

OXIDATIVE STRESS IN THE PATHOGENESIS OF DISEASE AND AGING: OPPORTUNITY FOR INTERVENTION

Richard E. DuBois, M.D., F.A.C.P.
Chief of Internal Medicine, Atlanta Medical Center

Contact information: ID Group of Atlanta,
L.L.C. 340 Boulevard, Suite 210 Atlanta, GA
30312 dubmelt@pol.net

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ABSTRACT

Normal metabolism produces free radical molecules. Oxidative stress is the excess of free radical production beyond the capacity of the antioxidant cascade. This stress is associated with the pathogenesis of multiple disorders and even with the rate of aging. Nutrition includes the ingestion of physiologic doses of antioxidants from fruits, vegetables and grains. These phytonutrients, in conjunction with endogenous antioxidants provide an interdependent network of buffers and scavengers against free radical damage. Nutrition from whole food sources should not be confused with medication. Medication is the ingestion of pharmacologic, unbalanced, and incomplete doses of components from chemical or herbal sources such as traditional vitamin pills. Nutrition is the foundation of health and disease prevention. The foundation of nutrition is a diet rich in fruits and vegetables.

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Introduction

Free radical chemistry and molecular biology have given new insight into the pathogenesis of disease. Oxidative stress caused by free radical molecules results in damage to macromolecules, which, in turn, leads to disease and aging. Insight into this process will help physicians give antioxidant nutritional advice to patients. This will provide the opportunity for prevention of disease and retardation of aging, which could save trillions of dollars and untold human misery.

Physicians do not generally recommend food supplements to patients. Even when they do, it is often in the form of isolated vitamins or man-made nutraceuticals, such as vitamin E, vitamin C, beta-carotene, or folic acid. Such nutraceuticals provide pharmacologic doses and, by definition, are incomplete nutrition. The balance of nutrition that is needed can only be obtained from whole food sources.

Normal metabolism produces large numbers of free radicals: namely, hydroxyl, hydrogen peroxide, and superoxide. Interestingly, these are the same free radicals as those produced by radiation. A typical rat cell produces twenty billion free radical molecules per day. The rat cell is metabolically seven times more active than a human cell; therefore, it is estimated that the average human generates one to three billion free radicals per day, per cell.¹

Antioxidants neutralize free radicals and protect against oxidative damage. Unless protected by antioxidants, macromolecules, such as RNA, DNA, proteins, and lipids, are damaged by these free radicals.² The lipid damage occurs to circulating lipids, semi-permeable membrane lipids, and lipid components of such essential molecules as axonal sheaths of the central nervous system.

Antioxidants are a complicated and interdependent cascade.³ Some are endogenous, meaning that they can be made by human tissue itself. These include:

Catalase	Glutathione peroxidase	Peroxisomes
Ceruloplatin	Glutathione S-transferases	Proteases
Ferritin, transferrin	Glycosylases	Superoxide dismutase

Others are exogenous, meaning that they must be eaten. These nutritional chemicals (phytonutrients) come from fruits, vegetables, and grains. There are thousands of phytonutrients⁴ that have not yet been designated as vitamins, due to the fact that a deficiency disease has not been identified for them. They, nonetheless, have important roles in human nutrition. Antioxidants are themselves oxidized and therefore must be replenished or reconstituted continuously - that is, we must eat them every day.

It takes an entire cascade of antioxidants (similar to our coagulation cascade) to decrease free radical damage. To substantiate this point, efforts to reduce oxidative stress (lipid peroxides) in-vivo with five different doses of vitamin E failed to show benefit;⁵ whereas nutrition capsules of powdered juice from whole food sources* reduced lipid peroxides by 75%, and in a third of the subjects reduced lipid peroxides to undetectable levels.⁶

* Juice Plus+®

American Nutrition

Americans, of all ages and on every level of society, are facing a nutritional crisis. The magnitude of the problem is alarming. According to the Centers for Disease Control and Prevention (CDCP), at the end of 2001, 44.3 million Americans were obese (20.9%), and 16.7 million were diabetic (7.9%). The CDCP has declared this "an epidemic." Seventy-seven percent of American adults don't get five servings of fruits and vegetables per day; and, only 13% of American families with children get five servings of fruits and vegetables per day.

Even for those individuals who do eat well, some foods have lost much of their micro-nutritional value. Foods that have been cooked, stored, or irradiated may have had some damage to the phytonutrient content. For instance, cooking can destroy up to 98% of free folic acid.⁷ The shelf life of any food depends upon several factors: the food itself, packaging, temperature, and humidity. Foods stored at inappropriate temperatures or in unsuitable containers will obviously be compromised. Radiation of foods results in an inability to sprout, e.g., potatoes and onions. It is therefore clear that even though the protein, carbohydrate, and fat content is unchanged by irradiation, other critical changes in the food quality have resulted. This is in addition to the beneficial effects of killing microorganisms. Americans are not getting all of the vital, viable phytonutrients their bodies need.

Nutritional problems begin in childhood.^{8 9} Ninety-nine percent of American children don't get the USDA recommended number of servings of the five food groups per day. The following table shows the proportion of youth, ages 2-19 years, who meet USDA recommendations for each food group:¹⁰

Food group	% adherence
Grain	31.6
Vegetable	36.4
Fruit	26.0
Dairy	33.2
Meat	28.0
All groups	1.0
No group	16.0

Eighty-eight percent of Americans consume less than 400 meg of folate per day." One third of the elderly have micronutrient deficiencies.¹² "It would be prudent to opt for suitable micronutrient supplementation in modest amounts for all elderly individuals to achieve maximum physiological health benefit with the least toxicity."¹³

The metabolic syndrome (formerly Syndrome X) affects 47,000,000 Americans¹⁴ with up to 3.6 times greater probability of death from coronary heart disease and 3.2 times greater probability of death from any cause.¹⁵ Yet these outcomes are not inevitable since 30 minutes of exercise daily for five days per week and reduction of weight by 7% (average of 15 pounds) resulted in a 58% decrease in the onset of Type 2 diabetes; and, for those subjects over age 60, Type 2 diabetes was reduced by 70%.¹⁶

Consideration of our poor nutrition is critical in decreasing the economic burden and magnitude of human misery caused by disease. That's why most countries have programs promoting five or more servings of fruits and vegetables per day. The evidence is overwhelming that phytonutrients significantly impact those aspects of human physiology associated with disease and aging. Let's review those aspects of physiology and some of the evidence.

Aging

Aging is inevitable; however, the rate of aging is nutrition- and oxidative stress-dependent.¹⁷ "Laboratory control of free radical metabolism can extend the maximum life span of multi-cellular species six-fold."¹⁸ The same life extension by control of human free radical metabolism would allow a human to live seven hundred years.

