Chapter 4

"Fire in the Heart": New Developments in Diagnosis, Prevention & Treatment of Cardiovascular Disease

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ABSTRACT

The aim of this paper is to discuss the integration of conventional cardiology and alternative cardiology. The world of cardiology is moving fast and in multiple directions. In this paper we will discuss the importance of inflammation and how nutraceuticals can be used in the fight against cardiovascular disease.

Keywords: inflammation; insulin; detoxification; nutraceuticals; omega fatty acids; CoEnzyme Q10

INTRODUCTION

Most of us have some idea of what inflammation is. If a wound gets hot, turns red, hurts, and swells, we recognize that inflammation is at work. In this instance, inflammation is a beneficial process, serving to immobilize and rest the area of injury as the rest of the immune system mobilizes to heal.

Regardless of the source of assault on our bodies, inflammation is the "first alert" mechanism that calls into action the cells responsible for surveillance and protection, heralding them to go to work and limit the damage. These cells attack and destroy the invaders, and clean up the damaged cells, repairing and clearing as they go until a healthy state is restored. As such, inflammation is your body's first line of defense against injury or infection.

Researchers now recognize another kind of inflammation: silent inflammation, or SI, which is very different from the type of inflammation described above. This type of internal inflammation has an insidious nature and is the culprit behind the many chronic diseases that are primarily caused by poor lifestyle habits and environmental pollutants. The chronic and continuous low-level demand that silent inflammation places on the body's defense systems results in an immune system breakdown. In SI there is no regulated progression of a healthy inflammatory response, no planned sequence from the first alarm to the formation of the last new cell. Many of these reactions become intermingled and hamper one another.

The body tissues themselves may lose their ability to recognize cells that are "self" from those that are not, and the body may mistakenly identify its own cells as foreign invaders. This internal programming error, if you will, continues to trigger and re-trigger immune responses, setting the stage for what we call autoimmune diseases, such as lupus, multiple sclerosis and scleroderma. The result is chaos,

and what is even more disturbing is that this process may be happening year after year without us even being aware of it.

We now know that SI also plays a central role in the chronic illness that remains our number 1 killer: coronary artery disease. In fact, elevated markers of silent inflammation: such as homocysteine, C-reactive protein (CRP), lipoprotein a (Lp(a)), and interleukin-6 (IL-6), have been found to be more predictive of heart disease than traditional risk factors such as elevated cholesterol levels. In fact, 50% of patients hospitalized for heart disease have normal cholesterol levels.

A landmark study showed that people with high levels of CRP, one of the cardinal markers of inflammation, were over four times more likely to have heart attacks than those with low levels of CRP. Researchers then began to link CRP, along with other markers of inflammation, to a wide range of chronic diseases including Alzheimer's disease, arthritis, Parkinson's disease, and even cancer. It is now accepted that chronic SI is a warning that something is drastically out of balance with one's overall health.

Although chronic SI can cause a variety of disorders, many of us (and unfortunately this includes many physicians) are not aware of the warning signs of this kind of inflammation, or of the best ways to treat it. This knowledge is critical because should a person have one inflammatory condition, the odds that they will develop another skyrocket drastically. Researchers have discovered, for example, that a woman with rheumatoid arthritis has a 100% increased risk of experiencing a myocardial infarction. Very recent research has now demonstrated that higher CRP levels are also associated with age-related macular degeneration. Thus, the same individual may suffer from more than one condition caused by SI. For all these reasons, slowing down this chronic inflammation syndrome is also a major factor for age management, therefore it is crucial that everyone is aware of SI, and that they understand its causes, and now how to take measures to stop it.

CAUSES OF INFLAMMATION

The many factors that trigger SI are found in both our internal and external environments and include over-consumption of hydrogenated oils, excessive insulin levels, obesity, cigarette smoking, radiation exposure, environmental toxins (mercury, heavy metals), free-radical damage, bacterial and viral infections like nanobacteria and cytomegalovirus (CMV), spirochetes such as the borrelia that causes Lyme disease, periodontal disease, emotional stress, and even some pharmacological drugs.

Insulin

The most powerful drug you can consume is the food you eat each day. Depending on the ratio of macronutrients (carbohydrates, fats, proteins) you take in at each meal, your daily diet will either keep you in an optimum "zone" for good health, or it won't.

The "zone" is a physiological state in which the hormones (especially insulin) influenced by the diet are within ranges consistent with optimal health. A "zone meal" is comprised of macronutrients that are kept within ideal balance. The perfect zone meal is proportioned as follows:

Carbohydrates	40-45%
Fat	30%
Protein	25-30%

Combining macronutrients according to the ratio listed above, will keep you "in the zone." The goal is to keep fasting insulin levels lower than 12 µIU/ml, although an ideal level is 5 µIU/ml. We now know that a diet that follows this ratio helps keep weight, insulin, and eicosanoids (hormone-like substances) at ideal levels, which in turn assuages SI in the body. It is important to remember the health consequences of failing to keep insulin levels at bay (<17 µIU/ml): insulin resistance, obesity, Type II diabetes, and heart disease are just a few of the many health complications that may arise from this condition.

Controlling Insulin

Insulin control is achieved through balancing the ratio of protein and carbohydrates at each meal to maintain stable blood-sugar levels for four to six hours. We agree with our colleague Dr. Barry Sears who states, "Hormonally, you are only as good as your last meal, and you will be only as good as your next meal." This means that, for optimal health, you have a dietary choice to make every four to six hours. Accordingly, the following is advised:

- Try to eat a Zone meal within one hour of waking.
- Every time you eat, aim to balance protein, carbohydrates, and fat.
- Try to eat five times a day: three meals and two light snacks.
- Eat more vegetables and fruit, less bread, pasta, rice, and potatoes.
- Always supplement your diet with fish oil and other nutraceuticals.
- Eat a serving of slow-cooked oatmeal topped with seasonal fruit twice a week for fiber, phytonutrients and gamma linolenic acid (GLA).
- Use monounsaturated oils (olive oil) whenever possible on salads and vegetables.
- Use low glycemic carbohydrates whenever possible.

