Glutathione:

Life-Extending "Master Antioxidant"

By Ward Dean, MD

Glutathione (GSH) is a tripeptide molecule composed of glutamic acid, cysteine and glycine. It is one of the main nonprotein antioxidants in the cell, and has been referred to as the body's "master antioxidant."

Glutathione is present in nearly all living cells, and without it they can't survive. The major functions of glutathione in the body include protecting cells against the destructive effects of free radicals; detoxifying external substances such as drugs, environmental pollutants and carcinogens; maintaining cell membrane stability; regulating protein and DNA biosynthesis and cell growth; enhancing immunologic function through its influence on lymphocytes; prostaglandin synthesis; and amino acid transport.

Clearly, with such widespread functions, glutathione has major effects on health at the molecular, cellular and organ levels.1,2 Glutathione and its related enzymes glutathione peroxidase (GPx), and glutathione reductase (GR), constitute what is known as the "glutathione system" (Fig. 1).3

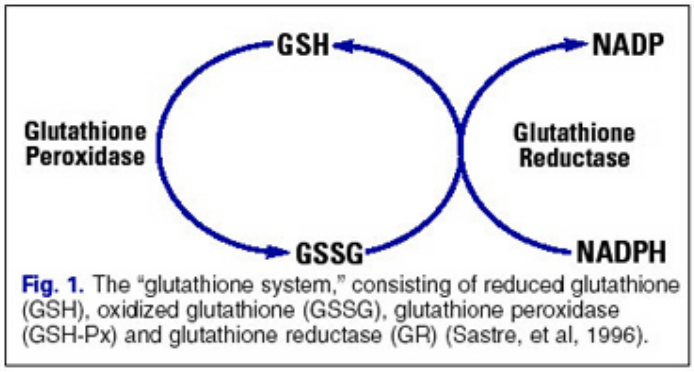

Fig. 1. The "glutathione system," consisting of reduced glutathione (GSH), oxidized glutathione (GSSG), glutathione peroxidase (GSH-Px) and glutathione reductase (GR) (Sastre, et al, 1996).

Mitochondrial glutathione is critical to the healthy cell, and is probably the most important antioxidant defense system within the mitochondria. Age-related alterations in these enzymes can have a profound adverse effect on health, as this article will explain.

Age-Related Changes in Glutathione

Drs. J.P. Richie and Calvin Lang, of the Department of Biochemistry, University of Louisville, were the first to propose that a glutathione deficiency might be a biochemical cause of the aging process. They demonstrated that glutathione levels decline with age in a number of organisms, including mosquitoes, mice, and man. They proposed that restoring glutathione tissue concentrations to those of younger organisms might result in an extension of the lifespan.

These scientists first tested their hypothesis using adult mosquitoes. They fed magnesium

thiazolidine-4-carboxylic acid (MgTCA) (which is known to increase glutathione) to the mosquitoes, and measured the insects' glutathione levels and lifespans. The MgTCA supplementation increased GSH levels by 50-100 percent, and increased www. lifespans by 30-38 percent over control values (Fig. 2), confirming the GSH deficiency hypothesis and demonstrating a specific biochemical mechanism of aging that can be nutritionally modified.4

