

## FAQs

### WHAT IS GLUTATHIONE?

#### As an Antioxidant

Glutathione (GSH) is your body A.I.D. (A-antioxidant, I- immune system, D- detoxifier). It is a small protein molecule formed from the amino acids cysteine, glycine and glutamic acid. It is produced normally by the body in response to today's environment such as pollution in the air we breath, water we drink, chemicals & pesticides in the food we eat that cause damages in our cells & system.

Glutathione is often referred to as Master Anti-oxidant in the body.

“small molecule made up of linked amino acids and anti-oxidant naturally produced in the body. It has been widely heralded for its importance for good health and long life. Glutathione in increased dose posts an remarkable good 'side effect' such as SKIN WHITENING”.

Its skin whitening regimen (whitening capsule) has been widely used in Asia and has been reported to be the Asian Most Prescribed Oral Skin Whitener among the skin whitening products. And often referred to as bleaching pill, bleaching capsule, whitening pill or whitening capsule in Asia. There are several L Glutathione preparations in the market but not all can really guarantee a good result.

“the greater the exposure to toxins, the faster the body uses up its supply glutathione. Without the protection of Glutathione, cells die at a faster rate, making people age quicker & putting them at risk for toxin induced diseases including cancer” .

Glutathione is considered to be the most powerful, most versatile, and most important of the body's self-generated antioxidants. Among glutathione's many important properties are:

1)

Is found in almost all living cells. The liver, spleen, kidneys, pancreas, and the lens and cornea, have the highest concentrations in the body.

2)

It is a powerful antioxidant and thus neutralizes free radicals and prevents their formation

3)

Important role in immune function via white blood cell production and is one of the most potent anti-viral agents known

4)

It is one of the strongest anti-cancer agents manufactured by the body,

5)

Glutathione is able to reduce oxidized Vitamin C and Vitamin E back to their unoxidized state,

6)

It is used by the liver to detoxify many toxins including formaldehyde, acetaminophen, benzpyrene and many other compounds and plays a key role in Phase I and Phase II detoxification reactions

7)

It is an antioxidant necessary for the protection of proteins; is involved in nucleic acid synthesis and plays a role in DNA repair,

8)

It maintains the cellular redox potential

9)

Glutathione levels decrease with age. It is involved in cellular differentiation and slows the aging process

10)

Protects the integrity of red blood cells

11)

Glutathione is involved in maintaining normal brain function

## USES / BENEFITS OF L GLUTATHIONE

## Good Health

- 

As your body's MASTER ANTIOXIDANT -because glutathione participates directly in the destruction of reactive oxygen compounds. Glutathione destroys free radicals, is involved in the detoxification of foreign compounds and supports the normal active functioning of the immune system.

- 

## Require in detoxifying nicotine

- 

## Body's defense against pollutants and ultraviolet radiation

- 

Highest concentration of glutathione is found in the liver w/c is the principal organ involved in the detoxification and elimination of toxic materials. Interestingly, glutathione also acts to reconstitutes vit C and E after they have been oxidized, and therefore plays a determinant role in their function. (Convert fat-soluble substances into water-soluble GSH conjugates, in order to facilitate their excretion). Its main purpose is to detoxify the liver of many harmful substances that accumulate over the years but cannot be purged naturally. These toxins include alcohol, heavy metals such as mercury, lead and cadmium, and pesticides which glutathione extracts from the body so they can be expelled through urine or bile.

- 

Plays an important role in cancer prevention and treatment.

- 

“ANTI-AGING CAPSULE” by aiding in the breakdown of oxidized fats.

- 

Increases sperm count for men with low sperm counts.

- 

Low glutathione levels are found in immune compromised individuals, Neuro-degenerative diseases such as multiple sclerosis, ALS, Alzheimer, and Parkinson's disease, arteriosclerosis, male infertility, pregnancy complications, cataracts, damage from many pharmaceutical drugs, cancer and poor survival rate for patients with AIDS.

- 

High levels of Glutathione appear to protect against the dangers of cancer, heart disease, premature aging, autoimmune disease and chronic illness.