Besides excess insulin, increased blood sugar, free radicals, and elevated cortisol levels accelerate heart disease and aging. All these contributing factors can be modified by the Zone diet, which works to establish hormonal equilibrium in the body.

The essential fatty acids omega-6 and omega-3 are also key dietary components. When these two types of essential fatty acids are metabolized, they produce eicosanoid hormones, which can have dramatically different physiological reactions. Eicosanoids have been labeled as either "good" or "bad", depending upon their effect on the body. "Good" eicosanoids, which are produced from omega-3 fatty acids, are anti-inflammatory by nature, while "bad" eicosanoids, for example arachidonic acid, cause inflammation within the body. The synthesis of each type of eicosanoid depends upon the types of dietary fat we consume as well as endogenous production and metabolism.

Essential fatty acid metabolism is ultimately controlled by one particular enzyme found in the body, delta-5-desaturase, which produces arachidonic acid (AA), a long-chain omega-6 fatty acid that is the precursor of the proinflammatory eicosanoids.

Two dietary constituents profoundly affect the activity of delta-5-desaturase: levels of long-chain omega-3-fatty acids, such as eicosapentaenoic acid (EPA), and levels of insulin. The AA/EPA balance, as measured in the blood, represents the balance of "bad" and "good" eicosanoids throughout the body. Arachidonic acid causes platelet aggregation by triggering the release of thromboxane A2. This kind of endothelial cell unfriendly process is the perfect scenario to set the stage for chronic SI, while promoting blood clotting at the same time. High levels of EPA will counteract the negative effects of AA production and keep inflammation at bay. The ideal AA/EPA ratio is 1.5.

Too much insulin in the body exacerbates AA production and therefore catalyzes inflammation. If you eat an imbalance of (too many) carbohydrates, refined sugars, and proteins at each meal, you will provoke a greater insulin response. Chronic excess insulin will accelerate inflammation, heart disease, obesity, and Type II diabetes; as such hyperinsulinemic patients also have elevated CRP levels.

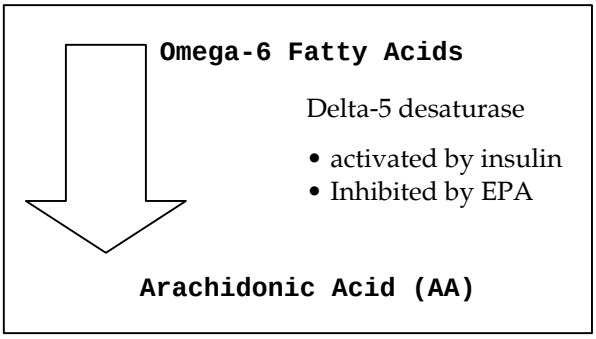

Figure 1. The Production of Arachidonic Acid by Delta-5 Desaturase

Heavy Metals

There are numerous published papers describing adverse clinical effects with aluminum, cadmium, copper, iron, lead and mercury. According to data from the US Toxics Release Inventory, in the year 2000 industry in the United States released 4.3 million pounds of mercury and mercury compounds into the environment, and generated 4.9 million pounds of mercury compounds in toxic waste. This toxic metal burden increases low-grade inflammation at the cellular level, which interferes with mitochondrial function and energy production, and therefore has a very negative effect on the endocrine (glandular), immune, and metabolic systems.

The cardiovascular system is extraordinarily sensitive to mercury. In one small study of 13 biopsied patients with idiopathic dilated cardiomyopathy, investigators found mean mercury concentrations in excess of 22,000 times that of normal levels. Higher mercury levels were thus implicated as causes of this form of cardiomyopathy. Researchers speculated that toxic mercury levels adversely affected mitochondrial activity and the subsequent decrease in myocardial metabolism was a profound metabolic factor in the etiology of idiopathic dilated cardiomyopathy. And how do we become mercury toxic in the first place? Quite simply: breathing contaminated air and eating contaminated fish.

Most mercury vapors arise in the atmosphere from the industrialization of coal. Mercury is then inhaled into the lungs, and transmitted to tissues. And the precipitation of mercury vapors in the water supply is another important factor. Rainfall precipitates mercury into ponds, lakes and streams. Bacteria and algae (your main entree if you're a fish) sequester mercury. First, small (bait) fish ingest algae-laden methylmercury, and then the bigger fish eat these smaller fish. Thus, the larger the fish, the more time it has had to accumulate more mercury from its diet of smaller fish. When we enjoy a dinner with a mercury-overloaded fish, that heavy metal has made it into our food chain.

Salonen and colleagues studied the association between fish intake and myocardial infarction, using hair analysis and urinary excretion to measure mercury levels in 1,833 men. Their results showed that men in the highest tertile for hair mercury content had twice the incidence of acute myocardial infarction and almost 3 times the incidence of cardiovascular death as those with lower hair mercury content. Both hair and urinary mercury increase immune complex oxidized LDL, and high levels of oxidized LDL prime the pump for further inflammation.

Although somewhat controversial, dental amalgams are another source of unwanted mercury toxins in the body. The removal of old, tired, and cracked amalgams by a biological dentist should be strongly considered by anyone with signs and symptoms of mercury overload, such as headache, tremor,

cardiac disease of unknown etiology, confusion, weakness, weight loss, insomnia, joint pain, and fatigue to mention a few.

The easiest way to diagnose heavy metal toxicity is to ingest a dose of oral DMSA (dimercaptosuccinic acid) and collect the urine for twenty-four hours. In our respective practices, we commonly perform this test on patients with unexplained fatigue, fibromyalgia, neurological, and emotional problems, in addition to cardiac disease.

Free Radicals

Free radicals are highly reactive, imbalanced molecules produced during oxidation that steal electrons from cells to neutralize their charge. Free radicals interfere with enzymatic reactions, and cause significant metabolic stress, and thereby damaging cells and DNA. Oxidation may occur within the body through simple metabolic processes like eating, drinking, and breathing, which generate free radicals as byproducts of energy (ATP) production. Alcohol, drugs, poor diets, radiation, and other catalysts all accelerate the production of free radicals in the body. The danger of free radicals is that they fan the fires of inflammation and attack cell membranes, ultimately disrupting cellular communication. When free-radical damage disturbs the integrity of cell membranes, they leak, and excessive waste builds up inside the cells.