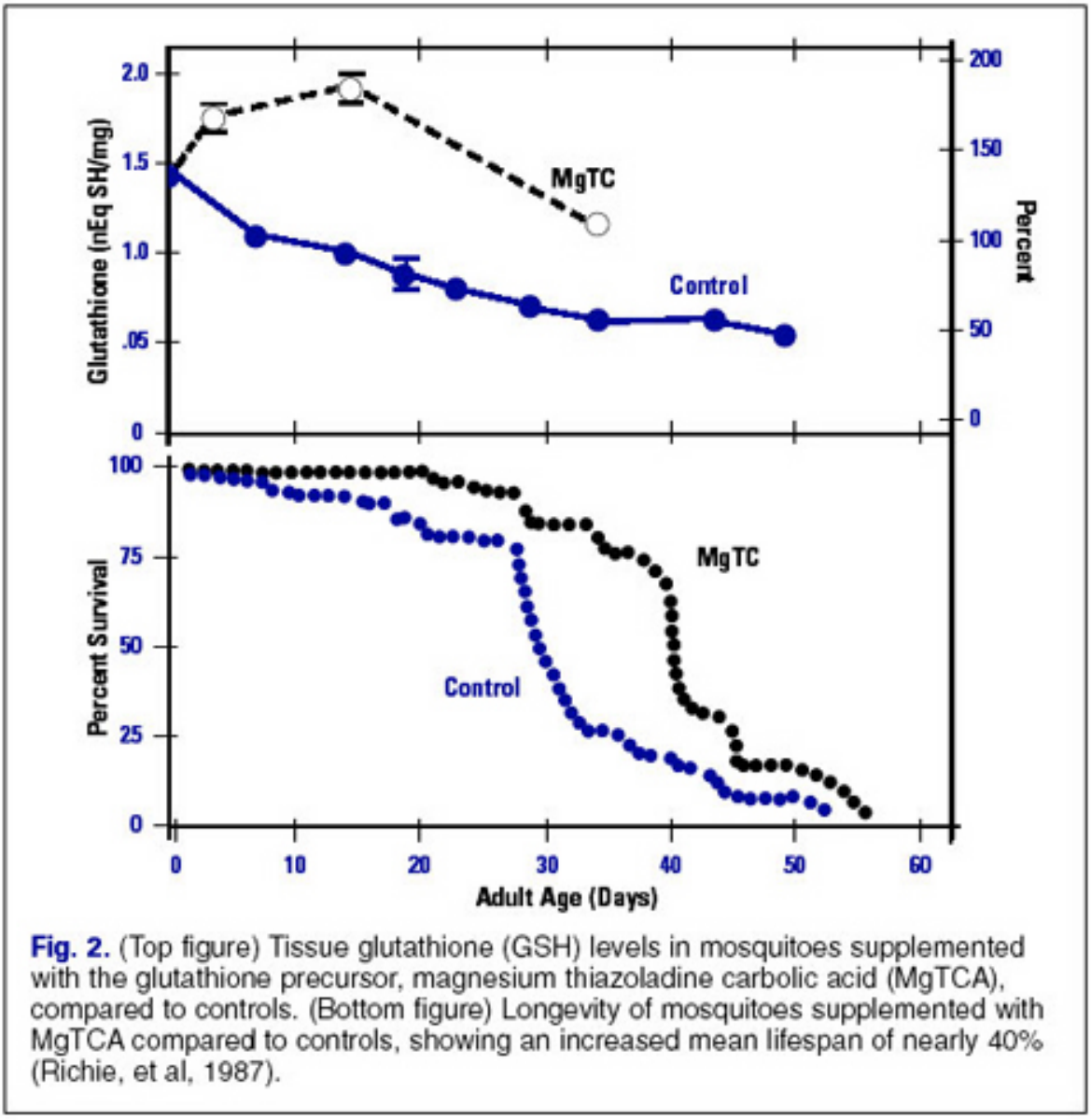

Fig. 2. (Top figure) Tissue glutathione (GSH) levels in mosquitoes supplemented with the glutathione precursor, magnesium thiazoladine carbolic acid (MgTCA), compared to controls. (Bottom figure) Longevity of mosquitoes supplemented with MgTCA compared to controls, showing an increased mean lifespan of nearly 40% (Richie, et al, 1987).

