How to boost your immune system and take advantage of your body's most powerful antioxidant and detoxifier

GLUTATHIONE

GSH

YOUR BODY'S MOST POWERFUL HEALING AGENT

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IMPORTANT NOTE

Glutathione as a Dietary Supplement

Before continuing we must clarify one particular aspect of the glutathione story. When people find out about GSH, they want to go to their health store, buy some and _take' it. Although it can be found in this form, eating glutathione has negligible effects on your health. It is quickly broken down in your digestive tract and eliminated. GSH must be manufactured within your cells, which is exactly where it appears—in every cell of your body. The only effective way to do this is to give your body the building blocks it needs to manufacture glutathione for itself. Some pharmaceutical drugs have been developed to provide these precursors and there are also natural ways to raise glutathione levels, notably the use of undenatured (bioactive) whey proteins. These are referred to throughout this book and are described in chapter 4.

CHAPTER 1 GLUTATHIONE

You may or may not have heard of _glutathione.' However, researchers and scientists continue to discover the importance of this substance in health and disease and in the next few years its name will become as well known as terms like _cholesterol' or _vitamin.' Your life depends on glutathione. Without it, your liver would shrivel up and die from the overwhelming accumulation of toxins, your cells would disintegrate from unrestrained oxidative stress and, as if you needed more problems, your body would have little resistance to bacteria, viruses or cancers. So many protective systems of the body, including its use of vitamins C and E, depend heavily upon this remarkable molecule.

THE IMPORTANCE OF GLUTATHIONE

Glutathione's importance to your health cannot be overstated. Your immune system is constantly on the prowl for pathogens—agents of cellular damage, toxicity and disease. To neutralize them the body needs a ready supply of glutathione. If it doesn't have enough, some of the invaders will get through, infecting the body and/or contributing to aging, long-term accumulative damage—even eventual cancer. We can't avoid illness and aging altogether—though a few scientists are pursuing the age-old dream of immortality—but by keeping our intracellular glutathione levels up we also keep our immune system on the ball and fully armed. GSH is fundamental to the immune system.

RESEARCH ON GLUTATHIONE

In the last twenty years the volume of research into GSH has grown immensely. A huge variety of theoretical papers, bench-top laboratory experiments, epidemiological studies, animal projects and—most importantly—clinical trials on humans, has linked glutathione to an extraordinary variety of

illnesses. The list is long and would be hard to believe were it not for the strength and credibility of the research. However, it is now clear that glutathione‘s role in the immune response, detoxification and antioxidation is pivotal. Without it, many bodily processes would fail.

All the information in this book is derived from the scientific reports listed at the end of each chapter. Hundreds of articles have described how elevated glutathione levels help combat the infirmities of aging, such as Parkinson‘s disease, Alzheimer‘s disease, cataract formation, macular degeneration, and cancers of aging (e.g. prostate cancer). You will find references to all these subjects listed in the index.

GSH is also known to play a crucial role in the cardiovascular system, helping prevent heart disease, stroke, atherosclerosis and reperfusion injury. In an ideal situation where the patient is exercising, eating properly, avoiding tobacco and maintaining a good general lifestyle, raising glutathione levels can actually help reverse atherosclerosis (see chapter 9).

In the digestive system glutathione helps the body fight inflammatory bowel disease, hepatitis, malnutrition, pancreatitis and peptic ulcer. Its antioxidant properties and its role in maintaining the immune response have led to interesting strategies against these all-too-common problems (see chapter 15).

Overdosing of certain drugs has been treated for some time with a variety of GSHenhancing drugs that have become mainstays in critical care medicine. However only recently has it been recognized that GSH is a powerful detoxifier of many other nasty substances—including those released from cigarette smoke and auto exhaust, such pollutants as heavy metals and pesticides, and many well-known carcinogens. Believe it or not, the evidence shows that GSH even helps prevent hearing loss from noise pollution (see chapter 17).

In infectious disease and immunology, glutathione‘s anti-viral properties help the body fight AIDS, hepatitis, herpes and the common cold. Its role in combating bacterial infection has also been clearly described. Although raised GSH levels do not affect a ―cure,‖ they elevate and sustain our natural immune response, providing reinforcement to deal with the threats at hand and minimizing damage. GSH also has potential applications against some autoimmune dysfunctions, chronic fatigue syndrome and states of immunosuppression.

The immune system is on constant alert against the threat of cancer. Glutathione helps prevent carcinogenesis (the transformation of normal cells into cancer cells) by eliminating carcinogens and mutagens from the body and by slowing down oxidative damage to DNA and other sensitive structures within the cell. In cases of diagnosed cancer, glutathione has been shown to suppress tumor growth, prevent the wasting disease associated with advanced cancer and ease the side effects of chemotherapy and radiotherapy (see chapter 5).

In pulmonary or respiratory medicine, raised glutathione levels have been used for many years in Europe and now increasingly in North America. Glutathione can break up mucus (especially in cystic fibrosis), reduce the danger of asthmatic attacks, aid in both acute and chronic bronchitis and fight emphysema and pulmonary fibrosis. All these mechanisms are described in chapter 14.

We have also included chapters on glutathione‘s many metabolic functions, including its role in complications of diabetes, reduction of cholesterol and oxidation of bad cholesterol (LDL), and its support of red blood cell levels in patients suffering from kidney failure.

Finally, we present research emphasizing the importance of glutathione in the healthy individual. For the physically active, GSH enhances athletic performance, decreases recovery time from physical stress and aids in immune function. For the average person, its role in health maintenance just can‘t be overestimated. Glutathione modulation is an essential part of staying young, active and healthy (see chapters 23 and 24).

In his book on antioxidants (What You Should Know About the Super Antioxidant Miracle) Dr. Earl Mindell states ―We literally cannot survive without this miraculous antioxidant.‖ Dr. John T. Pinto of the Sloan Kettering Cancer Center in New York proclaims, ―It is the master antioxidant.‖ Jean Carper in her book Stop Aging Now! Claims, ―You must get your levels of glutathione up if you want to keep your youth and live longer. High levels of GSH predict good health and a long life. Low levels predict early disease and death.‖

Closer to the raw science of glutathione, Dr. Gustavo Bounous, a researcher and leading authority on GSH and nutrition at McGill University in Montreal says, ―In view of existing scientific data, all we can expect from the environment is continued pollution, ozone depletion, and the increased virulence of infections. I think that enhancing glutathione levels will allow for a better quality of life.‖

You don’t have to be a scientist to understand that as society ‘progresses’ we become increasingly dependent upon technology and have to live with its many unhealthy byproducts. Not all of them are as tangible as toxic waste. There’s the stress and hurry of modern life---few of us take the time to listen closely to our bodies’ demands, to eat and exercise accordingly, nor even to rest as often as we might need. We are driven by forces that sometimes leave us numb to our spiritual and physical needs. Our whole being is affected, but a strong immune system can help take the physiological brunt of it. What it needs is regular maintenance and the all-important raw materials to make glutathione.

GSH—THE MOLECULE

Glutathione is the general term for glutathione sulfhydryl, abbreviated as GSH. The _SH‘ represents the critically active sulfur sulfhydryl group. GSH is a peptide (very small protein) that occurs naturally within the body, where it is assembled by individual cells from its three components—the amino-acids glycine, glutamate (glutamic acid), and the all-important cysteine. Because it contains three amino acids it is referred to as a tripeptide.

Of these three amino acids, cysteine is the hardest to find. Cysteine is a sulfur-containing amino acid that contributes the sulfydryl group to the molecule, making it also the most important of these raw ingredients. When cells have cysteine, they can efficiently manufacture GSH. However, this amino-acid is absent or deficient in many diets. Also, it must be in an accessible form. Cysteine has trouble surviving the trip from your mouth to your cells unless it‘s part of a larger protein.

