HEALTH AND STRESS

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VITAMINS, COENZYME Q10 AND PHYTOCHEMICALS

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As indicated in a recent Newsletter, many people take larger than recommended daily doses of vitamins C, E or beta-carotene in the belief or hope this will ward off various diseases and/or delay the ravages of aging. Large-scale studies designed to correlate health with dietary habits show that lower rates of heart disease and cancer and greater longevity are associated with a liberal intake of fruits, vegetables, whole grains and certain oils. Blood levels of these vitamins are relatively higher in this population which has led to the conclusion that it is their antioxidant properties that are responsible for any health benefits.

Most Americans don't ingest the recommended amounts of vitamin rich fruits, vegetables or grains on any regular basis. In addition, the vast majority would prefer to take a few pills every day if it could achieve the same results as eating more fruits and salads. In fact, **why wouldn't taking very large amounts of these vitamins be even better?**

Many people do take megadoses of vitamins C and E and possibly beta-carotene based on this assumption. Although this is rarely harmful, does it do any good? Let's face it. **For those of you who take a particular vitamin daily, how can you really tell if it is helping you? And if you take more than one supplement, how can you determine which, if any, are beneficial?** Most people say something subjective such as "I feel I have much more energy" or "I don't feel as tired as I used to". Others may claim that they used to get frequent colds and infections but that taking various supplements has boosted their immune system resistance.

This should not be misconstrued as implying that such self-reports are not truthful or accurate. The power of placebo phenomena should never be underestimated and is responsible for many of the benefits we attribute to conventional medications. As the Roman physician Celsus noted 2,000 years ago, "Part of the cure is the wish to be cured". **Since vitamins are taken for prophylactic reasons, few objective measures are available to determine their efficacy, much less optimal dosage.**

ALSO INCLUDED IN THIS ISSUE

There is increasing suspicion that vitamin supplements in any amount may fail to furnish the same benefits as those derived from dietary sources. Foods may contain phytochemicals necessary for vitamins to function optimally. Although difficult to prove, recent evidence tends to support this view.

How Do Substances Become Vitamins?

In addition to questions of efficacy, there are concerns that megadoses of vitamins may have adverse health consequences. In that regard, it is important to understand exactly what entitles a substance to be designated as a vitamin. It all started in 1897, when a Dutch physician named Christiann Eijkman proved there was an unusual ingredient in unpolished rice that was vital for the proper function of the nervous system. It was not present in polished rice, the main source of nutrition in some parts of Asia, where its deficiency resulted in severe weakness and even paralysis. In India, it was called "beri-beri", a Singhalese term meaning, "I cannot", signifying that the person was just too weak to do anything.

In 1911, the Polish-American chemist Casimir Funk isolated a substance from rice husks that appeared to contain this important factor. It could prevent the development of beri-beri and relieve its symptoms. He named it *vitamine*, from the Latin *vita* for life, and amine, since it appeared to fall into this chemical classification. This later became vitamin, and was used to refer to unrelated substances subsequently found in other foods that were also essential to prevent different diseases.

Funk had discovered vitamin B1, which became known as thiamin after its isolation in 1926. By the time it was synthesized ten years later, eight other vitamins had been isolated and their deficiency states described. Since then, five more have been added to the list, the most recent being folic acid.

However, it had long been recognized that specific foods seemed to have unusual healing powers in certain illnesses, which we now recognize as deficiency diseases. The Egyptians used liver to treat night blindness and pine needles and citrus fruits were later found to prevent and cure scurvy. When researchers learned how to produce deficiency diseases like beri-beri and scurvy in laboratory animals by feeding them deficient diets, they were amazed by the ability of minute amounts of the missing ingredient to restore health. Subsequent research was devoted to determining the minimum daily amounts of different vitamins that would be required to prevent deficiency diseases in humans.

The Recommended Daily Dietary Allowances for six of them were first published in 1943 by the National Research Council but many questioned their accuracy. There was so much controversy that in 1968 this was changed to Recommended Daily Allowance (RDA) to acknowledge varying requirements depending on age and other factors. Reference Daily Intake (RDI) is a more recent index of across the board recommendations for everyone not only for vitamins, but also calcium, protein, trace minerals and other essential nutrients. These are constantly being updated to incorporate the concept of risk reduction for chronic diseases rather than simply prevention of nutrient deficiencies or to acknowledge increased requirements of vitamin C for smokers, etc.

