Franklin Cardiovascular Six-Prong Approach To Wellness

About the Program

Nicholas DePace, M.D., F.A.C.C., is a board certified cardiologist who has various types of certifications; including nuclear cardiology, echocardiography, lipidology (study of cholesterol and related compounds), and internal medicine. He has been practicing clinical cardiology for 34 years, publishing extensively in the fields of cardiovascular disease and autonomic dysfunction. He has authored or coauthored nearly 100 abstracts and journal articles. He has also coauthored two books: *The Heart Repair Manual*, published by W.W. Norton (NY, NY) in 1992; and *Clinical Autonomic* Dysfunction—a medical textbook written with Colombo, Aurora, and Vinik—published by Springer Publishers (NY, NY) in 2015.

Dr. DePace treats and diagnoses various diseases that are cardiac or related to cardiology. His major patient population consists of patients with atherosclerosis. Atherosclerosis is derived from Greek and translates to, "hardening of the arteries". In addition, he treats patients with various disorders of cholesterol abnormalities, as he is a certified Lipidologist who has had training in lipid-board certification and lipidology. Many cases are very complex and are genetic in basis. In addition, Dr. DePace developed a program in the early 1990s, which he tabbed, "The Philadelphia Formula for Reversing and Halting Atherosclerosis". Components of it are within his book, *The Heart Repair Manual*. This program predated risk stratification by the famous Framingham Study, which came out several years later. The Framingham Study was an epidemiological study in which a cohort of subjects in Framingham, Massachusetts, was followed prospectively for several decades and risk factors were identified as causative agents for coronary heart disease.

In addition, Dr. DePace's program focuses on autonomic dysfunction. One of the main systems responsible for the capability and adaptability is the autonomic nervous system and the interplay between its two branches, which are the (1) parasympathetic and (2) sympathetic nervous systems. The autonomic nervous system is the regulatory branch of the nervous system. It consists of a central portion and a peripheral portion of the nervous system. The autonomic nervous system controls regulation of blood pressure, heart rate, airway size, airflow to lungs, digestive function, sweat production, bladder control, sexual function, nervous function (including depression and anxiety), gland and hormone function, and pupil size. The two components, parasympathetic and sympathetic, need to be

in balance. Autonomic dysfunction results when there is imbalance between the parasympathetic and sympathetic components. This is nicely explained in his introductory chapter, specifically page 3, of his coauthored textbook, *Clinical Autonomic Dysfunction*.

There are many disorders involving autonomic nervous system dysfunction. These include chronic fatigue; fibromyalgia; and various forms of fainting or pre-fainting, which we respectively term, "syncope", and "near syncope". Digestive problems, such as gastroparesis, gastroesophageal reflux disease, and irritable bowel syndrome, are also affected by autonomic nervous system dysfunction. Most importantly, a large percentage of patients in the world have what is termed, "orthostatic intolerance". This occurs when people are in the upright position—or standing or walking—and develop evidence of lack of cerebral perfusion, or blood flow to the head, which can present itself as dizziness, giddiness, brain fog, and cognitive dysfunction. This orthostatic intolerance syndrome is up to 97% of the time associated with chronic fatigue syndrome; which is defined as six months of significant exhaustion associated with oftentimes unrefreshing sleep, daytime somnolence, swollen lymph nodes, sore throat, depression, and an inability to function. It is felt that many of these disorders—including migraines; neurodegenerative diseases, such as Parkinson's, Alzheimer's, dementia and other more complicated neurological syndromes; asthma; and various forms of lung disease, such as COPD—may not only involve the autonomic nervous system, but also dysfunction in mitochondria of the cells in the body. We term these, "mitochondrial dysfunction disorders".

The mitochondria are small components of all the cells in the body, except for the red blood cells, for the most part. These are the power factories of the body. The mitochondria produce the energy molecule, ATP. ATP is derived from food products we derive, which become metabolized and eventually converted to this energy molecule, allowing us to perform our everyday activities. ATP is important for muscle contraction, for example. Lack of ATP can cause chronic fatigue syndrome and other disorders pertaining to autonomic and mitochondrial dysfunction. The mitochondria are special in that they produce a significant amount of harmful compounds in the body, called, reactive oxygen species (ROS). These compounds are very toxic and, if not neutralized by antioxidants (such as vitamin E, vitamin C, alpha lipoic acid, or coenzyme Q10), can cause damage to DNA particles, proteins, lipids, and other components of the body and cell membranes. This promotes disease, especially atherosclerosis and various forms of cancer.

The DePace formula is a six-prong approach in an attempt to maintain a healthy autonomic nervous system and mitochondria in the body. This program also attempts to slow down atherosclerosis production in blood vessels of the body.

The six-prong approach was developed after many years of empirical clinical experience with thousands of patients. It is partially based on valuable information obtained from the medical literature, including many significant studies. It also involves incorporating principles of biochemistry and theories of biological feasibility. While this program does not diagnose or treat diseases, it is very useful in promoting wellness. It does involve a combination of commonly-used pharmaceutical agents—for example, statins to lower cholesterol when necessary—along with various nutraceuticals, beneficial lifestyle behavior (including exercise and stress reduction), and a Mediterranean diet. It is the goal of this program to create an antioxidant milieu so that, in principal, oxidative stress—which occurs when there is an imbalance with too much reactive oxygen species compared to antioxidants—is depressed.

Pharmaceutical agents are developed by research and development companies and pass rigorous protocols before they are accepted by Food and Drug Administration agencies. They require prescriptions by licensed physicians, for the most part. They are primarily backed by what are known as randomized, controlled, clinical studies or similar-type well-designed studies, which demonstrate the efficacy of these medicines, especially in treating various ailments. Nutraceuticals are called "functional foods" and are part of functional medicine. A nutraceutical is a food product, such as a fortified food or supplemental dietary product, or vitamin that is believed to provide some health or medical benefit above its nutritional value. They are not used to diagnose or treat diseases.

Hippocrates, the father of ancient medicine, said, "Let food be your medicine." The Mediterranean Diet has been shown in numerous studies to be efficacious and perhaps the most valuable diet in reducing incidence of heart disease and cancer in large populations of patients. It is very similar to the Japanese Diet in many respects. Fish is a component, as is the omega-3 fatty acid, which is a component of fish. The Mediterranean Diet is a plant-based diet consisting of three major components: olives, grapes, and wheat. Small quantities of wine are allowed and organ meats are limited. Healthy dairy products, such as yogurt, may be included. Since the Seven Countries Study was started in the 1970s by Dr. Ancel Keys, numerous studies have validated the importance of this particular diet in maintaining wellness and have demonstrated advantages in weight loss, cardioprotective ability, cancer-protective ability, improvement in diabetes or insulin resistance, and providing other major advantages.

Exercise is a key component of wellness as it beneficially affects the antioxidant environment, reduces inflammation in the body, maintains ideal weight, enhances the good cholesterol in the body to work as a vacuum cleaner, reduces blood pressure, reduces weight, reduces stress, and improves both

autonomic dysfunction and potentially the function of the millions of mitochondria cells in the body. There is no better modality, including pharmacological agents, that can do all of these things.

Psychosocial stress is a major risk factor for heart disease. This was highlighted in the INTERHEART Study, which involves 52 countries and showed a significant risk of heart attack in individuals experiencing psychosocial stress. Reduction of psychosocial stress is one aim of the six-prong approach to wellness in the DePace program. It can involve meditation, yoga, exercise, biofeedback, relaxation and breathing exercises, or other recreational activities that produce beneficial effects.

Three types of nutraceuticals are utilized in this program. Omega-3 fatty acids are extremely important as anti-inflammatory molecules. The others are nitric-oxide-promoting compounds or food products, such as L-arginine, L-citrulline, L-carnitine, and beet root extract (which is a source of inorganic nitrates from the diet). For beneficial antioxidant effects, which we term a mitochondrial approach (since most oxidants in the body are produced in the mitochondria), we use specifically alpha lipoic acid and coenzyme Q10 in concentrations we feel are optimal. Also, folic acid, B vitamins, vitamin D, and magnesium are very important.

Dr. DePace graduated from the Mt. Sinai School of Medicine in New York in 1978. He did his medicine training and cardiology training at Hahnemann Hospital, which was founded by Dr. Hahnemann, the father of homeopathic medicine. Homeopathic medicine is a medical philosophy practice using a holistic natural approach to treat illnesses based on the concept that the body can heal itself. It involves a concept of homeopathic dilution that is, "like heals like". DePace's program modifies this somewhat in that it treats patients holistically with the lowest doses of agents that are necessary to combat a disease.

Dr. DePace has studied many of the works of the famous physician, Sir William Osler (1849-1918). Sir Osler, the father of modern medicine and one of the four founding professors of John Hopkins University, was a physician, pathologist, historian, philosopher, author, teacher, and bibliophile. He created the first residency program for specially-trained physicians. He brought students out of lecture halls and into wards. He has a great impact on modern medicine. Dr. Osler taught, "One of the first duties of physicians is to educate the masses not to take medicine." While he did not believe that no medicines were necessary, it certainly appears that he prescribed to the concept that more is not better; that is, too much medicine may not be beneficial. He also stated, "The person who takes medicine must recover twice, once from the disease and once from the medicine." He went on to state, "The good physician treats the disease. The great physician treats the patient who has the disease." Lastly, he said, "Gentleman, I have a

confession to make. Half of what we have taught you is in error, and furthermore, we cannot tell you which half it is." He was a very honest and forthcoming physician whose didactics persist to this day in medical wards.

Dr. DePace has always believed that there needs to be a proper balance between pharmacological agents that are taken and lifestyle changes. There needs to be a proper balance between both parts of the autonomic nervous system, the parasympathetic and sympathetic branches. There also needs to be a balance between oxidants and antioxidants, as too many oxidants will favor the process of oxidative stress, which creates a surplus of reactive oxygen species (ROS) that damage tissues and proteins and promote many diseases, as are mentioned above. He also believes there should be a balance between work and relaxation (lack of stress), a yin and yang balance emphasized in this program.

I. Omega-3 Fatty Acids

In regards to the first prong of the program, he addresses omega 3 fatty acids. Omega 3 fatty acids are used to lower triglycerides and make the bad or "lousy" LDL particles more buoyant and less sticky so that they do not stick to the artery walls. Also, the fish oil components prevent the oxygen from combining with the bad cholesterol particles in the body. When oxygen combines with bad cholesterol particles in the body it creates oxidized LDL cholesterol which becomes incorporated in the blood vessel wall after being engulfed by scavenger cells called macrophages and forms foam cells. It attempts to avoid the formation of foam cells, which occur in teenage years and onward, by lowering serum cholesterol with statins or other related medicines if necessary, fish oils and lifestyle changes and diet. Keeping LDL and bad cholesterol low, there is less chance of an abundance of these foam cells to form and become plaque in the arteries. Dr. DePace also attempts to keep an antioxidant environment in the body so as to prevent these bad cholesterol particles from becoming oxidized and more easily becoming incorporated in the blood vessels of the body. Fish oil or omega 3 compounds are one component of promoting an antioxidant type environment. Therefore, fish oils impair oxidation of the bad or "lousy" LDL particles and lipoproteins in the body and may prevent the initial step of atherosclerosis production which is the production of foam cells.

Dr. DePace's program involves a brain-heart theory which shows how the brain and heart connect and effect all of the organs of the body. One of the major components is inflammation in the body to promote disease. Fish oils are superb anti-inflammatory molecules called Resolvins and Protectins which are metabolites which can resolve inflammation. Inflammation is important in promoting many diseases including atherosclerosis, various forms of cancer and autonomic dysfunction disorders.

Various epidemiological and observational studies have shown that fish reduce cardiovascular mortality. Greenland Eskimos and Japanese fishing village inhabitants have lower incidents of heart disease than other non-fish consuming cultures. The Zutphen, Netherlands Study was a 20 year study which showed an inverse relationship between fish consumption and mortality from coronary heart disease published in the New England Journal of Medicine. The MRFIT study was another study which showed the benefits of consuming fish. The Chicago Western Electric Study fish consumption was a 30 year study of risk of heart attack published in the New England Journal of Medicine in 1997 and also showed beneficial effects of consumption of fish. Numerous studies have shown that populations that consume fish have a lower incidence of coronary heart disease.

Omega 3 fatty acids are the main type of saturated fat in fish products especially oily fish. Two main types are Eicosapentaenoic acid (EPA) which is a 20 carbon chain molecule and Docosahexaenoic acid (DHA) a 22 carbon atom. These are known as natural anti-inflammatories or membrane molecules since they go into the membranes of the body and prevent inflammation. One way to prevent inflammation is by impairing the ability of another type of omega 3 called omega 6 fatty acid from entering the membranes and they displace them. Omega 3 fatty acids are anti-inflammatory, anti-thrombotic and antioxidant whereas omega 6 fatty acids which we obtain from vegetable oil such as corn oil or sunflower oil can be prothrombotic, inflammatory and promote oxidation, all of which are harmful to the body. Another source of omega 3 fatty acid is from plants and is an 18 carbon known as alpha lipoic acid which is found in linseed oil. This is also beneficial.