Without adequate cysteine, cells can‘t produce enough GSH and the body suffers on three fronts: cellular oxidation contributes to general decline and aging, toxins accumulate in the body causing further damage, and the immune system is compromised, leaving us vulnerable to disease.

On the other hand, there are many benefits for the body with elevated glutathione levels.
Its metabolic functions include:

- Enhanced immune function
- Elimination of toxins
- Elimination of carcinogens
- Antioxidant cell protection
- Protection against ionizing radiation
- DNA synthesis and repair
- Protein synthesis
- Prostaglandin synthesis
- Leukotriene synthesis
- Amino acid transport
- Enzyme activation and regulation
-

These functions can be summarized into three general categories:

1. **Antioxidant**—GSH is the most powerful antioxidant occurring naturally in your body. The effectiveness of other antioxidants like vitamins C and E depends on glutathione. This is described in the following pages.
2. **Detoxifier**—Dozens of toxins are eliminated by the GSH enzyme system, including drug metabolites, pollutants, carcinogens and radiation damage.
   It's no surprise that GSH concentrations are highest in the liver, the body's major detoxifying organ (see chapter 2).
3. **Immune System Enhancer**—The immune system is dependent upon GSH for its proper functioning, in particular the creation and maintenance of
   T-cell lymphocytes, the body's frontline defense against infection.
   See chapter 3 for details.

These three functions are not separate. As far as the immune system is concerned, it is just using GSH to do its job. A GSH molecule may neutralize a free radical, be recycled by the GSH system and then eliminate a stray toxin. The remainder of part 1 describes these functions in detail and how we can maintain them. Before we look at its antioxidant role we must describe the process of oxidation.

Oxidation and Antioxidation

Today there is enormous growth in the markets for preventative and anti-aging medicine, and much time and money has been spent looking into the wear and tear of living, breathing and eating. This non-stop activity places continuous stress on every cell of the body, and every cell must respond or suffer damage. Terms like oxidation, free radical, oxyradical and antioxidant are used to describe these processes. What do they mean?

Each and every cell in the body is a biological machine that is gradually worn down by the work of staying alive. It's an imperfect system. Like all machines, cells derive their energy from the consumption (oxidation) of fuel—nutrients and oxygen—but at a price. This process produces harmful waste products (free radicals or oxyradicals). One of our cells' most routine tasks is to

neutralize and remove these wastes, and the key substance it uses is glutathione. Glutathione is the body‘s principal antioxidant. When it runs out, oxyradicals proliferate, slowly but surely wreaking havoc. In Part Two you will see that severe GSH deficiency is common to many diseases, especially in their advanced, chronic conditions.

How do oxyradicals form? If you were to look inside a cell you‘d see thousands of tiny chemical reactions that use oxygen to metabolize nutrients and release energy. This is the necessary process of oxidation. But oxidation produces harmful byproducts— oxyradicals, or unstable atoms.

An atom is a nucleus orbited by electrons. By working in pairs like children on a seesaw electrons maintain a balanced and stable orbit. But sometimes during oxidation an electron is knocked off its orbit, leaving its partner unbalanced. The remaining electron spontaneously corrects the imbalance by stealing a neighbor‘s electron, which then does the same again. Imagine a playground full of children jumping from seesaw to seesaw. The resulting chain reaction of disrupted molecules can cause untold damage to individual cells. Fortunately, our cells are equipped with natural antioxidants—agents that neutralize free radicals by giving them an electron, rather as a playground monitor ensures that each child has a partner.

This process of oxidation and antioxidation occurs continuously. Oxidation isn‘t a bad thing—after all, it provides energy and is also a frontline defense against bacteria and viruses. But if our diet lacks certain nutrients or vitamins, or if our body experiences excessive oxidative stress and increased oxyradical production, individual cells inevitably suffer. This isn‘t surprising. After all, oxidation causes metal to rust, apples to rot and butter to turn rancid. It also causes natural aging in humans. But its effects don‘t end there. Free radicals can damage or destroy cell walls, cause cell death (apoptosis) and disrupt DNA patterns, potentially leading to cancer.

Lipid peroxidation (precipitous oxidative chain reaction) is responsible for the breakdown of fats, particularly _bad‘ cholesterol (LDL-cholesterol) which damages arteries and leads to blocked blood vessels, heart disease and stroke (see chapter 9). The list of ailments caused by oxidation and free radical formation grows longer every day. In fact, a whole new field of medicine has developed, called _Free Radical Biology.‘ It studies the diseases and potential damaging effects of oxidative stress. Today there is no doubt that antioxidants help diminish cell damage, lessen the threat of disease and slow the harmful effects of aging.

Many factors contribute to oxidative stress. Some of them are poor diet, pollution, drugs, radiation, stress, trauma, injury, burns, aging and infection by bacteria or viruses. Each time your immune system confronts a threat, free radicals are released. Free radicals are also created in large numbers during exercise, when more energy is used and the rate of oxidation increases, and every time your body encounters fatigue, illness, inflammation, pollution, toxins and radiation. As you will see in the following paragraphs, glutathione is the body‘s key natural antioxidant. You can minimize oxidative damage by raising intracellular GSH levels and keeping them there.

GLUTATHIONE—THE MASTER ANTIOXIDANT

How does GSH work with other antioxidants? They all have their advantages and disadvantages. You should never stop using established supplements like vitamins C and E. These substances act synergistically with GSH—i.e., they enhance each other‘s effectiveness. We call GSH the master antioxidant because it replenishes the action of many other antioxidants. When vitamins C and E pick up an oxyradical they must hand it off to the GSH system so they are free to go back and get

others. GSH similarly neutralizes peroxide and lipoic acid. In fact, all of these antioxidants help to neutralize each other, and glutathione is at the center of cellular antioxidation. It is GSH—not the vitamin—that ultimately neutralizes the radical. A GSH molecule encounters a destructive, positively-charged hydroxyl radical and gives it an electron, turning it into harmless water. The GSH molecule has not become a radical but pairs up with another radicalized GSH molecule to from neutral, non-toxic GSSG.

Another synergistic antioxidant is selenium. Studies show it to be clinically similar to glutathione and it is an integral component of the important enzyme GSH –peroxidase. For this reason selenium is considered a GSH-booster.

None of these important but lesser antioxidants occur naturally in the cell—only glutathione. All others are obtained from the food we eat. GSH is a vital, natural component of your cells—an endogenous antioxidant. It is manufactured within from amino-acid precursors. If you want to boost your body‘s defenses against oxidation, your best bet is to give it the raw materials it needs to produce glutathione. GSH is at the heart of cellular antioxidation. It works, in conjunction with the secondary (exogenous) antioxidants peroxide, lipoic acid, vitamin C and vitamin E, relieving them of destructive charged ions and enabling them to return to the battle.

GSH—THE IMMUNE SYSTEM ENHANCER

A body well-stocked with intracellular glutathione fights illness more effectively than one that depends on exogenous (dietary) antioxidants. GSH helps prevent pathogens from gaining a foothold. And when they do get through they are confronted by an enhanced immune system. Glutathione therefore provides both preventative and therapeutic advantages. This is mainly because elevated glutathione levels enable the body to produce more white blood cells. These constitute the most important division of the immune system‘s ground-troops. Glutathione‘s overall role in the immune response is discussed in chapter 3.

GSH—THE DETOXIFIER

We inhale and ingest natural and synthetic toxins every day of our lives and can‘t possibly avoid them, especially in our technological times, our congested, polluted cities and with our engineered food supplies. As long as it has the health and nourishment it needs the body goes to great lengths to eliminate toxins and protect itself. Our main organ of detoxification is the liver—the largest organ in the body and also the depository of the body‘s highest concentrations of glutathione. Experimental studies have shown that low glutathione levels lead to poor liver function, and result in unnecessarily large quantities of toxins circulating through the body. There, they continuously damage individual cells and organs. Chapter 2 describes the role of glutathione in detoxification. The liver and its function are described in chapter 11.

