GLUTATHIONE

Your Best Defense Against Aging, Cellular Damage and Disease

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INTRODUCTION

Imagine a single item that could thoroughly clean your home, wash your clothes, purify the air you breathe, protect you against tainted food, and defend you and your family from a criminal attack.

While such an amazing entity doesn't exist in stores, it can be found in every cell of your body. It's a tripeptide named glutathione (pronounced *glue-ta-thigh-own*) and it is arguably the body's most powerful antioxidant. It was discovered more than a century ago, but still languishes in the shadows of mainstream medicine.

Glutathione functions as an antioxidant and an antitoxin, protecting us from the ravages of our increasingly toxic environment and our own foibles. In addition, it is a protector of our immune defense system and a promoter of efficient blood flow and production, yet it is not even mentioned in major clinical textbooks.

While some of us have been dependent on glutathione to detoxify the effects of "one too many," your family physician has probably never heard about its remarkable abilities. In fact, I would not have known of the importance of glutathione to health and the quality of life if my patients, problems hadn't encouraged me to study nutrition.

To explain the challenges I encountered in changing my approach to medicine, I'd like to share with you a brief glimpse of my journey.

First of all, glutathione was taught as a mere footnote, if at all, in my four years of rigorous medical school training. During internship, residency and fellowship training at prestigious medical establishments, I can honestly say that I do not recall hearing the word antioxidant, much less glutathione.

During my medical training and career, I spent 20 to 30 hours per week studying scientific and medical literature. Throughout two decades of exciting discoveries in academic medicine in the fields of Immunology and

Hematology, the terms antioxidant and/or glutathione rarely surfaced.

I might add that the generally held belief in mainstream medicine that nutritional supplements had few, if any, health benefits and were all hype, gave me little incentive to search "outside the box."

What then happened? In a word, my patients happened. While reviewing laboratory data on my patients, I encountered the same unusual laboratory anomaly (low uric acid) repeatedly. After months of noting it and dismissing it as a laboratory-generated error*, I decided to research its meaning.

After spending many hours on the database for the National Institutes of Medicine and the National Library of Medicine, called PubMed (www.pubmed.com), I discovered that uric acid was used in the body as "the last line of defense" when all other antioxidants had been expended.

If this represented the last line of defense, then, I wondered if there might be a "first line of defense," a primary or most important antioxidant in maintaining health and quality of life?

After many false starts and blind alleys in PubMed, an epiphany! I discovered **GLUTATHIONE**. At that time (1997) there were 66,000 literature citations concerning glutathione alone and not counting searches such as oxidative stress. At the time of this writing (Dec. 2007), there are more than 77,000 scientific studies in the English literature alone.

One might ask why glutathione's importance has remained so under-appreciated. I believe there are at least two separate but interrelated reasons. The first involves the fact that most articles on glutathione involve scientific research which most practicing physicians are just too busy to read.

**In medicine and science, as in life, we are all 'prisoners of our training' and tend to dismiss things we haven't learned and/or don't understand rather than embracing them as opportunities to expand our knowledge.*

The second reason can be found by examining the history of medicine.

Remember, nutritional supplements, including antioxidants, are largely dismissed by mainstream medicine perhaps because they were embraced first by practitioners of alternative medicine.* Whatever the reasons, an apt analogy to changing medical status quo would be like trying to make a 180-degree turn in a fully loaded oil supertanker - not easy or quick!

The history of medicine is littered with the contempt and in some cases, literal destruction, of those who dared to challenge prevailing medical wisdom. A few examples include Pasteur's radical theory that germs caused disease; Semmelweis' notion that hand washing could prevent the transmission of infections; and Baltimore and Temin's heretical concept that some viruses could be RNA and not just DNA as prevailing dogma dictated (think of HIV/AIDS). These groundbreaking discoveries brought their creators derision and professional ostracism.

Justice does eventually prevail. The ultimate result for Baltimore and Temin was the awarding of a Nobel Prize. Pasteur and Semmelweis are considered medical heroes for their discoveries and all of these discoveries are now considered intuitively obvious.

Is it glutathione's turn? Since mainstream medicine and federal regulatory bodies still largely dismiss the importance of nutritional supplements, I hesitate to predict. Read the following pages and decide for yourself! I believe glutathione will one day take its rightful place as the most powerful and life-sustaining antioxidant in the human body.

**There are multiple arbitrary divisions of medicine including: allopathic, osteopathic, chiropractic, alternative or complementary; homeopathic, naturopathic, etc. These divisions are a paradigm of the parable of the four*

blind men feeling and then describing an elephant. I have learned over the last quarter century that there is only one kind of medicine; ***THAT WHICH WORKS*** *and it encompasses aspects from all of the arbitrary divisions.*

JUST A NOTE

I have written this monograph for the interested novice. I apologize in advance if I slip occasionally into scientific jargon.

As I was trained as both a physician and research scientist, I would be remiss, however, if I didn't include sufficient information for the scientist, healthcare practitioner, nutritionist or anyone with a burning desire for more information. To that end, I have included a selected bibliography at the end of the monograph for each relevant section.

For those who wish more than the information contained herein, I invite you to visit my second home, the website of the National Library of Medicine: www.pubmed.com for further information. For all who read these pages, however, I hope you incorporate the information into your life as it will make a difference both now and in the future. I hope you enjoy reading my monograph as much as I have enjoyed writing it and incorporating the benefits from the information garnered into my life.

SECTION ONE
GLUTATHIONE: WHAT IS IT?

Glutathione is a tripeptide (3-amino acid protein-like structure) composed of glutamic acid, cysteine and glycine. Its chemical structure (makeup) is depicted in **Figure 1.**

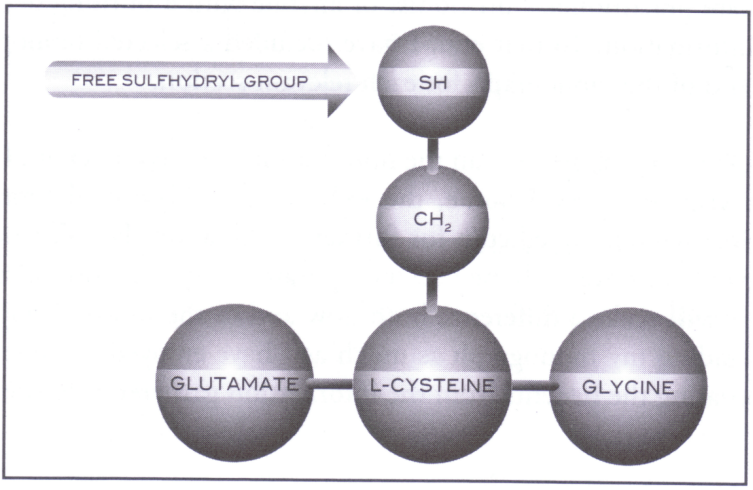

Figure 1-*Schematic of glutathione molecule adapted from J. Gutman, "Your Body's Most Powerful Healing Agent," G&SHealth Books, Montreal, Canada.*

Of the three components, cysteine is the most important. Cysteine limits the production of glutathione (rate limiting) and is considered a conditionally essential amino acid, meaning if the body cannot make enough; it must be ingested. It contains a sulfhydryl group (SH), which means it can easily donate an electron thus neutralizing (quenching) a free radical or interact with another molecule containing a sulfhydryl group.

The whole free radical quenching/electron donating process may sound complex but each of us has experienced this phenomenon. The smell of rotten eggs is the result of the same chemical reaction (oxidation). An eggshell is cracked and the sulfhydryl group (SH) of cysteine, one of the amino acids in egg whites, reacts with a free radical from the

environment and donates an electron, thus rebalancing (neutralizing) the molecule. The result of this reaction is, however, a very characteristic and unpleasant smell. Perhaps we should be thankful that we cannot smell the processes occurring continuously inside our body.

To simplify names, we shall call all oxidants free radicals, although the term Reactive Oxygen Species (ROS) and Oxidative Stress are essentially equal and interchangeable.

Glutathione is found in every cell of the body. It is particularly concentrated in the liver (detoxifier) and spleen (immune defense system) but the highest amount of glutathione is found in the skin (the largest organ in the body). Glutathione reaches concentrations that are thousands of times that of the commonly advertised vitamins such as C, E, and/or A.

It has multiple functions that include, among others:
Ferrying (transporting) proteins between cells and among the compartments of a cell.
Effectively detoxifying heavy metals, pesticides, food preservatives and environmental pollutants among others (Phase II Detoxification) after the liver initially detoxifies them (Phase I Detoxification) by changing them into FREE RADICALS. .
Activating the immune (defense) systems' Delta Forces (first responders) to attack the invader and protecting it from self-annihilation (free radical generation).
Regenerating a wide variety of other antioxidants.

Glutathione's major function, however, is as the MASTER ANTIOXIDANT

In fact, glutathione is:
• The most concentrated and important intracellular (inside the cell) thiol
• Low molecular weight
• Sulfhydryl-containing (primed to neutralize free radicals)
• Peptide (small protein)
• Found in all mammalian cells
• The most important free-radical trap (antioxidant) in humans

That is why I call it the most important antioxidant in your body and why, in a sense, it creates **FEAR** in the hearts, so to speak, of free radicals.

Glutathione exists in two basic forms: GSH and GSSG. The antioxidant (functional) or reduced form of glutathione is conventionally designated as "glutathione" and abbreviated chemically as "GSH."

The oxidized (spent or used) form of glutathione has been changed chemically into a second oxidized glutathione molecule and is designated as GSSG. The process of GSH neutralizing a free radical and then complexing with a second oxidized glutathione molecule is depicted in **Figure 2**.

This represents but one of the unique features of glutathione because all other antioxidants (except antioxidant enzymes) become free radicals themselves when they quench a free radical.

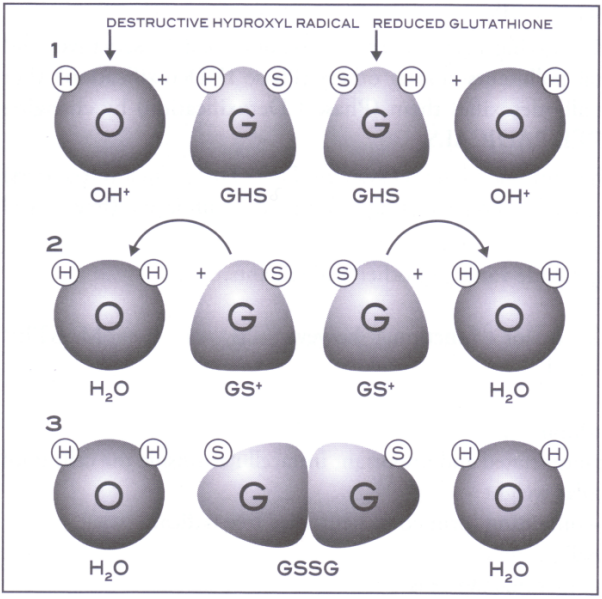

Figure 2- *Glutathione neutralizes the hydroxyl free radical, the most destructive in the body and then complexes with another used (spent) glutathione molecule. This process is unique as the used glutathione avoids becoming a free radical itself and the combined oxidized glutathione complex induces sleep. Adapted from Gutman.*

Other antioxidants, such as vitamin C, vitamin E and vitamin A therefore, need to be neutralized again. This may explain, at least in part, the need for multiple antioxidants creating a chain of reactions to neutralize free radicals in order to protect the body.

Glutathione, however, requires no such chain reaction and is found in all animals, plants and microorganisms. Its continued presence among such diverse living organisms, alone, suggests its vital importance as nature does not conserve anything that is not extremely useful. Glutathione is water soluble and is concentrated mainly in the water-containing parts of the body including the blood and most importantly, the cytosolic compartment of every cell.

The cytosol of a cell is its internal fluid where most cell metabolism occurs. You can imagine the importance of glutathione in cell cytosol to safeguard metabolic processes.

Glutathione concentrations are very tightly controlled, both within and outside the cell. A decrease in functional glutathione, GSH, signals the cell to produce more enzymes which synthesize glutathione and glutathione peroxidase. (Glutathione peroxidase is an enzyme requiring glutathione that detoxifies hydrogen peroxide and organic peroxides.) If glutathione levels begin to reach a maximum concentration inside the cell, enzymes are synthesized to transport excess glutathione into the blood (plasma).

Finally, if too much of the intracellular glutathione is in GSSG or the oxidized state (in youth, 90 percent of glutathione exists as GSH) enzymes are produced/activated to regenerate reduced glutathione (GSH). This is described in **Figure 3** and is a common occurrence in the liver, the organ with the highest per cell concentration of glutathione.

While providing itself with sufficient GSH to function as the detoxifier (washing machine) of the body, the hepatic (liver) parenchymal cells export GSH to the plasma where it serves to quench free radicals and neutralize toxins and heavy metals in the blood.

Although there are rare genetic abnormalities where glutathione may reach potentially toxic levels, under normal conditions, elevated (harmful) levels of GSH are a physical impossibility.

On the other hand, there are a number of genetic abnormalities which make it difficult for the body to maintain normal glutathione levels. These difficulties in synthesizing sufficient glutathione have been linked recently to cases of Tylenol poisoning, where small, “safe” doses of acetaminophen in conditions of nausea and vomiting resulted in liver failure and death.

The importance of adequate levels of glutathione to life cannot be denied and should not be underestimated. Jean Carper, in her book, *Stop Aging Now* states “you must get your levels of glutathione up if you wish to keep your youth and live longer.”

