Ubiquinone, or coenzyme Q (CoQ), was discovered in 1957 by Fred Crane. Its chemical structure was determined a few years later by Karl Folkers, who later won the Priestley medal from the American Chemical Society. CoQ plays an important role in the production of chemical energy in the mitochondria. In its reduced form, ubiquinol, CoQ also serves as an antioxidant. Ubiquinol inhibits lipid peroxidation in biological membranes and in low-density lipoprotein (LDL), and it also protects membrane proteins against oxidative damage. While ubiquinol does not require vitamin E for its antioxidant activity, it can regenerate the vitamin from its oxidized form, the alpha-tocopheroxyl radical, a process that otherwise relies on water-soluble vitamin C. This interaction with vitamin E is thought to be particularly important for the protection of LDL and other lipoproteins from oxidative damage, and we now have evidence that directly supports an antioxidant function of ubiquinol against LDL oxidation in blood vessels. On the other hand, the discovery of the semiquinone form of CoQ in the mitochondria raises the question of a possible role of the ubisemiquinone radical in the generation of superoxide radicals in the course of respiration. However, to date there is no convincing evidence that CoQ acts as a pro-oxidant in vivo.

CoQ is the only lipid-soluble antioxidant that is synthesized in our bodies. In humans ubiquinone-10 (CoQ10, containing 10 isoprenoid units) is the major form, whereas rats and mice predominantly make CoQ9. CoQ is present in all cellular membranes and in lipoproteins. Levels of CoQ10 in plasma are substantially less than those of vitamins E and C and vary greatly in tissues, where the concentrations of CoQ exceed those of vitamin E. Although the relative tissue distribution of CoQ varies by species, the highest concentrations are found in liver, heart, muscle, kidney, and brain. At the sub-cellular level, CoQ is found mainly in Golgi vesicles, which control protein traffic, the inner mitochondrial membrane, and lysosomes, where macromolecules are digested.

CoQ10 is also a micronutrient. However, its bioavailability is limited compared to that of other lipid-soluble antioxidants like vitamin E. We know that uptake of CoQ occurs in blood, blood vessels, liver, and spleen, but generally not in other organs, although some uptake has been reported in mouse kidney and rat brain. Interestingly, in cases of severe CoQ10 deficiency resulting from enzyme defects, muscular and organ functions are drastically improved by dietary CoQ10.
supplements, suggestive of an effective uptake. It appears that the extent of uptake correlates with the degree of tissue deficiency. This view is supported by recent observations that oral supplementation of CoQ in rats for 2 months increased muscle and brain levels of CoQ in old but not in young rats. Also, there is evidence that oral supplements increase the concentration of CoQ in the hearts of patients suffering from cardiomyopathies and heart failure. During gastrointestinal uptake, dietary CoQ is efficiently reduced to the antioxidant-active ubiquinol form that enters the circulation within lipoproteins for potential uptake by tissues.

There are a number of conditions in which CoQ tissue concentrations are altered with functional consequences. Oxidative stress generated by, for example, physical exercise increases tissue ubiquinone levels by increasing biosynthesis, as does administration of drugs like clofibrate. In contrast, aging is generally associated with decreases in tissue CoQ levels. For example, levels of CoQ10 in the skin are low in childhood, reach a maximum at around 20-30 years of age, and then decrease steadily with increasing age. Topically applied CoQ10 can penetrate into the living cell layers of the skin and attenuate both the depth of deep wrinkles characteristic of photoaging, as well as the turnover of epithelial cells. CoQ10 is also highly effective in protecting skin cells known as keratinocytes from oxidative DNA damage induced by ultraviolet light. Similar to what is observed in human skin, the concentration of CoQ in various mouse and rat tissues changes with age; the highest level occurs at about the age of 30 days, followed by a subsequent decrease with increasing age. The observed decrease in tissue content of CoQ10 could accentuate the age-related oxidative damage of lipids and proteins, although this question remains to be answered. It is also important to determine whether CoQ10 cellular deficiency is general or affects only certain organelles, such as the mitochondria.

