Exhibit A

The clinical use of HMG CoA-reductase inhibitors (statins) and the associated depletion of the essential co-factor coenzyme Q_{10}; a review of pertinent human and animal data.

By Peter H. Langsjoen, M.D., F.A.C.C.[1]

Introduction

HMG CoA-reductase inhibitors or statins are clearly the most effective class of drugs for lowering LDL cholesterol. Those drugs have been associated with a beneficial impact on cardiovascular morbidity and mortality. As such, statins have become some of the most widely prescribed drugs in the United States with many millions of patients taking them on a regular basis. According to the most recent NCEP (National Cholesterol Education Program) guidelines, the indications for the use of statins have been broadened such that patients with even low normal LDL cholesterol levels are now being treated in hopes of favorably altering the incidence of stroke and myocardial infarction. Statins are frequently used in the elderly and have gained very broad acceptance in the medical community. Statins have been noted to have significant anti-inflammatory and plaque-stabilizing effects which has added to their broader usage.

It is well established that the mevalonate pathway is involved not only in the biosynthesis of cholesterol but also in the biosynthesis of the essential co-factor required for energy production, coenzyme Q_{10} (CoQ_{10}, ubiquinone). As such, HMG CoA reductase inhibitors block the cellular production of cholesterol and of coenzyme Q_{10} (Rudney 1981, Goldstein 1990). This drug-nutrient interaction has been reviewed (Bliznakov 1998, Bliznakov 2002).

The peer-reviewed scientific evidence supports the following findings:

1. Statins block the endogenous biosynthesis of both cholesterol and CoQ_{10} by inhibiting the enzyme HMG CoA reductase, thus decreasing mevalonate, the precursor of both cholesterol and CoQ_{10}.

2. CoQ_{10} is essential for mitochondrial ATP production and is a potent lipid soluble antioxidant present in cell membranes and carried in the blood by LDL. CoQl0 is biosynthesized in the body and available fiom dietary sources.

3. Statin-induced decreases in CoQ_{10} are more than just hypothetical drug-nutrient interactions. Good evidence exists of significant CoQ_{10} depletion in humans and animals during statin therapy.

4. Scientific evidence confirms the existence of detrimental cardiac consequences from statin-induced CoQ10 deficiencies in man and animals.

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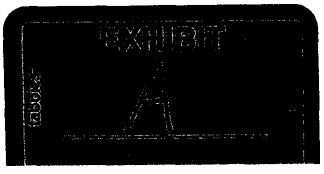
[1] Dr. Langsjoen's curriculum vitae is attached.



5. Statin-induced CoQ_{10} deficiency is dose related and the clinical consequences are notable most in the elderly and in settings of pre-existing congestive heart failure (CHF).

6. Statin-induced CoQ10 deficiency can be completely reversed by supplemental CoQ_{10}.

7. Supplemental CoQ_{10} is safe and has no adverse effect on statin cholesterol-lowering or on statin anti-inflammatory effects.

8. We are in the midst of a congestive heart failure epidemic in the United States. Approximately 4.8 millions Americans are diagnosed with congestive heart failure. Half of those patients will die within 5 years. Each year, there are an estimated 400,000 new cases of CHF (Congestive Heart Failure Data Fact Sheet, www.nhlbi.nih.gov/health/public/heart/other). Although the causes of this epidemic are unknown, statin-induced CoQ_{10} deficiency has not been excluded as a possible contributing factor.

9. All large-scale statin trials excluded patients with NYHA class III and IV heart failure such that the long term safety of statins in patients with heart failure has not been established.