-

Protects individual cells & tissues of arteries, brain, heart, immune cells, kidneys, lens of eyes, liver, lungs and skin against oxidant damage.

## Whitens Skin

Have you ever wondered how comes so many Black, Asian and Indian celebrities are all very light skinned? Have you wondered why early childhood photos of many top celebrities show a much darker skin color than they have now? Glutathione in INCREASED DOSE helps whiten skin by modifying conversion of eumelanine (dark/brown/yellow pigmentation) to phaeomelanin (reddish white pigmentation). This is the main reason whiter skin are produced. Most dermatologists in Asia uses and recommends Glutathione as a whitening capsule or bleaching pills that is were proven to be very safe and effective.

- In Asia, Glutathione is mostly used as whitening and anti aging pill mostly used by celebrities and models. Recommended by dermatologist and skin care experts.

\*

## Dark spots remover

\*

## Prevents pimples and removes blemishes

\*

Whitens the skin / help cure MELASMA

\*

Anti-aging and anti-wrinkles (delaying the sign of aging)

\*

Makes skin stay supple, smooth, fresh and radiant

\*

Treats skin ulceration

\*

Enhance healing of wounds

\*

Nourishes skin

## WHO NEEDS GLUTATHIONE?

Here are the people who will need L Glutathione supplement: smoker; alcohol drinker; those 40 years old and above; those who exercise excessively/body builders; low sperm count; those with liver problems; those with cataracts; those with MELASMA problem,those recovering from chemotherapy; those exposed to chemicals and pesticides; the immunocompromised; low immune system; those who want fairer and whiter skin; and consumers of fish oils.

## IS IT SAFE IN THE LIVER?

Regarding the safety of glutathione in the liver, it is said that “the levels of glutathione in the liver is critically linked to the liver’s capacity to detoxify.” This means that the higher the glutathione content, the greater the liver’s capacity to detoxify harmful chemicals. Typically, when we are exposed to chemicals like alcohol which can damage the liver, the concentration of glutathione in the liver is substantially reduced. This reduction makes the liver susceptible to damage.

## IS IT SAFE TO THOSE PERSONS WITH THYROID PROBLEMS?

YES.

“...both hypothyroidism and hyperthyroidism are associated with enhanced oxidative stress involving antioxidants.”

Reschu, Helsel, et. Al.

November, 2002

“...has a direct relationship with free radical formation and inverse relationship with levels of erythrocyte glutathione and glutathione peroxidase in human subjects.”

Turkish Journal of Endocrinology & Metabolism, Feb.,2001

## TOXICITY:

No toxicities have been reported or suspected as being associated with glutathione.

## CONTRAINDICATIONS:

None known, except for use during some forms of chemotherapy and radiation where antioxidants are contraindicated due to their inhibition of the free radical formation which is an integral part of the therapeutic mechanism.

## INTERACTIONS:

Nutrient affecting drug – CISPLATIN

Nutrient affected by drug and affecting drug – HALOPERIDOL

## OVERDOSAGE

There have been no reports of glutathione overdosage in the literature.

## DOSAGE AND ADMINISTRATION

Glutathione is available as a single ingredient dietary supplement or in combination products. Dosage ranges from 50 to 1000mg.

## ADVERSE REACTIONS

Oral doses of up to 1000 milligrams daily are well tolerated. There are no reports of adverse reactions.

## WHAT IS THE DOSAGE?

### ANTIOXIDANT/ ANTI-AGING:

10 mg/kg/day

Ex. 50kg male

50kg body weight x 10mg = 500 mg/day

### SKIN WHITENING (double increased dose)

20-40 mg/kg/day

Ex. 50 kg female

50kg body wt x 30mg (median of 20 & 40) = 1500mg/ day in 3 divided doses

Duration of Intake for skin whitening:

If your skin is medium brown, take it for at least one to three months. A person with dark brown skin will need glutathione for at least three to six months. Those with very dark skin should take it for six to 12 months. A person with dark skin may need L-glutathione for at least two years or even more. Once a person has her desired skin color, the maintenance dose will just be 500mg once a day.

