



From the Desk of Dr. Stephen Sinatra

Alternative Medicine for the Conventional Cardiologist

Stephen T. Sinatra, M.D., F.A.C.C., F.A.C.N., C.N.S., C.B.T

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Today's cardiologist faces a daily dilemma concerning how best to refer patients for diagnostic procedures and how to select surgical and/or pharmaceutical interventions based on those test results. But the evaluations they order and the treatments they select may actually create unnecessary risks for the patients that are out of proportion to the benefits they experience. Continuing technological advances, although necessary, add to the complexity of the decision-making process. As increasing numbers of our patients are turning to alternative therapies, a paradigm shift is required in medicine to evaluate the efficacy of these therapies and effectively incorporate them into the conventional medical model. In this review, alternative treatment options are highlighted, with emphasis on understanding the psychoemotional component of heart disease and the use of modern "nutriceutical" agents. Accepting complementary therapies as equally judicious treatment interventions requires a shift in perspectives that may allow for more integrated care strategies for those who have been seeking a more expanded approach to heart disease.

Alternative medicine has become a striking presence and a persuasive attraction in our modern, orthodox medical system.¹ Somewhere in our reliance on "high-tech," conventional medicine, something has gone amiss. More and more of our patients are seeking out alternative practitioners. Who are they? Why has there been so much distrust of practitioners of conventional medicine by the people we are attempting to heal? What is driving even our most conservative, doctor-seeking patients to look to other forms of complementary healing? Obviously the medical consumer is searching for less invasive, safer, and lower cost medical interventions. Some of this comes out of necessity; managed care plans have driven our patients to put a lot more energy into seeking cost-effective medical service delivery as more of their healthcare dollars come out of their own pockets.

The trends are noteworthy. Consider that in 1990, 33% of the population spent 22% of their out-of-pocket dollars on alternative therapy, and that number is increasing.² In 1997 an estimated four out of ten adults included some form of alternative therapy, including herbal medicine, massage, and mega vitamins. Startling revelations have also

indicated that consumers made more visits to alternative medical practitioners, such as chiropractors, naturopaths, and massage therapists, than they did to primary care physicians: an estimated 629 million versus 386 million visits.³ And for 1998, the estimates were even higher.

Given these statistics, the public is clearly becoming more and more disenchanted with high-tech, conventional medicine. Because there is now a perceived availability of effective natural alternatives for the treatment of a wide range of cardiovascular disorders, including angina, arrhythmia, and congestive heart failure (CHF), many patients are questioning the need for potentially life-threatening drug and other invasive interventions that not only carry considerable morbidity but also mortality as well.

Any clinical cardiologist managing acutely ill patients on a day-to-day basis has been thankful for the life-saving pharmacologic medications, especially antiarrhythmic drugs, that are a crucial part of practicing conventional cardiology. However, as we are all so acutely aware, our greatest assets always simultaneously have the potential to be our Achilles heel. For example, many of us have most likely had to face a dreaded torsades de pointes, a type of ventricular tachycardia, on one or more occasion. I'm sure that there is no cardiologist prescribing antiarrhythmic medications on a daily basis who does not have a respectful sense of vigilance regarding the proarrhythmic side of these pharmacologic agents.

The 1994 statistics for the United States reinforce our concern: ranking fourth among the top ten causes of death were medications *properly* prescribed in a hospital setting.⁴ Following in ninth place was invasive heart treatment.⁵

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From the University of Connecticut School of Medicine, Farmington, Connecticut, and the Eastern Connecticut Health Network, Manchester, Connecticut.

Address correspondence to Stephen T. Sinatra, MD, Assistant Clinical Professor of Medicine, Director of Medical Education, 483 West Middle Turnpike, Manchester, CT 06040-3683.

Many of us have been deeply concerned by these alarming findings and have asked ourselves the rhetorical question, "How can I better protect my own patients from some of the risk that traditional medications present?"

Are there occasions when there actually are safer alternatives that have the same potential benefit to treat the symptoms or underlying disease process? And just like properly prescribed medications can have a dark side, the risk of acute interventions (angiography, angioplasty) and surgical revascularization can have serious implications, with unexpected morbidity and mortality.

This question has driven researchers to evaluate the outcomes of more conventional treatment protocols to determine when it is in the patient's best interest to follow an aggressive, sometimes invasive, intervention course and when a conservative strategy may be more efficacious. A brief review of the literature on outcome data for follow-up studies of invasive cardiology procedures reiterates that we have good reason to look at other possible approaches.

The VANQWISH trial⁶ explored just that issue and recently published their findings in the *New England Journal of Medicine*. They compared two groups of patients with non-Q wave myocardial infarction (MI), randomly assigning 920 patients to either invasive assessment or a conservative management plan. Their results confirmed that patients in the invasive group had increased mortality.

The results of the FRISC II trial,⁷ however, showed that for patients with intractable angina and objective electrocardiographic and biochemical markers of myocardial injury the preferred management was stabilization with aggressive antiischemic and antithrombotic treatment (with aspirin and preferably low molecular weight heparin), followed by a speedy invasive approach. These findings reinforce the need to determine which patients benefit from invasive procedures and which patients are better served with conservative management, a selection process we have been fine-tuning for decades. Although invasive evaluation for acute coronary syndromes appears to offer significant benefit to those deemed to be at the highest risk, what about assessment in patients with coronary artery disease (CAD) who are at less risk and whose condition is more stable?

Boden et al⁶ are not the first to challenge the routine use of angiography recommended by many cardiologists. Researchers followed 168 patients referred for cardiac catheterization for determination of native anatomy and possible angioplasty or revascularization. Outcome data revealed that 80% of patients did not warrant cardiac catheterization and could be evaluated successfully with other methods. The authors suggested that an estimated 50% of angiographic procedures are unnecessary. The study group experienced a rate of annual fatal heart attack of only 1.1% over a 5-year period. This rate is considerably lower than the mortality rate associated with coronary artery revascularization or angioplasty, indicating that more conservative follow-up is not associated with a higher mortality rate.⁸ Patients treated in the FRISC II trial had a mortality rate of

2.1% 30 days after coronary artery bypass surgery, versus 7.7% found in the VANQWISH participants.⁹

And what of another group of our patients, those who have significant lesions found on angiography? When should angioplasty or revascularization be performed? Are some patients better candidates than others? We know, for example, that revascularization is most helpful for patients with symptomatic angina who have compromised ejection fractions (in the 35% to 50% range).¹⁰ When evaluating the selection of patients for surgical interventions, however, only 56% of surgical procedures were performed for appropriate reasons. Researchers reported that approximately 30% of these procedures were performed for stable angina alone, and 14% should not have been performed in the first place.¹¹

The Coronary Artery Surgery Study (CASS)¹²⁻¹⁴ reported that the severity of blockage as confirmed by angiography alone is not directly proportional to the patient's risk of heart attack. Those with single, double, and even triple vessel disease did exceedingly well without surgery in the presence of normal ejection fractions. Regardless of the severity of the anatomic changes, each group had a similar rate of death (~1% per year).¹² The mortality rate for patients in whom revascularization is performed is much higher. Thus, once the invasive treatment protocol has been followed to angiography, surgical selection becomes a real dilemma.