Background

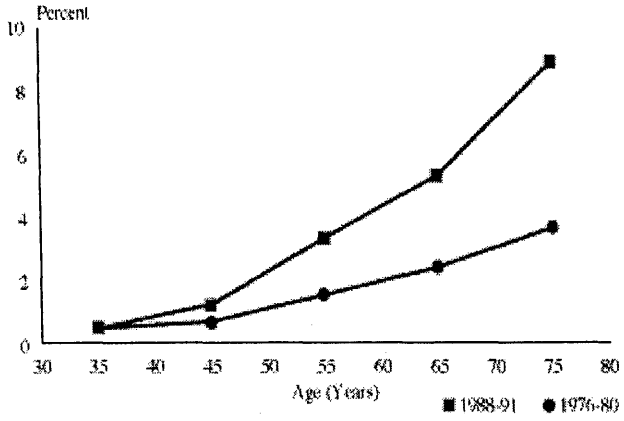
Coenzyme Q_{10} is the coenzyme for mitochondrial enzyme complexes involved in oxidative phosphorylation in the production of ATP (Mitchell 1976, Mitchell 1990, Lenaz 1991). That bioenergetic effect of CoQ_{10} is believed to be of fundamental importance in its clinical application, particularly as it relates to cells with exceedingly high metabolic demands such as cardiac myocytes. The second fundamental property of CoQ_{10} involves its antioxidant (free radical scavenging) functions (Beyer 1990, Villalba 1997). CoQ_{10} is the only known naturally occurring lipid soluble antioxidant for which the body has enzyme systems capable of regenerating the active reduced ubiquinol form (Ernster 1993). CoQ_{10} is carried in the blood with low density lipoprotein and serves to diminish the oxidation of LDL cholesterol in settings of oxidative stress (Alleva 1997). CoQ_{10} is known to be closely linked to Vitamin E and serves to regenerate the reduced (active) alpha-tocopherol form of Vitamin E (Constantinescu 1994) as well as the reduced form of ascorbate (Rodriguez-Aguilera 1995). Other more recently discovered aspects of CoQ_{10} function include its involvement in extramitochondrial electron transfer, e.g. plasma membrane oxidoreductase activity (Villalba 1997), involvement in cytosolic glycolysis (Lawen 1994), and potential activity in both Golgi apparatus and lysosomes (Gille 2000). CoQ_{10} also plays a role in improvement in membrane fluidity (Lenaz 1985). The multiple biochemical functions of CoQ_{10} have recently been reviewed by Crane (Crane 2001).

Coenzyme Q_{10} is essential for all cellular ATP production and is of particular importance in heart muscle function given that tissue's extreme energy requirements. **A** deficiency of CoQ_{10} in the blood and the heart muscle has been documented in congestive heart failure (Kitamura 1984, Folkers 1985). An Australian group of cardiovascular surgeons has recently documented impairment in myocardial function secondary to age-related CoQ_{10} deficiency in patients undergoing coronary artery bypass surgery (CABG). That impairment was completely

eliminated with incubation of the atrial myocardium with CoQ_{10} (Rosenfeldt 1999). Later the researchers performed a trial of preoperative supplemental CoQ_{10} therapy and found improved outcomes in coronary artery bypass surgery (Pepe 2001). The clinical experience with supplemental CoQ_{10} in cardiovascular disease, including congestive heart failure, ischemic heart disease, hypertensive heart disease and heart surgery has been recently reviewed (Langsjoen 1998, Langsjoen 1999).

In the US we are presently in the midst of a congestive heart failure (CHF) epidemic, with a significant increase in the incidence of congestive heart failure over the past decade (see the figure below as reproduced from the National Center for Health Statistics NIH & NHLB Institute). The annual number of deaths directly from CHF increased from 10,000 in 1968 to 42,000 in 1993. The rate of hospitalizations for heart failure increased more than three times between 1970 and 1994. In the largest health system study of its kind, researchers at the Henry Ford Heart and Vascular Institute in Detroit found that the annual number of heart failure cases more than doubled from 1989-1997. Over that nine-year period, 26,442 cases were identified in the Henry Ford Health System in Detroit. Strikingly, the annual prevalence rose from 9 to 20 cases per 1000 health system patients (Eurekalert.org reference). Those results were compiled in the Resource Utilization Among Congestive Heart Failure (REACH) study (McCullough 2002).

Figure 5
Prevalance of CHF, by Age, 1976-80 and 1988-91



Source: National Health and Nutrition Examination Survey (1976-80 and 1988-91), National Center for Health Statistics.

Figure 1. Congestive Heart Failure: A New Epidemic.
Reproduced from figure 5 at http://www.nhlbi.nih.gov/health/pub ic/heart/other/CHF.htm

Statins were first given pre-market approval in the US in 1987. Since that time, there has been a slow but steady accumulation of scientific evidence that the coenzyme Q_{10}-lowering effect of statin medications has clinical relevance and should be considered by all physicians when prescribing this class of medication.