CONCLUSION

Glutathione carries out many crucial functions in our body, of which three stand out. GSH is 1) the most important naturally-occurring antioxidant in our cells, 2) a key enzyme system for the detoxification of countless noxious substances and 3) a critical element that sustains the functioning and well-being of our immune system. These vital roles are now beyond doubt and considerable research is underway to uncover the full range of clinical applications for the preventative and therapeutic roles of elevated GSH levels.

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TOXINS, GLUTATHIONE AND HEALTH

Medical science and public health measures have measurably reduced death rates and prolonged the average life span, especially in developed countries. But development has its downside. Our environment contains tens of thousand of confirmed toxic substances, and the pace of life and consumer-oriented marketing promote bad lifestyle habits which we all adopt to some extent. We in the twentieth-century can expect a longer life span than our ancestors, but one potentially burdened by chronic ailments. The full promise of longevity is blunted.

What‟s remarkable is that we don‟t succumb even earlier to the daily onslaught of toxins in our food, air and water. We have our body‟s defense mechanisms to thank, notably the GSH detoxification process. But like all biological systems, even this can be overwhelmed by extensive or prolonged attack and may eventually begin to function poorly.

Although GSH was discovered in 1888 by De-Rey-Pailhade, it was not until the 1970‟s that its detoxifying role was recognized. Over the past thirty years scientific understanding of this process has unfolded slowly, but the huge resurgence of interest in preventive medicine and in GSH is giving rise to new discoveries. The liver and the kidney are the major organs of detoxification and elimination and have the highest levels of intracellular GSH in the body (see figure 7). GSH is the most important thiol (sulfurcontaining amino-acid) in living systems. It plays a critical role not only in humans and mammals, but in all vertebrates and even in insects, plants and microorganisms.

***Figure 7* – Organ GSH content in lab animals**	
ORGAN	**GSH (u-mol/g)**
Liver	**7.3**
Kidney	**4.0**
Lung	**2.9**
Heart	**2.4**
Brain	**1.5**

The team of biochemists D.P. Jones, L.A. Brown, and P. Sternberg from Emory School of Medicine in Atlanta wrote, “GSH has multiple functions in detoxification and its depletion has been associated with an increased risk of chemical toxicity…GSH can be depleted by different agents (and GSH) plasma levels vary with gender, age, race and dietary habits.” They go on to suggest that by monitoring glutathione levels we can measure an individual‟s risk of falling prey to environmental toxins.

H. Lew and A. Quitanihila, physiologists at the University of California, verified the upside of this discovery. The increased liver GSH levels seen in actively trained, physically fit individuals leave them better equipped to handle toxic threats from such substance as acetaminophen. R.J. Flanagan and T.J. Meridith at the Poisons Unit of Guy‟s Hospital in London reviewed the use of N-acetyl-cysteine (NAC) – a GSHenhancing drug – as a detoxifying treatment. They believe that besides its common use as a treatment for acetaminophen overdose, research will show its potential to detoxify the body of carbon monoxide, carbon tetrachloride, chloroform, and other harmful compounds.

CASE STUDIES

Whether accumulated over the years or ingested in one dose, many organic and inorganic toxins are cleared from the body by the action of GSH. Without sufficient glutathione supplies, these toxins can push the body into a slow or precipitous decline. Fortunately, drug-induced or dietary supplementation to raise GSH levels can sometimes help reverse this process. The following stories illustrate this.

Lara, a 28-year-old technical writer, did what she could to live a healthy life-style. He exercised regularly but found it increasing difficult over the years to get what she needed nutritionally. Many foods she had previously enjoyed – including dairy and meat products – left her feeling bloated, cranky and fatigued. She found herself taking various supplements to round off her dietary needs, but felt she was "left short". In addition, trips downtown were fraught with episodes of itchy, runny eyes and nose, headache and shortness of breath. Perfumes, auto exhaust and other odors made her feel „sick" so she avoided crowds. Fortunately, the nature of her job allowed her to do most of her work at home. After a visit to a local clinic she was diagnosed as agoraphobic. This made no sense to her because she loved going out. A nutritionist suggested that she was in fact suffering from multiple chemical sensitivity and prescribed the GSH-enhancing drug NAC for detoxification. After a few weeks of cramps, diarrhea, sweating and considerable urination she began to improve. She started cautiously reintroducing previous favorites back into her diet. She remains on her low dose of NAC and her tolerance of external smells continues to improve.

Linda was a recently unemployed 24 year-old office manager whose common-law husband had abruptly moved out of their apartment. After drinking two bottles of wine, she swallowed 30-40 tablets of extra strength (500 mg) acetaminophen. The next morning, after the effects of the alcohol had worn off, she showed up at the emergency department of the local hospital. Her stomach was not pumped because it had been so long since she took the pills. Her acetaminophen blood level was at 150 micrograms per milliliter (ug/ml) – enough to damage the liver if left untreated – and her initial liver enzyme profile was already showing mild abnormalities. A dose of NAC (N-acetylcysteine) treatment was given immediately and continued every four hours for the next three days. Oral charcoal was also used on the first day. Her liver enzyme abnormalities worsened over the first forty-eight hours but were finally reversed and returned to normal. Although suffering from nausea and cramps during her hospital stay, she was glad to be alive. After being cleared by the psychiatric consultant, she was sent home.

PREVENTION

A serious shortcoming of traditional medicine is its focus on treatment rather than prevention. This isn"t without cause. The need to see people who are sick or suffering is always more pressing than the good intentions to meet those in good health. And there"s no shortage of disease out there – if anything, there"s a shortage of doctors. It has fallen to other branches of the healing arts to address the issue of maintaining well-being.

Nutrition-sensitive approaches can teach us a great deal. But the real strength of such health maintenance is self-awareness. We must study for ourselves, and learn to take control of the conditions that affect our well-being. As much as possible, we should avoid whatever harmful influences we can, then identify the unavoidable ones and provide our body with whatever resources it needs to fight them.

SMOKING AND TOBACCO

Medically, statistically and economically, the greatest risk to health in North America is tobacco use. The huge body of scientific evidence accumulated over the past decades leaves no doubt that cigarette smoking profoundly increases the risk of contracting Chronic Obstructive Pulmonary Disease (COPD, including asthma, chronic bronchitis and emphysema), cancer and cardiovascular disease. Despite years of successful lobbying and denial, the tobacco industry has recently been forced to admit what the medical community has known for ages – cigarettes kill.

Cigarette smoke releases thousands of different chemicals and a single puff contains literally trillions of free radicals. The smoke actually burns away antioxidant vitamins like C and E and other nutrients, but even worse is the inflammation it causes in the lungs. This is the principal source of oxidative stress. The degree of lung inflammation and injury is directly related to the extent of oxidation caused by cigarette smoke. In addition, the tar from tobacco products contains potent carcinogens that cause not only lung cancer but all sorts of other tumors. GSH is well known to scavenge these free radicals and to neutralize many of the toxins by conjugation and elimination. If you‟re not ready to quit smoking, or if you can‟t avoid second-hand smoke, elevated GSH levels will help protect you.

Many studies have outlined the role of GSH in preventing or suppressing the damage caused by smoking. Clinicians have even gone as far as attempting to treat some of these consequences – not just prevent them – with glutathione-enhancing drugs like NAC. A more detailed analysis and review of clinical studies can be found in chapter 14.

RADIATION

Ionizing radiation is a known cause of cancer, and does other kinds of harm as well. It is one of the most extensively studied of all carcinogens and accounts for about three percent of all cancers. Some radiation comes from natural sources such as cosmic rays and natural radioactive minerals. The most common source is sunlight, which carries the increased threat of ultraviolet radiation due to depletion of the protective ozone layer. Other sources include nuclear waste from energy plants, industrial waste, weapons test residue and certain building materials. X-rays from radiographs, mammograms, CTscans and other medical test equipment are all weak, but have a cumulative effect over time.

