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The feature subject in this issue concerns coenzyme Q10 and heart health, with emphasis on heart failure. This disorder is of particular concern because of its remarkable prevalence as the number-one cause for hospital admission among those over 65 years of age. CoQ10, as this chemical is frequently called, is probably one of the most effective over-the-counter supplements available today and is the poster child for the alternative medical treatment of heart failure and other heart problems. It is ignored by mainstream medicine.

Two recent negative studies will most certainly reinforce this view, but as will be discussed, both are flawed, deceptive, and ignore a considerable body of positive data, some compelling. One study downplays the potential adverse effects of statins in inhibiting the endogenous production of CoQ10. Consideration of a 2007 study, discussed in detail, will make it clear that patients with heart failure are the big losers. Also discussed is the problem of bioavailability of CoQ10 which appears to have been successfully addressed.

Other topics discussed include the continued prevalence of serious conflicts of interest as the new diagnostic manual of psychiatry is being prepared, the diagnosis of male hypogonadism, the impact of diabetes and the metabolic syndrome on the incidence and progression of coronary atherosclerosis, the remarkable protection provided by curcumin in the context of post-operative heart attacks after on-pump revascularization, and finally, a brief review of a just-published observation which appeared in the "British Medical Journal" and illustrates how drug companies manipulate the system in the U.S. to extend patent protection for blockbuster drugs.

If you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

COENZYME Q10 AND HEART HEALTH

Coenzyme Q10 (Q10) was discovered in 1957 and there followed a considerable amount of research in animals and with cell cultures. Many international symposia were held with hard cover proceedings that gather dust on library shelves. It was found that Q10 was essential for the cellular energy production processes centered in the mitochondria. Q10 was observed to be low in patients with heart failure and this connection between low Q10 levels and heart failure was seen years ago both in Q10 status determined by blood levels and in heart biopsy samples. This is important since heart failure is the number one diagnosis

in hospitalized individuals over age 65. Recently, there has been considerable interest in benefit from high levels of Q10 in the context of a number of other disorders, both cardiovascular and otherwise. The well-known cardiologist Stephen Sinatra provides a good review of Q10 in his book *The Sinatra Solution,* which individuals with heart disease should find of interest.[1]

The range of Q10 levels in self-reported normal, healthy individuals is quite large. In a study of 38 subjects, the distribution of blood Q10 levels was found to be <0.4 µg/L, 2%; 0.4-1.6 µg/mL, 81%; and > 1.6 µg/mL 17%.[2] It is interesting that in this study no decline with age was seen. The age range was infant to 94 years. There was also no gender dependence. Blood levels of Q10 can be elevated with oral supplementation. Today there are a number of preparations available over the counter, which claim high bioavailability. These mostly use the reduced form of Q10 called ubiquinol, whereas the oxidized form is ubiquinone, the molecule generally implied by the term coenzyme Q10. In the blood, Q10 is mostly in the reduced form, but the traditional supplement has been the oxidized form.

Food is a minor source of this enzyme. The pathway that leads to the endogenous synthesis of Q10 is also the pathway to cholesterol. Drugs called HMG-CoA reductase inhibitors, better known as statins, inhibit this pathway with the resultant large decrease in both cholesterol and Q10. This fact prompted concern over the impact of reduced Q10 levels, not only in the context of the mitochondrial respiratory energy chain, but the possibility of Q10 deficiency being involved in a number of age associated disorders and statin side effects. In fact, Q10 is a powerful and critical endogenous antioxidant. The concern over the impact of the widespread use of statins in this context is mounting as the pressure to have everyone on statins, from newborn children to the frail elderly, intensifies.