The genetic code of life is contained on our chromosomes, which are made of double-stranded chains of DNA. Chromosomal DNA tips are called telomeres. They shorten with each eeli division, and are gone after about fifty divisions.¹⁹ When the telomeres are gone, the chromosome dies, and hence, the eeli. In other words, telomeres determine eeli life and, ultimately, an organism's longevity. Telomerase is a normal human reverse transcriptase that maintains telomere length in germ eelis, allowing an infinite number of eeli divisions for perpetuation of the species. A mutation in the expression of telomerase allows malignant eelis to survive by maintaining telomere length through innumerable eeli divisions; witness the HeLa eeli Une that has been prospering for over fifty years. In normal human eelis, telomere length determines quality and duration of life.²⁰

Similarly, activating telomerase on normal human eelis renders them immortal.²¹ Thus "ends the debate" about whether oxidative stress and telomere length determine the rate of aging.²²

Progeria is a syndrome of congenitally short telomeres, resulting in death from degenerative disease by the age of puberty. Aids is associated with rapid loss of telomere length. The CD8 eeli telomere of a patient with AIDS is the equivalent length of 100 years.²³

Excess free radicals or those separated from the antioxidant cascade produce oxidative stress. Oxidative stress causes peroxidation of lipids in cytoplasmic semipermeable membranes. When cellular "damage rate" exceeds "repair rate," mitosis is necessary to produce new eelis. With each eeli division, shortening of the telomere occurs. Increasing rates of eeli turnover increase telomere shortening, which results in aging, disease, and death at a cellular level, and ultimately, an organism level. **"Clearly free radical damage underlies much of aging which ultimately determines our health and our maximum life span. ... Free radical damage increases with age and is less well contained and repaired by aged eelis."**²

Cancer

Humans sustain ten thousand mitochondrial and nuclear DNA oxidative "hits" to every eeli in the body every day, and the damage is cumulative. Lymphocytes from elderly humans mutate at a rate that is nine times greater than the mutation rate of lymphocytes from infants.¹

DNA damage must be repaired; otherwise, there is mutation, which in turn increases the risk of cancer and of eeli system malfunction caused by mitochondrial toxicity. DNA repair enzymes depend on methylation of adenine in the original DNA template in order to differentiate the original from the new mirror image strand. Methyl groups are supplied by methionine and by 5-methyl and 5,10-methylene tetrahydrofolate, but S-adenosyl methionine (SAME) is 1,000 times more efficient in donating methyl groups to DNA.²⁴ Hypo-methylation of adenine results in the lack of identification of the original template and a greater chance for error (mutation). Furthermore, hypo-methylation of cytosine allows for release of oncogenes. In addition, deficiencies of methionine or folate create substitution errors of uracil (found only in RNA) for thymidine in DNA strands.^{25,26,27,28}

In addition to the free radicals produced from normal aerobic metabolism, hydroxyl free radicals are generated every day by the microflora of the bowel at a rate corresponding to that produced by exposure to

10,000 rads of gamma radiation every day.²⁹ Gamma-tocopherol is the principle antioxidant of colon contents; therefore, significant colon levels of gamma-tocopherol are needed to counteract the magnitude of oxidative stress produced by the microflora. This is accomplished by the liver, which preferentially excretes gamma-tocopherol when the serum levels of tocopherols and tocotrienols are satisfactory. Inadequate levels of serum tocopherol and tocotrienol result in retention of gamma-tocopherol in the serum at the expense of antioxidant balance in the colon.³⁰ Folic acid is also important in decreasing rates of colon cancer.³¹

"If you don't get enough antioxidants, it is the equivalent of irradiating yourself. ... It's the same as stepping unprotected in front of an x-ray machine."³²

DNA damage can be measured by urinary 8-hydroxy deoxyguanosine. Urinary excretion increases with smoking, but is not decreased by all antioxidants. For example, beta-carotene is not effective, whereas Brussels sprouts, which are high in folic acid, can decrease urinary 8-hydroxy deoxyguanosine levels.³³

Similarly, DNA damage can be measured by Comet assay on individual cell types. A study³⁴ of nutrition capsules of powdered juice from whole food sources*, administered to twenty elderly patients (average age, sixty-eight years) for eighty days, showed 66% decrease in DNA damage in peripheral blood lymphocytes. This was true for males/females and smokers/non-smokers.

A review of 172 case-controlled prospective studies, comparing low versus high quartile of food consumption, showed that low fruit and vegetable consumption resulted in double the risk of cancer for most sites:³⁵

Cancer Site	Protection / Studies	Risk
Lung	15 / 24	2.2
Oral	9/9	2.0
Larynx	4/4	2.3
Esophagus	15 / 16	2.0
Stomach	17/19	2.5
Pancreas	9/11	2.8
Cervix	7/8	2.0
Colorectal	20/35	1.9
Breast	8/14	1.8
Prostate	4/14	1.3
Totals	117/145	

In summary, the authors stated: **"In 1854, John Snow stopped a cholera epidemic simply by taking the handle off the (Broad Street) pump. Consumption of fruits and vegetables may be a handle that if manipulated by public policy, clinical advice and public education could have a substantial impact on a wide range of cancers."**

Additionally, 150 scientists reviewed 4,500 research studies on the relationship between nutrition and cancer.³⁶ It is the most comprehensive review and evaluation of scientific evidence on diet and cancer since the National Academy of Science's 1982 report *Diet, Nutrition, and Cancer*.¹¹ They found overwhelming evidence that fruits, vegetables, and grains can prevent cancer. Their report states that 3-4 million cases of cancer could be

prevented annually by a modification of diet. In 1996, more than 10 million people in the world developed cancer, and at least 6 million died from cancer. Compare this to only 2.65 million deaths from cancer in 1985.³⁷

The National Cancer Act of 1971 declared war on cancer. The death rate per 100,000 population was 6% higher in 1994 than in 1970, having increased from 189.6 in 1970 to 200.9 in 1994. Despite the expenditure of thirty billion dollars, **"the effect of new treatments and early intervention has been disappointing. The most promising approach to the control of cancer is a national commitment to prevention."**^{38,39}

It has been shown that high dietary intake of a variety of vegetables rich in alpha-carotene, beta-carotene, or lutein provides a two- to four-fold decrease in the risk of cancer of the lung for males and females, compared to low dietary intake.⁴⁰

In large epidemiologic studies (Basel I-III) of 6,000 patients, cancer mortality is associated with low levels of beta-carotene and vitamin C.^{41,42}

A study of 99 cases of lung cancer showed the lowest quintile of vitamin E was associated with 2.5 times greater risk for having any type of lung cancer and the lowest quintile of beta-carotene was associated with 4.3 times greater risk for squamous-cell lung cancer.⁴³

From 1975 to 1990, a study of 15,161 women for cervical cancer⁴⁴ looked at levels of total carotenoids, alpha- and beta-carotene, lycopene, and cryptoxanthin. There were lower levels than controls in 50 cases. As shown below, the lower levels had double to triple the risk of cancer compared to the highest level.

Carotene	Relative Risk
total carotenoid	2.7
alpha-carotene	3.1
beta-carotene	3.1

Levels of retinol, alpha- and gamma-tocopherol, as well as selenium were not related to risk of cancer, but smoking was.

A study from 1986-1992 of 47,894 men for prostate cancer⁴⁵ showed 812 cases. There was 45% less prostate cancer in men with the highest quintile of lycopene intake, compared to those with the lowest. This was not surprising, in light of the following:

1. Normal serum lycopene is twice that of beta-carotene.
2. Lycopene is the most abundant carotenoid in the prostate, having a tropism for that gland.
3. Lycopene quenches singlet oxygen with more than twice the efficiency of beta-carotene.

Sadly, 40,000 American men still die from prostate cancer annually, when it is clear that nutrition, especially carotenoids and specifically lycopene, can prevent a large proportion of the cases. Lycopenes were also associated with protection against most forms of intestinal cancer, including mouth, esophagus, stomach, intestine, colon, and rectum.^{46,47}

In 1973, the Food and Drug Administration authorized the inclusion of 400 meg of folic acid in standard multi-vitamin/mineral capsules. Subsequently, a decrease in cancer of the colon in male and female Caucasian Americans was documented to have begun in the late 1980's.⁴⁸ Folic acid supplementation for 15 years is

associated with a decrease in colon cancer.³¹ **Hypo-methylation of colon mucosa DNA is the first step in colon cancer and is folate-dependent. This is due to the critical role that folate plays in the conversion of homocysteine to methionine and ultimately to SAMe, and the fact that SAMe is the primary donor of methyl groups to DNA.**²⁷²⁸

