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A Present Day Pandora's Box**

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Coenzyme Q₁₀, Lipid-Lowering Drugs (Statins) and Cholesterol: A Present Day Pandora's Box

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ABSTRACT

The advent of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) has reshaped the treatment of hypercholesterolemia and associated cardiovascular diseases (CVD). Unfortunately, this inhibition of the mevalonate pathway restricts the biosynthesis of other nonsteroidal products of this loop, including coenzyme Q₁₀. In humans, the fat-soluble nutrient coenzyme Q₁₀, also known as CoQ₁₀ or ubiquinone (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone), is a major participant in electron transfer during oxidative phosphorylation in the mitochondria. In addition to its role in intracellular energy generation, CoQ₁₀ is a potent antioxidant and free radical scavenger, and is a membrane stabilizer that preserves cellular integrity. Oxidative stress and energy deficiency are implicated in the pathogenesis of many disease states: the cardiovascular system is frequently the first victim. A large number of clinical trials demonstrate the relationship between CoQ₁₀ deficiency and CVD, and the slowdown of CVD progression with CoQ₁₀ supplementation.

Statins are prescribed to reduce cardiovascular morbidity and mortality. However, statins suppress the biosynthesis of CoQ₁₀, essential for optimal cellular function. This

self-defeating outcome is compounded by side effects such as myopathies and rhabdomyolysis that suggest generalized mitochondrial injury and CoQ₁₀ involvement.

A logical deduction is to consider complementing extended statin therapy with CoQ₁₀ to support the deficient cellular bioenergetic state and ameliorate oxidative stress.

INTRODUCTION

For decades, the major cause of mortality in industrialized Western countries has been cardiovascular disease (CVD). Clinical studies and epidemiological analysis established the relationship between high cholesterol level, atherosclerosis, and CVD. Therefore, reducing the level of cholesterol decreases susceptibility to CVD, and in high risk individuals, prolongs life.¹

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), constitute a new class of cholesterol-lowering drugs.² They competitively inhibit the enzyme HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol biosynthesis, that is, the conversion of HMG-CoA to mevalonate.³ In the blood, cholesterol circulates attached to low density lipoprotein (LDL) particles, whose function is to provide cells with cholesterol.⁴ The statin-induced inhibition of HMG-CoA reductase is thought to decrease the cellular cholesterol content and thus to stimulate the production of LDL receptors. This, in turn, leads to an increased cellular uptake of circulating LDL particles and ultimately to lower total serum cholesterol and LDL cholesterol levels.

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Table 1 lists the statin drugs marketed in the USA since 1987. Sales of the leading cholesterol lowering drug (Lipitor®) were 2.2 billion in 1998, and are expected to reach 4.8 billion in the year 2010.⁵

