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William R. Ware, PhD - Editor

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Rather than having a main theme, this issue covers a variety of currently important health issues such as flu vaccination, the alarming increase in autism, the lack of evidence for low blood pressure targets in the context of heart disease prevention, more vitamin D news and the continued accumulation of evidence for the merits of the Mediterranean diet.

Also discussed is a paper remarkable for its presence in a major mainstream cancer journal that points out the slight or negligible increases in overall cancer survival associated with certain astronomically priced chemotherapy agents. In countries or situations where health care is rationed or where the absence of health insurance is common, one hears of cases where someone is denied "lifesaving therapy" because no one will pay for it. This makes good human interest material for the media, but it is likely that the therapy is in fact not lifesaving, and the huge expenditure that is being resisted may extend life by a period measured in days or a month or two at best, and there is in addition a treatment associated mortality that accompanies this lifesaving therapy.

This issue also contains a short research review which addresses the importance of coenzyme Q-10 in the context of heart health and in particular heart failure. Physicians practicing integrative and alternative medicine have been using this enzyme routinely for many years in this context, but mainstream medicine has been steadfast in its resistance. It is a supplement available, even in highly absorbable forms, without prescription. Furthermore, statins appear commonly used in the treatment of heart failure, and yet they decrease the blood levels of this enzyme and probably also its tissue levels. This review attempts to deal with this paradox.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

H1N1 VACCINES

In a Centers for Disease Control (CDC) summary in their publication *Morbidity and Mortality Weekly Report* (MMWR) of October 9, 2009, there is a list of four monovalent H1N1 vaccines currently approved for use in the U.S. In spite of the all the talk and concern over adjuvants (chemical additives to enhance the effectiveness of the vaccine), they are, according to the CDC, absent from these vaccines. Also, vaccines for injection or intranasal application supplied in prefilled syringes are either free of mercury or contain < 1.0 microgram per dose.

Vaccines that are administered by withdrawing from a multidose vial contain about 25 micrograms of mercury per dose. The summary indicates that children can receive 2 doses, independent of whether or not the vaccine is mercury free. No vaccine appears to have been approved for children under 6 months. The injectable vaccines contain inactivated virus, whereas the intranasal formulation contains live attenuated virus. According to the CDC document, the intranasal vaccine should not be given to children under 2 years of age, adults over 49, pregnant women, people with medical conditions that put them at higher risk for flue complications, and children under 5 who have had a wheezing episode within a year. All the vaccines contain protein from eggs. For more information, go to the MMWR or CDC websites.

According to a report in *The Globe and Mail,* in Canada one of the vaccines health authorities have decided to use contains adjuvants, something that has not been previously approved for influenza vaccines in this country. Approval is expected shortly, apparently based on a clinical trial done in Germany on 130 healthy adults. According to media reports, the Canadian government like the U.S. government will protect the manufacturer from lawsuits.

An interesting article just appeared in the *Atlantic Monthly* magazine titled "Does the Vaccine Matter?" which raises questions regarding the studies that are used to justify the seasonal vaccination program. These questions are based on peer reviewed papers suggesting serious bias and confounding due to preferential receipt of vaccine by relatively healthy seniors.[1,2] It is available online at http://www.theatlantic.com/doc/2009.

PREVALENCE OF AUTISM APPEARS TO BE INCREASING

A study just published online in the journal *Pediatrics*[3] found that the prevalence of children being diagnosed with autism has doubled since 2003 and is now at 1 in 91. Even when the rate was half of this it was alarming. Considering the impact on both the affected child and its caregivers, this represents a disaster and a crisis.

The study had some limitations. It was based on parent reported diagnosis, but studies suggest that this approach has moderate-to-high sensitivity. Also, excluded from the final count were children who earlier had been reported as diagnosed with autism but were no longer labelled as such. Strengths of the study include a large population-based sample.

In the May 2009 issue of this newsletter, successful so-called biomedical treatments of autism were described. In connection with the question of what causes autism, the opinion of a physician who treats autism via the biomedical approach was discussed. He believes that the causes are multifactorial and include genetic predispositions, toxic environment and nutrient deficiencies and these factors are magnified by over use of medications such as antibiotics and vaccinations. Thus in his view, autism is a complex, multisystem disorder rooted in toxic insults, infections and their treatment, and allergic reactions. Incidentally, some of the toxic insults are now though to come from not only mercury, the traditional suspect, but from dietary excitotoxins such as monosodium glutamate, the Chinese food flavour enhancer which is widely used in prepared foods with its presence concealed with strange pseudonyms, aspartame, the diet soda sweetener also found in prepared foods, fluoride, and aluminum, and mechanisms have very recently been proposed to describe how these individual chemicals act on the brain and the rest of the body to produce the autism spectrum of disorders.[4] The case histories presented in the May issue highlight the extent to which the autistic child's biochemistry is impaired and a cause and effect association is implied by the interventions described which reduce or eliminate the symptoms that lead to the diagnosis of autism.

The biomedical approach appears to use only one prescription drug, an anti-fungal for treating yeast overgrowth in the gut. Interested readers are referred for more information on the biomedical approach to treating autism to the book *Gut and Psychology Syndrome* by Dr. Natasha Campbell-McBride, MD, which was briefly reviewed in the July-August newsletter. Primary prevention appears highly complex since exposure can occur both during the prenatal period and in early childhood when sensitivity may be very high to the adverse effects of the vast assortment of toxic chemicals to which we are all exposed, dozens of vaccinations, unfriendly gut bacteria, poor nutrition, vitamin D

deficiency, frank deficiencies in some micronutrients which serve as vital cofactors in numerous biochemical processes, excitotoxic food additives, etc. It is clear that primary prevention is not only a scientific problem but also a political problem, and this latter aspect suggests that progress will be slow. The popular notion that autism is a "brain disorder" distracts from preventing or treating systemic problems. If we are really at a prevalence of about 1 in a hundred, then it would appear that a crash program of research is needed which is not controlled by special interests or influenced by dogmatic preconceived notions.