Human Trials

From 1990 to date there have been 15 published studies in humans evaluating the effects of statins on CoQ_{10}. Nine were controlled trials and eight of those demonstrated significant CoQ_{10} depletions secondary to statin therapy.

Human observations on the interaction between statins and coenzyme Q_{10} were first published in 1990 by Folkers et al, who observed that five patients with pre-existing cardiomyopathy exhibited a significant decline in blood coenzyme Q_{10} level and clinical deterioration following lovastatin (Folkers 1990) treatment. That decrease in coenzyme Q_{10} blood level and decline in clinical status was reversed through an increase in supplemental coenzyme Q_{10}.

In 1993, Watts et al studied 20 hyperlipidemic patients treated with a low cholesterol diet and simvastatin and compared them to 20 hyperlipidemic patients treated with diet alone and 20 normal controls (Watts 1993). Patients treated with simvastatin had significantly lower plasma coenzyme Q_{10} levels and a lower coenzyme Q_{10} to cholesterol ratio than either patients on diet alone or normal controls. The depletion of plasma CoQ_{10} was significantly inversely associated with the dose of simvastatin. It was concluded that simvastatin may lower plasma coenzyme Q_{10} concentration and that the reduction may be proportionally greater than the reduction in cholesterol. The authors felt that the adverse effect of simvastatin on the biosynthesis of coenzyme Q_{10} may be clinically important and requires further study.

In 1993, Ghirlanda et al studied 30 hypercholesterolemic patients and 10 healthy volunteers in a double-blind controlled trial, comparing placebo with either pravastatin or simvastatin for a three-month treatment period (Ghirlanda 1993). Both of those HMG CoA-reductase inhibitors showed significant reduction in total cholesterol and plasma CoQ_{10} levels, not only in hypercholesterolemic patients but also in the normal healthy volunteers.

In 1994, Bargossi et al performed a randomized controlled trial evaluating 34 hypercholesterolemic patients treated with either 20 mg of simvastatin for six months or 20 mg of simvastatin plus 100 mg of supplemental coenzyme Q_{10} (Bargossi 1994). The study demonstrated that simvastatin lowered LDL cholesterol and lowered plasma and platelet coenzyme Q_{10} levels. The depletion of CoQ_{10} in both plasma and platelets was prevented in the supplemental Coenzyme Q_{10} group without affecting cholesterol lowering caused by simvastatin.

In 1995, Laaksonen et al. documented a significant decrease in serum Coenzyme Q_{10} levels in hypercholesterolemic patients treated with four weeks of simvastatin, with no reduction in skeletal muscle ubiquinone (Laaksonen 1995).

In 1996, Laaksonen et al evaluated skeletal muscle biopsy specimens in 19 hypercholesterolemic patients treated with simvastatin at 20 mg per day and found no

depletion of skeletal muscle ubiquinone concentration as compared to control subjects (Laaksonen 1996).

In 1996, De Pinieux et al evaluated 80 hypercholesterolemic patients (40 patients treated with statins, 20 patients treated with fibrates, and 20 untreated controls) (De Pinieux 1996). Further, they evaluated 20 non-hyperlipidemic health controlled patients. Serum ubiquinone levels were significantly lower in statin treated patients and were not depleted in fibrate treated patients or in untreated controls. Lactate to pyruvate ratios were significantly higher in statin treated patients, indicating mitochondrial dysfunction in patients treated with statins, which was not observed in untreated hypercholesterolemic patients or in healthy controls.

In 1997, Palomaki et al. studied 27 hypercholesterolemic men in a double-blind placebo controlled crossover trial with six weeks of lovastatin at 60 mg per day (Palomaki 1997). Lovastatin therapy was associated with a significant decline in serum ubiquinol content as measured per LDL phosphorus, and there was an increased oxidizability of LDL in the lovastatin treated patients.

In 1997, Mortensen et al studied 45 hypercholesterolemic patients in a randomized double-blind trial with either lovastatin or pravastatin for 18 weeks (Mortensen 1997). A dose-related significant decline in total serum coenzyme Q_{10} was found in the pravastatin group from 1.27 +/- 0.34 to 1.02 +/- 0.31 mmol/L. In the lovastatin group, there was a more pronounced decrease in serum CoQ_{10} level from 1.18 +/- 0.36 to 0.84 +/- 0.17 mmol/L $p<0.001$. The authors concluded that although HMG CoA-reductase inhibitors are safe and effective within a limited time horizon, possible adverse consequences fiom coenzyme Q_{10} lowering was an important factor in long-term therapy.

