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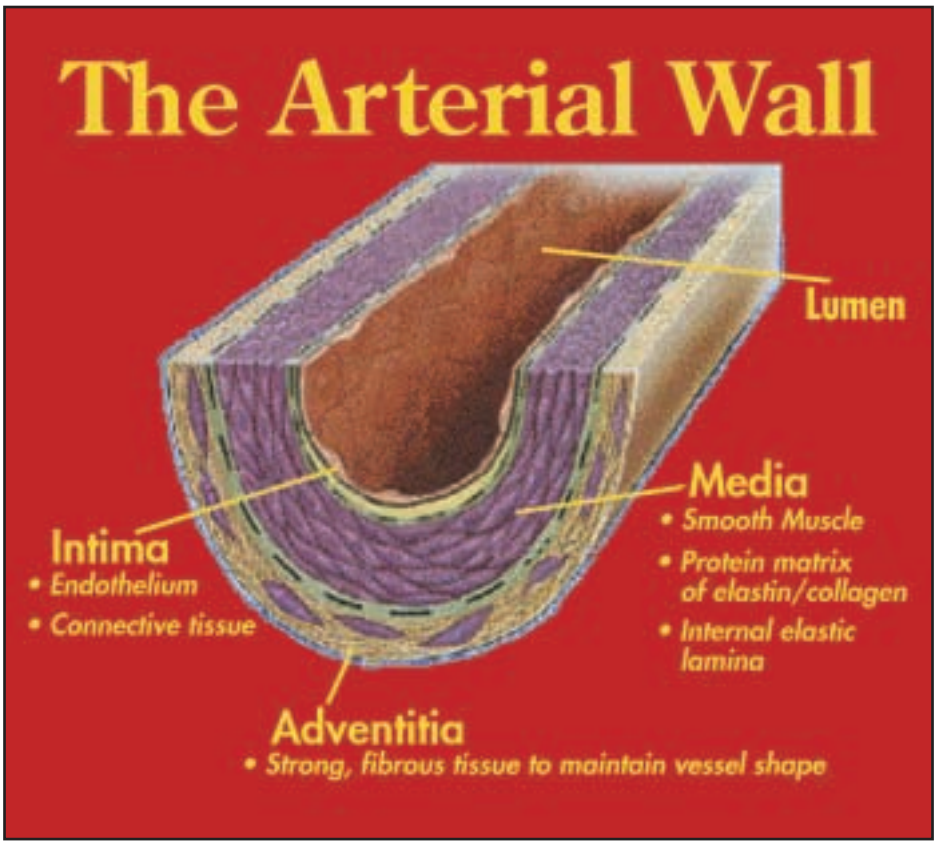

The Role of Vascular Biology, Nutrition and Nutraceuticals in the Prevention and Treatment of Hypertension

Mark C. Houston, MD, SCH, FACP, FAHA

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EDITORIAL COMMENTARY

Commentary on "The Role of Vascular Biology, Nutrition, and Nutraceuticals in the Prevention and Treatment of Hypertension"

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Malnutrition is a leading cause of disease in both emerging and developed economies.[1] While the spectrum of health problems resulting from calorie-protein undernutrition is different from the "empty-calorie" overfeeding, both can have devastating consequences on both quality of life and longevity (Table 1). The review article by Dr. Mark Houston, "The role of vascular biology, nutrition, and nutraceuticals in the prevention and treatment of hypertension," represents a comprehensive synopsis of the current evidence that the food and supplements we ingest have a major impact on our cardiovascular health. The article confirms the wisdom of centuries-old advice (Table 2)[2] that eating fruits and vegetables is the healthy choice.[3] The evidence cited spans the spectrum from cellular and molecular to clinical and epidemiological. Moreover, the grave dangers accompanying obesity, reported nearly 80 years ago, are being clearly being rediscovered and the mechanisms by which this leading manifestation of malnutrition impact health are being explained.[4]

This article by Dr. Houston also continues his personal tradition of timely and superb, state-of-the art reviews. This paper will be essential reading for every clinician and academician with a professional interest in evidence-based nutritional approaches to cardiovascular disease prevention. However, this article will also be useful and informative to a wide range of professional and lay readers. The review also delivers more than the title indicates. It addresses the metabolic or insulin-resistance syndrome and associated vascular pathobiology. Hypertension is but one of many facets. In fact, Dr. Houston points out that the metabolic syndrome is often manifest before the blood pressure reaches levels regarded as hypertensive. Malnutrition is a major contributor to the expression of the metabolic syndrome, and those with a genetic predisposition are more likely to manifest its adverse consequences, *i.e.,* gene-environment interactions lead to expression of the syndrome.

The review article is an impressive tour de force with 749 references. Dr. Houston strikes a fine balance between multiple scientific domains. The cell and molecular mechanisms leading to vascular pathobiology and clinical manifestations of cardiovascular disease are examined. The active components of various foods and supplements on cardiovascular disease are explored at both a basic cellular and pathophysiological as well as the clinical-epidemiological level. As one example, the article reviews the cellular signal transduction mechanisms by which oxidative stress impacts endothelial and vascular smooth muscle function. It then progresses to the pathophysiological and clinical consequences of the disordered cellular function and the mechanisms by which a wide range of naturally-occurring compounds abrogate those adverse effects and potentially alter outcomes. At the outset, Dr. Houston identifies gene-environment interactions in the pathogenesis of most cardiovascular disease, and he proceeds to buttress that position with overwhelming scientific evidence. There can be no doubt that what we eat impacts gene transcription, protein expression, and enzyme function that ultimately determine our cardiovascular health.

Table 1. Some health consequences of malnutrition: Protein-calorie undernutrition and obesity.[1]

Emerging economies Protein-Calorie Undernutrition	Developed economies Obesity
↓ Muscle mass	Metabolic syndrome with ↑ risk of
↓ cardiac and renal mass	CVD, CHF, PVD, ESRD,
Numerous skin changes	↑ cancer risk, especially, endometrial
Normocytic, normochromic anemia	breast, prostate and colon.
Fatigue, listlessness	↑ gall bladder disease
↓ cell-mediated immunity	Osteoarthritis, gout
Pneumonia, opportunistic infections	Polycystic ovaries, infertility
Impaired wound healing	Sleep apnea
↓ Fertility	Fatigue

CVD = cardiovascular disease, CHF = congestive heart failure, PVD = peripheral vascular disease, ESRD = end-stage renal disease.

This article clearly documents that nutritional research has long since moved past the stage of soft science and is solidly entrenched in the exciting era of cellular and molecular biology. It would appear that clinical practice has fallen behind the science and may help explain why so many patients are turning to alternative solutions to major health care concerns.

In the summary and conclusions, which promises to become a classic reference source, no fewer than 20 naturally-occurring foods and specific compounds have angiotensin-converting enzyme inhibitor activity. Some of these substances appear to have ACEI activity comparable to that of commercially marketed pharmaceutical products. Moreover, 11 naturally-occurring substances are noted to have calcium channel blocker activity, 11 diuretic activity, and 11 enhance nitric oxide. Nine naturally-occurring compounds have angiotensin receptor-blocking properties, 16 direct vasodilator properties, and 14 improve insulin sensitivity. This summary provides a foundation for a rational, "stepped-care" or multi-dimensional nutritional and nutraceutical approach to the primary and secondary prevention of cardiovascular disease.

The review focuses mainly on the positive evidence that nutrition and nutraceuticals positively affect cardiovascular disease risk and outcomes. This is not a major criticism but simply to alert the reader that there are credible studies, *e.g.,* the Heart Outcomes Prevention Evaluation (HOPE), which clearly did not find benefits of one specific antioxidant, in this case, vitamin E, on cardiovascular outcomes in high-risk patients. To his credit, Dr. Houston repeatedly and correctly points out that the evidence for benefit is much stronger when multiple foods and nutraceuticals are considered together rather than as isolated components.

Table 2. Wisdom of nutritional advice through the millennia.[3]

Genesis 2:9. And the Lord God made all kinds of trees grow out of the ground—trees that were pleasing to the eye and *good* for *food* (i.e., fruit).

Daniel 1:12, 15. (Daniel said) "Please test your servants for 10 days. Give us nothing but vegetables to eat and water to drink." At the end of 10 days they looked healthier and better nourished than the young men who ate the royal food.

Proverbs 23:1–3. Avoid rich foods and gluttony. When you sit to dine with a ruler, note well what is before you, and put a knife to your throat if you are given to gluttony. Do not crave his delicacies, for that food is deceptive.

The comments on pharmacological approaches to the management of hypertension are relatively brief, but unlike the review of nutrition and nutraceuticals, much less evidence-based. To his credit, Dr. Houston clearly acknowledges this limitation.

This is an excellent and very important review article. Although significant time is required to read through this 34-page article, it is time well spent. For anyone seriously interested in nutrition and health, this is essential and enjoyable reading.

REFERENCES

1. Denke M, Wilson JD. Protein and energy undernutrition. Obesity. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Long DL, eds. *Harrison's Principles of Internal Medicine*, 14th ed. New York: McGraw Hill; 1998:452-462.
2. Weder AB. Your mother was right: eat your fruits and vegetables. *Curr Hypertens Rep.* 1999;1:11–12.
3. Holy Bible. New International Version. Zondervan Publishing House, Grand Rapids, Michigan, 1984.
4. Preble WE. Obesity: observation on one thousand cases. *Bost Med and Surg J.* 1923;88:617–621.

EDITORIAL COMMENTARY

Nutraceuticals and Vascular Biology: Are They Ready For Prime Time Use?

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Roughly one-third of adults use nutraceuticals and 15 million Americans use them together with conventional medicines.[1] Their use is of tremendous importance to the medical community. A recent prevalence study from the Mayo clinic found that 61% of those 18 years of age and older had used a nutraceutical over the past year.[2] A significant boost in use began in 1994, when Congress passed the Dietary Supplement Health and Education Act (DSHEA). These "dietary supplements," defined as a vitamin, mineral, herb, or other botanical, were now excluded from the rigorous scientific evaluation that ensured both the safety and the effectiveness required of "drugs" presented before the Food and Drug Administration. Although manufacturers were no longer allowed to make specific disease claims, their products were often positively promoted and accepted by the public to affect one's health, despite their certainty for benefit.

With sales of nutraceutical products increasing 25% per year in the United States, their influence on blood pressure control has been of great importance, but rarely written about. In this issue of *JANA,*[3] Houston comprehensively reviews the "evidence" that both genetic and lifestyle choices affect the vascular biology of endothelial function, which, when altered, can lead to hypertension. He suggests that certain nutraceutical supplements as well as certain vitamins and minerals, when optimally integrated with proper nutrition, exercise, and weight loss, can effectively prevent, delay, and control blood pressure in those with hypertension, regardless of their need for drug therapy. Although there is biologic plausibility to his theory, one needs to ask, "where is the clinical evidence"?

Large, well-designed hypertension trials evaluating lifestyle changes such as sodium restriction, weight loss, aerobic exercise, as well as the Dietary Approaches to Stop Hypertension (DASH)4 and DASH-Sodium5 diets, emphasizing fruits, vegetables, grains, and low-fat dairy products, have achieved a favorable effect on reducing blood pressure and are endorsed by national guidelines. The results, however, with supplemental magnesium, calcium, potassium, omega fatty acids, garlic, tea, mushrooms, and seaweed have been inconsistent, and should not be recommended for blood pressure reduction. On the other hand, observational studies with vitamins E and C, as well as Coenzyme Q-10 and L-arginine, have been associated with more consistent blood-pressure-lowering effects in those with hypertension. Accordingly, Houston suggests that "there is a role for the selected use of single and component nutraceuticals, vitamins, antioxidants, and minerals in the treatment of hypertension based on scientifically controlled studies as a complement to optimal nutritional, dietary, and other lifestyle modifications." Before the hypertension community endorses this recommendation, however, several important questions remain. What is the exact dose and dose-frequency of these agents that will allow clinical benefit? How homogeneous is the production of these products so that their bioavailability can be assured? These are just a few issues that will need to be carefully evaluated in clinical hypertension trials before these agents are widely endorsed by the practicing community.

So where do we stand on these agents in the control of hypertension? For sure, our patients will continue to use nutraceuticals in an effort to prevent as well as treat their hypertension, hoping to favorably affect their vascular biology. Although their clinical benefit may be debated, our patients remain enthused about these preparations and physicians must be aware of their use. Only through a detailed history and knowledge of all prescribed as well as over-the-counter and dietary preparations taken by our patients will we begin to be able to evaluate the effective-

ness of the patient's total health care. As emphasized in "The Sixth Report on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," a detailed history should be obtained on the use of herbal and alternative medications in the evaluation of those with hypertension as they may raise blood pressure or interfere with the effectiveness of antihypertensive drugs."[6] As more than two-thirds of patients never tell us about their use, the importance of a detailed history concerning nutraceuticals cannot be overstated. However, until well-designed evidence-based trials evaluate these compounds in those with hypertension, nutraceuticals are not "ready for prime-time" in those at risk for or being treated for hypertension, even though our patients may continue to believe so.

REFERENCES

1. Eisenberg DM, Kessler RC, Foster C, *et al.* Unconventional medicine in the United States: prevalence, costs, and patterns of use. *N Engl J Med.* 1993;328:246-252.
2. Harnack LJ, Rydell SA, Stang J. Prevalence of use of herbal products by adults in the Minneapolis/St Paul, Minnesota, metropolitan area. *Mayo Clin Proc.* 2001;76:688-694.
3. Houston MC. The role of vascular biology, nutrition, and neutreuticals in the prevention and treatment of hypertension. *JANA.* 2002;5 (suppl)1:S5-S72.
4. Appel LC, Moore TJ, Obarzanek E, *et.al.* A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med.* 1997;336:1117-1124.
5. Sacks FM, Svetkey LP, Vollmer WM, *et.al.* Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med.* 2001;344:3-10.
6. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med.* 1997;157:2413-2446.

REVIEW ARTICLE

The Role of Vascular Biology, Nutrition and Nutraceuticals in the Prevention and Treatment of Hypertension

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ABSTRACT

Vascular biology plays a primary and pivotal role in the initiation and perpetuation of hypertension and subsequent target organ damage. Endothelial activation and dysfunction, oxidative stress and vascular smooth muscle dysfunction (hypertrophy, hyperplasia, remodeling) may be some of the first events that trigger essential hypertension. Nutrient-gene interactions determine specific phenotypic consequences of either vascular health, vascular disease or hypertension. Optimal nutrition, nutraceutical supplements, vitamins, antioxidants, minerals, weight loss, exercise, smoking cessation and judicious restriction of alcohol and caffeine as well as other lifestyle modifications can prevent, delay the onset, reduce the severity, treat and control the essential hypertension of many patients. An integrative and synergistic approach combining these lifestyle modifications with appropriate pharmacologic treatment is most likely to achieve new goal blood pressure levels, reduce risk factors for vascular disease, improve vascular biology and vascular health, optimize target organ protection and reduce coronary heart disease, stroke, congestive heart failure and renal disease. This paper will review the expanded scientific roles for nutrition and nutraceutical supplements in the prevention and treatment of essential hypertension with specific emphasis on mechanisms of action, clinical use and integration with drug therapy as indicated, based in part on the Joint National Committee's 6th Report (JNC-VI) and other national and global hypertension guidelines.

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INTRODUCTION

Hypertension is a consequence of the interaction between genetics and the internal environment of the body. Macronutrients and micronutrients are crucial in the regulation of blood pressure (BP) and subsequent target organ damage (TOD). Nutrient-gene interactions, oxidative

stress and subsequent gene expression have positive or negative influences on vascular biology in humans. Endothelial dysfunction and vascular smooth muscle dysfunction are the initiating and perpetuating factors in essential hypertension. The correct combination of macronutrients and micronutrients significantly influences the prevention and treatment of hypertension and its vascular complications. Our genes determine who we are, how we look and even how we think. However, our lifestyle and nutritional choices will influence our physical and mental health and ultimately our fate.[1]

Nutritional needs have changed as we have evolved from a pre-agricultural, hunter-gatherer milieu to a highly technological agricultural industry dependent on mechanical processing for our food supply.[1,2] Movement from the Paleolithic diet with low sodium, high potassium, high fiber, low fat, lean animal protein, low refined carbohydrate, and low cholesterol intake composed of fruits, vegetables, berries, nuts, fiber, fish, fowl, and wild game to our modern diet has resulted in an epidemic of nutritionally-related diseases. These diseases include hypertension, atherosclerosis and target organ diseases (TOD) such as coronary heart disease (CHD), congestive heart failure (CHF), cerebrovascular accidents (CVA), myocardial infarction (MI), renal insufficiency (RI), and renal failure (RF).[2]

Short-term reduction in blood pressure (BP) by nutritional means translates into intermediate and long-term improvements in morbidity and mortality, including CVA, CHD and MI.[3,4] In the Health Professionals Followup Study,[3] diets rich in potassium reduced CVA by 41% in hypertensive subjects. In the Lyon Diet Heart Study,[4] a Mediterranean-type diet reduced the incidence of a second MI by 76%. These and other studies to be addressed testify to the importance of micronutrients, macronutrients and specific nutraceuticals in the prevention and treatment of hypertension and its cardiovascular sequelae. Many national and global organizations (such as the JNC-VI,[5] the Nutrition Committee of the American Heart Association,[6] the World Health Organization (WHO) and the Institute of Medicine) report to Congress[7] on the nutritional needs of the elderly, INTERSALT[8] and numerous others recognize the impact of nutrition in hypertension, CHD, atherosclerosis, CVA and overall disease prevention.[7,8,9]

NUTRITION AND DISEASE PREVENTION

A wise healer uses that which works. An integrative and synergistic approach that embraces nutrition, nutraceuticals, weight loss, exercise, judicious limited use of alcohol, and tobacco cessation with appropriate pharmacologic therapy (antihypertensive drugs) is clearly the optimal means to lower BP and reduce TOD in specific subsets of essential hypertensive patients. Lower BP goals in essential hypertensive patients will make combining lifestyle modifications and drug therapy a requirement for many patients, including those[5] with multiple risk factors, TOD or clinical cardiovascular disease (CCD). These include hypertensive patients with diabetes mellitus, renal insufficiency (RI), proteinuria or microalbuminuria, those with present or previous TOD (cerebrovascular accident [CVA], coronary artery bypass graft [CABG], left ventricular hypertrophy [LVH], transient ischemic attack [TIA], nephropathy, peripheral arterial disease, retinopathy) and those with concomitant CHD risk factors such as dyslipidemia, homocysteinemia, insulin resistance, hyperglycemia, diabetes mellitus, tobacco use, being elderly, being male, being a postmenopausal woman, or having a family history of premature cardiovascular disease (women < 65, men < 55) (Table 1 and Table 2).

These lifestyle modifications may prevent, delay the onset, reduce BP levels and its progression, potentiate the effects of antihypertensive drugs (which allow for fewer drugs and/or lower doses) and provide additive or synergistic improvements in risk factors, BP and vascular function, structure and health.[10,11] Patients with high normal BP (BP 130-139/85-89 mm Hg) or Stage 1 hypertension (BP 140-159/90-99 mm Hg) who have no risk factors, TOD or clnical cardiovascular disease (CCD) (Risk Group A), should be treated with lifestyle modification for up to 12 months[5] (Table 1 and Table 2). These same patients in Risk Group B with only one risk factor (excluding diabetes) and no TOD or CCD should be treated with lifestyle modification for up to six months.[5] If the BP remains elevated beyond six months, then antihypertensive drug therapy should be initiated (Table 1 and Table 2).

However, a large percentage of essential hypertensive patients are appropriate candidates for initial and prolonged lifestyle modifications as long as the BP is frequently evaluated and clinical TOD, CCD or significant risk factors are not present at that time and do not develop later. As many as 50 to 60% of essential hypertensive patients may fall into this classification.[11,12,13] Nutrition, nutraceutical supplements, weight loss, exercise, cessation of tobacco use, and judicious limited use of alcohol are effective therapy in these patients and provide excellent adjunctive therapy in patients on antihypertensive drugs. The lifestyle modifications mentioned above should always be continued following initiation of drug therapy.[10,11,12,13]

This paper will review the basic science and clinical studies of nutrition, nutraceutical supplements, vitamins, antioxidants, minerals, macronutrients, micronutrients, exercise, weight loss, weight management, and alcohol and caffeine consumption and their role in the prevention and treatment of hypertension. Correlations and mechanisms of action based on vascular biology will provide a unique framework for understanding the clinical use of these lifestyle modifications. A review of pharmacologic therapy with antihypertensive drugs is beyond the scope of this paper, but some general discussion is provided to emphasize the importance of "balance" when treating essential

hypertension. Extreme opinions about lifestyle modifications or treatments with alternative non-drug therapy versus drug therapy serve little purpose except to polarize ideas and health care providers at the expense of their patients' welfare. Therapeutic choices must be based on good science, not on whims, misconceptions and ignorance. It is time to integrate nutrition and nutraceutical science with traditional drug therapy to reduce BP, TOD and improve the dismal BP control in the U.S. and other countries.[5,14,15,16,17]

Indeed, the wise healer will use what works, is safe and based in good science. Our goal is to improve our patients health and quality of life. Let fruitful scientific and rational discussions begin and the rhetoric end. A belief that certain treatments are true or untrue, or thinking that it is counter-intuitive or unproven can no longer be considered acceptable medical practice. The truth awaits to be revealed.

"The doctor of the future will give no medicine, but will interest his patient in the care of the human frame, in diet and in the cause and prevention of disease" - Thomas Edison.

EPIDEMIOLOGY OF HYPERTENSION

Approximately 25% of the United States adult population (over 50 million people) have hypertension as defined by a BP reading over 140/90 mm Hg.[5,14,15,18] This percentage increases with age, such that 50% of adults over age 60, and 80% of adults over age 70 have hypertension.[5,14,15,18] Although 90 to 95% of hypertension is genetic, environment (nutrition and exercise) influences its age of onset and severity.[5,14] In general, African Americans, men and the elderly have more severe hypertension and increased target organ damage (TOD) at similar BP levels compared to Caucasians, women and younger patients.[5,14,15,18] However, after age 60, women have a greater incidence of hypertension than men.[5,14] About 70% of patients with essential hypertension have BP ≤ 160/105 mm Hg.[10]

Hypertension is the leading cause of cardiovascular and cerebrovascular complications, the most common reason for visits to physician offices, and the number one reason for drug prescriptions in the U.S.[5,14,19,20] The annual expenditure for antihypertensive drug prescriptions is over 10 billion dollars,[14] an amount projected to exceed 25 billion dollars by 2007. The National Health and Nutritional Examination Survey III (NHANES III) found that only 27% of the hypertension population had controlled their blood pressure to a goal of less than 140/90 mm Hg.[5,14,15,17] This percentage is less than in 1990, yet the expenditure on antihypertensive medications has doubled.[5,14,15,17]

Cardiovascular and cerebrovascular disease increase dramatically with small increases in BP, even while remaining within normal range.[5,21] In fact, 32% of CHD deaths secondary to hypertension occur with a systolic blood pressure (SBP) of less than 140 mm Hg.[22] Reducing BP results in impressive decreases in CHD, MI, CHF, CVA and RI.[5,18,23,24] A reduction in diastolic blood pressure (DBP) of 5 mm Hg reduces CHD by 15%, CHF by 52% and CVA by 40%.[5,18,23] A 3 mm Hg reduction in SBP reduces CHD by 5% and CVA by 8%.[18,24] Even with adequate BP control on antihypertensive medications, hypertensive patients still have a substantially and significantly 30% higher risk of cardiovascular morbidity and mortality compared to untreated, normotensive patients.[25] The reasons for this are not established, but a negative influence of diuretics and beta blockers on CHD risk factors, the presence of the hypertension syndrome and its constellation of risk factors or abnormalities of vascular biology may be important contributing factors.[25]

CLASSIFICATION OF HYPERTENSION

The Joint National Committee's 6th Report has classified BP into four major groups (Table 1).[5] Hypertension is stratified into Stage 1, 2 and 3 based on either systolic (SBP), or diastolic blood pressure (DBP) (Table 1).[5] Treatment is determined by BP level, risk factors, TOD, CCD or presence of diabetes mellitus (DM) (Table 2).[5] It should be emphasized that lifestyle modification or non-pharmacologic therapy is recommended for up to 12

Table 1

JNC-6 Classification of BP for Adults[5] Aged 18 Years and Older

	BP, mmHg		
Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Hypertension			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	≥ 180	or	≥ 110

Table 2[5]

Risk Stratification and Treatment*

BP Stages (mmHg)	Risk Group A No risk factors No TOD / CCD†	Risk Group B At least one risk factor, not including diabetes No TOD/ CCD†	Risk Group C TOD / CCD‡ and/or diabetes, with or without other risk factors
High -normal (130-139 / 85-89)	Lifestyle modification	Lifestyle modification	Drug Therapy†
Stage 1 (140-159 / 90-99)	Lifestyle modification (up to 12 months)	Lifestyle modification (up to 6 months)	Drug Therapy
Stages 2 and 3 (≥ 160 / ≥ 100)	Drug Therapy	Drug Therapy	Drug Therapy

* Lifestyle modification should be adjunctive therapy for all patients recommended for pharmacologic therapy
** For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.
‡ TOD / CCD = target organ disease / clinical cardiovascular disease
† For those with heart failure or renal insufficiency or those with diabetes

months in patients with Stage 1 hypertension in Risk Group A and up to six months in Risk Group B.[5] These patients have BP ≤ 160/100 mm Hg without DM, TOD, or CCD, but may have one CV risk factor (Group B). Group C patients with TOD, CCD, DM, or more than one CV risk factor should immediately receive drug therapy. Nonpharmacologic therapy should be adjunctive treatment for all patients on pharmacologic therapy regardless of Stage or Risk Group.[5] Patients with Stage 2 and 3 hypertension should initially receive antihypertensive drug therapy (BP > 160/100 mm Hg) regardless of Risk Group category, and continue on lifestyle modifications as well.[5]

The primary TOD in hypertension includes CHD, MI, CHF, (both systolic CHF and diastolic CHF), CVA, RI or RF, large arterial disease (aorta and peripheral vascular disease) and retinopathy.[5,14] Goal BP levels should be approximately 110/70 mm Hg in patients with DM, chronic renal insufficiency (CRI), proteinuria, CHD or a history of CVA.

RISK FACTORS AND HYPERTENSION

The most common and important risk factor for the development of hypertension is genetics. A positive family history in a parent results in a 25 to 50% chance of a child developing the polygenic and multifactorial disorder called hypertension.[5,14] Other risk factors include unhealthy nutrition, obesity, alcohol, high sodium intake, chronic and acute stress, increased unrefined carbohydrate and sugar intake, sedentary lifestyle, age, ethnicity, gender, tobacco use and possibly caffeine intake.[14] Oxidative stress has assumed a major role in the initiation and perpetuation of hypertension.[26,27,28,29,30]

Numerous studies have shown that appropriate nutrition, macronutrients, micronutrients and other lifestyle changes can prevent or significantly reduce the incidence of hypertension in any age group, gender or race.[31,32,33,34,35] In the Trials of Hypertension Prevention Phase 2 (TOHP-2), sodium restriction, weight loss, or a combination reduced the incidence of hypertension at year four by 18-22% compared to the control group of a middle-aged, obese, nonhypertensive population.[31] The incidence of hypertension in the control group was 7.3% versus 4.5% in the sodium restricted group, 4.2% in the weight reduction group, and 2.7% in the group with combined sodium restriction and weight loss.[31] Sodium restriction in normotensive newborns of hypertensive parents administered for six months resulted in a reduced BP and prevented BP elevation that was maintained for fifteen years.[35] Elderly patients with hypertension are quite sensitive to sodium restriction. In the Trial of Nonpharmacologic Interventions in the Elderly (TONE),[32] a 40 mmol/day reduction of sodium decreased the need for hypertensive medications in 40% of subjects at three months. In addition, a weight loss of 10 pounds reduced the need for medication by 36%, and the combination of sodium restriction and weight loss reduced the need for medication by 53% in those subjects with an initial BP ≤ 145/85 mm Hg. African American hypertensive patients tend to have a greater reduction in BP than Caucasians with the same dietary interventions.[33,34]

HYPERTENSION SYNDROME

Hypertension is associated with a constellation of clinical, metabolic, biochemical and structural abnormalities in over 70% of cases.[36,37,38,39,40,41,42] These abnormalities may actually precede the development and/or diagnosis of hypertension by many years.[37,39,40] The hypertension syndrome consists of endothelial dysfunction, reduced arterial and ventricular compliance, abnormal glucose metabolism and insulin resistance, endocrine and neurohormonal dysfunction, renal function changes, clotting changes with a thrombotic tendency, left ventricular hypertrophy (LVH), diastolic dysfunction, accelerated atherogenesis, abnormal lipid metabolism and central obesity.[20,36,37,38] Hypertension is a disease of the blood vessel in which the vascular biology is altered and dysfunctional.

It appears that many of the changes in vascular structure and function antedate the onset of hypertension by decades and may be responsible for its ultimate development.[37,39,40] Identification of the syndrome, followed by aggressive, appropriate nutrition, exercise, weight management and nutraceutical treatment of these patients before hypertension becomes chronically established will improve and even reverse cardiovascular disease.[37,39,40,41]

Dyslipidemia and hypertension are genetically inherited and genetically linked, but are variables that occur independently of each other. Approximately 80% of hypertensive patients have concomitant dyslipidemia.[39,40] Dyslipidemia in patients with a positive family history of hypertension is significantly more frequent than in those without a family history of hypertension despite being normotensive.[39,40]

Left ventricular hypertrophy (LVH) precedes the development of hypertension in young, normotensive adults who have a positive family history of hypertension and is significantly more common compared to age-matched normotensive controls without a family history of hypertension.[39,40] Thus, LVH, although commonly associated with hypertension in over 50% of patients, is also genetically determined, may be independent of and precede the onset of hypertension. Similarly, diastolic dysfunction or reduced ventricular compliance precedes hypertension and is more common in normotensive patients with a positive family history of hypertension compared to normotensive controls with a negative family history of hypertension.[39,40]

Reductions in arterial compliance with increased arterial stiffness occur before the onset of hypertension,[39,40] follow a similar family history, may not worsen with increasing BP,[39] but it is associated with the pathophysiology of

elevated BP and is a marker for an increased incidence of adverse cardiovascular outcomes.[39,40]

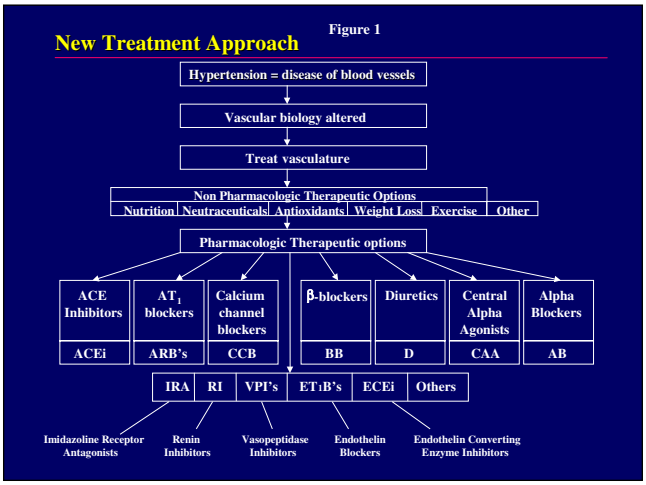
Insulin resistance occurs in 50% of untreated hypertensive patients.[39,40,41] The resulting hyperinsulinemia may cause endothelial dysfunction (ED), hypertension, dyslipidemia, central obesity, hypercoagulable state, VSM hypertrophy, atherosclerosis, sodium retention, increased SNS activity and glucose intolerance or DM, which may be exacerbated by diuretics and beta blockers.[39,40,41] Insulin resistance and all of its consequences can be treated and reversed with the implementation of a low fat (reduced saturated and trans fats with more polyunsaturated omega-3 fatty acids and monounsaturated fats), unrefined-carbohydrate diet without caloric restriction.[41]

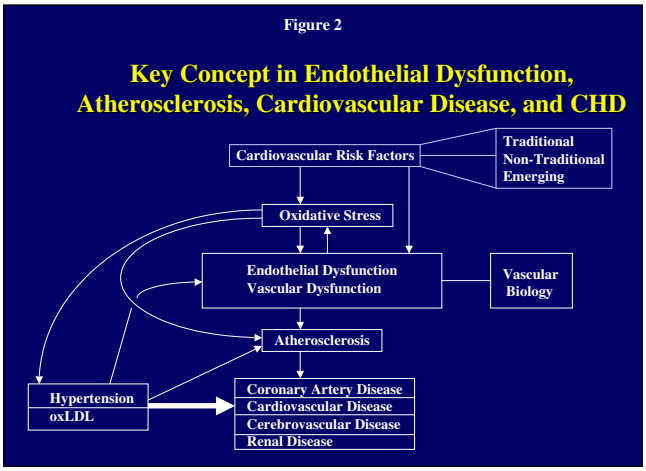
Abnormalities in renal function have been demonstrated in children of parents with hypertension compared to children of normotensive parents.[39,40] These include the inability to increase creatinine clearance after a protein load, more microalbuminuria and hyperuricemia.[39,40] These renal changes precede the onset of hypertension.

Neuroendocrine changes such as significantly elevated plasma renin activity (PRA) and plasma norepinephrine (NE) levels occur in normotensive children with hypertensive parents more often than normotensive children without a family history of hypertension, and these neuroendocrine changes precede the development of hypertension.[39,40]

It is apparent that normotensive children or adults with a family history of hypertension have a cardiovascular risk profile that is similar to hypertensive patients. This has led to the term "normotensive hypertension" to indicate that these subjects have not yet developed hypertension, which may be a late cardiovascular marker of vascular damage, but they are at risk to develop significant cardiovascular disease. The therapeutic implications of the hypertension syndrome are enormous. Early detection, aggressive lifestyle modifications including optimal nutrition, exercise, weight management, nutraceuticals, risk factor control and other daily lifestyle changes are mandatory to prevent cardiovascular disease and hypertension.

Hypertension is not just a simple disease consisting of elevated blood pressure, but is part of a complex syndrome. It is imperative that a new approach to prevention and treatment of hypertension be directed at treating the blood vessel, to optimize control of these abnormalities to maximally decrease TOD (Figure 1).





ARTERIOSCLEROSIS AND ATHEROSCLEROSIS

Although there are clear differences in arteriosclerosis and atherosclerosis, recent research in vascular biology indicates similar mechanisms that adversely effect the blood vessel and result in both processes. There is much overlap in pathogenesis, as well as in functional and structural outcomes (Table 3).[43] Treatment directed at endothelial dysfunction, vascular smooth muscle dysfunction and abnormal arterial compliance may slow or halt progression to arteriosclerosis and atherosclerosis.

ENDOTHELIAL DYSFUNCTION, OXIDATIVE STRESS, ATHEROSCLEROSIS, CARDIOVASCULAR RISK FACTORS AND CORONARY HEART DISEASE

Many traditional, nontraditional, and emerging cardio-

Table 3[43]

Arteriosclerosis and Atherosclerosis

Atherosclerosis	Arteriosclerosis (increased vascular stiffness, decreased vascular compliance)
-Focal, occlusive	-Diffuse, dilatory
-Inflammatory	-Fibrotic (elastin replaced by collagen)
-Endothelial dysfunction	-Adventitial and medial hypertrophy
-Related to LDL cholesterol oxidation	-Related to age and blood pressure
-"Inside-out"	-"Outside-in"
-Sensitive to angiotensin-II and other substances	-Sensitive to angiotensin-II and other substances

Dzau, Arch Intern Med 1993; 153: 937-42[43]

vascular risk factors can directly cause oxidative stress or endothelial dysfunction (ED) and vascular dysfunction leading to atherosclerosis, arteriosclerosis and TOD (Figure 2). Oxidative stress may induce hypertension and oxidize LDL cholesterol resulting in further ED, atherosclerosis and TOD. This cycle becomes self-perpetuating with progressive vascular damage and high cardiovascular morbidity and mortality.

THE BLOOD VESSEL

The blood vessel becomes the primary and central organ in the pathogenesis of cardiovascular disease and hypertension. The blood vessel structure is shown in Figure 3 and consists of the intima (endothelium and connective tissue), the media (vascular smooth muscle, a protein matrix of elastin and collagen, and an internal elastic lamina), and the adventitia with strong fibrous tissue to maintain vessel shape.[44,45]

The vascular endothelium is the largest endocrine organ and the largest organ in the body.[46] It is 14,000 ft^2 in surface area, the size of 6 1/2 tennis courts in square area, and 5 times the heart size in mass with a total weight of about 2 kilograms.[46,47,48,49,50,51] It is a metabolically active organ with endocrine, paracrine, autocrine and intracrine functions.

The vascular endothelium under normal, healthy physiologic conditions forms a continuous sheet of organized monolayer polyhedral cells that becomes disorganized at extremes of hemodynamic shear stress (hypotension and hypertension).[46,47,48,49,50,51]

Endothelial cells create a conduit that regulates blood flow through the tissues. Small vessels and capillaries consist primarily of endothelial cells, while larger vessels have additional components including connective tissue and smooth muscle that add strength and tone to the vessel.[46,47,48,49,50,51]

The endothelium, which forms a barrier between the blood and the tissues, is a living organ with multiple functions. The endothelial cells are tightly interlocked so that passage of products from the blood occurs through the endothelial cell. These cells are both a passive filter and a metabolically active organ that secretes substances into and out of the blood and into the underlying vascular smooth muscle, which regulates the local milieu.[46,47,48,49,50,51]

ENDOTHELIAL FUNCTION

The strategic location of the endothelium allows specific modulation of elements in the blood and vascular smooth muscle cell (Figure 4).[49,51] Modulation in the circulating blood controls platelet function, coagulation, monocyte and leukocyte adhesion and inflammation. Modulation of the vascular smooth muscle cells (VSMC) determines permeability, contractile state, proliferative or growth response, migratory response and redox state. The endothelium maintains vascular health by a carefully controlled balance of

Table 4[47,48,50,51]

Vascular Endothelial Function
Vasomotor Tone

Vasodilators	Vasoconstrictors
• Nitric Oxide (N0)	• Angiotensin-II (Ang-II)
• Prostacyclin (PGI_2)	• Endothelin-1 (ET-1)
• Endothelium -Derived Hyperpolarizing Factor (EDHF)	• Angiotensin-I (Ang-I)
	• Angiotensin-III (Ang-III)
• Bradykinin (BK)	• Thrombin
• Serotonin (S)	• Endoperoxides
• Histamine (H)	• Prostaglandin 2 (PG-2)
• Substance P (SP)	• Prostaglandin H_2 ($PG-H_2$)
• Angiotensin (1-7) (Ang 1-7)	• Thromboxane A_2 (TxA_2)
• C-Type Natriuretic Peptide (CNP)	• Serotonin (S)
• Adrenomedullin (AM)	• Arachidonic Acid (AA)
• Angiotensin (1-9) (Ang 1-9)	• Nicotine
	• Angiotensin-IV (Ang-IV)
	• Platelet Derived Growth Factor (PDGF)

Table 5[46,47,48,50,51]

Vascular Endothelial Function
Oxidative Stress
REDOX

Antioxidant	Oxidant
• Nitric Oxide (NO)	• Angiotensin-II (Ang-II)
• Bradykinin (BK)	• Endothelin-I (ET-1)
• COX-1, COX-2	• Cytokines
• Mn SOD, Cu / Zn SOD	• Growth Factors

Figure 3[44,45]

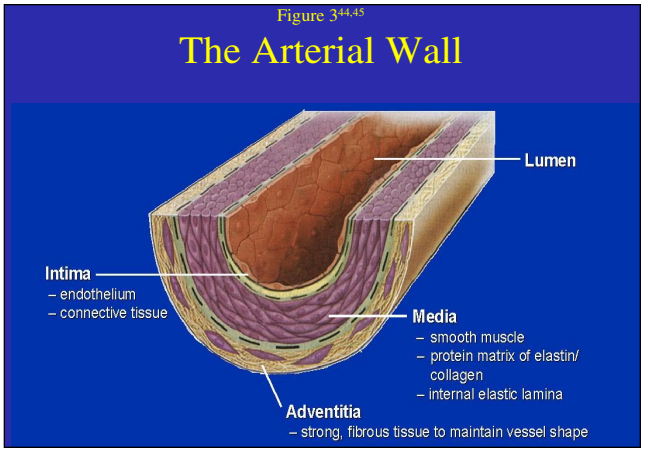
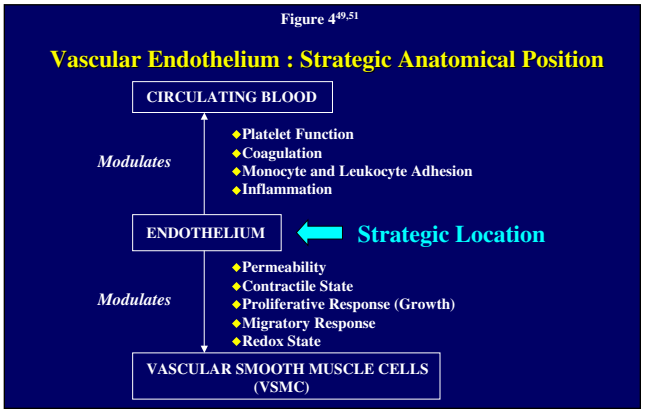
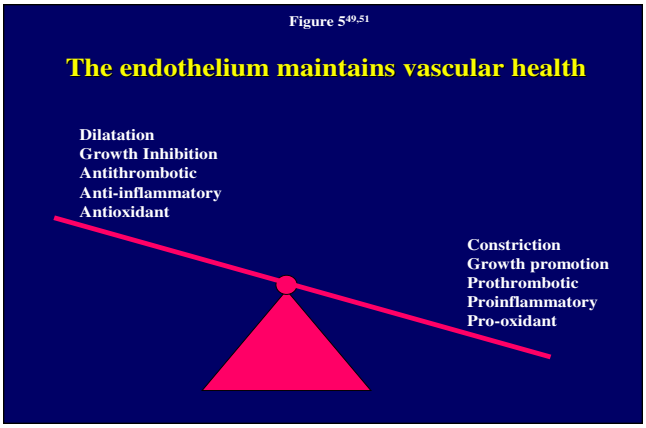


Figure 4[49,51]





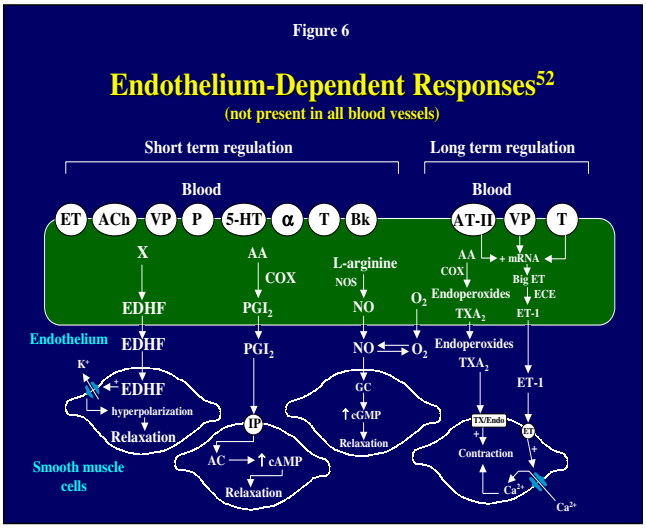
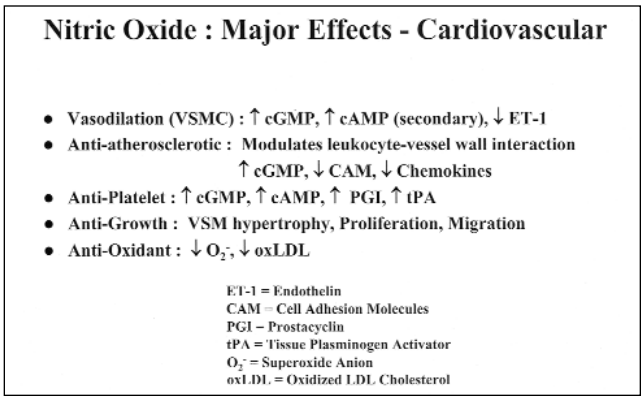
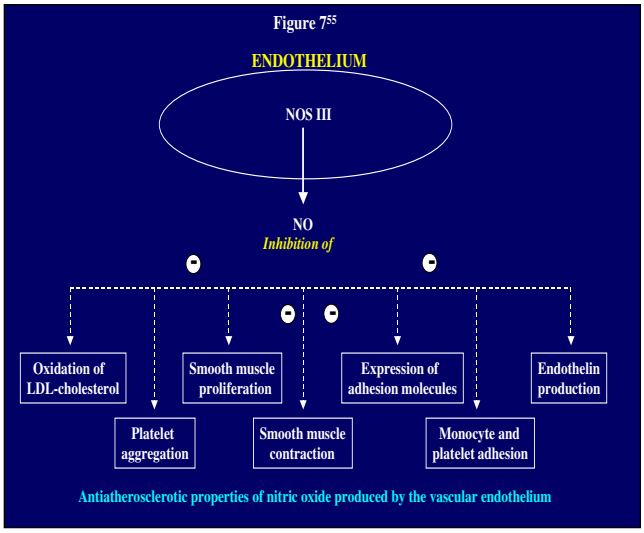


Table 6[57]





"good" or "bad" mediators (Figure 5).[49,51] Mediators that are involved in vascular tone[47,48,50,51] and redox state[46,47,48,50,51] are listed in Tables 4 and 5 respectively.

Endothelial activation and subsequent responses are shown in Figure 6.[52] Activation of endothelial receptors can stimulate nitric oxide (NO) synthase (NOS) with the production of NO and cyclooxygenase (COX), which produces prostacyclin [PGI_2] from arachidonic acid [AA]) and can lead to the release of endothelium-derived hyperpolarizing factor (EDHF). NO causes relaxation by activating the formation of cyclic GMP (cGMP) from guanosine triphosphate (GTP) by soluble guanylate cyclase (SGC). Prostacyclin (PGI_2) causes relaxation by activating adenylate cyclase (AC) leading to the formation of cyclic AMP (cAMP). EDHF produces hyperpolarization and relaxation by opening K^+ channels. Any increase in cytosolic calcium causes the release of relaxing factors. In certain blood vessels, contracting substances can be released from the endothelial cells, which include superoxide anions (O_2^-), thromboxane A_2 (TXA_2), endoperoxides and possibly endothelin-1 (ET-1). Thromboxane A_2 and endoperoxides activate specific receptors (TX/Endo) on the vascular smooth muscle, as does ET_1. Such activation causes an increase in intracellular Ca^{2+} leading to contraction. The production of ET-1 (catalyzed by endothelin converting enzyme [ECE]) can be augmented by angiotensin II (ATII), vasopressin (VP) or thrombin (T). The neurohumoral mediators, which induce the release of endothelium-derived relaxing factors (and sometimes contracting factors) through activation of specific endothelial receptors include: acetylcholine (ACh); adenosine diphosphate (ADP); bradykinin (BK); endothelin (ET); adrenaline (A); serotonin (5HT); thrombin (T); vasopressin (VP).

NITRIC OXIDE: CARDIOVASCULAR EFFECTS

Nitric oxide is the most powerful endogenous vasodilator. It maintains basal vascular tone, but is also produced and released both tonically and under stimulation.[48,52,53,54,55,56] It inhibits the atherosclerotic process and lowers blood pressure. Nitric Oxide is synthesized in the endothelium and vascular smooth muscle by nitric oxide synthase with a very short half-life of only a few seconds. Nitric Oxide is involved in numerous biologic functions,[57] but only its cardiovascular effects which include vasodila-

tion, anti-atherosclerotic, anti-platelet, anti-growth and anti-oxidant effects, will be considered here (Table 6)[57]. The results of NO inhibition are shown in Figure 7.[55]

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction occurs when the vascular endothelium undergoes a phenotypic modulation to a non-adaptive state characterized by the loss or dysregulation of critical homeostatic mechanisms that normally operate in healthy endothelial cells.[51] The endothelial cell, VSMC and emigrated leukocytes (EML) are all oxidant stress sensors and the source of the biologic modification response.[51]

The two major paradigms of endothelial activation are biochemical and biomechanical (Figure 8).[51] Activation results in release of numerous mediators with endocrine, paracrine, autocrine and intracrine actions. Endothelial activation and dysfunction is the key, initial event in vascular disease, present with only risk factors, but no atherosclerosis.[46,48,49,51,52,55,57,58] Endothelial dysfunction precedes intimal thickening by a decade and clinical atherosclerosis by several decades. Endothelial dysfunction has a high correlation with future cardiovascular events such as MI, percutaneous transluminal angioplasty, coronary artery bypass graft and sudden death.[58] Hypertensive patients demonstrate a reduction in endothelial vasodilators (EDV) in both peripheral and coronary arteries.[57] Some of the pathophysiologic stimuli and consequences are shown in Figure 9.[51] ED begets numerous vascular consequences, setting up a vicious cycle of increasing ED (Figure 10).[59] ED, therefore, leads to inappropriate vasoconstriction, reduced NO, PGI2, PGE, PGE3, increased platelet aggregation, thrombosis, vascular hypertrophy, proliferation, oxidative stress and vascular permeability that result in numerous vascular diseases such as atherosclerosis, hypertension, CHD and CVA.[60,61,62,63,64,65,66]

HYPERTENSION AND OXIDATIVE STRESS IN ANIMAL MODELS

Excess production of oxidants (reactive oxygen species [ROS]) and a deficiency of antioxidant systems contribute to hypertension and ED with endothelial-dependent impairment of vascular relaxation in the spontaneously hypertensive rat (SHR).[67] In fact, in the spontaneously hypertensive rt (SHR), the increase in reactive oxygen species (ROS) precedes the development of hypertension.[68] Increased ROS production in vitro and in vivo has been demonstrated in several animal models of hypertension.[68] These studies suggest that ROS participate in the development and maintenance of hypertension in the SHR. These ROS may be an early event in the pathogenesis of human hypertension.