Because of the interdependent cascade of phytonutrient function, it's important to point out that individual phytonutrients will not accomplish what can be derived from whole food nutrition. A carefully conducted study from the University of Milan in Italy showed that tomato puree supplementation resulted in striking increases in lycopene serum concentrations, and that this was associated with marked decreases in DNA damage of circulating lymphocytes, compared to controls on a tomato-free diet. However, when the tomato puree supplementation was discontinued, there was an immediate return of DNA damage with no carry-over protection. This occurred despite high levels of serum lycopene for a week after supplementation was stopped. This shows that lycopene by itself is not sufficient for protection of DNA, and that thousands of other phytonutrients from the tomato are working synergistically with the lycopene for DNA protection.⁴⁹

A very important point to make is that even though these examples show how important individual phytonutrients are, as discussed throughout this document, multiple attempts to change metabolism by the addition of individual phytonutrients have been unsuccessful. This is due to the synergy, checks and balances, and interdependence of phytonutrient cascades in-vivo. There is accumulating data that suggests that the following phytochemicals also play a significant role in cancer prevention:

PEITC (Isothiocyanates)	Chlorogenic acid
Allylic sulfides	Sulforane
Genistein	3-Indol carbinols
Capsaicin	Coumeric acid
Phenols	Flavenoids
Dithiolthiones	Ellagic acid

Excellent reviews of the efficacy of whole food nutrition, phytonutrients, and nutraceuticals for prevention and treatment of cancer have been done.⁵⁰⁵¹⁵² This research is ongoing and increasingly enhances the significance of whole food nutrition as the cornerstone of cancer prevention. The National Institutes of Health Center for Complementary and Alternative Health is leading the way with research. The United Nations and World Health Organization have initiated campaigns to encourage nations to decrease carbohydrates and increase fruit and vegetable consumption in an effort to decrease the burden of cancer.

Coronary Disease

The etiology of coronary heart disease is multi-factorial, but there is overwhelming data to emphasize that oxidative stress is central to the disease.⁵⁴ Low density lipoprotein (LDL) is subjected to oxidative stress unless protected by antioxidants. The trigger that peroxidates LDL is homocysteine thiolactone, a cyclic compound that results from spontaneous auto-oxidation of homocysteine. If nitric oxide and other serum antioxidants, such as glutathione and ascorbic acid, become depleted by oxidative stress, direct endothelial damage, smooth muscle proliferation, and peroxidation of LDL occur.⁵

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Serum levels of antioxidants and of homocysteine are dependent upon ingestion of phytonutrients. Each LDL particle contains seventeen hundred molecules of cholesterol esters and seven hundred molecules of free cholesterol. In addition, however, the particle is armed with an array of antioxidants designed to protect it from oxidative damage (lipid peroxidation): six molecules of alpha-tocopherol, a number of other lipid soluble

carotenoids, as well as gamma-tocopherol.

Peroxidation of LDL cannot occur until the alpha-tocopherol content has been depleted, and accelerates linearly once all lipid soluble antioxidants have been depleted. Increasing the alpha-tocopherol content increases the duration of protection for the LDL particle. Carotenoids work less effectively, but synergistically with tocopherols in this regard. The ascorbic acid (vitamin C) content of the surrounding plasma in turn reconstitutes the LDL surface alpha-tocopherol. Similarly, the ascorbic acid is reconstituted by glutathione, which in turn is reconstituted by glutathione reductase, which in turn requires selenium.^{56 " 58 59}

According to the Nobel Prize-winning work of Drs. Michael S. Brown and Joseph L. Goldstein at The University of Texas Health Science Center at Dallas, under ordinary circumstances cells ingest LDL particles by receptor mediated endocytosis, one particle at a time. However, peroxidized LDL particles become large foreign body aggregates, which are phagocytosed by endothelial macrophages, creating foam cells. These foam cells die, depositing a concentration of their debris and toxic lipid contents into the center of a growing lesion of the vessel wall, called a vulnerable plaque. Pro-coagulant and inflammatory mediators abound in the microenvironment of these vascular endothelial plaques. Rupture of the vulnerable plaque results in coronary thrombosis and sudden death.^{60 6162 o M}

Homocysteine levels are directly affected by a number of factors, including folate, and vitamins B₆ and B₁₂.^{65 66} Levels increase with age, male gender, renal failure, certain medications, coffee, and methionine challenge. In the post-prandial state, methionine rapidly demethylates to homocysteine, which is transsulfurated to cysteine, and then combines with glutamate to become glutathione. This transsulfuration is vitamin B₆ and cystathione beta-synthetase dependent.

Congenital lack of this enzyme was shown by Dr. Kilmer McCully to result in homocysteinuria, which leads to death from atherosclerosis in childhood. If not genetically enzyme-deficient, post-prandial homocysteine level is dependent on vitamin B₆ concentration. This is not a threshold phenomenon, since homocysteine level is inversely related to the vitamin B₆ level.

Furthermore, homocysteine can be remethylated to methionine in the presence of 5-methyl tetrahydrofolate and vitamin B₁₂. Again this is not a threshold phenomenon, but is folate-driven and vitamin-B ^-dependent. The powerful methyl donor S-adenosyl methionine (S AMe) is derived by the addition of ATP to methionine. The control of post-prandial and fasting homocysteine levels can be achieved with increasing intake of folate, and vitamins B₁₂ and B₆.^{67 55 60}

There is data to support this science. Consider the following:

- Latitude and growing season affect a nation's ability to consume fresh fruits and vegetables. Heart disease mortality in England, Wales, Scotland, Norway and Israel was inversely correlated with the calculated ascorbic acid intake, measured ascorbate, carotenoid, and other antioxidant levels.⁶⁸
- In a large prospective study of 6,000 patients (Basel study, I-III), heart attack and stroke mortality was associated with low levels of any major antioxidant.⁴¹⁴²
- In a study of 1,883 men with hyperlipidemia followed for 13 years, the lowest quartile of carotenoid levels had 40% more coronary events than the highest quartile.⁶⁹
- In a study of 25,802 patients studied for 14 years, the lowest quintile of serum beta-carotene was associated with 2.3 times the risk of subsequent coronary event compared to the highest quintile.⁷⁰

- A study of 39,910 male doctors (ages 40-75) showed 667 coronary events. Consumption of more than 60 IU of vitamin E was associated with 36% fewer coronary events.⁷¹
- A study of 87,245 female nurses (ages 34-59) showed 552 coronary events. Vitamin E supplementation was associated with 40% fewer coronary events.⁷²
- A study of 34,486 postmenopausal women for seven years showed 242 coronary deaths. Intake of vitamins A, C, and E from food or supplements was the parameter measured. Risk of death from coronary disease in the lowest quintile of dietary vitamin E intake was 58% greater than the highest quintile. There was no evidence that vitamins A, C, and E taken as supplements were helpful. Nor was there benefit shown from dietary intake of vitamins A or C.⁷³
- A study conducted from 1970 to 1985 of 5,056 patients showed that the risk of death from coronary heart disease was 69% greater with folate levels in lowest quartile compared to highest quartile. Folate deficiency (levels <3.0 ng/ml) were present in 27% of men and 23% of women.⁷⁴
- A study of 80,000 nurses showed 939 heart attacks. There was a linear decrease in risk of coronary disease by 6% for every increment of 100 mcgm/d of folic acid in the diet and every milligram of vitamin B₆ consumed.⁷⁵
- The NHANES I study followed 9,608 patients for 19 years and found an inverse relationship between the amount of fruit and vegetables consumed and the mortality from heart disease and all cause mortality.⁷⁶

Homocysteine has been established as an independent risk factor for coronary disease and as an independent risk factor for death from any cause.^{77 78 79 so}