In another investigation, patients with well preserved ventricular function who refused revascularization and had been given medical treatment had good long-term survival with remission of symptoms.¹⁵ In a 10-year follow-up of patients after coronary artery revascularization in Scotland,¹⁶ however, only 25% remained symptom free, 29% had recurrent anginal symptoms, 13% had repeat coronary artery bypass graft or angioplasty, and an alarming 33% died. The researchers stated that "the long-term benefits of coronary artery bypass surgery were disappointing."¹⁶ In addition, rates of complications from revascularization, such as MI, infection, and central nervous system dysfunction, also were disturbing. For example, central nervous system disorders were observed in an alarming 61% of patients 6 months after coronary artery bypass surgery.¹⁷ Considering surgical mortality, morbidity, cost of the procedure, and lack of long-term survival benefits, patients for whom this surgery has been recommended are pursuing more second opinions to validate the need for these operations. They are also looking for less risky and invasive alternatives.

Clearly, when medical therapy has failed to correct a patient's symptoms, consideration of surgical intervention to improve quality of life and possibly enhance longevity is a mindful approach. Unfortunately, however, in our firm belief in the benefits of technological advances, many surgical operations are performed on the basis of anatomic findings alone.¹¹

The new push to practice integrative medicine (the use of complementary methods as adjuncts to traditional medicine) is supported by clear research findings. The evidence

is accumulating and confirming the safety and efficacy of integrating such mind-body and nutritional strategies in specific clinical situations.

THE PHILOSOPHICAL DILEMMA

Most cardiologists would agree that simple dietary and lifestyle changes can significantly reduce the risk of cardiovascular disease. Many of these same well trained, conventional cardiologists, however, have been resistant to recommend or even learn more about new nutritional and metabolic modalities despite published data in the peer-reviewed literature indicating that these adjunctive therapies support established conventional treatments for heart disease. For example, we all know cardiologists who themselves have taken vitamin E for years but often will not advise their patients to do the same. Other physicians have been outwardly negative, discouraging their patients from "wasting money on supplements," and many even tell their patients that there are "no published data" on the nutritional supplements that they inquire about.

On rare but significant occasions, I have even known of peers who have refused to treat a patient if they continue to use alternative therapy, or who have dismissed them outright for doing so. Is it any wonder then that many even longtime patients do not advise us if they are seeing an alternative practitioner or using a different modality, such as nutritional supports, for fear of reprisals or rejections? You may be totally unaware of how many people in your own practice are already using complementary approaches without your knowledge.

Rather than dismiss their entreaties for guidance or refuse to prescribe for them out of fear of potential drug interactions, it behooves us to understand the range of complementary therapies available and when they can be safely integrated into medical practice. Only then can we truly help our clients "come out of the closet," so to speak, so that we might be more involved in and safely supervise their overall care in an atmosphere of open communication. For example, consider patients being prescribed coumadin who are also taking unprescribed natural blood thinners such as garlic, ginger, fish oil, ginkgo biloba, and even excessive amounts of vitamin E at the same time. Such a combination is clearly a potential risk for both patient and physician!

Perhaps there is no greater time than now to seriously question our own attitudes and beliefs, taking the risk to explore any negative bias we may still have toward some of these alternative approaches that were never a part of our practical training. Educating ourselves is the first step. The first shift is already happening in the education of undergraduate physicians and established ones.

A 1998 report demonstrated that 64% of American medical schools offered elective courses in alternative medicine.¹⁸ In the December 17, 1997 issue of the *Journal of the American Medical Association (JAMA)*¹⁹ the editors made a call for papers on complementary, alternative, unconventional, and integrative medicine. They also reported that their physician readers identified alternative medicine as the

seventh of 73 most important topics for publication in the Journal. A subsequent analysis showed that increasing numbers of medical professionals are accepting alternative medicine.²⁰

One of the major obstacles to evaluating the benefits of any alternative therapeutic interventions, however, has been related to the claim that there is a lack of scientific data on the subject. Although most conventional wisdom is subject to the current gold standard of evidence-based scientific-controlled studies, more and more alternative therapies are demonstrating these rigorous standards of controlled analysis.

For example, in a previous communication in this journal, the benefits of L-carnitine in a wide variety of cardiovascular diseases were discussed, including the evidence supported by controlled trials.²¹ Also of significance is the fact that the United States National Institute of Health (NIH) responded to public demand, creating an Office of Alternative Medicine Department in 1992. Congress appropriated \$50 million in the fiscal year 1998 for the study of complementary and alternative medicine, emphasizing the need to seriously investigate these other modalities in healing.²² Failing to keep up with the transition toward this paradigm shift in medicine may place some orthodox physicians in a position of vulnerability.

Perhaps for the cardiologist, the two major areas in which the scientific evidence is most strikingly significant are the effects of psychological stress on the heart, and the use of targeted nutritional supports for the cardiovascular system. A brief analysis of each is presented below.

MIND-BODY MEDICINE

Most cardiologists accept the growing body of compelling scientific evidence demonstrating the link between chronic emotional stress and heart disease. We know that statistics show that 50% of cases of heart disease cannot be explained by the standard risk factor analysis, including parameters such as high cholesterol, smoking, or sedentary lifestyle.²³ Cardiovascular research suggests that chronic stress may potentiate underlying structural heart disease and that acute psychological situations may actually precipitate unexpected cardiac events.²⁴ One group of researchers described the high levels of anxiety, depression, and sleep deprivation found in cardiac patients.²⁵ Other investigators have reported the high incidence of MI and sudden cardiac death found in patients with acute psychological stress superimposed on a background of underlying depression.²⁶ The recent research findings on the correlation between states of high arousal and cardiac sequelae are too alarming to ignore.

In one study of cardiac patients conducted at the Mayo Clinic, acute psychological stress was the single strongest predictor of future cardiac events, including heart attack, cardiac arrest, and sudden cardiac death.²⁷ Other investigators have reported that men acknowledging having states of high anxiety were as much as six times more likely to experience sudden cardiac death than those who were described as calmer and more in touch with their emotions.²⁸

A Harvard Medical School study of 1,623 heart attack survivors documented that when patients got angry during emotional conflicts, their risk of subsequent MI was more than double that of those who remained tranquil.²⁹

Anger can be an Achilles heel for the cardiovascular system.³⁰ Although some of the evidence is more anecdotal, the recognition of the powerful connection between the mind and the body is not. There are even personal excerpts from historical figures attesting to the dilemma thrust on them by their emotions. For instance, the well known anatomist John Hunter died suddenly during a heated argument after having written that "my life is in the hands of any rascal that cares to annoy or tease me."³⁰

We also have had the opportunity to report a case in which a middle-aged man developed a Type I aortic dissection in a self-reported "fit of rage."³¹ The effects of emotional stress on the heart also have been reported in the literature for those who are lonely, socially isolated, and lacking in social support, all of which correlate with an increased mortality rate after MI.³² In a recent study of heart attack survivors, researchers observed that the quality of interpersonal relationships after MI was a prognostic predictor as significant as disease severity.³³ Unresolved grief also has been linked to a higher risk of cardiac events.³⁴

The literature on heart disease and psychological factors also has its roots in the study of personality traits, behavior, and cardiac risk. Although most cardiologists are familiar with and accepting of the findings of early researchers such as Ray Rosenman, Meyer Friedman, et al,^{35,36} who identified compulsive traits and driven "type A" behaviors as cardiac risk factors, some are skeptical about the possible roots of this personality trait as a compensation for a lack of unconditional love in childhood. For many of our cardiac patients, the expression of controlling, aggressive, and narcissistic behavior may represent a defense mechanism to protect the vulnerability of a wounded heart.³⁷

Understanding and treating heart disease requires that the modern day cardiologist understand and include underlying mind-body relationships to better treat the whole person. We have data to prove that this approach can be successful. For example, participation in a cardiac rehabilitation program has been associated with considerable improvements in well being, quality of life, and mortality, particularly when targeted psychotherapeutic interventions have been program components.³⁸ Many of these programs not only assessed and addressed behavioral and psychosocial needs, but also included dietary and nutritional modifications with the basic exercise focus.

