

Part I: Cardiovascular Disease Risk Factors and Fundamental Nutrition

BY DECKER WEISS, N.D.

ABSTRACT: *Cardiovascular disease (CVD) is the leading cause of death in the United States, representing 42% of all deaths each year. While genetic influences can play a role in the onset of CVD, the prevalence of this disease is largely attributable to modifiable risk factors such as smoking, physical inactivity, and poor diet. In addition, chronic stress can damage the cardiovascular system through multiple pathways and may contribute to the development of CVD. Counseling of patients on*

appropriate lifestyle modifications is an essential first step in the prevention of CVD. In addition, a great deal of research conducted over the last few decades has identified several nutrients that can have a profound effect on the cardiovascular system. These nutrients include vitamin E and coenzyme Q10 for their cardioprotective benefits, magnesium and B-complex vitamins for a healthy stress response, and essential fatty acids and garlic for their blood pressure lowering effects.

The Prevalence of CVD

For decades, the major cause of death in many industrialized Western countries has been cardiovascular disease (CVD), which includes heart disease and stroke. In the United States, CVD accounts for more deaths than from all cases of cancer, chronic obstructive pulmonary disease, pneumonia and influenza, diabetes, and AIDS/HIV combined. Almost one million people die annually, or more than 2,600 daily, from CVD. It is currently estimated that 60 million Americans suffer from some form of CVD and the economic drain, including health expenditures and loss of productivity, approaches \$274 billion annually.¹

Risk Factors of CVD

CVD is the product of multiple genetic, metabolic, behavioral, and environmental influences, which fall into modifiable and non-modifiable categories. Well-known or traditional risk factors include elevated stress levels, hypertension, physical inactivity, poor diet, and diabetes.¹ These risk factors will be discussed, along with specific nutrition and lifestyle recommendations aimed at reducing their incidence and consequent impact on the cardiovascular system.

Psychosocial Stress and Its Role in CVD

Stress is a hallmark risk factor in CVD mainly due to its affect on arterial blood pressure, levels of atherosclerotic promoters, and neuroendocrine reactions.² Recent studies show clear and compelling evidence that psychosocial factors such as stress contribute significantly to the development and manifestation of heart disease. For instance, studies on monkeys exposed to psychosocial stress demonstrated an increased number of injured endothelial cells in the descending thoracic aorta, and exacerbated atherosclerosis via

a heightened response of the sympathetic nervous system.^{3,4} In humans, data links sympathetic nervous system hyperresponsivity to accelerated development of carotid atherosclerosis.²

Poor circulation can be exacerbated with exposure to stress. In one recent study, ischemia developed in 106 of 183 patients with documented coronary disease during a mental stress test.⁵ Furthermore, those patients with daily life ischemia exhibited a heightened generalized response to mental stress. Another recent study examined the effects of stress on plasma concentrations of homocysteine, an amino acid that has been implicated in the development of CVD.⁶ In this study on 34 healthy women, acute psychological stress induced rapid and significant elevations in plasma homocysteine levels, with a return to baseline during recovery. These findings indicate that plasma homocysteine may be an important factor in the correlation of stress and risk of heart disease.⁶

Substantial epidemiological evidence indicates that hypertension is related to psychosocial factors such as chronic exposure to stress.^{7,8} For instance, animal and human models associate chronic social conflict with hypertension. In addition, occupational stress has been associated with hypertension and risk of CVD.⁷ One study, using the Karasek Job Content Survey (a known predictor of heart disease), found that men in high strain jobs (high demands/low control) are more likely to show hypertension and left ventricular hypertrophy than men in less stressful positions.⁸ In addition, type A behavior, which is associated with coronary heart disease, predicts a greater increase in left ventricular hypertrophy in men with essential hypertension.⁹ Stress management interventions, along with specific nutrition, can help reduce levels of daily stress and their effects on the body.

Stress Management

Stress management interventions can measurably improve performance on cardiac function tests.^{10,11} Thirteen patients with heart disease, who also exhibited type A behavior, were found to have multiple episodes of silent myocardial ischemia over a 48-hour period.¹⁰ After 14 months of type A behavior counseling with 10 of these patients, time urgency and hostility diminished by 53% and 59%, respectively, and the mean frequency of ischemic episodes declined from 6.6 to 3.1 per 24 hours.¹⁰ The remaining 3 uncounseled patients did not show a significant change in these measures. Group psychotherapy, health education, and behavior modification in major lifestyle areas may be important for the secondary prevention of coronary artery disease.