The increased ROS in the SHR inactives NO, which reduces bioactive NO leading to vasoconstriction and hypertension.[69,70,71,72,73,74,75,76,77,78,79] Superoxide anion

Figure 8[51]

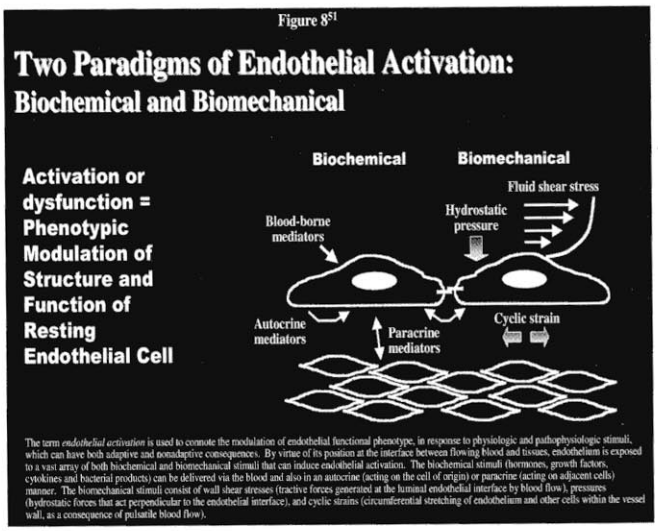


Figure 9[51]

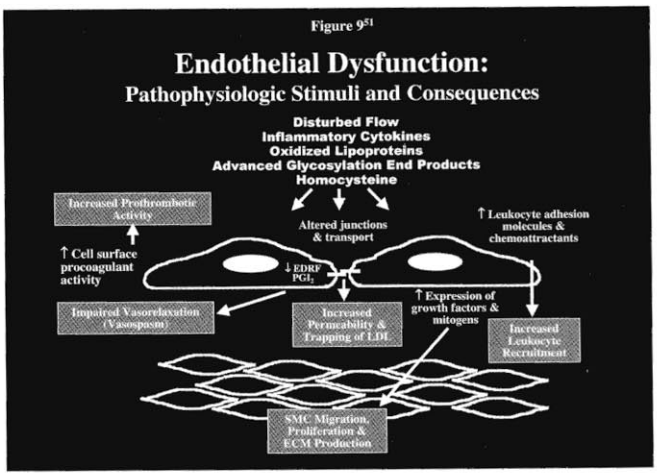
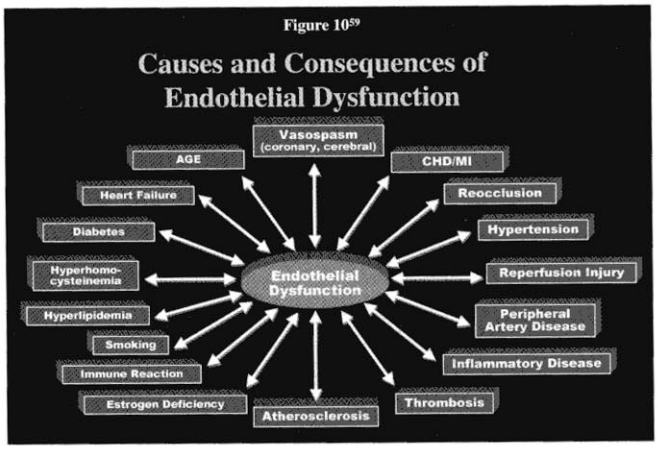


Figure 10[59]



(O_2^-) and other ROS have been shown to act avidly with NO and cause its inactivation with subsequent ED.[76,77,78,79,80,81,82,83,84] There is marked upregulation of renal, cardiac and vascular expressions of endothelial (eNOS), inducible (iNOS) and NOS proteins in young SHR.[69,70,71,72,73,74,75] This is due to ROS mediated reduction in NO bioavailability and reduced negative feedback on the regulation of NOS expression.

The proposed mechanisms of ROS induced hypertension in the SHR include inactivation of endothelium-derived NO,[76,78,84] nonenzymatic generation of vasoconstrictive F-2-isoprostanes from arachidonic acid peroxidation[79] and depletion of the NOS cofactor-tetrahydrobiopterin (BH_4).[77] Angiotensin II (A-II) will increase superoxide production (O_2^-) by the NAD(P)H oxidase in endothelial cells.[68,85,86]

Antioxidant administration ameliorates hypertension in the SHR supporting the concept that ROS play a role in the genesis and maintenance of hypertension.[26,78,79,87,88,89,90] Administration of tempol, a cell- permeable superoxide dimutase (SOD) to SHR lowers BP and increases NO.[78] Antioxidant treatment with ascorbic acid, glutathione, aminotriazol and vitamin E also reduces BP in SHR.[67] The vitamin E fortified diet in SHR will increase NO, reduce endothelial nitric oxid (eNOS) and lower BP.[69] Numerous antioxidants have the same effect, but these effects are not due to a nonspecific action of the antioxidant therapy. Antioxidant administration in the normotensive animal in the absence of oxidative stress does not change BP, urinary NO excretion, or NOS expression.[69,83,91]

There is emerging evidence that dietary factors, nutrients, vitamins and antioxidants play an important role in modulating endothelial dysfunction. Specifically, essential fatty acids (EFA), vitamins C and E, folic acid, arginine, coenzyme Q_{10} and others have a beneficial effect on endothelial function and possibly in preventing cardiovascular disease.[92,93]

HYPERTENSION AND OXIDATIVE STRESS IN HUMANS

Oxidative stress with an imbalance between ROS and the antioxidant defense mechanisms may contribute to the etiology of human hypertension, its initiation, maintenance, pathogenesis, pathophysiology and cardiovascular complications.[26,27,28,29,30,93] Oxidative stress has been implicated in many hypertensive disorders including lead-induced,[83,94,95,96] uremic, cyclosporin induced,[97,98,99,100] salt-sensitive,[101,102] preeclampsia, essential hypertension,[27,103,104,105,106,107] diabetes mellitus[108,109] and in hypertension induced by high fat, high refined carbohydrate diets.[110,111,112,113]

Hypertensive patients have an impaired endogenous and exogenous antioxidant defense mechanism.[27,28,29,30,114,115,116,117,118,119,120,121] This includes increased lipofuscin,[27,28,30,114] increased lipid peroxidation,[115,116] elevated plasma malondialdehyde (MDA) ($p < .05$),[27,28,30,114,116] reduced superoxide dismutase (SOD) in erythrocytes ($p < .005$)[115,116] and plasma,[27,116] reduced glutathione peroxidase ($p < .05$),[28,116,118] reduced vitamin A ($p < .05$),[114,116] reduced vitamin C,[114] reduced copper ($p < .005$),[116] reduced vitamin E ($p < .001$),[114,115, 116] lower NO levels,[27] and polyunsaturated fatty acids (PUFA) in red cell membranes,[28,120] reduced glutathione,[28,29] normal to reduced selenium levels,[116,121] and increased plasma hydrogen peroxide (H_2O_2) production.[119,122]

In addition, hypertensive patients have more oxidative stress with more ROS produced and a greater than normal response to oxidative stress.[67,68,85,86,115,116,119,122,123] This includes increased lipid peroxidation in serum and urine,[115,116] increased MDA in serum and urine,[27,28,30,114] elevated H_2O_2,[119] increased production of O_2^- by polymorphonuclear leukocytes (PMN's),[27,68,115] increased NADPH oxidase activity[86] and increased plasma zinc ($p < .001$).[116]

The proposed mechanisms of ROS-induced hypertension in humans is shown in Table 7.[27,28,29,30,124,125,126] Nitric oxide exerts a negative feedback on NOS expression in cultured human endothelial cells.[127] This leads to a compensatory upregulation of NOS by reducing NO bioavailability similar to that seen in lead,[83,91,94] uremic[100] and cyclosporin induced hypertension.[97] An imbalance of vasodilators (such as NO) and vasoconstrictors (such as A-II) and their interaction with ROS contribute to the initiation and perpetuation of hypertension (Figure 11).[128]

Antioxidant deficiency and excess free radical production have been implicated in human hypertension in numerous epidemiologic, observational and interventional studies.[84,86,93,123,129,130,131,132,133,134] Serum ascorbic acid (AA)

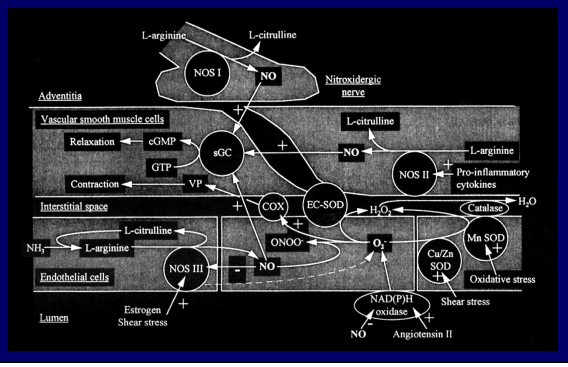
Table 7[27,28,29,30,124,125,126]

Hypertension and Oxidative Stress
ROS in Hypertension

Mechanisms of ROS in HBP
A. Direct action on endothelial cell with structural and functional damage
B. Degradation of NO by ROS
C. Effects on eicosanoid metabolism in endothelial cell
D. Oxidative modification of LDL-C (oxLDL)
E. Hyperglycemia
F. Hyperinsulinemia
G. ↑ Fatty acid mobilization
H. ↑ Catecholamines
I. Ang-II increase O_2 via NADPH oxidase

Figure 11[128]

ROS and NO



had the highest inverse association with systolic blood pressure (SBP) among risk factors for CVA, CVD, hypertension and hyperlipidemia.[131,135] Ceriello et al[132] demonstrated significant hypotensive effects with various antioxidants including ascorbic acid, glutathione and thiopronine in subjects with hypertension and diabetes mellitus. Normotensive control patients had no significant change in blood pressure.

Vitamin C increases endothelial vasodilation (EDVD) of epicardial coronary arteries in hypertensive patients.[136] Intravenous vitamin C, thiopronine and glutathione each significantly reduced BP in hypertensive patients.[132] In an eight week, placebo-controlled study of hypertensive subjects *vs* normotensive subjects,[137] the SBP was significantly reduced by 9 mm Hg ($p < .01$) and urinary NO (UNox) was reduced. A regimen of vitamin C 500 mg qd, vitamin E 600 IU qd, beta-carotene 30 mg qd and zinc 200 mg qd was prescribed. Combinations of various antioxidants may have additive or synergistic effects in neutralizing ROS, increasing NO and improving EDVD and lowering BP.

A summary of the present research and conclusions of the role of oxidative stress in animal and human hypertension is shown in Table 8. The interrelations of neurohormonal systems, oxidative stress and cardiovascular disease is shown in Figure 12.[138] The increased oxidative stress in human hypertension is thus a combination of increased generation of ROS, an exacerbated response to ROS and a decreased antioxidant reserve.[138,139] The ED, arachidonic acid metabolites, renin angiotensin aldosterone system (RAAS) and sympathetic nervous system contribute to increased ROS. Reduced antioxidant reserve is due to low intracellular, extracellular, enzymatic and nonenzymatic antioxidants (Table 9).[138]

Reactive oxygen species damage virtually every organelle, cell, and tissue in the body (Table 10).[138,139] Their primary and ultimate mechanism of damage is intracellular calcium overload secondary to injury of subcellular organelles.[138,139] ROS are actually second messengers that are involved in redox-sensitive transcription pathways mod-

Figure 13[140]

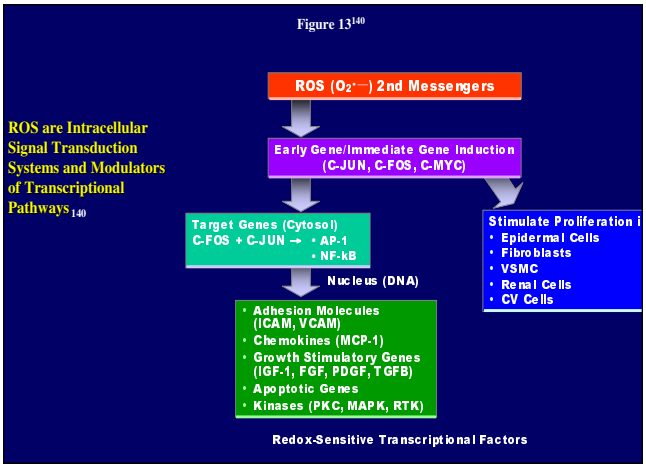


Table 8

Hypertension *and* Oxidative Stress
Animal Models *and* Human Studies

- **Impaired anti-oxidant status (Endogenous and Exogenous)**
- **More oxidative stress, more ROS production**
- **Greater than normal response to oxidative stress**
- **ROS contribute to E.D. in aorta and resistance arteries with imbalance of vasoconstrictors and vasodilators**
- **ROS is both cause and consequence of hypertension**
- **Antioxidants as single or combined agents reduce BP**
- **Inverse relationship between BP and antioxidant intake in observational and interventional studies.**
- **ED leads to VSM contraction, increased SVR and BP**

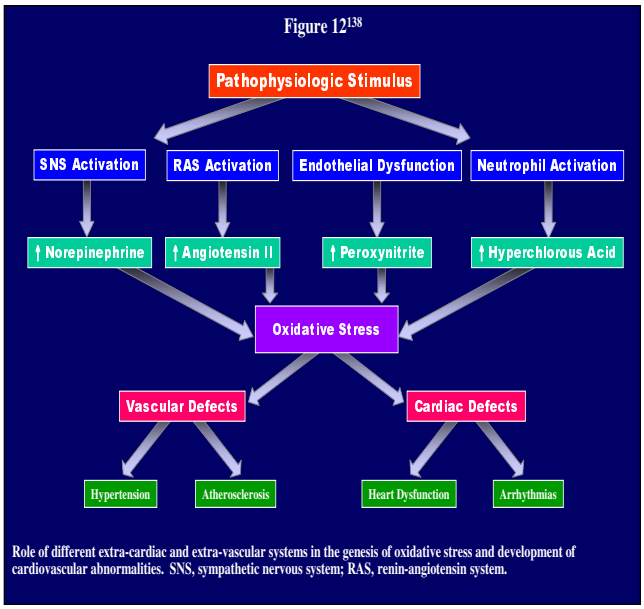
Table 9[138]

The Cytotoxic Reactive Oxygen Species and the Natural Defense Mechanisms

Reactive Oxygen Species		**Antioxidant Defense Mechanisms**	
Free Radicals		*Enzymatic Scavengers*	
$O_2^{\cdot -}$	Superoxide anion radical	SOD	Superoxide dismutase
$OH^{\cdot}$	Hydroxyl radical		$2O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + O_2$
$ROO^{\cdot}$	Lipid peroxide (peroxyl)	CAT	Catalase (peroxisomal-bound)
$RO^{\cdot}$	Alkoxyl		$2H_2O_2 \rightarrow O_2 + H_2O$
$RS^{\cdot}$	Thiyl	GTP	Glutathione peroxidase
$NO^{\cdot}$	Nitric oxide		$2GSH + H_2O_2 \rightarrow GSSG + 2H_2O$
$NO_2^{\cdot}$	Nitrogen dioxide		$2GSH + ROOH \rightarrow GSSG + ROH + 2H_2O$
$ONOO^-$	Peroxynitrite		
$CCl_3^{\cdot}$	Trichloromethyl	*Nonenzymatic scavengers*	
		Vitamin A	
Non-radicals		Vitamin C (ascorbic acid)	
H_2O_2	Hydrogen peroxide	Vitamin E (α-tocopherol)	
HOCl	Hypochlorous acid	β-carotene	
$ONOO^-$	Peroxynitrite	Cysteine	
$^1O_2$	Singlet oxygen	Coenzyme Q	
		Uric Acid	
		Flavonoids	
		Sulfhydryl group	
		Thioether compounds	

The superscripted bold dot indicates an unpaired electron and the negative charge indicates a gained electron. GSH, reduced glutathione; GSSG, oxidized glutathione; R, lipid chain. Singlet oxygen is an unstable molecule due to the two electrons present in its outer orbit spinning in opposite directions.

Figure 12[138]



Role of different extra-cardiac and extra-vascular systems in the genesis of oxidative stress and development of cardiovascular abnormalities. SNS, sympathetic nervous system; RAS, renin-angiotensin system.

ulating early and late gene induction with production of adhesion molecules, chemokines, cytokines, growth stimulatory genes, apoptotic genes and kinases in virtually all cells (Figure 13).[140]

Touyz and Schiffrin[141] studied vascular smooth muscle cells (VSMC) from peripheral resistance arteries of normotensive and hypertensive subjects. The generation of ROS, particularly H_2O_2 by angiotensin II (A-II) is augmented in the VSMC of the hypertensive subjects. These NAD(P)H oxidase-dependent processes are associated with increased activation of phospholipase D (PLD), which may influence the redox-sensitive pathways through protein kinase C (PKC) and phosphatidic acid that contribute to vascular structural changes in human hypertension.

Essential hypertension is not only associated with oxidative stress, but the level of BP is partially related to the level of oxidative stress.[142] Hypertensive patients compared to normotensive controls have significantly elevated GSSG/GSH index (oxidized glutathione / to reduced glutathione index), a measure of oxidative stress status, increased malondialdehyde (MDA), a lipid peroxidation product, elevated 8-OXO-2' deoxyguanosine (a measure of DNA damage), and decreased activity of three major enzymatic antioxidants including superoxide dimutase (SOD), catalase (CAD) and glutathione peroxidase (GPX). These indicators of oxidative stress correlate with urinary albumin excretion (UAE), left ventricular mass index (LVMI) and partially to BP. Hypertension-induced target organ damage is related to the level of oxidative stress, but this is, in part, independent of BP levels.[143]

WEIGHT LOSS AND HYPERTENSION

Observational and experimental studies indicate that excess weight (body mass index [BMI] > 25) and visceral obesity (waist circumference over 35 inches [88 cm] in women and over 40 inches [102 cm] in men) is positively and directly associated with elevated blood pressure[18] as well as dyslipidemia, diabetes, and CHD morbidity and mortality. Weight loss is one of the most effective means to significantly reduce BP[18,144,145,146,147,148,149] in overweight hypertensive patients,[150] overweight persons with high normal BP[150] and in nonobese, hypertensive patients, or those with high normal BP.[148] Reductions in BP occur before and often without weight loss to ideal body weight (IBW)[18,151] related to the beneficial effects of calorie restriction.[20] In the Trial of Hypertension Prevention I and II (TOHP I and II)[150,152,153] a 4.4 kg weight loss resulted in a 7/5 mm Hg reduction in BP in the short and long term evaluation (36 months).[150] A two pound weight loss reduced SBP 1 mm Hg and DBP 1.4 mm Hg. There was a direct weight-BP response relationship with greater weight loss resulting in greater BP reduction.[150] Even a modest weight loss reduced the risk of developing hypertension.[150] The short term and long term BP reduction persists as long as the weight is maintained.[18,32,154,155] Unfortunately, only 13% of subjects in TOHP II maintained weight loss at 3 years.[150] In a meta-analysis of 11 clinical trials, the average BP reduction was 1.6 mm Hg per kg for SBP and 1.1 mm Hg per kg for DBP.[18,151] Weight loss potentiates other nonpharmacologic and pharmacologic treatments[149] for hypertension and improves concomitant risk factors (glucose, insulin resistance and lipids).[5] The mechanisms[151] include lower insulin levels, improved insulin resistance, reduced intravascular volume and sympathetic nervous system activity with concomitant increased parasympathetic nervous system activity, decreased systemic vascular resistance, sodium/water diuresis, lower plasma renin and aldosterone levels, improvement in sleep apnea and decreases in levels of tumor necrosis factor alpha (TNF-a), macrophage migration-inhibitory factor (MMIF), interleukins and cytokines.[20,156,157,158,159,160,161,162,163,164,165,166,167]

In view of the crucial importance of a balance of macronutrients (protein, fats, carbohydrates) and micronutrients (Na^+, K^+, Mg^{++}, Ca^{++}, vitamins and antioxidants) in preventing and controlling BP through various pathophysiological pathways, weight loss should be achieved without imposing any nutritional deficiencies.[20] These goals were achieved in the HOT Study (Hypertension Optimal Treatment) at 30 months in which the weight loss group used fewer antihypertensive medications to achieve the same BP level as the control group.[149]

Table 10[138,139]

Oxidative Stress and CV Disease

ROS EFFECTS

- Lipid Peroxidation: (PUFA in membrane lipid bi-layer)
- Protein Oxidation: induces lipid and CHO auto-oxidation proteolysis
- Carbohydrate Oxidation
- DNA oxidation and damage
- Organic molecule oxidation
- Genetic machinery and gene expression
  Transcription factors and DNA synthesis

Table 11[175]

Relative Risk *for* Coronary Heart Disease *According to* Levels of Physical Activity*

	Energy expended in exercise each week (in KJ)				
	< 2100	2100-4199	4200-8399	8400-12,599	≥ 12,600
No. of men	2002	2354	3481	2145	2534
Relative CHD risk	1	0.9	0.81	0.8	0.81

* 1983 through 1997

Relative risk adjusted for age, body mass index, alcohol intake, hypertension, diabetes mellitus, smoking status, and early (< 65 y) parental death.

EXERCISE AND HYPERTENSION

Regular aerobic exercise significantly reduces established BP,[5,168,169,170] glucose, lipids, sympathetic nervous system (SNS) activity;[171] it reduces the risk of developing hypertension,[5,172] reduces cardiovascular disease risk,[173,174] lowers CHD risk,[175] and decreases all-cause mortality.[173,174] A meta-analysis of 13 controlled studies of regular exercise found a mean reduction in BP of 11.3 mm Hg/7.5 mm Hg.[168] A regimen of 5 to 7 days a week of exercise at 50 to 75% of VO_2 max (maximum oxygen consumption) for 30-45 minutes daily was required to sustain this effect.[5,168,176] In a recent study by Sesso et al,[175] an expenditure of 4,200 Kcal per week resulted in the optimal decrease in CHD risk.[175] Increases in exercise above this level to over 12,600 Kcal per week did not further reduce CHD beyond the 19% reduction noted at 4200 Kcal per week (Table 11). Exercise increases eNOS and NO, improves endothelial function in coronary and system circulation, which improves coronary artery blood flow to the ischemic myocardium, decreases systemic vascular resistance (SVR) and reduces BP.[171,177] Regular aerobic exercise and resistance training improve lean muscle mass, reduce total body fat, increase caloric expenditure and should be included as part of every hypertensive treatment program.

SMOKING AND TOBACCO

Cigarette smoking is a major risk factor for cardiovascular disease and hypertension.[5,178] A significant increase in blood pressure accompanies smoking. Smoking reduces the protection against cardiovascular disease from antihypertensive therapy.[178] The cardiovascular benefits of discontinuing tobacco use can be seen within one year in all age groups.[179] The lower amounts of nicotine contained in smoking cessation aids usually will not raise blood pressure.[180] Smoking causes vasoconstriction, increased sympathetic nervous system (SNS) activity, ED, hypertension, CVA and CHD.[10] All tobacco products should be completely eliminated.

EVOLUTIONARY NUTRITION

We have evolved from a pre-agricultural, hunter-gatherer society to one of commercial agriculture and highly processed, refrigerated and fast foods. This has imposed upon humans an unnatural and unhealthy nutritional selection process. Our genetic makeup is 99.9% that of our Paleolithic ancestors, yet our nutritional, vitamin and mineral intakes are vastly different.[181] The macronutrient and micronutrient variations of protein, fats, carbohydrates, fiber, sodium, potassium, magnesium and various vitamins and minerals contribute to the higher incidence of hypertension and other cardiovascular diseases through a complex nutrient-gene interaction (Table 12).[181,182,183,184] Poor nutrition, coupled with obesity, a sedentary lifestyle and minimal exercise, has resulted in an exponential increase in nutritionally-related pathophysiology and disease.[182] In particular, the high Na^+/K^+ ratio of modern diets has contributed to hypertension, stroke, CHD, CHF and renal disease.[33,148,185,186,187] In addition, the relatively low intake of omega-3 polyunsaturated fatty acids (PUFA), increase in omega-6 PUFA and trans fatty acids, has contributed to the high incidence of CHD, hypertension, and other cardiovas-

Table 12[181]

Evolutionary Nutritional Impositions[181]

Evolution from pre-agricultural, hunter-gatherer milieu to an agricultural, refrigeration society has imposed an unnatural and unhealthy nutritional selection process.

	Paleolithic Intakes	Modern Intakes
K^+	> 10,000 meq / day (256 Gms)	150 meq / day (6 Gms)
Na^+	< 50 mmol / day (1.2 Gms)	175 mmol / day (4 Gms)
Na^+ / K^+ ratio	< 0.13 / day	> 0.67 / day
Fiber	> 100 Gms / day	9 Gms / day
Protein	37%	20%
Carbohydrate	41%	40% - 50%
Fat	22%	30% - 40%
P/S Ratio	1.4	0.4

Ratio = Polyunsaturated to saturated fats

Table 13

Examples of Nutrient - Gene Interactions

- PUFA (Omega-3) : Cell differentiation, Growth, Energy metabolism, Energy balance and Insulin sensitivity[182,198,199]
- Sodium
  - QTL (Quantitative Trait Loci) in rats chromosome 10 and 12 with HSP (Heat Shock Protein) 27 gene ↑ stress response and ↑ SNS (Sympathetic Nervous System) activity with ↑ Na^+ intake[201]
  - Montreal Study : Na^+ + ETOH increases in BP more with low Ca^{++} intake[202]
  - Angiotensinogen Gene : AA vs GG in Na^+ BP response AA genotype had best response to low Na^+ intake, as well as to weight loss (TOPH) and DASH diet[152,153,193,200]
- Potassium[201,203]
  - Lower BP
  - ↓ CVA in SHR (Spontaneously Hypertensive Rats) and humans
  - ↑ Na^+/K^+ ATPase in VSMC (Vascular Smooth Muscle Cells) and SNS, increase in urinary kallikrein
- Obesity : ↓ leptin receptor gene → ↑ leptin → ↑ SNS → ↑ BP[201]
- Fetal Growth Retardation and Low Birth Weight due Abnormal GLUT-4 (Glucose Transport) gene Insulin Resistance → VSMH(Vascular Smooth Muscle Hypertrophy) → ↓ AC (Aortic Compliance) → ↑ BP + insulin resistance and NIDDM[201]

Figure 14[182,183,184,194,195,196,197]

Nutrient-Gene Interactions and Gene Expression ("The Interaction of Nature and Nurture")

- Nutrients determine amount and activity of specific proteins produced by human genome by functioning as regulators of:
  - A. Gene Transcription
  - B. Nuclear RNA processing
  - C. Messenger RNA stability and degradation

Determine and influence

- •Energy Metabolism
- •Cell Differentiation
- •Cell Growth

Table 14[201]

Forms of Genetic -Environmental Factors / Interactions

Factor	Type-I	Type-II	Type-III	Type-IV
Genetics Only	-	-	+	+
Environment Only	-	+	-	+
Genetics + Environment	++	++	++	++
Examples	Dahl Salt Sensitive HBP rat	NIDDM Pima Indians	Liddle's Syndrome	Obesity

cular and metabolic disorders such as diabetes mellitus and hyperlipidemia.[188,189,190,191,192]

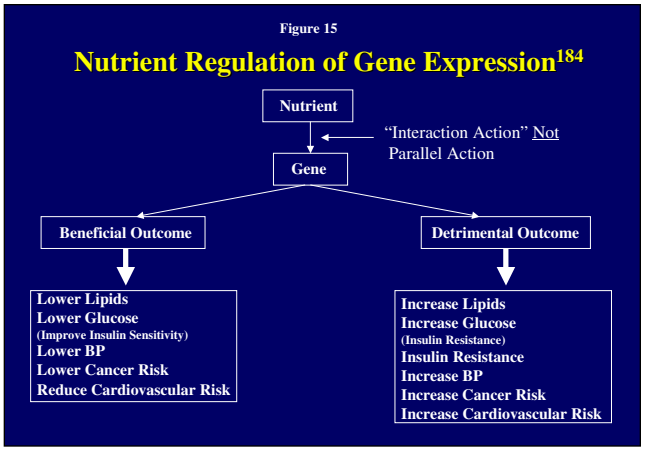
NUTRIENT-GENE INTERACTIONS

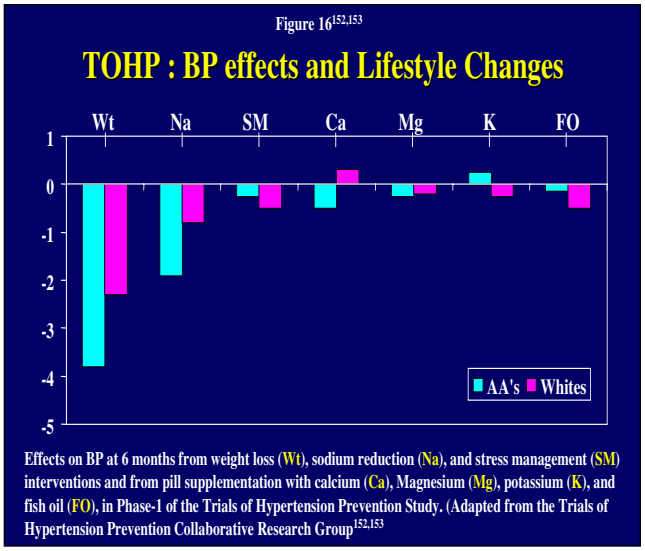
The human genetic pool remains basically unchanged for the past 35,000 years.[181] We are still genetically geared to a pre-agricultural, hunter-gatherer nutritional and exercise lifestyle. This includes, at a minimum, a low Na^+ intake (less than 2 grams per day), high K^+ intake (over 500 mEq per day), a K^+/Na^+ ratio > 5:1, low saturated fat (less than 10% total calories), high omega-3 PUFA, more monounsaturated fats with a total fat intake of 20-25% of total calories, high fiber (> 50 grams per day), moderate protein (30-35% total calories), moderate unrefined carbohydrate (35-40% total calories), no trans fatty acids and regular aerobic and resistance exercises performed daily.[33,148,182,186,187,188,189,190,191,192,193] Perhaps some alternating feasting and hunger would be healthful as well, as this was part of the Paleolithic lifestyle.

Nutritionally-related diseases such as diabetes mellitus, CHD, hypertension, CHF, cancer, and hyperlipidemia have reached epidemic levels in the U.S.[182,184] This is due, in part, to the drastic change in the amount and frequency of human exposure to selected undesirable and unhealthy macro- and micronutrients.[183]

Nutrients are powerful, influential factors to which the human genome is exposed. These nutrients determine the amount and activity of specific proteins by functioning as regulators of gene transcription,[182,184,194,195] nuclear RNA processing[182,184,196] and messenger RNA stability and degradation.[182,184,197] These factors, in turn, determine and influence energy metabolism, cell differentiation and cell growth[182] (Figure 14).

The clinical outcomes of nutrient regulation of gene expression can be beneficial with reduction of cardiovascular disease, BP, glucose and lipids or detrimental with an increase in cardiovascular disease, BP, glucose and lipids[184] (Figure 15). The omega-3 PUFA are strong determinants of cell growth, energy metabolism, energy balance and insulin sensitivity.[182,198,199] A ratio of omega-3 to omega-6 PUFA of between 1:1 to 4:1 is considered beneficial to cardiovascular health and approaches that of our Paleolithic ancestors and the Inuit Eskimos.[181]





Some examples of nutrient-gene interactions are shown in Table 13 for PUFA,[182,198,199] the Dietary Approaches to Stop Hypertension (DASH) diet[193,200] and the Trials of Hyperestion Prevention (TOHP) diet,[152.153] sodium[152,153,201,202,203] potassium,[201,203] obesity,[201] and fetal growth retardation.[201]

GENETICS OF HYPERTENSION

Hypertension is a complex interplay of susceptibility genes and environmental factors.[201] It is a multifactorial trait with multiple genes (polygenetic) involved in BP regulation and pathogenesis.[203,204] The multiple genes contribute to the specific phenotypes through epistasis (interactive effect of nonallelic genes on a phenotype) and pleiotropy (simultaneous effects of a single gene on multiple phenotypes).[201] The genetic-environmental action is not parallel, but is an interaction.[201]

Hypertension before age 55 is 3.8 times more common in patients with a positive family history than in those with

Table 15[18,148,152,153,187,193,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225]

Nutritional Intervention, Prevention and Treatment of Hypertension Trials
1 Health Professionals Follow-up Study : CVA reduction (K^+ intake)
2 Health Professionals Follow-up Study : CHD / MI reduction
3 Multiple Risk Factor Intervention Trial (MRFIT) : CHD reduction
4 Lyon diet Heart Study : CHD / MI reduction
5 Trials of Hypertension Prevention (TOHP-I & II) : BP prevention
6 Trial Of Non-pharmacologic intervention in Elderly (Tone) : BP reduction
7 Treatment Of Mild Hypertension Study (TOMHS) : BP reduction
8 Dietary Approaches to Stop Hypertension (DASH-I) : BP reduction
9 Dietary Approaches to Stop Hypertension (DAHS-II-Na^+) : BP reduction
10 Neonatal sodium restriction study : BP prevention x 15 years
11 Mediterranean Diet : BP reduction
12 Intermap : BP reduction (non-animal protein)
13 JNC-6 : BP reduction
14 AHA nutritional committee (BP reduction)
15 Cardiovascular Risk Reduction Dietary Intervention Trial (CVRRDIT)
16 Intersalt : BP reduction
17 Nurses Health Study
18 US Male Health Study
19 National Diet Heart Study
20. Vanguard Study

a negative family history.[201] Approximately 30-60% of the BP variations in a population are secondary to genetic factors. The remainder are secondary to the environment.[203,204] Monogenic hypertension due to a single gene mutation is quite rare and includes apparent mineralocorticoid excess (AME), Liddle's Syndrome (LS) and glucocorticoid suppressible hyperaldosteronism (GSH).[204]

Examples of genetic-environmental factors and interactions are shown in Table 14.[201] An inherited perturbation in renal sodium handling plays a significant role in genetic hypertension.[203] More than 50% of hypertensive patients are "salt sensitive," demonstrating increases in MAP of about 10% with increased sodium intake and reduction in BP with sodium intake reduction.[203] Potassium, magnesium and calcium are natriuretic and ameliorate salt-sensitive hypertension; whereas refined carbohydrates, saturated fats and trans fatty acids have anti-natriuretic and hypertensive potential.[203] In the Trials of Hypertension Prevention I (TOHP-I), the G-6A angiotensinogen gene was associated with responsiveness to dietary interventions.[152,153] Caucasians with the AA genotype of G-6A had lower BP and reduced incidence of hypertension from either reduced sodium intake or weight reduction compared to the GA or GG genotypes.[152,153] Similarly, in the (DASH-I[193,200] and DASH-II[187] studies, the best BP response occurred in individuals with the AA genotype, and the least response was in those with the GG genotype.

NUTRITIONAL INTERVENTION TRIALS IN HYPERTENSION[18,92,146,148,152,153,187,193,205-238]

Numerous nutritional intervention trials for the prevention and treatment of hypertension have demonstrated significant reductions in BP and target organ damage in hypertensive subjects, prevention of progression to higher BP in mildly hypertensive or subjects with high normal BP levels and reduction in antihypertensive medication use (Table 15).[18,92,146,148,152,153,187,193,205-238] The Trials of Hypertension Prevention (TOHP-I) noted significant reductions in BP with various lifestyle changes over a six month period[152,153] (Figure 16). The combination of weight loss and sodium restriction in TOHP-II resulted in a 60% reduction in incident hypertension at six months.[153]

Table 16[418]

Lifestyle Changes and SBP Meta-analysis of Clinical Diet Trials

Intervention	Reduction in SBP (mmHg)
↑ Mg^{++}	0-1
↑ Ca^{++}	2
↑ K^+	4
↓ ETOH	4
Fish Oil	6
↓ Na+	6
↓ Weight	8
Exercise	10
DASH diet	12

A recent meta-analysis of clinical nutritional and lifestyle changes evaluated the effects of numerous interventions on systolic BP[148] (Table 16). The most effective intervention was the DASH diet followed by exercise, weight loss, sodium restriction and fish oil supplements. The least effective were increased intake of magnesium, calcium and potassium, or reduction in alcohol intake.[148] This meta-analysis and other nutritional/diet studies emphasize the importance, the additive or synergistic effect of multiple nutrients, whole food and whole food concentrates with their nutrient combinations in a natural complex form to reduce BP and CVD.[18,92,146,148,205-217,225,239,240-244]

SINGLE VERSUS MULTINUTRIENT EFFECT

Single nutrient effects such as only sodium reduction or only increased intake of calcium, potassium or magnesium were not as effective in reducing BP as were seen in the Mediterranean diet,[205,206,207,208] the Cardiovascular Risk Reduction Dietary Intervention Trial (CVRRDIT),[208,209,210,211,212,213,214,215] the Treatment of Mild Hypertension Study (TOMHS),[208,216] the DASH-I[193]/DASH-II diets,[187] the Vanguard Study,[225] or the China Trial.[245]

The Mediterranean diets have effectively reduced BP, cardiovascular disease and MI.[205,206,207,208] In the Cardiovascular Risk Reduction Dietary Intervention Trial (CVRRDIT), 1141 subjects were studied over a four year period in a multicenter trial utilizing a comprehensive nutritional program with prepared meal plans *vs* controls.[208,209,210,211,212,213,214,215] Subjects with hypertension, hyperlipidemia and type II DM demonstrated significant

Table 17[193]

DASH-I Results
Overall : Hypertensives + Non-hypertensives

	Control	F + V	Combined
SBP	↓2 mmHg	↓4 mm Hg	↓7 mmHg
DBP	↓1 mmHg	↓2 mmHg	↓4 mmHg

- Non-hypertensive / borderline 3.5 / 2.1 mmHg (combined)
- Hypertensive patients 11.4 / 5.5 mmHg (combined)

Table 18[193]

DASH-I : Results
Hypertensive Patients

	SBP	DBP
Control	.72 mmHg	.28 mm Hg
F + V	7.3 mmHg	3.24 mmHg
Combined	11.4 mmHg	5.5 mmHg

Combined Diet = Pharmacologic Treatment Trials of Mild Hypertension

Table 19[187]

DASH-II Sodium Diet Results / Conclusions

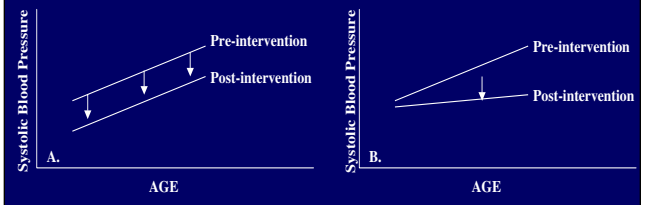
- Hypertensive Patients : Control High Na^+ vs DASH Low Na^+
  - SBP 11.5 mmHg ($p < 0.001$)
  - DBP 6.8 mm Hg ($p < 0.001$)
- Overall : Control High Na^+ vs DASH Low Na^+
  - SBP 8.9 mm Hg ($p < 0.001$)
  - DBP 4.5 mm Hg ($p < 0.001$)

reductions in BP, lipids, glucose, homocysteine levels and weight, with a concomitant increase in quality of life and increase in nutrient levels in the blood. In subjects with hypertension alone, the average reduction in BP was 6.4/4.2 mm Hg. In subjects with hypertension and hyperlipidemia, the reduction in BP was 12.4/7.2 mm Hg. These data suggest that subjects with more cardiovascular risk factors and greater vascular damage (more ED or reduced aortic compliance) have the greatest benefit from nutritional intervention. A five kg weight loss was maintained in most subjects at the end of four years.[215]

The DASH-I combination diet and the Treatment of Mild Hypertension Study (TOMHS) diets reduced BP to levels that can be achieved by drug therapy in patients with mild hypertension (i.e. 10.7/5.2 mm Hg).[193,208,216] Both diets emphasize eating fruits, vegetables, grains and low fat

Figure 17

Models of Hypertension Prevention[18]



A. Downward shift in age-related rise in blood pressure, without change in slope.
B. Downward shift in age-related rise in blood pressure, with change in slope.

dairy products similar to vegetarian diets. Observational and prospective clinical trials consistently show that vegetarians have lower rates of hypertension,[241] lower BP levels[18,217,241] and do not have the steep rise in systolic BP with age.[241] Vegetarians have mean arterial pressures of 10-15 mm Hg lower than non-vegetarians; and among vegetarians, those with the strictest vegetarian diets (no animal products) had the lowest BP.[239,240,241,242] The mechanism of BP reduction may be due to a combination of factors including combinations of natural micronutrients (K^+, Mg^{++}, Ca^{++}, Na^+), macronutrients such as MUFA, PUFA, low saturated and trans fatty acids, reduced total fat, elevated P/S ratio and fiber.[18,217,239,243,244] Both PUFA and MUFA incorporate into lipid membranes, improve fluid characteristics, permeability and increase Na^+/K^+ ATPase.[243] In addition, the omega-3 fatty acids increase vasodilatory prostaglandins, reduce systemic vascular resistance and lower BP.[244]

Approximately 15 to 60% of hypertensive patients withdrawn from antihypertensive drugs remain normotensive for nine months to three years following strict lifestyle modifications of alcohol and Na^+ restriction, weight loss and other nutritional and exercise counseling.[218,219,220,221,222,223,224]

Two models of hypertension prevention have been proposed.[18] Lifestyle modifications may cause a downward shift in age-related rise in blood pressure without a change in slope or cause a downward shift in age-related rise in blood pressure with a change in slope (Figure 17).

The Linxian China Randomized Nutritional Intervention Trial of 29,584 subjects over five years showed variable results on hypertension, stroke, and total mortality depending on the nutritional supplement that was used.[246] Subjects receiving Factor C (molybdenum and vitamin C) or Factor B (riboflavin and niacin) had small, but insignificant decreases in SBP and DBP of 0.50/0.24 mm Hg or 0.57/0.37 mm Hg respectively. Subjects receiving Factor D had reductions in total mortality of 9%, cancer reduction mortality of 13%, and stroke reduction of 9%. Factor D contained lipid soluble antioxidants and vitamins including beta-carotene, alpha-tocopherol, and selenium.

WHOLE FOOD BASED CONCENTRATES: FRUIT, VEGETABLE, AND FIBER EXTRACTS

Combinations of natural phytonutrients in a balanced form appears to provide better antioxidant protection, BP and CVD reduction than single "bullet type" nutrient supplementation as has been discussed.[18,92,146,148,152,153,187,193,205-224,239-246] Whole food concentrates of fruits, vegetables and fiber may provide additional nutrient value to the recommended eight to ten servings of fruits, vegetables and grains a day (about 400 grams/day) or ensure better nutrition in the form of an "insurance policy" when dietary intake is suboptimal for a variety of reasons. Several prospective clinical human trials have been published or are in progress on such a product..[247-254] These studies in humans have shown significant increases in serum[247,251] and lymphocyte antioxidant and vitamin levels[252] following oral ingestion, reduced oxidative stress,[247,251,252] weight reduction with increased lean body mass and reduced total body fat,[248] improved cellular immune function in lymphocytes,[249] reduced DNA damage in lymphocytes,[250] improved brachial artery flow-mediated vasodilation and improved endothelial function,[253] improved arterial compliance,[254] and a reduction in homocysteine and BP levels.[254] A two-year prospective trial is ongoing to evaluate the effects of this whole food concentrate on CHD regression or stabilization by Electron Beam Tomography (EBT).[254]

THE DASH DIETS[187,193] (DASH-I AND DASH-II-SODIUM) (Dietary Approaches to Stop Hypertension)

The DASH-I diet published in 1997 was a landmark nutritional trial in reducing blood pressure in hypertensive patients.[193] The DASH-II sodium diet published in 2001 confirmed the value of DASH-I, but proved that moderate to severe sodium restriction further enhanced BP reduction.[187] These nutritional studies are so important in the nonpharmacologic management of hypertension that they will be presented in detail.

The DASH-I diet was a two-month, multicenter, randomized, controlled prospective clinical trial of 379 subjects with borderline or Stage I hypertension (SBP ≤ 160 mm Hg and DBP 80-95 mm Hg), no concomitant diseases and on no antihypertensive drugs.[193] The average age was 45 years, two-thirds were minorities (60% black, 6% other races and 34% white). The design of the study and prescribed nutrition for the three treatment groups, which included control subjects, the fruit and vegetable (F + V) group and the combined diet (C) group, are shown in Figure 18. After a three week control diet in all subjects, randomization was to one of the three treatment groups above for eight weeks. The sodium content remained the same in all three groups at three grams per day. All diets were prepared and were well tolerated with a 93% adherence rate. There was no change in alcohol intake, weight, or sodium excretion during the study. Subjects met weekly with the investigators.

Table 20[187]

DASH-II Sodium Conclusions

- Reduction of sodium intake to 50 mmol/day from current recommendations of 100 mmol/day significantly reduces BP
- DASH combination diet with low sodium intake of 50 mmol/day lowers BP more in combination than either singly.
- Level of dietary sodium had twice BP reducing effect with the control diet than with DASH diet ($p < 0.001$)
- BP reductions occurred in all patients regardless of age, gender, ethnicity, or BP level (normals)
- Hypertensive patients, blacks and women had greatest BP reductions
- Low Na^+ intake attenuated the hypotensive effects of K^+ and Ca^{++}

Table 21[187,193]

Summary of BP Reductions in DASH-I and DASH-II Na^+ Diets Hypertensive Patients and Overall

	SBP	DBP
DASH-I Overall Combination Diet vs Control Diet	-5 mmHg	-3 mmHg
Dash I Hypertensive Pts. Comb. Diet vs Control Diet	-10.7 mmHg	-5.2 mmHg
DASH-II Overall Comb. Low Na^+ DASH Diet vs vs. Control high Na^+ Diet	- 8.9 mmHg*	- 4.5 mmHg*
DASH-II Hypertensive Pts. Comb. Low Na^+ DASH Diet vs Control high Na^+ Diet	-11.5 mmHg*	- 6.8 mmHg*

* = $p < 0.001$

The results of this clinical trial (shown in Tables 17, and 18 and Figure 19) demonstrate significant reductions in BP with controlled feeding and the described dietary modifications of increasing whole grains, nuts, poultry, fish, fruits, vegetables, K^+, Mg^{++} and Ca^{++} while reducing intake of saturated and trans fatty acids, red meat, sweets, sugars and other refined carbohydrates. The hypertensive subjects on the combined diet had the greatest BP reduction of 11.4/5.5 mm Hg. Minority subjects, especially blacks,[34] had greater reductions in BP compared to white subjects, and hypertensive subjects had greater BP reductions than normotensive subjects. Urinary Mg^{++} and K^+ increased in the "F + V" and "C" groups, while urinary Ca^{++} decreased in the "F + V" group. The urinary Na^+ remained constant in all three groups.

The reduction in BP occurred immediately, reaching near maximum levels at two weeks, but was sustained throughout the eight-week study. In addition, the quality of life improved in subjects on the "F + V" and "C" diets.[255] The combined treatment group had reductions in BP that were equal to that obtained with pharmacologic treatment of mild hypertension.[208,216] DASH-I emphasizes the importance of combined nutrients as they occur in natural food.

