

COENZYME Q-10: EFFICACY, SAFETY, AND USE

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OBJECTIVES

Upon completion of this article, participants should be able to do the following:

1. Comprehend the functions of CoQ-10 in mammalian metabolism.
2. Evaluate the preclinical and clinical literature on CoQ-10 supplementation that supports (or in some cases does not support) its therapeutic uses.
3. Apply this knowledge of potential therapeutic applications and health benefits of CoQ-10 supplementation to clinical practice.
4. Understand the dosage, formulation and safety issues related to the use of CoQ-10 as a supplement.

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In 1957, Crane and coworkers isolated from mitochondrial lipids in bovine heart a compound they named "coenzyme Q," which they proposed was a mediator of electron transport within the cellular respiratory chain.¹ Subsequent structural determination revealed that the compound was identical to an earlier described quinone, named *ubiquinone* because of its widespread occurrence.²

In 1975, the International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology (IUPAC-IUB) Commission on Biochemical Nomenclature established this name as the "official" scientific designation for the compound, referring to its quinoid structure. This permitted easy reference to the partially reduced (ubisemiquinone) and fully reduced (ubiquinol) forms of the compound that reversibly interconvert via redox reactions. This property is key to ubiquinone's roles in electron and proton transport in mitochondrial respiration coupled to synthesis of adenosine triphosphate (ATP) and its use as a powerful lipophilic antioxidant.²

CHEMISTRY

More commonly known as CoQ-10, ubiquinone is widely distributed in nature, where it is biosynthesized *de novo* in animals (including humans), plants, and microbes. Additionally, several homologues of CoQ-10 are known from various organisms. The homologues differ from CoQ-10 in the length of the lipophilic isoprenoid side chain.³ In birds, fish, and most mammals, only CoQ-10 itself is found. The major exception is a rodent that has the major CoQ-10 homologue called coenzyme Q-9 (the homologue of CoQ-10 containing 9 isoprene units) in addition to smaller amounts of CoQ-10. Rodent CoQ-10 biochemistry differs in that it also features shorter homologues of CoQ-10, including coenzyme Q-7 and coenzyme Q-8 in various tissues.⁴

CoQ-10 biosynthesis in mammals is characterized by the convergence of 2 metabolic pathways. The quinone moiety is derived from tyrosine or phenylalanine, which are converted over several steps to 4-hydroxy-benzoate. The isoprenoid side chain is biosynthesized from acetyl-Coenzyme A (acetyl-CoA) via

the mevalonate pathway, through which cholesterol is produced as well. Acetyl-CoA is converted via several enzymatic steps to farnesyl-pyrophosphate, the common precursor to both CoQ-10 and cholesterol. Farnesyl-pyrophosphate is then converted to decaprenyl-pyrophosphate (or solanesyl-pyrophosphate in rodents) and condenses with 4-hydroxy-benzoate, producing decaprenyl-4-hydroxy-benzoate, which results in CoQ-10 after several more biosynthetic steps.²

As noted previously, CoQ-10 is a fundamental redox component of the respiratory chain within inner mitochondrial membranes. All respiratory chain enzymes except cytochrome oxidase require CoQ-10 as a coenzyme.³ As lipophilic, freely diffusible components of the mitochondrial membrane, both CoQ-10 and cytochrome-c mediate the electron transfer between complexes. This flow of electrons (from redox pairs with a more negative redox potential to pairs with a more positive redox potential) drives proton pumps that generate an electrochemical gradient (via the flow of protons from the mitochondrial matrix). The resulting "proton motive force" across the inner mitochondrial membrane is used to drive ATP synthase (complex V of the respiratory chain), whereby the protons are channeled back into the mitochondrial matrix where ATP, the "cellular currency of energy," is produced.³

THERAPEUTIC APPLICATIONS

In one study, CoQ-10 status was determined to be inadequate in 40% of women and 24% of healthy people more than 90 years of age.⁵ An experimental study of aging in the rat has shown some decrease of mitochondrial CoQ-10 content in the heart, and even greater decrease in the liver and skeletal muscle. The authors reason that CoQ-10 administration may be beneficial in the elderly because of the aging body's increased demand for antioxidants.⁶

Mitochondrial CoQ-10 levels are influenced by numerous factors, including dietary fat and physical exercise. A study conducted by Mataix et al⁷ suggests monounsaturated dietary fats increase CoQ-10 mitochondrial contents, whereas polyunsaturated fats decreased CoQ-10 levels. Another study found that the highest mitochondrial CoQ-10 content was found in a diet supplemented with corn oil.⁸ A possible interpretation is that oil subjected to thermal treatment represents an oxidative insult, subsequently provoking a net decrease in endogenous CoQ.⁷ Only in the polyunsaturated fat diet were CoQ-10 levels elevated in response to aerobic performance.⁷

New studies have shown that CoQ-10's unique biochemistry has diverse applications in all cellular membranes. One important function of CoQ-10 is in plasma membrane electron transport. CoQ-10 potentiates the activation of signaling protein kinases related to gene expression in cellular proliferation. In addition, CoQ-10 has recently been found to function as a co-antioxidant with tocopherol (within membranes) and ascorbate (both intracellularly and extracellularly, via CoQ-10's ability to maintain both of these compounds in their reduced states).¹

The ubiquinol/ubiquinone ratio in plasma has been proposed as a marker of oxidative stress.⁹ Oxidative stress has been defined as a disturbance in pro-oxidant/antioxidant balance,

which is biased toward greater pro-oxidant activity. Pro-oxidant activity is alleged to be a factor in aging as well as in various pathological conditions. Patients who experience oxidative stress have more CoQ-10 than ubiquinol compared to healthy patients.¹⁰ CoQ-10 levels reach their peak in most tissues by the time a person reaches the age of 20 and then fall slowly thereafter. This decrease in CoQ-10 content during aging is consistent with the "free-radical theory of aging," as demonstrated by the inverse correlation between longevity and peroxide-producing potential in mammalian tissues. Disorders observed during the process of aging may relate to the diminished capacity of an organism to maintain adequate ubiquinol levels in relation to the necessity for protection from oxidative insult.²

The role of the ubisemiquinone radical in respiratory chain redox cycling has raised the question of the possible role of this compound in the generation of oxygen radicals; that is, a pro-oxidant effect.² An increasing body of evidence, however, refutes the assumption that free-radical generation is an inevitable side effect of respiration.¹¹ Schnurr and colleagues have reported another type of pro-oxidant effect for CoQ-10 that involves 15-lipoxygenase in the biologically programmed degradation of mitochondria during the maturation of red blood cells.¹¹

To date, the main application of CoQ-10 has been the treatment of cardiological disease, including congestive heart failure, hypertension, angina pectoris, and arrhythmias.^{12,13} Doses were usually 100 mg/d,¹³ and in some trials up to 240 mg/d.¹² Male patients with effort angina and ischemic heart disease have shown normal levels of CoQ-10 in muscles of the diaphragm, gastrocnemius, and vastus lateralis, but levels in intercostal muscles were lower compared to those of healthy individuals.¹⁴ Levels of endogenous CoQ-10 and succinate-CoQ-10 oxidoreductase, key components of complex II of the mitochondrial respiratory chain, are reported to be depressed in myocardial tissue and blood samples of patients with cardiomyopathy and other cardiac diseases. The magnitude of these deficiencies is proportionate to the severity of disease, and decreasing levels of CoQ-10 are correlated with a decline in patient status.¹³ Data on the effective treatment of cardiomyopathy with CoQ-10 suggest that a myocardial deficiency of CoQ-10 may be one cause of cardiac dysfunction.

PRECLINICAL STUDIES

Cardiovascular and Circulatory Functions

Hypertension. In stroke-prone, spontaneously hypertensive rats, CoQ-10 treatment attenuated the blood pressure elevation, the degradation of membrane phospholipids, and the enhanced phospholipase A₂ activity in the renal membrane. Researchers speculated that these effects were due to a renal membrane-stabilizing activity of CoQ-10.¹⁵

Ischemia-Reperfusion Injury. Several reports exist in the literature indicating a protective role of CoQ-10 against ischemia-reperfusion injury. A study was conducted in swine hearts to determine the mechanism of action by which CoQ-10 protects heart tissue.

➤ The results of the study demonstrated that pigs fed CoQ-10 (5 mg/kg/d) for 30 days fared significantly better: they had less

myocardial infarction and less creatine kinase release. The hearts of animals fed CoQ-10 had higher levels of CoQ-10, higher levels of the intracellular antioxidants ascorbate and thiol, and an increased amount of ubiquitin gene expression, all of which may contribute to the observed increased resistance to ischemic injury.¹⁸ Results of this study suggest that nutritional supplementation with CoQ-10 renders the heart resistant to ischemia-reperfusion injury, probably by reducing oxidative stress.

