HEALTH AND STRESS

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STATINS, STRESS, CORONARY DISEASE AND HYPERTENSION

KEYWORDS: Coenzyme Q10 and congestive failure, inflammation, polytherapy perils, plasma renin assay, salt-volume (V) vs. renin-angiotensin (R) hypertension

It's hard to go through the week without learning about some sensational new indication for statins or being updated on their triumphs in lowering your "cholesterol number" and preventing heart attacks. Small wonder that some now view statins as some sort of panacea. A constant barrage of advertisements has also made them the most profitable prescription drugs ever. Lipitor sales are projected to hit $10 billion in 2005 and Zocor is not far behind. While statins may be useful medications there are growing concerns about the guidelines for prescribing them as well as repeated claims that they are unusually safe and well tolerated.

The Framingham study originally found that heart attacks were largely due to three controllable risk factors: high cholesterol, hypertension and smoking cigarettes. These were additive but cholesterol was clearly the most important. However, many heart attack patients have none of these risk factors and about half have normal or low cholesterol values.

Furthermore, in the Framingham 30-year follow-up report, cardiac death rates showed no relationship to cholesterol. Men over 47 with low cholesterol died just as frequently as those with high values; elevated cholesterol was not a risk factor for women and was actually associated with reduced mortality in the elderly. A variety of drug trials also failed to show that lowering cholesterol had any benefits.

We were subsequently told that the real culprit was LDL "bad" cholesterol and that a new class of statin medications effectively reduced LDL as well as heart attack and death rates. The prestigious National Research Council reported in 1989 that "LDL has the strongest and most consistent relationship to individual and population risk of CHD (coronary heart disease)". A leading proponent of the cholesterol-heart disease hypothesis subsequently wrote, "Evidence is abundant that elevated LDL is a major cause of CHD and that lowering LDL reduces CHD risk."

Save for rare cases of rhabdomyolysis and liver disease that were readily detectable, statins were also allegedly

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remarkably safe. As detailed in prior Newsletters, there was not only little to support these claims but also abundant evidence that they were erroneous and dangerously deceptive. **Recent reports provide further proof that statins are not as harmless as generally believed and that their benefits are not due to lowering LDL or other lipid effects.**

The May 2003 Weston Price Conference

Many of these issues were discussed at the recent Weston A. Price Foundation conference entitled *Heart Disease In The 21st Century: Beyond The Lipid Hypothesis*. Uffe Ravnskov's opening presentation, "High Cholesterol Protects Against Disease" reviewed a number of studies showing higher rates of infectious disease, cancer, and AIDS in patients with low cholesterol levels. Higher death rates from respiratory and digestive disorders were also associated with low cholesterol. In the Framingham follow-up study, subjects whose cholesterol fell the most had the highest coronary and overall death rates. In the only cholesterol lowering trial that included autopsies, atherosclerosis was more pronounced in the treatment group. Ravnskov, author of *The Cholesterol Myths*, has assembled an international group of similar cholesterol skeptics, (www.thincs.org) some of whom also participated in this conference. Duane Graveline, a retired physician and former NASA scientist/astronaut recounted his personal experience with Lipitor, which caused global amnesia on two occasions. He has collected a considerable number of cases demonstrating the adverse cognitive side effects of statins and is publishing a book and some papers detailing these.

Kilmer McCully, who first demonstrated that homocysteine caused atherosclerosis in laboratory animals decades ago, reviewed a subsequent wealth of literature proving that increased homocysteine is an independent risk factor for vascular disease in humans. This is most often the result of a deficiency of folic acid and other B vitamins that can be readily corrected. Recent research studies suggest that the mechanism of action may involve increased production of certain free radical species. Further investigations could lead to the development of compounds to retard the development of cancer, atherosclerosis and degenerative diseases associated with aging.