One of the primary ways we can protect ourselves from free-radical damage is to take oral antioxidants. Because cell membranes are composed mostly of fat, fat-soluble antioxidants like alpha lipoic acid, CoEnzyme Q10, and vitamin E can best penetrate into the cell. Antioxidants slow the aging process by promoting cellular repair, inhibiting inflammation, and preventing production of the inflammatory substances that accelerate aging.

Cardiologists frequently cite the process of lipid peroxidation as a focal point for the origin of atherosclerosis. Many antioxidants, particularly CoEnzyme Q10 and quercetin (found in onions), actively block the oxidation of LDL that contributes to SI.

Nanobacteria

Although oxidized LDL cholesterol helps to set the stage for atherosclerosis, there are other causes of cardiovascular disease. Oxidized LDL may be part of the story, but it's not the entire explanation. The controversial Nanobacteria Story may well be an important initiating event behind atherosclerosis.

Nanobacteria, formally known as *nanobacterium sanguineum*, are so minute that they eluded researchers for decades. They are $1/100^{th}$ of the size of normal bacteria, and until recently, nobody believed that anything so small could even be alive. It turns out, however, that nanobacteria are not only very vital and thriving, but may cause damage to our health in more ways than we could imagine.

One of our missions has been to explain how and why heart disease occurs in people who do not exhibit the traditional risk factors. If we can identify the cause, then we can help prevent thousands of unexplained deaths each year. There have been numerous hypotheses, but so many never pan out. Take *Chlamydia pneumoniae*, the pathogen that causes acute respiratory disease, for example.

In news reports, from just a few years ago, authorities proclaimed that infection with this bacterium probably accounted for much of the unexplained plaque in people. They hoped that doctors could treat the *C. pneumoniae* and thereby eradicate the plaque. Well, further research uncovered that *C. pneumoniae* was only found in a small percentage of all plaque and was certainly not pervasive enough to be a major cause for it.

An Apt Analogy

To help illustrate what the discovery of nanobacteria could ultimately mean for our health, it is important to consider the relationship between *Helicobacter pylori* and ulcers. It was only after years of having patients undergo gastric surgery that doctors learned the real culprit in many ulcers was a

bacterium known as *helicobacter pylori*. Surgeons were putting their patients with ulcers through major surgery, cutting their vagus nerve, and revamping part of their small intestine when, in most cases, the only treatment needed was antibiotics.

In the same way in another alarmingly common procedure, cardiac surgeons have been cutting and pasting blood vessels to "bypass" plaque-filled arteries. We may learn, instead, that a course of the right antibiotic is all that is needed for severely calcified arteries.

Scientists from the Hungarian Academy of Sciences have reported finding nanobacteria in more than 60% of carotid artery-clogging plaques studied. The Hungarians also validated previous research reports of how truly miniscule these bacteria are, and how easily they can enter the body via blood exchange and blood products. Their protective calcified apatite coat makes nanobacteria highly resistant to heat, radiation, and all antibiotics with the exception of tetracycline. Nanobacteria have been implicated in nephrolithiasis, polycystic kidney disease, and renal stone formation.

More research will determine whether nanobacteria are the real culprit behind coronary arteriosclerosis. For now it's prudent to keep in mind that microbes could play a substantial factor in the genesis of silent inflammation that could culminate in cardiovascular disease. We'll now discuss some of the research that looks at other viruses and spirochetes as well as the relationship of periodontal disease and the heart.

Spirochetes

In 1982, Willy Burgdorfer discovered the cause of Lyme disease when he isolated spirochetes of the genus *Borrelia* from the mid-gut of Ixodes ticks. Some researchers believe that as many as 60 million people in the US are infected with *Borrelia*, but that Lyme disease occurs in them only when their immune systems become overloaded.

Lyme disease has been reported in forty-seven states and on four continents, and ticks are not the only sources. Blood transfusions, fleas, mosquitoes, sexual intercourse, and unpasteurized cow's and goat's milk have also transmitted the disease. People with Lyme disease are often simultaneously co-infected with other viruses and bacteria.

The spirochetes responsible for Lyme disease do best in an anaerobic (low-oxygen) environment and cannot tolerate large quantities of oxygen. They can change their shape and chemical structure, and are more evolved than bacteria in many ways. Furthermore, these spirochetes can turn off several surface proteins, which have the effect of keeping the immune system from being able to detect them. This stealth-type camouflage prevents antibodies from attaching to them, and prevents the enzymes in the blood from finding and destroying them. In this way, the spirochete can penetrate virtually any tissue in our body including blood vessels, heart, brain and oral cavity.

Periodontal Disease

Multiple microbes including spirochetes, bacteria, and viruses can be cultured in and around the teeth and periodontal sections of the oral cavity. There is a significant relationship between gum disease and chronic inflammation. Low-grade inflammation, particularly in the periodontal areas of the mouth can cause immune system decline. Chronic persistent low-grade inflammation can raise CRP levels. In one study of 50 patients referred for angiography and assessed for periodontal disease, there was a significant relationship between the extent of coronary atherosclerosis and periodontal disease.

Cardiologists are especially cognizant of the relationship between oral hygiene, edentulous teeth, gum disease, halitosis and a strong probability of subsequent cardiovascular disease. Practicing good oral hygiene, taking antioxidants, magnesium, essential fatty acids and CoEnzyme Q10 can help support gum health, thereby reducing chronic inflammation.

Toxic Blood Syndrome

Many heart attacks and strokes occur when arteries are only one-third narrowed, so it is not the blood vessels that are of interest to us, but the blood flow when it is compromised by plaque rupture. Inflammation is the primary culprit responsible for vascular disease. In fact, 95% of chronically sick patients are hypercoagulable. Many of these patients have "toxic blood syndrome," which is characterized by elevated levels of oxidized LDL, CRP, fibrinogen, homocysteine, Lp(a), and ferritin. Elevated CRP was the most significant of 12 markers in 28,263 healthy postmenopausal women as a predictor of future cardiac events. It was the strongest risk factor associated with an acute coronary event such as plaque rupture and myocardial infarction. In acute myocardial infarction there has also been an increased mortality in patients with higher CRP levels when compared to age-matched cohorts with lower levels.