#### IMPORTANT:

A person taking L glutathione should take Vitamin C two to three times more than the dose of L Glutathione. Why is Vitamin C needed? This is to keep L Glutathione in its absorbable or reduced form. This will release the potential of Vitamin C's derivatives' whitening properties. It also prevents GSH from being oxidized and raises GSH by helping the body manufacture it.

#### What the Experts Say about Glutathione:

"Many neurological and psychiatric disease processes are characterized by high levels of oxidative stress and free radical formation, as well as abnormalities in glutathione metabolism and antioxidant defenses."

Source Dr. Gutman M.D. Glutathione GSH

"Glutathione is a substance, the levels of which in our cells are predictive of how long we will live. There are very few other factors which are as predictive of our life expectancy as is our level of cellular glutathione. Glutathione has been called the "master antioxidant", and regulates the actions of lesser antioxidants such as vitamin C, and vitamin E within the body. "We literally cannot survive without this antioxidant," Earl Mindell, R.Ph., Ph.D. "What You Should Know about the Super Antioxidant Miracle"

"No other antioxidant is as important to overall health as glutathione. It is the regulator and regenerator of immune cells and the most valuable detoxifying agent in the human body. Low levels are associated with hepatic dysfunction, immune dysfunction, cardiac disease, premature aging, and death." The Immune System Cure, Lorna R. Vanderhaeghe & Patrick J.D. Bouic, Ph.D.

- 

"...that everyone should take antioxidant supplements and recommends about 4000mg of Vitamin C per day as a part of that regimen"

Dr. Anthony Verlangieri, Director of thetherosclerosis  
Reseach Laboratory and Professor of Pharmacology  
Toxicology of the Univ. of Mississippi states

•

GSH is one of the 14 “Superfoods” listed in SuperFoods Rx : Fourteen Foods That Will Change Your Life, co-authored by Dr. Steven Pratt, an authority on food and ageing.

•

“Without GSH, other important antioxidants such as vitamins C and E cannot do their job adequately to protect your body against disease”

Allan Somersall, Ph.D., M.D., and Gustavo Bounous, M.D. FRCS(c) in Breakthrough in Cell Defense.

•

“Blood GSH levels rose nearly 50% in healthy individuals taking 500mg of Vit. C because it raises GSH by helping the body manufacture it and at the same time prevent GSH from being oxidized.”

– Dr. Murray's Newsletter 7/30/2003

Supplemental detoxicants become necessary as our environment becomes increasingly polluted. Our food and water sources are contaminated with chemicals. One of our main defenses against pollutants is glutathione, which is present in the liver in high concentrations. Glutathione acts as a detoxifying agent by combining with undesirable substances and ridding the body of them through urine and bile. It is important to note that unless the Colon, Liver and Blood are also detoxified, the benefits of Glutathione as a detoxicant may be minimized.

### To Get a Little More Technical About Glutathione

"Glutathione is a ubiquitous tripeptide molecule, consisting of three amino acids joined together. These are cysteine, glutamic acid and glycine - three of the twenty two amino acids which comprise the building blocks of all known proteins. In general, the amino-end of one amino acid combines with the acid-end of another to form a peptide bond with the elimination of water. Chains of amino acids are called proteins. The sequence of amino acids and the arrangement in space of each peptide bond defines some specific structural features of all proteins and oligopeptides (few amino acids in sequence) that relate to their function."

### Functions of Glutathione

Enhancing the Immune System - Your bodies immune activity, involving unimpeded multiplication of lymphocytes and antibody production, requires maintenance of normal levels of glutathione inside the lymphocytes.

Antioxidant and Free Radical Scavenger - Glutathione plays a central protective role against the damaging effects of bacteria, viruses, pollutants and free radicals.

Regulator of Other Antioxidants - Without glutathione, other important antioxidants such as vitamins C and E cannot do their job adequately to protect your body against disease.

A Detoxifying Agent - Another major function of glutathione is in the detoxification of foreign chemical compounds such as carcinogens and harmful metabolites.