Vitamins act as catalysts to facilitate essential intracellular enzyme activities but the distinction between vitamins and coenzymes and cofactors that also function in this fashion is becoming increasingly blurred. **It is also essential to distinguish between the physiologic function of vitamins in preventing deficiency diseases and purported pharmacological effects, which are quite different.**

Can Vitamin Supplements Be Harmful?

Certainly not when taken in accordance with governmental regulations. The problem is that most people take much more than this and in some cases, massive amounts. That is not apt to be a problem with B-complex water soluble vitamins, but other fat soluble vitamins can accumulate in the body to eventually reach levels that could be toxic. While not common, such problems have been reported, especially with vitamins A and D.

Vitamin A is present in nature in two forms, retinol and beta-carotene. Retinol comes from animal sources and toxic effects usually do not occur unless dosages exceed 30,000 IU daily. Retinol can be stored in the body and there is enough vitamin A in the liver of a well-nourished adult to last for about two years of deprivation. Toxicity has occurred in individuals who consume polar bear liver, which contains 2,000,000 IU of vitamin A per 100g. **It is estimated that one in 57 birth defects in the U.S. results from excess vitamin A** and pregnant women should avoid taking more than 10,000 IU daily. Beta-carotene, found in vegetables, is a precursor of vitamin A and can be converted into retinol in the body if required and is generally not considered to be toxic. However, some health fanatics who drink gallons of carrot juice have turned yellow because excess beta-carotene is stored under the skin.

Excess consumption of Vitamin D can elevate blood levels of calcium because of increased absorption from the gut and resorption of calcium from bone. This can result in calcium deposits that damage the heart, blood vessels and kidneys. Administering excess vitamin D is sometimes used to produce experimental hypertension in laboratory animals but toxicity in humans is uncommon. Vitamin K can interfere with the action of anticoagulants but toxic effects are rare, with the exception of vitamin K3. Large doses of this synthetic compound can cause flushing and sweating and jaundice and anemia have also been reported. Very large doses of vitamin E can cause headache, visual complaints, and hemorrhagic complications, including stroke.

Large clinical trials to demonstrate the efficacy of various vitamins in doses many people take have also led to concerns. One designed to test the ability of a combination of beta-carotene and vitamin A to reduce coronary disease and cancer was terminated after four years because supplement-takers who smoked had a 28% higher incidence of lung cancer and a 17% higher death rate. In another, which compared the effects of vitamin E, beta-carotene and a placebo in heavy smokers, **the beta-carotene group had 18% more lung cancer and overall death rates were 87% higher than controls**. Those who took vitamin E not only demonstrated no increased health benefits, but had a higher incidence of hemorrhagic stroke.

A trial to see if these two vitamins could reduce the incidence of a second heart attack reported significantly more coronary deaths among those who took beta-carotene supplements compared to placebos and there was a trend toward more deaths in the vitamin E group. Some believe that vitamin A supplements should never be taken, especially by anyone who smokes. Earlier this year, the National Academy of Sciences lowered the adult daily requirement for vitamin A intake to 3,000 IU and for the first time, established an upper limit of 10,000 IU for adults and less than half of this for children and infants. Vitamin A capsules containing 25,000 units are still on the shelves in some stores as are products containing much more than the maximum recommended daily dose for adults and children.

High intake of vitamin E from foods seemed to be associated with protection against heart disease and cancer in early observational studies. However, two recent clinical trials showed no such benefits from taking 400 to 666 IU daily of vitamin E (alpha-tocopherol) for three to six years. It seems likely that foods contain other tocopherols and phytochemicals that may provide greater health benefits.

Megadoses of Vitamin C can cause bowel complaints. In addition, large doses of this, as well as beta-carotene, can have a harmful prooxidant rather than protective antioxidant effect under certain circumstances.

Will Phytochemicals Replace Vitamins?