Evidence is accumulating for a role of CoQ10 in the treatment of mitochondrial disorders and neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). A number of case reports suggest a beneficial effect of supplemental CoQ in patients with known mitochondrial disorders. Perhaps the strongest evidence for a beneficial effect of CoQ supplements comes, however, from animal studies. Oral administration of CoQ10 produces dose-dependent neuroprotective effects against lesions produced by mitochondrial toxins. CoQ10 also protects against 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in mice. Furthermore, CoQ10 supplementation exerts neuroprotective effects in transgenic mouse models of familial ALS and Parkinson's disease. The potential efficacy of CoQ10 in Parkinson's and Huntington's disease is currently being evaluated in human clinical trials.

The first studies indicating a CoQ10 deficiency in myocardial tissue of patients with cardiovascular disease date to the early 1970s—findings that were confirmed in the 1980s. Old rats supplemented with CoQ10 show a significantly higher level of CoQ in their left ventricle, and the hearts of these animals are better protected
against functional impairment induced by acute oxidative stress. There is also evidence that CoQ supplements can protect the heart against functional damage induced by ischemia-reperfusion (lack of blood flow followed by resupply), as well as provide tolerance of the aging heart tissue to aerobic stress, although it remains unclear whether this protective effect is the result of an antioxidant and/or bioenergetic activity of CoQ. In human heart tissue, the CoQ10 content in the atrial trabeculae (connective tissue) is decreased in older subjects, and, compared to their younger counterpart, the trabeculae from older individuals have impaired recovery after simulated ischemia. Presently, we don’t know to what clinically relevant extent supplemental CoQ10 can increase the heart tissue content of the antioxidant in humans.

Heart disease is the leading cause of mortality in developed countries, and atherosclerosis is the major underlying cause of heart disease. As pointed out in the Spring/Summer 2002 issue of *The Linus Pauling Institute Newsletter*, prospective trials with antioxidants, principally vitamin E, have not consistently lessened clinical outcomes in patients with cardiovascular disease. However, this does not necessarily rule out the possibility that an antioxidant activity of CoQ could ameliorate atherosclerosis and related cardiovascular disease. For example, an overall lack of benefit of supplemental vitamin E could be explained partly on the basis that the concentration of vitamin E does not become limited during disease progression. Also, some studies have found that supplementation with vitamin E alone can increase the oxidizability of LDL, a process commonly thought to contribute to atherogenesis. Ubiquinol effectively prevents this pro-oxidant activity of vitamin E, and enrichment with ubiquinol strongly inhibits LDL oxidation under all conditions tested. Compared to vitamin E, few studies have examined the anti-atherogenic potential of CoQ10, although such an effect of CoQ10 has recently been reported in rabbits. Perhaps more convincingly, supplementation with CoQ10 alone or together with vitamin E has been shown to significantly reduce atherosclerosis in apolipoprotein E gene-deficient mice. Whether CoQ10 supplements affect atherosclerosis in humans still remains unknown. The human studies carried out to date are limited to the dysfunction of blood vessel cells, a process that occurs early in atherogenesis and predicts the progression of the disease. The results obtained thus far are inconclusive.

A topical question is whether cholesterol-lowering treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) decreases tissue CoQ, and, if so, whether this may attenuate the overall decrease in cardiovascular morbidity and mortality in patients with cardiovascular disease and/or in healthy men at risk for coronary heart disease seen with statins. A potential decrease in CoQ levels could conceivably arise from the inhibition of the synthesis of CoQ by statins. Indeed, there is now evidence that statin therapy lowers plasma concentrations of CoQ, although it remains to be established whether this has clinical consequences.

Over the past few years CoQ10 has gained considerable attention as an agent
capable of influencing cellular bioenergetics and counteracting some of the damage caused by free radicals. Animal studies provide increasing support for a beneficial effect of CoQ10 supplements in disease, particularly neurodegenerative diseases and atherosclerosis. These results are encouraging and warrant further investigation, including clinical studies that directly assess a health benefit of CoQ10 supplements in humans.

For more information on CoQ10 and health, see the Linus Pauling Institute's Micronutrient Information Center.

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