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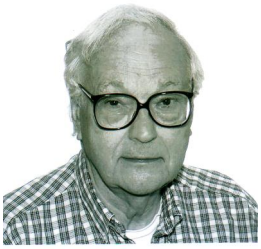

For eons longevity has been a topic of interest to humans and of late has been the subject increased scientific study. Some researchers have studied the subject by examining populations which have experienced extraordinary longevity. Books like "The Blue Zone" by Dan Buettner and "The Okinawa Program" by Willcox, Willcox and Suzuki document some of the most successful investigations and illustrate the complexity of the problem and the intertwining of culture, philosophy of life and nutrition. Some aspects of the culture and philosophy of the longest-lived people are simply not transferable to modern societies but the question and challenge of human longevity remains.

Coupled with the desire for longevity is the desire that the extended lifespan be healthy and satisfying. Unfortunately, chronic age-related diseases have cast a depressing shadow over the increased life expectancy witnessed in the past century. Retiring from work with little to do and then dealing with cancer, heart disease, diabetes, cognitive and other degenerative mental problems and finally social problems has unfortunately become common. A visit to the dining rooms and common rooms of nursing homes and hospital palliative care floors allow one to capture the many aspects of the picture in an instant. Thus the challenge of longevity must ultimately include minimizing these problems. A solution which looks to pharmaceutical intervention (a pill for everything) may be doomed to failure.

Of all the relevant recently studied interventions, only calorie restriction has been found effective in producing significant life extension and this intervention in fact appears to be successful for a broad spectrum of living creatures from flies, worms, and rodents to non-human primates, the latter offering a unique opportunity to conduct experiments, the results of which closely relate to humans, without encountering the practical or ethical problems associated with long-term human studies. Observing human behavior is also very suggestive in that eating more, and frequently much more than necessary is a common phenomenon. In this issue we feature a review of some of the recent research.

The remainder of this issue is devoted to recent developments the prevention and treatment of diabetes and cardiovascular problems. Cholesterol and statins continue to appear prominently in these discussions. Finally, a recent small study from Harvard calls attention to the serious problem of bisphenol (BPH) leaching from the plastic coatings that line cans used for a huge variety of food products.

In this issue your editor is pleased to present a Research Review by Hans Larsen which discusses many important aspects of heart failure.

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

CALORIE RESTRICTION, LONGEVITY AND DISEASE PREVENTION

INTRODUCTION

Over the last century life expectancy has dramatically increased, especially in developed countries. Lifespan was about 45 years at the start of the 20th Century it is now about 77 years in developed countries such as Western Europe, the US, Canada, Japan, Australia and New Zealand. But it is important to distinguish between longevity and healthy living. This increase in lifespan has been accompanied by an increasing burden of chronic diseases. Approximately 80% of older adults (> 65 years) have at least one of the following: abdominal obesity, type 2 diabetes, lower respiratory disease, Alzheimerôs disease, cardiovascular disease, cerebrovascular disease, and cancer. In addition, 50% have at least two chronic diseases.[1] Clearly, longevity is a mixed blessing and the challenge is maintain or increase the current lifespan while at the same time decreasing the disease burden associated with aging. This is an area where research continues to accelerate.

While the search for the fountain of youth goes back centuries with the most famous early effort Ponce de Leonôs futile quest, over the past several decades gerontologists have actively searched for interventions that consistently extend the lifespan in multiple species. One notable discovery involves the reduction of macronutrients, i.e. calorie restriction (CR), which was first demonstrated in rats in the 1930s. These early results have been repeatedly replicated in yeast, flies, worms, fish mice, rats, dogs and Rhesus monkeys. Human studies, especially long-term, are obviously more difficult, but suggestive data are accumulating.

Calorie restriction is generally defined as a reduction in calorie intake without malnutrition. Micronutrient deficiencies are addresses with supplementation if necessary. CR can be viewed as a corrective intervention to eliminate the detrimental effects of overeating energy-dense foods, a national pastime in parts of the developed world. Typical calorie reductions from baseline are about 30%. Advocates point to many benefits, but conservative nutritionists and researchers are quick to come up with lists of contraindications and warnings. One is reminded of the Atkins saga.

WHAT HAS BEEN LEARNED FROM THE RHESUS MONKEYS

While dramatic life extension was observed in 1935 with calorie restriction in rodents, these studies had serious limitations if it is desired to extrapolate to humans. The same applies even more strongly to studies involving fruit flies and worms. These studies taken together are simply hypothesis generating and strongly suggest the role of CR in longevity and chronic age-related disease prevention. The nonhuman primate provides a vital link between flies, worms, rodents and humans and studies involving primates have proved highly informative. The favourite species is the captive rhesus monkey. These primates have a 93% sequence identity with the human genome and are similar with respect to anatomy, physiology, neurology, endocrinology, immunology and behavior. They progress through stages of life that are complimentary to the human life cycle, but with time compression. They develop many of the age-related disorders common to humans, including cataracts, cancer, osteopenia and cardiovascular disease. The captive rhesus monkey has a median lifespan of about 26 years with a maximum of 40 years which is about 1/3 that of humans. However, the rate of aging from birth to sexual maturity to menopause and old age does not parallel that of humans in that the 1/3 factor cannot be generally applied. Also, in the context of CR and aging, the evaluation of cognition and behavior is challenging since food is the primary motivator and tool used in testing. Nevertheless, the age-related diseases and their biomarkers and clinical manifestations that these monkeys share with humans make them highly attractive surrogates.[2]