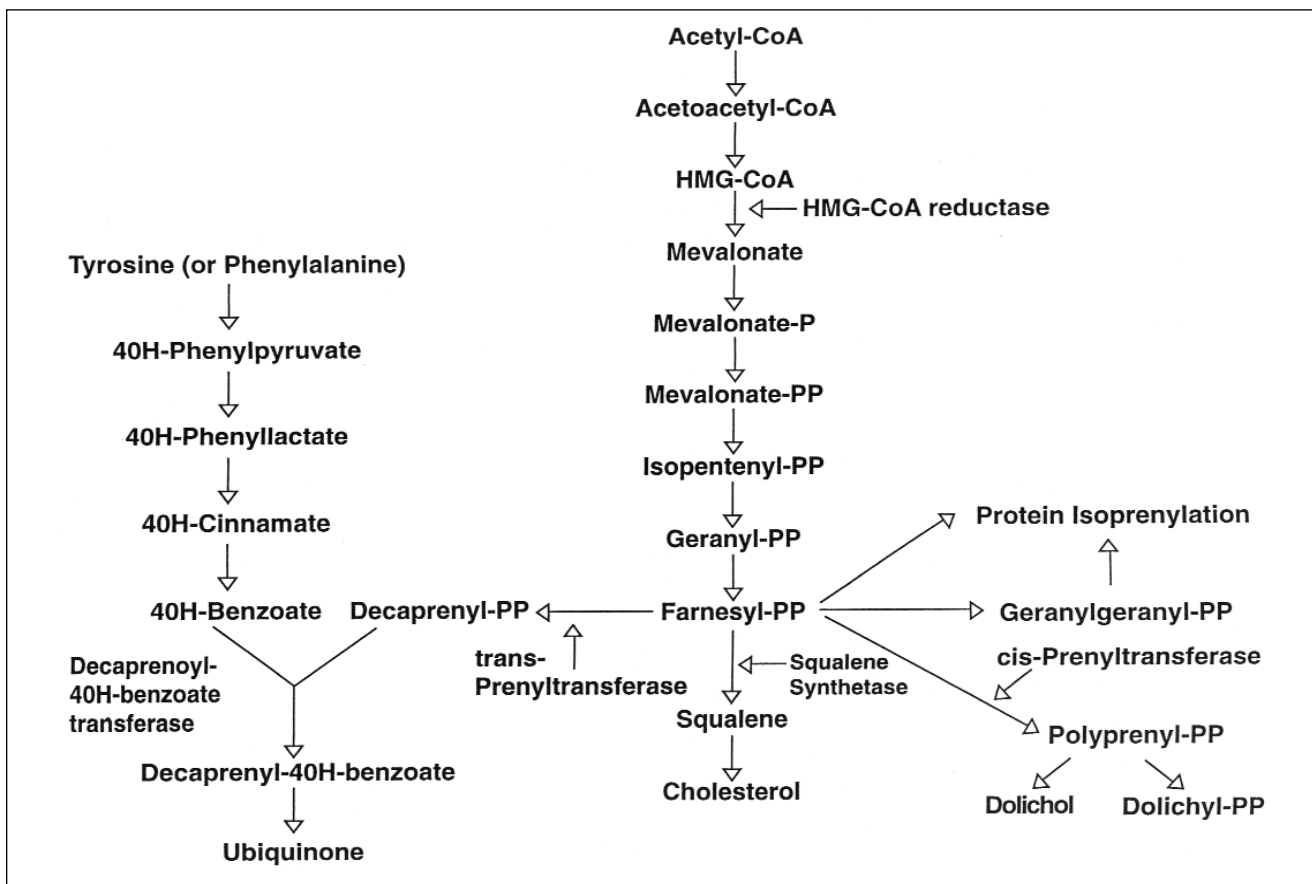
Undermining this advancement is the proverbial “other side of the coin.” Mevalonate is the precursor not only of cholesterol, but also of many nonsteroidal isoprenoid compounds vital to diverse cellular functions, including cell proliferation (Figure 1). These isoprenoids include dolichols, required for glycoprotein synthesis and coenzyme Q, involved in intracellular electron transport and energy generation.⁶ Thus, while inhibition of the mevalonate pathway suppresses cholesterol production; it also reduces CoQ bioavailability, causing CoQ deficiency.

It is now well established that oxidative stress resulting from the formation of intracellular or extracellular free radicals and reactive oxygen species (ROS) is a major factor in the pathogenesis of CVD. More specifically, oxidized cholesterol has deleterious effects, including carcinogenicity, mutagenicity, and initiation or acceleration of the atherosclerotic process.^{4,7,8} However, systems undoubtedly exist to protect LDL-cholesterol particles in the blood from

Table 1. Listing of HMG-CoA reductase inhibitors (statins), marketed in the USA since 1987. Cerivastatin (Baycol) was withdrawn from the market on August 8, 2001 by the manufacturer Bayer AG.

HMG-CoA reductase inhibitors (statins)	Year of US introduction
lovastatin (Mevacor)	1987
pravastatin (Pravachol)	1991
simvastatin (Zocor)	1992
fluvastatin (Lescol)	1994
atorvastatin (Lipitor)	1997
cerivastatin (Baycol)	1997

Figure 1. Reaction pathway of the biosynthesis of coenzyme Q₁₀ (ubiquinone), cholesterol, and dolichols. HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A, (PP = pyrophosphate)



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oxidative damage. Attention has mostly been directed at fat-soluble antioxidants, such as alpha-tocopherol, beta-carotene and coenzyme Q, that are present in LDL in quantities that can be modified by dietary food intake or oral supplementation.⁸ Clearly, the depletion of CoQ by statins is a serious clinical concern, since this depletion can initiate or intensify LDL-cholesterol oxidation.

In his book *The Antioxidant Miracle*, Packer⁹ wrote that antioxidants function better in a coordinated manner with one another, which he calls the "antioxidant network". In particular, the interaction of CoQ with vitamin E is critical to the overall antioxidant defense and has important clinical ramifications.