Exposure to radiation results in the formation of hydroxyradicals – the most reactive of all free radicals. Many studies have shown that GSH plays a key role in neutralization. Some physicians are raising GSH levels of patients in radiotherapy. This tends to reduce the side-effects they experience and can even enhance the effectiveness of the therapy itself.

L.A. Applegate at the Swiss Institute for Experimental Cancer Research conducted studies on human cells cultured in the laboratory. First, his team depleted their glutathione levels with the drug BSO, then they exposed the cells to radiation. They found a significantly higher proportion of DNA mutations, and therefore an increased risk of developing cancer. J. Navarro and a team of Spanish doctors showed that humans exposed to radiation suffered from significant GSH abnormalities.

V.N. Bhattathiri led a research team in India to study patients suffering from oral cancer. Each patient‟s GSH levels before radiation therapy was measured and correlated to the side-effects of the therapy. It was clear that the lower their initial GSH levels, the more injury they suffered. Following these tests the team felt able to identify any patient‟s susceptibility to radiation damage by

measuring their GSH levels. They recommended that treatment dosages be adapted to the individual‟s ability to withstand the therapy.

A group of genetic researchers at the University of Nurnberg in Germany studied the potential use of NAC (a GSH-enhancing drug) to protect human white blood cells from X-ray damage. Cells pretreated with NAC clearly had a protective advantage over untreated ones. Glutathione and its role in cancer, chemotherapy, and radiotherapy are discussed in chapter 5.

Enhanced GSH levels can also reduce the damaging effects of sunburn. It is believed that skin damaged by sunburn can develop various forms of skin cancer. Chapter 21 reviews some important studies relating to sun exposure, ultraviolet-radiation damage and glutathione.

HEAVY METAL TOXICITY

Heavy metals are metals from periodic table groups IIA through VIA. The semi-metallic elements boron, arsenic, selenium, and tellurium are often included. Many are essential in small quantities but can accumulate to toxic levels. Absorbed from the environment and food chain, they gradually build up in biological systems – from plants to the human body – and can grow into a significant health hazard. Such metals as arsenic are actually used as poisons. Nutritional supplements like iron or medications like bismuth are helpful or essential at appropriate doses, but quickly become toxic at higher levels. Here is a list of potential heavy metal toxins:

Arsenic	Copper	Selenium
Arsine	Gold	Silver
Bismuth	Iron	Thallium
Cadmium	Lead	Tin
Chromium	Mercury	Vanadium
Cobalt	Nickel	Zinc

Heavy metals exert their influence on all sorts of tissue and can affect many bodily systems. The nervous system, the renal (kidney) system, the cardiovascular (heart and circulation) system, the hematological (blood) system, the gastrointestinal (digestive) system and many others are affected one after the other. Heavy metals exact their damage by generating free radicals or by interfering biochemically with normal metabolic functions.

Glutathione and its associated enzymes help regulate and eliminate many of these metals. Clinical studies have outlined the role of GSH in heavy metal toxicology and its role has been described in the way cells process arsenic, arsine, bismuth, cadmium, chromium, cobalt, copper, gold, iron, lead, mercury, nickel, selenium, silver, thallium, tin, vanadium and zinc. Of all these substances, mercury seems to be the most GSH-depleting.

MERCURY TOXICITY

The heavy metal mercury is an insidious but potent toxin that warrants special attention. It is all too common in our environment and is fraught with controversy, most notably when the topic of mercury amalgams (dental fillings) comes up. I have seen usually staid and sober medical and dental professionals coming close to blows over this issue at educational conventions. However, one of the tenets of the Hippocratic oath is, “Above all, do no harm”. There certainly is sufficient clinical evidence to force a much closer look at the use of this important neurotoxin in clinical applications.

Mercuric substances can be either organic or inorganic. Inorganic forms include pure or elemental mercury (quicksilver), or the salts of mercury (mercuric chloride, mercuric oxide and others). These can be inhaled or ingested. High-risk occupations include dentistry, manufacture of batteries, explosives and jewelry, photographic development and taxidermy. Organic mercury comes in many forms, methyl-mercury being the most common – and also highly toxic. Poisoning by this form usually follows accidental ingestion. Farm workers, embalmers and producers of pesticides, fungicides, insecticides, bactericides, drugs and preservatives are all at risk.

Although primarily a neurotoxin (nerve poison), mercury can cause a broad range of problems, including kidney failure, severe nausea and vomiting, diarrhea, oral lesions (stomatitis), lung inflammation (pneumonitis) and rashes. It affects the nervous system with symptoms as subtle as emotional instability, anxiety, memory loss, and lethargy. The expression "Made as a hatter" has an interesting basis in fact. Hat-makers in the nineteenth century used elemental mercury to form and weight down their hats, and often paid a high neurological price for repeatedly handling this toxin. Serious mercury poisoning includes tingling or loss of sensation in the extremities, poor coordination, tremors, slurred speech and tunnel vision. These symptoms can progress to paralysis, coma and death.

Traditional treatment of mercury toxicity requires binding of the metal to larger organic molecules, a process call chelation. Chelating agents may be administered orally (e.g. Dpenicillamine), intramuscularly (e.g. Dimercaprol, BAL) or intravenously. Once chelated, the mercury complex is eliminated through normal excretion of urine or stool.

It has been long known that glutathione is a primary cellular defense against mercury toxicity. It starts out by effectively quenching the formation of free radicals. Even more critical is its ability to bind directly to mercuric compounds, enabling the cell to expel and the body to excrete them.

A recent article from the International Archives of Occupational and Environmental Health measured the impact of mercury exposure on glutathione levels. Forty-two workers from a chloralkali factory exposed to elemental mercury were compared to seventy-five non-exposed workers from a lime production plant. As expected, blood levels of mercury were higher in mercury workers, but so were levels of lipid peroxidation. Evidently, the detoxifying effects of glutathione peroxidase were significantly decreased.

In the laboratory, many studies have shown how glutathione protects cells from toxicity. By raising GSH levels, a team of toxicologists from the University of Arizona was able to decrease mercury-induced kidney damage. An Argentinean team had equal success using NAC to preserve renal (kidney) function. Similar positive results were found using glutathione monoester, selenium, and other agents to enhance GSH levels.

Experimentation on the liver, nerve and small intestine and other tissues, and even in fetal development verify that mercury drains the glutathione system, that decreased GSH levels lead to increased toxic damage by mercury, and that elevating or sustaining glutathione significantly protects cells against mercury poisoning.

DENTAL AMALGAMS

There"s quite a controversy surrounding the alleged ill-effects of mercury from dental fillings (amalgams). The mercury in these so-called „silver" fillings makes them malleable and strong. It has been a mainstay of dentistry for decades. Studies show that for average individuals not otherwise exposed to mercury, these filling represent the predominant source of exposure. The same studies also indicate that urinary mercury excretion is significantly higher in individuals with these fillings, and that these excretion levels correspond to the amount of filling in their mouths. A German study determined that the long-term excretion of mercury could be cut by five-fold after amalgam removal. A recent study from the Journal of Dental research by G. Sandborgh-England concluded that "…the process of removing amalgam fillings can have a considerable impact on Hg (mercury) levels in biological fluids".

The sixty-four thousand dollar question is whether or not this higher level of mercury exposure actually produces ill-effects. A recent study by the Australian W. Blumer looked at 80 patients with dental amalgams who also showed symptoms of chronic mercury toxicity. Using the chelators EDTA to flush mercury from the body, it was found that the urine of patients with fillings had significantly higher levels of mercury. The fillings were removed and patients continued to take oral chelators along with selenium supplementation (to raise glutathione peroxidase). After three months patients were either symptom-free or greatly improved.

Proponents of the amalgam-toxicity school of thought are seeking ways to detoxify both patients and the dental professionals who are exposed daily to mercury vapors. Merely removing the exposure is not enough – like other heavy metals, mercury remains imbedded intracellularly in deeper tissues unless appropriately chelated or removed.

