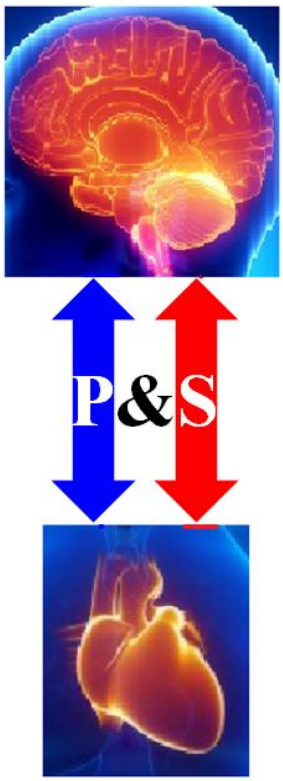
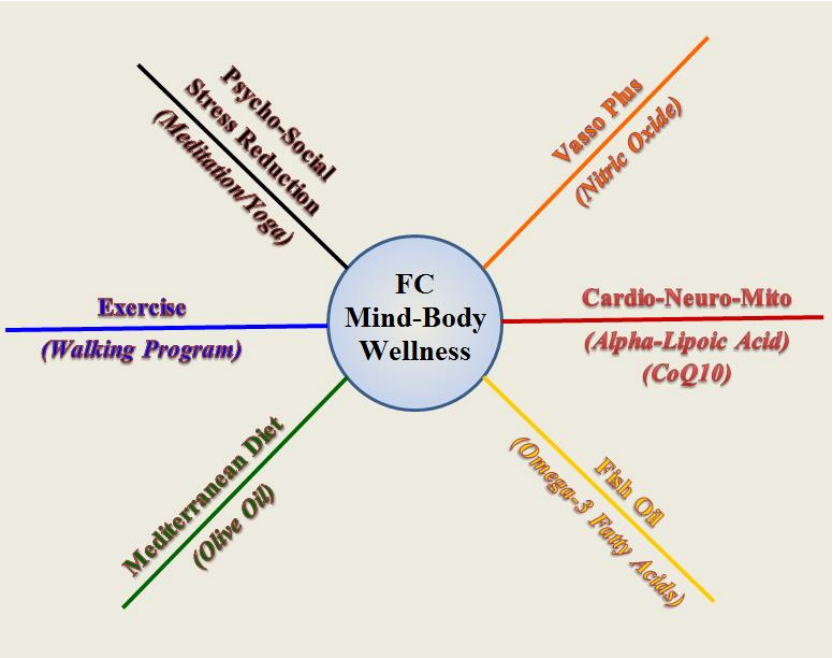
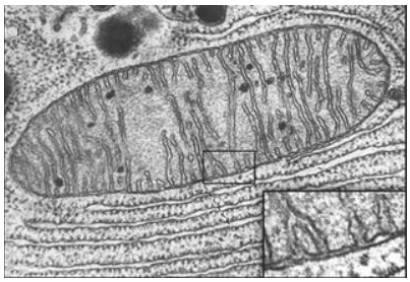


Summary FRANKLIN CARDIOVASCULAR MIND-BODY WELLNESS PROGRAM



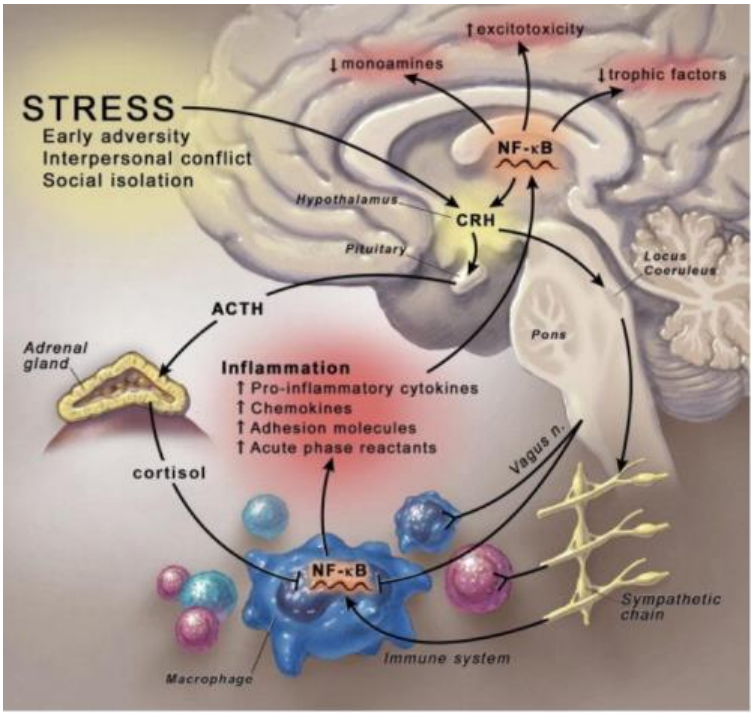
by
Nicholas L. DePace, MD, FACC
and J. Colombo, PhD



FRANKLIN CARDIOVASCULAR MIND-BODY WELLNESS PROGRAM

by

Nicholas L. DePace, MD, FACC and J. Colombo, PhD



Anxiety is the world's single most diagnosed disorder. Psychosocial stress is arguable the leading contributor. Often poor diet and the lack of exercise exacerbates the condition by causing additional stresses on your body. Prolonged anxiety and chronic stress pre-disposes individuals to diseases, by causing inflammation. Prolonged inflammation compromises your immune system and increases oxidation throughout your body. Oxidative stress and inflammation, for example, may cause cognitive dysfunction and accelerates the onset of dementia. Oxidative stress and inflammation also instigates the development of atherosclerosis which leads to heart disease. Someone in the US dies of heart disease every 90 seconds. Despite taking statins and lowering cholesterol by 33%, two-thirds (2/3) of these patients still have major adverse cardiovascular events (MACE; *e.g.*, heart attack, sudden death, or stroke), including repeat events.

Patients are not always protected from MACE just because they are on a statin. The **Franklin Cardiovascular Mind-Body Wellness Program** (**FC Mind-Body Wellness Program**, or **Mind-Body Wellness Program**) lifestyle recommendations and supplements help to protect the two-thirds sub-population; thereby, closing that gap. Furthermore, these lifestyle recommendations and supplements, if started early in life help to prevent MACE and avoid needing pharmaceuticals to begin with. Unfortunately, you will never hear any of this from the Parmaceutical industry. However, there are peer-review articles in prestigious medical journals that support a lifestyle and supplement, non-pharmaceutical, approach. The Pharmaceutical industry will not promote a lifestyle and supplement progam such as this **Mind-Body Wellness Program** because it will require less of their product and detract from their ecomnomic profits.

> **The person who takes medicine must recover twice, once from the disease and once from the medicine.**
> **– Sir William Osler, Bt**

As depicted on the cover of this booklet, the six-prongs of the **Franklin Cardiovascular Mind-Body Wellness Program** includes (1) **Omega-3, Fish Oil**; (2) **Cardio-Neuro-Mito**™; and (3) **Vasso-Plus**™, as the three supplements; and (4) **Mediterranean Diet**, (5) **Exercise**, and (6) **Psychosocial Stress Reduction** as the three lifestyle recommendations.

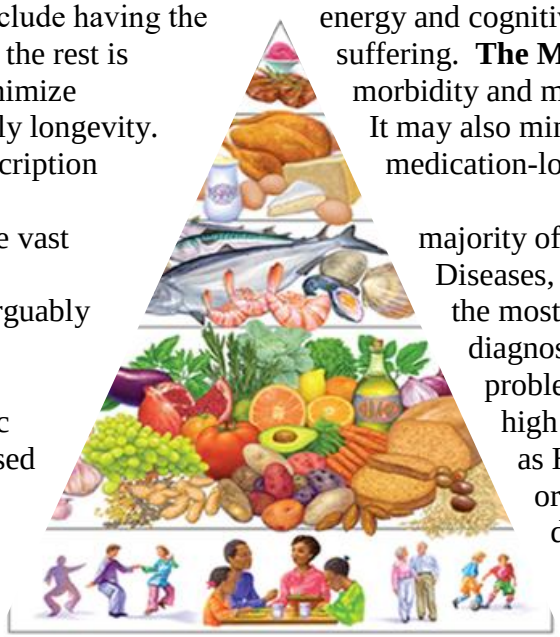
After doing hospital-based work for over 35 years, we have noted a trend towards less preservation of life and a low threshold placed to order comfort care. Many of these hospice and comfort care indications are justified. However in many of them, especially in younger patients, this type of care is not completely justified, especially at the premature stage at which this type of care is initiated. In particular, there was a patient of ours who had a diagnosis of mitochondrial disease. She was young, in her 50s. She had come in with a COPD exacerbation and pneumonia and was intubated. The issue of mitochondrial dysfunction was not clarified and whether this was truly a genetic mitochondrial disorder or a diagnosis that the patient had been labeled with based on an abnormal blood test was not known. As in this example, hospital personnel will use the pretense that they want to ease the patient's suffering and institute palliative care protocols and comfort care protocols. While this again is true of many instances, many times we have seen this to be a false pretense.

Human life is something that needs to be weighed very carefully and evaluated very carefully. Age of course, is a factor that must be considered, but should not be the predominant factor in making decisions about using comfort care measures, or hospice care. We are particularly distressed when patients that are young in their 40s and 50s or even 60s in some cases are put on these protocols without sufficient time to treat and attempt to stabilize their conditions. The bottom line is that patients (or patients' caregivers) must be aware of their (patient's) condition and be proactive to remain as healthy and well as possible. Adopting the **Mind-Body Wellness Program** even on your 30s, as those little nagging things begin to present (because you are no in your 20s any more) can help you to be proactive. If you are not 30 anymore, the **Mind-Body Wellness Program** is still able to help you to establish and maintain wellness. This program should be adopted for life. While you will experiment with other supplements and may need to take pharmaceuticals (at least periodically) we know and have evidence that this program will improve the efficacy of, and reduce the need for pharmaceuticals. They will also reduce the severity of the effects of the diseases you may encounter.

Again, some of the most ubiquitous diseases are caused by stress, including psychosocial stress, and stress due to Anxiety, Depression, Diabetes, being overweight, excessive processed and fast foods, sedentary lifestyles, Pain, etc. They may all lead to heart and vascular diseases that cause the risk of MACE, as well as Anxiety, Depression, Diabetes, ADD/ADHD,

Dementia, etc.; in other words, the diseases of this generation. As you know, pharmaceuticals are not always sufficient to restore quality of life (QOL) and normal lifespans. The fish oils, antioxidants (*e.g.*, Alpha-Lipoic Acid), olive oil diet, and exercise recommendations of the **Mind-Body Program**, may do more than any pharmaceutical; without the myriad of side effects and risks, including suicide risk.

Our point is that despite pharmaceuticals our patients are still suffering poor QOL (due to increased morbidity risk) and shortened life-spans (reduced longevity due to increased mortality risk). It may be argued that a younger adults' basic definition of QOL is eating (upper GI health) and sleeping well (restful sleep), normal bathroom habits (lower GI and bladder health), having sex (proper erectile function and vaginal lubrication), and not getting dizzy when you stand up (perhaps not in that order). Now-a-days, not having high blood pressure, not having cognitive difficulties ("brain-fog"), and having good levels of energy should probably be added. Even when these functions are diminished with time, older adults' QOL would include having the energy and cognitive faculties to spend time with grand-children, even if the rest is suffering. **The Mind-Body Wellness Program** is designed to minimize morbidity and mortality risk, thereby optimizing QOL and possibly longevity. It may also minimize the number of pharmaceutical agents (prescription medication-load) required to maintain health.



As another example, the vast majority of patients with Anxiety, Diabetes, Heart and Kidney Diseases, and more, have high blood pressure (BP). It is arguably the most common condition measured. High BP is not a diagnosis. Consider it more of a warning. High BP is not a problem to be diagnosed until it becomes chronic. Chronic high BP is known as the "silent killer" and is diagnosed as Hypertension. You must demonstrate high BP in two or more consecutive doctor visits in a row before being diagnosed with Hypertension. Chronic high BP (Hypertension) will:

- damage organs like the kidneys (increased morbidity risk) leading to renal failure (increased mortality risk);
- damage blood vessels (increased morbidity risk) leading to atherosclerosis, aneurysms, and stroke (increased mortality risk);
- over-work the heart (increased morbidity risk) leading to heart failure or heart attack (increased mortality risk);
- damage nerves and nervous tissue, including the brain, (increased morbidity risk) leading to dementia (*e.g.*, Alzheimer's or Parkinson's Disease) and autonomic neuropathy (increased mortality risk); and more.

Chronic high BP accelerates the aging process, making you look and feel older before your time.

Over fifty percent (50%) of patients with Hypertension are not adequately controlled with Pharmaceuticals alone. They may continue to suffer from: headaches or migraines; cognitive difficulties, including "brain fog;" fatigue; lightheadedness or dizziness; anxiety or panic attacks; sleep disorders; and more. Often times weight-loss and diet alone or with anti-hypertensives are also not enough. We are missing a piece of the puzzle. The internal and external stress must also be addressed. The **Mind-Body Wellness Program** (see six-prong figure on cover**Error! Reference source not found.**) addresses this inadequacy; the chasm between well controlled and the current state of most patients. As listed above the **Mind-Body Wellness Program** includes six-prongs. All six-prongs are equally important and must be taken all together. No one prong can substitute for anyother. As in this example for the patients with persistent *Hypertension*:

1. the **Mediterranean Diet** provides fuel and energy, some antioxidants and anti-inflammatories, as well as vitamins, minerals, and nutrients that are the building blocks for repair and healing, and health and wellness;
   - The Mediterranean Diet is a "heart healthy" diet which has been proven to reduce or prevent *Hypertension* among other diseases, including heart disease and dementia.
2. **Exercise**, yes exercise. Exercise is not a bad word! What we mean is an active lifestyle. Think of life before automobiles, elevators, television remotes and cell phones. Walking, taking the stairs, gardening, housework, yoga, dancing, and the like, even horseback riding, are all considered exercise in this case. Exercise is another anti-oxidant, and it ensures proper cirulation with nutrient and oxygen delivery and waste removal from all cells in your body, and reduces stress;

   - More anti-oxidants, more appropriate circulation and less stress adds-up to reduced or prevented *Hypertension*;
3. **Reduced Psycho-Social Stress** is another antioxidant and anti-inflammatory, it reduces the damaging effects of oxidation and inflammation, especially to the power-plants of your body, the Mitochondria (see the micrograph on the front cover), which together with proper blood flow keeps the brain and nervous system (the largest consumers of energy in your body) healthy and well, thereby properly controlling all systems of the body, including the cardiovascular and immune systems, thereby helping to keeping your body healthy and well;
   - With the brain supplied with proper amounts of oxygen and nutrients, including anti-oxidants, it reduces the demand for more blood on the heart and vasculature by increasing blood pressure or heart rate (Anxiety, for example, may be fueled by "adrenalin storms" initiated by the brain as a call for more blood to receive more oxygen and nutrients), thereby reducing *Hypertension* and palpitations);

4. **Vasso-Plus™** increases nitric oxide to promote endothelial health. The endothelium is the sheet of cells that line all of the blood vessels of the body, and other linings separating the body from the outside world. Improved endothelial health provides better circulation to all cells, and it is another anti-oxidant;

- Nitric oxide promotes proper (smooth) blood flow, preventing or reversing atherosclerosis, and maintains flexible and more relaxed blood vessels; both of which lowers blood pressure. Smooth blood flow and lower blood pressure help to protect the heart among many other organs, thereby reducing or preventing *Hypertension*;

5. **Cardio-Neuro-Mito™** provides more antioxidants (you can never have too many antioxidants) and other nutrients (incliding amino-acids) as essential building blocks to further decrease oxidative stress, maintain proper Antioxidant-Oxidant balance, increase energy production (especially from mitochondria), and prevent or slow the progression of chronic disease;
   - **Cardio-Neuro-Mito** supports the brain and the nervous system, especially the Autonomic Nervous System (ANS), including its two branches: the Parasympathetic and Sympathetic (P&S) Nervous Systems. **Cardio-Neuro-Mito** promotes a proper balance between the P&S nervous systems helping to prevent and minimize the affects of Chronic diseases, including *Hypertension*; and
6. **Omega-3, Fish Oil** increases the "good" fats[1], creating a proper HDL-LDL balance, helping to unclog your vasculature and keep it unclogged, it is a membrane stabilizer, as well as an anti-inflammatory and antioxidant, it gets energy and nutrients to all parts of the body by maintaining healthy cell membranes and endothelial function;
   - By keeping arteries and veins clear *Hypertension* is reduced and prevented.

A healthy side effect of a combination of **Vasso-Plus** and **Omega-3**, will establish and maintain a healthy cholesterol balance[2]. A healthy cholesterol balance is furthered through the combination of the **Mediterranean Diet**, **Exercise**, and **Omega-3 Fatty Acids**.

Cardio-Neuro-Mito includes Alpha-Lipoic Acid (ALA) and Co-Enzyme Q10 (CoQ10). These are two of the most powerful antioxidants produced in the body. Unfortunately, due to stress, chronic disease and aging, the body produces less and less of these antioxidants, starting as

[1] Technically speaking there are no "bad" fats; however, the "bad" fats are the fats that actually become bad when they exist in quantities that are excessive for the individual. In small quaitities, "bad" fats are very important for proper nerve function, among other functions.

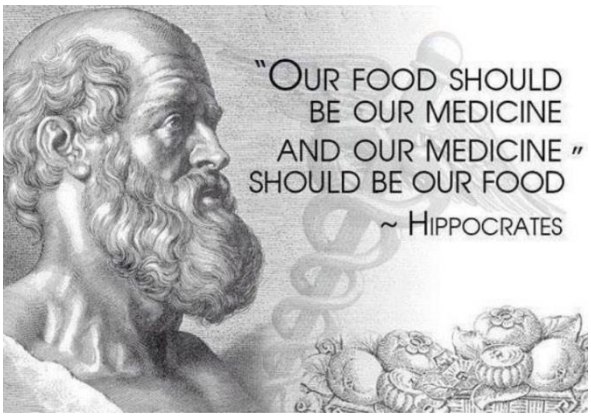
[2] Cholesterol balance is the "good" to "bad" lipoprotein balance (HDL to LDL). The body does need a, very, little, relatively speaking, of the "bad" cholesterol (LDL), or fat, for normal nerve function. While this is not a specific target of the **Mind-Body Wellness Program** is a benefit.

early as in your 30's. Fewer antioxidants accelerate the aging process and slow the body's energy production due to increased oxidation[3] of the Mitochondria in

[3] Oxidation is burning, a chemical raction that burns to destroy. A fire is the oxidation of carbon. Like fire, a little is good for cooking and heating, but too much (like a a house burning) or not enough (like freezing) are not good. In the terms of this book too much oxidation is known as "Oxidative Stress." A proper Antioxidant-Oxidant balance eliminates Oxidative Stress.

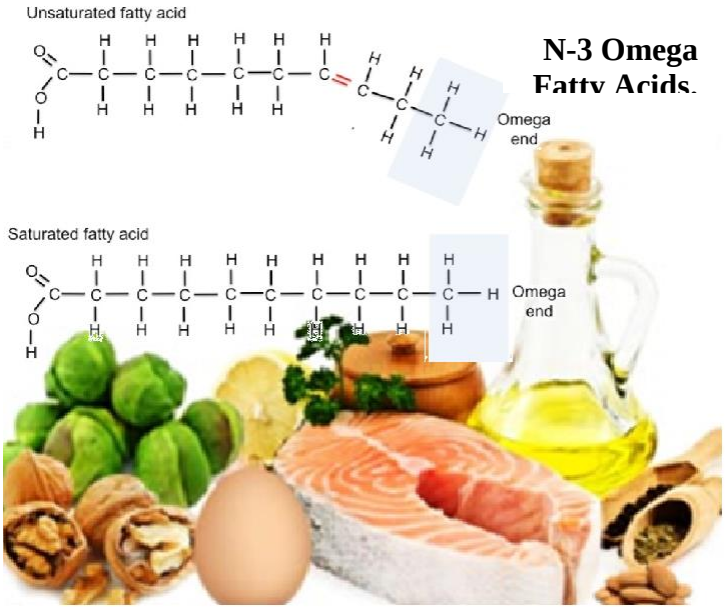
your cells. The healthier your mitochondria, the more energy you have for brain function as well as muscle function, including yor heart.

A high stress lifestyle works to reduce the levels of these powerful antioxidants. This reduces your QOL and how long you may live (longevity). A high stress lifestyle is compounded by the American diet (fast food and pre-prepared foods) and lack of exercise. Of course going to the gym and running and weight lifting, etc., are good, but they can also injure.



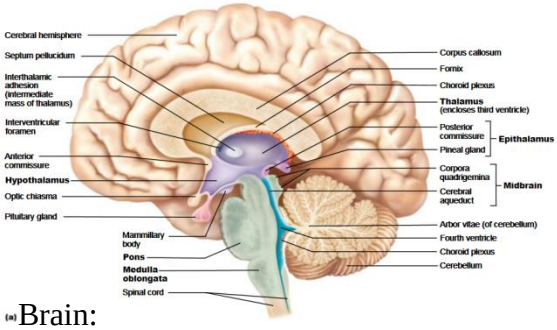
EXERCISE IS THE MOST POWERFUL OF ALL ANTIOXIDANTS, and includes many other health beenfits, including: Happier Moods; Reduced Pain; Immune Health; Better Sleep Quality; Improved Concentration & Creativity; Reduced Anxiety; Mental Fitness; Parasympathetic and Sympathetic (P&S) Health; Neuroendocrine Health; Heart & Vascular Health; Stress Reduction; Weight Control (Loss); Reduced Risk of Type 2 Diabetes and Metabolic Syndrome; Reduced Cancer Risk; Healthier Bones, Muscles, and Joints; and Increased Longevity – promotes living longer *with a healthier Quality of Life!*

CAUTION: Always consult your physician before starting an exercise regimen. The wrong types of exercise may do more harm than good, including increasing body fat (and thereby body weight), fatigue and pain due to the fact that the body is programmed to over-react to stresses. Under these conditions, the body sees exercise as stress and works to protect itself against the stress. With certain diseases (*e.g.*, some arrhythmias, diabetes, stroke or aneurysm risk, or heart disease), the wrong type of exercise may also lead to heart attack, stroke or sudden death. It is best to start slow and build up and always listen to your body. Until you build endurance, you may not reach recommendations for a while. This is not bad, be patient and keep at it until you are able to reach your goals. (Dying before we get you well is *definitely* counter-productive! ☺) The health benefits of physical activity far outweigh the risks of getting hurt.

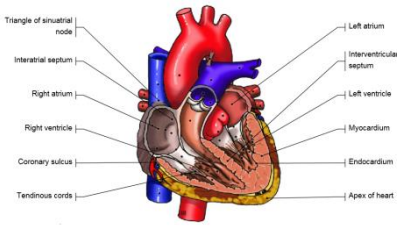


N-3 Omega Fatty Acids

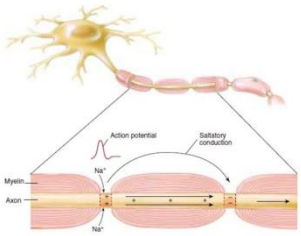
The Mind-Body Wellness Program focuses on the P&S Nervous Systems. This is the portion of the nervous system that forms the brain-heart and mind-body connection (see the brain-heart figure on the cover). The P&S nervous systems regulate blood pressure, heart rate, airway size, airflow to lungs, digestion, the bladder, sexual function, depression, anxiety, gland and hormone function, and all of the rest of the functions of our bodies that we do not want to have to think about. In fact the P&S



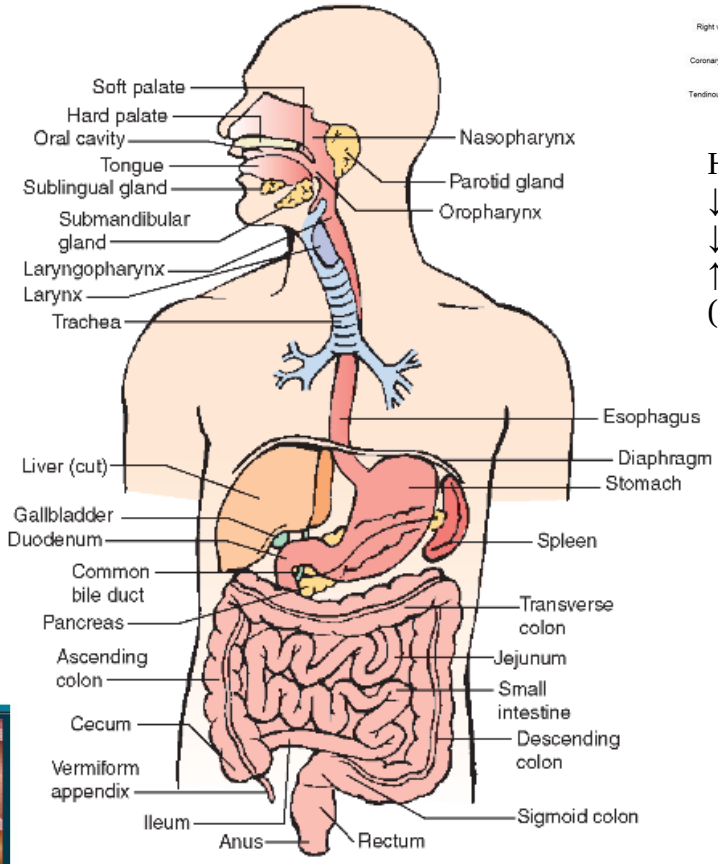
Brain:
↓ Inflammation at Blood Brain Barrier
↑ Cognitive function & Memory



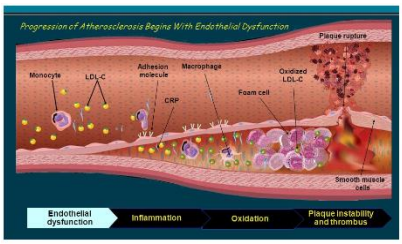
Heart:
↓ Heart rate
↓Arrhythmia
↑ Vagal
(Parasympathetic) tone



Myelin Sheath:
↑ production/repair

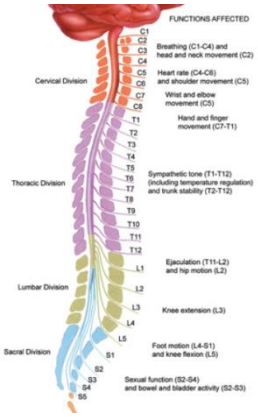


Liver:
↓ Triglyceride production
↓ Blood viscosity



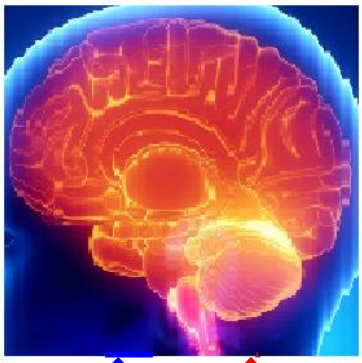
Endothelium:
↓ Blood pressure
↓Endothelial dysfunction
↑ Blood vessel Vassodilation

Digestive System:
↓ Production of Arachidonic Acid & Eicosanoids
↑ n-3 metabolites

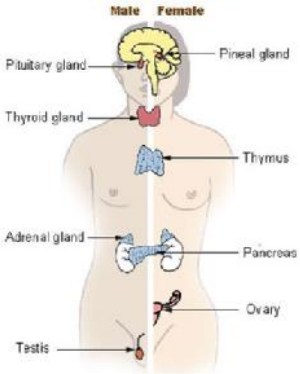


Nervous System:
↑ Autonomic funciton
↑Vagal (Parasympathetic) tone

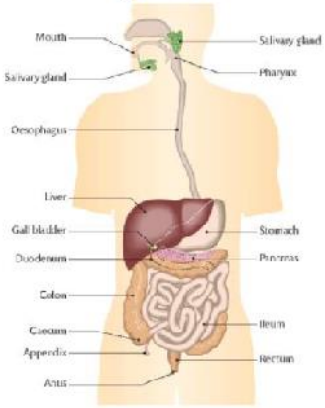
Physiologic effects of n-3 omega fish oils.