COENZYME Q (UBIQUINONE)

Coenzyme Q (coenzyme Q₀ or CoQ₁₀ in humans, (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) is a naturally occurring, fat-soluble nutrient, with characteristics common to vitamins and, like vitamins, is essential for the optimal functioning of an organism. CoQ was discovered in 1957 by Crane and his associates¹⁰ as a component of beef heart mitochondria. In 1958 Folkers and his associates determined its chemical structure.¹¹ Peter Mitchell was awarded the Nobel Prize in Chemistry in 1978 for his elucidation of the "Q-cycle."

The essential role of CoQ for cellular energy production in eukaryotes is well established.¹² A vital electron and proton carrier, CoQ supports adenosine triphosphate (ATP) synthesis in the mitochondrial inner membrane and stabilizes cell membranes, thus preserving cellular integrity and function. CoQ₁₀ is a potent and versatile antioxidant that blocks oxidative injuries to DNA, lipids, proteins, and other essential molecules. This well-documented function prevents or retards the development of many cardiovascular, neoplastic, and probably neurodegenerative diseases. Several publications illustrate how, diet-derived antioxidants participate in protection against these diseases.¹² It has been reported¹³ that the normal level of CoQ in mitochondrial membranes is below that required for kinetic saturation. This finding strongly indicates that CoQ might be a rate-limiting component in the respiratory chain, especially in the mitochondria of injured Tissues.¹⁴

The biosynthesis of CoQ is an elaborate 17-step process, first described by Folkers¹⁵ that requires the availability of several vitamins or their coenzyme forms: vitamins B2, B6, B12, C, folic acid, niacinamide, pantothenic acid, as well as many trace elements. Deficiencies of one or more of these building blocks will result in CoQ deficiency, with subsequent impairment of certain vital functions. The clinical manifestations of CoQ deficiency are diverse and are determined by the cells and organs involved. Additionally, an age-dependent decline of CoQ₁₀ level¹⁶ is postulated to be responsible,

in part, for the diseases of aging. Bioenergetic degradation resulting from CoQ₁₀ deficiency affects first and most intensely the cardiovascular and immune systems, whose cells and organs place the highest energy demands of all body systems. Working with suboptimal energy, a cascade of functional impairment begins in these systems, as do overt clinical manifestations. Not surprisingly, cardiovascular and neoplastic diseases are the most common causes of morbidity and mortality in the elderly.

Interest in the use of antioxidants for prevention and treatment of human diseases has been sustained for at least two decades. Developments in both therapeutic and nutritional fields have been punctuated by successes and some failures. It is important to note that in his book on CoQ₁₀, Littarru¹⁷ devoted 71% of the content to the CoQ₁₀ defense against oxidative damage.

Most CoQ₁₀ clinical research is focused on the large, heterogeneous group of cardiovascular diseases (CVD). The published results of 34 controlled clinical trials and several open-labeled and long-term studies were critically reviewed by Langsjoen *et al.*¹⁸ The summary of their comprehensive evaluation reveals that out of 58 early and current clinical trials involving 5,727 CVD participants, three trials reported negative results (1.7%) experienced by 110 participants total (1.9%). A more general review was published by Sinatra¹⁹ who compiled a list of 39 placebo-controlled clinical trials since 1972 in patients with heart diseases, as a part of more than 100 general clinical CoQ₁₀ studies. Of the 39 placebo-controlled trials, 36 showed a beneficial CoQ₁₀ effect (92.3%).²⁰ Impressively, the largest reported single study in patients with various forms of CVD involved 2359 patients who participated with cardiologists in 173 Italian health centers.²¹ Moreover, based on elaborate statistical analysis, Jameson²² proposed that a strict relationship exists between CoQ₁₀ levels and a prognosis for CVD.

Since 1960, the biochemistry, physiology, and clinical effectiveness of CoQ₁₀ have been presented at 15 specialized international symposia whose published proceedings total over 4,600 pages. The results substantiate the postulated earlier relationship between CVD and CoQ₁₀ deficiency, with clinical improvement after CoQ₁₀ treatment, and substantiate as well the lack of side effects or defined adverse reactions.

The involvement of CoQ as a modulator of the effectiveness of the immune system in neoplasia, infections (including retroviral), and aging was proposed on the basis of extensive research.^{23,24} Since then, this novel concept has been confirmed in experimental and clinical studies. Certainly, the CoQ immunomodulating effect links directly with the atherosclerotic process. The involvement of some compartments of the immune system in the formation, progression, and repair of vascular injuries is well documented. A recently published review by Nicoletti *et al.*²⁵ evalu-

ated the role of the immune system in atherosclerosis and the possibility of immunomodulator use in prevention and treatment of the atherosclerotic process.