Dr. Earl Mindell in his book, *What you Should Know about the Super Antioxidant Miracle*, said this about glutathione: "We literally cannot survive without this miraculous antioxidant.” The ultimate proof of the importance of glutathione to life, however, may be the experimental studies demonstrating that an absence of glutathione is fatal.

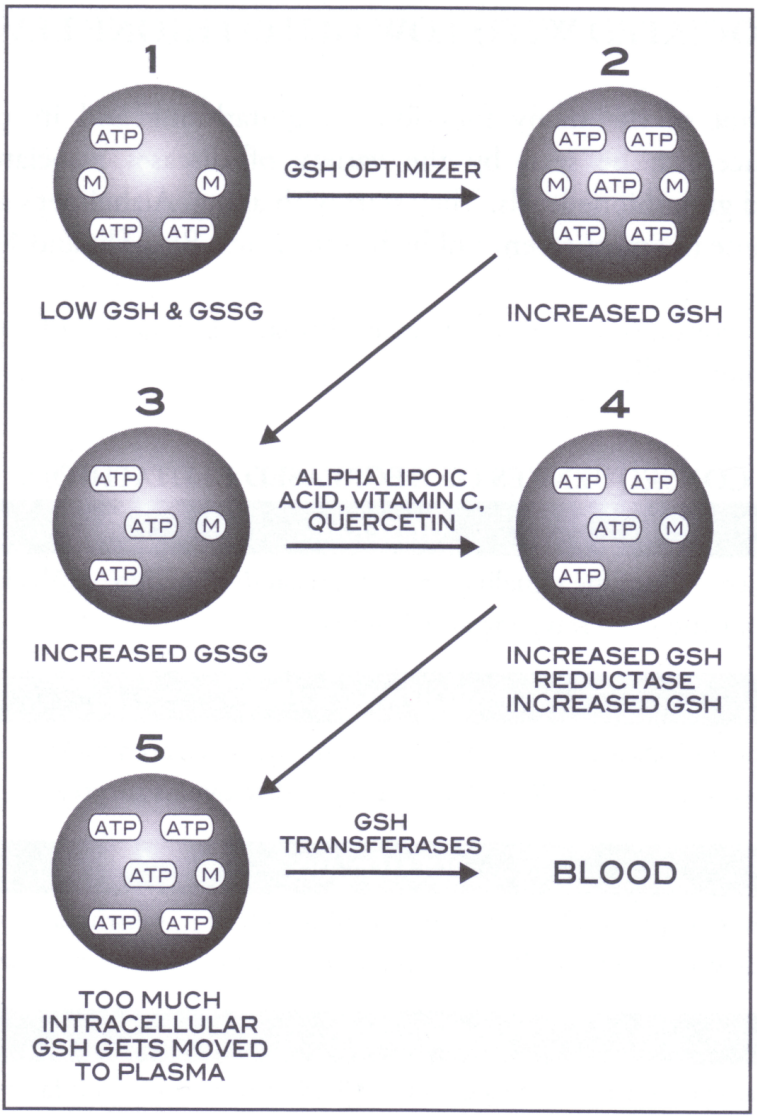

Figure 3-*The sequential steps in the production, function, regeneration and cellular control of glutathione in the presence of the patented glutathione optimizer.*

SECTION TWO
MEDICAL CONDITIONS
ASSOCIATED WITH LOW GLUTATHIONE LEVELS

A snapshot of the many functions of glutathione and its potential importance can be seen by the variety of diseases associated with decreased glutathione levels. They start with aging, Alzheimer's and acne and include the most recent public health scares, Bird Flu and MRSA.

Table 1 contains a list of diseases impacted because of decreased glutathione levels.

CONSEQUENCES OF DECREASED GLUTATHIONE

GENERAL
• Obesity • Immune signaling • Endothelial dysfunction • Alcoholism • Inflammation • Heavy metal poisoning
CARDIOVASCULAR
• Angina and spastic angina • Unstable angina • Heart attacks • Positive stress tests • Reperfusion after cardiac bypass surgery
PULMONARY
• Emphysema (COPD) • Pulmonary Fibrosis (IPF) • Asthma • Muscle wasting in COPD • Chronic bronchitis • Tobacco abuse
NEURO/PSYCH
• Migraine headaches • Alzheimer's • Parkinson's • Multi infarct dementia • Autism • ADHD (Attention Deficit Hyperactivity Disorder) • Bipolar disease • Schizophrenia • Lou Gehrig's disease • Huntington's chorea • Multiple Sclerosis (MS) • Depression
OPTHAMOLOGY
• Cataracts • Macular Degeneration

Table 1

INFECTIOUS DISEASE/IMMUNOLOGY
• Hepatitis A, B, and C • Herpes simplex • Herpes zoster/shingles • Influenza and Bird Flu • HIV • MRSA • Common viral infections (upper respiratory, gastroenteritis) • Others
RHEUMATOLOGY
• Systemic Lupus Erythematosus (SLE) • Rheumatoid arthritis (RA) • Multiple Sclerosis (MS) • Systemic Sclerosis (Scleroderma) Syndrome • Behcet's Syndrome • ME/CFS • Fibromyalgia • Others
DERMATOLOGY
• Wrinkles, sagging • Acne • Psoriasis • Atopic dermatitis • Eczema • Others
ONCOLOGY Every cancer studied including:
• Brain • Head and neck • Thyroid • Lung • Esophagus • Stomach • Intestine • Liver • Pancreas • Kidney • Uterine • Ovarian • Prostate • Leukemia (acute and chronic) • Lymphoma • Multiple myeloma • Others
OB/GYN
• Infertility • Spontaneous abortions • Pre Menstrual Syndrome

Table 1 (continued)

Unfortunately, reduced glutathione levels in these many diseases does not prove a causal relationship between decreased glutathione and disease onset and/or progression as science demands a cause and effect relationship.

Other than acetaminophen (Tylenol™) poisoning and cystic fibrosis, few scientifically rigorous studies have demonstrated that increasing glutathione levels will improve the outcome of any disease or clinical condition. This knowledge gap will be discussed further in a subsequent section.

You might question why glutathione has not been studied more intensely in the treatment of disease. It is my personal opinion that the failure of the pharmaceutical industry to create a glutathione-elevating drug to date and their inability to patent naturally occurring substances for use as drugs have effectively persuaded "Big Pharma" not to fund the expensive but mandatory cause and effect studies.

On the other hand, FDA regulations banning nutritional companies from making health claims (i.e. that a nutritional product improves any clinical disease) provide little incentive for conventional nutritional companies to fund such costly studies.

The Effects of a Glutathione Shortage

To understand the importance of glutathione and why I am so excited about bringing its amazing importance to a larger audience, I want you to know about the devastating consequences of reduced glutathione levels:

- Without glutathione, every cell in your body would die prematurely from its own waste products
- Without glutathione your entire defense (immune) system would surrender to the first virus you encountered and cease to function
- Without glutathione, your liver, which cleanses all the toxins you ingest or inhale and acts as a washing machine, could no longer cleanse any poison or toxin, as glutathione is, in a sense, the detergent for the washing machine
- Without glutathione (and I mean a *complete* absence) oxygen-based life (us) would be impossible

Reviewing this list of conditions impacted by decreased levels of glutathione may give you a deeper appreciation for all it does to preserve and support health.

SECTION THREE
FREE RADICALS, OXYGEN AND GLUTATHIONE

In order to comprehend the function of glutathione as the body's master antioxidant, I believe it is important to understand the nature of a free radical or oxidant, where they are created and the damage they cause.

A free radical is a molecule that is chemically unstable because it is missing an electron. Or put more simply, it is unbalanced. This creates a problem as your body will not tolerate anything unbalanced.

All free radicals are extremely reactive chemically, meaning they are in a heightened energy state. They will seek out and acquire an electron at any cost to reduce their energy state. They represent a prime example of "robbing Peter to pay Paul," since when they steal an electron from another molecule, that molecule itself becomes a free radical and is damaged. Free radicals are capable of damaging and thereby changing the structure of every bio-molecule in your body.

A few examples of these include:

- Damaging the lipids (fats) in blood vessel walls, resulting in arterial hardening or stiffening, hypertension (high blood pressure), heart attacks and strokes
- Damaging DNA, the blueprint of the body leading to mutations (changes) that promote aging and cancer
- Damaging the synovial producing cells in joints (chondrocytes) resulting in arthritis
- Damaging proteins which results in Advanced Glycation End products (AGE), producing age spots, wrinkling and sagging (elastin damage) in the skin alone

The major free radicals produced include:

- Superoxide
- Hydroxyl
- Hydroperoxyl
- Alkoxyl peroxide
- Nitric oxide

In addition, other molecules are produced which function as free radicals. They are chemically different but produce similar damage and include:

• Singlet oxygen • Hydrogen peroxide
• Hypochlorous acid (better known as bleach)

As you know, both hydrogen peroxide and bleach are used to clean cuts and clothes respectively. Imagine their effect on the delicate structures of the cells of your body!

Given their potentially damaging characteristics, one might question why free radicals exist. The answer is simple. Like the Energizer Bunny, we need a source of energy to function. In fact, simply reading this monograph is creating millions if not billions (if you are really concentrating) of free radicals, which must be quenched in order to perform future activities.

Think of your computer. It functions on energy, but it loses up to one half of the energy as heat. In a simplistic sense, the energy created by your cells is ATP and the heat generated (inefficiency or oxygen loss) to produce the energy is the free radicals.

Imagine the consequences if your cells were as inefficient as the computer. The damage produced during the thousands of energy producing (ATP) reactions in each cell every second would be devastating to the function, if not the very existence of the cell.

There are numerous studies that validate this concept. They involve comparisons of the Maximum Life Span Potential (MLSP)* of various animal species as well as humans. They reveal that MLSP is inversely correlated strongly with mitochondrial damage. Stated simply, this means that the more the mitochondrial damage, the shorter the lifespan.

Although these studies involve comparisons among different species of animals, other studies strongly support the concept that the greater the mitochondrial damage, the shorter **OUR** lifespan.

**The MLSP for humans is calculated to be 122 years.*

There are four primary sources of free radicals in humans and in every other living organism:

1. Mitochondrial energy production
2. Hepatic (liver) detoxification
3. The immune system
4. Metabolizing (chemically changing) the fats we eat

Mitochondria and Free Radical Production

The first and most abundant source of free radicals that occurs during normal life is the generation of energy (ATP) within the mitochondria (energy producing factory) of each cell. In fact, there are tens to thousands of these energy factories in every cell of the body and they are most prevalent in the energy using organs of your body, the brain, the heart and the liver.

Mitochondria account for up to 90 percent of the bio-energy your whole body creates. They use oxygen as well as chemicals produced in the body from the food you ingest to produce energy. The actual biochemical processes are quite complex although we will discuss a simplified version later.

As an analogy, however, it is similar (although not completely accurate scientifically) to the computer mentioned above. The computer battery produces electricity, which powers the computer and the ATP produced by the mitochondria powers each cell. The loss of energy (heat) determines the efficiency of the computer and the loss of oxygen during the mitochondrial ATP production results in free radicals (burning substances) and determines the efficiency of the cell.

Thank God we are not computers. The computer loses up to 50 percent of its energy as heat, but our cells lose only a very small amount (1-3 percent) as lost oxygen (free radical production) while we are young and healthy.

Unfortunately, this oxygen loss results in the production of superoxide and subsequently hydroxyl and peroxide free radicals. Perhaps even more

unfortunately, these free radicals are the ones which inflict the most damage to the very structures in the mitochondria which are responsible for replenishing the chemicals in the energy (ATP) producing factory.

The Liver and Free Radical Production

A second major source of free radicals is the liver. As mentioned previously, the liver functions as the detoxifier for substances which include, but are not necessarily limited to those depicted in **Figure 4.**

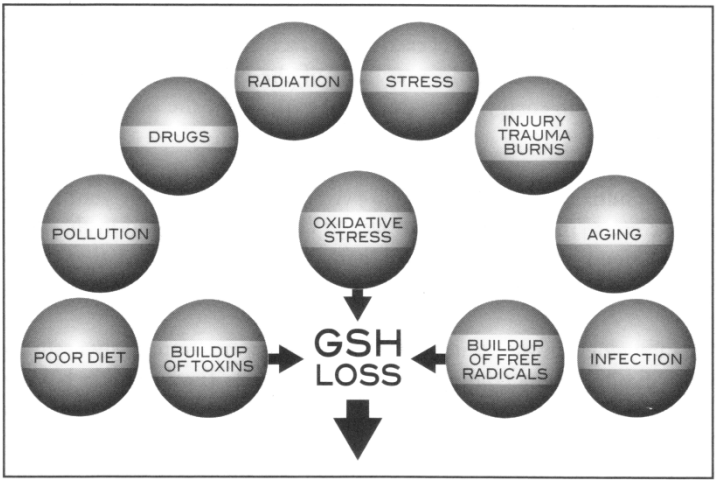

Figure 4-A partial list of the physiologic, pathologic processes and the life choices which deplete glutathione. Expanded from Gutman.

The liver functions in a two-step process. The first (called Phase I Detoxification) involves a group of enzymes collectively called the Cytochrome p45O system which accepts the offending agent and converts it to an intermediate substance.

The problem is that this intermediate substance is itself; a FREE RADICAL. A common example of this process is the detoxification of alcohol. In the first step, the alcohol is converted to acetaldehyde, similar chemically to formaldehyde (embalming fluid).