In 1998, Palomaki et al evaluated 19 men with hypercholesterolemia and coronary artery disease treated with lovastatin with or without ubiquinone supplementation (Palomaki 1998). The lag time in copper mediated oxidation of LDL increased by 5% ($p=0.02$). It was observed that the faster depletion of LDL ubiquinol and shortened lag time in conjugated diene formation during lovastatin therapy may partially be restored with ubiquinone supplementation.

In 1999, Miyake et al studied 97 non-insulin-dependent diabetic patients treated with simvastatin and observed a significant decrease in serum CoQ_{10} concentrations along with the decrease in serum cholesterol (Miyake 1999). Oral CoQ_{10} supplementation in diabetic patients receiving simvastatin significantly increased serum coenzyme Q_{10} levels without affecting cholesterol levels. Furthermore, the supplemental coenzyme Q_{10} significantly decreased cardiothoracic ratios from 51.4 +/- 5.1 to 49.2 +/- 4.7% ($p<0.03$). The authors concluded that serum coenzyme Q_{10} levels in diabetic patients are decreased by statin therapy and may be associated with subclinical diabetic cardiomyopathy, reversible by coenzyme Q_{10} supplementation.

In 1999, De Lorgeril et al. studied in a double-blind fashion 32 patients treated with 20 mg of simvastatin compared to 32 patients treated with 200 mg of fenofibrate (De Lorgeril 1999). Serum coenzyme Q_{10} levels were significantly reduced after treatment with simvastatin but

not with fenofibrate. No significant change in left ventricular ejection fraction could be determined after 12 weeks of therapy. They observed a loss of myocardial reserve with a flattening of the ejection fraction response to exercise, which could be explained by the statin-induced diastolic dysfunction in those patients. Unfortunately, only systolic measurements of ejection fraction were obtained in this study.

In 2001, Bleske et al. failed to show a depletion in whole blood CoQ_{10} in 12 young, healthy volunteers with normal cholesterol levels treated with either pravastatin or atorvastatin for four weeks (Bleske 2001).

Also in 2001, Wong et al. documented that the beneficial anti-inflammatory effect of simvastatin on human monocytes was completely reversible with supplemental mevalonate but not with coenzyme Q_{10}, indicating that supplemental coenzyme Q_{10} would not interfere with this important statin-mediated anti-inflammatory effect (Wong 2001).

The most recent statin/CoQ study was a randomized controlled trial by Jula et al., published in JAMA (Jula 2002). Simvastatin at 20 mg per day caused a reduction in serum CoQ_{10} of 22% ($p<0.001$). The clinical consequences of this significant CoQ_{10} deficiency were not evaluated in this short term trial.

In summary, in human trials evaluating coenzyme Q_{10} in statin therapy, there appears to be frequent and significant depletion in blood CoQ_{10} levels, particularly when statins are taken at higher doses and most notably in the elderly. In one study involving patients with preexisting CHF, the depletion in blood coenzyme Q_{10} levels was associated with a drop in ejection fraction and clinical deterioration. Supplemental coenzyme Q_{10} has been found to prevent the depletion of CoQ_{10} in blood and in one study also to prevent the depletion measured in platelet CoQ_{10}. The serum depletion of CoQ_{10} was associated with an elevation in lactate to pyruvate ratio, suggesting an impairment in mitochondrial bioenergetics, secondary to statin-induced CoQ_{10} depletion. Furthermore, two trials demonstrated enhanced oxidizability of LDL cholesterol related to the lowering of serum CoQ_{10} by statins. Supplemental CoQ_{10} has been shown to increase the CoQ_{10} content in low density lipoproteins and to decrease significantly LDL cholesterol oxidizability (Alleva 1997). One trial demonstrated no significant CoQ_{10} depletion in 12 young normolipidemic volunteers treated with statins and one trial found no skeletal muscle depletion of CoQ_{10} in statin treated hypercholesterolemic patients. In diabetic patients, the CoQ_{10} depletion with statin therapy appears to be associated with subclinical cardiomyopathy, with significant improvement in cardiothoracic ratios upon CoQ_{10} supplementation.