BENEFITS OF TREATING HYPERTENSION—EVIDENCE BASED OR MYTHOLOGY?

This question might be better phrased as follows: Are what is considered normal for blood pressure and the threshold and targets set for therapy evidence-based? This is an important question because millions of individuals worldwide are treated for hypertension based on the belief that there is benefit. But while mainstream medicine considers the above question settled there always seems to be pressure to lower thresholds. Two recent studies relate to this question and should prompt renewed interest in some earlier literature which has been completely ignored.

The first study was already reviewed in the July/August Newsletter. It involved a very large and indiscriminate meta-analysis of 147 studies.[5] The conclusion was that blood pressure drugs should be offered to people with all levels of blood pressure and discouraged even measuring it. The justification was the reduction of coronary heart disease (CHD) events and stroke. The study was criticized because of the failure to discriminate between studies with variable degrees of evidence quality.

A study from the well known Cochrane Collaboration, a research organization specializing in high quality, definitive meta-analyses of important medical questions, has just appeared which addresses the importance of blood pressure targets as assessed by the impact on endpoints such as total mortality, cardiovascular mortality, non-cardiovascular mortality, heart attacks and major cardiovascular events.[6] It was found that when comparison was made between the target ≤ 135/85 compared to ≤ 140-160/90-100 mm Hg, there was no difference in the above endpoints. In other words, lowering blood pressure below the range of 140-160/90-100 carried no benefit for the endpoints generally evoked as being benefited by therapy. This analysis involved 22 trials selected for high quality with 22,089 participants.

These studies relate to the belief, which has influenced the mainstream view on hypertension for decades, that there is a continuous, graded and strong relationship between systolic blood pressure and the risk of death and that there is no evidence of a threshold. Already in 1980 this was questioned by Keys. In 2000, a reanalysis of the Framingham data by Port *et al* from the University of California at Los Angeles demonstrated that in fact there was a threshold followed by a rapid increase in risk which was in fact greater than found by the Framingham investigators.[7,8] They found a threshold at the 70th to 80th percentile which was age dependent but fell between 150 and 160 mm Hg for systolic blood pressure. For the age group 65-74, 22% of men and 40% of women fell in the range between 140 mm Hg and the 70th percentile, i.e. even though they had what would be considered high blood pressure, they were still below the threshold. The presence of a threshold was also seen in data for diastolic pressure.

But the matter is not as simple as these results suggest. As Port *et al* take pains to point out, a number of studies have demonstrated cardiovascular benefits, but they are for the most part independent of the magnitude of the blood pressure lowering and dependent on the class of hypotension medication employed. Thus the blood pressure lowering effects of these drugs may just be an "inconsequential" side effect. They cite 5 studies to support this contention. The similarity with cholesterol-lowering drugs is interesting since anti-hypertensives and statins are the chief weapons in modern medicine's arsenal in the context of "fighting" cardiovascular disease.

While the notion of Wald and Law that everyone and especially those over 65 should be on anti-hypertensives and there is no need even to measure blood pressure seems wild, the non-blood pressure lowering effects of anti-hypertensives appear to support this notion. The problem is, which

drug is indicated for which set of risk factors since it is evident that some produce benefits and others do not for a given cardiovascular endpoint. It is also interesting that both ACE inhibitors and calcium channel blockers are implicated in reducing the prevalence and/or progression of coronary plaque and thus atherosclerosis.[9,10] Pulse pressure (the difference between the systolic and diastolic pressures) has also been found to be a component of hypertension associated with the presence and progression of atherosclerosis.[11] However, conventional anti-hypertensive drug therapy does not appear to prevent the increase of pulse pressure with age.[12]

Thus it still appears important to identify individuals with blood pressure above the thresholds identified by Pont *et al* and by the latest meta-analysis by the Cochran Collaboration since these individuals appear at real risk for adverse hypertension associated events. It is noteworthy that these two studies agree in the location of this threshold. Whether or not anti-hypertensive drugs such as ACE inhibitors and calcium channel blockers will ultimately be found useful for evidence based therapy to control atherosclerosis remains to be seen. It will require carefully designed studies to show that the effects are not related to blood pressure lowering but to what are called pleiotropic effects.

Other examples can be quoted. Hypertension also increases the risk of dementia and the use of anti-hypertensive drugs for a number of years reduces the risk of incidence, independent of the drug used.[13] Tight control of systolic blood pressure in non-diabetic patients with hypertension has been found to beneficially influence left ventricular hypertrophy.[14] Finally, untreated hypertension is a risk factor for kidney problems. These examples reinforce the argument that it is in general important to measure blood pressure and intervene, but the question of appropriate targets, given the diversity of health problems where hypertension is a factor, appears to merit additional research and generalization of the studies related to cardiovascular disease does not appear justified.

The reader is also referred to a study of modifiable risk factors associated with the risk of developing hypertension that appeared in the October 2009 Newsletter and which found potential risk reductions of up to 90% without medication.

MEDITERRANEAN DIET AND NEED FOR DRUG THERAPY IN TYPE 2 DIABETES

A study just published in the *Annals of Internal Medicine*[15] randomized over 200 overweight patients newly diagnosed with type 2 diabetes to either the diet recommended by the American Diabetes Association, which is essentially a low-fat diet, or to a Mediterranean-style diet. Fairly intensive counseling was given on an ongoing basis and the patients were followed for 4 years. At the end, 44% of patients on the Mediterranean diet and 70% those on the low fat diet required pharmaceutical intervention to control blood glucose. The absolute change was a decrease of 26 percentage points. Those assigned to the Mediterranean diet had greater improvements in some glycemic control and coronary risk measures than those on the low-fat diet, and they lost more weight even though there was no increase in physical activity or decrease in caloric intake.