Phyto comes from the Greek word for plant. Phytochemicals are substances that protect plants from damage caused by strong sunlight, winds and other environmental hazards and function much like antioxidants do in humans. While phytochemicals may have no specific nutritional value, many appear to be effective in preventing and treating diseases, particularly certain malignancies. More than 900 different phytochemical compounds have been identified, including:

- **Allyl sulfides** (in garlic, onion and chives)
- **Indoles, glucosinolates, sulforaphane, isothycyanates** (cruciferous vegetables like broccoli, cauliflower, cabbage, Brussel sprouts, kale, turnips and kohlrabi)
- **Lycopene** (in solanaceous vegetables such as tomatoes and peppers)
- **Carotenoids, phthalides, polyacetylenes,** (umbelliferous vegetables including carrots, celery, cilantro, parsley and parsnips)
- Oranges, lemons, grapefruit and other citrus fruits are rich in **monoterpenes (limonene) and flavonoids (naringenen and hesperiden)**
- Other fruits (berries, cherries, apples, cantaloupe and other melons) supply **ellagic acid, phenols, and flavonoids like quercetin**.
- Soybeans, oats, barley, brown rice, whole wheat and flaxseed contain **phytic acid and isoflavones, another type of flavonoid**.
- **Flavonoids, as well as gingerols and monoterpenes** are found in herbs and spices such as ginger, mint, rosemary, thyme, oregano, sage, basil, fennel and turmeric.

All phytochemicals have antioxidant actions but some may provide specific benefits, like **glycyrrhizin** in licorice root and **silymarin** in artichoke, which are used to protect liver cells from damage due to infection or toxins.

Polyphenols in wine, tea, chocolate and coffee may reduce rates of cancer and coronary heart disease but it is important to recognize that there are many types of polyphenols that seem to have different properties. **Catechins** are the components that provide the above benefits but they also vary in type and concentration, not only in different foods, but even green, black and oolong teas.

Polyphenols have several subcategories, one of which, the **flavonoids**, includes not only **catechins** but also **lignins** (nuts), **proanthocyanins** (grapes), **anthocyanine** (brightly colored fruits, vegetables and berries), **tannins** (tea, nuts), **isoflavones** like **genistein** and **daidzein** (soybeans) as well as **quercetin**, **hesperidin, naringenen** and others previously mentioned. While "flavonoid" or "polyphenol" are often used as substitutes for some of these strange names, it is important to recognize that they are not synonyms.

Terpenes represent another large class of phytochemicals that include limonoids, saponins and carotenes. **Limonoids** are found in the peels of citrus fruits and are used for their cardioprotective effects and to reduce respiratory infections. **Saponins** from soy and legumes have anti-cancer and cholesterol lowering effects. **Carotenes** are the most important terpenes and **over 600 different carotenoids have been identified**. They are usually present in groups of 40 to 50 that contribute to the distinguishing colors of various vegetables and fruits. We are most familiar with **beta-carotene** as a source of vitamin A but there are also alpha-, delta-, and gamma-carotenes as well as other important carotenoids, like **lutein, lycopene** and the **xanthophylls**.

It is this combination and ratio of specific phytochemicals that gives various foods their differing and distinctive disease fighting properties. **It has been estimated that one serving of vegetables can contain well over 100 different phytochemicals!** It seems doubtful that any vitamin or mixture of vitamins in any dosages could reduplicate the benefits of combinations of nutrients that are the result of millions of years of evolution. The surprising finding that beta-carotene caused increased cancer rates in smokers is believed to be due to the fact that it was administered in an isolated form rather than as a component of naturally occurring carotenoid complexes. Indeed, under certain circumstances, giving large doses of vitamins alone could turn them into harmful pro-oxidants, as has been demonstrated with vitamin C when it is taken with iron or in megadoses that could damage DNA.

Should We All Become Vegetarians?

One might get that impression after looking at the numerous nutritional rewards that fruits and vegetables have to offer. Animal foods also supply a variety of

vitamins from a single source and are the only source of vitamins D and B12. Eggs contain significant amounts of six vitamins as well as important fats and proteins, and are one of the most nutritious foods available. Pure vegetarians are very susceptible to vitamin B12 deficiency and would also be lacking in Coenzyme Q10, carnitine and possibly selenium and calcium unless they took supplements.