The DASH-II diet took the DASH-I diet one step further, proving that moderate to severe Na^+ restriction

Figure 18[193]

DASH-I : Trial Design

- Borderline or Stage-I hypertension (SBP < 160, DBP 80-95)
- Age average 45 yrs ; 2/3 minorities n=379
- No Anti-hypertensive drugs, otherwise healthy
- Protocol

Control diet x 3 weeks (C)

Na = 3 Gms / day
K+, Mg++, Ca++ = 25% U.S. average
Macronutrients = U.S. average (F + V 4 servings)
Na+ / K+ Ratio = 1.7
Fiber = 9 Gms / day

Control Diet	Fruit + Vegetable Diet (F + V)	Combined Diet (Comb)
	Na+ = 3 Gms / day	Na+ = 3 Gms/day
	K+, Mg++, Ca++ = 75% U.S. average	K+, Mg++, Ca++ = Same (75%)US ave
	F + V = 8.5 servings / day	F + V = 10 servings / day
	Na+ / K+ Ratio = 0.7	Na+ / K+ Ratio = 0.6
	Fiber = 31 Gms / day	Fiber > 31 Gms / day
		Low Fat Dairy = 2.7 servings/day

8 Weeks (all Diets)

Figure 19[193]

Mean Systolic and Diastolic BP at baseline and during each intervention week, according to Diet for 379 Subjects

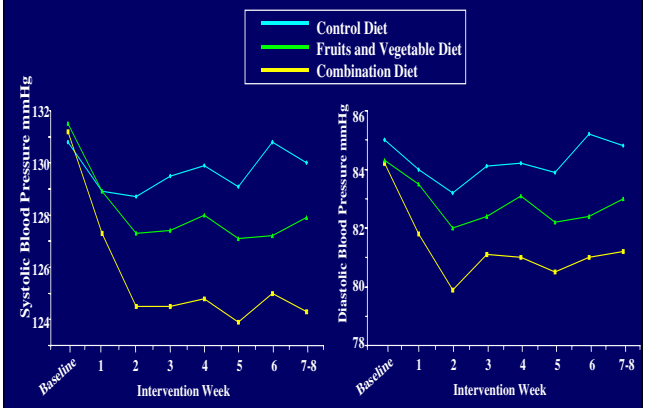
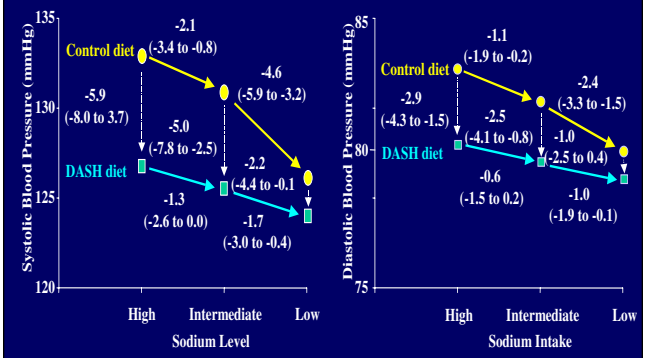


Figure 20[187]

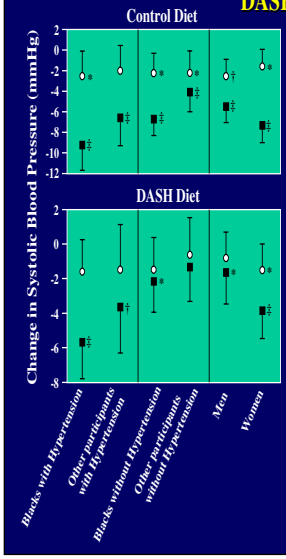
DASH-II Sodium Diet : Results



Sacks FM et al; *NEJM 2001; 344: 3-10 with permission*

Figure 21[187]

Effect of Dietary Na+ Intake on Subgroups in the Control & DASH Diet groups

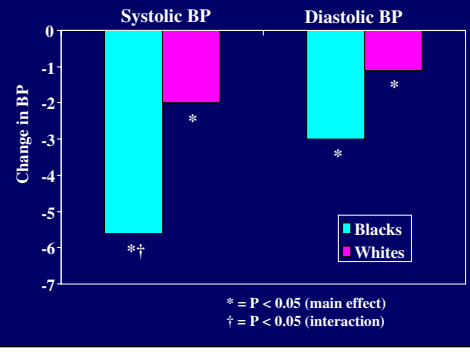


The error bars represent the 95 percent confidence limits of the changes in BP for each subgroup. Hypertension was defined as an average SBP of 140 to 159 mmHg or and average DBP of 90 to 95 mmHg during the three screening visits. The "other" category of race and ethnic group is composed primarily of non-Hispanic whites. Asterisks ($p \leq 0.05$), daggers ($p < 0.01$), and double daggers ($p < 0.001$) indicate significant differences between levels of sodium intake.

Sacks FM et al; *NEJM 2001; 344: 3-10 with permission*

Figure 22[33]

Effects *of* K+ Supplementation *on* BP *in* Trials *that* Enrolled Predominantly Blacks (>80%) *or* Whites: Results of a Meta-analysis

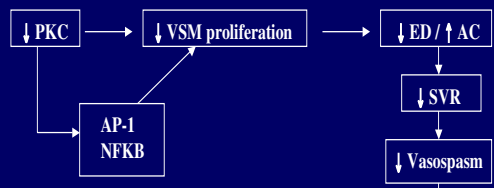


* = P < 0.05 (main effect)
† = P < 0.05 (interaction)

Figure 23[544,545,546,547,548,549,550]

Vitamin E : Mechanism in Hypertension and Vascular Disease

- α-Tocopherol inhibits thrombin-induced endothelin secretion in vitro at least partly through inhibition of PKC



- Insulin Sensitivity Improves
- Increased Total Antioxidant Status
- Increased NOS and NO
- Increased membrane and intracellular Mg++
- Increased Serum Glutathione Levels
- Reduces OxLDL

reduced BP even more in all three study groups.[187] This was a multicenter, randomized, controlled prospective study of 412 subjects on either a control diet or one of three DASH-Na^+ diets for 30 days (150 mmol, 100 mmol or 50 mmol Na^+ intake). The SBP and DBP reductions were significant with each incremental decrease in Na^+ intake (Figure 20, Table 19). The important conclusions and results of this study are shown in Table 20. Hypertensive subjects, blacks and women had the greatest BP reductions (Figure 21).

A comparison of the relative BP reduction in DASH-I and DASH-II in hypertensive subjects is shown in Table 21. The net BP reduction versus the control patient reduction was greatest in the DASH-II combination, low Na^+ (50 mmol) diet (-11.5/6.8 mm Hg).[187,193] The message from these two studies is clear. Hypertensive patients can achieve significant BP reductions that are equivalent to drug therapy used in mild hypertensive patients by combining a more severe Na^+ restriction of 50 mmol/day with the combination DASH-I diet. These benefits are immediate, sustainable, inexpensive, and improve nutrient levels and the individual's quality of life.

VANGUARD STUDY

Resnick and Oparil *et al*[225] recently published an important, unique and provocative clinical hypertension nutrition trial that confirms the results of DASH-I, DASH-II and other nutritional intervention trials, and added a new dimension by measuring biochemical parameters. Seventy-one untreated hypertensive or hypertensive-hyperlipidemic patients were given a prepared meal plan, CCNW (Campbell Center for Nutrition and Wellness), and compared to 87 normotensive, hyperlipidemic control subjects on a self-selected diet based on nutritional counseling for 10 weeks in a multicenter, randomized, controlled trial.

The BP fell significantly more in the hypertensive compared to the normotensive patients, -8/5 mm Hg *vs* -2/-2 mm Hg ($p < 0.0001$) respectively and on the CCNW versus the self-selected diet ($\triangle$ SBP/$\triangle$ DBP = $p = 0.033/p = 0.002$). Nutritional-induced weight loss had the highest correlation with BP change (SBP $p < 0.0001$ and DBP $p < 0.0001$). Some of the changes in SBP were correlated with fasting glucose ($p = 0.009$) and cholesterol ($p = 0.006$) in the multivariate analysis of the weight change effect on BP. Independent of weight, the nutritional-induced reduction in SBP significantly correlated with changes in urinary potassium excretion ($p < 0.001$), urinary magnesium excretion ($p < 0.003$), urinary calcium to sodium ratio ($p < 0.021$), serum potassium ($p = 0.002$), serum phosphorous ($p = 0.001$), parathyroid hormone (PTH) ($p = 0.0006$) and 1,25 dihydroxy vitamin D (1,25 vitamin D) ($p = 0.017$), but not to sodium per se (NS).

These results confirm the ability of a nutritionally sound diet to reduce BP, and also the importance of, and additive effects of, multiple nutrients, minerals and other dietary components in BP control. All study subjects on both diets had significant reductions in BP, but the CCNW diet had the largest effect especially in the combined hypertension-hyperlipidemic patients. The improved mineral metabolism mediated by vasoactive mineral-regulating hormones such as the parathroid (PTH) and 1,25 vitamin D correlated significantly and positively with urinary K^+, Mg^{++} and Ca^{++}/Na^+ ratio. The data are consistent with the DASH Diet Trial reflecting additive effects of multiple dietary components such as K^+, Mg^{++} and Ca^{++}, but supporting the significance of Na^+ only in relation to other minerals such as Ca^{++}, rather than as Na^+ per se. The enhanced antihypertensive effect of a multinutritional diet as opposed to single specific nutrient was seen in patients with more vascular disease or more CV risk factors (*i.e.* the hypertensive-hyperlipidemic patients). If these beneficial results can be sustained with a long-term nutrition program with education, nutritional counseling and possibly prepared meal plans, then hypertension control will be more easily achieved.

This trial and others[152,187,193,209,216,225] have recently focused on the role of naturally occurring nutrients in whole food as opposed to isolated dietary components in BP reduction. This, as we shall see with a few exceptions, is the key to controlling BP and the hypertension syndrome.

SODIUM (Na^+)

The average sodium intake in the U.S. is 5,000 mg per day though in some areas of the country people consume 15,000 to 20,000 mg per day.[14] However, the minimal requirement for sodium is probably about 500 mg per day.[14] Epidemiologic, observational and controlled clinical trials have clearly shown that an increased sodium intake is associated with higher blood pressure.[256] A reduction in sodium intake in hypertensive patients, especially the salt-sensitive patients, will significantly lower blood pressure with average reductions of 4-6 mm Hg systolic BP and 2-3 mm Hg diastolic BP.[18,24,187,257,258,259] The blood pressure reduction is proportional to the severity of sodium restriction.[18,187,260,261]

In the Trial of Hypertension Program I study (TOHP-I),[31] a 100 mmol sodium intake per day (2,400 mg) reduced the incidence of hypertension by 20% in a group of high risk subjects, improved hypertension control in elderly subjects on medications in the TONE Study,[32] reduced cardiovascular disease in obese subjects[186] and reduced proteinuria and progression of renal disease.[18,261,262] The TOHP-II Trial had a mean BP reduction of 2.9 mm Hg $\pm$ 1.6 mm Hg with moderate sodium restriction.[150] There was no rebound increase in sodium excretion at the end of intervention in TONE, indicating that the preferred amount of sodium in food is smaller after reduction in the sodium intake.[155]

The effect of dietary sodium on BP is modulated by other components of the diet.[20,228,245,263] A severe sodium restriction may concomitantly decrease other essential dietary compo-

nents such as calcium, potassium, fiber and protein that would adversely affect BP and cardiovascular risk.[263,264] Sodium chloride-induced hypertension is augmented by diets low in potassium,[20,228,245] calcium and magnesium[228,263,265] and attenuated by high potassium, magnesium and calcium (especially Na^+ sensitive). This is true only of sodium with chloride, not other anions.[263] An increased dietary intake of simple carbohydrates also augments the BP response to sodium chloride. The DASH-II diet is particularly instructive in this regard.[187] Gradual reductions in sodium from 150 mmol to 100 mmol to 50 mmol per day in association with a high fruit, vegetable and low fat dairy intake with adequate potassium, calcium, magnesium and fiber intake was the most effective in reducing BP.

Despite the enormous body of literature on "salt and hypertension", debate still exists as to a true causal relationship.[20,266,267] Nevertheless, sodium does have a major impact on cardiovascular, cerebrovascular and renal disease.[267-282] Studies have documented a direct relationship between sodium intake and increased platelet reactivity,[268] stroke (independent of BP),[269,270] left ventricular hypertrophy,[271] MI,[271] CHF,[271] sudden death[271] and left ventricular filling.[272] The renal plasma flow falls and glomerular filtration and glomerular filtration rate increase leading to an increase in intraglomerular capillary pressure, microalbuminuria, proteinuria, glomerular injury and renal insufficiency.[271,273,274,275,276] Sodium also reduces arterial compliance independent of BP changes.[277,278]

Salt sensitivity ($\geq$ 10% increase in MAP with salt loading) is a key factor in determining the cardiovascular, cerebrovascular, renal and blood pressure response to dietary salt intake.[279,280,281,282] Cardiovascular events are more common in the salt-sensitive patients than in salt resistant ones, independent of BP.[281,282] This may reflect specific target organ sensitivity and vulnerability to sodium that is unrelated to BP. In addition, salt sensitivity is most pronounced in elderly patients with isolated systolic hypertension and it is modified by polymorphisms of the angiotensinogen gene.[284] Salt sensitive patients do not inhibit their sympathetic nervous system activity[285] or increase NO production with salt loading.[286]

The evidence is very suggestive that reduction of dietary salt intake reduces target organ damage (brain, heart, kidney and vasculature) that is both dependent on the small BP reduction, and also independent of the decreased BP. However, it should be noted that higher sodium consumption has actually been associated with lower BP suggesting that nutritional deficiencies and relative serum levels or total body stores (K^+, Mg^{++}, Ca^{++}, vitamins, antioxidants and essential fatty acids) and not excess sodium cause hypertension.[20,225,228,287,288,289,290] On the other hand, strict dietary sodium restriction may increase the risk of nutrient, mineral, vitamin and antioxidant deficiencies due to a narrow and limited nutritional intake that could elevate BP.[20,287,288,289,290] Clearly, a balance of sodium with other nutrients is important, not only in reducing and controlling BP, but also in decreasing cardiovascular and cerebrovascular events.

In the Montreal Study on the relationship of Ca^{++} and Na^{++},[228] salt intake influenced BP only in those with a low Ca^{++} intake. Increased calcium intake has a depressor effect to increased Na^+ intake.[225] Other studies[234,291,292,293] have demonstrated that the response to calcium is closely linked to the effect of salt; the more that salt elevated BP, the more Ca^{++} lowered it. A decreased Ca^{++}/Na^+ ratio in the diet or a decreased urinary Ca^{++}/Na^+ ratio may predispose to higher BP in "salt-sensitive" hypertensive patients, which can be reversed by restricting Na^+ and/or increasing Ca^{++} intake.[225]

POTASSIUM (K^+)

The average U.S. dietary intake of potassium(K^+) is 45 mEq per day with a potassium to sodium ratio of less than 1:2.[14] The recommended intake of K^+ is 650 mEq per day with a K^+/Na^+ ratio of over 5:1.[14] Numerous epidemiologic, observational and clinical trials have demonstrated a significant reduction in BP with increased dietary K^+ intake.[14,18,294,295] The magnitude of BP reduction with a K^+ supplementation of 60 to 120 mEq per day is 4.4 mm Hg systolic and 2.5 mm Hg diastolic in hypertensive patients and 1.8/1.0 mm Hg in normotensive patients.[18,33,148,203] A meta-analysis of all K^+ supplementation clinical trials in the treatment of hypertension demonstrated a racial difference with black subjects having a more substantial reduction in BP compared to whites[33] (Figure 22). A high potassium intake is most effective in reducing BP in patients with diuretic induced hypokalemia,[18] those with a high Na^+ intake,[18,33,296,297] patients with salt-sensitive hypertension,[297] severe hypertension or a positive family history[297] and patients who are of African American[297] and Chinese descent.[296] Alteration of the K^+/Na^+ ratio to a higher level is important in both antihypertensive as well as cardiovascular and cerebrovascular effects.[265,296] High potassium intake reduces the incidence of cardiovascular and cerebrovascular accidents independent of the BP reduction.[20,148,185] Improvements in vascular smooth muscle function and structure, natriuresis, modulation of baroreflex sensitivity, direct vasodilation, reduced vasoconstrictive sensitivity to norepinephrine and angiotensin II, increased serum and urinary kallikrein, increased Na^+/K^+ ATPase activity and DNA synthesis and proliferation in vascular smooth muscle cells and sympathetic nervous system cells are some of the proposed mechanisms for the beneficial cardiovascular, cerebrovascular and antihypertensive effects of K^+.[20,203,297,298]

Gu *et al*[296] recently demonstrated for the first time that potassium supplementation at 60 mmol of KCl per day for 12 weeks significantly reduced SBP of –5.0 mm Hg (range –2.13 mm Hg to –7.88 mm Hg) ($p < 0.001$) in 150 Chinese

men and women aged 35 to 64 years. This study confirmed that the higher the initial BP, the greater the response. Finally, it showed that the urinary sodium-potassium ratio correlates best with BP reduction as does the dietary sodium-potassium ratio[265] compared to either urinary sodium or potassium individually.[296]

In addition, K^+ may have a Ca^{++}-conserving effect that would further minimize the effects of a high Na^+ intake.[299] The interactions of Na^+, Ca^{++}, K^+ and Mg^{++} are more important in BP control than are isolated changes in one mineral.[187,193,225,228,234,291,293,299]

MAGNESIUM (Mg^{++})

A high dietary intake of magnesium of at least 500-1,000 mg per day reduces BP in most of the reported epidemiologic, observational and clinical trials, but the results are less consistent than those seen with Na^+ and K^+.[14,18,148,152,203,256,300-306] In most epidemiologic studies, there is an inverse relationship between dietary magnesium intake and BP.[20,148,289,302,303,306,307,308,309,310,311] A study of 60 essential hypertensive subjects given magnesium supplements showed a significant reduction in BP over an eight week period documented by 24 hour ambulatory BP, home and office blood BP.[301] However, in the TOHP-I Trial, magnesium had a small insignificant and inconsistent effect on BP.[152] The intake of multiple minerals in a natural form such as Mg^{++}, K^+ and Ca^{++} is more effective than Mg^{++} alone in reducing BP.[203] Magnesium may also be effective in acute MI and atherosclerosis.[300]

Magnesium competes with Na^+ for binding sites on vascular smooth muscle and acts like a calcium channel blocker (CCB), increases PGE, binds in a necessary-cooperative manner with potassium, inducing (EDV) vasodilation and BP reduction.[14,256,289,311,312,313]

Witteman *et al* [314] treated 91 middle-aged and elderly women with mild to moderate hypertension on no antihypertensive medications in a double-blind placebo controlled study given magnesium asparate-HCL, 20 mmol per day (485 mg of Mg^{++}) *vs* placebo for six months. The SBP fell 2.7 mm Hg ($p < 0.18$), DBP fell 3.4 mm Hg ($p < 0.003$), urinary Mg^{++} increased, but the lipid profile did not change. The BP response was not associated with baseline magnesium status.

Magnesium is an essential co-factor for the delta-6-desaturase enzyme that is the rate-limiting step for conversion of linoleic acid (LA) to gamma-linolenic acid (GLA).[289,315,316,317] GLA elongates to form DGLA (dihomo-gamma-linoleic acid), the precursor of prostaglandin E_1 (PGE_1), a vasodilator and platelet inhibitor.[289,315] In hypomagnesemic states, insufficient amounts of PGE_1 are formed, leading to vasoconstriction and increased BP.[289,316]

Magnesium regulates both SBP, DBP, intracellular Ca^{++}, Na^+, K^+ and pH as well as left ventricular mass, insulin sensitivity and arterial compliance.[310,311] Newer techniques such as P-Nuclear Magnetic Resonance (NMR) and Mg^{++}-specific ion-selective electrodes (ISE) that measure intracellular and extracellular free levels of magnesium will enhance the understanding of the role of Mg^{++} in hypertension.[310]

CALCIUM (Ca^{++})

While population studies show a link between hypertension and calcium,[14,148,318] clinical trials that administer calcium supplements to patients have shown inconsistent effects on BP.[18,319,320] Higher dietary calcium is not only associated with a lower BP, but also with a decreased risk of developing hypertension.[148,321] A 23% reduction in the risk of developing hypertension was noted in those individuals on greater than 800 mg per day compared to those on less than 400 mg per day.[148,322]

A recent meta-analysis of the effect of Ca^{++} supplementation in hypertensive patients found a reduction in systolic BP of 4.3 mm Hg and diastolic BP of 1.5 mm Hg.[293,323,324] Foods containing Ca^{++} were more effective than supplements in reducing BP.[293,324] Karanja *et al*[325] assessed the effects of $CaCO_3$ (calcium carbonate) *vs* calcium contained in the diet and found significant increases in magnesium, riboflavin and vitamin D in the dietary group that correlated with Ca^{++} intake. There is an additive or synergistic effect on BP reduction with combination minerals and vitamins as compared to Ca^{++} alone.[187,193,225]

The TOHP-I tested the individual effects of several micronutrients and other dietary factors on BP[152] in hypertensive patients with a DBP of 80-89 mm Hg. Increases in dietary Ca^{++} and Mg^{++} had little effect on BP, whereas Na^+ restriction and weight loss produced significant decreases in BP.[152]

The response to Ca^{++} intake may be dependent on the population or hypertensive subtype that has been studied.[203,321.326] Those patients with the most reduction in BP with Ca^{++} supplements include blacks, those with low-renin hypertension, the elderly, pregnant women (pregnancy-induced hypertension [PIH]), Na^+ sensitive hypertensives, those on a high Na^+ intake, type II DM and postmenopausal women.[203,321,326]

The heterogeneous responses to calcium supplementation have been explained by Resnick.[327] There are two underlying calcium-related mechanisms. One is salt-sensitive, low renin and calcium antagonist-sensitive, which is dependent on impaired cellular calcium uptake from the extracellular space. The other is salt-sensitive, renin-dependent and calcium-antagonist-insensitive, which is dependent on increased cellular calcium released from intracellular sites. Reduced dietary calcium may deplete calcium from all membrane storage sites causing a less stable membrane of vascular smooth muscle cells.[327,328]

When calcium is present in optimal concentrations, it stabilizes vascular membranes, blocks its own entry into cells and reduces vasoconstriction.[20,316,329] Calcium in combination with other ions such as Na^+, K^+ and Mg^{++} provides ionic balance to the vascular membrane, vasorelaxation and reduced BP.[289,330]

This "ionic hypothesis"[331] of hypertension, cardiovascular disease and associated metabolic, functional and structural disorders is characterized by the following:[331-344]

1. Increased intracellular free Ca^{++} and reduced intracellular free Mg^{++} which determine the relative vasoconstriction or vasodilation.[332,333]
2. Elevated glucose and LDL-C increase the intracellular Ca^{++} and/or lower intracellular Mg^{++} in VSM cells.[334,335]
3. Hypertension, insulin resistance and type II DM are characterized by increased intracellular Ca^{++} and decreased intracellular Mg^{++} and all respond to weight loss.[336,337,338]
4. Weight loss decreases intracellular Ca^{++} levels.[236]
5. Dietary Ca^{++} suppressible hormones like PTH, 1,25 vitamin D are vasoactive and promote Ca^{++} uptake in VSM cells and cardiac muscle.[339,340,341]
6. The higher the PTH level, the greater the fall in BP and the greater the reduction in PTH and 1,25 vitamin D, the greater the BP reduction.[225]
7. Salt-sensitive and Ca^{++}-sensitive hypertension have elevated intracellular Ca^{++}, PTH and 1,25 vitamin D, but low intracellular Mg^{++}.[342]
8. Dietary Ca^{++} reverses abnormal calcium indices and lowers BP.[343]
9. Dietary K^+ reduces urinary Ca^{++} excretion and 1,2 vitamin D plasma levels.[235]
10. Mg^{++} intake reduces tissue Ca^{++} accumulation.[344]

The overall effect of nutrition and diet on BP is thus determined by the net contribution of multiple nutritional components on cytosolic free mineral ions such as Ca^{++} and Mg^{++}. Direct ionic effects on glucose or Ca^{++} and ionic effects on hormones (PTH, 1,25 vitamin D) regulate these steady-state mineral concentrations.[225]

ZINC (Zn^{++})

Low serum zinc levels in observational studies correlate with hypertension as well as CHD, type II DM, hyperlipidemia (especially hypertriglyceridemia and low HDL-C), elevated lipoprotein a (Lp(a)), two-hour postprandial plasma insulin levels and possibly insulin resistance.[345] Elderly hypertensives with very low plasma renin activity (PRA) have high urinary excretion of Zn^{++} and low serum levels a condition partially corrected by the administration of oral calcium > 800 mg per day.[346] There is a close relationship between Zn^{++}, Ca^{++}, Na^{++}, Mg^{++} and K^+ in various hormonal systems (SNS, RAAS) that modulate BP.[346,347]

Galley *et al* administered antioxidants to 40 hypertensive and normotensive adult subjects in a randomized, double-blind, crossover design placebo-controlled study for eight weeks.[137] The antioxidants administered were zinc sulfate 200 mg per day, ascorbic acid 500 mg per day, alpha-tocopherol 600 mg per day, and beta carotene 30 mg per day. The SBP decreased significantly in the hypertensive subjects ($p < 0.01$) and decreased in the normotensive subjects ($p < 0.067$). Increases in plasma levels of antioxidants and increased urine nitrate excretion occurred in the hypertensive subjects, suggesting an increased bioavailability of NO.[137]

Bergomi *et al*[348] evaluated Zn^{++} and Ca^{++} status in 60 hypertensive compared to 60 normotensive control subjects. An inverse correlation of BP and serum Zn^{++} was observed, but there was a direct correlation with serum Ca^{++}. The BP was also inversely correlated to a Zn^{++} dependent enzyme-lysyl oxidase activity. Zn^{++} inhibits gene expression and transcription through nuclear factor kappa-beta (NFK-B) and activated protein-1 (AP-1).[345] These effects plus those on insulin resistance, membrane ion exchange, RAAS and SNS effects may account for Zn^{++} antihypertensive effects.[345,347] Zinc intake should be between 15-30 mg per day.

PROTEIN

Observational and epidemiologic studies indicate an association between high protein intake and a reduction in BP in Japanese rural farmers, Japanese-American men in Hawaii, American men in two cohort studies, British men and women, Chinese men and women and American children.[18,349,350,351,352] The protein source is an important factor in the BP effect; animal protein is less effective than nonanimal protein.[18,353] However, lean or wild animal protein with less saturated fat and more essential omega-3 and 6 fatty acids may reduce BP, lipids and CHD risk.[352,353,354] The Intermap Study, a large international observational study showed an inverse correlation of BP with total protein intake and with protein intake from nonanimal sources.[353]

The Intersalt Study[350] supported the hypothesis that higher dietary protein intake has favorable influences on BP. The study evaluated 10,020 men and women in 32 countries worldwide and found that SBP and DBP were 3.0 mm Hg and 2.5 mm Hg lower respectively on average for those whose dietary protein was 30% above the overall mean than for those 30% below the overall mean (81 gm/day versus 44 gm/day).

Fermented milk supplemented with whey protein concentrate significantly reduced BP in animal models (rats) and human studies.[355] Kawase *et al* studied 20 healthy men

given 200 ml of fermented milk/whey protein BID for eight weeks. The SBP was reduced ($p < 0.05$), HDL-C increased ($p < 0.05$) and TG fell ($p < 0.05$) in the treated compared to the control group.[355] Natural bioactive substances in milk and colostrum including minerals, vitamins and peptides have been demonstrated to reduce BP.[356] Milk ingestion increases protein, vitamins A, D and B_{12}, riboflavin, pantothenate, calcium, phosphorous, magnesium, zinc and potassium.[357] These findings are consistent with the combined diet of fruits, vegetables, grains and low fat dairy in DASH-I and DASH-II studies in reducing BP.[187,193]

Soy protein at intakes of 25 to 30 grams/day lowers BP and increases arterial compliance[358,359] as well as reducing LDL-C and total cholesterol (TC) by 6 to 7% and reducing LDL-C oxidation.[358,359] Soy contains many active compounds that produce these antihypertensive and hypolipidemic effects including isoflavones, amino acids, saponins, phytic acid, trypsin inhibitors, fiber and globulins.[358,359]

Laplante *et al*[360] recently evaluated the effects of genistein, an active ingredient in soy, on the BP of angiotensin-treated hypertensive rats. Blockade of tyrosine kinase (TK) pathway with genistein significantly reduced SBP ($p < 0.05$) when exposed to A-II infusion. In addition, the superoxide anion radical concentration in aortic tissue decreased ($p < 0.05$), and the extracellular signal-regulated kinases-mitogen activated protein kinases (ERK-MAPK) pathway activity was suppressed ($P < 0.05$). These results suggest that genistein lowers BP by decreasing ERK-MAPK activity and superoxide anion radical in A-II related hypertension. Other studies have shown that genistein inhibits tyrosine kinase activity, reduces ROS by a direct antioxidant effect or protects tyrosine phosphatases, which shifts the balance of protein phosphorylation-dephosphorylation reactions.[361] Phosphorylation of proteins by tyrosine kinases and other protein kinases escalates signal transduction pathways, which induces growth promotion, platelet aggregation, VSM hyperplasia and hypertrophy, increased vascular resistance and BP.[361] Numerous foods are abundant in genistein and daidzein such as currants, raisins, hazelnuts, peanuts, coconuts, passion fruit, prunes, as well as many other fruits and nuts.[362]

In two unpublished studies by Pitre *et al*[363] in SHR, hydrolyzed ion-exchange whey protein isolate (BioZate-1™, Davisco, Eden Prairie, Minnesota) demonstrated significant reductions in mean arterial pressure and heart rate compared to an ion-exchange whey protein isolate. BioZate-1™ at an oral dose of 30 mg/kg, 75 mg/kg, and 150 mg/kg reduced mean arterial pressure by 10 to 18% and HR 10% that was sustained for 24 hours ($p < 0.05$ for both). The maximum effect was at one to six hours after dosing. These data indicate that the whey protein must be hydrolyzed in order to exhibit an antihypertensive effect, and the maximum BP response is dose dependent.

Bovine casein-derived peptides and whey protein-derived peptides exhibit ACEI activity.[355,356,364,365] These components include B-caseins, B-lg fractions, B2-microglobulin and serum albumin. Whey protein hydrolysates exhibit both *in vitro* and in vivo ACEI and antihypertensive activity *in vivo* animal and human studies.[355,356,357,363,364,365] The enzymatic hydrolysis of whey protein isolates releases ACEI peptides.[363] The relative in vitro ACEI activity (IC50 – the amount of the substance that causes a 50% inhibition of ACE activity – is 0.45 mg/ml for BioZate-1™, 376 mg/ml for whey protein isolate, compared to 1.3×10^{-6} for captopril).

Sardine muscle protein, which contains Valyl-Tyrosine (VAL-TYR), significantly lowers BP in hypertensive subjects.[366] Kawasaki *et al* treated 29 hypertensive subjects with 3 mg of Valyl-Tyrosine sardine muscle concentrated extract for four weeks and lowered BP 9.7 mm Hg/5.3 mm Hg ($p < 0.05$).[366] Levels of A-I increased as serum A-II and aldosterone decreased indicating that Valyl-Tyrosine is a natural angiotensin converting enzyme inhibitor (ACEI). No adverse effects were noted during the clinical study.

A similar study using a wheat germ hydrolysate, which contains Ile-Valyl-Tyrosine (ILE-VAL-TYR) significantly reduced BP in the SHR model.[367] The mean arterial pressure MAP fell between 10.3 and 19.2 mm Hg after intravenous injection of 5 mg/kg to 50 mg/kg of the wheat germ hydrolysate. This hydrolysate has the natural ACEI (ILE-VAL-TYR), which is also metabolized by aminopeptidase to Valyl-Tyrosine (VAL-TYR), an ACEI.

In addition to ACEI effects, protein intake may also alter catecholamine responses and induce natriuresis.[368] The optimal protein intake, depending on level of activity, renal function, stress and other factors, is about 1.0 to 1.5 gm/kg/day.[369,370]

Table 21A[239]

FATS and BP
Meta-Analysis and Study Review 1994

• Total Fat :	one : ↓ SBP	
	two : ↑ BP	
	8	: No change BP
• PUFA :	9	: No change BP
	1	: ↓ BP
• N-6 PUFA :	1	: ↓ BP
	1	: No change BP
• N-3 PUFA	1	: ↓ BP
• PUFA / SFA Ratio	5	: No change in BP
• MUFA	2	: ↓ BP
	5	: No change in BP
• SFA		: No change in BP

PUFA = Polyunsaturated Fatty Acids
SFA = Saturated Fatty Acids
MUFA = Monounsaturated Fatty Acids

FATS

Observational, epidemiologic, biochemical, cross-sectional studies and clinical trials of the effect of fats on BP have been disappointing and inconsistent.[239,371,372,373,374] However, many of these studies have probably missed small associations, were prone to inaccurate measurement of diet through recall or recording, had inadequate or incorrect BP measurement and did not correct for numerous dietary or nondietary confounding factors.[239] An exhaustive meta-analysis and review of these studies is reported by Morris (Table 21A).[239]

In the National Diet Heart Study, there was no change in BP with a polyunsaturated to saturated fat ratio (P/S ratio) in the range of 0.3 to 4.5 in 1,218 subjects over a 52-week study period.[239,371] The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated that consumption of an extra six grams of trans fatty acids (TFA) per day increased SBP 1.4 mm Hg and DBP 1.0 mm Hg.[372] However, the addition of two grams per day of linolenic acid reduced mean BP by 1.0 mm Hg.

Two large prospective clinical studies, the Nurses Health Study (NHS)[373] and the U.S. Male Study (USMS),[374] showed a neutral effect on BP by all fats studied. In the NHS, 58,218 disease free nurses were evaluated for the incidence of hypertension over a four-year period. A diet questionnaire was used; all confounding factors were controlled during the study. Multivariate analysis showed that the incidence of hypertension was not associated with total fat, saturated fat, and polyunsaturated fat (linoleic acid), or trans fatty acids.[373] Similarly, in the USMS, of 30,681 U.S. male health professionals, which was also a four year study that controlled for confounding factors, the incidence of hypertension was not associated in multivariate analysis by total fat, saturated fat, polyunsaturated fat or trans fatty acids.[374]

However, the type of fat, total daily intake, and relative ratios of fat intake may be more important in determining the BP effect in patients. This is particularly true of the polyunsaturated fats (PUFA) and monounsaturated fats (MUFA), which include omega-3 fatty acids (W-3), omega-6 fatty acids (W-6) and omega-9 fatty acids (W-9) (Table 22 and Table 23). The W-3 FA and W-6 FA are essential fatty acid families, whereas W-9 FA (oleic acid) can be manufactured by the body from the dietary precursor stearic acid.

OMEGA-3 PUFA (OMEGA-3)

Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) comprise the primary members of the omega-3 PUFA family (Table 23). Omega-3 fatty acids are found in cold water fish (herring, haddock, Atlantic salmon, trout, tuna, cod and mackerel), fish oils, flax, flax seed, flax oil and nuts.[14,375] Omega-3 PUFA significantly lowers BP in observational, epidemiologic and some small prospective clinical trials.[14,18,239,376,377,378,379,380,381,382] A meta-analysis of 31

Table 22

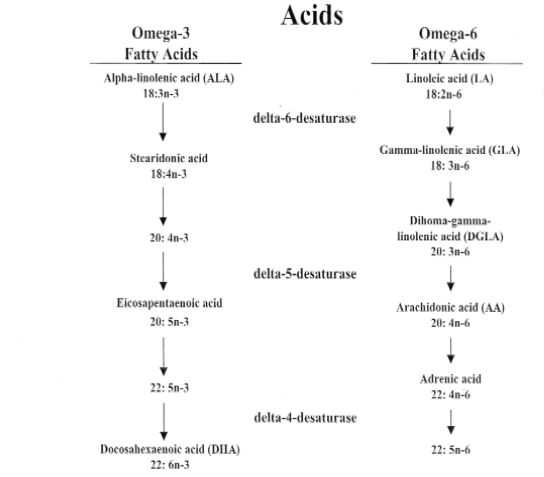
Nomenclature of Major Families of Unsaturated Fatty Acids [a]

Parent Compound	Number of Double Bonds	Family Name [b]	Structural Abbreviations [c]
Oleic acid	one	Omega-9 (ω-9)	18: 1n-9 or 18: 1ω-9
Palmitoleic acid	one	Omega-7 (ω-7)	16: 1n-7 or 16: 1ω-7
Linoleic acid	two	Omega-6 (ω-6)	18: 2n-6 or 18: 2ω-6
Alpha-linolenic acid [d]	three	Omega-3 (ω-3)	18: 3n-3 or 18: 3ω-3

[a] Adapted from Vaisey-Genser M in: Flaxseed: Health, Nutrition and Functionality, Winnipeg, MB: Flax Council of Canada, 1994, P 11
[b] The family name denotes the position of the first double bond as the number of carbon atoms from the methyl end of the fatty acid chain
[c] Number of carbon atoms: number of double bonds (fatty acid family).
[d] Also designated α-linolenic acid, Alpha-linolenic acid is distinct from gamma-linolenic acid [γ-linolenic acid (18: 3n-6)], which is an intermediate in the omega-6 metabolic pathway and is a major component of evening primrose, borage and black currant oils.

Table 23

Metabolic Pathways *of the* Omega-3 *and* Omega-6 Fatty Acids



studies on the effects of fish oil on BP showed both a dose-related response in hypertension as well as a relationship to the specific concomitant diseases associated with hypertension.[289,383,384,385,386,387,388,389] At fish oil doses of < 4 gm/day, there was no change in BP in the mildly hypertensive subjects. At 4 to 7 grams of fish oil per day, BP fell 1.6 mm Hg to 2.9 mm Hg and at over 15 grams of fish oil per day, BP decreased 5.8 mm Hg to 8.1 mm Hg.[289,383,384,385,386,387,388,389] There was no change in BP in the normotensive subjects. However, in those subjects with atherosclerotic disease and hypertension, hyperlipidemia and CHD, BP was reduced as shown below:

	Mean Fish Oil Dose	**Mean BP Reduction**
Disease	Per Day (gm)	(mm Hg)
Hypertension	5.6	2.3 – 3.4
Hyperlipidemia	4.0	4.1
Coronary Heart Disease	4.8	2.9 – 6.3

A study of 399 healthy males showed that a 1% increase in adipose tissue alpha-linolenic acid (ALA) content was associated with a 5 mm Hg decrease in SBP, DBP and MAP.[301]

Knapp *et al*[381] demonstrated a significant reduction in BP ($p < 0.01$) in a group of hypertensive subjects given 15 grams per day of fish oil. Bao *et al*[375] studied 69 obese, hypertensive subjects for 16 weeks treated with fish oil (3.65 grams omega-3 FA per day), evaluated by 24-hour ambulatory BP monitoring (24 hour ABM). Group I subjects on 3.65 grams per day of omega-3 FA alone reduced 24-hour ABM by 6/3 mm Hg ($p < 0.01$). Group II subjects who lost an average of 5.6 kg of weight, but received no fish oil, had a 5.5/2.2 mm Hg reduction in BP ($p < 0.01$). The best BP results were seen in Group III subjects on combined fish oil (omega-3 FA) and weight loss whose BP fell 13.0/9.3 mm Hg and heart rate fell an average of 6 beats/minute.

Mori *et al*[198] studied 63 hypertensive, hyperlipidemic subjects treated with omega-3 FA, 3.65 grams/day for 16 weeks, and found significant reductions in BP ($p< 0.01$), increase HDL_2-C ($p < 0.0004$), decrease in HDL_3-C ($p < 0.026$), decrease in triglycerides (29%), but no change in LDL-C, TC or total HDL-C. Serum glucose and insulin levels also declined.

Studies indicate that docosahexanoic acid (DHA) is very effective in reducing BP and heart rate.[376,377] However, formation of EPA and ultimately DHA from ALA is decreased in the presence of increased linoleic acid in the diet (omega-6 FA), increased dietary saturated fats and trans fatty acids, alcohol and aging through inhibitory effects, or reduced activity of delta-6-desaturase, delta-5-desaturase or delta-4-desaturase (Table 23).[20,376,377] Eating cold water fish three times per week is as effective as high- dose fish oil in reducing BP in hypertensive patients.[14,382] The BP is usually unaffected in healthy non-hypertensive patients.[382,388]

OMEGA-6 FATTY ACIDS (OMEGA-6 FA)

The omega-6 FA family, which includes linoleic acid (LA), gamma-linolenic acid (GLA), dihomo-gamma linolenic acid (DGLA) and arachidonic acid (AA) do not usually lower BP significantly[18,239] (Table 23), but may prevent increases in BP induced by saturated fats.[288,390] The omega-6 FA are found in flax, flax seed, flax seed oil, conjugated linoleic acid (CLA), canola oil, nuts, evening primrose oil, borage oil and black currant oil. The ideal ratio of omega-3 FA to omega-6 FA is between 2:1 to 4:1 and a polyunsaturated to saturated (P/S) fat ratio greater than 1.5 to 2:1.[391] Hydrogenated or partially hydrogenated vegetable oils with trans fatty acids should be avoided as they will increase BP and CHD risk.[372] They also have high omega-4 FA concentrations with little or no omega-3 FA.[14]

GLA and DGLA will enhance synthesis of vasodilating prostaglandins PGE^1 and PGI_2 preventing the increase in BP by feeding saturated fats.[289,390] GLA also completely blocks stress-induced hypertension[392,393] due to increased PGE_1,[394] decreased plasma aldosterone and reduced adrenal angiotensin II receptor density and affinity.[393] Both PGE_1 and PGI_2 regulate nerve conduction, mental function and neurotransmitter release and action that normalizes stress-induced changes in the hypothalamus and endocrine organs in hypertensive patients given GLA supplementation.[289,393,394,395,396] The conversion from LA to GLA and DGLA requires cofactors such as magnesium, potassium, zinc, calcium, vitamin B_6, vitamin A and beta carotene, vitamin C, niacin, selenium and sodium.[289,315,316,317,394]

OMEGA-3 FATTY ACIDS – OTHER CLINICAL EFFECTS

The omega-3 FA have a multitude of cardiovascular effects whose interplay modulates BP. These include reduction in fibrinogen,[381] anti-inflammatory,[377] anti-platelet,[377] anti-arrhythmic,[377,378] hypolipidemic,[397] anti-atherosclerotic[377] and vasodilatory effects (increases NO levels).[377]

OMEGA-3 FA: MECHANISM OF ACTION

The numerous proposed mechanisms of action of omega-3 FA are outlined in Table 24.[182,198,199,200,239,243,244,398-408] Alpha linolenic acid (ALA) competes for the same enzyme as linoleic acid (LA) - *i.e.* delta-6-desaturase thus reducing arachidonic acid (AA) formation and eicosanoid production of products such as thromboxane A_2 (TxA_2) (pro-coagulation) and leukotrienes (pro-inflammatory) while increasing production of vasodilatory prostacyclin I (PGI_2 and PGI^3).[239,243,244,289,409] In addition, there is modification of membrane phospholipids, improved membrane fluidity, reduced Ca^{++} exchange and increased Na^+/K^+ ATPase activity.[243,405,406,407,408] Stimulation of NO production,[377] improved insulin sensitivity,[182,198,199,200,398,399,400,401,402] and effects on

Table 24[182,198,199,200,243,244,377,399,400,402,403,404,406,407,408,]

Omega-3 and PUFA : Mechanism of Action

- Stimulates Nitric Oxide (NO)[377,405,406] and PGI but decreases TxA_2 and leukotrienes[244,405,406]
- Improves insulin sensitivity and lowers BP
  - N-3 skeletal muscle phospholipid content[199]
  - Membrane fluidity, membrane phospholipid content[243,405,406] regulate gene expression[402]
  - Mitochondrial up-coupling protein and FA oxidation in liver and skeletal muscle[399]
  - Thermogenesis gene induction (Reduces body fat)(increase heat production) energy balance improves[200,399,400]
  - Mitochondrial and peroxisomal oxidation in skeletal muscle[182]
  - ↓ TG droplets, ↑ Glucose uptake, Glycogen storage[198,199,200,399,400]
  - Improved glucose tolerance[185]
- Intracellular and inter organ fuel partitioners directing FA away from storage to oxidation.[182,403]
  - PPARα ligand activators (lipid oxidation)[182]
  - SREBP-1 suppression (↓ lipogenic genes)[403]
- Improved Cardiac Function[404]
- Improved Endothelial Dysfunction[375,382,388,406,407]
- Reduced plasma norepinephrine[405]
- Change Calcium Flux[406]

PPAR = Peroxisome Proliferator- activated receptor
SREBP-1 = Sterol Response Element - Binding Protein

intracellular and intraorgan fuel partitioning of fatty acids accounts for much of the observed BP-lowering effect.[182,399,403]

EPA blocks the activity of delta-5-desaturase, which reduces levels of arachidonic acid (AA) and increases DGLA levels and thus PGE_1.[409] AA is necessary for conversion of EPA to PGI_3 and EPA for conversion of DGLA to PGE_1.[387,409] Dietary caloric restriction will increase the activity of delta-6-desaturase, increasing levels of GLA, DGLA, EPA and DHA as well as PGE_1, PGI_2 and PGI_3.[289,317,409,410] The EFA all have ACE inhibitory activity.

A critical and optimal balance of omega-3 and omega-6 essential fatty acids with the nutrition cofactors of minerals, vitamins, antioxidants and electrolytes is important in vasoregulation, thrombosis, BP, vascular health and CVD reduction.

OMEGA-9 FATTY ACIDS (OMEGA-9 FA)

Olive oil is rich in monounsaturated fats MUFA (omega-9 FA) (oleic acid), which have been associated with BP and lipid reduction in Mediterranean and other diets.[14,18,412] Ferrara *et al* studied 23 hypertensive subjects in a double-blind, randomized, crossover study for six months comparing MUFA with PUFA.[412] Extra virgin olive oil (MUFA) was compared to sunflower oil (PUFA), rich in linoleic acid (W-6 FA). The SBP fell 8 mm Hg ($p \leq 0.05$) and the DBP fell 6 mm Hg ($p \leq 0.01$) in the MUFA-treated subjects compared to the PUFA-treated subjects. In addition, the need for antihypertensive medications was reduced by 48% in the MUFA group versus 4% in the PUFA (omega-6 FA) group ($p < 0.005$).

Strazzullo *et al* found an increase in SBP and DBP in patients when olive oil was replaced with saturated fatty acids.[413] Thomsen *et al* compared 16 hypertensive type II diabetics in a three-week crossover study comparing MUFA (olive oil) with PUFA. There was a significant reduction in clinic BP and 24-hour ABM.[414] However, in 47 normotensive healthy subjects given an olive-oil-rich diet versus a carbohydrate-rich-diet for 36 days, there was no change in BP.[415]

Olive oil is rich in oleic acid (omega-9 FA). Extra virgin oil has 5 mg of phenols in 10 grams of olive oil, a rich polyphenol antioxidant.[412,416] About 4 tablespoons of extra virgin olive oil is equal to 40 grams. The MUFA tend to increase HDL-C more than PUFA[417] and the oleate-rich LDL-C is more resistant to oxidation to OXLDL-C.[418] The combined antioxidant and antilipid effect of MUFA probably accounts for the BP effects by improved NO bioavailability, reduced ROS, improved endothelial function, vasodilation and inhibition of the OXLDL-stimulation of the angiotensin II receptor (A-II R).[26,27,28,29,30,115,116,128,132,138,139]

PALMITOLEIC ACID (POA)

Palmitoleic acid reduces the incidence of stroke in SHR-stroke prone (SHRSP) without any change in BP.[419] This may be due to a direct metabolic improvement in vascular smooth muscle. An extremely low saturated fat intake in the Asian population is associated with an increased risk of intra-cranial hemorrhage (ICH) in women.[420] This is also independent of BP. Perhaps some saturated fat and omega-6 FA from dairy products and red meat is essential for membrane integrity and reduction in ICH.

FIBER

The clinical trials with various types of fiber to reduce BP have been inconsistent.[18,421] Soluble fiber, guar gum, guava, psyllium and oat bran reduce BP and reduce the need for antihypertensive medications in hypertensive subjects, diabetic subjects and hypertensive-diabetic subjects.[422,423,424,425] Vuskan *et al*[423] reduced SBP 9.4 mm Hg in hypertensive subjects with the fiber glucomannan. Keenan gave oat bran (beta glucan) to hypertensive patients and reduced BP 7.5 mm Hg/5.5 mm Hg. The doses required to achieve these BP reductions is approximately 60 grams of oatmeal per day, 40 grams of oat bran (dry weight) per day, 3 grams of beta-glucan per day or 7 grams a day of psyllium.[358] In addition, the soluble and insoluble fibers reduce TC, TG, LDL-C and increase HDL.[358] The mechanisms for the BP reduction include improved insulin sensitivity,[422,426] reduced endothelial dysfunction,[422,426] natriuresis and reduced intravascular volume,[422,427] decreased sympathetic nervous system activity,[422,427] reduced OXLDL,[358] and mitigation of postprandial high-fat -meal induced hypertriglyceridemia, hyperglycemia with ED and vasoconstriction.[358]

GARLIC

Good clinical trials utilizing the correct type and dose of garlic have shown consistent reductions in BP in hypertensive patients.[14,377,428,429,430,431,432,433,434,435,436,437] Not all garlic preparations are processed similarly and are not comparable in antihypertensive potency.[438,439] In addition, cultivated garlic (allium sativum),[438,439] wild uncultivated garlic or bear garlic (allium urisinum)[438,439,440,441,442,443,444,445,446,447,448] and aged[301] or fresh garlic will have variable effects.[14,428,429] Mohamadi *et al*[439] found that wild garlic had the greatest antihypertensive effect in rats, probably mediated through the reduction in A-II levels, increased NO and decreased ROS by the higher content of allicin and other compounds. There is a consistent dose-dependent reduction in BP with garlic mediated through the RAAS and the NO system.[439] ALLICIN, a synthetic preparation of an active constituent of garlic, lowered BP, insulin and TG to a similar degree as enalapril in the Sprague-Dawley Rat Study by Elkayam *et al*.[449]

Approximately 10,000 mcg of allicin per day, the amount contained in four cloves of garlic (four grams) is required to achieve a significant BP lowering effect.[14,428,429] In humans the average reduction in SBP is 5 to 8 mm Hg.[450]

Garlic contains numerous active compounds that may account for its antihypertensive effects including gamma-glutamyl peptides (natural ACEI),[440,447,448] flavonolic compounds (natural ACEI),[440,448] magnesium (vasodilator and natural CCB),[438,440] ajoenes,[301,438,440] phosphorous,[438,440] adenosine,[442,443,444,445,446] allicin,[301,439] and sulfur compounds.[301] The proposed mechanisms of action of garlic in reducing BP are shown in Table 25. Garlic probably is a natural ACEI and CCB that increases BK and NO-inducing vasodilation, reducing SVR and BP and improving vascular aortic compliance.