The article contains a nice summary of the benefits of the Mediterranean diet in the context of various health issues. Included were

- Mediterranean-style diets may be more effective than low-fat diets when weight-loss is the goal.
- Mediterranean diets produce more favourable changes in plasma glucose and insulin levels than low-fat diets.
- Prospective studies show that the Mediterranean diet food pattern is associated with a reduction in the risk of type 2 diabetes in both healthy individuals and those who have had a heart attack.
- Three large prospective studies found that consumption of fruits and vegetables, an essential component of the Mediterranean diet, reduced the risk of diabetes.
- A recent meta-analysis of prospective studies found that as the score for adherence to a Mediterranean diet increased, the risk of overall mortality and cardiovascular-related mortality decreased.
- The Mediterranean diet is protective against chronic inflammation, insulin resistance and the metabolic syndrome.

MEDITERRANEAN DIET AND INCIDENCE OF DEPRESSION

An interesting study has just appeared in the *Archives of General Psychiatry*.[16] Over 10,000 individuals were followed for over 4 years. Participants were judged as having incident depression if they were free of depression and did not take antidepressant drugs at baseline, and later reported a physician-made diagnosis of clinical depression and/or the use of antidepressant medication. A score was generated for adherence to the Mediterranean diet pattern which was positively weighted for vegetables, fruit and nuts, cereal, legumes and fish, the mono-saturated fat ratio and moderate alcohol consumption. Meat and meat products and whole-fat dairy were negatively weighted. The risk of incident depression decreased by 26%, 34%, 51% and 42% as the dietary adherence score increased through the 4 upper categories. When the results were stratified by dietary component, inverse dose-response relationships were found for fruit and nuts, legumes and the mono to saturated fatty acid ratio.

The authors suggest that the beneficial effect of the Mediterranean diet may be due to its beneficial effect on endothelial function. The Mediterranean diet is considered healthy because it reduces vascular, inflammatory and metabolic processes through improvements in endothelia function, decreases in proinflammatory cytokines, and favourable changes in the mechanisms related to the occurrence of the metabolic syndrome. That the diet may help prevent depression is especially important since recurrent major depression is related to coronary calcification, i.e. directly measured coronary atherosclerosis, and therefore to the risk of eventually having clinically evident heart disease.[17] Major depression is not only widespread but presents a serious public health problem.

While the authors add the almost obligatory caution that trials are needed, the evidence for the benefits of the Mediterranean diet, seem so compelling, both in the context of this discussion and in general, that one should need little encouragement to investigate and implement such a diet.

PESTICIDE EXPOSURE AND CHILDHOOD CANCERS

Children and fetuses are considered particularly susceptible to adverse effects induced by pesticides, especially cancer. A study just published in the journal *Therapeutic Drug Monitoring* deals with evidence for enhanced risk of acute lymphoblastic leukemia (ALL) associated with exposure to household pesticides and in particular organophosphates.[18] Mother-child pairs where the child had diagnosed ALL were compared to an equivalent number of pairs where the child was free of the disease. It was found that more case mothers (33%) than control mothers (14%) reported using insecticides in the home. Urine analysis was employed to determine pesticide metabolites. Mother's pesticide levels were higher in cases than controls and statistically significant differences were found between children with ALL and controls for the metabolites of organophosphates commonly used in pesticides. Levels of a typical metabolite were 4 times higher in case-children than in controls. While the authors emphasize that this does not prove cause, it suggests the need for more studies. This appears to be an understatement.

Another recently published study addresses the risk of childhood brain cancer associated with parental exposure to pesticides.[19] As in the above study, it was of the case-control design. Parents' exposure was assessed by telephone interviews and included both domestic and workplace contact. The data concerned exposure in the 2-year period before the child's birth. A significant risk of brain cancer (astrocytoma, which includes one of the worst brain cancers, glioblastoma multiforme) was found to be associated with parental exposure to herbicides and the risk was reduced significantly for children whose fathers washed immediately after any pesticide exposure or who wore protective clothing. The enhanced risk of brain cancer from herbicide exposure was about a factor of 2 for either residential or combined residential and occupational exposure compared to those unexposed, but occupational exposure was not common in this cohort. Also, The authors point out that these results are consistent with some of the existing literature, but discuss inconsistencies in this literature. It is interesting that it has been demonstrated that levels of pesticides in a mother's blood correlate with those in the cord blood.

One of the arguments that there is no danger associated with trace amounts of toxic materials either inhaled or ingested is based on the fact that exposure involves minute amounts. But consider a typical organophosphate, dimethyl phosphate. Two micrograms of this chemical contains about 10^{16} molecules which is 1000 molecules for every cell in a child's body. For those who recall their elementary chemistry, Avogadro's number, the number of molecules in an amount equivalent to the molecular weight (a mole), is $6X10^{23}$, a very big number indeed. This is the number of molecules in 18 cc of water! For those toxic substances which accumulate or are slowly eliminated, the exposure increases with time and the toxin may become localized and thus concentrated in specific organs or cellular structures. Thus "trace" exposure can result in high local concentrations.

The number of chemicals made for release into the environment, added to or contaminating food, or available for leaching out of consumer products is huge. Real testing is impossible since definitive experiments are unethical. Indirect evidence is easily confounded, hard to collect, and the chemical industry has a conflict of interest associated with their own testing and a strong incentive to suppress unfavourable study results. While a sensible approach is to avoid inhaling or ingesting all manmade chemicals and avoiding skin exposure, this has become totally impossible. Quite the contrary, we are immersed in a sea of manmade chemicals from which it is almost impossible to escape unless one lives isolated from modern population and is able to grow all their own food for year-around consumption. Organic food is only a step in the right direction, but organic food is not *a priori* free of manmade chemicals. Not using pesticides or herbicides and using only "natural" soap, shampoo, shaving cream, toothpaste, etc. appears to offer some relief from the present-day levels of exposure, but this only scratches the surface of what may be a very big problem.