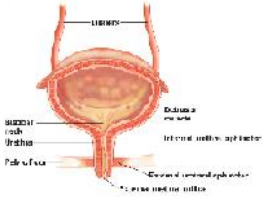
Glands

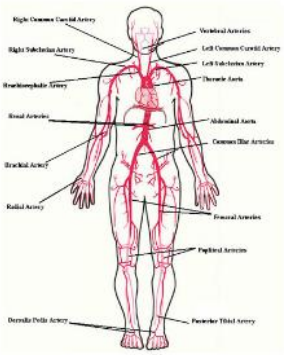


Digestive System

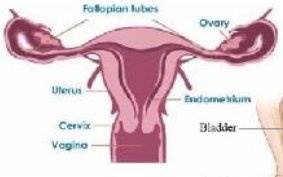


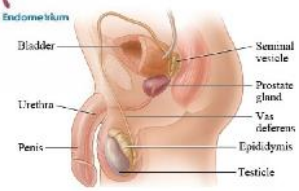
P&S





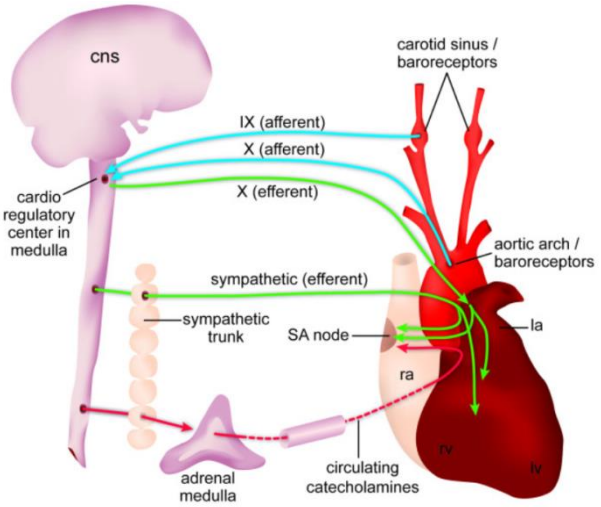
Vasculature





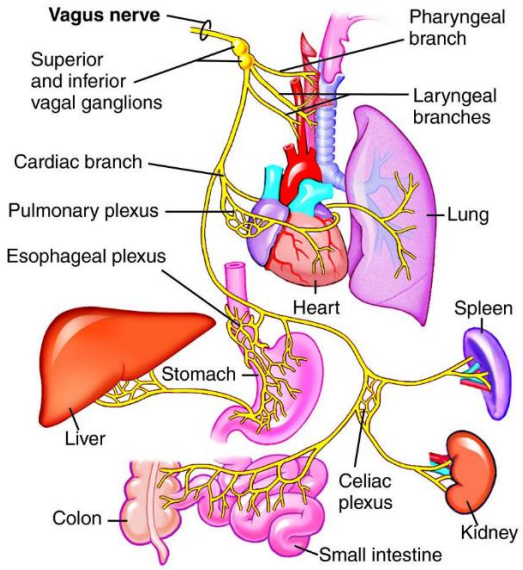
The P&S Nervous Systems form the Heart-Brain connection and together with the heart and brain connect the rest of the body's organ systems. Achieving a proper balance between the P&S, enables optimal control of the organs, helping to establish and maintain health and wellness.

nervous systems control or coordinate virtually all cells of the body and all organ and organ systems of the body, including the immune system. The Sympathetic nervous system is the reactionary nervous system (known as the "fight or flight" nervous system) and responds to stresses and generally expends energy. The Parasympathetic nervous system is the protective nervous system (known as the "rest and digest" nervous system) and generally conserves energy. The health of, and balance between, the P&S nervous systems defines QOL (in medical parlance, morbidity risk) and affects longevity (in medical parlance, mortality risk).



P&S connects the brain and the heart

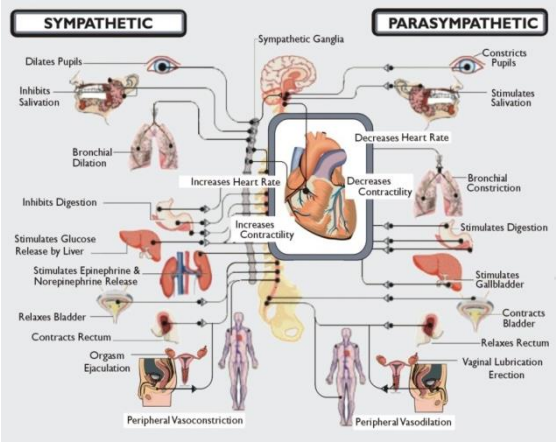
As mentioned, **The Mind-Body Wellness Program** also focuses on the Mitochondrial health.



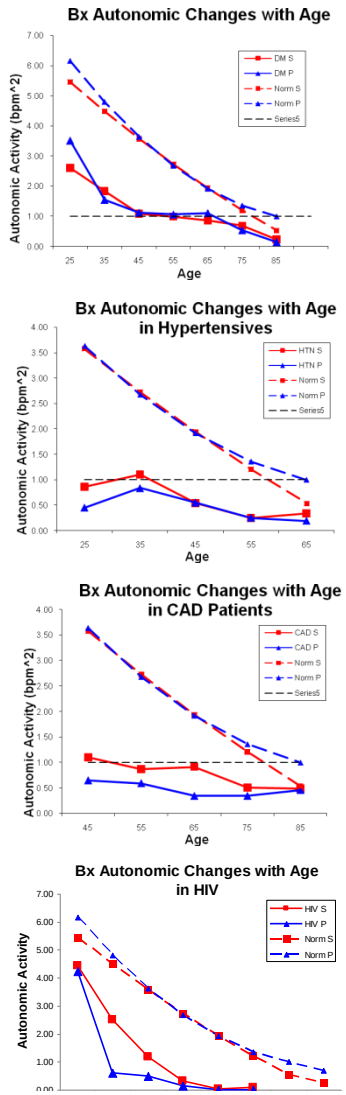
The Vagus Nerve, the major portion of the Parasympathetic Nervous System

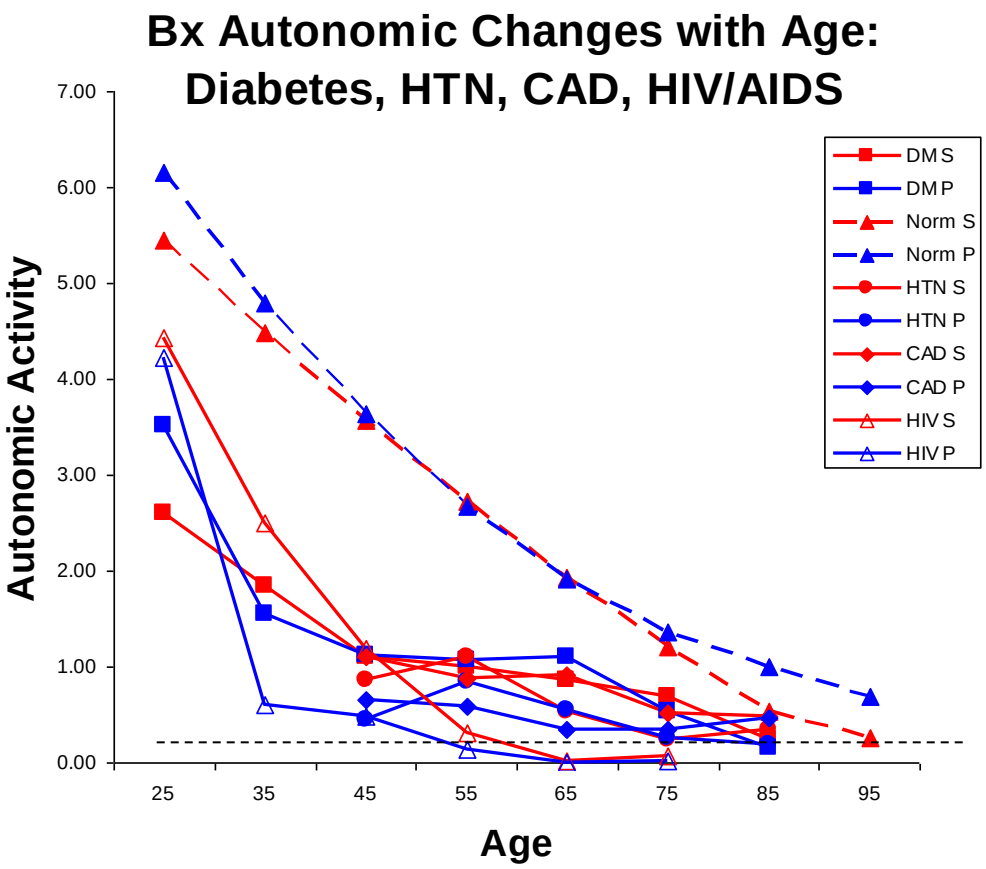
Nerves, including the brain, require lots of energy. Just sitting there, your brain consumes about 70% of the energy produced in your body to control all of the functions of your body. During periods of high activity (whether running or swimming, having an emotional experience like love or rage, or taking a final exam), your brain consumes up to 85% of the energy produced in your body to also control the additional activities. Many cognitive disorders may involve both autonomic and mitochondrial dysfunction. Mitochondria produce energy molecules known as Adenosine Tri-Phosphate (ATP). ATP is needed for all nerve functions and muscle contractions. Mitochondria are the power plants of your body and ATP is the energy molecule that powers all cellular functions.

A lack of ATP can cause chronic fatigue syndrome (CFS) and other disorders pertaining to Autonomic (P&S) and Mitochondrial dysfunction. Even moderate levels of P&S dysfunction is well known to involve many QOL dysfunctions. These may include: (1) difficult to control BP, blood glucose, or hormone level, (2) difficult to describe pain syndromes (including CRPS and Fibromyalgia), (3) difficult to manage weight-loss, (4) unexplained arrhythmia (palpitations) or seizure, and symptoms of (5) depression or anxiety, (6) fatigue, (7) exercise intolerance, (8) sex dysfunction, (9) sleep or (10) GI disturbance, (11) occasional to frequent lightheadedness or dizziness (Orthostatic Dysfunction or Syncope are arguably the most debilitating symptoms of autonomic

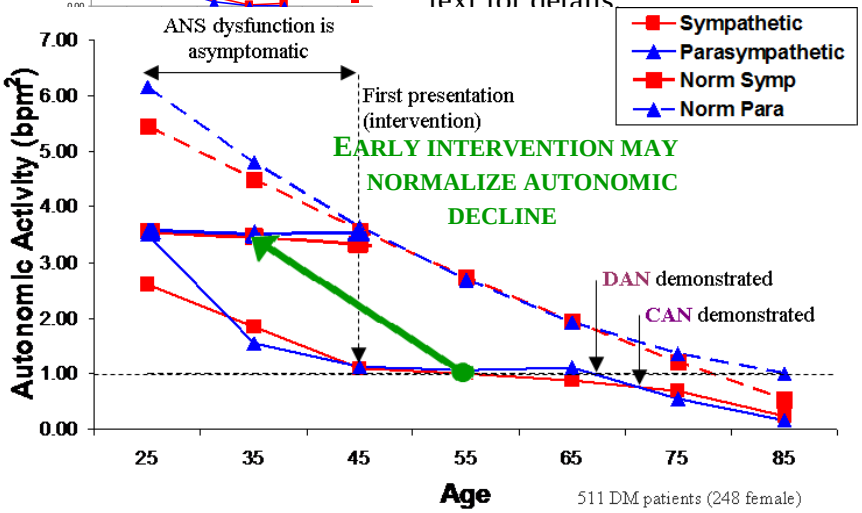


dysfunction), (12) cognitive dysfunction or "brain fog," (13) attention difficulties, or (14) frequent headache or migraine.



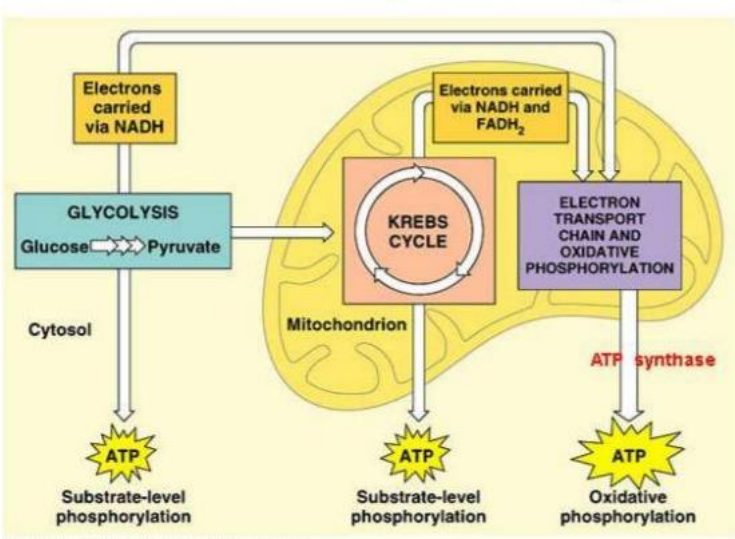


Chronic Disorders and Diseases, including high blood pressure and Hypertension accelerate aging. Age-matched comparisons between normal subjects and patients with diabetes, hypertension, CAD, and HIV/AIDS. See text for details.



The effects of restoring and maintaing Sympathovagal balance.

Often, none of these symptoms are treated as P&S dysfunctions. They are typically treated in isolation leading to many medications and often over-medication. Often this is because they occur early in the disease processes, when patients are younger. Furthermore, traditional therapies are often not very effective to, or only mask, P&S symptoms. Patients end-up trying many different physicians to no avail and are even recommended

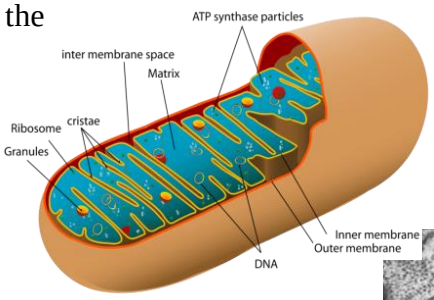


The heart of energy production is in Mitochondria

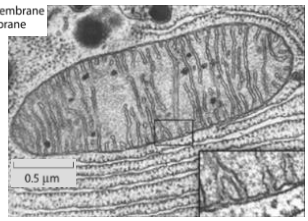
for psychiatric evaluation; at which time everyone loses. Everyone loses because the problem is not psychological, but *physiological*. The problem is that very few know about it. This level of P&S dysfunction was not taught in Medical School.

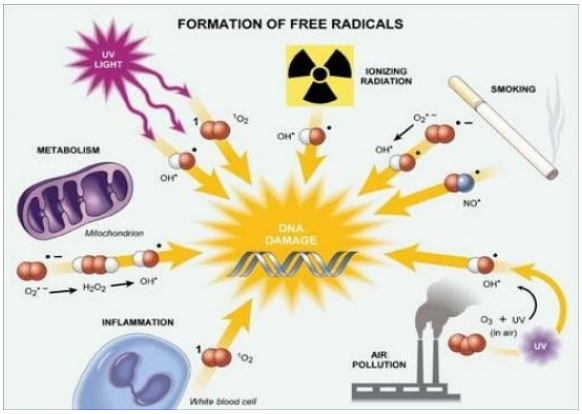
The stage at which these symptoms present is known as Advanced Autonomic Dysfunction (AAD), or for patients with Diabetes, Diabetic Autonomic Neuropathy (DAN); both of which carry a high morbidity risk (risk of secondary diseases or side-effects). Both of which are defined as low, resting P or S activity. AAD affects QOL. This is not reversible, the best we can do at this time is to preserve what is left. The better option is to start as early as possible to prevent the onset of AAD or DAN. The **Mind-Body Program** is designed to use lifestyle recommendations and supplements to delay or prevent the onset of these symptoms and thereby the conditions known as AAD or DAN.

Not long after AAD or DAN, late stage (end stage) autonomic dysfunction presents. This is known as Cardiovascular Autonomic Neuropathy (CAN). It is defined as very low, resting, Parasympathetic activity (*e.g.*, it is like having "no brakes" on your car; you are an accident waiting to happen). There are two forms of CAN: functional and structural. Functional CAN patients often find (temporary) relieved of CAN once their P&S balance is restored appropriately for them, the individual patient. Structural CAN is not reversible and carries the mortality risk. CAN risk is the same as in post-MI and post-CABG patients as documented in the Framingham Heart Study. For chronic patients, CAN has been found to carry the same 50% increase in the five-year mortality rate, as with diabetes. In other words, upon diagnosis, the risk of experiencing a heart attack, stroke, or other major cardiovascular event (MACE) within five years is 50% or more.



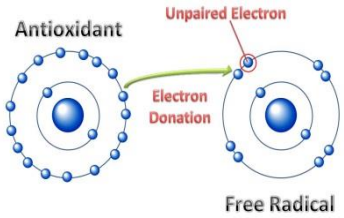
The functional structure of Mitochondria





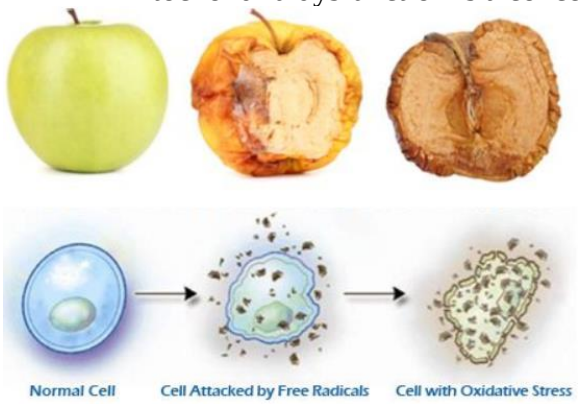
Free radicals come from many sources: internally (*e.g.*, "leaky" Mitochondria and inflammation), externally (*e.g.*, radiation and air pollution), and through lifestyle (*e.g.*, UV from sunbathing and air pollution from living or working in polluted areas, poor nutrition).

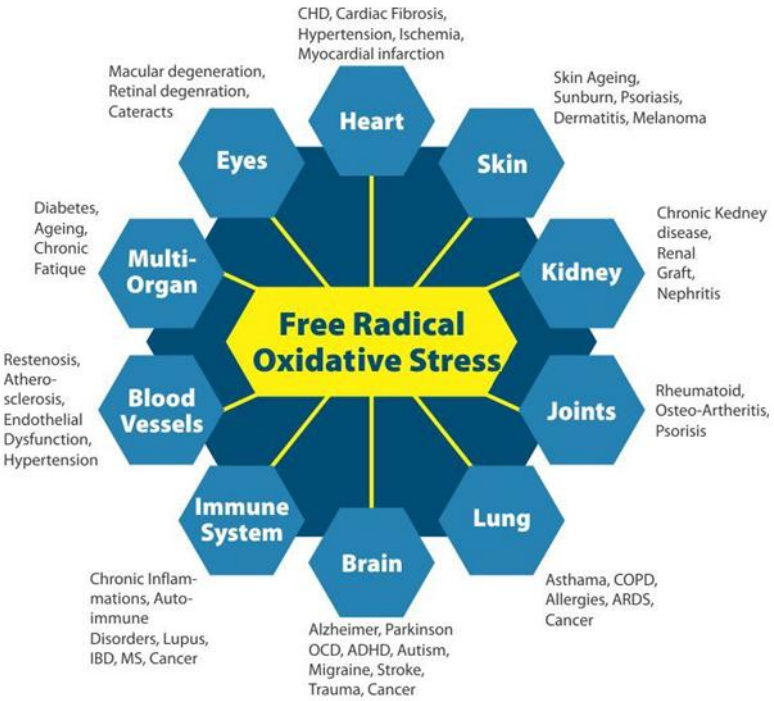
Typically, CAN is normal for post-MI, post-CABG, chronically ill, and geriatric patients. CAN is a normal part of the aging process. Again, CAN simply indicates risk of mortality. In other words, it is a sign



of age and people with CAN, who tend to be older, have a greater risk of dying than people without CAN, who tend to be younger and healthier. However, regardless of age, CAN with abnormal P&S balance is not normal. CAN with high P&S balance is high risk, and is associated with other risk factors, including 1) low ejection fraction; 2) poor cardiac output; 3) arrhythmias; 4) cardiomyopathies, including chronic heart failure; 5) poor circulation, including poor cardiac circulation (Angina or coronary artery disease); 6) greater mortality; and 7) greater morbidity, including silent myocardial infarction and early cardiac death. CAN with low P&S balance is associated with "Broken Heart Syndrome" and depression and depression-anxiety syndromes. Often, CAN leads to the need for cardiac intervention or an implanted cardiac device. CAN affects longevity.

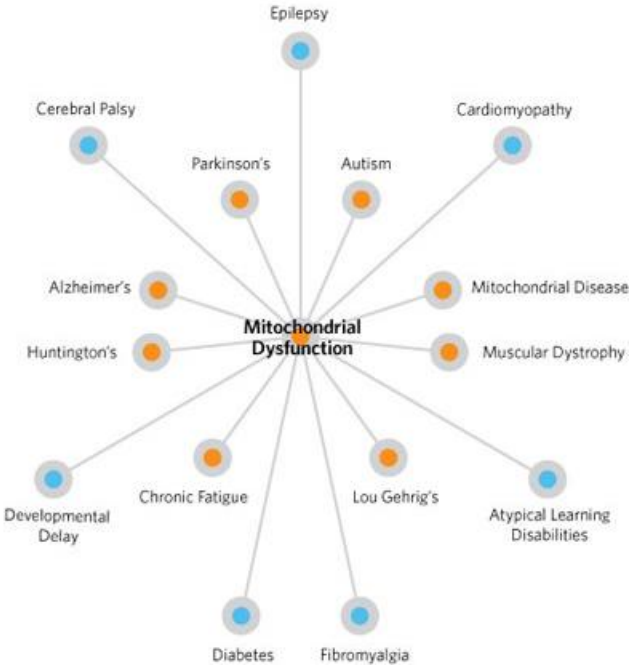
Mitochondria dysfunction is a concern in that it produces a significant amount of harmful compounds in the body, called, Reactive Oxygen Species (ROS) and free radicals. Free radicals are also caused by environmental and lifestyle affects. They all include an unpaired electron in their outer valence. Antioxidants neutralize free radicals by donating an electron to fill the pair. If the electron is not donated by an antioxidant, it will find one elsewhere, thereby, damaging the structure from which it takes the electron. On average, your body produces 300 Sextillion ($3x10^{23}$) free radicals *per day*! This number increases when you are sick. This is the reason for your need of antioxidants, and the **Mind-Body Wellness Program** is putting as many



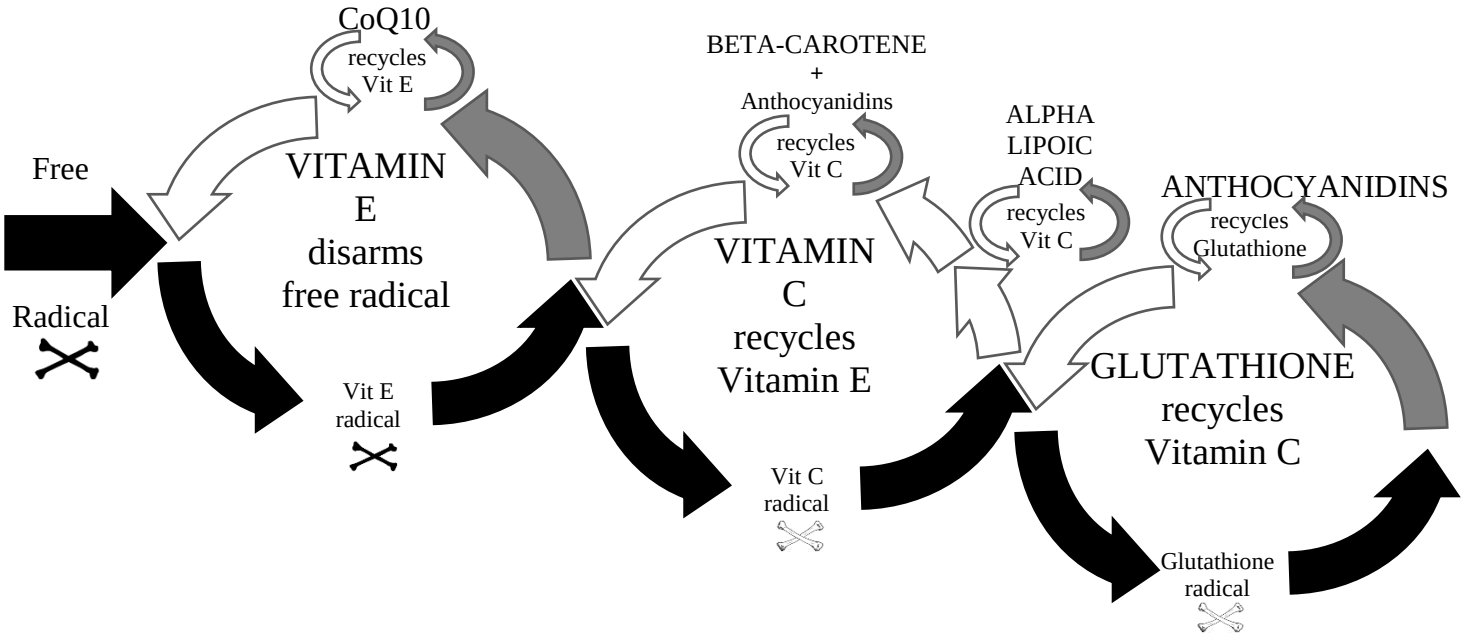


Systemic effects of oxidative stress.

potent antioxidants as possible into its supplements. Oxidation accelerates the effects of aging, as well; remember what it does to apples. Given the harm that is often induced by ROS and free



Mitochondrial dysfunction underlies Autonomic (P&S) Dysfunction which is associated with many diseases and disorders throughout the body, and morbidity and mortality risks. Mitochondrial and Autonomic dysfunction go together like Laurel and Hardy, Bud and Lou, Sears and Roebuck, or Funk and Wagnall.