Our recommendations and not that of any government agency is that if there is a family history of coronary heart disease, one should consider taking 600 mg of EPA plus DHA as a supplement. If there is a family history of sudden cardiac death or heart disease of significance, we recommend at least 1200 mg of EPA plus DHA. If an individual has a triglyceride level greater than 150, I will titrate the fish oil dosage upward also in an attempt the lower the triglycerides and use higher dosages. We have used up to 3 to 4 grams of fish oils in many patients especially those with high triglycerides and do monitor them for side effects such as excess bleeding.

Two major studies, the GISSI study published in Lancet in 1999 which was a study which showed that 11,324 patients with recurrent heart attacks taking 850 mg of EPA and DHA had, approximately, 50% lower instance of sudden cardiac death and the JELIS study published in Lancet in 2007 which involved 18,645 patients with high cholesterol and a five year follow up (all patients were on statins) showed a major event reduction of 19% with omega 3 fatty acids. This occurred despite no benefit of omega 3 lowering LDL counts. These two studies highlighted the importance and potential beneficial effects of how supplementation with omega 3 fatty acids can reduce heart disease including sudden cardiac death. Other studies have not shown such dramatic effect but have not included such large population of patients or such large dosage of fish oils as these have and in other studies, patients have been on more modern medications such as statins which may have reduced the efficacy of the fish oil supplements. Despite that, the American Heart Association has recently recommended in March of 2017 that fish oils are acceptable after heart attack and heart failure and that even a modest 10% reduction of heart disease manifestation would justify treatment with relatively safe therapy. Therefore, the conclusion of the American Heart Association (AHA) in its recent circulation article published by the American Heart Association in March of 2017 concluded that it was acceptable to take fish oil after heart attacks

and heart failure, however, did not see any new evidence for use in primary prevention of cardiovascular disease. American Heart Association has previously stated that omega 3 fatty acids should be part of a healthy diet and has recommended 1.5 g to 3 g a day of alpha lipoic acid as also being beneficial either through plant based foods or supplement capsule.

The American Heart Association dietary guidelines recommend at least two servings of fish per week in a healthy diet which includes vegetable oils such as soybean, canola, walnut, flax seed and food such as walnuts and flax seeds all of which are good sources of alpha lipoic acid.

Another omega 3 fatty acid, omega 9, is also anti-inflammatory. This is found in olive oil and will be discussed under the area of Mediterranean Diet. One brief note regarding fats. Saturated fats have no double bonds. Monounsaturated fats are relatively stable but not as stable as saturated fat. They only have one double bond. Polyunsaturated fats are the least stable but are the most flexible fats. They have more than one double bond. Omega 3 and fish oils omega 6 and vegetable oils omega 9 all have double bond and are considered polyunsaturated fats. Omega 3 fatty acids are found in fish and flax seed as mentioned. Omega 6 are found in various seeds and nuts and vegetable oils. Omega 9 is found in extra virgin or virgin olive oil. The body needs fats for structure of membranes and low fat diets may not be the best option as we originally once thought. The body needs some fat. The key is to pick the right fats. Omega 3 and omega 9 are considered most important. Therefore, DePace's formula employs intake of olive oil omega 9 and fish oil omega 3 liberally.

Fish oils, in addition to being antithrombotic in that they impair clotting and anti-inflammatory in that they impair inflammation, also dilate blood vessels by increasing nitric oxide. Nitric oxide is the messenger molecule of the body which improves the lining of the arteries or the endothelial cells of the arteries and promotes relaxation in the blood vessels. These endothelial cells produce an abundance continuously of nitric oxide (NO). Omega 3 fatty acids by keeping endothelial cells and blood vessels healthy permit them to continuously function and produce this beneficial nitric oxide compound which dilates and opens up the blood vessels of the body. This lowers blood pressure.

In addition, omega 3 have been shown to reduce vagal tone and lower heart rate which is cardioprotective. Vagal tone is a major component of the parasympathetic nervous system of the body and helps balance the autonomic effects of high sympathetic tone. Sympathetic tone is a fight or flight response which increases heart rate and blood pressure. Fish oils have been shown to produce an increased vagal effect which lowers the heart rate and may be the protective mechanism for sudden cardiac death with omega 3 fatty acids and fish oils.

Fish is also brain food. Omega 3 helps myelin sheaths of the nerve cells remain healthy. These are the passage ways which connect one nerve cell to the other. The nerve fibers are aligned with a substance called myelin and these membranes need to stay strong. By doing so, the body's cognitive function may stay sharp and mood is stabilized. Fish products and specifically fish oils are thought to be extremely protective in maintaining the integrity of these myelin sheaths which protect nerve fibers and facilitate transportation of nerve impulses throughout the body. In essence, fish is brain food because it keeps the nerve fibers healthy.

Brain cells have the most mitochondria. As mentioned, mitochondria are the battery storage areas of cells that produce energy and ATP. By keeping brain cells healthy, mitochondria can continue to produce significant ATP for brain energy.

The myelin sheaths are important to protect. When they are damaged they become repaired and omega 3 is also thought to be helpful in repairing damaged myelin sheaths.

Therefore, the first prong of the DePace formula involves taking at least 600 mg of omega 3 supplementation a day in addition to eating two to three fish oil meals a day, presumably, fatty fish such as salmon. This is highly encouraged. If an individual cannot eat fish they may need to consume more fish oil supplementation or if they have established heart disease, a higher dose is often required. If the triglycerides are significantly above 150 higher dose of fish oil supplements are also used and there are also prescription formulations, Lovaza and Vascepa, which have been approved by the FDA for triglyceride lowering. As usual, one should consult their own private physician if they feel that any of the components of the DePace formula are of potential benefit to them as each individual has their own set of circumstances that are different and treatment will vary from individual to individual.

II. Nitric Oxide (NO)

The objective of the second prong is to increase one's natural nitric oxide (NO). Nitric oxide is a natural dilator of blood vessels. It increases blood flow and circulation. It is interesting that all six prongs of the DePace Franklin Cardiovascular Program increase nitric oxide either directly or indirectly. By keeping the small cells which line the blood vessels throughout the body, the endothelial cells, healthy nitric oxide is more easily produced. When the endothelial cells become damaged, diseased or defaced, then nitric oxide deficiency occurs. Nitric oxide mediates distinct signaling profiles depending on the concentration and antioxidant buffer balance in the body. In the body, it is naturally produced by using the amino acid L-arginine. Nitrous oxide synthase (NOS) is the enzyme involved. Nitric oxide is a gas with a low solubility in water which only lasts for a short period of time but communicates but is important in communicating as a messenger between cells in the body. Also, nitric oxide is a potent inhibitor of oxidation of cholesterol especially the lousy LDL cholesterol. When the LDL cholesterol that is carried by lipoproteins in the body becomes oxidized by oxygen it becomes an abnormal modified particle which is taken up by scavenger cells in the blood vessel walls and form foam cells. These foam cells begin the process of atherosclerosis and plaque formation.

The endothelial cell is the largest organ system in the body and if it was stretched out would form several football fields. It functions as a barrier and prevents harmful substances from reaching our organ tissues. It is a monolayer of cells and regulates blood flow and blood pressure. It also controls growth of new blood vessels and controls clotting and inflammation. When there is damage to these endothelial cells, nitric oxide is not produced in abundance and clotting is facilitated as is inflammation. This can cause stoppage of circulation and cause heart attacks and strokes.

There is a cofactor BH4 which helps NOS produce nitric oxide. Folic acid is important in influencing this important cofactor BH4. Therefore, we encourage use of folic acid both in diet and supplements. Folic acid is important in reducing homocysteine levels. Homocysteine is a substance which is toxic to blood vessel cells and endothelial if allowed to become elevated. It also allows for another harmful substance ADMA which is an L-arginine derivative to be produced and cause damage to tissues.

The NOS system is known as the endogenous system and causes continuous production of nitric oxide in the body. The exogenous system also known as the alternate nonenzymatic pathway is where we produce nitric oxide in the body by taking in beet root and green leafy vegetables. These are a source of inorganic nitrates which can get converted to nitrates by mouth bacteria then eventually to

NO. Both routes of production of NO vasodilate or open up blood vessels, are important for killing invading bacteria by enhancing immune function, cause neurotransmission between nerve cells which is important for avoidance learning and may also dilate the bronchioles in the lung and decrease inflammation.

Asymmetrical dimethyl arginine is produced in cytoplasm in cells from methylation process. We abbreviate it as ADMA. It is elevated by oxidized LDL cholesterol and may be derived from homocysteine. It impairs medicines like statins from lowering cholesterol and raising nitric oxide levels. ADMA competes with L-arginine for NOS enzyme. There is a ratio of L-arginine to ADMA which is important and if it becomes reduced, it is a significant risk factor for cardiovascular disease. B vitamins and folic acid attenuate the abnormal effects of ADMA on competing with the enzyme NOS and are beneficial. They may do this through reducing homocysteine as one potential mechanism. Therefore, B vitamins are extremely important as is folic acid in maintaining continuous production of nitric oxide in the body.

There are many processes in the body which elevated this harmful ADMA molecule. These include high cholesterol, smoking, diabetes, erectile dysfunction, congestive heart failure, liver failure, high homocysteine levels, preeclampsia, hypertension, chronic renal disease and arterial sclerosis. By giving L-arginine exogenously and beneficially affecting a ratio of L-arginine to ADMA we believe we can induce the enzyme NOS in the endothelial cells to produce more beneficial nitric oxide. This will prevent ADMA for competing with this enzyme and producing harmful oxidants instead of nitric oxide which can cause tissue damage. L-arginine is more beneficial in people with established illness and older subjects than healthy young subjects in this regard.

L-arginine and L-citrulline are both important substrates which help sustain nitric oxide levels. While they can be obtained through diet, one would have to take significant quantities of dietary substances to achieve what can be achieved in supplements. Watermelon is an excellent source of L-citrulline. One would have to take over 2 lbs. of watermelon to give 1 g of L-citrulline. L-citrulline is easily absorbed and goes to the liver where it is converted to L-arginine which becomes nitric oxide. It appears that half the dose of L-citrulline is required to produce the same amount of nitric oxide as the dose of L-arginine that is needed. L-arginine and L-citrulline can interconvert into each other.

Three physicians were awarded the Nobel Prize in 1998 for elucidating the function of nitric oxide in the body. Today we know nitric oxide has many important functions which include but are not limited to acting as transporter or transmitter, acting as an antimicrobial or bactericidal agent, and acting as an anti-inflammatory agent in inhibiting white blood cells from adhering to blood vessels. Nitric oxide is an important antioxidant which also inhibits LDL cholesterol from

becoming oxidized and eventually becoming foam cells in the arterial wall. This would be the start of atherosclerosis. Nitrous oxide functions to help regulate the immune system and enhances T cell function. Nitrous oxide also promotes sexual health, vasodilates blood vessels and lowers blood pressure. We have found that L-arginine and L-citrulline and even beet root extract by increasing nitric oxide levels do lower blood pressure in many patients and many times have to use lower concentrations to prevent too much lowering of blood pressure. Nitric oxide is also antithrombotic in that it prevents platelets from clumping together to clot off blood vessels. It may promote better cerebral circulation and we have seen it improve "Brain Fog" symptoms in individuals with autonomic dysfunction. Nitric oxide also functions to promote local growth and is antiproliferative. Therefore, nitric oxide has many beneficial functions in the human body and it is incumbent on us to preserve our endothelial cells which produce nitric oxide and also to supply the necessary substrates to keep nitrous oxide continuously being produced.

Interestingly, nitric oxide may balance autonomic nervous system. It increase vagal tone which slows heart rate and decrease sympathetic tone which decreases blood pressure. By virtue of this, it would be cardioprotective also.

We like to think of nitric oxide of acting as the policeman of the circulation or the blood vessel system of the body by regulating hemostatic mechanisms of blood flow. It also acts as the fireman of the body by preventing white blood cells from adhering to blood vessel walls and causing inflammation, in essence it is the fireman that extinguishes fires from occurring by preventing inflammation. Nitric oxide can also be represented by the Red Cross Ambulance and first aid crew because it is a reparative gas. Lastly, by stopping clots from forming and causing traffic jams, it acts as the engineer and architect in the building of new roads and throughways in which our blood vessels act in the circulatory system in our body.

Arginine, a conditional amino acid, is essential in the urea cycle to excrete urea form ammonia. Therefore, it has a detoxification role. It can also go to other compounds such as citrulline which we have already discussed in forming nitric oxide, ornithine which is important in urea cycle for disposing of ammonia in the form of urea through the kidneys, creatine important in energy production and nitric oxide of course.

We believe that nitric oxide is the true "anti-atherosclerotic" molecule. One third of deaths in America are cardiovascular including heart disease, stroke and other vascular diseases and any advantage in combating atherosclerosis would be welcomed. Increasing nitric oxide levels are very useful tool in the armamentarium to fight atherosclerosis.