Peter Langsjoen, a Texas cardiologist who specializes in the treatment of heart failure, warned that this problem has reached epidemic proportions, possibly due to statin depletion of coenzyme Q10. Biopsy studies show that the severity of heart failure is directly correlated with low CoQ10 levels. Numerous animal studies and clinical trials have documented statin induced Co Q10 depletion, which affects the heart more than other structures since the heart has the highest requirements of this essential vitamin-like substance. This can be prevented by administering CoQ10 supplements, which are readily available without a prescription. Langsjoen has been using these with great success over the past two decades for the prevention and treatment of heart failure as well as other cardiac problems. He is also a member of the International Coenzyme Q10 Association (www.coenzymeQ10.org). They, as well as other concerned groups, have petitioned the FDA to put a black box label warning on all statin containers.

Leslie Kevay, a prominent nutrition researcher, noted that Western diets are often low in copper and that this might contribute to coronary heart disease. Copper deficiency elevates cholesterol, uric acid and blood pressure, impairs glucose tolerance and promotes thrombosis and oxidative damage. More than 80 anatomical, chemical and physiological similarities between animals deficient in copper and ischemic heart disease patients have now been identified. For additional coverage of this conference, visit www.westonaprice.org

Statins, Cancer, CRP, CHD And Stress

My own presentation was devoted to explaining why statins are not as safe as generally claimed and that they work by reducing inflammation rather than lowering LDL. Current therapy goals of reaching arbitrary LDL levels that are difficult to achieve are dangerous. They will only lead to higher doses and longer duration of treatment, both of which will result in increased complications. In addition to rhabdomyolysis and liver dysfunction, these include: muscle pain, weakness and fatigue,

biopsy evidence of myopathy and tendinopathy in the absence of abnormal blood tests, memory loss, global amnesia, poor concentration, insomnia, erectile dysfunction, problems with temperature regulation (feeling hot or cold, having sweats), difficulty in managing diabetes, and peripheral neuropathy. In one report, the incidence of new cases of peripheral neuropathy was 16 times higher in patients taking statins.

All statins have been shown to be carcinogenic in experimental animals in dosages that approximate those given to patients. Although the lag time between exposure to a carcinogen and clinical detection is often a decade or more, a disturbing twelve-fold increase in breast cancer was reported in one study and more skin malignancies were noted in another. Statins can contribute to malignant growth by blocking the production of Coenzyme Q10 and/or squalene. Both of these intermediate compounds in the synthesis of cholesterol have been shown to have anticancer effects in animal and human studies. Statins lower DHEA, which has anticancer and immune stimulating effects and reduce bile production. This could lead to bowel cancer by increasing the transit time of food in the gut. In addition, statins can stimulate the growth of new and existing blood vessels that cancers require to promote their spread.

Statin cardioprotective effects are seen far too rapidly to be due to lowering LDL and are achieved regardless of baseline LDL levels or the degree to which they are reduced. Finally, if statins worked by lowering LDL there should be some linear dose-response relationship. This has never been shown in any study.

Cardioprotective benefits are seen in the elderly, where LDL is not a CHD risk factor. Statins also prevent ischemic stroke, another disorder that is unrelated to LDL levels. According to recent reports, statins are now allegedly beneficial for everything from Alzheimer's and atrial fibrillation to multiple sclerosis. Statins even reduce stress as assessed by lower hostility, depression and anxiety score measurements. None of these can be explained by lowering LDL.

Reducing inflammation, thrombotic factors and endothelial damage would be a much better explanation. In the CARE trial, CRP levels were found to be the best predictor of recurrent coronary events. The efficacy of statin therapy was directly related to the degree of inflammation and completely independent of any lipid response. Atherosclerotic plaque has all the hallmarks of an inflammatory response to infection and there is considerable evidence to support such an etiology in many cases, particularly for *Chlamydia pneumoniae*. Homocysteine, angiotensin II, aldosterone and a host of other inflammatory agents have also been implicated.

Stress can contribute to coronary heart disease via increased catecholamine secretion and other neuroendocrine activities. For what it's worth, stress has a much more profound influence on cholesterol levels than dietary fat intake. Stress can similarly contribute to hypertension, smoking and increased homocysteine. With respect to inflammation, most conditions associated with high CRP levels are also seen with increased stress. CRP concentrations correlate best with abdominal obesity, which has been shown to be largely due to cortisol activities that promote visceral fat cell production of inflammatory cytokines. These have been shown to contribute to coronary disease, hypertension, diabetes and other manifestations of metabolic syndrome.