A large and significant ongoing study of CR, longevity and age-related disorders is being conducted at the Wisconsin National Primate Research center at the University of Wisconsin. The results to date have been summarized in a very recent review by Colman and Anderson[2] This project began in 1989 and involved 30 Indian-origin male rhesus monkeys ages 8-14. In 1994, 30 female monkeys of the same age range were added

along with 16 additional males aged 6-14. The investigators recognized the importance of maintaining as stress-free an environment as possible and thus as non-invasive as possible. Nevertheless, they were able to measure blood components commonly monitored in humans, examine age-associated changes in body composition, and examine the incidence of age-related muscle mass loss and glucose regulatory dysfunction. After *ad libitum* food intakes were quantified for each animal over 3-6 months, they were assigned as either controls or CR subjects and for the CR group, individualized calorie intake was reduced 10% per month until 30% was reached. Follow-up times were either 12 or 18 years, depending on the entry date of the subjects.

The results obtained thus far can be summarized as follows. Over the study period, the most significant differences between the CR and controls are that the former had lower triglycerides and more buoyant LDL particles. CR attenuated the age-associated decrease in HDL. CR opposed age-related changes in amino acid levels that relate to reduced muscle contribution to total body protein metabolism. The CR and control groups differed significantly in body weight which was mostly attributable to the controls progressively gaining weight, and this was attributed to differences in body fat. The CR monkeys had lower abdominal circumferences and abdominal fat compared to the controls. Skeletal muscle mass declined more rapidly with age in the controls than the CR group. At present, insulin sensitivity is approximately two-fold higher in the CR compared to age matched control monkeys.

HUMAN STUDIES

Human studies that would provide definitive evidence of the value of CR as it relates to longevity will probably never be accomplished. This is because there are no validated biomarkers for aging and it is impractical to conduct randomized, diet-controlled long-term survival studies involving normal subjects. Also, CR has a different meaning in animal studies as compared to human studies. For example, in animal studies the diet and control groups start from a baseline animal chow presumed to be healthy, whereas in human studies CR can refer to any calorie restriction independent of the weight of the subject and the diet, either or both of which in the case of humans can be at baseline highly undesirable with associated problems that CR probably will not address. For humans, CR should involve an energy intake that is sufficiently low to achieve or maintain normal body weight without causing malnutrition. Furthermore, those who demand randomized, controlled survival studies will probably not even be alive when significant results would be achieved. Thus it is necessary to focus on metabolic and physiological effects of CR.[1]

Data from observational studies are of interest. When Japanese inhabitants of Okinawa, who were known to consume fewer calories than residents of the main Japanese islands, were studied this population was found to have lower mortality from coronary heart disease and cancer and had the highest percentage of centenarians in the world. Other evidence came from studies of anthropometric and physiological parameters associated with forced CR of about 30% in inhabitants of the Biosphere 2. It was found that reductions occurred in body weight, blood pressure, fasting glucose, insulin, cholesterol, triiodothyronine and white blood cells. Ongoing studies involving members of the Calorie Restriction Society also found a number of beneficial changes in marker and parameters related to health associated with CR of 30%.[1] Morley ***et al*** have summarized both the positive and negative aspects of CR currently recognized.[3]

CALORIE RESTRICTION PROS AND CONS BASED ON HUMAN STUDIES

PROS

- Weight loss, potentially down to a desired weight
- Maintenance of the desired (optimum?) weight
- Decreased triglycerides
- Decreased LDL
- Lower blood pressure
- Decreased metabolic rate and body temperature
- Improved glucose tolerance
- Decreased CRP
- Lower pulse rate
- Decreased liver fat
- Decreased visceral fat
- Decreased IGF-1, the insulin like growth factor which activates a number of critical pathways
- Decreased TNF-Ŭ, the tumor necrosis factor, a cytokine involved in systemic inflammation.
- Improved left ventricular function
- Attenuation of cytokine related aging processes
- Attenuation of oxidative damage

- Attenuation of mitochondrial DNA mutations
- Potential for increased longevity
- Potential for cognitive benefits

CONS

- Probable need to initially count calories
- Muscle loss
- Decrease in bone mineral density
- Deficiency in certain amino acids
- Potential decreased work capacity.
- Very limited human studies, especially concerning cognitive and longevity benefits and long-term risks.

Among the drawbacks of CR, those that appear serious can be the subject of monitoring and correction.

Many of the beneficial effects observed in human studies are also found in animal studies. For example, limited evidence from human studies but a large body of evidence from animal studies suggests that calorie CR provides powerful protection for the aging heart and vasculature. These benefits, in combination with those derived from CR that are associated with protection against obesity, diabetes, hypertension, and cancer lead to the view that CR may have a major beneficial effect on the duration of health, lifespan and quality of life in humans.[4]

It is generally recognized that most people will probably prefer not to restrict their diet in the presence of an abundant food supply. The parallel with dieting in general and its common failure is obvious. Thus there is growing interest in what are called calorie restriction mimeties (CRMs). These are agents which are consumed in food or water which would increase longevity and decrease age-associated diseases without requiring a change in calories. This approach is entirely consistent with the modern philosophy that the path to health and happiness (and in this case longevity) is to be found in a pill, no doubt obtainable from the pharmacy not the health food store.[5] However, it has been argued that such ñdrugsò can never be developed because aging is the results of a random accumulation of damage, some of which is inevitable and irreversible. Furthermore, while continued incremental progress can be expected in delaying mortality, significant increases in longevity will require modification of the fundamental processes of aging.[6] It is in the mammalian animal studies that really significant increases have been observed, and this has been accomplished by CR, not a mixture of several chemicals in a pill or drink.