### Glutathione (Psychoneurobiology)

"Free radicals and oxyradicals have been recognized by psychoneurobiologist as playing an important role in the development and progression of many of these disorders. The brain is particularly susceptible to free radical attack because it generates more oxidative-by-products per gram of tissue than any other organ. The brain's main antioxidant is glutathione- its importance cannot be overstated."

"Oxidative stress and glutathione are important factors in such various disorders as brain injury, neurodegenerative disease, schizophrenia, Down syndrome and other pathologies."

### Disorders of the brain and nervous system that are linked to oxidative stress

Brain Injury

Neurodegenerative disease

Others

Brain injury

Parkinson's disease

Schizophrenia

Trauma

Alzheimer's dementia

Down syndrome

Stroke

Multiple sclerosis (MS)

Tardive dyskinesia

Ischemia

Lou Gehrig's disease (ALS)

Sleep deprivation

Toxicity of lead, mercury, etc.

Lipofuscinosis (Batten's disease)

Huntington's chorea

"Many neurological and psychiatric disease processes are characterized by high levels of oxidative stress and free radical formation, as well as abnormalities in glutathione metabolism and antioxidant defenses."

Source Dr. Gutman M.D. Glutathione GSH

Dr. Perlmutter: "Eighty to ninety percent improve dramatically. It's felt that the mechanism that allows it to work is in increasing the sensitivity to certain receptors to dopamine. Glutathione doesn't raise dopamine levels, but it allows the dopamine in the brain to be more effective. That's not a new idea in medicine. Diabetic drugs work not by increasing insulin, but by increasing the receptors to insulin. Glutathione not only increases sensitivity to dopamine, but also to serotonin, which may explain why many of our depressed PD patients have a remarkable improvement."

Increasing glutathione in the body has been proven to be essential in the treatment of disease. Antidepressants and other medications deplete the body and brain of glutathione.

- 

Glutathione is a substance, the levels of which in our cells are predictive of how long we will live. There are very few other factors which are as predictive of our life expectancy as is our level of cellular glutathione. Glutathione has been called the "master antioxidant", and regulates the actions of lesser antioxidants such as vitamin C, and vitamin E within the body. "We literally cannot survive without this antioxidant," Earl Mindell, R.Ph., Ph.D. "What You Should Know about the Super Antioxidant Miracle"

- 

"Without glutathione, other important antioxidants such as vitamins C and E cannot do their job adequately to protect your body against disease." Breakthrough in Cell Defense, Allan Somersall, Ph.D., M.D., and Gustavo Bounous, M.D. FRCS(C)

- 

"No other antioxidant is as important to overall health as glutathione. It is the regulator and regenerator of immune cells and the most valuable detoxifying agent in the human body. Low levels are associated with hepatic dysfunction, immune dysfunction, cardiac disease, premature aging, and death." The Immune System Cure, Lorna R. Vanderhaeghe & Patrick J.D. Bouic, Ph.D.

- 

Glutathione (L-gammaglutamyl-L-cysteinylglycine) is a tri-peptide of the amino acids cysteine, glycine, and glutamic acid. Glutathione is an antioxidant compound found in living animal and plant tissue. It takes up and gives off hydrogen and is important in cellular respiration. A deficiency of glutathione can cause hemolysis (destruction of red blood cells, leading to anemia) and oxidative stress. Glutathione is essential in intermediary metabolism as a donor of sulfhydryl groups which are essential for the detoxification of acetaminophen. [PDR Medical Dictionary. Spraycar. 1999] Selenium is a structural component of, and a co-factor for the antioxidant enzyme glutathione peroxidase.

## OVERDOSAGE

There have been no reports of glutathione overdosage in the literature.

## DOSAGE AND ADMINISTRATION

Glutathione is available as a single ingredient dietary supplement or in combination products. Dosage ranges from 50 to 600 milligrams daily.

## ADVERSE REACTIONS

Oral doses of up to 600 milligrams daily are well tolerated. There are no reports of adverse reactions.