NAC (N-acetylcysteine) raises GSH levels and has been used to detoxify organic mercury. Researchers from the Department of Environmental Medicine at the University of Rochester, NY showed that oral NAC profoundly accelerates urinary methylmercury excretion to levels as much as ten times more than usual. NAC is able to detoxify mercury compounds.

One of the foremost scientists dealing with heavy metal and mercury toxicity is Dr. David Quig of Chicago, Illinois. He has elaborated the interplay of mercuric compounds, glutathione, cysteine and other metallothioneins (organic metal-sulfur compounds). He feels the long-term effects of consistent low-level mercury exposure have been underestimated. According to him, the most effective way to eliminate these toxins from deep tissue like the brain is by eating high-quality whey protein. Although the bioactivity of natural whey can easily be denatured, good quality whey protein can have significant GSH-enhancing properties. Studies using the whey protein Immunocal® are currently underway by several research groups. The protein precursors of GSH act here as oral chelating agents.

High levels of mercury poisoning are often treated by emergency dialysis (blood filtration). American military doctors at their Health Sciences Department of Pharmacology at Bethesda, Maryland carried out an experiment to improve this treatment, with revealing results. Using dialysis they investigated the ability of ten different chelating agents to remove mercury from blood fluid. Most kidney specialists were surprised to find that NAC was very effective, even surpassing more traditional agents. Clinicians are now starting to apply this knowledge to their daily practice, using GSH therapy as a compliment to their usual emergency treatments.

CASE STUDY

Sheryl was a 32-year-old mother of four who had fallen ill following the caesarian delivery of her last child two years earlier – the surgical incision was taking far too long to heal. Her gynecologist was puzzled, and noted some muscular atrophy. She experienced periods of such profound weakness that she was bedridden for days. Over the next 18 months this weakness recurred and she was eventually admitted to hospital. Various diagnoses were considered, including multiple sclerosis and chronic fatigue syndrome, but supportive treatment for these conditions didn‟t help. Then her dentist suggested that mercury toxicity might be a contributing factor so she had her mercury amalgams removed.

Herbal supplementation was attempted to rid her of residual mercury. Her symptoms improved modestly. Some internet research led the dentist to Immunocal, which he suggested to Sheryl. Within five days she experienced a marked increase in strength. After ten days she was walking without pain. Two weeks later she rode her bike for the first time in 2 ½ years. Three weeks later, she felt "almost back to normal".

She still feels well and continues to raise an active family.

LEAD POISONING

Plumbism – lead poisoning – is a public health problem that dates back to Roman times. The name comes from the use of lead (Latin: plumbium) in plumbing. Other forms of exposure have been common for centuries through cooking and eating utensils, pottery, and the use of lead in paints (fortunately discontinued in most house-paints). Moonshine liquor is sometimes prepared using automobile radiators, pipes and barrels soldered with lead. Mechanics, battery manufacturers, solderers and other trades people are subject to occupational exposure.

Lead poisoning is often difficult to diagnose. The symptoms can be subtle and very nonspecific. Nevertheless, acute poisoning can be accompanied by severe nausea and vomiting, diarrhea, kidney failure, seizures, coma, paralysis, and death. Continuous, repeated exposure can result in anemia, weakness, aches and pains and irritability, not to mention a host of intellectual dysfunctions from learning disabilities to profound mental behavioral changes. The treatment is removal of the source of exposure and chelation therapy.

Like mercury, lead is detoxified at the cellular level by the glutathione enzyme system. The pro-oxidant effect of lead is counterbalanced by the antioxidant capabilities of GSH and the lead molecule itself can be conjugated or bound to glutathione, after which it is eliminated from the body.

Lead toxicity affects many tissues including the central and peripheral nervous system, the liver, the kidneys and red blood cells. Depleted GWSH stores usually indicate increased severity of the disease. Restoration of glutathione levels is protective and helps eliminate lead. Raising GSH levels with agents like NAC, and the use of selenium have been shown to be a useful compliment to traditional therapies, acting at the level of the liver, kidney, red blood cells and even the lens of the eye to counteract the deleterious effect of lead poisoning.

The anemia (loss of red blood cells) that is characteristic of lead toxicity is caused by several different factors, among them high levels of oxidative stress. This leads to lipid peroxidation of the red blood cell membrane, followed by cell disruption. A Japanese research group studied workers with a high occupational lead exposure by measuring their lipid peroxidation levels, lead

concentration and glutathione peroxidase activity. The results show that lead levels and peroxidation levels seem to be directly related, and levels of the essential GSH-peroxidase fell as lead levels rose.

Figure 9 – A short list of substances detoxified by GSH conjugation; there are countless others

- **Acetaminophen** (Tylenol, Atasol, others)
- **Other pharmaceuticals** (Adriamycin, etc.)
- **Acetone** (common solvent, cleaner, industrial agent)
- **Aflatoxin B1** (natural toxin, carcinogen from moldy nuts, etc.)
- **Aliphatic hydrocarbons** (vinyl chloride, hexachlorohexane, plastics etc.)
- **Aromatic hydrocarbons** (solvents, fuels, bromobenzenes, chlorobezenes, etc.)
- **Nitrosamines** (smoked foods, salami, hot dogs, etc.)
- **Benzopyrenes** (barbecued foods, fuel exhaust, cigarettes, etc.)
- **Heavy metals** (lead, mercury, cadmium, cobalt, copper, etc.)
- **Organophosphate pesticides** (parathione, others)
- **Peroxides** (lipid peroxides, cholesterol peroxides, others) **Isothiocyanates**
- **Carbamates, thiocarbamates**
- **Arylamines, arylhalides** (industrial exposures, etc.)
- **Sulfates, nitrocompounds, naphthalene** (fuel, fuel by-products, etc.)

ENVIRONMENTAL ILLNESS

Chronic exposure to xenobiotics (substance foreign to the body) can lead to subtle and hard-to-pinpoint changes in health. It may also lead to full-blown syndromes known as Environmental Illness (EI). These often reveal themselves in a combination of minor complaints – such as headaches, fatigue and lethargy – that tend to confuse diagnosis. They may be quite profound, as in the case of MCS (multiple chemical sensitivity) which has only recently become accepted as a legitimate diagnosis. For similar reasons, it was years before the medical community recognized Gulf War Syndrome as a specific illness.

There are many sources of xenobiotic exposure around the home. Carpets may hide pesticides carried in on footwear; steamy bathrooms contain chloroform; dry-cleaned clothes hanging in your closet give off fumes of perchloro-ethane and trichloro-ethane; fireplaces produce benzene and household cleaners contain paradichlorobenzene. In the office, photocopy toner releases formaldehyde and styrene, among other chemical pollutants. Enclosed parking garages are another source of benzene, among other chemicals. The air outdoor in the city or even the country contains many different compounds that we should ideally avoid. And of course, rooms in which people are smoking tobacco contain dozens of carcinogens and other toxic chemicals. We should be careful when using mildew removers, mothballs, scented detergents, fabric softeners, lawn fertilizers, pesticides, solvents and cleansers, paints, heating fuels, certain insulation materials and even products used to manufacture mattresses and furniture. A brief list of substances detoxified by GSH conjugation is shown in figure 9. Fortunately, a wealth of published information can help you keep track of these substances and where they are used. You‟ll find some excellent guides at your local bookstore.

Because the number of poisons in the general environment is large, exposure to environmental pollutants is unavoidable. In addition, concentrations of specific substances are high in certain

workplaces. In an article on chemical toxicity in industrial workers, D.V. Parke and A. Sapota made a powerful statement about threats that can be counteracted by GSH.

They claim that many industrial workers with symptoms of systemic inflammation are often misdiagnosed as suffering from rheumatoid arthritis, viral infections, connective tissue diseases and other such maladies. Physicians need to be informed more thoroughly about the ability of chemical pollutants to imitate inflammatory diseases.