Approximately 30 hypertensive clinical trials have been completed to date and 23 reported results with placebo control, 4 used non-placebo controls and 3 did not report results.[450] These trials studied BP as the primary outcome and 7 excluded concomitant antihypertensive medications. Significant reductions in DBP of 2-7% were noted in three trials and reductions in SBP of 3% in one trial when compared to placebo. Other trials reported BP reductions in the garlic-treated subjects (within group comparisons). Many studies did not provide numerical data about BP or did not have an *a piori* hypotheses regarding BP reduction.

TEA: GREEN AND BLACK

The effects of chronic green or black tea ingestion on blood pressure in humans has not been studied extensively and results are inconsistent.[451,452,453,454,455,456] However, green tea, black tea and extracts of active components in both teas have demonstrated reduction in BP in the SHR model.[457,458,459]

Norwegians consuming black tea had a significant decrease in BP in an observational study.[454] Normotensive subjects consuming six mugs of black tea per day for four weeks had no change in BP.[455] Elderly hypertensive subjects had their postprandial reduction in BP attenuated with black tea,[456] but there was no change in 24-hour ABM in another study.[451]

Hodgson *et al*[451] evaluated the effects of acute and chronic ingestion of 4-5 cups of green tea, black tea, caffeine or water in a group of normotensive, borderline hypertension, or mild systolic hypertension (SBP 130-150 mm Hg) subjects in a Latin square and crossover study design. In the acute study, there were increases in BP of 5.5/3.1 mm Hg at 30 minutes with green tea, but no change at 60 minutes. The black tea group had an increase in BP of 10.7/5.1 mm Hg at 30 minutes, but no change at 60 minutes. The chronic study demonstrated no significant change in office or 24 hour ABM, SBP, or DBP with green or black tea. Tea contains many active compounds that may alter BP, including flavonoids, which are polyphenolic compounds with vasodilatory and antioxidant effects,[452,453] theanine,[459] theobromine,[451] quercetin,[451] epigallocatechin-3-0-gallate (EGCG),[460] gamma-glutamylmethylamide (GMA),[461] thearubigins and theaflavins.[462] Additional studies in humans will be required to accurately assess these BP effects.

Table 25 [301,431,438,439,440,441,442,443,444,445,446,447,448]

Garlic : Mechanism of Action

- ACEi (GAMMA-Glutamyl peptides, flavonolic compounds)[438,439,440,441,447,448]
- Increase NO[431,439]
- Decrease sensitivity to NE[431,439]
- Increase Adenosine[431,439,442,443,444,445,446]
- Vasodilation and reduced SVR[301,439]
- Inhibit AA metabolites (TxA_2)[301,439]
- Reduced aortic stiffness[301]
- Magnesium (Natural CCB vasodilator)[438,440]
- Decreased ROS[439]

MUSHROOMS

The effects of mushrooms on BP in humans has not been studied. However, in the SHR, shiitake and maitake mushrooms reduce BP and serum lipids.[14,463,464,465] Mushrooms are low in carbohydrate, have no sugar, but also have high amounts of zinc and other vitamins and minerals that may reduce BP. In addition, the cellulose provides a small amount of fiber.

SEAWEED

Wakame (*Undaria pinnatifida*) is the most popular, edible seaweed in Japan.[466] In the SHR, wakame has similar ACEI activity to captopril with similar reductions in BP.[466] In humans, 3.3 grams of dried wakame for four weeks reduced the SBP 14 $\pm$ 3 mm Hg and significantly reduced DBP ($p < 0.01$).[467] In a study of 62 middle-aged, male subjects with mild hypertension given a potassium-loaded, ion-exchanging sodium-adsorbing potassium-releasing seaweed preparation showed significant BP reductions at four weeks on 12 and 24 gm/day of the seaweed ($p < 0.01$).[468] The MAP fell 11.2 mm Hg ($p < 0.001$) in the sodium-sensitive subjects and 5.7 mm Hg ($p < 0.05$) in the sodium-insensitive subjects, which correlated with plasama renin activity (PRA). The urinary sodium excretion decreased, urinary potassium increased and the sodium/potassium urinary excretion ratio decreased indicating that the MAP reduction was dependent on the reduced intestinal absorption of sodium and increased absorption of potassium released from the seaweed preparation. A similar mechanism of BP and stroke reduction was reported in SHR given 10% alginic acid in a seaweed fiber.[469]

Seaweed and sea vegetables contain most all of the seawater's 77I minerals and rare earth elements, fiber and alginate in a colloidal form.[466] However, the concentration of these minerals and alginate are lower than the effective dose needed to reduce BP in most cases.[466] The primary effect of wakame appears to be through its ACEI activity from at least four parent tetrapeptides and possibly their dipeptide and tripeptide metabolites, especially those containing the amino acid sequence TYR-LYS in some combination.[466] Its long-term use in Japan has demonstrated its safety. Other varieties of seaweed may reduce BP by reducing intestinal sodium absorption and increasing intestinal potassium absorption.[468,469]

NATURAL ACEI'S

Many other foods have demonstrated ACEI activity *in vitro*, but whether they are active after oral ingestion *in vivo* remains to be proven in human studies (Table 26).[440,443,447,448,466,470-486]

VITAMIN C

Vitamin C is a potent water-soluble antioxidant that recycles vitamin E, improves endothelial dysfunction and produces a diuresis.[377,487,488,489,490,491] Numerous epidemiologic, observational and clinical studies have demonstrated that the dietary intake of vitamin C or plasma ascorbate concentration in humans is inversely correlated to SBP, DBP and heart rate.[132,135,137,492-509] Studies in the SHR have shown fairly uniform reductions in BP with vitamin C administration.[510] Long-term epidemiologic and observational follow-up studies in humans also show a reduced risk of CVD, CHD and CVA with increased vitamin C intake.[500,502,511,512] However, controlled intervention trials have been somewhat less consistent or inconclusive as to the relationship of vitamin C administration and BP.[135,495,502,503,504,505,513] Numerous reasons exist for these variable results, including lack of a control group, no baseline BP, small study population, short trial duration, variable vitamin C doses, variable demographics and study population, unknown premorbid vitamin C status or premorbid general vitamin or antioxidant status, concomitant or unknown multivitamin intake and unknown nutritional status, existing concomitant diseases, confounding factors such as smoking, alcohol, weight changes, fiber, etc. were not stated or evaluated, plasma ascorbic acid levels were not measured, the P-value and confidence intervals were not reported, variable BP measurement techniques were employed (clinic or office, home, 24-hour ABM) unknown genetic polymorphisms exist or there was publication bias.[135]

Ness *et al*[135] published in 1997 a systematic review of MEDLINE-listed peer review journals on hypertension and vitamin C and concluded that if vitamin C has any effect on BP, it is small. However, in the 18 studies that were reviewed worldwide, 10 of 14 showed a significant BP reduction with increased plasma ascorbate levels and 3 of 5 demonstrated a decreased BP with increased dietary vitamin C.[135] In four small, randomized clinical trials of 20 to 57 subjects, one had significant BP reduction, one had no significant BP reduction and two were not interpretable.[135] In two uncontrolled trials, there was a significant reduction in BP.[135]

Table 26[466]

ACEi Activity in Foods and Nutraceuticals

A. Sour milk will ↓ BP in humans[470]
B. Casein[471,472]
C. Zein[473,474]
D. Geletin[475]
E. Sake[476]
F. Sour milk[477]
G. Sardine muscle[478,479]
H. Tuna muscle[480]
I. Dried salted fish[481]
J. Dried bonito[482]
K. Fish sauce[483]
L. Porhyda yezoensis[484]
M. Hijikia fusiformis[485] and seaweed (wakame)[467]
N. Garlic[440,443,447,448]
O. Hawthone[14,377,466,665]
P. Pycnogenol[486]
Q. Egg yolk (chicken)
R. Hydrolyzed whey protein[355,363]
S. Omega-3 fatty acids[142,405,406]

Koh [5]*et al* [507] in 1984 evaluated 23 hypertensive women with a BP range of 140-160/90-100 mm Hg over a three month period. Administration of one gram of vitamin C per day reduced office SBP 7 mm Hg ($0.05 < p < 0.10$) and reduced DBP 4 mm Hg ($0.05 < p < 0.10$). Ceriello *et* al in 1991[132] gave IV vitamin C to hypertensive patients with DM and reduced BP significantly.

Trout *et al* in 1991[499] gave one gram of vitamin C orally to 12 hypertensive subjects in a randomized crossover study for six weeks. The plasma ascorbate levels increased by 20 umol/liter ($p < 0.001$), SBP fell 5 mm Hg ($p < 0.05$) and DBP fell 1 mm Hg $\pm$ 2 (NS)

Duffy et al[495] in 1999 evaluated 39 hypertensive subjects (DBP 90 mm Hg to 110 mm Hg) in a placebo-controlled four-week study. A 2000 mg loading dose of vitamin C was given initially followed by 500 mg per day. The SBP was reduced 11 mm Hg ($p = 0.03$), DBP decreased by 6 mm Hg ($p = 0.24$) and MAP fell 10 mm Hg ($p < 0.02$). The plasma ascorbate increased to 49 umol/liter at four weeks ($p < 0.001$) showing an inverse correlation with MAP and plasma ascorbate levels ($p < 0.03$). There was no change in cyclic GMP (CGMP), urinary 6 keto-prostaglandin-Fl $\propto$, or urinary 8 epi-prostaglandin-F2 $\propto$.

Fotherby *et al* (2000)[506] studied 40 mild hypertensive and normotensive subjects in a double-blind, randomized, placebo-controlled, crossover study for six months. Men and women age 60 to 80 years (mean age 72 $\pm$ 4 years)

were given vitamin C 250 mg twice daily for three months, then crossed over after a one-week washout period. The plasma ascorbate increased to 35 umol/liter ($p < 0.001$), but clinic BP did not change significantly. However, the 24-hour ABM showed a significant decrease in SBP 2.0 $\pm$ 5.2 mm Hg ($p < 0.05$), but there was no significant change in DBP. However, the higher the BP, the greater the response to vitamin C. Therefore, when the normotensive or borderline hypertensive subjects were excluded, the BP reduction was more pronounced and significant. A significant increase in HDL-C was seen in women ($p < 0.007$), but not in men. The LDL-C did not change in either group. The conclusion from this study was that vitamin C reduced primarily daytime SBP as measured by 24 hour ABM in hypertensive, but not normotensive subjects. In the hypertensive subjects, SBP was reduced by 3.7 mm Hg $\pm$ 4.2 mm Hg ($p < 0.05$) and DBP fell 1.2 mm Hg $\pm$ 3.7 mm Hg (NS).

Block *et al* (2001)[514] in an elegant depletion-repletion study of vitamin C demonstrated a significant inverse correlation of plasma ascorbate levels, SBP and DBP. During this 17-week controlled diet study of 68 normotensive men aged 39 to 59 years with mean DBP of 73.4 mm Hg and mean SBP of 122.2 mm Hg, vitamin C depletion at 9 mg/day for one month was followed by vitamin C repletion at 117 mg/day repeated twice. All confounders were eliminated, including smoking, exercise, alcohol, weight change and other nutritional intake during the study. Plasma ascorbate was inversely related to DBP ($p < 0.0001$, correlation -0.48) and to SBP in logistic regression. Persons in the bottom quartile of plasma ascorbate had a DBP 7 mm Hg higher than those in the top quartile. One-fourth of the DBP variance was accounted for by plasma ascorbate alone. Of the other plasma nutrients examined, only ascorbate was significantly and inversely correlated with DBP ($p < 0.0001$, $r = -0.48$) for the five week plasma ascorbate levels. Each increase at week five in the plasma ascorbate level was associated with a 2.4 mm Hg lower DBP at week nine.

Hajjar *et al*[515] evaluated 31 subjects with Stage I hypertension in a double-blind, randomized, placebo, four- week, run-in trial utilizing three doses of vitamin C at 500 mg, 1000 mg, or 2000 mg per day for eight months. The mean age was 62 $\pm$ 2 years, 52% male, 90% white with good compliance of 48 $\pm$ 2%. The SBP fell significantly by 4.5 $\pm$ 1.8 mm Hg ($p < 0.05$) and DBP fell by 2.8 $\pm$ 1.2 mm Hg ($p < 0.05$) at one month and persisted during the study. No dose response was demonstrated. The BP decrease was not significant, but was lower in the vitamin C group. There was no difference in BP response between the three groups ($p = 0.48$) and no significant change in serum lipid levels from baseline or between groups although the vitamin C group had an overall trend to improve lipids: TC ($p = 0.75$), TG ($p = 0.87$), HDL ($p = 0.32$) or LDL ($p = 0.52$).

Ness *et al*[493] evaluated subjects aged 45-74 in a population based cross sectional analysis and found that an increase in plasma ascorbate of 50 umol/liter reduced BP by 3.6/2.6 mm Hg. Bates *et al*[492] in a similar cross sectional analysis on 914 elderly patients over 65 years of age confirmed that an increase in plasma ascorbate of 50 umol/liter reduced SBP by 7 mm Hg. In most of the epidemiologic studies, there is a clear inverse relationship between plasma ascorbate levels, dietary intake and BP with a reduction in SBP of 3.6 to 17.8 mm Hg for each 50 umol/liter increase in plasma ascorbate.[135,492,493,497,498,499,500,501]

In the post hoc analysis in the ADMIT study (Arterial Disease Multiple Intervention Trial),[513] a prospective, double-blind, placebo-controlled study of 363 subjects with PAD (peripheral arterial disease) treated with vitamin C 1000 mg/day, vitamin E 800 IU/day and beta carotene 24 mg/day versus placebo, there was no difference in BP in the normotensive or hypertensive subjects (N = 177). Other studies, however, have shown synergy of combination antioxidants and vitamins in reducing BP, increasing NO, PGE_1 [289,317,516] and PGI_2 levels,[137,506,517,518] and reducing TxA_2 levels. The study by Miller *et al*[519] in 297 elderly patients showed no difference in BP in the treated group given vitamin C, E and beta carotene vs placebo group. However, 87% of all subjects were permitted to take their own multivitamins.

MECHANISM OF VITAMIN C ON BLOOD PRESSURE

Vitamin C improves ED in hypertensive[377,489] and hyperlipidemic[488] patients and reduces BP in a dose related manner with higher pharmacologic doses.[377,487] The improvement of ED in hypertensive patients occurs in conduit arteries, epicardial coronary arteries and forearm resistance arteries.[136,488,520,521] Vitamin C restores NO-mediated flow-dependent vasodilation in patients with CHF.[521] Hypertensive patients exhale less NO than healthy patients.[496] Following vitamin C administration, there is an increase in exhaled NO that correlates with BP reduction, especially SBP.[496] Acute oral or intravenous administration

Table 27

Mechanisms Vitamin C

- Reduces ED and Improves EDVD and lowers BP and SVR in HBP, HLP, CHD, Smokers[136,377,487,488,489,490,491,493,494,496,506,509,520,521]
- Diuresis[377]
- Increase NO and PGI_2[499,506,527,528,529]
- Decrease adrenal steroid production[506,527]
- Improve sympathovagal balance[506,530]
- Decrease cystosolic Ca^{++}[498]
- Antioxidant[377,498]
- Recycles Vit-E, Glutathione, Uric Acid[377,498]
- Reduces neuroendocrine peptides[506,528,529]
- Reduces thrombosis[498,506,531] and decreases TxA_2[529]
- Reduces Lipids (↓TC, ↓LDL, ↓TG, ↑HDL)[506,532,533]
- Reduces Leukotrienes[498,499]
- Improves Aortic Collagen, Elasticity and Aortic Compliance[514,534]
- Increase cGMP and Activate VSM K^+ channels[509]

of vitamin C reverses ED and causes acute vasodilation in humans with CHD[490] and in smokers.[491] The multitude of proposed mechanisms for vitamin C in hypertension and other cardiovascular diseases is outlined in Table 27. Grossman *et al*[509] proposed recently that ascorbic acid modulates the redox state of soluble guanylyl cyclase, activating cGMP-dependent potassium channels that hyperpolarize VSMC-inducing vasodilation.

VITAMIN C - A PERSPECTIVE

Combined nutrients, vitamins, minerals, and antioxidants have clearly been shown to lower BP in DASH-I,[193] DASH-II,[187] NHANES-III,[522] Vanguard,[225] and other studies.[137,506,517,518] Although these varied diets confer more antihypertensive and cardiovascular benefits than any single nutrient, it is also quite probable that vitamin C as a single nutrient plays a significant role in the regulation of BP in both normotensive and hypertensive patients. Almost all studies and reviews reported have shown an inverse relationship to vitamin C intake and plasma ascorbate levels that is reasonably consistent among different study groups, populations and the variable study designs.[135,492,493,495,497,498,499,500,501,506,507,514] Hypertensive subjects were found to have significantly lower plasma ascorbate levels compared to normotensive subjects (40 umol/liter *vs* 57 umol/liter respectively).[523] Evidence supports the fact that plasma ascorbate is inversely correlated with BP even in healthy normotensive individuals.[514] The NHANES-II Study found 20% of U.S. males have plasma ascorbate levels below 27 umol/liter and 30% of U.S. black males were below 27 umol/liter.[524] This could partially account for the higher prevalence of hypertension in blacks.

Pharmacokinetic studies have documented the existence of at least three or more ascorbate compartments of which plasma is only one.[525,526] Human organs such as adrenal, pituitary, liver, spleen, pancreas, brain, and lens of the eye actively concentrate ascorbate against a concentration gradient and achieve levels 20-to 100-fold greater than plasma.[526] It is possible that during vitamin C deprivation, these organs gain relative priority over the vascular system and other organs as to ascorbate concentrations.[514] The body stores of vitamin C then may be more relevant than plasma levels as it correlates with BP. This vascular tissue-organ depletion theory is consistent with many of the proposed mechanisms of vitamin C shown in Table 27.[136,377,487-491,493,494,496,498,499,506,514,520,521,527-534] Vitamin C is not pro-oxidant and, in fact, significantly reduces oxidative stress as measured by the ratio of urinary 8-oxoguanine to 8-oxoadenine.[535,536,537]

SUMMARY AND CONCLUSIONS VITAMIN C AND BLOOD PRESSURE

The present conclusions based on these available studies correlating vitamin C and BP are shown in Table 28. The observational, epidemiologic and prospective clinical trials point strongly to a role of vitamin C in reducing BP in hypertensive subjects and normotensive subjects as well as those in other disease categories. A dose relationship is suggested, but the efficacy of "supraphysiologic" doses of vitamin C and BP effects are yet to be confirmed. More sound clinical trials are welcomed and needed.

VITAMIN E

The relationship of vitamin E and BP has been studied *in vitro*,[528] extensively in animals (SHR),[538,539,540,541,542,543] but limited studies have been done in humans.[544,545] Alpha tocopherol inhibits thrombin-induced endothelin secretion *in vitro* at least partially through protein kinase C (PKC) inhibition.[546] Reduced PKC levels reduce vascular smooth muscle (VSM) proliferation through inhibition of activated protein-1 (AP-1) and nuclear factor kappa-B (NFKB). This, in turn, improves ED, lowers SVR and reduces BP.

Newaz *et al*[538] gave gamma-tocotrienol 15 mg/kg to SHR and found significant reductions in lipid peroxides in plasma and in blood vessel walls, increased superoxide dismatase (SOD) activity, increased total antioxidant status (TAS) and lowered BP ($p < 0.001$). In a similar study, Newaz *et al*[539] gave 34 mg/kg of alpha-tocopherol to SHR and WKY rats. Lipid peroxide levels were decreased in plasma and in vascular walls, plasma SOD activity increased, TAS increased and BP fell ($p < 0.001$). In a follow-up, dose response study,[540] Newaz administered alpha-tocopherol to SHR in doses of 17 mg/kg, 34 mg/kg or 170 mg/kg. Nitric oxide synthase (NOS) increased significantly ($p < 0.01$) only at the 34 mg/kg dose and BP fell the most at the 34 mg/kg dose ($p < 0.001$).

Table 28

Vitamin C: Conclusions

1. BP is inversely correlated with Vitamin C intake and plasma ascorbate levels in humans and animals in epidemiologic, observational, cross sectional and controlled prospective clinical trials
2. A dose response relationship between lower BP and higher plasma ascorbate levels is suggested
   - A. DBP fell about 2.4 mmHg per plasma ascorbate quartile in a depletion repletion study
   - B. SBP fell 3.6 to 17.8 mmHg for each 50 μmol/L increase in plasma ascorbate level
   - C. BP may be inversely correlated to tissue levels of ascorbate.
   - D. Doses of 100 to 1000 mg per day are needed.
3. SBP is reduced proportionately more than DBP, but both are decreased. 24 hour ABM indicates a predominate daytime SBP reduction and lower HR. Office BP show a reduction in SBP and DBP as well
4. The greater the initial BP, the greater the BP reduction
5. BP is reduced in hypertensives, normotensives, hyperlipidemics, diabetics and in patients with a combination of these disease.
6. Improves ED in HBP, HLP, PAD, DM, CHD, CHF, smokers and in conduit arteries, epicardial coronary arteries and forearm resistance arteries
7. Long term epidemological studies indicate an inverse correlation of Vitamin-C intake and ascorbate levels with RVR of CVD, CHD, and CVA
8. The lipid profile seems to be beneficial with small reductions in TC, TG, and LDI and oxLDL and with increases in HDL (women)
9. Combinations of Vitamin-C with other antioxidants such as Vitamin-E, Beta-carotene or selenium provide synergistic anti-hypertensive effects.

Other animal studies have shown beneficial results of alpha-tocopherol on hypertension and stroke in the SHR,[541] membrane fluidity and BP in SHR and WKY rats[542] and prostacyclin production, serum lipids and BP using a mixture of alpha-tocopherol and tocotrienols.[543]

Human studies of vitamin E in doses of 400 to 1000 IU/day, although limited, have shown beneficial effects on improving insulin sensitivity,[544] lowering serum glucose,[544] inhibiting TxA_2,[529] increasing serum glutathione levels,[544] increasing intracellular magnesium,[544] improving arterial compliance (·37 to 44%) (independent of arterial pressure),[547] reducing ED and vascular resistance[547,548] and decreasing OXLDL.[548] However, reductions in BP in hypertensive subjects have been inconsistent, limited to small numbers of subjects, or it has been difficult to interpret the results for a variety of reasons.[544,545,549]

Barbagallo *et al*[544] evaluated 24 hypertensive subjects in a double-blind, randomized, placebo-controlled study who received vitamin E 600 IU/day for four weeks. The BP in both treatment and placebo groups was decreased significantly ($p < 0.001$ for SBP and $p < 0.005$ for DBP), but both groups received furosemide 25 mg per day. The effects of vitamin E on BP cannot be interpreted in this study.

Palumbo *et al*[545] administered 300 IU vitamin E per day to 142 treated hypertensive subjects in a randomized, open-labeled trial for 12 weeks. Clinic and 24 hour ABM showed no change in SBP and a small decrease in 24-hour ABM, DBP of –1.6 mm Hg (95% confidence intervals –2.8 to 0.4 mm Hg at $p = 0.06$). However, the mean BP at entry was 147/88 mm Hg in the vitamin E group, indicating reasonably good BP control by JNC-VI criteria. The day and night changes in mean ABM were not significant. The antihypertensive treatment clearly restricted the possibility of actually measuring a BP-lowering effect of vitamin E.

Lino *et al*[549] performed a double-blind, placebo-controlled study of the effects of dl-alpha-tocopherol nicotinate in 94 hypertensive subjects with cerebral atherosclerosis. Subjects received 3000 mg of the study vitamin for four to six weeks. In subjects with hypertension, the SBP declined from 151.0 $\pm$ 22.1 mm Hg to 139.2 $\pm$ 16.8 mm Hg ($p < 0.05$), but DBP did not change.

If vitamin E has an antihypertensive effect, it is probably small and may be limited to untreated hypertensive patients or those with known vascular disease or other concomitant problems such as diabetes or hyperlipidemia.[547,548,549] However, vitamin E does improve ED through numerous mechanisms that could improve vascular health, reduce vascular and target organ damage that is BP-dependent or independent[546,550] (Figure 23). Hypertensive patients, compared to normotensive patients, have significantly lower plasma and cell content of vitamins E and C with increased lipid peroxidation.[550]

VITAMIN D

Epidemiological, clinical and experimental investigations all demonstrate a relationship between the plasma levels of $1_125\ (OH)_2\ D_3$ (1,25-dihydroxycholecalciferol), the active form of vitamin D and BP.[551,552,553,554,555,556,557] This includes a vitamin-D-mediated reduction in BP in hypertensive patients. Although the mechanism of action of vitamin D on vascular tone and BP is not completely understood, both a direct effect on cell membranes and an indirect effect on calcium transport, metabolism and excretion have been shown.[551]

It has been difficult to dissociate the effects of calcium from vitamin D on BP in humans. Numerous studies have verified the finding of an inverse relationship between dietary calcium intake and BP.[558] This relationship applies to all ages, gender, racial, and socioeconomic groups.[551] A low serum ionized calcium level is particularly common in salt-sensitive, low-renin, hypertensive patients who have increased intracellular calcium concentration in platelets, lymphocytes and renal proximal tubular cells.[551,558,559,560]

Vitamin D may have an independent and direct role in the regulation of BP[551,552,553] and insulin metabolism.[552,553] A study of 34 middle-aged men demonstrated that serum levels of $1_125\ (OH_2)\ D_3$ were inversely correlated to BP ($p < 0.02$), VLDL triglycerides ($p < 0.005$) and to triglyceride removal after intravenous fat tolerance test ($p < 0.05$).[552] Serum levels of $25\ (OH)_2\ D_3$ were correlated to fasting insulin ($p < 0.05$), insulin sensitivity during clamp ($p < 0.001$) and lipoprotein lipase activity in adipose tissue ($p < 0.005$) and skeletal muscle ($p < 0.03$).[552] Holdaway *et al* found no difference in $25\ (OH)_2\ D_3$ levels in a group of hypertensive versus normotensive subjects.[561] The Tromso Study analyzed calcium and vitamin intake in 7,543 men and 8,053 women and found a significant linear decrease in SBP and DBP with increasing dietary calcium intake in both sexes ($p < 0.05$); however, vitamin D intake had no significant effect on BP.[562]

In the deoxycorticosterone acetate salt model of hypertension, dietary manipulation of vitamin D has been shown to reduce BP without a change in calcium levels, indicating a direct effect on BP regulation.[551,563,564] Vascular tissue contains receptors for both calcium-regulating hormones PTH and $1_125\ (OH)_2\ D_3$.[564] MacCarthy demonstrated that $1_125\ (OH)_2\ D_3$ antagonizes the mitogenic effect of epidermal growth factor on proliferation of vascular smooth muscle cells.[565]

Lind, in double-blind, placebo-controlled studies, found that BP was lowered with vitamin D during long-term treatment of patients with intermittent hypercalcemia.[554,555] In another study, Lind *et al* demonstrated that total and ionized calcium levels were increased, but DBP was significantly decreased, and the hypotensive effect of vitamin D

was inversely related to the pretreatment serum levels of 1_125 $(OH)_2$ D_3 and additive to antihypertensive medications.[556] Pfeifer *et al* showed that short-term supplementation with vitamin D_3 and calcium is more effective in reducing SBP than calcium alone.[557] In a group of 148 women with low 25 $(OH)_2$ D_3 levels, the administration of 1200 mg calcium plus 800 IU of vitamin D_3 reduced SBP 9.3% more ($p < 0.02$) than did 1200 mg of calcium alone. The HR fell 5.4% ($p = 0.02$), but DBP was not changed.[557]

VITAMIN B-6 (PYRIDOXINE)

Low serum vitamin B_6 levels are associated with hypertension in rats[328,566,567,568,569,570] and humans.[566,571,572,573,574,575,576,577] Vitamin B_6 is a readily metabolized and excreted water soluble vitamin.[578] Six different B_6 vitamins exist, but pyridoxal 5 / phosphate (PLP) is the primary and most potent active form that is produced by rapid hepatic oxidation by pyridoxine phosphate oxidase and pyridoxine kinase in the presence of zinc and magnesium.[578,579] Numerous PLP-dependent enzymes exist that are involved in metabolic pathways that include carbohydrate metabolism, sphingolipid biosynthesis and degradation, amino acid metabolism, heme biosynthesis and hormone and neurotransmitter biosynthesis such as steroid hormones, thyroid hormone, gamma amino butyric acid (GABA), histamine, norepinephrine (NE) and serotonin.[577,578] Vitamin B_6's participation in neurotransmitter and hormone biosynthesis, amino acid reactions with kynureninase, cystathionine synthetase, cystathionase and membrane L-type calcium channels account for much of its antihypertensive effects.[578,579] Vitamin B_6 (PLP) is involved in the transsulfuration pathway of homocysteine metabolism to cysteine.[578]

Animal studies in specific rat strains have demonstrated an increase in BP, NE and epinephrine plasma levels, increase in the NE cardiac turnover, reduced CNS brainstem NE, GABA and serotonin content that completely reverses after vitamin B_6 repletion.[579] Pyridoxine at 10 mg/kg in B_6-deficient rats (B6DHT) reduced BP from 143 mm Hg to 119 mm Hg within 24 hours ($p < 0.05$).[579] In these B6DHT rats, PLP enhanced binding of CCB's to the vascular membrane indicating that PLP corrects membrane abnormalities and is an endogenous modulator of DHP-sensitive (dihydropyridine-sensitive) calcium channels.[568,580] Low calcium levels and low B_6 levels potentiate BP increases in rats, whereas replacement of both will reduce BP.[328] Vitamin B_6 plus tryptophan reduced BP more than monotherapy with each in rats, probably related to effects on brain stem serotonin and kynurenine.[567] There is a structural similarity of the B_6 vitamins to the DHP-CCB's, and CCB's are most effective in B_6 deficient rats.[566]

Supplemental vitamin B_6 in the diets of prehypertensive, obese, Zucker and sucrose-induced hypertensive rats, and SHR reduces BP by increasing the synthesis of cysteine from methionine.[581,582,583] Cysteine acts directly on aldehydes and neutralizes their effects. Aldehydes bind sulfhydryl groups of membrane proteins and alter calcium channels (L-type), which increase cytosolic free calcium, cause VSM constriction and elevate BP.[583] Aldehydes also induce hyperglycemia and promote insulin resistance.[583] Cysteine is also a precursor of glutathione, which neutralizes aldehydes and further improves BP and glucose metabolism.[583] Thus, vitamin B_6 reduces both movement of calcium into cells (cytosolic Ca^{++}) and decreases intracellular sarcoplasmic reticulum release of calcium.

One human study by Aybak *et al*[577] proved that high dose vitamin B_6 significantly lowered BP. This study compared 9 normotensive men and women with 20 hypertensive subjects, all of whom had significantly higher BP, plasma NE and HR compared to control normotensive subjects. Subjects received 5 mg/kg/day of vitamin B_6 for four weeks. The SBP fell from 167 $\pm$ 13 mm Hg to 153 $\pm$ 15 mm Hg, an 8.4% reduction ($p < 0.01$) and the DBP fell from 108 $\pm$ 8.2 mm Hg to 98 $\pm$ 8.8 mm Hg, a 9.3% reduction ($p < 0.005$). Plasma NE was reduced from 1.80 $\pm$ .21 nmol/l to 1.48 $\pm$ .32 nmol/l (18% reduction, $p < 0.005$); plasma epinephrine fell from 330 $\pm$ 64 pmol/l to 276 $\pm$ 67 pmol/l (16% reduction, $p < 0.05$). There was no significant change in heart rate.

The proposed mechanisms of hypertension in vitamin B_6 deficient animals and humans includes:[578,579]

1. Central nervous system, and brain stem depletion of neurotransmitters such as NE, serotonin and GABA, which lead to an increase in sympathetic outflow.
2. Increased peripheral SNS activity.
3. Increased VSMC calcium uptake and increased intracellular calcium release.
4. Increased end-organ responsiveness to glucocorticoids and mineralocorticoids (aldosterone).
5. Increased aldehyde levels.
6. Insulin resistance.

In summary, vitamin B_6 has multiple antihypertensive effects that resemble those of central alpha agonists (i.e. clonidine), calcium channel blockers (i.e. DHP-CCB like amlodipine) and diuretics. Finally, changes in insulin sensitivity and carbohydrate metabolism may lower BP in selected hypertensive individuals with the metabolic syndrome of insulin resistance. Chronic intake of vitamin B_6 at 200 mg per day is safe and has no adverse effects. Even doses up to 500 mg per day are probably safe.[578]

FLAVONOIDS

Over 4,000 naturally occurring flavonoids have been identified in such diverse substances as fruits, vegetables, red wine, tea, soy and licorice.[520,584,585,586,587,588,589] Flavonoids (flavonols, flavones and isoflavones) are potent free radical scavengers that inhibit lipid peroxidation, prevent atherosclerosis, promote vascular relaxation and have antihypertensive properties.[520,584] In addition, they reduce stroke,[589] and provide cardioprotective effects that reduce CHD morbidity and mortality[589] in the Zutphen Elderly Study,[590] Finnish Study[591] and U.S. Health Professionals Study.[592] Various flavonoids have undergone extensive scientific studies that demonstrate a wide variety of protective cardiovascular effects. Soy, which contains diadzein and genistein, lowers total cholesterol, low density lipoprotein cholesterol (LDL-C), BP and reduces coronary and generalized thrombosis.[360,520,585] Red wine contains quercetin, which reduces oxidation of LDL (OxLDL) and decreases platelet aggregation.[520,584] Blueberries (*vaccinium myrtillus*) are rich in antioxidants, reduce oxidized LDL and are more potent than vitamin C on a molar basis as an antioxidant.[520,586] Licorice root (*glycyrrhiza glabra*) is a potent antioxidant, anti-inflammatory, antiplatelet and anti-viral, but it may lower potassium, increase sodium retention and elevate BP due to a mineralocorticoid action when used in high doses.[520,587,588]

Very few studies have been done in hypertensive humans to determine the effects of flavonoids on BP. Hodgson *et al*[593] studied 59 subjects with high normal SBP (SBP $\geq$ 125 mm Hg) (range 125-138 mm Hg) in a randomized, double-blind, placebo-controlled two-way parallel design for eight weeks. The treatment group received one capsule daily containing 55 mg of isoflavonoids from a soy product with 30 mg genistein, 16 mg biochann A, 1 mg daidzein and 8 mg formononetin. The clinic and 24-hour ABM showed no significant change in BP. This study has many limitations; it was not a true hypertensive population, so effects on BP would be minimal at best, it was limited to a soy product extract with limited number and combinations of isoflavonoids, and the dose administered may have been too small.

Genistein and diadzein inhibit tyrosine kinase activity, which decreases vascular smooth muscle contraction (VSMC), lowers BP and inhibits oxidation activity in the blood vessel.[360,593] However, Hodgson *et al*[594] were unable to demonstrate any reduction in urinary F-2 isoprotanes in human subjects with high normal BP given a 55 mg daily isoflavanoid supplement for eight weeks. Urinary F-2 isoprostanes are the best available marker for *in vivo* lipid peroxidation.

Asgary *et al*[595] evaluated the flavonoid rich plant, *achillea wilhelmssi*, in a group of 120 hypertensive, hypercholesterolemic men and women for six months. Significant reductions in TC, LDL, TG, and increased HDL as well as significant reductions in SBP and DBP were found ($p< 0.05$).

Dietary flavonoids may reduce CVA,[589,596] CHD, and MI[589] independent of any effect on BP. Additional studies are needed to determine the type and amount of dietary flavonoids required to produce significant effects on BP.

LYCOPENE (CAROTENOID)

Lycopene is a non-provitamin-A carotenoid, potent antioxidant found in tomatoes and tomato products, guava, pink grapefruit, watermelon, apricots, and papaya in high concentrations.[597] Lycopene has recently been shown to produce a significant reduction in BP, serum lipids and oxidative stress markers.[598,599] Paran *et al*[599] evaluated 30 subjects with Grade I hypertension, age 40-65, taking no antihypertensive or antilipid medications treated with a tomato lycopene extract for eight weeks. The SBP was reduced from 144 to 135 mm Hg (9 mm Hg reduction, $p < 0.01$) and DBP fell from 91 to 84 mm Hg (7 mm Hg reduction, $p < 0.01$). A similar study of 35 subjects with Grade I hypertension showed similar results on SBP, but not DBP.[598] Serum lipids were significantly improved in both studies without change in serum homocysteine.

COENZYME Q-10 (UBIQUINONE)

Coenzyme Q_{10} (CoQ10) is a potent lipid phase antioxidant, free radical scavenger, co-factor and coenzyme in mitochondrial energy production and oxidative phosphorylation that regenerates vitamins E, C, and A, inhibits oxidation of LDL, membrane phospholipids, DNA, mitochondrial proteins, lipids, reduces TC, and TG, raises HDL-C, improves insulin sensitivity, reduces fasting, random and postprandial glucose, lowers SVR, lowers BP and protects the myocardium from ischemic reperfusion injury.[14,397,501,520,600,601,602,603,604,605,606,607] CoQ_{10} improves mitochondrial energy production, enhancing myocardial infusion with improved diastolic function, left ventricle (LV) function, Left ventricle wall tension (LVWT) and NYHA (New York Heart Association) class for CHF.[397,501]

Serum levels of CoQ_{10} decrease with age and are lower in patients with diseases characterized by oxidative stress such as hypertension, CHD, hyperlipidemia, DM, atherosclerosis, and in those who are involved in aerobic training, patients on total parenteral nutrition (TPN), those with hyperthyroidism and patients who take statin drugs.[501,600,605] Enzymatic assays showed a deficiency of CoQ_{10} in 39% of 59 patients with essential hypertension versus only 6% deficiency in controls ($p < 0.01$).[608] There is a high correlation of CoQ_{10} deficiency and hypertension. Most foods contain minimal CoQ_{10}, which is primarily found in meat and seafood. Supplements are needed to maintain normal serum levels in many of these disease states and in some patients taking statin drugs for hyperlipidemia.[501]

Numerous animal studies in SHR, uninephrectomized rats treated with saline or deoxycortisone and in experimentally-induced hypertension in dogs, have demonstrated significant reductions in BP following oral administration of CoQ_{10} at doses of 60 mg per day or more.[609,610,611,612]

Human studies have also demonstrated significant and consistent reductions in BP in hypertensive subjects following oral administration of 100 mg to 225 mg per day of CoQ_{10}.[397,535,600,602,603,607] Digiesi *et al*[600] studied 26 hypertensive subjects with an average BP of 164.5/98.1 mm Hg given Co-Q-10, 50 mg oral bid for 10 weeks. The SBP fell from 164.5 mm Hg to 146.7 mm Hg, an 11% reduction ($p < 0.001$). The DBP was reduced from 98.1 mm Hg to 86.1 mm Hg, a 12% reduction ($p < 0.001$). The CoQ_{10} serum levels increased by .97 ug/ml ($p < 0.02$), which was highly correlated with the BP reduction. In addition, the 24-hour ABM showed significant reductions in SBP and DBP of 18 mm Hg and 10 mm Hg respectively ($p < 0.001$). The TC fell 10 mg% ($p < 0.005$), HDL rose 2 mg% ($p < 0.01$) and SVR fell 29% ($p < 0.02$). There was no significant change in plasma renin activity (PRA), serum K^+, serum Na^+, urinary K^+ or Na^+ or urine aldosterone. Finally, the serum endothelin level, EKG, and echo were not significantly different.

Langsjoen *et al*[397] placed 109 hypertensive subjects taking antihypertensive medications on 225 mg per day of CoQ_{10} for four months and demonstrated significant reductions in mean SBP from 159 to 147 mm Hg, a reduction of 12 mm Hg ($p < 0.001$) and mean DBP from 94 mm Hg to 85 mm Hg, a reduction of 9 mm Hg ($p < 0.001$). Serum CoQ_{10} levels were adjusted to an average of 3.02 ug/ml, but all subjects had levels therapeutic at > 2.0 ug/ml. The Co-Q-10 dose varied from 75 to 360 mg/day. There was improvement in diastolic LV function, LVWT, LVH and NYHA class ($p < 0.001$), thought to be mediated secondary to a neurohormonal response with reduction in serum catecholamines and a fall in BP. In addition, improved bioenergetics were noted with improved adrenal function and vascular endothelial function.[613] About 51% of subjects were able to discontinue between one to three antihypertensive drugs (37% stopped one drug, 11% stopped two drugs, 4% stopped three drugs) at an average of 4.4 months after starting Co-Q-10. No side effects were noted. The reduction in drug use by category was 16.7% decrease in digitalis, 40% decrease in diuretics, 59% decrease in beta blockers, 27.5% decrease in calcium channel blockers, 31.7% decrease in angiotensin-converting enzyme inhibitors, and a 35% decrease in other antihypertensive drugs.[397]

Yamagami *et al*[614] observed a CoQ_{10} deficiency in 29 subjects with essential hypertension and found significant improvement in their BP and correction of the Co-Q-10 deficiency following oral intake of 1-2 mg/kg/day. Tsuyuaki *et al*[615] found that CoQ_{10} at 30 mg/day when added to a beta blocker, reduced the negative inotropic effect and lowered BP. Richardson *et al*[616] demonstrated a significant reduction in systolic and diastolic blood pressure in 16 subjects with essential hypertension on 60 mg/day of CoQ_{10} treatment for 12 weeks as well as normalization of their cardiac output. Hamada *et al*[617] did not see a significant change in BP in 12 hypertensive subjects treated with CoQ_{10} at 60 mg/day for four weeks, but the negative inotropic effect of a beta blocker was reduced, and the malaise and fatigue in the patients improved. Yamagami et al[613] showed a significant decrease in SBP in 20 essential hypertensive subjects with low CoQ_{10} levels (less than 0.9 ug/ml) who were randomized to receive either placebo or CoQ_{10} at 100 mg/day for 12 weeks. The BP decreased significantly in the CoQ_{10} group between 8-12 weeks. Montaldo *et al*[618] studied 15 hypertensive subjects on 100 mg/day of Co-Q-10 for 12 weeks and noted a significant reduction in BP at rest and exercise as well as a significant improvement in myocardial stroke work index.

Digiesi *et al*[607] in 1992 evaluated 10 subjects with essential hypertension treated with oral CoQ_{10}, 50 mg BID for 10 weeks. The SBP fell from 161.5 $\pm$ 5.1 mm Hg to 142.2 $\pm$ 5.3 mm Hg ($p < 0.001$) and the DBP fell from 98.5 $\pm$ 1.7 mm Hg to 83.1 $\pm$ 2.0 mm Hg ($p < 0.001$). Plasma CoQ_{10} levels increased from 0.69 $\pm$ 0.1 ug/ml to 1.95 $\pm$ 0.3 ug/ml ($p < 0.02$). In addition, TC decreased from 227 $\pm$ 24 mg% to 203.7 $\pm$ 20.6 mg% ($p < 0.01$) and serum HDL cholesterol increased from 42 $\pm$ 3.0 mg% to 45.9 $\pm$ 3.0 mg% ($p < 0.01$). The PRA, urine K^+, Na^+ and aldosterone did not change. The SVR decreased significantly and correlated directly with BP reduction.

Digiesi *et al* in 1990[603] evaluated 18 subjects with essential hypertension, off all antihypertensive drugs, treated with CoQ_{10}, 100 mg orally per day for 10 weeks versus placebo, then subjects were crossed over to the opposite study group after a two week treatment suspension. Compared to the placebo subjects, there was a significant reduction in SBP from 166 $\pm$ 2.6 mm Hg to 156 $\pm$ 2.25 mm Hg and DBP from 102.9 $\pm$ 1.2 mm Hg to 95.2 $\pm$ 1.04 mm Hg, both significant at $p < 0.001$. The placebo group had no significant reduction in BP. The antihypertensive effect of CoQ_{10} was observed during the third and fourth week of treatment, remained constant for the entire duration of treatment and ceased seven to ten days after the end of drug treatment. No adverse effects were noted.

Recently, Singh *et al*[602] evaluated 30 treated hypertensive subjects with CHD treated with CoQ_{10}, 60 mg BID, for eight weeks versus a vitamin B complex. The CoQ_{10} treated subjects had a reduction in SBP from 168 $\pm$ 9.6 mm Hg to 152 $\pm$ 8.2 mm Hg (16 mm Hg reduction, $p < 0.05$) and a DBP reduction from 106 $\pm$ 4.6 mm Hg to 97 $\pm$ 4.1 mm Hg

(9 mm Hg reduction, $p < 0.05$). In addition, the heart rate fell from 112 ± 7.8 to 85 ± 4.8 per minute ($p < 0.05$). Fasting and two hour insulin fell 45% and 35% respectively ($p < 0.05$), as fasting glucose decreased 33% ($p < 0.05$). Serum TG fell 10% and HDL-cholesterol increased significantly ($p < 0.05$), lipid peroxides decreased ($p < 0.05$), malondialdehyde fell ($p < 0.05$) and olene conjugates were reduced ($p < 0.05$). Serum vitamin A, C, E and beta carotene levels increased. The only changes in the B-vitamin complex group were increases in vitamin C and beta carotene ($p < 0.05$).

The mechanism of action of CoQ_{10} includes a reduction in SVR, decreased degradation of membrane phospholipids, decreased membrane phospholipase A_2 activity, membrane stabilizing activity, decreased catecholamine and aldosterone levels, improved insulin sensitivity, decreased OxLDL, antioxidant effects on endothelium and vascular smooth muscle (VSM) with increased NO, decreased VSM hypertrophy, vasodilation, decreased ED and improved mitochondrial energy production with less vascular ischemia.[397,602,603,607]

In summary, CoQ_{10} has consistent and significant antihypertensive effects in patients with essential hypertension. The major conclusions from *in vitro*, animal and human clinical trials indicate the following:

1. Compared to normotensive patients, essential hypertensive patients have a high incidence of CoQ_{10} deficiency documented by serum levels 2. Doses of 120 to 225 mg per day of CoQ_{10}, depending on the delivery method and concomitant ingestion with a fatty meal, are necessary to achieve a therapeutic level of over 2 ug/ml. This is usually 1-2 mg/kg/day of CoQ_{10}. The best studied and most bioavailable CoQ_{10} supplement is Q-Gel, (Tishcon Corp, Westbury, New York). Use of this special delivery system allows better absorption and lower oral doses.
3. Patients with the lowest CoQ_{10} serum levels may have the best antihypertensive response to supplementation.
4. The average reduction in BP is about 15/10 mm Hg based on reported studies.
5. The antihypertensive effect takes time to reach its peak level, usually at about four weeks, then BP remains stable. The antihypertensive effect is gone within two weeks after discontinuation of CoQ_{10}.
6. Approximately 50% of patients on antihypertensive drugs may be able to stop between one and three agents. Both total dose and frequency of administration may be reduced.
7. Even high doses of CoQ_{10} have no acute or chronic adverse effects.

Other favorable effects on cardiovascular risk factors include improvement in the serum lipid profile and carbohydrate metabolism with reduced glucose and improved insulin sensitivity, reduced oxidative stress, reduced heart rate, improved myocardial LV function and oxygen delivery and decreased catecholamine levels.

ALPHA LIPOIC ACID (ALA)

Alpha lipoic acid (ALA) is a potent and unique thiol compound-antioxidant that is both water and lipid soluble.[377] Alpha lipoic acid helps to recirculate tissue and blood levels of vitamins and antioxidants in both lipid and water compartments such as vitamin C and vitamin E, glutathione, and cysteine.[377,619,620] To date, only animal studies in the SHR have been performed to determine the effects of ALA on the vasculature and BP.[377,619,621] Vasdev *et al* [619] administered 500 mg/kg/day in their feed, which was equivalent to 26 mg/kg body weight of ALA to the SHR for nine weeks. There was a significant decrease in SBP ($p < 0.001$), as well as reduction in cytosolic and platelet, calcium, glucose, insulin levels, tissue aldehyde conjugates in the liver, kidney and aorta. Most important, there was evidence of structural improvement in the vasculature with reduced vascular damage, hypertensive VSMH and atherosclerotic changes. The reduction in SBP in the ALA-treated SHR was from a mean of 180 mm Hg to 140 mm Hg ($p < 0.001$); whereas the untreated SHR had an increase in SBP from a baseline of 180 mm Hg to 195 mm Hg over the nine-week study period. The decrease in BP was gradual and did not show a further decrease after five weeks of ALA treatment.

The vascular changes in the kidneys of the untreated SHR showed hyperplasia of the smooth muscle, thickening and narrowing of the lumina of the small arteries and arterioles, vacuoles and PAS-positive material in the walls of the arteries. On the other hand, the ALA-treated SHR kidneys had minimal smooth muscle cell hyperplasia, minimal thickening of the wall and no narrowing of the lumina in the small arteries and arterioles. Thus, ALA attenuated the renal vascular hyperplasia in the SHR. In this study of the SHR, ALA reduced blood pressure, biochemical and histologic changes. The dose that would be required for an average 70 kg human patient would be about 2,000 mg per day of ALA. However, it should be emphasized that no dose response study in human hypertension has been done to date.