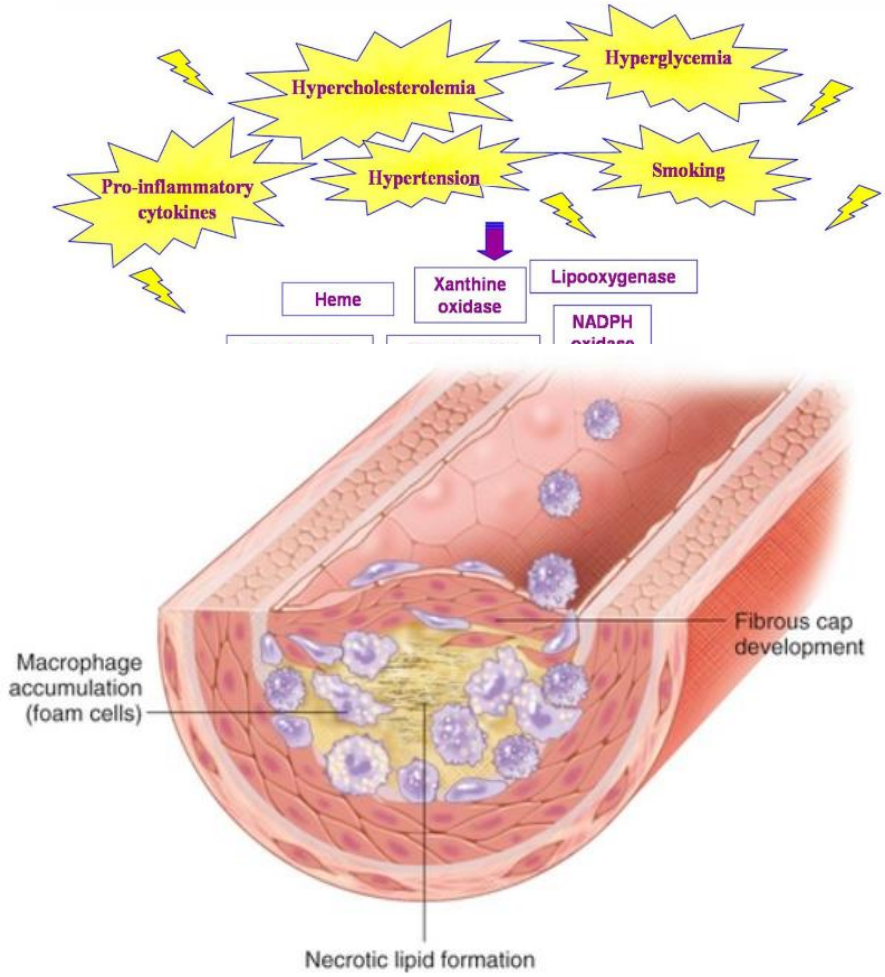


Antioxidant recycling. The antioxidants work together to maintain a healthy antioxidant buffer and to prevent themselves from becoming oxidants. In this example, a free radical is eliminated by Vitamin E, which will be recovered by Vitamin C. Vitamin C then will be recycled by Glutathione, which will be restored by Anthocyanidins. Coenzyme Q10, Beta-Carotene, and Alpha-Lipoic Acid help each other.

radicals, the importance of antioxidants cannot be understated.

The noxious effects of ROS, generated during cellular respiration at the mitochondrial level, are directly involved in aging processes. However, ROS actually may have a beneficial physiological role. They act as messengers in cellular signaling, regulating controlled production of reactive oxygen and nitrogen species (RONS). RONS act as second messengers for the expression of several health factors, help to regulate immune responses, programmed cell death (when cells are worn out), and more.

However, like all things in life, too much of a good thing is no longer good. Too much oxygen burns (fire is an oxygen reaction, oxygen reactions literally burn structures) and destroys. A derangement in oxygen management results in sustained levels of oxidative stress, can play a significant role in the development of major human diseases characterized by chronic inflammation, chronic activation of wound healing and tissue fibrogenesis (essentially excessive scarring, both inside and out).



Atherosclerotic lesion progression. This illustration shows an advanced atherosclerotic plaque with uptake of oxidized LDL by macrophages, which become Foam Cells. Reactive oxygen species induce necrosis and apoptosis, leading to a necrotic core. Inflammatory cells promote cytokine and growth factor release that stimulates fibrous cap formation. *Modified from Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999;*

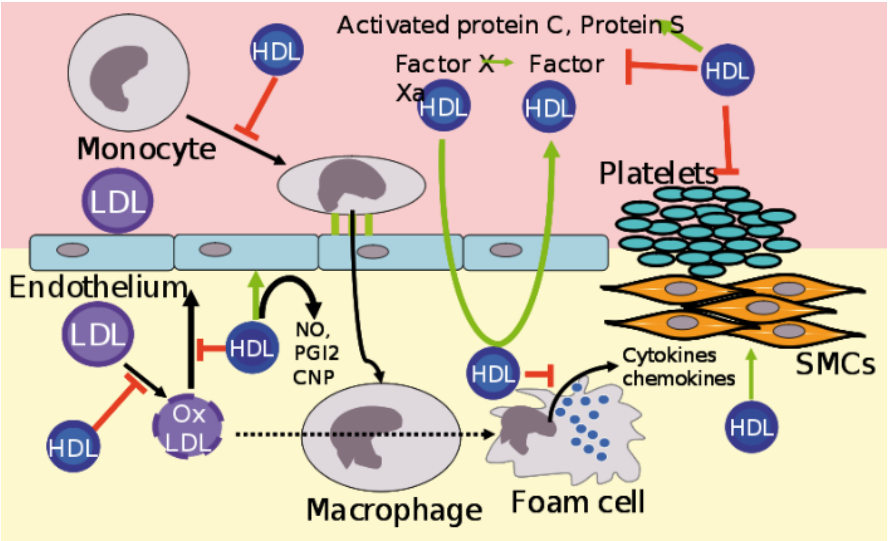
Anti-oxidant Recyclic Figure, above).

Oxidative stress effects pathways by injecting too much energy into the normal oxidative reaction, permitting an incomplete oxygen (or nitrogen) atom to be attached to compounds that are used normally. These harmful compounds are very toxic and, if not neutralized by antioxidants, they cause damage. This damage promotes disease, especially various forms of cancer and atherosclerosis. Preventing this damage, antioxidants promote QOL (reducing morbidity risk) and longevity (reducing mortality risk). "Sick" Mitochondria can be the greatest producer of oxidants and oxidative stress, because they become leaky and inefficient. As medicine has discovered, mitochondrial disease and autonomic disorders are intimately linked, in health and wellness the two work together to maintain eachother, and thereby the body, in wellness. In sickness the two can exacerbate eachother. This is another reason to take more antioxidantswhen sick; such as Vitamin C, or better yet: Alpha-Lipoic Acid (see

Both Dr. DePace and Dr. Colombo have long believed that there needs to be a proper balance to promote wellness. A proper balance must be individualized for the patient, given the patient's family medical history, personal medical history, age, lifestyle, and genetics. So far we

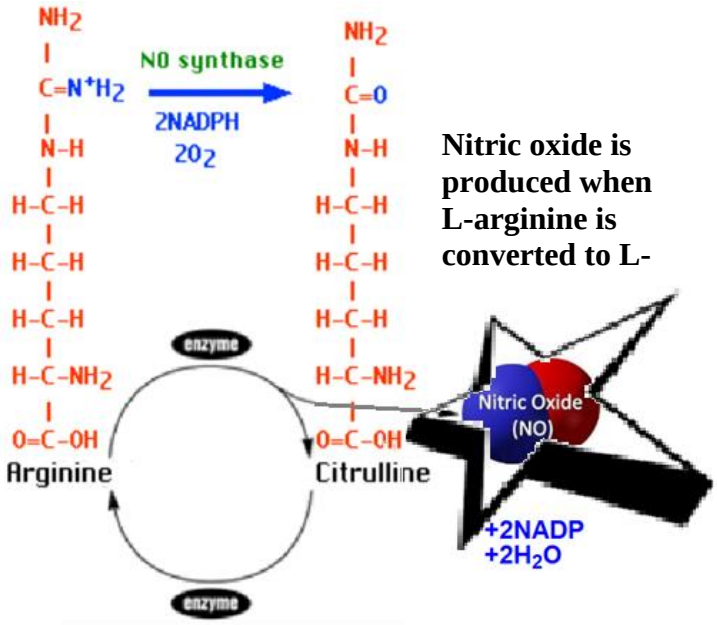
> **The good physician treats the disease; the great physician treats the patient who has the disease.**
> **– Sir William Osler, Bt**

have discussed the need for a proper balance between pharmacological agents that are taken and supplements and lifestyle changes, and a proper balance between the P&S nervous systems. To prevent or reduce atherosclerosis, oxidized-LDL levels must be lowered. While more HDL enables less LDL, too little LDL is also unhealthy, and leads to nerve and neuro-muscular disorders and cognitive dysfunction. Therefore, there needs to be a proper balance between LDL and HDL cholesterol. Omega-3 Fatty Acids help to establish and maintain this balance. The **Mind-Body Wellness Program** provides extra **Omega-3, Fish Oil** to help ensure this healthy balance between oxidants and antioxidants, as well as the other benefits of Omega-3 fatty acids. Too many oxidants will favor the process of oxidative stress, which creates a surplus of RONS that damage tissues and proteins, prolong inflammation, and promote many diseases. The **Mind-Body Wellness Program** also provides extra antioxidants through **Cardio-Neuro-Mito**™ to help ensure a healthy antioxidant-oxidant balance, like a balance between work and relaxation (lack of stress), are types of "Yin and Yang" balance emphasized in the **Mind-Body Wellness Program**.



HDL helps to prevent atherosclerosis by helping to (1) block LDLs from being oxidized, (2) macrophages from becoming Foam Cells, (3) Foam Cells from sticking to vessel walls, (4) Foam Cells from releasing inflammatory products, including cytokines, and (5) platelets from aggregating.

In addition to preventing and reversing atherosclerosis by keeping blood vessel walls smooth and slippery, nitric oxide helps to prevent inflammation. It is a messenger that is ubiquitously available throughout the body helping to reduce the aging effect, increase energy, enhance memory and cognitive function, increase blood flow to organs, boosts exercise performance and endurance, regulates Insulin to manage Diabetes and prevent complications due to Diabetes, improves sex performance, lowers blood pressure and LDL cholesterol, and reverses kidney disease and failure. The **Mind-Body Wellness Program** provides extra nitric oxide through **Vasso-Plus**™ to help ensure healthy levels to promote all of the benefits of nitric oxide.

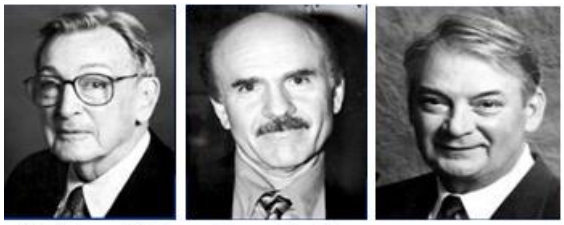


Nitric oxide is produced when L-arginine is converted to L-

Nitric oxide is produced when L-arginine is converted to L-citrulline. The doctors recognized for the discoveries of nitric oxide as a signaling molecule won the Nobel prize in Physiology or Medicine in 1998. Nitric oxide is found throughout the body. It is interesting that all six prongs of the **Mind-Body Wellness Program** increase nitric oxide either directly or indirectly. By keeping endothelial cells healthy throughout the body, nitric oxide is more readily produced. When endothelial cells become damaged, diseased or defaced, nitric oxide deficiency occurs. This leads to increased morbidity (quality of life) risk and if prolonged, mortality risk. When endothelial dysfunction is treated by increasing nitric oxide levels in the body, cardiovascular risk is reduced. Also, when cardiovascular risk factors are treated the endothelial dysfunction is reversed. Endothelial dysfunction is an independent predictor of cardiac events.

Nitric oxide works as a neurotransmitter and vasodilator. It is bactericidal fighting infections, and an anti-inflammatory reducing or preventing inflammation. Very importantly, it is antioxidant and performs many antioxidant activities, including neutralizing free radicals and ROS. It can promote cerebral (brain) circulation, so that people who have brain fog actually feel better and have fewer cognitive difficulties. Nitric oxide promotes sexual health, including erectile dysfunction, and possibly vaginal lubrication and other reproductive functions.

As stated before, nitric oxide is known as the "Anti-Atherosclerotic Molecule." It prevents LDL-oxidation leads to "Foam Cells" that are the beginning of atherosclerosis. Unfortunately, this process occurs very easily.



Robert F. Furchgott **Louis J. Ignarro** **Ferid Murad**

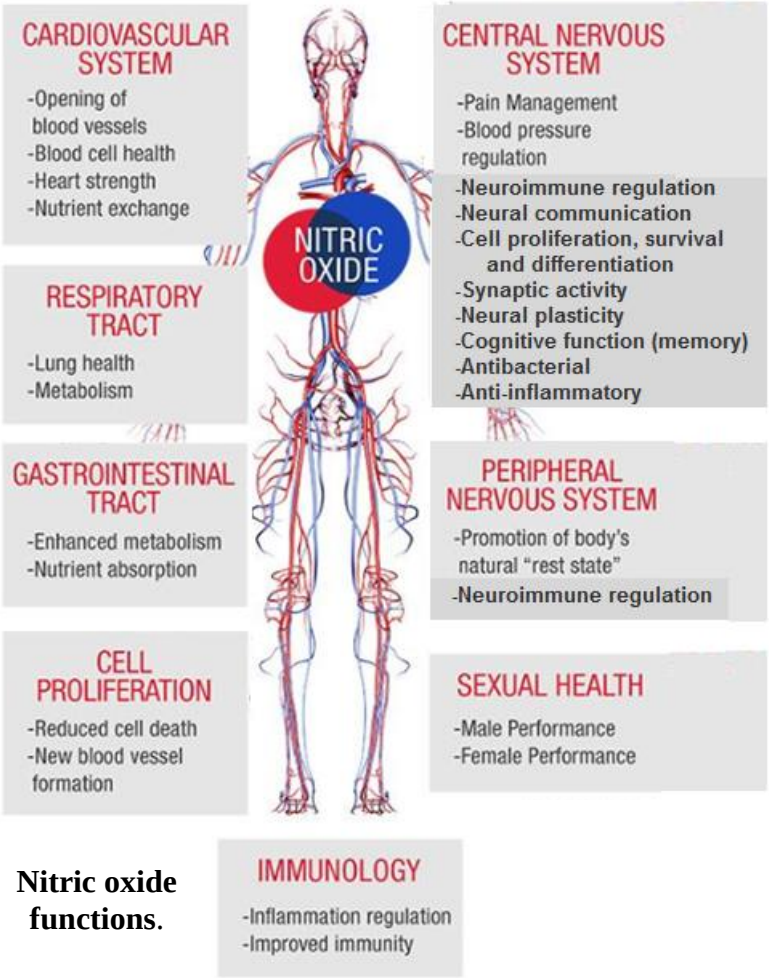
The doctors that shared the 1998 Nobel prize for discoveries of nitric oxide as a signaling molecule.

Nitric oxide is a ubiquitous messenger, also known as the "universal messenger".

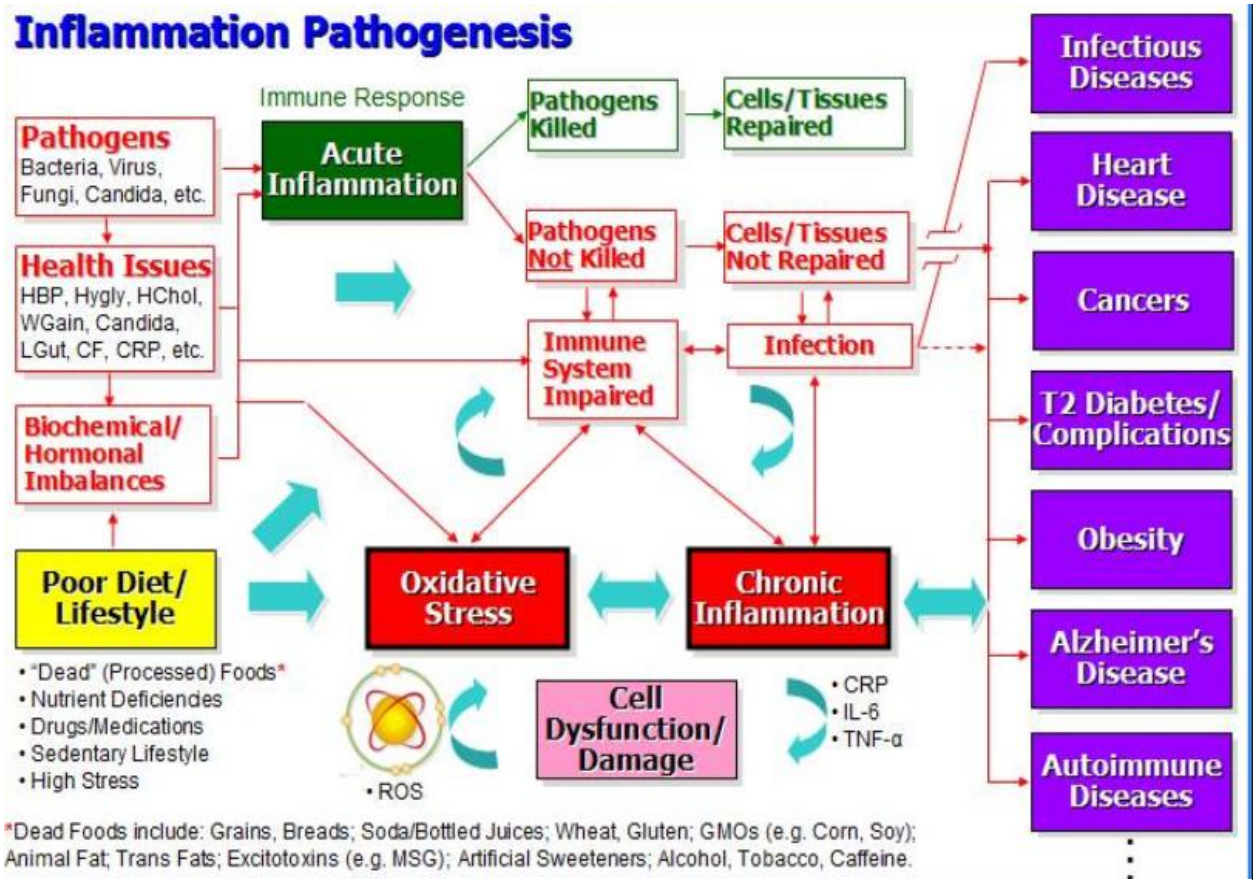
Nitric oxide protects the arteries from the adverse effects of "sticky" or too many platelets leading to blood clots which further clogs blood vessel. As a result, nitric oxide is an anti-thrombotic; it prevents clotting.

In the cardiovascular system, nitric oxide acts 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 firemen of the body by preventing white blood cells from adhering to blood vessel walls and causing inflammation (in essence it is the firemen 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.

Nitric oxide prevents leukocyte (white blood cell) adhesion which causes inflammation of, and damage to, endothelial cells promoting plaque build-up leading to atherosclerosis. Therefore, nitric oxide is also an anti-inflammatory. Nitric oxide insufficiency and the resulting inflammation, stimulates the Sympathetic nervous system leading to too much Cortisol and Adrenaline throughout the body which exacerbates inflammation. Excessive, Sympathetic activity pulls the Autonomic nervous system out of balance, promoting the risk factors (*e.g.*, Diabetes induced heart disease, high cholesterol, high blood pressure, persistent obesity). The Sympathetics get higher, suppressing the protective Parasympathetics, and there is even more Adrenaline type compounds around. In the extreme, suppressed Parasympathetic activity cannot prevent heart attack, stroke, aneurysms, sepsis, and other, potentially, life-ending (MACE) events.



Nitric oxide functions.

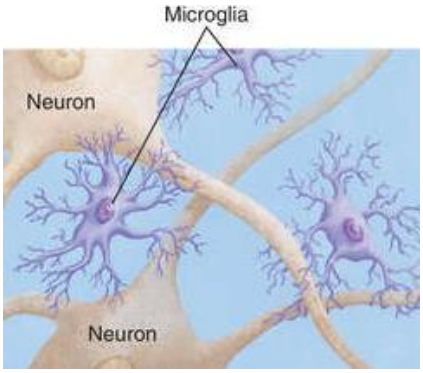


Inflammation Pathogenesis. Inflammation has many sources, including poor diet or lifestyle, which lead to acute inflammation (which is normal and healthy) and oxidative stress (including an over-production of ROS, which is not normal or healthy). Sources from pathogens and acute (short-term) health issues responded to in a normal, healthy manner (text in green at the top) lead to the pathogens being killed and cells and tissues being repaired. Long-term health issues, including imbalances (which involve P&S imbalances), lead to pathogens not being killed, and cells and tissues not being repaired. The abnormal responses (text in red) lead to chronic inflammation and cell damage, which lead to chronic diseases including diabetes, cancers, and heart (cardiovascular) disease, as well as neurological diseases, arthritis, and pulmonary diseases. The Mediterranean diet, exercise, anti-oxidants, and anti-inflammatories from the **Mind-Body Wellness Program** helps to prevent the abnormal responses and negative outcomes..

Nitric oxide is the neurotransmitter of the family of Parasympathetic neurons known as Nitrergic neurons, adding to the well known Cholinergic family. Through its mediation of Parasympathetic activity by Nitrergic neurons, nitric oxide reduces Sympatethetic activity (balancing the ANS), reducing cortisol and adrenaline, helping to reduce inflammation and symptoms associated with Sympthetic excess. By increasing Parasympathetic tone, helping to decrease Sympathetic activity, nitric oxide helps to reduce stress throughout the body and has a good balancing effect on the P&S nervous systems, helping to protect the heart and the other systems of the body; that is a whole lecture in and of itself, and is for another time.

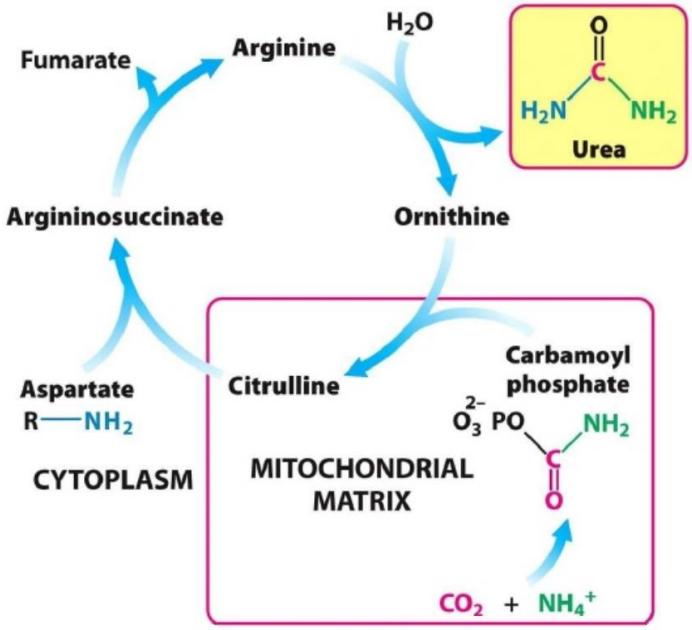
Resting Parasympathetic activation is known to stimulate microglia (see below right insert). Microglia are a type of immune (glial) cell located throughout the brain and spinal cord, and

account for 10–15% of all cells found within the brain. As the resident scavenger (macrophage) cells, they act as the first and main form of active immune defense in the central nervous system (CNS). Microglia are known to be mobilized with brain injury. Resting Parasympathetics are activated when organs require protection or healing and activates the immune system. For example, by the third concussion a persistent dynamic Parasympathetic Excess (PE) is typically demonstrated. PE is only measured by P&S Monitoring technology. Evidence indicates that with brain injury the Parasympathetics shift immune priority to the brain, leaving other organs, *i.e.*, the lungs, susceptible to infections leading pneumonia and high risk of death.



Sympathetic activation promotes inflammation. In the acute stage (short-term) this helps to protect and heal. Excessive Sympathetic activation (SE) leads to disorder and disease. Chronic (resting) Sympathetic activation due to stressful life styles is well known to lead to disorder and disease. Dynamic PE promotes SE. The Parasympathetics set the threshold around which the Sympathetics react. Dynamic PE is an abnormal autonomic response to stress, causing an excessive stress reaction. It is possible that nitric oxide is the Parasympathetic agent mediating microglial proliferation. Therefore, the possible proliferative pathway is PE leads to SE which leads to Chronic Inflammation which leads to excess Microglia proliferation which causes continued brain injury and diseases of the brain, including ADHD, Alzheimer's, Parkinson's, and MS.

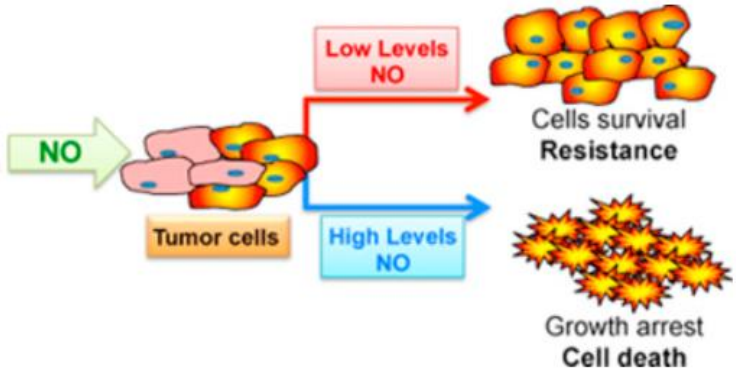
Nitric oxide benefits the immune system outside the brain also. It is an antimicrobial with probiotic activities, and it upregulates the immune system, including facilitating T-cells. Nitric oxide regulates processes involved in sepsis defense. It strengthens the body's defense against infection, retards tumor growth by enhancing immune function, and through an ample production of nitric oxide in white blood cells, it kills invading bacteria and parasites. Every day from birth, your body produces millions of cancer cells. Finding them and eliminating them is one of the functions of your immune system. Nitric oxide helps with tumor suppression. It is potentially one of the strongest, yet little-known, cancer-fighters. However, nitric oxide is also a promoter of cell growth. So it can be both a cancer tumor promoter under certain circumstances, as well as a cancer suppressor. One of the most powerful ways it can help heal cancer is by encouraging the growth of healthy cells by modulating different cancer-related events including angiogenesis, apoptosis, cell cycle, invasion, and metastasis. It appears that high levels of of nitric oxide are toxic for tumor cells; whereas, low level activity can have the opposite effect and promote tumor growth. Although



Simplified Urea Cycle.