Unfortunately if the liver is overwhelmed by "one too many," the acetaldehyde lingers and the result is commonly termed a "hangover." The process of detoxification of alcohol is chemically depicted below in **Figure 5.**

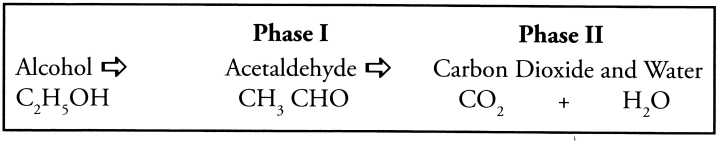

Figure 5 *- Alcohol Detoxification*

Detoxifying Stages

The second step (called Phase II Detoxification) involves a number of enzymes. It is distinguished by two facts. The primary function of Phase II Detoxification is the conversion of the free radicals to useful or harmless water-soluble substances and this process is **dependent** on available glutathione.

Inadequate function of either of these steps (failure of GSH dependent Phase II is much more common) results in the accumulation of poisons within the cells which further decreases mitochondrial energy production.

The Immune System and Free Radicals

The third source of free radicals is again, a by-product of a function essential for life, your immune (body defense) system. In fact, members of your defense system called macrophages or phagocytes (part of the

Delta force or first responders) actually produce a variety of free radicals to attack germs (bacteria, viruses, parasites) as depicted in **Figure 6.**

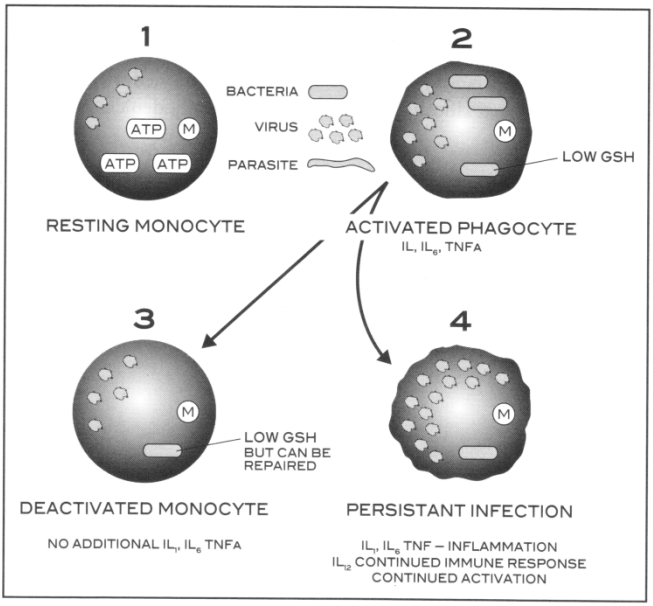

Figure 6 *- Immunologic activation by foreign substances causes production of inflammatory cytokines and expends GSH and energy. If invaders killed, system becomes quiet. If invader persists, continued expenditure of GSH and energy (ATP) and persistent inflammation.*

In limited circumstances, this is beneficial as it begins the process of immune activation which ultimately destroys the invader. When the invader is destroyed a number of negative feedback mechanisms are then activated which return the system to a quiescent or balanced state. Consider, however, a state of chronic immune activation such as HIV, other chronic viral infections, prolonged stress or even a lack of adequate sleep.

Continued activation of the defense system produces a literal storm of free radicals resulting in more and more collateral damage to the cell structures including the mitochondria.

It is little wonder, then, that glutathione levels have been reported to be an independent predictor of outcome in HIV/AIDS and that a nutritional containing a patented glutathione enhancement technology has been shown to actually improve the defense system (CD4 Helper T Cell numbers) and reduce the enemy (HIV viral activity) in HIV/AIDS.

Metabolizing Fats and Free Radicals

To be complete, the fourth source of free radicals involves organelles (little cells), called peroxisomes, which degrade fatty acids (do you really want that Big Mac?). This process is called lipid peroxidation. It will be discussed later in the following section on glutathione's protection of mitochondrial DNA damage.

SECTION FOUR
GLUTATHIONE - THE MASTER ANTIOXIDANT

The public has been bombarded regarding the importance of antioxidants such as vitamin C, vitamin E, vitamin D3 and a plethora of others in foods and nutritional supplements. All of them are important, but pale in comparison to those your body creates every day.

These internally produced (endogenous) antioxidants, although few in number, are far more powerful and in the case of glutathione, far more prevalent (higher in concentration) than anything we might ingest.

There are just four main endogenous antioxidants:
- Glutathione
- Superoxide dismutase
- Catalase
- Coenzyme Q 10 (CoQ10)

Of these antioxidants, multi-talented glutathione reigns as the king (or queen) of antioxidants.

Why Do We Need Antioxidants?

Think of a fire in a fireplace. It warms you up with its heat and brightens your mood as the flames dance among the logs. In a real sense, the process is akin to mitochondrial energy production. The logs are the fuel (food); the dancing flames are similar to the electron transport chain creating energy and the ashes are the free radicals produced. Now imagine how delightful it would be to have the warmth of the fire and the dance of the flames without the annoyance (damage) of cleaning out the ashes the next morning.

Although not totally analogous, the major function of glutathione is to clean up (neutralize) the free radicals (ashes) and prevent damage to adjacent molecules (the logs). There were many cold mornings in Minnesota and Wisconsin when I wished for the log-preserving, ash-preventing "fireplace glutathione."

Another example, although far less whimsical and with far more serious implications for health and life, is cigarettes. In fact, smoking is the number one preventable cause of a shortened life span in humans (8 fewer years of life for a smoker) and is associated causally with a variety of life-threatening diseases.

As with the fire in the fireplace, smoking one cigarette produces billions, if not trillions, of free radicals. In addition, cigarettes contain numerous carcinogens (cancer-causing substances) and finally, smoking inflames the lining of the breathing tubes of the lung (bronchitis).

In today's environment, however, one does not need to smoke to sustain this damage. Second-hand smoke as well as other volatile pollutants from household and industrial chemicals, car, truck and airplane exhaust among others, produces a similar, if less intense, effect.

One must question, however, how much is enough to produce disease? The answer, unfortunately, is quite variable and depends on both genetics (nature) and lifestyle habits (nurture). As a result, smoking cigarettes is very similar to playing "Russian Roulette" with your life and being unaware of how many chambers in the gun are loaded.

One factor reported to offer some protection (in human and animal studies) against the damage caused by cigarette smoke is elevated lung glutathione levels. Studies have demonstrated that N-acetyl cysteine (NAC), a glutathione-promoting supplement, which will be discussed in detail in a later section, reduces the pulmonary (lung) and systemic damage caused by exposure to cigarettes.

As an interesting side note, in 1994 during tobacco litigation, the five major cigarette companies incorporated the glutathione-precursor ingredient N-acetyl cysteine as the 599th additive to tobacco in cigarettes.

One can but speculate on the health effects of never starting or quitting smoking AND nutritional supplementation with glutathione-promoting substances.

Glutathione a Totally Unique Antioxidant

What then distinguishes glutathione from all of the other antioxidants? I believe the answers include the following:

Regenerative abilities for itself and other antioxidants
Antioxidant capacity (the most concentrated intracellular antioxidant)
Generation of and an integral component in the chemical structure of antioxidant enzymes (glutathione peroxidases, glutathione transferases)
Energy (the amount used by cells to continually synthesize, monitor and maximize intracellular glutathione concentrations)

This represents another suitable acronym. When the components of **RAGE** and **FEAR** are combined, the diverse functions and power of glutathione can begin to be understood. It must be emphasized, however, that the individual

components of both **RAGE** and **FEAR** are physiologically interdependent and work as a team to quench free radicals and prevent damage.

One could argue that its position as the most prevalent (concentrated) antioxidant in the human body, alone, would crown it as the MASTER ANTIOXIDANT. Science, however, demands proof not logic. Of course, absolute scientific proof is beyond the realm of experimental possibility but the following unique characteristics of glutathione in the antioxidant universe offer additional strong evidence of its primacy.

- GSH is the most concentrated intracellular antioxidant.
- More than six percent of the total energy (ATP) production of the whole body may be used to synthesize and regulate intracellular glutathione levels.
- GSH, alone in the antioxidant world, regenerates (recycles) directly and indirectly a variety of other antioxidants including vitamin C, alpha lipoic acid, vitamin E and vitamin A. This is described in **Figure 7.**
- GSH is the only non-enzyme antioxidant that does not itself became a free radical after it has quenched a free radical.

• GSH not only acts as a multifunctional antioxidant itself but is an essential component of antioxidant enzymes including glutathione peroxidases and the genetically determined family of glutathione transferases.

There are more enzymes involved in the regulating of intracellular glutathione concentration than for any other antioxidant.

The preceding represents additional strong circumstantial evidence for Glutathione's supremacy but still falls short of absolute proof. Perhaps an even more convincing argument for GSH as the Master Antioxidant derives from its function as an integral protector of the mitochondrial energy (ATP) factory, the Electron Transport Chain (ETC).

Although this is a very complex molecular biologic concept, I believe a basic understanding is critical to grasping the importance of glutathione. I apologize, in advance, however, it if proves to be too complex and/or technical for the reader.

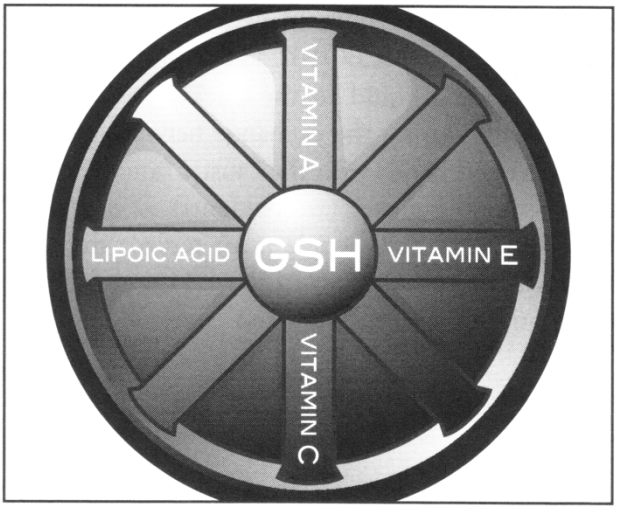

Figure 7*-A depiction of the antioxidant-regenerating capacity of glutathione.*

The (Rather Complicated) Energy Cycle

The (OXPHOS) Electron Transport Chain is composed of a series of enzymes that pass oxygen and three products from the food we eat (TCA or Krebs cycle) through a series of five enzymatic reactions which ultimately generate energy.

Think of it as a bucket brigade passing pails of liquid down a chain of people. It is an amazingly efficient process (while cells are healthy) as it "spends" only four molecules of ATP to generate thirty-two ATP molecules. That represents as eight hundred percent return on investment (ROI); a feat rarely achieved in the stock market or any other investment.

This efficiency, however, depends on protecting and perhaps more importantly, replenishing the components of the Electron Transport Chain (the people in the chain). The mitochondria (which produce energy) are bombarded by a continuous storm of the free radicals produced by the chemical reactions in the ETC and are damaged even in the presence of adequate antioxidants, GSH, superoxide dismutase (SOD) and coenzyme Q 10 (CoQ10).

This is analogous to the liquid in the bucket passed along the chain being caustic; spilling during the exchange between people (ETC) and burning their arms and hands with the caustic liquid (free radicals) even though they are wearing gloves (antioxidants). When they are burned too severely to function, new people must replace them in the bucket brigade. Similarly, the components of the ETC must be replaced. And that's where we run into a problem.

Fragile DNA?

Regeneration of the ETC components and, in fact, the very mitochondria, themselves, depends totally on a unique form of DNA, called mitochondrial (mt) DNA. This unusual DNA was appropriated by humans in their formation and is passed on only by the mother. It differs from your cellular DNA, the blueprint for new cells, in two important ways.

First, cellular DNA contains two strands of complementary base pairs (DNA strands) but mtDNA contains only a single strand. As a result, it is more susceptible to damage.

Second, and equally, if not more important, cellular DNA has developed multiple defenses against free radical damage but these protections are absent or have not yet developed in mtDNA.

As a result, mtDNA, the factory for the components of the ETC (replacements for those burned in the bucket brigade), is subject to massive damage from the very components (ETC chemical reactions) it produces. In fact, mtDNA in biopsies from 90 year olds compared to 5 year olds, reveal that only 5 percent of the mtDNA in the 90-year-old specimens is normal.

In youth, mitochondria divide (replicate) when needed in order to produce (replenish) new ETCs components (replacement people for the bucket brigade). As we age, and free-radical-induced injuries (burns) accumulate, the mtDNA is damaged, the mitochondria cannot divide and new ETC cannot be formed. With injured (burned) people in the chain (ETC) there is a progressive loss of efficiency (more free radical formation) and a progressive decrease of ATP (energy) production.

During ETC reactions, superoxide is the first free radical produced. Unfortunately, in the process of quenching it, the antioxidant enzyme superoxide dismutase (SOD) converts it to a hydroxyl group (OH) and

hydrogen peroxide (H_2O_2), both of which are themselves, free radicals. Worse still, it is these obligate if unfortunate products of energy (ATP) production (OH and H_2O_2) that do the most damage to mtDNA.

Thus in the very process of performing its job, the ECT unwittingly damages the mtDNA on which the very existence of present and future mitochondrial energy production and the future health of the mitochondria, themselves, depend. This process is, indeed, a paradigm of self-destructive behavior.

Fortunately, however, nature has countered with the perfect antidote, **glutathione.** Not only does glutathione efficiently and effectively quench hydroxyl free radicals thereby protecting mtDNA but by neutralizing hydroxyl and peroxide radicals, it prevents them from interacting with other molecules and creating a host of other free radicals including peroxynitrite, and oxidized lipids (fats contained in cell membranes and the plasma).