Nutritional Support

While stress management is obviously important in reducing recurrent and chronic stress at the psychological level, certain nutrients are important for limiting the effects of the stress response at the physiological level. Antioxidant nutrients such as coenzyme Q10 (CoQ10) and vitamin E are beneficial due to the increase in oxidative stress associated with psychosocial stress.¹² In addition, nutrients such as magnesium and the B-complex vitamins play important roles in healthy nervous system function.¹³ Magnesium deficiency increases susceptibility to physiologic damage produced by stress;¹⁴ in addition, magnesium is often depleted in stress, leading to an increased risk of cardiovascular damage.¹⁵ B-complex vitamins also help regulate the mood and emotional well-being by facilitating carbohydrate metabolism (which affects serotonin levels) and the cellular conversion of glucose to usable energy.¹³ Furthermore, deficiencies of B vitamins including B₆, B₁₂, and folate have been implicated in the exacerbation of psychological distress itself and symptoms such as depression, irritability, tiredness, and other psychiatric disturbances.^{16,17}

Many herbs, and combinations thereof, have been used in Chinese herbal tradition to help alleviate the psychological and physiological effects of stress. Herbs such as rehmannia root (*Rehmannia glutinosa*), dong quai root (*Angelica sinensis*), schizandra fruit (*Schizandra chinensis*), scrophularia root (*Scrophularia ningpoensis*), salvia root (*Salvia miltiorrhiza*), and codonopsis root (*Codonopsis pilosula*) soothe irritability and restlessness, produce a calming effect on the central nervous system, and have anti-hypertensive qualities.^{18,19}

Vitamin E and CoQ10: Fundamental Protective Factors

The heart and coronary blood vessels are highly susceptible to free radical oxidative stress. The effects of oxidative stress are believed to contribute to CVD through a number of acute and chronic pathways, including reperfusion and ischemia, endothelial damage, and chronic oxidative changes occurring in low-density lipoprotein (LDL).¹² During oxidative stress, free radicals produce structural changes in serum LDL.^{12,13} These damaged LDL are then recognized as foreign and phagocitized by macrophages. These macrophages fill up with lipids, forming “foam cells” which aggregate and adhere to the blood vessel surface. They facilitate the development of lesions on the artery wall, initiating a cascade of events ultimately leading to CVD. These foam cells compose the characteristic “fatty substance” in atherosclerotic plaque. Cardioprotective nutrients such as vitamin E and CoQ10

have powerful antioxidant capabilities that enable them to prevent the initial damage to LDL and endothelial tissues that contributes to the development of CVD.¹²

Vitamin E

Over the past few decades, research has continuously shown that vitamin E offers significant protection against CVD.¹² Not only does vitamin E reduce the risk of heart attack, inhibit platelet aggregation, and impede atherosclerosis, it can also increase the survival rate of patients undergoing bypass surgery and plays a role in decreasing other heart ailments, including angina.

The Cambridge Heart Antioxidant Study tested the hypothesis that treatment with vitamin E would reduce the risk of myocardial infarction (MI).²⁰ In this randomized, placebo-controlled, double-blind study of 2,002 patients with proven coronary heart disease, vitamin E proved to reduce the rates of non-fatal MI, with beneficial effects apparent after 1 year of treatment. The patients were divided into 3 groups and treated for 510 days. Group 1 (n=546) received 800 IU/daily, Group 2 (n=489) received 400 IU daily, and Group 3 (n=967) received a placebo. Plasma vitamin E levels rose in Groups 1 and 2 (from a baseline mean of 34.2 micromol/L to 64.5 and 51.1, respectively), but did not change in the placebo group. During the study period, 14 patients in Groups 1 and 2 had non-fatal MIs compared to 41 events in Group 3 (placebo).