In mainstream medicine, Q10 has two strikes against it. First, it is not a prescription drug (read patentable). Supplements obtained at the health food store are the subject of almost universal disdain. The second problem concerns dose and bioavailability. There is a quite considerable variation in how humans convert oral doses into serum and tissue levels. There is also very significant variations in bioavailability depending on the form used since Q10 supplements can now contain either ubiquinone or ubiquinol. Human or for that matter mammalian metabolism utilize both forms and convert back and forth as the occasion demands, but the ubiquinol form appears much more bioavailable orally. Modern routine laboratory assays generally measure total Q10. Studies that address such important questions as the impact of Q10 supplementation on heart failure and cardiac mortality generally use doses that are too low and some look at only baseline Q10 levels, not the increased levels obtainable through oral supplementation. Thus literature is often cited describing negative trial results from trials doomed to failure because the Q10 dose was too low or the range in a cohort in the absence of supplementation was too low. These negative studies have a huge impact on mainstream attitudes. As will be discussed below, this is one reason why the conventional wisdom today regards Q10 as of doubtful importance in heart failure or heart health and the measurement of levels and effective interventions to bring these levels up to values described in the literature as necessary for successful therapy are not part of standard practice. Furthermore, two recently reported trials will further damage the image of Q10.

In 2011 Fumagalli *et al*[3] reported on a small randomized placebo controlled trial involving 67 patients with heart failure (HF) randomized to receive either a placebo plus the usual care or a combination of a Q10 preparation and creatine for 8 weeks plus the usual care. The Q10 dose was 34 mg/day, a very low dose by any standard. Outcomes were exercise tolerance, peak oxygen consumption from an exercise test, and what was called a sickness impact profile. Small improvements were found, mostly of no statistical significance or of questionable clinical significance. Q10 blood levels were not reported in spite of the novel nature of the Q10 source.

In 2010 a sub study of the CORONA study by McMurray *et al* reported which examined the impact of rosuvastatin (Crestor) and Q10 on heart failure.[4] This was an industry sponsored study with the majority of the investigators having close financial ties to the sponsor. The average age of subjects was about 72. Q10 was measured but the only intervention was with rosuvastatin. All the subjects had significant to severe heart failure. The statin reduced the mean Q10 levels in each of three tertiles of Q10 from 0.49 to 0.35, 0.75 to 0.46 and 1.10 to 0.53 µg/ml respectively. It was observed

that patients with lower Q10 levels were older and had more advanced heart failure (HF). Mortality was significantly higher among patients in the lowest vs. highest Q10 tertile, but the difference was not significant on multivariate analysis and Q10 was not found upon extensive statistical manipulation to be an independent predictor of worsening or fatal HF nor did statin treatment results in worse outcomes.

These studies put the icing on the cake for the current mainstream opinion that Q10 is not particularly important and its reduction with statins has no significant cardiac consequences. The problem is that these studies in fact tell us almost nothing! In the first study, Q10 levels were not measured and the dose was very low. It was thus not surprising that very small or non-significant results were obtained. In the second study, the Q10 range among subjects was low and basing conclusions regarding the association between Q10 and HF using the range available was doomed to failure for reasons already known and discussed below.

In addition, a study published in 2008 did indeed find an impact of Q10 on survival in HF patients. Molyneux *et al* [5] examined the relationship between Q10 blood levels and survival among patients with chronic heart failure (CHF). Two hundred thirty six patients, mean age 77, admitted to hospital with HF were followed for a mean of 2.7 years. The mean Q10 blood level was 0.58 µg/mL. They found a significant difference in survival over the period studied (about 4 years) when a cut-point of 0.63 µg/mL was used (survival of about 70% vs. 50%). Patients below this cut point had a range of Q10 blood levels of 0.11 to 0.63 whereas those above had a range of 0.62 to 1.50 µg/mL.

Perspective concerning these observations can be gained by considering the views of Dr. Peter H. Langjoen, a cardiologist who has been involved on Q10 research since 1985 and has published extensively in this area. He was recently interviewed and the transcript is available on the internet.[6] He points out that early on, it was believed that HF patients typically had a Q10 level of 0.5 µg/mL and normal individuals had levels of around 1. Then if one was trying to impact HF, supplementation to bring the value up to about 1 was indicated. When this was tried, not much improvement was seen. Further research revealed that there was a significant blood level threshold at about 2.5 µg/ml above which HF patients appeared to have some benefit and severe HF patients were helped by supplementation once the level achieved was greater than 3.5 µg/mL. This was pointed out in a 2008 paper in *Biofactors*.[7] Even an earlier paper (1999) by Langsjoen and Langsjoen[8] in the same journal justified the > 3.5 µg/mL blood level based on earlier studies. The results of 15 years of research are clearly simply being ignored.