Exposure to certain chemicals in the workplace has been connected to the development of cancer. R.K. Ross and his colleagues at the University of Southern California linked a deficiency of GSH enzymes to bladder cancer in workers exposed to Arylamines – are also present in cigarette smoke.

CHRONIC FATIGUE SYNDROME, GULF WAR SYNDROME AND MULTIPLE CHEMICAL SENSITIVITY

These three health problems are dealt with together here for several reasons. They are mutually connected to a combination of environmental exposure to toxins, inappropriate immunological response and genetic predisposition. Because symptoms may be intermittent and vary from one person to another, many doctors are reluctant to offer firm clinical diagnoses, and these disease names and definitions have taken the medical community a long time to accept. Some small groups of physicians still feel these diseases are just various manifestations of a psychological disease.

Multiple chemical sensitivity is an environmental disease in which the buildup of various toxins reaches a dangerous threshold with few or minor symptoms. Any additional toxicological load may be the last straw that triggers a cascade of symptoms, often mimicking other diseases. Such circumstances make clear diagnosis very difficult. The onus is on the patient to avoid further exposure. The health practitioner must suggest detoxification strategies. The use of glutathione-enhancing treatments will undoubtedly become standard in the future.

A recent article in the American Journal of Medicine by I.R. Bell, C.M. Baldwin and G.E. Schwartz at the University of Arizona set out to summarize the relation of chronic fatigue syndrome to chemical sensitivity. They determined that severe chemical sensitivity is a factor in about one-fifth to one-half of chronic fatigue patients, and in about 5% of the American population. Between 15 and 30% of the general population report at least minor problems with chemical intolerances.

A paper entitled “Gulf War Illnesses: complex medical, scientific and political paradox”, was published by the Institute for Molecular Medicine in California. It also points to a link with chronic fatigue syndrome. There is a higher incidence of CFS among Gulf War Veterans than in the general population. Because Gulf War Syndrome may mimic other chronic multi-organ or immunological dysfunctions, there is danger of misdiagnosis and mistreatment.

Scientists at the Center for Environmental Hazards Research in New Jersey have determined that even when chronic fatigue syndrome and multiple chemical sensitivity syndrome are diagnosed among Gulf War Veterans, their symptoms differ substantially from the CFS and MCS diagnosis in the population at large. Discrepancies are found in immunological parameters, demographics and prognosis.

A discussion of chronic fatigue syndrome (CFS), also called chronic fatigue/immune dysfunction syndrome (CFIDS) would not be out of place in our chapter on immunology (chapter 3). From a

casual point of view, CFS is less of a toxicological problem and more typical of an immune disorder. It is best classified as a post-viral or post-infectious syndrome. The casual sequence often begins with an acute viral illness. This is usually followed by an overactive lymphatic response – swollen glands or lymph node enlargement (a symptom of "glandular fever"). For unknown reasons, some people develop an abnormal immunological and neuro-endocrinological response. This inability to fight health threats combines with an imbalance in the body‟s hormonal secretions, then begins to produce the symptoms of CFS.

Rheumatologists have now better defined the syndrome to enable more accurate diagnosis. It is characterized by persistent fatigue, musculo-skeletal pain, sleep disturbance and cognitive and psychological abnormalities. A clear test for CFS does not yet exist, but researchers are trying to elaborate the many subtle biochemical and physiological changes that take place. One such group is led by Dr. Paul Cheney, one of the first clinicians to describe the syndrome in the late 1980‟s and early 90‟s. Founder and director of the Cheney Clinic in North Carolina, his research is on the cutting edge of our understanding of chronic fatigue. He believes that although the initial event may be viral, it is subsequent abnormalities in protein synthesis and enzyme production that lead to liver and intracellular detoxification failure.

Dr. Cheney initially used oral glutathione or injectable glutathione and later the GSH precursor drug NAC (N-acetylcysteine), all with modest success. When the bioactive whey protein Immunocal became available, many patients responded with dramatic results. This dietary source of GSH precursors is described in chapter 4.

The well-organized German immunochemist Dr. Wulf Droge has coined the term "Low CG Syndrome" to describe a number of disease states associated with a depletion of cysteine and glutathione. These include chronic fatigue syndrome, AIDS, certain cancers, sepsis, Crohn‟s disease, ulcerative colitis, major trauma and others.

CASE STUDY

William, a lawyer from Alabama, noticed a change in his health at age 39. His initial visits to a number of physicians were neither conclusive nor accurate in their diagnoses, nor were any treatment options helpful. He was unable to carry on his usual demanding workload and was forced to end his law practice in 1994. His own research led him to a local CFS support group. They suggested that he consult a prestigious south-eastern clinic specializing in chronic fatigue. Initial treatment with vitamins, nutrients and dietary changes proved minimally successful. The head of this clinic was investigating the use of Immunocal and after William was on the product 12 weeks, improvements were noticeable. Three months later, he woke up one morning and "felt well again". That day he picked up his golf clubs for the first time in five years. Today he is shooting in the low 90‟s and will be restarting his practice in t he fall.

CONCLUSION

The number of toxins our bodies must deal with every day is truly remarkable. To cope with this burden a fit, rested, well-fed person must maintain adequate immunological and biochemical defenses. The role played by GSH in these defense systems cannot be overstated. Glutathione detoxifies a large number of pollutants, carcinogens, heavy metals, herbicides, pesticides and radiation. We are exposed every day to toxins like cigarette smoke, automobile exhaust, food preservatives and dental amalgam and our body depends on GSH for their removal. Substances that

raise GSH levels are being used with increasing frequency in the field of toxicology with considerable success.

GSH AND THE IMMUNE SYSTEM

THE IMMUNE SYSTEM

It‟s surprising how many people still believe that catching a cold is the result of sitting in a draft or going out with wet hair. It is a simple and well-established fact that the common cold is a contagious, transmittable disease. We don‟t catch colds from cold air, in spite of the disease‟s name. Both the expression and the misconception are deeply ingrained in our culture. But it is exposure to the actual virus that causes illness.

Others might blame their cold on being stressed out, overworked or having exercised too much. They are much closer to the truth. Although these factors in themselves do not *cause* a cold, they do make us more susceptible to the cold virus. By overdoing it, these patients have temporarily diminished their immune resources and suffer the consequences – the virus overpowers them. Most visits to the doctor follow the failure of the immune system to deal with a particular threat. The good news is, the immune system can be reinforced.

Few people are aware of this, even those who consciously work at their well-being. Many of us know well enough how to take care of the heart and muscles, but only a few pay attention to the immune system, even though this is our front line defense against all infectious and destructive attacks. To maintain a good immune response we should exercise regularly (45 to 60 minutes, 3 times weekly), eat regular and varied meals, maintain an ideal body weight, sleep regularly (8 hours for young adult, less for elderly), supplement our diet with vitamins, minerals and micronutrients, avoid undue stress and, funnily enough, laugh a lot. We should also avoid radiation and toxins, abuse of tobacco, alcohol and caffeine and the unnecessary use of antibiotics and steroids. See figure 10.

The immune defense is an extraordinarily sophisticated system. A microscopic examination of any part of the human body shows it teeming with microorganisms such as bacteria, parasites and fungi, and that‟s just inside us. The environment from which we get our air, water and food is also saturated with microorganisms. It is amazing that we survive at all.

Traditionally, we consult a physician only when a disease has actually taken hold. Often, the doctor launches an offensive or „attack‟ strategy with antibiotics, antiviral compounds or chemotherapy in an attempt to exterminate the invader. Despite drug side-effects and other drawbacks this offensive strategy has proven widely effective. It‟s the best way we‟ve found to fight the war.