Vitamin E's role in stimulating the regression of existing arterial lesions and its protective effect against the development of atherosclerosis are well supported by epidemiological and clinical studies.²¹⁻²³ For instance, it has been shown that 100 IU/day or more of vitamin E can significantly decrease coronary artery lesion progression.²¹ Results from a clinical intervention trial showed that 1600 mg/day (800 IU) vitamin E taken for 5 months reduced LDL susceptibility to oxidation by 50%.²² In another study, regression of existing atherosclerosis was demonstrated in a group of middle-aged men who had coronary bypass surgery and an intake of over 100 IU/day of vitamin E.²³

Recently, the benefit of mixed tocopherol vitamin E has been examined with special reference to alpha- and gamma-tocopherol.^{12,24-26} Studies have demonstrated that although alpha-tocopherol is an effective antioxidant in and of itself, gamma-tocopherol is required to more effectively remove specific free radical species (peroxynitrite-derived nitrating species) and prevent lipid hydroperoxide formation in liposomes.²⁴⁻²⁶ Secondly, large doses of alpha-tocopherol can displace gamma-tocopherol in plasma and other tissues to a significant degree.²⁴⁻²⁶ The synergistic action of these two tocopherols provides a greater level of protection against oxidative damage, and better reflects the ratios found in a healthy diet.

Coenzyme Q10

Coenzyme Q10, or ubiquinone, is found in the mitochondria, Golgi apparatus, and lysosomes of animal cells, and is therefore omnipresent in body tissues. It is also present in all plasma membranes including low-density lipoproteins. CoQ10 is a vital component in the ATP-generating process by acting as an electron acceptor/proton donor; hence, its presence in the body is fundamental to the support of cellular life. Not surprisingly, CoQ10 is found highly concentrated in organs that require a large energy

supply, including the heart. In its reduced form, ubiquinol, CoQ10 functions as a chain-breaking antioxidant and is believed to regenerate vitamin E.²⁷ Most of the research on CoQ10 relates to its cardioprotective and free radical scavenging abilities.²⁸

Individuals with cardiac disorders have been identified as having abnormally low levels of CoQ10. In a study conducted over an 8-year period, the usefulness of CoQ10 in clinical cardiology was assessed.²⁹ Statistically significant improvements in myocardial function were evident. The diagnostic categories (ischemic cardiomyopathy, dilated cardiomyopathy, primary diastolic dysfunction, hypertension, mitral valve prolapse, and valvular heart disease) were evaluated according to the New York Heart Association (NYHA) functional scale. Of 424 patients, 58% improved by one functional class, 28% by two classes, and 1.2% by three classes. Overall medication requirements dropped, with 43% of the patients discontinuing between one and three drugs. Only 6% were required to add one drug.

In another study on 40 patients undergoing elective coronary artery bypass surgery, pretreatment with CoQ10 at 150 mg/day for 7 days served a protective role against oxidative compounds.³⁰ Not only were the concentrations of oxidative compounds decreased in the treatment group, but this group also had a significantly lower incidence of arrhythmias during the recovery period.

CoQ10 plays a vital role as an antioxidant in cellular membranes and plasma lipoproteins. Studies illustrate CoQ10's protective action against the oxidative modifications that make LDL atherogenic.^{28,31} One study showed that treatment of healthy volunteers with CoQ10 led to a parallel increase of CoQ10 in plasma and plasma lipoproteins and to an enhanced resistance of LDL oxidation.³¹ When CoQ10 in LDL samples were isolated from volunteers taking 300 mg of CoQ10 daily for 11 days, they showed an increase of almost four times that of basal levels. When these CoQ10 enriched samples were exposed to an oxidative initiator, they developed only one third the amount of lipid peroxides produced by LDL from untreated controls.

The stability and bioavailability of CoQ10 supplements for therapeutic use should be considered. Due to its molecular instability, low melting point, light sensitivity, and lipophilic nature, CoQ10 must be manufactured under stringent pharmaceutical standards. In addition, because CoQ10 is a fat-soluble nutrient, lipid carriers within the formula can positively impact bioavailability.³² For instance, in a study comparing two different CoQ10 formulations, it was shown that a formula containing vitamin E (30 IU), rice bran oil (221.4 mg) and CoQ10 (30 mg) increased absolute blood levels of CoQ10 from 0.8 mcg/ml to 2.77 mcg/ml versus an increase to only 1.72 mcg/ml by a formula containing the same levels of dry ingredients (dry CoQ10, rice bran powder, and dry vitamin E). Intestinal absorption rate was found to be 9.3 mcg/minute in the lipid based formula versus 3.42 mcg/minute in the dry formula, indicating a relative difference in bioavailability of 273%.³³

In addition to the fundamental roles performed by vitamin E and CoQ10, various other nutrients perform roles that reduce traditional risk factors and therefore the progression of CVD.

