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ABSTRACT—The heart is the most susceptible of all the organs to premature aging and free radical oxidative stress. Clinical research has clearly documented the role of free radical damage and the progression of numerous degenerative diseases, particularly cardiovascular disease. This may be the result of acute ischemia-reperfusion injury, endothelial damage of hyperhomocysteinemia, as well as chronic oxidative damage secondary to lipid peroxidation. Fortunately, although highly responsive, and therefore vulnerable to the effects of oxidative stress, the heart is also receptive to the benefits of targeted phytonutrients, antioxidants, and nutritionals.

The effects of antioxidant nutrients have been extensively evaluated in epidemiological, population, and clinical studies. Phytonutrients such as the natural flavonoids and carotenoids found in fresh fruits and vegetables or vitamins C, E, and beta-carotene have powerful antioxidant effects. In addition, minerals like selenium and nutrients such as coenzyme Q10 will minimize free radical risk and optimize a favorable outcome from the ubiquitous presence of oxidative stress on the cardiovascular system.

The B complex, particularly folic acid, B12, and B6 are also essential in the prevention of hyperhomocysteinemia, another major risk factor for the circulatory system. Measures to minimize accumulation of heavy metals in the body, especially iron and copper, which are capable of initiating adverse free radical reactions, will also help to assuage oxidative stress. Thus, the combination of a healthy diet supplemented with antioxidants and phytonutrients may be useful in the prevention and promotion of optimum cardiovascular health.

ALTHOUGH oxygen is necessary for aerobic life, the metabolism of oxygen has ominous metabolic consequences. Abundant circumstantial evidence has suggested that oxidant by-products of normal metabolism (free radicals) are involved in the pathogenesis not only of the degenerative diseases of the 20th century, but also in aging itself. However, free radicals also play a key role in normal biological functions. This obviously seems to represent a paradox. Although research has shown that free radicals may play a fundamental role in supporting life processes such as mitochondrial respiration,[1] platelet activation,[2] leukocyte-phagocytosis,[3] and prostaglandin synthesis,[4] these unstable, highly charged, and deleterious atoms have been incriminated as a cause of extensive damage to lipid membranes, organelles, and even DNA itself. This paradox of free radical chemistry has generated interest among health-care professionals, especially those interested in preventive medicine.

Free Radicals and Endogenous Antioxidant Systems

A free radical is a molecule with an odd number of electrons. Stable chemical molecules such as oxygen contain paired electrons. In contrast, many highly unstable or extremely reactive compounds contain unpaired electrons. The activation of oxygen may lead to the creation of a number of free radicals by producing unpaired electrons. The mitochondrial inner membrane reduces

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oxygen to water by the addition of a sequential transfer of four electrons. This involves a mechanism in which the oxygen molecule undergoes reduction, gaining electrons and subsequently forming molecular fragments with unpaired electrons and very high chemical reactivity.[5] As unpaired electrons can be transferred to a nonradical, these potential reactions create another free radical, thereby setting up a chain reaction of electron transfer. Such chain reactions may proceed thousands of times before the reaction is terminated.

Once the reduction of oxygen has occurred, inevitable by-products called reactive oxygen species (ROS) are formed, the first of which is the superoxide anion (O_2^-). Superoxide is very toxic and travels great distances. Hydrogen peroxide (H_2O_2) is generated by the interaction of two superoxide anions. A reaction between the superoxide anion and the hydrogen peroxide leads to the formation of the most damaging hydroxyl radical (OH) (Table 1).[6] The hydroxyl radical is highly reactive and can set off toxic free radical chain reactions. A major source of endogenous free radicals occurs during normal oxidative metabolism in the respiratory mitochondrial chain. Under normal conditions, 95% to 98% of molecular oxygen consumed by cells is reduced to water by the addition of four electrons. The remaining 2% to 5%, however, are reduced by a univalent pathway giving rise to reactive free radicals even during daily homeostatic oxidative stress (Table 2).[7]