## Where is it found?

Dietary glutathione is found in fresh and frozen fruits and vegetables, fish, and meat.<sup>26</sup> Asparagus, avocado, and walnuts are particularly rich dietary sources of glutathione.

## Glutathione: Systemic Protectant Against Oxidative and Free Radical Damage

Dedicated to the memory of Professor Daniel Mazia, my PhD mentor and a pioneer in cell biology.

Parris M. Kidd, Ph.D.

## Glutathione Deficiency in Liver Diseases

GSH depletion has been suggested to represent an important contributory factor to liver injury, and to enhanced morbidity related to liver hypofunction<sup>[4]</sup>. In one small study, subnormal plasma concentrations of GSH were observed in cirrhosis patients, independent of their diet.<sup>47</sup> A larger study demonstrated a four- to eight-fold decrease in plasma GSH in 48 cirrhotic patients versus 18 healthy volunteers.<sup>48</sup> A significant decrease in cysteine in severe cirrhosis also was observed.

Altomare and collaborators measured liver GSH and GSSG in chronic alcoholics, in patients with nonalcoholic liver diseases (fatty liver, acute and chronic hepatitis, cirrhosis), and control patients (admitted for uncomplicated abdominal procedures).<sup>49</sup> They found GSH decreased in the alcoholic and nonalcoholic liver disease groups, compared with the control groups; GSSG was also significantly higher in these groups. The investigators postulated that decreased GSH and/or increased GSSG could have contributed to liver injury susceptibility and toxic risk in these patients, while altering fundamental cell functions such as protein synthesis, enzyme activities, transport processes, microtubular and other structural support, and secretion mechanisms. Other studies also have documented plasma and liver GSH decreases in patients with acute viral hepatitis, and in chronic cases of hepatitis, alcoholic liver disease, or nonalcoholic cirrhosis.<sup>50,51</sup>

Deficiency of GSH caused by one toxin may render the liver more vulnerable to other toxins. One example is acetaminophen intake superimposed on the alcohol-damaged liver.<sup>51</sup> In a group of chronic alcoholics with GSH deficiency, acetaminophen did not lower GSH unless gamma-glutamyl transferase (GGT) was high to begin with. Those subjects with abnormally elevated GGT manifested abnormally lowered plasma GSH after acetaminophen intake, and were therefore more predisposed to further liver damage from other toxic agents.

## Glutathione and Lung Diseases

Being directly in the path of airborne materials, the lung tissue is particularly at risk from oxidative stressors such as cigarette smoke, atmospheric pollutants, and other inhaled environmental toxins.<sup>28</sup> GSH and GSH-associated enzymes present in the epithelial lining fluid (ELF) of the lower respiratory tract may be the first line of defense against such challenges.<sup>41,52,53</sup> Sustained oxidative challenge to the lung results in depletion of GSH and other antioxidants from the lungs.

GSH deficiencies have been documented in a number of pulmonary diseases, including acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and neonatal lung damage.<sup>4</sup> Patients with ARDS and sepsis have a deficiency of GSH in the ELF as compared with healthy subjects,<sup>52,53</sup> and a greater percentage of the total ELF glutathione is in the oxidized form (GSSG), indicating increased oxidative stress in the lower respiratory tract.<sup>53</sup> When GSH was repleted in their ELF using intravenous N-acetylcysteine, patients in intensive care regained independent lung function and left the intensive care unit significantly faster.<sup>54</sup>

Airway inflammation in asthma also features increased generation of free radical oxidants. As earlier indicated from animal experiments, subjects with mild asthma seemingly have the capacity to adaptively increase their antioxidant defenses, as manifested in their alveolar GSH concentrations being significantly higher than healthy volunteers.<sup>55</sup> By contrast, in patients with idiopathic pulmonary fibrosis, GSH concentrations in the ELF are a mere 25% of normal, and may contribute to the pathophysiology of this disease.<sup>41</sup>

Infants born prematurely at 25 weeks average gestational age were found to have significantly lower pulmonary GSH than did infants born at 40 weeks.<sup>56</sup> Among infants born at 35 weeks, those with lower GSH levels in their ELF were found more susceptible to subsequent chronic lung disease. These findings suggest that poor lung GSH status at birth may predispose the infant to respiratory pathologies.