Nutrients for Lowering Blood Pressure and Improving Circulation

Hypertension appears to aggravate the atherosclerotic process, possibly by weakening the artery walls that are already stiffened and narrowed by plaque. As the heart struggles to pump blood, blood pressure continues to increase. This increase forces the left ventricle of the heart to work harder; in time, left ventricular hypertrophy can result and chronic heart failure may develop. Hypertension can also upset the electrical conduction system of the heart, triggering arrhythmias.¹³

Magnesium, Calcium, and Potassium

Epidemiologic data suggest a relationship between blood pressure and calcium, potassium, and magnesium intake. A recent report concluded that adequate amounts of these minerals should be consumed to help prevent and treat hypertension.³⁴ Studies have shown that their consumption has an independent and significant inverse association with hypertension and may have multiple blood pressure-lowering effects, including inducing vascular smooth muscle relaxation and, thus, peripheral resistance.¹³ These minerals may also be able to control the electrical conduction system and reduce the incidence of arrhythmia.³⁵

In addition, magnesium plays a role in neuromuscular transmission activity and ion exchange, whereby it acts as a muscle relaxer and directly influences vascular tone and reactivity.^{36,37} In one study on 60 patients with essential hypertension, the effects of magnesium supplementation on ambulatory, home, and office blood pressures was studied. All blood pressures were significantly lower during the magnesium supplementation period of 8 weeks, as compared to an 8-week control period.³⁸

Research has shown that the intestinal absorption and metabolism of minerals in the form of amino acid chelates is superior to that of inorganic metal salts.³⁹ Amino acid chelates, due to their stability, are not altered in the digestive process. Furthermore, their similar characteristics to dipeptides and tripeptides allows them to easily travel through the intestine.³⁹ This factor is especially important in the case of magnesium, often found in oxide, citrate, or sulfate forms, which can be difficult to absorb and carry a laxative effect. Magnesium glycinate represents a true amino acid chelate with dipeptide characteristics, making it an ideal mineral form for therapeutic uses.

Essential Fatty Acids (EFAs)

Omega-3 and omega-6 fatty acids act to reduce the production of inflammatory thromboxanes, which reduces the likelihood of platelet aggregation and consequently reduces blood pressure. In a double-blind crossover study, 46 elderly hypertensives with systolic blood pressure of greater than 160 mm Hg or diastolic blood pressure greater than 90 mm Hg received 9 g/day of omega-3 fatty acids or 9 g/day of omega-6 fatty acids.⁴⁰ Following a 4-week baseline period, treatment was given for two 8-week periods with a 3-week washout period between them. During the first treatment period, both omega-3 and omega-6 EFAs lowered diastolic blood pressure by 5.1 mm Hg and 0.72 mm Hg, respectively. No further lowering of blood pressure was attained during the second treatment period.

To study the long-term effects of beneficial dietary fats on blood pressure, researchers conducted adipose-tissue fatty acid composition analysis on 399 healthy males.⁴¹ Stepwise regression analysis showed that an absolute 1% increase in tissue alpha-linolenic acid (omega-3) content was associated with a decrease of 5 mm Hg in the systolic, diastolic, and mean blood pressures.

Garlic

Garlic extracts have been used since the early part of this century for treatment of elevated blood pressure.⁴² Active constituents of garlic (allicin, ajoene, and other sulfur compounds) are believed to decrease the sensitivity of peripheral blood vessels to adrenaline, promote dilation of blood vessels, inhibit angiotensin-converting enzyme and arachidonic acid metabolites, and increase adenosine levels in the blood stream.⁴² Adenosine directly enlarges peripheral blood vessels and is involved in the regulation of blood flow in coronary arteries. For instance, in a study on the effect of allicin in animal tissues, significant vasodilating activity in the vascular bed was observed.⁴³

A double-blind crossover study comparing the effect of aged garlic extract with a placebo showed a 5.5% decrease in systolic blood pressure and a modest reduction of diastolic blood pressure.⁴⁴ In a meta-analysis of garlic's effect on lowering blood pressure, it was concluded that the overall pooled difference in systolic and diastolic blood pressure, as compared to baseline measures, was greater in garlic-treated subjects than in placebo groups.⁴⁵ Furthermore, chronic garlic intake has been associated with a decrease in the aortic stiffness related to aging, thereby supporting the elastic properties of a healthy aorta.⁴⁶