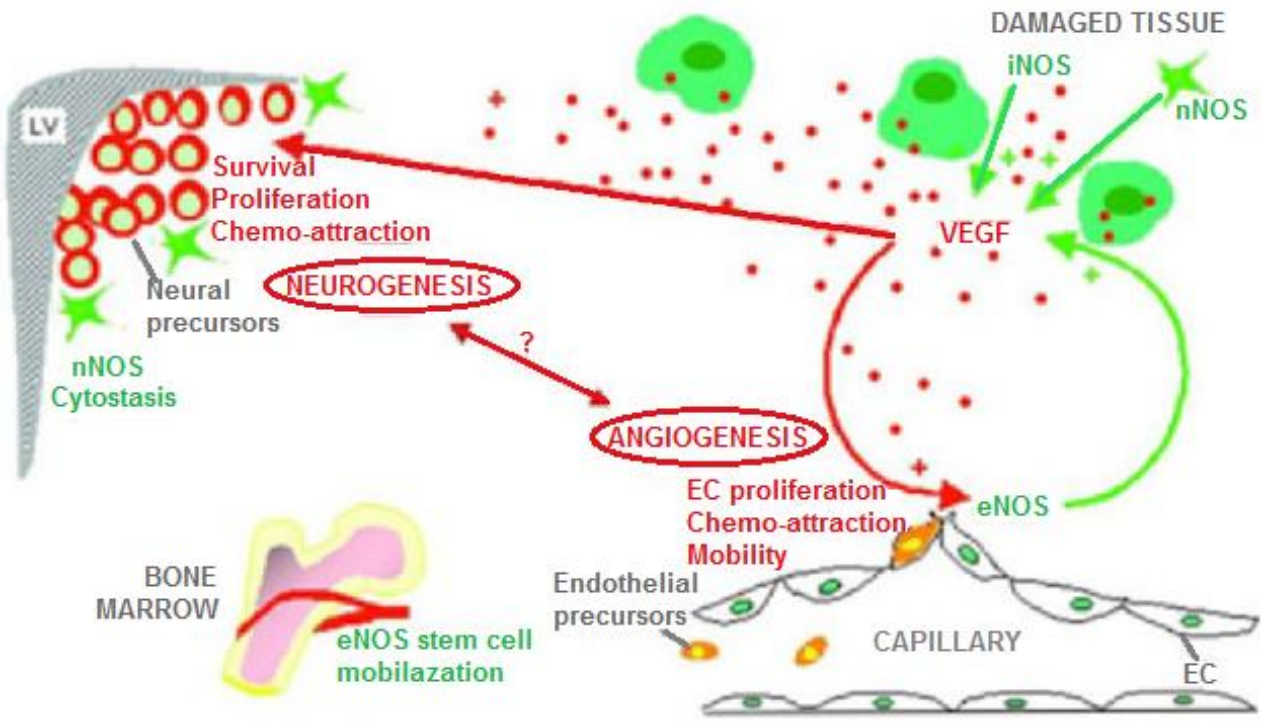
the jury is still out as to the exact "low point" at which nitric oxide may increase cancer tumor growth, what is crystal clear (and verified by countless studies) is that nitric oxide at a high level is a tumor suppressor. Being proactive with prevention by increasing nitric oxide levels naturally may help prevent and even heal cancer. This is a reason for Vasso-Plus™ as part of the **Mind-Body Wellness Program**.

Nitric oxide prevents cells from dying too soon or nitric oxide can make cells die that are no longer healthy, helping to remove damaged, dead, or alien cells. Therefore, it regulates cell death, especially blood vessel cells. Nitric oxide enhances a process called angiogenesis which is the process of forming new blood vessels out of old blood vessels, and helps to to repair other tissues, including nerve cells and brain cells. Damage anywhere in the body releases nitric oxide and the released nitric oxide stimulates the repair or new tissue generation process. Nitric oxide helps form the endothelial cells in bone marrow to support the formation of new blood vessels. Taken all together, nitric oxide is significantly involved in the repair of injury.

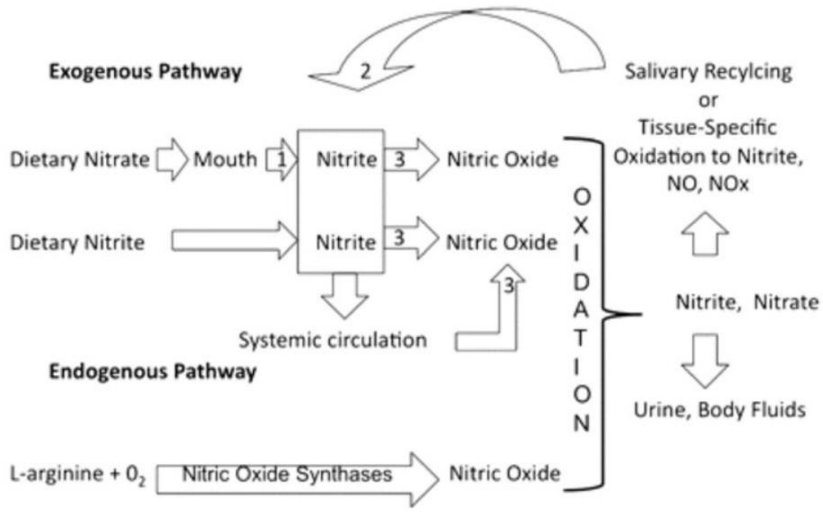


Nitric oxide level determines activity in cancer cells.

Nitric oxide promotes bone remodeling and healing, may improve bone density. It has a role in stimulating the Hypothalamus-Pituitary axis. Nitric oxide can release growth hormone. Having as much of it around as healthy, is very helpful for our bodies to keep maintaining these important properties and functions, but still (like oxygen and water) not too much.



A model of nitric oxide – VEGF action in the brain. This model includes both angiogenesis (repair of blood vessels, capillaries in this illustration) and neurogenesis (repair of brain cells). In damaged areas, VEGF and nitric oxide synthase (specifically, the neural type, nNOS, and the inducible type, iNOS) are up-regulated; generating nitric oxide. A positive feedback is created in which nitric oxide enhances VEGF expression and VEGF increases endothelial type nitric oxide synthase (eNOS) expression in capillary damaged endothelial cells, thereby increasing the quantity of nitric oxide. Together nitric oxide and VEGF cause migration and proliferation of new capillary endothelial cells, which form the foundation for the new capillaries. The foundation of new endothelial cells cause chemo-attraction and homing of hematopoietic stem cell-derived endothelial precursors, generating more endothelial cells, leading to angiogenesis. Meanwhile VEGF increases nNOS expression generating more nitric oxide on the brain side of the blood-brain barrier, enhancing proliferation of neural precursors, neuroblasts, and the migration of neuroblasts to the lesion area. nNOS generated nitric oxide also promotes the survival of the remaining and repairable neurons in the lesion area. VEGF also acts as a chemo-attractor for material needed to repair surviving brain (nerve) cells. In addition, nitric oxide produced by eNOS in the bone marrow promotes hematopoietic stem cell mobilization and, therefore, contributes to angiogenesis and re-vascularization of the damaged area. Meanwhile, continued expression of nitric oxide attracts scavenger cells to isolate, remove and recycle unrepairable and necrotic tissue.



A schematic of the physiologic disposition of nitrate, nitrite, and nitric oxide from exogenous (dietary) and endogenous sources. Key: 1) The action of bacterial nitrate reductases on the tongue and enzymes that have nitrate reductase activity in tissues, 2) Bacterial nitrate reductases , 3) Enzymes with nitrite reductase activity.

Nitric oxide helps as a detoxifying agent. The body makes ammonia (NH_3), especially during exercise, for example, in the muscles. Ammonia is highly toxic and needs to be detoxified and eliminated. The Urea Cycle is the process that rids the body of ammonia. The Urea Cycle occurs in the liver. As discussed, L-arginine can become nitric oxide and L-citrulline. Ammonia is taken into the Urea Cycle. In the Urea Cycle, L-citrulline couples with the ammonia to start detoxification. The modified ammonia is then coupled with L-arginine, using water, to complete the detoxification process and produce urea. This is a reason to maintain healthy levels of these amino acids to maintain wellness. The processing occurs partially in the cytoplasm of liver cells and partially in those cells' mitochondria. The urea is then passed into the blood stream and filtered by the kidneys to be excreted as urine. Nitric oxide is a product of the Urea Cycle and helps to regulate ammonia detoxification.

L-citrulline takes part in two important processes: (1) L-citrulline is active in the production of nitric oxide, and 2) L-citrulline is important for the removal of ammonia from the blood in the form of urea. Both processes are equal in the body. As a supplement, L-arginine is readily broken down before most of it reaches the blood. L-citrulline, on the other hand, is not susceptible to breakdown in the stomach, and therefore, makes it into the body where it eventually produces L-arginine which supports both pathways: the Urea Cycle and the Nitric Oxide Cycle.

Nitric oxide is involved in various detoxification or neutralization processes. The lungs deactivate nitric oxide by adding an oxygen to make Nitrogen Dioxide (NO_2). Saliva reduces Nitrogen Dioxide to nitrogen gas, an inert product which composes over 75% of the air we breathe. In the blood, nitric oxide is involved in other functional nitrate groups serving to transmit nitric oxide bioactivity and to regulate protein function. In the bowels, functional nitrate groups are reclaimed leaving behind ammonia which is collected and transferred to the liver for detoxification.

Nitric oxide, like oxygen, could potential be damaging as well. Excess nitric oxide becomes an oxidant under the right circumstances. Maintaining a proper anti-oxidant milieu prevents nitric oxide from becoming an oxidant, restoring proper levels of nitric oxide to act as its own anti-oxidant.

Nitric oxide production diminishes with age. When one is in their 20s, 100% of the healthy levels of nitric oxide is available. By age 60, it is down to as little as only 15%. With aging, 85% of the ability to make nitric oxide is lost. Taking nitrates in a diet, such as with beet root, is

an excellent way to increase nitric oxide. Studies have shown that beet root consumption does improve endothelial function. Generally, nitrate ingestion from any dietary rich source helps to increase nitric oxide. However, it is important to emphasize that supplements cannot take the place of medications that are prescribed (*e.g.*, antihypertensive or cholesterol lowering pharmacological agents). 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.

Properties of L-Arginine. These properties are in addition to helping to produce nitric oxide.

Promotes wound healing	Helps to build Collagen
Aids in waste removal	Detoxifies Urea in the Urea Cycle
Aids in releasing hormones	Especially growth hormone
Aids in healing gastric ulcers	Inhibits gastric hyperacidity
Aids in reducing atherosclerosis	Improves the function of Statins and helps to close the "Statin GAP"
Improves Insulin sensitivity	Increases Insulin release and recovery of Beta Cells
Important for Immune function	Has anti-carcinogenic effects
Beneficial in weight loss	Improves exercise tolerance, due to improved blood flow to the lower extremities

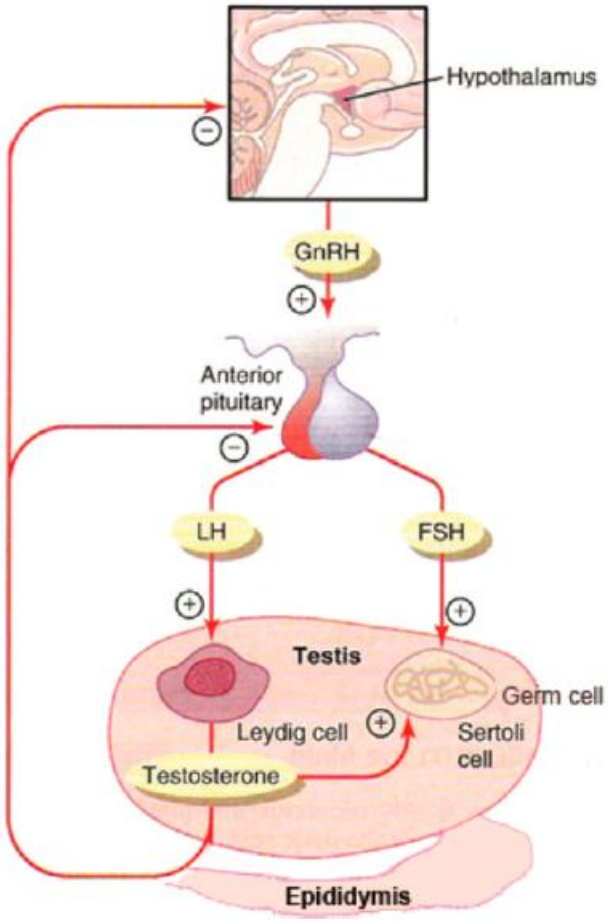
L-Arginine directly or indirectly through nitric oxide, is involved or promotes many functions throughout the body. It can be found in the diet in highest concentrations in turkey and chicken, pumpkin seeds, soybeans, and peanuts. It is purported to have the potential to enhance physical performance and stamina. L-arginine has been demonstrated to improve peripheral circulation, renal function, and immune function. It also possesses anti-stress capabilities. L-arginine stimulates the release of growth hormone, pancreatic insulin and glucagon, and pituitary hormones. The antioxidant property of L-arginine has been well documented in several reports. Nebulized L-arginine significantly increased exhaled nitric oxide concentrations. Manufacturers have tried to enrich apples with L-arginine. L-arginine increases the antioxidant in both: apples themselves include antioxidants and L-arginine itself is an antioxidant. L-arginine and apples appear to be a good combination. This supports the old saying that an apple a day keeps the doctor away. We would say take L-arginine with an apple a day, and you may not only keep the doctor away, but you may keep the hospital away. In other words, they augment each other.

L-citrulline is the other compound created in the formation of nitric oxide from L-arginine. L-citrulline is a non-essential amino-acid, since it can be produced from L-arginine. In the diet, L-citrulline can be found in watermelon (where it was discovered), and in very low-levels, cucumbers, cantaloupe, and milk. L-citrulline operates primarily in the liver, in the Urea Cycle to help to detoxify the body of ammonia. In the Nitric Oxide Cycle, L-citrulline is recycled to L-arginine to produce more nitric oxide. Because L-citrulline can be converted into L-arginine again and vice versa, it can promote and do the things L-arginine can do. In fact, a significant synergism between the two taken together has been documented in studies, especially, with blood flow (including to the brain to reduce fatigue) and erectile dysfunction. This is because together they help to produce more nitric oxide to help maintain optimal levels of that messenger throughout the body. L-citrulline is well absorbed by the GI tract. It is more well absorbed than

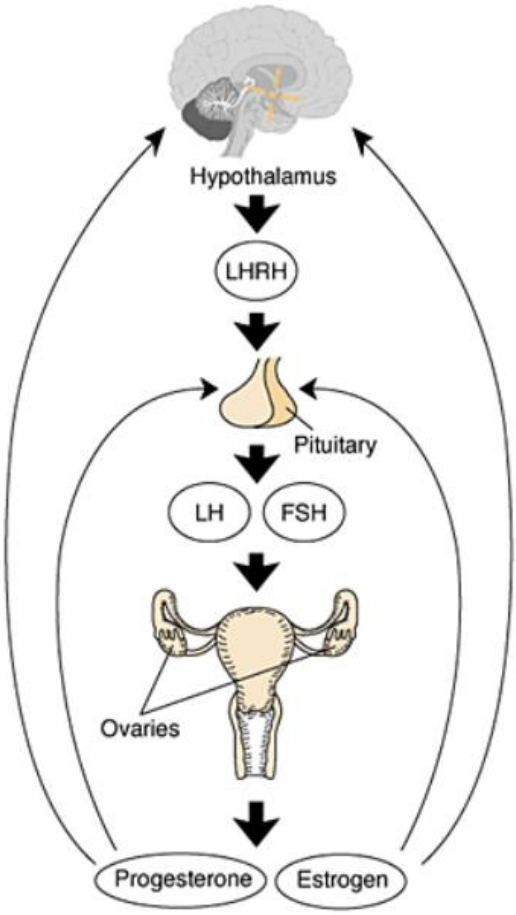
L-arginine. As stated above, only about 40% of the L-arginine ingested is absorbed through the GI tract. Virtually all of the L-citrulline ingested is absorbed. Therefore, L-citrulline makes for a more efficient supplement. To that end, only about half the amount of L-citrulline is required to make as much L-arginine in the body as compared to the amount of L-arginine needed to be consumed to achieve the same levels. Therefore, we recommend the two of them together.

L-citrulline is an alternative to think about. If a patient is reluctant to take statins or they only want to take it in low dose, they should think about the antioxidant benefit of L-arginine and L-citrulline to keep oxidizing of LDL from happening, and utilize the nitric oxide mechanism to restore and promote healthy blood vessels. That is how the "Statin Gap" is closed. As stated above, closing the statin-gap is important since statins are not 100% protective. Patients are still having major cardiac events (MACE) while they are taking the statins. Statins may also damage the myelin sheath of nerves causing patients to complain of muscle weakness and reduced coordination. This is due to the fact that statins not only reduce the LDLs in the blood stream to prevent oxidation and the process leading to atherosclerosis, but they also reduce the LDLs needed to repair and refurbish the myelin required for healthy, functioning nerves.

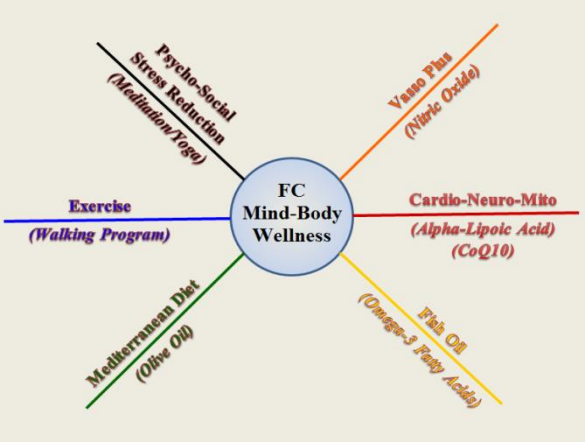
L-carnitine is an antioxidant as well as an anti-inflammatory. It is important for 1) ATP and energy genetation in the mitochondria, 2) keeping the blood vessels open, and 3) helping nitric oxide signal and improve endothelial function. It has been labeled as a fat burner. L-carnitine is made in the body by glycine and methionine and helps to oxidize fats, fatty acids, and brings them into the Mitochondria produce ATP. However, in reality, it is not a great fat burner unless the patient is L-carnitine deficient. If normal, there is no additional fat burning effect by taking supplemental L-carnitine. It is not recommend as a fat burner or for weight loss in the majority of people if they don't have a deficiency. It is recommended for mitochondrial wellness if a mitochondrial disorder is suspected. It is healthy for the endothelial system because it promotes the nitric oxide signaling; therefore, it has multiple advantages as an antioxidant and an anti-inflammatory. In this regard, L-carnitine is an important component in the **Mind-Body** cocktail.



Male regulation of hypothalamic-pituitary axis. 1) Nitric oxide (NO) stimulates LHRH secretion from the hypothalamus. 2) LHRH effects release of LH from the pituitary gland. 3) LH effects testosterone secretion in the testis. 4) testosterone effects germ cell apoptosis and survival. 5) germ cell survival leads to secretion or absorption of epididymal fluids and spermatozoa maturation. 6) Nitric oxide also regulates testicular micro-circulation. Abbreviations: LHRH, luteinizing hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

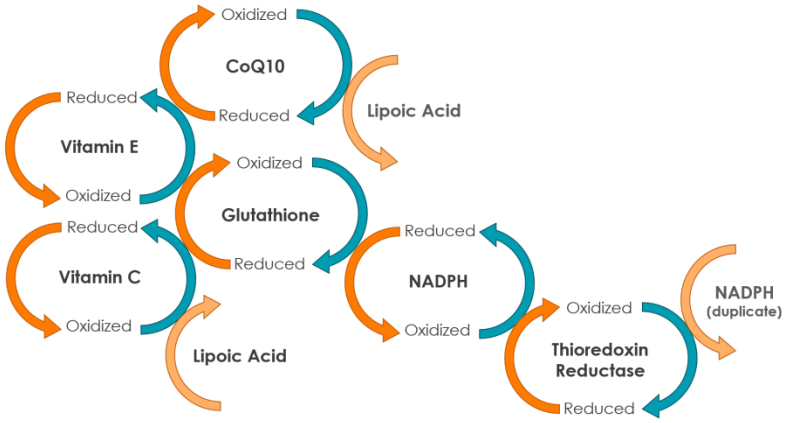


Female regulation of hypothalamic-pituitary axis. 1) Nitric oxide (NO) stimulates LHRH secretion from the hypothalamus. 2) LHRH effects release of LH from the pituitary gland. 3) LH effects progesterone and estrogen secretion in the ovaries. 4) progesterone and estrogen effects ovulation. 5) Nitric oxide also regulates uterine micro-circulation. Abbreviations: LHRH, luteinizing hormone-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.



The antioxidant prong of the **Franklin Cardiovascular Mind-Body Wellness Program** actually focuses on reducing oxidative stress. The purpose is to (1) decrease ROS and free radicals when they are harmful to the body, and (2) increase antioxidant defenses to establish and maintain an appropriate antioxidant-oxidant balance that promotes health and wellness. In essence, the goal of this **Program** is to increase antioxidant buffer capacity as much as possible. To this end the **Program** provides: (1) the greatest of all anti-oxidants, **Exercise**; (2) the powerful antioxidants in **Cardio-Neuro-Mito**™; (3) the effective anti-oxidant in **Psycho-Social Stress Reduction,** which is arguably the most pervasive of all oxidative stresses; and the anti-oxidants (as well as anti-atherosclerotic, and anti-inflammatory components) in the (3) **Mediterranean Diet**, (4) **Omega-3** Fatty Acids from **Fish Oil**, and (5) nitric oxides in **Vasso-Plus**™. All of these antioxidants work together to contribute to reduce (6) **Oxidative Stress**.

As stated above, sources of oxidative stress are ubiquitous. They are internal as well as external. Antioxidants themselves, once they have given up their electron, become oxidants and need an electron from somewhere else. If this electron comes from atoms or molecules in healthy positions or situations, the oxidative process is perpetuated. Fortunately, there is an antioxidant network where many antioxidants work together to keep the giving and receiving of electrons "within the family." The network helps to prevent other molecules from having to get involved. This is known as the antioxidant buffer. Even critical processes generate oxidants. As we have discussed, Mitochondria generate oxidants as a normal course of function. In small quantities, nitric oxide is a natural oxidant. The immune system recruits oxidants to combat invading pathogens. Oxidative stress affects many pathways. However, it is not all bad. Like nitric oxide, a little (in time and space) is healthful. In addition to helping the immune system, they are used in signaling, among other physiologic activities. As with everything else in life, moderation; a little is actually good. This moderation is the antioxidant-oxidant balance. The way red blood cells carry oxygen from the lungs to the rest of the body is an oxidation reaction. The iron atoms in the red blood cells literally rust (oxidize) as they collect oxygen to enable the red blood cell to carry the oxygen



Antioxidant Network. Antioxidant buffer requires several antioxidants, in surplus, working together to share electrons between themselves to remain antioxidants and provide electrons to neutralize ROS, RNS, and free radicals before they damage healthy tissue.

(that is why they are red, from the rust). Remember oxidation is a type of burning, and the body uses oxidation to literally help to "burn the trash." Definitely, though, too much oxidation is

Neurological

ADHD	Autism
Alzheimer's Disease	Multiple Sclerosis
Anxiety & Depression	Parkinson's Disease
Asperger syndrome	Multiple Sclerosis

Cardiovascular

Cardiovascular Disease	Hypertension
Angina Pectoris	Atherosclerosis

Multi-System Effects

Diabetes	Chronic Fatigue Syndrome
Cancer	Metabolic Syndrome
Inflammation	Anxiety
Fibromyalgia	Hyperthyroidism
Lyme Disease	Sleep Apnea

Respiratory

COPD	Asthma

Gastrointestinal Disorders

Crohn's Disease	Celiac Disease
GERD	Functional Dyspepsia
Gastric Ulcers	

Joints/Skin

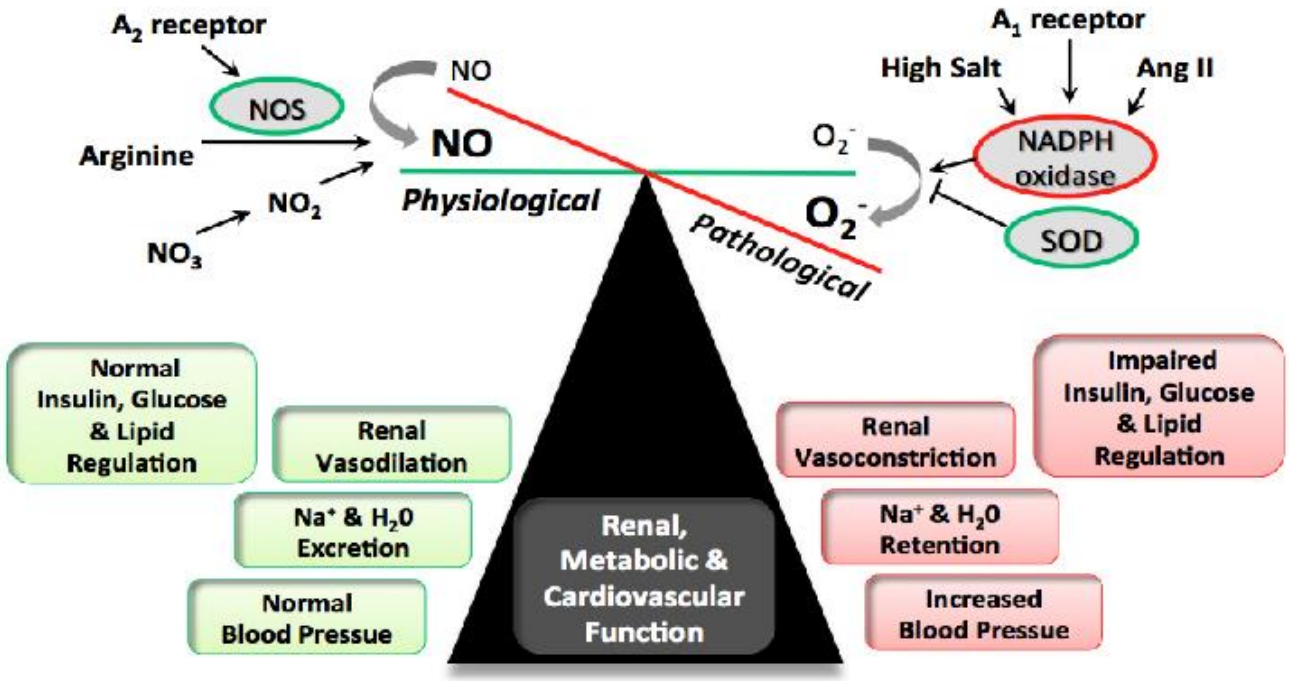
Gout	Rheumatoid Arthritis
Dermatitis	Carpal Tunnel

Clinical examples of the effects of chronic oxidative stress.