The opposite of calorie restriction is overeating. In a study to be presented at the annual meeting of the American Academy of Neurology in April, Yonas Geda and colleagues from the Mayo Clinic in Scottsdale, Arizona will present data indicating that overeating among seniors age 70-89 increased the chance of mild cognitive impairment by 140%, a statistically significant result from a multivariate analysis that adjusted for a large number of confounders including CHD, diabetes and body mass index. Comparison was with a reference group that consumed 600 to 1526 calories/day. The overeaters consumed between 2140 and 6000 (!) calories/day. Mild cognitive impairment generally precedes dementia and Alzheimerôs disease.

Readers interested in CR may find useful information regarding initiation and maintaining CR as well as the risks involved by visiting the website of the Calorie Restriction Society.
http://www.calorierestriction.org/Home

STATINS AND DIABETES IN POSTMENOPAUSAL WOMEN

A very large follow-up study of women participating in the Womenôs Health initiative has just reported. It examined the association between statin use and the incidence of diabetes.[7] After over a million person-years of follow-up covering about 10 years it was found that there was a 71% increase in the risk of developing diabetes if statins were used, a results that was statistically significant. The absolute risk increase was 3.5%, which corresponds to needing to treat only 28 women over the study period to produce one case of diabetes attributable to the therapy. This result was only modestly modified by multivariate analysis (48% risk increase) and was observed for all types of statins. This raises concerns regarding the merits of statin therapy in the context of cardiovascular disease in women and also the actual risk in this population of women in general presented by elevated cholesterol levels, which must be weighed against adverse effects.

A pooled analysis involving 15 observational studies and about 125,000 women examined the question of total cholesterol and all-cause, cardiovascular, and coronary heart disease mortality.[8] Only events that occurred Ó 5 years after the study baseline were considered and the reference was 160-199 mg/dL. Hazard ratios adjusted for age, diastolic blood pressure, BMI, and alcohol and smoking were derived. For total cardiovascular mortality, there was no significant association with cholesterol levels. For coronary heart disease mortality, the association became significant at levels Ó 240 mg/dL but this may have included individuals with familial hypercholesterolemia, which confuses the issue because of the non-lipid related triggers for acute coronary events associated with this disorder.

In 2004, Walsh and Pignone reported on a pooled analysis of 6 lipid lowering trials involving women with endpoints of CHD and total mortality and CHD events.[9] Follow-up was from 3 to 5 years and 5 of the 6 studies used statins. For women without cardiovascular disease, lipid-lowering was not associated with total or CHD mortality. For CHD events, the data was insufficient to permit a conclusive result. A more recent meta-analysis found that for women without prior cardiovascular disease, statin therapy did not reduce CHD events nor the risk of total mortality.[10] A similar conclusion was reached in a study motivated by legal aspects of drug company claims of efficacy which was also based on a meta-analysis.[11] It is unusual to see a study on this subject in a legal journal, although one of the two authors was a professor of medicine at Harvard.

The famous JUPITER trial was the first to find benefit of lipid-lowering for women. This study enrolled men and women with relatively low LDL (<130 mg/dL, mean 108 mg/dL) with C-reactive protein levels > 2 mg/L.[12] While described as healthy, 42% of the cohort had the metabolic syndrome and most were overweight and some obese. The study was prematurely terminated at a median follow-up of about 2 years with maximum follow-up of 5 years, even though the number of events was very small. If the tabulated events during the study are used, the absolute risk reduction for any heart attack was 0.41% and for combined heart attack, stroke or death from cardiovascular causes, it was 0.83%. Since these results span a considerable range of follow-up times of up to 5 years, the small absolutes risk reductions appear more meaningful than approximate numbers needed to treat which one might calculate. Women and men had similar relative risks, and thus the absolute risk reductions for women were also very small, although the relative risk reductions were very large. What is generally not recognized about this trial is that Crestor is unique in its very strong influence on vitamin D levels. The increase in vitamin D levels could easily account for the small absolute cardiovascular benefits.[13] Until this potential confounding is taken into account, JUPITER should be viewed with reservations. Serious problems with JUPITER have also been discussed by de Logeril.[14] Put simply, some of the numbers do not make any sense clinically.

Thus from the above studies one may reasonably conclude that TC or LDL are only very weak or non-existent risk factors for acute coronary events for women. This of course accounts for the interest from the legal profession. It is important to recognize that women younger than 50 years have such low risk of CHD that studies of events are difficult due to the very large number of participants needed to obtain useful data. This is no doubt also the reason why, historically, women were under-represented in studies conducted to justify drug therapy.

This brief summary suggests that the risk of diabetes is much greater than the benefit derived from statins, which may in fact be negligible for women. Thus the risk of diabetes must be added to the other side effects of statin therapy which include mild to severe to fatal muscle problems, cognitive problems and sudden complete amnesia, and depleted coenzyme Q-10 levels which, among other things, increase the risk of heart failure, to just mention a few of the many adverse effects of this class of drug. Readers are referred to www.spacedoc.net for extensive side effect information and a list of highly recommended books on this subject.