Hawthorn

Active constituents found in the leaves, flowers, and berries of hawthorn (*Crataegus oxyacantha*) may help lower blood pressure and pressure rate product (an indicator of economization of cardiac work) and increase ejection fraction—the percentage of blood leaving the heart during each beat.^{47,48} The higher the ejection fraction, the better the heart's ability to pump oxygen-rich blood throughout the body. All of these parameters may contribute to reducing the load on the heart in individuals with congestive heart failure. Hawthorn is also believed to dilate coronary blood vessels, reduce peripheral vascular resistance, and increase myocardial perfusion.⁴⁷ In animal studies, hawthorn has been shown to increase peripheral and coronary artery blood flow and decrease arterial blood pressure.^{47,49}

Horse Chestnut

Horse chestnut seeds (*Aesculus hippocastanum*) contain a complex mix of flavonols, including quercetin, kaempferol, rutin, and aescin. These flavonols function to increase the tone of the veins, thereby improving blood flow.⁵⁰ Capillaries become excessively permeable when any factor, such as thrombus formation, destroys the integrity of the capillary wall. Increased permeability facilitates the passage of electrolytes, proteins, and water through the venous walls, thereby producing edema and chronic venous insufficiency.^{51,52}

A study conducted by Bisler et al. showed that horse chestnut has an inhibitory effect on edema formation via a decrease in

transcapillary filtration, thus improving edema-related symptoms in venous disease of the legs.⁵³ Twenty-two patients with proven chronic venous insufficiency were given a horse chestnut seed extract (600 mg providing 50 mg aescin) or a placebo. Three hours after administration, the capillary filtration coefficient decreased by 22% in the patients given horse chestnut seed extract. Aescin is believed to be able to exert anti-inflammatory properties as well as decrease capillary permeability by reducing the number and size of the small pores of the capillary wall, thus restricting water from leaving the capillaries. In addition to aescin, rutin is commonly used to help decrease capillary fragility and restore normal permeability.⁵⁴

Incorporating these nutrients, which are summarized in Table 1 below, into a cardiovascular support program can have a profound impact on the health of the patient. In addition, counseling patients on appropriate lifestyle modifications is also an essential part of CVD prevention.

Table 1. Cardiovascular Benefits of Select Nutrients and Herbs

<i>Fundamental Protective Factors</i>	
Vitamin E (400-800 IU) Coenzyme Q10 (100-300 mg)	Prevent lipid oxidation. Cardioprotective.
<i>Stress</i>	
Folate (0.4-0.8 mg) Vitamin B ₁₂ (0.4-0.5 mg) Vitamin B ₆ (10-45 mg)	Support the health of the nervous system. Decrease homocysteine.
Traditional Chinese Herbal Formula Containing: rehmannia root, dong quai root, schizandra fruit, scrophularia root, salvia root, and codonopsis root	Soothe irritability and restlessness, calm the nervous system, and invigorate.
<i>Hypertension and Circulation</i>	
Magnesium (300-900 mg) Calcium (800-1000 mg) Potassium (400-900 mg)	Decrease blood pressure by inducing smooth muscle relaxation. Promote healthy electrical conduction.
Essential Fatty Acids (5,000-10,000 mg)	Reduce inflammation and platelet aggregation thereby lowering blood pressure.
Garlic (400-600 mg raw garlic concentrate)	Promotes dilation of blood vessels. Decreases aortic stiffness.
Hawthorn (160-250 mg of hawthorn flower, standardized to 2% flavonoids and 18.75% procyanidins)	Vasodilator that reduces peripheral resistance. Decreases blood pressure and increases ejection fraction.
Horse Chestnut (600-700 mg of horse chestnut seed, standardized to 16%-21% aescins)	Decreases capillary permeability through improved venal tone. Improves blood flow.

Lifestyle and Dietary Factors

Exercise

Regular exercise has been proven to have beneficial effects on a variety of chronic disease conditions, and cardiovascular disease is no exception.¹ Although there are no controlled trials proving that exercise reduces the risk of developing CVD to date, it is generally accepted as a viable adjunct recommendation. Various studies have verified that exercise is effective in reducing CVD risk factors including hypertension, dyslipidemia, and glucose tolerance.⁵⁵ Sedentary individuals should begin a program that involves aerobic activity (brisk walking, swimming, bicycling, etc.) that is sustained for a period of 30 minutes at least three times per week.