From these studies, one can conclude that supplemental coenzyme Q_{10} prevents the statin induced CoQ_{10} deficiency state without altering the cholesterol-lowering ability of these drugs and appears to have benefit both in terms of decreasing the oxidizability of low density lipoprotein cholesterol, as well as preventing or reversing observed detrimental clinical changes.

Animal Studies

From 1990 through 2001 there have been 15 published animal studies involving six different animal species (six rat studies, three hampster studies, three dog studies, one rabbit study, one guinea pig study and one study looking at squirrel monkeys, mini pigs and hampsters) evaluating the effect of statins on coenzyme Q blood and/or tissue levels. Nine of these 15 studies looked specifically at the adverse consequences of this statin-induced CoQ depletion: decreased ATP production, increased injury after ischemia/reperfusion, increased mortality in cardiomyopathy, and skeletal muscle injury and dysfunction. Some of the animals use coenzyme Q_9 which is a shorter chain homologue of coenzyme Q_{10} and in those cases the term coenzyme Q or CoQ is used.

Some of the first animal data was published in 1990 by Willis et al. and documented statistically significant decreases in coenzyme Q (CoQ) concentration in blood, heart and liver in 45 adult male Holtzman rats. This blood and tissue CoQ deficiency could be completely prevented by supplementing the lovastatin treated animals with coenzyme Q_{10} (Willis 1990).

In 1992, Low et al. found similar decreases in ubiquinone in liver and heart in rats treated with lovastatin (mevinolin), confirming observations by Willis et al (Low 1992).

1993, Fukami et al. studied simvastatin treated rabbits and specifically looked at those animals with elevations in creatinine kinase, lactate dehydrogenase, and skeletal muscle necrosis (Fukami 1993). The simvastatin treated rabbits were noted to have significantly reduced liver and cardiac muscle coenzyme Q content as compared to the control group. Interestingly, skeletal muscle ubiquinone content in this study was not affected.

In 1993, Belichard et al studied lovastatin in cardiomyopathic hamsters and found a 33% decrease in ubiquinone content in heart muscle as compared to control (Belichard 1993). Cholesterol lowering in cardiomyopathic hamsters with fenofibrate did not lower coenzyme Q_{10} levels. Statins are the only class of lipid-lowering drugs that axe known to block the synthesis of mevalonate.

In 1994, Diebold et al documented a depletion in Coenzyme Q_{10} content in heart muscle in guinea pigs when treated with lovastatin in older age (2 years of age) animals, and further observed no significant depletion in coenzyme Q_{10} content in heart muscle in the guinea pigs in the younger age group (2 to 4 months of age) (Diebold 1994). The authors evaluated mitochondrial function as measured by the potential to phosphorylate ADP to ATP, and again documented a decrease by up to 45% in cardiac mitochondria in the 2-year-old animals treated with lovastatin, and no significant decrease in phosphorylation in the younger age group animals. This sensitivity for older animals to show clinically relevant heart muscle CoQ_{10} depletion is of concern in humans as older patients are treated with statin medications and are observed to be more fragile and more susceptible to side effects.

In 1994, Loop et al. documented again that lovastatin decreased coenzyme Q content in rat liver that could be completely prevented with supplemental coenzyme Q_{10} (Loop 1994).

In 1995, Satoh et al evaluated ischemic reperfusion in dog hearts and documented that simvastatin significantly decreased myocardial coenzyme Q_{10} levels and worsened ischemia reperfusion injury (Satoh 1995). Water soluble pravastatin was also studied in this dog model and did not appear to cause worsening of mitochondrial respiration in the dog heart muscle, nor did the pravastatin reduce myocardial CoQ_{10} levels. It is believed that the lipid soluble simvastatin may be more detrimental in this model due to better membrane penetration of that fat soluble drug.

In 1997, Morand et al studied hamsters, squirrel monkeys, and mini pigs, and documented CoQ_{10} depletion in heart and liver with simvastatin treatment (Morand 1997). They saw no decrease in coenzyme Q_{10} in heart and liver using the experimental cholesterol lowering drug 23-oxidosqualene:lanosterol cyclase, which blocks the synthesis of cholesterol below the mevalonate level and thus does not impair the biosynthesis of coenzyme Q_{10}.