In the study by McMurray *et al* the upper end of the range of Q10 serum blood levels was too low to be of significance in the context of HF, especially in multivariate analysis looking for an independent effect and the lowering of Q10 caused by the statin was too small to be of interest in this special class of patients with a need for very high levels.

Molyneux used a somewhat different statistical approach and found Q10 levels were an independent predictor of mortality in HF. However, the researchers did not stratify the cohort by the NYHA Class system for HF. But this study also involved HF patients with low Q10 levels and the study only divided the cohort in to two groups, thus making it difficult to assess the impact for those at the upper end of the Q10 range. The effect was also not large.

The authors of the intervention study discussed above do cite the 1999 paper which justified therapeutic levels > 3.5 µg/mL for HF patients. They state that their daily dose was equivalent to 34 mg of “native CoQ10” and provide a reference to a guinea pig study where the novel preparation was given interperitoneally. They ignored the 1999 paper. The dose used appears about 10 or more times too small to have a therapeutic effect, based on what was then known about dose vs. serum levels. It is not surprising that the results were clinically insignificant.

The most interesting study which should not have been ignored in the context of the above discussion appears to be that of Langsjoen and Langsjoen cited above,[7] They report on seven *consecutive* patients who had worsening HF (NYHA Class IV) who were on maximal medical therapy and taking

large doses of the ubiquinone form of Q10 which was not, from their point of view using the >3.5 µg/mL threshold, adequately elevating blood levels in the context of severe HF. Some patients were taking 900 mg/day! In the absence of blood level data, this could have been written up and presented as a negative study demonstrating without a doubt that Q10 supplementation did not work at all for severe HF. Not so. Patients were switched to the ubiquinol form with a change in average blood Q10 going from 1.6 to 6.5 µg/mL during the course of the revised therapy. The table below provides the detailed results of ejection fraction (EF) and NYHA class change indicating the change in the severity of HF, after ubiquinol was used.

Case #	Blood Q10 Change (µg/mL)	EF % Change	NYHA Class HF Change	Treatment Duration (mo)
1	2.0 -> 9.3	15 -> 60	IV -> I	20
2	0.9 -> 2.6	35 -> 50	IV -> III	3
3	1.5 -> 8.9	10 -> 10	IV -> III	12
4	1.7 -> 5.1	35 -> 60	IV -> I	10
5	1.5 -> 5.6	30 -> 55	IV -> II	9
6	2.0 -> 5.7	10 -> 20	IV -> II	10
7	1.6 -> 6.5	22 -> 39	IV -> II	10

The NYHA Class I HF is asymptomatic. Class II involves mild shortness of breath and/or angina with little limitation of ordinary activity. Class III involves significant limitation of activity due to symptoms, even to the point of problems walking short distances. Class IV is sufficiently severe as to apply mostly to bed ridden patients. Thus the HF class changes listed above are impressive and obviously of huge significance to most of the patients involved. Note the high baseline Q10 levels, which are at the upper extreme of the modern laboratory reference range, and yet the individuals had Class IV HF which was then strongly impacted by changing the supplement to achieve greater bioavailability and thus achieving very high Q10 levels. Note also the individual variations. This table in fact nicely states the case for treating HF patients to a high target even if their Q10 levels are already high by normal standards.

At the time Langsjoen and Langsjoen carried out their case study, it was already becoming apparent that while ubiquinone bioavailability was increased when administered in a capsule where the chemical was dispersed in an oil, much higher levels of blood Q10 could be achieved by replacing the oxidized form with ubiquinol.[9,10] In fact, Hosoe *et al* found that supplementation with 300 mg ubiquinol in oil over a period of 28 days raised the Q10 level on average from 0.66 to 7.28 µg/mL. This level was much higher than that achieved with a single dose (2.56 µg/mL) and thus there is a cumulative effect which must be taken into account in evaluating single dose studies. They used the commercial preparation *Kaneak QH*, a Japanese preparation which is available today over the internet from several supplement suppliers. Another comparable preparation is LiQ-NOL CoQ10 which also uses the ubiquinol from Kaneka Corporation.