Diet

Most inhabitants of industrialized countries consume diets that are atherogenic. Epidemiological data and in vivo studies show that a reduction of dietary saturated fats, cholesterol, fried foods, sugar, and animal proteins positively affects CVD risk. Conversely, the consumption of a diet high in fiber and fruits and vegetables is recommended. The goal of dietary intervention is mainly to affect the lipid profile positively, i.e., reduce triglycerides, cholesterol, and low-density lipoproteins and increase high-density lipoproteins.⁵⁶ In addition, patients are often advised to reduce their intake of alcohol and caffeine containing beverages.

Diabetes

Up to 70% of the deaths in persons with diabetes are from coronary artery disease and concomitant congestive heart failure.⁵⁷⁻⁵⁹

Although the role of dietary carbohydrate in CVD is not well established, the American Nurses' Study has reported that diets with high glycemic indexes, which are characterized by rapid absorption and high postprandial glucose and insulin responses, increase the risk of CVD.^{57,58} Low insulin sensitivity is linked to CVD because excess carbohydrates are utilized preferentially over triglycerides and other lipids for energy. This effect is most dramatic in "carbohydrate sensitive" individuals—people who respond to sucrose with abnormally high glucose levels. As such, fasting lipid profiles, including triglycerides, HDL, LDL, total cholesterol, and apolipoproteins, are important laboratory markers for diabetic related cardiovascular disease.⁵⁹ In Type II diabetes, which constitutes the majority of diabetes cases in the U.S., a reduction of carbohydrates (most specifically simple/refined) and the addition of factors such as chromium, vanadium, fenugreek, and B vitamins that help stabilize blood glucose, increase insulin sensitivity, and metabolize carbohydrates are important preventive measures.⁶⁰⁻⁶³

Researchers are beginning to realize that while clinical care is necessary and important, it often falls short in the realm of prevention. Furthermore, it is now being understood that the sooner preventive measures against risk factors are employed, the more likely they will be to hasten or prevent the development of CVD.¹ In addition to the well-known risk factors discussed in this paper, research has uncovered clinical markers that can further identify those at risk of CVD. In *Part II: Cardiovascular Disease—Nutritional Management of Clinical Markers*, the importance of these markers and specific nutritional interventions are discussed.