In addition to swine hearts, the effects of CoQ-10 on ischemia-reperfusion injury have also been studied in rat livers. Pentoxifylline (PTX) is a hemorrheologic drug that improves capillary blood flow by increasing erythrocyte flexibility and reducing blood viscosity. Portakal et al¹⁹ have investigated whether the addition of CoQ-10 to PTX treatment affects the outcome of laboratory-induced ischemia-reperfusion injury. Whereas PTX treatment alone did not cause beneficial effect in the measured outcome variables, the combination of CoQ-10 and PTX pretreatment proved useful. This combination prevented glutathione depletion and curbed the elevation of malondialdehyde, catalase, and superoxide dismutase typically seen in ischemia-reperfusion injury.

Thrombosis, Hemostasis, and Embolism. In a randomized, placebo-controlled study in female pigs, Serebruany et al²⁰ found that CoQ-10 (100 mg twice a day for 20 days) decreased levels of eicosanoids and endothelin-1, a potent endothelium-derived vasoconstrictor. Abnormal hemostasis plays an important role in the pathogenesis of coronary artery disease, and free radicals have strong platelet proaggregatory properties. Dietary CoQ-10 supplementation was examined in experiments using swine (chosen for their hemostatic parameters, which are similar to those of humans). Serum levels more than doubled after 20 days of supplementation with 200 mg of oral CoQ-10. This was correlated with decreases in ADP-induced platelet aggregation, eicosanoid levels, and levels of endothelin-1. Researchers surmised that some of the reported clinical benefits with regard to cardiovascular morbidity and mortality of CoQ-10 supplementation may be due to improved hemostatic profile and a reduction in possible thrombotic and thromboembolic complications.

The effect of CoQ-10 was assessed on aortic lipoprotein lipid peroxidation and atherosclerosis in apolipoprotein-E -/- mice fed a high-fat diet. CoQ-10 treatment significantly decreased atherosclerotic lesions in the aortic root and descending aorta and decreased the absolute concentrations of hydroperoxides of cholesteryl esters and triacylglycerols.²¹

Rabbits fed a diet rich in trans fatty acids were supplemented with 3 mg/kg/d of CoQ-10 in a randomized, single-blind, controlled trial. Intervention with CoQ-10 was associated with changes indicative of decreased oxidative damage. The aortic and coronary artery plaque sizes and the atherosclerosis scores of each were significantly lower in the CoQ-10 group versus placebo. Aortic and coronary plaque frequencies, as well as frequencies of ulceration, thrombosis, or hemorrhage and cracks and fissures, were also significantly lower in the CoQ-10 group. These and other markers from the study suggest that CoQ-10 can have a beneficial effect on the chemical composition of atheroma.²²

Metabolic and Nutritional Functions

Antioxidant Activity. CoQ-10 potentiates the antioxidant efficacy of vitamins E and C via its ability to recycle them from their oxidized states (ie, to reduce the oxidized forms of both). Vitamin E is recycled within membranes and low-density lipoproteins (LDL), and vitamin C from inside and outside the cell.^{1,2}

Subarachnoid hemorrhage in humans can be complicated by the development of a delayed cerebral vasospasm (an arteriopathy), which can result in ischemic brain damage and permanent neurological deficits.²³ Putative causal mechanisms for this kind of vasospasm include immunologically mediated inflammatory changes as well as epithelial damage to cerebral arteries via hemoglobin-generated free-radical peroxidation of membrane lipids. Researchers also have noted similarities between atherosclerosis and arteriopathy that occurs after subarachnoid hemorrhage, suggesting a common mechanism involving free-radical-induced peroxidation of low-density lipoprotein (LDL). A rabbit model of subarachnoid hemorrhage uses carotid artery ligation, followed at 2 weeks by injection of autologous blood into the subarachnoid space. Using this system, Grieb et al²⁴ treated rabbits with oral CoQ-10 (10 mg/kg/d) or inactive fluid. A third of the untreated group died before the end of the experiment, and all surviving rabbits showed moderate to severe neurological deficits. All untreated animals had widespread brain lesions associated with disappearance of neurons and loss of myelin. All CoQ-10-treated animals survived, no brain lesions could be found, and no neurological deficits could be observed. The researchers surmised that the central nervous system damage in this model was due to free radicals generated from auto-oxidation of hemoglobin in the autologous blood injection, rather than the initial ligation, and that the resulting peroxidized plasma LDL was the ultimate mediator of the brain damage. Grieb et al²⁴ inferred that the affinity of CoQ-10 for LDL and its antioxidant activity were responsible for the observed positive effects in this model.

CoQ-10 has been shown to occur throughout all mammalian cells, where it likely has a membrane-stabilizing function in addition to its redox and antioxidant activities.⁴ CoQ-10 is discharged to a limited extent into the blood, where it is bound to serum lipoproteins.²

CoQ-10 inhibits initiation and propagation of lipid peroxidation as well as oxidation of proteins and DNA.² The antioxidant efficacy of CoQ-10 is due to its access to the proton motive cycle within the mitochondrial respiratory chain. After quenching a free radical, CoQ-10 may be recycled within plasma membranes and cytosol by quinone reductases.^{2,25,26}

Unlike cholesterol, endogenous CoQ-10 is not distributed among different tissues via circulation.² In the tissues of humans and other mammals, a portion of the endogenous CoQ-10 (ubiquinone) is found as ubiquinol, the reduced form in which it is active as an antioxidant. The ratio of reduced to oxidized species varies from one tissue type to another. In humans it can range from as low as ~25% in lung and brain to 95% to 100% in intestine, liver, and pancreas.² Quinone reductases have been identified in cytosol and plasma membranes, which function to maintain CoQ-10 in the reduced state.^{25,26}

Studies in rats with altered oxidative metabolism (eg, low-temperature acclimation or thyroid hormone treatment) revealed changes in CoQ-10 levels in highly aerobic tissues that paralleled the increases in metabolic rate and resultant free-radical production. The increase in CoQ-10 levels following thyroid hormone treatment paralleled the increase in metabolic rate, suggesting that the increase was an adaptation to the oxidative rate increase rather than the cause of it.²

Pharmacokinetics. CoQ-10 pharmacokinetics were investigated in rat tissues after oral treatment. CoQ-10 passed quickly from plasma into tissues such as the liver, which showed maximal CoQ-10 concentrations. The results indicated that oral treatment makes it possible to obtain good tissue levels of CoQ-10 that might be of clinical value against endogenous CoQ-10 insufficiencies due either to pathological alterations or to drug administration.²⁷ More recently, researchers reported that a 2-month treatment with orally administered CoQ-10 increases cerebral cortex concentrations in rats by 30%.^{28,29}

Kommuru et al³⁰ examined the bioavailability of a commercially marketed CoQ-10 oil-based formulation and powder-filled capsule products in beagle dogs in an open, randomized, multiple-dose crossover design study. The oral absorption of both formulations proved slow and poor, and while not significantly different in terms of pharmacokinetic parameters, the results were in agreement with bioavailability studies in humans that showed a lack of significant difference between oil-based and granular (soft gelatin and tablet, respectively) forms of CoQ-10. In shelf-life tests, most degradation of CoQ-10 occurred at temperatures of 45°C and 55°C (113°F and 131°F). Stability was improved more by the addition of EDTA (.1%) and ascorbic acid (5%) than by the addition of propyl gallate (PG), butylated hydroxy anisole (BHA), or butylated hydroxy toluene (BHT). Kommuru et al noted that when BHA concentrations were increased by 400% or PG concentrations by 300%, degradation of CoQ-10 accelerated. They added that CoQ-10 appears yellow upon exposure to light and turns a dark yellow as it decomposes. Preparations of CoQ-10 in solution are more prone to degradation in light than are solid preparations. Shelf life at room temperature was 6.3 years, based on time to reach 90% potency, and no degradation occurred at 37°C (98.6°F) for a period of 12 months. Preliminary (unpublished) studies by Kommura and colleagues indicate that some commercial CoQ-10 products lack a stable shelf life. In conclusion, they suggest that stable formulations of the supplement may be possible by formulating with EDTA (.1%) and ascorbic acid (5%).