Think of a stone tossed into the pond as the hydroxyl radical and the inevitable series of ripples produced by the stone as the variety of other free radicals produced. Glutathione neutralizes the stone (hydroxyl radical) before it can cause damage to the mtDNA or any other molecule.

In addition, glutathione as an integral component of glutathione peroxidase (an antioxidant enzyme) quenches the peroxide free radicals formed and prevents the secondary waves (other free radicals) produced, similar to the result of the stone's displacing water.

Glutathione and glutathione peroxidase (Gxp) act in combination, to prevent any damage to the mtDNA caused by the ETC free-radical production (inefficiency) and preserve the viability and of present and future mtDNA, which is solely responsible for producing the components of the Electron Transport Chain.

Glutathione and glutathione peroxidase also prevent the collateral damage to proteins and lipids caused by the hydroxyl and peroxide radicals producing other free radicals. This later process includes lipid peroxidation which has been demonstrated to be a major factor in the development of heart disease.
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"Convincing" Proof

Other proof of glutathione's importance to the quality and perhaps even the length of life comes from a number of experimental and observational studies that demonstrate the following:

- GSH levels decrease with age
- GSH is better maintained in well (healthy) subjects compared to ill subjects independent of age
- Although GSH decreases with age, subjects who reach 100 years of age have higher concentration of GSH than any group except young (20 to 30-year-old), healthy adults
- Calorie restriction, the only proven technique to prolong life (in animal studies) is correlated with increased levels of GSH
- Increased GSH is associated with increased phase III mitochondrial reactivity (increased ATP production) required for sustained physical and/or mental activity
- Decreased GSH is associated with increased phase IV and decreased phase III mitochondrial activity (phase IV produces reduced or maintenance levels of ATP) associated with being sedentary, inactive or stated simply a "couch potato." Perhaps you should consider this when your health care practitioner tells you that your age is the reason you can no longer perform a physical activity which you excelled at in your youth
- N-acetyl cysteine and alpha lipoic acid, both of which individually and collectively increase GSH, increase ATP production, reverse the inability to maintain phase III mitochondrial activity associated with the decreased

GSH levels in aged or ill subjects and have been reported to even reverse mtDNA damage and increase SIRT1 , the gene associated with anti-aging that was discovered in the animal caloric restriction studies.

Of course, none of the above scientifically proves beyond a shadow of a doubt, the primacy of glutathione in the universe of antioxidants. Nonetheless, there is overwhelming evidence that glutathione is, in fact, the reigning monarch of antioxidants and lends credence to the title of Dr. Earl Mindell's book on glutathione: *What You Should Know About the Super Antioxidant Miracle.*

SECTION FIVE
GLUTATHIONE: METHODS TO MAXIMIZE GSH LEVELS, HEALTH AND LIFE

Before discussing foods or supplements that will raise your glutathione levels, a word to the wise is in order. Consuming all the glutathione-containing or producing supplements listed in a "Google search" will not fully cancel the effects of poor lifestyle choices and/or habits.

I would be negligent if I didn't briefly mention the major areas involved in good lifestyle habits. There are, of course, many others that are very important, but they are beyond the scope of this monograph. The major ones, I submit, are:

- **Good sleep**
- **Good nutrition**
- **Exercise**
- **Good hydration**

As there are countless articles and books written on these subjects to which the reader is referred for more information, they will be discussed but briefiy. There may be some disagreement in rank ordering them, but there is little argument scientifically about their vital and preeminent importance.

My grandmother, whom I called Oma and who was a natural, if untrained, immunologist, termed sleep "God's good medicine." It is of paramount importance in maintaining the well-being (balance) of all

living organisms. For humans, this requires an appropriate amount of uninterrupted sleep. Textbooks define the appropriate period as eight hours during youth and less as we age.

Except in children, however, this is counterintuitive, as aging should generate more, not less, damage to repair (think of sleep as the period when your body eliminates the damage created from the environment, your daily activities and the stresses of the day).

I would choose to offer another definition of "a good night's sleep," which is not based on time. It involves two requisites; first, awakening refreshed, alert and ready for the day **without an alarm clock** and second, remembering your dreams. Although it would require volumes to explain and validate these requisites, the data does exist to support both concepts.

Thus, rather than a statistical average (8 hours), each person can decide for themselves if their body had sufficient sleep to repair yesterdays damage and restore their body's balance **(aging is related directly to your cumulative sleep deficit).**

A second major foundation of good health involves nutrition. In this day and age, when we are bombarded by functional food ads (milk with omega 3 fatty acids, yogurt with added probiotics (good bacteria), etc.) one would think our nutritional habits and health should be improving. Given the marked increase in the prevalence of obesity and type II (adult onset) diabetes, among others, however, the data would suggest that our "love affair" with fast food, the proliferation of energy drinks (like Pepsi Max and Red Bull to counter the effects of fatigue or decreased energy production), and many other factors have resulted in poorer, not improved, nutrition compared to previous generations despite the statistical increase in our average lifespan.*

Suffice it to say that poor nutrition results in inflammation (increased free radicals) in your intestines and has been implicated causally in every disease of aging. In addition, detoxifying the preservatives, hormones, antibiotics and pesticides in foods generates increased free radicals, increased work for your liver and decreased glutathione levels. (Remember the studies on glutathione and lifespan.)

Finally, in an engine that requires premium fuel (the cells of your body) to function maximally (Phase III mitochondrial ATP production), imagine the effect of less-than-ideal fuel.

**The US population has one of the shortest average lifespan of all industrialized countries despite the fact that the US per capita health care expenditure is twice that of most industrialized countries.*

A little discussed, but important example of this problem is the R value of proteins. The R value refers simply to the percentage of the protein that is absorbed in a form that can be used by your body. The R value of undenatured whey protein and egg white is 1 (100% usable). The R value of a rare or medium filet mignon is between .7 and .6 (70-60% usable). Would you care to guess the R value of a Big Mac? Perhaps this should be considered the next time you "fill up" to empower your body.

Another critical element to your health and quality of life is exercise. I believe a simple, but perhaps not easy, way of remembering its importance is a phrase that was repeated frequently during my medical training. Use it or lose it.

In fact, this holds true not only for muscle and joint strength and flexibility as we age, but for glutathione protection itself. Prolonged intense physical activity has been reported to decrease glutathione levels. For instance, decreased glutathione levels and weakened immune function (protection) have been reported in marathon runners. Moderate exercise for 30 minutes to an hour spread over the day, on the other hand, actually increases the enzymes (GSH synthetase, GSH reductase, ere.) responsible for producing and recycling glutathione.

Again, the articles and books on the importance of exercise to health are legion. Sadly, the simple relationship of exercise to glutathione levels is rarely included.

Finally, I would be remiss if I didn't mention the importance of good clean hydration (water) to your health. Remember your body is more than ninety percent water and the very function of every cell in your body depends on maintaining adequate internal fluids.

A good analogy is the difference associated with starting a car on a winter morning in Minnesota compared to Florida. In one case, the water molecules are compressed (reduced functionally), the oil (plasma, intracellular fluid) is thickened and the car (your body) rarely starts smoothly.

In the other case, the water molecules have expanded (comparatively) the oil is slippery and the car responds immediately. Although not precisely similar, your body is a biomechanical machine and lubrication is of great importance to its smooth function.

Were that not enough, there is one other factor (probably many more) that requires consideration when discussing hydration and water. It is clear that the increasing consumption of bottled water is contributing significantly to global warming, creating environmental pollutants (plastic manufacturing, transportation) which increases the work of your liver and glutathione in detoxifying them. It is equally clear, however, that global warming contributes to acid rain, the main source of municipal water, and that municipal water treatment with chlorine, fluoride and probably many other chemicals that aren't divulged also increase the work of hepatic detoxification and produce a glutathione deficit. This is a proverbial "Catch 22." I have no answers but will end simply with the admonition "*Caveat Emptor*" (let the consumer beware).

Pure Foods?

A major, if not the primary reason, for mainstream medicines dismissive attitude towards nutritional supplements is the generally held belief that all of the requisite factors (including vitamins and antioxidants) required for health can be obtained from food.

In a perfect world, I would agree completely. Organically raised, properly harvested, locally grown and properly prepared food remains the quintessential source for everything your body needs to function maximally

As you examine the sentence above, however, the number of red flags included should alarm you as the conditions above represent the ideal not, I submit, practical reality. Again the number of less than "ideal" factors introduced into the food chain during the production, transportation and packaging of food, not even counting the vagaries of preparation, is legion.

As a result, only a few of the more particularly harmful practices that adulterate our food will be mentioned. They include but are not limited to; hormones and antibiotics used in raising animals; pesticides and other chemicals used to improve crop yield; the incredible amount of environmental pollutants including diesel fuel exhaust which produces xenoestrogens (man-made estrogens that mimic the effects of natural estrogen) produced during transportation; and our increasing practice of packaging food in plastics, which by their very composition and/or their interaction with foods produce additional xenoestrogens.

Think of buying a fresh, moist, delectable appearing package of blueberries, which are rich in antioxidants (actually blackberries and strawberries have more antioxidants). Now consider that they were probably grown in pesticide-contaminated soil and were genetically modified to improve crop yield; transported thousands of miles producing tons of diesel fuel exhaust and other pollutants and packaged for presentation on the store shelf in plastic.

Imagine the work involved in detoxifying all of the negatives (pesticides, environmental pollutants, and xenoestrogens, among others) by your liver and the attendant reduction of glutathione, the master antioxidant, in achieving this feat, before your body can enjoy the antioxidant benefits of the blueberries. Given the above, I cannot but wonder if this is even a zero sum game.

I believe scientific examination of the negative (oxidant producing) aspects of food production suggests strongly that foods alone cannot provide the requisite antioxidants, vitamins, etc., necessary for "good health."

Despite those problems, foods still do supply the bulk of the components (including antioxidants) required for both the maintenance and health of our bodies as the alternative would require hundreds, if not thousands, of pills and/or capsules (both of which have their own negatives) per day.

As a result, no monograph on glutathione would be complete without

mentioning foods that are rich in glutathione (remember it is largely destroyed in the stomach and intestine) as well as the foods rich in the component amino acids (glutamine, cysteine, glycine) required for the cells in your body to produce (synthesize) glutathione.

Given all of the problems with our food supply, however, I believe a discussion of glutathione producing/promoting supplements and their relative advantages and disadvantages is warranted as I believe they are necessary for "good health." Finally, I would beg the reader's indulgence to create, using the available scientific data, an ideal glutathione producing/promoting supplement.

The wide variety of foods containing glutathione itself or the component parts (the amino acids glutamine, cysteine and glycine) are listed in **Table 2**. It is important, however, to mention the problems with ingesting these foods and expecting increased glutathione levels.

FOODS CONTAINING GLUTATHIONE AND GLUTATHIONE COMPONENTS

CHEMICAL	FOOD SOURCES
Glutathione	**Animal sources:** red meat (fresh),fish, poultry **Vegetable sources:** fresh and frozen fruits: blackberries, strawberries, blueberries, leafy green vegetables (raw or steamed), particularly asparagus, avocados and nuts (walnuts)
Glutamine	**Animal sources:** meat, fish, poultry, milk, eggs, yogurt, whey protein and cottage cheese **Vegetable sources:** beans, spinach, parsley, cabbage
Cysteine	**Animal sources:** eggs, milk, whey protein, yogurt, cottage and ricotta cheeses, pork, sausages, poultry and lunch meats **Vegetable sources:** red peppers, garlic, onions, leeks, broccoli, Brussels sprouts, granola and wheat germ
Glycine	**Animal sources:** meat, poultry, fish, milk, eggs, yogurt, whey protein, ricotta and cottage cheeses **Vegetable sources:** leafy green vegetables, legumes

Table 2

Glutathione, itself as a tripeptide, protein-like structure, is very efficiently disassembled by a powerful one-two punch from your body. The first involves the production of hydrochloric acid (HCI) from your stomach. It has a pH below 3, would burn through your finger if you spilled it, and effectively breaks the bonds between the amino acids of glutathione similar to its action on the proteins (amino acids) of your skin.

Even though the production of hydrochloric acid decreases significantly with age, along with the protein necessary to absorb vitamin B12 (remember Phase III and Phase IV ATP production), glutathione is still, at least partially, destroyed by hydrochloric acid even in old age or illness. If the HCI doesn't complete the job, however, pepsin, and a series of peptidases, protein-dissolving enzymes from your stomach and pancreas respectively will deliver the second and final blow.

This creates a dilemma. By disassembling glutathione, free cysteine is liberated. Whether the cysteine comes from breaking the bonds among the amino acids of glutathione or ingesting cysteine as in the foods listed in **Table 2** (remember the R values of proteins), free cysteine creates a problem. With its free sulfhydryl group (SH), cysteine has a higher energy state than other (non-SH) containing amino acids.

As such, sulfhydryl radicals are similar to the free radicals we discussed previously. In contradistinction to free radicals, however, they are neutralized by complexing with another free sulfhydryl group, rather then by grabbing an electron from another biomolecule, except in states of inflammation. In the digestive tract, this is most commonly accomplished by complexing to another cysteine molecule, forming cystine (two cysteines linked together) which produces a disulfide bond (two SH groups linked together) and a lowered energy state.

While this solves one problem, it creates another and is an excellent example of the oft used phrase, "Short-term gain for long-term pain." In order to break the bond (SH-HS), the cell needs to perform work (expend

energy “create free radicals”) to recreate free cysteine for use in glutathione synthesis. Were this required energy expenditure not a sufficient problem, there is another that is perhaps even more dangerous.