- The European Concerted Action Project (750 cases of vascular disease and 800 controls) showed homocysteine elevation associated with double the risk of vascular disease. Cases had homocysteine levels 16% higher than controls.⁸¹
- A prospective study of practicing physicians showed 5% had homocysteine levels greater than 14.0. However, if the homocysteine level was 15.8 or greater, the risk of acute myocardial infarction within five years was 3.1 times greater than the rest of the study population.⁸²
- In a study of 1,160 elderly male and female survivors of the original Framingham Study (ages 68-98), homocysteine levels greater than 14.0 micromol/L were present in 29%, which reflects the age factor of homocysteine elevation. Of these, 67% of the high homocysteine levels were associated with low levels of B₁₂, B₆, or folate. Homocysteine levels were inversely related to folate level.⁸³
- In 20 case-controlled studies of more than 2,000 patients, heart attack cases showed higher levels of homocysteine than controls, even though most of the levels were "within what has been considered normal range."⁸⁴

Folate supplementation given to women for 70 days showed confirmation of homocysteine lowering capability:⁸⁵

Folate supplement mcg/d	Folate level ng/mL	Homocysteine level micromol/L
200	2.9	12.6
300	3.3	8.4
400	6.5	7.7

A 5.0 micromol/L decrease in homocysteine level should achieve a 50-70% reduction in coronary heart disease risk. There is a 10% decrease in risk for coronary disease for every 1.0 micromol decrease in plasma homocysteine level.⁸⁶

Renal failure patients with normal folate, B₁₂, and B₆ levels showed elevated fasting and post-methionine challenge homocysteine levels that were correctable with supplementation. The fasting levels improved with folate and vitamin B₁₂ supplementation, whereas the post-prandial challenge levels required vitamin B₆ supplementation.⁸⁷

The Congressional mandate to increase heat-stable folate in bread, cereal, and flour is aimed at decreasing neural tube defects; however, there is evidence that the amount added is insufficient to do this, and even further evidence that it will be insufficient to decrease homocysteine levels.^{88 89}

A double-blind, prospective, placebo-controlled study of nutrition capsules of powdered juice from whole food sources* demonstrated a decrease of homocysteine by 8.4% in only 30 days.⁹⁰

Vitamin E for Coronary Disease

It has been traditional for physicians to recommend vitamin E for lipid protection against coronary disease. However, careful studies continue to confirm little, if any, benefit from this supplementation.

- An entire edition of *Archives of Internal Medicine* was devoted to the subject, and the editorial stance taken after reviewing all of the evidence was "Don't paint the walls without treating the termites!"⁹¹
- The Heart Outcomes Prevention Evaluation (HOPE) study was terminated prematurely when it became statistically clear that vitamin E was of no benefit in prevention of death from coronary disease or death from any cause.⁹²
- A study of 83,639 physicians for 5.5 years showed no decrease in death from coronary heart disease while taking supplements of vitamins C, E, or multi-vitamin.⁹³
- A meta-analysis of prospective randomized studies, including 81,788 patients in vitamin E trials and 138,113 patients in beta-carotene trials, concluded:⁹⁴
 1. Vitamin E did not provide benefit in mortality compared to control treatment or significantly decrease risk of cardiovascular death or stroke.
 2. Beta-carotene led to a small but significant increase in all-cause mortality and with a slight increase in cardiovascular death.
 3. The lack of salutary effect was seen consistently for various doses of vitamins in diverse populations.

- In July of 2003, the U.S. Preventive Services Task Force, working independently, agreed with the meta-analysis and found no reason for or against the recommendation of vitamins A, C, E, multi vitamins with folic acid, or antioxidant combinations for the prevention of cancer or cardiovascular disease.⁹⁵ They did, however, recommend that beta-carotene singly or in combination NOT be taken for the prevention of cancer or cardiovascular disease. Their comprehensive review of the data is available.⁹⁶

In contrast to this failure of beta-carotene, vitamin E, and multi-vitamin/mineral supplements, whole food nutrition has been shown to benefit primary and secondary prevention of death from coronary disease.

- A follow-up of the NHANES I study (First National Health and Nutrition Evaluation Survey) followed 9,608 patients. It showed that, after 19 years, there was an inverse relationship between intake of fruits and vegetables and death from coronary disease or death from any cause.⁷⁶
- In the Lyon Diet Heart Study, 605 patients were randomized after they had survived their first heart attack. A Mediterranean diet, rich in alpha-linoleic acid, was associated with a 70% decrease in death from a second heart attack after two years, when compared to the American Heart Association Step I diet.⁹⁷
- Tricopoulou and others did a comprehensive population-based, prospective investigation of 22,043 adults in Greece, with 44 months of follow-up. It measured adherence to the Mediterranean diet, based on a point system with maximum adherence point score of 9 and minimal of zero. A two-point increase in the dietary adherence score was associated with a decrease in all-cause mortality of 25%. There was also a significant decrease in mortality from coronary disease and cancer.⁹⁸

One intriguing aspect of this study is that despite the robust inverse association between the overall Mediterranean-diet score and mortality, no appreciable associations were seen for most of the individual dietary components used to construct the score. One possible explanation is that the effects of single nutrients or foods may be too small to detect, whereas the cumulative effects of multiple dietary components may be substantial. In addition, there may be synergistic or interactive effects among the nutrients or foods, which the score automatically takes into account.⁹⁹

It is clear that fruits, vegetables, and whole grain nutrition plays an important role in the prevention of coronary disease, and that lack of this nutrition is associated with its causation.

Stroke

The process of oxidative stress implicated in coronary heart disease also applies to the etiology of stroke. The Framingham Study followed 832 men for 20 years. During this time, there were 97 stroke events. Analysis of nutrition showed that there was a 22% decrease in incidence of stroke for each increment of three [1-cup] servings of fruits and vegetables ingested per day.¹⁰⁰

Subsequent analysis showed carotid artery stenosis rate was double for patients with the highest homocysteine levels (>14.4 micromol/L) compared to those with the lowest (<9.1). Carotid artery stenosis was inversely associated with plasma folate and vitamin B₆. It is important to note that the risk was a continuum and not a threshold.¹⁰¹

Endothelial Function

A microenvironment is a very specific set of physical, biological, and nutrient factors immediately surrounding an organism. The microenvironment surrounding the vascular endothelium, for example, is teeming with cytokines and vasoactive substances affected by oxidative stress. These factors play a critical role in the function of the endothelium. This can be favorable or unfavorable. For example:

- Patients with Non-Insulin-Dependent Diabetes Mellitus have hyperglycemia, which is associated with increased free radicals and reduced free radical scavenging capacity.¹⁰² This results in increased levels of oxidative stress, leading to glutathione depletion. Glutathione is required to convert organic tri-nitroglycerol to the active inorganic nitric oxide necessary for vasodilation. Depletion results in decreased vasoactive responsiveness to nitroglycerin therapy.¹⁰³
- Paradoxical effects on blood rheology occur when the nitroglycerin cannot be converted to nitric oxide. This is correctable by pre-medication with vitamin E for seven days and/or glutathione given intravenously for 30 minutes.¹⁰⁴
- Hypercholesterolemia can reduce the bioavailability of nitric oxide, but is reversible with the implementation of lipid-lowering therapy.^{105 106} Flow-mediated vasodilatation, which is nitric oxide-dependent, was impaired by methionine (a precursor of homocysteine). Antioxidant therapy with vitamin C or E was shown to decrease this methionine induced impairment.¹⁰⁷
- Homocysteine toxicity can be modulated by nitric oxide if it has not been consumed by other oxidative stress.¹⁰⁸
- A 50-gram, high-fat meal disabled endothelial function, as measured by flow-mediated vasodilatation for over four hours. This dysfunction could be avoided by pretreatment with vitamin E or C¹⁰⁹ and by nutrition capsules of powdered juice from whole food sources*.¹¹⁰
- Hormone replacement (estrogen has antioxidant qualities) therapy was associated with improvement of nitric oxide to endothelin-1 ratios.¹¹¹
- Active smoking which depletes serum ascorbate (antioxidant capacity) reduces endothelial dependent aortic elasticity by 27%. Passive smoking is almost as bad, reducing elasticity by 21%.¹¹²

Since the microenvironment of the endothelium is so active, it is likely that more research will elucidate the continuing role of antioxidant benefit in preventing or ameliorating cardiovascular disease. It is likely that antioxidant therapy will eventually show benefit for intervention in acute coronary syndromes as well.