Homocysteine

Hyperhomocysteinemia is not only a risk factor for cardiovascular disease; it has also been implicated in osteoporosis, low birth weight, neural tube defects, certain cancers, and Alzheimer's disease. Homocysteine is directly toxic to blood vessels in the brain and heart. Elevated levels wreak oxidative stress, and cause endothelial dysfunction, neuronal DNA damage, and even mitochondrial membrane weakening. High homocysteine levels in the brain cause cerebral microangiopathy and apoptosis of neural cells.

Hyperhomocysteinemia has been shown to double the incidence of Alzheimer's disease. In one study of 1092 people who were "dementia free" over an eight-year follow-up, 111 developed dementia and 83 developed full-blown Alzheimer's disease. Those with homocysteine levels of 14 µmol/L and above doubled their risk, and for every 5µmol/L increase their risk of developing Alzheimer's disease rose by 40%. The correlation between homocysteine levels and Alzheimer's was independent of age, gender and APOE genotype.

One of the most important factors in lowering homocysteine is the use of various B vitamin components including folic acid, calcium folinate, vitamin B6, vitamin B12, pyridoxal phosphate, and betaine hydrochloride (trimethylglycine). Garlic, beets, broccoli, and SAMe are also potent methyl donors in reversing toxic homocysteine back to harmless methionine.

It is important to be aware that approximately 40% of the population has genetic polymorphisms of 5,10-methyltetrahydrofolate reductase (MTHFR). What this means is that a large percentage of people, particularly those of European and French Canadian decent, cannot adequately metabolize synthetic folic acid. For these patients, refractory homocysteine levels will persist despite the use of B vitamin components and natural methylators.

People with hyperhomocysteinemia, that are resistant to usual B vitamin and methylator treatment, need Metafolin (HS Fighters: 877.877.1970), a very highly bioavailable form of methyltetrahydrofolate that also readily crosses the blood brain barrier.

What are acceptable levels of homocysteine? A homocysteine level of less than 7 µmol/L is ideal. Levels over 10 are unacceptable, especially in those with presenile dementia or arteriosclerotic cardiovascular disease. High homocysteine levels are treacherous, especially in the company of elevated Lp(a) because together they can induce the binding of Lp(a) to fibrin, a clot promoting mechanism . On an anecdotal note, Dr Sinatra has seen elevated homocysteine in the company of high Lp(a) in many of his patients who have heart disease, and treats it aggressively in them as well as those at risk for developing it.

Lipoprotein (a)

Lipoprotein (a) is a cholesterol particle with a disulfide bridge that is highly inflammatory and thrombotic. In a ten-year follow-up of myocardial infarction in 5,200 participants, those with the highest Lp(a) levels had a 70% increased incidence of myocardial infarction. For the clinical cardiologist Lp(a) is

probably the most difficult risk factor to neutralize. Because statin therapy is known to increase Lp(a), it is important that physicians track Lp(a) levels whenever treating hypercholesterolemia with statin therapy.

We have found that targeted nutraceuticals, especially liver supporting nutrients, CoEnzyme Q10, policosanol, and Omega-3 essential fatty acids, i.e., fish oils, in combination with niacin, and/or Niaspan will often neutralize the toxic effects of Lp(a).

Fibrinogen

Fish oils, garlic, bromelain, and natural Cox 2 inhibitors such as ginger and green teas will also help to alleviate high fibrinogen levels, a phenomenon observed in smokers and postmenopausal women with more frequency. Levels greater than 360 mg/dl are undesirable and have been associated with coronary calcification. This coagulation protein has been successfully neutralized with the nutrients mentioned above as well as enzymes that will be discussed later in this chapter.

Ferritin

Serum ferritin (high levels of stored iron) is also associated with increased risk for myocardial infarction. The high levels of iron that can oxidize LDL cholesterol may reflect iron overload or hereditary hemochromatosis. In the setting of high iron overload it is important to cut iron consumption to a minimum and use high-dose vitamin C with caution, as mega doses of greater than 500mg daily may enhance iron absorption from the diet.

In summary, it is important to assess all these "toxic blood" components, particularly when treating an individual with a family history of early-onset, or what we call premature, cardiovascular disease. Certainly, homocysteine and Lp(a) associations can have a genetic predisposition. The assessment of arteriosclerosis needs to go beyond cholesterol and triglyceride monitoring, and the toxic blood components cited are a good place to start in light of the fact that these inflammatory and thrombotic components are the most undesirable factors in the generation and promotion of plaque.

Younger plaque is soft and covered by a thinner fibrous cap, loaded with cholesterol. It is also quite volatile. It is this young plaque that so often goes unnoticed on angiograms. To some extent many of us have atherosclerosis; thus the real question should be, "Do you have an unstable plaque?" Inside fatty plaques, macrophages can become engorged, becoming incompetent to do the job they are designed to do. Instead, they evolve into angry foam cells, releasing pro-inflammatory toxic substances that may result in further instability to the plaque.

It used to be thought that cholesterol was the major marker for atherosclerosis. This is no longer the case. Pro-inflammatory messengers, referred to as cytokines and leukotrienes, are now recognized as behind-the-scene culprits. When inflammation is present, specific cytokine messengers are heralded into service to instruct the liver to increase intermediary inflammatory substances that are released into the blood and serve as measures of underlying chronic inflammation. CRP is one of those intermediary substances. By interrupting and arresting inflammation we can help to prevent atherosclerosis, hypertension, heart disease, stroke, and even sudden death. Let us look at what we can do to lower inflammatory mediators and minimize SI in the body.

WAYS TO REDUCE INFLAMMATION

Detoxification

The chemical cocktail of stress, pesticides, industrial wastes, poor diet, heavy metals, chronic infections, and drugs greatly contribute to the SI in our bodies as we age. As the toxic load increases, so does the incidence of chronic disease (Figure 2).

We believe that regular detoxification should become part of a healthy lifestyle. Although you should always avoid obvious toxins whenever possible, it is extremely difficult to avoid many toxins that are present everywhere in the environment today.