Taking supplements alone might not achieve the same effects as when they are ingested in foods containing phytochemicals that could potentiate their benefits, or as in the case of beta-carotene, reduce adverse effects. As a result, we are likely to be bombarded by a host of products claiming to reproduce the concentrations of phytochemicals found in fruits, vegetables, grains, nuts and oils. Manufacturers are already hyping new mixtures of beta-carotene and other carotenoids that allegedly provide the same benefits as eating fruits and vegetables. Pills called "concentrates" that make similar claims are also being promoted despite analyses that clearly dispute this and occasionally show no active ingredients at all.

It is doubtful that such approaches will be of much value for several reasons. We simply don't know what ingredients in foods are responsible for their ability to promote health. The original assumption that this was due to their content of certain antioxidant vitamins seems incorrect. We may be making the same mistake by now shifting to specific antioxidant phytochemicals as the essential ingredients. High consumption of tomato products is associated with reduced prostate cancer rates, presumably because tomatoes are rich in lycopene, a powerful antioxidant. However clinical trials showed no effect of lycopene supplements alone on prostate cancer. It may be that another tomato constituent or constituents are responsible for this protective action and/or that lycopene requires these or nutrients like selenium and vitamin E to be effective.

Another problem is that nutritional supplements don't have to demonstrate safety. Several years ago, impurities in the manufacture of l-tryptophan resulted in at least 40 deaths and there are concerns that this could happen again with DHEA since the FDA has no control over manufacturing procedures. FDA requirements for safety and efficacy are strict for any additives used to make foods look or taste better or to help prevent spoilage. A regulation is issued detailing what specific foods can contain the additive and in what amounts and no approval is permanent.

Nutritional supplements, including DHEA, melatonin and body building steroids like androstenedione are exempt from all this. Some of these require a prescription in other countries and are banned by athletic organizations here, but there is nothing to prohibit their addition to so-called "functional foods" in order to imply certain health benefits. Ginseng, echinacea, St. John's wort, kava kava and ginkgo biloba have all been added to "improve endurance, support the immune system, elevate mood, reduce stress and anxiety, improve memory" etc. A citizen's group petitioned the FDA to ban over 75 functional foods, claiming that "Food companies are spiking fruit drinks, breakfast cereals, and snack foods with illegal ingredients and then misleading consumers about their health benefits." There is also no guarantee that what is stated on the label of a nutritional supplement container corresponds with its contents. "Over 200 lbs. of vegetables in a bottle" claims one supplement but there is no information on its actual nutrient content.

One argument against being a strict vegetarian is that meat supplies particularly important vitamins and other nutrients because animals need these very same substances to stay alive. Cattle, sheep, goats and other ruminants have bacteria in their stomachs that utilize building blocks from ingested grasses and grains to make high-quality nutrients like Coenzyme Q10 and L-carnitine that are only found in meats. This might be unfortunate for some vegetarians unless they took supplements. **In my opinion, almost all adults could benefit from a daily dose of Coenzyme Q10.**

From Gum Disease To The Nobel Prize

Like many other important scientific breakthroughs, the discovery of Coenzyme Q10 (CoQ10) illustrates Pasteur's observation that "chance favors the prepared mind." CoQ10 is also an example of how some medical discoveries are recognized and utilized in other countries long before they are accepted in the U.S., even when they have originated here. Researchers at the University of Wisconsin were looking for information on how the body was able to transform forces from foods that were consumed into a form of energy that could be utilized immediately or stored for future use. They focused their attention on the mitochondria: tiny cucumber-shaped components that are the "power plants" of all cells.

In 1957, they noted some curious yellow crystals in a test tube containing an extract from beef heart mitochondria. They sent some of this material to Dr. Karl Folkers at Merck Pharmaceutical Company in New Jersey. Folkers determined its molecular structure and together with co-workers tried to get the company to do studies to determine its possible clinical applications, especially in patients with cardiovascular disease.