The formation of free radicals in neutrophils is also a normal intracellular physiological process involved in defending the body against invading microorganisms. However, when reactions of phagocytosis and inflammation are overwhelming, free radicals may then be released into the extracellular space and injure the surrounding tissue. Such overwhelming inflammation, and other high free radical situations such as radiation, arachidonate metabolism, and the extraordinary radical flux occurring during reperfusion/ischemia can cause widespread damage to cells, basement membranes, mitochondria, and even DNA itself. Sudden bursts of ROS under abnormal conditions undergo inadequate detoxification by the organism's natural endogenous enzyme defense systems. This results in cellular injury. Such oxidative stress resulting from reperfusion injury in myocardial ischemia may also occur with thrombolytic therapy in myocardial infarction or during coronary artery bypass surgery.[8]

Table 1.—Free Radical Species

$$2O_2 + NADPH \longrightarrow 2O_2^- + NADP^+ + H^+$$
$$O_2^- + O_2^- + 2H \longrightarrow H_2O_2 + O_2$$
$$O_2^- + H_2O_2 \xrightarrow{FE} OH^\cdot + OH^- + O_2$$

During coronary artery bypass surgery, there is a period of cross-clamping which reduces oxygenation to the heart. With reperfusion (unclamping) free radical oxidative stress and lipid peroxidation cause considerable damage to cellular tissues.[8] A similar mechanism occurs during clot lysis by thrombolytic therapy during myocardial infarction. There are several potential sources of oxygen-derived free radicals in ischemic tissue. The most crucial and best studied is endothelial-derived xanthine oxidase which, in tissue, is a dehydrogenase that cannot reduce molecular 0_2. During ischemia, however, xanthine dehydrogenase in the endothelial cells is converted to xanthine oxidase. Adenosine triphosphate (ATP) is a product of Krebs cycle activity providing energy to the cell. A degradation product of ATP is hypoxanthine.

During postischemic reperfusion, oxygen enters the cell at high tension (increased flow) combining with hypoxanthine in the presence of xanthine oxidase. This results in the generation of superoxide anions and other free radicals that cause widespread lipid peroxidation and damage to cellular membranes (Table 3).[6,7,8]

Overwhelming free radical activity in the early phase of reperfusion injures the endothelial lining resulting in the loss of endothelium derived vasorelaxants, such as nitric oxide endothelial cell releasing factor (EDRF-NO). The myocardial effects of such free radical stress include denaturation of proteins, tissue edema, and by-products of lipid peroxidation causing monocyte injury and death.[6]

Reperfusion injury in myocardial ischemia has been extensively studied in animal models.[9-11] Pretreatment of animals with free radical scavengers such as vitamin E,[9] superoxide dismutase, and catalase has been shown to protect left ventricular function following ischemia.[10,11] In the human model, pretreatment with coenzyme Q10 (antioxidant, membrane stabilizer, free radical scavenger)

Table 2.—Univalent Pathway/Electron Transfer in Mitochondrial Chain

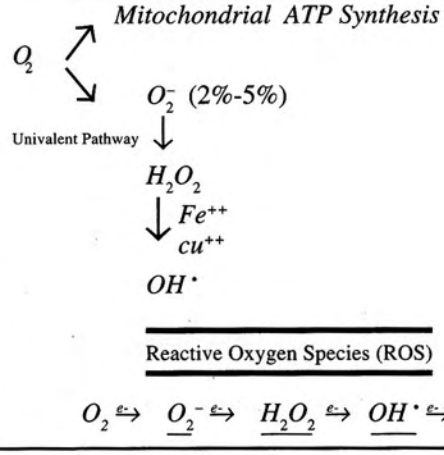

Table 3.—Myocardial Ischemia/Reperfusion
Formation of Super Oxide Radicals

Ischemia → *Xanthine DeHydrogenase* → *Xanthine Oxidase*

$ATP \xrightarrow{\text{Catabolism}}$ Hypoxanthine

Reperfusion → O_2 + *Hypoxanthine* + *Xanthine Oxidase* → $2O_2^-$

was effective in preserving left ventricular function in patients undergoing revascularization and coming off heart-lung pump bypass.[12,13] Since the heart may be the most vulnerable of all organs to oxidative stress, research is now aimed at preserving left ventricular function and limiting infarct size via neutralization of ROS in situations of ischemia and reperfusion. Oxidation is also believed to contribute to acute tissue damage in situations of acute myocardial infarction[14] and thrombotic stroke,[15] as well as to the oxidative changes occurring in serum low-density lipoproteins (LDL) over time,[16] or to the atherosclerotic lesions of homocysteinemia.