The mechanisms by which ALA reduces BP and promotes improvement in vascular function and structure are numerous.[619,620,622-632] It is known that endogenous aldehydes bind sulfhydryl groups (-SH) in membrane proteins that alter membrane calcium channels (especially L-type calcium channels), which increase cytosolic free calcium, increase vascular tone, SVR and BP.[619] Thiol compounds, such as ALA and N-acetyl cysteine (NAC), bind these endogenous aldehydes, normalize the membrane calcium channels and decrease cytosolic free calcium. In addition,

Table 29

Alpha Lipoic Acid (ALA) : Mechanism of Action[619,620,622,623,624,625,626,627,628,629,630,631,632]

1. Increases levels of glutathione, cysteine, Vitamin-C and E[619,624]
2. Binds endogenous aldehydes, reduces production and increases excretion[619,622,623,624]
3. Normalizes membrane calcium channels by providing sulfhydryl groups (-SH) which reduces cytosolic free calcium, SVR, Vascular tone and BP. DHLA is redox partner of ALA[619]
4. Improves insulin sensitivity and glucose metabolism, reduces advanced glycosylation and products (AGE's) and thus Aldehydes[619,622,623,625,626,627,628,629]
5. Increases NO levels, stability and duration of action via increase nitrosothiols such as S-nitrosocysteine and S-nitroglutathione which carry NO[631]
6. Reduces cytokine-induced generation of NO (iNOS)[620,621,631]
7. Inhibits release and translocation of NF-KB from cytoplasm into nucleus of cell which decreases controlled gene transcription and regulation of endothelin-I, Tissue Factor, VCAM-1[620,621]
8. Improves ED through beneficial effects on NO, AGE's, Vitamin-C and E, glutathione, cysteine, endothelin, Tissue Factor, VCAM-1, Linoleic and myristic acid[619,620,622,623,625,626,627,628,629,631,632]
9. Reduces monocyte binding to endothelium (VCAM-1)[620,632]
10. Increase linoleic acid and reduce myristic acid[630]

ALA increases levels of glutathione and cysteine, which bind aldehydes and increase their excretion, and increase antioxidant-vitamin levels of ascorbic acid and vitamin E, which improve endothelial dysfunction. ALA acts like a calcium channel blocker (CCB) through these indirect mechanisms (Figure 24 and Figure 25). A detailed summary of the mechanism of action of ALA is shown in Table 29. Glutathione, which supplies 90% of nonprotein thiols in the body, is depleted in SHR and human hypertension; thus, ALA by increasing levels significantly, reducing aldehydes and closing L-type calcium channels in cell membranes may reduce vascular tone, SVR and BP.[625,626,627,628,629]

N-ACETYL CYSTEINE (NAC)

N-acetyl cysteine (NAC), a source of sulfhydryl groups, is a potent thiol compound and antioxidant that scavenges radical oxygen species (ROS) and supports intracellular glutathione synthesis by binding to endogenous aldehydes, reducing their production and increasing excretion to non-toxic compounds.[633,634,635,636,637] N-acetyl cysteine also increases interleukin 1-B (IL-1B)-induced nitrite production by increasing (Nitric Oxide Synthase - messenger RNA) transcription and protein expression, elevating NO levels, reducing SVR and BP. These antihypertensive effects of NAC have been shown in SHR, but no human hypertensive studies have been published to date. Similar to ALA, NAC improves the L-type calcium channel in cell membranes, which decreases cytosolic calcium, SVR and BP through aldehyde binding.[634,635,636,637]

N-acetyl cysteine in doses of 600 mg per day improved capillary blood flow velocity in smokers through its antioxidant effect by improving glutathione levels, reducing ROS, increasing NO, decreasing peroxynitrate and improving ED.[638] Furthermore, NAC lowers homocysteine[639,640,641,642] and lipoprotein (a)[639] and potentiates nitroglycerin-mediat-

Table 30

Nutrients and Nutraceuticals *with* Calcium Channel Blocking (CCB) Activity

1. Alpha Lipoic Aacid (ALA)
2. Magnesium (Mg^{++})
3. Vitamin B-6 (Pyridoxine)
4. Vitamin C
5. Vitamin E ? (↑ cytosolic Mg^{++} with ↓ Ca^{++})
6. N-Acetyl Cysteine (NAC)
7. Hawthorne
8. Celery
9. Omega-3 fatty acids (EPA + DHA)
10. Calcium
11. Garlic

Figure 24[619,620,622,623,624,625,626,627,628,629,630,631,632]

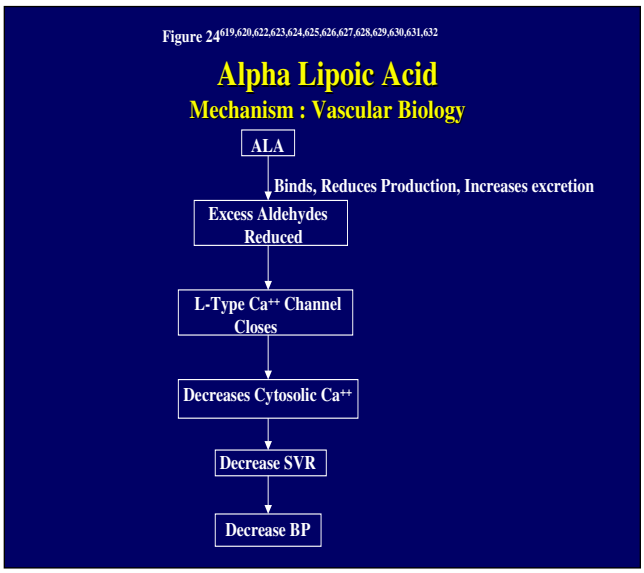
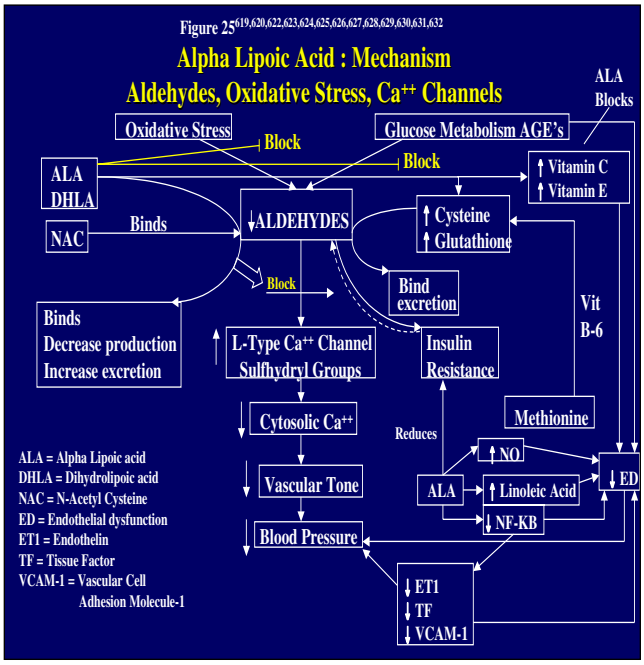


Figure 25[619,620,622,623,624,625,626,627,628,629,630,631,632]



ed vasodilation[643] and reversal of platelet aggregation.[644] All of these effects may have beneficial effects on the vascular system and BP. N-acetyl cysteine, like ALA, magnesium, vitamin B_6, vitamin C and possibly vitamin E, have natural calcium channel blocking activity (Table 30).

Cabassi *et al*[645] have recently shown that NAC treatment in the SHR improves SBP, HR, aortic endothelial function, peroxynitrite-induced impairment of endothelial-independent relaxation, aortic oxidized/reduced glutathione balance (GSSG/GSH), malondialdehyde (MDA) content and 3-nitrotyrosine (3-NT). NAC may have both an antihypertensive effect as well as a protective effect against aortic vascular dysfunction.[545]

L-ARGININE

L-arginine is the primary precursor for the production of nitric oxide (NO)[646,647] (Figures 6, 7 and 11), which has numerous cardiovascular effects[57,535,647] (Table 6), mediated through conversion of L-arginine to NO by eNOS to increase cyclic GMP levels in VSM, improve ED and reduce vascular tone and BP.[648] Patients with hypertension, hyperlipidemia and atherosclerosis have elevated serum levels of ADMA, which activates NO.[535,649] Administration of L-arginine in humans at doses of 10 grams per day will increase coronary artery blood flow, reduce angina and improve peripheral blood flow and peripheral vascular disease symptoms.[535,650,651,652]

Hypertension induced by NACL loading in the Dahl sensitive rats,[653,654,655] in adrenocorticotrophin (ACTH)-induced hypertension in the Sprague-Dawley rats[656] and in the SHR (spontaneously hypertensive rats) can be prevented and partially reversed by chronic and acute dietary L-Arginine supplementation. L-Arginine reduced BP, SVR, LV mass, collagen content, improved coronary hemodynamics and restored plasma Nox (nitrite/nitrate) and citrulline concentrations.[656,657]

Human studies in hypertensive and normotensive subjects of parenteral and oral administrations of L-arginine demonstrate an antihypertensive effect.[648,658,659,660] The intravenous administration of large doses of L-Arginine acutely reduces BP in normotensive and in salt-sensitive, hypertensive individuals,[658,659,660] but not in cortisol-induced hypertension in humans. Siani *et al*[648] evaluated six healthy,[661] normotensive volunteers in a single-blinded, controlled study utilizing three different isocaloric diets with equal sodium content in each (180 mmol/day) administered in a crossover design in random sequence, each for a one week period. Diet one was the control diet containing 3.5 to 4 grams of L-arginine per day. Diet two contained natural arginine enriched foods at 10 grams of L-arginine per day. Diet three consisted of diet one plus an L-arginine supplement of 10 grams per day. It should be noted that the average arginine intake per day is 5.4 grams/100 grams of protein, which is found especially in lentils, hazelnuts, walnuts and peanuts.[648] The BP decreased significantly in both diets two and three. In diet two, the BP fall was 6.2/5.0 mm Hg ($p < 0.03$ for SBP and $p < 0.002$ for DBP). In diet three, the BP fell 6.2/6.8 mm Hg ($p < 0.01$ for SBP and $p < 0.006$ for DBP). In addition, in diet three, creatinine clearance increased ($p < 0.07$), glomerular filtration rate increased ($p < 0.07$) and fasting glucose fell ($p < 0.008$). The reduction in TC and TG with increased HDL in diet two was thought to be secondary to the natural high fiber intake.

L-arginine is not normally the rate limiting step in NO synthesis.[662] Alternative mechanisms may exist whereby L-arginine lowers BP through direct effects of the amino acid on the vasculature or endothelium, as well as release of hormones, vasodilating prostaglandins, improved renal NO, or endothelial NO bioavailability.[648]

L-arginine produces a statistically and biologically significant decrease in BP and improved metabolic effect in normotensive and hypertensive humans similar in magnitude to that seen in the DASH-I diet.[193,648] This reduction in BP was seen whether L-arginine was provided through natural foods or as a pharmacologic supplement when given at approximately a two-fold dietary increase (doses of 10 grams per day).[648] Although these doses of L-arginine appear to be safe, no long term studies in humans have been published at this time. A good supplemental source of L-arginine is the Heart Bar™ (Cooke Pharmaceuticals, Inc., Silver Springs, Maryland), which supplies 3.3 grams of L-arginine per bar.

HAWTHORN

Hawthorn may reduce SVR and BP,[14,301,377,663,664] decrease the pressure-rate product in the myocardium, improve ejection fraction and CHF,[301,663,664] improve arrhythmias,[663,664] lower cholesterol,[663] dilate coronary arteries and improve myocardial perfusion and angina.[301,664] The mechanism of some of these effects is the angiotensin converting enzyme inhibition (ACEI) effect of Hawthorn.[14,377,665] No controlled clinical trials in hypertensive individuals have been reported to date. Doses of about 160 to 900 mg per day of a standardized extract of Hawthorn have been used to achieve these cardiovascular effects, which appears to be safe.[663,664] Hawthorn contains oligomeric procyanidins, flavonoids, hyperoside, quercetin, vitexin and vitexin rhamnoside, which may also have beta-blocking, calcium-channel-blocking and diuretic effects.[663] The hypolipidemic effects are due to beta-sitosterol, catechin, chromium, fiber, linoleic acid, magnesium, pectin and rutin, all of which may also reduce BP as well.[663]

ALCOHOL

Acute and chronic alcohol intake elevates BP[666,667,668,669] and is a risk factor for stroke.[5] Alcohol also causes a biphasic hemodynamic response with initial vasodilation and a subsequent pressor response.[670] Epidemiologic observational studies indicate that more than 20 grams of alcohol per day (more than three drinks a day) is associated with both the incidence and severity of hypertension and resistance to antihypertensive therapy.[5,18,666,671] Tsuruta *et al*[672] reported a 12 year prospective study of 325 normotensive Japanese men with a mean BP $\leq$ 140/90 mm Hg. The odds ratio was 2.39 to develop hypertension with an alcohol intake of over 46 gm/day versus those consuming less than 46 gm/day, adjusted for age, BMI, SBP, tobacco use and family history. The BP levels were significantly different at $p < 0.01$ at the conclusion of the study with a BP of 125.2/75 mm Hg in nondrinkers and 134.9/80.2 mm Hg in heavy drinkers. However, this study did not adjust for sodium intake or exercise, and alcohol consumption was self-reported. In the Atherosclerosis Risk in Communities Study (ARIC), consumption of all alcoholic beverages in amounts of $\geq$ 210 grams per week was an independent risk factor for hypertension.[666]

Numerous observational and clinical studies have consistently demonstrated that reduction or moderation in alcohol intake as well as complete cessation lowers BP and concomitantly increases serum magnesium and potassium.[18,673,674,675,676,677,678,679,680] It is recommended that hypertensive patients limit alcohol intake to less than 20 grams per day; that is the equivalent of 10 ounces of wine, 24 ounces of beer or 2 ounces of hard liquor . These amounts do not elevate BP and may be associated with a lower risk of CHD[5,681] and cancer, and all cause mortality, especially in wine drinkers.[681] The relative risk for death from all causes among wine drinkers was 0.66 (CI 0.55 to 0.77) compared to nondrinkers, and the CHD mortality was significantly lower ($p = 0.0007$)[681]

CAFFEINE

The hemodynamic and blood pressure effects of caffeine remain controversial and inconclusive.[5] Caffeine elevates BP acutely, but tolerance to this effect develops with chronic ingestion.[5] Most epidemiologic studies do not show a direct relationship between elevated BP and caffeine intake.[5]

Consumption of caffeine at a dose of 3.3 mg per kg will acutely increase SBP 5 to 9 mm Hg and DBP 3 to 8 mm Hg for 30 to 60 minutes in subjects who have avoided caffeine for 12 hours or more.[451,682,683,684] Individuals consuming caffeine 250 mg three times daily for seven days showed significant increase in DBP ($p < 0.05$) 24 hours after the first intake, but this disappeared in the subsequent days.[684]

Consumption of two to three cups of coffee per day increased BP and cortisol secretion at rest and during stress.[685,686,687,688,689,690,691,692] The combination of caffeine and stress will elevate BP more than either alone with a mean increase in BP of 12/8 mm Hg.[685] Other studies suggest that the hypertensive and cortisol responses to caffeine occur in habitual users, not just acutely, and there is no tolerance to caffeine's effects.[685] There are obvious individual variations to caffeine's hemodynamic and BP effects. It would be prudent to eliminate or restrict caffeine in most hypertensive patients to less than 100 mg per day.

L-CARNITINE

L-carnitine is a nitrogenous constituent of muscle primarily involved in the oxidation of fatty acids in mammals.[693] Clinical and experimental studies demonstrate significant therapeutic benefits in L-carnitine and its derivative, propionyl-L-carnitine (PLC) in the treatment of diabetes mellitus,[535,694] hypertension,[695] ischemic heart disease,[535,694,696] acute MI,[535,694] CHF,[535,694,697,698,699] arrhythmias and peripheral vascular disease with claudication[535,693,694,700,701,702] and dyslipidemia.[535,694]

Human studies on the effects of L-carnitine are small and limited.[695] Digiesi *et al*[695] compared three groups of subjects with essential hypertension. Group A-1, with 14 subjects, received antihypertensive drugs (ACEI and/or CCB) and L-carnitine 2 grams a day. Group A-2, with 14 subjects, received only antihypertensive drugs (ACEI or CCB). Group B, with 9 subjects, was treated with L-carnitine only at 2 grams per day. Group A-1 and B subjects received oral L-carnitine, 2 grams per day for 22 and 10 weeks respectively. Group A-1 subjects had reductions in extrasystoles, improved electrocardiograms (signs of minor changes of ventricular repolarization), less asthenic symptoms (decrease by 90% versus only a 10% decrease in control subjects) and lower TG levels ($p < 0.025$), but no change in total cholesterol or HDL-C. The group B subjects had improvement in left ventricular ejection fraction from 57.89% to 64.33% ($p < 0.001$), reduced TC ($p < 0.02$), and increased HDL-C ($p < 0.05$) with no change in TG. The BP decreased from a SBP of 155 ± 4.86 mm Hg to 150.89 ± 5.39 mm Hg (NS) and DBP fell from 97.22 ± 1.88 mm Hg to 94.78 ± 2.90 mm Hg (NS).

Carnitine may be useful in the treatment of essential hypertension, type II DM with hypertension, hyperlipidemia, cardiac arrhythmias, CHF and cardiac ischemic syndromes.[695,703,704,705,706,707,708,709,710]

Ghidini *et al*[703] administered L-carnitine, 1 gram, orally twice daily to 38 patients with hypertensive or ischemic heart disease and congestive heart failure in a 45-day placebo-controlled study. Both groups had significant improvement compared to baseline with subjective and objective parameters such as reductions in heart rate ($p < 0.01$), SBP ($p < 0.01$), DBP ($p < 0.05$), edema ($p < 0.01$), dyspnea ($p <$

0.01), daily digitalis consumption ($p < 0.01$) and weight ($p < 0.01$). All patients had a significant diuresis ($p < 0.01$), improved angina, less arrhythmias, ventricular extrasystoles, echocardiographic changes and moved to a lower NYHA category. However, only the lipid changes and digitalis use were significantly different between groups even though the carnitine-treated patients trended toward more improvement in all parameters. This may have been due to the limited size of the trial population. The TC and TG were significantly reduced only in the carnitine-treated patients ($p < 0.05$ for TC and $p < 0.001$ for TG).

TAURINE

Taurine is a sulfonic beta-amino acid that is considered a conditionally-essential amino acid, which is not utilized in protein synthesis, but rather is found free or in simple peptides with its highest concentration in the brain, retina and myocardium.[711,712] In cardiomyocytes, it represents about 50% of the free amino acids and has a role of an osmoregulator and inotropic factor and has been used to treat hypertension,[713] hypercholesterolemia, arrhythmias, atherosclerosis, CHF and other cardiovascular conditions.[711,712,714,715]

Animal studies have shown consistent and significant reductions in BP.[716,717,718,719,720,721,722,723,724,725,726] Taurine inhibited the alcohol-induced hypertension in SHR by reducing acetylaldehyde and changing membrane cation handling.[716] In the SHR-high sodium model, taurine reduced proteinuria and lowered BP 20-25%,[722] and reduced LVH, urinary epinephrine, and dopamine.[717,726] The DOCA-salt rat model had BP reduction due to decreased sympathetic nervous system (SNS) activity centrally[718,720] due to an opiate-mediated vasodepressor response.[721,724] Taurine increases renal kallikrein[725] and has an anti-atherosclerotic effect.[723]

Human studies have noted that essential hypertensive subjects have reduced urinary taurine as well as other sulfur amino acids.[727,728] Taurine lowers BP[713,714,715,728,729,730] and HR,[715] decreases arrhythmias,[715] CHF symptoms[715] and SNS activity,[713,715] increases urinary sodium[729,731] and decreases PRA, aldosterone,[731] plasma norepinephrine,[730] and plasma and urinary epinephrine.[713,732] This diuretic effect is seen in normal subjects as well as hypertensive and cirrhotics with ascites.[729,730,731,732] In doses of 6 grams per day for three weeks in 22 healthy, normotensive, male volunteers, taurine reduced SNS activity, urinary epinephrine, TC and LDL, but increased TG, while BP and BMI did not change significantly.[732] Another study of 31 Japanese males with essential hypertension placed on an exercise program for 10 weeks showed a 26% increase in taurine levels and a 287% increase in cysteine levels. The BP reduction of 14.8/6.6 mm Hg was proportional to both taurine level elevations and plasma norepinephrine reduction.[730] Fujita *et al*[713] reduced BP 9/4.1 mm Hg ($p < 0.05$) in 19 hypertension subjects given 6 grams of taurine for seven days.

The mechanisms by which taurine exerts its cardiovascular and antihypertensive effects include diuresis[712,731] and urinary sodium loss,[731] vasodilation,[712] increased atrial natriuretic factor (ANF),[712] reduced homocysteine,[711] improved glucose and insulin sensitivity,[727] increased sodium space,[719] reduced SNS activity and opiate mediated vasodepressor response,[721,724] increased renal kallikrein,[725] reduced PRA and aldosterone,[731] and a glycine mediated CNS response with decreases in both BP and HR.[733]

Concomitant use of enalapril with taurine provides additive reductions in BP, LVH, arrhythmias[734,735] and platelet aggregation.[735] The recommended dose of taurine is two to three grams per day at which no adverse effects are noted, but higher doses may be needed to reduce BP significantly.[713]

CELERY

Animal studies have demonstrated a significant reduction in BP using a component of celery oil, 3-N-butyl phthalide.[736,737] There was a dose response relationship in SBP with a 24 mm Hg fall (14%) ($p < 0.05$) in the Sprague-Dawley hypertensive rat model.[737] Significant decreases in plasma norepinephrine, epinephrine and dopamine were also highly dose dependent. Celery, celery extract and celery oil contain apigenin, which relaxes VSM, CCB-like substances and components that inhibit tyrosine hydroxylase, which reduces plasma catecholamine levels, and lowers SVR and BP.[737,738] Consuming four stalks of celery per day, eight teaspoons of celery juice three times daily, or its equivalent in extract form of celery seed (1,000 mg twice a day), or oil (one-half to one teaspoon three times daily in tincture form) seems to provide a similar antihypertensive effect in human essential hypertension.[663,738,739,740] In a Chinese study of 16 hypertensive subjects, 14 had significant reductions in BP.[738,739,740] Celery also has diuretic effects that may reduce BP.[738,739,740] In addition, celery has been used to treat CHF, fluid retention, anxiety, insomnia, gout, and diabetes.[738,739,740]

MISCELLANEOUS

1. Nicotinamide Adenine Dinucleotide (NADH)

Nicotinamide adenine dinucleotide (NADH) was shown to significantly reduce SBP in SHR compared to the placebo rats after a 10 weeks oral NADH supplement ($p < 0.001$). In addition, TC decreased ($p < 0.002$), LDL decreased ($p < 0.02$) and measures of renal oxidative stress decreased ($p < 0.001$).[741] No human studies in essential hypertension with NADH have been done, but therapeutic doses for other medical problems range from 2.5 mg to 20 mg per day orally as the formulation ENADA.

2. Chlorella

A study of 24 hypertensive patients given 10 grams of chlorella tablets and 100 ml of chlorella extract per day had no significant mean change in BP.[742] However, a small subgroup of six patients had a reduction in DBP from 96.5 mm Hg to < 90 mm Hg. Effects on ED, SNS or the replacement of K^+, Mg^{++}, Ca^{++} and fiber may account for the antihypertensive effect.[742]

3. Guava Fruit

Singh *et al*[743] evaluated 72 patients with essential hypertension treated with 0.5 to 1.0 kg of guava fruit daily for four weeks in a randomized, single-blind, placebo-controlled trial. The patients receiving guava had a net decrease in mean BP of 7.5/8.5 mm Hg ($p < 0.05$). The high content of soluble fiber and potassium may account for the BP lowering.[743]

4. Herbs

Various herbs and plants have been reported to have antihypertensive effects in animals or humans, but the studies are small and less conclusive or they have only anecdotal-folk uses.[663,664,738] These include ashwagandha, jiaogulan, onions and onion oil (botanical relative of garlic), maitake mushrooms, dill, lemon or lemon peel (flavonoids), purslane, yinyanghuo, devil's claw, kudzu root or tea (isoflavone), guar gum and kaffie potato (forskolin or coleonol),[663,664,738,744] reishi,[745] skull cap,[745] siberian ginseng,[745] capsicum (cayenne),[745] fumitoroy (diuretic),[745] ginger (diuretic),[745] angelica,[744] anise,[744] banana,[744] baytree,[744] cashew,[744] echinacea,[744] eucalyptus,[744] german chamomile,[744] ginkgo biloba,[744] indian mulberry,[744] lotus,[744] neem,[744] nutmeg,[744] puncture vine[744] and St. John's wort.[744]

NUTRITIONAL AND DIETARY SUPPLEMENTS: QUALITY CONTROL AND CERTIFICATION: DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT (DSHEA)

In 1994, the United States Congress passed the Dietary Supplement Health and Education Act (DSHEA),[746] allowing for the marketing of a product claimed to affect the structure or function of the body as a "dietary supplement" without the approval of any government agency, provided the labeling includes a disclaimer saying that is has not been evaluated by the FDA and the product is not intended to diagnose, treat or prevent any disease. A "dietary supplement" in this act is defined as "a vitamin, a mineral, an herb or other botanical or an amino acid". If a question about safety arises, the burden of proof is on the Food and Drug Administration (FDA), not the manufacturer. No requirement to prove purity exists for dietary supplements sold in pharmacies, health food stores and supermarkets in the United States.[747]

During the past 10 years, however, dietary supplements have been reported to have fewer and less serious side effects than prescription drugs, estimated to be 100,000 deaths per year.[747,748] Certified, high quality supplements with standardized ingredients that are bioavailable and potent with 100% purity, no toxicity or adverse effects and have accurate labeling and expiration dates should be sought by the wise consumer. The terms "all natural", "organic", "herbal", etc., do not necessarily imply potency, purity, safety, or efficacy.

Table 31[10,11,12,13]

SUBSETS OF HYPERTENSION APPROACH TO THE SELECTION OF ANTIHYPERTENSIVE DRUGS

These eight parameters allow for logical individualized, pathophysiologic and clinical selection of drugs based on recent clinical hypertension outcome trials.

1. Pathophysiology: Membranopathy, ion transport defects, structural factors, smooth muscle hypertrophy (vascular, cardiac, cerebral, renal), functional factors, vasoconstrictive forces, endothelial dysfunction.
2. Hemodynamics: SVR, CO, arterial compliance, organ perfusion, BP. Select the appropriate therapy to reverse the circulatory dysregulation.
3. End-organ damage: Reduce risk factors for *all* end-organ damage.
4. Concomitant medical diseases and problems: Select antihypertensive medications with favorable or neutral effects.
5. Demographics: Race, age, gender.
6. Adverse effects of drugs and quality of life.
7. Compliance with medication regimen.
8. Total health care costs: Direct and indirect costs.

MEDICATIONS, TOXINS OR DRUGS THAT INCREASE BLOOD PRESSURE

Numerous medications, toxins or drugs have the potential to elevate BP directly or interfere with antihypertensive medications.[5,10] These include oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAID's), cyclooxygenase inhibitors (COX-2), decongestant/antihistamine combinations with ephedrine, pseudoephedrine and phenylpropanolamine, corticosteroids, mineralocorticoids, anabolic steroids, ephedra, "energy pills", "diet pills", amphetamines, licorice, tricyclic antidepressants, monoamine oxidase inhibitors (MAO), ergot alkaloids, lead, cadmium, thallium, red ginseng, "herbal phen-fen", cocaine, cyclosporine, erythropoietin, bromocriptine, nasal decongestants, caffeine, tacrolimus, alcohol and others.[5,10] These should be decreased or eliminated in patients with hypertension.

ANTIHYPERTENSIVE DRUG TREATMENT

Approximately 40 to 50% of patients with essential hypertension may require antihypertensive drug therapy

once a diagnosis of essential hypertension is firmly established by JNC-VI guidelines.[5,10] These drugs should be used in conjunction with the lifestyle modifications, nutritional guidelines, nutraceutical supplements, weight loss, exercise, tobacco cessation, and limited use of alcohol and caffeine as discussed in this paper. Goal BP levels are well established depending on the concomitant medical diseases, risk factors, TOD, and CCD reported in JNC-VI and these should be met to reduce TOD.[5] Selection of drugs and dose will depend on many factors that are best determined by using the Subsets of Hypertension Approach[11,12,13] (Table 31).

The primary goal in the treatment of essential hypertension is to prevent and reduce *all* end-organ damage, not simply to reduce BP. Hypertension is associated with an increased risk of cerebrovascular, cardiovascular and renal morbidity and mortality. Pharmacologic therapy has reduced some, but not all, of these complications. To achieve optimal decreases in morbidity and mortality in hypertensive-related diseases, the overall impact of antihypertensive drug therapy on the pathogenesis of damage to each end organ must be considered.[10]

Although a higher percentage of deaths occurs in patients with diastolic blood pressure (DBP) $\geq$ 105 mm Hg, patients with DBP $\leq$ 105 mm Hg actually account for more deaths. The majority of patients (60 to 70%) with essential hypertension have DBP $\leq$ 105 mm Hg. The risks of therapy versus the benefits of therapy are particularly critical in this group. Pharmacologic therapy of essential hypertension with DBP $\leq$ 110 mm Hg has reduced the complications of most pressure-related (arteriolar) damage, such as CVA, CHF, and some cases of CRF, but the atherosclerotic complications (CHD, angina, MI, and sudden death) have not been reduced to the extent predicted by the degree of BP reduction in those prospective clinical trials in which diuretics and beta blockers were the primary antihypertensive drugs used.[10,11,12,13] The role of beta blocker monotherapy in reducing CHD in the elderly has been questioned.[10] In addition, beta blockers induce insulin resistance, hyperglycemia, hyperuricemia and dyslipidemia.[10] The indiscriminate use of diuretics may be associated with a higher incidence of colon and renal cell carcinoma, progressive proteinuria and renal insufficiency, induce hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, insulin resistance, homocysteinemia, dyslipidemia, thrombosis and do not seem to optimally reduce CHD.[10]

A more sophisticated and pathophysiologically oriented pharmacologic approach based on our knowledge of vascular biology, endothelial dysfunction, and the complex interplay of the *hypertension/atherosclerotic syndrome* is needed. The newer drugs such as calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) appear to offer some distinct advantages in both surrogate end points, improvement in vascular remodeling, arterial compliance, endothelial dysfunction and target organ damage, compared to older drugs (diuretics, beta blockers).

The currently FDA-approved single antihypertensive drugs and combination drugs are listed in Table 32 and Table 33.[10,749] Newer drugs such as CCB, ACEI, and ARB's have distinct advantages on vascular biology (function and structure) as well as many clinical endpoints. These agents also have better metabolic profiles and meet most of the criteria for selection based on the subsets approach to hypertension. They are also coming closer to the "characteristics of an ideal antihypertensive drug" (Table 34).[10] In the author's opinion, CCB, ACEI and ARB's as monotherapy or in low dose combination are superior to diuretics and beta blockers for the drug treatment of hypertension.

The addition of lifestyle modification with low dose combination antihypertensive drugs (CCB, ACEI, ARB) provides additive or synergistic BP reduction, improved risk factors and metabolic parameters, improved vascular structure and function, allows for lower doses and number of drugs with reduced side effects and may be superior in reducing TOD.

Table 32[10,749]

ORAL DRUGS FOR HYPERTENSION APPROVED CURRENTLY BY THE FDA

Drug	Daily Adult Maintenance Dosage
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS	
Benazepril – *Lotensin* (Novartis)	10-80 mg in 1 or 2 doses
Captopril – average generic price	12.5-150 mg in 2 or 3 doses
Capoten (Apothecon)	
Enalapril – average generic price	2.5-40 mg in 1-2 doses
Vasotec (Merck)	
Fosinopril – *Monopril* (Bristol-Myers Squibb)	10-40 mg in 1 or 2 doses
Lisinopril – *Prinivil* (Merck)	5-40 mg in 1 dose
Zestril (AstraZeneca)	
Moexipril – *Univasc* (Schwarz)	7.5-30 mg in 1 or 2 doses
Perindopril – *Aceon* (Solvay)	4-8 mg in 1 or 2 doses
Quinapril – *Accupril* (Parke-Davis)	5-80 mg in 1 or 2 doses
Ramipril – *Altace* (Monarch)	1.25-20 mg in 1 or 2 doses
Trandolapril – *Mavik* (Knoll)	1-4 mg in 1 dose

Drug	Daily Adult Maintenance Dosage
ANGIOTENSIN II RECEPTOR ANTAGONISTS	
Candesartan cilexetil – *Atacand* (AstraZeneca)	8-32 mg in 1 dose
Eprosartan – *Teveten* (Unimed)	400-800 mg in 1 or 2 doses
Irbesartan – *Avapro* (Bristol-Myers Squibb)	150-300 mg in 1 dose
Losartan – *Cozaar* (Merck)	25-100 mg in 1 or 2 doses
Telmisartan – *Micardis* (Abbott Pharm)	40-80 mg in 1 dose

Table 32[10,749] Continued

Drug	Daily Adult Maintenance Dosage
ANGIOTENSIN II RECEPTOR ANTAGONISTS	
Valsartan – *Diovan* (Novartis)	80-320 mg in 1 dose
BETA-ADRENERGIC BLOCKING DRUGS	
Atenolol – average generic price	25-100 mg in 1 or 2 doses
Tenormin (AstraZeneca)	
Betaxolol – average generic price	5-40 mg in 1 dose
Kerlone (Searle)	
Bisoprolol – average generic price	5-20 mg in 1 dose
Zebeta (ESI Lederle)	
Metoprolol – average generic price	50-200 mg in 1 or 2 doses
Lopressor (Novartis)	
extended release	
Toprol-XL (AstraZeneca)	50-400 mg in 1 dose
Nadolol – average generic price	20-320 mg in 1 dose
Corgard (Apothecon)	
Propranolol – average generic price	40-240 mg in 2 doses
Inderal (Wyeth-Ayerst)	
Extended release –average generic price	60-240 mg in 1 dose
Inderal-LA (Wyeth-Ayerst)	
Timolol – average generic price	10-40 mg in 2 doses
Blocadren (Merck)	
Beta-Blockers with Intrinsic Sympathomimetic Activity	
Acebutolol – average generic price	200-1200 mg in 1 or 2 doses
Sectral (Wyeth-Ayerst)	
Carteolol – *Cartrol* (Abbott)	2.5-10 mg in 1 dose
Penbutolol – *Levatol* (Schwartz)	20 mg in 1 dose
Pindolol – average generic price	10-60 mg in 2 doses
Visken (Novartis)	
Beta-Blockers with Alpha-1 Blocking Activity	
Carvedilol – *Coreg* (GlaxoSmithKline)	12.5-50 mg in 2 doses
Labetalol –average generic price	200-1200 mg in 2 doses
Normodyne (Key)	
Trandate (GlaxoSmithKline)	
DIURETICS	
Thiazide-Type (Usually once daily)	
Chlorothiazide – average generic price	125-500 mg
Diuril (Merck)	
Hydrochlorothiazide – average generic price	12.5-50 mg
Esidrix (Novartis)	
Microzide (Watson)	
Chlorthalidone – average generic price	12.5-50 mg
Indapamide – average generic price	1.25-5 mg
Lozol (Aventis)	
Metolazone – *Zaroxolyn* (Medeva)	1.25-5 mg
Mykrox (Medeva)	0.5-1 mg

Table 32[10,749] Continued

Drug	Daily Adult Maintenance Dosage
Loop	
Bumetanide – average generic price	0.5-5 mg in 2 or 3 doses
Bumex (Roche)	
Ethacrynic acid – *Edecrin* (Merck)	25-100 mg in 2 or 3 doses
Furosemide – average generic price	20-320 mg in 2 or 3 doses
Lasix (Aventis)	
Torsemide – *Demadex* (Roche)	5-20 mg in 1 or 2 doses
Potassium-Sparing	
Amiloride – average generic price	5-10 mg in 1 or 2 doses
Midamor (Merck)	
Spironolactone – average generic price	12.5-100 mg in 1 or 2 doses
Aldactone (Pharmacia)	
Triamterene – *Dyrenium* (SK Beecham)	50-150 mg in 1 or 2 doses
CALCIUM-CHANNEL BLOCKERS	
Diltiazem – extended-release	120-360 mg in 2 doses
average generic price	
Cardizem SR (Biovail)	
extended-release (once per day)	
average generic price	
Cardizem CD (Biovail)	120-360 mg in 1 dose
Dilacor XR (Watson)	120-480 mg in 1 dose
Diltia XT (Andrx)	120-480 mg in 1 dose
Tiazac (Forest)	120-480 mg in 1 dose
Verapamil – average generic price	120-480 mg in 2 or 3 doses
Calan (Searle)	
extended-release	120-480 mg in 1 or 2 doses
average generic price (tablets)	
Calan SR (Searle)	
Covera-HS (Pharmacia)	180-480 mg in 1 dose
average generic price (capsules)	
Isoptin SR (Knoll)	
Verelan (Wyeth-Ayerst)	120-480 mg in 1 dose
Dihydropyridines	
Amlodipine – *Norvasc* (Pfizer)	2.5-10 mg in 1 dose
Felodipine – *Plendil* (AstraZeneca)	2.5-10 mg in 1 dose
Isradipine – *DynaCirc* (Novartis)	5-10 mg in 2 doses
Extended-release – *DynaCirc CR*	5-10 mg in 1 dose
Nicardipine – average generic price	60-120 mg in 3 doses
Cardene (Roche)	
extended-release	60-120 mg in 2 doses
Cardene SR (Roche)	
Nifedipine – extended-release	30-90 mg in 1 dose
average generic price	
Adalat CC (Bayer)	
Procardia XL (Pfizer)	
Nisoldipine – *Sular* (AstraZeneca)	10-60 mg in 1 dose

Table 32[10,749] Continued

Drug	Daily Adult Maintenance Dosage
ALPHA-ADRENERGIC BLOCKERS	
Prazosin – average generic price	First day: 1 mg at bedtime
Minipress (Pfizer)	Maintenance: 1-20 mg in 2 or 3 doses
Terazosin – average generic price	First day: 1 mg at bedtime
Hytrin (Abbott)	Maintenance: 1-20 mg in 1 dose
Doxazosin – average generic price	First day: 1 mg at bedtime
Cardura (Pfizer)	Maintenance: 1-16 mg in 1 dose
CENTRAL ALPHA-ADRENERGIC AGONISTS	
Clonidine – average generic price	0.1-0.6 mg in 2 or 3 doses
Catapres (Boehringer Ingelheim)	
transdermal – *Catapres TTS*	one patch weekly (0.1 to
(Boehringer Ingelheim)	0.3 mg/day)
Guanabenz – average generic price	4-64 mg in 2 doses
Wytensin (Wyeth-Ayerst)	
Guanfacine – average generic price	1-3 mg in 1 dose
Tenex (Robins)	
Methyldopa – average generic price	250 mg-2 grams in 2 doses
Aldomet (Merck)	
DIRECT VASODILATORS	
Hydralazine – average generic price	4-200 mg in 2-4 doses
Minoxidil – average generic price	2.5-40 mg in 1 or 2 doses
Loniten (Pharmacia & Upjohn)	
PERIPHERAL ADRENERGIC NEURON ANTAGONISTS	
Guanadrel – *Hylorel* (Medeva)	10-75 mg in 2 doses
Reserpine – average generic price	0.05 – 0.1 mg in 1 dose

Table 33[10]

SELECTED COMBINATION ANTIHYPERTENSIVE DRUGS

Beta-Adrenergic Blockers and Diuretics	
Atenolol, 50 or 100 mg/chlorthalidone, 25 mg	Tenoretic
Bisoprolol fumarate, 2.5, 5, or 10 mg/hydrochlorothiazide, 6.25 mg	Ziac
Metoprolol tartrate, 50 or 100 mg/hydrochlorothiazide, 25 or 50 mg	Lopressor HCT
Nadolol, 40 or 80 mg/bendroflumethiazide, 5 mg	Corzide
Propranolol hydrochloride, 40 or 80 mg/ hydrochlorothiazide, 25 mg	Inderide
Propranolol hydrochloride (extended release), 80, 120, or 160 mg/hydrochlorothiazide, 50 mg	Inderide LA
Timolol maleate, 10 mg/hydrochlorothiazide, 25 mg	Timolide

Table 33[10] Continued

ACE Inhibitors and Diuretics	
Benazepril hydrochloride, 5, 10, or 20 mg/ hydrochlorothiazide, 6.25, 12.5, or 25 mg	Lotensin HCT
Captopril, 25 or 50 mg/hydrochlorothiazide, 15 or 25 mg	Capozide
Enalapril maleate, 5 or 10 mg/hydrochlorothiazide, 12.5 or 25 mg	Vaseretic
Lisinopril, 10 or 20 mg/hydrochlorothiazide, 12.5 or 25 mg	Prinzide, Zestoretic
Angiotensin II Receptor Blockers and Diuretics	
Valsartan, 80 or 160 mg/hydrochlorothiazide, 12.5 mg	Diovan HCT
Losartan potassium, 50 mg/hydrochlorothiazide, 12.5 mg	Hyzaar
Calcium Antagonists and ACE Inhibitors	
Amlodipine besylate, 2.5 or 5 mg/benazepril hydrochloride, 10 or 20 mg	Lotrel
Diltiazem hydrochloride, 180 mg/enalapril maleate, 5 mg	Teczem
Verapamil hydrochloride (extended release) 180 or 240 mg/trandolapril, 1, 2, or 4 mg	Tarka
Felodipine, 5 mg/enalapril maleate, 5 mg	Lexxel
Other Combinations	
Triamterene, 37.5, 50, or 75 mg/hydrochlorothiazide, 25 or 50 mg	Dyazide, Maxide
Spironolactone, 25 or 50 mg/hydrochlorothiazide, 25 or 50 mg	Aldactazide
Amiloride hydrochloride, 5 mg/hydrochlorothiazide, 50 mg	Moduretic
Guanethidine monosulfate, 10 mg/hydrochlorothiazide, 25 mg	Esimil
Hydralazine hydrochloride, 25, 50, or 100 mg/ Hydrochlorothiazide, 25 or 50 mg	Apresazide
Methyldopa, 250 or 500 mg/hydrochlorothiazide, 15, 25, 30, or 50 mg	Aldoril
Reserpine, 0.125 mg/hydrochlorothiazide, 25 or 50 mg	Hydropres
Reserpine, 0.10 mg/hydralazine hydrochloride, 25 mg/ Hydrochlorothiazide, 15 mg	Ser-Ap-Es
Clonidine hydrochloride, 0.1, 0.2, or 0.3 mg/chlorthalidone, 15 mg	Combipres
Methyldopa, 250 mg/chlorothiazide, 150 or 250 mg	Aldochlor
Reserpine, 0.125 or 0.25 mg/chlorthalidone, 25 or 50 mg	Demi-Regroton
Reserpine, 0.125 or 0.25 mg/chlorothiazide, 250 or 500 mg	Diupres
Prazosin hydrochloride, 1, 2, or 5 mg/polythiazide, 0.5 mg	Minizide

Table 34[10]

CHARACTERISTICS OF THE IDEAL ANTIHYPERTENSIVE DRUG

1. Efficacious as a monotherapy in more than 50% of all patients.
2. BP control during all activities for 24 hours.
3. Once-a-day dosing with high trough to peak ratio.
4. Hemodynamically logical and effective: reduces SVR, improves arterial compliance, preserves CO and maintains perfusion to all vital organs.
5. Lack of tolerance or pseudotolerance: no reflex volume retention or stimulation of neurohumoral mechanisms.

Table 34[10] Continued

6. Favorable biochemical effects, metabolic effects and risk factor profile.
7. Reverses structural, vascular smooth muscle and cardiac hypertrophy; improves systolic and diastolic compliance and left ventricular contractility and function; reduces ventricular ectopy, if present.
8. Reduces all end-organ damage: cardiac, cerebrovascular, renal, retinal and large artery.
9. Maintains normal hemodynamic response to aerobic and anaerobic exercise.
10. Low incidence of side effects, good quality of life.
11. Good compliance with drug regimen.
12. Good profile for concomitant diseases or problems.
13. Reasonable cost.
14. No withdrawal symptoms and prolongation of BP control with missed dose due to long biological half-life and efficacy of drug.

Table 35

NATURAL ANTIHYPERTENSIVE COMPOUNDS

CATEGORIZED BY ANTIHYPERTENSIVE CLASS

Diuretics

1. Hawthorne Berry
2. Vitamin B-6 (Pyridoxine)
3. Taurine
4. Celery
5. GLA
6. Vitamin C (Ascorbic Acid)
7. K^+
8. Mg^{++}
9. Ca^{++}
10. Protein
11. Fiber
12. Coenzyme Q-10
13. L-Carnitine (?)

Beta Blockers (BB)

1. Hawthorne Berry

Central Alpha Agonists (CCA) (Reduce SNS Activity)

1. Taurine
2. K^+
3. Zinc
4. Na^+ Restriction
5. Protein
6. Fiber
7. Vitamin C
8. Vitamin B-6
9. Coenzyme Q-10
10. Celery
11. GLA/DGLA
12. Garlic

Direct Vasodilators

1. Omega-3 FA
2. MUFA (Omega-9 FA)
3. K^+
4. Mg^{++}
5. Ca^{++}
6. Soy
7. Fiber
8. Garlic
9. Flavonoids
10. Vitamin C
11. Vitamin E
12. Coenzyme Q-10
13. L-Arginine
14. Taurine
15. Celery
16. ALA

Table 35 Continued

Calcium Channel Blockers (CCB)

1. Alpha Lipoic Acid (ALA)
2. Vitamin C (Ascorbic Acid)
3. Vitamin B-6 (Pyridoxine)
4. Magnesium (Mg^{++})
5. N-Acetyl Cysteine (NAC)
6. Vitamin E
7. Hawthorne Berry
8. Celery
9. Omega-3 Fatty Acids (EPA and DHA)
10. Calcium
11. Garlic

Angiotensin Converting Enzyme Inhibitors (ACEI)

1. Garlic
2. Seaweed – various (Wakame, etc.)
3. Tuna protein/muscle
4. Sardine protein/muscle
5. Hawthorne Berry
6. Bonito Fish (dried)
7. Pycnogenol
8. Casein
9. Hydrolyzed Whey Protein
10. Sour Milk
11. Geletin
12. Sake
13. Essential Fatty Acids (Omega-3 FA)
14. Chicken Egg Yolks
15. Zein
16. Dried Salted Fish
17. Fish Sauce
18. Zinc
19. Hydrolyzed Wheat Germ Isolate

Angiotensin Receptor Blockers (ARB's)

1. Potassium (K^+)
2. Fiber
3. Garlic
4. Vitamin C
5. Vitamin B-6 (Pyridoxine)
6. Co-Enzyme Q-10
7. Celery
8. Gamma Linolenic Acid (GLA) and DGLA

NATURAL ANTIHYPERTENSIVE COMPOUNDS CATEGORIZED BY ANTIHYPERTENSIVE CLASS

As has been discussed previously, many of the natural compounds in food, certain nutraceutical supplements, vitamins, antioxidants, or minerals function in a similar fashion to a specific class of antihypertensive drugs. Although the potency of these natural compounds may be less than the antihypertensive drug, when used in combination with other nutrients and nutraceuticals, the antihypertensive effect is magnified. In addition, many of these nutrients and nutraceuticals have varied, additive, or synergistic mechanisms of action in lowering BP. Table 35 summarizes these natural compounds into the major antihypertensive drug classes such as diuretics, beta blockers, central alpha agonists, CCB, ACEI and ARB's.

SUMMARY AND CONCLUSIONS

1. Vascular biology (ED and VSM dysfunction) plays a primary role in the initiation and perpetuation of hypertension, CVD, and TOD.

2. Nutrient-gene interactions are a predominant factor in promoting beneficial or detrimental effects in cardiovascular health and hypertension.

3. Nutrition (natural whole food, nutraceuticals) can prevent, control and treat hypertension through numerous vascular biology mechanisms.

4. Oxidative stress initiates and propagates hypertension and cardiovascular disease.

5. Antioxidants can prevent and treat hypertension.

6. Whole food and whole food concentrates of fruits, vegetables and fiber with natural combinations of balanced phytonutrients, phytochemicals, antioxidants, vitamins, minerals and appropriate macronutrients and micronutrients are generally superior to single component or isolated artificial or single component natural substances for the prevention and treatment of hypertension and CVD.

- However, there is a role for the selected use of single and component nutraceuticals, vitamins, antioxidants and minerals in the treatment of hypertension based on scientifically controlled studies as a complement to optimal nutritional, dietary intake from food and other lifestyle modifications.
- Exercise, weight reduction, smoking cessation, and alcohol and caffeine restriction, as well as other changes in lifestyle must be incorporated.