That is why each of us should incorporate certain daily detoxification strategies to help flush out the toxins that are circulating in the blood or are lodged in soft tissues and vital organs.

These strategies should include diets such as the Omega Zone diet, bathing, infrared saunas, massages, and liver and colon cleansing on a regular basis. Also, a detoxifying nutraceutical formula can provide additional protection from the various toxins. Such detox formulas should include liver supporting nutrients like milk thistle, artichoke, and L-Carnitine. Alpha lipoic acid and other sulfur-containing nutraceuticals will help chelate heavy metals. Indole-3-carbinol will also assist in the conjugation of the metabolites of petrochemicals like xeno-estrogens out of the body.

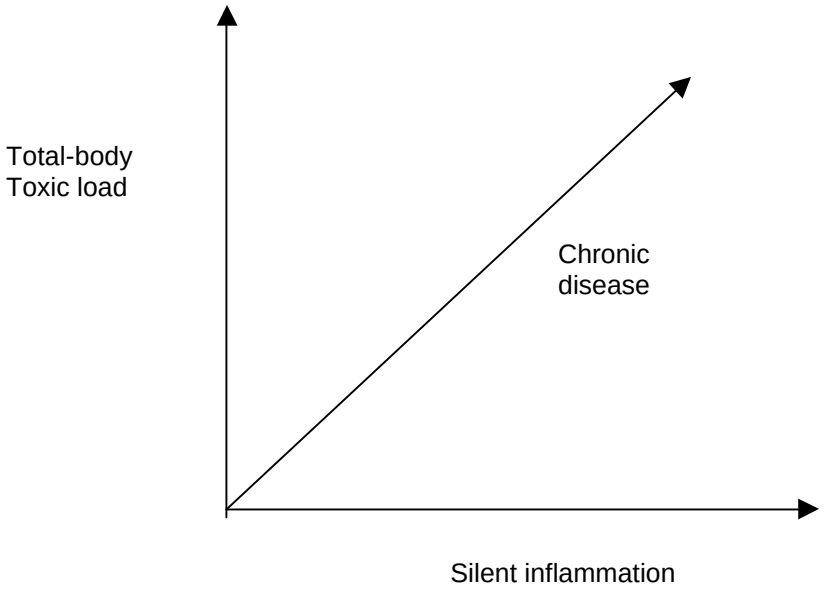

Figure 2. Silent Inflammation and Chronic Disease

Diet/Weight Loss

More than 65% of the US population is now overweight. Researchers speculate that obesity will replace tobacco as the major risk factor for disease and death in America today. Recent research suggests that adipocytes have become the "home" for inflammatory cytokines. This is probably one of the major reasons obese people tend to get more cancer, Type II diabetes, and heart disease, as well as other inflammatory disorders. The obesity and diabetes epidemics are linked to the "metabolic syndrome," with its deadly quartet of:

a. High insulin levels
b. Weight gain (apple shape)
c. Elevated triglycerides (TG) and decreased HDL
d. Elevated blood pressure

Metabolic syndrome also places patients at a much-increased cardiovascular risk. In fact, the most important finding in treating hypertension in the last decade has been an understanding of metabolic syndrome and its relationship with insulin resistance, a condition that can only be reversed through diet and exercise. Hippocrates knew best, many years ago, when he proclaimed: "Let food be your medicine."

For a diet to become a lifestyle, it must be convenient and not too complex. Most people become

overwhelmed deciding what they should and should not eat, based on the latest medical news. Designing a Zone meal is simple and involves dividing a plate into three sections. First, fill one-third of it with a protein (a typical portion is approximately the size of the palm of your hand), and fill up the other two-thirds of the plate with low-glycemic vegetables (broccoli, cauliflower, dark leafy greens, and others that won't raise your blood sugar rapidly), and fruit. Finally, add a dash of heart-healthy fat like olive oil to your salad or greens, avocados, or almonds. This is the way we have been genetically designed to eat. Dr. Sinatra prefers a Pan Asian Modified Mediterranean (PAMM) way of eating using the Zone principles because cultural societies following traditional Asian and Mediterranean diets have the lowest rates of cancer and heart disease in the world.

Nutraceuticals

Nutraceuticals are components of foods or dietary supplements that support healing. They include antioxidants, enzymes, vitamins and minerals, Co-Q10 and L-carnitine, garlic, green tea, and fish oil to mention a few. At the microscopic level, many of these nutrients and antioxidants penetrate into the cell and help eradicate free-radical damage, while decreasing inflammation at the same time.

Flavonoids and carotenoids are nutraceuticals that can have a positive impact on the body. For example, dietary antioxidant flavonoids, especially quercetin, were studied in the Zutphen Elderly Study. In this European study reported in the *Lancet*, researchers looked at mortality in elderly men. Results showed that a higher death rate was associated with a lower flavonoid intake. The dietary flavonoids consumed by the male subjects came primarily from onions, green tea, and green apples. Their results confirmed that all-cause mortality was reduced in those men consuming greater than 30 mg of flavonoids per day.

The cardiovascular benefits of similar oligomeric proanthocyanidins (OPCs), which add the bright colors to many fruits and vegetables, and also belong in the flavonoid class of nutrients, have also been noteworthy. OPCs inhibit xanthine oxidase, a promoter of the superoxide radical, platelet aggregation, and the oxidation of LDL. They improve blood vessel elasticity and integrity, and additionally have an "ACE effect" on lowering blood pressure. In animal research, OPCs have also demonstrated a cholesterol lowering effect.

Most people have heard of the "French Paradox," a term that describes the discrepancy between the traditional pate-rich, high-fat French diet and their comparatively low incidence of heart disease. It has been suggested that red wine consumption offsets the evils of a high-fat diet. But why, you ask? Researchers believe that OPCs named quercetin and resveratrol, as well as other flavonoids, present in grape skins are responsible for this victory over heart disease.

Magnesium

Magnesium is a mineral with favorable cardiovascular benefits: it acts like a calcium channel blocker to prevent spasm in blood vessel walls. Magnesium has a profound positive influence on vascular tone and reactivity, as well as platelet aggregations. In fact, a magnesium deficiency has been observed in those with insulin resistance and the diabetic syndrome. Taking 400-800 mg of bioavailable sources is recommended to anyone looking to lower blood pressure, block coronary artery spasm and Raynaud's, and even relieve symptoms of mitral valve prolapse.