In 1969 McCully first proposed his hypothesis concerning vascular pathology resulting from homocysteinemia.[17] Unfortunately, he was many years ahead of his time. His hypothesis of homocysteinemia and premature atherosclerosis was not accepted by the medical community. However, over the last few years, there have been several studies demonstrating the connection between high plasma homocysteine levels and occlusive arterial disease including coronary atherosclerosis, peripheral vascular disease, and carotid artery disease.[18-25] These studies, including the Harvard Physician and Framingham studies, indicated that high plasma homocysteine levels are indeed a risk factor for cardiovascular disease. Unfortunately, plasma homocysteine has not received the attention that it deserves. Hypercholesterolemia is still the major metabolic risk factor that most physicians accept.

Although, the possibility of interactions of synergy between cholesterol and homocysteine has already been noted,[23] most cardiologists do not consider homocysteine as an independent risk factor for cardiovascular disease. Measuring plasma homocysteine concentrations may be academic in some instances, but it should be considered in any young patient with myocardial ischemia.

It is also important to note that hyperhomocysteinemia is not limited to men. In one study, women with coronary disease had higher homocysteine levels than did the control group.[24] In another study comparing men and women with high homocysteine levels, women evidenced greater carotid thickening ratios than their male counterparts.[25] Although the mechanism of homocysteine associated endothelial damage remains unclear, the fact that it may be inhibited by the addition of catalase suggests that the free radical hydrogen peroxide produced during the oxidation of homocysteine plays a role.[26] Thus, free radical oxidative stress is believed to contribute to cardiovascular disease through a number of acute and chronic pathways, including reperfusion and ischemia, direct toxicity to endothelium by homocysteine, and the chronic oxidative changes occurring in LDL over time.

Antioxidant Defense

Fortunately, the body has a complex antioxidant defense system against free radicals. If it were not for the quick action of these protective antioxidant defense systems, thousands of chain reactions of free radicals, generated within seconds, could quickly cripple and destroy cellular functions. The body's natural antioxidant systems include superoxide dismutase, catalase, and glutathione peroxidase. Most of these naturally occurring enzymes deactivate free radicals by using them to generate safer chemical reactions. The most effective line of defense against hydrogen peroxide is catalase. The first line of defense is far from efficient, particularly in mitochondria under high oxygen stress. The fate of superoxide is destruction by the enzyme superoxide dismutase. Some superoxide reacts with water to form hydrogen peroxide which is known to exist in high concentrations in the innermost compartment of the mitochondria. The most potent destructive free radical, the hydroxyl radical (OH), is generated from the hydrogen peroxide molecule in the presence of transition metals such as copper and iron. It is the hydroxyl radical that is the most potent factor in the chain reaction formation of the polyunsaturated fatty acids (PUFA) peroxides.

Polyunsaturated Fatty Acids (PUFA)

Fatty acids in the body found in cellular membranes are especially susceptible to oxidative damage. Highly unsaturated fatty acids are more susceptible to oxidation than saturated fatty acids. Although saturated fatty acids are least susceptible to oxidation, they are more atherogenic. Saturated fatty acids affect the level of liver lipoprotein receptors which cause an elevation in plasma cholesterol. Evidence suggest that dietary oils containing a greater proportion of monounsaturated fats such as olive oil, may provide the best protection for lowering cholesterol and reducing susceptibility to lipid peroxidation at the same time. Polyunsaturated fatty acids commonly found in vegetable oil, such as safflower, sunflower, canola, and corn oil, are highly susceptible to lipid peroxidation. These polyunsaturated fatty acids, like free radicals, represent a paradox. Although they are essential building blocks for providing cellular elasticity and pliability, they

are easily broken down by free radicals. PUFA peroxides and their degradation products are toxic to living systems, especially the cardiovascular system. It has been suggested that PUFA peroxides play the major role in the aging of the eyes[27] and a significant role in the development of atherosclerosis.[28] As lipid peroxides destroy membrane integrity and decrease membrane flexibility and elasticity[29,30] they are implicated in the "response to injury" theory.