In conclusion, CoQ₁₀ is an essential nutritional factor, not a drug. This indisputable fact, unfortunately, hinders its acceptance by most conventional clinicians despite the reported clinical and experimental results. Arthur Schopenhauer (1788-1860), an authority on the philosophy of pessimism, wrote prophetically:

“All truth passes through three stages:

First, it is ridiculed; Second, it is violently opposed; and Third, it is accepted as self-evident.”

COENZYME Q AND STATINS

In an extensive review in 1998, we evaluated the literature assessing inhibition of the CoQ biosynthesis by statins.¹² We also searched for the connection between CoQ deficiency and the development of side effects after statin treatment.

As early as 1990, Folkers and his group reported²⁶ that lovastatin treatment was associated with a decrease of CoQ₁₀ blood levels and resulted in a measurable decline of cardiac function. Since then, many other studies confirmed the connection between statin treatment and CoQ biosynthesis. Supporting this observation is the report by Caliskan *et al.*²⁷ that simvastatin reduces also the ATP blood level in mice by 49% and alters the composition, and probably also the function, of cell membrane lipids. Similar results were disclosed by Satoh *et al.*²⁸ in dogs using simvastatin. The authors concluded that cholesterol inhibition by simvastatin may influence myocardial energy generation, particularly under pathophysiological conditions. It is likely that the beneficial hypocholesterolemic effect of lipophilic statins may be negated by the adverse effects of the inhibition of the mitochondrial energy-generating system. Additional investigations showed a statin-induced CoQ decrease in the blood can be compensated by oral CoQ₁₀ administration without affecting the cholesterol-lowering effect of statins.²⁹

Despite clinical trials documenting a “generally good safety record”, side effects resulting from statin treatment occur.³⁰ Some adverse reactions — myalgia, myopathies, and rhabdomyolysis; peripheral neuropathies; gastrointestinal symptoms, including hepatic injury; initiation or accelerated progression of cataracts and neoplasia — could be a direct or indirect result of CoQ₁₀ deficiency consequent to statin treatment. Once more, the literature survey¹² suggested or confirmed a causal relationship between side effects of statins and lowered CoQ level. Significantly, mevalonate, the CoQ precursor, was able to prevent the side effects of statins.³¹⁻³³

Hebert *et al.*³⁴ evaluated 16 clinical statin trials and noted that in the CARE study, 12 cases of breast cancer occurred in the pravastatin group, compared with one case in the placebo group ($p=0.002$). Of the trials evaluated only

CARE provided information on breast cancer. Reviewing the accumulated evidence for a connection between lipid-lowering drugs and carcinogenicity, Newman *et al.*³⁵ concluded that treatment with fibrates and statins should be avoided, except in patients at high, short-term risk of coronary heart disease. In general, low serum cholesterol has been associated by some investigators with an increased risk of cancer and other noncoronary heart disease mortality,³⁶⁻³⁸ including suicide, violence, and accidents.³⁹

Fat-soluble nutrients, including cholesterol, are solubilized and transported in the plasma by specific carrier lipoproteins.^{40,41} The serum concentration of these nutrients depends not only on the dietary nutrient concentration, but also on the concentration of circulating lipoproteins. In humans 47% to 76% of CoQ₁₀ in the blood is carried by LDL as reported by Appelkvist *et al.*⁴¹ and Littarru *et al.*⁴² Yet statins, as part of their therapeutic effectiveness, restrict LDL by 25% to 60%.⁴³ One should be able to foresee the creation of a far-reaching problem during treatment with statins — an impairment of CoQ₁₀ transport to tissues and to cells. Since LDL are also carriers for other lipid-soluble nutrients,⁴³ the question of competition between several molecules for incorporation in the transportation process provided by lipoproteins remains un contemplated.

Package inserts and publicity material for various marketed statins usually ignore the CoQ₁₀ statin relationship. Nevertheless, two US patents granted in 1990 describe a method for counteracting statin-associated myopathy⁴⁴ and potential liver damage⁴⁵ by adjunctive administration of statin and CoQ₁₀. A publication by MacDonald³³ is quoted in support of the patent claims. In that study, coadministration of mevalonate and lovastatin prevented increases in transaminase levels, an indication of liver injury. The author concluded that transaminase elevation produced by lovastatin and other statins is a direct consequence of inhibiting mevalonate synthesis, thus implicating again the role played by CoQ₁₀ in statin side effects. Yet, for more than 12 years, statin producers did not act on this information and failed to reveal the vital statin-CoQ₁₀ link to the millions of statin users and even to medical professionals.