But humans are now in an almost no-win situation. A recent report on the pesticide residue status of European fruits and vegetables found higher levels than allowed bylaw in some samples tested (www.telegraph.co.uk, September 24, 2009).

MULTICOMPONENT APPROACH TO CONTROLLING CORONARY PLAQUE PROGRESSION

Contrary to the almost universal belief that LDL cholesterol drives atherosclerosis, a notion reinforced in drug company ads during prime time TV, non-invasive coronary artery imaging studies during the last 10 years appear to falsify this hypothesis. Not only is there no statistically significant connection between the prevalence or progression of coronary plaque and serum LDL, recent randomized controlled studies indicate that statin therapy has no influence on the progression of coronary plaque.[20] A recent open-label study designed to look beyond LDL lowering is of interest. The study was motivated by the several trials where LDL lowering failed to arrest plaque progression or reduce coronary plaque. Combined therapy involved statins for most subjects plus niacin, omega-3 fatty acids from fish oil, and vitamin D3 supplementation. The non-LDL goals consisted of triglycerides ≤ 60 mg/dL, HDL ≥ 60 mg/dL, and 25 hydroxyvitamin D serum levels of ≥ 50 ng/mL. Subjects had elevated triglycerides, low HDL and a wide range of coronary calcium scores with a quite high median value. The mean follow-up with a repeat calcium scan was 18 months. Compared to expected calcium score progression, 49% achieved slower plaque growth and in addition, 44% had a substantial reduction in calcium score.[21] No information was acquired regarding the relative importance of the individual components of the intervention. However, given that it is unlikely that the results were produced by a synergism between statins and the supplements employed, and that studies indicate that statins do not influence the endpoints used, this study should be followed with one that attempts to determine the relative benefits from the non-statin component of the intervention. In addition, one of the targets was the elimination of so-called dyslipidemia associated with triglycerides and HDL which most would agree is a desirable goal in general.

CURCUMIN, VITAMIN D AND ALZHEIMER'S DISEASE

The prevalence of Alzheimer's disease (AD) in the U.S. in the population over 71 years of age is about 10% whereas in India, for the population over 65 it is just over 1%.[22,23] The global prevalence is predicted to double every 20 years. One hypothesis concerning this huge geographical difference is that in India the spice turmeric (curcumin) is much more widely and heavily used for seasoning in India than in the U.S. This suggestion is supported by a recent study which found that 1-alpha 25-dihydroxyvitamin D (1,25D), also called vitamin D hormone, and compounds in curcumin interact to stimulate the clearance of amyloid-beta mediated by macrophages in patients with AD.[24] Amyloid-beta appears to be the main component of amyloid plaques in brain tissue, is implicated in the pathology of AD and is currently a therapeutic target for plaque prevention and regression.

It is important to recognize that vitamin D hormone is distinct from the metabolite 25-hydroxyvitamin D in that the former is tightly regulated and rather insensitive to an individual's vitamin D status or intake from sun or supplements. Thus while there are dozens of reasons for maintaining a high level of 25-hydroxyvitamin D, in the context of the synergism under discussion, manipulating the concentration of curcuminoids derived from curcumin appears to be indicated. Thus increasing the intake of curcumin while maintaining high vitamin D status may have very beneficial effects on the incidence and progression of AD. Randomized intervention trials would be very informative. However, it is not required to consume foods heavily seasoned with turmeric since curcumin is available as a supplement, and some vendors provide a highly bioavailable preparation. Curcumin is also thought to play a preventive or therapeutic role in cancer, diabetes, cardiovascular disease, arthritis and inflammatory disorders such as irritable bowel syndrome.[25]

HIGH COST OF EXTENDING CANCER SURVIVAL TIMES WITH CHEMOTHERAPY

Advocates of adult cancer chemotherapy claim significant overall survival benefit whereas critics point out that the absolute increase in overall survival is small to trivial and one must factor in serious and sometimes fatal side effects. However, it is important to first identify the adult cancer types or sites where there is much less if any debate as to clear benefit. These appear to include ovary, testis, non-Hodgkin's lymphoma and Hodgkin's disease.[26] This leaves a large number of other types and sites where the percentage contribution to 5-year survival due to chemotherapy falls in the range of 0.7% to 5.4%. If all types and sites of cancer are considered, the average percentage is 2.3%, but if those with obvious benefit are excluded, the average percentage drops to 1.7% A recent commentary in the *Journal of the National Cancer Insititute*[27] is of interest in this context, not only for what is says but also where it was published. The inspiration came from the 2008 meeting of the American Society of Clinical Oncology where the overall survival advantage of the chemotherapeutic agent Cetuximab (Erbitux) used against lung cancer was heralded as a breakthrough. In fact the increase in overall survival was 1.2 months and was barely statistically significant. Nevertheless, in the meeting press briefing it was stated that this therapy "…sets a new standard for the first-line treatment of patients with non-small cell lung cancer."

The authors present an interesting table of cost and overall survival for four chemotherapeutic agents.