The anxious cardiac patient is fairly easy to recognize in an office visit. Many cardiologists will prescribe anxiolytic agents for them, and antidepressants for those in whom depression is more obvious. It is important to remember, however, that depression is oftentimes underreported to physicians, especially by men, who may see depression as a sign of weakness. Therefore, obtaining a careful history is still imperative for eliciting psychological concerns.

An alternative approach is to include a diet rich in proteins and essential fatty acids to support brain function and to consider herbs, such as St. John's Wort, to treat milder cases of depression and referring patients to psychotherapists for follow-up evaluation. Body-oriented psychotherapies, such as bioenergetic therapy,³⁹ can be extremely helpful for patients to learn methods in which to assuage emotional behaviors that increase their risk for cardiac illnesses.

Patients who are socially isolated and/or lacking in physical contact, such as the widowed or those caring for chronically ill spouses, can benefit from massage and other forms of body work. There is evidence of central nervous system down-regulation as a result of interventions such as relaxation, imagery, meditation, prayer, blood pressure lowering, and even premature ventricular contraction suppression.⁴⁰

Cardiologists need to find and network with well credentialed alternative practitioners in their area and make appropriate referrals to them. Problem-solving actions, such as asking patients about personal issues and emotional conflicts, and collaborating with complementary therapists, often are interpreted as caring gestures by patients, reinforcing their confidence in the doctor-patient relationship. We must also consider that psychological stress is a major contributor to the release of hormones, such as catecholamines and cortisol.

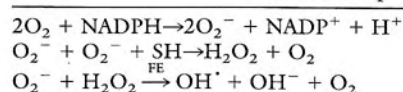
Acute psychological arousal and states of vigilance increase sympathetic activity, promoting the discharge of catecholamines and cortisol, which results in an excessive free radical metabolic load that can lead to arterial damage and facilitate malignant cardiac arrhythmia.⁴¹ It is important that the cardiologist recognize the multiple situations in which free radical mediated reactions exacerbate the atherosclerotic process, and how to employ antioxidant and phytonutrient support to help neutralize this dangerous process.⁴² Although some of the early research into many complementary interventions has been either anecdotal or fraught with extraneous variables, clinical trials on supplements have been designed in the same scientific fashion as those for pharmacologic agents, and the data are impressive.

THE RATIONALE FOR TARGETED NUTRITIONAL SUPPLEMENTS FOR CARDIOVASCULAR HEALTH

The heart is one of the most susceptible of all organs to free radical oxidative stress and premature aging. Fortunately, it is also highly responsive to the benefits of targeted nutritional agents, such as phytonutrients, antioxidants, and nutraceuticals.

The term "nutraceutical" includes a wide variety of non-prescription nutritional supplements normally found in the body or natural sources (such as vitamins, amino acids, and herbals). We now have strong scientific evidence from large and repeated clinical trials that have confirmed their efficacy and safety, and guidelines for patient selection, dosage, and potential medication interactions.⁴³ To best understand why targeted nutritional supports, such as basic antioxidants, are appropriate in cardiology situations, a familiarity

TABLE 1
Free radical species



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with the effects of free radicals, oxidative stress, and oxidized low-density lipoprotein (LDL) is essential.⁴⁴

Free Radicals

Although oxygen is necessary for aerobic life, the metabolism of oxygen and its byproducts can have ominous metabolic consequences. Free radicals, the normal byproducts of oxidative metabolism, have been implicated as culprits in the pathogenesis of many degenerative diseases, especially vascular disease. Although abundant clinical research has documented that free radical oxidative stress plays a significant role in supporting life processes such as mitochondrial respiration,⁴⁵ platelet activation,⁴⁶ leukocyte-phagocytosis,⁴⁷ and prostaglandin synthesis,⁴⁸ these volatile, unstable, and highly charged electrons also have been identified as a source of extensive damage to lipid membranes, organelles, and even DNA itself.

A free radical is a molecule with an odd number of electrons. Stable compounds such as oxygen contain paired electrons, one in each of two different orbitals. Because the oxygen molecule has room for two more electrons (one for each orbital that already contains one electron), it can remove a total of two electrons from other substances. This is what oxidation is: the removal of two electrons from a molecule, which then become attached to the O_2 molecule.

The mitochondrial membrane reduces oxygen to water by addition of a sequential transfer of four electrons. This involves a mechanism in which the oxygen molecule undergoes reduction, gaining electrons and subsequently forming new species that have high chemical reactivity.⁴⁹ These new species are not always radicals themselves, but once they have accumulated more electrons, they need to get rid of them. This sets up a chain reaction of electron transfers. 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 a molecule that results from oxygen gaining one electron. It can be very toxic if it is not handled properly by the body. Hydrogen peroxide (H_2O_2) can be generated by the interaction of two superoxide anions or by another additional electron added to the superoxide. A reaction between the superoxide anion and the hydrogen peroxide leads to the formation of the relentless and most damaging hydroxyl radical, $\text{OH}^\cdot$ (Table 1).⁵⁰ This highly reactive hydroxyl radical sets off toxic free radical chain reactions.

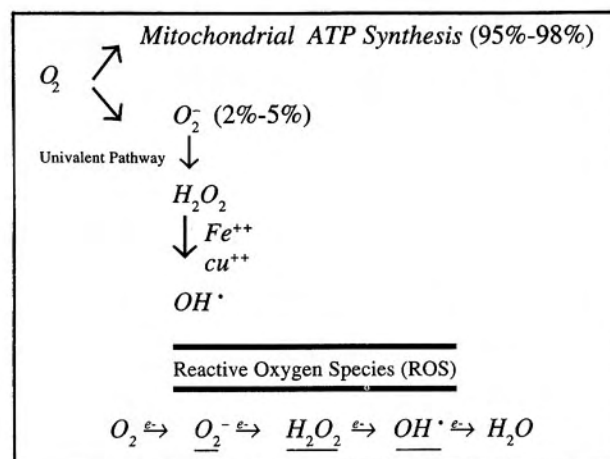


Figure 1. Univalent pathway/electron transfer in mitochondrial chain. Reproduced with permission from Sinatra and DeMarco.⁴⁴

Under normal conditions, 95% to 98% or more of the molecular oxygen consumed by cells is reduced to water by the addition of four electrons (and four protons, H^+). The remaining 2% to 5%, however, are reduced by a univalent pathway, giving rise to reactive free radicals that can become toxic to cells (Figure 1). Obviously, we need some form of protection from these processes.