7. Specific mechanism of actions of nutrition and nutraceuticals include:

- **ACEI activity:** garlic, seaweed, tuna, sardine, dry salted fish, zein, fish sauce, chicken, egg yolks, hydrolyzed whey protein, hawthorne, sour milk, gelatin, sake, bonito, pycnogenol, casein, omega-3 fatty acids, zinc, wheat germ hydrolysate.
- **CCB activity:** ALA, vitamin C, vitamin B_6, Mg^{++}, NAC, vitamin E, hawthorne, celery, omega-3 fatty acids, Ca^{++}, garlic.
- **ARB activity:** K^+, fiber, garlic, vitamin C, vitamin B6, coenzyme Q-10, celery, GLA and DGLA.
- **Diuretic**: hawthorne, vitamin B_6, taurine, celery, GLA, vitamin C, K^+, Mg^{++}, Ca^{++}, protein, fiber.
- **Beta blockers**: hawthorn
- **NO increased:** L-arginine, omega-3 PUFA, garlic, vitamin C, vitamin E, ALA, NAC, Mg^{++}, K^+, MUFA, Co Q_{10}.
- **Reduced activity or sensitivity to angiotensin-II and NE:** K^+, fiber, garlic, vitamin C, vitamin B6, CoQ_{10}, taurine, celery, GLA and DGLA, zinc, protein, Na^{++} restriction.
- **Gene expression NF_KB:** Zn, vitamin E, ALA.
- **AGE and RAGE:** omega-3 PUFA, fiber.
- **PPAR alpha ligand:** omega-3 PUFA.
- **SREBP-1:** omega-3 PUFA.
- **Antioxidants**: neutralize ROS, O_2^-: numerous other effects.
- **Insulin sensitivity:** fiber, omega-3 PUFA, vitamin C, vitamin E, vitamin D, vitamin B_6, CoQ_{10}, ALA, taurine, K^+, Mg^{++}, Zn, L-arginine, L-carnitine.
- **Increased PGI_2, PGE_1, PGE_3:** vitamin C, niacin, Zn, omega-3 fatty acids, vitamin E, selenium, Ca^{++}, Mg^{++}, GLA and DGLA (omega-6 FA), L-arginine
- **PKC inhibition:** vitamin E.
- **Increased cytosolic Mg^{++}:** vitamin E.
- **TK inhibition:** SO_4, flavonoids, genistein, diadzein.
- **↓PRA, ↓aldo:** Taurine, GLA, DGLA, vitamin B_6, CoQ_{10}.

↑ANF: Taurine.

- **Improved arterial compliance:** Na^+ restriction, K^+, Mg^{++}, soy, garlic, vitamin E, ALA.
- **Reduced VSM hypertrophy:** Na^+ restriction, K^+, vitamin E, COQ_{10}, ALA.
- **Microalbuminuria reduction:** Na^+ restriction.
- **Modulates baroreceptor sensitivity:** K^+.
- **Direct vasodilation:** K^+, Mg^{++}, Ca^{++}, fiber, garlic, vitamin C, flavonoids, COQ_{10}, ALA, L-arginine, taurine, celery, MUFA, soy, omega-3 FA, vitamin E.

RECOMMENDATIONS

Nutrition	Daily Intake
1. DASH I and DASH II-Na^+ diets	
2. Sodium restriction	50 – 100 mmol
3. Potassium	60 – 100 mEq
4. Potassium/sodium ration > 5:1	
5. Magnesium	500 – 1000 mg
6. Calcium	1000 – 1500 mg
7. Zinc	25 mg
8. **Protein:** total intake (40% total calories)	1.0 – 1.5 mg/kg
A. Nonanimal sources preferred but lean or wild animal protein in moderation is acceptable	
B. Hydrolyzed whey protein	5 grams
C. Soy protein (fermented is best)	30 grams
D. Hydrolyzed wheat germ isolate	2 – 4 grams
E. Sardine muscle concentrate extract	3 mg
F. Cold water fish, fowl poultry	
9. **Fats:** 25% total calories	
A. Omega-3 fatty acids (30%) PUFA (DHA, EPA, ALA, cold water fish)	3 – 4 grams
B. Omega-6 fatty acids (10%) PUFA (flax, CLA, canola oil, nuts)	

C. Omega-9 fatty acids (30%) MUFA ....4 tablespoons (extra virgin olive oil)
D. Saturated FA (lean, wild animal meat) (30%)
E. P/S ratio (polyunsaturated/saturated) fats > 2.0
F. Omega-3/Omega-6 PUFA, ratio 2:1 – 4:1
G. No trans-fatty acids (0%) (hydrogenated margarines, vegetable oils)
H. Nuts: almonds, walnuts, hazelnuts, etc.
10. **Carbohydrates** (35% total calories)
A. Reduce or eliminate refined sugars and simple carbohydrates
B. Increase complex carbohydrates and fiber
whole grains (oat, barley, wheat)
vegetables, beans, legumes
i.e. oatmeal .....60 grams
oatbran (dry).....40 grams
beta-glucan .....3 grams
psyllium .....7 grams
11. Garlic .....4 cloves/4 grams
12. Mushrooms (shiitake and maitake)
13. Guava fruit.....500 – 1000 mg
14. Wakame seaweed (dried).....3.0 – 3.5 grams
15. Celery
celery stalks .....4 stalks
celery juice .....8 teaspoons TID
celery seed extract .....1000 mg BID
celery oil (tincture).....1/2 - 1 teaspoon TID
16. Lycopene .....10 mg
Tomatoes and tomato products,guava, watermelon, apricots, pink grapefruit, papaya

Nutrition	Daily Intake
Exercise	
• Aerobic	7days/weeks
45 minutes daily	
4200 Kcal/week	
• Resistance training daily	
Weight Loss	
• To ideal body weight	
• Lose 1 – 2 pounds/week	
• BMF ≤ 25	
Waist circumference	
< 35 inches in female	
< 40 inches in male	
• Total body fat	
< 16% in males	
< 22% in females	
Increase lean muscle mass	
Alcohol Restriction	< 20 grams/day
Wine < 10 ounces	
Beer < 24 ounces	
Liquor < 2 ounces (100 proof whiskey)	
Caffeine Restriction	< 100 mg/day
Tobacco and Smoking	STOP
Avoid drugs and interactions that increase BP (see list)	

VITAMINS, ANTIOXIDANTS AND NUTRACEUTICAL SUPPLEMENTS

Daily Intake

Vitamin C.....250 to 500 mg BID
Vitamin E.....400 to 800 IU QD
Vitamin B-6 .....100 mg QD to BID
Co-enzyme Q-10 (QGEL®).....60 mg QD to BID
Lipoic Acid .....100 to 200 mg BID
N-Acetyl Cysteine .....500 mg BID
L-Arginine (Heart Bar®) (3.3 grams) ..one bar BID
(plus lentils, hazelnuts, walnuts, peanuts)
Hawthorne Standardized Extract.....160 – 900 mg QD
L-Carnitine.....1000 mg BID
Taurine .....1.0 to 1.5 grams BID
ΣNADA .....2.5 to 5.0 mg BID

BID - Twice daily; QD - Daily

REFERENCES

1. Weder AB. Your mother was right: eat your fruits and vegetables. *Curr Hypertens Rep.* 1999;1:11-12.
2. Eaton SB, Eaton SB III, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. *Eur J Clin Nutr.* 1997;51:207-216.
3. Ascherio A, Rimm EB, Hernan MA, *et al.* Intake of potassium, magnesium, calcium and fiber and risk of stroke among US men. *Circulation.* 1998;98:1198-1204.
4. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon diet heart study. *Circulation.* 1999;99:779-785.
5. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the joint national committee on the prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med.* 1997;157:2413-2446.
6. Krauss R, Deckelbaum R, Ernst N, *et al.* Dietary guidelines for healthy American adults: a statement for health professionals from the nutrition committee, American Heart Association. *AHA Medical/Scientific Statement.* 1996;94:1795-1800.
7. Institute of Medicine. The role of nutrition in maintaining health in the nation's elderly: evaluating coverage of nutrition services for the medicare population. Washington, DC: National Academy Press; 2000.
8. INTERSALT Cooperative Research Group. INTERSALT: an international study of electrolyte excretion and blood pressure: results for 24-hour urinary sodium and potassium excretion. *BMJ.* 1988;297:319-328.
9. Geleijnse JM, Grobbee DE, Hofman A. Sodium and potassium intake and blood pressure change in childhood. *BMJ.* 1990;300:899-902.

10. Houston MC, Meador BP, Schipani LM. *Handbook of Antihypertensive Therapy.* 10th edition. Philadelphia: Hanley and Belfus, Inc.; 2000:1-176.

11. Houston MC. New insights and approaches to reduce end-organ damage in the treatment of hypertension: subsets of hypertension approach. *Am Heart J.* 1992;123:1337-1367.

12. Houston MC. New insights and new approaches for the treatment of essential hypertension: selections of therapy based on coronary heart disease risk factor analysis, hemodynamic profiles, quality of life, and subsets of hypertension. *Am Heart J.* 1989;117:911-951.

13. Houston, MC. Hypertension strategies for therapeutic intervention and prevention of end-organ damage. *Primary Care Clin North Am.* 1991;18:713-753.

14. Warner MG. Complementary and alternative therapies for hypertension. *Complementary Health Practice Review.* 2000;6:11-19.

15. Burt VL, Whelton P, Roccella EJ, *et al.* Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991 (comments). *Hypertension.* 1995;25:305-313.

16. Sheps SG, Roccella EJ. Reflections on the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Curr Hypertens Rep.* 1999;1:342-345.

17. Use of Antihypertensive Drugs. http://www.americanheart.org/statistics/10econom. html. June 2000.

18. Appel LJ. The role of diet in the prevention and treatment of hypertension. *Curr Atheroscler Rep.* 2000;2:521-528.

19. Alderman MH. Which antihypertensive drug first – and why? *JAMA.* 1992;267:2786-2787.

20. Undurti DN. Nutritional factors in the pathobiology of human essential hypertension. *Nutrition.* 2001;17:337-346.

21. MacMahon S, Peto R, Cutler J, *et al.* Blood pressure, stroke, and coronary heart disease: part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990;335:765-774.

22. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med.* 1993;153:598-615.

23. Collins R, Peto R, MacMahon S, *et al.* Blood pressure, stroke, and coronary heart disease: part 2, short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet.* 1990;335:827-838.

24. Stamler J, Rose G, Stamler R, *et al.* INTERSALT study findings: public health and medical care implications. *Hypertension.* 1989;14:570-577.

25. Isles CG, Walker LM, Beevers GD, Brown I, Cameron HL, Clarke J, *et al.* Mortality in patients of the Glasgow Blood Pressure Clinic. *J Hypertens.* 1986;4:141-156.

26. Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inque M. Does superoxide underlie the pathogenesis of hypertension? *Proc Natl Acad Sci U S A.* 1991;88:10045-10048.

27. Kumar DV, Das UN. Are free radicals involved in the pathobiology of human essential hypertension? *Free Radic Res Commun.* 1993;19:59-66.

28. Koska J, Syrova D, Blazicek P, Marko M, Gizna JD, Kvetnansky R, Vigas M. Malondialdehyde, lipofuscin, and activity of antioxidant enzymes during physical exercise in patients with essential hypertension. *J Hypertens.* 1999;17:529-535.

29. Sagar S, Kallo U, Kaul N, Ganguly NK, Sharma BK. Oxygen free radicals in essential hypertension. *Mol Cell Biochem.* 1992;111:103-108.

30. Parik T, Allikmets K, Teesalu R, Zilmer M. Oxidative stress and hyperinsulinaemia in essential hypertension: different facets of increased risk. *J Hypertens.* 1996;14:407-410.

31. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, Phase II. *Arch Intern Med.* 1997;157:657-667.

32. Whelton PK, Appel LJ, Espeland MA, *et al.* Efficacy of sodium reduction and weight loss in the treatment of hypertension in older persons: main results of the randomized, controlled trial of nonpharmacologic interventions in the elderly (TONE). *JAMA.* 1998;279:839-846.

33. Whelton PK, He J, Cutler JA, *et al.* Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA.* 1997;277:1624-1632.

34. Svetkey LP, Simons-Morton D, Vollmer WM, *et al.* Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med.* 1999;159:285-293.

35. Geleijnsse J, Hofman A, Witteman J, *et al.* Long-term effects of neonatal sodium restriction on blood pressure. *Hypertension.* 1997;29:913-917.

36. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA.* 1996;275:1571-1576.

37. Weber MA, Smith DHG, Neutel JM, Graettinger WF. Arterial properties of early hypertension. *J Hum Hypertens.* 1991;5:417-423.

38. Dzau VJ, Gibbons GH. Vascular remodeling: mechanisms and implications. *J Cardiovasc Pharmacol.* 1993;21:S1-S5.

39. Neutel JM, Smith DHG, Weber MA. Is high blood pressure a late manifestation of the hypertension syndrome? *Am J Hypertens.* 1999;12:215S-223S.

40. Neutel JM, Smith DHG. Hypertension control: multifactorial contributions. *Am J Hypertens.* 1999;12:164S-169S.

41. Roberts CK, Vaziri ND, Liang KH, Barnard JR. Reversibility of chronic experimental syndrome X by diet modification. *Hypertension.* 2001;37:1323-1328.

42. Kahn AM, Allen JC, Zhang S. Insulin increases CGMP in vascular smooth muscle cells (VSMC) – role of NO and redox state. *Am J Hypertens.* 2001;14:26. Abstract.

43. Dzau VJ. Tissue renin-angiotensin system in myocardial hypertrophy and failure. *Arch Intern Med.* 1993;153:937-942.

44. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med.* 1999;340:115-126.

45. Mulvany MJ, Aalkjaer C. Structure and function of small arteries. *Physiol Rev.* 1990;70:921-961.

46. Sherman DL. Exercise and endothelial function. *Coron Artery Dis.* 2000;11:117-122.

47. Caterina R. Endothelial dysfunctions: common denominators in vascular disease. *Curr Opin Lipinol.* 2000;11:9-23.

48. Contreras F, Rivera M, Vasquez J, *et al.* Endothelial dysfunction in arterial hypertension. *J Hum Hypertens.* 2000;14:S20-S25.

49. Ruschitzka F, Corti R, Noll G, Luscher TF. A rationale for treatment of endothelial dysfunction in hypertension. *J Hypertens.* 1999;17:S25-S35.

50. Pepine CJ. A symposium: endothelial function and cardiovascular disease: potential mechanisms and interventions. *Am J Cardiol.* 1998;82:1S-64S.

51. Gimbrone MA, Topper JN. Biology of the vessel wall: endothelium. In: Chien KR, ed. *Molecular Basis of Cardiovascular Disease.* Orlando, Fl:WB Saunders Co; 1999:331-348.

52. Van Houtie PM. How to assess endothelial function in human blood vessels. *J Hypertens.* 1999;17:1047-1058.

53. Panza JA, Cardillo C. Potential mechanisms of endothelial dysfunction in patients with essential hypertension. *J Hypertens.* 1998;16:S43-S48.

54. Intengan HD, Schiffrin EL. Role of endothelium in modulation of structural changes of small arteries in hypertension: effects of therapeutic intervention. *J Hypertens.* 1998;16:S97-S101.

55. John S, Schmieder RE. Impaired endothelial function in arterial hypertension and hyperlipidemia: potential mechanisms and differences. *J Hypertens.* 2000;18:363-374.

56. Chun TH, Itoh H, Saito T, *et al.* Oxidative stress augments secretion of endothelium-derived relaxing peptides, C-type natriuretic peptide and adrenomedullin. *J Hypertens.* 2000;18:S75-S80.

57. Panza JA. Nitric oxide in hypertension. In: Oparil S, Weber MA, eds. *Hypertension: A Companion to Brenner and Rector's: The Kidney.* Orlando, Fl: WB Saunders Co; 2000:158-165.

58. Suuardi JA, Hamasaki S, Higano ST, *et al.* Long term followup of patients with mild coronary artery disease and endothelial dysfunction. *Circulation.* 2000;101:948-954.

59. Rubanyi GM. The role of endothelium in cardiovascular homeostasis and diseases. *J Cardiovasc Pharmacol.* 1993;22:S1-S14.

60. Moncada S. Nitric oxide in the vasculature: physiology and pathophysiology. *Ann NY Acad Sci.* 1997;811:60-67.

61. Kumar KV, Das UN. Are free radicals involved in the pathobiology of human essential hypertension? *Free Rad Res Commun.* 1993;19:59-66.

62. Uwabo J, Soma M, Nakayama T, Kanmatsuse K. Association of a variable number of tandem repeats in the endothelial constitutive nitric oxide synthase gene with essential hypertension in Japanese. *Am J Hypertens.* 1998;11:125-128.

63. Vapaatalo H, Mervaala E, Nurminen ML. Role of endothelium and nitric oxide in experimental hypertension. *Physiol Res.* 2000;49:1-10.

64. Rees D, Ben-Ishay D, Moncada S. Nitric oxide and the regulation of blood pressure in the hypertension-prone and hypertension-resistant Sabra rat. *Hypertension.* 1996;28:367-371.

65. Bode-Boger SM, Boger RH, Kielstein JT, Leffler M, Schaffer J, Frohlich JC. Role of endogenous nitric oxide in circadian blood pressure regulation in healthy humans and in patients with hypertension or atherosclerosis. *J Investig Med.* 2000;48:125-132.

66. Cachofeiro V, Sakakibara T, Nasjletti A. Kinins, nitric oxide, and the hypotensive effect of captopril and ramiprilat in hypertension. *Hypertension.* 1992;19:138-145.

67. Akpaffiong MJ, Taylor AA. Antihypertensive and vasodilator actions of antioxidants in spontaneously hypertensive rats. *Hypertension.* 1998;11:1450-1460.

68. Kitiyakara C, Wilcox CS. Antioxidants for hypertension. *Opin Nephrol Hypertens.* 1998;7:531-538.

69. Vaziri ND, Ni Z, Oveisi F, Trnavsky-Hobbs DL. Effect of antioxidant therapy on blood pressure and NO synthase expression in hypertensive rats. *Hypertension.* 2000;36:957-964.

70. Akiba Y, Yamaguchi N, Amano H, Fujii T, Fujimoto K, Suzuki T, Kawashima K. Role of nitric oxide in control of blood pressure in young and adult spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol Suppl.* 1995;1:S142-S143.

71. Gil-Longo J, Fernandez-Grandal D, Alvarez M, Siera M, Orallo F. Study of in vivo and in vitro resting vasodilator nitric oxide tone in normotensive and genetically hypertensive rats. *Eur J Pharmacol.* 1996;310:175-183.

72. Tomita T, Onda T, Mashiko S, Hamano M, Tomita I. Blood pressure-related changes of endothelium-dependent relaxation in the aorta from SHRSP at developmental stages of hypertension. *Clin Exp Pharmacol Physiol Suppl.* 1995;1:S139-S141.

73. Hayakawa H, Coffee K, Raij L. Nitric oxide activity is enhanced in the vasculature and renal medulla of spontaneously hypertensive rats, but fails to control hypertension. *J Am Soc Nephrol.* 1996;7:1562. Abstract.

74. Wu CC, Hong HJ, Chou TC, Ding YA, Yen MH. Evidence for inducible nitric oxide synthase in spontaneously hypertensive rats. *Biochem Biophys Res Commun.* 1996;228:459-466.

75. Hayakawa H, Raij L. Nitric oxide synthase activity and renal injury in genetic hypertension. *Hypertension.* 1998;31(pt 2):266-270.

76. Tschudi MR, Mesaros S, Luscher TF, Malinski T. Direct in situ measurement of nitric oxide in mesenteric resistance arteries: increased decomposition by superoxide in hypertension. *Hypertension.* 1996;27:32-35.

77. Cosentino F, Patton S, D'Uscio LV, Werner ER, Werner-Felmayer G, Moreau P, Malinski, T, Luscher TF. Tetrahydrobiopterin alters superoxide and nitric oxide release in prehypertensive rats. *J Clin Invest.* 1998;101:1530-1537.

78. Schnackenberg CG, Welch WJ, Wilcox CS. Normalization of blood pressure and renal vascular resistance in SHR with a membrane-permeable superoxide dismutase mimetic: role of nitric oxide. *Hypertension.* 1998;32:59-64.

79. Schnackenberg CG, Wilcox CS. Two-week administration of tempol attenuates both hypertension and renal excretion of 8-isoprostaglandin F_{2a}. *Hypertension.* 1999;33:424-428.

80. Halliwell B. What nitrates tyrosine?: is nitrotyrosine specific as a biomarker of peroxynitrite formation in vivo? *FEBS Lett.* 1997;411:157-160.

81. Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, the ugly. *Am J Physiol.* 1996;271:C1424-C1437.

82. Eiserich JP, Butler J, van der Vliet A, Cross CE, Halliwell B. Nitric oxide rapidly scavenges tyrosine and tryptophan radicals. *Biochem J.* 1995;310:745-749.

83. Vaziri ND, Liang K, Ding Y. Increased nitric oxide inactivation by reactive oxygen species in lead-induced hypertension. *Kidney Int.* 1999;56:1492-1498.

84. Cosentino F, Sill JC, Katusic ZS. Role of superoxide anions in the mediation of endothelium-dependent contractions. *Hypertension.* 1994;23:229-235.

85. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADDH oxidase activity in cultured vascular endothelial smooth muscle cells. *Circ Res.* 1994;74:1141-1148.

86. Sagar S, *et al*. Oxygen free radicals in essential hypertension. *Mol Cell Biochem.* 1992;110:103-108.

87. Suzuki H, DeLano FA, Parks DA, Jamshidi N, Granger DN, Ishii H, Suematsu M, Zweifach BW, Schmid-Schonbein GW. Xanthine oxidase activity associated with arterial blood pressure in spontaneously hypertensive rats. *Proc Natl Acad Sci USA*. 1998;95:4754-4759.

88. Suzuki H, Swei A, Zweifach BW, Schmid-Schonbein GW. In vivo evidence for microvascular oxidative stress in spontaneously hypertensive rats: hydroethidine microfluorography. *Hypertension.* 1995;25:1083-1089.

89. Grunfeld S, Hamilton CA, Mesaros S, McClain SW, Dominiczak AF, Bohr DF, Malinski T. Role of superoxide in the depressed nitric oxide production by the endothelium of genetically hypertensive rats. *Hypertension.* 1995;26:854-857.

90. Yoshioka M, Aoyama K, Matsushita T. Effects of ascorbic acid on blood pressure and ascorbic acid metabolism in spontaneously hypertensive rats. *Int J Vitam Nutr Res.* 1985;55:301-307.

91. Vaziri ND, Ding Y, Ni Z. Nitric oxide synthase expression in the course of lead-induced hypertension. *Hypertension.* 1999;34:558-562.

92. Brown AA, Hu FB. Dietary modulation of endothelial function: implications for cardiovascular disease. *Am J Clin Nutr.* 2001;73:673-686.

93. Nayak DU, Karmen C, Frishman WH, Vakili BA. Antioxidant vitamins and enzymatic and synthetic oxygen-derived free radical scavengers in the prevention and treatment of cardiovascular disease. *Heart Disease.* 2001;3:28-45.

94. Gonick HC, Ding Y, Bondy SC, Ni Z, Vaziri ND. Lead-induced hypertension: interplay of nitric oxide and reactive oxygen species. *Hypertension.* 1997;30:1487-1492.

95. Vaziri ND, Ding Y, Ni Z, Gonick HC. Altered nitric oxide metabolism and increased oxygen free radical activity in lead-induced hypertension: effect of lazaroid therapy. *Kidney Int.* 1997;52:1042-1046.

96. Ding Y, Vaziri ND, Gonick HC. Lead-induced hypertension, II: response to sequential infusions of L-arginine, superoxide dismutase, and nitroprusside. *Environ Res.* 1998;76:107-113.

97. Vaziri ND, Ni Z, Zhang YP, Ruzicks EP, Maleki P, Ding Y. Depressed renal and vascular nitric oxide synthase expression in cyclosporine-induced hypertension. *Kidney Int.* 1998;54:482-491.

98. Navarro-Antolin J, Hernandez-Perera O, Lopez-Ongil S, Rodriguez-Puyol M, Rodriguez-Puyol D, Lamas S. CsA and FK506 up-regulate eNOS expression: role of reactive oxygen species and AP-1. *Kidney Int Suppl.* 1998;68:S20-S24.

99. Lopez-Ongil S, Hernandez-Perera O, Navarro-Antolin J, Perez de Lema G, Rodriguez-Puyol M, Lamas S, Rodriguez-Puyol D. Role of reactive oxygen species in the signaling cascade of cyclosporine A-mediated up-regulation of eNOS in vascular endothelial cells. *Br J Pharmacol.* 1998;124:447-454.

100. Vaziri ND, Oveisi F, Ding Y. Role of increased oxygen free radical activity in the pathogenesis of uremic hypertension. *Kidney Int.* 1998;53:1748-1754.

101. Atarashi K, Ishiyama A, Takagi M, Minami M, Kimura K, Goto A, Omata M. Vitamin E ameliorates the renal injury of Dahl salt-sensitive rats. *Am J Hypertens.* 1997;10:116S-119S.

102. Swei A, Lacy F, DeLano FA, Schmid-Schonbein GW. Oxidative stress in the Dahl hypertensive rat. *Hypertension.* 1997;30:1628-1633.

103. Kitiyakara C, Wilcox C. Antioxidants for hypertension. *Curr Opin Nephrol Hypertens.* 1998;7:531-538.

104. Lacy F, O'Conner DT, Schmid-Schonbein GW. Plasma hydrogen peroxide production in hypertensives and normotensive subjects at genetic risk of hypertension. *J Hypertens.* 1998;16:291-303.

105. Tse WY, Maxwell SR, Thomason H, Blann A, Thorpe GH, Waite M, Holder R. Antioxidant status in controlled and uncontrolled hypertension and its relationship to endothelial damage. *J Hum Hypertens.* 1994;89:843-849.

106. Romero-Alvira D, Roche E. High blood pressure, oxygen radicals and antioxidants: etiological relationships. *Med Hypotheses.* 1996;46:414-420.

107. Roggensack AM, Zhang Y, Davidge ST. Evidence for peroxynitrite formation in the vasculature of women with preeclampsia. *Hypertension.* 1999;33:83-89.

108. Giugliano D, Ceriello A, Paolisso G. Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress? *Metabolism.* 1995;44:363-368.

109. Orie NN, Zidek W, Tepel M. Reactive oxygen species in essential hypertension and non-insulin dependent diabetes mellitus. *Am J Hypertens.* 1999;12:1169-1174.

110. Faure P, Rossini E, Lafond JL, Richard MJ, Favier A, Halimi S. Vitamin E improves the free radical defense system potential and insulin sensitivity of rats fed high fructose diets. *J Nutr.* 1997;127:103-107.

111. Aliev G, Bodin P, Burnstock G. Free radical generators cause changes in endothelial and inducible nitric oxide synthases and endothelin-1 immuno-reactivity in endothelial cells from hyperlipidemic rabbits. *Mol Genet Metab.* 1998;63:191-197.

112. Roberts CK, Vaziri ND, Wang XQ, Barnard RJ. Enhanced NO inactivation and hypertension induced by a high-fat, refined carbohydrate diet. *Hypertension.* 2000;36:423-429.

113. Barnard RJ, Roberts CK, Varon SM, Berger JJ. Diet-induced insulin resistance precedes other aspects of metabolic syndrome. *J Appl Physiol.* 1999;84:1311-1315.

114. Wen Z, Killalea S, McGettigan P, Feely J. Lipid peroxidation and antioxidant vitamins C and E in hypertensive patients. *Ir J Med Sci.* 1996;165:210-212.

115. Kumar KV, Das UN. Are free radicals involved in the pathology of human essential hypertension? *Free Radic Res Commun.* 1993;19:59-66.

116. Russo C, Olivieri O, Girelli D, Faccini G, Zenari ML, Lombardi S, Corrocher R. Antioxidant status and lipid peroxidation in patients with essential hypertension. *J Hypertens.* 1998;16:1267-1271.

117. Laursen JB, Rajagopalan S, Galis Z, Tarpey M, Freeman BA, Harrison DG. Role of superoxide in angiotensin II-induced but not catecholamine-induced hypertension. *Circulation.* 1997;95:588-593.

118. Loverro G, Greco P, Capuano F, Carone D, Cormio G, Selvaggi L. Lipoperoxidation and antioxidant enzymes activity in pregnancy complicated with hypertension. *Eur J Obstet Gynecol Reprod Biol.* 1996:70:123-127.

119. Tse WY, Maxwell SR, Thomason H, Blann A, Thorpe GH, Waite M, Holder R. Antioxidant status in controlled and uncontrolled hypertension and its relationship to endothelial damage. *J Hum Hypertens.* 1994;8:843-849.

120. Villar J, Montilla C, Muniz-Grijalvo O, Muriana FG, Stiefel P, Ruiz-Gutierrez V, *et al.* Erythrocyte Na^+ -Li^+ countertransport in essential hypertension: correlation with membrane lipid levels. *J Hypertens.* 1996;14:969-973.

121. Mihailovic MB, Avramovic DM, Jovanovic IB, Pesut OJ, Matic DP, Stojanov VJ. Blood and plasma selenium levels and GSH-Px activities in patients with arterial hypertension and chronic heart disease. *J Environ Pathol Toxicol Oncol.* 1998;17:285-289.

122. Lacy F, O'Connor DT, Schmid-Schonbein GW. Plasma hydrogen peroxide production in hypertensives and normotensive subjects at genetic risk of hypertension. *J Hypertens.* 1998;16:291-303.

123. Huang A, Sun D, Kaley G, Koller A. Superoxide released to high intra-arteriolar pressure reduces nitric oxide-mediated shear stress- and agonist-induced dilations. *Circ Res.* 198;83:960-965.

124. DeFronzo R, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, and atherosclerotic cardiovascular disease. *Diabetes Care.* 1991;14:173-194.

125. Singal PK, Beamish RE, Dhalla NS. Potential oxidative pathways of catecholamines in the formation of lipid peroxides and genesis of heart disease. *Adv Exp Med Biol.* 1983;161:391-401.

126. Paolisso G, Giugliano D. Oxidative stress and insulin action: is there a relationship? *Diabetologia.* 1996;39:357-363.

127. Vaziri ND, Wang XQ. cGMP-mediated negative-feedback regulation of endothelial nitric oxide synthase expression by nitric oxide. *Hypertension.* 1999;34:1237-1241.

128. McIntyre M, Bohr DF, Dominiczak AF. Endothelial function in hypertension. The role of superoxide anion. *Hypertension.* 1999;34:539-545.

129. McCarron DA, Morris CD, Henry HJ, *et al.* Blood pressure and nutrient intake in the United States. *Science.* 1988;48:1226-1232.

130. Salonen JT, Salonen R, Ihanainen M, *et al.* Blood pressure, dietary fats, and antioxidants. *Am J Clin Nutr.* 1988;48:1226-1232.

131. Yoshioka M, Matsushita T, Chuman Y. Inverse association of serum ascorbic acid level and blood pressure or rate of hypertension in male adults aged 30-39 years. *Int J Vitam Nutr Res.* 1984;54:343-347.

132. Ceriello A, Giugliano D, Quatraro A, *et al.* Antioxidants show an anti-hypertensive effect in diabetic and hypertensive subjects. *Clin Sci.* 1991;81:739-742.

133. Sagar S, Kallo IJ, Kaul N, Ganuly NK, Sharma BK. Oxygen free radicals in essential hypertension. *Mol Cell Biochem.* 1992;111:103-108.

134. Parik K, Allikmets K, Teesalu R, Zilmer M. Evidence for oxidative stress in essential hypertension: perspective for antioxidant therapy. *J Cardiovasc Risk.* 1996;3:49-54.

135. Ness AR, Chee D, Elliot P. Vitamin C and blood pressure–an overview. *J Hum Hypertens.* 1997;11:343-350.

136. Solzbach U, Just H, Jeserich M, Hornig B. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. *Circulation.* 1997;96:1513-1519.

137. Galley HF, Thornton J, Howdle PD, Walker BE, Webster NR. Combination oral antioxidant supplementation reduces blood pressure. *Clin Sci.* 1997;92:361-365.

138. Dhalla NS, Temsah RM, Netticadam T. The role of oxidative stress in cardiovascular diseases. *J Hypertens.* 2000;18:655-673.

139. Koska J, Syrova D, Blazicek P, *et al.* Malondialdehyde, lipofuscin and activity of antioxidant enzymes during physical exercise in patients with essential hypertension. *J Hypertens.* 1999;17:529-535.

140. Wolf G. Free radical production and angiotensin. *Curr Hypertens Rep.* 2000;2:167-173.

141. Touyz RM, Schiffrin EL. Increased generation of superoxide by angiotensin II in smooth muscle cells from resistance arteries of hypertensive patients: role of phospholipase D-dependent NAD(P)H oxidase-sensitive pathways. *J Hypertens.* 2001;19:1245-1254.

142. Saez G, Tormos MC, Giner V, Lorano JV, Chaves FJ. Oxidative stress and enzymatic antioxidant mechanisms in essential hypertension. *Am J Hypertens.* 2001;14:248A. Abstract P-653.

143. Giner V, Lozano JV, Saez G, Tormo MC, Chaves FJ. Oxidative stress and early organ damage in essential hypertension. *Am J Hypertens.* 2001;14:248A. Abstract P-654.

144. NHLBI. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults–the evidence report. *J Obesity Res.* 1998;6:51S-209S.

145. Reisen E, Abel MD, Modan M, Silverberg DS, Eliahou HE, Modan B. Effect of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. *N Engl J Med.* 1978;298:1-6.

146. Conlin PR. Dietary modification and changes in blood pressure. *Curr Opin Nephrol Hypertens.* 2001;10:359-363.

147. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and aldosterone levels in obese patients. *N Engl J Med.* 1981;304:930-933.

148. McCarron DA, Reusser ME. Nonpharmacologic therapy in hypertension: from single components to overall dietary management. *Prog Cardiovasc Dis.* 1999;41:451-460.

149. Hansson L, Zanchetti A, Carruthers SG. Effects of intensive blood pressure lowering and low dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomized trial. *Lancet.* 1998;351:1755-1762.

150. Steven VJ, Obarzanek E, Cook NR, Lee I-MN, Appel LJ, *et al.* Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. *Ann Intern Med.* 2001;134:1-11.

151. Staessen J, Fagard R, Lijnen P, Amery A. Body weight, sodium intake, and blood pressure. *J Hypertens.* 1989;7:S19-S23.

152. The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. *JAMA.* 267:1213-1220.

153. Hunt SC, Cook NR, Oberman A, *et al.* Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension: trials of hypertension prevention, phase II. *Hypertension.* 1998;32:393-401.

154. Neaton J, Grimm R, Prineas R, *et al.* Treatment of Mild Hypertension Study (TOMHS): final results. *JAMA.* 1993;270:713-724.

155. Kostis JB, Shindler DM, Lacy CR. Non-drug therapy for hypertension: do effects on weight and sodium intake persist after discontinuation of intervention. *Am J Med.* 2000;109:734-735.

156. Landsberg L. Role of the sympathetic adrenal system in the pathogenesis of the insulin resistance syndrome. *Ann N Y Acad Sci.* 1999;892:84-90.

157. Young JB, Landsberg L. Suppression of sympathetic nervous system during fasting. *Science.* 1977;196:1473-1475.

158. Young JB, Rosa RM, Landsberg L. Dissociation of sympathetic nervous system and adrenal medullary responses. *Am J Physiol.* 1984;247:E35-E40.

159. Young JB, Landsberg L. Stimulation of the sympathetic nervous system during sucrose feeding. *Nature.* 1977;269:615-617.

160. Walgren MC, Young JB, Kaufman LN, Landsberg L. The effects of various carbohydrates on sympathetic activity in heart and interscapular brown adipose tissue (IBAT) of the rat. *Metabolism.* 1987;36:585-594.

161. Schwartz JH, Young JB, Landsberg L. Effect of dietary fat on sympathetic nervous system activity in the rat. *J Clin Invest.* 1983;72:361-370.

162. Das UN. GLUT-4, tumor necrosis factor, essential fatty acids and daf-genes and their role in insulin resistance and non-insulin dependent diabetes mellitus. *Prostaglandins Leukot Essent Fatty Acids.* 1999;60:13-20.

163. Uysal KT, Wesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature.* 1997;389:610-614.

164. Hughes K, Aw TC, Kuperan P, Choo M. Central obesity, insulin resistance, syndrome X, lipoprotein(a) and cardiovascular risk in Indians, Malaysians and Chinese in Singapore. *J Epidemiol Community Health.* 1997;51:394-399.

165. Das UN. Possible beneficial action(s) of glucose-insulin-potassium regimen in acute myocardial infarction and inflammatory conditions: a hypothesis. *Diabetologia.* 2000;43:1081-1082.

166. Waeber G, Calandra T, Bonny C, Bucala R. A role for the endocrine and pro-inflammatory mediator MIF in the control of insulin secretion during stress. *Diabetes Metab Res Rev.* 1999;15:47-54.

167. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey JK. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature.* 2000;405:458-462.

168. American College of Sports Medicine. Physical activity, physical fitness and hypertension: position stand. *Med Sci Sports Exerc.* 1993;25:55-60.

169. Jennings GL, Nelson L, Nestel P, *et al.* The effects of changes in physical activity on major cardiovascular risk factors, haemodynamics, sympathetic function, and glucose utilization in man: a controlled study of four levels of activity. *Circulation.* 1986;73:30-39.

170. Martin JE, Dubbert PM, Cushman WC. Controlled trial of aerobic exercise in hypertension. *Circulation.* 1990;81:1560-1567.

171. Higashi Y, Sasaki S, Sasaki N, Nakagawa K, *et al.* Daily aerobic exercise improves reactive hyperemia in patients with essential hypertension. *Hypertension.* 1999;33:591-597.

172. Blair SN, Goodyear NN, Gibbons LW, Cooper KH. Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA.* 1984;252:487-490.

173. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical activity level and other lifestyle characteristics with mortality among men. *N Engl J Med.* 1993;328:538-545.

174. Kokkinos PF, Narayan P, Colleran JA, *et al.* Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. *N Engl J Med.* 1995;333:1462-1467.

175. Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and coronary heart disease in men. The Harvard Alumni Health Study. *Circulation.* 2000;102:975-980.

176. U.S. Department of Health and Human Services. Physical activity and health: a report of the surgeon general. Atlanta, Ga: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.

177. Hambrecht R, Wolf A, Gielen S, *et al*. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med.* 2000;342:454-460.

178. Greenberg G, Thompson SG, Brennan PJ. The relationship between smoking and the response to antihypertensive treatment in mild hypertensives in the Medical Research Council's trial of treatment. *Int J Epidemiol.* 1987;16:25-30.

179. U.S. Department of Health and Human Services. The health benefits of smoking cessation: a report of the surgeon general. Rockville, MD: Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; DHHS publication no. (CDC) 90-8416;1990.

180. Khoury Z, Comans P, Keren A, Lerer T, Gavish A, Tzivoni D. Effects of transdermal nicotine patches on ambulatory ECG monitoring findings: a double-blind study in healthy smokers. *Cardiovasc Drugs Ther.* 1996;10:179-184.

181. Eaton SB, Eaton SB III, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. *Eur J Clin Nutr.* 1997;51:207-216.

182. Price PT, Nelson CM, Clarke SD. Omega-3 polyunsaturated fatty acid regulation of gene expression. *Curr Opin Lipidol.* 2000;11:3-7.

183. Berdanier CD. Nutrient-gene interactions. In: Ziegler EE, Filer LJ Jr, eds. *Present Knowledge in Nutrition.* 7th ed. Washington, DC: ILSI Press; 1996:574-580.

184. Talmud PJ, Waterworth DM. In vivo and in vitro nutrient-gene interactions. *Curr Opin Lipidol.* 2000;11:31-36.

185. Khaw K-T, Barrett-Connor E. Dietary potassium and stroke-associated mortality: a 12-year prospective population study. *N Engl J Med.* 1987;316:235-240.

186. He J, Ogden LG, Vupputuri S, *et al.* Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA.* 1999;282:2027-2034.

187. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, *et al.* Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med.* 2001;344:3-10.

188. Broadhurst CL. Balanced intakes of natural triglycerides for optimum nutrition: an evolutionary and phytochemical perspective. *Med Hypotheses.* 1997;49:247-261.

189. Ravnskov U. The questionable role of saturated and polyunsaturated fatty acids in cardiovascular disease. *J Clin Epidemiol.* 1998;51:443-460.

190. Gillman MW, Cupples A, Millen BE. Inverse association of dietary fats with development of ischemic stroke in men. *JAMA.* 1997;278:2145-2150.

191. Ascherio A, Willett WC. Health effects of trans fatty acids. *Am J Clin Nutr.* 1997;66:1006S-1010S.

192. Tavani A, Negri E, D'Avanzo B, *et al.* Margarine intake and risk of nonfatal acute myocardial infarction on Italian women. *Eur J Clin Nutr.* 1997;51:30-32.

193. Appel LJ, Moore TJ, Obarzanek E, *et al.* A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med.* 1997;336:1117-1124.

194. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev.* 1999;20:649-688.

195. Jump DB, Clarke SD. Regulation of gene expression by dietary fat. *Ann Rev Nutr.* 1999;19:63-90.

196. Stabile LP, Klautky SA, Minor SM, Salati LM. Polyunsaturated fatty acids inhibit the expression of the glucose-6-phosphate dehydrogenase gene in primary rat hepatocytes by a nuclear posttranscriptional mechanism. *J Lipid Res.* 1998;39:1951-1963.

197. Weiss SL, Sunde RA. Selenium regulation of classical glutathione peroxidase expression requires the 3 untranslated region in Chinese hamster ovary cells. *J Nutr.* 1997;127:1304-1310.

198. Mori TA, Bao DQ, Burke V, Puddey IB, Watts GF, Beilin LJ. Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose and insulin metabolism in overweight hypertensive subjects. *Am J Clin Nutr.* 1999;70:817-825.

199. Baur LA, O'Connor J, Pan DA, Kriketos AD, Storlien LH. The fatty acid composition of skeletal muscle membrane phospholipid: its relationship with the type of feeding and plasma glucose levels in young children. *Metabolism.* 1998;47:106-112.

200. Svetkey LP, Moore TJ, Sacks FM, *et al.* Genetic determinants of BP response to DASH dietary patterns. *Am J Hypertens.* 2000;13(4):76A (ABSTRACT D 010).

201. Pausova Z, Tremblay J, Hamet P. Gene-environment interactions in hypertension. *Curr Hypertens Rep.* 1999;1:42-50.

202. Hamet P, Mongeau E, Lambert J, *et al.* Interactions among calcium, sodium, and alcohol intake as determinants of blood pressure. *Hypertension.* 1991;17:I150-I154.

203. Preuss HG. Diet, genetics and hypertension *J Am Coll Nutr.* 1997;16:296-305.

204. Tan KT, Dempsey AA, Llew CC. Cardiac genes and gene databases for cardiovascular disease genetics. *Curr Hypertens Rep.* 1999;1:S1-S8.

205. De Lorgeril M, Salen P, Martin J-L, *et al.* Effect of a Mediterranean type of diet on the rate of cardiovascular complications in patients with coronary artery disease: insights into the cardioprotective effect of certain nutriments. *J Am Coll Cardiol.* 1996;28:1103-1108.

206. Renaud S, de Lorgeril M, Delaye J, *et al.* Cretan Mediterranean diet for prevention of coronary heart disease. *Am J Clin Nutr.* 1995;61:1360S-1367S.

207. Willett WC. Diet and health: what should we eat? *Science.* 1994;264:532-537.

208. McCarron DA, Reusser ME. The power of food to improve multiple cardiovascular risk factors. *Curr Atheroscler Rep.* 2000;2:482-486.

209. McCarron DA, Oparil S, Chait A, *et al.* Nutritional management of cardiovascular risk factors: a randomized clinical trial. *Arch Intern Med.* 1997;157:169-177.

210. Haynes RB, Kris-Etherton P, McCarron DA, *et al.* Nutritionally complete prepared meal plan to reduce cardiovascular risk factors: a randomized clinical trial. *J Am Diet Assoc.* 1999;99:1077-1083.

211. Metz JA, Kris-Etherton P, Morris CD, *et al.* Dietary compliance and cardiovascular risk reduction with a prepared meal plan compared to a self-selected diet. *Am J Clin Nutr.* 1997;66:373-385.

212. Hatton DC, Metz JA, Kris-Etherton PM, *et al.* Healthier diets improve quality of life while reducing cardiovascular disease risk factors. *Dis Manage Clin Outcomes.* 1998;1:106-113.

213. Chait A, Malinow MR, Nevin DN, *et al.* Increased dietary micronutrients reduce serum homocysteine in patients at high risk for cardiovascular disease. *Am J Clin Nutr.* 1999;70:881-887.

214. Pi-Sunyer FX, Maggio CA, McCarron DA, *et al.* Multicenter randomized trial of a comprehensive prepared meal plan program in type 2 diabetes. *Diabetes Care.* 1999;22:191-197.

215. Metz JA, Stern JS, Kris-Etherton PM, *et al.* Improved weight loss on a prepared meal plan in overweight and obese patients: impact on cardiovascular risk-reduction: a randomized trial. *Arch Intern Med.* 2000;160:2150-2158.

216. The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423.

217. Rouse IL, Armstrong BK, Beilin LJ, Vandongen R. Blood pressure lowering effect of a vegetarian diet: controlled trial in normotensive subjects. *Lancet.* 1983;1:5-9.

218. Reid CM, Maher T, Jennings GL. Substituting lifestyle management for pharmacological control of blood pressure: a pilot study in Australian general practice. *Blood Press.* 2000;9:267-274.

219. Alderman MH, Lamport B. Withdrawal of drug therapy. A component of the proper management of the hypertensive patient. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis, and Management.* New York: Raven Press; 1990:2:2301-2308.

220. Fletcher AE, Franks PJ, Bulpitt CJ. The effect of withdrawing antihypertensive therapy: a review. *J Hypertens.* 1988;6:431-436.

221. Blaufox MD, Langford HG, Oberman A, Hawkins CM, Wassertheil-Smoller S, Cutter GR. Effect of dietary change on the return of hypertension after withdrawal of prolonged antihypertensive therapy (DISH). *J Hypertens.* 1984;2:179-181.

222. Stamler R, Stamler J, Grimm R, *et al.* Trial of control of hypertension by nutritional means: three year results. *J Hypertens.* 1984;2:167-170.

223. Straand J, Fugelli P, Laake K. Withdrawing long-term diuretic treatment among elderly patients in general practice. *Fam Pract.* 1993;10:38-42.

224. Pahor M, Guralnik JM, Corti M-C, Foley DJ, Carbonin P, Havlik RJ. Long-term survival and use of antihypertensive medications in older persons. *JAGS.* 1995;43:1191-1197.

225. Resnick LM, Oparil S, Chait A, Haynes RB, Kris-Etherton P, Stern JS, *et al.* Factors affecting blood pressure responses to diet: the Vanguard Study. *Am J Hypertens.* 2000;13:956-965.

226. McCarron DA, Morris CD, Cole C. Dietary calcium in human hypertension. *Science.* 1982;217:267-269.

227. Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation.* 1998;98:1198-1204.

228. Hamet P, Daignault-Gelinas M, Lambert J, Ledoux M, Whissell-Cambiotti L, Bellavance F, Mongean E. Epidemiological evidence of an interaction between calcium and sodium intake impacting on blood pressure: a Montreal study. *Am J Hypertens.* 1992;5:378-385.

229. Resnick LM. Therapeutic implications of calcium intake in hypertension. More analyses, a little progress, and a different approach. *Am J Hypertens.* 1999;12:82-83.

230. Addison WLT, Clark HG. Calcium and potassium chloride in the treatment of arterial hypertension. *Can Med Assoc J.* 1925;15:913-915.

231. Kempner W. Treatment of hypertensive vascular disease with rice diet. *Am J Med.* 1948;4:545-577.

232. Laragh JH, Pecker MS. Dietary sodium and essential hypertension: some myths, hopes, and truths. *Ann Intern Med.* 1983;98:735-743.

233. McCarron D, Morris C. Blood pressure response to oral calcium in persons with mild to moderate hypertension: a randomized, double-blind, placebo-controlled crossover trial. *Ann Intern Med.* 1985;103:825-831.

234. Resnick L, DiFabio B, Marion R, James G, Laragh J. Dietary calcium modifies the pressor effects of dietary salt intake in essential hypertension. *J Hypertens.* 1986;4:S679-S681.

235. Lawton WJ, Fitz AE, Anderson EA, Sinkey CA, Coleman RA. Effect of dietary potassium on blood pressure, renal function, muscle sympathetic nerve activity, and forearm vascular resistance and flow in normotensive and borderline hypertensive humans. *Circulation.* 1990;81:173-184.

236. Jacobs DB, Sowers JR, Hmeidan A, Niyogi T, Simpson L, Standley P. Effects of weight reduction on cellular cation metabolism and vascular resistance. *Hypertension.* 1993;21:308-314.

237. Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, Phase II. *Arch Intern Med.* 1997;157:657-667.

238. Sacks FM, Willett WC, Smith A, Brown LE, Rosner B, Moore TJ. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. *Hypertension.* 1998;31:131-138.

239. Morris MC. Dietary fats and blood pressure. *J Cardiovasc Risk.* 1994;1:21-30.

240. Sacks F, Kass E. Low blood pressure in vegetarians: effects of specific foods and nutrients. *Am J Clin Nutr.* 1988;48:795-800.

241. Sacks F, Rosner B, Kass E. Blood pressure in vegetarians. *Am J Epidemiol.* 1974;100:390-398.

242. Rouse I, Armstrong B, Berlin L. The relationship of blood pressure to diet and lifestyle in two religious populations. *J Hypertens.* 1983;1:67-71.

243. Sacks F, Stampfer M, Munoz A, McManus K, Canessa M, Kass E. Effect of linoleic and oleic acids on blood pressure, blood viscosity, and erythrocyte cation transport. *J Am Coll Nutr.* 1987;6:179-185.

244. McGiff J, Carroll M, Escalante B. Arachidonate metabolism and kinins in blood pressure regulation. *Hypertension.* 1991;18:V150-V157.