As we said, sulfhydryl radicals want to chemically complex to other sulfhydryls to reduce their energy state (redox). Unfortunately the SH group they attach to is whatever is in the neighborhood (available in the chemical environment) and whether cysteine complexes to another SH containing amino acid or is, in fact, oxidized depends on the local chemical environment.

When the body is inflamed (remember the effects of poor nutrition, etc, on your GI tract), the cysteine molecule acts like a free radical and is actually oxidized to reduce its energy state. This results in the formation of homocysteine, which is strongly associated with an increased risk of cardiovascular disease including heart attacks, strokes, and multi-infarct dementia.

Despite their pitfalls, the component amino acids of glutathione participate in a variety of other important biochemical actions in the body. These are listed briefly in **Table 3.** It can be seen from their diverse physiological uses that there is significant competition among the various organs (brain, liver, blood, etc) and biochemical processes for them. I believe this illustrates but one more reason for the necessity of nutritional supplements, especially when the zero sum game of food consumption is considered.

There are a variety of glutathione promoting supplements. They can be conveniently, if arbitrarily, divided among prescription drugs, natural glutathione promoting/protecting substances and cofactors which augment the production/protection of glutathione. These are listed in **Table 4.**

MAJOR FUNCTIONS OF GLUTATHIONE PRECURSORS

AMINO ACID	PHYSIOLOGIC USES
Glutamine	• Conditionally essential (must be ingested) in illness or injury • GSH production • GI health; Strengthens GI barrier to entry of abnormal substances • Promotes intestinal cell production • Accelerated wound healing • Alternate source of fuel for brain cells • Major role in protein synthesis • A substrate (necessary building block) for DNA synthesis • Aids in immune function
Glutamic Acid	• Form of glutamine used in GSH synthesis • Complexed to nitrogen waste products for safe elimination (UREA) • Excitatory neurotransmitter (NMDA) • Precursor to inhibitory neurotransmitter (GABA)
Cysteine	• Antioxidant by itself • Can become antioxidant in states of inflammation • GSH production • Binds to heavy metals • Involved in apoptosis (programmed cell death or cell suicide)
Glycine	• Inhibitory neurotransmitter in the brain • Major component of collagen (35%) • Component of blood (hemoglobin) and muscle (myoglobin) proteins

Table 3

GLUTATHIONE PROMOTING DRUGS, SUPPLEMENTS AND CO FACTORS

DRUGS	SUPPLEMENTS	CO FACTORS
Glutathione	Glutamine	Selenium
N Acetyl Cysteine	N-Acetyl Cysteine	Vitamin B1
OTC	Sam-E	Vitamin B2
OTZ	Melatonin	Vitamin B3
Procysteine	Alpha Lipoic Acid	Vitamin B5
GSH monoesters	Silymarin	Vitamin B6
GSH diesters	Cordyceps	Vitamin B12
Quercetin	Quercetin	Folic Acid
	Low Temp Extracted Ion Exchanged (Bioactive) Whey	Vitamin E Vitamin D3
	Protein	Beta Carotene (Vitamin A)

Table 4

The N-Acetyl Cysteine Story

The only substances listed in the drug category above that have been approved by the FDA to date are N-acetyl cysteine and glutathione itself both of which are usually administered intravenously. All others in that category have demonstrated significant problems and are not considered safe for long term use.

Nonetheless, it is estimated that pharmaceutical companies have spent billions of dollars to develop a glutathione producing/promoting drug. Given the relative obscurity of glutathione in mainstream medicine, don't you find Big Pharma's intense and costly interest curious?

With the scarcity of available drugs and their restricted uses imposed by the FDA and health insurance companies, it is clear, to me at least, that

nutritional supplements are needed to maintain maximum glutathione levels (for health, quality and perhaps even length of life).

One substance that occupies a position both as a prescription drug and a supplement is N-acetyl cysteine (NAC). Of course the difference is that a prescription drug (NAC) must be pharmaceutical (highest) grade whereas supplements containing NAC may, but are not required to be, pharmaceutical grade. In fact, most of them are food grade. As such, drug NAC is purer but not necessarily more effective (comparative studies Don't exist). Both drugs and supplements taken orally have the same potential gastrointestinal side effects (stomach ache, nausea, vomiting) if administered at greater than 800mg/ m2 per dose.

Stated simply, this is about 1200 milligrams (mgs) for a 150-pound person. Some of the other negatives such as statements that NAC supplements raise glutathione levels only transiently (temporarily), however, require more critical examination.

Glutathione is synthesized within the cytosol of cells. The studies demonstrating that NAC raises GSH levels only transiently measure glutathione in the serum (blood). In a previous section, we mentioned that glutathione transrerases transport glutathione out of cells when intracellular levels exceed the cells requirements. Although the ORAC test (Oxygen Radical Absorbance Capacity) may measure GSH levels in serum, remember neither serum glutathione elevations nor its duration accurately depicts the conditions within the cell. In fact, there are a few important articles in the research literature that speak directly to this controversy.

In one study, animals were given NAC every four hours. The studies revealed that intracellular glutathione levels increased with the initial dose; increased again with the second dose; and only plateaued after the third dose. Of note, the doses used were thousands of times the equivalent human dose.

In another study, animals were fed NAC, again at doses hundreds of times the equivalent human dose, over a prolonged period (the equivalent of approximately four years in humans). Examination of all the organs of the animals after the experiments were completed demonstrated no abnormalities in any tissue. In addition, comprehensive chemistry evaluation revealed only one minor abnormality in liver enzyme levels, but glutathione and glutathione peroxidase levels were elevated significantly.

Finally, an interesting study in baby animals demonstrated that 20 grams (20,000 mgs) in a baby chick weighing less than 100 grams (the ideal human is 70,000 grams) demonstrated increased growth compared to a group of baby chicks receiving no NAC. It must be noted that if 30 and 40 grams of NAC was given, the chicks actually demonstrated decreased growth rate compared to a placebo-fed group, but at doses at least thousands of times the human dose, NAC increased the growth of the baby chicks. This finding gains importance as babies of any species grow more quickly that adults and therefore, any problem associated with NAC should be magnified.

In addition, these are the very studies required by the FDA before human clinical trials can begin (animal toxicity studies) and are worthy of mentioning even though the results of animal studies cannot be extrapolated to humans. Given the beneficial effects at doses thousands of times any human dose, they call into question any statement concerning the possible toxicity associated with long-term use of N-acetyl cysteine. These studies suggest strongly that NAC or other "protected" cysteines serve our integral purpose in any GSH promoting supplement.

Other GSH-Promoting Supplements

Silymarin (milk thistle) and alpha lipoic acid are commonly included in glutathione promoting supplements due to their known effects of increasing hepatic (liver) ATP synthesis and recycling glutathione respectively. Selenium is also included as it is a necessary component of

the enzyme antioxidant, glutathione peroxidase.

Notably absent from most lists, however are a number of other valuable nutritional supplements. They include but are not necessarily limited to: cordyceps, which increases hepatic ATP synthesis equivalently to silymarin; pycnogenol, from pine bark which increases glutathione reductase; and resveratrol, from grapes which increases glutathione synthetase.

In addition, the active ingredients of the most marketed juice antioxidant drinks, including green tea, by one mechanism or another, all promote/ protect glutathione. Of course, many of these nutritional supplements have other important functions, but they are all linked to glutathione. One must wonder then if protection/promotion of glutathione may be the "final common pathway" for the body's conservation of its most important "first line of defense."

In fact, a thorough review of all of the proposed antioxidants in PubMed failed to discover any nutritional supplement which didn't in some way protect or promote glutathione.

SECTION SIX

THE FORMULA FOR AN IDEAL GLUTATHIONE OPTIMIZER

Having discussed the commonly known antioxidants, I would again beg the reader's indulgence. Reviewing the literature extensively in preparation for writing this monograph, I believe I am in a unique position to create a theoretical optimum glutathione promoting supplement. The components of this "Ideal Glutathione Optimizer", I believe, should include:

- Components to improve the gastrointestinal absorption
- Components in a balanced chemical formula to maximize intracellular GSH production
- Components to continuously promote glutathione recycling (GSSG) to 2 molecules of GSH

- Components to stimulate/maximize enzymes involved in controlling intracellular glutathione functionality and levels
- Cofactors to facilitate both glutathione and ATP production

Of course, depending on sleep, nutrition, exercise, hydration and lifestyle choices, there is no "one size fits all." Nonetheless, given the various problems discussed previously, perhaps it would be prudent to include each of these components in a glutathione optimizer.

In order to facilitate absorption, it is necessary to include components which have been demonstrated to promote gastrointestinal healing. These include, but are certainly not limited to: glutamine which has been discussed previously and N-acetyl d-glucosamine (NAG). NAG is a chemical cousin of glucosamine sulfate, which has been shown to stop and perhaps even reverse the progression of age-related arthritis (osteoarthritis). Not only does recent evidence suggest NAG may be more effective than glucosamine in arthritis, but a small study in children with bowel disease revealed that NAG reduced symptoms. Another possible, although less studied, supplement possibility is ginger.

NAG, as well as ginger, functions, at least in part, by promoting the synthesis of intestinal mucopolysaccharides, the protective covering (slime layer) for the intestinal cells. To summarize, glutamine stimulates production of intestinal cells and N-acetyl glucosamine promotes a protective covering for them.

Clearly, this combination would be inadequate to treat or improve serious intestinal disease. Under normal physiologic circumstances, however, it should promote and perhaps increase the functional integrity of intestinal absorption.

The individual components of amino acids of glutathione have been discussed previously in Tables II and III and will not be covered further except for N-acetyl cysteine. We have discussed and offered compelling evidence against the possible problems associated with NAC including

GI toxicity, the transient effects of it on increased glutathione levels and its potential long term toxicity. A discussion of the reasons for its inclusion in a "potentially ideal" glutathione supplement, therefore, seems warranted.

Since N-acetyl cysteine is embroiled in controversy, the question could be asked, why use it? The answer reminds me of Sir Winston Churchill's quip about democracy "It is the worst form of government except all the rest." A few reasons for including NAC include:

- The acetyl group stabilizes ("hides") the SH group and prevents its oxidation or attachment to another SH group
- It cannot act as a free radical in states of inflammation and form homocysteine (contributing to heart disease)
- It is ten times more absorbable than cysteine
- There is a separate mechanism in the membrane of cells to absorb it specifically from the plasma (the body, I submit, does not make mistakes)
- It is a conditionally essentially amino acid (when the body needs more due to inflammation and disease, it must be ingested)

Although the actual biochemical processes are quite complex, to paraphrase Churchill "it is the worst clinical form of cysteine except every other form."

In summary, then, glutamine should be included in the ideal glutathione accelerator both for its healing properties in the GI tract which facilitate absorption and the fact that it is a conditionally essential amino acid.

Likewise, NAC (or an alternate source of "protected" cysteine) should be included as it too is a conditionally essential amino acid; is the most absorbable form of cysteine; has a separate and distinct biochemical absorption pathway in the cell membrane and cannot contribute to homocysteine formation.

Glycine, however, is unnecessary as sufficient quantities are contained in all human diets (even fast foods). As such, nature (the body) then can balance the absorption of the component amino acids rather than science (man) introducing an arbitrary amount of glycine.

Other Important Components

Although improving absorption and introducing the components of glutathione in balanced amounts might be sufficient, there are other components which will maximize the production/protection of intracellular glutathione and thus should be included, I submit, in an "Ideal Glutathione Optimizer." Although the mechanisms of actions in producing and/or protecting glutathione have not been defined biochemically in many cases, these nutritional supplements include, but may not be limited to:

- Milk thistle (Silymarin)
- Cordyceps
- Quercetin

Milk thistle has been used medicinally for over 2000 years for the treatment of liver disease. An extract from the seeds called silymarin is believed to be the biologically active ingredient. Although there are many studies on its uses in cirrhosis, cancer prevention and diabetes to name a few, there is no scientifically rigorous support for its use in any disease (remember the correlative evidence for glutathione).

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One indisputable fact that has emerged from numerous animal studies, however, is that silymarin improves ATP production in hepatic (liver) cells by more than 50 percent. As efficient ATP production is intimately linked to glutathione (remember the ETC bucket brigade), silymarin must improve glutathione production although the exact biochemical mechanism of action remains undefined. Nonetheless, its improvement of hepatic ATP production, alone, warrants its inclusion in an "Ideal Glutathione Optimizer."

A similar and equally cogent argument can be made for the inclusion of cordyceps. There are many species of this fungus with various properties. The best, based on the literature, is *Cordyceps sinensis*, which prior to modern times was reserved for the Imperial Family in China. There have been many books written about its potentially amazing properties, to which the reader is referred for more information.

As with silymarin, however, few scientifically rigorous studies have been reported concerning cordyceps proposed medical benefits in treating diabetes, preventing various cancers and improving sexual performance to name a few. Further research, therefore, is needed before any clinical benefit can be proven (remember the problems involving clinical studies on natural substances).

Again, however, basic science studies are illustrative. Among many others, three functions of cordyceps warrant its inclusion in an "Ideal Glutathione Optimizer." First, similar to silymarin, it increases hepatic (liver) cell ATP production by more than half and thus is linked to improved glutathione production. Second, it has been shown to directly quench hydroxyl (OH) free radicals and, thus, has a direct glutathione sparing effect. Its third property, however, may even offer a more compelling argument for its inclusion.