Unlike the U.S., Canadian ads for statins must state they lower CoQ10 and have not been shown to prevent heart attacks. They can only claim reduction in "relative risk", which is deceptive and very different than "absolute risk". A good illustration is provided by the preposterous "Polypill" proposal.

The Phenomenal Polypill Panacea

Forget about the alchemist's magical "Elixir of Life" and Ponce De Leon's "Fountain of Youth". These fantasies have recently been replaced by a combination pill concocted not by some "kook", but two distinguished scientists, Nicholas Wald, Professor and Head of the Wolfson Institute of Preventive Medicine in London and Malcolm Law, a Professor at the University of London and University of Auckland in New Zealand. These

researchers believe they can prevent almost nine out of ten heart attacks as well as four out of five strokes in anyone with cardiovascular disease and everyone age 55 and older. All you need to do is to take their powerful Polypill daily.

So what's in this latest magic bullet? A statin to lower LDL, three different antihypertensive drugs (a beta blocker, diuretic and ACE inhibitor), aspirin to reduce clotting tendencies and folic acid to prevent high homocysteine levels. There is no vitamin C or vitamin E, omega-3 fatty acids, Coenzyme Q10 or other ingredients that have also been shown to reduce heart disease. There are no dietary restrictions or recommendations nor any need to exercise more and stop smoking.

The Polypill was introduced with much fanfare in a lead article entitled "A strategy to reduce heart disease by more than 80%". It appeared in the June 28 issue of the *British Medical Journal* accompanied by two enthusiastic editorials. Richard Smith, the editor, started out by stating that this was possibly the most important issue of the journal in the last 50 years. He suggested that everyone save their copy since it would likely become a collector's item because of the Wald and Law contributions. A guest editorial by Anthony Rogers, co-director of the Clinical Trials Research Unit, University of Auckland, was not quite as gushy. However, it also seemed to endorse the authors' claim that the Polypill would have "a greater impact on the prevention of disease in the Western world than any other known intervention"! Not surprisingly, the professors filed a patent application for their formulation and a trademark application for the name Polypill over three years ago

Their contention is that one in three people over the age of 54 could look forward to an additional 11 or 12 years of life free from cardiovascular disease by taking a daily Polypill. All the ingredients are readily available and not protected by patent so the price of the pill would be minimal, especially when purchased in huge quantities. There are apparently few concerns about safety because of the relatively lower than normal dosages used. Although all antihypertensive drugs are prescribed at "half standard doses", efficacy is presumably maintained because of some synergistic effect.

These conclusions seem somewhat premature, if not preposterous, for several reasons. The first is that no studies have ever been done with the Polypill since it does not exist. It is not clear if this will be manufactured as a tablet, capsule containing powder or gelcap, and the various different fillers required or formulation of the covering may not be compatible with all the constituents. Proximity to meals and time of day of administration may influence efficacy. Simvastatin and beta blockers are more effective when given in the evening, but a thiazide diuretic taken at the same time could significantly interfere with a good night's sleep. Some of the ingredients have significant side effects or are relatively contraindicated in common conditions like diabetes and asthma. In addition, desired responses may be suppressed and/or unwanted actions augmented when certain of these drugs are taken simultaneously.

The claims for the efficacy and safety of the Polypill are based solely on meta-analyses and statistical evaluations of more than 750 clinical trials involving some 400,000 participants. Many of these study groups involved individuals with evidence of or at increased risk for coronary heart disease and hypertension. Extrapolation of such results to a population with no increased risk for cardiovascular disease other than having reached the age of 55 seems unwarranted and potentially dangerous. They hardly justify converting millions of healthy people into perpetual patients, some of whom may well develop complaints like chronic cough and bleeding tendencies.

Relative Versus Absolute Risk And NNT

The promise that 88% of heart attacks and 80% of strokes will be prevented and that a decade or more of healthy life will be added for those who take a daily Polypill is very appealing. It is also very misleading since there are no actual studies that demonstrate this as many may be led to believe. These, as well as the claims of safety, are based solely on statistics derived from meta-analyses of randomized trials that reflect relative risk, which is very different than absolute risk. This is a great example of Harry Truman's advice, "If you can't convince them, confuse them".