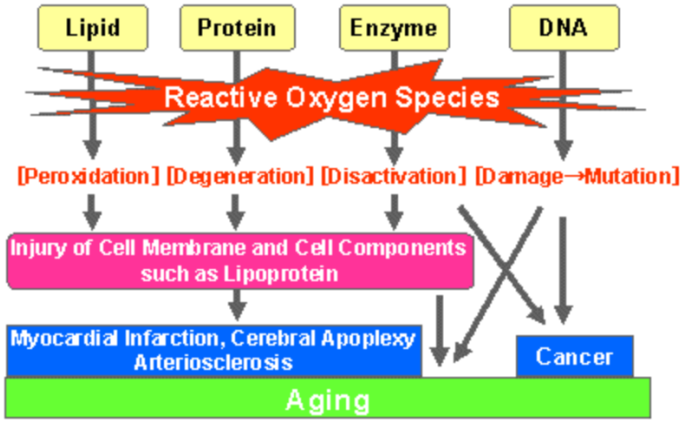
never good. Again, small fires are helpful (cooking, staying warm, and burning trash). Large fires destroy.

To reduce oxidative stress, first a balance between oxidants and anti-oxidants must be achieved. Then to maintain the balance and promote wellness, an antioxidant buffer must be established and maintained. A healthy diet and exercise are important, but may not be enough; supplements may add the antioxidants that may be deficit or missing, especially as systems age (physiologic age may be years ahead of chronoclogical age due to injury, diease, lifestyle, or genetics). Reducing oxidative stress, including by quitting cigarette smoking (cigarette smoke contains a number of free radicals and chemical compounds, representing the major source of inhaled RONS) helps to relieve the effects of chronic oxidative stress listed above. Supplements to help reduce oxidative stress and to minimize the risk of, or help to relieve, these disorders and diseases include, Alpha-Lipoic Acid, Coenzyme Q10, Vitamins A, C & E, Beta Carotene, Cysteine, and Zinc. Note, Alpha-Lipoic Acid and Coenzyme Q10 provide bonus antioxidant action, in that they also recycle the vitamins. "Healthy aging" is a result of the **Mind-Body**

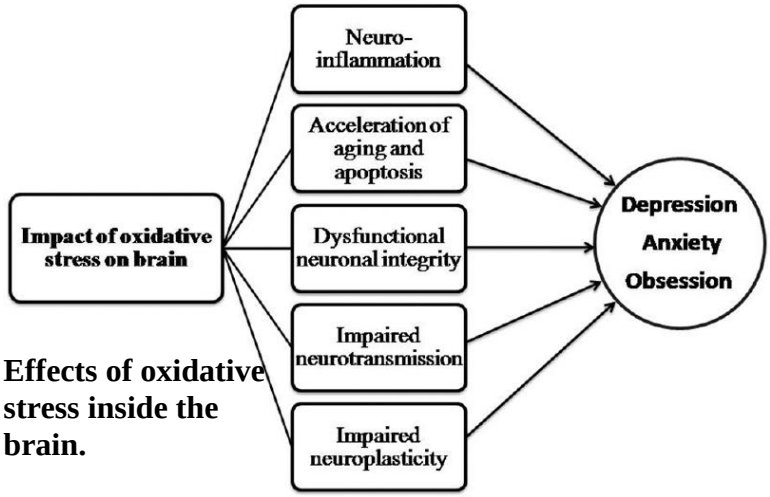
Program. It is why we promote all six prongs, they all support proper endothelial function, blood flow, and P&S nerve balance enabling proper P&S nerve function and control and



An example of the effects of balance and imbalance between antioxidants and oxidants. Imbalance between nitric oxide (NO) and reactive oxygen species (ROS) signaling has been linked to renal dysfunction, metabolic syndrome, cardiovascular disease and type 2 diabetes.

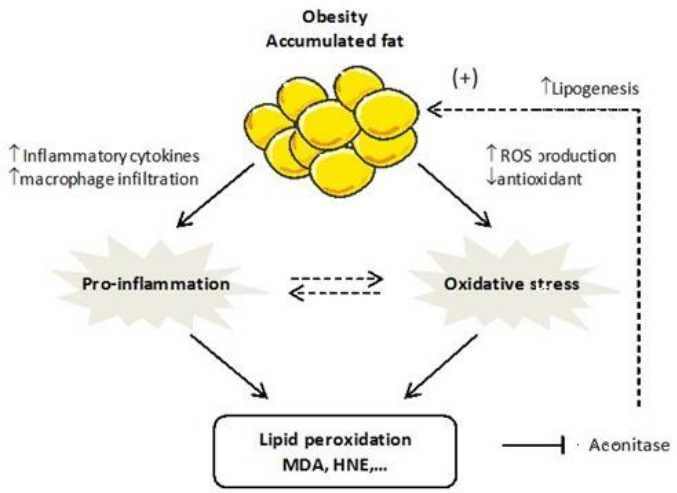


Proper antioxidant balance minimizes cell and tissue damage by Reactive Oxygen Species (ROS).



Effects of oxidative stress inside the brain.

coordination of all organs and systems of the body. Proper endothelial function, blood flow, and P&S nerve function requires healthy levels of nitric oxide, omega-3 fatty acids, and antioxidants.



The obesity – oxidative stress vicious circle.

All six prongs of the **Mind-Body Wellness Program** directly and indirectly support all three healthy levels, which slows the aging process of all cells throughout the body.

ALA, is a key component of the antioxidant cocktail in the **Program**. ALA prevents the development of glucose-induced insulin resistance by decreasing oxidative stress in both fat cells (adipocytes) and muscle cells. ALA 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 disease, and autonomic and peripheral neuropathies; especially diabetic neuropathy. It is a healthy supplementation to the Mediterranean Diet.

Sufficient amounts of natural vitamins and antioxidants from fruits and vegetables are intrinsic to the Mediterranean Diet. ALA, along with CoQ10 (Ubiquinol) which is also derived from this diet, recycle the natural vitamins and antioxidants; causing their effective levels to be physiologic (see figure above). It is not surprising, therefore, that synthetic vitamins such as A, E, C, and so forth have no or negative effects when they are not with the powerful antioxidants ALA and CoQ10 to ensure their proper levels to recycle other less powerful antioxidants. All together they help to maintain health and wellness in Mitochondria the vasculature, and and the P&S nerves.

One of the lifestyle prongs of the **Franklin Cardiovascular Mind-Body Wellness Program** focuses on food! Obviously, food is central to life. There are many sayings about food, ranging from the conservative (*e.g.*, "eat to live, not live to eat") to the liberal (*e.g.*, "eat what you want, you only live once"). Hippocrates, the father of ancient medicine, said, "Let food be your medicine." It has been suggested that some who live in the more affluent countries and the more affluent areas of those countries, live in a time of "food stress." When we were "cave-people," there was no fast-food or processed food. Food was a local phenomenon. If it was not in season you simply did not eat it. There were many fewer food allergies and food sensitivies, because food lived in the same region as its consumers, and was subject to the same conditions as the consumers. So the food carried allergens (in very small quantities) which "innoclated" the locals to the things we are now allergic to today. This causes many fewer allergies and promotes health and wellness. There was no refrigeration, or even preservatives until salt was discovered. In fact, salt was so important a discovery, as a preservative, that the word 'salary' is derived from the latin word for salt ('*salis*'). Half of the Roman soldier's salary came in the form of salt, not coin. Have you ever noticed that cuisines from countries near to the equator are significantly more spiced (not

Let food be your medicine and let medicine be your food.
– Hippocrates, c.460 BC – c.377 BC

necessarily hot, but more highly flavored) than foods from near to the poles? Peoples nearer to the poles had natural refrigeration and were able to keep foods longer. Peoples nearer to the equator did not, and they needed to stretch the use-ability of foods. Therefore, they covered the early spoiled flavor with spices, before foods became rancid (poisonous).

With technology "shrinking" the world, foods of all sources are readily available everywhere. More than ever, a saying accredited to Hippocrates is vital for health and wellness: "Let food be your medicine and let your medicine be your food." If you known a little about the nutritional value of the foods you eat, or better, the foods you cook with, Hippocrates' saying comes alive. For example, if you have women at your dinner table, adding some celery or spinach to their diet provides extra iron to their meal and helps replace that which may be lost once a month. If you have people at your table that are sad or depressed or anxious, green leafy vegetables and other foods rich in Vitamins B_6 and B_{12} and Magnesium affect the Parasympathetic nervous system to restore proper autonomic balance, thereby helping to elevate and stabilize the mood disorders. An apple a day truly does keep the doctor away, including the trace levels of Arsenic in apple seeds that are anti-carcinogenic. Of course all of these foods are better fresh, when picked ripe and eaten ripe. "You are what you eat." Eating healthy is living healthy. If this is your lifestyle, then the occasional indulgence is easily tolerated by your body. As a good doctor once said, if you do not eat the "bad" things once in a while, how will your body 'know' what is "good"? The contrary is absolutely NOT true.

Now everything has changed. Many people eat without really thinking about it, and spend as little time as possible cooking. A hectic morning may mean that you are worn out by

lunchtime. This is exacerbated by no breakfast, a steady diet of pre-processed, high-glycemic foods with little nutritional value. Then lunch is all pre-processed: a can of soda and a fast-food "meal." In the evening you are even more tired, and you have not even said "Hello" to your children. So dinner comes from a can, a box, or other fast-food or pre-prepared food source. Health has been relegated to a pill or a multi-vitamin. We hope to make up for the American lifestyle by distilling the needed nutrients into pills, hoping that fresh from the factory, "natural," chemistry can be replaced by "factory-fresh" from nature. The American lifestyle involves waking-up and perking-up with chemicals. We help relax and sleep with chemicals. The average American does indeed believe that there is better living through chemistry. Food has become medicine, in the shape of a pill. While this sounds like what Hippocrates said, unfortunately it is not anything like what he meant. The pill is now seen as a substitute, not as a supplement (as too many people glibly state without recognition). Most, if not all, people cannot eat enough, nor do they live in regions where times of the year provide enough, of the proper foods. Therefore, supplements are still needed. Especially as we age and our bodies do not produce or assimilate the necessary nutrients, supplements are still needed. However, they should not be the primary source, *only the supplementary source*.

The growing and aging processes were the original reasons for developing supplements. Then food became modernized and made convenient. Food is comprised of both macro- and micro-nutrients. Macro-nutrients constitute the majority of what is consumed: protein, carbohydrtes, fat, alcohol, and fiber. These provide energy and the raw materials to adapt, grow, and heal. Micro-nutrients are found in very small amounts and include vitamins and minerals and other trace elements that are vital to health and wellness. Processing of foods to make them convenient, tends to retain the macro-nutrients and dispose of, or destroy, the micro-nutrients. Wheat is a prime example of this loss. White wheat flour has lost 60% or more of the nutrients of the plant. Whereas whole wheat flour retains more than 90% of its nutrients. While this has become well known and recognized, as evidence by the growing restaraunt fad of "farm-to-table" (even if the "farm" is in a flower box in the back alley or is too many miles away), it still does not make up for what is disposed of in everything else. Now supplements are required by all, not just by children and the aged or sick.

The processing, pasturizing, homogenizing, irradiating, ultra-preserving, etc., of the majority of the foods the aveage American eats is literally killing America; albeit slowly. It affects mental and nervous health, cardiovascular health, quality of life, and eventually mortality (continuation of life). It is now affect our children in elementary schools, underlying ADD/ADHD, obesity, and fatigue all causing poor grades and low levels of creativity. Food is medicine, but like all medicines, not all are healthy for everyone.

My Sicilian great-grandmother helped to teach me to select the freshest and ripest foods to cook with (even in the middle of Manhattan, in New York City) and to prepare it in a way to preserve the flavor and "value" (as she put it – meaning so much more than just flavor) of the food itself. In fact, the only times I was truly sick in my life were the times when I was not near a garden of my own (growing "organically" – not in the sense of what the government permits producers to claim as organic), or a local farmer I knew (farmer's markets are a real "windfall" – pun intended). True the foods in this diet help establish and maintain health and wellness; however, the hidden benefit is in the fact that true adherence to this diet involves eating and

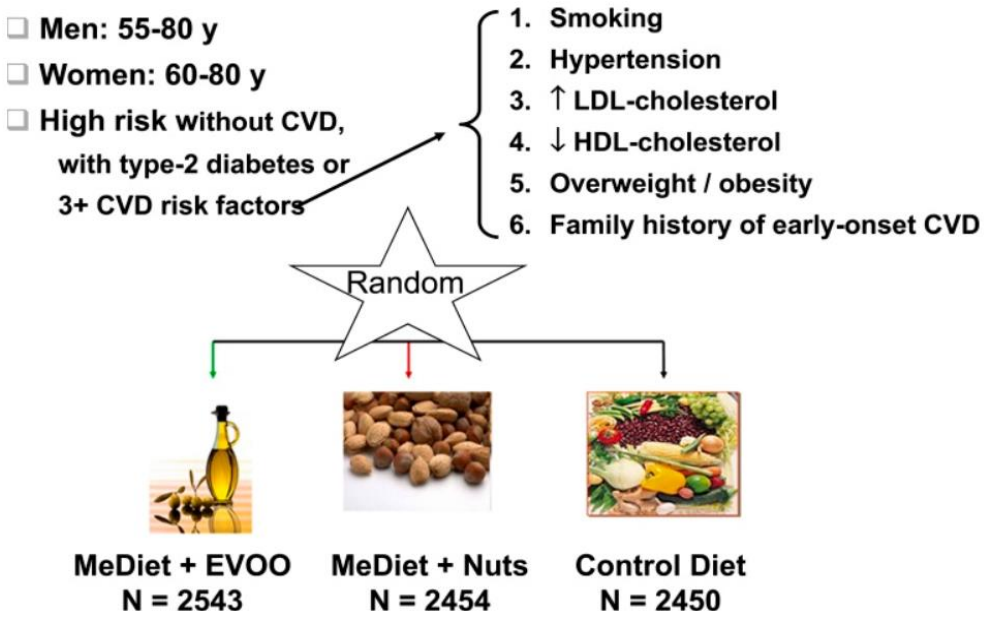
cooking with fresh, whole, locally grown, un-pre-processed foods so that the nutrients and health benefits are preserved and ingested when consumed – and you get to enjoy it with a little wine!

The Mediterranean Diet is probably the healthiest dietary pattern. It is a traditional diet found in many of the countries that border the Mediterranean Sea, including Gibraltar, Spain, France, Monaco, Italy, Slovenia, Croatia, Bosnia, Herzegovina, Greece, and the Middle East. It is a plant-based diet where vegetables, fruits and whole grains along with legumes and nuts are consumed in high amounts, with the "stars" of the diet being the Olive, the Grape, and Wheat. It primarily consists of vegetables and olive oil with moderate protein. The primary protein source in the **Mediterranean Diet** is fish, including shellfish. Red meat is consumed on a monthly basis. White meats are preferred and saturated fats are limited. Fish and shell fish are consumed on a weekly basis. Olive oil is the primary source of fat. Whole grains, fruits, vegetables, and nuts are typically natural and unprocessed. Dairy products, especially yogurt products are used along with certain cheeses such as goat cheese. Processed foods and foods that are high in sugars are eaten very infrequently, including desserts. From the grape, wine is the primary alcoholic beverage consumed. One glass of wine (5 ozs.) for women and up to two glasses for men (under age 65) is recommended.

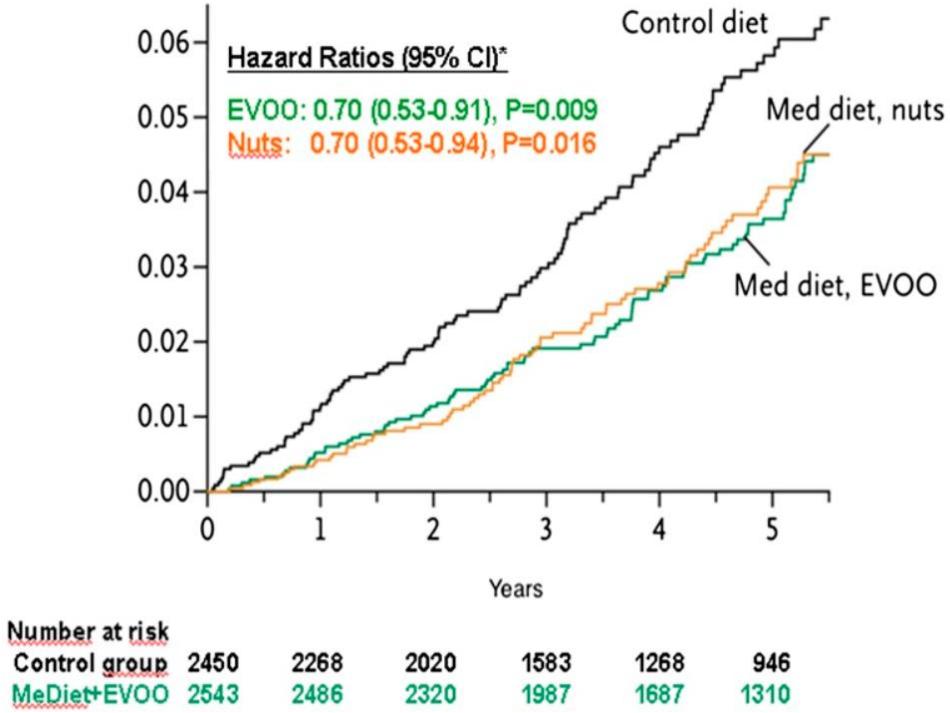
Overall, in addition to providing the nutrients, vitamins and minerals that serve as antioxidants, anti-inflammatories, and the fuel and building blocks needed for health and wellness, the **Mediterranean Diet** reduces the risk of oxidized LDL cholesterol. Lower ox-LDL, reduces or prevents atherosclerosis, which reduces or prevents endothelial disease, which reduces or prevents cardiovascular disease. Therefore it is an anti-sclerotic. The health benefits of the **Mediterranean Diet** extend beyond just cardiovascular disease. It seems clear from the evidence that the Mediterranean Diet is very healthy and may help prevent some of the world's leading killers, including cancer. It is definitely a much better option than the standard low-fat diet that is still being recommended all around the world.

In addition to its cardio-protective and cancer-protective abilities, the **Mediterranean Diet** has been validated to maintain wellness due to its demonstrated advantages in (1) weight loss (reduced body-mass index), (2) improvement in diabetes or insulin resistance, and (3) providing other major advantages, including decreased dementia (*i.e.*, cognitive difficulties and Alzheimer's disease). Many of the nutrients found in the **Mediterranean Diet**, including **Omega-3 Fatty Acids**, **Antioxidants**, and **nitric oxide**, are also provided in the **Mind-Body Wellness Program** to ensure proper dosages and help the body to properly assimilate them, especially as we age or battle chronic diseases.

An easy way to transition to the Mediterranean Diet is to start by eating 7 to 10 servings of vegetables and fruits per day and switch to whole grains, including whole grain cerals, rice, and pasta. Also, keep nuts, tahini, and natural peanut butter close for snacks. Then add one to 2 meals with fish per week. Avoid butter, instead use olive oil or canola oil. Avoid frying the fish and use canola or olive to cook, if necessary. Avoid red meat, sausage, bacon and other fatty meats and high fat dairy. For dairy (to ensure a source of calcium), consume low fat dairy: 2% or less milk, low fat cheese or ice cream, or fat free yogurt.



PREDIMED study design. Abbreviations CVD, cardiovascular disease; EVOO, extra-virgin olive oil; MeDiet, Mediterranean diet.



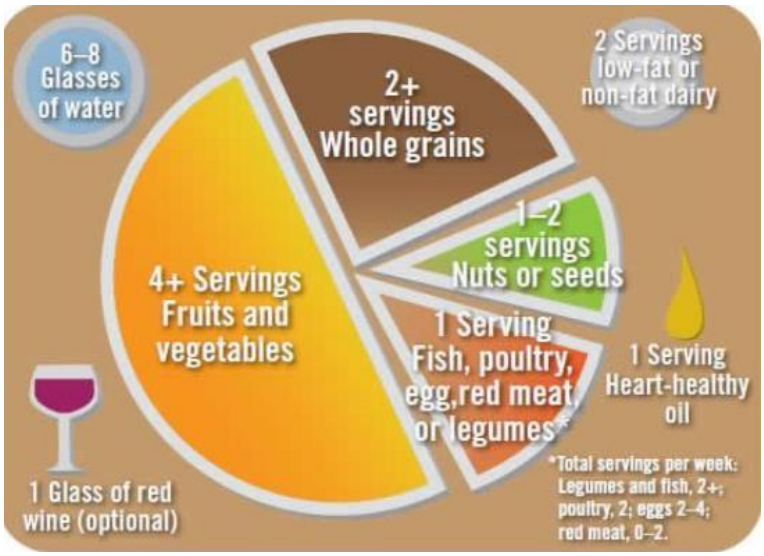
Incidence of cardiovascular disease by intervention group in the PREDIMED study; see text. Abbreviations: EVOO, extra-virgin olive oil; Med diet and MeDiet, Mediterranean diet.

Table: 20 common foods with the most antioxidants.

Rank	Food item	Serving size	Total antioxidant capacity per serving size
1	Small Red Bean (dried)	Half cup	13,727
2	Wild blueberry	1 cup	13,427
3	Red kidney bean (dried)	Half cup	13,259
4	Pinto bean	Half cup	11,864
5	Blueberry (cultivated)	1 cup	9,019
6	Cranberry	1 cup (whole)	8,983
7	Artichoke (cooked)	1 cup (hearts)	7,904
8	Blackberry	1 cup	7,701
9	Prune	Half cup	7,291
10	Raspberry	1 cup	6,058
11	Strawberry	1 cup	5,938
12	Red Delicious apple	1 whole	5,900
13	Granny Smith apple	1 whole	5,381
14	Pecan	1 ounce	5,095
15	Sweet cherry	1 cup	4,873
16	Black plum	1 whole	4,844
17	Russet potato (cooked)	1 whole	4,649
18	Black bean (dried)	Half cup	4,181
19	Plum	1 whole	4,118
20	Gala apple	1 whole	3,903

An example of what you might eat in a day:

- **6 to 8, 8 oz glasses of water per day** to stay properly hydrated. This is equally important to the rst of the Mediterranean diet.
- **Breakfast:** a slice of sourdough bread with chopped tomatoes, red onion, fresh herbs with crumbled feta and drizzle of olive oil and balsamic vinegar. You might add a slice of melon with tea or Greek coffee (or espresso).
- **Snack:** fresh fruit (pear, small bunch grapes, a couple of figs) or small handful of nuts (walnuts, almonds, or hazelnuts).
- **Lunch:** Mediterranean vegetable bake (Briami) with small serving of rice.
- **Afternoon snack:** Greek plain natural yoghurt drizzled with honey and a few crushed walnuts.



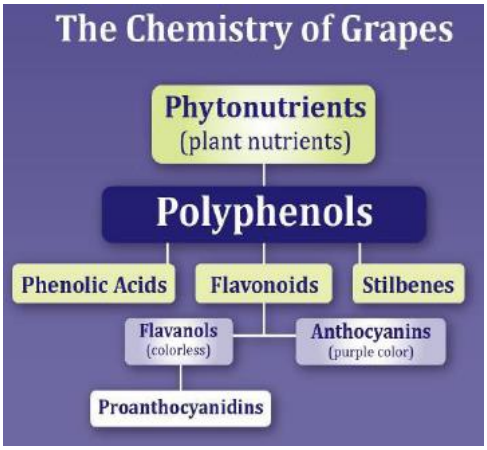
- **Dinner:** baked or grilled snapper (or other oily fish) with salad of fresh leafy greens drizzled with olive oil and lemon juice, and a small glass of wine.

- **After dinner:** a small plate of fresh fruit to share (melon, grapes, figs, stone fruits).

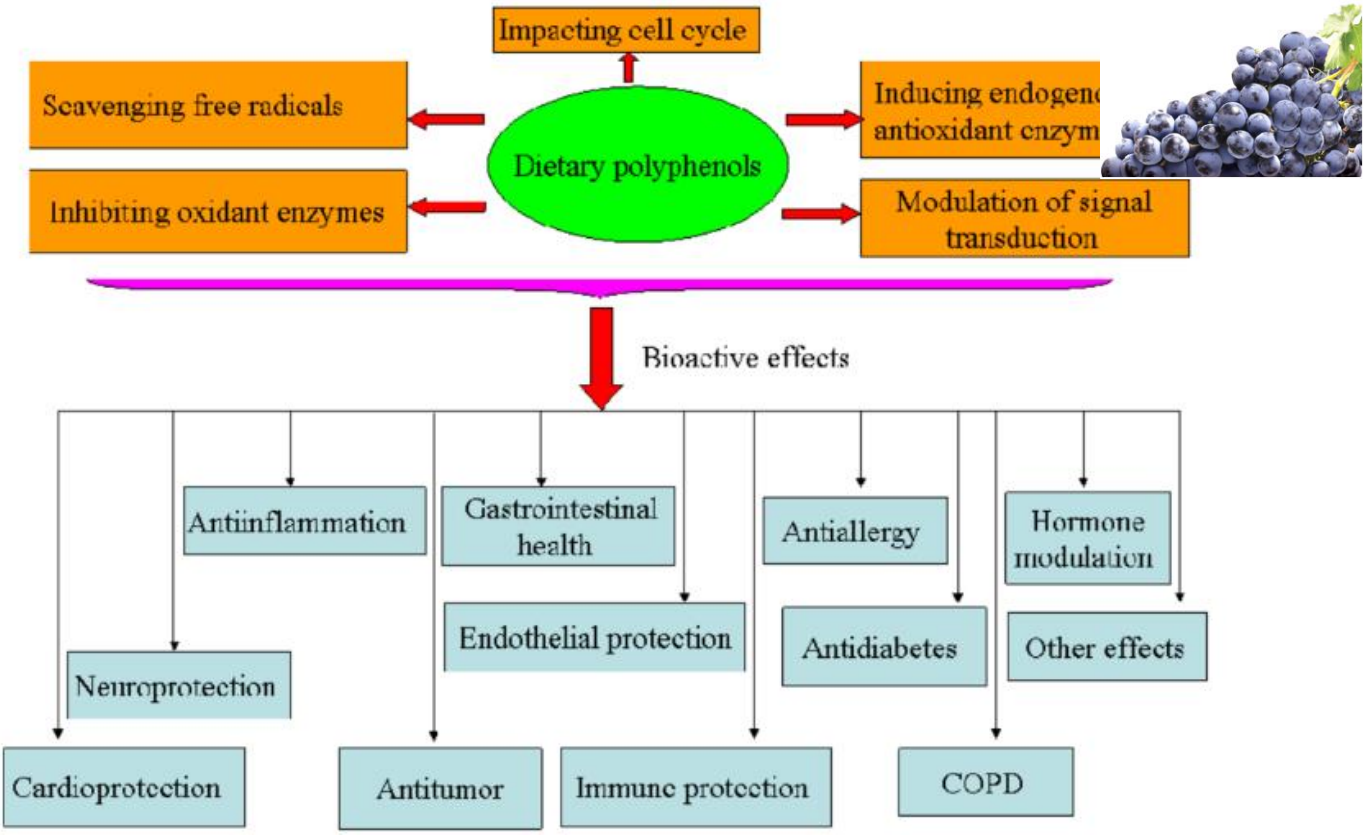
Olive oil is central to a healthy lifestyle, and the **Mediterranean Diet**. Olive oil helps to increase levels of Omega-3 fatty acids, antioxidants, and nitric oxide, to reduce oxidative stress. Olive oil helps to maintain Brain-Heart health. The main health constituents of olive oil are its polyphenols, including Estradiol. In humans Estradiol is converted to Estrogen, the primary female sex hormone and is important in the regulation of the estrous and menstrual cycles in the female reproductive system. Estradiol is essential for the development and maintenance of female reproductive tissues such as the breasts, uterus, and vagina during puberty, adulthood, and pregnancy. While estrogen levels in men are lower compared to those in women, estrogens have essential functions in men. In both genders, it has important effects in many non-reproductive tissues, including bone, fat, skin, liver, and the brain. In women estradiol is produced primarily in the follicles of the ovaries. In both genders it is produced in endocrine (*e.g.*, adrenal glands) and nonendocrine tissues, including fat, liver, breast, and neural tissues.