This theory has been advanced to postulate the presence of a chemical pathway responsible for the development of atherosclerosis. According to this theory, atherosclerosis is a patchy and "inflammatory" disorder involving the circulatory tree that has been subject to injury as a result of mechanical shear forces and localized chemical instability along tortuous arterial walls. These hemodynamic factors are believed to result in localized areas of endothelial cell injury dangerously increasing cellular permeability. The next step in this cascade is arterial platelet interaction and smooth muscle proliferation

Reactive oxygen species (ROS) in combination with polyunsaturated degradation products present in both serum and arterial wall lipid medium drive the inflammatory process that will initiate the concentration of toxic oxidation by-products in the subendothelial space. Lipid peroxidation and excessive free radical production disrupt plasma membrane integrity and permeability causing alteration of intracellular lipids.[31,32] This process, causing damage to the intima cells, has been suggested as the initial event in the pathogenesis of atherosclerosis.[28,33]

As the hydroxyl radicals initiate the breakdown of phospholipids in cellular and inner mitochondrial membranes, the viability of the cell is threatened.[34] The chemical modification by these free radicals result in an oxidized LDL which in contrast to native LDL, facilitates atherogenesis.[6,16,35-36]

Oxidized LDL as opposed to native, harmless unoxidized LDL is quickly picked up by endothelial cells and systemic monocytes and acts as a chemical attractant for other monocytes. By-products of such oxidized LDL are directly cytotoxic to endothelial cells resulting in a decreased level of endothelial cell releasing factor (EDRF), which is now believed to be nitric oxide.[6,37] Oxidized LDL in the presence of platelets can generate thromboxane (TxA_2). Thus, increased vascular tone and thrombogenesis are more readily activated.[6] Since one of the first reactions in the oxidative modification of LDL is the peroxidation of polyunsaturated acids,[36] it has been suggested that accumulation of LDL in macrophages is the process that drives the formation of foam cells, the key component of the fatty streak.[39] Therefore, it is the oxidation of LDL, which is now believed to be the focal pivotal step in the process of atherosclerosis.

LDL extracted from atherosclerotic lesions show biochemical and immunoreactive properties similar to those of in vitro oxidized LDL.[40] Investigators have presented evidence to suggest that autoantibodies present in oxidized LDL were predictive of pathological situations including myocardial infarction.[41] Thus, it appears that oxidized LDL induced by lipid peroxidation in the presence of autoantibodies to it not only begins the process of atherosclerosis, but also accelerates it. Therefore, it is logical to consider that the prevention of oxidation may retard the progression of atherosclerosis. In addition, the fact that antioxidant therapy slows the progress of early atherosclerotic lesions[42,43] does provide evidence that oxidized LDL does play the pivotal pathogenic role in the mechanism of atherosclerosis.

Strategies to Prevent Free Radical Damage: Antioxidants and Phytonutrients

There is overwhelming evidence that a diet rich in fruits, vegetables, and grains is protective against cardiovascular disease. This may be due to the antioxidants they contain and/or the many phytonutrients present. There have been numerous clinical studies including epidemiological, population, in vitro, animal, and case-control demonstrating the positive effect of targeted nutritional supplements on the cardiovascular system.

Preventing the oxidation of LDL may be the most powerful means of preventing cellular injury leading to atherosclerosis. Many of these studies present convincing evidence that dietary micronutrients with antioxidant properties such as alpha-tocopherol, beta-carotene, ascorbate, and coenzyme Q10 can prevent LDL oxidation and, hence, atherosclerosis.[44-47] Consider the research on vitamin E.