In a related study, Dr. G. Buonous of the Montreal General Hospital Research Institute, Quebec, studied the effects of a whey-rich diet on tissue glutathione concentrations and survival of 21-month-old mice (equivalent to a human age of about 55-60). The study was performed over six months, until the mice were the human equivalent of about 80 years old. As in the MgTCA-fed mosquitoes, glutathione tissue concentrations and longevity of the

whey-fed mice increased significantly above control levels.5

Dr. Lang and his colleagues, as well as a number of other scientists, found that blood glutathione levels predictably declined with age in healthy men and women ranging in age from 20 to 94, just as they do in mosquitoes, mice and rats.1,6

Scientists at the University of Pavia found that glutathione peroxidase (GSH-Px) levels also follow this age-related pattern up to about age 75 (Fig. 3), after which they noted a slight increase with age in a cross-sectional study (Fig. 4). They interpreted this as a self-selection process, which enabled those with the highest glutathione peroxidase levels to survive the longest.7

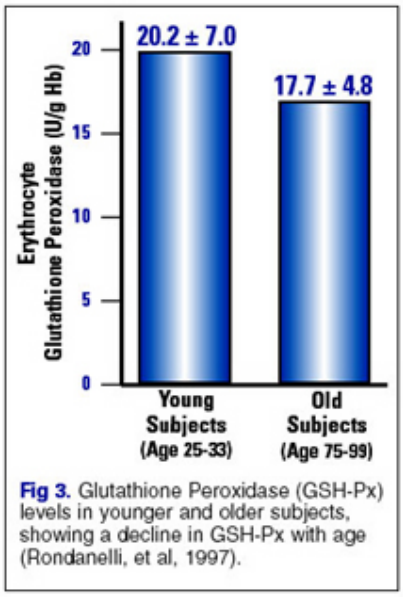

Fig 3. Glutathione Peroxidase (GSH-Px) levels in younger and older subjects, showing a decline in GSH-Px with age (Rondanelli, et al, 1997).

In another study of enzyme activity in the very old, Dr. Helle Anderson and colleagues at Odense University in Denmark compared the levels of glutathione reductase (GR) in 41 centenarians between 100-105 years old, to that in 52 community controls between the ages of 60-79. They found that the mean glutathione reductase (GR) activity was significantly higher in centenarians than in the group of younger elderly subjects, and that centenarians with the best functional capacity tended to have the highest GR activity.

They concluded that high GR activity appears likely to be associated with increased survival.8 In a later study, Lang's group evaluated glutathione levels in 87 women in excellent physical and mental health, ranging in age from 60 to 103. The scientists found that all subjects had very high blood glutathione levels. They followed these women for five years, and concluded that "high blood glutathione concentrations … are characteristic of long-lived women."9