Merck dropped the ball but Japanese researchers were excited about the potential for CoQ10. They had already demonstrated the value of a related compound in congestive failure and in 1965, the first clinical trial of CoQ10 in cardiovascular disease was conducted in Osaka University. In the early 1970's, Folkers and Italian investigators demonstrated that CoQ10 levels were often low in patients with periodontal disease as well as cardiovascular disease. A Japanese double blind study found CoQ10 to provide statistically significant improvement in gum disease and to be superior to conventional treatment approaches. Periodontists here subsequently confirmed that healing of gum disease was often dramatic following daily oral CoQ10 supplementation. **It is now well established that periodontal disease is a risk factor for coronary artery disease so that administering CoQ10 provides benefits for both of these disorders.**

It was not until 1974 that Japanese scientists were able to perfect the technology needed to produce enough pure Coenzyme Q10 to conduct large clinical trials. By 1976, the benefits of CoQ10 were so obvious that it was placed on the formulary of Japanese hospitals. Within six years it was one of the five top selling medications in Japan. One of the factors responsible for this, in addition to its efficacy and extreme safety, was that in 1978, Peter Mitchell, an English scientist, received the Nobel Prize for explaining how CoQ10 played an essential role in facilitating energy transfer processes in the mitochondria of all cells.

Things moved fairly quickly following this and by 1985, one Japanese review article listed some 65 scientific clinical studies showing the benefits of CoQ10 in myocardopathies, arrhythmias and cardiovascular damage resulting from drugs, hypertension and stroke. Interest also picked up in the U.S with Per Langsjoen's double-blind studies confirming the dramatic effects of CoQ10 in severe cardiomyopathy. By the early 1990's, there was an explosion of interest in CoQ10 in the health food and nutritional supplement industry. Cardiologists here were also beginning to take CoQ10 seriously and requesting its addition to hospital formularies.

However, little was known about dosage requirements for different disorders, all sorts of CoQ10 products were available making competitive claims of superiority based on increased bioavailability, laboratory measurements were not widely available or standardized, and there was little unanimity of opinion on what the optimal blood levels should be for treating different complaints, since some cardiac conditions required larger doses. In addition, the vast majority of people were taking it to prevent disease. At the 1996 9th annual CoQ10 conference in Ancona, Italy, it was agreed that blood levels of at least 2.5 μg/ml were needed. Most of the other problems have been resolved since then and although CoQ10 is now mainstream medicine, few physicians or dentists are aware of its benefits because it is not promoted by drug companies.

Why Ubiquinone Is Unique

Coenzyme Q10 is also known as ubiquinone because it belongs to a class of organic compounds called quinones and is so widely distributed in all tissues and cells that it is truly ubiquitous. It essentially fulfills the criteria for being a vitamin, which may be defined as an organic compound essential in minute amounts for normal body functions by acting as a coenzyme. Coenzymes are compounds required for more complex vital enzyme systems to function correctly.

CoQ10 is the crucial coenzyme for at least three enzyme systems that are responsible for the mitochondrial production of a remarkable compound known as adenosine triphosphate (ATP). It is ATP's high-energy phosphate bonds that supply the fuel for all cells in the body, regardless of their location or function. That helps to explain why CoQ1O supplementation can be effective in so many different disorders. Normal values for CoQ1O in blood and certain tissues are now fairly well established and significantly decreased levels have been reported for various diseases. This may be due to poor dietary intake, impaired CoQ10 biosynthesis in the body, excessive utilization, or a combination of all three.

Most CoQ1O is manufactured in the body in a complicated 17-step process that requires at least seven vitamins (riboflavin, folic acid, niacinamide, pantothenic acid, pyridoxine, vitamin B12, vitamin C) as well as several trace elements. A lack of any of these would impair production and since insufficient nutrient intake is so common, many authorities believe that current range for "normal" or "average" CoQ1O values are suboptimal and that the very low levels often observed in certain disease states are only the tip of a deficiency iceberg. Support for this comes from evidence that in addition to its value in treating cardiovascular complaints ranging from angina and arrhythmia to hypertension and congestive failure, CoQ1O has been found to benefit patients with periodontal disease, diabetes, cancer, infertility and may have applications for the treatment of Parkinson's disease and other neurodegenerative disorders.