Alpha-tocopherol is the principal lipid-soluble, chain-breaking antioxidant in tissues and plasma. As the predominant antioxidant present in the LDL particle, it blocks the chain reaction of lipid peroxidation by scavenging intermediate peroxyl radicals.[48,49] The evidence that alpha-tocopherol blocks LDL oxidation has been shown in vitro when oxidation is mediated by transition pro-oxidant metals.[50,51] Vitamin E appears especially promising because it is carried directly in LDL particles. Reaven et al showed that long-term suppplementation with large doses of vitamin E alone, but not beta-carotene or vitamin C, increased LDL resistance to oxidative damage.[52] Vitamin E supplementation increased vitamin E levels in LDL by 2.5 fold and reduced lipid peroxidation in LDL by as much as 40%. Although several studies have shown that vitamin E will retard LDL oxidation, the dose required for maximum suppression of LDL oxidation has yet to be determined.

However, in a study by Jialal and others,[53] the investigators noted a relationship between dose-dependent plasma tocopherol level and susceptibility to LDL oxidation.

Their results led the researchers to conclude that the minimum dose of vitamin E needed to decrease susceptibility of LDL to oxidation was 400 IU. They noted no side effects at this level of supplementation or any adverse effect on plasma lipoprotein levels. Other large epidemiological and population studies conducted at the Harvard School of Public Health, have correlated significant reductions in cardiovascular disease with variable dosages of vitamin E supplements. In the Nurses Health Study involving a cohort of approximately 87,000 women, Stamfer reported a 41% reduction in risk of heart disease in nurses taking vitamin E for more than two years.[54] The authors concluded that the apparent benefit was primarily attributed to the use of vitamin E from supplements.

The average intake in the lowest risk group was 200 IU. However, in the Health Professions follow-up study involving almost 40,000 men, Rimm found that men who were taking vitamin E for more than two years had a 37% lower risk of heart disease compared to men who had not taken vitamin E.[55] The average vitamin E intake in the lowest risk group was 400 IU. Thus, in the male population, higher dosages of vitamin E may be required to retard LDL oxidation. In Jialal's study, 48 healthy men were investigated. It appears that in men, the optimal dose is probably 400 IU. However, in women, until a randomized placebo-controlled dose-response design study is performed (like Jialal's study in men), 200 IU of vitamin E should be considered the recommended dose.

There are several other lines of evidence to support the inverse relationship of plasma alpha-tocopherol and atherogenesis. For example, in a major European study of middle aged men, fatality from heart disease was strongly correlated with lowest levels of plasma vitamin E.[56] In another epidemiological study involving a cohort of 5,133 Finnish men and women initially free from coronary heart disease, the association between dietary intakes of vitamin C, vitamin E, carotenoids, and subsequent mortality was studied over a mean follow-up period of 14 years. A total of 244 cases of fatal coronary heart disease occurred during this time. There was a significant inverse relationship between dietary vitamin E intake and coronary heart disease mortality in both men and women. The relative risk of heart disease mortality was 32% lower for men and 65% lower for women in the highest tertile of vitamin E intake when compared to the lowest tertile. Women with both dietary vitamin E and carotenoid intakes in the highest tertile had an 84% lower adjusted relative risk of coronary heart disease mortality than women with both vitamin intakes in the lowest tertiles.[57] The clinical research suggests that vitamin E, whether incorporated in a diet or taken as a supplement, can have major implications on cardiovascular risk.