CARDIOVASCULAR HEALTH. NEW FOCUS OF THE AMERICAN HEART ASSOCIATION (AHA)

The AHA recently developed a set of seven ideal health metrics to be used in measuring progress toward their 2020 goals of cardiovascular health. A retrospective follow-up study has just examined the

ability of adherence to these goals to impact all-cause and cardiovascular mortality.[15] The data was derived from the U.S. National Health and Nutritional Examination Survey from 1999 to 2002 with mortality information obtained from the National Death Index. The metrics were not smoking, body-mass-index < 25, physical activity at goal levels and a diet containing three or more daily servings of fruits and vegetables. To this were added total cholesterol < 200 mg/dL, diastolic blood pressure < 80 mm Hg, and fasting plasma glucose < 100 mg/dL. The researchers used HbA1c as a surrogate for fasting blood glucose, and the Healthy Eating Index for dietary assessment. Follow-up was for a median of 5.8 years.

Compared to those who did not meet any of the ideal metrics, those meeting five or more had an age and gender adjusted 78% rate reduction per 1000 person years in all-cause mortality and an 88% reduction in cardiovascular mortality. Absolute unadjusted risk reductions were similar in magnitude. Furthermore, there was a more or less linear decrease in the age-adjusted rate per 1000 person years as the number of metrics increased from zero to 5. This trend persisted when adjusted hazard ratios were calculated, although statistical significance was achieved only for 3 or more metrics. In the total cohort of 7622 adults, 1% met all seven metrics, 13.5% met five, 5.4% met 6 and 1.5% met none. The researchers were not surprised with these results since earlier studies have also indicated a large impact on adherence to a significant number of health-related metrics of cardiovascular health.

However, what they claimed to be surprising was the poor predictive power of hypercholesterolemia, which they describe as one of three cardinal risk factors for coronary heart disease and a risk factor for all-cause mortality. However, it is quite interesting that the sole reference for the statement regarding mortality was a study of young men only; whereas this study covered both men and women with a wide age range and the mean age of deceased subjects was 67 years. The hazard ratios for total cholesterol, when referenced to subjects where the metric indicated poor health were consistently completely non-significant for all-cause mortality and diseases of the circulatory system across those deemed to have intermediate health and ideal health values for the cholesterol metric. It was a total non-issue even though four models for data adjustment were employed. Poor, intermediate and ideal values for total cholesterol were Ó 240 mg/dL, 220-239 mg/dL and < 200 mg/dL. In the maximally adjusted model where cholesterol failed to achieve statistical significance as a predictor of all-cause mortality, only smoking statues, physical activity, Healthy Eating Index Score, blood pressure and HbA1c retained their statistical significance.

ANOTHER PILLAR OF THE CHOLESTEROL—CARDIOVASCULAR DISEASE ASSOCIATION CRUMBLES

The traditional biomarkers used to predict ischemic (occlusive rather than a bleed) stroke have been total and LDL cholesterol. Critics of this approach are also traditionally ignored. A large case-control study just published in the American Heart Association journal ***Stroke*** strengthens the critics' position significantly.[16] Stroke cases were drawn from over 82,000 postmenopausal women followed for a mean of 7.9 years. The first-confirmed stroke cases (972) were matched with an equivalent number of controls and comparisons made to determine blood lipid risk factors for stroke. Fourteen lipid biomarkers were examined--total cholesterol, the total cholesterol/HDL ratio, triglycerides, HDL, HDL particle size and number, intermediate density lipoproteins, LDL, LDL particle size and number, very low density triglycerides and their particle numbers and size, and lipoprotein(a). The risk of stroke was presented in terms of odds ratios according to quartiles of measures of these biomarkers, with the lowest quartile taken as reference and the ratios were adjusted for all the standard risk factors in a multivariate analysis. The results were striking. Statistically significant results were only found in the highest quartile and for only triglycerides, intermediate density lipoprotein particle number, and very low density lipoprotein particle size. Very large P values for trend with serum levels, indicating no trend at all, were found for LDL, total cholesterol, HDL particle number and LDL size.

Thus according to these results, total cholesterol, the popular total cholesterol/HDL ratio, and LDL cholesterol were insignificant biomarkers of risk for serum levels in any of the three quartiles above the reference, and there was not even a trend evident that came close to qualifying as significant. In a

quote from an interview with *theheart.org*, the lead investigator said ñthe study calls into question the traditional measures of stroke risk.ò Perhaps an understatement. There appears to be no evidence for the biomarkers that have dictated the standard of practice for two or more decades, at least in the case of stroke in older women. This is of course what the critics have been saying all along, but they represented a voice crying in the wilderness. Also, this study complements the study reviewed above regarding the failure of cholesterol to make the grade as a metric in a scheme to improve heart and vascular health.

CALL TO ABANDON LDL CHOLESTEROL TARGETS IN NEW GUIDELINES BEING FORMULATED

Updated guidelines for cholesterol testing and management are due to be published in 2012. Readers will recall the National Cholesterol Education Program 2001 Adults Treatment Panel (ATP III) and subsequent updates which had a profound impact on statin prescriptions. In an open letter to the ATP IV committee, three medical scientists from the University of Michigan medical school, the Veterans Affairs Ann Arbor Healthcare System and Yale School of Medicine have presented arguments for abandoning the presently popular ñtreat to targetò approach for LDL cholesterol and call for a fundamental revision of the guidelines and standards of practice.[17] They make the following points:

- No randomized clinical trial has tested the benefits of treating patients based on LDL targets. All trials indicate that the use of statins, not the recommended target, is responsible for risk reduction. They argue against the belief that those without other CV risk factors benefit from statin treatment just because their LDL is high by citing numbers needed to treat that range from 125 to 83 to prevent one CV event over 5 years of treatment.
- LDL levels are not a very useful factor in determining who is at risk for cardiovascular disease or how much that risk will be reduced by a statin.
- The guidelines that are based on LDL targets to promote treatment have not been shown to be safe. If there is benefit for these patients, it is likely to occur only after decades of treatment. Safety information is not available for more than 5-7 years of treatment.
- To argue that merely the fact that statins lower cholesterol is not sufficient rationale for promoting their use and ignores a number of recent examples of trusting surrogates.
- Randomized controlled studies clearly suggest that LDL levels do not help identify patients who are more likely to benefit from a statin.