A reasonable evidence-based conclusion appears to be that HF patients are significantly helped by Q10 but the dose must be individualized and blood levels measured to test the impact of the intervention. One cannot generalize on the oral dose because of the wide variation in both commercial preparations and individual absorption. Thus monitoring is essential. As pointed out by Langsjoen in the interview cited above, it took some time before it was demonstrated that using doses of 100 mg/day of ubiquinone was not effective in many cases of HF. Thus early studies found in many cases only small effects. In his interview, Langsjoen is emphatic that there are no side effects or drug interactions to high doses, He does however point out that Q10 therapy for HF, once heart function improves, reduces the need for some of the “standard treatment” drugs and in particular blood pressure medications. Improvements can be easily assessed by ejection fraction or simply an improvement in daily functioning and quality of life. Also, there appears to be no doubt that statins reduce serum Q10 levels quite significantly—something that has been known for a long time and appears to be a class action that can be rectified by supplementation.

The above discussion is also a good example of the challenges and pitfalls of going to the literature to answer what appear to be simple questions. Find the recent clinical trials, download the papers, examine the methods and the tables in detail, and try to make a judgement. In this case, in the two most potentially influential recent papers, there is the implicit assumption that if Q10 were important, one would see differences or benefits if patients were at the upper end of the normal range. This ignores 15 years of research culminating in the result that blood levels of Q10 must be brought up to much higher values for there to be any clinically significant association between Q10 and serious HF. There is no mention of this "study limitation" in the discussion sections. The readers of the studies discussed would almost certainly not know this and conclude that the case against Q10 was now complete and evidence based. This is of course nonsense. This is also an example of an imperfection in the peer review process held in such high esteem by mainstream medicine. But it is important to understand that anecdotal evidence such as the study by Langsjoen and Langsjoen is held in low regard by mainstream medicine unless it conforms to conventional wisdom.

The reader is referred to the March 2012 issue of the Newsletter for a detailed discussion by Hans Larsen of alternative treatments for HF.

NEW *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS* CONFLICTS OF INTERESTS ARE ALIVE AND WELL

Most readers of this Newsletter have heard of this manual, universally called the DSM, or by some in the psychiatric profession, the *Bible.* The current volume is the fourth edition and DSM-V is due out in 2013. With DSM-IV, no disclosures of financial conflicts of interest (FCIOs) were required but the information was out there and subsequently dug up. The FCIOs were staggering with some writing groups (mood disorders, psychotic disorders) having 100% of the members with ties to the industry supplying the psychiatric drugs they were recommending.

For the new edition the American Psychiatric Association, the publisher of the manual, required for the first time a certain level of disclosure. A paper has just appeared in PLoS Medicine[11] which reveals the FCIOs of the new writing groups for DSM-V and compares the numbers with the DSM-IV results acquired by digging. Three-fourths of the writing groups continue to have a majority of their members with ties to the pharmaceutical industry. For the group concerned with delirium, dementia, amnesia and cognitive disorders, the FCOI jumped from 25% to 89%, sleep disorders from 50 to 100% and psychotic disorders dropped from 100% to 83%. For the task force as a whole, the conflicts of interest increased from 57% to 69%. Clearly, the APA has accomplished nothing that effectively addressed the issue of conflicts of interest by requiring disclosure.

The PLoS paper discusses a number of interesting points. One is the possibility that disclosure simply "Shifts the problem from one of 'secrecy of bias' to 'openness of bias'" In addition, the authors suggest that when panel members disclose every affiliation they have ever had, including those from federal agencies, it creates a "signal-to-noise problem" obscuring the truth about what they term deeply problematic financial relationships between writing groups and the industry supplying the drugs being recommended. Also, Speakers Bureau memberships are lumped with honoraria although there is a significant distinction. Furthermore, the DSM-V disclosure policy excludes unrestricted grants from industry, but it can be argued that there is still a potential conflict of interest. The actual amount of money received from the pharmaceutical industry is also not part of the required disclosure.

The new DSM is rumoured to contain over 100 new mental disorders added to the existing ensemble of over 300. We are fast approaching the point where everyone will at some time be diagnosed as mentally ill and many medicated (adding prolonged bereavement as a mental disorder will help

make this happen). A list of the pharmaceutical companies ranked by percent sales in psychiatric drugs with information on the number of new drug in their pipelines should be of interest to investors.