The oxidative hypothesis of lipids states that when lousy or bad LDL cholesterol gets oxidized it becomes incorporated into the vessel walls it becomes foam cells and plaques. We attempt to keep the LDL particles under 100 in people

who are at high risk for heart disease and diabetics who are at very high risk to keep it under 70 mg/dL. However, this may not be enough and we do concentrate on an oxidative environment so that LDL is not as susceptible to becoming oxidized. The statin gap is a phenomenon whereby we believe that even lowering LDL cholesterol on the average still is only 33% protective. Two thirds of patients still may have cardiac events. We believe this may be because the remaining LDL particles that are left, even though they become reduced, still get oxidized and are insufficiency antioxidant defenses. Our six prong program including increasing nitric oxide attempts to create a more beneficial oxidant and create a more beneficial antioxidant defense.

Nitric oxide production diminishes with age. When one is in their 20s, 100% of nitric oxide is available. By age 60, on 15% of nitric oxide may be available. As we age, we lose 80% of our ability to make nitric oxide. Taking nitrates in a diet such as beet root is an excellent way to increase your nitric oxide and studies have shown that beet root consumption does improve endothelial function as measured by brachial flow dilatation with various testing techniques. Beet juice is also effective in improving submaximal exercise tolerance and blood pressure in older patients with heart failure and preserved ejection fractions. Beet root juice has also been shown to be an excellent blood pressure lowering agent. We have used beet juice in combination with L-arginine and L-citrulline to lower blood pressure in patients with hypertensive disorders in many instances reducing their preexisting blood pressure medicines or even getting them off of them. However, it is important to emphasize that supplements cannot take the place of antihypertensive pharmacological agents or cholesterol lowering pharmacological agents but only supplemental. An individual must consult with their physician when working with supplements in conjunction with pharmacological agents. Also, supplements may cause adverse interactions with other pharmacological agents and one's personal physician input is important in this regard.

In regard to erectile dysfunction the following should be noted. ED affects endothelial dysfunction. Medications such as Viagra and Cialis inhibit an enzyme known as phosphodiesterase 5 which is important in permitting blood vessels to dilate since this enzyme prevents the vasodilatation process. L-citrulline and L-arginine reduce ED by increasing nitric oxide through the NOS pathway a different mechanism which may be complimentary to phosphodiesterase 5 inhibition in addition to Viagra, Cialis and other related medicines. Some data has shown that L-citrulline, L-arginine and PDE5 inhibitors work synergistically to reverse ED.

III. Oxidative Stress Reduction

The third prong of the DePace Franklin Cardiovascular Program focuses on reducing oxidative stress. The purpose is to decrease reactive oxygen species (ROS) and free radicals that may be harmful in the body and increasing the antioxidant defenses. In essence, the goal of this approach is to increase antioxidant buffer capacity.

In regards to circulatory diseases, improvement in circulation is very important. Impaired blood flow to muscles and organs causes dysfunction, morbidity and chronic illnesses. We have identified traditional risk factors for circulatory diseases and developed excellent pharmacological and lifestyle measures to improve those. Traditional risk factors include diabetes, high LDL cholesterol, low HDL cholesterol, family history of premature cardiovascular disease (this is considered a non-modifiable risk factor along with male sex), hypertension, being sedentary, aging, obesity and tobacco. Nontraditional risk factors include psychosocial stress, inflammation, endothelial dysfunction, kidney disease and brachial index measurements. Oxidative stress has not been considered typically a nontraditional risk factor since it is difficult to measure and measurements are usually done in experimental situations in a laboratory.

Oxidative stress affects the mitochondria and all of the cells of the body significantly. These are organelles in cells and there are more than 100,000 in the body. They require oxygen for cellular respiration. They make the ATP which is the energy molecule in the body. However, the major source of the reactive oxygen species (ROS) that are produced in the body is actually the mitochondria through a leak in the electron transport chain. Therefore, the mitochondria are small organelles in the body most susceptible to being damaged.

The mitochondria are the factory or powerhouses of the cells and are the key organelles in the process of cellular respiration. Here, carbohydrates such as glucose combine with oxygen to form carbon dioxide, water and ATP. The ATP are the energy molecules. A very important component of ATP are glycolysis, the Kreb cycle, and electron transport chain. The electron transport chain or mitochondrial respiratory chain complex is where the ATP molecules are produced in most abundance. Here, however, occasionally in 1% to 3% of the time there is only partial reduction in oxygen and not complete reduction and ROS are produced. Key ROS products produced include the superoxide radical ($O2^{\cdot}$) The hydroperoxyl radicals ($HOO^{\cdot}$-), the hydroxyl radical ($OH^{\cdot}$), the lipid peroxyl radical ($ROO^{\cdot}$). In addition, nitric oxide ($NO^{\cdot}$), peroxynitrate ($ONOO^{\cdot}$) and the singlet oxygen which is not a free radical and hydrogen peroxide (H_2O_2) are involved.

Mitochondrial dysfunction is characterized by a loss of efficiency in the electron transport chain in reduction of synthesis of high energy ATP molecules. It is characteristic of aging in essentially all chronic diseases (Nicolson, GL, Alternative Therapies, Volume 20, supplement 1).

Mitochondrial dysfunction can cause mitochondrial disease. These are often diseases which are genetic and inherited from infancy when they are primary mitochondrial diseases. In primary mitochondrial disorders, stroke like syndromes, migraines, cortical blindness, developmental delays, seizures, muscle weakness, peripheral neuropathies and many other abnormalities are associated. In these mitochondrial disorders, increased ROS, abnormal calcium regulation and reduced synaptic plasticity are seen. However, the more common types of mitochondrial dysfunction that occur, occur with aging. The mitochondria, because of oxidative stress and accumulation of ROS can become reduced and actually shrivel up and reduce the amount of ATP produced. Decreasing ATP which are an energy source can produce chronic fatigue. Other disorders associated with mitochondrial dysfunction are autonomic dysfunction, most likely, the result of damage to mitochondria to neurons and decreased production of energy to neurons. Therefore, we often see autonomic dysfunction associated with chronic fatigue in mitochondrial dysfunction entities. Mitochondrial dysfunction can also affect the GI tract, cause chronic pain, muscle myopathies, fibromyalgia syndromes, seizure disorders and many cognitive dysfunction states. These we often term as acquired and are not genetic although there may a genetic susceptibility in some individuals who develop mitochondrial dysfunction during their lifetime compared to others who do not. There indeed may be familiar connections with mitochondrial dysfunction and several familial diseases. While it has been established with cardiomyopathies, various developmental delays and muscular dystrophies research is ongoing to assess how mitochondrial dysfunction is associated with autism, Parkinson's, epilepsy, learning disability, ALS, fibromyalgia, chronic fatigue, diabetes, developmental disease, Alzheimer's disease, Huntingdon's disease, cerebral palsy, and other neurodegenerative diseases.

Dysfunction of the mitochondria can affect all organ systems including the brain causing brain ischemia, neurotoxicity, neurodegenerative diseases, cardiovascular system, myocardial infarction, atherosclerosis, diabetes complications, the liver (ischemic injury, fatty liver, iron overload) and the kidney (ischemic injury, various forms of nephritis).

Antioxidant agents are agents with sequestered reactive oxygen species and prevent or repair damage to tissues. There are many different types and classifications of antioxidants and many are intrinsic to the human body. Important antioxidants include bioflavonoids such as n lipoic acid, ascorbic acid

(vitamin C), vitamin E or tocopherol, selenium, coenzyme Q10, and lycopene. Lipoic acid has been shown to regenerate vitamin E and bioflavonoids, ascorbic acid and beta carotene. Also, ascorbic acid has been shown to regenerate vitamin E. Therefore, antioxidants can act among each other to regenerate other antioxidants in a synergistic fashion. Of those, lipoic acid and coenzyme Q10 are the most important.

It is the goal to have a positive antioxidant to oxidant balance. When there are too many pro-oxidants there is tissue damage and the see saw tips towards the side of oxidative stress. When there is more defense or antioxidants, The see saw will tip away from oxidative stress and towards host defense and protection of cells and membranes.

Oxidative stress is what we seek to limit in the DePace Franklin Cardiovascular Program. Especially in prong 3, we target it with antioxidant approaches in the form of supplements. Oxidative stress was first coined by Helmut Sies in 1985 and occurs when antioxidant defenses are overwhelmed by ROS. This can occur with a dramatic increase in ROS or decrease in activity of antioxidants or both. While more sophisticated definitions have evolved since that time the basic definition for the purpose of this program will be adhered to. Moderate oxidative stress can accelerate the aging process of senescence and can promote tumorgenesis. Overt oxidative stress can cause cell death which we call aptosis. Therefore, reducing oxidative stress may have antiaging capabilities. Formation of free radicals from external sites such as UV radiation, inflammation from viruses and bacteria and toxins such as cigarette smoking and ionizing radiation can cause DNA damage and should be avoided.

The key process involved with the function of antioxidants is that they donate electron to a free radical which is in need of an electron because it may have an isolated electron and electron shell which is unpaired. By doing this, it prevents the free radical from damaging other tissues and stealing their electrons.

In oxidative stress, we worry about oxidative damage not only in proteins and nucleic acids but also in lipids. Oxidative damage to lipids can form foam cells and begin atherosclerotic process and cause it to propagate. Therefore, reducing oxidative stress in lipids is extremely important in delaying or preventing atherosclerosis.

Free radicals and increased oxidative stress have been associated with disease entities similar to what we see with mitochondrial dysfunction since both mitochondrial dysfunction and formation of free radicals and oxidative stress are interconnecting. Virtually every organ system can be affected by free radicals oxidative stress and cause mitochondrial dysfunction.

In regards to lipid oxidation, lipid membranes get oxidized and promote cell death called lipid peroxidation. Fatty acids, which are polyunsaturated, are targets

of ROS especially the omega 6 fatty acid cell membranes. This is one reason why we want more omega 9 such as the components of olive oil and omega 3 such as the components of fish oils and cell membranes and not the components of omega 6 which are seen in linoleic acid. Once lipoproteins and cholesterol particles get oxidized, they are engulfed by macrophages and foam cells in atherosclerosis is promoted. Unfortunately, vitamin E by itself does not prevent the formation of these oxidized lipids and more than just vitamin E alone is required. Also, just lowering the LDL cholesterol particle count with statins, pharmacology or other dietary measures will not prevent atherosclerosis since we need to also prevent the oxidation of these lipids even though they are in lower quantity.

It is no wonder why studies involving just vitamin E supplements have not been shown to be effective and there are many reasons for this. This is why the DePace Franklin Cardiovascular Program is so important in taking a multi-prong approach to possibly preventing or limiting lipid oxidation. While we endorse statins or other pharmacological agents to lower total LDL cholesterol, we also attempt to increase the oxidant balance and produce an antioxidant milieu with lifestyle changes and supplements.

One of the disadvantages of oxidative stress is that when LDL and lipoprotein particles become oxidized and enter the artery system in the form of foam cells they increase platelets to aggregate and clump together and form clots, decrease nitric oxide and PGI2 which are vasodilating substances and cause the endothelial cells to dysfunction. They can actually damage endothelial cells and promote inflammation. Therefore, oxidized LDL particles promote heart disease and need to be prevented. It has been shown that statins have the ability to actually remove oxidized LDL cholesterol from plaques and this can be measured in very sophisticated scientific experiments. However, preventing the plaque from forming or limiting its formation is the true goal of the DePace Franklin Cardiovascular Program.

Virtually, all diseases may be related to oxidative stress including cancers, asthma, Parkinson's disease, blood vessel diseases, COPD, aging, hepatitis, chronic fatigue, macular degeneration, inflammatory bowel disease, kidney disease, skin disorders, Alzheimer's disease, diabetes, heart disease and even autism.

When one wants to see an example of how oxidative stress causes progressive aging and tissue damage, one can look at an apple which, if left in the open air and combines with oxygen, slowly shrivels up, deteriorates, shrinks and becomes necrotic.

Antioxidants are a key component of combating oxidative stress. Vitamin E and vitamin C are powerful antioxidants located in our bodies. Glutathione in cells are a powerful antioxidant. Lipoic acid and coenzyme Q10 are important

antioxidants in the body and are important in regenerating many of the natural antioxidants in addition. Antioxidants are obtained from the diet and may be obtained in supplements. Important antioxidants include vitamin C, vitamin E, alpha lipoic acid, coenzyme Q10, fruits, leafy vegetables and folic acid.

Oxidants promote lipid peroxidation, nucleic acid damage and protein oxidation. This is the process of oxidative stress. Antioxidants attempt to block that progression.