This viewpoint is consistent with the study reviewed above where the AHA metric involving cholesterol failed to have any significance in the context of overall or cardiovascular mortality in a large study. However, a much stronger case could have been made when examining the LDL target issue by taking into account age and gender and acknowledging the extensive data demonstrating that LDL is not a risk factor at all for the prevalence or progression of coronary atherosclerosis.[18,19]

ATP III put forward their guidelines in 2001, complete with references. LDL targets became an integral component of the standard care. Presumably most clinicians believed they were evidence based. This was taught to medical students and justified treatment decisions. Now we are told that they are not evidence based. This is the sort of situation that undermines the confidence in the system. Nevertheless, anyone reading the literature carefully or even checking up on the references in the ATP III paper should have realized the merit to the view presented in this recent paper. But because this literature went against the conventional wisdom, i.e. dogma, and one might, with trepidation, say the mythology, it was ignored. Those who supported it no doubt were sincere in their belief regarding the truth and that it was justified to ignore falsifying studies. This practice continues today and the innocent victims are patients. The lifetime of falsified dogma is probably between one and two decades.

HUMAN INTAKE OF BPH FROM CANNED SOUP MEASURED

Most individuals concerned with health issues have heard of the potential problems associated with bisphenol A (BPH). In fact, anyone who listens to the TV news or reads the newspapers has heard of the plastic water bottle controversy. The question of health risks associated with BPH present a challenge: (a) controlled experiments where humans are dosed with BPH are not ethical; (b) finding homogeneous populations where non-exposed individuals can be identified and used as controls is nearly impossible; (c) BPH production is measured in million metric tons with annually increasing demand; (d) BPH is a building block for polycarbonate plastics and epoxy resins and turns up in plastic bottles, liners for food and beverage containers and packaging, and coatings for a vast number of consumer products. Dermal absorption can occur from products containing BPH and even from cash register receipts printed on thermal paper. Its use is so widespread that exposure can occur via inhalation of dust. In short, only the most energetic and informed efforts allow one to minimize but not eliminate exposure. Furthermore, the metabolite of BPH is rapidly eliminated, mostly in the urine, and health-related studies must contend with a serious problem of measuring exposure.

Proposed adverse effects off BPH include insulin resistance and disruption of glucose metabolism, diabetes, interference with brain development, male and female reproductive effects, mammary and prostate cancers, impaired immune response, increase adiposity, brain sexual differentiation, altered behavior and cardiovascular disease.[20,21] The chemical industry uses the standard defenceð the available evidence indicates that BPH exposure represents no noteworthy risk to health of the human population, including newborns. A recent review concerning this subject in the journal *Clinical Reviews in Toxicology*[22] included several authors declaring industrial ties or ties to advocacy groups that could contribute to bias. The conclusions in this review mirror the industry position. To examine the hundreds of cited references in this review for evidence of bias would be a monumental task since many journals do not require conflict-of-interest declarations and unearthing the conflicts becomes a major research project.

In this context, a short paper just published in the JAMA[23] is of interest. Researchers at Harvard compared the BPH intake from canned soup with controls consuming fresh soup prepared without canned ingredients. They used a wash-out period followed by a cross-over design where controls and canned soup consumers were switched for the second half the study period. They found that consumption of one serving of canned soup daily over 5 days was associated with more than a 1000% increase in urinary BPH. The absolute urinary BPH concentrations observed were among the most extreme reported in a non-occupational setting.

In the paper, the researchers highlighted the potential risks by reference to a JAMA paper published in 2008 which found in human studies that higher urinary concentrations of BPH were associated with increased prevalence of cardiovascular disease, diabetes diagnosis and liver-enzyme abnormalities. The prevalence increase for the latter was 29% and for cardiovascular and diabetes diagnosis the increases were both 39%. All these results were statistically significant. But as indicated above, the range of disorders potentially impacted by BPH is huge. In fact, recent evidence suggests that, contrary to popular belief, BPH is not a weak environmental estrogen but may have a potency similar to estradiol itself in stimulating some cellular responses and BPH may influence multiple endocrine-related biological pathways.[20]

This all adds up to rather depressing news since, as pointed out above, avoiding exposure is extremely difficult. But a first step, aside from not using plastic water bottles, might be to avoid canned food and beverages. The seemingly simplistic ruleð don't eat anything that your great grandmother or even your grandmother would fail to recognize as real food--has merit, and it is worth recalling that canned foods historically were in glass jars with just a rubber sealing ring for the glass lid. Today, the when glass jars are used, even for home canning, the metal lid will probably have a plastic coating.