The PLoS article calls for an unbiased DSM, evidenced based and free from any conflicts of interest. The DSM is more or less a gold standard and "transparency cannot alone mitigate bias." Perhaps this will be the case when DSM-VI comes out a decade from now. In the meantime, the stage is being set for a real epidemic of overdiagnosis and overtreatment in this important area.

The reader is referred to the February and March 2011 issues of the Newsletter for a two-part Research Review concerning the use and abuse of psycho-pharmaceuticals.

PREDICTING MALE HYPOGONADISM

Hypogonadism translates to decreased functional activity of the gonads (testicles) and thus lower testosterone production. The list of symptoms suggesting hypogonadism is quite long and includes poor libido, fatigue, muscle weakness, glucose intolerance, poor sleep, difficulty in concentrating, memory loss, depression anxiety, osteoporosis, infertility, testicular shrinkage, and dry skin or cracking nails. Such a list is rather too long to be very useful. The measurement of serum testosterone is frequently used to assess the possibility of the presence of hypogonadism, especially for individuals with diabetes, obesity, corticosteroid and opiate use, depression and loss of muscle mass, or complaints regarding libido.

A study recently appeared in the *Journal of Urology*[12] which begins with the assertion that the investigators regarded the best laboratory test for initial screening for hypogonadism to be in fact unknown. The problem is the ability of the sex-hormone binding globulin (SHBG) to strongly bind testosterone. Obesity, diabetes and aging affect circulating SHBG levels and thus circulating total testosterone (TT) without necessarily impacting the free testosterone (FT) and weakly bound (to albumin) testosterone, the two forms that are regarded as bioavailable. The popular initial screening test, however, is simply the TT. While the measurement of FT is considered the gold standard for the diagnosis of hypogonadism, direct measurement is costly, time-consuming and not generally used in clinical practice. Rather, it is calculated with one of several validated formulas based on measured serum TT, SHBG and albumin, but SHBG and albumin determinations are not part of the initial screening protocol. The commonly used practice guidelines recommend initial screening with TT followed by the determination of bioavailable testosterone only when TT is near the lower limit of the range regarded as normal and in whom alterations in SHBG are suspected. There are reasons to believe that this is unsatisfactory.

This study cited above addressed the critical question, i.e. how well does TT perform as a predictor of FT, which is generally taken as the benchmark for biochemical confirmation of hypogonadism. To undertake this type of study, one accumulates a group of men where all have both a measured TT and a value for FT, generally the calculated value from SHBG and albumin. Once this data is in hand, a benchmark must be set for the diagnosis of HG which means setting a level of FT, above which HG is regarded as absent. This then defines true or false results of the test in question, namely TT. One cannot examine the validity of a diagnostic test without knowing the actual diagnosis of each member of the study cohort! The diagnostic test yields either positive or negative indications, and this is determined by the threshold for the parameter used in the test. In the above study, various levels of TT were examined to see how they perform in establishing the probability that a positive result of the diagnostic, i.e. above or below the TT level, was indeed true in that the individual had the disorder as defined by the diagnostic test taken as perfect (FT). It is the nature of the statistical arithmetic that as the TT threshold is lowered; the probability of a positive diagnostic result being true goes up. This is because the pool of individuals with the disorder is constant, and as TT threshold is lowered, the true positives decrease and the

false negatives of necessity increase, simply because the lower the threshold, the more individuals will be labelled disorder-free who in fact have the disorder and there will be fewer individuals correctly identified as having the disorder (true positives), all because the total number who actually have the disorder is constant. This may sound complicated, but it is the standard way of testing a screening test.

In the study cited, medical records of 3,672 men were examined. The subjects had been evaluated for hypogonadism from 1997 to 2007 in a number of VA hospital outpatient clinics. All had data regarding TT, SHBG, albumin and thus calculated free testosterone. When the researchers used a threshold of FT of < 34 pg/mL to define the presence of HG, the commonly used TT threshold of 280 ng/dL produced a 91% probability that those below this level had HG (sensitivity of the test). However, the probability that those having TT above this cut-off, i.e. judged by the diagnostic test to not have the disorder, in fact did not have the disorder, i.e. it was ruled out (specificity of the test) was 68%, Lowering the TT threshold to 200 ng/dL decreased the sensitivity to 77% but increased the specificity to 93%. Thus using a low TT such as 200 ng/dL to examine the question of the presence or absence of HG worked rather well to rule out the disorder, but the chance was only about 3 out of 4 that when the individual had a TT below this threshold, a positive test result, they actually had the disorder.