Many prescription medicines have antioxidant effects such as ACE Inhibitors, beta blockers such as Carvedilol, antiplatelet medications, and statins. Ways to reduce oxidative stress include antioxidants including supplements and dietary products, omega 3, nitric oxide production, exercise, stress reduction with yoga and meditation. Other agents that can reduce oxidative stress include coffee and black and green tea which have significant antioxidant potential. Immunomodulators and corticosteroids have also been shown to decrease oxidative stress. There are enzymatic antioxidants which are primary enzymes and secondary enzymes (SOD and glutathione reductase) and nonenzymatic antioxidants such as minerals, vitamins, antioxidant cofactors (coenzyme Q10, alpha lipoic acid), polyphenols (olive oil), low molecular weight antioxidants, carotenoids and minerals such as zinc and selenium.

When can actually measure the biomarkers of oxidative stress in the body. For example, the more cups of coffee one consumes per day, the lower biomarkers and oxidative stress can be seen as coffee has antioxidant potential. In these studies, the compound F_2-isoprostanes was measured.

Nitric oxide can act as an antioxidant but usually does when there is an antioxidant environment or milieu and there is an abundance of antioxidants which can sequester free radicals. In this way, it acts anti-atherosclerotic. However, during times of oxidative stress when there are many free radicals, nitric oxide can act as a pro0oxidant and produce peri-nitrate or ONOO- which can promote tissue injury. Therefore, normally in health nitric oxide blocks or reverses endothelial dysfunction as anti-atherosclerotic but during times of oxidative stress, it can promote more oxidative stress by producing reactive airway ROS. In periods of oxidative stress the compound ADMA becomes produced in abundance and can increase nitrogen reactive species and prevent nitric oxide from forming. L-arginine supplements and surplus of L-arginine is a way to combat this. The compound ADMA seen in oxidative stress is often produced in abundance in oxidative stress environments. This prevents L-arginine being a substrate for the production of nitric oxide. Instead, ADMA is the substrate and peri-nitrate nitrogen oxygen species are produced which are damaging cells. Abundance of L-arginine may overcome this process. While nitric oxide is an anti-atherosclerotic molecule and promotes healthy endothelial, it can also become an oxidant when

there are too many antioxidants in the environment by its ability to be transformed to peri-nitrate.

There are many diseases mentioned previously that are associated with oxidative stress. The common ones in primary care are diabetes, asthma, migraine, chronic fatigue, fibromyalgia and simple aging process along with anxiety, depression and obsessive compulsive behavior. In cardiovascular practice, we see hypertension, atherosclerosis and heart failure as manifestations of increased oxidative stress. All risk factors promote oxidative stress including hypertension, diabetes, smoking, and also high homocysteine can along with high angiotensin II levels which are powerful vasoconstrictors which are actually produced in the bloodstream. Oxidative LDL cholesterol produces significant oxidative stress. The end result in the blood vessel is endothelial dysfunction. Nitric oxide can improve endothelial dysfunction if an antioxidant milieu is present but if there is too much of an oxidant environment, nitric oxide can act as an oxidant and not be protective.

It is believed that chronic fatigue is caused by oxidative stress which is a manifestation of mitochondrial dysfunction. Other diseases like fibromyalgia, migraine and other autonomic dysfunction states can likewise be the result of chronic oxidative stress. It is for this reason, that the DePace Franklin Cardiovascular Program uses a strong antioxidant approach to treat autonomic dysfunction disorders and chronic fatigue syndrome.

Coenzyme Q10 is a very important antioxidant and is a key component of the antioxidant approach. It is a cofactor or coenzyme, not a vitamin. It is lipid soluble. It is produced and regenerated in the body. It sequesters active ROS especially in mitochondria. It protects cell membranes and prevents lipid oxidation and, hopefully, atherosclerosis from propagating. Unfortunately, coenzyme Q10 levels decline with age. It can be measured by blood assays to attain concentrations in the blood and it is believed to beneficial to have a high concentration of coenzyme Q10 in the blood.

Much research has been done with coenzyme Q10 as the major energy molecule and antioxidant. It has been studied in cardiovascular health including congestive heart failure, hypertension, aging, fatigue, dental health, eye health, renal health, migraine syndromes, and neural diseases. It has also been studied in conjunction with statin therapy to prevent myalgias. Coenzyme Q10 decline with age. It is believed that a person supplementing with coenzyme Q10 will have much slower decline with age.

Studies have shown that subjects with coronary artery disease have lower plasma levels of coenzyme Q10. Higher levels of coenzyme Q10 have been associated with reducing the risk of coronary artery disease. Therefore, the theory

of the potential cardioprotective impact of coenzyme Q10 has been raised in the past.

Coenzyme Q10 is an important coenzyme in the electron transport chain where most ATP is made. In 1% to 3% of instances, oxygen is incompletely reduced and ROS are formed in the electron transport chain and this is called the electron leak. Coenzyme Q10 is believed to be beneficial in limiting this electron leak production of ROS which cause oxidative stress and mitochondrial damage and dysfunction. Supplements are a good source of coenzyme Q10. It is believed that the reduced form of ubiquinol may be better absorbed and better utilized in this regard.

Coenzyme Q10 can recycle vitamin E which is a lipid soluble vitamin and important antioxidant in a body. It can recycle vitamin C which is water soluble vitamin and antioxidant. Coenzyme Q10 can lower blood pressure believed to be the result of improving endothelial function and, hence, more production of nitric oxide making the nitric oxide work better. Some studies have shown coenzyme Q10 can lower by as much as 17 mm of Hg. There has been meta-analysis by Rosenfeldt which showed that coenzyme Q10 has the potential in hypertensive patients to lower systolic blood pressure by up to 17 mm and diastolic blood pressure by up to 10 mm without significant effects.

Coenzyme Q10 has been studied and shown to improve endothelial function. It has also been used in heart failure studies although these studies have been small. The results have been encouraging. Increase in ejection fraction or strength of the left ventricle of the heart have been shown in patients with heart failure. Encouraging results have also been shown in chronic fatigue, migraine, Parkinson's, cognitive dysfunction and other mitochondrial dysfunction disorders in various studies.

Coenzyme Q10 has also been shown to decrease inflammatory markers (CRP, IL-6 and TNF-α).

Coenzyme Q10 has been shown to be useful in some studies to treat both skeletal muscle and cardiac muscle. It has been shown to be safe in long term treatment of idiopathic dilated cardiomyopathy a condition where the heart is enlarged and poorly contracting. It has been shown to be safe in long terms treatments in patients with heart failure by improving symptoms major cardiovascular events in one large study with 420 patients.

Coenzyme Q10 has been used to treat patients with statin myopathy as the tail portion of coenzyme Q10 is manufactured in the pathway which produces cholesterol. This pathway is blocked by statins and this is one reason statin depletes the body of coenzyme Q10. Some studies have shown that increasing coenzyme Q10 blood levels can prevent or treat the myopathy which occurs with patients consuming statins to lower cholesterol. Coenzyme Q10 has also been shown to be safe in long term treatment of idiopathic dilated cardiomyopathy

which is a condition with weak heart muscle and enlargement of heart muscle. In one large randomized controlled trial of 420 patients Coenzyme Q10 was shown to be effective and improve symptoms of heart failure for up to two years. It was safe and reduced major cardiovascular events.

Studies have shown that in fibromyalgia syndrome reduced levels of coenzyme Q10 decrease mitochondrial membrane function.

Chronic fatigue syndrome is a very common ailment in primary practice. Also, 97% of people with chronic fatigue syndrome may have orthostatic intolerance. Orthostatic intolerance is present when an individual when standing has evidence of increased symptoms of dizziness or inability to focus or concentrate and has to sit down or lie down for relief. Orthostatic hypotension and postural orthostatic hypotension or POTS syndrome forms of orthostatic intolerance. Brain fog, near fainting and fainting have all been seen. Orthostatic intolerance and chronic fatigue syndrome are usually interrelated and involve mitochondrial dysfunction. Most forms of autonomic dysfunction are believed to be associated with mitochondrial dysfunction. As antioxidants such as coenzyme Q10 can be used to buffer radicals they are used to treat chronic fatigue syndrome in patients with orthostatic intolerance along with another important cofactor alpha lipoic acid.

There are many triggers for autonomic dysfunction besides external toxins such as cigarette smoke or radiation. Emotional stress, viruses, and concussions can cause mitochondrial dysfunction.

Chronic fatigue syndrome consists of symptoms which last more than six months with at least four of the following: subjective memory impairment, tender lymph node, muscle pain, joint pain, headache, unrefreshing sleep, and post exertional tiredness more than 24 hours.

Fibromyalgia is a common syndrome in a person with pain and tenderness in many joints, muscles, tendons and tissues. It has been linked to chronic fatigue and also other sleep problems, headaches, irritable bowel syndrome, depression, and anxiety. The cause is unknown. Triggers include physical and emotional stress. Individuals have abnormal pain responses. No virus has been identified that can cause this. It is often seen in women between the ages of 20 and 50. They may have chronic neck pain, chronic fatigue, and depression in addition. The symptoms of fibromyalgia may mimic hypothyroidism, Lyme disease or various organic sleep disorders and these need to be excluded. Fibromyalgia is also believed to be a disease of mitochondrial dysfunction. It is also associated with orthostatic intolerance.

Orthostatic intolerance is a symptoms. Orthostatic hypotension and orthostatic tachycardia are measureable components, namely, decrease in blood pressure with standing and an increase in heart rate with standing respectively. Basically, orthostatic intolerance is defined by symptoms when upright that are relieved by

lying down. They are very difficult to treat. We target pharmacology, lifestyle changes, volume changes and also antioxidant approaches to treat these disorders as they are, in our opinion, closely linked to mitochondrial dysfunction.

Orthostatic intolerance is interrelated to migraine syndrome, sleep apnea, anxiety depression temperature dysregulation, chronic fatigue syndrome, gastroesophageal reflux, irritable bowel syndrome, tinnitus, syncope and pre=fainting syndromes. POTS disease is diagnosed as an increase in heart rate over 30 beats from lying to standing within 10 minutes and for adolescents more than a 40 beat rise. One has to exclude orthostatic hypotension which is a drop in systolic blood pressure of 20 mm or a drop in diastolic blood pressure of 10 mm within 3 minutes of standing in these patients. Symptoms of orthostatic intolerance in POTS lasts more than 6 months and are exacerbated by standing and are improved by lying down. Dehydration has to be excluded. We often treat these patients with increased salt and volume, compression stockings, eating smaller meals and fewer carbohydrates, avoiding caffeine and various medications of which Midodrine is one of the key medications if tolerated. An antioxidant cocktail is also employed by us which we have developed in our practice which is empirically useful.

Patients who faint or have syncope is often a vagal phenomenon which is a form of autonomic dysfunction. However, there are various forms of fainting which we can diagnostically work up and treat and, oftentimes, respond also to antioxidant cocktails.

L-carnitine is an ammonia compound found in the body. It increases nitric oxide signaling. It is synthesized from amino acids lysine and methionine in the body. It improves endothelial function and reduces oxidative stress. When fatty acids undergo beta oxidation in mitochondria, L-carnitine facilitates transports of fatty acids into the matrix of the mitochondria and this is called the “L-carnitine fatty acid shuttle”. Fatty acid oxidation does produce energy in the form of ATP. L-carnitine is important for ATP production, nitric oxide production and vascular and endothelial wellness. It is a key component in our cocktail systems. L-carnitine 1000 mg a day has been shown to be significantly positively correlated with antioxidant enzyme activity and significant reduction in oxidative stress and increase in antioxidant activity in patients with coronary artery disease.

There are several forms of L-carnitine. It is naturally produced in the body and is used in fat burning supplements, although, when people are not deficient it has little effect in losing weight. It is also found naturally in the body as acetyl L-carnitine (ALCAR) and easily crosses the blood brain barrier and may provide mental focus and better memory. L-carnitine/L-tartrate (LCLT) provides antioxidants, is found in fruits, is usually a preferred form and is the most stable. Glycine Propionyl-L-carnitine (GPLC) promotes strong blood flow to muscles,

compensates oxygen loss during workout, enhances fat metabolism and has been shown in many studies to be an excellent exercise enhancer. It increases nitric oxide and blood flow. Increase in nitrite and nitrate plasma levels is seen after four weeks of supplementation with GPLC. Remember, nitric oxide has many health benefits. It may have anti-aging benefit, cognitive ability benefits, limit cigarette damage, may promote increased libido, prevent kidney disease, promote better cholesterol profile and prevent oxidation and lower blood pressure. It also may prevent diabetes by regulating insulin, may increase physical endurance, increase blood flow and energy production.

L-carnitine is not only important as an energy producer and nitric oxide booster, but by transporting long chain fatty acids to the mitochondria, effects the limiting step in fatty acid oxidation and is important in fatty acid oxidation. In essence it has a significant metabolic role in fat reduction. However, we do not believe its primary function is in weight loss as people, unless they are L-carnitine deficient, do not lose weight while on this supplement and we do not recommend this as a fat burner even though it has been labeled as such because it doesn't really burn fat significantly and cause weight loss. We recommend it for mitochondrial and endothelial wellness in some patients.