For example, your doctor tells you that there is a new blockbuster statin drug with no side effects and if you take it every day for the next five years it will significantly "reduce your risk" of heart attack. How likely is it that you would take the drug based on the following clinical studies?

1. Over five years, patients taking this drug had 34% fewer heart attacks compared to controls who took a placebo. (*Sounds pretty convincing*)
2. Over five years, only 2.7% of patients taking this drug had a heart attack compared to 4.1% taking a placebo. (*Also not bad*)
3. If seventy-one people take this drug every day for five years it will prevent one of them from having a heart attack. However, there is no guarantee that you will be that person. (*These odds are not very attractive*)

All these scenarios are accurate and are based on the same data but the statistics have been presented in very different ways. To avoid becoming confused, it is essential for you to be able to distinguish between relative risk reduction (RRR), absolute risk reduction (ARR) and number-needed-to-treat (NNT).

Scenario 1:

34% is the relative risk reduction. 4.1% taking the placebo had heart attacks; compared to only 2.7% for those taking the drug, a RRR of 34%.

Scenario 2:

1.4% is the absolute risk reduction. When you compare the percentage of the 4.1% in the placebo group who had heart attacks with the 2.7% of statin-takers who had heart attacks, the ARR is 1.4%. That's about 25 times less than the RRR figure advertised.

Scenario 3:

How many people need to take the drug to prevent just one heart attack? Your doctor would have to treat 71 people just like you for five years to prevent one of them from having a heart attack but there is no way of knowing who this will be. This is called the number needed to treat (NNT) and would probably not persuade many healthy patients to take this pill for the rest of their life.

The statin manufacturers are able to persuade physicians to prescribe their products by citing Relative Risk Reduction statistics and these are also featured in direct advertising to consumers, who may not be aware of their true significance. The fact is that none of the primary prevention statin trials have demonstrated a decrease in overall mortality rates and most show no significant decrease in the incidence of heart attacks or strokes.

The Polypill proponents have done the same thing. Many will interpret their claims to mean that taking a pill every day for the rest of their lives will reduce the likelihood of having a heart attack by 88 per cent and lower their chances for stroke by 80 per cent. If the meta-analyses results were reported as absolute percentages (ARR) and number needed to treat (NNT), quite a different picture would be painted according to a rapid response entitled "Patients before populations" posted on the *BMJ* web site by two British physicians. They wrote, "We are duty bound to inform our healthy 55-year-old that if he or she takes the Polypill for the next 10 years there will be less than 1% chance per year of benefit and a 6% overall chance of side effects, some of which (e.g. aspirin related GI haemorrhage) may be life threatening. Furthermore if the Polypill is successful, our patient's chance of dying from cancer, trauma and degenerative brain disease will increase *pari passu* with the effectiveness of the Polypill, as sadly even on the Polypill, mortality will remain stubbornly around the 100% mark."

Not mentioned were the possible adverse effects of statin induced Coenzyme Q10 depletion, beta blocker fatigue and impotence, etc. The selection of three antihypertensive drugs at "half standard doses" shotgun approach raises other important objections.

Buckshot Or Bullets For Blood Pressure?

The Polypill authors make some reckless presumptions with respect to treating "essential hypertension" and preventing its development in older individuals. The decision to combine three antihypertensive drugs is based on the belief that most patients will eventually require three or more medications to achieve

satisfactory blood pressure control. These drugs are administered at half their customary doses in the hope that a satisfactory synergistic response will result but there are no studies to support this. Lower doses may reduce individual side effects but this could be offset by reactions with other medications. Beta blockers can deplete levels of CoQ10 and potentiate adverse reactions to statins such as fatigue and weakness and there may be other unanticipated polytherapy perils. The problem with the Polypill is that it is targeted to treat a set of statistics rather than a person.