Protection from Adriamycin-induced Cardiotoxicity. Doxorubicin (adriamycin), an anthracycline type of antimalignant tumor agent, is widely used in chemotherapy regimes, but the severity of side effects, such as cardiotoxicity and suppression of bone marrow functions, limits its clinical use. The mechanism of adriamycin (ADM)-induced toxicity may be mediated by microsomal lipid peroxidation resulting from cell membrane damage.³¹ CoQ-10 may stabilize the heart microsomal membrane lipid or may improve the myocardial mitochondrial functions under such insult.³²

When CoQ-10 was given to rats in conjunction with ADM treatment, no significant change in mitochondrial electron transport chain was observed in cardiac cells. Without CoQ-10, significant decreases were noted in complex I activity of the transport chain.³³ Other research suggests that the beneficial effect of CoQ-10 against ADM-induced cardiotoxicity appears not to be the result of its role in the respiratory chain, but a consequence of its antioxidant action.³⁴

Neurological, Psychological, and Behavioral Functions

Neurotoxicity and Neuroprotection. Matthews et al²⁹ reported neuroprotective effects from CoQ-10 powder in studies with 12- and 24-month-old male rats given a high dose (200 mg/kg/d orally for 2 months) as part of their normal diet. The 12-month-old rats experienced an increase in cerebral cortex levels of CoQ-10 of about 30%, levels usually found in animals 2 to 3 months old. Cerebral cortex mitochondrial levels of CoQ-10 also showed a significant increase after 60 days, compared to controls. An increase in CoQ-10 levels of about 8% in the 24-month-old rats after 1 month of the diet was also significant ($P < .05$). Rats that received the same diet for 1 week before receiving 3-nitropropionic acid-induced striatal lesions (resembling those of Huntington's) disease developed lesions significantly reduced in size compared to controls ($P < .001$). Using a transgenic model of familial amyotrophic lateral sclerosis in transgenic mice (of the G1 line) that express high levels of human superoxide dismutase, the same diet resulted in a significant increase in animal survival ($P < .05$) compared to controls on the same diet without CoQ-10 supplementation. Similar effects were not found with vitamin E supplementation, though vitamin E does reduce disease onset in these mice. Matthews et al concluded that CoQ-10 might be a useful adjunct in treating Huntington's disease and other neurodegenerative diseases.

The symptoms of Huntington's disease might arise from glutamate-mediated excitotoxicity and abnormalities in mitochondrial energy production. Using a mouse model, Shilling et al³⁵ determined that supplementation with a combination of CoQ-10 and remacemide hydrochloride produced a transient improvement in motor performance 3 weeks after therapy was initiated. The combination therapy was ineffective at prolonging survival time in this study.³⁵

CLINICAL STUDIES

Cardiovascular and Circulatory Disorders

Cardiotonics and Cardioprotection. From a meta-analysis of the main placebo-controlled clinical trials on CoQ-10 (1986-1995), Soja and Mortensen³⁶ concluded that scores for various parameters of cardiac function were significantly better for patients treated with CoQ-10 than for patients given placebo. An average 73% of patients treated with CoQ-10 displayed improved cardiac output ($P < .05$), 76% ($P < .005$) had increased stroke volume, cardiac index was improved in 87% ($P < .001$), diastolic index in 88% ($P < .001$), and ejection fraction in 92% ($P < .001$).

Watson et al³⁷ reported no significant benefit from CoQ-10 in 30 men with congestive heart failure (aged 44 to 66 years)

diagnosed with chronic left-ventricular dysfunction (echocardiography less than 35%) secondary to idiopathic or ischemic dilated cardiomyopathy. The randomized, double-blind, placebo-controlled, crossover trial found no difference of any significance after treatment with CoQ-10 compared to placebo in functional capacity, well-being (quality of life according to the Minnesota Living With Heart Failure questionnaire), cardiac volumes, or left-ventricular ejection fraction; nor were changes of any significance evident in the hemodynamic data. Watson et al noted that both the dosage and duration of the therapy (33 mg orally 3 times daily for 3 months) were comparable to those used in other trials of CoQ-10. The patients had a history of chronic heart failure of 6 months to 6.25 years, left-ventricular dysfunction for 3 months or more, and were clinically stable on angiotensin-converting enzyme inhibitor. Daily medications taken concurrently with CoQ-10 during the trial by the vast majority of patients consisted of digoxin, nitrates and hydralazines, and furosemide. Watson et al commented that resting left ventricular ejection fraction did not improve under therapy with CoQ-10. However, no adverse events occurred, no altered hematologic parameters or deleterious changes in renal or hepatic function were found, and the patients achieved plasma levels of CoQ-10 of about double their baseline readings.

Singh and Niaz³⁸ examined the effect of CoQ-10 (Hydrosoluble Q-gel; Tishcon Corp, Westbury, NY) on serum alpha-lipoprotein in a randomized, double-blind, placebo-controlled trial in 35 patients diagnosed with acute coronary artery disease and a moderate elevation of alpha-lipoprotein. Alpha-lipoprotein is associated with both the occurrence and recurrence of cardiac death and myocardial infarction. The placebo group received a vitamin B-complex while the CoQ-10 group received a dose of 120 mg twice daily for the same 28 days. The results showed that, compared to placebo, there was a significant increase in the CoQ-10 group in levels of high-density lipoprotein (HDL) cholesterol and significant decreases in fasting blood glucose, malondialdehyde (MDA), diene conjugates, lipid peroxides, and especially alpha-lipoprotein ($P < .001$), which dropped by 31.0%, versus 8.2% in the placebo group. LDL and total cholesterol showed no change. Adverse events, mostly nausea (36%), vomiting (24%), and hypotension in the first week of therapy (24%), occurred in 30 subjects in the CoQ-10 group, compared to 13 subjects in the placebo group, and were assessed as mild.³⁸

Taggart and colleagues³⁹ studied the effects of short-term supplementation of CoQ-10 on myocardial protection during cardioplegia in a double-blind, placebo-controlled study of patients having well-preserved ventricular function. The CoQ-10 treatment group received 2 oral doses of 300 mg, the first on the evening before and the second on the morning of the cardiopulmonary bypass operation. These researchers found no difference between treated and untreated groups with regard to biochemical markers of cardiac injury, and no cases of low cardiac output requiring inotropic support; however, preoperative blood tests revealed no difference in plasma CoQ-10 levels between treated and untreated groups. These researchers suggested that this was

due to rapid uptake of exogenous CoQ-10 into plasma lipoproteins and subsequent concentration in liver, myocardium, and other sites, and that longer treatment durations led to a greater steady-state concentration of CoQ-10 in plasma. They also noted that their patient groups had relatively well-preserved ventricular function and short ischemic times. Taggart and colleagues concluded that patients whose myocardial function was the most impaired, with clear evidence of a deficiency in endogenous CoQ-10 such as those in heart failure or undergoing valve replacement, would benefit most from CoQ-10 supplementation.³⁹

Hofman-Bang et al⁴⁰ examined the effect of CoQ-10 in a double-blind, crossover, placebo-controlled study in which the treatment was an adjunct to conventional therapy. Patients were all diagnosed with stable chronic congestive heart failure. Thirteen of the patients were diagnosed at class II on the New York Heart Association (NYHA) functional scale, 60 at class III, and 6 at class IV. The vast majority were receiving treatments with diuretics, digitalis, and angiotensin-converting enzyme inhibitors. Hofman-Bang and colleagues reported that in their 3-month trial, compared to placebo, 100 mg/d of CoQ-10 (Pharmacia, Stockholm, Sweden) produced no significant differences in measurements of the ejection fraction, the primary endpoint of their study. However, CoQ-10 produced a significant increase ($P < .05$) in ejection fraction during the volume-load test with legs up, as well as significant improvement ($P < .05$) in maximum exercise tolerance. Also significant ($P < .05$) was the decrease in the end-of-exercise score for leg fatigue and dyspnea, and the difference in the quality-of-life questionnaire total score versus placebo ($P < .05$), in which life satisfaction and physical activity scores were significantly higher than those in the placebo group. No significant changes were found in blood specimens, and no patients were changed from their initial NYHA classification. An insignificant difference was found in the number of patients in each phase of the study who reported side effects, none of which could reasonably be ascribed to CoQ-10. The authors concluded that, though the changes were significant in quality of life and exercise capacity, these were still only slight improvements, and the clinical importance of these differences remained unclear.⁴⁰

Langsjoen et al⁴¹ recorded the clinical outcomes of 424 cardiovascular disease patients who received CoQ-10 as an adjunct therapy over a period of 8 years. Doses averaged 242 mg/d (75 to 600 mg/d), and in many cases the goal was to reach a whole-blood level of ≥ 2.0 mg/mL. An average whole-blood level of 2.92 mg/mL was achieved in 297 subjects. Regardless of the different categories of patients, clinical responses were evaluated according to the NYHA functional scale. Compared to baseline readings, significant improvements were recorded in the majority in fatigue, chest pain, palpitations, and dyspnea, along with improvements in the NYHA functional scale according to classes of function; 247 subjects improved by 1 class; 120 subjects improved by 2 classes. The authors point out that, apart from 1 subject reporting transient nausea, there were no side effects from CoQ-10, and improvements were gradual and sustained.⁴² It is interesting to note that these researchers found that over time, absorption of CoQ-10 commercial products

could be enhanced by chewing and swallowing a fat-containing food; for example, peanut butter.