There is a molecular switch in every cell of your body which controls inflammation. The switch is more active in your immune defense system

cells (white blood cells) and other active tissues. The switch is called nuclear factor kappa beta (NFkB). Activation results in a cascade of biochemical reactions resulting in increased free radical production and inflammation. Cordyce fewer free radicals, less need for the spectrum of antioxidants to control inflammation-generated free radicals and thus protection (conservation) of glutathione for its primary purpose, protection and production of mitochondrial DNA and the Electron Transport Chain responsible for cellular energy (ATP production).

Finally, the inclusion of a powerful and multi-functional antioxidant which is more glutathione protective than promotive would be desirable in an "Ideal Glutathione Optimizer" supplement to both bolster the effects of the other components as well as provide additional benefits.

After an exhaustive review of the antioxidant literature, one such supplement, quercetin, comes to the fore. It is a member of a class of supplements, chemically termed bioflavonoids, and has many functions. It has a variety of possible health benefits including reduction of allergic symptoms, improving varicose veins, and preventing/treating prostate cancer. As with silymarin and cordyceps however, the true medical potential of quercetin requires additional cause and effect studies.

One exception to the general lack of direct studies, however, may be in HIV/AIDS. Studies have shown that quercetin as an integral component of a multi-component anti-IV drug (PBS 119), effectively reduces HIV viral activity while significantly improving the immune system. As previous *in vitro* studies have demonstrated, the quercetin both inhibits HIV binding to target cells (CD4 helper cells) and interferes with the function of HIV enzymes required for the HIV virus to survive, much less divide, these in vivo clinical studies, offer possible proof of a cause and effect relationship.

In an "Ideal Glutathione Optimizer," quercetin offers multiple benefits. It is known to independently recycle vitamin C and there is some evidence that it has a similar effect on alpha lipoic acid (ALA). This would offer

a dual benefit to glutathione as it would both "excuse" GSH from its requirement to recycle these antioxidants while simultaneously improving the (ALA, vitamin C) glutathione-recycling mechanism.

In addition, quercetin, similar to cordyceps, directly inhibits the cellular inflammatory switch (NFkB). Of interest, quercetin and cordyceps appear to inhibit NFkB activity by independent mechanisms although further research will be required to define precisely their biochemical mechanism(s) of action. These data would suggest, however, that inclusion of both in an "Ideal Glutathione Optimizer" provides, at least, an additive effect in reducing inflammation and thereby "protecting" glutathione for its primary function.

Including all of the components discussed above in a balanced formula should constitute a complex, yet extremely functional, "Ideal Glutathione Optimizer." This is not to say that other antioxidants could not be included but the scientific literature suggests that other supplements added to the formula would add too little to its "functionality" to warrant inclusion.

There is one area, however, where this statement could and should be questioned. It is the necessity of adequate amounts of bioavailable cofactors necessary to "maximize the efficiency" of all of the biochemical processes required for glutathione synthesis and ATP production.

Of course, these can be obtained from a good multivitamin formula, containing the Institute of Medicine's RDI (recommended daily intake) not the FDA's recommended daily allowances (RDA). They must, however, be obtained from food (remember the pitfalls) or from a nutritional supplement. Of course, the question could and should be posed about why they are not included in the "Ideal Glutathione Optimizer" formula itself. The answer is "they could" but I would choose to exclude them for four practical reasons.

First, most healthy people ingest sufficient quantities of each of them so that inclusion seems unnecessary. For aged or ill people, however, a supplement may well be required.

Second, there is a practical consideration of the quantity (pill burden) required to achieve a sufficient balanced quantity of any "Ideal Glutathione Optimizer."

Third, and perhaps the most practical of the four, is the issue of cost. Remember, I begged your indulgence to create the "Ideal Glutathione Optimizer" but even under "ideal" circumstances, practical reality must be considered.

Fourth, and the most cogent reason for including them as an adjunct to the "Ideal Glutathione Optimizer" is our current knowledge of a variety of vitamins and trace minerals. Any inclusive list of them however, I believe, represents a "moving target" as the literature is continually changing.

As additional studies are published (there have been over 20,000 mentioning glutathione, directly or indirectly, in the last five years) additional cofactors and/or trace elements will be discovered that also warrant inclusion. They represent cofactors which will enhance the function of food utilization chains (the TCA or Krebs cycle); improve mitochondrial DNA (mtDNA) and/ or the ATP factory (ETC) production and/or add efficiency to glutathione control factors.

As of this writing, they include various B vitamins, vitamin D3, trace minerals, and selenium, which is necessary for the synthesis of glutathione peroxidase (GPx). Given the proliferation and intensity of research, however, any listing of them may well prove obsolete before it is published. As such, I have elected to relegate them to "adjuncts" (see Table 4) as I believe the list might prove incomplete regardless of the amount of research I reviewed.

As a result of all my research, I believe the minimal components for an "Ideal Glutathione Optimizer" would include: glutamine, N-acetyl cysteine, N-acetyl D-glucosamine, vitamin C, quercetin, alpha lipoic acid, cordyceps, and milk thistle (silymarin).

SECTION SEVEN

A POSSIBLE ROADMAP FOR FUTURE STUDIES IN CARDIOVASCULAR DISEASE, CANCER AND NEURODEGENERATIVE DISEASES

There are three (actually many more) general areas that because of their impact on the health, well-being and life itself, deserve at least a general discussion. To maintain fairness and balance (the yin and yang of our present state of knowledge), I shall attempt to detail both the potential power and the present problems in assigning a role for glutathione in these devastating diseases. Of course, any listing of these illnesses is arbitrary, but I submit, these three, due to their current or expected prevalence and their ability to "rob" quality of life and even life itself, warrant their primacy. They are:

- Atherosclerotic cardiovascular disease (heart attacks, strokes, and multiple little strokes (infarcts) causing dementia)
- Cancer
- Neurodegenerative disease (Alzheimer's, Parkinson's and one I consider a childhood variant, autistic disorders)

It is impossible to argue that these are not devastating illnesses and a myriad of studies have associated them causally with inflammation. The question that remains is, if they are associated with increased free radical production (a given in states of inflammation) will "rebalancing" the system with antioxidants prove clinically beneficial?

We know that increased free radical production ("oxidative stress") causes disease. This was proven conclusively in the 1940's when premature infants were given 100 percent oxygen to sustain their life. It worked. They lived,

but the law of unintended consequences prevailed. The extremely high levels of oxygen resulted in excessive “lost oxygen” in mitochondrial ATP production and the clinical result was blindness.

Similarly, in the 1970-80’s the use of oxygen concentrations greater than 50 percent for prolonged periods in patients with chronic obstructive lung disease and other pulmonary problems resulted in “burning” the lungs, a clinical condition named “acute respiratory distress syndrome" (ARDS), which frequently resulted in death.

Cardiovascular Disorders

What about heart disease? Interestingly, McCully, a professor at Harvard, implicated inflammation as a causal factor/ promoter of heart disease in the l970’s. Unfortunately, as so many others, he was dismissed and derided (remember the oil tanker). In fact, it was not until 2000 that inflammation gained "medical credibility” as a causative factor in cardiovascular disease. It is now considered intuitively obvious (sound familiar?).

It is well beyond the scope of this monograph to detail all of the studies that prove the link(s) among free radicals, inflammation and cardiovascular disease. Again the reader is referred to the many books and articles written on the subject for further information. A balanced portrayal (the power and the problems) of a few selected studies, however, will be discussed.

First, I submit, we should have known that atherosclerotic cardiovascular disease (ASHD) involved more than just elevated cholesterol or more precisely elevated “bad cholesterol,” Low Density Lipoproteins-LDL, when autopsies on 18- to 25-year-old soldiers killed in the “Korean Conflict” revealed significant atherosclerotic lesions (plaques) in up to 75 percent of the autopsies. As “kids” shouldn’t have enough “time" to develop such severe lesions (the prevailing wisdom was that the presence of “too much” cholesterol over decades resulted in the plaques) there must be another explanation.

Enter free radicals. Remember free radicals can damage (burn) any biomolecule. Using simple logic then, the more LDL (bad) cholesterol you have and the more free radicals you produce that aren't quenched, the greater the odds you will burn (damage) LDL. This has, in fact, been proven scientifically to be the first domino in a multi-domino cascade of reactions, the result of which is cardiovascular disease in its varied forms.

This illness (the number one cause of death in the US) is the result of damage to the blood vessels of the heart resulting in disruption of the plaques and activation of the platelets causing a heart attack and death to the heart muscle supplied by those blood vessels. If the heart wall damage is severe and/or occurs in areas involving control of the heart rhythm, the result is sudden death.

There is a minor variant named "angina." I doubt, however, that anyone experiencing "angina" which is a temporary decrease in blood flow to the heart caused by the same free radical induced lesions that cause heart attacks, would consider it "minor."

In a similar way, damage to the blood vessels of the brain, from the same multi-domino reaction starting with excess, unquenched, free radicals results in cerebrovascular accidents (strokes) or the "minor" variant transient ischemic attacks (TIAs). Alternatively, there can be multiple and repeated damage to smaller blood vessels in the brain resulting in multiple very small strokes. At some point, which remains undefined, this cumulative damage results in multi-infarct dementia, which is difficult to distinguish clinically from Alzheimer's disease.

Given the above, you should be screaming by now, "where are the studies on antioxidants as a possible treatment for cardiovascular diseases?" Sadly, they are largely nonexistent. There are studies which demonstrate that people who consume more fruits and vegetables have a decreased risk of cardiovascular disease. When it comes to interventional studies, however, the statement made previously, **"we are all prisoners of our training"** assumes great importance

as most of the studies used single antioxidants (remember the antioxidant chain reaction necessary with antioxidants other than glutathione) including vitamin C, vitamin E and beta carotene (Vitamin A). As might be expected, the results were mixed. Traditional medicine, while acknowledging the importance of unquenched free radicals and inflammation in the development of cardiovascular disease, is still waiting for "the intuitively obvious" cause-and-effect studies.

There are correlative studies however, which demonstrate, that both glutathione and glutathione peroxidase are decreased in cardiovascular disease. In addition, there are a few human studies that suggest that increasing glutathione is protective against experimentally induced coronary artery disease and there are many studies demonstrating the protective effects of increased glutathione in animal models of heart disease. Nonetheless, proof sufficient to alter "acceptable dogma" is lacking. One can but wonder about the results of a gold standard, double-blind, placebo-controlled, crossover study using the "Ideal Glutathione Optimizer."

Cancer

A second general disease state, cancer, also merits consideration. In my opinion, there is no diagnosis either rendered by a physician or heard by a patient that causes more shock and fear than "cancer." In addition, I believe that the reticence to use antioxidants in cancer is a prime example of disservice to patients engendered by traditional medicines "show me" attitude.

There are thousands of correlative studies demonstrating that antioxidants and even glutathione cofactors (selenium) reduce the incidence of various forms of cancer. A major reason for the current dogma of avoiding antioxidant supplements in cancer patients, however, is the well proven fact that glutathione levels are elevated in cancer cells. It is argued, therefore, that using glutathione producing/protecting supplements would exacerbate the cancer as antioxidants protect cancer cells against the effects of chemo and radiation therapy (both work, at least in part, by creating free radicals).

The argument, although plausible, is not supported by the facts. There are numerous *in vitro* and animal studies (remember that clinicians largely don't read basic science literature) demonstrating that using glutathione producing/promoting supplements has two separate and opposing effects. Although they appear counterintuitive, the numerous independent studies demonstrating similar results suggest that the conclusions are correct and, at the very least, demand their consideration.

Stated simply, glutathione producing/promoting supplements actually decrease, rather than increase further, glutathione levels in cancer cells and increase GSH levels in immune cells. The ultimate result of these opposite effects, then, make the cancer cells more susceptible to therapy (less GSH to quench free radicals) and empower the bodily defenses (immune system) to fight the cancer.

One interesting proof comes from the recent spate of articles about the prevalence of vitamin D_3 deficiency in the US population and the protective effects of high normal (75-90mlg/ml) levels of vitamin D, in the development of various cancers. In fact, in colon cancer, the third most prevalent form of cancer, people with the highest compared to the lowest levels of vitamin D_3 have more than a 70 percent chance of never developing colon cancer. Similar if less startling protection occurs with lung, breast, prostate and other cancers.

One could ask why a simple vitamin could offer such robust protection against so many forms of this dreaded disease. The answer, again, can be found, at least in part, in the basic science literature. Vitamin D_3 decreases levels of glutathione and glutathione peroxidase and increases free radical production in every type of cancer cell studied.

Although the molecular mechanism of action awaits further study, the take home message is clear. Vitamin D_3 protects against cancer and works, at least partially, by "robbing" the cancer cells of one of their major tricks and important protectors against destruction, **glutathione**. As GSH producing/promoting supplements have been reported to have

a similar "glutathione robbing effect" on cancer cells while increasing glutathione in immune/defense cells, one is left to wonder again about the results of a double-blind, placebo-controlled, crossover study (the FDA "gold standard") using the "Ideal Glutathione Optimizer" in vitamin D_3 optimized patients as an adjunct in the therapy of cancer.

Neurodegenerative Diseases: Alzheimer's

The final group of diseases that merits consideration is termed neurodegenerative diseases. These include multi-infarct dementia, which was mentioned previously, Alzheimer's and Parkinson's.

Any listing which uses the common mechanisms of increased free radical production (reactive oxidative stress) and inflammation as the defining characteristics, however, would also include Amyotrophic Lateral Sclerosis (Lou Gehrig's disease), Huntington's chorea and in fact, a large, although precisely undefined proportion of children with autistic disorders.

Although autism and Alzheimer's are rarely discussed together, the similar problems of increased (unquenched) free radicals, inflammation and the resultant disruption of neuro circuits in both conditions suggest strongly a pathophysiologic relationship. We, in science, tend to pigeonhole diseases rather than acknowledging that biology is a continuum and not a series of pigeon holes. Imagine the potential of extrapolating medical advances in one "pigeonhole" to the continuum of other mechanistically similar illnesses.