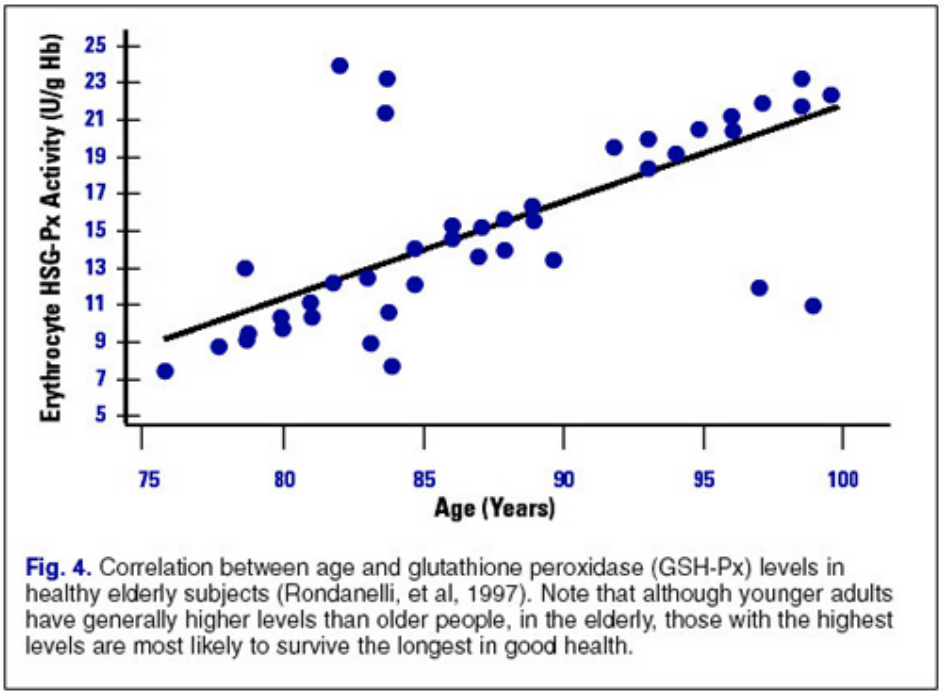

Fig. 4. Correlation between age and glutathione peroxidase (GSH-Px) levels in healthy elderly subjects (Rondanelli, et al, 1997). Note that although younger adults have generally higher levels than older people, in the elderly, those with the highest levels are most likely to survive the longest in good health.

Glutathione in Health and Disease

Just as high glutathione levels are related to increased survival and longer life in all organisms tested so far, lower levels are related to poorer health and a number of chronic degenerative diseases, including heart disease, arthritis, hypertension, diabetes, cancer, genitourinary, gastrointestinal, and musculoskeletal diseases, age-related macular degeneration (ARMD), preeclampsia, cataracts, chronic renal failure, leukemia, respiratory diseases like COPD and adult respiratory distress syndrome (ARDS), hearing loss, and AIDS.1,10-14

Lang concluded that decreased GSH is a risk factor for chronic diseases and may be used to monitor the severity and progress of the diseases.15 Conversely, Dr. Mara Julius of the Department of Epidemiology, University of Michigan, in a study of 33 subjects over the age of 60, found that higher glutathione levels were associated with fewer illnesses and higher levels of self-rated health, lower cholesterol, lower body mass index and lower blood pressures. The author noted that this was the first study that showed an association of higher glutathione levels with higher levels of physical health in a community-based sample.16

Glutathione and Detoxification

One of glutathione's primary roles in the body is to detoxify a number of drugs and toxins. Acetaminophen (APAP, i.e., Tylenol) has been studied intensively in regard to its glutathione-depleting properties, and with regard to glutathione's ability to prevent APAP-induced liver

and kidney damage.

Since GSH levels decrease with aging in all tissues, including the liver and kidney, older organisms are thus at even greater risk to APAP-induced liver and renal damage than younger organisms.

Lang's group studied the effect of APAP on the livers of mice of different ages, and the extent of GSH depletion and recovery. In control animals, GSH concentrations decreased about 30 percent over the lifespan of the aging mouse, compared to younger animals.

Four hours after APAP administration, GSH levels of the young, growing (3- to 6-month-old), mature (12-month-old), and old (31-month-old) mice decreased about 70 percent. The growing and mature mice recovered to near control values by 24 hours (94 and 66 percent, respectively). In contrast, old mice recovered only 41 percent in 24 hours (Fig. 5).