Cardioplegia is the process by which cardiac function is temporarily arrested via hypothermia, medication, or electrical stimuli to reduce myocardial oxygen demand during cardiopulmonary bypass. Chen et al⁴³ reported that a double-blind trial of the effectiveness of oral CoQ-10 pretreatment (150 to 200 mg/d for 5 to 7 days, 1000 mg total) on myocardial preservation during cardioplegia revealed the following:

- Treated patients displayed better preservation of myocardial function, as demonstrated by a slightly decreased incidence of low cardiac output and wider pulse pressure.
- Treated patients' right and left ventricular myocardial structure was better preserved.
- No demonstrable benefit could be found regarding preservation of atrial myocardium.

Chen and coworkers noted that in both groups, atrial function was less well preserved because of the following:

- Topical cooling of the atrium was less effective because of its position during cardioplegia (maintenance of profound hypothermia is paramount in protecting myocardial tissue).
- Noncoronary collateral blood flow caused early washout of the cardioplegia solution.
- Cardioplegic solution was delivered differentially; all atrial regions received approximately half as much solution per gram of tissue as did the ventricles.

Chen et al⁴³ concluded that CoQ-10 helps preserve ventricular myocardial function during cardioplegic arrest, most likely via its effects on cellular energetics, membrane stability, and myocardial oxidative load.

Permanetter and colleagues⁴⁴ conducted a placebo-controlled, double-blind, crossover study with CoQ-10 (33.3 mg given orally 3 times/day) in 25 chronic heart failure patients (aged 31 to 71 years) diagnosed with dilated cardiomyopathy. Four patients were symptom free at NYHA class I, 7 were at class II, and 15 were at class III. The 2 groups of patients were well-balanced except that 15 patients in group 2 were taking digitalis, compared to 8 patients in group 1. CoQ-10 was suspended in soya oil and provided in capsules (Zyma GmbH; Munich, Germany). The other accompanying medications were diuretics, nifedipine, and nitrates. Results showed that while only 1 patient had to be excluded because of the need for a heart transplant, there were no significant differences between placebo and CoQ-10 in any measurements, either in the cardiothoracic ratio, maximum exercise capacity, exercise tolerance, echocardiography of the left ventricle, left ventricle ejection time, stroke volume index, or cardiac index. No side effects could be ascribed to CoQ-10, and function tests of liver and kidneys, blood count, and serum levels of electrolytes showed nothing out of the ordinary. The authors commented that 1 reason for the equivalent results might have been that other trials involved patients in worse condition than theirs.⁴⁴

Judy et al⁴⁵ recorded improved long-term survival for patients with NYHA class IV congestive heart failure who were treated with CoQ-10, when compared with a conventionally treated control

group. Congestive heart-failure patients on CoQ-10 were also found to relapse when taken off this treatment. Judy et al studied the short-term effect of CoQ-10 (100 mg/d for 90 days) in 14 NYHA class IV patients, aged 52 to 76 years, who had been diagnosed with cardiac failure. The randomized, double-blind, placebo-controlled, crossover study found that patient response to CoQ-10 varied, with some patients showing improvements in cardiac function after 30 to 45 days and others showing improvements after 60 to 90 days. CoQ-10 treatment for 90 days resulted in patients' cardiac index attaining normal levels; however, left ventricular end diastolic volume index and ejection fraction showed no normalization, nor was there improvement after a year of treatment with CoQ-10 in these patients. Judy et al concluded that their results supported previous findings with CoQ-10 in congestive heart failure, adding that if CoQ-10 treatment is stopped, a gradual decrease in cardiac function ensues at variable rates from 1 patient to the next. Patients who showed declining cardiac function during the placebo phase showed improvement when they were treated again with CoQ-10 after 180 days.

Poggesi and colleagues⁴⁶ conducted a double-blind, placebo-controlled, crossover study of the effects of CoQ-10 (100 mg/d orally for 60 days) in patients with dilative cardiomyopathy. Significant improvement in left ventricular systolic function was noted following CoQ-10 treatment. After a 30-day washout period, effects returned to baseline levels, indicating that functional improvement was linked to drug administration and, therefore, to serum and myocardial levels of CoQ-10. Since the improved function was seen in both ischemic and idiopathic cardiomyopathies, the therapeutic efficacy of CoQ-10 was independent of coronary blood flow. These researchers concluded that oral CoQ-10 is a safe and effective treatment for dilative cardiomyopathies of different etiology and that this efficacy may be due to CoQ-10's supportive and enhancing effect on myocardial tissue energetics.⁴⁶

Serra et al⁴⁷ reported beneficial results from CoQ-10 (60 mg/d orally for 28 days) added to "usual treatment" in a randomized, double-blind, crossover, placebo-controlled study of 20 chronic ischemic heart disease outpatients (aged 44 to 70 years, with 15 in NYHA class II and 5 in class III) diagnosed with symptoms of stable-effort angina, sinus rhythm, and mild or moderate heart failure. The condition of 13 of the patients resulted from chronic artery disease; the condition of the remainder was from left ventricular hypertrophy resulting from left ventricular hypertension. Study results showed that, compared to placebo, CoQ-10 produced a significant improvement in heart failure scores, cardiothoracic ratio, number of angina attacks per week, stroke volume, cardiac output, exercise duration (26 minutes versus 3 minutes for placebo, $P < .01$) and endpoint, workload, and a significant reduction in the number of nitrate tablets consumed per week ($P < .01$). At the end of the treatment period, 4 of the 5 patients in NYHA class III were diagnosed class II, and 4 of the 15 NYHA class II patients improved to NYHA class I. Side effects from CoQ-10 were insignificant, with 3 patients reporting slight gastralgia.⁴⁷

A double-blind, double-crossover, placebo-controlled trial involving 19 patients with chronic, stable, moderately advanced myocardial disease found that treatment with oral CoQ-10 (33 mg

3 times daily for 24 weeks) resulted in improvements in myocardial function that were positively correlated with increasing blood levels of CoQ-10, demonstrating that CoQ-10 deficiencies in humans are treatable through supplementation. A decline in cardiac function was correlated with a decrease in CoQ-10 levels when patients were moved to placebo, indicating that the causes of the initial deficiency were not affected. Clinical improvement was demonstrated by tolerance of increased activity in 95% of the patients; some of the physical improvements were reported to be remarkable. No adverse reactions to the drug were reported.¹³

These researchers¹³ theorized that the remarkable clinical improvement in the patients' cardiomyopathy resulted from improved bioenergetics, which support improved cardiac function of impaired but still viable myocardial cells. The reappearance of symptoms of dysfunction when CoQ-10 was replaced by placebo suggested to these researchers that CoQ-10 deficiency might be a major cause of cardiomyopathy and that lifetime therapy with CoQ-10 may be mandatory for the cardiac patient.

Hypertension. Singh et al⁴⁸ studied the effect of 60 mg of CoQ-10 (Q-gel hydrosoluble CoQ-10 Softules; Tishcon Corp, Westbury, NY) given twice daily for 8 weeks in 64 coronary artery disease patients being treated with antihypertensive medication for more than 1 year to test the hypothesis that CoQ-10 could decrease oxidative stress and blood pressure in these patients. The randomized, double-blind trial was performed as part of a main trial of CoQ-10 in acute coronary artery disease (previously published⁴⁹). The control group received a B-vitamin complex in capsules. When compared to the placebo group, a significant decrease was found in the men treated with CoQ-10 in diastolic and systolic blood pressure, waist-to-hip ratio, and heart rate. Fasting triglyceride levels, 2-hour plasma insulin, fasting insulin, and plasma glucose levels all showed a significant decrease in the CoQ-10-treated patients compared to placebo. HDL cholesterol levels were significantly increased compared to the control group, and significantly fewer patients treated with CoQ-10 used sublingual trinitrate every day, experienced angina pectoris, or used diltiazem, enalapril malate, metoprolol, or nitrate compared to the placebo group. Indicators of free radical stress (diene conjugates, lipid peroxides, and MDA) also decreased significantly in the CoQ-10 group, and this group's levels of vitamins C, E, and beta carotene showed a significant increase. The B-vitamin control group showed a significant increase only in beta carotene and vitamin C. CoQ-10 treatment resulting in decreased blood pressure has previously been reported by others.⁵⁰

A 12-week, randomized, double-blind, placebo-controlled trial with twice daily oral administration of 60 mg CoQ-10 resulted in a mean reduction in systolic blood pressure of 17.8 ± 7.3 mm Hg. All subjects discontinued any existing antihypertensive therapy before participation in the study. Analysis of individual patient data revealed that 55% of patients in the CoQ-10 treatment group achieved a reduction in systolic blood pressure of >4 mm Hg, while 45% of patients were nonresponders. In the subset of patients who were responders, the average reduction in systolic blood pressure was 25.9 ± 6.4 mm Hg.⁵¹

Thrombosis, Hemostasis, and Embolism. Serebruany et al,⁵² in an open-label study, treated 12 normal volunteers with oral CoQ-10 (200 mg/d). At day 20 of treatment, serum levels of CoQ-10 had increased from a mean of .6 mg/mL to 1.8 mg/mL. This was correlated with a decrease in platelet size and platelet vitronectin receptor expression. Platelet size is positively correlated with platelet activity, and vitronectin is a serum glycoprotein that promotes cell adhesion, among other processes. The researchers speculated that some of the known clinical benefits of CoQ-10 for cardiovascular disorders were partially due to inhibition of platelet activity.