Olive oil has many functions, including as an antioxidant, anti-inflammatory, anti-atherosclerotic, anti-cancer activities, antimicrobial activities, antiviral activities, hypolipidemic and hypoglycemic effects. The anti-oxidant effects promote healthy DNA repair, fewer Mitochondria defects, and reduced aging factors. Olive oil prevents angiogenesis, reduces inflammation, is a probiotic, improves endothelial function, and stabilizes membranes, helping them to be more flexible and resilient, improving cellular signaling, and membrane transport. It blocks adrenaline receptors to reduce BP. The pharmacological properties of olive oil, the olive fruit and its leaves have been recognized as important components of medicine and a healthy diet from the time before Hippocrates. Eating about two tablespoons or 23 g of olive oil a day is recommended for it may reduce the risk of coronary heart disease.

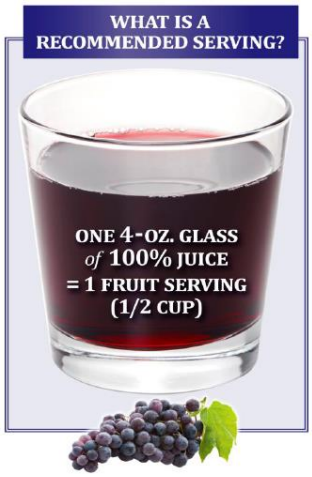
Grapes help to satisfy the Mediterranean diet recommendation of four or more servings of fruits and vegetables per day. Grapes can become wine, which at moderate levels (one to two 5 oz glasses per day) is also recommended with the **Mediterranean Diet**. Grapes also offer additional benefits. Like olives, grapes contain polyphenols. Grape polyphenols give grapes their color. Grape polyphenols are found in the skins and seeds of grapes. They function naturally as antioxidants (including to scavenge free radicals) and as an anti-atherosclerotic (keeping



arteries more flexible). They help to maintain healthy platlet aggregation (anti-clotting), stimulate nitric oxide production (reduce blood pressure), and more is being discovered. All of this benefits cardiovascular and nervous system health.

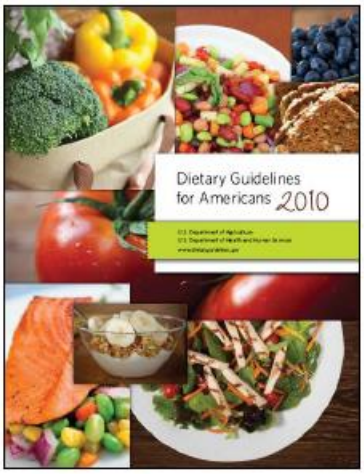


The bioactive effects of olive oil.



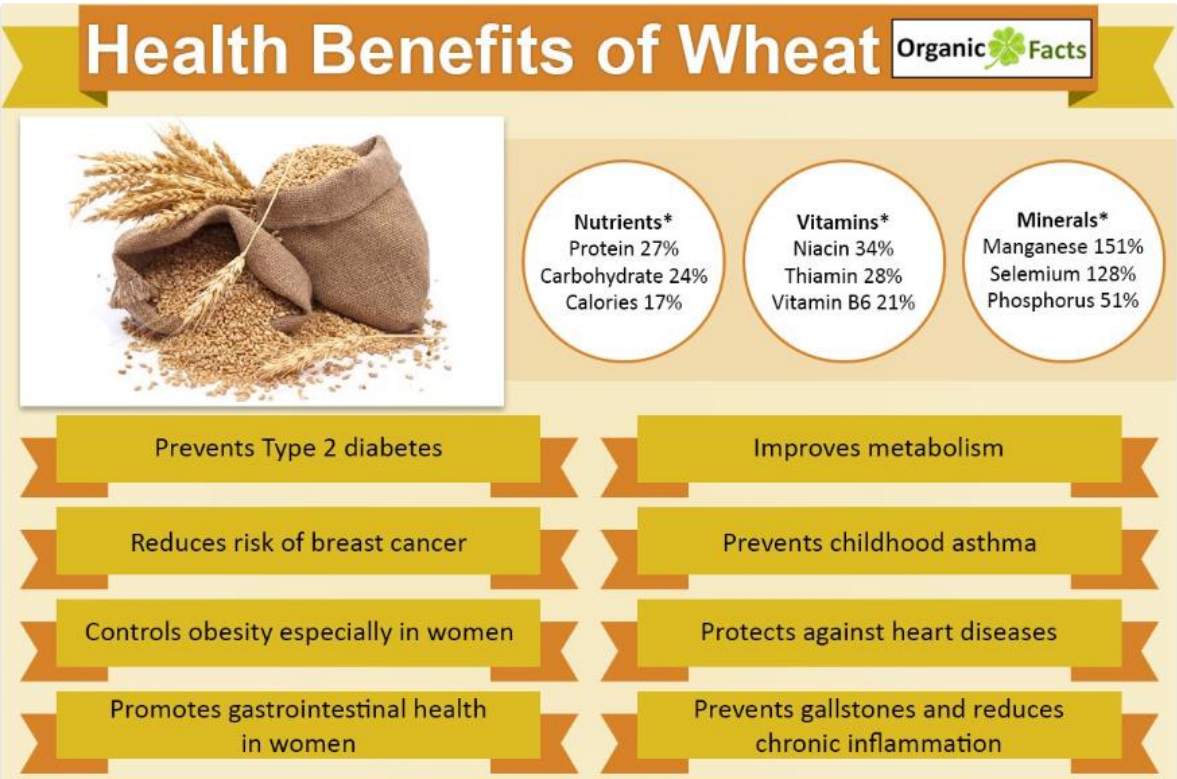
Flavonoids are the largest and most studied sub-group of polyphenols. In grapes, Flavonoids are particularly found in the skins and seeds. **G**rape juice has a greater polyphenol concentration than many other juices. The antioxidant, anti-platelet and anti-clotting potential of red grape juice vs. red wine is about the same. The flavonoids in grape juice help manage the effects of LDL cholesterol, including protecting LDL cholesterol from oxidation. Purple grape juice (including red wine) polyphenols increases nitric oxide production, improves endothelial function and reduces oxidation of LDLs all helping to keep arteries more flexible (by promoting endothelial health), improving circulation and reducing blood pressure. Grape consumption explains the low rate of heart disease attributed to the French national habit of moderate wine consumption. The health benefits of grape juice (including wine, especially red wine) may also include reducing blood glucose levels and supporting cognitive and immune health. As a component of the **Mediterranean Diet**, wine helps slow and possibly even reverse age-related cognitive, including memory, decline. While the **Mediterranean Diet** promotes higher consumpton of fruits and vegetables, not all fruits and vegetables are created equally. Darker-colored fruits typically offer more phytonutrients than lighter options. Dark-skinned blue and purple fruits also have unique plant nutrients not found in many other colors of fruits and vegetables.

The third "star" of the **Mediterranean Diet** is wheat. The health benefits of wheat are now well known. The benefits are due to the B-



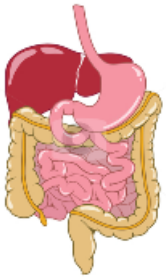
vitamins (thiamin, folate, and vitamin B_6), and the minerals (magnesium, zinc, and manganese) it provides. Wheat is probably the most common cereal available world-wide and is even higher in demand in recent years due to its abundant health benefits. Over the years, it has shown itself to be one of the most successful and sustainable cereal crops in the world. It originated in southwestern Asia, but today it is grown in countless countries. Wheat is primarily used for baking bread products, foods like bread, pasta, crackers, bagels, cakes, and muffins are just a few common examples of wheat sources.

Wheat is believed to be one of the most wholesome food items, and it ensures a diet rich in nutrients. Wheat is extremely beneficial for healthy living. It considerably lowers the hazards of heart diseases, owing to its comparatively low fat content. It also regulates insulin and blood glucose levels in diabetic patients. Patients who suffer from Diabetes are able to keep their sugar levels under control by replacing white rice with wheat in their diet. Wheat is able to provide an immense energy source from all parts of the grain kernel, including the bran, germ, and endosperm. The nutrient value of wheat is retained even after processing it into (whole wheat) flour. However, if you wish to get the maximum benefit out of wheat products, it's advisable to choose those products that are made from whole-wheat flour rather than the refined varieties (*e.g.*, white flour). The health benefits of wheat greatly depends on the form in which you consume it. Whole wheat is extremely nutritious and retains 100% of the nutrients found in wheat. Bleached white flour losses 60% of the nutrients found in whole wheat.



After personal experimentation in the kitchen, a mix of two-thirds bleached white flour to one-third whole wheat flour returns much of the nutrients lost in the processing. With this ratio of white to brown, most recipes for white flour (breads, rolls, biscuits, cookies, cakes, etc.) do not change; except (optional – personal preference) for perhaps a little more yeast, or chemical levening, if a lighter product is desired. This same two-thirds to one-third ratio may be used in noodles and pasta, as well as with rice where a little more water may be desired (since levening is not required).

The wheat germ component of whole wheat is by itself a rich source of nutrients, containing many of the vitamins and minerals attributed to whole wheat, particularly Vitamin E. Wheat germ oil improves strength and increases life span. Many of the minerals in wheat optimize many chemical reactions in the body including immune responses against excessive inflammation and cancer. Conditions like anemia, mineral deficiencies, gallstones, breast cancer, chronic inflammation, obesity, Asthenia, Tuberculosis, pregnancy problems and breastfeeding problems are quickly improved by consuming whole wheat. It is also recommended to treat sterility, gastrointestinal conditions, skin diseases, respiratory illnesses, and cardiovascular ailments. It is also known to help balance cholesterol levels and protect the heart. Due to its antisclerotic nature, the effectiveness of pharmaceuticals for heart disease, such as ACE-inhibitors and β-blockers are significantly enhanced by whole wheat and other whole grains as part of the **Mediterranean Diet**; and they have less of an impact on the rest of the body's systems due to their balanced composition.



Whole wheat has a natural ability to control weight in everyone, but this ability is more pronounced among women. Whole grains like wheat are immensely effective on patients with metabolic disorders. Common types of metabolic syndromes include visceral obesity, also known as the "pear shaped" body, high triglycerides, low levels of (protective) HDL cholesterol, and high blood pressure. It protects against all of these conditions. The majority of fiber works to help the digestive process in the body and improve the overall metabolism. Having a whole wheat diet is probably the most effective, quick, and enjoyable way to reduce metabolic syndrome, but also to stay slim and healthy throughout your life.

Wheat aids in the prevention of chronic inflammation as found in most types of rheumatic pains and also some rheumatic diseases. By lowering the risk of chronic inflammation it helps to relieve or prevent other ailments like osteoporosis, heart disease, dementia, Alzheimer's disease, and cognitive decline. It may well be that the best modality to preventing or slowing down the development of such as Alzheimer's disease even more than pharmaceuticals. Wheat is the most popular and easily available bulk laxative. Three cups of wheat consumption per day is enough for an individual to live a long, healthy and disease-free life. Wheat breads and cereals that are high in bran, reduces

EATING TO REDUCE
OXIDATIVE STRESS

pain, flatulence, nausea, constipation, and distension. Diverticulitis often occurs due to inflammation with lower intestinal pains. This can also lead to chronic constipation and unnecessary straining, which can result in a sac or a pouch in the wall of the colon. Such cases can be easily dealt with naturally by keeping up with a fiber-rich diet and including whole wheat on a regular basis. However, like everything else in life, too much is not healthy either. Too much wheat can lead to crystallization, thereby causing gallstones, kidney stones, and gout.

Whole wheat acts as an anti-carcinogenic agent, particularly in women. Wheat bran enhances the metabolic rate of estrogen. Excessive levels of estrogen may lead to breast cancer. Components of whole wheat block estrogen from binding and thereby being excessively active, reducing the risk for breast cancer. Whole wheat reduces the risks of colon cancer. In total, whole wheat provides a balanced result. It provides the benefit as well as the limiter to keep the system in balance. In fact most natural, unprocessed, foods or nutriceuticals which offer health benefits also, in the same product, provide the buffers to prevent the health benefit from becoming unhealthy. (Remember oxygen: too little causes low energy, not healthy, and too much burns or oxidizes, and destroys, not healthy; we only need just enough to be healthy and well.) Approximately 30 grams of whole wheat consumed per day is recommended, especially pre-menopausal women. This amount has been found to reduce the risks of breast cancer by up to 41% compared with equivalent amounts of other forms of fiber.

Wine is allowed and 4 to 6 ounces is usually consumed with dinner. The benefit of wine over other sources of alcohol is the fact that it is absorbed slowly because it is (1) often eaten with meals, which (2) causes a sustained level of alcohol in the blood, and (3) it is rich in flavonoids which produce antioxidants, as discussed above.

The **Mediterranean Diet** is also associated with a non-sedentary lifestyle. **Physical activity**, preferably a moderate level of daily exercise, and the **Mediterranean Diet** are complimentary. Again, physicial **Exercise** is arguably the strongest of all antioxidants. Exercise raises core body temperature which is like the passive immune response of a fever, reducing the need for the immune system to involve oxidants in neutralizing pathogens. It increases circulation to all areas of the body helping to passively remove wastes and contaminants, increase oxygen supplies to all areas of the body, boost active immune responses, and much more.

In the **Mind-Body Wellness Program**, all components work together. The **Program** recommends NO smoking (better lifestyle). Prediabetic or insulin resistant patients are often started on medications such as Metformin in an attempt to delay the need for further drug treatment of type 2 Diabetes. The **Mediterranean Diet** has been shown to also delay or prevent the need for drugs in patients with newly diagnosed type 2 Diabetes.

The **Mediterranean Diet** is known as a stress reducing diet. Certain foods consumed such as those with 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. These are stresses on the body, especially on the P&S nervous systems and thereby the cardiovascular system. This has been linked to higher incidences of heart attacks and vascular events, including stroke. By limiting obesity and frequent insulin peaks and valleys, the **Mediterranean Diet** reduces stress, including 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 people to seek foods with high glycemic indices leading to high insulin levels, increasing abdominal fat, and higher risk of Diabetes, heart disease and cancer. Also, the antioxidant properties of the Diet have been thought to delay aging.

The **Mediterranean Diet** is associated with a reduced risk of cancer incidents and mortality, including in the elderly. The **Diet** is associated with decreased epithelial cancers, digestive and laryngeal tract cancers, and upper airway digestive tract cancers. In women it has a protective effect against cancers of their genital tract (*e.g.*, endometrial cancer) and urinary tract, and other epithelial neoplasm. In contrast, refined grains and the consequently high glycemic loads, were associated with increased risks of cancers.

The *'Mediterranean way of drinking*', that is, regular, moderate consumption of wine mainly with food, increases longevity, reduces the risk of cardiovascular disease, stroke, and dementia, and does not appreciably influence the overall risk of cancer. However, heavy alcohol drinking is associated with digestive, upper respiratory tract, liver and breast cancers; therefore, avoidance or restriction of alcohol consumption to two drinks/day in men and one drink/day in women is a global public health priority. Light to moderate alcohol intake has a protective effect on all-cause and cardiovascular-type mortality in the United States adults. Heavy or binge drinking was associated with increased risk of cancer-specific and all-cause mortality.

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** improves exercise capacity. It reduces oxidative stress. Not all plant-based foods are equally healthy. Diets that adhere to (1) whole grains as the main form of carbohydrates, (2) unsaturated fats as the predominant form of dietary fat, and (3) an abundance of fruits and vegetables and adequate omega-3 fatty acid intake are the only diets that reduce the effects of, or prevent, chronic diseases.

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 with associated lifestyle factors.

Again, no one component of the **Mind-Body Wellness Program** alone stands out. In essence, the **Mediterranean Diet** acts in a team effort just as an American football team requires all components such as a great coach, offensive line, defensive line, quarterback, running backs, receivers, and so

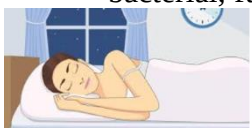
forth. All work in conjunction to produce the desired effect, namely, winning the ball game, which in our case is longevity of good health.

Exercise is another prong of the **Franklin Cardiovascular Mind-Body Wellness Program**. 'Exercise' is not a bad word! It does not have to be drudgery. Perhaps a better description is "active lifestyle," which may include exercise, but it should reflect the life style of people before elevators, television remotes automobiles, can be a single (preferably and cell phones. It physical exertion or muscular daily) acute bout of expends energy above one's activity that level. Exercise can also be a day long habit of activity: household chores, taking the stairs, shoppping, gardening, walking, playing with children. The physiologic and psychologic benefits of exercise are numerous. It is better than any supplement or pill available. It is probably better than any combination of supplements or pills or possibly even pharmacological agents. In fact, as mentioned throughout the book, exercise with supplements, etc., including diet which supports exercise is the best combination for minimizing morbidity risk, which optimizes quality and continuation of life, and minimizing mortality risk, which optimizes longevity and minimizes the impact of disease if and when it happens. It does so many beneficial things to the body.

Happier Moods from the release of endorphins in the brain, and other brain chemicals that elevate mood. Regular physical activity (3 to 5 times a week for 30 to 60 minutes each time) reduces risk of depression.

Reduced Pain. Endorphins are natural pain killers and can help to provide temporary pain relief.

Immune Health from two aspects of exercise: 1) Physical activity raises the body's core temperature, simulating a fever, 20 minutes or more of exercise, three or more times per week helps to prevent disease before is starts; 2) Exercise, as stated above, is arguably the strongest antioxidant available and provides all of the benefits detalied below, plus defeating (promoting the oxidation of) all types of infections: viral, bacterial, fungal, etc.



Better Sleep Quality. Five or six hours after workout, the decreased body core temperature signals the body to sleep, promoting less time to fall asleep and sounder sleep cycles; resulting in less daytime drowsiness. Also, less weight may mean less risk of Sleep Apnea and snoring.

Improved Concentration & Creativity. Exercise increases circulation, thereby increasing tissue oxygenation and removal of wastes from throughout (detoxifies) the body. In the brain this improves brain function, including concentration, creativity, and productivity. In addition to an improved cardiovascular system, the endorphins released stimulate the mind for more creative thoughts.

Reduce Stress Levels & Anxiety. "Too busy" is a logical excuse to skip a work out, but physical activity actually helps alleviate stress and promotes productivity. Exercise increases the body's ability to handle stress.

It produces higher levels of norepinephrine, a chemical that regulates areas of the brain that send stress signals. The more you train your body with the healthy physical stress of mild to moderate exercise, the better the body responds to emotional stress.

Maintain Mental Fitness. Through aging, our brainpower decreases and the brain actually grows smaller. Mental decline can start as early as 24 years of age. Elderly who exercise show less brain shrinkage than those who do not. Exercise may also reverse brain shrinkage. Regular physical activity (3 to 5 times a week for 30 to 60 minutes) helps maintain or sharpen thinking, learning, and judgment skills with age, and increases memory by increasing the volume of gray matter in the brain.

Parasympathetic and Sympathetic (P&S) Nervous Systems. The P&S (autonomic) nervous systems control and coordinate all of the organs and "involuntary" functions of the body. A proper balance is needed, both at rest and during activity. Note, sleeping is an activity and so is sitting at a desk and working, but sitting watching television is not. Exercise by itself can balance the P&S nervous systems better than any supplement or diet alone. Again, the best is when exercise and diet and the rest of the **Mind-Body Wellness Program** are taken together! Establishing and maintaining P&S balance should always be a goal, and exercise is an excellent adjunct to pharmacology and other lifestyle measures, including diet in this regard.

Neuroendocrine Health. Exercise reduces cortisol release for better neuroendocrine balance. It helps to keep insulin levels healthy and increases insulin sensitivity. It boosts sex hormones. It helps to maintain healthy thyroid and hypothyroid hormone levels, including levels of growth hormones, which in adulst help with healing and repair.

Heart & Vascular Health. Physical activity engages the entire body, and a healthier cardiovascular system means the heart is better able to circulate blood to all parts of the body, including in older individuals. Heart disease and stroke are two of the leading causes of death in the United States. Following physician recommendations and getting at least 150 minutes a week (2½ hours) of moderate-intensity activity reduces the risk for these diseases. The more exercise the more that risk is reduced. Regular physical activity improves almost all cardiac risk factors, including by increasing HDL cholesterol, lowering LDL cholesterol (clears arteries), lowering blood pressure, increasing cardiovascular fitness, and making the blood less prone to thrombosis or clotting.

Stress Reduction. Exercise reduces stress, reducing cortisol levels (as mentioned above), reducing psycho-social stress, reducing anxiety, depression (as mentioned above), and fatigue. It reduces oxidative stress, improving endothelial function, increasing nitric oxide production and the numbers of Mitochondria for more energy.

Weight Control (Loss). Diet and physical activity play a critical role in weight management. Weight gain occurs when the calories burned, including those burned during physical activity, are less than the calories consumed. The amount of physical activity required for weight management varies greatly, depending on metabolism (genetics), age (including stage of development), environment, and more. Physical activity can help with weight loss as well as weight maintenance. Establishing and maintaining a healthy weight requires both regular physical activity and a healthy eating plan.

Reduced Risk of Type 2 Diabetes and Metabolic Syndrome. Regular physical activity reduces risk of developing type 2 Diabetes and Metabolic Syndrome. Metabolic Syndrome includes a combination of (1) too much fat around the waist, (2) high blood pressure, (3) low HDL cholesterol, (4) high triglycerides, or (5) high blood sugar. Lower rates of these conditions are seen with 120 to 150 minutes (2 to 2½ hours) a week of at least moderate-intensity aerobic activity. The more exercise the more the risk is reduced. Regular physical activity also helps control blood glucose levels and can reverse type 2 Diabetes and Metabolic Syndrome.

Reduced Cancer Risk. Regular physical activity reduces risk of cancers as compared with people who do not exercise regularly. Physically active people have a lower risk of colon cancer. Physically active women have a lower risk of breast cancer. Regular physical activity reduces risk of endometrial and lung cancer. Improve your quality of life. Cancer survivors who exercise regularly have improved quality of life and physical fitness over those wo do not.

In association with leisure time, physical activity was associated with a lower risk of 13 cancers including esophageal, lung, kidney, gastric, cardiac, 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. Lifestyle factors are important for cancer development and a 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 and an ideal weight with BMI of 18.5 to 27.5.

Strengthen Bones and Muscles. Bones and joints, as well as muscles, change with activity level and age. They also need more protection with age. Physical activity strengthens them, which protects bones and joints. Strong and healthy bones, joints, and muscles promote an active lifestyle. Adding a proper diet ensures the necessary micronutrients to maintain bone, joint, and muscle health. Physical activity of at least a moderately-intense level slows the loss of bone density that comes with age. All together, exercise helps to reduce the risk of falling in elderly, either due to fewer leg bone fractures and improved muscle strength. Hip fracture is a serious

health condition that often, negatively effects quality of life, especially for older adults (*e.g.*, climbing stairs, grocery shopping, or playing with the grandchildren). However, 2 to 5 hours of at least moderate-intensity aerobic activity each week lowers risk of hip fracture.

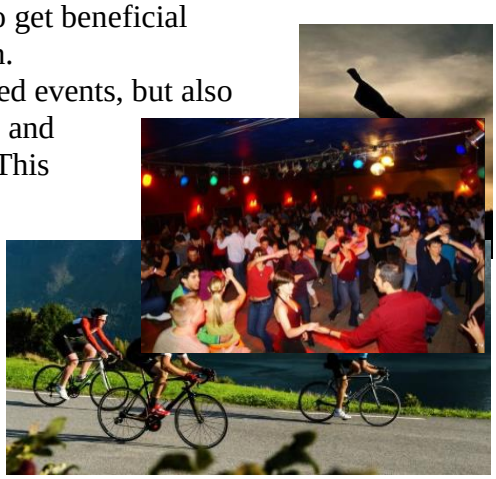
Regular physical activity reduces risk of developing, and helps to manage, arthritis and other joint disorders. For arthritis, 2 to 2½ hours a week of moderate-intensity, low-impact activity improves the ability to manage pain and do everyday tasks, and improves quality of life, not just from the pain, but also in terms of range of motion.

Muscle-strengthening activities helps increase or maintain muscle mass and strength. Gradually increasing the amount of weight and number of repetitions provides even more benefits, including endurance, no matter your age. Regular physical activity helps to return and improve quality of life, reduces morbidity risk (including dizziness and litghtheadedness, thereby reducing fall risk), and mortality risk; at any age.

Increases Longevity (promotes living longer) by reducing mortality risk, increasing the antioxidant milieu, boosting immune activity, reducing stress (including pain), and maintaining nervous system and cardiovascular health (P&S balance, **Mind-Body Wellness**). Only a few lifestyle choices have as large an impact on health as physical activity. People who are physically active for about 7 hours a week have a 40% lower risk of dying early than those who are active for less than 30 minutes a week; and this activity does not have to be vigorous, moderate-intensity is sufficient. Everyone may gain the health benefits of physical activity. Age, ethnicity, shape or size does not matter.