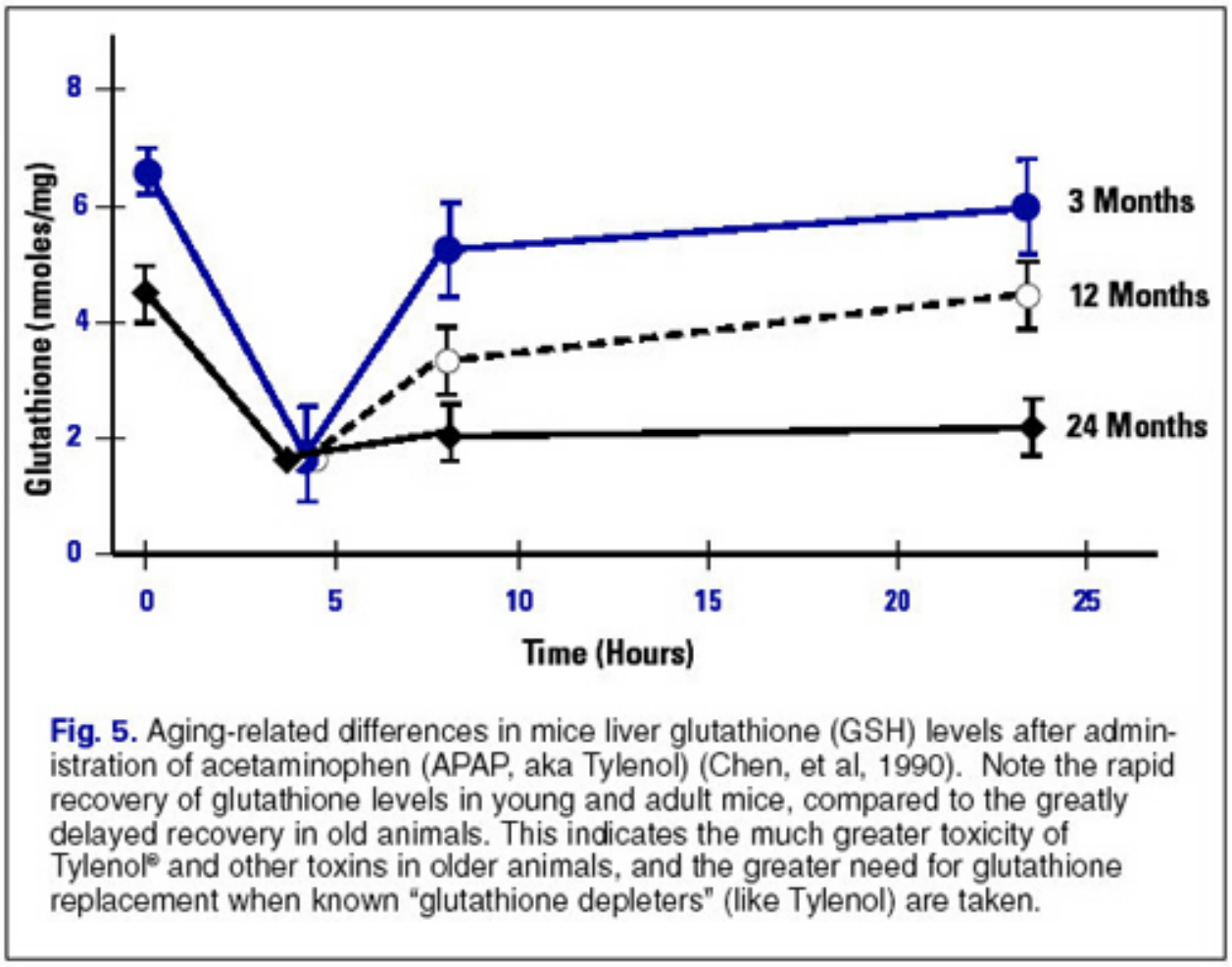

Fig. 5. Aging-related differences in mice liver glutathione (GSH) levels after administration of acetaminophen (APAP, aka Tylenol) (Chen, et al, 1990). Note the rapid recovery of glutathione levels in young and adult mice, compared to the greatly delayed recovery in old animals. This indicates the much greater toxicity of Tylenol® and other toxins in older animals, and the greater need for glutathione replacement when known "glutathione depleters" (like Tylenol) are taken.

These results clearly demonstrate that the aging mouse liver is not only deficient in GSH, but has a reduced recovery capacity.17,18 This illustrates the danger of chronic administration of glutathione-depleting drugs like Tylenol-especially to older people.

Increasing Tissue Glutathione Levels

It is clear that those with the highest glutathione levels are likely to live the longest in the best of health. A number of ways have been demonstrated to increase glutathione (GSH) and the glutathione enzymes, glutathione peroxidase (G-Px) and glutathione reductase (GR).