In an open-label study,⁵² CoQ-10 decreased platelet aggregation and also decreased platelet size in healthy volunteers (aged 24 to 43 years) of both sexes who were given 100 mg CoQ-10 twice a day for 20 days. In an 8-week open-label study,⁵³ CoQ-10 decreased blood viscosity in ischemic-heart-disease patients (mean age 49 ± 16 years) given 20 mg CoQ-10 3 times daily. CoQ-10 decreased blood viscosity without affecting the patients' hematocrit or fibrinogen levels.

In an 8-week study,⁵³ Kato et al found that blood viscosity (expressed as yield shear stress) was reduced in their 12 subjects, while hematocrit (red blood cell count) and fibrinogen levels were not affected. Since hematocrit and fibrinogen levels were not affected by CoQ-10 treatment, these researchers speculated that the effects of CoQ-10 on membrane properties were the cause of the observed effect by diminishing erythrocyte aggregation and improving erythrocyte deformability.

Congestive Heart Failure. In a randomized, double-blind, controlled trial, the effect of coenzyme Q-10 was assessed in 55 patients with congestive heart failure. Although the mean serum concentration of CoQ-10 increased in patients who received active treatment, the ejection fraction, peak oxygen consumption, and exercise duration remained unchanged in both CoQ-10 and placebo groups. Subjective parameters were not monitored in the study.⁵⁴

Endocrine and Hormonal Disorders

Diabetes. Miyake et al⁵⁵ conducted a comparative treatment study with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (simvastatin and pravastatin) on CoQ-10 levels in 97 noninsulin-dependent diabetes mellitus patients and 53 healthy volunteers. In noninsulin-dependent diabetes patients with undiagnosed hypercholesterolemia who were subsequently treated with HMG-CoA reductase inhibitors, cholesterol levels decreased along with levels of CoQ-10. Oral CoQ-10 supplementation (Neuquinon; Eisai Co, Ltd, Tokyo, Japan; 30 mg/d for 6 months) had no effect on cholesterol levels and resulted in a highly significant increase in serum CoQ-10 levels. In 14 of 17 patients,⁵⁵ there was a significant decrease in the cardiathoracic ratio, suggesting a previously undiagnosed subclinical diabetic cardiomyopathy that may have responded to treatment with CoQ-10. Treatment with CoQ-10 caused no side effects.

In diabetics with certain types of mitochondrial DNA mutations, and in those with multiple deletions, oral CoQ-10 treatment (150 mg/d for 3 years) has been shown⁵⁶ to significantly improve insulin secretory response. Exercise-induced blood

lactate concentrations also were reduced significantly in patients with the mitochondrial DNA multiple deletions. Treatment did not improve diabetic complications or neurosensory deafness.

Oral CoQ-10 treatment (30 mg/day given orally) has been reported to stimulate insulin synthesis and peripheral glucose utilization and decreases fasting blood sugar levels in diabetics.⁵⁷

Immune Disorders

Cancer. Increasing evidence implicates free radicals in the pathogenesis of cancer development. In an attempt to determine whether reactive oxygen species are associated with malignant cells, Portakal et al⁵⁸ found an overexpression of antioxidant enzymes and depleted concentrations of CoQ-10 in the breast tissue of tumor and surrounding tumor-free tissues following mastectomy. The authors suggest that CoQ-10 levels may be depleted by excessive reactive oxygen species and that supplementation may provide protection against the development of breast cancer.

Complete regression of cancer in some high-risk cases was thought⁵⁹ to be due to CoQ-10 supplementation. Similar cases have been reported where complete disappearance of metastases accompanied CoQ-10 administration as an adjunct to chemotherapy and radiation. While the use of these standard techniques makes the ascription of sole therapeutic efficacy to CoQ-10 problematic, the excellent results seen in preliminary studies are thought by some workers to be due to the immunological activities of CoQ-10.

Chemotherapy Adjunct Treatments. CoQ-10 has been used as a treatment for the cardiotoxicity induced by cancer chemotherapeutic agents. The concurrent use of CoQ-10 during 4'-epidoxorubicin (epirubicin) chemotherapy for breast cancer was associated with an amelioration of epirubicin-induced cardiac dysfunction.⁶⁰ Treatment with CoQ-10 after discontinuation of chemotherapy has been associated with partial reversal of adriamycin-induced cardiotoxicity.⁶¹ There are possible contraindications for this practice, namely that concurrent use of CoQ-10 and adriamycin may be problematic due to high kidney and heart concentrations of adriamycin's primary metabolite (as noted in mice treated with CoQ-10). Isoprenoids are known to increase the cytotoxicity of anticancer agents through enhanced uptake of the drug and/or its metabolites.³¹

Adult patients treated with anthracyclines had a lower myocardial and blood CoQ-10 content than controls.¹⁴ Conversely, a similar study conducted by Eaton et al⁶² demonstrated a highly significant increase in plasma CoQ-10 levels during a course of doxorubicin treatment. Whereas the former study was conducted on adults, some of whom had evidence of cardiotoxicity, the subjects in the latter study were children and adolescents, none of whom had clinical evidence of cardiotoxicity. Interestingly, in rats exposed to doxorubicin,³³ no significant decrease in the activity of complex I of the mitochondrial electron transport chain was observed in rats aged 13 weeks, but significant decreases in the activity in rats aged 35 weeks were observed when compared to control groups. Age and evidence of dysfunction may be factors of significant importance when determining the appropriateness of supplementation during such therapy.

HIV/AIDS. In a blinded study, Bui et al⁶³ found plasma levels of CoQ-10 in HIV-positive patients significantly lower than in normal individuals and lower in a more progressed stage (Centers for Disease Control level 4 or 5) compared to a less advanced stage of infection (level 2 or 3).

CoQ-10 (200 mg/d) increased the ratios of thymus-derived lymphocytes (T4 helper to T8 suppressor cells) in some AIDS patients⁶⁴ and in 12 of 14 apparently healthy control subjects of both sexes (aged 34 to 66 years) given 100 mg/d for 2 months in an open-label study.⁶⁵

Immune Modulation. CoQ-10 (60 mg/d in some cancer, diabetes, and cardiovascular disease patients) increased levels of immunoglobulin G, stimulated the host defense system, and enhanced phagocytic activity in murine models.^{59,66,67}

Lockwood et al⁵⁹ reported that a percentage of cancer patients display a marked deficiency in serum CoQ-10. These researchers noted that oral CoQ-10 (60 mg/d) increased levels of gamma G immunoglobulin in cancer patients, an effect presumed to be due to transcriptional increases in messenger RNA and a translational increase in apoenzymes for CoQ-10 enzymes.