Cataracts

There is convincing data to show that antioxidant nutrition, which ameliorates oxidative stress, can thereby prevent the development of cataracts.

- Pregnant rats subjected to oxidative stress give rise to offspring with cataracts, but this can be prevented with antioxidant therapy.¹¹³
- A 15-year study in Finland showed a three-fold greater risk of cataracts in patients with the lowest levels of alpha-tocopherol and beta-carotene.¹¹⁴
- In 1996, 1.2 million cataracts were removed in the United States at a cost of \$3.4 billion. Multiple studies confirm that cataracts have an oxidative etiology. Five epidemiologic studies have shown cataract prevention with dietary ascorbate, tocopherol, and carotenoids.¹¹⁵

Age-Related Macular Degeneration (AMD)

Vitamins A, C, and E did not prevent AMD, but consumption of green leafy vegetables was associated with 43% less AMD, and a serving of green leafy vegetables on a daily basis was associated with 86% less risk of AMD.¹¹⁶ Lutein/zeaxanthin is the antioxidant associated with protection of the macula.¹¹⁷ It is found in abundance in green leafy vegetables.

Exercise

Multiple studies have shown exercise, particularly distance running, produces oxidative stress and cumulative damage, with increased risk of infection. In exercise-exhausted animals, free radical accumulation is increased 2- to 3-fold, with resultant lipid peroxidation, mitochondrial damage, and vitamin E depletion. Athletes given vitamin E, 1200 IU per day for two weeks, significantly decreased lipid peroxidation, as measured by a Pentane breath test during strenuous exercise. However, increased performance was not readily demonstrated except at high altitudes. Mountain climbers at high altitudes experienced deterioration in physical performance associated with lipid peroxidation, unless they received supplementation with vitamin E.¹¹⁸¹¹⁹¹²⁰¹²¹

Critical Care Medicine

The importance of oxidative stress in critical care medicine has been recognized for some time. "**Oxidant injury constitutes one of the major pathologic processes in the critically ill patient.... In fact, lipid peroxidation by toxic oxygen radicals and resultant cell membrane disruption is thought to be the final common pathway in cellular death**".¹²²

Most critical care patients receiving total parenteral nutrition get an ampule of 12 vitamins and trace elements. In some centers, because of the expense and scarcity of the parenteral vitamins, even less is administered.¹²³ Instead of getting thousands and thousands of phytonutrients of known or suspected nutritional and antioxidant value, they are getting a minimal amount of twelve or less.

It would seem that critical care patients who are undergoing severe, if not maximal, oxidative stress are not getting enough antioxidants to suffice for even non-stress situations.

More recently, oxidative stress and the effects of antioxidants have been studied in septic shock and ARDS with potential benefit demonstrated.¹²⁴¹²⁵ Oxidative stress and lipid peroxidation occur with total parenteral nutrition.¹²⁶ The need for increased attention to therapy with antioxidants is clear.¹²⁷ Recognition of oxidative stress and antioxidant therapy will soon become standard practice in critical care medicine.¹²⁸

Depression

Depression is associated with a need for serotonin contact at the receptor sites of efferent neurons. Selective serotonin reuptake inhibitors (SSRIs) act by sustaining levels of serotonin at the synapse. However, increased serum levels of folic acid can increase the amount of serotonin at the synapse. Homocysteine remethylates to methionine, which in turn is converted to S-adenosyl-methionine (S-AdoMet). This is a vitamin B₁₂-dependent reaction, but is driven by folate. S-AdoMet is responsible for over thirty reactions within the central nervous system, including steps in the conversion of phenylalanine and 5-hydroxytryptamine to serotonin, dopamine, norepinephrine, and epinephrine.

In several studies, 15-38% of depressed patients were found to be deficient in folic acid as defined by RBC folate <200 ng/ml or plasma values <2.5 ng/ml. Compared to normal or to non-depressed psychiatric patients, depressed patients had lower serum folate or red blood cell folate levels. Further, among the depressed patients, those with lower folate levels had higher ratings of depression. "These findings seem to indicate that folate deficiency is associated with the emergence and perhaps the severity and duration of depressive illness."¹²⁹

- In a two-year study of 81 patients with bipolar disorder on lithium and 26 patients with unipolar disorder on lithium, the highest folate levels were associated with the lowest "affective morbidity". This was not a threshold phenomenon.¹³⁰
- Duration of depressive episode has been shown to be inversely related to the level of folate.¹³¹
- Studies of patients with depression show poorer response to electro-convulsant, anti-depressant, and tryptophan therapies if folate deficiency is present.¹³²¹³³
- A study of 235 patients with depression showed that low serum folate levels predicted poorer response to SSRI therapy.¹³⁴
- Folate-deficient, depressed patients who had folic acid replacement therapy had shorter length of stay, better social functioning, and mood improvement when compared to those who did not.¹³⁵
- A double-blind controlled study of folate supplementation of unipolar/bipolar patients on Lithium therapy showed that 200 meg of folate reduced the occurrence and duration of mood disorders.¹³⁶
- In a randomized, placebo-controlled study of 24 depressed patients with folate deficiency, 15 mg/d of methyltetrahydrofolate showed significant improvement at three and six months, compared to controls.¹³⁷
- Depressed patients treated exclusively with 50 mg/d of methyltetrahydrofolate showed 81% improvement in six weeks.¹³⁸

Alzheimer Disease

"The pathogenesis of Alzheimer disease may involve oxidative stress and the accumulation of free radicals, leading to excessive lipid peroxidation and neuronal degeneration in the brain."

A double-blind, placebo-controlled study of 341 patients with Alzheimer disease compared the monoamine oxidase inhibitor selegiline, with or without 1200 units of vitamin E, and placebo for two years. Results demonstrated a significant delay to death or institutionalization in the treatment group.¹³⁹

The role of oxidative stress in Alzheimer disease is highlighted by an association with high levels of homocysteine. Patients with levels greater than 14.0 were shown to have twice the risk of Alzheimer disease and to progress to death twice as fast.¹⁴⁰

Two other studies looking at nutrition and incidence of Alzheimer disease found a 35% and 70% reduction in the incidence of Alzheimer disease associated with dietary intake of vitamin E, but no benefit from vitamin C or E supplementation.^{141 142 143}

HIV/AIDS

Oxidative stress plays an important role in Human Immunodeficiency Virus Infection (HIV) and Acquired Immune Deficiency Syndrome (AIDS). The following research findings suggest the potential value of antioxidant therapy:

- Levels of antioxidants have been shown to be low even before the development of AIDS, with corresponding elevated levels of lipid peroxides.^{144 145}
- Levels of the antioxidant glutathione were shown to be low in patients with HIV. These levels could be improved with selenium supplementation, but not with beta-carotene.¹⁴⁶
- Low levels of the antioxidant glutathione could be improved with acetylcysteine, and a survival advantage was demonstrated in patients with AIDS.¹⁴⁷
- Oxidative stress has been shown to be the physiologic mediator of apoptosis, and HIV disease represents the extreme example of disordered apoptosis.¹⁴⁸
- Research has suggested that antioxidant therapy with acetylcysteine may decrease HIV production and cellular oxidative stress.¹⁴⁹
- Therapy with nucleoside reverse transcriptase inhibitors is associated with inhibition of mitochondrial DNA polymerase-gamma, which results in mitochondrial toxicity. Mitochondrial toxicity is at least partially responsible for adverse effects such as muscle cramps, lactic acidosis, hepatic steatosis, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, respiratory chain enzyme depletion, and the lipodystrophy syndrome.¹⁵⁰ DNA polymerase-gamma is primarily involved with repair of DNA damage and is the template for respiratory chain enzymes. Since the major factor leading to DNA damage is free radical oxidative stress, it would seem sensible to reduce the oxidative stress with phytonutrient antioxidants and thereby reduce the DNA damage. Such a reduction should logically result in less impairment of the DNA polymerase-gamma function and, therefore, a decrease in mitochondrial toxicity.