Drug	Site	Overall Survival Increase	Treatment Cost
Erbitux	Lung	1.2 months	$ 80,352
Avastin	Breast	1.5 months	$ 90,816
Tarceva	Pancreas	10 days	$ 15,752
Nexavar	Kidney	2.7 months	$ 34,373

Even before considering the impact of treatment on quality of life and the risk of therapy related mortality, these numbers speak for themselves. The distributions of treated and untreated survival times generally overlap strongly, and all that is quoted to patients may be the relative change in the mean,

whereas one needs to know the actual mean survival times accompanied by the standard deviation. The chances that the therapy will be of no benefit whatsoever can be very high when the distributions overlap strongly. Thus cancer patients should insist disclosure of absolute increases in survival time in days, weeks or months, not relative increases, and weigh these against the side effects which should also be described in detail including the risk of treatment-caused death. To those uninitiated in how the system operates, this would seem to constitute a reasonable minimum for informed consent, but such detailed questioning may produce a very unfavourable reaction. To ask for supporting literature with references would really shake the system up and probably result in a hostile reaction.

NEWS BRIEFS

DIABETES DRUG MAY CAUSE ACUTE PANCREATITIS

According to a report in Reuters (September 26, 2009) U.S. health officials have indicated that they suspect that Merck's blockbuster drug (definition: sales > 1 billion per year) Januvia, a diabetes drug, may be linked with acute pancreatitis, a potentially fatal disorder. The concern centers on the fact that of the 88 cases reported so far, 19 developed soon after initiation of the drug therapy and 47 resolved after the drug was discontinued. A variation of this drug is Merck's Janumet, and a similar drug Byetta, marketed by another pharmaceutical company have also been linked to acute pancreatitis. Reuters quotes the FDA as saying it was working with Merck to add information about this problem to the so-called labels of the two drugs. No mention was made of the association between pancreatitis and pancreatic cancer. Reuters also quotes a security analyst from a major European bank as suggesting that this will not impact the sales of the two Merck drugs, estimated at 2.7 billion for 2009. Interesting situation. The readers are left to draw their own conclusions.

WALKING TO IMPROVE GLUCOSE TOLERANCE

A recent randomized study of individuals with impaired glucose tolerance but normal fasting glucose examined the impact of increased walking on glucose metabolism parameters. Two groups, one using a pedometer, were encouraged increase their walking by about 3000 steps per day (30 minutes walking per day). It was found that at 12 months, participants using a pedometer and increased their walking by a mean of about 1000 steps (about 10 minutes additional walking) had a drop in 2 hour glucose in the glucose tolerance test of 24 mg/dL compared to a control group. Fasting glucose decreased by 6 mg/dL. The goal was actually an increase of 3000 steps but not all in the intervention group achieved this. There were no changes in weight or waist circumference observed that could explain the results. The group who were to increase walking but did not use a pedometer had no significant benefit. The study incorporated a structured educational program. It was concluded that this plus using a pedometer to help achieve walking goals could have important implications for future diabetes prevention.[28]

VITAMIN D AND COGNITIVE IMPAIRMENT

In a study of 752 women age ≥ 75 years, it was found in a cross-sectional study (snapshot of present status) that those deficient in vitamin D were approximately twice as likely to be cognitively impaired, a result that persisted after adjusting for confounding. The cognitively impaired group had a mean 25-hydroxyvitamin D level of 7.2 ng/mL whereas those deemed normal had a mean of 20.1 ng/mL. The threshold was ≤ 10 ng/L. Interestingly, all of the participants were, by modern standards, deficient with some more so than others.[29]

VITAMIN D AND RISK OF DEVELOPING HYPERTENSION

A study presented at a recent American Heart Association meeting found that low vitamin D status was associated with increased risk of developing hypertension. While the abstract is short on details, the study examined 559 women in 1992 with measurements of blood pressure and 25-hydroxyvitamin D. At that time, 5.5% with deficiencies had high blood pressure compared to 2.8% who were deemed to have normal D status. In 2007, more than 10% of the women with baseline vitamin D deficiencies had high blood pressure whereas only 3.7% with sufficient D levels were hypertensive (Reuters, September 23, 2009).

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RESEARCH REVIEW

STATINS AND HEART FAILURE. A TREATMENT PARADOX

William R. Ware, Ph.D.

INTRODUCTION

Heart failure (HF) is a condition where the heart is unable to supply sufficient blood flow to meet the body's demand. The term congestive heart failure (CHF) is approximately synonymous and emphasizes the problem of low cardiac output and problems of blood congestion backing up into the lungs and tissues. Causes include reduced blood supply to the heart (ischemic heart disease), an enlarged heart with diminished pumping efficiency (dilated cardiomyopathy) and valvular heart disease.[1] One manifestation of HF frequently used in diagnosis and as a study endpoint is the ejection fraction, generally that associated with the left ventricle. It is the fraction of the blood content of the ventricle ejected relative to the amount present at peak capacity. It is generally determined by echocardiography, a non-invasive procedure widely used in cardiology. The left ventricle ejection fraction in healthy adults ranges from 50 to 65%.

HF is an enormous social and medical problem affecting more than 2% of the U.S. population or almost 5 million people. The mortality is high and 30-40% die within 1 year of diagnosis. It can also be disabling and severely impact the quality of life.[2] This Research Review will look at one aspect, statin therapy, since there appears to be an interesting paradox associated with the current guidelines.

The 2005 and 2009 American Heart Association (AHA) guidelines for the treatment of heart failure (HF) recommend that for patients at high risk of HF and those with various stages of established HF, part of the standard treatment protocol should include "treat lipid disorders" which presumably translates into establishing and attempting to reach low LDL targets.[3] The only drug in common use is the statin.

However, statins reduce levels of a critical enzyme, coenzyme Q-10 (CoQ-10), and there is a fairly extensive literature concerning the adverse effect of low CoQ-10 on muscle function (including heart muscle) related in part to the role of this enzyme in mitochondrial energy production. Statins inhibit the mevalonate pathway involved in CoQ-10 synthesis. Furthermore, several small but significant studies indicate that there is an *inverse* association among individuals with HF between total cholesterol, LDL cholesterol and mortality. The effect is in fact rather strong and would suggest cholesterol elevation, not reduction, as an appropriate therapeutic target in this context. Also, it has been suggested on a number of occasions that there is a distinct possibility that in some patients, statins may actually contribute to the severity of HF. It has been repeatedly pointed out that HF has

increased in lock-step with the use of statins. As will be discussed below, statin treatment of HF patients appears to provide no benefit in terms of overall mortality or fatal cardiovascular events.