The ratios of T4 helper to T8 suppressor cells are used as immunological parameters in both HIV infection and cancer. The T4/T8 ratio is depressed in both disorders, and the magnitude of the depression is correlated with the severity of the disease.⁶⁶ AIDS patients have also been reported to experience significant cardiac dysfunction, which some researchers believe is causally correlated with a marked serum deficiency of CoQ-10.⁶⁴ Folkers and coworkers⁶⁴ treated 14 normal subjects with oral CoQ-10 (100 mg/d for 2 months) to determine whether supplementation could increase serum T4/T8 levels. By the end of the treatment regimen, the T4/T8 ratios in the normal subjects had increased 25% (from 2.8 to 3.5), suggesting to these researchers that CoQ-10 might have utility in maintaining the immunologic status of patients suffering from AIDS.⁶⁵

Metabolic and Nutritional Disorders

Coenzyme Q-10 Deficiency and Respiratory-Chain Deficiencies. Mitochondrial encephalomyopathies represent a heterogeneous group of genetic disorders caused by various types of respiratory-chain dysfunction. Several hundred cases of deficiencies within the 5 major complexes of the respiratory chain have been described. Symptoms include mitochondrial encephalomyopathy with central nervous system and skeletal-muscle abnormalities, epileptic seizures, kidney failure, cognitive impairment, general weakness, and exercise intolerance. Thus far, these disorders have largely been untreatable. Rotig et al⁶⁸ identified widespread CoQ-10 deficiency in 2 siblings presenting with severe encephalomyopathy and kidney failure, thus identifying a potentially treatable subclass of respiratory-chain dysfunction. Treatment with 5 mg/kg/d of CoQ-10 resulted in a substantial improvement of the siblings' condition over 3 years of therapy.⁶⁸

Antioxidant Activity. Dlugosz and Sawicka⁶⁹ conducted a comparative study of CoQ-10 in a group of 24 workers (mean age 46 years) who had worked in the lacquer and paint industry for 8

to 38 years. Twelve of the workers received 10 mg CoQ-10 3 times daily for 4 weeks, while the other 12 received double the dose (30 mg 2 times daily) for 4 weeks. A separate reference group consisted of 20 healthy volunteers who were not employed in the industry (mean age 39 years). Compared to the lacquer and paint workers, subjects in the reference group showed a significantly lower level ($P < .01$) of peroxidation products in their blood serum as measured by levels of MDA with 4-hydroxynonenal (4-HNE). After week 4 of the treatment period, the researchers found no significant changes in total cholesterol, HDL, LDL, or triglyceride levels, although in some instances there were positive changes in the latter, more so in the high-dose group than the low-dose group (60% versus 42%). Compared to the reference group, a significant decrease in MDA with 4-HNE was noted in all the CoQ-10-treated groups ($P < .01$), with those having worked in the industry more than 20 years showing a greater decrease than those in the industry less than 20 years. Changes in superoxide dismutase and hydrogen peroxide were statistically insignificant.⁶⁹

Using a solubilized form of CoQ-10 (Hydrosoluble Q-gel; Tishcon Corporation, Westbury, NY), Singh et al⁴⁹ conducted a randomized, double-blind, placebo-controlled trial using 144 patients diagnosed with acute myocardial infarction or unstable angina. Patients were enrolled no later than 72 hours from the time of acute myocardial infarction symptoms. Those in the placebo group were given capsules containing B-complex vitamins; the active treatment group received 60 mg of CoQ-10 twice a day for the same 28-day trial period. Both groups received their other required treatments, including aspirin, nitrates, streptokinase, and nifedipine. The subjects were well matched except that the CoQ-10 group had significantly more smokers (28, compared to 18 in the placebo group, $P < .05$) and more patients taking nifedipine (20, compared to 10 in the placebo group). The results showed that compared to patients in the placebo group, patients in the CoQ-10 group developed significantly increased plasma levels of antioxidants (beta-carotene and vitamins A, C, and E) and significantly decreased levels of diene conjugates, lipid peroxides, and MDA (all $P < .05$ except vitamin E, $P < .01$). Regarding symptoms, the CoQ-10 group showed significantly less cardiac arrhythmia and poor function of the left ventricle (both $P < .05$) compared to the placebo group, as well as a significantly smaller number of total cardiac events ($P < .02$). The CoQ-10 group also showed a tendency toward fewer nonfatal infarctions and cardiac deaths compared to placebo, but not significantly fewer adverse events: hypotension in the first 7 days of treatment (16% compared to 7%), headache (12.3% versus 0%), body aches (6.8% versus 0%), epigastric discomfort (12.3% versus 9.8%), nausea (38.3% versus 15.4%), and vomiting (21.9% versus 9.8%). The authors note that cessation of smoking by the patients while they were in the hospital may have affected the outcome.⁴⁹

Oxidation of LDL plays an important role in the pathogenesis of atherosclerosis. In support of this, a Finnish study⁷¹ of 70 healthy volunteers measured the total peroxy radical trapping capacity of plasma LDL phospholipids. Trapping capacity was found to be significantly lower in those over 50 years of age. In

men, LDL-ubiquinol did not vary with age, and there was a statistically insignificant decrease in LDL-tocopherol for those over age 50 years. In women, mean trapping capacity, LDL-ubiquinol, and LDL-tocopherol levels did not vary with age. When 17 of the study participants were treated with oral CoQ-10 (100 mg/d), a significant increase in LDL-ubiquinol concentration was noted. The researchers concluded that LDL antioxidant defenses tend to decrease with age in the Finnish male population, and the decline is most notable in those under 50. In addition, the antioxidant defenses tend to remain stable at a low level in those over age 50 years. CoQ-10 supplementation increases the ubiquinol content of plasma LDL and may inhibit its oxidation and, therefore, the process of atherosclerosis.

Kucharska et al⁷² studied CoQ-10 levels and other parameters reflecting cellular bioenergetics in an open-label comparative study using heart transplant patients and patients with cardiomyopathies of unknown etiologies. They found mitochondrial respiration, phosphorylation, CoQ-10 levels, and creatine kinase activity similarly depressed in both groups of patients, with mitochondrial energy metabolism in cardiomyopathy patients comparable to that in posttransplant patients suffering from Degree I rejection. The researchers theorized that pathological changes in mitochondrial energetics, decreased CoQ-10 levels, and increased active oxygen species participate in the development of rejection in posttransplant patients. They noted that the most sensitive parameter studied was CoQ-10 concentration, which is depressed before rejection can be histologically detected. These workers proposed that CoQ-10 levels in endomyocardial biopsies be used as a biochemical marker of rejection and that CoQ-10 supplementation could be useful as an antioxidant and cardioprotective defense for posttransplant patients.

Kidney Disease. In 1 study,⁷³ CoQ-10 levels were lower in patients with nephropathy who underwent conservative treatment with peroral substitution. After substitution with CoQ-10, blood and plasma concentrations of CoQ-10 increased to values within the reference range. The authors claim that the treatment was well-tolerated and recommend the complementary administration of CoQ-10 in the treatment of nephropathy.

Metabolism and Nutrient Utilization. CoQ-10 preserves or increases levels of ATP, phosphocreatine, and creatine kinase, which are important in cellular metabolism. CoQ-10 is especially effective at boosting cellular bioenergetics during myocardial and neurologically pathological states, as well as cancer.

Kucharska et al⁷² reported finding significantly lower levels of CoQ-10 in blood and endomyocardial biopsy samples from patients who had had heart transplants and showed rejection of the organ than in samples from those who had not experienced rejection.

Walker and Byrne³ reviewed the various clinical studies of CoQ-10 (in which subjects were given from 6 to 150 mg/d) in the treatment of respiratory-chain encephalomyopathies. They found that while some studies reported improvements in serum lactate levels, muscle strength, ocular movement parameters, exercise ergometry, and cardiac and neuronal conduction, there

were other studies that showed no improvements with CoQ-10, despite subjects receiving 200 and 300 mg/d.

Laaksonen et al⁷⁴ found that muscle and serum levels of CoQ-10 in healthy subjects vary greatly and that serum levels depend largely on the quantities of circulating lipoproteins that contain CoQ-10. Because no correlation between serum and muscle tissue levels of CoQ-10 were established, the authors concluded that this suggests CoQ-10 levels are independently regulated in these areas.

Chen et al⁴³ conducted a prospective randomized, double-blind controlled study in patients who, before undergoing cardiopulmonary bypass surgery, received CoQ-10 (150 to 200 mg/d for 5 to 7 days). Significant differences compared to controls, who did not receive CoQ-10 before the same surgery, were found in pulse pressure and in better preservation (less ischemic injury) of both left and right ventricular myocardial ultrastructure.

Performance and Endurance Enhancement. The documented efficacy of CoQ-10 supplementation in correcting deficiencies and enhancing aerobic performance in sedentary subjects as well as patients suffering cardiovascular and respiratory chain pathologies has raised questions about its application to performance enhancement in athletics.⁷⁵ A recent study⁷⁶ of adult male cyclists using CoQ-10 supplements failed to demonstrate an improvement in physiological or metabolic parameters when compared to controls. The cyclists taking 100 mg/d of CoQ-10, however, reached muscular exhaustion at higher workloads. The authors conclude that the improvement of tolerance may be due to the antioxidant activity of CoQ-10.