Age-Related Immune Deficiency

Age-related immune deficiency is very common and is caused in part by micronutrient deficiency. At least some of this immune deficiency is reversible and should be preventable.

- In a placebo-controlled study of 88 ambulatory patients over 65 years of age, vitamin E supplementation at 200 mg/d showed 65% improvement in cellular immunity (response to delayed hypersensitivity skin test) and six-fold increase in humoral immunity (response to hepatitis B immunization and tetanus booster). The 200 mg/d dose was superior to placebo and to a 60 mg/d dose, and paradoxically was also superior to an 800 mg/d dose. Additionally, the vitamin E patients had 30% fewer infections during the 4.5 month study than the placebo group.¹⁵¹
- Another study of elderly hospitalized patients compared vitamins A, C, and E taken for four weeks vs. placebo. There was an increase in CD4 and CD8 counts as well as lymphocyte mitogen response.¹⁵²
- Yet another study looking at the effect of vitamin E and/or multi-vitamin/mineral supplementation in 652 elderly subjects over a two-year period showed no decrease in infections in any of the three treatment groups compared to placebo, and paradoxically showed the severity of respiratory infections to be worse in the vitamin E-treated groups.¹⁵³
- A study¹⁵⁴ of nutrition capsules of powdered juice from whole food sources* in 48 elderly patients for 80 days showed improvement in all parameters of immune function that were measured:
 1. Spontaneous proliferation of peripheral blood mononuclear cells increased significantly ($p < .0001$).
 2. Natural killer (NK) cell cytotoxicity significantly increased at effector to target ratios of 100:1 ($p < .0001$), 50:1 ($p < .0005$) and 25:1 ($p < .005$).
 3. Supernatant from peripheral blood mononuclear cells stimulated with phytohemagglutinin (PHA; 10 mcg/ml) resulted in significant two-fold increases in interleukin-2 (IL-2) ($p < .0001$).
 4. Statistically significant increases in IL-2 production were observed in smokers ($p < .005$).
 5. Significant increases were found in the serum antioxidants when baseline values were compared with day 80; lutein/zeaxanthin ($p < .005$), alpha-carotene ($p < .0001$), beta-carotene ($p < .0001$), lycopene ($p < .05$), and alpha-tocopherol ($p < .005$).

Other Oxidative Stress-related Diseases

There is a growing body of knowledge regarding the role of oxidative stress in multiple other diseases, as well as its detrimental effects on those aspects of physiology that contribute to disease and aging.

- Inflammatory bowel disease has increased magnitude of oxidative stress.¹⁵⁵¹⁵⁶
- Male infertility is associated with oxidative stress and can be associated with increased levels of 8-hydroxy deoxyguanosine in the semen.¹⁵⁷¹⁵⁸¹⁵⁹
- Eclampsia of pregnancy is strongly associated with oxidative stress and trials of calcium and aspirin have failed to reduce the incidence of pre-eclampsia; however, serendipitously, antioxidants have shown a 68% reduction in pre-eclampsia.¹⁶⁰¹⁶¹

- Asthma has been associated with oxidative stress. Lipid peroxidation of arachidonic acid, which is the major active product of omega-6 fatty acid nutrition, produces F2-isoprostanes, which are bronchoconstricting. Urinary F2-isoprostanes show a dramatic increase when the lungs of asthmatics are subjected to allergenic challenge.¹⁶²
- Furthermore, the severity of asthma is inversely correlated with the plasma levels of beta-carotene and ascorbate.¹⁶ In asthmatics treated with theophylline, pyridoxal-5'-phosphate (vitamin B₆ coenzyme) becomes depleted and homocysteine levels rise disproportionately in response to methionine challenge. This is reversible with B₆ supplementation.¹⁶⁴

These examples show the broad range of physiologic disturbances resulting or at least contributing to human disease. We can expect that the science will continue to evolve and the role of "antioxidant" nutrition from whole food sources to show continuing efficacy.

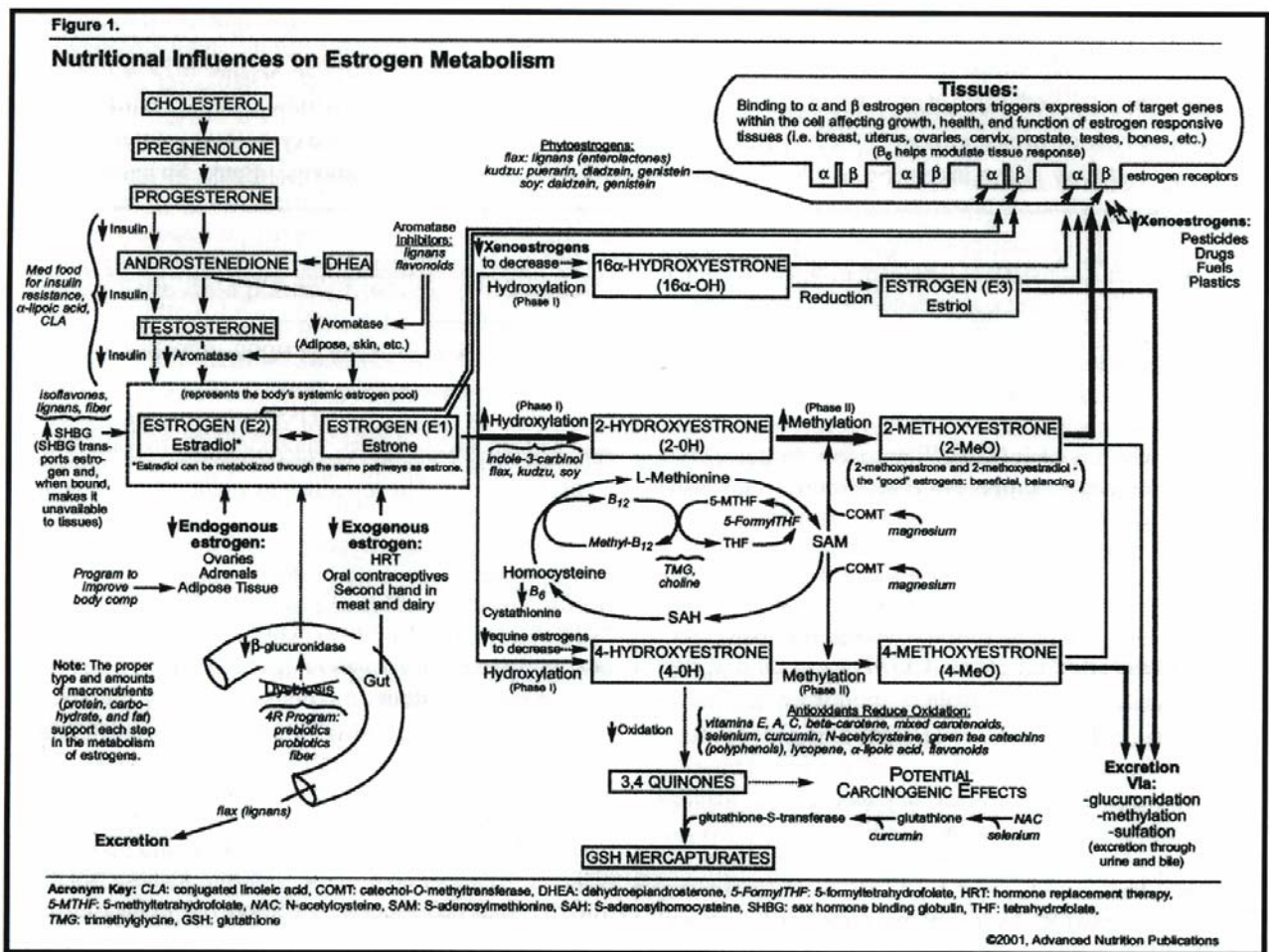


Diagram reproduced with permission from the *Journal of the American Nutraceutical Association*. (Liska DJ, Leupp LR. Estrogen metabolism: A Complex Web. JANA. 2002;5(3):4-14.)