The direct association of antioxidant vitamin intake on the progression of coronary atherosclerotic lesions had not been explored until the June 1995 landmark study of Hodis and colleagues comparing supplementary vitamin E intake and the progression of coronary heart disease using quantitative coronary angiography as their method of evaluating atherosclerotic lesions

In a cohort of 156 men aged 40 to 59 years with a history of coronary artery bypass surgery, subjects given vitamin E intake of 100 IU per day or greater demonstrated less coronary artery lesion progression than their untreated counterparts. These results indicate an association between supplementary vitamin E intake and angiographically proven reduction in coronary artery lesion progression.[58]

Animal models have also demonstrated decreased atheroma formation when supplemented with vitamin E. In one randomized trial monkeys who were fed an atherogenic diet and given vitamin E supplementation had less atherosclerosis than those given placebo.[59] In another study hypercholesterolemic rabbits fed vitamin E had a 25% reduction in aortic atherosclerotic lesions.[60] Although we have to consider the limitation of applying the results of animal studies to humans, the fact remains that vitamin E shows great promise in preventing LDL oxidation, offering a tremendous impact on cardiovascular disease. The antioxidant activity in vitamin E and other dietary nutrients such as flavonoids and carotenoids (found in fresh fruits and vegetables) may help to explain the preventive benefit of some dietary factors in addition to fat intake in the epidemiological differences in coronary heart disease. Consider, for example, the 25-year follow-up of the seven-country study.[61]

In this study, serum cholesterol was linearly related to coronary heart disease mortality among various cultures. It is interesting to note that absolute coronary heart disease mortality rates and given cholesterol levels support the idea that indicators, other than serum cholesterol, are important in coronary heart disease prevention. The authors of the study indicate "it is not enough to focus solely on serum cholesterol levels to decrease the burden of coronary heart disease in populations." The authors revealed that dietary factors that influence LDL oxidation are of great importance. The Mediterranean and Japanese diets, not only low in saturated fat but rich in antioxidants, may explain the lower coronary heart disease mortality in comparison to other cultures. It is important to note that fresh fruits and vegetables contain not only valuable antioxidant vitamins, but considerable flavonoids, polyphenols, and carotenoids.

Consider that countries with a low fruit and vegetable intake, ie, Scotland, have a higher rate of cardiovascular disease than do countries with a high intake of fresh fruits

and vegetables such as Greece. Southern Europeans consume significantly greater amounts of fresh fruits and vegetables than do northern Europeans.

This high intake correlates with lowêr coronary heart disease incidence.[62,63] Similar findings were noted in France. However, the French diet includes high-fat cheeses, sauces, gravies, pâtés, and other highly saturated fats. This obviously represents a paradox. Why should the incidence of coronary heart disease be lower in the French population, especially when they consume so many foods with high saturated fats? Perhaps, the routine consumption of red wine and vegetables containing vital phytonutrients including tocopherols, carotenoids, flavonoids, phenols, catechins, quercetin, and others may affectively reduce peroxidative tendencies and retard the several interactions involved in arthrogenesis and thrombosis.[64]

In a subsequent study done in the Netherlands, the utilization of dietary bioflavonoids, phenolic acids, and flavonoids with specific ingestion of quercetin reduced the incidence of heart attack and sudden death. The end point of this study was mortality in a male population aged 64 to 85. The results indicate an inverse relationship between the amount of quercetin ingested and the death rate. Green tea, apples, and onions were the foods evaluated which contain generous quantities of quercetin similar to the quercetin found in the red grapes of aged wine.[65]

The effect of red wine and antioxidant activity in serum was addressed in a small study of volunteers drinking red wine.[66] The experiment showed that two glasses of red wine taken before a meal gave considerable antioxidant protection for at least four hours. Those volunteers not consuming red wine had much lower antioxidant activity in their serum. Thus, this small study shows that red wine, indeed, increases antioxidant activity via the flavonoid-polyphenol effect. Carotenoids, however, are an entirely different class of compounds.

Serum carotenoids have also been extensively studied in the prevention of coronary heart disease. Carotenoids are found predominantly in fresh fruits and vegetables with carrots the primary source of beta-carotene and tomatoes the best source for lycopene. Although lycopene has twice the antioxidant activity of beta-carotene, the latter has been the primary focus in studies. This may be due to the fact that beta-carotene has the potential to promote vitamin A synthesis. Research has correlated a high dietary intake of beta-carotene with a reduction in the incidence of cardiovascular disease.[67] Another study reported increased beta-carotene content of subcutaneous fat was also negatively correlated with risk of myocardial infarction.[68]