The Franklin Cardiovascular cocktail for autonomic dysfunction/mitochondrial dysfunction along with exercise, stress reduction and Mediterranean diet consist of the following:

1. Alpha lipoic acid 400 to 800 mg a day
2. Coenzyme Q10 200 to 300 mg a day
3. L-carnitine 1 g a day
4. L-arginine 2 to 3 g a day
5. L-citrulline 1 g a day
6. Beet root extract 500 mg a day (important source of inorganic nitrates)
7. Lysine
8. Folic acid, B vitamins, magnesium and vitamin D
9. Omega 3 fatty acid 1200 mg a day

We emphasize that this is a cocktail that we have used empirically in our practice for many years and is based on our independent research of the medical literature and is only a recommendation for individual patients that we see and treat. It is not applicable to all patients that we see and treat. You should consult with your own personal physician as your condition may preclude all or some components of this cocktail.

A comment about brain fog. Brain fog is a medical term but basically defines patient's lack of clarity or thinking when usually in the upright position. This is a major feature in orthostatic intolerance. People with brain fog may have sluggish mentality, speaking difficulties, low mental energy, and low cognition, difficulty

paying attention, mental fatigue, a hazy or confused feeling and difficulty concentrating and focusing. They are often seen in conjunction with chronic pain which is also a component of fibromyalgia and with chronic fatigue symptoms which are associated with mental fatigue of brain fog. Word use and recall is difficult, short term memory problems occur, people have multi-task difficulties, directional disorientation, confusion, and trouble concentrating. They may have problems in preforming simple math. It is a key symptom seen in orthostatic intolerance and autonomic dysfunction syndromes. Antioxidants are one facet of treating this along with pharmacology, lifestyle changes, volume changes and other factors depending on the individual patient.

In regards to autonomic testing, there are many tests that are available. We use tilt test, heart rate variability with time domain parameters at rest and with provocation, cardiorespiratory testing, and sometimes look at pseudo motor or stress testing. Also, responses to exercise stress testing including recovery time are also important. The brain-heart connection involves:

1. Nitric oxide signaling
2. Autonomic input and output
3. Oxidative stress

Most ailments in cardiovascular disease require treating brain and heart at the same time. Therefore, we look at the patient as a whole when treating an illness involving one organ system. Often the brain and nervous system along with the organ system involved is important.

In the brain-heart connection, autonomic dysfunction is particularly paid attention to. Nitric oxide and signaling pathways of the endothelial system need to be operating well. Vascular tone is influenced by both the autonomic nervous system and nitric oxide. It is our goal to delay the aging of type C fibers in the autonomic nervous system to preserve this brain-heart connection and we believe antioxidant, especially alpha lipoic acid, may be useful. Also, we believe that delaying aging in the endothelial system and dysfunction is important in the brain-heart connection and we believe enhancing the secretion of nitric oxide along with antioxidants is also important. Promoting a healthy lipid profile is also important.

Alpha lipoic acid is a key component of the antioxidant cocktail we use in the Franklin Cardiovascular program. It is a sulfur coenzyme and was isolated in 1951. It is also known as thioctic acid. It is both lipid and water soluble and is not a vitamin. It sequesters free radicals in ROS. It regenerates vitamin E and vitamin C. It aids in cardiac function. It aids in improving autonomic and sensory nerves in diabetics. It has been shown to help burn carbohydrates and bring glucose metabolic products into the mitochondria. It acts as both antioxidant and anti-inflammatory.

Good sources in foods include broccoli, spinach, carrots, red meats and organ meats, brussel sprouts, brewer's yeast, tomatoes, beets and peas. It also helps to regenerate other antioxidants such as glutathione in addition to vitamin C and vitamin E. It modulates inflammation.

Alpha lipoic acid has been called the universal antioxidant. It is unique because it is both fat and water soluble. It protects both the interior and exterior part of cells from cell damaging free radicals. Its unique ability to regenerate other antioxidants makes it extremely versatile.

Alpha lipoic acid is produced endogenously by the body but levels can be increased through supplements. Not only is it involved in free radical scavenging but also protein repair and chelation of metals.

Alpha lipoic acid may be useful in migraine and vision problems, helping reduce the risk of type 2 diabetes by increasing insulin sensitivity and metabolic syndrome by improving brain function. It has been used as an effective remedy for migraines and headaches compared to pain killers by some physicians. It is a very viable treatment for diabetic neuropathy and studies have been done with it, both intravenous and oral. It has been tested in diabetic sensory and motor neuropathy. It is evidenced that 200 mg twice a day is beneficial on painful diabetic neuropathy. Also, cardiac autonomic neuropathy progression appears to be slowed down with alpha lipoic acid according to Tankova in a randomized open label study. Other studies have shown three week treatment of alpha lipoic acid in diabetic neuropathy were effective at 600 mg a day.

Alpha lipoic acid is a natural cofactor in the body and is seen both in the enzyme pyruvate dehydrogenase and in an enzyme in the Kreb Cycle. In fact, arsenic is lethal and kills individuals because it complexes with lipoic acid in the pyruvate hydrogenase complex. Lipoic acid lowers blood pressure because it enhances nitric oxide production.

Because alpha lipoic acid can lower glucose, one must be careful not to promote hypoglycemia if one is on oral diabetic medicines. Lipoic acid decreases insulin resistance. It also increases acetylcholine levels and may have benefits in this regard with autonomic dysfunction. It has been shown to lower lipids in the liver and may be effective in treating fatty liver and we have tried this empirically in our practice. Most importantly, alpha lipoic acid appears to increase energy and ATP and we have used it in chronic fatigue syndromes. Lipoic acid reduces lipid peroxidation and may be important in treating atherosclerosis.

Some data suggests that it does protect against memory loss and aging and may be beneficial in treating patients with Alzheimer's disease and stroke victims. It increases blood flow to nerve endings and is helpful in neuropathy. Therefore, it has many vascular and neurological potential benefits. In addition, because of its

wellness promoting effects on mitochondrial function, it appears to be very versatile.

We are currently testing alpha lipoic acid and coenzyme Q10 in patients with autonomic dysfunction with cardiorespiratory testing.

Alpha lipoic acid has been used as an anti-obesity and for its lipid lowering properties in studies.

In summary, alpha lipoic acid enhances nitric oxide production, lowers blood pressure, makes insulin work better, increases ATP, is a potent antioxidant and anti-inflammatory compound both lipid and water soluble, and may have potential uses in weight loss, fatty liver use, autonomic and peripheral neuropathy and especially diabetic neuropathy. Research is ongoing. It is a healthy supplementation to the Mediterranean diet.

IV. Mediterranean Diet

The Mediterranean diet is probably the healthiest dietary pattern. It is a plant based diet where vegetables, fruits and whole grains along with legumes and nuts are consumed in high amounts. In the Mediterranean diet, high consumption of fish including shellfish is noted. Dairy products, especially yogurt products are used along with certain cheeses such as goat cheese. White meats are preferred and saturated fats are limited. Processed foods and foods that are high in sugars and red meats are eaten very infrequently. The principal components of this plant based diet are (1) the olive, (2) the grape, and (3) wheat. Wine is allowed and is usually consumed in between 4 to 6 ounces with dinner. The benefit of wine over other sources of alcohol is the fact that it is absorbed slowly because it is often eaten with meals and a sustained blood level of alcohol which is rich in flavonoids and antioxidants is produced.

The Mediterranean diet is also associates with a non-sedentary lifestyle. Physical activity, which moderate exercise is an additional prong in the DePace Franklin Cardiovascular Program, are complimentary.

The Mediterranean diet utilizes good fats. These include omega 3 fatty acids which are seen in fish oil products and omega 9 fatty acid profile which is seen with a high content of monounsaturated fatty acids found in virgin and extra virgin olive oil. Also in the Mediterranean diet, there is a high consumption of dietary fiber with a low glycemic index and low glycemic load which means that the type of sugar consumed influences how insulin is secreted. For example, table sugar or sucrose is the most common sweetener. It is composed of glucose and fructose. Glucose is absorbed by the blood and leads to rapid rise in blood sugar whereas fructose only slightly affects blood sugar. Glucose has a glycemic index of 100. Fructose has a glycemic index of only 19. Sucrose, table sugar, has a glycemic index of 68. The higher the glycemic index the worse health effect on the body. Fructose is found in all fruit and in honey. It is 30% sweeter than ordinary sugar and is healthier because it has a lower glycemic index. It is obtained in fruits that are consumed in the Mediterranean Diet.

Lactose which is milk sugar is found in mild and other dairy products. It has a glycemic index of 46. Yogurt is a preferred dairy product and source of lactose in the Mediterranean diet. Actually in yogurt, which is a fermented dairy product, the lactose has been broken down and these products are more digestible. The bacteria are probiotic and beneficial bacteria. Yogurt is a main component of the Mediterranean diet. In addition, prebiotic fibers from vegetables, legumes, oats and barley are non-digestible ingredients that found in the Mediterranean diet that stimulate the growth of good intestinal flora.

Maltose or malt sugar has the highest glycemic index since it is composed of two glucose molecules. Its glycemic index is 105 to 110 which is one of the highest. It is found in beer. Therefore, beer is limited or omitted in the Mediterranean diet. Beer is not good for individuals who are overweight. In a 2000 calorie diet one should take no more than 1 ½ oz. or 50 g of added sugar a day. Fruit juices are not consumed in the Mediterranean diet as a 7 oz. glass can contain up to 20 g of sugar whereas 3 oz. of strawberries contains just 5 g of natural sugar. Strawberries also have dietary fiber and vitamin C.

In the Mediterranean diet pasta is made from durum wheat and certain types of rice especially brown, basmati and long grain rice which is easily cooked. These have a lower glycemic index than white flour. However, they are rich in carbohydrates and are limited to some degree in the Mediterranean diet. Remember, excess carbohydrates are converted into the body into fat. Also, stone ground whole wheat flour is healthier than ordinary white flour. The Mediterranean uses a minimum of white flour.

The Mediterranean diet has many anti-inflammatory or antioxidant effects which have already been discussed in the prongs on fish oil and antioxidants such as omega 3 and coenzyme Q10.

The endothelial cells as mentioned is a monolayer of cells important for smooth muscle function and vascular tone in all of the blood vessels of the body. It causes nitric oxide to be secreted and blood vessels to dilate. The endothelial produce not only nitric oxide but other vasodilating substances such as endothelium derived hyperpolarizing factor and beneficial prostacyclin. These counteract the constricting substances that are produced by the endothelial cells which are known as thromboxane A2 and endothelin-1. We can measure endothelial function with an ultrasound technique known as brachial vasodilator response to reactive hyperemia after inflating blood pressure cuff and then releasing it. The increase in blood flow gives us an indication of the reserve of the endothelial cells in producing nitric oxide and some of the other vasodilating properties.

In the 6 prong approach to the DePace Franklin Cardiovascular Program, all components enhance the endothelial function and increase the production of nitric oxide and dilate the blood vessels. This has been shown in many studies involving brachial vasodilator responses using an ultrasound technique noninvasively. These include long chain omega 3 fatty acids (prong 1), nitric oxide and L-arginine and related compounds (prong 2), antioxidants, folic acid, vitamin D and vitamin B12 (prong 3), the Mediterranean diet (prong 4), exercise (prong 5) and stress reduction (prong 6). One of the reasons the Mediterranean diet with moderate alcohol consumption, moderate to high physical activity levels and nonsmoking (better lifestyle) were associated with lower mortality from all types of coronary heart

disease, cardiovascular disease and cancer during prolonged follow up studies of approximately 10 years was because of beneficial effects on keeping the endothelial cells healthy and producing nitric oxide. The Mediterranean diet is rich in fruits, vegetables, legumes, whole grains, fish, olive oil, L-arginine, folic acid, soy products, antioxidants such as C and E, beta carotene, lutein, selenium, high fiber, red wine, black and green tea, almonds and walnuts all improve endothelial cell function. In fact, all components of the Mediterranean diet are beneficial and are necessary to operate in conjunction to improve endothelial function and wellness. Not one component alone is integral. Even olive oil, which many people consider most important component of the Mediterranean diet, in and of itself is not the sole factor responsible. In essence, the Mediterranean diet acts in a team effort just as a football team requires all components such as a great coach, offensive line, defensive line, quarterback, running backs, receivers, and so forth. All work in conjunction to produce the desired effect, namely, winning the ball game of longevity. There are many definitions of the Mediterranean diet. Perhaps the specific diet that was followed in Crete was the most beneficial. However, most of the southern countries that border the Mediterranean diet have healthy lifestyles and diets with chief components that have been outlined above. Unfortunately, people from Mediterranean countries have strayed from traditional Mediterranean diet and are beginning to consume sugared soft drinks, sweets, hidden saturated fats in bakery products and snacks and using refined flour. This is a less healthy diet.