It is beyond the scope of this monograph to review comprehensively each of these disorders. The reader is again referred to the mountains of scientific literature published on each disease and urged to remember the continuum, not the pigeonholes, when reading them.

I have chosen, arbitrarily, to briefly summarize two illnesses in the spectrum, Alzheimer's disease (AD) and autism, due to their similarities, explosive increase in prevalence and devastating effects on both the

individual and the family.

In both, there is evidence of a genetic predisposition in some patients. In both, there has been and continues to be a very scary increase in the numbers afflicted. In AD, it is estimated that the worldwide incidence will increase 10 fold in the next decade and in Florida alone, autism has catapulted from approximately 400 cases 10 to 15 years ago to approximately 40,000 today with no end of the upward spiral in sight. In Alzheimer's disease, the hallmark lesion has been the presence of plaques in the brain. This has recently been challenged, however, as all people over the age of 65* who have been autopsied demonstrated the same plaques. As only 10 percent of people over age 65 are affected, how can plaques which are present in virtually all autopsies of people over age 65 cause Alzheimer's?

What, then, distinguishes those who develop AD from those who simply have plaques? There are, of course, no definitive answers. Nonetheless, a number of correlative studies linking AD to other health problems offers a tantalizing glimpse into one possible cause, at least, being increased: unquenched free radical production and inflammation.

One study that demands particular attention is that people with borderline diabetes (insulin resistance, the precursor for diabetes which is associated with increased free radical production and inflammation) have a 70 percent increased risk of developing AD. This is corroborated by another study demonstrating that in patients diagnosed with adult onset diabetes (type II), those with the worst control of blood sugar (highest in free radical production) are at the greatest risk of developing dementia.

These studies, of course, do not prove a causative link but they merit consideration. In fact, a number of nutritional interventional studies bolster the relationship. They have demonstrated that vitamin B12, which reduces homocysteine (remember the effect of inflammation and increased free radicals on cysteine), omega-3 fatty acids (natural anti-inflammatory agents) and a number of studies employing various single

and multiple antioxidants have all demonstrated some benefit as have correlative studies demonstrating that people who consume the largest amount of fruits and vegetables and who exercise (remember the effects of exercise on glutathione) have the lowest risk of developing AD.

** Perhaps even more worrisome is 50 percent of people over age 85 demonstrate clinical signs of Alzheimer's and the average lifespan in the US is approaching 80 years.*

In addition, Big Pharma (remember them?) is spending hundreds of millions of dollars to develop a therapeutic "anti-inflammatory" for the treatment, or at least to prevent the progression of AD.

Remember, however, that inflammation is the result, not the cause of increased unquenched free radical production. An exciting, although very preliminary study that reinforces the possibility of increased free radical production as the first domino (along with brain plaques) in the cascade that results in AD, demonstrated that N-acetyl cysteine (NAC) reduced the effects of increased free radical production and slowed the progression of AD in an animal model. And a preliminary human study demonstrating that a monoclonal antibody which blocks the effects of TNF alpha, an inflammatory cytokine which causes increased free radical formations, demonstrates a dramatic, albeit temporary, reversal of Alzheimer's symptoms.

As stated before, no definitive conclusion can be drawn, but I believe the above warrants serious consideration in any "Roadmap of Future Studies."

Neurodegenerative Diseases: Autistic Spectrum Disorders

In a similar vein, although not usually linked, autism or autistic spectrum disorders shares many similarities. These include, but may not be limited to:

- A genetic cause in some cases
- Excess nervous system immune activity
- Evidence of increased free radical production
- Evidence of increased pro-inflammatory cytokines

- Evidence of mitochondrial dysfunction
- An explosive increase in incidence (and/or improved diagnosis)
- Anecdotal evidence of improvement of symptoms with IV glutathione administration

Again, however, as the immune, neurologic and endocrine (hormone) systems are intricately linked and may, in fact, be simply different parts

of a singular biochemical system, a singular cause for either of these or any other neurodegenerative disease may be similar to "a quest for the Holy Grail."

Remember, the brain, as the heart, has the most mitochondrial activity of all organs (except the liver) and is the most susceptible to unquenched free radicals and mitochondrial damage (remember the bucket brigade). Since the mitochondria produce the energy for all cells, is it surprising that an organ, the brain, with the highest mitochondrial activity and thus the highest risk of unquenched free radical production and mitochondrial damage should suffer the clinical consequences of Alzheimer's, Parkinson's and even autism, all of which are associated with mitochondrial dysfunction?

It is equally unsurprising that these clinical diseases, along with cardiovascular disease, hepatitis and diabetes, are associated with pronounced decreases in glutathione levels. What I do find surprising is the absence of rigorous scientific interventional studies of the effect of promoting glutathione in these devastating diseases. I can but hope that the information I have outlined will stimulate interest in such studies.

TESTIMONIALS

Having covered some general areas where there is abundant correlative evidence that reduced glutathione is associated with disease states, and suggests that studies of cause and effect are warranted, I will now include selected testimonials. As I was told by Dr. John C. Nelson, the past president of the American Medical Association, "One thousand stories don't equal a study."

Testimonials represent a single person's experience, and are not meant to suggest that the glutathione supplement will treat or improve any medical condition. Nonetheless, I believe they do represent a valid road map for future rigorous scientific studies whenever the barriers to this research are removed.

Serge, Age 46, Improved Cellular Function

Back in 2005, I suffered a heart attack, three weeks before my 44th birthday. I remember thinking, "What's going on? I'm too young for this!" But it did happen. Since then, I was plagued with chronic fatigue, heart palpitation, headaches, and more.

I started taking the glutathione supplement last spring, and after 3 days of taking it my palpitation had ceased. Then, one week later, my fatigue was gone and so were my headaches.

But one thing I did not expect. Since I was very young, I chewed my fingernails (I was always a nervous child) and one day, after about 3 months on the glutathione supplement, I started to notice fingernails growing for the first time in 40 years. My stress levels had gone down so gradually that I did not notice that I did not chew my nails in a few days, and have not had the urge to chew my nails since then. I've also noticedthat my E.D., as a result of my heart attack, had also been corrected. My sleep patterns have also been much better, as well as my mental focus.

Jillyn, Improved Cellular Function-Musculoskeletal

In February 2006, working as a teacher I, Jillyn, at 52 years old was tripped in the hall and landed on my left knee. It immediately swelled up and I struggled to walk. I was sent to two doctors, one was an orthopedic surgeon. I had X-rays, and an MRI done. I was told my MRI showed a meniscus cartilage tear. It hurt so bad I couldn't sleep and I walked with severe pain. I was given Prednisone and Amitriptyline to bring down the inflammation and the pain, but to no avail. I was on crutches for a month but that didn't help either.

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Then in April 2007, over a year later and still in pain, I was then sent to another orthopedic surgeon who really is a specialist in knees. He said I definitely needed surgery. But I am allergic to a lot of anti-inflammatories so I wanted to think about it for a few weeks. I then heard about the glutathione supplement and started taking

it to see if it would help my fibromyalgia which I was diagnosed with in 1980 by a rheumatologist. Some symptoms of fibromyalgia, besides pain and lack of energy that I also struggle with, are severe insomnia where many nights I did not sleep at all and a lack of mental clarity.

The longer I was on the glutathione supplement, the better I felt. After about 2 months of taking it I noticed increased mental clarity, my energy level was up and there was less stiffness in my joints and muscles. I sleep better and I feel better than I have in 27 years! I am sleeping all night, every night, and my knee is NOT painful anymore.

Now 1 ½ years since the fall, Oct. 1, I had a follow up with the knee specialist, the orthopedic surgeon who I saw last April. I was concerned about the surgery and when to have it. After my exam he wrote up the results and asked if l wanted a copy. In those results he wrote:

"PLAN: Because her symptoms have shown signs of resolution and her exam is benign today, I would recommend holding off on surgery for now. Continue to follow on a conservative basis using the glutathione supplement. Since the inflammation is now resolving, it will take another 6 months or so for complete healing."

My orthopedic surgeon then explained that by keeping the inflammation down with the glutathione supplement my body has been able to work on healing my meniscus cartilage tear. He then recommended careful exercise to build my knee strength, so the very next day I walked ONE mile on it, which I had not dared do, and my knee felt fine. I am ecstatic! My knee is doing wonderful, NO surgery needed, my fibromyalgia seldom bothers me anymore, I have more energy, better mental clarity and I sleep every night.

For years I have also had severe allergies. And after four months on the glutathione supplement, I was able to keep my allergies completely under control. I felt normal and even forgot about my allergies until one day my husband asked me why I wasn't suffering with them. I said I was only taking my glutathione supplement and had no allergy symptoms.

Frank and Judy, Improved Cellular Function

I am 46 years young and I live in Peachland, BC.

In 1997, we were hit with the news that I was being diagnosed with Multiple Sclerosis, a neurological disease which leaves little hope for the future. Our children were young teens at the time and needless to say this was terrifying for all of us. With MS comes many different types of symptoms, muscle pain and spasm, mental and physical fatigue, poor balance, I can go on and on. Activities had to be well planned so that I could be well rested. I hated feeling like a burden to my family.

As things go, over the next years so many well intentioned friends and friends of friends were convinced they could "cure" my MS with their various products etc. Being somewhat of a realist I didn't want any part of bouncing from product to product, I did my research, there is no cure for MS!

In January of 2005, my husband had a heart attack, yet another blow for us! Two surgeries and 11 stints later he is taking huge doses of Lipitor (80 mg daily).

Our children now being young adults and heading out on their own, I wanted a change for us so we moved to Peachland and semi-retired.

In June of 2007 my husband was introduced to a glutathione supplement. I was willing to try it.

About two weeks into taking the glutathione supplement, I had to admit that I was feeling so much better than I had in years! Less spasm, less pain, less fatigue and more energy than I had in some time! WOW and this gets better. After two months on the product, my husband's medication was reduced by 20% to 60 mg of Lipitor daily.

Glutathione has been so much more than a supplement. It has and is changing our lives daily. ***I still have MS but MS doesn't have me!*** *We are looking forward to a much longer life and a better quality of life than we ever could have imagined!*

Jean, Improved Cellular Function-Neurologic

I am a 52 year old woman with Parkinson's. I was diagnosed in 2002, at the age of 47. My neurologist is Ali H. Rajput, OC, SOM, MBBS, FRCPC, of Royal University Hospital, Saskatoon, Canada. I was last seen by Dr. Rajput in December of 2006, when it was determined I could no longer work (I was a bakery manager at the time). This is a part of his letter to my family doctor. "Jean was examined 3 hours and 30 minutes after the last dose of Sinemet. There was 2+ resting tremor in the left upper limb and 1+ resting tremor in all other limbs. There is 2+ postural tremor in the right upper limb and 1+ in the left upper limb. Her pronation/supernation is at 2+ on the left side and 1+ on the right side, and heel tapping is 3+ on the left and 1+ on the right. There is 1+ rigidity. Her posture is stable; she is therefore at Stage 2 disability."

I first started taking the glutathione supplement in late May 2007. I started with three capsules in the morning and three in the afternoon. I felt nauseated, weak, developed a headache, and broke out in hives. So I then started taking only 1 capsule twice daily for three days. Then I went to 1 and 2 for 3 days. I still did not feel really well. Then I went to 2 and 2. By day 10, I started to feel really good. I actually slept for 4 hours straight, something that had not happened in the last 2 years. By day 12, I was feeling great! My medication did not "wear off" in one to one-and-a-half hours like it usually did, but lasted 3 hours before wearing off! My pain level went from about an 8 to a 2. For the first time since about January of 2007, I did not have to use a cane to walk! What a wonderful feeling that was! There was no more Parkinson's shuffle, and the cramping in my left arm and leg was minimal. And instead of sleeping half the afternoon away, I only need about a 15-minute nap. I started taking 3 and 3 capsules on about day 30. The hives have gone away and no more headaches. So, to sum up the first 3 months:

1) My energy level increased (from about a 2 to a 6)
2) I sleep for about three hours straight and for a total of about 6 hours per night, whereas before, I was lucky to get a total of 4 hours per night.
3) My medications last 3 to 3-and-a-half hours instead of 1 to 1-and-a-half hours, resulting in:
   a) Less tremors
   b) Less muscle cramping

c) Less muscle rigidity

d) Do not lose my voice very often

e) Do not have as much trouble swallowing

f) Pain in joints is minimal (as opposed to all day)

g) Do not need cane to walk

h) Less depression

i) My thinking is a lot clearer, not so foggy in the morning

j) Panic attacks are less

k) I feel more confident in such things as my driving, going out alone, etc.

l) Overall, more "on" time than "off" time

In September, I felt the glutathione supplement was not working as well, so I started taking 3 in the morning, 3 just after lunch, and 3 at around 4 or 5 p.m. This seems to be working well.

Shirley, Improved Cellular Function

About three months ago, I had problems with my joints, bones and muscles, I wasn't very good company. I felt old, much older than my age. I couldn't walk upstairs or hills. Just standing after sitting for a while would give me excruciating pain. I never felt good about anything in my life for about 10 years. Although I was skeptical, I started taking the glutathione supplement.

In one week, I started to notice little things, like going about the house humming. The first time I caught myself humming in the morning before coffee, WOW! Then I was walking upstairs without stopping halfway or on my hands and knees. Now I feel so good I can walk up a hill, that before I would have had to stop three or four times before reaching the top. Now I just keep on going without getting out of breath or feeling any pain whatsoever.