245. Liu ZQ, Yang JJ, Mu YM, Liang YX, Wang DJ, Zhu CF, Sun TY. Adding potassium and calcium to the dietary salt as a hypertension–preventive approach in adolescents with higher blood pressure and their family members: a single blind randomized-controlled trial. *Am J Hypertens.* 2001;14:145A. Abstract P-345.

246. Mark SD, Wang W, Fraumeni JF, Li JY, Taylor PR. Do nutritional supplements lower the risk of stroke or hypertension? *Epidemiology.* 1998;9:9-15.

247. Wise JA, Morin RJ, Sanderson R, Blum K. Changes in plasma carotenoid, alpha-tocopherol, and lipid peroxide levels in response to supplementation with concentrated fruit and vegetable extracts. *Current Therapeutic Research – Clinical and Experimental.* 1996;57:445-461.

248. Kaats GR, Wise JA, Morin R, Pullin D, Squires W, Hesslink R. Positive effects of nutritional supplements on body composition biomarkers of aging during a weight loss program. *JANA.* 1998;1:1-6.

249. Inserra PF, Jiang S, Solkoff D, Lee J, Zhang Z. Immune function in elderly smokers and nonsmokers improves during supplementation with fruit and vegetable extracts. *Integrative Med.* 1999;2:3-10.

250. Smith MJ, Inserra PF, Watson RR, Wise JA, O'Neill KL. Supplementation with fruit and vegetable extracts may decrease DNA damage in the peripheral lymphocytes of an elderly population. *Nutrition Research.* 1999;19:1507-1518.

251. Leeds AR, Ferris AE, Staley J, Ayesh R, Ross F. Availability of micronutrients from dried, encapsulated fruit and vegetable preparations: a study in healthy volunteers. *J Hum Nutr Disease.* 2000;13:21-27.

252. Ellithorpe RR. Pilot study of whole food based nutritional supplementation yields superior antioxidant protection. *JANA*. 2001;2:44-48.

253. Plotnick GD. The effects of dietary supplements on endothelial function: results of a recent clinical study evaluating the effect of a phytonutrient product on brachial artery flow mediated vasoactivity. In: Program of The American Nutraceutical Association's Nutraceutical and Medicine Conference. Nashville, Tennessee; October 12-13, 2001.

254. Houston MC, Olafsson BJ, Raggi P, Asher JR. Evaluation of coronary heart disease regression by EBT (electron beam tomography) in patients treated with concentrated fruit and vegetable extracts. Unpublished data.

255. Plaisted CS, Lin P-H, Ard JD, *et al.* The effects of dietary patterns on quality of life: a substudy of the Dietary Approaches to Stop Hypertension trial. *J Am Diet Assoc.* 1999;99:384-389.

256. Kotchen TA, McCarron DA. AHA Science Advisory. Dietary electrolytes and blood pressure. *Circulation.* 1998;98:613-617.

257. Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials [comments]. *JAMA.* 1996;275:1590-1597.

258. Cutler JA, Follmann, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr.* 1997;65:643S-651S.

259. Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. *JAMA.* 1998;279:1383-1391.

260. Svetkey LP, Sacks FM, Obarzanek E, *et al.* The DASH diet, sodium intake, and blood pressure (the DASH-Sodium Study): rationale and design. *JADA.* 1999;99:S96-S104.

261. Egan BM, Lackland DT. Biochemical and metabolic effects of very-low-salt diets. *Am J Med Sci.* 2000;320:233-239.

262. Cianciaruso B, Bellizzi V, Minutolo R, Tavera A, Capuano A, Conte G, DeNicola L. Salt intake and renal outcome in patients with progressive renal disease. *Miner Electrolyte Metab.* 1998;24:296-301.

263. Kotchen TA, Kotchen JM. Dietary sodium and blood pressure: interactions with other nutrients. *Am J Clin Nutr.* 1997;65:708S-711S.

264. Morris CD. Effect of dietary sodium restriction on overall nutrient intake. *Am J Clin Nutr.* 1997;65:687S-691S.

265. Hu G, Tian H. A comparison of dietary and non-dietary factors of hypertension and normal blood pressure in a Chinese population. *J Hum Hypertens.* 2001;15:487-493.

266. Messerli FH. Salt and hypertension: going to the heart of the matter. *Arch Intern Med.* 2001;161:505-506.

267. Aviv A. Salt and hypertension: the debate that begs the bigger question. *Arch Intern Med.* 2001;161:507-510.

268. Nara Y, Kihara M, Nabika T, Mano M, Horie R, Yamori Y. Dietary effect on platelet aggregation in men with and without a family history of essential hypertension. *Hypertension.* 1984;6:339-343.

269. Perry IJ, Beevers DG. Salt intake and stroke: a possible direct effect. *J Hum Hypertens.* 1992;6:23-25.

270. Reid R, Lindop G, Brown W, Lever AF, Lucie N, Webb D. Similar blood pressure but different outcome in rats with DOC and post-DOC hypertension. *J Hypertens.* 1983;1:303-310.

271. Messerli FH, Schmieder RE, Weir MR. Salt: a perpetrator of hypertensive target organ disease? *Arch Intern Med.* 1997;157:2449-2452.

272. Langenfeld MRW, Schmieder RE, Schobel HP, Friedrich A. Dietary salt intake and left ventricular diastolic function in early essential hypertension. In: Program and Abstracts of the XVI Scientific Meeting of the International Society of Hypertension. Glasgow, Scotland; June 26, 1996. Abstract 128.2.

273. Gu J-W, Anand V, Shek EW, et al. Sodium induces hypertrophy of cultured myocardial myoblasts and vascular smooth muscle cells. *Hypertension.* 1998;31:1083-1087.

274. Yu HCM, Burrell LM, Black MJ, *et al.* Salt induces myocardial and renal fibrosis in normotensive and hypertensive rats. *Circulation.* 1998;98:2621-2628.

275. Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int.* 1989;36:272-279.

276. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med.* 1996;125:201-204.

277. Safar ME, Asmar RG, Benetos A, London GM, Levy BI. Sodium, large arteries and diuretic compounds in hypertension. *J Hypertens Suppl.* 1992;10:S133-S136.

278. Draaijer P, Kool MJ, Maessen JM, *et al.* Vascular distensibility and compliance in salt-sensitive and salt-resistant borderline hypertension. *J Hypertens.* 1993;11:1199-1207.

279. Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. *Am J Med.* 1978;64:193-198.

280. Weinberger MH. Salt sensitivity of blood pressure in humans. *Hypertension.* 1996;27:481-490.

281. Morimoto A, Usu T, Fujii T, *et al.* Sodium sensitivity and cardiovascular events in patients with essential hypertension. *Lancet.* 1997;350:1734-1737.

282. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure and death in normal and hypertensive humans. *Hypertension.* 2001;37:429-432.

283. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and characteristics of sodium sensitivity and blood pressure resistance. *Hypertension.* 1986;8:127-134.

284. Johnson AG, Nguyen TV, Davis D. Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects. *J Hypertens.* 2001;19:1053-1060.

285. Miyajima E, Yamada Y. Reduced sympathetic inhibition in salt-sensitive Japanese young adults. *Am J Hypertens.* 1999;12:1195-1200.

286. Cubeddu LX, Alfieri AB, Hoffmann IS, Jimenez E, Roa CM, et al. Nitric oxide and salt sensitivity. *Am J Hypertens.* 2000;13:973-979.

287. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. *Science.* 1984;224:1392-1398.

288. McCarron DA. Diet and blood pressure–the paradigm shift. *Science.* 1998;281:933-934.

289. Das UN. Minerals, trace elements, and vitamins interact

with essential fatty acids and prostaglandins to prevent hypertension, thrombosis, hypercholesterolaemia and atherosclerosis and their attendant complications. *IRCS Med Sci.* 1985;13:684.

290. Department of Health and Human Services. DHSS Publications (PH 5). London. 1983;83.

291. Saito K, Sano H, Furuta Y, Fukuzaki H. Effect of oral calcium on blood pressure response in salt-loaded borderline hypertensive patients. *Hypertension.* 1989;13:219-226.

292. Resnick L, Sosa R, Corbett M, Gertner J, Sealey J, Laragh J. Effects of dietary calcium on sodium volume *vs*. renin-dependent forms of experimental hypertension. *Trans Assoc Am Physicians.* 1986;99:172-179.

293. Birkett NJ. Comments on a meta-analysis of the relation between dietary calcium intake and blood pressure. *Am J Epidemiol.* 1998;148:223-228.

294. Whelton PK, He J. Potassium in preventing and treating high blood pressure. *Semin Nephrol.* 1999;19:494-499.

295. Siani A, Strazzullo P, Giacco A, Pacioni D, Celentano E, Mancini M. Increasing the dietary potassium intake reduces the need for antihypertensive medication. *Ann Intern Med.* 1991;115:753-759.

296. Gu D, He J, Xigui W, Duan X, Whelton PK. Effect of potassium supplementation on blood pressure in Chinese: a randomized, placebo-controlled trial. *J Hypertens.* 2001;19:1325-1331.

297. Barri YM, Wingo CS. The effects of potassium depletion and supplementation on blood pressure: a clinical review. *Am J Med Sci.* 1997;3:37-40.

298. Ma G, Mamaril JLC, Young DB. Increased potassium concentration inhibits stimulation of vascular smooth muscle proliferation by PDGF-BB and bFGF. *Am J Hypertens.* 2000;13:1055-1060.

299. Karanja N, Roullet JB, Aickin M, O'Brien K, Vogt TM, Cutler J, McCarron DA. Mineral metabolism, blood pressure, and dietary patterns: findings from the DASH trial. *J Am Soc Nephrol.* 1998;9:151A. Abstract.

300. Ahsan SK. Magnesium in health and disease. *J Pak Med Assoc.* 1998;48:246-250.

301. Weiss D. Cardiovascular disease: risk factors and fundamental nutrition. *Int J Integrative Med.* 2000;2:6-12.

302. Widman L, Wester PO, Stegmayr BG, Wirell MP. The dose dependent reduction in blood pressure through administration of magnesium: a double blind placebo controlled crossover trial. *Am J Hypertens.* 1993;6:41-45.

303. Paolisso G, Gambardella A, Balbi V, Galzerano D, Verza M, Varricchio M, D'Onofrio F. Effects of magnesium and nifedipine on insulin action, substrate oxidation and blood pressure in aged subjects. *Am J Hypertens.* 1993;6:920-926.

304. Kisters K, Krefting ER, Barenbrock M, Spieker C, Rahn KH. Na^+ and $Mg2^+$ contents in smooth muscle cells in spontaneously hypertensive rats. *Am J Hypertens.* 1999;12:648-652.

305. Sanders GM, Sim KM. Is it feasible to use magnesium sulfate as a hypotensive agent in oral and maxillofacial surgery? *Ann Acad Med Singapore.* 1998;27:780-785.

306. Altura BM, Altura BT, Carella A. Magnesium deficiency-induced spasms of umbilical vessels: relation to preeclampsia, hypertension, growth retardation. *Science.* 1983;221:376-378.

307. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta.* 2000;294:1-26.

308. Sudhakar K, Sujatha M, Rao VB, Jyothy A, Reddy PP. Serum and erythrocyte magnesium levels in hypertensives and their first degree relatives. *J Indian Med Assoc.* 1999;97:211-213.

309. Corica F, Corsonello A, Buemi M, De Gregorio T, Malara A, Mauro VN, Macaione S, Ientile R. Platelet magnesium depletion in normotensive and hypertensive obese subjects: the role of salt-regulating hormones and catecholamines. *Magnes Res.* 1999;12:287-296.

310. Resnick LM. Magnesium in the pathophysiology and treatment of hypertension and diabetes mellitus: where are we in 1997? *Am J Hypertens.* 1997;10:368-370.

311. Laurant P, Touyz RM. Physiological and pathophysiological role of magnesium in the cardiovascular system: implications in hypertension. *J Hypertens.* 2000;18:1177-1191.

312. Haenni A, Johansson K, Lind L, Lithell H. Magnesium improves endothelium-dependent vasodilation in the human forearm. *Am J Hypertens.* 2001;14:68A. Abstract P-116.

313. Siegel G, Walter A, Gustavsson H, Lindman B. Magnesium and membrane function in vascular smooth muscle. *Artery.* 1981;9:232-252.

314. Witteman JCM, Grobbee DE, Derkx FHM, Bouillon R, DeBruijn AM, Hofman A. Reduction of blood pressure with oral magnesium supplementation in women with mild to moderate hypertension. *J Clin Nutr.* 1994;60:129-135.

315. Das UN. Nutrients, essential fatty acids and prostaglandins interact to augment immune responses and prevent genetic damage and cancer. *Nutrition.* 1989;5:106-110.

316. Das UN. Essential fatty acids: biology and their clinical implications. *Asia Pacific J Pharmacol.* 1991;6:317.

317. Das UN, Horrobin DF, Begin ME, *et al.* Clinical significance of essential fatty acids. *Nutrition.* 1988;4:337.

318. McCarron DA. Role of adequate dietary calcium intake in the prevention and management of salt sensitive hypertensive. *Am J Clin Nutr.* 1997;65:712S-716S.

319. Cappuccio FP, Elliott P, Allender PS, *et al.* Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. *Am J Epidemiol.* 1995;142:935-945.

320. Allender PS, Cutler JA, Follmann D, *et al.* Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. *Ann Intern Med.* 1996;124:825-831.

321. McCarron DA. Calcium metabolism in hypertension. *Keio J Med.* 1995;44:105-114.

322. Witteman JCM, Willett WC, Stampfer MJ, *et al.* A prospective study of nutritional factors and hypertension among US women. *Circulation.* 1989;80:1320-1327.

323. Bucher HC, Cook RJ, Guyatt GH, *et al.* Effects of dietary calcium supplementation on blood pressure. A meta-analysis of randomized controlled trials. *JAMA.* 1996;275:1016-1022.

324. Griffith L, Guyatt GH, Cook RJ, *et al.* The influence of dietary and nondietary calcium supplementation on blood pressure: an updated meta-analysis of randomized clinical trials. *Am J Hypertens.* 1999;12:84-92.

325. Karanja N, Morris CD, Rufolo P, *et al.* The impact of increasing dietary calcium intake on nutrient consumption,

plasma lipids, and lipoproteins in humans. *Am J Hypertens.* 1994;59:900-907.

326. Whiting SJ, Wood R, Kim K. Calcium supplementation. *J Am Acad Nurse Pract.* 1997;9:187-192.

327. Resnick LM. Calcium metabolism in hypertension and allied metabolic disorders. *Diabetes Care.* 1991;14:505-520.

328. Lal KJ, Dakshinamurti K. The relationship between low-calcium-induced increase in systolic blood pressure and vitamin B6. *J Hypertens.* 1995;13:327-332.

329. Miller GD, DiRienzo DD, Reusser ME, McCarron DA. Benefits of dairy product consumption on blood pressure in humans: a summary of the biomedical literature. *J Am Coll Nutr.* 2000;19:147S-164S.

330. Kolata G. Does a lack of calcium cause hypertension? *Science.* 1984;225:705-706.

331. Resnick LM. Cellular ions in hypertension, insulin resistance, obesity, and diabetes: a unifying theme. *J Am Soc Nephrol.* 1992;3:S78-S85.

332. Kuriyama H, Uyshi I, Sueuk H, Kitamura A, Itoh T. Factors modifying contraction-relaxation cycle in vascular smooth muscles. *Am J Physiol.* 1982;243:H641-H662.

333. Altura BM, Altura BT. Magnesium ions and contraction of vascular smooth muscles: relationship to some vascular diseases. *Fed Proc.* 1981;40:2672-2679.

334. Resnick LM, Barbagallo M, Gupta RK, Laragh JL. Ionic basis of hypertension in diabetes mellitus: role of hyperglycemia. *Am J Hypertens.* 1993;6:296-301.

335. Weisser B, Locher R, de Graaf J, Vetter W. Low density lipoprotein subfractions and [Ca2+] in vascular smooth muscle cells. *Circ Res.* 1993;73:118-124.

336. Erne P, Bolli P, Burgissen E, Buhler F. Correlation of platelet calcium with blood pressure: effect of antihypertensive therapy. *N Engl J Med.* 1984;319:1084-1088.

337. Resnick LM, Gupta RK, Laragh JH. Intracellular free magnesium in erythrocytes of essential hypertension: relation to blood pressure and serum divalent cations. *Proc Natl Acad Sci USA.* 1984;81:6511-6515.

338. Resnick LM, Gupta RK, Bhargava KK, Gruenspan H, Alderman MH, Laragh JH. Cellular ions in hypertension, diabetes and obesity: a nuclear magnetic resonance spectroscopic study. *Hypertension.* 1991;17:951-957.

339. Resnick LM. Calcium-regulating hormones and human hypertension. In: Crass MF, Avioli LV, eds. *Calcium-Regulating Hormones and Cardiovascular Function.* Boca Raton, Fla: CRC Press; 1995:295-320.

340. Bogin E, Massry SG, Harrary I. Effect of parathyroid hormone on rat heart cells. *J Clin Invest.* 1981;67:1215-1227.

341. Bian K, Ishibashi K, Bukoski RD. $1,25(OH)_2D_3$ modulates intracellular Ca^{2+} and forces generation in resistance arteries. *Am J Physiol.* 1996;270:H230-H237.

342. Resnick L, Muller F, Laragh J. Calcium regulating hormones in essential hypertension: relation to plasma renin activity and sodium metabolism. *Ann Intern Med.* 1986;105:649-654.

343. Lijnen P, Petrov V. Dietary calcium, blood pressure and cell membrane cation transport systems in males. *J Hypertens.* 1995;13:875-882.

344. Zhang Z, Cheng TPO, Altura BM. Magnesium regulates intracellular free ionized calcium concentration and cell geometry in vascular smooth muscle cells. *Biochim Biophys Acta.* 1992;1134:25-29.

345. Singh RB, Niaz MA, Rastogi SS, Bajaj S, Gaoli Z, Shoumin Z. Current zinc intake and risk of diabetes and coronary artery disease and factors associated with insulin resistance in rural and urban populations of North India [see comments]. *J Am Coll Nutr.* 1998;17:564-570.

346. Zozaya JL. Nutritional factors in high blood pressure. *J Hum Hypertens.* 2000;1:S100-S104.

347. Garcia Zozaya JL, Padilla Viloria M. Alterations of calcium, magnesium, and zinc in essential hypertension: their relation to the renin-angiotensin-aldosterone system. *Invest Clin.* 1997;38:27-40.

348. Bergomi M, Rovesti S, Vinceti M, Vivoli R, Caselgrandi E, Vivoli G. Zinc and copper status and blood pressure. *J Trace Elem Med Biol.* 1997;11:166-169.

349. Obarzanek E, Velletri PA, Cutler JA. Dietary protein and blood pressure. *JAMA.* 1996;274:1598-1603.

350. Stamler J, Elliott P, Kesteloot H, Nichols R, Claeys G, Dyer AR, Stamler R. Inverse relation of dietary protein markers with blood pressure. Findings for 10,020 men and women in the Intersalt study. Intersalt Cooperative Research Group. International study of salt and blood pressure. *Circulation.* 1996;94:1629-1634.

351. He J, Welton PK. Effect of dietary fiber and protein intake on blood pressure: a review of epidemiologic evidence. *Clin Exp Hypertens.* 1999;21:785-796.

352. Zhou B. The relationship of dietary animal protein and electrolytes to blood pressure. A study on three Chinese populations. *Int J Epidemiol.* 1994;23:716-722.

353. Elliott P, Dennis B, Dyer AR, *et al.* Relation of dietary protein (total, vegetable, animal) to blood pressure: INTERMAP epidemiologic study. Presented at the 18th Scientific Meeting of the International Society of Hypertension, Chicago, Il, August 20-24, 2000.

354. Wolfe BM. Potential role of raising dietary protein intake for reducing risk of atherosclerosis. *Can J Cardiol.* 1995;11:127G-131G.

355. Kawase M, Hashimoto H, Hosoda M, Morita H, Hosono A. Effect of administration of fermented milk containing whey protein concentrate to rats and healthy men on serum lipids and blood pressure. *J Dairy Sci.* 2000;83:255-263.

356. Groziak SM, Miller GD. Natural bioactive substances in milk and colostrum: effects on the arterial blood pressure system. *Br J Nutr.* 2000;84:S119-S125.

357. Barr SI, McCarron DA, Heaney RP, Dawson-Hughes B, Berga SL, Stern JS, Oparil S. Effects of increased consumption of fluid milk on energy and nutrient intake, body weight, and cardiovascular risk factors in healthy older adults. *J Am Diet Assoc.* 2000;100:810-817.

358. Hasler CM, Kundrat S, Wool D. Functional foods and cardiovascular disease. *Curr Atheroscler Rep.* 2000;2:467-475.

359. Tikkanen MJ, Adlercreutz H. Dietary soy-derived isoflavone phytoestrogens: could they have a role in coronary heart disease prevention? *Biochem Pharmacol.* 2000;60:1-5.

360. Laplante MA, Wu R, Champlain JD. Hypotensive effect of genistein in angiotensin-treated hypertensive rats; implication of the ERK-MAPK pathway and the superoxide anion radical. *J Hypertens.* 2001;19:S130. Abstract P 2.91.

361. Schoene NW, Guidry CA. Genistein inhibits reactive oxy-

gen species (ROS) production, shape change, and aggregation in rat platelets. *Nutrition Research.* 2000;20:47-57.

362. Liggins J, Bluck LJC, Runswick S, Atkinson C, Coward WA, Bingham SA. Daidzein and genistein content of fruits and nuts. *J Nutr Biochem.* 2000;11:326-331.

363. Pitre M, Santure M, Bachelard H. Antihypertensive effects of whey protein hydrolysates in conscious, unrestrained spontaneously hypertensive rats. Hypertension Research Unit, Pavillon CHUL Research Center, Laval University, Ste-Foy, Quebec, Canada. (Unpublished data by permission).

364. Yamamoto M, Akino A, Takano T. Antihypertensive effect of the peptides derived from casein by a cell-wall proteinase from Lactobacillus helveticus CP790. *J Dairy Sci.* 1994;77:917.

365. Yamamoto N, Akino A, Takano T. Antihypertensive effect of different kinds of fermented milk in spontaneously hypertensive rats. *Biosci Biotechnol Biochem.* 1994;58:776-778.

366. Kawasaki T, Seki E, Osajima K, Yoshida M, Asada K, Matsui T, Osajima Y. Antihypertensive effect of valyl-tyrosine, a short chain peptide derived from sardine muscle hydrolysate, on mild hypertensive subjects. *J Hum Hypertens.* 2000;14:519-523.

367. Matsui T, Li CH, Tanaka T, Maki T, Osajima Y, Matsumoto. Depressor effect of wheat germ hydrolysate and its novel angiotensin I-converting enzyme inhibitory peptide, Ile-Val-Tyr, and the metabolism in rat and human plasma. *Biol Pharm Bull.* 2000;23:427-431.

368. Kuchel O. Differential catecholamine responses to protein intake in healthy and hypertensive patients. *Am J Physiol.* 1998;275:R1164-R1173.

369. Millward DJ. Optimal intakes of protein in the human diet. *Proc Nutr Soc.* 1999;58:403-413.

370. Lemon PWR. Is increased dietary protein necessary or beneficial for individuals with a physically active lifestyle? *Nutr Rev.* 1996;54:S169-S175.

371. National Diet Heart Study Research Group. The National Diet Heart Study final report. *Circulation.* 1968;37-38:1228-1230.

372. Chee D, Stamler J. Relationship of dietary linolenic acid and omega-3 PUFA to BP: results from the MRFIT #2. AHA 40th Annual Conference on Cardiovascular Disease Epidemiology and Prevention. San Diego. March 1-4, 2000.

373. Witteman J, Willett W, Stampfer M, Golditz G, Sacks F, Speizer F, *et al.* A prospective study of nutritional factors and hypertension among US women. *Circulation.* 1989;80:1320-1327.

374. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ. A prospective study of nutritional factors and hypertension among US men. *Circulation.* 1992;86:1475-1484.

375. Bao DQ, Mori TA, Burke V, *et al.* Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. *Hypertension.* 1998;32:710-717.

376. Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension.* 1999;34:253-260.

377. DeBusk RM. Dietary supplements and cardiovascular disease. *Curr Atheroscler Rep.* 2000;2:508-514.

378. Alexander JW. Immunonutrition: the role of omega-3 fatty acids. *Nutrition.* 1998;14:627-633.

379. Toft I, Bønaa KH, Ingebretsen OC, Nordøy A, Jenssen T. Effects of w-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension: a randomized, controlled trial. *Ann Intern Med.* 1995;123:911-918.

380. Bønaa KH, Bjerve KS, Straume B, Gram IT, Thelle D. Effect of eicosapentaenoic and docosahexanoic acids on blood pressure in hypertension: a population-based intervention trial from the Tromso study. *N Engl J Med.* 1990-322:795-801.

381. Knapp HR, FitzGerald GA. The antihypertensive effects of fish oil: a controlled study of polyunsaturated fatty acid supplements in essential hypertension. *N Engl J Med.* 1989;320:1037-1043.

382. Appel LJ, Miller ER, Seidler AJ, Whelton PK. Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. *Arch Intern Med.* 1993;153:1429-1438.

383. Engler MM, Engler MB, Goodfriend TL, Ball DL, Yu Z, Su P, Koretz DL. Docosahexaenoic acid is an anti-hypertensive nutrient that affects aldosterone production in SHR. *Proc Soc Exp Biol Med.* 1999;221:32-38.

384. Prisco D, Paniccia R, Bandinelli B, Filippini M, Francalanci I, Giusti B, Giurlani L, Gensini GF, Abbate R, Neri Serner GG. Effect of medium-term supplementation with a moderate dose of n-3 polyunsaturated fatty acids on blood pressure in mild hypertensive patients. *Thromb Res.* 1998;91:105-112.

385. Rousseau D, Moreau D, Raederstorff D, Sergiel JP, Rupp H, Muggli R, Grynberg A. Is a dietary n-3 fatty acid supplement able to influence the cardiac effect of psychological stress? *Mol Cell Biochem.* 1998;178:353-366.

386. Health effects of omega–3 polyunsaturated fatty acids in seafoods. In: Simopoulos AP, Kifer RR, Martin RE, Barlow SM, eds. *World Review of Nutrition and Dietetics. Vol. 66.* Basel: Karger; 1991:1-592.

387. Woodcock BE, Smith E, Lambert WH, Jones WM, Galloway JH, Greaves M, Preston FE. Beneficial effect of fish oil on blood viscosity in peripheral vascular disease. *BMJ.* 1984;288;592-594.

388. Morris M, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation.* 1993;88:523-533.

389. Engler MB, Ma YH, Engler MM. Calcium-mediated mechanisms of eicosapentaenoic acid-induced relaxation in hypertension rat aorta. *Am J Hypertens.* 1999;12:1225-1235.390.

390. Hassall CH, Kirtland SJ. Dihomo-gamma-linolenic acid reverses hypertension induced in rats by diets rich in saturated fat. *Lipids.* 1984;19:699-703.

391. Eaton SB, Eaton SB III, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. A review. *Eur J Clin Nutr.* 1997;51:207-216.

392. Mills DE, Ward R. Attenuation of psychosocial stress-induced hypertension by gamma-linolenic acid (GLA) administration in rats. *Proc Soc Exp Biol Med.* 1984;176:32-37.

393. Engler MM, Schambelan M, Engler MB, Ball DL, Goodfriend TL. Effects of gamma-linolenic acid on blood

pressure and adrenal angiotensin receptors in hypertensive rats. *Proc Soc Exp Biol Med.* 1998;218:234-237.

394. Mamalakis G, Kafatos A, Tornaritis M, Alevizos B. Anxiety and adipose essential fatty acid precursors for prostaglandin E1 and E2. *J Am Coll Nutr.* 1998;17:239-243.

395. Williams LL, Kiecolt-Glaser JK, Horrocks LA, Hillhouse JT, Glaser R. Quantitative association between altered plasma esterified omega-6 fatty acid proportions and psychological stress. *Prostaglandins Leukot Essent Fatty Acids.* 1992;47:165-170.

396. Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res.* 2000;42:7-17.

397. Langsjoen P, Willis R, Folkers K. Treatment of essential hypertension with coenzyme Q10. *Mol Aspects Med.* 1994;15:S265-S272.

398. Allmann DW, Gibson DW. Fatty acid synthesis during early linoleic acid deficiency in the mouse. *J Lipid Res.* 1969;6:51-62.

399. Baillie RA, Takada R, Nakamura M, Clarke SD. Coordinate induction of peroxisomal acyl-CoA oxidase and UCP-3 by dietary fish oil: a mechanism for decreased body fat deposition. *Prostaglandins Leukot Essent Fatty Acids.* 1999;60:351-356.

400. Hill JO, Peters JC, Lin D, Yakubu F, Greene H, Swife L. Lipid accumulation and body fat distribution is influenced by type of dietary fat fed to rats. *Int J Obes.* 1993;17:223-236.

401. Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS. Fish oil prevents insulin resistance induced by high fat feeding in rats. *Science.* 1987;237:885-888.

402. Podolin DA, Gayles EC, Wei Y, Thresher JS, Pagliassotti MJ. Menhaden oil prevents but does not reverse sucrose-induced insulin resistance in rats. *Am J Physiol.* 1998;274:840-848.

403. Xu J, Nakamura MT, Cho HP, Clarke SD. Sterol regulatory element binding protein-1 expression is suppressed by dietary polyunsaturated fatty acids. *J Biol Chem.* 1999;274:23577-23583.

404. Leaf A, Kang JX. Prevention of cardiac sudden death by N-3 fatty acids: a review of the evidence. *J Intern Med.* 1996;240:5-12.

405. Chin JP. Marine oils and cardiovascular reactivity. *Prostaglandins Leukot Essent Fatty Acids.* 1994;50:211-222.

406. Mori TA, Watts GF, Burke V, *et al.* Differential effects of eicosapentaenoic acid and docosahexaenoic acid on forearm vascular reactivity of the microcirculation in hyperlipidaemic, overweight men. *Circulation.* 2000;102:1264-1269.

407. Goodfellow J, Bellamy MF, Ramsey MW, *et al.* Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. *J Am Coll Cardiol.* 2000;35:265-270.

408. Hashimoto M, Hossain S, Yamasaki H, *et al.* Effects of eicosapentaenoic acid and docosahexaenoic acid on plasma membrane fluidity of aortic endothelial cells. *Lipids.* 1999;34:1297-1304.

409. Das UN. Biological significance of arachidonic acid. *Med Sci Res.* 1987;24:1485.

410. Kumar KV, Das UN. Effect of cis-unsaturated fatty acids, prostaglandins, and free radicals on angiotensin-converting enzyme activity in vitro. *Proc Soc Exp Biol Med.* 1997;214:374-379.

411. Suryaprabha P, Das UN, Koratkar R, Sagar PS, Ramesh G. Free radical generation, lipid peroxidation and essential fatty acids in uncontrolled essential hypertension. *Prostaglandins Leukot Essent Fatty Acids.* 1990;41:27.

412. Ferrara LA, Raimondi S, d'Episcopa I, *et al.* Olive oil and reduced need for antihypertensive medications. *Arch Intern Med.* 2000;160:837-842.

413. trazzullo P, Ferro-Luzzi A, Siani A, *et al.* Changing the Mediterranean diet: effects on blood pressure. *J Hypertens.* 1986;4:407-412.

414. Thomsen C, Rasmussen OW, Hansen KW, Vesterlund M, Hermansen K. Comparison of the effects on the diurnal blood pressure, glucose, and lipid levels of a diet rich in monounsaturated fatty acids with a diet rich in polyunsaturated fatty acids in type 2 diabetic subjects. *Diabet Med.* 1995;12:600-606.

415. Mensink RP, Janssen MC, Katan MB. Effect on blood pressure of two diets differing in total fat but not in saturated and polyunsaturated fatty acids in healthy volunteers. *Am J Clin Nutr.* 1988;47:976-980.

416. Papadopoulos G, Boskou D. Antioxidant effect of natural phenols in olive oil. *J Am Oil Chem Soc.* 1991;68:669-671.

417. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. *Arterioscler Thromb.* 1992;12:911-919.

418. Reaven P, Parthasarathy S, Grasse BJ, Miller E, Steinberg D, Witzum JL. Effects of oleate-rich and linoleate-rich diets on the susceptibility of low density lipoprotein to oxidative modification in mildly hypercholesterolemic subjects. *J Clin Invest.* 1993;91:668-676.

419. Yamori Y, Nara Y, Tsubouchi T, Sogawa Y, Ikeda K, Horie R. Dietary prevention of stroke and its mechanisms in stroke-prone spontaneously hypertensive rats–preventive effect of dietary fibre and palmitoleic acid. *J Hypertens.* 1986;4:S449-S452.

420. Iso H, Stampfer MJ, Manson JE, *et al.* Prospective study of fat and protein intake and risk of intraparenchymal hemorrhage in women. *Circulation.* 2001;103:856-863.

421. He J, Whelton PK. Effect of dietary fiber and protein intake on blood pressure: a review of epidemiologic evidence. *Clin Exp Hypertens.* 1999;21:785-796.

422. Pereira MA, Pins JJ. Dietary fiber and cardiovascular disease: experimental and epidemiologic advances. *Curr Atheroscler Rep.* 2000;2:494-502.

423. Vuksan V, Jenkins DJA, Spadafora P, *et al.* Konjac-Mannan (Glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. *Diabetes Care.* 1999;22:913-919.

424. Keenan JM, Pins JJ, Frazel C, *et al.* Oat ingestion reduces systolic and diastolic blood pressure among moderate hypertensives: a pilot trial. *J Fam Pract.* 2000.

425. Pins JJ, Geleva D, Keenan JM, *et al.* Whole grain cereals reduce antihypertensive medication need, blood lipid and plasma glucose levels. *J Am Coll Nutr.* 1999;18:529. Abstract.

426. Katakam P, Ujhelyi MR, Hoenig ME, *et al.* Endothelial dysfunction precedes hypertension in diet induced insulin resistance. *Am J Physiol.* 1998;275:R788-R792.

427. Scherrer U, Sartori C. Defective nitric oxide synthesis: a

link between metabolic insulin resistance, sympathetic overactivity and cardiovascular morbidity. *Eur J Endocrinol.* 2000;142:315-323.

428. Auer W, Eiber A, Hertkorn E, Hoehfeld E, Koehrle U, Lorenz A, Mader F, Marx W, Otto G, Schmid-Otto B. Hypertension and hyperlipidaemia: garlic helps in mild cases. *Br J Clin Pract.* 1990;69:3-6.

429. McMahon FG, Vargas R. Can garlic lower blood pressure? A pilot study. *Pharmacotherapy.* 1993;13:406-407.

430. Lawson LD. Garlic: a review of its medical effects and indicated active compounds. In: Lawson LD, Bauer R, eds. *Phytomedicines of Europe: Chemistry and Biological Activity.* Washington, DC: American Chemical Society; 1998:176-209.

431. Pedraza-Chaverri J, Tapia E, Medina-Campos ON, de los Angeles Granados M, Franco M. Garlic prevents hypertension induced by chronic inhibition of nitric oxide synthesis. *Life Sci.* 1998;62:71-77.

432. Orekhov AN, Grunwald J. Effects of garlic on atherosclerosis. *Nutrition.* 1997;13:656-663.

433. Ernst E. Cardiovascular effects of garlic (Allium sativum): a review. *Pharmatherapeutica.* 1987;5:83-89.

434. Silagy CA, Neil AW. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens.* 1994;12:463-468.

435. Silagy C, Neil A. Garlic as a lipid lowering agent: a meta-analysis. *J R Coll Physicians Lond.* 1994;28:39-45.

436. Ojewole JAO, Adewunmi CO. Possible mechanisms of antihypertensive effect of garlic: evidence from mammalian experimental models. *Am J Hypertens.* 2001;14:29A. Abstract.

437. Kleinjnen J, Knipschild P, Ter Riet G. Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol.* 1989;28:535-544.

438. Reuter HD, Sendl A. Allium sativum and Allium ursinum: chemistry, pharmacology and medicinal applications. *Econ Med Plant Res.* 1994;6:55-113.

439. Mohamadi A, Jarrell ST, Shi SJ, Andrawis NS, Myers A, Clouatre D, Preuss HG. Effects of wild versus cultivated garlic on blood pressure and other parameters in hypertensive rats. *Heart Disease.* 2000;2:3-9.

440. Clouatre D. *European Wild Garlic: The Better Garlic.* San Francisco: Pax Publishing; 1995.

441. Sendl A, Elbl G, Steinke B, Redl K, Breu W, Wagner H. Comparative pharmacological investigations of Allium ursinum and Allium sativum. *Planta Med.* 1992;58:1-116.

442. Sendl A, Schliack M, Losu R, Stanislaus F, Wagner H. Inhibition of cholesterol synthesis in vitro by extracts and isolated compounds prepared from garlic and wild garlic. *Atherosclerosis.* 1992;94:79-85.

443. Wagner H, Elbl G, Lotter H, Guinea M. Evaluation of natural products as inhibitors of angiotensin I converting enzyme (ACE). *Pharmacol Lett.* 1991;15-18.

444. Das I, Khan NS, Soornanna SSR. Potent activation of nitric oxide synthase by garlic: a basis for its therapeutic application. *Curr Med Res Opin.* 1994;13:257-263.

445. Torok B, Belagyi J, Rietz B, Jacob R. Effectiveness of garlic on the radical activity radical generating sytems. *Arzneimittelforschung.* 1994;44:608-611.

446. Jarrell ST, Bushehri N, Shi S-J, Andrawis N, Clouatre D, Preuss HG. Effects of Wild Garlic (Allium ursinum) on blood pressure in SHR. *J Am Coll Nutr.* 1996;15:532. Abstract.

447. Mutsch-Eckner M, Meier B, Wright AD, Sticher O. Gamma-glutamyl peptides from Allium sativum bulbs. *Phytochemistry.* 1992;31:2389-2391.

448. Meunier MT, Villie F, Jonadet M, Bastide J, Bastide P. Inhibition of angiotensin I converting enzyme by flavonolic compounds: in vitro and in vivo studies. *Planta Med.* 1987;53:12-15.

449. Elkayam A, Mirelman D, Peleg E, Wilchck M, et al. The effects of Allicin and Enalapril in fructose-Induced hyperinsulinemic, hyperlipidemic, hypertensive rats. *Am. J. Hypertens* 2001;14:377-381

450. Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, Lawrence VA. Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med.* 2001;161:813-824.

451. Hodgson JM, Puddey IB, Burke V, Beilin LJ, Jordan N. Effects on blood pressure of drinking green and black tea. *J Hypertens.* 1999;17:457-463.

452. Fitzpatrick DF, Hirshfield SL, Ricci T, Jantzen P, Coffey RG. Endothelium-dependent vasorelaxation caused by various plant extracts. *J Cardiovasc Pharmacol.* 1995;26:90-95.

453. Fitzpatrick DF, Hirshfield SL, Coffey RG. Endothelium-dependent vasorelaxing activity of wine and other grape products. *Am J Physiol.* 1993;265:H774-H778.

454. Stensvold I, Terdal A, Solvol K, Foss OP. Tea consumption. Relationship to cholesterol, blood pressure and coronary and total mortality. *Prev Med.* 1992;21:546-553.

455. Bingham SA, Vorster H, Jerling JC, Magee E, Mulligan A, Runswick SA, *et al.* Effect of tea drinking on blood lipids, blood pressure and aspects of bowel habit. *Br J Nutr.* 1997;78:41-45.

456. Rakic V, Beilin LJ, Burke V. Effect of coffee and tea drinking on postprandial hypotension in older men and women. *Clin Exp Pharmacol Physiol.* 1996;23:559-563.

457. Abe Y, Umemura S, Sugimoto K, Hirawa N, Kato Y, Yokoyama N, *et al.* Effect of green tea rich in gamma-aminobutyric acid on blood pressure of Dahl salt-sensitive rats. *Am J Hypertens.* 1995;8:74-79.

458. Yokozawa T, Oura H, Sakanaka S, Ishigaki S, Kim M. Depressor effect of tannin in green tea on rats with renal hypertension. *Biosci Biotechnol Biochem.* 1994;58:855-858.

459. Yokogoshi H, Kato Y, Saesaka YM, Takihara-Matsuura T, Takeuchi N. Reduction effect of theanine on blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats. *Biosci Biotechnol Biochem.* 1995;59:615-618.

460. Uchida S, Ozaki M, Akashi T, Yamashita K, Niwa M, Taniyama K. Effects of (-)-epigallocatechin-3-0-gallate (green tea tannin) on the lifespan of stroke-prone spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol.* 1995;22:S302-S303.

461. Yokogoshi H, Kobayashi M. Hypotensive effect of gamma-glutamylmethylamide in spontaneously hypertensive rats. *Life Sci.* 1998;62:1065-1068.

462. Riemersma RA, Rice-Evans CA, Tyrell RM, Clifford MN, Lean ME. Tea flavonoids and cardiovascular health. *QJM.*

2001;94:277-282.

463. Kabir Y, Yamaguchi M, Kimura S. Effect of shiitake (lentinus edodes) and maitake (grifola frondosa) mushrooms on blood pressure and plasma lipids of spontaneously hypertensive rats. *J Nutr Sci Vitaminol (Tokyo).* 1987;33:341-346.

464. Adachi K, Nanba H, Otsuka M, Kurada H. Blood pressure-lowering activity present in the fruit body of grifola frondosa (maitake). I. *Chem Pharm Bull (Tokyo).* 1988;36:1000-1006.

465. Kabir Y, Kimura S. Dietary mushrooms reduce blood pressure in spontaneously hypertensive rats (SHR). *J Nutr Sci Vitaminol (Tokyo).* 1989;35:91-94.

466. Suetsuna K, Nakano T. Identification of an antihypertensive peptide from peptic digest of wakame (undaria pinnatifida). *J Nutr Biochem.* 2000;11:450-454.

467. Nakano T, Hidaka H, Uchida J, Nakajima K, Hata Y. Hypotensive effects of wakame. *J Jpn Soc Clin Nutr.* 1998;20:92.

468. Krotkiewski M, Aurell M, Holm G, Grimby G, Szckepanik J. Effects of a sodium-potassium ion-exchanging seaweed preparation in mild hypertension. *Am J Hypertens.* 1991;4:483-488.

469. Yamori Y, Nara Y, Tsubouchi T, Sogawa Y, Ikeda K, Horie R. Dietary prevention of stroke and its mechanisms in stroke-prone spontaneously hypertensive rats – prevention effect of dietary fibre and palmitoleic acid. *J Hypertens.* 1986;4:S449-S452.

470. Hata Y, Yamamoto M, Ohni M, Nakajima K, Nakamura Y, Takano T. A placebo-controlled study of the effect of sour milk on blood pressure in hypertensive subjects. *Am J Clin Nutr.* 1996;64:767-771.

471. Maruyama S, Mitachi H, Awaya J, Kurono M, Tomizuka N, Suzuki H. Angiotensin I-converting enzyme inhibitory activity of the c-terminal hexapeptide of as1-casein. *Agric Biol Chem.* 1987;51:2557-2561.

472. Kohmura M, Nio N, Kubo K, Monoshima Y, Munekata E, Ariyoshi Y. Inhibition of angiotensin-converting enzyme by synthetic peptides of human b-casein. *Agric Biol Chem.* 1989;53:2107-2114.

473. Miyoshi S, Ishikawa I, Kaneko T, Fukui F, Tanaka M, Maruyama S. Structures and activity of angiotensin-converting enzyme inhibitors in an a-zein hydrolysate. *Agric Biol Chem.* 1991;55:1313-1318.

474. Yano S, Suzuki K, Funatsu G. Isolation from a-zein of thermolysin peptides with angiotensin I-converting enzyme inhibitory activity. *Biosci Biotechnol Biochem.* 1996;60:661-663.

475. Ohshima G, Shimabukuro H, Nagasama K. Peptide inhibitors of angiotensin-converting enzyme in digests of gelatin by bacterial collagenase. *Biochim Biophys Acta.* 1979;566:128-137.

476. Saito S, Wanezaki (Nakamura) K, Kawato A, Imayasu S. Structure and activity of angiotensin I converting enzyme inhibitory peptides from sake and sake lees. *Biosci Biotechnol Biochem.* 1994;58:1767-1771.

477. Nakamura Y, Yamamoto N, Sakai K, Okubo A, Yamazaki S, Takano T. Purification and characterization of angiotensin I-converting enzyme inhibitors from sour milk. *J Dairy Sci.* 1995;78:777-783.

478. Suetsuna K. Study on the inhibitory activities against angiotensin I-converting enzyme of the peptides derived from sardine muscle. Doctoral Thesis, Tohoku University, Miyagi, Sendai, Japan; 1992.

479. Matsufuji H, Matsui T, Ohshige S, Kawasaki T, Osajima K, Osajima Y. Antihypertensive effects of angiotensin fragments in SHR. *Biosci Biotechnol Biochem.* 1995;59:1398-1401.

480. Kohama Y, Oka H, Kayamori Y, Tsujikawa K, Mimura T, Nagase Y, Satake M. Potent synthetic analogues of angiotensin-converting enzyme inhibitor derived from tuna muscle. *Agric Biol Chem.* 1991;55:2169-2170.

481. Astawan M, Wahyuni M, Yasuhara T, Yamada K, Tadokoro T, Maekawa A. Effects of angiotensin I-converting enzyme inhibitory substances derived from Indonesian dried-salted fish on blood pressure of rats. *Biosci Biotechnol Biochem.* 1995;59:425-429.

482. Yokoyama K, Chiba H, Yoshikawa M. Peptide inhibitors for angiotensin I-converting enzyme from thermolysin digest of dried bonito. *Biosci Biotechnol Biochem.* 1992;56:1541-1545.

483. Okamoto (Kaimura) A, Matsumoto E, Iwashita A, Yasuhara T, Kawamura Y, Koizumi Y, Yanagida F. Angiotensin I-converting enzyme inhibitory action of fish sauce. *Food Sci Technol Int.* 1995;1:101-106.

484. Suetsuna K. Purification and identification of angiotensin I-converting enzyme inhibitors from the red algae Porphyra yezoensis. *J Mar Biotechnol.* 1998;6:163-167.

485. Suetsuna K. Separation and identification of angiotensin I-converting enzyme inhibitors from peptic digest of Hizikia fusiformis protein. *Nippon Suisan Gakkaishi.* 1998;64:862-866.

486. Blaszó G, Gáspár R, R?ve HJ, Rohdewald P. ACE inhibition and hypotensive effect of a procyanidins containing extract from the baric of pinus pinaster sol. *Pharm Pharmacol Lett.* 1996;1:8-11.

487. Sherman DL, Keaney JF, Biegelsen ES, et al. Pharmacological concentrations of ascorbic acid are required for the beneficial effect on endothelial vasomotor function in hypertension. *Hypertension.* 2000;35:936-941.

488. Ting HH, Creager MA, Ganz P, Roddy MA, Haley EA, Timimi FK. Vitamin C improves endothelium-dependent vasodilation in forearm resistance vessels of humans with hypercholesterolemia. *Circulation.* 1997;95:2617-2622.

489. Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. *Circulation.* 1998;97:2222-2229.

490. Levine GN, Frei B, Koulouris SN, Gerhard MD, Keaney JF, Vita JA. Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation.* 1996;93:1107-1113.

491. Heitzer T, Just H, M?nzel T. Antioxidant vitamin C improves endothelial dysfunction in chronic smokers. *Circulation.* 1996;94:6-9.

492. Bates CJ, Walmsley CM, Prentice A, Finch S. Does vitamin C reduce blood pressure? Results of a large study of people aged 65 or older. *J Hypertens.* 1998;16:925-932.

493. Ness AR, Khaw K-T, Bingham S, Day NE. Vitamin C status and blood pressure. *J Hypertens.* 1996;14:503-508.

494. Moran JP, Cohen L, Green JM, Xu G, Feldman EB, Hames CG, Feldman DS. Plasma ascorbic acid concentrations relate inversely to blood pressure in human subjects. *Am J Clin Nutr.* 1993;57:213-217.

495. Duffy SJ, Gokce N, Holbrook M, *et al.* Treatment of hypertension with ascorbic acid. *Lancet.* 1999;354:2048-2049.

496. Schilling J, Holzer P, Guggenbach M, Gyurech D, Marathia K, Geroulanos S. Reduced endogenous nitric oxide in the exhaled air of smokers and hypertensives. *Eur Respir J.* 1994;7:467-471.

497. emila H. Vitamin C and lowering of blood pressure: need for intervention trials? *J Hypertens.* 1991;9:1076-1077.

498. Feldman EB. The role of vitamin C and antioxidants in hypertension. *Nutrition and the M.D.* 1998;24:1-4.

499. Trout DL. Vitamin C and cardiovascular risk factors. *Am J Clin Nutr.* 1991;53:322-325.

500. Salonen JT, Salonen R, Ihanainen M, *et al.* Blood pressure, dietary fats, and antioxidants. *Am J Clin Nutr.* 1988;48:1226-1232.

501. Enster L, Dallner G. Biochemical, physicological and medical aspects of ubiquinone function. *Biochim Biophys Acta.* 1995;1271:195-204.

502. Simon JA. Vitamin C and cardiovascular disease: a review. *J Am Coll Nutr.* 1992;11:107-125.

503. Osilesi O, Trout DL, Ogunwole J. Glover EE. Blood pressure and plasma lipids during ascorbic acid supplementation in borderline hypertensive and normotensive adults. *Nutr Res.* 1991;11:405-412.