## Glutathione, Immunity, and HIV Disease

As with other cell types, the proliferation, growth, and differentiation of immune cells is dependent on GSH. Both the T and the B lymphocytes require adequate levels of intracellular GSH to differentiate, and healthy humans with relatively low lymphocyte GSH were found to have significantly lower CD4 counts.<sup>57</sup> Intracellular GSH is also required for the T-cell proliferative response to mitogenic stimulation, for the activation of cytotoxic T "killer" cells,<sup>58</sup> and for many specific T-cell functions, including DNA synthesis for cell replication, as well as for the metabolism of interleukin-2 which is important for the mitogenic response.<sup>59</sup>

Experimental depletion of GSH inhibits immune cell functions, sometimes markedly,<sup>58,60</sup> and in a number of different experimental systems the intracellular GSH of lymphocytes was shown to determine the magnitude of immunological capacity.<sup>58</sup> These and other findings indicate that intracellular GSH status plays a central role in the functioning of immune cells.

In the auto-immune diseases of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and as seen in aging, T lymphocytes demonstrate depressed responsiveness to antigens and mitogens, perhaps because of insufficient IL-2 production (see reference 60 for a review). Patients with RA had low blood sulfhydryl (-SH) status,<sup>60</sup> as did patients with Type II diabetes or with ulcerative colitis.<sup>13,60</sup>

Chronic viral infections may trigger GSH depletion in circulating immune cells or GSH/GSSG imbalance. Patients chronically infected with the hepatitis C virus were found to have low GSH in their circulating monocytes.<sup>13</sup> Monocyte GSH levels were abnormal in early HIV-1 disease,<sup>61</sup> then in patients with advanced disease the GSH levels normalized in monocytes but the GSH/GSSG ratio became abnormal. Significant decreases in the plasma levels of both cysteine and cystine also were documented in subjects with HIV-1 infection.<sup>61-63</sup> Since cysteine is a rate-limiting precursor for GSH synthesis, an associated decrease of GSH in the lung ELF was highly suggestive of a systemic GSH insufficiency

in these subjects.<sup>64</sup> The most marked GSH decreases occurred in subjects who were asymptomatic but had CD-4 counts below 400. Both the abnormal cytokine expression and the progression to weight loss seen in HIV-1 disease may be linked (at least in part) to abnormalities in the uptake of GSH precursors by immune cells of HIV-1 subjects, and/or to abnormalities in their synthesis of GSH.

## Neurodegeneration Related to Glutathione Depletion

Perhaps the most challenging aspect of the clinical research on free radicals and antioxidants has been to relate oxidative stress to disease causality. Thus, GSH depletion has been hard to position as "the smoking gun" at the scene of the "crime." However, few experts in this field seriously continue to doubt that free-radical propagation and associated antioxidant depletion are involved in at least some types of degenerative tissue breakdown.<sup>25</sup> Numerous studies link free-radical damage with degenerative brain conditions.

The brain is particularly susceptible to free radical attack: it is highly oxygenated, which makes it vulnerable to endogenous oxygen radical production, and it has a high proportion of unsaturated lipid which makes it vulnerable to peroxidation. In addition, those brain regions that are rich in catecholamines are exceptionally vulnerable to free radical generation. The catecholamines adrenaline, noradrenaline, and dopamine can spontaneously break down (auto-oxidize) to free radicals, or become metabolized to radicals by the endogenous enzymes known as MAO Ñthe monoamine oxidases.<sup>65,66</sup> One such region is the substantia nigra (SN), where a connection has been established between antioxidant depletion (including GSH) and tissue degeneration.

Parkinson's Disease (PD) is based primarily in the SN. It is to date the most suggestive example of likely causality of oxidative stress in neural degeneration. Lipid peroxidation had been reported increased in this condition, although causality was not established;<sup>67</sup> then studies found GSH levels were dramatically decreased in PD.<sup>68,69</sup> Jenner et al<sup>69</sup> suggested GSH depletion might have particular significance in PD, especially since such depletion often predates the emergence of clinical symptoms.