This admittedly sounds like snake oil, and some of the nutritional supplement ads that make anti-aging and other extravagant claims tend to reinforce this impression. In order to separate the wheat from the chaff, it is necessary to understand how CoQ1O works in the mitochondria as part of the assembly line that transforms the food we eat into high energy electrons for immediate utilization or stored for future use. This involves complex metabolic activities that break down carbohydrates, fats and proteins to molecules that ferry energy to what is referred to as the electron transport chain. This is a series of "pumps" that use oxygen and protons to transfer this energy to ATP and CoQ1O is essential for these pumps to operate.

Although most of the oxygen used ends up as a component of water or carbon dioxide and is excreted during respiration, some oxygen molecules lose an electron and become "charged" oxygen free radicals that are very damaging to cell membranes and set up a chain reaction of destruction. CoQ1O also acts as a very powerful antioxidant because it has the ability to neutralize these dangerous oxygen particles without becoming destabilized itself. CoQ1O also facilitates the antioxidant effects of vitamin E and works in conjunction with L-carnitine.

L-carnitine is a small molecule derived mainly from meat that assists CoQ1O by working in the "shipping and receiving department" of the mitochondria. Security here is very tight and carnitine is required to escort long chain fatty acids into the mitochondrial matrix. It also helps out as part of the cleanup crew by binding to metabolic waste products and escorting them out of the body. Think of the mitochondria as the furnace, CoQ1O as the generator that sparks cellular activity, and carnitine as the delivery service for important fuels and part of the hazardous waste removal crew. Carnitine potentiates CoQ1O effects in so many ways that the two are often given together, especially for cardiac complaints. This seems reasonable, but what are the correct dosages to use for prevention and treatment and are all brands of supplements equal?

Nutritional Supplements: Which Ones Should You Take And How Much?

The honest and correct answer is that nobody really knows. Things used to be fairly simple. Free radicals were the "bad guys" that caused cancer, coronary disease, cataracts and gray hair. These problems were normally prevented or minimized by the body's natural antioxidants but our ability to manufacture these "good guys" falls off sharply as we grow older. Manufacturers, the media and most authorities reassured us that vitamins C, E, and beta-carotene were also powerful antioxidants that could more than make up for any deficit, since they could be taken in huge amounts without any concerns about safety or adverse side effects.

This view has now changed as scientific studies have failed to confirm that these popular vitamins provide any benefits in larger than recommended dosages and could actually prove harmful. Some believe that beta-carotene should never be taken. The current official recommendations are that vitamin A supplements are not needed, Vitamin C supplements should not exceed 2000 mg. daily and that vitamin E should be limited to 200 mg. of alpha-tocopherol with an equal amount of mixed tocopherols. When *Consumer Reports on Health* (October 2001) asked 16 leading researchers in the field if they thought that taking larger doses of vitamin E could help reduce cancer rates as some had previously claimed, only 3 now believed there might be possible benefits and 2 of them limited this to prostate cancer. Six said there was no good evidence that vitamin E helped to prevent heart disease and the remainder felt "the jury was still out."

This debunking development has been very disappointing and embarrassing since I was an early and enthusiastic supporter of Linus Pauling. I followed his advice about taking large amounts of vitamin C and urged family, friends and readers to do likewise. I also took large doses of vitamin E, beta-carotene and other antioxidants that allegedly would help prevent disease and slow down the aging process. Taking all of these and occasionally some that promised to increase pep or improve memory definitely gave me a sense of confidence and control. Even though there was no proof that my daily regimen provided any benefits, my attitude was if it couldn't hurt and might help, why not continue taking them? Now I'm not so sure because COQ10 might suffice.

My wife and I have been taking CoQ10 daily ever since she stopped Lipitor because of memory problems. As l pointed out in the November 21 issue of the *Journal of The American Medical Association*, statin drugs lower CoQ10 levels and memory loss associated with statin therapy improves following CoQ10 supplementation. This was certainly Marguerite's experience and there has also been a progressive improvement in her periodontal problem. COQ10 (30-50 mg. in a gel cap) should be taken with a meal containing some fat to increase absorption and I also take a B complex combination. Although 1000 mg. of C in divided doses and the tocopherol schedule noted above seems reasonable, still somewhat confused and not certain about this - so stay tuned.

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