In 1998, Nakahara et al. evaluated simvastatin (a lipophilic inhibitor of HMG CoA-reductase) or pravastatin (a hydrophilic inhibitor) (Nakahara 1998). In group I, rabbits were treated with simvastatin at 50 mg/kg per day for four weeks. There was a 22% to 36% reduction in ubiquinone content in skeletal muscle and the observation of skeletal muscle necrosis and elevated CK levels. Group II rabbits were treated with pravastatin at 100 mg/kg per day for four weeks, which did not cause skeletal muscle injury and reduced coenzyme Q_{10} in skeletal muscle by 18% to 52%. In group III, treated with high dose pravastatin at 200 mg/kg per day for three weeks followed by 300 mg/kg per day for another three weeks, there was a greater reduction in ubiquinone skeletal muscle content from 49% to 72% depletion and evidence of skeletal muscle necrosis and CK elevation.

In 1998, Sugiyama observed that pravastatin caused significant decrease in the activity of mitochondrial complex I in diaphragm skeletal muscle in rats age 35-55 weeks (Sugiyama 1998). The authors concluded that careful clinical examination of respiratory muscle function is necessary in patients treated with pravastatin, particularly in the elderly.

In 1999, Ichihara et al studied the effect of statins on ischemia reperfusion in dogs and observed that pretreatment of the dogs with the lipophilic HMG CoA-reductase inhibitors simvastatin, atorvastatin, fluvastatin, and cerivastatin all worsened recovery of myocardial contraction after ischemia reperfusion, but the water soluble pravastatin had no detrimental effect on myocardial contraction in this model (Ichihara 1999).

In 2000, Satoh et al further observed a detrimental effect fiom atorvastatin, fluvastatin, and cerivastatin in dog ischemia reperfusion, confirming that lipophilic HMG CoA-reductase inhibitors enhance myocardial stunning in association with ATP reduction after ischemia and reperfusion (Satoh 2000).

In 2000, Caliskan et al studied rats treated with simvastatin and found significant reductions in plasma cholesterol and ATP concentrations, indicating an impairment in bioenergetics related to CoQ depletion (Caliskan 2000).

In 2000, Marz et al studied hamsters with inherited cardiomyopathy and concluded that lovastatin but not pravastatin at a dose of 10 mg/kg body weight significantly increased the mortality of cardiomyopathic hamsters, as a result of inhibition of myocardial ubiquinone (Marz 2000).

Finally, the most recent animal study by Pisarenko et al in rats treated with simvastatin at 24 mg/kg for 30 days showed a significant decrease in ATP and creatinine phosphate in myocardium, again indicating that statin-induced CoQ_{10} depletion has a detrimental impact on energy production in the heart muscle (Pisarenko 2001).

In summary, animal studies to date uniformly document varying degrees of coenzyme Q depletion in blood and in tissue with statin therapy, and that the coenzyme Q deficiency is associated with adverse effects in cardiomyopathic hamster models, in the ischemia reperfusion injury in dog models, as well as in liver and cardiac coenzyme Q content in rabbits with skeletal muscle damage. **A** decrease in cardiac CoQ content and in ATP production has been documented in 2-year-old (elderly) guinea pigs. Significant CoQ depletion was documented in the heart and liver in hamsters, squirrel monkeys, and mini pigs. It is also noteworthy that the lipid soluble statins appear to show more animal toxicity, particularly in the ischemia reperfusion dog models. One can surmise from these animal studies that statins have the potential to produce clinically meaningful coenzyme Q depletion in several animal species and that the depletion is dose related. In all animal studies where supplemental coenzyme Q was given to the animals prior to the institution of statins, the coenzyme Q blood and tissue depletion was completely prevented.

Safety and Drug Interactions

Coenzyme Q_{10} is sold in the United States and abroad as an over-the-counter dietary supplement and is widely recognized as completely safe with no reported toxicity in over a thousand published human and animal trials. The most recent animal safety study was published in 1999 by Williams et al. Potential CoQ_{10} toxicity was assessed in rats administered CoQ_{10} by oral gavage for 1 year at 100, 300, 600, and 1200 mg per kg body weight per day. No adverse changes in mortality, clinical signs, body weight, food consumption, or clinical pathology results occurred.