The melanized catecholaminergic cells found in large quantities in the SN contain less GSH peroxidase and tend to bind to redox-active metals, which makes them more vulnerable to free radical generation from their easily oxidizable melanin complement. Several studies have demonstrated increased levels of such metals, especially iron, in PD brains compared with controls (reviewed by Lohr and Browning<sup>67</sup>).

Several antioxidants have been measured decreased in PD tissue.<sup>4,69</sup> Indicators such as the disappearance of melanin from the SN, the increase of total iron and ferric iron, the marked decrease of GSH in the SN, the decreases in antioxidant enzyme activities, and the substantial increases of lipid peroxidation indicators, all argue for oxidative stress playing a role in the initiation and/or progression of PD.<sup>69</sup> In a study using high-dose antioxidants, Fahn<sup>70</sup> found that a combination of vitamin E (3,200 IU per day) and vitamin C (3,000 mg per day) could slow PD progression. Further controlled studies are needed that involve GSH precursors, administered preferably in combination with other antioxidants.

Tardive dyskinesia (TD), a movement disorder centered in the basal ganglia, has been linked to long-term treatment with neuroleptic drugs. The basal ganglia are exceptionally vulnerable to free-radical overload because they are so rich in dopamine as well as other catecholamines. By blocking dopamine receptors, neuroleptics may cause dopamine buildup in the basal ganglia that then increases free-radical production. Glutamate excess may also contribute to the free-radical overload in TD. Lohr and co-workers<sup>67</sup> also found elevated lipid peroxide levels in the cerebrospinal fluid of patients maintained on neuroleptics and exhibiting symptoms of TD. They succeeded in decreasing the severity of TD using high doses of vitamin E, and called for further trials with combinations of antioxidants.

Schizophrenia may have a component of free-radical overload. Lipid peroxides have been found elevated in the blood, and Phillips and co-workers found increased pentane gas, a marker for lipid peroxidation, in the breath of schizophrenics as compared with normal volunteers and with patients having other psychiatric illness.<sup>71</sup> The enzyme SOD (superoxide dismutase, which metabolizes superoxide radicals) was found increased, possibly as an adaptive response to free radical overload. Studies of antioxidant treatment in schizophrenia have been few; two recent studies that examined only vitamin C yielded conflicting results.<sup>67</sup> Especially since GSH peroxidase was also found to be reduced,<sup>72</sup> future trials with antioxidants in schizophrenia should include selenium and GSH precursor nutrients.

Down's Syndrome (DS), the classic mental deficiency disease resulting from a trisomy of chromosome 21, is known to feature increased systemic oxidative stress.<sup>39</sup> The 50% overexpression of SOD on chromosome 21 contributes to heightened fluxes of superoxide in all the tissues. Yet DS does not manifest until after birth; the mother's antioxidant defenses may protect the fetus until delivery. Reportedly, parents have experienced success with nutritional antioxidants in conserving their DS children's mental resources after birth.<sup>73</sup> DS children are also at greatly increased risk for an Alzheimer's-type dementia as they age,<sup>67</sup> and it should prove exciting to determine whether potent nutritional supplementation from birth can delay the onset of dementia in DS subjects.

Alzheimer's Disease (AD), though almost certainly multifactorial in its etiology, has both direct and indirect indications of free radical involvement. Increased lipid peroxides have been reported from the temporal and cerebral cortex of patients with AD as compared with controls.<sup>67</sup> Jenner<sup>69</sup> reported that iron was raised and GSH was decreased in the cortical areas; and Richardson and co-investigators<sup>74</sup> added iron to homogenates of frontal cortex from AD patients and found significantly higher lipid peroxide generation. Fibroblast cells cultured from patients with AD exhibited increased susceptibility to free-radical damage over controls; the sites of their increased vulnerability may be the mitochondria.<sup>67</sup> Glutathione metabolism may also be abnormal in AD; Adams and co-investigators<sup>68</sup> found GSH to be lower in the hippocampus, the primary site of short-term memory initiation, and Jenner<sup>69</sup> found that GSH was decreased in the cortical areas.