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RESEARCH REPORT

Treatment of Congestive Heart Failure

by *Hans R. Larsen MSc ChE*

Heart failure is defined as the inability of the heart to supply sufficient blood flow to meet the needs of the body. The term ñcongestive heart failureò implies that the impaired blood flow is causing fluid retention in the lungs, legs, ankles or feet. Other common symptoms include shortness of breath when lying down or during exercise, fatigue and weakness, reduced exercise capacity, and rapid or irregular heartbeat.

Coronary artery disease (atherosclerosis) and heart attack are the most common causes of heart failure along with high blood pressure, faulty heart valves, damage to the heart muscle, inflammation (myocarditis), and congenital heart defects. Untreated chronic heart arrhythmias, especially atrial fibrillation, may also lead to heart failure as may the presence of diabetes, severe anemia and thyroid problems. Finally, there is evidence that heart failure is associated with a deficiency of thiamine (vitamin B1) which is exacerbated with the use of thiazide diuretics.

The primary diagnostic markers of heart failure are left ventricular ejection fraction of less than 40% and a blood (plasma) level of brain natriuretic peptide (BNP) in excess of 100 pg/mL. An elevated blood (serum) level of C-reactive protein is also associated with heart failure.

Conventional Treatment

Regardless of the cause and manifestation of the disease (left-sided heart failure, right-sided heart failure, systolic heart failure or diastolic heart failure) the medications commonly prescribed for heart failure are as follows:

- ACE inhibitors such as enalapril, lisinopril and captopril which dilate blood vessels to lower blood pressure, improve blood flow, and decrease the workload on the heart.
- Angiotensin II receptor blockers such as losartan (Cozaar) and valsartan (Diovan) which have effects similar to those of ACE inhibitors.
- Beta-blockers such as bisoprolol and carvedilol which slow heart rate and reduce blood pressure.
- Digoxin (Lanoxin) which slows the heart beat and increases the strength of heart muscle contractions. Unfortunately, it has many serious adverse effects and is probably not that effective. See www.afibbers.org/resources/digoxin.pdf for further reading.
- Diuretics such as butmetanide and furosemide which help prevent and eliminate fluid build-up.
- Aldosterone antagonists such as aldosterone and eplerenone. These are potassium-sparing and may help reverse scarring of the heart and help patients with severe heart failure live longer.

The most recent *AHA/ACCF Guidelines for the Management of Heart Failure*[1] recommend the following treatment protocol for patients with structural heart disease (valve problems) and symptoms of heart failure[2]:

- Treatment of hypertension if present
- Treatment of high cholesterol if needed
- Regular exercise
- No smoking and limited alcohol intake
- Restricted salt intake

- Routine drug therapy with diuretics, ACE-inhibitors, beta-blockers
- Selected drug therapy with aldosterone antagonists, angiotensin II receptor blockers, digoxin.

The following comments in the guidelines regarding potassium are of particular interest[3]:

> *"Patients with HF (heart failure) should be monitored carefully for changes in serum potassium, and every effort should be made to prevent the occurrence of either hypokalemia or hyperkalemia, both of which may adversely affect cardiac excitability and conduction and may lead to sudden death. Activation of both the sympathetic nervous system and renin-angiotensin system can lead to hypokalemia and most drugs used for the treatment of HF can alter serum potassium. Even modest decreases in serum potassium can increase the risks of using digitalis and antiarrhythmic drugs, and even modest increases in serum potassium may prevent the use of treatments known to prolong life. Hence, many experts believe that serum potassium concentrations should be targeted in the 4.0 to 5.0 mmol per liter range."*

Alternative Treatment

The goal of alternative and complementary therapies is to increase the pumping efficiency of the heart and to alleviate the adverse effects of conventional treatment. Several natural substances have been found effective in the treatment of heart failure. Substantial evidence of efficacy is available for the following:

- Coenzyme Q10
- Pycnogenol
- L-carnitine
- Thiamine
- Magnesium
- Potassium
- D-ribose
- Fish oil
- Hawthorn
- Vitamin D
- Arginine
- Taurine

Coenzyme Q10

Coenzyme Q10 (ubiquinone, ubiquinol) is an essential component of the mitochondria, the energy-producing unit of every cell of our body. Heart failure is associated with a pronounced coenzyme Q10 deficiency, and low coenzyme Q10 levels are associated with increased mortality in heart failure patients.[4,5] There are several clinical trials which clearly show that supplementation with coenzyme Q10 (150 ï 650 mg/day) markedly improves heart function in heart failure patients.[6-9] More recent research has shown that ubiquinol, the reduced form of coenzyme Q10 is even more effective in the treatment of heart failure.[10]

Coenzyme Q10 supplementation is of extreme importance in heart failure patients on statin drugs. Research has shown that these drugs seriously impede the synthesis of coenzyme Q10 leading to such adverse effects as
myalgia (muscle pain), fatigue, breathing difficulties, memory loss, and peripheral neuropathy. Fortunately, supplementation with coenzyme Q10, preferably in conjunction with discontinuation of statin drugs, can completely reverse these effects.[11-14]

Well-functioning heart cell mitochondria are essential to heart health. Coenzyme Q10 is the ñspark plugò that powers the mitochondria. Recently, a new supplement, pyrroloquinoline quinone (PQQ) has been developed which markedly increase the formation of new mitochondria.[15-17] Thus, it would seem that a protocol which combines ubiquinol (3 x 100 or 3 x 200 mg/day) with PQQ (20 mg/day) would be greatly beneficial.