Thus it appears that, paradoxically, there is evidence that one of the treatments recommended for HF may in fact provide no benefit. This may perhaps be due to the balance between adverse effects and non-lipid-lowering beneficial effects. Under some circumstances, statin therapy may aggravate HF. This is just part of a larger subject related to the consequences of inhibiting a major biological pathway and thus reducing the levels of a number of important endogenous biochemicals just in order to reduce the synthesis of one target molecule, in this case cholesterol. It is interesting that one of the major statin manufacturers actually acquired patents for a combination of CoQ-10 and their statin but never marketed the combined medication. Instead, the industry appears to be in a state of denial regarding potential problems associated with the inhibition of the mevalonate pathway.

The mevalonate pathway directly involves over 13 biochemicals, only one of which is cholesterol. These chemicals are each involved in a number of other processes and pathways leading to additional biochemicals. There is considerable variation in the extent of understanding of the role of each of these molecules and in many cases research is ongoing. Inhibiting this pathway with a statin inhibits the synthesis of these biochemicals from mevalonic acid and as well those further down the line from it. The effects of this inhibition are thus profoundly complex, not as yet fully understood by any means, and may have serious long term adverse effects, either not as yet identified or attributed to other causes. Nevertheless, it is widely believed that aside from what are termed minor side effects, the interruption of this pathway presents no risk. The safety of statins is "evidence based" we are told. Critics point out that studies of side effects have frequently involved too few subjects and that the post-introduction reporting is notorious for its inadequacy, with the typical estimate that only 1% of side effects are reported and officially recorded, and that in fact the rate of adverse effects is large and significant.[4,5] The widespread belief that statins are safe also leads to a failure to associate observed problems with the drug. Rather, they are easily attributed to the effects of aging and other disorders. When Dr. Duane Graveline had his two disabling episodes of transient global amnesia he was simply told by cardiologists that "statins did not do that." In fact the evidence is now compelling that they do.[4] Given this background, we will briefly examine the apparent paradox outlined above.

STATINS DECREASE CoQ-10 IN THE CIRCULATION AND MUSCLE TISSUE

In a review in 2007, Littarru and Langsjoen[6] list a large number of studies from 1990 to 2005 which demonstrate that there is significant circulating CoQ-10 depletion secondary to statin therapy. The effect is particularly important at high doses and most notable among the elderly. Blood markers suggest impairment of mitochondrial bioenergetics which impacts muscle energetics. In addition, they cite evidence of enhanced LDL oxidizability associated with lower CoQ-10 levels. The review also discusses the impact of statins on muscle levels of CoQ-10. While the data is somewhat less consistent, the weight of the evidence favors a statin induced decrease of CoQ-10 in muscle tissue.

In a review available online,[7] Peter Langsjoen puts this decline of CoQ-10 and its relation to HF in perspective. CoQ-10 is essential for all cellular ATP production and is of particular importance in heart muscle function given that this tissue has extreme energy requirements. He points out that already in 1984 and 1985 a deficiency in CoQ-10 both in the blood and heart muscle was documented in cases of congestive HF, and age-related CoQ-10 deficiency was associated with myocardial dysfunction in patients undergoing coronary bypass surgery in Australia. In addition, preoperative supplementation with CoQ-10 was found to improve outcomes in bypass surgery. He also points out that that the steady increase in the prevalence of HF coincides with the advent and increased use of statin drugs.

CoQ-10 BLOOD LEVELS ARE AN INDEPENDENT PREDICTOR OF HF MORTALITY

A study reported in 2008 in the *Journal of the American College of Cardiology* examined the association between blood levels of CoQ-10 and mortality in chronic heart failure. Blood samples were obtained from 236 patients admitted to hospital with chronic heart failure with a median follow up of about 2.7 years. A detailed statistical analysis (multivariate) allowed for the standard predictors of survival—age, gender, previous heart attack, a peptide marker, and a measure of kidney function. It was found that low CoQ-10 was an independent predictor of survival which persisted in a model that also included statin treatment. Thus the depletion of CoQ-10 appears associated with worse outcomes in chronic heart failure.[8]

STATINS MAY INCREASE RISK OF HF BY INHIBITING THE SELENOPROTEIN PATHWAY

The element selenium, acting through selenium containing proteins called selenoproteins, plays an important role in development, metabolism and antioxidant defence. There are over 25 selenoproteins including the highly critical glutathione peroxidase which provides protection from oxidative damage, and a class of selenoproteins which govern thyroid metabolism. The synthesis of these proteins depends on a special RNA molecule containing selenocysteine, an amino acid where the sulphur atom in cysteine has been replaced by selenium. For this RNA to function it must be modified by a chemical reaction that involves a molecule which is a direct metabolite of mevalonate, the production of which is inhibited by statins. This is one view of the connection between statins and the inhibition of the synthesis of essential selenium containing proteins.[9]

In a recent review, de Lorgeril and Salen present evidence supporting the role of selenium in the prevention and treatment of HF.[10] Unfortunately, there do not appear to be clinical studies published to date that examine the effect of selenium supplementation on the risk of coronary heart disease, heart disease mortality or overall mortality. The authors mention a few epidemiologic studies which document associations between serum glutathione peroxidase activity and cardiovascular disease, but none provide data specifically about HF. Recently, however, a case history describes a 55-year-old woman with documented heart failure who presented with a significant selenium deficiency. Her symptoms resolved in 3 weeks with daily IV selenium treatments of 100 micrograms. Beta-blockers and ACE inhibitors, two standard treatments, were not tolerated because of very low blood pressure. Her ejection fraction measured by an echocardiogram went from 30% to 65% over the treatment period.[11]

Thus it can be argued on general principles that it is not a good idea to mess with the pathway involved with such an important class of biochemical as the selenoproteins, and that there is some indirect evidence that inhibiting the selenoprotein pathway may adversely impact heart failure. Selenium status appears to be rarely measured in patients presenting with HF.