SUMMARY

Side Effects of Statin Drugs

The multiplicity of effects of statins has been the center of attention over the past few years. Referred to as pleiotropic effects, statins influence a wide range of physiological functions, such as vasodilative, antithrombotic, antioxidant, antiproliferative, anti-inflammatory,^{46,47} and even immunosuppressive, anticoagulant, and bone-formation-inducing capabilities. New pleiotropic effects of statins are continuously described⁴⁸ but their clinical relevance has not been established. Most of them, without crit-

ical evaluation, are added to the long list of beneficial effects. Only a few investigators regard some of the pleiotropic effects as controversial or of adverse consequence, accounting in part for the side effects of statins.⁴⁶ Related to this is a long-overlooked but grave problem, perhaps a present day Pandora's box, treated in a short note: an analysis at the University of California at San Francisco of studies on "a heart drug" showed that 96% of authors with drug company ties declared it to be safe, compared with only 37% of authors with no ties.⁴⁹ Similar thorny conclusions were reached also by Wazana.⁵⁰

Wheeler⁴⁷ predicted that statins are likely to be prescribed with increasing frequency, even to individuals with normal plasma cholesterol levels. One step closer to fulfillment of this prophecy is the attempt by two pharmaceutical companies to obtain FDA approval to market two statins as OTC drugs, not requiring prescriptions.

A development, unforeseen by many statin advocates, materialized on August 8, 2001, when the Food and Drug Administration (FDA)⁵¹ announced that Bayer Pharmaceutical Division (Bayer AG, Germany) withdrew Baycol® (cerivastatin) from the U.S. market because of reports of sometimes fatal rhabdomyolysis, an acute disease characterized by destruction of skeletal muscle. While all statins create a risk for rhabdomyolysis and other adverse side effects, only Baycol® has been determined to be so dangerous that it is no longer sold. Over 700,000 Americans took Baycol® during the three years it was on the market in the United States.

On January 18, 2002, CNN television network reported that over 100 deaths had been linked to the use of Baycol®, double an earlier estimate of 52. This lipid-reducing drug was distributed in 80 countries, with 6 million patients treated. The respected German publication *Frankfurter Allgemeine Zeitung*⁵² christened this event the "Baycol Katastrophe" a news-line reported extensively in Europe, but less so in the US.

Almost one year following the withdrawal of Baycol® our professional organization, the American Medical Association, remains silent on this issue. In a letter to the editor of the *Archives of Internal Medicine* (a publication of AMA), Suzanne Simpson of Houston, Texas, pointed out that "in a case report published in the *ARCHIVES* in March, 2001, Garcia-Valdecasas-Campelo *et al.*,⁵³ write that 'no [previous] cases of rhabdomyolysis associated with cerivastatin therapy have been described. Yet even my quick PubMed search showed at least 5 reports published in 1999 or 2000 of rhabdomyolysis in cerivastatin users.'⁵⁴⁻⁵⁸ Ms. Simpson concluded with the observation, "it strikes me that there was a serious breakdown in the peer review process of the *ARCHIVES*, especially given that claims of primacy should always be viewed with some skepticism. Had your peer reviewers been more careful, perhaps clinicians would

have been more aware of a problem that would lead to a drug's withdrawal."⁵⁹

At the present time, it is premature to evaluate with objectivity the evolving statin controversy and its complex medical, financial, societal, and ethical ramifications.

CoQ₁₀ Depletion

It should be noted that in addition to statins, other popular drugs deplete or interfere with the biosynthesis of CoQ₁₀. A comprehensive useful overview of depletion of various nutrients, including CoQ₁₀, by drugs widely used in clinical practice was published in 1999.⁶⁰ The CoQ₁₀ list contains the names of 49 drugs.

In humans, CoQ₁₀ is of dual origin, as is cholesterol. Part is of exogenous origin (food intake) and part is biosynthesized intracellularly from other nutrients, as discussed earlier. Today, routine CoQ₁₀ food intake is probably much lower; many dietetic and nutritional choices are responsible for this phenomenon, such as avoiding foods high in fats, which have a high CoQ₁₀ content.¹² This affects other essential nutrients as well.