Antioxidant Defense Mechanisms

Antioxidants are molecules that react with free radicals to make them less toxic. Antioxidants act like friendly guardians or bodyguards, neutralizing free radicals before they can do damage. The aim is not to halt the important process of oxidation in the mitochondria that produces energy, but to minimize the negative impact of the resulting free radicals. The integrity of every cell in the body depends on the balance of free radicals and antioxidants. Biologic antioxidants can be single nutrients, such as coenzyme Q10, vitamin E, or vitamin C, or they can be elaborate enzyme systems.

Classification of Antioxidant Defenses

The body has many types of defense systems set up to eliminate free radicals. Were it 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 function. Most of these systems deactivate free radicals by generating safer molecules via chemical reactions. The major antioxidant enzymes that can do this are superoxide dismutase, catalase, and glutathione peroxidase.

Superoxide dismutase converts superoxide (the toxic oxygen molecule) to hydrogen peroxide and water. Two different forms of superoxide dismutase are found in the body: one in the mitochondria, which requires manganese for proper functioning, and the other in the cellular fluid (cytosol). But the hydrogen peroxide generated from superoxide dismutase can be toxic to our cells too, so another enzyme called catalase safely converts hydrogen peroxide to water and oxygen. Ultimately, it is these two key en-

TABLE 2

Sources of free radicals and antioxidant defenses

Sources of Free Radicals	Antioxidant Defenses
Inflammation	Vitamin E
Cigarette smoke	Vitamin C
Exercise	β -Carotene
Air pollutants	Other carotenoids
Radiation	Ubiquinol (CoEnzyme Q10)
High PUFA diet	Superoxide dismutases
Ischemia/reperfusion	Catalase
Carcinogens	GSH peroxidases
Adriamycin	Selenium
Acetaminophen	Uric Acid

Adapted with revision from Machlin LJ. Implications for the Biomedical Field. In, Williams GM (ed): *Antioxidants: Chemical, Physiological, Nutritional and Toxicological Aspects*. Princeton, NJ: Princeton Scientific Publishing Co., 1992:383-387.

zymes, superoxide dismutase and catalase, that assist in elimination of the toxic ROS formed in the mitochondria during respiration.

If the hydrogen peroxide generated by superoxide dismutase is not immediately detoxified by catalase, however, the more destructive hydroxyl radical may be formed. This often occurs if minerals, such as iron or copper, are in the vicinity of the hydrogen peroxide. The presence of these metals can cause the peroxide to yield the hydroxyl radical through a chemical reaction discovered by Fenton (Figure 1). Interestingly, we have yet to identify the specific system in our body that detoxifies the hydroxyl radical.

Glutathione peroxidase helps eliminate the free radicals that form on lipid membranes from ROS. These types of radicals are called lipid hydroperoxides. Glutathione peroxidase also can reduce other peroxides, such as hydrogen peroxide. Selenium, another antioxidant mineral, is incorporated into glutathione peroxidase, only acting as an antioxidant after incorporation into the enzyme.

The available concentration of antioxidants, vitamins, and minerals requires a complicated balance. Because many endogenous antioxidant enzymes are produced through elaborate biochemical processes, it is difficult to relate simple nutrient intake to direct antioxidant usefulness. There is a growing body of evidence to suggest that those whose lifestyles render them susceptible to low vitamin and mineral intake, excessive oxidative damage from cigarette smoking, environmental toxins, excessive radiation, insecticides, chemicals, carcinogens, etc., or pharmacologic drugs that interfere with endogenous nutrient production are compromised by physiologic abnormalities. Benefits can be derived from supplementation with key metabolic intermediates, such as coenzyme Q10, carotenoids, flavonoids, minerals, vitamin E, vitamin C, magnesium, and others (Table 2).⁵¹ The implications for the cardiologist range from primary and secondary prevention to acute intervention.

For example, consider the extraordinary free radical activity in the heart that occurs during reperfusion/ischemia, which creates widespread damage to cells, basement membranes, mitochondria, and even DNA itself. Sudden bursts of ROS, under abnormal conditions, undergo inadequate

TABLE 3

Myocardial ischemia/reperfusion formation of super oxide radicals

Ischemia $\rightarrow$ Xanthine Dehydrogenase $\rightarrow$ Xanthine Oxidase
 ATP $\xrightarrow{\text{Catabolism}}$ Hypoxanthine
 Reperfusion $\rightarrow$ O₂ + Hypoxanthine + Xanthine Oxidase $\rightarrow$ 2O₂⁻

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detoxification by natural endogenous enzyme defense systems, resulting in cellular injury. The injurious reperfusion oxidative stress after myocardial ischemia can occur during MI, thrombolytic therapy, and coronary artery bypass surgery.⁵²

During revascularization, there is a period of cross-clamping that reduces vital oxygenation to the heart. With reperfusion (unclamping), highly oxygenated blood reenters the previously ischemic area, inducing additional free radical stress, causing a firestorm of free radicals and resulting in considerable damage to cellular tissues.⁵² A similar mechanism occurs during the episodic ischemia of an evolving acute MI and clot lysis by thrombolytic therapy. There are several potential sources of oxygen-derived free radicals in ischemic tissue.

The most crucial and best studied source is endothelial-derived xanthine oxidase, a tissue dehydrogenase that cannot reduce molecular oxygen. During ischemia, however, xanthine dehydrogenase in endothelial cells is converted to xanthine oxidase. Adenosine triphosphate (ATP) is broken down to hypoxanthine. During postischemic reperfusion, an increased flow of oxygen combines with hypoxanthine in the presence of xanthine oxidase, generating an enormous release of superoxide anions and other free radicals that cause widespread lipid peroxidation and subsequent damage to cellular membranes (Table 3).

Such reperfusion injury has been extensively studied in animal models. Pretreatment of animals with free radical scavengers, such as vitamin E,⁵³ superoxide dismutase, and catalase, has been shown to protect left ventricular function after ischemia.^{54,55} In the human model, pretreatment with coenzyme Q10 (an antioxidant, membrane stabilizer, free radical scavenger) was effective in preserving left ventricular function for revascularization patients during weaning from cardiopulmonary bypass pump.^{56,57} Surgical patients about to undergo hypothermic cardioplegic arrest receiving pretreatment with coenzyme Q10 demonstrated an improvement in right- and left-sided myocardial ultrastructures.⁵⁸

Because cardiac cells may be the most vulnerable of all tissues to oxidative stress, research is underway to evaluate preservation of left ventricular function and limitation of infarct size in situations of acute myocardial ischemia and reperfusion by neutralization of ROS. For example, in one randomized double-blind, placebo-controlled trial, the effects of 2 g of L-carnitine were compared with placebo in 101 patients with suspected heart attack. The treatment period lasted 4 weeks. At the end of the 28-day protocol, the area of tissue damage was assessed. Infarct size was

found to be significantly reduced in the carnitine group compared with the matched control group.⁵⁹ Similar protective findings, including a reduction in cardiac death and nonfatal infarction, were reported by the same group of investigators with the use of coenzyme Q10 in patients with acute MI.⁶⁰

COENZYME Q10

Coenzyme Q10, a vitamin-like nutrient native to the inner mitochondrial membrane, is vital for oxidative phosphorylation. Q10 acts like an antioxidant, stabilizing membrane activity and preventing depletion of the metabolites necessary for the resynthesis of ATP. As an antioxidant, the reduced form of coenzyme Q10 inhibits lipid peroxidation in both cellular membranes and serum LDL, and also protects DNA from oxidative stress.