MARKED INCREASE IN HF MORTALITY ASSOCIATED WITH LOW CHOLESTEROL

Two studies provide evidence for the hypothesis that low total cholesterol is associated with an increase in mortality from HF. Horwich *et al*[12] studied 1,134 patients with advanced HF who presented at a single center for HF management. Survival was observed over 5 years. Total cholesterol, LDL, HDL and triglyceride levels all predicted survival with improved survival at *higher* levels. When other risk factors were taken into account, those in the lowest quintile of total cholesterol had twice the mortality risk as those in the highest. These results were confirmed in a study by Rauchhaus *et* al[13]. They found that the chance of survival increased 25% with each *increase* of one mmol/L (approximately 40 mg/dL) of total cholesterol. It was concluded that patients with lower serum total cholesterol had a worse prognosis in the context of HF. Thus a treatment protocol which includes aggressively lowering cholesterol may be counterproductive in this context.

STUDIES REGARDING STATINS AND HEART FAILURE

It might seem that one approach to resolving the problem of statins and heart failure would be to do clinical studies. But there immediately arises the question of appropriate endpoints. Some studies use hospitalization for a cardiovascular indication, but the reasons associated with the admission may not be directly or even indirectly related to heart failure. Death from coronary heart disease has also been used, but this is too general and includes a heart attack, not necessarily the first, or sudden cardiac death which may be directly related to an arrhythmia problem, not a failure of the heart due to a chronic inability to pump enough blood. Thus studies that look at large databases of causes of hospitalization and mortality can be fatally confounded if one is trying to directly relate events to heart failure. Furthermore, coronary heart disease and heart failure are closely coupled and any treatment that impacts the former can impact the latter if it is related to muscle damage or weakness due to ischemia. Overall mortality is not informative because it does not zero in on heart failure as the cause. Also statins have an amazing number of non-lipid lowering effects which might impact heart failure favourably, and in fact, statins are given immediately post MI with almost instantaneous beneficial results that can not be explained by lipid lowering. Also, in studies the expectation is that there will be benefit, and when there is harm it may be ignored.

Thus while statins have the potential to increase the risk of heart failure or mortality directly related to heart failure and there is considerable evidence to back up this belief, they also have the potential to provide beneficial

effects. These beneficial effects may vary considerably with the type of statin and in addition have a dose dependence which would lead the unwary to conclude that it was lipid lowering that was providing the benefit whereas it is merely the increase in the dose of a drug that is acting independent of lipid lowering. This in fact is a fundamental problem with the position of those who believe that statins provide benefit because they lower cholesterol, especially in the case of individuals with coronary heart disease, This belief is so widespread that is has all the characteristics of a dogma, and yet the logic is fatally flawed.

Thus studies that result in null results, or sets of studies that are inconsistent, may reflect both endpoint problems and a balance between benefit and harm which results in a wash. If the latter is true, then a more sensible approach would be to use different drugs that might have the beneficial actions without the adverts effects of the enzyme inhibition caused by statins. The resistance to this approach is in part based on the belief that statins are good for the heart, period.

STATINS IN RANDOMIZED CLINICAL TRIALS DO NOT DECREASE HF MORTALITY

While observational studies suggest that statin therapy is beneficial for individuals with HF with and without prior heart attack, some medical scientists, as a matter of principle, have suspended judgment pending randomized placebo-controlled trials. Two such trials have recently reported which do not support the observational studies. The first (CORONA) randomized about 5000 patients with HF to either 10 mg/day of rosuvastatin (Crestor) or a placebo. The primary endpoint was death for cardiovascular causes, non-fatal heart attack or non-fatal stroke. Secondary outcomes included death from any causes, any coronary event and the number of hospitalizations. Statin treatment did not reduce the primary outcome or the number of deaths from any cause although the drug did slightly reduce the number of cardiovascular hospitalizations (2.1% absolute difference). The second study (GISSI-HF) randomized approximately 4600 patients with CHF to the same protocol as CORONA. The primary endpoints were time to death, admission to hospital for cardiovascular reasons. It was found that 10 mg daily of rosuvastatin did not affect clinical outcomes in patients with CHF of any cause.

For those who believe that in the hierarchy of trials and studies, the randomized placebo controlled trial provides the strongest evidence, then the use of statins for the treatment of HF does not appear to be evidence-based. Many of the investigators in both studies had ties to the maker of rosuvastatin, a fact that some would say in this case strengthens the credibility of the study and the validity of the negative results. The GISSI-HF investigators took the position that the prescription of rosuvastatin, or in fact any statin, to patients with heart failure should be discouraged.

EVIDENCE THAT CoQ-10 SUPPLEMENTATION IMPROVES CARDIAC FUNCTION

From the above discussion it appears that age related decline in CoQ-10 leads to the impairment of cardiac function and perhaps HF. It also appears that statins potentially exacerbate this disorder. Evidence appeared as early as 1990 when Folkers *et al*[14] described a few cases of cardiac patients supplemented with CoQ-10 where HF worsened when lovastatin was added to their therapy. This deterioration was reversed upon increasing the daily dose of CoQ-10. More recent evidence that there is the potential for benefit from supplementing with CoQ-10 mainly derives from the work of cardiologist Peter Langsjoen and coworkers in Texas. Four studies are of interest. The studies suggest that the impact of CoQ-10 depletion is multi-factorial.