To date, there have been at least 34 placebo controlled trials using CoQ_{10} in cardiovascular disease involving a total of 2152 patients with no toxicity or drug interactions reported in the CoQ_{10} group as compared to the placebo group. Most of these controlled trials have been reviewed (Langsjoen 1998, Langsjoen 1999). In addition to these controlled trials there have been many open-label long term trials using CoQ_{10} in doses up to 600 mg per day with up to eight year follow up, again with a complete lack of toxicity. In heart failure alone there have been at least 39 open trials with supplemental CoQ_{10} published involving 4498 patients again with remarkable safety with the only reported side-effects being rare cases of mild nausea.

Long term safety and tolerability of CoQ_{10} was documented by Langsjoen in 1990 in a six year study of 126 heart failure patients (Langsjoen 1990). Later, in 1993, Morisco published a double blind controlled trial on 641 heart failure patients treated with either placebo or CoQ_{10} for one

year (Morisco 1993). The investigators found a significant reduction of hospitalizations for worsening of heart failure in the CoQ_{10} group and no evidence of side effects. In 1994 Baggio published an open-label multi-center trial on 2664 patients with heart failure, treated with 150 mg CoQ_{10} per day for three months and reported good tolerability (Baggio 1994). Also in 1994 Langsjoen published long term observations on 424 cardiac patients, treated with 75 to 600 mg of CoQ_{10} per day for up to eight years with no adverse effects or drug interactions. One out of the 424 patients experienced transient nausea.

There have been two case reports published claiming potential interaction between CoQ_{10} and coumadin (warfarin), suggesting that CoQ_{10} has a vitamin K-like effect (Spigset 1994, Landbo 1998). This has not been corroborated by other investigators and was the subject of a prospective trial which was presented at the most recent coenzyme Q_{10} conference of the International Coenzyme Q10 Association in Frankfurt, Germany, Dec 1-3, 2000 (Engelsen 2000). Physicians wisely and routinely follow prothrombin times very closely in patients on coumadin, particularly after any change in diet, medication or over-the-counter supplements. In this author's 18 year experience with the use of CoQ_{10} in many thousands of cardiac patients we have yet to see a single case of CoQ_{10}-coumadin interaction at doses up to 600 mg of CoQ_{10} per day (unpublished observations).

Discussion and Conclusions

The widely prescribed HMG CoA-reductase inhibitors block the endogenous biosynthesis both of cholesterol and of coenzyme Q_{10}, and the decrease in both substances is related to the dose as well as the potency of those drugs. The depletion of the essential co-factor required for energy production, coenzyme Q_{10}, appears to be well tolerated in younger and healthier patients, particularly in the short term, but the data reveal detrimental cardiac effects in humans with pre-existing cardiac dysfunction and in several animal models, particularly in older animals. CoQ_{10} is known to be deficient in congestive heart failure (CHF), with the degree of deficiency in blood and cardiac tissue correlating with the severity of the CHF (Kitamura 1984, Folkers 1985). Normal whole blood levels of CoQ_{10} are about 1.0+/-0.2 :g/ml with deficiency in the range of 0.6+/-0.2:g/ml. It is also known that CoQ_{10} levels steadily fall after the age of 40 (Kalen 1989, Soderberg 1990). The best recent data documenting impairment in myocardial function secondary to age-related CoQ_{10} deficiency in older patients undergoing coronary artery bypass graft surgery is by an Australian group of cardiovascular surgeons who obtained atrial muscle from patients at the time of open heart surgery and evaluated it for a post-ischemic contractile recovery. Older patients had significantly lower myocardial tissue levels of CoQ_{10}. Incubation of the atrial myocardium with CoQ_{10} completely abolished the difference between the contractile recovery of the senescent atrial tissue (greater than the age of 70) as compared to the atrial tissue from patients under the age of 60 (Rosenfeldt 1999). Later those researchers performed a randomized, double-blind, placebo controlled trial of preoperative supplemental CoQ_{10} therapy and found improved outcomes in coronary artery bypass surgery. The results of that trial were presented at the 2001 American Heart Association Scientific Sessions in Anaheim (Pepe 2001). Certainly, patients undergoing bypass surgery may be more susceptible to statin-induced lowering of coenzyme Q_{10} cardiac tissue levels, and elderly patients who are on statin therapy would greatly benefit from supplemental CoQ_{10}.