However, the recent Finnish trial on supplemental beta-carotene failed to show a reduction in lung cancer or cardiovascular disease among heavy smokers.[69] Thus, the enthusiasm for beta-carotene as the "magic bullet" for the prevention of cardiovascular disease has been dampened. However, the Finnish study had serious flaws and limitations in both product intervention and study design. In another investigation of 3,806 men with hyperlipidemia, participants with higher serum carotenoid levels had a decreased risk of coronary heart disease. This finding was also stronger among men who had never smoked.[70]

The Physician's Health Study, now in its final year, followed physicians between the ages of 45 and 80 with a history of a single heart attack or angina who were taking beta-carotene supplements. The results demonstrated a 50% reduction in subsequent coronary events over a five-year period.[71] It was also interesting to note that in this same study a small subset of 333 physicians, taking both beta-carotene and aspirin, did not have a single coronary event over a five year period. In another investigation, Gaziano et al showed the association between fresh fruits and vegetables high in beta-carotene content and subsequent cardiovascular mortality. In this prospective cohort of 1,299 elderly people in Massachusetts, the investigators showed a significant inverse relationship between beta-carotene score and cardiovascular death.[72]

Beta-carotene is not the only carotene with antioxidant activity. Other carotenes present having substantial concentrations in human plasma include alpha-carotene, lutein, lycopene, and beta-cryptoxanthin. There are approximately 600 carotenoids present in nature. Some, as mentioned, have greater antioxidant activity than others. In addition to the modification of LDL, carotenes may also have a favorable effect on prostaglandins.[73] Since beta-carotene represents only one quarter of the total serum carotenoid activity, perhaps there are other carotenoids capable of modifying both LDL oxidation and prostaglandins as well as offering unknown protective properties.

There is a variety of mechanisms providing defenses against free radical damage. Antioxidant vitamins can react in both the aqueous phase and lipid phase thereby protecting tissues against damage by trapping free radicals. Water-soluble vitamin C can quench singlet oxygen radicals. Beta-carotene is the most potent quencher of singlet oxygen and is most effective at low oxygen partial pressures.

Vitamin E is the primary lipid-soluble antioxidant capable of quenching the singlet oxygen radical and is effective at relatively higher oxygen partial pressures.[74] Because the oxidized form of vitamin E can be reduced by coenzyme Q10, the interplay between vitamin E regeneration is significantly improved by the addition of the vital nutrient—coenzyme Q10.

Coenzyme Q10 is another known antioxidant that may stabilize membrane activities as well as prevent the depletion of metabolites necessary for the resynthesis of ATP. Coenzyme Q10 has been demonstrated to scavenge free radicals, especially those produced by peroxidation.[7,75] The pretreatment of coenzyme Q10 in patients undergoing hypothermic cardioplegic arrest demonstrated an improvement in right and left ventricular myocardial ultrastructure.[76]

Other studies have demonstrated the effect of coenzyme Q10 on myocardial protection in coronary artery bypass surgery. These studies suggest that pretreatment with IV or oral coenzyme Q10 is effective in preventing left ventricular depression.[12,13] Perhaps the major impact of coenzyme Q10 is in congestive heart failure and dilated cardiomyopathy. Several studies[7,77-81] of coenzyme Q10 supplementation have demonstrated improvements in left ventricular function, ejection fraction, exercise tolerance, and diastolic dysfunction. Another important action of coenzyme Q10 is its synergistic action with selenium, another powerful antioxidant. In one study there was improved survival in patients taking a combination of selenium and coenzyme Q10 for one year following myocardial infarction. Out of 61 patients, there were six cardiac deaths in the control group (20%) and only one noncardiac death in the experimental group.[82]

The mineral selenium is crucial for the proper functioning of the heart. Selenium levels have been negatively correlated with atherosclerosis. In an observational study of approximately 1,000 men ages 55 to 74, low-serum selenium levels were more frequently associated with coronary heart disease, stroke, and claudication.[83] In another study, plasma selenium levels were measured in 126 hospitalized patients undergoing coronary arteriography for suspected coronary heart disease. The highest levels of selenium were seen in normal coronaries with the lowest levels noted in situations of triple vessel disease.[84] Selenium deficiency has also been reported in cardiomyopathy.[85] Perhaps the major biological importance of selenium, however, is the formation of glutathione peroxidase, the major natural endogenous antioxidant which neutralizes lipid peroxides and hydroperoxides. Selenium, in combination with vitamin C, is essential in the formation of glutathione peroxidase.