When I graduated from medical school a half century ago, "essential hypertension" was often called "benign" hypertension since most patients had no complaints and some seemed to tolerate their condition for years without suffering any ill effects. "Malignant" hypertension meant that there was some evidence of retinopathy, cardiac enlargement or impaired renal function and the diastolic pressure was over 120 mm. Hg. This could arise without warning but in other instances was a worsening of a previously benign course. There were few safe blood pressure lowering drugs available for such patients and treatment was usually sodium restriction, diuretics, or sedatives depending on symptoms. If nothing worked and diastolic pressures over 140 persisted, bilateral sympathectomy was the only option to prevent blindness, encephalopathy and a certain and sometimes prompt death.

Whether or how to treat patients with benign hypertension could also be challenging. We suspected that most patients would likely have problems down the line but there was little we could do about it. Because stress or psychogenic factors were thought to play an important role, the usual therapy was phenobarbital along with advice to "slow down" and "take it easy".

Reserpine, the first widely available blood pressure lowering drug was isolated in 1952 from *Rauwolfia serpentina*, the snakeroot plant. The plant's root had been used in India for centuries to treat mental disorders and insomnia and in addition to having a tranquilizing effect, reserpine (Serpasil) also promoted vasodilatation and lowered heart rate. Unfortunately, it had disturbing side effects such as severe depression, especially at the higher doses often required to achieve normal blood pressure levels. It was difficult to justify continued treatment that significantly impaired the quality of life with no guarantee that this would be offset by preventing future problems.

A decade later, although there were now around ten additional drugs that could lower an elevated blood pressure, there was no rush to use them in patients with no complaints. Most doctors recognized that many individuals had what was later called "white coat hypertension" and that measurements were probably normal outside of the office. There were also numerous instances of patients who had well-documented and alarmingly high blood pressures for a decade or more without any related complaints. Arturo Toscanini, who was still vigorously conducting at age 90, allegedly had pressures in the 230/140 range for years with no signs or symptoms other than evidence of left ventricular enlargement.

The 1962 edition of Harrison's *Principles of Internal Medicine* noted that many physicians believed "Treatment of hypertension per se is unjustified" and the dangers and side effects of "specific" therapy "may be worse than the natural course of the disease." Authorities urged us to avoid making patients "blood pressure conscious" by prescribing drugs or diets that might not be necessary. "The first principle of the therapy of hypertension is the knowledge of when to treat and when not to treat. . . . **A woman who has tolerated her diastolic pressure of 120 for ten years without symptoms or deterioration does not need immediate specific treatment for hypertension**." Taking that advice today would be grounds for malpractice since everybody now knows that hypertension is "The Silent Killer" and must be treated immediately and aggressively.

Aggressive treatment should not be a problem since we now have over 100 medications available and new ones in the pipeline. You can choose from a variety of diuretics that act at different sites, beta blockers with varying degrees of

cardioselectivity, ACE inhibitors, calcium channel antagonists, angiotensin-receptor antagonists, alpha blockers as well as all kinds of combinations of these. The problem is that although we may have some clues based on race, age, or comorbidity problems like diabetes, there is no algorithm to positively predict which pill will prove best for any given person. Patients are usually started out on a diuretic or beta blocker and doses are increased or different drugs are added or subtracted based on lack of a satisfactory response or disturbing side effects. Most patients eventually wind up having to take more than one medication and often three or four.

Despite this, we have not been very successful in either controlling hypertension or allaying the fears that have now been firmly instilled in our patients. A survey published in the July 9 issue of *The Journal of the American Medical Association* revealed that nearly one in three U.S. adults now have hypertension. Of the estimated 58 million affected, "almost 30% were unaware of their illness, 42% were not being treated, and at the time that their BP was measured, 69% did not have their hypertension controlled." Things may be worse in Europe, where the prevalence of hypertension is 50% higher than in North America.

Another survey reported in the *British Medical Journal* three weeks earlier also found that four out of five patients taking antihypertensive medications had significant concerns. These included the desire to lower blood pressure without drugs, wondering whether they still needed medication, worries about negative effects they had not been informed about and the possible dangers of life long treatment. **A total of 97% had suffered from side effects at some time and 17% continued to do so. The facts are that things have been getting progressively worse rather than better and hypertension and stroke rates will probably rise even more** as the obesity epidemic persists and the over 80 population continues to swell.