Numerous studies both epidemiologically, observation and randomized studies have shown the Mediterranean diet is associated with lower instances of mortality from all causes including cardiovascular disease, diabetes type 2 diabetes, certain types of cancers and neurodegenerative type diseases. Studies have shown beneficial effects on cognitive behavior in patients who have followed the Mediterranean diet and perhaps decreased incidence of dementia and Alzheimer's disease. The first study of significance was the Seven Countries Study by Keyes and coworkers which began in the early 1970s which demonstrated that individuals in countries such as Southern Italy had lower cardiac event rates than people who consume diets in Northern Italy or other countries remote from the Mediterranean basin. Studies such as the PREDIMED Study which was published in 2013 and included almost 7,500 individuals at high risk for cardiovascular disease showed that a Mediterranean diet whether enhanced with added extra virgin oil or nuts performed better than a low fat controlled diet. The risk of heart attack, stroke and death were reduced by approximately 30% in the Mediterranean diet groups. Analysis of the data in this particular study showed that levels of oxidized LDL cholesterol which are very harmful in the beginning stages of atherosclerosis and even later stages decreased with the Mediterranean but not the low fat control

group. Incidence of type 2 diabetes was also decreased in this study. Other studies such as the Lyon diet heart study which included a Mediterranean type diet supplemented with an omega rich margarine compared to a prudent Western diet had a 70% less likely incidence of heart attack or dying from heart disease. These were individuals who already had a heart attack (secondary prevention study). Large studies subsequently published in the New England Journal of Medicine showed the benefit of the Mediterranean diet in primary prevention. Studies have shown that the Mediterranean diet reduced the incidence of metabolic syndrome by improving endothelial function and decreasing inflammatory markers such as high sensitive CRP and also decreasing insulin resistance. Also, weight loss was greater in the Mediterranean diet than low fat diets as shown in other studies. Studies have also shown better blood pressure lowering effects with the Mediterranean diet and better effects on triglycerides and serum lipids with Mediterranean diet rather than low fat diet. Some of the results have been very impressive. For example, in the Lyon diet heart study, the Mediterranean diet group was 45% less likely to die over a 4 year period compared to the low fat diet group. Many have concluded that the Mediterranean diet is the most successful diet intervention trial in history. It is our opinion that the Mediterranean diet is the most successful dietary intervention of all diets available.

When patients are prediabetic or insulin resistant we often start medications such as Metformin in an attempt to delay the need for further drug treatment of type 2 diabetes. The study by Esposito in 2009 showed the Mediterranean diet could delay or prevent the need for drugs in patients with newly diagnosed type 2 diabetes.

It has often been stated that the Mediterranean diet is a stress reducing diets. Certain foods consumed such as high glycemic loads can actually increase stress by producing extra insulin when a rapid rise in blood sugar occurs. Blood sugar falls quickly after a high glycemic load and produces post prandial hypoglycemia or low blood sugar. This has been linked to higher incidences of heart attacks and vascular events. By limiting obesity, the Mediterranean diet reduces stress by promoting a better pattern of cortisol secretion. Elevated cortisol increases your appetite and craving for sugar and high glycemic foods. It is said that foods that are rich in both carbohydrates and fat have a calming or antidepressant effect. Unfortunately, stress and high cortisol levels cause us to seek foods with high glycemic index leading to high insulin levels, increasing abdominal fat, and higher risk of diabetes, heart disease and cancer. The Mediterranean diet because of its omega 3 content with fish has anticlotting properties and may prevent thrombosis in addition. Also, the antioxidant properties of the Mediterranean diet have been thought to delay aging since oxidative stress does promote the aging process and senescence. The Mediterranean diet is very similar to Japanese diet and a new

trend towards a Japomediterranean diet is now in vogue and includes olive oil, wine, fish, nuts beans, seeds, soya, vegetables, fruits, bread, rice, seaweed, dairy products and mushrooms. The Japanese diet has also been shown to have beneficial effects similar to the Mediterranean diet. We do promote aspects of the Japanese diet in our program. This is because Japanese traditional diets share a number of features of Mediterranean diets including seafood, beans, vegetables, fruits and grains that are seen mutually in both diets. However, the dietary consumption of alcohol is different. Wine is used in the Mediterranean diet and sake which is made from rice or corn in the Japanese diet. For the most part, the Mediterranean and Japanese diet have low glycemic loads which contribute to decreased risk of cardiovascular disease, some cancers, most chronic diseases and less oxidative stress.

Many studies including meta-analysis and observational studies have shown the Mediterranean diet has been associated with decreased risk of developing cognitive disorders. It may well be that the best modality to preventing or slowing down the development of dementia such as Alzheimer's disease even more than pharmacology. Further research is ongoing.

In addition, the green leafy vegetables in the Mediterranean diet are great source of inorganic nitrates to promote nitric oxide production. The high intake of extra virgin and cold pressed olive oil serves as a great antioxidant.

In regards to cancer, the association between the Mediterranean diet and cancer risk have been studied and reviewed in observational studies and meta-analysis as noted. Veberne and coworkers in 2010 published an analysis after reviewing 12 observational studies. Ten of these studies, six cohort and four case controlled provided evidence that the Mediterranean diet was associated with a reduced risk of cancer incidents and mortality. A study by Tyrovolas also showed that the effects on cancer reduction were shown in the elderly. Analysis of data by Pelucchi in Nutritional Cancer 2009 showed that the Mediterranean diet is associated with decreased epithelial cancers, digestive and laryngeal tract cancers, and upper airway digestive tract cancers. In contrast refined grains and consequently glycemic loads were associated with increased risks of cancers. Increasing vegetable consumption were associated with decreasing epithelial cancers and increasing fruit consumption with decreased digestive tract and laryngeal cancers. In a review by LaVecchi in Public Health Nutrition in 2004 was noted that a protective effect of the Mediterranean diet was also seen for female genital tract, urinary tract and other epithelial neoplasms.

Giacossa in European Journal of Cancer Prevention 2013 emphasizes that the Mediterranean diet may be related to the favorable effects of balance ratio of omega 6 to omega 3 essential fatty acids and a high amount of fiber, antioxidants, and polyphenols found in fruits, vegetables, olive oil and wine. However, he

emphasized that heavy alcohol drinking is associated with digestive, upper respiratory tract, liver and breast cancers and, therefore, moderation in limiting wine and alcohol intake is important and perhaps only two drinks a day in men and one drink a day in women. We, likewise, prescribe to that in advising our patients. Interestingly, endometrial cancer has been associated with dietary fat intake and is not protective by the Mediterranean diet (Dalvi, Cancer Causes Control 2007). To reduce the risk of endometrial cancer a plant based diet low in calories from fat is recommended rich in legumes, fiber, whole grains, vegetables and fruits. Therefore, females should consult with their physician as to what aspects of the Mediterranean diet they should individually follow especially if they are at risk of cancer such as endometrial cancer. Since none of these studies have been double blinded completely controlled trials, one cannot state with certainty that the Mediterranean diet will prevent certain types of cancers. However, dietary pattern emphasizing the consumption of fruits, vegetables, whole grains, legumes, nuts, seeds and low fat dairy products are highly recommended for most people especially those at risk for cancer (Konto UN et al, Journal of Medical Food 2011).

Lastly, in regards to extra virgin olive oil the following can be said. It is a beneficial fatty acid which contains modest amounts of vitamin E and vitamin K. It is replete with numerous antioxidants. Olive oil is a natural oil extracted from olives, the fatty fruit from olive trees. Its predominant fatty acid is a monounsaturated fat called oleic acid which is extremely helpful and reduces inflammation. It is an excellent antioxidant. It may also beneficially affect certain genes which are linked to cancer. Also, monounsaturated fats in extra virgin olive oil are resistant to high heat making it a healthy choice when used in cooking. Some studies have shown olive oil reduces inflammatory markers such as CRP. One large review of 841,000 subjects found that olive oil is the only source of monounsaturated fat associated with a reduced risk of stroke and heart disease. One theory of how olive oil reduces heart attack and stroke is that it prevents LDL cholesterol from becoming oxidized and improves endothelial function and clotting. Olive oil has also been shown to lower blood pressure in some studies and may reduce the need for blood pressure medicines by a large percent in certain individuals. Also, olive oil has not been shown to increase weight. In some studies it has been shown to actually cause weight loss. In studies with rodents olive oil has been shown to remove plaques from brain cells that may promote Alzheimer's disease and dementia.

In conclusion, olive oil combined with the Mediterranean diet have significant beneficial effects on health.

The Mediterranean diet is a plant based diet that consists of three major products olives, grapes and wheat or complex carbohydrates. There are many

definitions for the Mediterranean diet. In many respects, it is similar to the Japanese diet. Both have shown beneficial effects on reducing cardiac mortality and cardiac events and also cancer and other comorbidities.

Various pyramids have been constructed in regards to the Mediterranean diet. Daily physical activity is oftentimes one of the basic components. Bread, pasta, rice, polenta and whole grains are often added to vegetables, fruits, beans, legumes and nuts. Olive oil is a key component. Dairy products such as cheese and yogurt are often included as are fish. Higher up on the triangle is poultry and eggs. There is a reduced amount of meats, particularly red meats and sweets. Wine, in moderation, is often allowed.

The Mediterranean diet includes healthy fats which are omega 3 and omega 9 (virgin olive oil). One attempts to have no more than 35% of daily calories come from fat. As the Mediterranean diet is an excellent diet for weight loss, oftentimes, women are limited to 1,500 calories a day and men 1,800 calories a day.

Recognition from individuals in Southern Europe and Mediterranean basin were at lower risk of death from various disorders was heightened by the work of Ansel Keyes, an epidemiologist, who launched the Seven Countries Study in the early 1970s. Initially, Keyes pursued the very important question of how dietary fat influenced cholesterol. Mediterranean diet uses good fats and not the so called bad fats or saturated fats within the diet.

In the Mediterranean diet we strive to use polyunsaturated fat such as olive oil and omega 3 fatty acids which are found in fish. Low saturated fats are preferred to saturated fats. Carbohydrates with a low glycemic index are used. Foods are non-processed. High fiber and high antioxidants are employed. Omega 3 in fish and alpha-linolenic acid in grains are the omega 3 fatty acids that are utilized. One other goal of the Mediterranean diet is to lower the omega 6 to omega 3 ratio for any given cholesterol level. Omega 6 fatty acids have detrimental effects whereas omega 3 have protective effects in the body. One attempts to get this ratio to as close to 1 as possible whereas in the western diet it is usually 10:1 omega 6 to omega 3. Low ratio of omega 6 to omega 3 has been protective for coronary heart disease. For a given cholesterol level, if one has a very low omega 6 to omega 3 level, they have a much lower risk for coronary heart disease.

Vegetables commonly used in the Mediterranean diet include tomatoes, cucumbers, onions, carrots, lettuce, bell peppers, cabbage, squash, parsley, chives, zucchini and garlic. Spices are also used. While cinnamon is not considered a key spice in the Mediterranean diet, it is an extremely useful spice for antioxidant and insulin sensitivity affects. Sweet potatoes are also seen in the Mediterranean diet to some degree. In the Japomediterranean diet, coriander is also used. We attempt to use as much red beets uncooked as possible in the Mediterranean diets because

they are an excellent source of inorganic nitrates which promote nitric oxide production.

Fruits used in the Mediterranean diet include figs and grapes. Other fruits often seen are apples, bananas, oranges, lemons, grapefruit, watermelon (an excellent source of citrulline) clementine, cantaloupe, strawberries (an excellent source of fiber), kiwi, plums, apricots, peaches, and pears.

Legumes such as white and red beets, fava beans, lima beans, split peas, chick peas, lentils of all types and black eyed peas are often seen in the Mediterranean diet. Grains, such as breads with whole wheat or rye are often used. Rice such as basmati, brown and wild is preferred. Wheat pasta is also used. Bulgur and barley are very healthy grains.

It should be stressed that the Mediterranean diet is much more than a simple diet. It is a lifestyle change. Physical activity and low stress environments are often inherently associated with this diet. The Mediterranean diet by nature of its association with healthy lifestyle changes and healthy dietary patterns, lowers cancer risk, heart disease risk, obesity, diabetes, and other chronic diseases and promotes weight loss. It is in essence a "more holistic fulfillment of healthy living".

Not just the Seven Countries Study but other studies have shown that patients with higher percentages of omega 6 fatty acid compared to omega 3 are associated with higher death rates. This has been shown in the MRFIT, the Quebec Urban study, the Japan Elderly Study and Greenland Studies.

It has been analyzed which component of the Mediterranean diet are most important. All components are important and work in a team effort. Olive oil is a very important component but in and of itself is not responsible for the excellent health effects of the Mediterranean diet. Several studies have shown the benefit of each component contributing individually.

In addition, the Mediterranean diet, in randomized controlled studies, observational studies and meta-analysis, has been shown in both primary and secondary prevention of cardiovascular disease.

The Mediterranean diet is cardioprotective in many ways. It reduces blood pressures by improving nitric oxide utilization and endothelial function. It reduces inflammation and reduces reactive oxygen species (ROS). One can see and improved reactive hyperemic indices which reflect increased endothelial function. In addition, the Mediterranean diet is important for weight reduction and this and of itself improve reactive oxygen species, improve lipid profiles and reduce blood pressure. The Mediterranean diet also improves exercise capacity. In regards to lipids, it has been shown to reduce LDL, triglycerides and total cholesterol levels and increase HDL level but more importantly it reduces the LDL oxidation levels. In essence, the Mediterranean diet reduces oxidative stress. It does this by

improving antioxidant capacity, reducing LDL oxidation, reducing ROS and reducing isoprostanes substances which are harmful.