504. Lovat LB, Lu Y, Palmer AJ, Edwards R, Fletcher AE, Bulpitt CJ. Double blind trial of vitamin C in elderly hypertensives. *J Hum Hypertens.* 1993;7:403-405.

505. Ghosh SK, Ekpo EB, Shah IU, Girling AJ, Jenkins C, Sinclair AJ. A double-blind placebo controlled parallel trial of vitamin C treatment in elderly patients with hypertension. *Gerontology.* 1994;40:268-272.

506. Fotherby MD, Williams JC, Forster LA, Craner P, Ferns GA. Effect of vitamin C on ambulatory blood pressure and plasma lipids in older persons. *J Hypertens.* 2000;18:411-415.

507. Koh ET. Effect of vitamin C on blood parameters of hypertensive subjects. *J Okla State Med Assoc.* 1984;77:177-182.

508. Block G, Mangels AR, Patterson BH, Levander OA, Norkus E, Taylor PR. Body weight and prior depletion affect plasma ascorbate levels attained on identical vitamin C intake: a controlled-diet study. *J Am Coll Nutr.* 1999;18:628-637.

509. Grossman M, Dobrev D, Himmel HM, Ravens U, Kirsh W. Ascorbic acid-induced modulation of venous tone in humans. *Hypertension.* 2001;37:949-954.

510. Yoshioka M, Aoyama K, Matsoshita T. Effects of ascorbic acid on blood pressure and ascorbic acid metabolism in spontaneously hypertensive rats. *Int J Vitam Nutr Res.* 1985;55:301-307.

511. Enstrom JE, Kanim LE, Klein M. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology.* 1992;3:194-202.

512. Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. *BMJ.* 1995;310:1563-1566.

513. Egan DA, Garg R, Wilt TJ, *et al.* Rationale and design of the arterial disease multiple intervention trial (ADMIT) pilot study. *Am J Cardiol.* 1999;83:569-575.

514. Block G, Mangels AR, Norkus EP, Patterson BH, Levander OA, Taylor PR. Ascorbic acid status and subsequent diastolic and systolic blood pressure. *Hypertension.* 2001;37:261-267.

515. Hajjar IM, George V, Kochar M. Effect of vitamin C supplementation on systolic, diastolic, pulse pressure and lipids: a randomized controlled trial. *Am J Hypertens.* 2001;14:143A. Abstract P-339.

516. Das UN. Hypertension and ascorbic acid. *Lancet.* 2000;355:1273.

517. Salonen R, Korpela H, Nyyssonen K, Porkkala E, Salonen JT. Reduction of blood pressure by antioxidant supplementation: a randomized double-blind clinical trial. *Life Chem Rep.* 1994;12:65-68.

518. Toivanan JL. Effects of selenium, vitamin E and vitamin C on human prostacyclin and thromboxane synthesis in vitro. *Prostaglandins Leukotrienes Med.* 1987;26:265-280.

519. Miller ER III, Appel LJ, Levander OA, Levine DM. The effect of antioxidant vitamin supplementation on traditional cardiovascular risk factors. *J Cardiovasc Risk.* 1997;4:19-24.

520. Cooke JP. Nutraceuticals for cardiovascular health. *Am J Cardiol.* 1998:82:43S-45S.

521. Hornig B, Arakawa N, Kohler C, Drexler H. Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure. *Circulation.* 1998;97:363-368.

522. Hajjar IM, Grim CE, George V, Kotchen TA. Impact of diet on blood pressure and age-related changes in blood pressure in the US population. *Arch Intern Med.* 2001;161:589-593.

523. Pierdomenico SD, Constantini F, Bucci A, De Cesare D, Cuccurollo F, Mezzetti A. Low-density lipoprotein oxidation and vitamins E and C in sustained and white-coat hypertension. *Hypertension.* 1998;31:621-626.

524. National Center for Health Statistics, Fulwood R, Johnson CL, Bryner JD. *Hematological and Nutritional Biochemistry Reference Data for Persons 6 Months–74 Years of Age: United States, 1976-80.* Washington, DC; US Public Health Service; 1982 Vital and Health Statistics series 11, No. 232, DHHS publication No. (PHS) 83-1682.

525. Kallner A, Hartmann D, Hornig D. Steady-state turnover and body pool of ascorbic acid in man. *Am J Clin Nutr.* 1979;32:530-539.

526. Hornig DH. Distribution of ascorbic acid, metabolites and analogues in man and animals. *Ann N Y Acad Sci.* 1975;258:103-118.

527. Witte K. Lemmer B. Signal transduction in animal models of normotension and hypertension. *Ann NY Acad Sci.* 1996;783:71-83.

528. Beetens JR, Herman AG. Ascorbic acid and prostaglandin formation. *Int J Vitam Nutr Res Suppl.* 1983;24:131-143.

529. Siow RC, Richards JP, Pedley KC, Leake DS, Mann GE. Vitamin C protects human vascular smooth muscle cells against apoptosis induced by moderately oxidized LDL containing high levels of lipid hydroperoxides. *Arterioscler Thromb Vasc Biol.* 1999;19:2387-2394.

530. Nakazato T, Shikama T, Toma S, Nakajima Y, Masuda Y. Nocturnal variation in human sympathetic baroreflex sensitivity. *J Auton Nerv Syst.* 1998;70:32-37.

531. Shimizu M, Hatta Y, Hayashi H, *et al.* The effect of ascorbic acid on fibrinolysis. *Acta Haematol Jpn.* 1970;33:137-148.

532. Dobson H, Muir M, Hume R. The effect of ascorbic acid on

the seasonal variations in serum cholesterol levels. *Scott Med J.* 1984;29:176-182.

533. Bates CJ, Burr MK, St Ledger AS. Vitamin C high density lipoproteins and heart disease in elderly subjects. *Age Ageing.* 1979;8:177-182.

534. Siow RC, Richards JP, Pedley KC, Leake DS, Mann GE. Vitamin C protects human vascular smooth muscle cells against apoptosis induced by moderately oxidized LDL containing high levels of lipid hydroperoxides. *Arterioscler Thromb Vasc Biol.* 1999;19:2387-2394.

535. Kendler BS. Nutritional strategies in cardiovascular disease control: an update on vitamins and conditionally essential nutrients. *Prog Cardiovasc Nurs.* 1999;14:124-129.

536. Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P, Lunec J. Vitamin C exhibits pro-oxidant properties (letter). *Nature.* 1998;392:559.

537. Podmore ID, Griffiths HR, Herbert KE, *et al.* Does vitamin C have a pro-oxidant effect? (letter). *Nature.* 1998;395:232.

538. Newaz MA, Nawal NNA. Effect of ?-tocotrienol on blood pressure, lipid peroxidation and total antioxidant status in spontaneously hypertensive rats (SHR). *Clin Exp Hypertens.* 1999;21:1297-1313.

539. Newaz MA, Nawal NNA. Effect of a-tocopherol on lipid peroxidation and total antioxidant status in spontaneously hypertensive rats. *Am J Hypertens.* 1998;11:1480-1485.

540. Newaz MA, Nawal NNA, Muslim N, Gapor A. a-tocopherol increased nitric oxide synthase activity in blood vessels of spontaneously hypertensive rats. *Am J Hypertens.* 1999;12:839-844.

541. Igarashi T, Nakajima Y, Kobayashi M, Ohtake S. Anti-hypertensive action of DL-alpha-tocopheryl esters in rats. *Clin Sci Mol Med Suppl.* 1976;3:163s-164s.

542. Pezeshk A, Derick Dalhouse A. Vitamin E, membrane fluidity, and blood pressure in hypertensive and normotensive rats. *Life Sci.* 2000;67:1881-1889.

543. Koba K, Abe K, Ikeda I, Sugano M. Effects of alpha-tocopherol and tocotrienols on blood pressure and linoleic acid metabolism in the spontaneously hypertensive rat (SHR). *Biosci Biotechnol Biochem.* 1992;56:1420-1423.

544. Barbagallo M, Dominguez LJ, Tagliamonte MR, Resnick LM, Paolisso G. Effects of vitamin E and glutathione on glucose metabolism. The role of magnesium. *Hypertension.* 1999;34:1002-1006.

545. Palumbo G, Avanzini F, Alli C, Roncaglioni C, *et al.* Effects of vitamin E on clinic and ambulatory blood pressure in treated hypertensive patients. *Am J Hypertens.* 2000;13:564-567.

546. Martin-Nrard F, Boullier A, Fruchart JC, Duriez P. Alpha tocopherol but not beta-tocopherol inhibits thrombin-induced PKC activation and endothelin secretion in endothelial cells. *J Cardiovasc Risk.* 1998;5:339-345.

547. Mottram P, Shige H, Nestel P. Vitamin E improves arterial compliance in middle-aged men and women. *Atherosclerosis.* 1999;145:399-404.

548. Skyrme-Jones RA, O'Brien RC, Berry KL, Meredith IT. Vitamin E supplementation improves endothelial function in type I diabetes mellitus: a randomized, placebo-controlled study. *J Am Coll Cardiol.* 2000;36:94-102.

549. Iino K, Abe K, Kariya S, Kimura H, Kusaba T, *et al.* A controlled, double-blind study of dl-alpha-tocopheryl nicotinate (Juvela-Nicotinate) for treatment of symptoms in hypertension and cerebral arteriosclerosis. *Jpn Heart J.* 1977;18:277-286.

550. Wen Y, Killalea S, McGettigan P, Freely J. Lipid peroxidation and antioxidant vitamins C and E in hypertensive patients. *IJMS.* 1996;165:210-212.

551. Dakshinamurti K, Lal KJ. Vitamins and hypertension from Simopoulos AP, ed: Nutrients in the control of metabolic diseases. *World Rev Nutr Diet.* Basal, Karger. 1996;69:40-73.

552. Hanni LL, Huarfner LH, Sorensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. *Am J Hypertens.* 1995;8:894-901.

553. Boucher BJ. Inadequate vitamin D status: does it contribute to the disorders comprising syndrome 'X'? *Br J Nutr.* 1998;79:315-327.

554. Lind L, Wengle BO, Junghall S. Blood pressure is lowered by vitamin D (alphacalcidol) during long term treatment of patients with intermittent hypercalcemia. *Acta Med Scand.* 1987;222:423-427.

555. Lind L, Lithell H, Skarfos E, *et al.* Reduction of blood pressure by treatment with alphacalcidol. *Acta Med Scand.* 1988;223:211-217.

556. Lind L, Wengle BO, Wide L, Sorensen OH, Ljunghall S. Hypertension in primary hyperparathyroidism–reduction of blood pressure by long-term treatment with vitamin D (alphacalcidol). A double-blind, placebo-controlled study. *Am J Hypertens.* 1988;1:397-402.

557. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab.* 2001;86:1633-1637.

558. McCarron DA. Calcium metabolism and hypertension. *Kidney Int.* 1989;35:717-736.

559. McCarron DA. Low serum concentrations of ionized calcium in patients with hypertension. *N Engl J Med.* 1982;307:226-228.

560. Resnick LM. Dietary calcium and hypertension. *J Nutr.* 1987;117:1806-1808.

561. Holdaway SR, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxycholecalciferol concentration in newly detected hypertension. *Am J Hypertens.* 1995;4:429-432.

562. Jorde R, Bonaa KH. Calcium from dairy products, vitamin D intake and blood pressure: the Tromso Study. *Am J Clin Nutr.* 2000;71:1530-1535.

563. Kurtz TW, Morris RC. Dietary intake of vitamin D as a determinant of deoxycorticosterone hypertension. *Hypertension.* 1986;8:833. Abstract.

564. Bukoski RD, McCarron DA. Altered aortic reactivity and lowered blood pressure associated with high Ca^{++} intake in the SHR. *Am J Physiol.* 1986;251:H976-H983.

565. MacCarthy EP, Yamashita W, Hsu A, *et al.* 1,25 dihydroxy vitamin D3 and rat vascular smooth muscle cell growth. *Hypertension.* 1989;13:954-959.

566. Lal KJ, Dakshinamurti K. Calcium channels in vitamin B6 deficiency-induced hypertension. *J Hypertens.* 1993;11:1357-1362.

567. Fregly MJ, Cade JR. Effect of pyridoxine and tryptophan, alone and in combination, on the development of deoxycorticosterone acetate-induced hypertension in rats. *Pharmacology.* 1995;50:298-306.

568. Lal KJ, Krishnamurti D, Thliverv J. The effect of vitamin B6 on the systolic blood pressure of rats in various animal models of hypertension. *J Hypertens.* 1996;14:355-363.

569. Paulose CS, Dakshinamurti K, Packer S, Stephens NL. Hypertension in pyridoxine deficiency. *J Hypertens.* 1986;4:S174-S175.

570. Paulose CS, Dakshinamurti K, Packer S, Stephens NL. Sympathetic stimulation and hypertension in the pyridoxine-deficient adult rat. *Hypertension.* 1988;11:387-391.

571. Kleiger JA, Altshuler CH, Krakow G, Hollister C. Abnormal pyridoxine metabolism in toxemia of pregnancy. *Ann N Y Acad Sci.* 1969;166:288-296.

572. Brophy MH, Siiteri PK. Pyridoxal phosphate and hypertensive disorders of pregnancy. *Am J Obstet Gynecol.* 1975;121:1075-1079.

573. Brophy MH. Zinc, preeclampsia and g-aminobutyric acid. *Am J Obstet Gynecol.* 1990;163:242-243.

574. Brophy EM, Brophy MH. Pyridoxal phosphate normalization of the EEG in eclampsia. In: *Hypertension in Pregnancy.* Bologna; 1991:479.

575. Keniston R, Enriquez JI Sr. Relationship between blood pressure and plasma vitamin B_6 levels in healthy middle-aged adults. *Ann NY Acad Sci.* 1990;585:499-501.

576. Dakshinamurti K, Lal KJ. Vitamins and hypertension. *World Rev Nutr Diet.* 1992;69:40-73.

577. Aybak M, Sermet A, Ayyildiz MO, Karakilcik AZ. Effect of oral pyridoxine hydrochloride supplementation on arterial blood pressure in patients with essential hypertension. *Arzneimittelforschung.* 1995;45:1271-1273.

578. Bender DA. Non-nutritional uses of vitamin B-6. *Br J Nutr.* 1999;81:7-20.

579. Dakshinamurti K, Paulose CS, Viswanathan M. Vitamin B6 and hypertension. *Ann N Y Acad Sci.* 1990;575:241-249.

580. Dakshinamurti K, Lal KJ, Ganguly PK. Hypertension calcium channel and pyridoxine (vitamin B-6). *Mol Cell Biochem.* 1998;188:137-148.

581. Lehninger AL. *Biochemistry: The Molecular Basis of Cell Structure and Function.* 2nd edition. New York: Worth Publishers, Inc.; 1978:698.

582. Lal KJ, Dakshinamurti K, Thliveris J. The effect of vitamin B_6 on the systolic blood pressure of rats in various animal models of hypertension. *J Hypertens.* 1996;14:355-363.

583. Vasdev S. Ford CA, Parai S, Longerich L, Gadag V. Dietary vitamin B6 supplementation attenuates hypertension in spontaneously hypertensive rats. *Mol Cell Biochem.* 1999;200:155-162.

584. Formica JV, Regelson W. Review of the biology of quercetin and related bioflavonoids. *Food Chem Toxicol.* 1995;33:1061-1080.

585. Potter SM. Soy protein and serum lipids. *Curr Opin Lipidol.* 1996;7:260-264.

586. Laplaud PM, Lelubre A, Chapman MJ. Antioxidant action of Vaccinium myrtillus extract on human low density lipoproteins in vitro: initial observations. *Fundam Clin Pharmacol.* 1997;11:35-40.

587. Stromer FC, Reistad R, Alexander J. Glycyrrhizic acid in liquorice: evaluation of health hazard. *Food Chem Toxicol.* 1993;31:303-312.

588. Vaya J, Belinky PA, Aviram M. Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation. *Free Radic Biol Med.* 1997;23:302-313.

589. Moline J, Bukharovich IF, Wolff MS, Phillips R. Dietary flavonoids and hypertension: is there a link? *Med Hypotheses.* 2000;55:306-309.

590. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet.* 1993;342:1007-1011.

591. Knekt P, Reunanen A, Järvinen R, Seppänen R, Heliˆvaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol.* 1994;139:1180-1189.

592. Hollman PCH, Katan MB. Absorption, metabolism, and health effects of dietary flavonoids in man. *Biomed Pharmacother.* 1997;51:305-310.

593. Hodgson JM, Puddey IB, Beilin LJ, Mori TA, Burke V, *et al.* Effects of isoflavonoids on blood pressure in subjects with high-normal ambulatory blood pressure levels. A randomized controlled trial. *Am J Hypertens.* 1999;12:47-53.

594. Hodgson JM, Puddey IB, Croft KD, Mori TA, Rivera J, Beilin LT. Isoflavonoids do not inhibit in vivo lipid peroxidation in subjects with high normal blood pressure. *Atherosclerosis.* 1999;145:167-172.

595. Asgary S, Naderi GH, Sarrafzadegan N, Mohammadifard N, Mostafavi S, Vakili R. Antihypertensive and anti-hyperlipidemic effects of Achillea Wilelmsii. *Drugs Exp Clin Res.* 2000;26:89-93.

596. Keli SO, Hertog MGL, Feskens EJM, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke. *Arch Intern Med.* 1996;156:637-642.

597. Katz DL. *Nutrition in Clinical Practice.* Philadelphia: Lippincott Williams and Wilkins; 2001:370-371.

598. Paran E, Engelhard YN. Effect of lycopene, an oral natural antioxidant, on blood pressure. *J Hypertens.* 2001;19:S74. Abstract P -1.204.

599. Paran E, Engelhard Y. Effect of tomato's lycopene on blood pressure, serum lipoproteins, plasma homocysteine and oxidative stress markers in grade I hypertensive patients. *Am J Hypertens.* 2001;14:141A. Abstract P-333.

600. Digiesi V, Cantini F, Oradei A, Bisi G, Guarino GC, Brocchi A, Bellandi F, Mancini M, Littarru GP. Coenzyme Q-10 in essential hypertension. *Mol Aspects Med.* 1994;15:S257-S263.

601. Langsjoen PH, Langsjoen AM. Overview of the use of CoQ10 in cardiovascular disease. *Biofactors.* 1999;9:273-284.

602. Singh RB, Niaz MA, Rastogi SS, Shukla PK, Thakur AS. Effect of hydrosoluble coenzyme Q10 on blood pressure and insulin resistance in hypertensive patients with coronary heart disease. *J Hum Hypertens.* 1999;13:203-208.

603. Digiesi V, Cantini F, Brodbeck B. Effect of coenzyme Q10 on essential hypertension. *Curr Ther Res.* 1990;47:841-845.

604. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a

long-term multicenter randomized trial. *Clin Investig.* 1993;71:S134-S136.

605. Kontush A, *et al.* Plasma ubiquinol is decreased in patients with hyperlipidemia. *Atherosclerosis.* 1997;129:119-126.

606. Yokoyama H, *et al.* Coenzyme Q10 protects coronary endothelial function from ischemia reperfusion injury via an antioxidant effect. *Surgery.* 1996;120:189-196.

607. Digiesi V, *et al.* Mechanism of action of coenzyme Q10 in essential hypertension. *Curr Ther Res.* 1992;51:668-672.

608. Alternative Medicine Review. 1996;Vol. I(3):171-174.

609. Yamagami T, Iwamoto Y, Folkers K, Blomqvist CG. Reduction by coenzyme Q10 of hypertension induced by deoxycorticosterone and saline in rats. *Int J Vitam Nutr Res.* 1974;44:487-496.

610. Garashi T, Nakajima Y, Tanaka M, Ohtake S. Effect of coenzyme Q10 on experimental hypertension in rats and dogs. *J Pharmacol Exp Ther.* 1974;189:149-156.

611. Iwamoto Y, Yamagami T, Folkers K, Blomqvist CG. Deficiency of coenzyme Q10 in hypertensive rats and reduction of deficiency by treatment with coenzyme Q10. *Biochem Biophys Res Commun.* 1974;58:743-748.

612. Okamoto H, Kawaguchi H, Togashi H, Minami M, Saito H, *et al.* Effect of coenzyme Q10 on structural alterations in the renal membrane of stroke-prone spontaneously hypertensive rats. *Biochem Med Metabol Biol.* 1991;45:216-226.

613. Yamagami T, Takagi M, Akagami H, Kubo H, Toyama S, Okamoto T, Kishi T, Folkers K. Effect of coenzyme Q_{10} on essential hypertension, a double-blind controlled study. In:*Biomedical and Clinical Aspects of Coenzyme Q, Vol. 5.* Elsevier, Amsterdam; 1986:337-343.

614. Yamagami T, Shibata N, Folkers K. Study of coenzyme Q_{10} in essential hypertension. In: Folkers K, Yamamura Y, eds. *Biomedical and Clinical Aspects of Coenzyme Q, Vol. 1.* Amsterdam: Elsevier; 1977:231-242.

615. Tsuyusaki T, Noro C, Kikawada R. Mechanocardiography of ischemic or hypertensive heart failure. In: Yamamura Y, Folkers K, eds. *Biomedical and Clinical Aspects of Coenzyme Q, Vol. 2.* Amsterdam: Elsevier; 1980:273-288.

616. Richardson P, Drzewoski J, Ellis J, Shizukuishi S, Takemura K, Baker L, Folkers K. Reduction of elevated blood pressure by coenzyme Q_{10}. *Biomedical and Clinical Aspects of Coenzyme Q, Vol. 3.* Amsterdam: Elsevier; 1981:229-234.

617. Hamada M, Kazatani Y, Ochi T, Ito T, Kokubu T. Correlation between serum CoQ_{10} level and myocardial contractility in hypertensive patients. *Biomedical and Clinical Aspects of Coenzyme Q, Vol. 4.* Elsevier, Amsterdam; 1984:263-270.

618. Montaldo PL, Fadda G, Salis S, Satta G, Tronci M, DiCesare R, Reina R, Concu A. Effects of the prolonged administration of coenzyme Q_{10} in borderline hypertensive patients: a hemodynamic study. *Biomedical and Clinical Aspects of Conezyme Q, Vol. 6.* Amsterdam: Elsevier; 1991:417-424.

619. Vasdev S, Ford CA, Parai S, *et al.* Dietary alpha-lipoic acid supplementation lowers blood pressure in spontaneously hypertensive rats. *J Hypertens.* 2000;18:567-573.

620. Bierhaus A, Chevion S, Chevion M, Hoffman M, Quehenberger P, Illmer T, Luther T, Berentshtein E, Tritschler H, Muller M, Wahl P, Ziegler R, Nawroth PP. Advanced glycation end product-induced activation of NF-kappa B is suppressed by alpha lipoic acid in cultured endothelial cells. *Diabetes.* 1997;46:1481-1490.

621. Arivazhagan P, Juliet P, Panneerselvam C. Effect of dl-alpha-lipoic acid on the status of lipid peroxidation and antioxidants in aged rats. *Pharmacol Res.* 2000;41:299-303.

622. Jacob S, Henriksen EJ, Schiemann AL, Simon I, Clancy DE, Tritschler HJ, *et al.* Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. *Arzneimittelforschung.* 1995;45:872-874.

623. Henriksen EJ, Jacob S, Streeper RS, Fogt DL, Hokama JY, Tritschler HJ. Stimulation by a-lipoic acid of glucose transport activity in skeletal muscle of lean and obese zucker rats. *Life Sci.* 1997;61:805-812.

624. Busse E, Zimmer G, Schopohl B, Kornhuber B. Influence of a-lipoic acid on intracellular glutathione in vitro and in vivo. *Arzneimittelforschung.* 1992;42:829-831.

625. Phillips SA, Mirrlees D, Thornalley PJ. Modification of the glyoxalase system in streptozotocin-induced diabetic rats. *Pharmacology.* 1993;46:805-811.

626. Han D, Handelman G, Marcocci L, Sen CK, Roy S, Kobuchi H, *et al.* Lipoic acid increases de novo synthesis of cellular glutathione by improving cystine utilization. *Biofactors.* 1997;6:321-338.

627. Packer L. a-lipoic acid: a metabolic antioxidant which regulates NF-kB signal transduction and protects against oxidative injury. *Drug Metab Rev.* 1998;30:245-275.

628. anero DR, Burghardt B. Cardiac membrane vitamin E and malondialdehyde levels in heart muscle of normotensive and spontaneously-hypertensive rats. *Lipids.* 1989;24:33-38.

629. Uysal M, Bulur H, Sener D, ?z H. Lipid peroxidation in patients with essential hypertension. *Int J Clin Pharmacol Ther Toxicol.* 1986;24:474-476.

630. Vodoevich UP. Effect of lipoic acid, biotin, and pyridoxine on blood content of saturated and unsaturated fatty acids in ischemic heart disease and hypertension. *Vopr Pitan.* 1983;5:14-16.

631. Hoffmann PC, Souchard JP, Nepveu F, Labidalle S. Thionitrites as potent donors of nitric oxide: example of S-nitroso-and S,S'-dinitroso-dihydrolipoic acids. *C R Seances Soc Biol Fil* 1996;190:641-650.

632. Kunt T, Forst T, Wilhelm A, Tritschler H, Pfuetzner A, Harzer O, Englebach M, Zschaebitz A, Stofft E, Beyer J. Alpha lipoic acid reduces expression of vascular cell adhesion molecule-1 and endothelial adhesion of human monocytes after stimulation with advanced glycation end products. *Clin Sci (Colch).* 1999;96:75-82.

633. Jiang B, Haverty M, Brecher P. N-acetyl-L-cysteine enhances interlukin-1B-induced nitric oxide synthase expression. *Hypertension.* 1999;34:574-579.

634. Vasdev S, Longerich L, Ford CA. Role of aldehydes in hypertension. In: Sharma BK, Takeda N, Ganguly NK, Singal PK, eds. *Adaptation Biology and Medicine. Vol. 1.* New Delhi, India: Narosa Publishing House; 1997:326-339.

635. Vasdev S, Mian T, Ford CA, Longerich L, Parai S. Role of endogenous aldehydes in spontaneously hypertensive and disulfiram-induced hypertensive rats. *Nutr Metab Cardiovasc Dis.* 1996;6:130-140.

636. prince H, Parker CM, Smith GG, Gonzales LJ. Protection against acetaldehyde toxicity in the rat by L-cysteine, thiamin and L-2-methylthiazolidine-4-carboxylic acid. *Agents*

Actions. 1974;4:125-129.

637. Meister A, Anderson ME, Hwang O. Intracellular cysteine and glutathione delivery systems. *J Am Coll Nutr.* 1986;5:137-151.

638. Lu Q, Bjorkhem I, Xiu RJ, Henriksson P, Freyschuss A. N-acetylcysteine improves microcirculatory flow during smoking: new effects of an old drug with possible benefits for smokers. *Clin Cardiol.* 2001;24:511-515.

639. Gavish D, Breslow JL. Lipoprotein(a) reduction by N-acetylcysteine. *Lancet.* 1991;26:203-204.

640. Wiklund O, Fager G, Andersson A, Lundstam U, Masson P, Hultberg B. N-acetylcysteine treatment lowers plasma homocysteine but not serum lipoprotein(a) levels. *Atherosclerosis.* 1996;5:99-106.

641. Bostom AG, Shemin D, Yoburn D, Fisher DH, Nadeau MR, Selhub J. Lack of effect of oral N-acetylcysteine on the acute dialysis-related lowering of total plasma homocysteine in hemodialysis patients. *Atherosclerosis.* 1996;120:241-244.

642. Hultberg B, Andersson A, Isaksson A. The effects of homocysteine and copper ions on the concentration and redox status of thiols in cell line cultures. *Clin Chim Acta.* 1997;27:39-51.

643. Winniford MD, Kennedy PL, Wells PJ, Hillis LD. Potentiation of nitroglycerin-induced coronary dilatation by N-acetylcysteine. *Circulaton.* 1986;73:138-142.

644. Chirkov YY, Horowitz JD. N-acetylcysteine potentiates nitroglycerin-induced reversal of platelet aggregation. *J Cardiovasc Pharmacol.* 1996;28:375-380.

645. Cabassi A, Dumont EC, Girouard H, Bouchard JF, LeJossee M. Effects of chronic N-acetylcysteine treatment on the actions of peroxynitrite on aortic vascular reactivity in hypertensive rats. *J Hypertens.* 2001;19:1233-1244.

646. Cooke JP, Dzau VJ. Nitric oxide synthase: role in the genesis of vascular disease. *Annu Rev Med.* 1997;48:489-509.

647. Cooke JP, Tsao PS. Endothelial alterations in atherosclerosis: the role of nitric oxide. In: Webb D, Vallance P, eds. *Endothelial Function in Hypertension.* Heidelberg: Springer-Verlag; 1997:29-38.

648. Siani A, Pagano E, Iacone R, Iacoviell L, Scopacasa F, Strazzullo P. Blood pressure and metabolic changes during dietary L-arginine supplementation in humans. *Am J Hypertens.* 2000;13:547-551.

649. Vallance P, Leone A, Calver A, Collier J, Moncada S. Endogenous dimethyl-arginine as an inhibitor of nitric oxide synthesis. *J Cardiovasc Pharmacol.* 1992;20:S60-S62.

650. Boger RH, Bode-Boger SM, Thiele W, Junker W, Alexander K, Frolich JC. Biochemical evidence for impaired nitric oxide synthesis in patients with peripheral arterial occlusive disease. *Circulation.* 1997;95:2068-2074.

651. Drexler H, Fischell TA, Pinto FJ, Chenzbraun A, Botas J, Cooke JP, Alderman EL. Effect of L-arginine on coronary endothelial function in cardiac transplant recipients: relation to vessel wall morphology. *Circulation.* 1994;89:1615-1623.

652. Lerman A, Burnett JC Jr, Higano ST, McKinley LJ, Holmes DR Jr. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation.* 1998;97:2123-2128.

653. Chen PY, Sanders PW. L-arginine abrogates salt-sensitive hypertension in Dahl/Rapp rats. *J Clin Invest.* 1991;88:1559-1567.

654. Patel A, Layne S, Watts D, Kirchner KA. L-arginine administration normalizes pressure natriuresis in hypertensive Dahl rats. *Hypertension.* 1993;22:863-869.

655. Tomohiro A, Kimura S, He H, Fujisawa Y, Hishiyama A, Kiyomoto K, Aky Y, Tamaki T, Abe Y. Regional blood flow in Dahl-Iwai salt-sensitive rats and the effects of dietary L-arginine supplementation. *Am J Physiol.* 1997;272:R1013-R1019.

656. Wen C, Li M, Fraser T, Wang J, Turner SW, Whitworth JA. L-arginine partially reverses established adrenocorticotrophin-induced hypertension and nitric oxide deficiency in the rat. *Blood Press.* 2000;9:298-304.

657. Susic D, Francischetti A, Frohlich ED. Prolonged L-arginine on cardiovascular mass and myocardial hemodynamics and collagen in aged spontaneously hypertensive rats and normal rats. *Hypertension.* 1999;33:451-455.

658. Higashi Y, Oshima T, Ozono R, Watanabe M, Matsuura H, Kajiyama G. Effects of L-arginine infusion on renal hemodynamics in patients with mild essential hypertension. *Hypertension.* 1995;25:898-902.

659. Higashi Y, Oshima T, Watanabe M, Matsuura H, Kajiyama G. Renal response to L-arginine in salt-sensitive patients with essential hypertension. *Hypertension.* 1996;27:643-648.

660. Campese VM, Amar M, Anjali C, Medhat T, Wurgaft A. Effect of L-arginine on systemic and renal haemodynamics in salt-sensitive patients with essential hypertension. *J Hum Hypertens.* 1997;11:527-532.

661. Kelly JJ, Williamson P, Martin A, Whitworth JA. Effects of oral L-arginine on plasma nitrate and blood pressure in cortisol-treated humans. *J Hypertens.* 2001;19:263-268.

662. MacAllister RJ, Calver AL, Collier J, Edwards CMB, Herreros B, Nussey SS, Vallance P. Vascular and hormonal responses to arginine: provision of substrate for nitric oxide or non-specific effect? *Clin Sci.* 1995;89:183-189.

663. Duke JA. *The Green Pharmacy: Herbs, Foods and Natural Formulas to Keep You Young. Anti-Aging Prescriptions.* Philadelphia: Rodale Publishers St. Martin's Press; 2001:1-546.

664. Herbal medicine: expanded commission E monographs. In: Blumenthal, Goldbery, Brinckmann, eds. *American Botanical Society.* 2000:182-192.

665. Tauchert M, Ploch M, Hubner WD. Effectiveness of hawthorn extract LI 132 compared with the ACE inhibitor captopril: multicenter double-blind study with 132 NYHA stage II. *Muench Med Wochenschr.* 1994;136:S27-S33.

666. Fuchs FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G. Alcohol consumption and the incidence of hypertension: the atherosclerosis risk in communities study. *Hypertension.* 2001;37:1242-1250.

667. World Hypertension League. Alcohol and hypertension: implications for management. *WHO Bull.* 1991;69:377-382.

668. Altura BM, Zhang A, Cheng TP, Altusa BT. Ethanol promotes rapid depletion of intracellular free Mg in cerebral vascular smooth muscle cells: possible relation to alcohol-induced behavioral and stroke-like effects. *Alcohol.* 1993;10:563-566.

669. Zhang A, Altura BT, Altura BM. Ethanol-induced contrac-

tion of cerebral arteries in diverse mammals and its mechanisms of action. *Eur J Pharmacol.* 1993;248:229-236.

670. Rosito GA, Fuchs FD, Duncan BB. Dose-dependent biphasic effect of ethanol on 24-h blood pressure in normotensive subjects. *Am J Hypertens.* 1999;12:236-240.

671. MacMahon S. Alcohol consumption and hypertension. *Hypertension.* 1987;9:111-121.

672. Tsuruta M, Adachi H, Hirai Y, Fujiura Y, Imaizumi T. Association between alcohol intake and development of hypertension in Japanese normotensive men: 12-year follow-up study. *Am J Hypertens.* 2000;13:482-487.

673. Hsieh ST, Saito K, Miyajima T, Liu CM, Yokoyama M. Effects of alcohol moderation on blood pressure and intracellular cations in mild essential hypertension. *Am J Hypertens.* 1995;8:696-703.

674. Tokmak F, Schodjaian K, Musel E. Hohaye M, Kosch M, Rahn KH, Kisters K. Magnesium status and deficiency in cirrhosis of liver due to alcoholism. *Mag Bull.* 1999;21:35-38.

675. Martell N, Mateos J, Fernandez-Pinilla C, Fernandez-Cruz A, Luque M. Alcohol intake in normotensives and essential hypertensives, and its relation with plasma lipids. *J Hypertens.* 1997;15:S165-S166.

676. Kalbfleisch JM, Lindeman RD, Ginn HE. Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. *J Clin Invest.* 1963;42:1471-1475.

677. O'Callaghan CJ, Phillips PA, Krum H. The effects of short-term alcohol intake on clinic and ambulatory blood pressure in normotensive social drinkers. *Am J Hypertens.* 1995;8:572-577.

678. Puddey IB, Beilin LJ, Vandongen R, *et al.* Evidence for a direct effect of alcohol consumption on blood pressure in normotensive men: a randomized controlled trial. *Hypertension.* 1985;7:707-713.

679. Puddey IB, Beilin LJ, Vandongen R. Regular alcohol use raises blood pressure in treated hypertensive subjects. *Lancet.* 1987;1:647-651.

680. Cushman WC, Cutler JA, Hanna E, *et al.* The Prevention and Treatment of Hypertension Study (PATHS) effects of an alcohol treatment program on blood pressure. *Arch Intern Med.* 1998;158:1197-1207.

681. Grønbaek M, Becker U, Johansen D, Gottschau A, Schnohr P, *et al.* Type of alcohol consumed and mortality from all causes, coronary heart disease and cancer. *Ann Intern Med.* 2000;133:411-419.

682. Sung BH, Whitsett TL, Lovallo WR, Absi M, Pincomb GA, Wilson MF. Prolonged increase in blood pressure by a single oral dose of caffeine in mildly hypertensive men. *Am J Hypertens.* 1994;7:755-758.

683. Pincomb GA, Lovallo WR, McKey BS, Sung BH, Passey RB, Everson SA, *et al.* Acute blood pressure elevations with caffeine in men with borderline systemic hypertension. *Am J Cardiol.* 1996;77:270-274.

684. Cavalcante JW, Santos PR, Menezes MG, Marques HO, Cavalcante LP, Pacheco WS. Influence of caffeine on blood pressure and platelet aggregation. *Arq Bras Cardiol.* 2000;13:475-481.

685. Shepard JD, al'Absi M, Whitsett TL, Passey RB, Lovallo WR. Additive pressor effects of caffeine and stress in male medical students at risk for hypertension. *Am J Hypertens.* 2000;13:475-481.

686. Lane JD, Williams RB. Cardiovascular effects of caffeine and stress in regular coffee drinkers. *Psychophysiology.* 1987;24:157-164.

687. Pincomb GA, Lovallo WR, Passey RB, Wilson MF. Effect of behavior state on caffeine's ability to alter blood pressure. *Am J Cardiol.* 1988;61:798-802.

688. Lovallo WR, Pincomb GA, Sung BH, Passey RB, Sausen KP, Wilson MF. Caffeine may potentiate adrenocortical stress responses in hypertension-prone men. *Hypertension.* 1989;14:170-176.

689. Lovallo WR, Pincomb GA, Sung BH, Everson SA, Passey RB, Wilson MF. Hypertension risk and caffeine's effect on cardiovascular activity during mental stress in young men. *Health Psychol.* 1991;10:236-243.

690. Lovallo WR, al'Absi M, Blick K, Whitsett TL, Wilson MF. Stress-like adrenocorticotropin responses to caffeine in young healthy men. *Pharmacol Biochem Behav.* 1996;55:365-369.

691. Lane JD, Adcock RA, Williams RB, Kuhn CM. Caffeine effects on cardiovascular and neuroendocrine responses to acute psychosocial stress and their relationship to level of habitual coffee consumption. *Psychosom Med.* 1990;52:320-336.

692. al'Absi M, Lovallo WR, Pincomb GA, Sung BH, Wilson MF. Adrenocortical effects of caffeine at rest and during mental stress in borderline hypertensive men. *Int J Behav Med.* 1995;2:263-275.

693. Retter AS. Carnitine and its role in cardiovascular disease. *Heart Disease.* 1999;1:108-113.

694. Arsenian MA. Carnitine and its derivatives in cardiovascular disease. *Prog Cardiovasc Dis.* 1997;40:265-286.

695. Digiesi V, Cantini F, Bisi G, Guarino G, Brodbeck B. L-carnitine adjuvant therapy in essential hypertension. *Clin Ter.* 1994;144:391-395.

696. Bartels GL, Remme WJ, Holwerda KJ, *et al.* Anti-ischemic efficacy of L-propionyl carnitine–a promising novel metabolic approach to ischemia? *Eur Heart J.* 1996;17:414-420.

697. Anand IS, Chandrashekhar Y, de Giuli F, *et al.* Acute and chronic effects of propionyl-L-carnitine on the hemodynamics, exercise capacity, and hormones in patients with congestive heart failure. *Cardiovasc Drugs Ther.* 1998;12:291-299.

698. Caponnetto S, Canale C, Maspercone MA, *et al.* Efficacy of L-propionyl carnitine treatment in patients with left ventricular dysfunction. *Eur Heart J.* 1994;15:1267-1273.

699. Investigators of the Study on Propionyl-L-carnitine in Chronic Heart Failure. Study on propionyl-L-carnitine in chronic heart failure. *Eur Heart J.* 1999;20:70-76.

700. Brevetti G, Perna S, Sabba C, *et al.* Propionyl-L-carnitine in intermittent claudication: double-blind, placebo-controlled, dose titration, multicenter study. *J Am Coll Cardiol.* 1995;26:1411-1416.

701. Dal Lago A, De Martini D, Flore R, *et al.* Effects of propionyl-L-carnitine on peripheral arterial obliterative disease of the lower limbs: a double-blind clinical trial. *Drugs Exp Clin Res.* 1999;25:29-36.

702. Wiseman LR, Brogden RN. Propionyl-L-carnitine. *Drugs Aging.* 1998;12:243-248.

703. Cherchi A, Lai C, Angelino F, Trucco G, *et al.* Effects of L-carnitine in exercise tolerance in chronic stable angina: a multicenter, double-blind, randomized placebo-controlled crossover study. *Int J Clin Pharmacol Ther Toxicol.* 1985;23:569-572.

704. Digiesi V, Palchetti R, Cantini F. Utilità della terapia con L-carnitina nell'ipertensione arteriosa essenziale controlled diabete mellito tipo II. *Min Med.* 1989;80:227-231.

705. Ghidini O, Azzurro M, Vita G, Sartori G. Evolution of the therapeutic efficacy of L-carnitine in congestive heart failure. *Int J Clin Pharmacol Ther Toxicol.* 1988;26:217-220.

706. Mancini M, Rengo F, Lingetti M, Sorrentino G. Controlled study of the therapeutic efficacy of propionyl-L-carnitine in patients with congestive heart failure. *Arzneimittelforschung.* 1992;42:1101-1104.

707. Pola P, Tondi P, Dal Lago A, Serricchio M. Statistical evaluation of long-term L-carnitine therapy in hyperlipoproteinaemias. *Drugs Exp Clin Res.* 1983;9:925-934.

708. Regitz V, Shug A, Fleck E. Defective myocardial carnitine metabolism in congestive heart failure secondary to dilated cardiomyopathy and to coronary, hypertensive and valvular heart disease. *Am J Cardiol.* 1990;65:755-760.

709. Rizzon P, Biasco G, Di Biase M, Boscia F. High doses of L-carnitine in acute myocardial infarction: metabolic and antiarrhytmic effects. *Eur Heart J.* 1989;10:502-508.

710. Thomsen J, Shug A, Yap V, Patel A. Improved pacing tolerance of the ischemic human myocardium after administration of carnitine. *Am J Cardiol.* 1979;43:300-306.

711. Huxtable RJ. Physiologic actions of taurine. *Physiol Rev.* 1992;72:101-163.

712. Ciehanowska B. Taurine as a regulator of fluid-electrolyte balance and arterial pressure. *Ann Acad Med Stetin.* 1997;43:129-142.

713. Fujita T, Ando K, Noda H, Ito Y, Sato Y. Effects of increased adrenomedullary activity and taurine in young patients with borderline hypertension. *Circulation.* 1987;75:525-532.

714. Birdsall TC. Therapeutic applications of taurine. *Altern Med Rev.* 1998;3:128-136.

715. Huxtable RJ, Sebring LA. Cardiovascular actions of taurine. *Prog Clin Biol Res.* 1983;125:5-37.

716. Harada H, Kitazaki K, Tsujino T, Watari Y, Iwata S, *et al.* Oral taurine supplementation prevents the development of ethanol-induced hypertension in rats. *Hypertens Res.* 2000;23:277-284.

717. Dawson R, Liu S, Jung B, Messina S, Eppler B. Effects of high salt diets and taurine on the development of hypertension in the stroke-prone spontaneously hypertensive rat. *Amino Acids.* 2000;19:643-665.

718. Fujita T, Sato Y. The antihypertensive effect of taurine in DOCA-salt rats. *J Hypertens Suppl.* 1984;2:S563-S565.

719. Fujita T, Sato Y. Changes in blood pressure and extracellular fluid with taurine in DOCA-salt rats. *Am J Physiol.* 1986;250:R1014-R1020.

720. Sato Y, Fujita T. Role of sympathetic nervous system in hypotensive action of taurine in DOCA-salt rats. *Hypertension.* 1987;9:81-87.

721. Fujita T, Sato Y. Hypotensive effect of taurine. Possible involvement of the sympathetic nervous system and endogenous opiates. *J Clin Invest.* 1988;82:993-997.

722. Trachtman H, Del Pizzo R, Rao P, Rujikarn N, Sturman JA. Taurine lowers blood pressure in the spontaneously hypertensive rat by a catecholamine independent mechanism. *Am J Hypertens.* 1989;2:909-912.

723. Petty MA, Kintz J, DiFrancesco GF. The effects of taurine on atherosclerosis development in cholesterol-fed rabbits. *Eur J Pharmacol.* 1990;180:119-127.

724. Sato Y, Ogata E, Fujita T. Hypotensive action of taurine in DOCA-salt rats–involvement of sympathaoadrenal inhibition and endogenous opiate. *Jpn Circ J.* 1991;55:500-508.

725. Ideishi M, Miura S, Sakai T, Sasaguri M, Misumi Y, Arakawa K. Taurine amplifies renal kallikrein and prevents salt-induced hypertension in DAHL rats. *J Hypertens.* 1994;12:653-661.

726. Nakagawa M, Takeda K, Yoshitomi T, Itoh H, Nakata T, Sasaki S. Antihypertensive effect of taurine on salt-induced hypertension. *Adv Exp Med Biol.* 1994;359:197-206.

727. Kohashi N, Okabayashi T, Hama J, Katori R. Decreased urinary taurine in essential hypertension. *Prog Clin Biol Res.* 1983;125:73-87.

728. Ando K, Fujita T. Etiological and physiopathological significance of taurine in hypertension. *Nippon Rinsho.* 1992;50:374-381.

729. Meldrum MJ, Tu R, Patterson T, Dawson R, Petty T. The effect of taurine on blood pressure and urinary sodium, potassium and calcium excretion. *Adv Exp Med Biol.* 1994;359:207-215.

730. Tanabe Y, Urata H, Kiyonaga A, Ikede M, Tanake H, Shindo M, Arakawa K. Changes in serum concentrations of taurine and other amino acids in clinical antihypertensive exercise therapy. *Clin Exp Hypertens.* 1989;11:149-165.

731. Gentile S, Bologna E, Terracina D, Angelico M. Taurine-induced diuresis and natriuresis in cirrhotic patients with ascites. *Life Sci.* 1994;54:1585-1593.

732. Mizushima S, Nara Y, Sawamura M, Yamori Y. Effects of oral taurine supplementation on lipids and sympathetic nerve tone. *Adv Exp Med Biol*. 1996;403:615-622.

733. Bousquet P, Feldman J, Bloch R, Schwartz T. Central cardiovascular effects of taurine: comparison with homotaurine and muscimol. *J Pharmacol Exp Ther.* 1981;219:213-218.

734. Tao L, Rao MR. Effects of enalapril and taurine on left ventricular hypertrophy and arrhythmia in the renovascular hypertensive rat. *Yao Xue Xue Bao.* 1996;31:891-896.

735. Ji Y, Tao L, Rao MR. Effects of taurine and enalapril on blood pressure, platelet aggregation and the regression of left ventricular hypertrophy in two-kidney-one-clip renovascular hypertensive rats. *Yao Xue Xue Bao.* 1995;30:886-890.

736. Le OT, Elliott WJ. Mechanisms of the hypotensive effect of 3-N-butyl phthalide (BUPH): a component of celery oil. *Am.J. Hypertension* 1992;40:326A. Abstract.

737. Le OT, Elliot WJ. Dose response relationship of blood pressure and serum cholesterol to 3-N-butyl phthalide, a component of celery oil. *Clinical Research.* 1991;39:750A. Abstract.

738. Duke JA. *The Green Pharmacy Herbal Handbook.* Emmaus, Pennsylvania: Rodale Press; 2000:68-69.

739. Castleman M. *The Healing Herbs: The Ultimate Guide to the Curative Power of Nature's Medicines.* Emmaus, Pennsylvania: Rodale Press; 1991;105-107.

740. Heinerman J. *Heinerman's New Encyclopedia of Fruits and Vegetables.* Paramus, New Jersey: Prentice Hall; 1995:93-95.

741. Busheri N, Jarrell JT, Lieberman S, Mirdamadi-Zonozi N, Birkmayer G, Preuss HG. Oral reduced B-nicotinamide adenine dinucleotide (NADH) affects blood pressure, lipid peroxidation, and lipid profile in hypertensive rats (SHR). *Geriatr Nephrol Urol.* 1998;8:95-100.

742. Merchant RE, Andre CA. A review of recent clinical trials of the nutritional supplement chlorella pyrenoidosa in the treatment of fibromyalgia, hypertension and ulcerative colitis. *Alternative Therapies.* 2001;7:79-91.

743. Singh RB, Rastogi SS, Singh NK, Ghosh S, Gupta S, Niaz MA. Can guava fruit intake decrease blood pressure and blood lipids? *J Hum Hypertens.* 1993;7:33-38.

744. Ross IA. *Medicinal Plants of the World: Chemical Constituents, Traditional and Modern Medicinal Uses.* Totowa, New Jersey:Humana Press; 2001:Volumes I:1-415; Volume II:1-487.

745. Ritchason J. *The Little Herb Encyclopedia: The Handbook of Natures Remedies for a Healthier Life.* 3rd edition. Pleasant Grove, Utah: Woodland Health Books; 1995:1-402.

746. United States Congress: Dietary Supplements Health and Education Act of 1994. FDA/CFSAN Webpage, 1994. Washington, DC, U.S. Government.

747. Fillmore CM, Bartoli L, Bach R, Park Y. Nutrition and dietary supplements. Complementary therapies in physical medicine and rehabilitation. *Phys Med Rehabil Clin N Am.* 1999;10:673-703.

748. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA.* 1998;279:1200-1205.

749. Drugs for hypertension. *Med Lett Drugs Ther.* 2001;43:17-22.