Hormone Replacement Therapy (HRT)

The entire issue of equine estrogen with progestin therapy was exploded by the cessation of one arm of the Women's Health Initiative in July 2002.¹⁶⁵ The study showed greater risk of death from heart disease, stroke, and breast cancer with a greater incidence of deep vein phlebitis and pulmonary embolism. Subsequently it was shown that there was also a greater risk of dementia in the women on equine estrogen with progestin therapy. Most of the hormone replacement controversy focuses on the amount and duration of exposure to estrogen; however, it is important to emphasize that the type of estrogen replacement and the metabolism of estrogen are also critical factors. The estrogen metabolism is largely dependent upon diet and other lifestyle factors that are modifiable.¹⁶⁶ Central to this metabolism is the ingestion of cruciferous vegetables, green leafy vegetables, and a general diet of antioxidant-rich fruits, vegetables, soy, and green tea.

The Phase I metabolism of estradiol and estrone (the two major endogenous human estrogens) is by hydroxylation at carbons 2, 4, and 16. The "safe passage" of these estrogens is via the 2-hydroxy pathway. In a five-year study of 10,786 women, predominant 2-hydroxy estrogen excretion was associated with a 40% decrease in risk of breast cancer.¹⁶⁷

Another long-term study found postmenopausal women who developed breast cancer had a 15% lower ratio of 2-hydroxy to 16-hydroxy urinary estrogen excretion than control subjects, and women with the highest ratio had 30% less risk of breast cancer.¹⁶⁸ The principal determinant of the safe 2-hydroxy pathway over the 16-hydroxy pathway is the ingestion of cruciferous vegetables (broccoli, kale, cabbage, Brussels sprouts, and cauliflower).

The Phase II metabolism of the 2-hydroxy and 4-hydroxy (catechol estrogens) is methylation. Methylation is accomplished by catechol-O-methyltransferase (COMT) which depends upon S-adenosyl-methionine (SAME) for the methyl group. As previously discussed, the production of SAME is dependent upon ingestion of green leafy vegetables.

Finally, when SAME/COMT are slow to detoxify the catechol estrogens, these estrogens are oxidized to estrogenic quinones, which are both directly and indirectly carcinogenic. These estrogen metabolic steps are nutrition-dependent.

Also of importance is that COMT is responsible for the production of several neurotransmitters (catecholamines) such as dopamine, epinephrine, nor-epinephrine, and serotonin. During the luteal phase (days 18-25) of the menstrual cycle, COMT is occupied by the estrogen surge. This means that a change in the amount of neurotransmitters is possible, which may account for some of the symptoms of premenstrual syndrome (PMS). If so, PMS should be at least partially responsive to dietary intervention with green leafy vegetables.

The future of HRT will depend on identification of specific estrogen receptor molecules with appropriate agents to block or stimulate them, depending on the necessary effect. For example, tamoxifen blocks estrogen receptors of breast cancer cells and raloxifen stimulates receptors for bone density. Arimedex blocks the enzyme aromatase that converts adrenal cortical hormones into estradiol in adipose tissue, which is the only source of estrogen in the postmenopausal female.

Compare these specific molecules to conjugated equine estrogens that contain over 100 estrogenic compounds. Since these are administered orally, they must pass through the liver prior to reaching the systemic circulation where they are active. In so doing, the 100 estrogenic compounds are converted to over 600 compounds. None of these 600 is highly identified and none are bio-identical to the human molecules.¹⁶⁹ When

a physician decides a patient needs estrogen therapy, it would seem best to prescribe a bio-identical estrogen or an estrogen that is bio-identical after first hepatic passage (even better would be a topically applied bio-identical estrogen that would reach target organs prior to hepatic passage) AND to counsel his or her patient on the nutrition necessary to enhance "safe passage" of the metabolites. For those female patients who cannot or will not consume cruciferous and green leafy vegetables daily, nutrition capsules of powdered juice from whole food sources* would seem a wise choice.

Osteoporosis

It has been shown in the Framingham Study that each serving of fruit or vegetable consumed per day increases bone density by 1%.¹⁷⁰ To the contrary, supplementation with vitamin A has been shown to actually decrease bone density. For example, Scandinavian women have a seven-fold increase in fractured hips from osteoporosis compared to the rest of Europe, and the men of Scandinavia have an incidence of fractured hips equal to women in the USA. This is due to the fact that Scandinavians traditionally have a high intake of cod-liver oil, which is rich in vitamin A. Surprisingly, the estimated incidence of fractured hip from osteoporosis increases by 68% for every milligram of vitamin A consumed per day.¹⁷¹ This is because vitamin A inhibits osteoblastic activity, but not osteoclastic activity; therefore, vitamin A allows for a slow leaching of calcium out of bones without allowing for deposition. On the other hand, proretinol carotinoids, such as beta-carotene, are safely stored in the body; and, when needed, the molecule is cleaved to form two molecules of vitamin A.

Problems and Paradoxes

A study of colon polyps as an indicator of cancer risk showed that supplementation with vitamins C and E, and beta-carotene for a period of four years failed to protect against colon polyps.¹⁷²

In an attempt to demonstrate that antioxidants could prevent cancer and heart attacks in patients at risk, a study took place between 1985 and 1993 that involved 29,133 Finnish male smokers, who had, on average, smoked a pack of cigarettes every day for 36 years.^{173, 174} The interventional study was planned for ten years, but was aborted at eight years due to some disturbing findings.

- 1) Supplementation with beta-carotene showed:
 - an 18% increase in incidence of lung cancer.
 - an 8% increase in overall mortality.
- 2) Supplementation with alpha-tocopherol showed:
 - a 50% greater risk of hemorrhagic stroke (which was not statistically significant because of premature termination of the study).
 - a 2% increase in overall mortality.

In a subset analysis of the 29,133 smokers enrolled, 1,862 had already had a heart attack prior to enrollment.¹⁷⁵ In these smokers, antioxidant supplementation increased the risk of a second and fatal heart attack during the study. The beta-carotene group was 75% more likely to die from a second heart attack than the placebo group; and, the vitamin E group was 33% more likely to die from a second heart attack than the placebo group. Supplements were beta-carotene: 20 mg/d or vitamin E: 50 mg/d; both; or, placebo. Relative risk compares the treatment to the placebo. (The placebo's relative risk is 1.00, therefore 1.75 is a 75% increase in mortality; 2.00 would be double the risk — or a 100% increase.)

Group	Relative Risk of Coronary Event	
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	Nonfatal	Fatal
Placebo	1.00	1.00
Beta-carotene	0.67	1.75
Both	0.86	1.58
Vitamin E	0.62	1.33

Another study designed to demonstrate the benefit derived from taking antioxidants looked at 18,314 smokers and asbestos workers who would be expected to have a high risk of cancer. It was a double-blind, placebo-controlled study.¹⁷⁶ There was combination intervention with vitamin A: 25,000 IU/d and beta-carotene: 30 mg/d. The study was terminated 21 months prematurely because treatment resulted in the following:

- 28% more lung cancer,
- 46% more death from lung cancer,
- 26% more death from heart disease, and
- 17% more death from any cause.