I would recommend the glutathione supplement to anyone, at any age. ***I am now 68 going on 45 or50. Before I felt like 68 going on 80.***

Carvel, Improved Cellular Function

I am 66 years old. Using the glutathione supplement has changed my life. Yes, I have reentered life!

I experienced a significant benefit within 2 hours of using this product. I feel better now than I have in many years.

Here is my story:
I was in near perfect health, so I believed, through my late 50's. Then I was assaulted by serious mental and physical health challenges.

I had been an outdoor enthusiast. I ran my first marathon at age 47. I ran at least one marathon a year for 10 consecutive years. I did a lot of mountain biking and backpacking into the backcountry. Also, I snow skied - never at a high skill level, but I had the energy and strength to do it.

All that great outdoor stuff stopped when I became ill. I stopped exercising and gained 75 pounds. For several years I was not living life - I was merely surviving from one day to the next.

I was diagnosed with severe depression and an anxiety disorder. Every day for at least 5 years, I had pains in my chest; some days it was only at an uncomfortable level, but most days the pain was excruciating.

I was committing many thinking errors. It adversely affected every area of my life, including financial, spiritual, and social.

Nothing seemed to deliver relief. I was hospitalized 3 times. I sought help from several different medical doctors. Many different pharmaceutical medicines were prescribed and used. Still no relief.

I tried several alternative approaches to my health problems, including acupuncture, hypnosis and chiropractic. Nothing worked.

I spent a week with a holistic practitioner in Mexico. It didn't help.

I have forgotten all the nutritional products I consumed, including many different nutritional juices. They didn't help.

Many well intended people gave me advice - what to do - what to eat - what to drink - what to swallow, etc. Nothing worked.

I decided to take an early retirement. I retired from my career in 2003. Life was still very hard.

Then I decided to move from Utah to Hawaii. I made the move early November, 2006. I believe that helped, but I was still hurting. I woke up every morning with turmoil in my chest. I can best describe it by reporting that it felt like cats inside my chest clawing.

Sometime late December, 2006, I learned about the glutathione supplement. I began using it mid-January, 2007.

This is what happened. Within an hour or two after I first took the supplement, I felt a softening of the anxiety in my chest. The pain went away, and has not returned. It is an absolute miracle.

But the softening of the anxiety per se, is not the most miraculous part of my experience. Not only was my anxiety going down, but my energy was increasing.

Never before had I taken anything, good or bad, that increased my energy and also reduced the anxiety. Usually, when my energy increased, my anxiety cranked up.

So, my first two noticeable benefits were my anxiety reduced and my energy went up.

Here are some other benefits I have noticed:

* *Better sleep - that is, more restful slumber*
* *Natural color returning to my hair*
* *Old scar tissue on my right shin repairing*
* *Increased desire to accomplish things each day*
* *Increased sense of well being*

I do not use any prescribed medication. I feel discouraged sometimes, but I no longer suffer depression; I know the difference.

Yes, using this product has changed my life. It is true that I feel better than I have in many years.

I am not yet back to the point where I thought I was enjoying near perfect health. But, that is now up to me. I know I need to exercise more, and shed some pounds.

There is more, but I think I have captured, and shared the essence of my experience using the revolutionary product.

Shirley, Improved Cellular Function and Mood

I am 68 years of age. I have always been in very good health, eat organically and am a competitive athlete enjoying a great deal of energy. In 1995, I was run over by a car while practicing for a triathlon and had my leg crushed. I was 4 years in physio, in and out of a wheelchair along with 3 operations. The end result was - no more running, limited walking, leg could not fully extend and the pain of arthritis began.

I also suffered for many years with familial arthritis in my hands, twisted, swollen fingers along with 24/7 pain. I always continued with a healthy lifestyle, exercising regularly, Tai Chi and walking the doggies. I did not let the pain stop me from keeping fit. I was known among my friends as the gal who could do anything regardless of how difficult it was. I was a bit of a role model for some.

In 2006, my life changed for the worse, I became more and more depressed, had a total lack of energy, my previous mental drive became 'mush' and it was all I could do to drag myself for my doggies' daily walks. I was in fear of becoming one of those 'old ladies' that lie around eating bon-bons. It was hard to believe it was me!

The end of February 2007, I first took the glutathione supplement and three days later I returned with the vitality and drive that I had always enjoyed! I am talking three DAYS, not years! I was back to being me. Yes, I still had pain BUT, 3 days

after starting the supplement (2 packets a day) I commented to my husband that my eyesight was clearer as was my mental focus. It continued to improve to the point

that I no longer used my glasses while driving at night. After four months I had my eyes checked by my specialist and he confirmed that yes indeed, "your eyesight has improved!"

My mental focus changed immediately from being in a depressed state to one of excitement waking to a new day! I felt absolutely wonderful and in such a positive state. I have suffered with Restless Legs Syndrome and that was gone within a month — that was a delightful surprise. The next to go was the pain of arthritis — it took 5 weeks. Now my rings spin around on my fingers, no leg pain and I can enjoy lying down in bed. I am now back on the treadmill, doing walk/run for one hour at an incline and practicing for the New York Marathon. My gym workout is 3 days
a week. When I complete my walk/run (which I increase on a 2-week basis), I drop down and do 60 FULL pushups, then do stretches and yoga poses. I also do weapons Tai Chi weekly and Pilates. I also run my own business. My life is good — really good!

Cindy, Improved Cell Function and Anti-Inflammation
Hi, my name is Cindy M. I've suffered with severe scoliosis since I was 12 years of age. I also have a lower back problem that caused my scoliosis; which is known as Spondylolisthesis. I was in severe pain. I went through surgery at 13 and was in a body cast for 9 months and in bed for 6 months. I couldn't sit up or hang my leg off the bed, I was basically confined to my bed. They did the surgery to slow the curve down and I didn't have your typical surgery that you would have for scoliosis, because of my Spondylolisthesis. I had a Harrington type pin placed in my lower back instead of rods. Prior to all of this I wore a Milwaukee brace for two years. It didn't work because of my lower back, however. Now they would like to go in and put four Harrington rods in from top to bottom.

And also some stainless-steel pins in the front to secure what they would have to do in the back. My doctor at University of Michigan has told me that he would like to tell me that he's doing it to get rid of my pain but he is not. My spine not just

curving, but it's turning my torso and they would like to try to stop that. I have suffered every day of my life with this pain. I have tried several different natural methods and I didn't choose synthetic pain killers because this would be with me for the rest of my life, and I would have to take stronger doses with each passing year.

The day I was introduced to the glutathione supplement, I was in severe pain. I was very skeptical because of all the things I've tried. But

I was always praying something would work. So I took the glutathione supplement and I went and rested because I didn't think I was going to be able to go do errands that I had to do. Twenty minutes later, I started feeling better. I got up and started moving around and my pain was gone! I didn't say anything to my family because I was still skeptical, wondering, "was this really this supplement? How could it work this fast?"

So I finished the week's supply and two days went by without the glutathione supplement and I felt like I had been hit by a Mack truck. I was back to severe pain, calling everyone to see if I could get some more. I've never done crack, but I felt like an addict. I was looking for that fix. At that point I knew that it was the glutathione supplement. It's been almost four months now, and the glutathione supplement has changed my life. My quality of life has never been this good since I was a little girl. I know everybody is different. It might not work on some people as fast as it did on me, but it was like the forest fire was put out on my back. I still have scoliosis but I'm not living with pain anymore.

Joanne, Improved Cellular Function

I am 61 years young — feeling like I'm 39 and holding due to the glutathione supplement! I can think more clearly now (less senior moments), major pain nearly gone - more energy. I love to dance and there is no more lactic acid after dancing or exercise! Inflammation is the cause of almost all pain, but with the glutathione supplement and my positive attitude, I am experiencing major pain relief. But my life wasn't always this enriched — healthwise!

I was diagnosed with fibromyalgia and osteoarthritis back in the late '80s - early '90's. I have been in pain since that time! Fibromyalgia is a condition where you

hurt all over your body. I would take over-the-counter pain medicine to help with the pain — but it would help for a short time only. My doctor gave me antidepressants a few years ago. I told him that I wasn't depressed. He told me that antidepressants work for the pain in fibromyalgia. So I went home and tried it. I took one tablet— a few minutes later I was sick to my stomach. I threw the pills in the garbage. So over the years I put up with the pain, dealing with it as best I

could. Due to this condition, I only slept 3-4 hours a night as well. And we all know that as we sleep — our bodies are repairing themselves. A person needs their proper sleep or they can't function the next day!

But since learning about the glutathione supplement — I've been taking it since July 9, 2007 noticing AMAZING RESULTS within 48 HOURS! First of all, I noticed my pain was not as bad as it used to be — my arms and legs had a lot less pain. As the days went by, the pain got even less! I have a great sleep every night now and energy galore. An amazing supplement!

Kay, Improved Cellular Function

"This is Kay C. I am almost 96 years young and live in Burnaby, British Columbia, Canada. Since starting on the glutathione supplement about seven months ago, I have had a number of positive changes, but for one in particular, I am most grateful.

For several months I had been having a problem with my right eye being sore and "fuzzy" and I was using drops several times a day. I was afraid I was losing the sight in that eye. An eye doctor told me I had macular degeneration, confirmed later by an eye specialist. Neither gave me any positive help. Three days after starting on the glutathione supplement, I looked in the mirror and was surprised to note I could see a "little bit" better. After eight days, I was looking out the window and could not believe how well I could see, and couldn't remember when I had stopped using eye drops. That is the way the supplement works — all of a sudden you notice a positive change in problems that you were just living with as part of life. For example, itchy skin disappeared after many years, my hearing is a "bit" better, and I'm sleeping better. My right foot had intermittently been very painful. It was thought to be gout but recent blood test showed it was not. Although the pain

had gone, I had swelling and inflammation. One day I noticed that was gone. I also had shooting pains in different parts of my body, especially at night, but recently noticed they have disappeared. My energy level is great and at almost 96, I am living a very happy, healthy and active life. ***I have invitations out for my 100th birthday!***

Xarhis, Improved Cellular Function and Anti-Inflammation

I am absolutely excited about this glutathione supplement because it helped me with

two major health concerns: ileitis and lymphedema! The ileitis inflammation was located in the "terminal ileum" (area of the small intestine) just before the ileocecal valve to the large intestine. Apparently, this condition started some months prior from food poisoning. Over a period of months and delays in getting a correct diagnosis, I began to experience ongoing significant pain in the lower right area of my abdomen. It got to the point I literally could not sit, stoop, bend, wear tight clothing or walk without PAIN! Certain foods began to bother me, as well. The only way to get relief was to eat bland food, wear a robe and be in a reclining position.

Finally, I had a CT Scan that showed "thickening" in that area attributable to infection and inflammation. Upon seeing a specialist in gastroenterology, I was given an antibiotic for the "infection" (presumably, caused by an amoeba), but was told the "inflammation" would take a "long, long time" to heal. In fact, the specialist informed me that since this condition had been left that long, he believed this thickening could very well already be ulcerated putting me at risk for Crohn's disease. The recourse for that could be surgery or Prednisone. I wanted neither. I was encouraged to have a colonoscopy after the antibiotic. However, I postponed this exam because I only felt 90 percent better and had "some" continued pain. I also had an Alaskan cruise I wanted to take two weeks later; and I was concerned about the risk of possible perforation by the camera used in the exam (in my mind) designed for a colon and not a much smaller ileum.

All of this was stressful to me because in 1994 I faced the big "C" of cancer and I certainly didn't want to face another big "C" for Crohn's disease! I knew several people who had it and I didn't want it. Being into natural health alternatives, I

started on chlorophyll capsules and concentrated whole leaf aloe vera. It seemed to help some, but I was still having pain and knew I wasn't well enough for me to believe I could make the cruise.

I heard about the glutathione supplement and obtained a week's supply. On the first day, I noticed a lot of energy. By the second day, I began to have less pain and within days I was actually able to increase my activities. After only taking eight (8) packets of the supplement, I saw my physical therapist for a scheduled manual lymphedema massage. (During my bout with breast cancer, I worked with natural herbs in lieu of chemo or radiation and my cancer was gone, but I was still left with lymphedema. My surgeon removed auxiliary lymph nodes, although I was assured they would not be.) My therapist, within a few minutes of putting her hands on me, asked excitedly, "What are you taking? What are you doing differently?!" The glutathione supplement had reduced some of the swelling from retained fluids and it softened much of the tissue that was usually hardened by trapped fluids from adhesions that would often take the therapist 20 minutes just to soften it. Immediately, she noticed my tissue was different. Never had it been like this during all the eight years she treated me, nor when I had taken chlorophyll or aloe vera in the past, so, it had to have been the glutathione supplement! (By the way, my lymphedema is still improving and I feel like I'm getting my life back.)

After only 14 packets of the glutathione supplement, I also knew it had significantly helped my ileitis condition. There now was no question about packing for the trip! I was able to drive ten hours the first day toward Canada for the cruise, with no problem. Just two weeks prior, I still could not sit more than a half-hour without experiencing some level of pain. I made the cruise and handled it fine: sitting, walking, climbing stairs, dancing, wearing my pretty "tight" clothes, eating whatever I wanted now (gained 8 pounds) and had no problems whatsoever! Upon returning home, I took only four more packets of the supplement (making it a total of 18 packets) before my scheduled colonoscopy and "knew" even before the exam that I was fine — and I was! The specialist took the camera into the ileum and it was normal.

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I have attempted to select illustrative references that bear directly on the topics rather than include an encyclopedic listing.

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