But it‟s preferable to avoid the war altogether. After all, the battleground is your body. Even when medicine wins, the carnage remains. Drug side-effects and chemotherapy after-effects are like the random destruction of war in which innocent bystanders die. We can‟t overemphasize the usefulness of a defensive strategy – a preventive medicine that prevents invaders from establishing a beachhead and avoids all-out conflict. An optimized immune system is without question the best prevention. We can do this by nurturing and feeing it just as we tend to the rest of our body.

THE IMMUNE RESPONSE

The immune response seeks out, identifies, and attack threatening microorganisms, allergens, cancer cells and grafted tissue – collectively called antigens. The body‟s reaction is called an antigen response.

When a pathogen enters the blood stream, immune cells are activated. There are several types, including the polymorphonuclear cells that form pus. These large cells simply engulf pathogens and digest them. The smaller but much more sophisticated lymphocytes deal with pathogens by adapting a specific defense to them.

Figure 10 – The do's and don'ts of immune system maintenance

DO	**DON'T**
Exercise regularly (45-60 min., 3 times weekly) Eat regular & varied meals Maintain ideal body weight Sleep regularly (8 hours for young adult, less for elderly) Supplement your diet with vitamins, minerals & micronutrients Avoid undue stress Laugh a lot	• Abuse tobacco • Abuse alcohol Abuse caffeine Use antibiotics inappropriately • Use steroids inappropriately • Expose yourself to radiation Expose yourself to toxins

B-cell lymphocytes identify pathogens and mark them as targets for T-cell lymphocytes. Helper T-cells alert immune cells to join the battle, killer T-cells destroy the intruder and suppressor T-cells switch off the immune response when the job is done.

The healthy immune response can become compromised, however. There may not be enough immune cells, the cells themselves may be incompetent, or they may be overwhelmed by a particularly aggressive pathogen. In many cases, the adaptive side of the immune system identifies and subsequently remembers the chemical signature of a pathogen and is able to handle it more effectively the next time around. This leads to partial or complete immunity. For example, you only catch the measles once.

The immune system is impressive, but not infallible. It can sometimes respond to threats as if they were non-threats and to normal metabolic functions as if they were attacks on the body. We want our immune response to protect against infection, ignore harmless substances, accept transplanted organs, not attack ins own organs and protect the body against carcinogenesis and tumor growth. We want to avoid recurrent infection, allergic response to harmless substances, rejection of transplanted organs, auto-immune disease in which the body attacks its own systems, and cancer. See figure 11.

Figure 11 – Desired and undesired immune responses

	Desired response	**Undesired response**
Infectious agent	Protective immunity	Recurrent infection
Harmless substance	No response	Allergy

Transplant organ	Acceptance	Rejection
Self organ	Self tolerance	Auto-immune disease
Tumor	Tumor immunity	Cancer

The two most common examples of unwanted immune response are autoimmune disease and allergies. In autoimmune disease the body mistakes normal tissue for a foreign antigen and attacks it, leading to the destruction of healthy tissue. In the case of allergies, the immune system mistakes a harmless substance for a potentially dangerous one and reacts with an aggressive, sometimes deadly response. Some autoimmune diseases are:

- Lupus Polymyositis
- Myasthenia gravis Scleroderma
- Chronic fatigue syndrome Lou Gehrig‟s disease
- Rheumatoid arthritis Grave‟s disease
- Multiple sclerosis

THE IMMUNE SYSTEM AND GSH

Our account of polymorphonuclear cells and lymphocytes in the previous section describes only a part of the immune system. B-cell lymphocytes account for about 10% of all circulating lymphocytes and work by releasing immunoglobulins to attack and destroy invading pathogens. About 80% of lymphocytes are T-cells. When this system is disrupted the doors to infection open and health is compromised. For example, the human immunodeficiency virus (HIV) destroys helper T-cells and leaves killer T-cells cut off and powerless. As a result, invading microorganisms that the body would normally shrug off are able to cause the severe infections that characterize AIDS.

GSH plays a central role in the functioning of our immune cells. Dr. Gustavo Bounous, a leading expert on GSH says, “The limiting factor in the proper activity of our lymphocytes is the availability of GSH.” This is strikingly clear in the example of the human immunodeficiency virus, or HIV – the cause of AIDS (see chapter 12).

AIDS is essentially a T-cell dysfunction. Patients typically suffer from low GSH levels and especially from low T-cell GSH count. Several studies have shown that GSH levels can predict an AIDS patient‟s chances of survival and quality of life.

The healthy growth and activity of immune cells depends upon the availability of GSH. Experimental depletion of GSH has severely diminished the ability of these cells to fight pathogens and left the door wide open to disease. In numerous studies the level of intracellular GSH in the lymphocytes corresponds directly to the effectiveness of immune response. In the simplest terms, GSH is a short of „food‟ for the immune system.

In some autoimmune diseases such as rheumatoid arthritis (chapter 6), lupus (SLE) and in normal aging (chapter 6), T-cell lymphocytes show a weakened response to antigens. In addition, these chronic inflammatory conditions have been associated with low serum and red blood cell GSH concentrations.

A lymphocyte attacks a pathogen by releasing powerful oxidizing chemicals such as peroxide and protects itself against these chemicals by neutralizing them with GSH. Also, lymphocytes must replicate themselves over and over again (monoclonal expansion) in order to attack the whole pathogen population. This requires the use of oxygen and release further oxidants. In order to continue multiplying efficiently GSH is once again required to counteract the effects of oxidation. So fighting off infection consumes GSH in two ways – by using it to stabilize free radicals and also to grow immune cells. This is apparent in acute infections such as bacterial pneumonia. In chronic infections such as hepatitis C or AIDS, GSH depletion is even more pronounced. Recent research has demonstrated that elevated GSH levels enable the immune system to address these infections more effectively.

Doctor Bounous with his McGill University team measured the immune response of laboratory animals fed a whey protein isolate rich in GSH precursors (later trademarked Immunocal). These animals demonstrated both higher intracellular GSH levels and a heightened response to immune challenge. Interestingly, animals fed a similar diet of cysteine-enriched casein (see chapter 4) did not benefit from the same effects.

So the protective activity of GSH is two-fold – it enhances the activity of immune cells and also functions as an antioxidant within them.

A frightening number of antibiotic-resistant bacterial infections such as flesh-eating disease, vancomycin-resistant enterococcus and methicillin-resistant staphylococcus have made their way into our hospitals and communities. Some health professionals believe that viruses such as those causing AIDS and Hepatitis C are just the tip of the iceberg, and that a wave of newly emerging pathogens is on its way. Old foes like tuberculosis, previously thought to have been eliminated, are back with a vengeance and are no longer susceptible to previously successful treatments. Enhancing our GSH levels is a practical precaution against this ominous trend.

CONCLUSION

The immune system uses a variety of cells to fight off infection and other threats and the healthy growth and activity of these cells depends upon the availability of GSH. Glutathione is at the heart of all immune functions and low GSH levels are seen in many diseases, especially AIDS which is characterized by a severely compromised immune system.

Raising and maintaining GSH levels can minimize the risk of these diseases. Although only very ill people are severely deficient in GSH, those in good or fair health can benefit from GSH supplementation, especially in these days when we are exposed as never before to environmental toxins and drug-resistant bacteria. The use of GSH supplementation to fight specific diseases is discussed in part 2.

Without question, the best type of preventive medicine is an optimized immune system and a critical strategy to optimize it is by feeding it GSH.

RAISING GSH LEVELS

If glutathione is manufactured within the body, what can we do to maintain or increase GSH levels? Some pharmaceutical drugs can do it, and so can some natural sources. Eating glutathione cannot. There are many ideas about how to raise GSH levels in the body but only a few actually work – and some of them have side effects. In order to take advantage of the great potential of GSH in health and disease we must dispel the myths and clarify the facts. This requires an understanding of the biochemical makeup of this important protein.