The awareness of the effectiveness of coenzyme Q10 in clinical cardiology is increasing, and its biochemistry and clinical applications are now discussed in mainstream cardiology textbooks.⁶¹ As of the writing of this commentary, there have been 39 controlled trials on the clinical effect of coenzyme Q10 and cardiovascular disease, with 36 trials showing benefit and three showing no significant response.^{60,62-99} In the three trials demonstrating no efficacy, flaws in the study design are worthy of mention.

Serum levels of coenzyme Q10 were not determined in one study,⁸³ the duration of another was only 12 hours,⁹⁵ and the third group of researchers used subtherapeutic doses (100 mg daily) for only 12 weeks.⁹⁷ Blood levels were only two times above normal in the latter study.

Because heart biopsy specimens taken from patients with chronic CHF have shown decreased ATP concentrations and an impaired myocardial contractility, serious defects in the metabolism of myocytes are now believed to be present in patients with chronic CHF.¹⁰⁰ Improvement in quality of life for these patients can be accomplished by promoting ATP production, which helps to enhance the bioenergetics of the cell.

Bioenergetics is the study of energy transformation in living organisms, and in biochemical terms, it is referred to as cellular energy. Every cell must have a way of obtaining energy. Coenzyme Q10 acts as an essential component of the electron transport chain that involves a series of redox reactions within the oxidative phosphorylation pathways in which ATP is formed.⁶¹ Because CHF is literally an energy-starved heart, the role of coenzyme Q10 in replenishing ATP to exhausted heart cells is a logical treatment, especially within 2 years of its presentation. When higher blood levels of coenzyme Q10 are achieved (4 to 7 times normal or as high as 3.5 $\mu\text{g/mL}$) a substantial improvement is found in these patients.¹⁰¹ For patients who do not show clinical improvement at these blood levels, the addition of L-carnitine at daily doses of 2 to 4 g often offers a synergistic effect that reduces symptomatology and enhances quality of life for nonresponders. In addition to the proper dosage of coenzyme Q10, the bioavailability of the compound is yet another crucial issue for adequate absorption.¹⁰²

A recent outstanding clinical overview of the use of coenzyme Q10 in cardiovascular disease was reported by car-

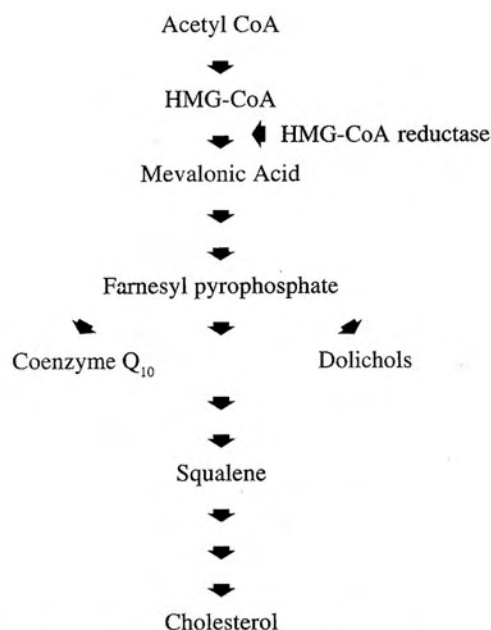


Figure 2. Biosynthetic pathway of cholesterol. Reproduced with permission from Sinatra ST. CoEnzyme Q10: a vital therapeutic nutrient for the heart with special application in congestive heart failure (*Conn Med* 1997;61:707-711).

diologist Peter Langsjoen and microbiologist Alena Langsjoen in *Biofactors*,¹⁰³ who reviewed 34 controlled trials. The authors concluded that coenzyme Q10 is a “deceptively simple molecule that lies at the center of mitochondrial ATP production and appears to have clinically relevant antioxidant properties manifested by tissue protection in the setting of ischemia and reperfusion.”¹⁰³ The results of a controlled study of patients with acute MI confirm this conclusion.⁶⁰ When should the conventional cardiologist consider using coenzyme Q10?

Given its utility in patients with angina,^{66,69,73,74,81} patients with CHF,^{68,70,71,79,80,84,91,94} myocardial preservation in heart surgery,^{65,75,85,90,93,96} and after acute MI,^{60,89} coenzyme Q10 should be at least considered for any patient with these conditions who has an unsatisfactory quality of life despite conventional medical treatment. In addition, anyone receiving a statin drug needs to take a coenzyme Q10 supplement to prevent deficiencies.^{81,88} Statins, powerful cholesterol killers, also block the metabolism of coenzyme Q10, which is generated through the same pathway (Figure 2).

Another crucial role of coenzyme Q10 in the prevention of cardiovascular disease is its ability to recycle the oxidized form of vitamin E back to its reduced form. Vitamin E regeneration is significantly improved by the addition of coenzyme Q10. Coenzyme Q10 also prevents the prooxidant effect of alpha tocopherol and increases resistance to LDL oxidation.¹⁰⁴

Preventing the oxidation of LDL may be one of the most powerful interventions to prevent the endothelial cell injury that lays the foundation for atherosclerosis. Many studies report convincing evidence that dietary micronutrient supplementation with antioxidants such as alpha tocopherol, ascorbate, and coenzyme Q10 can additionally

prevent LDL oxidation, perhaps the pivotal precursor to the atherosclerotic process. Consider the research on vitamin E, which are discussed below.

VITAMIN E

Alpha tocopherol is the key lipid-soluble, chain-breaking antioxidant found in tissues and plasma. As the predominant antioxidant present in the LDL particle, it blocks the chain reaction of lipid peroxidation by scavenging intermediate peroxy radicals.^{105,106} Research has shown that vitamin E supplementation can reduce lipid peroxidation in LDL by as much as 40%.¹⁰⁷ Results of several major studies have clearly demonstrated the cardioprotective effects of supplemental intake of vitamin E.

In the Nurses Health Study,¹⁰⁸ which involved a cohort of approximately 87,000 women, Stampfer et al reported a 41% reduction in the risk of heart disease in nurses taking vitamin E for more than 2 years. The average intake in the lowest risk group was 200 units.

In the Health Professional's follow-up study,¹⁰⁹ which involved almost 40,000 men, Rimm et al found that men taking vitamin E for more than 2 years had a 37% lower risk of heart disease compared with men who had not taken vitamin E. The average vitamin E intake in the lowest risk group was 400 units. In another investigation,¹¹⁰ men who took 100 units or more of vitamin E per day demonstrated less progression of coronary artery lesions than their untreated counterparts. In this study of 156 men 40 to 59 years with a history of coronary artery bypass surgery, supplemental vitamin E intake was associated with angiographically proven reduction in progression of coronary artery lesions.¹¹⁰

In the Cambridge Heart Antioxidant Study (CHAOS),¹¹¹ patients with atherosclerosis who received 400 to 800 units of vitamin E daily appreciated a 77% decrease in the relative risk of nonfatal MI; however, there was no difference in mortality overall. Although the CHAOS trial was a prospective, randomized trial, the findings have yet to be reproduced.