The Physicians' Health Study, conducted by Harvard Medical School, comprised 22,071 male physicians in a double-blind, placebo-controlled study. Cancer, heart disease, and overall mortality were the end points during the 12-year study. The conclusion was that neither benefit nor harm was demonstrated from beta-carotene: 50 mgs every other day.¹⁷⁷ Phase II of the study continued to run until June 2003, when it was terminated and the participants were informed as to whether they had been taking beta-carotene or placebo, and were advised not to take beta-carotene supplementation.

Looking at elderly patients, the group taking a vitamin C, E, or multi-vitamin supplement for several months showed no benefit in prevention of upper respiratory infections; however, the group taking vitamin E had greater intensity and longer duration of symptoms than the placebo group.¹⁷⁸ Therefore, isolated supplements of vitamins A or E and beta-carotene were shown to be of no benefit or even harmful.

Bioavailability and Efficacy

Natural vitamin E consists of four tocopherols and four tocotrienols. Absorption of synthetic (mostly alpha-tocopherol) vitamin E is inferior to that of natural vitamin E.¹⁷⁸

- A trial of volunteer athletes by M.S. Micozzi and others showed better bioavailability from beta-carotene capsules than from carrots. Capsules containing 12 and 30 mg increased beta-carotene levels more than 272 g of carrots containing the same amount (29 mg) of beta-carotene.¹⁷⁹

Carotene Intake	Serum Beta-carotene Level(nmol/L)
30 mg caps	7901
12 mg caps	3589
29 mg (272 g carrots)	1438

It is important to note, however, that beta-carotene capsules decreased lutein levels. This is because too much of a particular carotenoid saturates the serum capacity at the expense of other carotenoids.

- A study in West Java, Indonesia by S. DePee and others compared the efficacy of a daily supplement of enriched wafers to that of stir-fried, green leafy vegetables for breast-feeding anemic women. Taken over a period of 12 weeks, the enriched wafers contained the same amount of beta-carotene, folic acid, ascorbic acid, and iron as the vegetables, but in a simple matrix. A significant response of serum carotene and retinol, as well as breast milk retinol, occurred only from the wafers.¹⁸⁰ The poor absorption from vegetables may have been a result of phytonutrient capture in the cellulose content.
- A study in the United Kingdom by A.S. Zino and others asked subjects to increase their daily fruit and vegetable consumption from 2.2 servings to eight servings. They were able to increase servings to 7.7 daily. The results showed increases in levels of beta-carotene, alpha-carotene, and vitamin C, but no change in the level of alpha-tocopherol.¹⁸¹
- A study of nutrition capsules of powdered juice from whole food sources* (cellulose and hemicellulose removed by juicing) in 48 elderly patients for 80 days showed improvement in levels of the antioxidants beta-carotene, alpha-carotene, alpha-tocopherol, and lutein/zeaxanthin.¹⁵⁴
- Another bioavailability pilot study, conducted by J. Wise, of nutrition capsules of powdered juice from whole food sources* showed an increase in serum levels of the following phytochemicals:⁶

Phytochemical	Increase in serum level in 28 days
Beta-carotene	510%
Alpha-carotene	119%
Lutein/zeaxanthin	44%
Lycopene	2,046%
Alpha-tocopherol	58%

In this study, safety was demonstrated because there was no significant increase in retinol (vitamin A) levels. Accumulation of retinol could be potentially toxic for bone or liver. The body's homeostasis prevents breakdown of the pro-retinol carotenoids until vitamin A is needed, but this safety mechanism can be bypassed by vitamin A ingestion. There was a decrease of gamma-tocopherol by 38%, which is a presumptive indication of increased hepatic excretion into the gut. In the gut, gamma tocopherol functions as the principal antioxidant.³⁰ In the same study, there was a 75% decrease in circulating lipid peroxide levels and a third of the subjects achieved complete absence of circulating lipid peroxides. This is something that no dose of vitamin E can accomplish.⁵

- Other studies of nutrition capsules of powdered juice from whole food sources* have shown significant increases in folic acid, ascorbate, and selenium.⁹⁰ These studies establish that nutrition capsules of powdered juice from whole food sources* are bioavailable, safe, and efficacious in reducing oxidative stress.

Hence, Micozzi's data showed there is better bioavailability from beta-carotene capsules than from 272 grams of carrots per day, at what can be considered a maximum tolerable level of ingestion. DePee's data showed bioavailability of beta-carotene (leading to retinol) was inferior with stir-fried greens compared to specially-prepared wafers containing the same ingredients. The increased consumption of fruits and vegetables in Zino's study to what can be considered a maximum number of servings under reasonable life habits failed to increase levels of alpha-tocopherol. The data from the Wise study showed the bioavailability, safety, and efficacy of nutrition capsules of powdered juice from whole food sources* when the phytonutrients have been released from cellulose by juicing.

Opportunity for Intervention

George Bernard Shaw said it, and Bobby Kennedy paraphrased it: "Some people see things the way they are and ask 'Why?' Others see things the way they could be and ask 'Why not?'" We hear daily about the rising cost of health care, which has already ballooned to over \$1.4 trillion per year. Despite all of the dollars spent in its name, "health care" is really a misnomer, because the money is really being expended on "disease care." True health care dollars would be spent not on intervention, but on prevention of disease; and, not on reclamation of health, but on maintenance of health. "Disease care" fails to address the core cause of disease.

While there are billions of dollars spent on advertising fast food and junk food, the National Cancer Institute's "5 A Day for Better Health" campaign has only a \$2 million budget. Health requires a long-term commitment to prevention. As the quote suggests, what if we dare to dream?

What if:

- 58-70% of people with metabolic syndrome didn't progress to diabetes?¹⁶
- People could decrease oxidative stress every day by 75-100%?⁶
- 66% of cancers never occurred in the first place?³⁵³⁶⁴⁰⁴¹⁴²
- Everyone could experience 66% less DNA damage day after day, year after year?³⁴
- Women could increase the "safe passage" of estrogens to reduce breast cancer incidence by more than 40%?¹⁶⁶¹⁶⁷⁶⁸
- Everyone could have improved circulation and endothelial function?¹⁰⁹
- 69% of heart attacks never occurred in the first place?⁷⁴
- 70% of people who experience their first heart attack did not die from a second heart attack?⁹⁷
- Everyone could significantly decrease their homocysteine levels?⁷⁵⁷⁷⁷⁸⁷⁹⁸⁰⁸¹⁸²⁸⁴
- Everyone could improve the integrity of their immune systems?¹⁵⁴
- All of the disorders of oxidative stress outlined in this manuscript occurred less frequently and with less severity?

Bobby Kennedy would ask "Why not?" - and so should we. Why aren't prevention of disease and maintenance of health a real part of the "health care system"?

Granted, it is our personal responsibility to take charge of our health and nutrition, as well as the health and nutrition of our children, but counseling from health care providers can help. This manuscript has outlined the overwhelming evidence that oxidative stress plays a major role in the causation of disease and aging, and the equally compelling evidence that fragmented vitamin supplements are not beneficial and in some situations actually harmful.

Phytonutrition is the true opportunity for intervention. In the realm of health, phytonutrition allows individuals to respond to the challenge for us to examine the way things are and to change what can be changed. This phytonutrition should be from whole food sources - preferably raw, fresh fruits, vegetables, and whole grains. For supplementation, there are nutrition capsules of powdered juice from whole food sources* that have been shown to be bioavailable, safe, and efficacious in influencing those aspects of human physiology associated with disease causation. The efficacy has been shown in the reduction of oxidative stress; in the protection of DNA; in the enhancement of immune parameters; in the protection of circulation; and, in the reduction of homocysteine, which is an independent marker of probability of death from any cause. There is every reason to believe that eventually this efficacy will be extended to include the myriad other aspects of human physiology that have been shown to be associated with disease and aging.

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