A highly significant positive relationship between vastus lateralis muscle levels of CoQ-10 and marathon performance or exercise capacity was found in a study of healthy, physically active men.⁷⁷ The authors of the study explained that their results suggested CoQ-10 possesses a double role in the muscles, acting both as a "nonspecific" antioxidant and as a "mitochondrial coenzyme (CoQ-10)." A double-blind, placebo-controlled study on the efficacy of oral CoQ-10 supplementation (1 mg/kg/d for 4 weeks) in improving performance in endurance-trained male athletes (mean age 25.2±1.9 years) found the following:

- Plasma CoQ-10 concentration was significantly elevated from .91 to 1.97 mg/mL posttreatment.
- No significant effects were observed on oxygen uptake, ventilatory thresholds, blood lactate kinetics, heart rate, and blood glucose concentration at either submaximal or maximal exercise levels.
- A trend was observed during exercise and recovery toward elevated plasma triglyceride concentration and increased recovery rate of systolic blood pressure.⁷⁵

Two subjects in the treatment group and 3 in the placebo group demonstrated a deficiency in CoQ-10 (plasma level .66 mg/mL) before treatment, supporting previous findings that athletes may incur such a deficit during periods of intense training. The 2 subjects in the treatment group who were deficient in CoQ-10 displayed greater beneficial responses after treatment than those without such a deficiency, lending support to the argument that among healthy individuals, only those suffering

from a preexisting CoQ-10 deficiency will display obvious benefits from a CoQ-10 supplementation program.⁷⁵

A double-blind, placebo-controlled, crossover study⁷⁸ of the effects of oral CoQ-10 supplementation on exercise capacity was conducted in trained older (60 to 74 years) and younger men (22 to 38 years). Subjects receiving CoQ-10 (12 mg/d for 6 weeks) showed no change in time-to-exhaustion tests, and serum malondialdehyde concentrations were unaffected, either immediately following endurance exercise or before.

Burstein et al⁷⁹ conducted a double-blind, placebo-controlled study on the potential of CoQ-10 supplementation (50 mg given 3 times daily for 97 days) to minimize exercise-induced muscle membrane damage in healthy volunteers aged 18 to 20 years. After a prolonged military-style training period followed by a 45 km march, the placebo group and the CoQ-10 group showed no significant differences in muscle membrane damage (intracellular enzyme leakage into plasma). The authors concluded that supplementation with CoQ-10 was not effective in minimizing exercise-induced muscle membrane damage.

Neurological, Psychological, and Behavioral Disorders

Parkinson's disease. Certain neurodegenerative diseases can feature defects in the mitochondrial respiratory chain similar to those found in mitochondrial encephalomyopathies. Patients suffering from Parkinson's disease have been found to exhibit impaired respiratory chain complex 1 and complex 2 and 3 activities, as well as an endogenous CoQ-10 deficiency, when compared with age-matched controls. This deficiency is apparent even in early asymptomatic Parkinson's patients. Shults and coworkers⁸⁰ speculated that, due to the utility of benzoquinones in treating mitochondrial dysfunctions and the alleged role of these and free radicals in Parkinson's disease pathology, CoQ-10 might be useful in treating Parkinson's disease. Unfortunately, a pilot study using 200 mg of oral CoQ-10 twice, 3 times, or 4 times daily for 1 month in the treatment of patients with Parkinson's disease demonstrated no change in motor functions despite substantial increases in plasma CoQ-10 levels and some increase in complex 1 activity. These high doses were well tolerated, though mild, transient changes in urine were noted for the highest dose (800 mg/d).⁸¹

Platelet CoQ-10 redox ratios (reduced CoQ-10 to oxidized CoQ-10) were significantly decreased in de novo Parkinsonian patients.⁸² Platelet CoQ-10 redox ratios were further decreased by 3-hydroxy-L-tyrosine (L-DOPA) treatment (not significant), and selegiline treatment partially restored CoQ-10 redox ratios. The authors conclude that these results demonstrate either an impairment of electron transport or a higher need for reduced forms of CoQ-10 in the platelets of even de novo Parkinsonian patients. In this study, the CoQ-10 redox ratio was not correlated to disease severity but may be useful as an early state marker of Parkinson's disease.

Huntington's disease. CoQ-10 was investigated⁸³ to determine if supplementation slows the functional decline of early Huntington's disease. While CoQ-10 failed to produce statistically significant slowing in functional decline, patients treated with

300 mg twice daily showed a trend toward slowing in the decline of total functional capacity as well as beneficial trends in some secondary measures over the 30-month duration of the study.

Huntington's disease is a genetic disorder that eventually expresses itself as severe neurological damage in the striatum. Evidence for an energetic deficit in Huntington's disease includes reduced complex 2 and 3 activity in brain tissue, diminished phosphocreatine/inorganic phosphate ratios in resting muscle, and increased lactate/pyruvate ratios in cerebrospinal fluid, compared to normal controls. An earlier open-label trial of CoQ-10 in high oral doses (600 to 1200 mg/d for 6 months) found good tolerance but no significant effect. The following mild adverse effects were noted: heartburn, headache, fatigue, and an increase in involuntary movements.⁸⁴ Later work by the same group, however, demonstrated potential clinical benefit and a lack of serious adverse reactions. Treatment with CoQ-10 resulted in reduced elevations of basal and cortical ganglia lactate, as evidenced by magnetic resonance spectroscopy.²⁸

Retinopathies. In an open-label treatment using CoQ-10 (120 mg/d for 1 year), Bresolin et al⁸⁵ reported improved postexercise levels of serum lactate in 4 of 7 patients diagnosed with mitochondrial myopathy and chronic progressive external ophthalmoplegia when compared to controls.

Reproductive Disorders

Male Infertility. Mancini et al⁸⁶ reported that oligozoospermic varicocele patients show lower levels of cellular CoQ-10 in spermatozoa than normozoospermic varicocele patients, who showed CoQ-10 values similar to nonvaricocele patients. The authors hypothesize that CoQ-10 plays a functional role in sperm in oligozoospermic subjects and that higher intracellular concentrations of CoQ-10 represent a protective defense against sperm cell damage caused by oxidative mechanisms.

CoQ-10 is a putative treatment for male infertility where low endogenous ubiquinol content and high levels of hydroperoxide correlate with abnormal sperm morphology, low sperm count, and decreased motility in seminal plasma and fluid. CoQ-10 has been reported to show putatively favorable effects on male fertility. Clinical studies have shown a significant relationship between ubiquinol content and sperm count and motility in seminal plasma and fluid. A strong inverse relationship between ubiquinol content, hydroperoxide levels, and abnormal sperm morphology in seminal plasma and seminal fluid has also been demonstrated.⁸⁷ Researchers have theorized that ubiquinol inhibits hydroperoxide formation and, therefore, lipid peroxidation in seminal fluid and plasma. Because lipid peroxidation in spermatozoa is an important factor in male infertility, it is thought that ubiquinol could assume a diagnostic or therapeutic role in males suffering from infertility.⁸⁷ It has also been reported⁸⁸ that in 17 male patients with low fertilization rates following in vitro fertilization (intracytoplasmic sperm injection), treatment with oral CoQ-10 (60 mg/d for a mean of 103 days) produced a significant improvement in their fertilization rates (mean 10.3±10.5% before CoQ-10 treatment versus 26.3±22.8%

after), with no significant changes in other reproductive parameters. The researchers concluded that selected male patients suffering from infertility may benefit from CoQ-10 treatment.

DOSAGE

Most clinical studies demonstrating the therapeutic efficacy of oral CoQ-10 in the treatment of cardiovascular disorders have employed doses in the range of 100 to 240 mg/d. However, oral dosages as low as 60 mg/d result in greater than baseline serum concentrations and can improve certain hemodynamic parameters.^{12,13,43,53} Research indicates that therapeutic blood levels of CoQ-10 should be at least 2.5 mg/mL to elicit a biosensitive result.¹³

Effective treatment regimens for mitochondrial encephalomyopathies have employed oral doses of CoQ-10 in the range of 150 to 300 mg/d for extended periods of time (several months to several years). For these disorders, the literature suggests that shorter treatment periods are less likely to be beneficial.^{85,89-92}

Oral doses of CoQ-10 at 60 mg/d have been associated with improvement of some immunological parameters in cancer patients.⁵⁹ However, treatment protocols displaying results on tumor reduction and suppression used oral doses of CoQ-10 at 300 to 400 mg/d, which were well tolerated and free of side effects.^{59,61,67}

The optimum protective dose against adriamycin-induced cardiotoxicity was 10 mg/kg/d given orally in mice.³¹

Neurodegenerative diseases that feature mitochondrial respiratory chain deficits such as Huntington's disease and Parkinson's disease have been treated with high oral doses of CoQ-10: 600 to 1200 mg/d for Huntington's disease treatment protocols⁸⁴ and 200 to 800 mg/d for treatment of Parkinson's disease.⁸⁰

Moderate variability in the absorption of CoQ-10 has been observed, with some individuals requiring 2 or 3 times the amount needed by the average subject to attain the same blood level. Krone et al⁹³ observed several patients suspected of having *Candida albicans* overgrowth who did not respond as expected to CoQ-10 supplementation. An in vitro pilot study was conducted that suggested CoQ-10 was biologically functional in this yeast. The authors theorize that *C. albicans* overgrowth in the intestinal tract may lessen the amount of CoQ-10 available to the host, suggesting that the fungus uses the nutrient for its own mitochondrial respiratory chain.