The most likely person to provide a solution to this dismal state of affairs is John Laragh. He has long maintained that most patients with essential hypertension can be permanently controlled with one drug by determining whether the problem is primarily sodium (volume) related or due to increased renin actions. The key to this is being able to measure renin activity, a procedure that he and Jean Sealey pioneered over three decades ago. His credentials are impeccable. He founded the American Society of Hypertension, is Editor-in-Chief of the *American Journal of Hypertension*, past president of the International Society of Hypertension and Director of the Cardiovascular Center at the New York Presbyterian Hospital-Cornell Medical Center. The author of over 900 articles and several texts, he has been the recipient of numerous awards and was on *Time* magazine's cover in 1975 for his discovery of the role of the renin-angiotensin-aldosterone system in regulating blood pressure.

There have been a number of developments since then that support what is now referred to as the "Laragh Method". Many authorities are convinced that wider implementation of this treatment approach would significantly reduce the prevalence of poorly controlled hypertension as well as its complications and costs. It would certainly improve patient compliance and quality of life. I have known John for over 65 years since we both grew up in Northwest Yonkers. He has been a member of the Board of Trustees of The American Institute of Stress since its founding and we share some personal interests like golf as well as professional concerns, such as how the practice of medicine has changed. I have referred many patients to him over the years and have always found him to be a very caring as well as skilled clinician.

I am familiar with some details about how the Laragh Method evolved but in trying to explain this to you, thought it best to ask John a few questions to fill in some blanks. His responses were illuminating not only with respect to shedding light on the treatment of hypertension but also other problems that plague practicing physicians. More about this in a subsequent Newsletter.

The Laragh Method Of Treating Hypertension And Preventing Its Fatal Complications

As indicated, the complete interview will appear in a subsequent Newsletter since there is only enough space left for me to summarize a few key points. The Laragh Method is based on the hypothesis that essential hypertension is either salt-volume related or caused by renin-angiotensin. The key to differentiating these is the plasma renin activity (PRA) assay developed by Sealey and Laragh. Salt-volume (V) hypertension is associated with low renin values (PRA less than 0.65) and is seen in about a third of patients with high blood pressure. It is treated with natriuretic and anti-volume drugs such as spironolactone, thiazides, calcium channel blockers and alpha blockers. Renin-angiotensin mediated vasoconstrictive (R) hypertension is twice as common and is also more likely to result in heart attacks, congestive failure, strokes, and kidney failure. These patients are treated primarily with one of three types of antirenin medications, an angiotensin converting enzyme inhibitor, angiotensin receptor blocker or beta blocker. More details to follow but the bottom line is that **blood pressure can be controlled with one drug for life in over half of both (V) and (R) patients and probably in 60 - 80% of the total group**.

The difficulty I and many other physicians encountered 25 years ago was that the PRA assay was not widely available nor reimbursed by medical insurance and seemed to be very labor intensive. At the time, I served as a consultant for Paul Brown, who had founded Metpath Laboratories, and I recall hauling John over to Hackensack to meet with him. Metpath was well on its way to becoming the largest clinical laboratory in the U.S. and we wanted to add renin testing to the hypertensive profile. Nothing apparently came of that but Metpath subsequently became Quest Laboratories, which now offers an automated direct Renin assay. This has obviated some of the early problems although it may not be as sensitive or accurate in measuring low renin values.

It is also possible to bypass renin testing by single trials of a V or an R drug and discontinuing those that don't work. About 20% may need a V and an R medication but that's still preferable to the latest official recommendations. These advise starting out with a thiazide diuretic and to add other drugs until the blood pressure is controlled. Since diuretics are clearly not indicated in the 2 out of 3 patients with high renin hypertension, most have to keep adding other drugs and some can wind up taking four or more. **Placing high renin hypertensives on perpetual and often increasing doses of diuretics leads to potassium depletion, cardiac arrhythmia and a significant increase in diabetes. More importantly, it may deny these patients protection from cardiovascular complications that antirenin medications can provide.**

Hypertension is emerging as a complex metabolic disorder with adverse effects not solely related to the degree and duration of elevated blood pressure measurements. Governmental guidelines may be endangering the lives of millions of hypertensives unnecessarily and John Laragh's comments should be required reading for anyone with high blood pressure. - stay tuned!

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