Other prospective randomized trials¹¹² in which low doses of vitamin E, i.e., 50 units per day, were administered showed no difference in recurrence of progression of angina or major coronary events. In fact, in one investigation of patients with a history of MI, mortality was higher when vitamin E was combined with beta carotene.¹¹³ In the last of these studies with negative findings, low-dose synthetic vitamin E was administered to cigarette smokers. It is plausible that 50 mg of vitamin E may be too low a dose to be clinically significant, especially in high-risk populations such as smokers.¹¹⁴ It is also important to keep in mind that the oxidative modification of LDL cholesterol is a hypothesis and has yet to be proven,¹¹⁵ which raises the question of whether or not cardiologists should routinely recommend vitamin E to their patients.

Considering the many longitudinal epidemiologic studies and prospective randomized trials in which vitamin E consumption was associated with decreased cardiac risk, it is probably safe to say that vitamin E supplementation

should be considered for those individuals at risk for CAD or with documented CAD.

It is not unreasonable to consider a minimum of 100 IU of vitamin E daily as a supplement. For patients with documented CAD, a minimum dose of 200 to 400 IU per day is suggested. Whenever considering vitamin E supplements, gamma tocopherol should be included in the basic formula. Alpha tocopherol in the absence of a gamma tocopherol may be ineffective in inhibiting the oxidative damage caused by the reactive peroxynitrite radicals.¹¹⁶ Gamma tocopherol also can be obtained via diet, in the form of healthy nuts such as almonds, sunflower seeds, wheat germ, and wheat germ oil. Vitamin E (alpha tocopherol) and mixed tocopherols, including tocotrienols, may be the best combination of tocopherol biochemistry, which may play an even greater role in the oxidation of LDL.¹¹⁷

Recent data indicate that plasma levels of antioxidants are a more sensitive predictor of unstable angina than severity of atherosclerosis.¹¹⁸ The fact that free radical activity has been noted to influence the degree of coronary ischemia and spasm¹¹⁹ suggests that the beneficial effects of antioxidants in patients with CAD may result in part from a favorable influence on vascular reactivity, rather than a reduction in atherosclerotic plaque. Results of randomized double-blind, placebo-controlled clinical trials also have indicated that vitamins E and C can prevent nitrate intolerance,^{120,121} a major problem for patients who require long-term treatment with high-dose oral nitrates for relief of symptoms.

Investigational research suggests that nitrate intolerance is associated with increased vascular production of superoxides.¹²² When nitric oxide is released from administration of nitroglycerin, it reacts with superoxide anions, resulting in lower levels of cyclic guanosine monophosphate, an important intracellular intermediary that promotes vasorelaxation. There are key vitamins that warrant attention for the prevention of nitrate intolerance, including vitamin E, the main lipid phase antioxidant, and vitamin C, the main aqueous phase antioxidant. Supplementation with these nutrients boosts the free radical scavenging ability of the superoxide radical, promoting the prevention of nitrate intolerance. As the primary aqueous antioxidant, vitamin C—the major antioxidant in the aqueous phase—acts as the first line of defence against oxidative stress.

VITAMIN C

Vitamin C is not only a scavenger antioxidant, but also acts synergistically with vitamin E to reduce the peroxy radical. The synergistic relationship between vitamin E and vitamin C also has been documented in clinical research.¹²³

In addition to blocking lipid peroxidation by trapping peroxy radicals in the aqueous phase, vitamin C helps normalize endothelial vasodilative function in patients with heart failure by increasing the availability of nitric oxide.¹²⁴ Although the evidence linking vitamin C to human cardiovascular disease is still being evaluated, one study did report that vitamin C slowed the progression of atherosclerosis in men and women older than 55 years.¹²⁵ It is also well

known that many groups known to be at an increased risk for CAD have lower levels of vitamin C, such as men, the elderly, smokers, patients with diabetes, patients with hypertension, and possibly women taking oral estrogen contraceptives.¹²⁶ Because improved endothelial function has been observed with administration of vitamin C in patients with hypertension, hypercholesterolemia, and diabetes mellitus, vitamin C supplementation appears warranted.¹²⁷ We must also keep in mind the fact that at doses of 500 mg, vitamin C was able to increase red cell glutathione by 50%.¹²⁸ Glutathione is not only the major antioxidant responsible for inhibiting lipid peroxidation but is also a key contributing factor in stabilizing immune function.

We must avoid being overzealous, however, when prescribing supplementation for patients who are vulnerable to iron overload states.^{129,130} Such patients may accumulate harmful excess iron with higher doses of vitamin C, so caution must be employed for those with genetic diseases such as hereditary hemochromatosis, thalassemia major, or other diseases that promote iron overload. It has been suggested that vitamin C supplements may exacerbate iron toxicity by mobilizing iron reserves. Should cardiologists routinely recommend vitamin C supplementation to their patients?

Because several large-scale epidemiologic studies have observed that higher antioxidant levels limit the expression of CAD, the risk–benefit ratio argument suggests that it is not unreasonable to consider vitamin C supplementation. In the absence of relative contraindications for vitamin C, a dose range of 200 to 300 mg appears to impose negligible risks for the patient. When vitamin C is combined with dietary antioxidants such as vitamin E and beta carotene, a lower risk of CAD and greater life expectancy may be realized.¹³¹

CAROTENOIDS

Serum carotenoids have been extensively studied in the prevention of coronary heart disease. There are approximately 600 carotenoids found in nature, predominantly in fresh fruits and vegetables, with carrots being the primary source of beta carotene and tomatoes being the best source of lycopene. Although lycopene has twice the antioxidant activity of beta carotene, the latter has been the primary focus of study because of its activity as a precursor of vitamin A.

Research has associated a high dietary intake of beta carotene with a reduction in the incidence of cardiovascular disease.¹³² One study reported that increased beta carotene stores in subcutaneous fat were correlated with a decreased risk of MI.¹³³ However, more recent controlled studies have found that excessive supplemental beta carotene failed to lead to a reduction in rates of lung cancer or cardiovascular disease among heavy smokers.¹³⁴ An increased incidence of lung cancer was found in the beta carotene and retinol efficacy trial,¹³⁵ halting the study 21 months early when this alarming cancer incidence was observed among smokers and workers exposed to asbestos. Similarly, after the Physician's Health Trial¹³⁶ demonstrated that alter-

nate-day administration of 50 mg of beta carotene for 12 years showed no positive effects on coronary heart disease events, the enthusiasm for beta carotene as a magic bullet for prevention of cardiovascular disease was negated.

The use of excess synthetic beta carotene in the previously mentioned studies should be avoided in this high-risk population, because there are unidentified elements that may somehow impact cancer growth in vulnerable individuals. It is our opinion that pure beta carotene supplements are inappropriate and should not be administered to our patients. Safer and more efficacious is a mixed natural supplement combination of mixed carotenoids including beta carotene, lutein, lycopene, alpha-carotene, and beta-cryptoxanthin. Beta carotene is responsible for only approximately 25% of total serum carotenoid activity. Other carotenoids may offer additional protective qualities, such as modifying LDL oxidation.