Several small studies have shown that moderate, prolonged physical exercise increases glutathione and its related enzyme levels in the blood and skeletal muscles.19,20

Many vitamins and nutritional supplements are also glutathione boosters. Lipoic acid, pine bark extract (pycnogenol), melatonin, bilberry, grape extract, and turmeric have all been shown to elevate glutathione. Oral glutamine may also raise tissue glutathione levels,21 although there are conflicting reports.22

I used to think that oral glutathione was destroyed in the stomach, and was not effective in raising glutathione concentrations. However, Dr. Steve Edelson, of the Edelson Center for Environmental and Preventive Medicine in Atlanta, Georgia, kindly sent me a number of articles that convinced me otherwise. These articles demonstrated that about 80 percent of oral glutathione is absorbed intact, and that the blood levels remain elevated for about three hours (Fig. 6).23-26

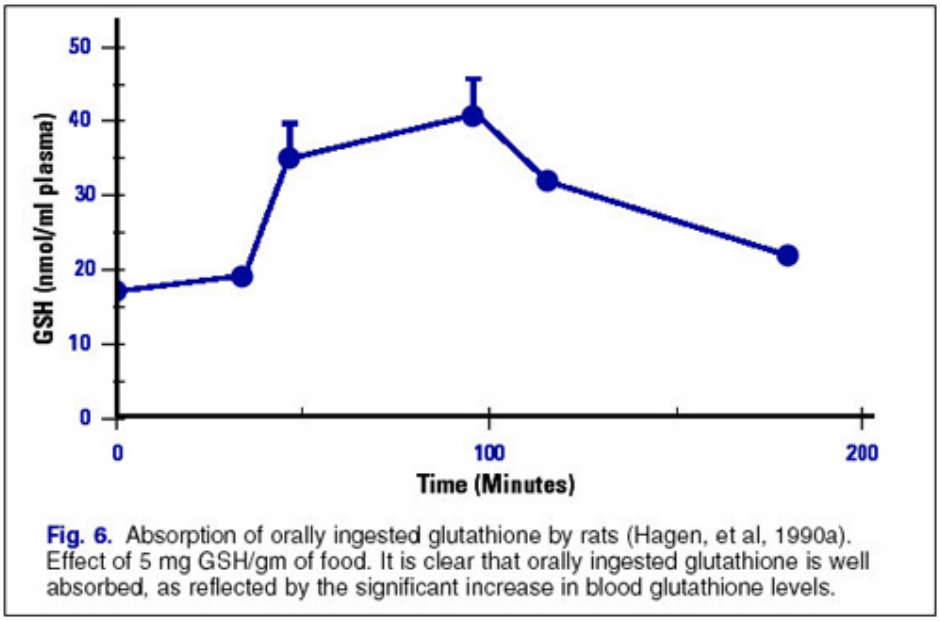

Fig. 6. Absorption of orally ingested glutathione by rats (Hagen, et al, 1990a). Effect of 5 mg GSH/gm of food. It is clear that orally ingested glutathione is well absorbed, as reflected by the significant increase in blood glutathione levels.

Foods that are high in glutathione include horseradish and cruciferous vegetables such as cauliflower, broccoli, cabbage, kale, and brussels sprouts. Dietary supplements that have been demonstrated to predictably raise blood glutathione levels are the glutathione precursors whey protein,5,27,28 and N-acetylcysteine (in a dose of 1,800-2,400 mg daily),12 or (as mentioned above) glutathione itself (recommended dose, 1-2 grams daily). A prudent person would probably use a combination of these modalities.

Many physicians are also using intravenous infusions of glutathione, ranging in dosages of 400-600 mg three to seven days a week for a number of conditions, including Parkinson's and Alzheimer's diseases, strokes, ALS, and other chronic degenerative diseases.29 Based on the work of Drs. Lang, Richie, Buonous, Perlmutter, and others, it appears that glutathione and its precursors should be used for the prevention and treatment of virtually every chronic degenerative disease.

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