When one looks at various measures to reduce cardiac risk such as aspirin, beta blocker, cholesterol lowering medications such as statins, medicines to block the angiotensin receptor pathway (ACE Inhibitors and angiotensin receptor blockers), one sees that the Mediterranean diet has a risk ratio reduction equivalent to if not better than those risk factors. Perhaps the only risk reduction factor that may be comparable to the Mediterranean diet in potency is smoking cessation if one is a smoker. Other cardioprotective activities shown to reduce cardiac risk with favorable risk ratios such as moderate alcohol intake, physical activity and omega 3 fatty acids are actually components of the Mediterranean diet.

Many have focused on olive oil as a key component of the Mediterranean diet. It is a polyphenol. It is an omega 3 molecule that displaces omega 6 in the membranes. It is an effective antioxidant. It must be emphasized, however, that by itself it is not solely responsible for the beneficial effects of the Mediterranean diet and all of the components act synergistically. Olive oil as a polyphenol, scavenges free radicals inhibits oxidant enzymes, and induces one's own antioxidant enzymes to work properly. Active effects of dietary polyphenols such as olive oil are effective in anti-inflammation, gastrointestinal health, anti-allergy, hormone modulation, has antidiabetic factors, endothelial protection and neural protection along with cardioprotection factors. They have been shown to have anti-tumor and immune protection. Also, they have shown to be effective in COPD. Olive oil will reduce ROS. As has been emphasized, ROS reduces DNA repair, creates mitochondrial defects, and increases aging factors and inflammatory factors.

Olive oil also stabilizes membranes, reduces inflammation and acts as an antioxidant and probiotic by being antimicrobial. It also has antihypertensive properties. It is interesting that a SCIs structure of oleic acid which is a component of olive oil fits nicely into the composite structures of membranes and alters receptor sites of the membrane to regulate blood pressure. Scientific evidence is limited although not conclusive but suggests eating about two tablespoons or 23 g of olive oil a day may reduce the risk of coronary heart disease due to the monounsaturated fats present in olive oil.

The Mediterranean diet has been compared head to head in several good studies with a low fat diet. The Mediterranean diet with extra nuts and olive oil has been shown to be more effective than a low fat composition diet in regards to reducing total death rates from any cause and rates of heart attack, stroke or death from heart attack. The Mediterranean diet also improves endothelial function more effectively than other diets. It has been shown to decrease the incidence of invasive breast cancer compared to controlled diets.

The Mediterranean diet is replete with antioxidant and incorporates weight loss, fitness or reduction of diabetes and metabolic syndrome. It is an anti-inflammatory diet that attempts to decrease the omega 6 to omega 3 ratio in cells. An interesting area of research has been the effects of the Mediterranean diet on cognitive function and dementia. Systemic reviews and meta-analysis show that adherence to the Mediterranean diet is associates with decreased risk of having cognitive dysfunction. Published studies suggest that a greater adherence to the Mediterranean diet is associated with slower cognitive decline and lower risk of developing Alzheimer's disease, although, further studies are required including long term randomized trial. Other conditions in which the Mediterranean diet has caused reduced risk include coronary heart disease, hypertension, diabetes, dyslipidemia, metabolic syndrome and diabetes. These have all been associated with mild cognitive impairment, dementia or Alzheimer's disease. Higher adherence to the Mediterranean diet improves insulin sensitivity and decreases oxidative stress. Oxidative stress increases have been observed in brains of patients with Alzheimer's disease. The Mediterranean diet has been shown to improve basic protein such as neurotrophins which protect neurons. The Mediterranean diet has been associated with decrease of CRP which is an inflammatory protein and has been suggested to be associated with Alzheimer's pathogenesis. Also, interleukin levels are reduced by the Mediterranean diet and these inflammatory molecules have been shown to be detrimental to human cells.

Of great interest are the systemic reviews and even several controlled trials have shown cardiovascular benefits of the Mediterranean diet in diabetes including patients who have had heart attacks. Evidence to date suggests that adopting the Mediterranean diet may actually help prevent type 2 diabetes and also improves the glycemic control in patients with established diabetes by increasing sensitivity. The Mediterranean diet has been shown to cause a risk reduction of 19% in regards to diabetes in meta-analysis performed by Schwingshack. Therefore, the Mediterranean diet is our diet of choice for both primary and secondary prevention. The Mediterranean diet is a good diet for those with busy lives. Today in America, we are too busy to stop and eat healthy. Fast foods, pizza, soft drinks and other dietary products taken on the run are almost always bad choices. Americans would rather ingest a pill to receive the proper antioxidants and nutrients that are inherent in the Mediterranean diet. However, taking a magic pill in the morning is not the answer and would not replace a good healthy diet such as the Mediterranean diet with its associated lifestyle factors.

V. Exercise

Exercise is better than any supplement or pill one can take. It is probably even better than any combination of supplements or pills or possibly even pharmacological agents. It does so many beneficial things to the body.

Exercise is a single acute bout of physical exertion or muscular activity that expends energy above one's basal or resting level. It usually, but not always, we result in voluntary muscle movement. Exercise sessions are usually planned out and structured with a goal to improve and maintain physical fitness. Physical activity is activity where the goal is different from exercise but also requires expending energy and often provides health benefits. If one walks from the parking lot to the job site, that is physical activity. But if one goes to a park or track and walks around at a predetermined heart rate or time schedule this is more consistent with exercise. Therefore, exercise is a type of physical activity which has a more specific goal or focus.

Exercise can be aerobic or anaerobic. It can also be continuous dynamic, rhythmical, static or a resistance exercise. Oftentimes, it is a combination of different modalities and involves muscle action.

Exercise intensity and exercise duration are important variables. Oftentimes, a physician or an exercise trainer, depending on the patient's level of fitness and health, will be able to write a prescription program. When individuals have certain physical restrictions such as cardiac restrictions, oftentimes, they may need to be monitor more carefully. For example, cardiac patients post heart attack are often monitored in a cardiac rehabilitation program with a monitor on exercising 3 times a week for 12 weeks and supervised by trained nurses. Exercise has many beneficial effects on the human body:

1. It can balance the autonomic nervous system better. One attempts to keep the sympathetic and parasympathetic system in balance and exercise is an excellent adjunct to pharmacology and other lifestyle measures and diet in this regard.
2. Exercise complements healthy diet.
3. Exercise reduces cortisol release for better neuroendocrine balance.
4. Exercise decrease psychosocial stress.
5. Exercise can increase nitric oxide production.
6. Exercise can boost the immune system.
7. Exercise reduces oxidative stress.
8. Exercise may increase the size and number of mitochondria.
9. Exercise can increase insulin sensitivity.
10. Exercise improves endothelial function.

11. Exercise has been shown to increase memory by increasing the volume of gray matter in the brain.
12. Exercise improves almost all cardiac risk factors, for example, it can increase the HDL or good cholesterol and lower blood pressure.
13. Exercise can increase blood flow and make the blood less prone to thrombosis or clotting.
14. Exercise can increase bone structure or strength.
15. Exercise can decrease central obesity.

Healthy individuals are recommended to partake in 150 minutes per week of moderate activity exercise. Young adults and adolescence may require up to 60 minutes a day. Individuals with chronic illnesses who are restricted may only be able to do a certain amount and not reach these duration goals.

It is the aim of cardio exercise to maintain or lose weight and strengthen the heart and lungs function al capacity in an individual. Exercise makes the heart function more efficiently. It can decrease the risk of heart disease. For example, it is also important in various cardiac conditions. Patients with myocardial infarction can increase their oxygen consumption with exercise. It causes a reduction in heart rate, blood pressure and improvement in blood lipid profile and sense of wellbeing. By reducing heart rate at rest and submaximal workloads, exercise can protect against cardiac arrhythmias. People with valvular heart disease can improve the working capacity of their skeletal muscles and be able to perform daily activities better with an exercise program. Even chronic heart failure, with improvement of skeletal muscle metabolism and distribution of blood throughout the body to various tissues can improve. Individuals with peripheral vascular disease with claudication and inability to walk far can begin increasing their exercise duration and distance. Exercise has been shown to be effective treatment in hypertension and reducing the rise in blood pressure over time and reduces both the resting systolic and diastolic blood pressure.

Exercise can also improve bone health and increase bone density. In individuals with arthritis, it improves fitness, decrease joint swelling and pain and can improve osteoporosis and slow down the age related decrease in bone mass. In various neurodegenerative diseases exercise increases strength and functional capacity and can improve physical fitness and functional performance in these individuals. Exercise has been shown to be important in reducing emotional outbursts. It creates a sense of wellbeing and can alleviate depression and anxiety symptoms.

In individuals who have insomnia or disease entities associated with poor sleep, exercise can improve sleep quality and energy levels of the individuals.

There is strong evidence that exercise can prevent premature death and is effective in combatting coronary heart disease. Evidence suggests exercise is

effective in stroke and high blood pressure prevention. It also has beneficial effects on lipids especially high triglycerides and low HDL. Exercise is important in treatment of type 2 diabetes and metabolic syndrome and preventing worsening or even emergence of these syndromes. Exercise has been shown to have health benefits in colon cancer and breast cancer. Exercise can also prevent weight gain and may affect weight loss especially when combined with reduced calorie diets. Importantly, because of its favorable effects on bone structure, it can prevent falls especially in geriatric patients. Exercise may also be effective in treatment of depression and anxiety or in ameliorating symptoms in such disorders. By improving aerobic fitness and muscle strength in general, exercise improves one's functional ability on a daily basis.

Exercise has also been shown to improve the immune system. Moderate aerobic exercise has been shown to increase the number and activity of white blood cells such as neutrophils which protect against bacterial infections. Exercise also increases phagocytic activity and secretion of substances called cytokines which fight infection and inflammation and are secreted by macrophages in the body. Also, exercise can increase the number of B and T cells which are immune regulating cells in the body. Certain cells known as NK and macrophages are important cells in our immune system defense against the spread of malignancies. Moderate exercise can increase the activity of NK cells and increase macrophage activity also.

In one study polished in JAMA Internal Medicine in 2006 in association with leisure time, physical activity was associated with a lower risk of 13 cancers including esophageal, lung, kidney, gastric cardia, endometrial, myeloid leukemia, myeloma, colon, rectal, bladder and breast. Interestingly, leisure time activity is associated with higher risk of malignant melanoma and prostate cancer. Smoking is shown to modify the association of lung cancer but no other smoking related cancers in that study. Another study in JAMA Oncology in 2006 showed that lifestyle factors were important for cancer development and that substantial cancer burden may be prevented through lifestyle modifications which include 75 rigorous intensity or 150 minutes of moderate intensity exercise per week among other lifestyle changes such as no smoking, moderate alcohol drinking or an ideal weight with BMI of 18.5 to 27.5.

In Journal of Circulation article published in 2003, it stated that moderate activities are comparable to walking briskly about 3 to 4 miles per hour and that 30 minutes of moderate activity daily equates to 600 to 1200 calories of energy expended per week. The article states that every American adult should participate in 30 minutes or more of moderate intensity activity on most and probably all days of the week. During exercise it is true there is a transient risk of having heart related complications such as a heart attack or cardiac arrhythmia and one should

always get clearance from a physician before undertaking moderate levels of exercise. In reality however, the majority of heart attacks, approximately 90%, occur in a resting state and not during physical activity. Initially, it was thought that if you were over the age of 45 and have two more risk factors for heart disease, you should consult your physician before starting any type of exercise program. However, we feel strongly that most individuals should consult with their physicians even in the absence of other risk factors and over the age of 45.

Beneficial effects of exercise include hypertrophy and hyperplasia of skeletal muscle, increasing flow of blood vessels, increasing insulin sensitivity and mitochondrial biogenesis and increases adipose "browning". Exercise can increase cardiac growth of cells with hypertrophy and can have cardioprotective effects against ischemic injury. It is believed that exercise improves the calcium handling of the myocardium. It has been shown that exercise can increase in blood vessels angiogenesis and also in the heart itself increase blood vessel growth. While thickening of the heart may be pathological or detrimental in conditions like hypertension, there may be a beneficial increase in heart muscle growth in a favorable remodeling way in individuals who exercise as the heart has considerable plasticity. Exercise training promotes efficient glucose and fatty acid handling as well as mitochondrial biogenesis.

We have noted that as one ages, mitochondrial dysfunction becomes more evident and this is linked to many disease processes. Exercise is one of the few proven methods improving mitochondrial function and decreasing the burden of mitochondria which are not healthy. Patients with mitochondrial disorders have a low maximal oxygen uptake which can lead to exercise intolerance and interfere with daily living activities.