For example, some researchers believe that the antioxidant lutein, which enters the high-density lipoprotein (HDL) and LDL particle, has favorable effects on LDL oxidation, which can retard CAD. In the Toulouse Study,¹³⁷ participants with greater lutein activity in the blood had a lower incidence of CAD. In fact, some researchers believe that the lutein found in a diet rich in green and yellow fruits and vegetables is more responsible for the inhibition of CAD than the red wine benefit referred to as the "French paradox."

FLAVONOIDS

How is it that the French, whose diet is steeped in high-fat cheese, rich sauce, gravy, pate, and other highly saturated fats, have a lower incidence of coronary heart disease? This paradoxical situation certainly challenges our American belief that a low-fat diet is protective against disease. What is it that could be offsetting the apparent time bomb that we see in the typical French diet? Perhaps it is the routine consumption of fresh fruits and vegetables that contain vital phytonutrients, including tocopherols, carotenoids, (especially lutein), flavonoids (quercetin), phenols, catechins, and others that may effectively reduce peroxidative tendencies and retard the varied interactions involved in atherogenesis and thrombosis.¹³⁸ Or is the secret really in the red wine?

The serum antioxidant activity of red wine was addressed in a small study of volunteers.¹³⁹ Their results essentially revealed that two glasses of red wine consumed before a meal offered considerable antioxidant protection for at least 4 hours. This small study showed that red wine increased antioxidant activity through a flavonoid–polyphenol effect. But is it necessary that you drink red wine to gain this benefit?

In a small study done in the Netherlands, the use of dietary bioflavonoids, phenolic acids, and quercetin reduced the incidence of heart attack and sudden death.¹⁴⁰ The end point for this study of 64- to 85-year-old men was death. The findings showed an inverse relationship between the amount of quercetin ingested and mortality. Quercetin-rich black tea, apples, and onions were the foods

evaluated, because they contain amounts similar to those found in the red grapes used in making wine. Now should cardiologists recommend red wine to their patients?

Because quercetin and other phenols are prevalent in many other foods (in fact, onions have perhaps the greatest quantity of quercetin), it is not our recommendation that red wine be routinely recommended for all patients. Remember, although the French may have the lowest incidence of coronary heart disease in Europe, they also boast the highest incidence of cirrhosis of the liver.

Flavonoids, like carotenoids, are found predominantly in brightly colored fruits and vegetables, and represent a safe alternative source of polyphenols and quercetin, which is believed to be the most active protective ingredient in preventing oxidation of LDL. Flavonoids are significant free radical scavengers that inhibit lipid peroxidation and contain antiinflammatory and antiallergenic properties as well. In addition, a diet rich in fresh fruits and vegetables is also an excellent source of magnesium.

MAGNESIUM

Magnesium exerts profound influences on coronary vascular tone and reactivity, and deficiencies have been shown to produce spasm of the coronary artery, rendering low magnesium states as possible culprits in nonocclusive MI. Hypomagnesemia can result in progressive vasoconstriction, coronary spasm, and even sudden death.¹⁴¹ For angina caused by coronary artery spasm, treatment with magnesium has been shown to be considerably efficacious.¹⁴² In fact, several studies have shown an association between intravenous magnesium supplementation during the first hour of admission for MI and reductions in both morbidity and mortality.¹⁴³

Magnesium deficiency, which is better detected by mononuclear blood cell magnesium than the standard serum level performed at most hospitals, predisposes to excessive mortality and morbidity in patients with acute MI.¹⁴⁴ In a setting of such acute ischemia, low magnesium levels are predictive of mortality in a hospital setting. Although trials of magnesium therapy in patients with acute MI have produced inconsistent results, the most efficacious use of magnesium, like thrombolytics, occurs with the earliest administration.¹⁴⁵ Why is magnesium so protective? Table 4 lists the physiologic activities of this mineral, one of which is its ability to help prevent serum coagulation.

Findings from a recent study of the inhibition of platelet-dependent thrombosis suggest that magnesium may have a positive preventive role for patients with CAD. In this double-blind, placebo-controlled study of 42 patients, median platelet-dependent thrombosis was reduced by 35% in 75% of patients taking oral administration of magnesium oxide tablets (800–1,200 mg daily) for 3 months.¹⁴⁶ This anti-thrombotic effect occurred despite the use of aspirin therapy in the study population.

Magnesium has also shown considerable efficacy in relieving symptoms of mitral valve prolapse (MVP).¹⁴⁷ In a double-blind study of 181 participants, serum magnesium levels were assessed in 141 patients with symptomatic MVP

TABLE 4

Possible cardioprotective mechanisms of magnesium

Antiarrhythmic effects
Calcium channel blocking effects
Improvement of LDL-C/HDL-C ratio
Improvement of nitric oxide release from coronary endothelium
Improved response to potassium repletion
Inhibition of platelet-dependent thrombosis
Protection against free radical-induced injury
Protection against reperfusion damage
Reduction in lipid levels
Reduction of potassium loss
Vasodilating effects (improved myocardial collaterals and reduced afterload)

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

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and compared with those of 40 healthy control subjects. Although decreased serum magnesium levels were found in 60% of the patients with MVP, only 5% of the control subjects showed similar decreases. The second leg of the study investigated response to treatment. Participants with magnesium deficits were randomly assigned to receive magnesium supplement or placebo. The results in the magnesium group were dramatic: the mean number of symptoms per patient was significantly reduced; significant reductions were noted in weakness, chest pain, shortness of breath, palpitations, and even anxiety; and decreases were noted in the amount of adrenalin-like substances in the urine. The researchers made two conclusions. First, many patients with MVP who have severe symptoms have low serum magnesium levels. Second, supplementation with this crucial mineral leads to improvement in symptoms and a decrease in adrenalin-like hormones. For these patients, magnesium supplementation may be the solution for reducing symptomatology and improving quality of life.

In our experience, the combination of magnesium and coenzyme Q10 has been promising, alleviating 70% to 80% of patients' symptoms, including chest pain, shortness of breath, easy fatiguability, and palpitations. This enhanced quality of life may be due to some improvement in diastolic dysfunction, which often is present in women with MVP.

Should cardiologists routinely recommend magnesium to patients suspected of having Prinzmetal's variant angina, coronary insufficiency, and MVP? In these symptomatic patient populations, the beneficial effects of magnesium outweigh the risk of negative side effects. The body can readily discard excess magnesium in the presence of normal renal function. A review of the research suggests that 400 to 600 mg of magnesium daily can be safely recommended to these groups of highly symptomatic patients.¹⁴⁵

B VITAMINS

Clinical cardiologists must be familiar with B vitamin support for their patients. We need to be wary of B vitamin depletion in any patient receiving high-dose diuretic ther-

apy, a common consequence of the conventional treatment for CHF.¹⁴⁸ In fact, B vitamin deficiency should be considered in patients with refractory CHF not responding to high-dose diuretic therapy. Nocturnal leg cramps, also associated with diuretic therapy, manifest as an involuntary, painful contraction of the calf muscles and other areas of the leg. B vitamin support in these patients has resulted in improved quality of life.