In one study, magnesium supplementation decreased many symptoms associated with mitral valve prolapse including weakness, chest pain, shortness of breath, palpitations, and anxiety. Because many patients with mitral valve prolapse have an associated diastolic dysfunction of the heart's left ventricle (LV), CoEnzyme Q10 therapy, which improves LV cardiodynamics, is also instrumental to help improve quality of life for these patients.

CoEnzyme Q10

CoEnzyme Q10 is an essential biological cofactor produced endogenously in the body that is also found in the food chain. As a critical component in the electron transport chain in mitochondria, CoEnzyme Q10 has a crucial role in cellular energy production (by recycling adenosine triphosphate (ATP) as well as being a cofactor in its production) as an electron and proton carrier. Because CoEnzyme Q10 is vital to mitochondrial energy production, it has become the cardinal nutrient in metabolic cardiology.

Since it takes more energy to fill the heart than to empty the heart, CoEnzyme Q10's ability to support heart cell bioenergetics translates into improved diastolic dysfunction. Because of this action, CoEnzyme Q10 is instrumental in addressing diastolic dysfunction, and subsequent systolic dysfunction, that could lead to heart failure. Those with hypertensive cardiovascular disease, mitral valve prolapse, infiltrative cardiomyopathy, and especially those with statin-induced diastolic dysfunction, have improved with the simple co-administration of CoEnzyme Q10.

Other potential therapeutic uses of CoEnzyme Q10 include treating stable and unstable angina, ventricular arrhythmia, mitral valve prolapse, hypertension, congestive heart failure and toxin-induced cardiotoxicity (such as that seen in Adriamycin therapy). CoEnzyme Q10 is also appropriate in the setting of myocardial ischemia, and should be used as a myocardial-preserving agent during chemical thrombolysis for reperfusion, urgent angioplasty, and coronary bypass surgery. In fact, pretreatment with CoEnzyme Q10 for weeks before elective coronary artery bypass grafting surgery has been shown to assist patients in weaning off of heart-lung bypass with improved cardiodynamics.

Since its discovery in 1972, there have been multiple controlled trials on the use of CoEnzyme Q10 with more than 40 showing some benefit, and 4 showing none. In one double-blind study of 641 patients receiving CoEnzyme Q10 (2 mg/kg or placebo for one year), a 20% reduction in hospitalizations in the CoEnzyme Q10 group was realized compared to those taking placebo. The CoEnzyme Q10 group had a better quality of life as well as lowered bills for medical care.

Another topic of special emphasis is statins: the number of these drugs prescribed every year is astounding, and may have a link to the increase number of cases of idiopathic cardiomyopathies that abound. Statin drugs can cause profound deficiencies in CoEnzyme Q10 because the HMG-reductase inhibitors "kill" cholesterol so successfully by interfering with the same biochemical pathway that produces endogenous CoEnzyme Q10 in the body. So, CoEnzyme Q10 should be supplemented by anyone receiving 3-hydroxy-3 methylglutaryl coenzyme A-reductase inhibitors (statins). CoEnzyme Q10 treatment has been noted to counteract the side effects of myalgias associated with statin therapy, and is appropriate to treat this side effect.

CoEnzyme Q10 production drops off with aging, and while its side effects (nausea, abdominal discomfort, and excess energy or anxiety) are rare, it is contraindicated for healthy pregnant or lactating women because the unborn and newborn produce sufficient quantities of the compound on their own. For further information on CoEnzyme Q10, the reader is referred to *BioFactors*, Volume 18, 2003. This journal is a peer-refereed review of original papers arising from the 3rd Conference of the International CoEnzyme Q10 Association held in London UK, November 2002. Several investigations discussed the complex biochemical and metabolic functions of CoEnzyme Q10.

Metabolic Cardiology

We believe that a new subspecialty in cardiology, i.e., "metabolic cardiology", will be driven by the biochemical interventions that will be utilized to optimize metabolism in cardiac myocytes. By supporting cellular function, such as ATP production, Coenzyme Q10 and other similar agents defend precious heart cells from the ravages of aging, toxins, and the myriad of other conditions that ultimately wear down mitochondrial function and eventually cause cardiovascular pathology. Metabolic cardiology is going to be one of the next great emerging fields, arising from a new emphasis on the relationship between ATP and energy in the heart. Coenzyme Q10, L-Carnitine, and D-ribose, will be the most

significant players.

The synergism of CoQ10 and L-Carnitine, for example, has been known for approximately 15 years. Italian researchers have demonstrated an extraordinary synergistic effect of these nutrients in several conditions, such as ischemia, reperfusion injury of the heart, fatty infiltration of the liver induced by alcohol, and hyperbaric oxygen toxicity in experimental animals. These nutraceuticals offer remarkable biochemical and metabolic complementary roles.

L-Carnitine has the unusual ability to enhance fatty acid oxidation in cells while removing excess harmful substances, such as acyl groups and free radicals, from inner mitochondrial membranes. Since 60% of cardiac energy comes from the beta-oxidation of fats, employing L-Carnitine is instrumental in treating angina, myocardial infarction, congestive heart failure, and peripheral claudication.

In the setting of acute and/or chronic ischemia, Coenzyme Q10 and L-Carnitine offer significant clinical advantages with absolutely no risk to the patient. These nutrients, while supporting cardiovascular function, also preserve the inner mitochondrial membrane and may even support vulnerable cells, particularly senescent myocardium from apoptosis. Recently, another new emerging compound has been gaining increasing support among our fellow "metabolic cardiologists."

D-ribose is a biochemical, five-sided sugar that has been extensively investigated in both animal and clinical models. Investigators believe that under certain cardiac conditions, especially during ischemic episodes like angina and myocardial infarction when the heart is deprived of oxygen, there is a profound depression of energy compounds such at ATP. A drop in ATP means a subsequent decrease in myocardial function causing the heart to struggle as a pump. This is probably one of the reasons that we see so-called "stunned myocardium" following acute coronary artery syndrome and myocardial infarction. Researchers are now learning that D-ribose plummets during ischemia, and that it takes considerable time to recover and regenerate ATP compounds. D-ribose helps to replenish the severely depleted adenosine nucleotide pool in the ischemic monocytes, a process that is critical to ATP synthesis.