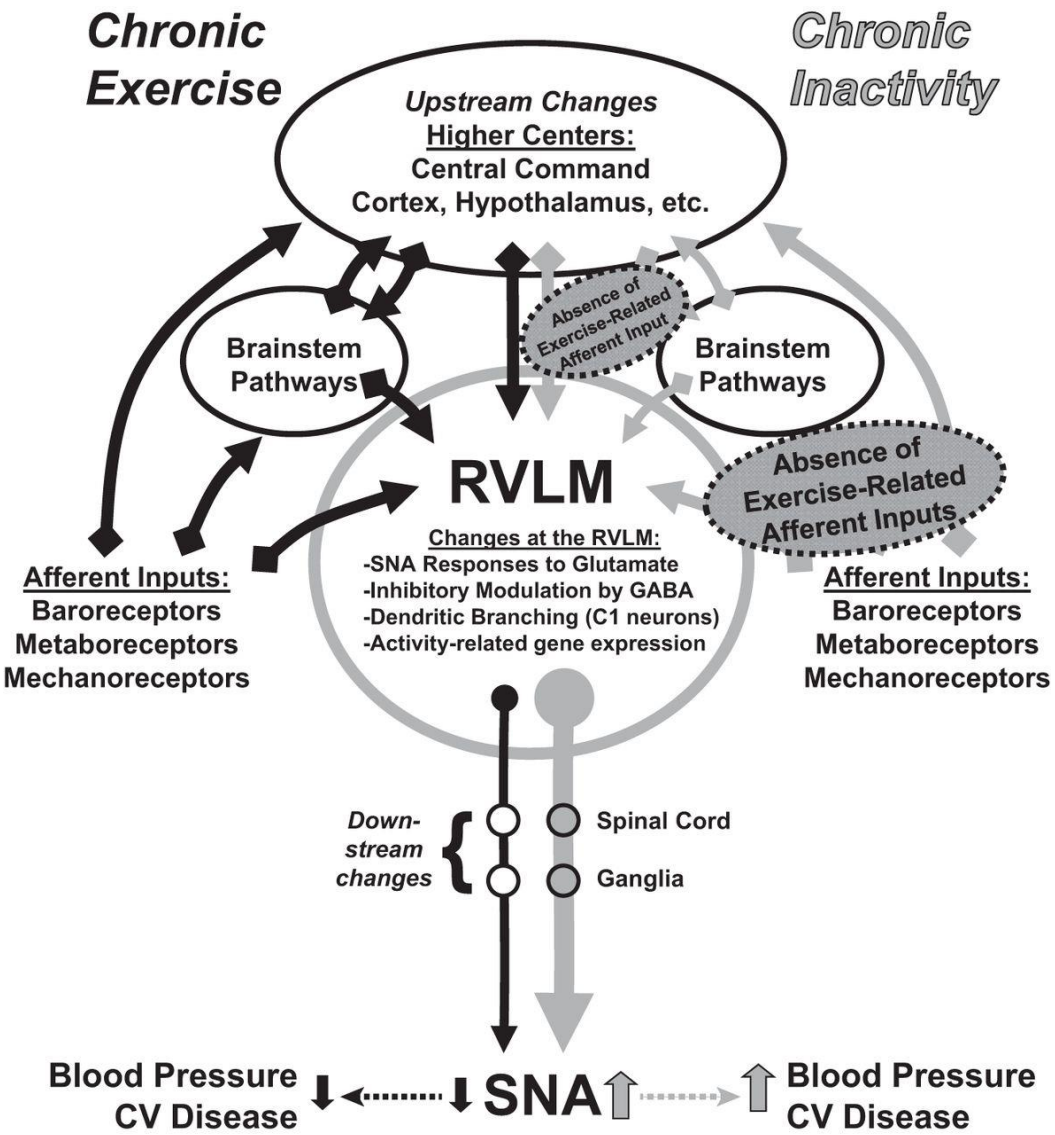
As with a pure Mediterranean diet, strict compliance with the recommended 150 minutes of exercise per week is not required to get beneficial effects. Smaller amounts of exercise are helpful, just not as much.

There is a portion of the brain stem that senses exercise-related events, but also senses the lack of exercise and has direct input to the brain, heart, and vascular system (the Rostral Ventrolateral Medulla, or RVLM). This brain stem center (or nucleus) regulates Sympathetic control over baroreceptor reflex and thereby blood pressure and hypertension, based on the levelof activity the body experiences. Physical inactivity independently contributes to the development of cardiovascular diseases and disorders that are becoming epidemic in the United States. The lack of normal healthy and regular exercise-related input (*e.g.*, at least 30 minutes of moderate exercise a day) leads to deleterious changes in the structure and function of RVLM neurons. These changes result in heightened Sympathetic outflow and end-organ damage, including damage to the vasculature, nerves, heart and kidneys.



This problem is not resolved with medication. Half of patients prescribed three or more anti-hypertensive medications are still hypertensive. There is no magic pill that can replace exercise. This is one of the dangers of eliminating recess from grade schools (in addition to being a cause of ADD/ADHD, Anxiety/Depression, Obesity, Fatigue, weak immune systems, and even poor grades). High blood pressure, and the hypertension that results from chronic high BP, is a common cause of diseases of the:

- Vasculature – Atherosclerosis, Arteriosclerosis, Aneurysms, and possibly Varicose Veins and Peripheral Artery Disease;
- Nervous System, including the Brain – Tension Headaches, some types of Migraines, Anxiety, Sleep Apnea and other sleep disorders, P&S dysfunction leading to Autonomic Neuropathy, Cognitive difficulties, "Brain Fog," Attention Disorders, Stroke, and Sudden Death;

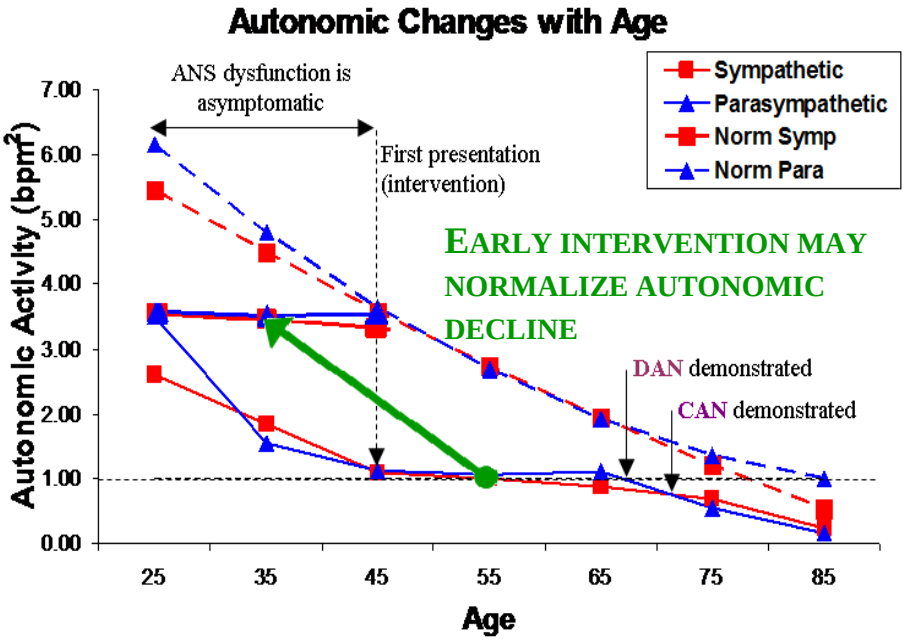


The effects of chronic exercise and chronic inactivity on the Rostral Ventrolateral Medulla (RVLM), Sympathetic nerve activity (SNA), and cardiovascular (CV) disease. The schematic depicts the RVLM as a key brain region in the integration of exercise-related input including peripheral and central afferents. Chronic exercise (*left*, black arrows) vs. chronic inactivity (*right*, gray arrows) produce central nervous system alterations that have opposite effects on BP and CV disease. With chronic inactivity, changes at the level of the RVLM seem to strengthen mechanisms of SNA. Significant neuroplasticity at the level of the RVLM explains exaggerated SNA observed in sedentary humans.

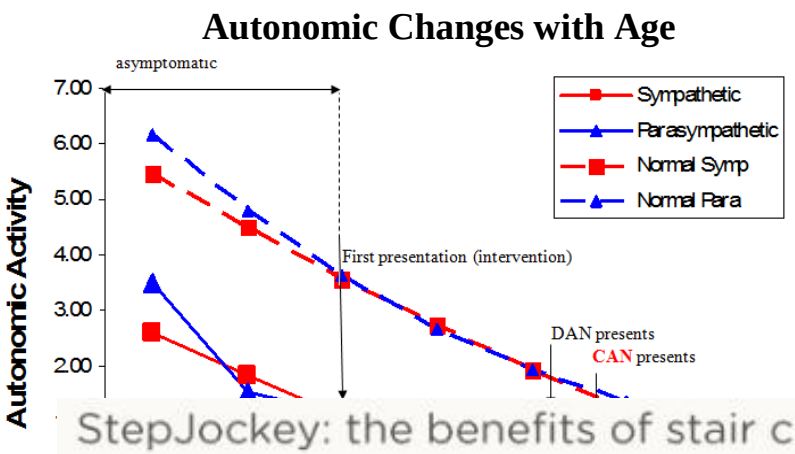
- Heart – Cardiomyopathy, Heart Failure, Heart Attack and Sudden Death;
- Kidneys – Renal Hypertension and Kidney Failure;
- Upper and Lower GI Systems – GERD, Diverticulitis, and Irritable Bowel Syndrome; and

- Other Systems – Diabetes, Insulin Resistance, Metabolic Syndromes, Retinal damage, Skin and complexion disorders, Obesity, some types of Cancers, and possibly Sex Dysfunction.

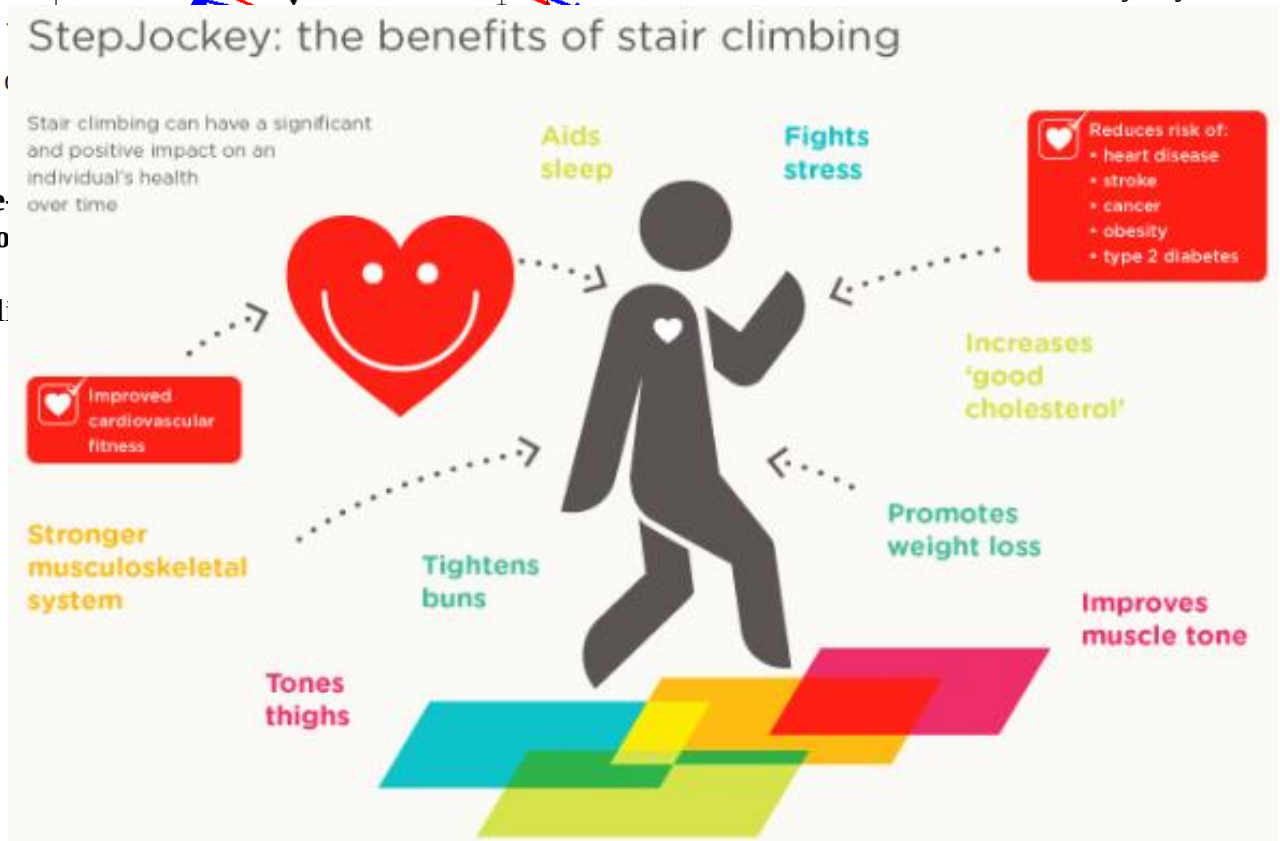
Inactivity promotes high BP by increasing Sympathetic activity and thereby the above cascade of diseases, many of which are compounding effects on the others, accelerating aging and death. Persistent Sympathetic Excess (SE) increases baroreceptor reflex, which increases BP, which causes Hypertension. SE with Hypertension accelerates the onset of the above diseases. SE also accelerates the onset of P&S dysfunction. Even as the Sympathetics decline, they typically remain stronger than the Parasympathetics, resulting in high Sympathovagal Balance (SB). High SB accelerates the onset of Advanced Autonomic Dysfunction (AAD, which is Diabetic Autonomic Neuropathy, if in a Diabetic), which increases morbidity risk and the presentation of the symptoms associated with the above cascade of diseases. Note how late in the progression of autonomic neuropathy do symptoms present. At this point in time in the progression of P&S (autonomic) decline, up to 80% of a patient's P&S function is lost; and the decline *was asymptomatic*! This is why a habit of regular (at least moderate) exercise is necessary, starting from an early age. Ultimately high SB and high BP accelerates the onset of the final stage of aging: Cardiovascular Autonomic Neuropathy (CAN) and its associated mortality risk. CAN is



The flat portion of the patients' P&S curves are the responses to the patients complying with therapy, including exercise and other lifestyle modifications. As shown here, with early intervention the "flat portion" can be realized earlier in life returning the patients to the normal subjects' path, preserving quality of life and minimizing morbidity and mortality risk.



end stage autonomic neuropathy. It is defined as very low Parasympathetic activity. Very low Parasympathetic activity is very dangerous (remember the Sympathetics are typically high compared with the Parasympathetics at this point). It means that the Parasympathetics are not strong enough to prevent a Sympathetically mediated Ventricular tachy-rhythm



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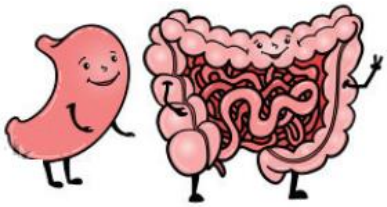
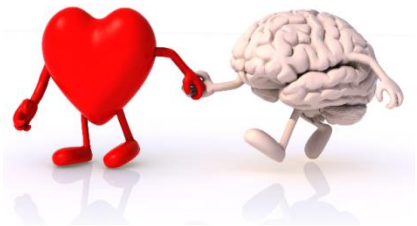
from becoming Ventricular Fibrillation and Sudden Death. In other words, it is like having no breaks on your car, so you cannot stop from having an accident (a heart attack).

Again, exercise is the most powerful antioxidant. It improves nerve function and blood flow, including by increasing the number of blood vessels and the volumes of the vessels in muscles. Exercise promotes antioxidant activities, including the scavenging of ROS, promoting healthy level of nitric oxide, which inhibits LDL oxidation and leukocyte adhesion, which prevents or reduces atherosclerosis. In this way it may augment statins. Overall, it is all about balance. Antioxidant-Oxidant balance is a dynamic balance established under conditions of homoeostasis between free radicals that are created (*e.g.*, by exercise) and those consumed (scavenged). A habit of healthy and regular exercise will prevent many of the diseases that have become epidemic in the US. However, exercise alone is not enough. Remember, all of the parts of the **Mind-Body Wellness Program** are needed and work together.

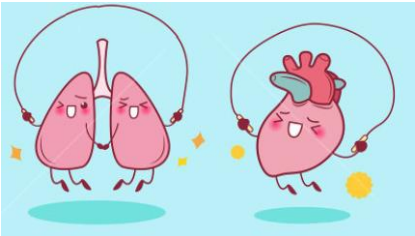
An example of exercise is Yoga. Yoga stimulates Parasympathetic activity. The Vagus Nerve (the major portoin of the Parasympathetic system) plays an important role in all aspects of health. Yoga stimulates the Vagus Nerve by movement, chanting, and breathing exercises. Vagus Nerve stimulation reduces neuronal excitability throughout the central nervous system. It is specifically associated with neuronal circuits that control fear and anxiety which results from over-excitation of these central nerves. Less stress helps dialate blood vessels and improves blood flow and endothelial function, reducing hypertension, risk for atherosclerosis and cadiovascular disease. The Parasympathetic nervous system controls the immune system (in and out of the central nervous system) and thereby includes antioxidant effects.



Again, exercise is not a dirty word! Think of exercise or physicial activity as in the time before automobiles, elevators, television remotes, and cell phones. As with the Mediterranean diet, physical activity was simply part of life. Even riding a horse requires a greater energy level than at rest. Many of the diseases that are "epidemic" in the world, were only found in the wealthy and ruling class, those who could afford carriages to ride in and servants to do their "leg-work." The "upper class" stopped their physical exertion, changed their diets, and under the delusion of "refinement" and "propriety" adopted much more stressful lifestyles. In fact, obesity was a sign of status. Only those who could afford it where obese. Today, most of society is based on the automobile. In fact the newer cities are designed to sprawl to enable the automobile. The older cities, built before the automobile, were designed so that the residents could reach their common destinations (grocery, butcher, church, physician, etc.), in a reasonable amount of time, by walking.



An active lifestyle (which involves physical activity) may be just as healthful as more modern lifestyles that include (planned) exercise. Exercise sessions are usually planned out and structured with a goal to improve and maintain physical fitness. It usually, but not always, involves voluntary muscle movement. 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.



The Surgeon General with the National Institutes of Health, the American Heart Association, a joint Centers for Disase Control and Prevention and American College of Sports Medicine consensus, all agreed that the benefits of moderate exercise generally occur by engaging in at least 30 minutes of modest activity on most, preferably all, days of the week. Walking briskly was defined as a pace that is about 3 to 4 miles per hour for about 30 minutes. "Activities" can include any other form of occupational or recreational activity that is dynamic in nature and of similar intensity, such as yard work, household tasks, cycling and swimming. This amount of exercise equates to approximately five to seven 30-minute sessions per week at an

intensity equivalent to 3 to 6 times the resting metabolic rate (approximately 70 calories per hour), or approximately 600 to 1200 calories expended per week.

The benefit of regular exercise depends on the type and intensity of the exercise. It is clinically important to select the appropriate intensity, duration, frequency and kind of exercise; please consult your physician before beginning a new exercise regimen. Patients should always get clearance from a physician before undertaking any exercise. Patients should continue to work with a physician to increase exercise levels to reach the moderate levels recommended.

The last prong of the **Franklin Cardiovascular Mind-Body Wellness Program** focuses on stress reduction, specifically Psychosocial Stress. Oxidative stress reduction discussed above is stress at the cellular and system level. Psychosocial Stress and other stresses, such as from Environmental, Temperature, and other factors are whole body stresses. These are the stresses we will discuss here. There are three stages to the acute stress response. First the stressor is detected with sensory organs. The second stage is the stress response: defense or escape. The third stage is when the acute become chronic. If the stressor cannot be avoided and it persists, then the third stage is entered; a state of exhaustion. Stress responses are coordinated by P&S nervous systems and the Hypothalamus-Pituitary-Adrenal axis. The stress response starts with the activation of the Sympathetic system. The Sympathetics stimulate the Adrenal Medulla to release Adrenaline and Noradrenaline. The two forms of Adrenaline (aka., Epinephrine[4]) increase heart rate and vasoconstriction. Concurrently, the Adrenal Cortex releases Glucocorticoids (such as Cortisol) mobilizing energy reserves (*i.e.*, Glucogenolysis in the Liver).

Under chronic stress, the immune system, metabolic pathways and cognitive processes in the organism gradually weaken until exhaustion and failure are reached. For example, repetitive Hypothalamus-Pituitary-Adrenal activation results in an excess of Glucocorticoids in the blood can lead to metabolic diseases such as Metabolic Syndrome or type 2 Diabetes. Strong emotion and mental stress are now recognized as playing a significant role in severe and fatal ventricular arrhythmias. The mechanisms include central processing at the cortical and brain stem level, the P&S nerves and the electrophysiology of the heart. This is part of the Mind-Body, Brain-Heart, connection. These mechanisms include regulatory processes which incorporate interactive feedforward and feedback mechanisms, and must be considered together, intact. These mechanisms underlie the colloquial beliefs that people may "die of fright" or are "worried to death." Strong emotions, as evidenced by the epidemic-like prevalence of the diagnosis of Anxiety clogging Emergency Rooms, may precipitate arrhythmias which may turn malignant and lead to sudden cardiac death.

Anxiety and other emotions and stress, both immediate, remembered, and imagined also affect other systems of the body, including the immune system. For example, "puppy love" responses, including flushing, cold sweat, "jitters", rapid breathing and pulse, "butterflies" in the stomach, and the need to evacuate bowels or bladder, are caused by the CNS communicating via brainstem nuclei through the P&S nervous systems to the viscera (the organs in the body). A bidirectional communication exists between the central nervous system and the immune system, via the P&S systems. The P&S nervous systems works in parallel with the Hypothalamic-Pituitary-Adrenal axis to modulate inflammatory events. The immune system, in turn, activates the CNS to orchestrate negative-feedback mechanisms that keep the immune response in check.

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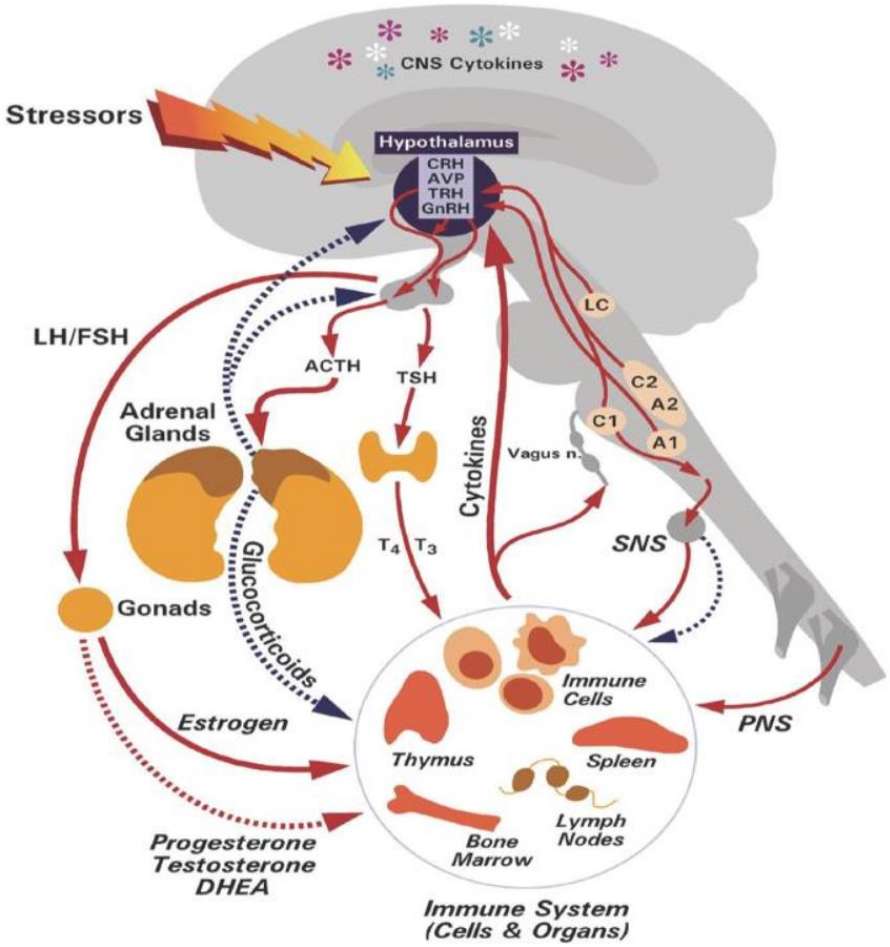
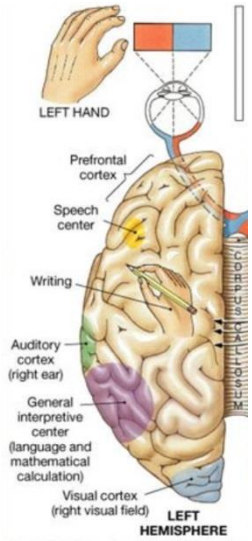
[4] Adrenaline and Epinephrine are the same molecule. They were discovered at the same time, both in America and England. The Americans called it Epinephrine and the British called it Adrenaline.

Disruption of these interactions has been associated with a number of syndromes including inflammatory, autoimmune, and cardiovascular diseases, metabolic and psychiatric disorders, and the development of shock.

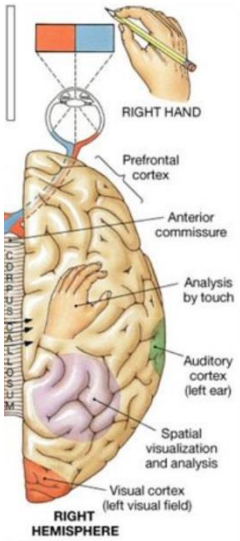


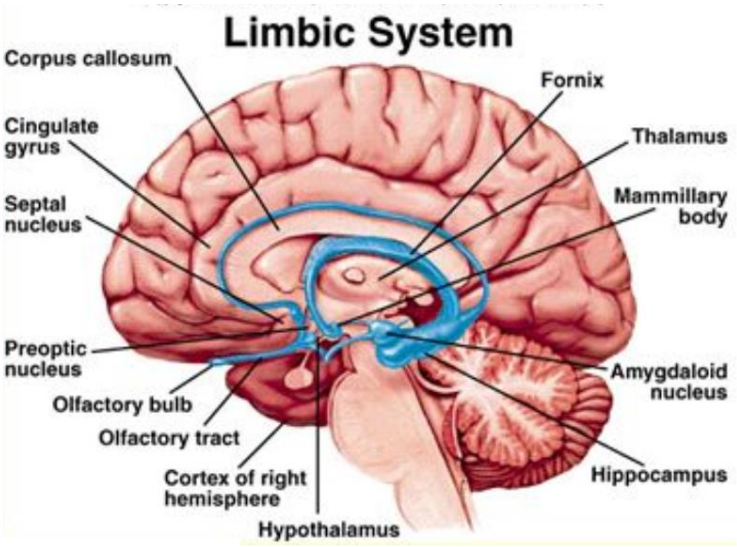
Bidirectional communication between the Hypothalamic-Pituitary axes, the P&S nervous systems, and the immune system. Hormones released by the adrenals and gonads, such as Glucocorticoids and Progesterone, respectively, work in parallel with neurotransmitters and neuropeptides to regulate the immune system. In turn, Cytokine signaling provides stimulus or feedback to the Hypothalamus to regulate the hormonal and neuronal response. Abbreviations: Broken lines represent negative regulatory pathways; Solid lines represent positive regulatory pathways; A1, C1, A2, C2, Brainstem adrenergic nuclei; ACTH, adrenocorticotrophin hormone; AVP, arginine vasopressin; CRH, corticotrophin-releasing hormone; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LC, locus ceruleus; LH, luteinizing hormone; PNS, peripheral nervous system; SNS, sympathetic nervous system; T3, tri-iodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; Vagus n., vagus nerve.