What does one conclude? The authors say that TT between 280 and 350 is not sensitive enough to reliably exclude HG. It must exceed 350 to 400 ng/dL to reliably predict normal FT. Furthermore, except when TT levels are less than 150 ng/dL can it be used for the biochemical diagnosis of HG. Thus, if one wants a definite answer rather than a threshold dependent answer, then they should probably demand a FT test and forget about total testosterone. But this requires a belief in the validity or clinical significance of the threshold of FT that will be used to say yes or no to the question, is HG present.

Many readers will be wondering about treating HG because of the association of testosterone and prostate cancer. They are referred to the September 2011 issue of the Prostate Monitor which accompanies the Newsletter of that date. A detailed discussion is provided regarding this question and information provided regarding the postulated saturation model which is the basis for some urologists strongly favouring the treatment of HG even if one has diagnosed prostate cancer.

DIABETES, METABOLIC SYNDROME, AND INCIDENCE AND PROGRESSION OF CORONARY CALCIUM

It is now well known that coronary artery calcium (CAC) provides evidence for subclinical atherosclerosis and is a significant predictor for future acute coronary events. It is also widely recognized that the metabolic syndrome (MetS) and diabetes (DM) increase the risk of acute cardiac events and mortality. However, no study has compared the incidence and progression of atherosclerosis as measured by CAC across these disorders.

This issue has now been explored as part of the Multiethnic Study of Atherosclerosis.[13] A cohort of almost 7000 individuals age 45 to 84 equally divided between men and women was followed for about 5 years. Incidence of CAC in subjects without CAC at baseline and progression of CAC in subjects with CAC at baseline was documented with cardiac computed tomography scans, taking into account the presence of MetS and/or DM, The results tabulated below were all statistically significant.

CAC	REF	MetS	DM	MetS & DM
Incidence (Odds Ratio)	1.0	1.7	1.8	2.2
Difference				
In Progression (Vol)	7.8	11.6	20.5	22.6

Thus there were rather dramatic increases in the incidence and progression of silent atherosclerosis in those with either the MetS or DM or both. Furthermore, progression of CAC corresponded to a 3 to 4 fold increase in the risk of coronary heart disease in those with Mets but no DM and those with both disorders when those in the highest tertile of CAC increase were compared with those with no increase.

HEART PROTECTIVE CURCUMIN

Curcumin (turmeric, an Indian spice) appears to be one of the most versatile and amazing natural medicines thus far investigated.[14] Unfortunately, most of the evidence comes from animal and cell culture studies, which are however voluminous. Impressive results have been obtained concerning its effectiveness as an antiproliferative and antiangiogenic agent, and as well a therapeutic agent in wound healing, diabetes, Alzheimer's disease, Parkinson's disease, cardiovascular disease, pulmonary disease and arthritis. Curcumin has been shown safe even at a daily dose of 12 g for 3 months.[15] Human studies are starting to accumulate. PubMed list 67 human clinical studies now published.

In a paper that has just appeared in the *American Journal of Cardiology*, an impressive effect of curcumin supplementation on the risk of heart attack (MI) after coronary artery bypass grafting (CABG) is described.[16] The investigators selected 121 consecutive patients who underwent on-pump CABG who were randomized into a curcumin group (n = 60) and a placebo group (n = 61) The Curcumin preparation was actually a curcuminoid mixture containing curcumin and two curcumin derivatives. The intervention group and the controls were very similar in a large number of relevant characteristics. In addition to standard therapy, also received by the control group, the intervention group received 4 g/day of the curcuminoid preparation starting 3 days before surgery and continuing until 5 days after surgery. The primary endpoint was in-hospital MI.

The incidence of in-hospital MI in the placebo group was 30% whereas the intervention group experienced an incidence of only 13.1% Multivariate analysis searching for independent risk factors for MI including curcuminoid therapy and CABG found odds ratios of 0.32 (protective) for the former and 5.35 (risky) for the latter, both statistically significant. Furthermore, levels of an oxidative stress marker (malondialdehyde) were almost identical prior to surgery in both groups but dramatically lower post-operatively in the curcuminoid group as compared to the placebo. CPR was also beneficially affected.