Pycnogenol

Pycnogenol is a powerful antioxidant and anti-inflammatory extracted from the bark of the French Maritime pine tree. It has an amazing range of beneficial effects including reduction of glucose levels, management of chronic asthma, reduction of platelet aggregation (as effective as aspirin, but without

the negative side effects), and regeneration of vitamins C and E. Of more immediate interest is a recent finding that pycnogenol, in combination with coenzyme Q10, materially improves the health of heart failure patients. An Italian clinical trial recently concluded that the combination of pycnogenol and coenzyme Q10 (50 mg/day Q10 and 15 mg/day pycnogenol) increased left ventricular ejection fraction and walking distance in a group of heart failure patients.[18]

Carnitine

Carnitine is a vitamin-like compound responsible for the transport of long-chain fatty acids into the mitochondria. Thus it, along with coenzyme Q10, is essential for cellular energy production. There is evidence that l-carnitine itself reduces symptoms of chronic heart failure[19], but research into the benefits of carnitine supplementation has largely focused on propionyl-l-carnitine, a naturally occurring derivative of l-carnitine. Several clinical trials have concluded that treatment with orally administered propionyl-l-carnitine (3 x 500 mg/day) is effective in increasing exercise capacity and left ventricular ejection fraction in heart failure patients.[20-22] Not surprisingly, a combination of l-carnitine and ubiquinol has also been found effective in reducing breathlessness, fatigue and palpitations, and improving walking distance in heart failure patients.[23]

Thiamine

Thiamine, also known as vitamin B1, is a prominent member of the water-soluble B-complex. It is required for the proper metabolism of proteins, carbohydrates and fats, and is intimately involved in ATP production (energy generation) in every cell. Clinical research has shown that about a third of hospitalized heart failure patients are deficient in thiamine and that from 55 to 98% of patients on the diuretic furosemide suffer from severe thiamine deficiency.[24,25] Fortunately, it is possible to reverse the adverse effects of thiamine deficiency by supplementing with 300 mg/day of thiamine.[26]

Magnesium

Magnesium is of key importance to human health. It participates in over 300 enzymatic reactions in the body. A deficiency has been linked to conditions such as irregular heartbeat, asthma, emphysema, cardiovascular disease, high blood pressure, mitral valve prolapse, stroke and heart attack, diabetes, fibromyalgia, glaucoma, migraine, kidney stones, osteoporosis, and probably many more. About 99% of the body's magnesium stores are found in the bones and tissues and heart tissue is particularly rich in this important mineral. Only 1% of the body's magnesium is actually present in the blood so a standard blood analysis is a very poor way of determining overall magnesium status.

Magnesium deficiency is widespread in the general population and especially pronounced in atrial fibrillation and heart failure patients, especially if treated with loop diuretics (thiazides), digoxin and ACE inhibitors.[27,28] There is evidence that magnesium deficiency is associated with a much lower survival rate in heart failure patients.[29] Fortunately, there is also evidence that replenishment of magnesium with oral supplementation, specially magnesium orotate, can markedly improve both clinical symptoms, survival and quality of life.[30]

A growing body of evidence points to a close connection between magnesium deficiency and mitral valve prolapse and, perhaps even more importantly, clinical trials have shown that supplementation with magnesium can partially or fully eliminate the symptoms of mitral valve prolapse.[31,32]

Intramuscular injections of magnesium sulfate and oral supplementation with chelated magnesium (magnesium glycinate) are effective means of increasing magnesium level in heart cells.

Potassium

Potassium is a very important electrolyte and an adequate level is essential to ensure proper heart function. As in the case of magnesium, potassium deficiency (hypokalemia) is widespread among heart failure patients and is further exacerbated if the patient is on loop diuretics (thiazides), digoxin and ACE inhibitors.[28] Scottish researchers have found that the optimum potassium level for heart failure patients is between 4.5 and 5.5 mmol/L (mEq/L). Levels lower than this increase the risk of ventricular arrhythmias and death. For those with low potassium levels, the researchers recommend

supplementation with potassium and magnesium combined with aldosterone blockade to prevent increased potassium excretion.[33] Aldosterone blockade can be achieved through the use of ACE inhibitors, angiotensin II type 1 receptor blockers, or aldosterone receptor blockers (spironolactone and eplerenone). Excessive potassium excretion can also be prevented through the use of potassium-sparing diuretics such as triamterene (Dyrenium) and amiloride (Midamor).[34]

Whichever protocol is used to achieve a potassium level between 4.5 and 5.5 mmol/L, it should be kept in mind that a low magnesium level (hypomagnesemia) increases potassium excretion, and it is very difficult to remedy hypokalemia without first attaining normal magnesium levels. One study found that 42% of people with low magnesium levels also had low potassium levels.[35,36]

D-ribose

D-ribose is a simple, five-carbon sugar which acts as fuel in the production of ATP, the body's source of energy. Clinical studies have shown that d-ribose is highly effective in increasing ATP production in heart failure patients and thus ameliorating symptoms of fatigue, improving the heart's pumping capacity, and generally resulting in a better quality of life.[37] Two clinical trials have found that supplementation with 5 grams of d-ribose 3 times daily is effective in improving heart failure symptoms.[38,39]