SAFETY PROFILE

Few adverse effects of CoQ-10 have been reported in the literature, and these are invariably of such a mild nature that they do not require cessation of treatment or medical intervention. As an example, an Italian multicenter, open-label, noncomparative, preliminary, postmarketing drug surveillance study was conducted on the safety and efficacy of oral CoQ-10 in the treatment of heart failure. Subjects received either 100 mg/d (78%) or 50 to 150 mg/d (22%). Following a 90-day treatment period, the incidence of side effects reported was no more than .7%. Ten adverse reactions were reported by 8 of 1113 patients studied, with only 5 of the reactions considered attributable to the treatment.⁸⁴ A subsequent drug surveillance study of all the participants in the trial reported a 1.5% incidence of side effects: 38 adverse reactions

were reported by 36 of 2664 patients, with only 22 of the reactions considered attributable to the treatment.⁶¹

Contraindications

Because CoQ-10 affects the metabolism of the quinone anti-cancer agent adriamycin (by increasing the concentrations of a putatively toxic adriamycin metabolite), CoQ-10 treatment should not be undertaken during chemotherapy with this agent.³¹ However, the use of CoQ-10 after cessation of chemotherapy has been reported as beneficial.⁶¹

Drug Interactions

Patients with hypertension receiving antihypertensive drugs may show decreased blood pressure, decreased oxidative stress, and a decreased insulin response, along with increased levels of antioxidant vitamins when antihypertensive drugs are taken concomitantly with CoQ-10. Patients may also show a decreased intake of medications and report less angina pectoris.⁴⁸

Lovastatin is clinically used to treat hypercholesterolemia. It successfully lowers cholesterol levels through the inhibition of HMG-CoA reductase, an enzyme in the mevalonate pathway involved in the biosynthesis of cholesterol from acetyl-CoA. Since inhibition of this enzyme also inhibits the biosynthesis of CoQ-10, it was hypothesized that the clinical use of lovastatin to reduce the risk of cardiac disease could constitute a new risk of cardiac disease, because CoQ-10 has been demonstrated to be indispensable for cardiac function.⁵⁵

Hypercholesterolemic noninsulin-dependent diabetic patients treated with simvastatin or pravastatin showed lower levels of CoQ-10 following treatment and significantly increased levels following CoQ-10 supplementation (30 mg/d for 6 months). It was suggested⁵⁵ that a significant decrease in cardiathoracic ratios in 14 of 17 patients treated with CoQ-10 and HMG-CoA reductase inhibitors may have been associated with an undiagnosed diabetic cardiomyopathy that was ameliorated by CoQ-10. However, whether mitochondrial dysfunction from treatment with statins can be associated with low-serum concentrations of CoQ-10 is uncertain.⁶⁶ Similarly, the cholesterol-lowering drug gemfibrozil is reported to decrease serum CoQ-10 levels in hyperlipidemic men.⁶⁷ In a 6-month clinical investigation, simvastatin (20 mg/d) lowered total serum CoQ-10 levels in hypercholesterolemic patients by 25% compared to untreated healthy controls. However, muscle CoQ-10 concentrations showed no appreciable difference compared to healthy controls, and the antioxidant capacity of LDL was not significantly different from baseline.⁶⁸ A double-blind, placebo-controlled crossover study of lovastatin (60 mg/d) combined with CoQ-10 supplementation (180 mg/d) also found no significant improvement in the antioxidative capacity of LDL, as measured by copper-mediated oxidation.⁶⁹

A new development in the field of cholesterol management is the use of the fungal product squalstatin 1 as an inhibitor of cholesterol synthesis. This compound is a potent, specific inhibitor of squalene synthetase. Because this enzyme occurs below the branch point in the mevalonate pathway leading to

CoQ-10, cholesterol synthesis is inhibited without affecting CoQ-10 or dolichol biosynthesis. Moreover, it has recently been reported that squalstatin 1 treatment can increase CoQ-10 levels 3- to 4-fold, presumably due to pooling of farnesyl pyrophosphate, the common precursor of cholesterol, dolichol, and CoQ-10.²

A decreased international normalization ratio has been reported in several elderly patients following their addition of CoQ-10 to treatment regimens with warfarin.¹⁰⁰ In 2 cases, the dose of CoQ-10 was known (30 mg/d). Correcting the problem may require temporarily increasing the dose of warfarin and ceasing supplementation with CoQ-10. CoQ-10 is structurally related to menaquinone (vitamin K₂) and may have procoagulant effects.¹⁰¹ The interaction may be the result of CoQ-10 antagonizing vitamin K, though this has yet to be shown *in vivo*.¹⁰²

Some evidence suggests that in male power athletes (aged 24 to 34 years) who abuse anabolic androgenic steroids (intramuscularly or orally), serum concentrations of endogenous CoQ-10 can become significantly increased (by 68%).¹⁰³

In mice, oral administration of CoQ-10 (10 mg/kg/d for 3 days), as a membrane stabilizer and antioxidant for prevention of cardiotoxicity before adriamycin chemotherapy, was associated with significantly elevated levels of an adriamycin metabolite in liver, heart, and kidney. Elevated levels of this metabolite are associated with decreased survival in murine models.³¹

Pregnancy and Lactation

No contraindications appear in the literature concerning the use of CoQ-10 during pregnancy and lactation. However, because of its hemodynamic, bioenergetic, and immunogenic effects, caution should be exercised when CoQ-10 is used during pregnancy.

Side Effects

During an open study⁸⁴ investigating the effectiveness of high oral doses of CoQ-10 (600 to 1200 mg/d) in the treatment of Huntington's disease, 6 of 10 patients reported the following adverse experiences, which were rated as mild and only possibly due to CoQ-10: headache, heartburn, fatigue, and an increase in the involuntary movements characteristic of the disorder. A second study in patients with Huntington's disease⁸⁵ reported an increased frequency of stomach upset with supplementation of 300 mg of CoQ-10 twice a day.

Similarly, a study of CoQ-10 in the treatment of Parkinson's disease⁸⁰ reported "mild, transient changes in the urine" at the highest oral dose tested: 200 mg given 4 times/daily.

When Singh et al⁴⁸ investigated their hypothesis that CoQ-10 could decrease oxidative stress and blood pressure in patients receiving antihypertensive medication, adverse effects were, in most instances, more frequently reported in the CoQ-10 group than in the control group: abdominal discomfort (2 in the CoQ-10 group, compared to 1 in the control group), headache (1, compared to 1), nausea (6, compared to 3), and vomiting (2, compared to 1).

Special Precautions

Patients undergoing chemotherapy with doxorubicin should not take CoQ-10 concurrently due to its ability to increase

levels of a potentially toxic doxorubicin metabolite.³¹ CoQ-10 has been used to treat the oxidative damage-induced cardiotoxicity caused by many antineoplastic drugs. Concurrent use of CoQ-10 and epirubicin during breast cancer chemotherapy is associated with an alleviation of the cardiac dysfunction seen when epirubicin is used alone.⁶⁰ CoQ-10 also successfully treats doxorubicin cardiotoxicity when administered after discontinuation of chemotherapy.⁶¹ Simultaneous use of CoQ-10 and doxorubicin, however, may be contraindicated. Tissue concentrations of doxorubicin and its major metabolite (aglycone 1) were examined in mice pretreated with CoQ-10. In the CoQ-10-pretreated group, the concentrations of aglycone 1 in the heart, liver, and kidney (at 1 hour and 3 hours) were significantly higher than in the control group. Elevated levels of this doxorubicin metabolite are associated with decreased survival in murine models; therefore, clinical application of CoQ-10 concomitant with antitumor drugs (especially doxorubicin) requires special caution.³¹

Animal studies indicate that treatment of human small-cell lung cancer with gamma radiation could be compromised by high doses of CoQ-10. A significant dose-dependent decrease in tumor responsiveness to radiation was found from oral administration of CoQ-10 to tumor-transplanted mice at doses equivalent to 40 mg/kg, given orally. This decreased response was borderline at the equivalent of 20 mg/kg. However, inhibited tumor susceptibility to radiation was not found at the equivalent of 10 mg/kg.¹⁰⁴

No documented reports of overdosage from CoQ-10 appear in the medical literature.

Toxicity in Animal Models

In a year-long treatment of male and female rats for signs of toxicity, CoQ-10 at daily oral dosages equivalent to 100, 300, 600, and 1200 mg/kg resulted in no adverse effects in body weight, clinical pathology, clinical signs, food consumption, or mortality.¹⁰⁵

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