Resistant exercises can increase strength and endurance exercise can improve exercise tolerance as well as biochemical enzyme activity (Nicolson, GL, Mitochondrial dysfunction and chronic disease, Alternative Therapies, Volume 20, supplement 1).

There is significant evidence that exercise counteracts the negative effects of aging. Regular exercise is associated with reduced deaths of all cause cardiovascular mortality and is associated with increased life expectancy. Besides reducing cardiovascular disease, type 2 diabetes, metabolic syndrome, colon cancer, obesity osteoporosis, anxiety and cognitive impairment, there are numerous disorders that are being beneficially effected by regular exercise. Also, exercise improves quality of life especially in elderly people.

Aging is associated with oxidative stress mainly due to what we term "leaky mitochondria" where partial reduction of the oxygen in the electron transport chain generate free radicals and reactive oxygen species. This causes damage of mitochondrial membrane lipids. Electron escape from the mitochondrion is a

pathological process and leads to progressive mitochondrial dysfunction and creates a vicious cycle with increasing ROS generation. Increasing ROS production occurs in skeletal muscles and other organs such as the heart and brain. Also, reduced protein synthesis, limits antioxidant defenses and repair capabilities. Aging is associated with progressive loss of muscle mass and strength. This increases muscle injury. Injured muscles will release inflammatory molecules. A condition known as sarcopenia is created when muscle mass and strength are lost. This leads to reduced physical activity and increased adiposity. Increasing fat cell accumulation is a state of low grade and chronic inflammation and many inflammatory cytokines such as TNFα and Interleukin 6 (IL-6) are increases and circulate. CRP is increased as well. There are also higher inflammatory cell counts such as neutrophils and myocytes. An important transcription factor known as nuclear factor Kappa B (NF-kB) are also released during oxidative stress.

Regular exercise has anti-inflammatory and antioxidant effects. Acute bouts of exercise cause break down of skeletal muscle and increasing inflammation. However, regular exercise reduces the level of systemic inflammation and markers such as CRP, IL-6 and TNFα both in young and old. This is especially true in exercise associated with weight loss. It is thought that some types of exercise may have more anti-inflammatory effects than others. For example, aerobic exercises may be more effective than resistant exercises in decreasing inflammation.

Obesity is associated with chronic inflammation especially adipose tissue that is visceral fat deposits where macrophages are trapped a significant inflammatory molecules are produced. Exercise induces the release of adiponectin for adipose tissue which exerts an anti-inflammatory and antioxidant effect. Exercise also inhibits the infiltration of macrophages into adipose tissue and switches them from a more inflammatory type to a less inflammatory type.

Aerobic exercise also regulates the immune system and activates the adaptive components with suppression of inflammation. This involves regulating T cells and B cells.

Also by stimulating mitochondrial biogenesis and enhancing mitochondrial oxidative capacity, exercise lessens mitochondrial aging and interrupts the viscous cycle of oxidative damage.

During regular exercise ROS production is reduced. Also, exercise training attenuates oxidative damage in the brain and other organs. This is especially true in the heart where regular exercise decreases age when associated with oxidative stress. Exercise has been shown to upregulate mitochondrial NADH cytochrome C reductase and other important enzymes in the electron transport chain.

Regular exercise also increases activity of beneficial antioxidant enzymes such as SOD in the brain. Exercise has also been shown to enhance the cellular repair process.

Very importantly exercises the content of brain derived neurotrophic factor (BDNF) which is a very important neurotrophic factor involved in higher cognitive function.

Clearly, more research is needed, however at the biochemical and cellular level, there are tremendous anti-inflammatory and antioxidant beneficial properties of regular exercise.

Being sedentary increases the risk for high blood pressure, metabolic syndrome, diabetes, cardiovascular disease and mortality. It is considered a cardiac risk factor. Individuals who are moderately active with exercise, but who sit significant periods of time have more risk than individuals who are moderately active with exercise who do not sit for significant periods of time. Habitual exercise and greater aerobic fitness have shown to be protective and associated with less coronary atherosclerosis.

Numerous mechanisms are proposed for the cardiovascular health benefit of exercise. One in particular, an improvement on sympathetic-parasympathetic balance and oxygen demand has recently been proposed as a mechanism for decreasing sudden cardiac death. Also, exercise has been proposed to improve vascular function and vascular collateralization and favorable remodeling of the plaque reducing the risk of rupture has been postulated. Also, exercise causes decreased risk of thrombosis and, in essence, stenting the blood from clotting. Some theories have discussed infarct sparing due to myocardial preconditioning. Decrease in psychosocial stress and chronic mental stress may be another cardioprotective mechanism of regular exercise. One thing for certain is that exercise does not appear to beneficially effect atherogenic lipids significantly. It will, however, increase the good HDL cholesterol or the vacuum cleaner. It can also increase the size of the LDL particle and make it more buoyant which may also be protective.

Exercise can improve insulin sensitivity and lower triglycerides which also is cardioprotective.

An improvement in BMI on exercising three times a week and percentage of body fat and glucose control has also been shown in studies.

Exercise does improve endothelial function.

Poor fitness has been associated with a higher incidence of premature death, diabetes and heart disease. Exercise by improving fitness can improve these percentages. There also appears to be a gradation of time spent with moderate exercise and an increase in percent of lowering risk for heart disease.

We attempt even in our more elderly and frail patients to get them to walk more each day. We suggest that they buy a pedometer and track the number of steps that they walk a day. Two thousand steps are equivalent to one mile. We

attempt to get as many patients as possible to walk six thousand steps or three miles a day and to build up to that if need be in a prescription exercise formula.

VI. Psychosocial Stress Reduction

Stress is a state of threatened homeostasis. The human body attempts to adapt to stress. It is difficult to control this stress with pharmacology alone. Also, removing oneself from what they consider a stressful environment is not always the answer. Many medicines that are used to alleviate stress have toxic side effects which include habituation. Also, a resistance to mediations can occur in time. This is called tachyphylaxis which occurs which chronic use of medicines to treat emotional stress.

Stress can affect the mind-body connection. Stress adversely affects the autonomic nervous system. It impairs vagal tone which is protective, increases cortisol levels which can promote stress further, increases adrenal medullary system in general producing more catecholamines which raises heart rate and blood pressure and increases oxidative stress and mitochondrial dysfunction.

Physiological effects of stress include and increased cholesterol and fatty acid level in the body for energy production system. Also blood pressure is increases with increasing stress. Local inflammation may cause redness, swelling, heat and pain in joints. Ongoing stress may cause the blood to clot faster and form more blood clotting elements. Psychosocial stress increases production of blood sugar for energy and increases stomach acids and gastric secretion which may promote gastric and esophageal irritation. Also, increasing stress can decrease protein synthesis and intestinal movement which is digestion. It may also impair immune responses and cause an allergic response system to be depressed. A faster heart beat and faster respiration are often consequences of stress effects on the autonomic nervous system by increasing metabolism.

Stressors produce cognitive, emotional, psychological and behavioral changes that can be harmful to one's physical and psychological wellbeing. Abnormal cognitive changes include worry and loss of concentration, memory loss especially short term memory loss, and an inability to make decisions. People can also have acute mental status changes. Emotional changes may include anxiety, apprehension, irritation, anger, shame, guilt, depression and so forth.

Not just the central nervous system and autonomic nervous system but the immune system can be affected by stress. The endocrine system can also be affected. Dry throat and mouth, trembling and muscle tension, cold hands and feet, headaches, fatigue, frequent illness and weakness can all be manifestation of chronic ongoing stress. Stress can adversely affect their relationships with others and their ability to perform at work. Stress can also increase exacerbation of asthma conditions and other chronic lung conditions including reactive airway disease. Menstrual disorders can worsen with strength as in recurrent vaginal infections in women and impotence and premature ejaculation in men. Skin

rashes, eczema and psoriasis can become worse. Diseases of the digestive tract such as gastritis and esophagitis can be worsened. Also, stomach ulcers can be produced. Irritable bowel syndrome is a common manifestation of ongoing stress. Stress by affecting the musculoskeletal system can cause neck and shoulder pain and a fibromyalgia type syndrome with musculoskeletal aches. Stress can also exacerbate low back pain. Stress has even been associated with hair loss and baldness. Stress, if it is acute can cause a shock like state to the heart muscle and a condition called Takotsubo cardiomyopathy. It can also cause restriction of arteries and spasm. When it occurs in the coronary arteries it can cause severe chest pain or heart attacks.

Psychosocial stress has been shown to the increase hazard ratio of heart attack more than twofold. This was shown in the landmark INTERHART Study published in Lancet in 2004. It is believed that stress can cause more vulnerability for plaques to rupture in the arteries around the heart. Also, stress increases blood clotting and blood pressure and this may be another mechanism by which it increases the incidences of heart attacks. Psychosocial stress is considered a nontraditional risk factor for heart attack. Also, chronic psychosocial stress has been linked to chronic atherosclerotic heart disease.

Chronic stress predisposes individuals and makes them more susceptible to infections. Immune function is depressed. People with chronic stress have been known to be predisposed to pulmonary embolism after long trips presumably because of increased clotting propensity. There may be an increase in viral cancers with stress in addition. Ongoing psychosocial stress may be a trigger for autoimmune diseases, migraines, obsessive compulsive behavior, post-traumatic stress, insomnia, depression, irritable bowel syndrome, reflux esophagitis and substance abuse.

Skin rashes, hives and ectopic dermatitis worsen with stress. Some authorities believe that degenerative neurological disorders like Parkinson's disease will worsen with psychosocial stress.

One adverse effect of chronic stress is that increased cortisol causes greater sensitization of the rewards center and stimulates pleasurable behavior which may cause individuals to seek drugs or excessive intake of palatable foods which are high in fat and high in sugar. Also, by increasing palatable food there is an accumulation of visceral fat and this creates central, leptin and insulin resistance. We have found that blood pressure elevation and arrhythmias are more difficult to treat when individuals are exposed to chronic psychosocial stress. Only after this stress is ameliorated or reduced are these abnormalities easier to control. Even serum lipid levels are difficult to control in individuals with psychosocial stress especially high triglyceride and low HDL levels in our experience. Some of this may be a reflection of diet noncompliance during times of stress. Of course,

obesity and weight gain are promoted during high levels of psychosocial stress. Therefore, obtaining ideal weight or ideal BMI is very difficult with ongoing chronic stress. It is thought that high emotional stress may be also be linked to promotion of ROS and increased oxidative stress states.

Identifying stress and stress management are crucial components of the Franklin Cardiovascular program. Unfortunately, it is difficult to monitor stress and quantitate it. We have developed a stress questionnaire in our first publication, *The Heart Repair Manual*, published by W.W. Norton in 1992. There are many questionnaires that have been proposed to test for stress.

There are many modalities to lower stress. These include:

1. Meditation
2. Progressive relaxation techniques
3. Biofeedback techniques
4. Acupuncture
5. Massage
6. Deep breathing exercises
7. Cognitive behavior therapy
8. Exercise
9. Yoga
10. Tai Chi

A recent publication disclosed a relationship between resting amygdalar activity and cardiovascular events. This was published in Lancet in February of 2017. It was the first study to link regional brain activity to subsequent cardiovascular disease. The amygdala is an area in the brain which has projections to the brain stem and participates in autonomic sympathetic responses to stress. By imaging metabolic activity with a technique using PET/CT scanning at the Massachusetts General Hospital in Boston following 293 patients over 3.7 years the researchers were able to show that increased activity in the amygdala portion of the brain was associated with inflammation with increased bone marrow activity and arterial inflammation and risk of cardiovascular events over that period of time.

Psychological stress has long been thought as an important human malady as the authors concluded. This study displays a mechanism of how chronic stress can affect the autonomic nervous system, in particular the sympathetic nervous system in the brain, and lead to cardiac events. The activation of the brain stress network had downstream consequences with inflammation in blood vessels and bone marrow. This study showed for the first time the relationship between neural tissue activity and subsequent cardiovascular event and emphasized the psychosocial or chronic stress aspect involving the brain-heart connection.

It is believed that stress suppression will beneficially affect this brain-heart connection and lead to cardiovascular morbidity and mortality. In essence, Stress to Brain, Stress to Heart" was the title of an editorial regarding this article written by Dr. Kuiper. Chronic psychosocial tress is associated with high levels of inflammatory protein such as CRP, IL-7 and tumor necrosis factor alpha. This is seen in depression, post-traumatic stress disorder, and almost any disorder associated with chronic ongoing stress.

The Franklin Cardiovascular Program helps individuals identify which factors are contributing to chronic psychosocial stress and encourages these individuals to seek stress reduction modalities they are most comfortable with in complying and pursuing. Whether it be a form of meditation, yoga, exercise or biofeedback. We strongly discourage tranquilizers such as benzodiazepine but are not adverse to cognitive behavioral therapy and pharmacotherapy especially under the guidance of a psychiatrist with the use of, SNRIs, SSRIs and tricyclics in an attempt to tailor such therapy in conjunction with autonomic test results and hemodynamic results including heart rate and blood pressure and exercise testing.