In a randomized, placebo-controlled, double-blind study¹⁴⁹ the efficacy of B complex was validated for the treatment of nocturnal leg cramps. In this study of 28 elderly patients, 86% taking vitamin B complex reported prominent remission of symptoms compared with no benefit in the placebo group. This has important implications for any cardiology practice; the usual treatment for nocturnal leg cramps is quinine, which can have serious side effects,¹⁵⁰ whereas B vitamins are virtually harmless.

Most of us are more familiar with the clinical significance of the need for B vitamins to lower hyperhomocysteinemia. In 1969, McCully¹⁵¹ first proposed the homocysteine hypothesis for accelerated vascular pathology as a sequelae to homocystinuria, a rare autosomal recessive disease caused by a deficiency of cystathione B-synthetase. Unfortunately, this hypothesis for premature artery disease was not readily accepted by the medical community until more recently.

In the last few years there have been several investigations confirming the proposed connection between high plasma homocysteine levels and occlusive arterial disease, including atherosclerosis, peripheral vascular disease, and CAD.¹⁵²⁻¹⁵⁹ Nonetheless, we have been hesitant to accept elevated plasma homocysteine as an independent risk factor, choosing instead to focus on hypercholesterolemia as our major metabolic concern.

Anyone with a family history of premature myocardial ischemia, MI, or sudden death should have a homocysteine concentration determined as part of their baseline assessment. The irony is that this high-risk trait usually goes unnoticed, and yet treatment for it is much easier and safer than that for lowering cholesterol levels. Further, hyperhomocysteinemia is not limited to men. In one study, women with coronary disease had higher homocysteine levels than matched control subjects.¹⁶⁰ In another study comparing men and women with high homocysteine levels, women demonstrated greater carotid thickening ratios than their male counterparts.¹⁵⁸

Although the mechanism of homocysteine-associated endothelial damage remains unclear, the fact that it may be inhibited by the addition of catalase incriminates the free radical hydrogen peroxide generated during the oxidation of homocysteine.¹⁶¹ Homocysteine also enhances thromboxane A₂ and platelet aggregation¹⁶² and increases the binding of lipoprotein (a) and fibrin.¹⁶³ Because the association between homocysteine and atherothrombotic vascular events has been shown to be consistent regardless of other factors, the conventional cardiologist must be aware that high levels are a significant marker for atherothrombotic vascular disease. Enzymatic deficiencies occur in as many as 5% of the population.¹⁶⁴ The fact that 28% of

patients with premature vascular disease have high blood levels of homocysteine¹⁶⁵ makes it imperative that we screen for and treat this lethal CAD marker.

Should future randomized trials correlate homocysteine lowering with a significant reduction in vascular events, then supplementation with B complex and multivitamin therapy must be strongly considered for patients with elevated levels,¹⁶⁶ but should the conventional cardiologist routinely recommend folic acid and vitamins B12 and B6 to his patients now, before these trials are completed?

Certainly, administration of these vitamins at the recommended daily allowance levels (folic acid = 400 µg; B6 = 2 mg; B12 = 6 µg) is safe and can be recommended routinely. Research shows a dose-dependent relationship between higher homocysteine levels and lower serum levels of B vitamins, so much higher doses need to be administered in those patients with severe hyperhomocysteinemia and documented CAD.^{166,167} It is also encouraging to note that the United States Food and Drug Administration (FDA) has required enriched grains to be fortified with folic acid, at a concentration that on average provides the average individual with an extra 100 µg of folic acid per day.

A potential hazard of folic acid therapy is subacute combined degeneration of the spinal cord with a subclinical vitamin B12 deficiency; folic acid may mask the development of hematologic manifestations in these patients.¹⁶⁶ This situation can be avoided by either ruling out B12 deficiency before initiating folic acid therapy, or by supplementing folic acid with vitamin B12.¹⁶⁶

DISCUSSION

As we approach the end of the twentieth century, medicine is poised on the edge of a transformation. Our old medical models of waiting for the body to break down before attempting to fix it cannot withstand the profound economic ramifications in the conventional managed care medical community. This approach has resulted in skyrocketing healthcare costs. Americans spend more than \$18 billion annually on coronary artery bypass surgery alone. The cost in terms of human suffering is even greater.

It is now obvious that the alternative involves a shift away from crisis-and-disease medicine toward prevention and health promotion, strengthening the body to restore balance and maintain health. New healing modalities have been created and ancient therapies have been reintroduced, although unfortunately some of these approaches have met with resistance from mainstream physicians.

Although rigidity and bias has been the Achilles heel of many conventional physicians, there are finally signs of a gradual change. The November 11, 1998 issue of the *Journal of the American Medical Association* was devoted entirely to alternative medicine.¹⁶⁸ It is obvious that the current biochemical model alone is inadequate for the future. The physician of tomorrow will need to be more flexible and adaptable, and to know how to choose the best from conventional and complementary options, tailoring treatment approaches to meet the patient's needs. Cardiologists

who are willing to incorporate the disciplines of nutritional, emotional, and mind-body interactions will become our most effective healers as we move into the next millennium. If physicians are to survive in today's climate, they must heed the message and listen to the outcry of the public.

Starving for information, massive numbers of patients are consulting alternative therapy practitioners or visiting book and health food stores in record numbers, creating a multibillion dollar industry completely outside the mainstream medical community (one cannot but think of the story of Nero fiddling while Rome burns).

Whose responsibility is it to examine all of the options that have the potential to ease human suffering? Who is best to partner with the patient in their quest to take charge of their health and well being? Who is better qualified than the highly trained medical professional to test the efficacy and safety of alternative and complementary therapies, under strict peer review, thereby protecting patients from quackery and "snake oil?" Once empowered with the knowledge of a wide variety of healing modalities, who is better able to provide patients with the best possible care? The conventional physicians, well grounded in orthodox, mainstream, scientific methodology will be the best health professional to incorporate alternative, anecdotal-based therapeutic approaches into their practice.

There are many reasons for the increase in the popularity of alternative medicine, including patient dissatisfaction with ineffective conventional treatments, pharmacologic drug side effects, high price of medications, and the fact that traditional medicine becomes too impersonal with involvement of high-tech modalities and time-limited office visits. People are literally screaming for an orthodox physician to be open to complementary methods in their practice.

Perhaps we need to step back and look at the wisdom of our previous teachers. More than 70 years ago, Dr. Francis Peabody, writing in the *Journal of the American Medical Association*,¹⁶⁹ wrote:

Disease in man is never exactly the same as disease in an experimental animal, for in man the disease at once affects and is affected by what we call the emotional life. Thus, the physician who attempts to take care of a patient while he neglects this factor is as unscientific as the investigator who neglects to control all the conditions that may affect his experiment. The good physician knows his patients through and through, and his knowledge is sought dearly. Time, sympathy and understanding must be lavishly dispensed, but the reward is to be found in the personal bond which forms a greater satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is caring for the patient.

Conventional cardiologists willing to embrace proven complementary modalities of nutritional, metabolic, and emotional healing will become the most effective healers, ready to meet the needs of a new tomorrow. Consideration of complementary therapies requires only an open mind, the willingness to add to our knowledge of conventional

methodology, and investigating alternatives that can improve quality of life and reduce human suffering. This paradigm shift in our medical system is the only logical and ethical thing to do.

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