REFERENCES

- Centers for Disease Control and Prevention. *Cardiovascular Disease* (July 14, 1999) (online). Retrieved via Microsoft Internet Explorer. <http://www.cdc.gov/nccdphp/cardiov.htm>.
- Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999;99:2192-2217.
- Watson SL, Shively CA, Kaplan JR, et al. Effects of chronic social separation on cardiovascular disease risk factors in female cynomolgus monkeys. *Atherosclerosis* 1998;137(2):259-66.
- Skantze HB, Kaplan J, Pettersson K, et al. Psychosocial stress causes endothelial injury in cynomolgus monkeys via beta1-adrenoceptor activation. *Atherosclerosis* 1998;136(1):153-61.
- Stone PH, Krantz DS, McMahon RP, et al. Relationship among mental stress-induced ischemia and ischemia during daily life and during exercise: the psychophysiological investigations of myocardial ischemia (PIMI) study. *J Am Coll Cardiol* 1999;33(6):1476-84.
- Stoney CM. Plasma homocysteine levels increase in women during psychological stress. *Life Sci* 1999;64(25):2359-65.
- Pickering TG, Devereux RB, James GD. Environmental influences on blood pressure and the role of job strain. *J Hypertens* 1996;14(suppl 5):S179-85.
- Pickering TG. Does psychological stress contribute to the development of hypertension and coronary heart disease? *Eur J Clin Pharmacol* 1990;39(Suppl 1):S1-7.
- Munakata M, Hiraizumi T, Nunokawa T, et al. Type A behavior is associated with an increased risk of left ventricular hypertrophy in male patients with essential hypertension. *J Hypertens* 1999;17(1):115-20.
- Friedman M, Breall WS, Goodwin ML, et al. Effect of type A behavioral counseling on frequency of episodes of silent myocardial ischemia in coronary patients. *Am Heart J* 1996;132(5):933-7.
- Allan R, Scheidt S. Group psychotherapy for patients with coronary heart disease. *Int J Group Psychother* 1998;48(2):187-214.
- Sinatra ST, DeMarco J. Free radicals, oxidative stress, oxidized low density lipoprotein (LDL), and the heart: antioxidants and other strategies to limit cardiovascular damage. *Conn Med* 1995;59(10):579-88.
- Guyton AC. *Textbook of Medical Physiology* 8th ed. Philadelphia (PA): W.B. Saunders; 1991.
- Galland L. Magnesium, stress and neuropsychiatric disorders. *Magnes Trace Elem* 1991;10:287-301.
- Seelig MS. Consequences of magnesium deficiency on the enhancement of stress reactions; preventive and therapeutic implications (a review). *J Amer Coll Nutr* 1994;13(5):429-46.
- Santhosh-Kumar CR, Hassell KL, Deutsch JC, et al. Are neuropsychiatric manifestations of folate, cobalamin and pyridoxine deficiency mediated through imbalances in excitatory sulfur amino acids? *Med Hypotheses* 1994;43:239-44.
- Baldewicz T, Goodkin K, Feaster DJ, et al. Plasma pyridoxine deficiency is related to increased psychological distress in recently bereaved homosexual men. *Psychosom Med* 1998;60(3):297-308.
- Bown D. *Encyclopedia of Herbs & Their Uses*. New York: Dorling Kindersley; 1995.
- Bensky D, Gamble A. *Chinese Herbal Medicine: Materia Medica*. Seattle: Eastland Pr; 1993.
- Stephans NG, Parsons A, Schofield PM, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study. *Lancet* 1996;347(9004):781-6.
- Hodis HN, Mack WJ, LaBree L, et al. Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis. *JAMA* 1995;273(23):1849-54.
- Reaven PD, Khow A, Beltz WF, et al. Effect of dietary antioxidant combinations in humans. Protection of LDL by vitamin E but not by beta-carotene. *Arter Thromb* 1993;13:590-600.
- Stampfer MJ, Rimm EB. Epidemiological evidence for vitamin E in prevention of cardiovascular disease. *Am J Clin Nutr* 1995;62(suppl):1365S-9S.
- Christen S, Woodall AA, Shigenaga MK, et al. gamma-Tocopherol traps mutagenic electrophiles such as NOX and complements alpha-tocopherol: physiological implications. *Proc Natl Acad Sci* 1997;94(7):3217-22.
- Wolf G. gamma-Tocopherol: an efficient protector of lipids against nitric oxide-initiated peroxidative damage. *Nutr Rev* 1997;55(10):376-8.