The incidence of post-operative MI may seem rather high in this study from Thailand. However, for comparison, a large multinational intervention study designed to test an agent to reduce MI/mortality after CABG with almost 6000 participants that reported in 2008, on-pump CABG had a 5-day post-operative rate in the placebo group of 21% for death or MI and about 19% for MI alone. Most of the MIs were non-Q-wave in both studies. The higher rate in the Thailand study may simply reflect the severity of the disease in the cohort studied. It may also reflect differences in the details of the on-pump protocol used and the small size of the study group.

The authors offer three proposed explanations for the beneficial effects of curcuminoids on the incidence of post-operative MI. First, oxidative stress and systemic inflammation may occur during CABG and may account for the ischemia/reperfusion injury inherent to the procedure. Curcuminoids and curcumin itself have been demonstrated to possess striking antioxidant and anti-inflammatory properties. The impact on malondialdehyde and CRP levels supports this view. Second, the curcuminoids may protect against cardiac injury through cell membrane stabilization and decrease the extent of myocardial necrosis. Third, there is evidence that curcuminoids inhibit human platelet activation which could decrease the probability of MI.

An interesting observation also made in this study was that on-pump CABG carried a much higher risk of post-operative MI than off-pump surgery. In fact, the latter group had an incidence of 35.5% whereas for the off-pump

group the incidence was 6.8%. Unfortunately, only the on-pump group were involved in the randomized trial.

The results reported in this trial seem to provide compelling evidence for the use of curcumin in the context of CABG surgery. Highly bioavailable curcumin is now available over the counter and may be approximately equivalent to or even better than the mixture used in this study. More research is obviously indicated, especially given the large effect size observed (the number of patents needed to treat to prevent one post-operative MI over 5 days was only 6).

The much broader question of the impact of curcumin on cardiovascular disease in general must await significant human studies. At present, all that appears to exist are strong positive indications regarding applications that would be of benefit.[14,15,17] However, Curcumin has been used since ancient times as a spice and studies indicate it is safe at large doses. Pharmaceutical companies would be expected to have no interest except in patentable derivatives of curcuminoids, an option that probably would take years to reach the pharmacy shelves if pursued. Clinical trials involving endpoints, such as enumerated above as possible target disorders, would require vast sums of money. Thus a case can be made for supplementation with highly bioavailable curcumin as a general preventive measure, since the evidence necessary to satisfy mainstream medicine and results in an official recommendation may never surface for more than an isolated situation.

The question has been asked that if statins are really acting mostly as anti-inflammatory agents, then why not look for something that offers more than numbers of one in a hundred needed to treat in primary prevention to prevent one adverse event? Perhaps Curcumin is one of the answers!

TRICKS OF THE TRADE

The blockbuster drug donepezil (Aricept) used to treat Alzheimer's disease was to come off patent in November 2010. Four months prior to this event (called going over the cliff) the FDA approved a new 23 mg dose of donepezil called *Aricept 23* and thereby extended the patent protection for three more years for this "new" drug. The approved generic doses of 5 and 10 mg did not add up to 23, which is evidentially a critical but curious aspect of this story. The new drug was approved over the objections of the FDA's medical and statistical reviewers. In a required study, the higher dose was responsible for increased side effects deemed potentially serious for Alzheimer's patients and the only benefit, a slight improvement in cognition, was considered without meaning in the medical review which also considered secondary endpoints.

The marketing (label and package insert and advertising) to physicians initially contained an erroneous and misleading but at the time legal statement regarding clinical benefits of the higher dose of the same old drug, an oversight only corrected on March 1, 2012, a delay of over a year and a half. But the overall approach to the patent problem appears to have worked well. Government and private insurance programs now cover the "new" drug and the drug company is reported having plans to seek approval in 16 countries in Asia and South America.

The above information was derived from an article just published in the *British Medical Journal*.[18] The article itself is protected from public view by requiring a subscription or library access, but a more detailed discussion of the BMJ article is available on the MedScape website at http://www.medscape.com/viewarticle/761345.

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