The Brain-Body connections:



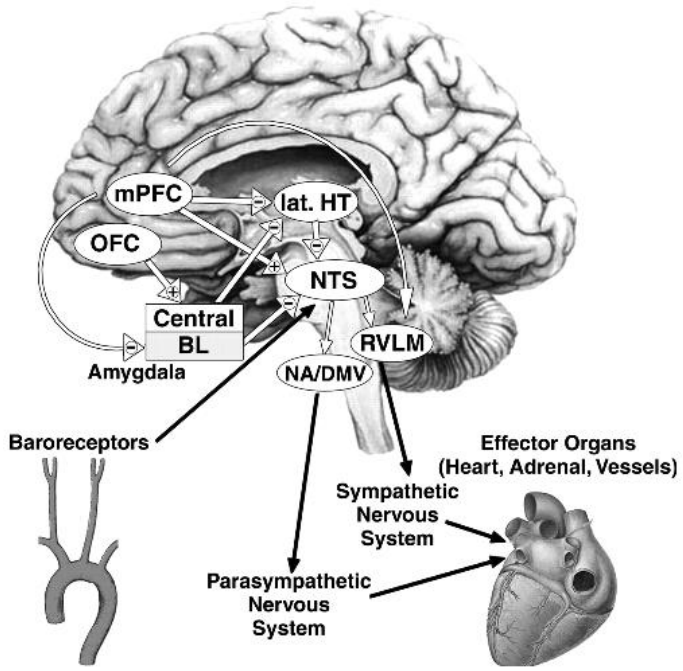
➔The right Cerebral Hemisphere (right insert) is associated with (1) holistic processing of multi-sensory input, (2) visual spatial skills, (3) memory stored in auditory, visual, & spatial modes, (4) remembering non-verbal material, and (5) color discrimination.
🡐The left Cerebral Hemisphere is (left insert) associated with (1) analytic and sequential thinking; (2) language, mathematics, abstraction and reasoning; (3) ability to name objects & their attributes; and (4) memory stored in language format.
🡓The Limbic system (insert below) consists of the hypothalamus, cingulated gyrus, amygdala, hippocampus, mamillary bodies and septum. It influences P&S nervous connected with pleasure center Accumbens), mediating sexual "high" from chemical agents. The mediates emotion Hippocampus, consolidates, and to long-term connected to the endocrine and systems. It is the brain's (the Nucleus thereby arousal and the natural and activities and Limbic System and through the stores, transitions short-memory. It is Pre-Frontal Cortex and is thereby related to the pleasure obtained from solving problems etc. Stimulation of specific areas of this system can also lead to feelings of dread, anxiety, and can also result in violent behaviors, including attack, defence, and explosive and emotional speech; in other words, anger.



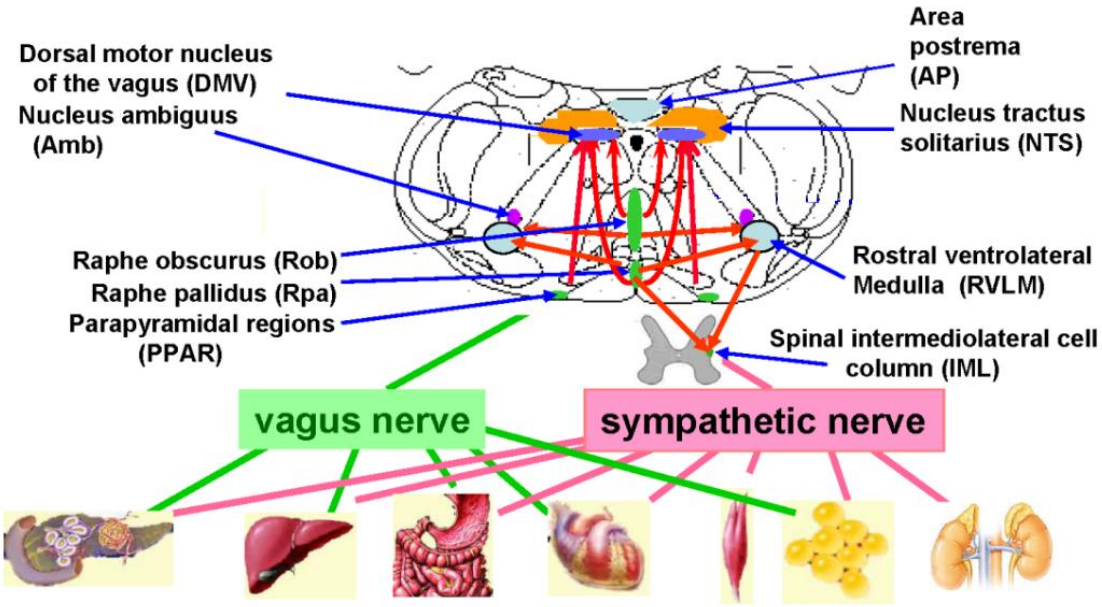


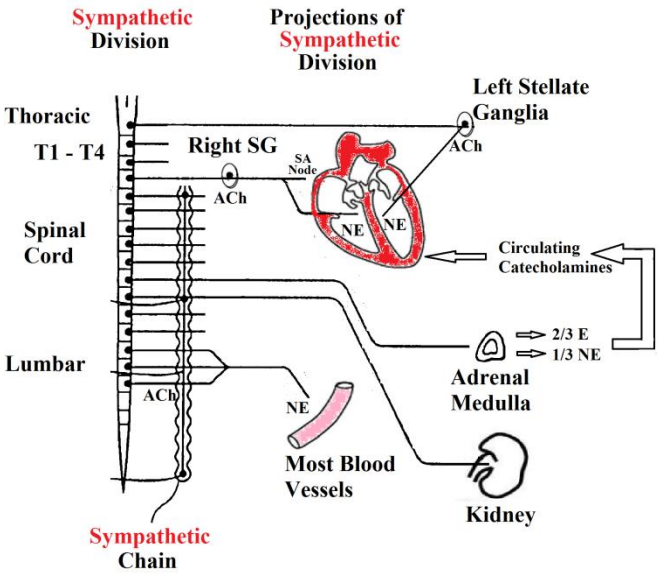
The Amygdala stores emotional memory. It is involved in the sense of smell, especially as it relates to memory and the sense of danger. It sends impulses to the mid-brain (*e.g.*, for sensory integration) and brain stem (*e.g.*, including medullary P&S nuclei), which results in the release of Adrenaline and Noradrenaline which may act as stress hormones. It seems to be the core of social networking, and organizes and approaises history and previous interpersonal encounters. As a result it seems to be the source of prejudice, gender bias, and “love at first sight.” It colors sensory informaton with emotion.

Hypothalamus connects the cortex to the Basal Ganglia, Thalamus, Midbrain, Pons, Medulla (*e.g.*, including P&S nuclei) and Spinal Cord. It regulates the functioning of the Pituitary gland and controls (1) Autonomic nerve function and (2) major endocrine effects (*e.g.*, water balance, appetite, and sex drive).



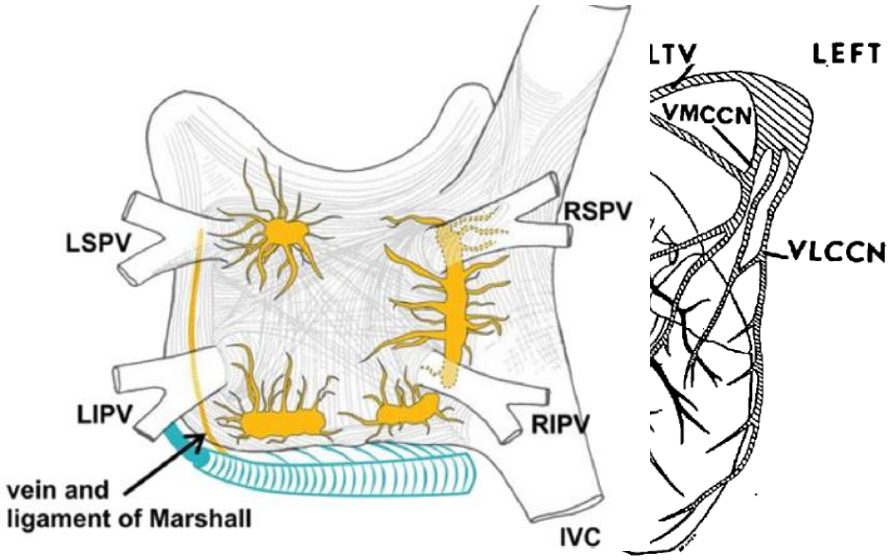
The Septal Nuclei play a role in reward and reinforcement, and is considered a pleasure zone. They also play a role in social behavior (play), espceially in females. Hypothalamus and Amygdala include projections to the Medullary Brain Stem P&S nuclei, thereby modulating cardiac, respiratory,vomiting and vasomotor centers. Through these projections, the Medulla mediates P&S and involuntary activities, *e.g.*, ventillation, plasma pH, heart rate, and blood pressure. The latter is mediated via the Sympathetic drive. In the Brain Stem, the Nucleus Tractus Solitarius (NTS), Nucleus Ambiguus (NA), and Dorsal Motor Vagal Nucleus (DMV) are important structures involved in efferent (from the brain) and afferent (to the brain) Vagal (Parasympathetic) activity. The nucleus of the Solitary Tract is a site of integration of both the afferent and efferent neural regulation of the cardiorespiratory as well as the immune system. The lateral Hypothalamus (lat HT) and the Amygdala with the Basolateral Nucleus (BL) generate inhibitory control over Parasympathetic structures in the Brain Stem during stressful events and in anxiety. To provide balance, the medial Prefrontal Cortex (mPFC) and the Orbitofrontal Cortex (OFC) facilitate Vagal output and inhibit the Rostral Ventrolateral Medulla (insert, left; (−) indicates primarily inhibitory influences; (+) indicates primarily facilitatory influences). Finally, emotions, including anxiety, depression, anger,and love, effect thoracic and viceral organs via projections from the DMV and NA, primarily via the Vagus Nerve, and the projections from the NTS and RVLM, primarily via the Sympathetic Chain.


Dorsal motor nucleus of the vagus (DMV)
Nucleus ambiguus (Amb)
Area postrema (AP)
Nucleus tractus solitarius (NTS)
Raphe obscurus (Rob)
Raphe pallidus (Rpa)
Parapyramidal regions (PPAR)
Rostral ventrolateral Medulla (RVLM)
Spinal intermediolateral cell column (IML)
vagus nerve
sympathetic nerve



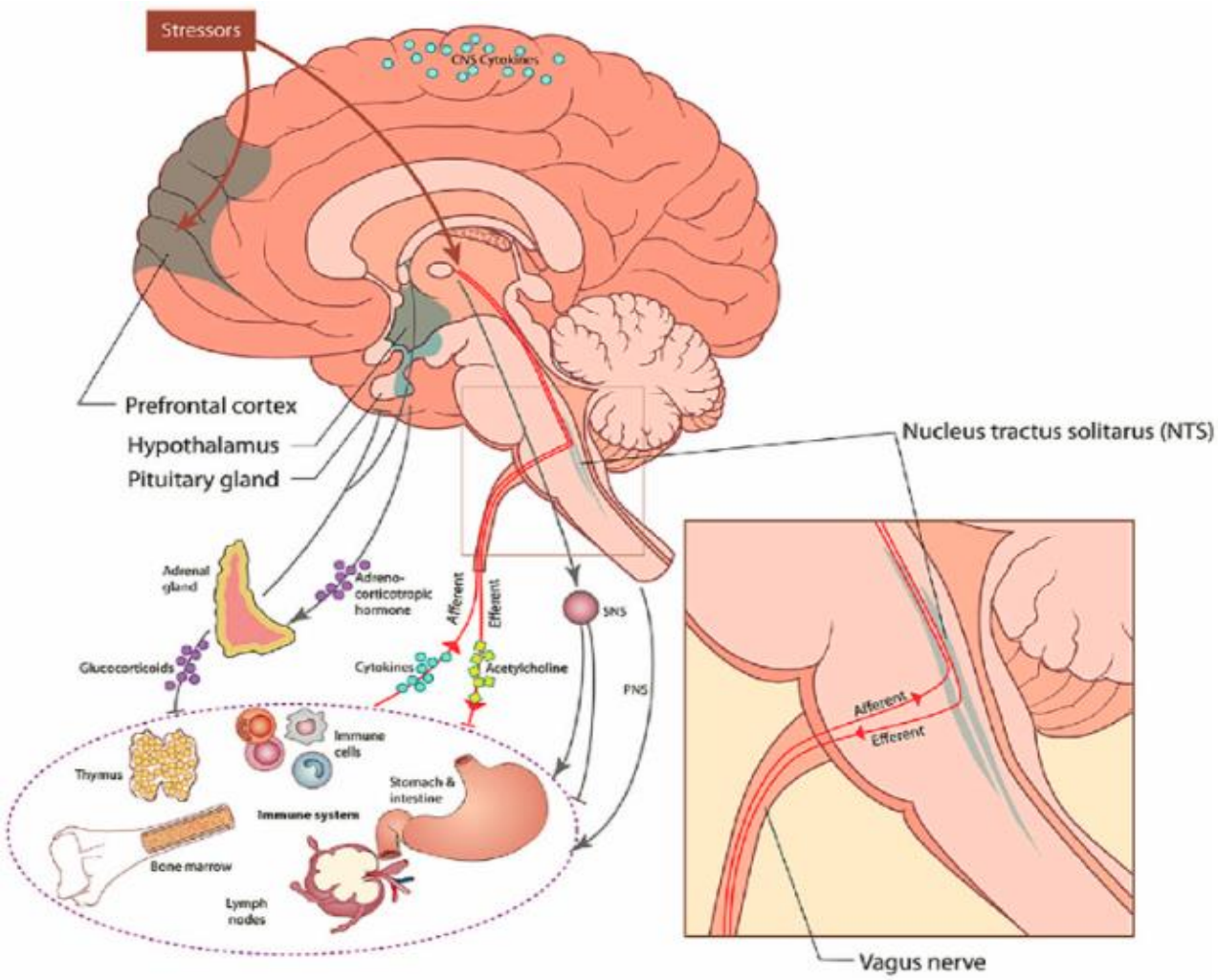
Cardiac Sympathetic Control. Abbreviations: ACh = Acetylcholine, E = Epinephrine, NE = Norepinephrine, SG = Stellate Ganglion.

Evidence suggests that the right cerebral hemisphere is predominantly concerned with negative emotion and Sympathetic activity, whereas the left hemisphere is predominantly concerned with positive emotion and Parasympathetic activity. P&S projections from the brainstem to the heart is mainly ipsilateral. There is also some degree of lateralization of the distribution of the right and left autonomic nerves on the heart. This asymmetric and inhomogeneous activation of the heart can become proarrhythmic when P&S balance is disturbed: too high, indicating Sympathetic Excess potentially leading to tachycardia and arrhythmia, or too low, indicating Parasympathetic Excess potentially leading to bradycardia and arrhythmia.



Parasympathetic Innervation of the Heart. Abbreviations: IVC – Inferior Vena Cava, LIPV – Left Inferior Pulmonary Vein, LSPV – Left Superior Pulmonary Vein, RIPV – Right Inferior Pulmonary Vein, RSPV – Right Superior Pulmonary Vein.

Sympathetic Stellate Control of the Heart. Abbreviations: CaV: Caudovagal N., CrV: Cranio-vagal N., LTV: Left Thoracic Vagus N., RC: Recurrent Cardiac N., RTV: Right Thoracic Vagus N., VLCCN: Ventrolateral Cervical Cardiac N., VMCCN: Ventromedial Cervical Cardiac N.

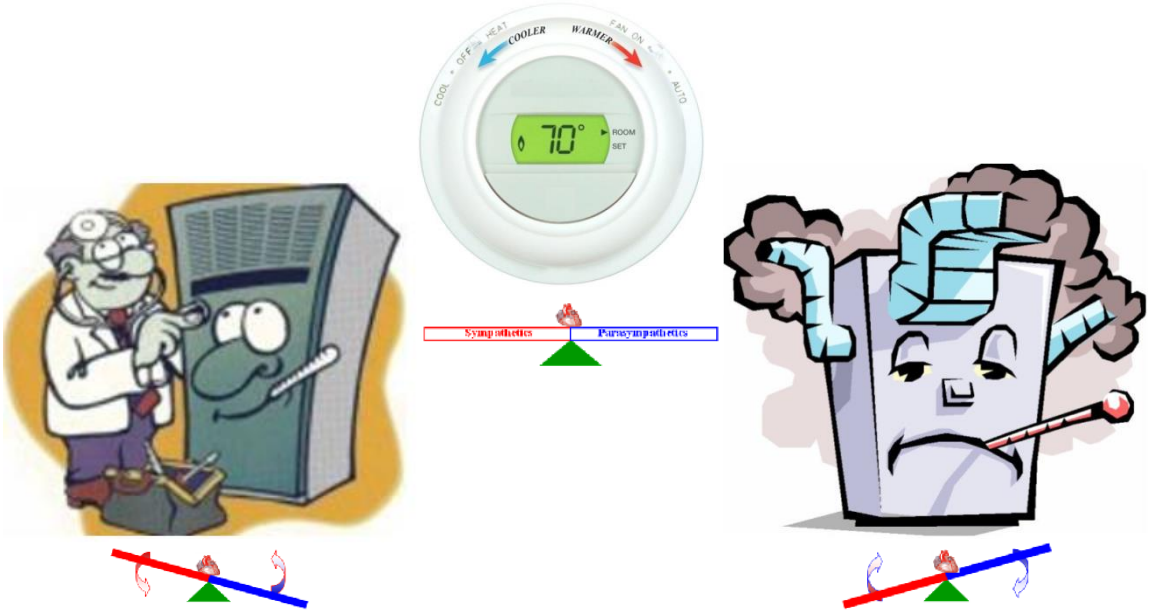


There is documented evidence of people dying almost immediately following highly charged (Sympathetic Excess-type) emotional events. There is also documented evidence of people dying from depression (Parasympathetic Excess conditions), including "Broken Heart Syndrome," where a long-time spounse or partner dies (or has a hgh risk of dying) in the month following the death of the partner. There is also documented evidence of people simply "giving up" and no longer wishing to live. These are types of Parasympathetic Excess where the nervous system, while mediating depression, suppresses the immune system, leaving the individual susceptible to infection (*e.g.*, Pneumonia) that becomes life threatening.

Anger as well as other stresses are associated with both increased plasma Catecholamines (a marker of increased Sympathetic activity), and decrease Vagal activity. Episodes of anger promote greater increases in Sympathetic activity compared with other emotions. Even anger recall in patients can make ventricular arrhythmias easier to induce and more difficult to terminate.

Emotions and abnormal brain function may cause many other disorders as well, for example, Post-Traumatic Stress Disorder (PTSD). PTSD does not always begin with physical trauma to the body or the brain. It can start with emotional trauma (harassment, bullying) or mental trauma (the sight of horrific events, or the experience of a life-threatening event – without physical trauma). PTSD is an interesting disorder from the point of view that we know when the trauma occurred, yet there is up to a three year onset latency, or more, before symptoms. What do you

think is happening during this time? The trauma (any type) pulled the nervous system out of balance and while it is the job of the nervous system to maintain normal organ function, even when itself is abnormal, this situation eventual ends in a catastrophic failure. Then the organs are no longer operated in a normal manner, and symptoms present. This is too late. The time to treat is immediately after trauma, but before symptoms. This is how wellness is maintained. Furthermore, treatment can be in the form of lifestyle modifications. It does not have to be medicinal.



You have a thermostat in your house to control temperature. Assume you like 70°F as comfortable. Assume you cannot hear, see, or access, or even know about your hearter (Sympathetic) or cooling (Parasympathetic) systems. Assume the cooling system is working well. Assume a very hot and humid day in the south and a $5 heater switch fails, and the heater comes on full. What happens to the temperature reading on the thermostat?..... *Nothing!* The heater amps up and compensates not only for the ambient, but also for the additional heat being produced by the heater. However, how long will this situation last until there is a catastrophic failure in one or the other systems. Then the temperature will change. Is that not too late? Which would you prefer, a $5 fix or a $5,000 system replacement (heating or cooling systems, or both). The thermosat is like your heart beating at 70 bpm. If one system becomes dysfunctional you are at risk for heart diseases, it does not necessarily happen immediately. However, when the P or S systems fail to maintain normal control, then the heart rate changes and may change to conditions that initiate a heart attack or worse sudden death or stroke. The **Mind-Body Wellness Program** helps to keep you well, not merely symptoms free, and this can be documented using P&S Monitoring.

To summarize, the **Franklin Cardiovascular Mind-Body Wellness Program** promotes all six of its prongs, which when working together optimizes wellness for the individual, including Quality of Life and Length of Life. The **Program** includes three supplements and three lifestyle changes. It itself is balanced. The three lifestyle changes recommended are the **Mediterranean Diet**, **Exercise**, and (**Psychosocial**) **Stress Reduction**. The three supplements are **Omega-3 , Fish oils**; the antioxidant compound **Cardio-Neuro-Mito™**; and the nitric oxide compound **Vasso-Plus™**. Without all six, some component will be lacking and total healing, leading to

wellness, is compromised. The ingredients of the three supplements are listed below. Stay in balance and enjoy an active life to the fullest! Stay well.

> **One of the first duties of the physician is to educate the masses not to take medicine.**
> **– Sir William Osler, Bt**

Nutrients included in the **Mind-Body Wellness Program** are listed below, in no particular order, with a brief description of their function or benefit:

- **Alpha Lipoic Acid** (ALA) – an anti-inflammatory and an antioxidant. At the cellular level ALA (1) reduces oxidative stress; (2) scavenges (through chelation) and sequesters free radicals, including ROS; (3) brings products to mitochondria; (4) regenerates other antioxidants, including vitamins C & E; (5) increases Nitric Oxide production; and (6) and boosts energy (ATP) production. At the system level, ALA (1) aids in P&S and sensory nervous system function; (2) lowers blood pressure (BP); (3) slows or relieves the progression of autonomic neuropathy in Diabetes and possibly in other chronic diseases.
- **Co-Enzyme Q10 (CoQ10)** – an antioxidant. At the cellular level CoQ10 (1) sequesters active ROS, (2) increases energy (ATP) production, (3) limits electron leak in the electron transport chain (also increasing (ATP) energy production), and (4) reduces mitochondrial dysfunction. At the system level, CoQ10 (1) decreases cholesterol, (2) increases immune function, (3) increases cardiac function by supporting cardiac muscle health, (4) supports skeletal muscle health, (5) reduces inflammation (including reducing inflammatory markers), and (6) lowers BP. A very important note: natural CoQ10 levels in the body decline with age.
- **B Vitamins**: Vitamins **B_6** & **B_{12}**, with **Magnesium** (**Mg**) are potent supporters of Parasympathetic nervous system health, and thereby help to elevate mood, and protect the heart, among other benefits, such as helping to improve mood and mental health.
    - **B_6 (Pyridoxine)** – supports nervous system function and boosts energy (ATP) production.
    - **B_{12} (Cobalamin)** – supports nervous system function and boosts energy (ATP) production.
    - **Folic acid (B_9)** – cofactor in producing Nitric Oxide, cofactor in Citric Acid Cycle to trap electrons, and a cofactor in reducing the toxin Homocysteine
    - **B_1 (Thiamine), B_2 (Riboflavin), B_3 (Niacin), B_5 (Pantothenic Acid) & B_9 (Folic Acid)** – boosts energy (ATP) production, as a cofactor in Citric Acid Cycle to trap electrons, and attenuates the abnormal effects of Asymmetric Dimethylarginine (ADMA) by competing with **L-arginine** for Nitric Oxide Synthase (NOS). The arginine part of ADMA, by replacing L-arginine in reactions with NOS, enables ADMA to impair NOS and the synthesis of Nitric Oxide.
- **Vitamin D_3** – helps to strengthen bones and teeth and helps to decrease Diabetes.
- **Vitamin E** – a fat soluble antioxidant protects cell membranes from ROS, thereby slowsthe aging process.
- **Vitamin K** – supports vascular health, reducing arterial calcification; supports halthy blood clotting and can slow cancer growth.
- **Minerals:**

- **Magnesium (Mg)** – supports Parasympathetic nervous system function, boosts energy (ATP) production and reduces anxiety
- **Zinc (Zn)** – supports immune function, and memory; decreases severity of chronic diseases that are age related; supports wound healing; and is involved in collagen synthesis and epithelialization (wound healing).
- **Copper (Cu)** – involved in collagen synthesis, supports energy (ATP) production and increases absorption of iron.
- **Manganese (Mn)** – supports nerve function, involved in fat and carbohydrate metabolism, helps to form connective tissue in bones, and supports blood clotting factors.
- **Selenium (Se)** – an antioxidant that boosts energy (ATP) production
- **Iron (Fe)** – key to red blood cell function, supports the immune system, involved in energy (ATP) production.

- **Amino Acids:**
  - **Glutathione** – an antioxidant that scavenges free radicals and heavy metals, and boosts energy (ATP) production.
  - **N-Acetyl Cysteine** – boosts **Glutathione** levels.
  - **L-Arginine** – produces Nitric Oxide naturally through the endogenous Nitric Oxide Synthase (NOS) system. By giving L-arginine exogenously as well, we can increase the L arginine to ADMA ratio and decrease tissue damage.
  - **L-Citrulline** – easily absorbed in the liver. L-Citrulline is converted to L Arginine and Nitric Oxide, thereby helping to maintain Nitric Oxide levels.
  - **L-Carnitine Tartrate** – (1) increases Nitric Oxide signaling, (2) improves endothelial function, (3) reduces oxidative stress (4) important as rate limiting step in fatty acid oxidation, that produces ATP, and (5) supports the metabolism of fat.
  - **L-Lysine** – Precursor to **L-Carnitine**, boosting **L-Carnitine** levels
- **Beet Root** – a potent, alternate, exogenous source of **N**itric Oxide promoting compounds that does not use the traditional Nitric Oxide Synthesis pathways that involve amino acids.
  - In the body, Nitric Oxide is generated quickly and dissipates quickly under normal situations. Systemically, Nitric Oxide increases endothelial function thereby enhancing exercise tolerance and lowering blood pressure. It is a natural Vassodilator and increases blood flow and circulation. **N**itric Oxide inhibits the oxidation of ("bad") LDL cholesterol into "Foam Cells" that are the precursors to atherosclerosis, as a result, it helps to reduce or lower atherosclerosis. Nitric Oxide also (1) kills bacteria, (2) enhances immune function, (3) aids neurotransmission, (4) decreases inflammation (5) may dilate bronchioles, (6) is an anti-thrombotic, (7) may promote better cerebral circulation, (8) increases Vagal (Parasympathetic) tone, (9) slows heart rate, and (10) lowers blood pressure. By increasing Parasympathetic tone, including slowing heart rate and lowering blood pressure, Nitric Oxide is therefore cardio-protective. However, it diminishes with age. By 60 years of age, we have lost, on average, 85% of our Nitric Oxide production abilities.