The evidence to date for possible oxidative stress in DS, PD, TD, schizophrenia and AD is suggestive, if not yet strongly persuasive. As pointed out by Jenner,<sup>69</sup> if oxidative stress does contribute to neural degeneration, whether it is eventually proven to be primary or secondary in the etiologic progression, the therapeutic rewards are likely to be great. Future trials are indicated with dietary GSH precursors, administered in combination with other antioxidants, antioxidant cofactors, and non-antioxidant brain-trophic nutrients such as phosphatidylserine.

#### Glutathione Abnormalities in Other Conditions

Human pancreatic inflammatory states, whether acute, acute recurrent, or chronic, have been linked to damage inflicted on the pancreatic tissue by oxygen free radicals.<sup>80</sup> Concomitantly, these patients suffered from a depletion of antioxidants. Many showed increased lipid peroxidation products in their pancreatic tissue, duodenal juice, and bile. After evidence of GSH over-oxidation (GSSG excess) in patients admitted to hospital with alcohol-provoked relapse of pancreatitis, one patient was treated with N-acetylcysteine (NAC), a precursor of GSH. Within 72 hours, the patient had improved significantly. This prompted a preliminary randomized trial of NAC on patients suffering from acute pancreatitis. Clinical status was significantly better on the second and third day in those patients with combined pancreatic and other organ failure who were treated with NAC.<sup>81</sup>

Chronic pancreatitis patients also have shown increased serum lipid peroxides, with those in relapse generally showing the greater increases.<sup>82</sup> Such patients often were deficient in several antioxidants. Uden and collaborators<sup>83</sup> did a small double-blind, crossover trial in which they gave selenium, vitamin A, vitamins C and E, and methionine (a cysteine precursor) to patients with pancreatitis (mixed acute and chronic). This therapy significantly reduced pain and prevented relapse, independent of the etiology and acuteness of the disease. Larger trials are needed, but to date supplementation with mixed antioxidants appears promising in pancreatic inflammatory states.

Metal storage diseases have become another area of focus for GSH and other antioxidant therapies. Both hepatic iron overload and copper overload feature increased lipid peroxidation and detectable free radical damage at the cell level.<sup>84</sup> Humans with thalassemia and secondary iron overload showed significant reduction in GSH reductase activity. Summer and Eisenburg examined copper-overloaded (Wilson's Disease) patients,<sup>85</sup> and found hepatic GSH markedly lower in biopsies of five out of six patients as compared with controls. Despite an impressive body of animal data indicating antioxidant depletion in iron and copper overload states, no randomized controlled trials have yet been conducted on humans.

Sickle cell anemia is a chronic hereditary anemia in which the lifespan of the red cell is markedly decreased, from an average 120 days to 17 days. Abnormal rod-like fibers of hemoglobin in the red cell cause an irreversible transition to a sickle shape, and "sickling crises" can be life-threatening. Sickling is associated with increased oxidative stress in the red cell, and depletion of antioxidants has been reported, including GSH.<sup>86</sup>

## Glutathione in Aging

Studies on GSH status with advancing age have been few, but to date there does appear to be a correlation between age-associated GSH depletion and poor health. Lang and collaborators<sup>87</sup> compared blood GSH concentrations between the healthy young and healthy elderly subjects. The 40 young subjects (20-39 years of age) had a blood GSH level 17% higher on average than the 60 elderly subjects (60-79 years). Julius et al<sup>88</sup> measured GSH in 33 persons of ages 60-79 years. Higher GSH concentrations were associated with good health, regardless of age; subjects with chronic diseases had lower mean GSH concentrations than those free of disease. Further studies should clarify whether systemic GSH status is indeed a predictor of good health with advancing age.<http://www.thorne.com/altmedrev/fulltext/glut.html>

## alpha lipoic acid

For use as a general antioxidant, a lower dosage of 20 to 50 mg daily is commonly recommended, although there is no evidence that taking lipoic acid in this way offers any health benefit.