It has been previously noted that coenzyme Q10 and L-carnitine increase exercise time and delay the onset of electrocardiographic evidence of ischemia during exercise stress testing of angina subjects. The pentose sugar D-ribose (15 grams daily) has been similarly noted to protect cardiac cells from ischemic episodes and increase exercise time before symptom onset due to angina. The combined antioxidant, membrane-stabilizing and metabolic activities of CoQ10, L-Carnitine, and D-ribose will play a significant role in the setting of silent and overt myocardial ischemia.

As new research unfolds, these nutraceuticals provide an exciting platform in cardiovascular disease to improve quality of life for patients suffering from progressive angina, unstable angina, acute coronary syndrome, diastolic dysfunction, and congestive heart failure. Metabolic cardiologists will upgrade the level of patient care as they gain further insight into this new great emerging field in cardiovascular medicine.

Enzymes

Within a single cell there are roughly 100,000 genes, the majority of which house enzymes, the workhorses of the living cell. All enzymes are proteins, and are also composed of long chains of amino acids. Also recognized as the corporeal life force, enzymes are involved in nearly every metabolic process in the body. As we age, or develop a disease, our body has fewer and fewer enzyme stores at its disposal. For example, a sixty-year-old has 50% fewer enzymes than a thirty-year-old.

Enzymes function as catalysts and make things work faster. They have the ability to initiate, accelerate, and terminate biochemical reactions in the body. Enzymes increase the activity of the cells that are important to a healthy immune system, and they are integral in maintaining homeostasis. Provided there are sufficient enzymes, cases of acute inflammation may be healed within a few days. With chronic SI, however, the continued shortage of enzymes leads to an eventual breakdown of the reactions needed to remove diseased tissue from the body and return it to normal health. Enzymes are important biological response modifiers and play a vital role in controlling inflammation and promoting heart health.

Although wobenzyme has been used exclusively by Olympic athletes over the years to reduce inflammations in tendons, muscles and joints, newer inflammatory mediators such as nattokinase have been gaining popularity for reducing inflammatory mediators such as CRP. In the future enzymes such as nattokinase and wobenzyme as well as fish oil will be utilized in reducing the total "inflammatory load" in the body.

Omega-3 Fatty Acids

Leading medical institutions worldwide have confirmed that daily supplementation with pharmaceutical-grade fish oil, rich in omega-3 essential fatty acids, is your most powerful weapon for assuaging inflammation.

Although the evidence in the cardiovascular literature resounding that omega-3 essential fatty acids are appropriate in the treatment and prevention of cardiovascular disease, the most recent noteworthy trial appeared in the *Lancet*. In this study of approximately of 11,000 Italian participants who suffered a myocardial infarction, the group given fish oil had a 45% lower incidence of sudden cardiac death and a 20% reduction in all-cause death over a three- year period. Those receiving fish oil also appreciated a reduction in blood pressure, suppression in platelet activity, drop in triglyceride levels, and a marked attenuation in cardiac arrhythmia. Perhaps the most noteworthy way fish oil seems to attain its beneficial effect is its favorable impact on heart rate variability (HRV). Omega-3 essential fatty acids also reduce plaque rupture by literally "getting inside plaque" to stabilize it and rendering it less vulnerable to rupture. Eating "healthy fish" or taking fish oil supplements is an absolute must, especially for the populations at risk for cardiovascular disease. In fact, just two fish meals per month will reduce an individual's risk of sudden cardiac death by 50%.

Unfortunately, because most fish have become contaminated with toxins, such as dioxins, mercury, and PCBs, consuming fatty cold-water fish as your primary source of omega-3s is now being questioned. To combat this situation, choose a pharmaceutical-grade fish oil that has been concentrated and purified to the highest standards possible. Pharmaceutical-grade fish oils are, as a result, toxin-free and can be ingested without any fear of toxins or contaminants found in the fish we eat, or as may be contained in more commonly available omega-3 supplements.

Control of Chronic Infections without Antibiotics

Current research from the National Institutes of Health (NIH) and elsewhere shows that while chronic infections are really never eradicated, they can be controlled as long as a person remains on an antimicrobial program. The disadvantages of living on antibiotics, however, do not make this an attractive or plausible way to live.

Research has shown that some people who have taken tetracycline for acne for years have less atherosclerosis. This previously anecdotal observation now makes sense when we recognize that many people have chronic infections, such as CMV and nanobacteria, which contribute to the SI and elevated CRP levels we see. It is our opinion that if we boost the body's natural immunity with select nutraceuticals and practice good oral hygiene, we can thwart many of these chronic infections. These formulas can be taken for an entire lifetime without any substantial risk.

We have already seen how most infections are masked by soluble fibrin monomers such as the ones in the protein coats of the agent that causes Lyme disease, and how useful enzymes like Wobenzyme are in the treatment of these chronic infections.

After studies done in Florida at Hemex Laboratories, researchers are now convinced that the presence of any form of infection is associated with inflammation and severely localized hypercoagulability (toxic blood). Therefore, to help get adequate blood flow to the infected tissues to completely extirpate these stubborn infections, we believe it is essential to take targeted nutraceuticals.

Garlic is also important because many microbials cannot grow well in its presence. Malic acid helps bind iron so that many harmful organisms requiring iron for their reproductive cycle are kept from replicating. We have found TOA-Free Cat's Claw, or Samento, to be very helpful for Lyme disease. Samento (*uncaria tomentosa*), is extremely potent and able to significantly strengthen the immune system. Samento also has powerful anti-inflammatory, antioxidant, and anti-tumor properties. Research shows that Samento eliminates dependence on steroids and inhalers, reduces HIV and hepatitis-C levels, drops CRP levels, and lowers some tumor markers, such as prostate specific antigen (PSA).

Other nutraceuticals, such as elements of colostrum, grapefruit seed extract, rice bran, rhodiola rosea (found in Northern Alpine regions), and many different mushrooms like shiitake and reishi, also have powerful effects in fighting chronic infections and inflammation.