26. Cooney RV, Franke AA, Harwood PJ, et al. gamma-Tocopherol detoxification of nitrogen dioxide: superiority to alpha-tocopherol. *Proc Natl Acad Sci* 1993;90:1771-5.
27. Papas AM. Other Antioxidants. In: Antioxidant Status, Diet, Nutrition, and Health. New York: CRC Pr; 1999.
28. Bagchi D. A review of the clinical benefits of coenzyme Q10. *J Adv Med* 1997;10(2):139-147.
29. Langsjoen H, Langsjoen P, Langsjoen P, et al. Usefulness of coenzyme Q10 in clinical cardiology: a long-term study. *Mol Aspects Med* 1994;15(Suppl):s165-75.
30. Chello M, Mastroberoberto P, Romano R, et al. Protection by coenzyme Q10 from myocardial reperfusion injury during coronary artery bypass grafting. *Ann Thorac Surg* 1994;58(5):1427-32.
31. Mohr D, Bowry VW, Stocker R. Dietary supplementation with coenzyme Q10 results in increased levels of ubiquinol-10 within circulating lipoproteins and increased resistance of human low-density lipoprotein to the initiation of lipid peroxidation. *Biochimica et Biophysica Acta* 1992;1126:247-54.
32. Kishi H, et al. Clinical application of coenzyme Q10 and the quality control of its preparations in Japan. In: Biochemical and Clinical Aspects of Coenzyme Q. Elsevier/North-Holland Biomedical Pr; 1981.
33. Judy WV. Coenzyme Q10 intestinal absorption study. (Unpublished study: SIBR 0.006-96) Soft Gel Technologies, Inc.; 1997.
34. Kendler BS. Recent nutritional approaches to the prevention and therapy of cardiovascular disease. *Prog Cardio Nursing* 1997;12(3)3-23.
35. Fotherby MD, Potter JF. Potassium supplementation reduces clinic and ambulatory blood pressure in elderly hypertensive patients. *J Hypertens* 1992;10(11):1403-8.
36. Mahan LK, Escott-Stump S. Krause's Food, Nutrition, & Diet Therapy. 9th ed. Philadelphia: W.B. Saunders; 1996.
37. Altura BM, Altura BT. Magnesium ions and contraction of vascular smooth muscles: relationship to some vascular diseases. *Federation Proc* 1981;40:2672-9.
38. Kawano Y, Matsuoka H, Takishita S, et al. Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. *Hypertension* 1998;32(2):260-5.
39. Ashmead HD. Comparative intestinal absorption and subsequent metabolism of metal amino acid chelates and inorganic metal salts. *Biol Trace Elem Res* 1991:306-19.
40. Margolin G, Huster G, Glueck CJ, et al. Blood pressure lowering in elderly subjects: a double-blind crossover study of omega-3 and omega-6 fatty acids. *Am J Clin Nutr* 1991;53:562-72.
41. Berry EM, Hirsch J. Does dietary linolenic acid influence blood pressure? *Am J Clin Nutr* 1986;44:336-40.
42. Koch HP, Lawson LD, eds. Garlic: The Science and Therapeutic Application of *Allium sativum* L. and Related Species. 2nd ed. Baltimore: Williams & Wilkins; 1996.
43. Kaye AD, Nossaman BD, Ibrahim IN, et al. Analysis of responses of allicin, a compound from garlic, in the pulmonary vascular bed of the cat and in the rat. *Eur J Pharmacol* 1995;276(1-2):21-6.
44. Steiner M, Khan AH, Holbert D, et al. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. *Am J Clin Nutr* 1996;64:866-70.
45. Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens* 1994;12(4):463-8.
46. Breithaupt-Grogler K, Ling M, Boudoulas H, et al. Protective effect of chronic garlic intake on elastic properties of aorta in the elderly. *Circulation* 1997;96(8):2649-55.
47. Busse W. Standardized *Crataegus* extract clinical monograph. *Quar Rev Natl Med* 1996(Fall):189-7.
48. Leuchtgens H. *Crataegus* special extract WS 1442 in NYHA II heart failure. A placebo controlled randomized double-blind study. *Fortschr Med* 1993;111(20-21):352-4.
49. Schussler M, Holz J, Fricke U. Myocardial effects of flavonoids from *Crataegus* species. *Arzneim Forsch* 1995;45(8):842-5.
50. Tyler VE. Herbs of Choice: The Therapeutic Use of Phytochemicals. New York: Pharmaceutical Products Pr; 1994.
51. Sherwood L. Human Physiology: From Cells to Systems. 2nd ed. New York: West Publishing; 1993.
52. Diehm C, Trampisch HJ, Lange S, et al. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *Lancet* 1996;347:292-4.
53. Bisler H, Pfeifer R, Klucken N, et al. Effects of horse-chestnut seed extract on transcapillary filtration in chronic venous insufficiency. *Dtsch Med Wochenschr* 1986;111(35):1321-9.
54. Schulz V, Hansel R, Tyler V. Rational Phytotherapy: A Physicians' Guide to Herbal Medicine. New York: Springer-Verlag; 1998.
55. Havranek EP. Primary prevention of CHD: nine ways to reduce risk. *Amer Fam Phys* 1999;59(6):1455-63.
56. Yu-Poth S, Zhao G, Etherton T, et al. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr* 1999;69:632-46.
57. Liu S, Stampfer MJ, Manson JE, et al. A prospective study of glycaemic load and risk of myocardial infarction in women. *FASEB J* 1998;12:A260.
58. Wolever TM. The glycemic index. *World Rev Nutr Diet* 1990;62:120-85.
59. Frost G, Leeds AA, Dore CJ, et al. Glycaemic index as a determinant of serum HDL-cholesterol concentration. *Lancet* 1993;353:1045-8.
60. Sharma RD, et al. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. *Eur J Clin Nutr* 1990;44:301-6.
61. Whitney EN, Rolfes SR. Understanding Nutrition. New York: West Publishing C; 1993.
62. Boden G, Chen X, Ruiz J, et al. Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin-dependent diabetes mellitus. *Metabolism* 1996;45(9):1130-5.
63. Anderson R, Polansky MM, Bryden NA, et al. Supplemental-chromium effects on glucose, insulin, glucagon, and urinary chromium losses in subjects consuming controlled low-chromium diets. *Am J Clin Nutr* 1991;54:909-16.