Fish oil

There is overwhelming evidence that consumption of fatty fish and supplementation with fish oil are highly beneficial in maintaining heart health. A fish oil intake of at least 1 gram/day reduces the risk of sudden cardiac death by as much as 80%, most likely through the ability of fish oil to increase heart rate variability, which is usually too low in heart failure patients.[40] The large GISSI-HF clinical trial found that supplementation with 1 gram/day of fish oil reduced hospital admissions and death in a group of 7000 heart failure patients.[41] A more recent trial involving 133 heart failure patients concluded that supplementation with fish oil increases left ventricular ejection fraction and exercise capacity, and reduces annual hospitalization rate from 30% to 6%.[42]

Hawthorn

Hawthorn (*Crataegus oxyacantha*) is a powerful heart tonic widely used in Germany in the treatment of heart failure, either on its own or in addition to standard medical treatment. Hawthorn increases the strength of the heart's contraction (inotropic effect similar to that exhibited by digoxin). It also increases blood flow in the heart, increases left ventricular ejection fraction and exercise tolerance, and relieves other symptoms of heart failure. The German Commission E has approved the use of hawthorn in stage II (NYHA classifi8cation) heart failure.

The product most widely used in Germany is WS1442 which is an extract of hawthorn leaf and flower standardized to contain 18.75% of oligomeric procyanidins. A recent Cochrane review of 10 clinical trials evaluating the effect of hawthorn in heart failure patients concluded that supplementation with hawthorn (most likely 450 mg of WS1442 twice daily) improved exercise tolerance and significantly reduced symptoms such as shortness of breath and fatigue. Most of the clinical trials used hawthorn as an adjunct to standard medical treatment. Adverse effects were infrequent, mild and transient. The Cochrane researchers conclude that ñ*there is a significant benefit in symptom control and physiologic outcomes from hawthorn extract as an adjunctive treatment for chronic heart failure*".[43]

Vitamin D

Vitamin D is not really a vitamin, but rather a hormone which the body can make using sunlight. The skin contains a cholesterol derivative, 7-dehydrocholesterol (provitamin D), which is converted to vitamin D when exposed to sunlight. Vitamin D is converted in the liver to 25-hydroxyvitamin D [25(OH)D] which in turn is converted, mostly in the kidneys, to the active hormone $1,25(OH)_2D$ or calcitriol. There are two forms of vitamin D supplements ï **vitamin D3** or cholecalciferol and **vitamin D2** or ergocalciferol. Vitamin D2 is synthetic and has only about half the efficacy of vitamin D3 when it comes to raising blood levels of 25(OH)D, the commonly used measure of vitamin D concentration.

Vitamin D deficiency is widespread and has been implicated in cancer, osteoporosis, hypertension, diabetes, rheumatoid arthritis and multiple sclerosis. Most researchers now consider a 25(OH)D level below 50 nmol/L (20 ng/mL) to be deficient and an optimum level to be about 75 nmol/L (30 ng/mL). A low vitamin D [25(OH)D] level is common among heart failure patients and is an indicator of a poor prognosis. Dutch researchers have found that heart failure-related mortality increases by 10% for each 10 nmol/L decrease in 25(OH)D level.[44] Fortunately, it is relatively simple to correct a vitamin D deficiency. It can be achieved slowly through oral supplementation with 2000 to 4000 IU/day of cholecalciferol over a 6-month period, or quickly by using one-time doses as high as 500,000 IU.[45,46]

Arginine

L-arginine is a semi-essential amino acid that acts as a physiological precursor of nitric oxide. Nitric oxide, in turn, plays a crucial role in regulating blood circulation, dilates blood vessels, and helps prevent the formation of blood clots. The effect of supplementation with arginine has been studied extensively and it has been found useful in the prevention and treatment of cardiovascular disorders including mild and moderate heart failure.[47] Supplementation with l-arginine has been found to increase exercise tolerance and improve right ventricular ejection fraction in heart failure patients.[48-50] Improvement may be seen in as little as 7 days using dosages of 2 to 3 grams three times daily.

Taurine

Taurine is an amino acid widely distributed in human tissue. It is essential for proper cardiovascular function, and the development and function of the central nervous system, retina and skeletal muscle. It is a powerful antioxidant and protects against toxicity of lead and cadmium. It has also been found effective in lowering cholesterol and by keeping potassium and magnesium inside of heart cells and excessive sodium out, it helps prevent arrhythmia (including atrial fibrillation), and acts as a diuretic.

Taurine deficiency is common among heart failure patients; thus, it is not surprising that Japanese researchers, 30 years ago, reported that taurine supplementation (2-3 grams/day) is effective and entirely safe in the treatment of congestive heart failure.[51-54] More recent research has shown that taurine supplementation (500 mg three times daily) for 2 weeks significantly increases exercise capacity in heart failure patients.[55] There is also evidence that taurine exerts an inotropic effect similar to that of digoxin (without the side effects), and that it has diuretic effects and counteracts the adverse effects of angiotensin II.[56,57] Thus taurine supplementation could potentially reduce the need for treatment with ACE inhibitors/angiotensin II receptor blockers and digoxin.

Summary

It is clear that heart failure patients are often deficient in nutrients crucial to proper heart function. In many cases, these deficiencies are exacerbated by drugs (digoxin, diuretics, statins and ACE inhibitors) prescribed as part of the standard medical treatment for heart failure. It is thus of utmost importance that patients

- confirm that their medications are indeed needed and that dosages are optimum ï minimizing digoxin dosage is particularly important.
- determine when possible if they are deficient in any of the critical nutrients discussed.
- rectify confirmed and likely deficiencies with appropriate supplementation.
- gradually wean off redundant medications as their condition improves as a result of the elimination of nutrient deficiencies.

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