Pharmacology

While many physicians are unaware of the important role of eicosanoids, the pharmaceutical industry is very cognizant of these powerful hormones because many of the more popular drugs used today alter eicosanoid levels. Most of these drugs inhibit the enzymes that synthesize eicosanoids and have little therapeutic effect in altering the balance of "good" and "bad" eicosanoids.

As an example, the cyclooxygenase enzymes (Cox-1 and Cox-2) are responsible for the synthesis of prostaglandins and thromboxanes, but they can be blocked by aspirin, Cox-2 inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs). Furthermore, the only drugs that can inhibit all types of eicosanoid synthesis are corticosteroids; while blocking the synthesis of "bad" eicosanoids may reduce inflammation, the anti-inflammatory and other beneficial properties of "good" eicosanoids are obstructed in the process. Unfortunately, the undesirable side effects make long-term corticosteroid usage inadvisable.

Recent research indicates that the cardiovascular benefits of statin drugs (first used to decrease cholesterol levels) may be due primarily to their anti-inflammatory actions that reduce CRP levels. As pointed out earlier, CRP is associated with generalized inflammation and is considered a significant biomarker for the development of heart disease. New research suggests that statin therapy also increases insulin levels and insulin resistance, which may amplify the future risk of heart disease, diabetes, and obesity.

Our position on statins was summarized in an editorial in the March 2003 issue of *The Southern Medical Journal*. Although there is little doubt that statin therapy can significantly reduce the incidence of coronary morbidity and mortality, especially for those who are at the greatest risk of developing coronary artery disease, over-utilization of statins in the population that does not have overt coronary artery disease or silent inflammation should be avoided.

However, recent interventions using electron beam computerized tomography (EBCT) to demonstrate an association between high coronary calcium burden (score greater than 1,000) and cardiac events suggest that statin therapy may prove to be a good intervention. In other words, in patients with myocardial infarction, coronary artery bypass surgery, stent emplacement, stable or unstable angina, and high coronary calcification, statin therapy should be utilized regardless of their cholesterol levels. In diabetics with high cholesterol and high inflammation indices determined by elevated CRP, homocysteine, LP(a), and other inflammatory cytokines, statin therapy is also beneficial. The use of statins in high-risk coronary patients, especially those with inflammatory markers, is good medicine.

However, overuse of these potent pharmacological agents with known and unknown side effects in otherwise healthy people is not considered smart medicine. We also do not know the long-term effect of statin therapy, especially since longitudinal studies for those taking statins for more than 10 years are lacking. Carcinogenicity and cardiomyopathy (diastolic dysfunction) associations with statin therapy may cause us to rethink our posturing on statin therapies in the future. For now, we implore physicians to select statin therapy to address the individual risks and health needs of each patient, and avoid prescribing

them simply to treat high cholesterol numbers alone.

Exercise and Stress Management

There is no doubt that exercise should be an indispensable part of any person's total health promotion program, not only because of its many benefits, but also because of the sense of well being that exercise provides.

The biological basis of all these benefits is that they are mostly a consequence of the hormonal and weight loss changes that various types of exercise induce. The real key is that the higher the intensity of exercise, the more the hormonal responses are affected. Moderate to higher-intensity aerobic exercise reduces insulin (and therefore inflammation), and increases glucagon levels: exactly as a Zone-favorable diet does. However, high intensity exercises such as marathon running, wrestling, boxing, and other professional and Olympic sports, to mention a few, can cause enormous oxidative stress and subsequent antioxidant insufficiency. The most common antioxidants that are depleted with regular intense exercise include CoEnzyme Q10, magnesium, and vitamin E. In a premenopausal female athlete severe iron deficiencies may also been noted. High intensity exercise, like emotional stress, can enhance the oxidation of LDL.

Emotional stress can cause inflammation just as easily as oxidized LDL. The medical community now recognizes that a supercharged sympathetic nervous system (SNS) can set you up for cardiac events and sudden death. Heart rate variability, an assessment of sympathetic and parasympathetic nervous system balance or imbalance, can now be performed in an office setting. Anger, hostility, and the inability to express feelings are also serious cardiovascular risk factors. In addition to exercise, various mind-body approaches can be very effective in altering SNS response and inflammation.

CONCLUSION

To underscore the importance of the concept of "fire in the heart," a front page article in the February 23, 2004 issue of *Time* magazine highlights the link between inflammation, cancer, heart attacks, Alzheimer's disease, and other diseases. Everywhere we turn we are facing evidence that inflammation plays a larger role in chronic disease than we physicians ever thought. We need to ask ourselves the rhetorical question "is your heart on fire?" To some degree, silent inflammation is insidiously eroding our vital organs.

One of our colleagues, neurologist Dr. David Perlmutter, would agree. His newest book, The *Better Brain Book* with Carol Colman, discusses the inflammatory and toxic environment of the aging brain. Plaque stabilization, whether in the brain, heart or other organs will eventually come under the domain of dietary Cox 2 inhibitors including green tea, ginger, curcumin, oregano, onions, garlic and fish oil. In addition, vital nutraceuticals such as folic acid, fish oil, enzymes, CoEnzyme Q10, magnesium, quercetin, L-Carnitine, D-ribose, and others will continue to be utilized by like-minded physicians as safe alternative options.

More integrative therapies will include statin therapy, ACE inhibitors, low-dose aspirin, antibiotics and leukotriene inhibitors as more conventional approaches to halting the ravages of inflammation. The integration of proven complementary therapies with conventional treatments in heart disease will allow physicians to offer many additional options to their patients.

We urge physicians to keep an open mind and harbor a willingness to support conventional methodologies while investigating alternatives that can improve quality of life and reduce human suffering. Choosing from the best conventional and complementary options is the only logical and ethical thing to do to help douse the inflammatory inferno in the heart.

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USEFUL RESOURCES

- Hemex Laboratories, www.hemex.com
- Nutramedix, www.nutramedix.com and www.samento.com.ec
- The Zone Lifestyle, www.zonecafe.com
- Sinatra S. and Simpson G., *Spa Medicine*, Basic Books, 2004

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