Vitamin C, a water-soluble antioxidant, not only regenerates tocopherol, but also enhances the body's total antioxidant system by raising levels of glutathione, a polypeptide amino acid and potent free radical scavenger. In a double blind study, experimental subjects were placed on 500 mg of ascorbate. Vitamin C increased red cell glutathione by 50%. The results of this study revealed that vitamin C in supplemental doses of 500 mg may help to maintain glutathione levels thus improving overall antioxidant status.[86] Although the evidence linking vitamin C to human cardiovascular disease is largely circumstantial, it is well known that many groups known to be at increased risk for cardiovascular disease have lower levels of vitamin C. An analysis of the literature indicates that those groups at risk for coronary heart disease such as men, the elderly, smokers, diabetics, hypertensives, and possibly oral estrogen contraceptive users, have lower plasma vitamin C levels.[87] The connection between vitamin C status and cardiovascular disease will need additional clinical research.

We also need to consider some of the data in the literature concerning the over-zealous use of vitamin C in patients who are prone to iron overload.[88-89] Such patients may accumulate harmful excess iron when given high-dose vitamin C supplements. However, this claim has been questioned by others.[90] Nevertheless, caution with vitamin C supplements should be utilized with patients definitely prone to iron overload such as individuals with genetic diseases, like hereditary hemochromatosis, thalassemia major, or other diseases that promote iron overload. It has been suggested that vitamin C supplements may, indeed, exacerbate iron toxicity, possibly by mobilizing iron reserves.

An overabundance of pro-oxidant metals such as iron and copper can initiate adverse free radical reactions in the body. Iron, copper, and other heavy metals such as lead, mercury, and cadmium can restrict the activities of sulfur and selenium-containing enzymes.[91] Thus, it is important to consider measures to minimize the accumulation of such metals in the body. For example, iron and copper supplements should not be taken unless recommended by the physician. Although iron is necessary for growing children, pregnant women, women athletes, and most menstruating young women, the use of iron in the male adult population should be avoided unless deemed medically necessary.

In summary, the heart is, indeed, the most susceptible of all the organs in the body to free radical oxidative stress. Free radical indices contribute to aging as well as degenerative disease such as cardiovascular pathology. Exogenous antioxidant defenses against this damage include ascorbate, tocopherol, carotenoids, flavonoids, and various other nutritional substances. At the present time, there are many controlled interventional trials with antioxidants that are being carried out world-wide. During the next several years, results from observational studies and randomized trials may permit specific public-health recommendations that go beyond the advice to eat a healthy diet of fresh fruits and vegetables.[92] It is important to counsel patients about dietary guidelines endorsed by the National Cancer Institute that suggest consuming between five and nine servings of fresh fruits and vegetables daily. Unfor-

tunately, fewer than 10% of Americans comply with these guidelines. Many people are, therefore, deficient in many vital nutrients rendering them sufficiently unprotected. Several clinical studies implicate that doses far greater than the RDA are necessary for protection against free radical oxidative stress. It is a simple and established fact that the prevention of premature coronary artery disease can be modified by a healthy lifestyle.

Primary prevention includes strategies such as maintaining ideal body weight and incorporating diets of fresh fruits and vegetables adequate in the essential nutrients designed to minimize damaging free radical reactions in the body. Measures should be taken to minimize the accumulation of toxic metals in the body such as iron and copper. Supplementing the diet with targeted nutritionals including antioxidants such as beta-carotene, vitamins C and E, coenzyme Q10, selenium, and other precious B vitamins is strongly recommended for promoting optimum health.[93,94]

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