- In a study of patients where statin therapy worsened left ventricular diastolic function as observed by Doppler echocardiography, supplementation with CoQ-10 resulted in a reversal in the abnormalities in the parameters of the diastolic function without stopping the statin.[15]

- A study of 50 consecutive patients presenting in a cardiology clinic were evaluated for statin side effects including various HF related symptoms. Statin treatment was terminated and CoQ-10 supplementation started at an average of 240 mg/day. Patients were followed for an average of 22 months. Improved ejection fraction was found in 50% of patients, whereas improved diastolic dysfunction was observed in between 46 and 50% of patients, depending on the measure. Fifty percent of patients with left ventricular enlargements improved with CoQ-10 treatment. In this group of patients, 64% also had myalgia, fatigue (84%}, shortness of breath (58%), memory loss (8%) and peripheral neuropathy (10%). Treatment with CoQ-10 resulted in these symptoms decreasing to much lower residual prevalence of 6%, 16%, 12%, 4%, and 2% respectively.[16]

- Some patients with advanced CHF receiving CoQ-10 supplementation for low levels of this enzyme have limited clinical improvement. Langsjoen and Langsjoen[17] hypothesized that this might be due to poor absorption due to intestinal edema. They identified seven such patients who failed to respond to 450 mg/day of CoQ-10. They switched the patients to the reduced form called ubiquinol which resulted in a dramatic normalization of serum Q-10 levels (mean 1.6 mg/L increased to 6.5 mg/L) and an improvement in the mean ejection fraction from 22% to 39%.[17] Ubiquinol is available from http://www.yourhealthbase.com/vitamins.htm and from health food stores.

- Berman *et al* in a small randomized placebo controlled trial examined the impact of CoQ-10 on patients with end-stage HF awaiting a heart transplant.[18] The treatment group showed significant improvement in a 6-min walk test, the stage of heart failure, nocturia and fatigue.[18] In a letter to the editor by the cardiologist Stephen Sinatra, it was pointed out that this study achieved a 3.5- to 4-fold increase in blood levels of CoQ-10 which brought the levels up to near normal using a highly bioavailable form of the enzyme. Sinatra also comments that in his own clinical experience he has had (as of 2004) two patients come off heart transplant waiting lists as a result of Q-10 therapy.[19]

In the book *The Sinatra Solution. Metabolic Cardiology*[20] Stephen Sinatra comments that 85% of his patients with CHF found CoQ-10 alone to be effective. For the remaining 15% he found that adding L-carnitine resulted in significant improvement. L-Carnitine is required in cells to facilitate the breakdown of lipids for the generation of metabolic energy. The protocol he uses for HF consists of daily supplementation with a multivitamin and a gram of fish oil to which he adds 300-360 mg of highly absorbable CoQ-10, 2 to 2.5 g of L-carnitine, 10-15 g of the sugar D-ribose, and 400-800 mg of magnesium. This protocol is frequently combined with conventional therapies such as diuretics and digitalis. His book, which provides the scientific background for this protocol, is highly recommended for anyone with heart problems. It contains an entire chapter on CoQ-10. He has also reviewed this subject in a recent paper in *Alternative Therapies* which includes a good discussion of CoQ-10 trials and in particular why some fail. He points out in this paper that in 23 controlled trials of supplemental CoQ-10 in CHF between 1972 and 2006, 20 showed benefit.[21]

One of the above studies highlights a problem with CoQ-10 supplementation, i.e. bioavailability or absorption. Over the past few years there has been a lot of effort put into developing preparations which result in higher blood levels. The use of ubiquinol is one result of this research and this reduced form is available without prescription at http://www.yourhealthbase.com/vitamins.htm. This is also something to keep in mind when purchasing supplements. It is also a factor to question when reading studies, especially those with null results. This may be one reason why data on the effect of CoQ-10 supplementation on myopathic symptoms are inconsistent, and why a recent review suggested that the routine use of CoQ-10 could not be recommended for patients treated with satins.[22] This appears overly conservative given that the prevalence of just myopathy alone appears much greater than admitted by the industry and points directly at a mitochondrial mechanism.[5] In the context of HF, the clinical experience of Dr. Stephen Sinatra and the literature cited would suggest that not addressing CoQ-10 depletion is a big mistake.

CONCLUSIONS

The above discussion clarifies the nature of the paradox represented by the use of statins to treat HF and the AHA recommendation of 2009 to treat lipid disorders in HF patients. While the GISSI-HF trial reported after the 2009 AHA guidelines were prepared, this is probably not true for the CORONA results which appeared in 2007. Nevertheless, research suggesting that statins are contraindicated in HF goes back a long way. However, it is fair to say that statins do not occupy a prominent position in the AHA guidelines which concentrate on diuretics, ACE inhibitors and beta-blockers as well as aldosterone antagonists, digitalis and hydralazine/nitrates. In addition, the guidelines encourage smoking cessation, regular exercise, and discourage alcohol intake, illicit drug use and control the metabolic syndrome. But there appears the potential for making the disorder worse if a HF patient is left on statins or prescribed this drug. At the very least, HF patients have enough problems without having to deal with the possible side effects of this class of drug, given that they appear to offer no significant therapeutic benefit in the context of either mortality or cardiovascular events.

For individuals who have a history of heart attack and/or symptomatic ischemia along with HF, statins appear to decrease the risk of secondary acute events associated with coronary artery disease. But, to quote Sinatra, “We

don't prescribe statin drugs to lower cholesterol. We selectively use statins to improve outcome in patients with risk markers known to respond well to this drug intervention."[23] This brings us in full circle to the necessity of always combining statin therapy when indicated with doses of CoQ-10 sufficient to elevate serum levels to a protective level.

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