Thus, all prescribing physicians should be notified that statin drugs produce a depletion in coenzyme Q_{10}, which in settings of pre-existing CoQ_{10} deficiency, such as in CHF (Folkers 1970, Littarru 1972, Kitamura 1984, Folkers 1985) and ageing (Kalen 1989), has the ability to markedly worsen myocardial function. As the potency of statin drugs increases and as the target LDL cholesterol level decreases, the potential for statin-induced cardiomyopathy must be seriously considered and must be prevented with the concomitant administration of CoQ_{10} with all statin medications. In addition, since CoQl0 is not obtainable fiom daily dietary sources sufficient to bolster flagging levels of statin-induced CoQ 10 deficiencies, the aforementioned concomitant administration must be in specific supplement form and within 100-200 mg.

A black box warning in the labeling for all statins sold in the Unites States should read as follows:

> Warning:
> HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q_{10}, 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). All patients taking HMG CoA reductase inhibitors should therefore be advised to take 100 to 200 mg per day of supplemental coenzyme Q_{10}.

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CURRICULUM VITAE

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EDUCATION: Temple High School, Temple, Texas, 1969-1972
The University of Texas at Austin, 1972-1975; Bachelor of Science in Chemistry with Honors.
The University of Texas Health Science Center, San Antonio, Texas, 1976-1980; M.D. degree 1980.
The University of North Dakota, Fargo, North Dakota, Internal Medicine Residency, 1980-1983.
Scott and White Memorial Hospital, Temple, Texas, Cardiology Fellowship, 1983-1985.

CERTIFICATIONS: Diplomate, American Board of Internal Medicine, 1983.
Diplomate, American Board of Internal Medicine, Cardiovascular Disease, 1985.

MEDICAL LICENSURE: 1980 - present, Texas

PROFESSIONAL SOCIETIES: Alpha Omega Alpha Honor Society
American College of Cardiology - Fellow
American College of Physicians - Member
Texas Club of Cardiologists - Member (President 1997-1998)
Texas Medical Association - Member
Smith County Medical Society - Member

The International Coenzyme Q_{10} Association
(http://wwwcsi.unian.it/coenzymeQ/index.html) - Founding Member of the Executive Committee (1997 to present)

EXPERIENCE:

1983-1985: Involved in the first controlled study of coenzyme Q_{10} in cardiomyopathy with Per H. Langsjoen, M.D., F.A.C.C. during cardiology fellowship at Scott and White Hospital, Temple, Texas.

1985-1990: Associate Professor of Medicine and staff invasive cardiologist at The University of Texas Health Center at Tyler, Tyler, Texas.

1986-1987: Performed the first exploratory treatment of AIDS patients with Coenzyme Q_{10} at the University of Texas Health Center in Tyler, Texas.

1990-present: Private practice of non-invasive cardiology, Tyler, Texas, specializing in congestive heart failure and other diseases of the heart muscle.

Presentations at the 6th, 8th and 9th International Symposiums on the Biomedical and Clinical Aspects of Coenzyme Q (held in Rome, Italy, 1990, in Stockholm, Sweden, 1993 and in Ancona, Italy, 1996, respectively), at the First Conference of the International Coenzyme Q_{10} Association (in Boston, USA, 1998) and many other presentations in the US and abroad

Numerous TV and radio appearances and interviews

1997 - Became a Founding Member of the Executive Committee of the International Coenzyme Q_{10} Association, based in Ancona, Italy and has served on the Executive and Scientific Committee of this Association since then.

Ongoing research into application of coenzyme Q_{10} to the treatment of the broad range of cardiovascular diseases, including long term follow up study in heart failure and later in primary diastolic dysfunction and hypertensive heart disease.

PUBLICATIONS:

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2. Langsjoen P.H. and Langsjoen A.M. Overview of the Use of CoQ_{10} in Cardiovascular Disease. *BioFactors* 1999;9(2-4):273-284.

3. Langsjoen P.H., Langsjoen **A.M.** Review of Coenzyme Q_{10} in Cardiovascular Disease with Emphasis on Heart Failure and Ischemia Reperfusion. Asia *Pacific Heart J* 1998;7(3):160-168.

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