All data demonstrate that multiple mechanisms acting alone or in concert contribute to the development of a CoQ₁₀ deficiency state, leading eventually to overt clinical manifestations. An inescapable and specific deduction is that extended therapy with statins should be complemented with CoQ₁₀ to support the deficient cellular bioenergetic state, as well as to minimize oxidative stress. This should be considered mandatory in patients with otherwise compromised, bioenergetic status (*e.g.*, elderly patients) treated with statins. Moreover, the distinct possibility of an additive or synergistic therapeutic effect of CoQ₁₀, when administered concomitantly with statins, should be further evaluated. Novel CoQ₁₀ formulations with improved bioavailability profile, as well as combinations of CoQ₁₀ with carnitine (another component of energy metabolism) and alpha lipoic acid (the so-called universal antioxidant), already available commercially, deserve serious consideration.

There are indications that the development of an advanced new generation of cholesterol-reducing drugs, effective below the farnesyl pyrophosphate branch point of the mevalonate pathway and not affecting CoQ₁₀ biosynthesis (Figure 1), is feasible.¹²

Citizen Petition Filed with FDA on Statin – CoQ₁₀ Depletion

On May 29, 2002, Julian Whitaker, MD, filed a citizen petition to the FDA asserting that 0.5 to 2.3% of the patients using statin drug therapies experience adverse events including myopathies.⁶¹ In his petition filed by Emord &

Associates of Washington, D.C., to FDA, Whittaker suggests that CoQ₁₀ supplementation could help reduce the incidence of these adverse events since it is an essential element in cellular energy production and in the functioning of the heart muscle due to the heart's extraordinary energy requirements. Whittaker further notes in his petition "the method by which statin drugs work to block cholesterol also causes them to block the production of CoQ₁₀." In his petition to FDA, Whittaker contends that between 125,000 and 575,000 who suffer from statin-induced liver dysfunction, cardiomyopathy or congestive heart failure would benefit from the use of CoQ₁₀ while on statin therapy. This estimate is based on data in the 1998 *Physicians' Desk Reference* indicating that 25 million patients use statins worldwide.

The citizen petition cites a risk assessment report on the dangers of CoQ₁₀ depletion prepared by cardiologist Peter Langsjoen, MD, FACC, to support its position. In his report, Dr. Langsjoen advises that "all prescribing physicians should be notified that statin drugs produce a depletion in coenzyme Q₁₀, which in settings of pre-existing CoQ₁₀ deficiency, such as in congestive heart failure and aging, has the ability to markedly worsen myocardial function. The potential for statin-induced cardiomyopathy must be seriously considered and must be prevented with the concomitant administration of CoQ₁₀." ⁶¹

Referring to Dr. Langsjoen's findings, Whittaker maintains CoQ₁₀ supplementation is an easy, economically-feasible remedy to prevent and/or reverse the dangerous CoQ₁₀ depletion effects of statins. For support of his position, Whittaker notes that Merck, the manufacturer of Mevacor (lovastatin) and Zorcor (simvastatin), holds two patents that cover compounds containing up to 80 mg of an HMG-CoA reductase inhibitor with 25 mg to 1 g of CoQ₁₀. Both patents note that concomitant use of CoQ₁₀ would benefit statin users and one patent (No. 4,933,165)⁴⁴ specifically says that "since CoQ₁₀ is of benefit in CHF patients, the combination with HMG-CoA reductase inhibitors should be of value in such patients who also have the added risk of high cholesterol levels." ⁶¹

The two patents held by Merck expire in May and June 2007 and currently, Merck does not market any combination of their statin drugs with CoQ₁₀. Whittaker's petition calls on the FDA to "act immediately to require that a medication guide warning of the dangers and explaining the need of CoQ₁₀ supplementation be included with statin drug prescriptions." ⁶¹

A separate petition was filed the same day by Emord & Associates on behalf of Whittaker and asks FDA to require a warning concerning the danger of CoQ₁₀ deficiency be added to the labeling of all HMG-CoA reductase inhibitors. The suggested warning would read: "HMG-CoA reductase

inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ is associated with impairment of myocardial function, with liver dysfunction, and with myopathies (including cardiomyopathy and congestive heart failure." ⁶¹

The proposed warning would advise physicians that "all patients taking HMG-CoA reductase inhibitors should therefore be advised to take 100 to 200 mg per day of supplemental coenzyme Q₁₀." ⁶¹

I encourage physicians in clinical practice who are prescribing statins to carefully consider the points raised in this paper that describe the potential for a drug-nutrient depletion of CoQ₁₀ by statin drugs. Furthermore, physicians may consider measuring CoQ₁₀ levels in patients on long-term statin therapy as this will support a physician-recommended supplementation of CoQ₁₀.

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