GSH is a tripeptide – a protein made up of three amino acids – in this case, glycine, glutamate (glutamic acid), and cysteine. The chemical structure of glutathione does not easily survive the digestive process, so eating it will not raise GSH levels. The body manufactures it within the cell from building blocks (precursors) of GSH in our food. Glycine and glutamate are readily available in North American diets, but cysteinecontaining proteins are much harder to come by. Figure 12 shows sources of these three component amino-acids of glutathione.

Cysteine – a sulfur-containing, or "thiol" amino acid – is responsible for the biological activity (bioactivity) of the whole molecule. Cysteine as an isolated amino acid has trouble getting from your mouth to your cells. Much of it is broken down or altered in the digestive tract and bloodstream. So we must take cysteine in a form that resists breakdown. If the body doesn‟t get these sulfur-containing amino acids into the blood, we can‟t make GSH.

Other thiol amino acids include cystine (different from cysteine) and methionine. Cystine is known as a "disulfide" amino acid because it contains two cysteine molecules connected by their sulfur atoms – a so-called dilsulfide bridge. Cystine is not generally found as a free amino acid. Methionine may serve as a glutathione building block, but it has the tendency to convert into homocysteine, which raises the risk of heart disease.

There are several ways to raise GSH levels. Both pharmaceutical and natural products are listed in figure 13 and described in this chapter. We also describe how GSH as a whole works with other nutrients or co-factors.

Figure 13 – GSH-promoting substances described in this chapter		
Drugs	**Natural products**	**GSH co-factors**
NAC	Oral Glutathione	Selenium
SAM	Cysteine	Vitamin B1
OTC	Methionine	Vitamin B2
OTZ	Melatonin	Vitamin B6
Procysteine	Glutamine	Vitamin B12
GSH monoesters	Lipoic Acid	Folate, Folic acid
GSH diesters	Silymarin (milk thistle)	Vitamin C
	Whey Proteins	Vitamin E
	Bioactive whey proteins (Immunocal®)	Other nutrients

GSH PRECURSORS & CELLULAR MANUFACTURE

The building blocks (precursors) glutamate, cysteine and glycine from any source must be in a form that can be transported from the mouth, through the digestive system, into the blood and finally

through the cell wall. Once there, the cell combines them into GSH. Glutamate is derived from food sources containing uncooked glutamic acid, glutamine and glutamate. It is found in protein supplements such as Immunocal and other whey derivates. Cysteine comes from such protein sources as eggs, raw milk, undenatured whey protein and in small amounts from other foods. The amino acid methionine can break down into cysteine. Various pharmaceutical drugs serve as cysteine delivery systems. Glycine is found in foods rich in the amino acids choline, glycine, serine and threonine. Only when these three precursors are absorbed by the body and have passed through the wall of individual cells can the body manufacture glutathione.

DRUGS

Many of the research studies described in this book were carried out using pharmaceutical drugs to raise GSH levels in test subjects. These drugs are described first. Afterwards, we discuss natural GSH-promoting substances.

NAC (N-ACETYL-CYSTEINE)

NAC is a potent glutathion precursor that has been available as a drug (Mucomist, Parvolex, etc.) and also on the shelves of health supplement stores for years. It is a variant of the amino acid L-cysteine, with an „acetyl" molecule attached. This greatly enhances the bioavailability (usefulness) of cysteine to the cell, enabling it to survive the trip from the digestive system into the blood, and finally through the walls of individual cells.

For many years this drug has been used to break up mucus in lung diseases such as cystic fibrosis, chronic bronchitis, asthma and emphysema and is still the standard treatment for acetaminophen overdose. Most GSH studies on humans used NAC. Together with other animal and laboratory experiments they measured the effectiveness of NAC against a host of diseases characterized by oxidative stress, free radical formation and glutathione depletion. Such diseases include infection by AIDS/HIV, cancer, heart disease, tobacco damage and heavy metal poisoning.

Its use in cancer therapy is exciting because it can substantially raise glutathione levels and has emerged as a promising anticarcinogen, especially for smokers and others at high risk for cancer. It is also known to have direct anti-tumor effects and its ability to detoxify normal cells helps it counteract the side effects of both chemotherapy and radiotherapy. However, its effectiveness depends on circumstances and it must be used wisely. Cancer patients wishing to take NAC must discuss it with their oncologist.

NAC has been used in AIDS research since the early 1990"s when it was found that HIV patients become profoundly glutathione deficient. Must data has resulted from studies at the National Institute of Health, Stanford University, and many other highly respected institutions around the world.

NAC therapy has two common problems: firstly, it is a pharmaceutical drug and carries a certain toxicity itself; secondly, NAC-induced GSH levels reach a rapid peak and decline within hours. The drug is thus described as having a short half-life. Rapid peaks are often followed by a rapid drop, often to below normal levels. To maintain constantly elevated GSH levels, NAC must be swallowed or injected several times per day, and this is very hard on the body. Many people eating NAC report unwanted symptoms, including rash, wheezing, nausea, vomiting, cramps and diarrhea. Others find the smell and taste unacceptable. Although rare, death has been reported in association with NAC. However, it is still the most commonly used way to raise glutathione levels in clinical settings.

Treating drug overdoses or acute pulmonary disease with NAC requires the monitoring of health professionals. Suggested non-prescription oral doses range from 200-2,400 mg/day depending on one‟s state of health.

SAM (S-ADENOSYL-METHIONINE)

SAM is a form of methionine that has already been partially converted to cysteine. It can be useful in the treatment of cirrhosis and cholestasis and is becoming popular as a mood stabilizing medication in Europe. Its possible use in America as an antidepressant is currently under investigation. SAM is expensive to synthesize and may react poorly with other antidepressants. Its side effects at therapeutic doses can include dry mouth, agitation and gastrointestinal problems.

OTC AND OTZ

OTC (ornithine decarboxylase, procysteine) and OTZ (Oxothiazolidine carboxylate) are synthetic delivery sources – a substrate for the enzyme 5-oxyprolinase which first converts them to S-carboxy-cysteine, and later hydrolyzes them to cysteine, which the liver uses to make GSH. However, the required enzyme 5-oxyprolinase is not present in all tissue and the value of OTC/OTZ is limited. Most studies have used either laboratory animals or human tissue cultures. Small studies have been conducted with AIDS and cancer patients, and further work is in progress. These drugs are not readily available to doctors or the general public.

GSH MONOESTERS, GSH DIESTERS

These synthetic compounds make quite effective GSH delivery systems but they can be metabolized into alcohol, which potentially depletes GSH. Very few studies have been carried out on humans, but well-recognized GSH researchers such as the late Alton Meister and Mary Anderson have been optimistic about further elaboration of its clinical applications. However, the long-term safety of these products is open to question.

NATURAL PRODUCTS

ORAL GLUTATHIONE

Why not just eat GSH? After all, it is freely available in fresh fruits, vegetables and meats. It is also commercially available in pill form or powder from a variety of chemical companies. Unfortunately, pre-manufactured GSH is not particularly helpful to the body. A small amount of reduced protein-bound GSH may make it into the blood stream, but most is lost to the digestive process and cannot effectively raise intracellular GSH levels. Researchers have demonstrated oral GSH‟s poor bioavailability, especially in the liver where it is most needed. E.W. Flagg and his team at Emory university, Atlanta even point to a possible decrease in blood GSH after oral ingestion of GSHcontaining foods. To put it in medical terms, oral GSH has negligible effect on immunologic parameters.

CYSTEINE (L-CYSTEINE)

The availability of cysteine determines how much GSH we can synthesize. Why not just eat this non-essential amino acid? It is available through pharmacological supply outlets and at health food stores and may in fact raise intracellular GSH to a small degree. However, cysteine as a dietary supplement can promote hypercysteinemia and potential toxicity. Because cysteine is easily oxidized in the digestive tract, its absorption into the bloodstream and cells is limited. Cysteine that manages to reach the bloodstream is further oxidized into potentially toxic by-products, some of

which contain the hydroxyl radical – a highly reactive oxidant. This defeats its intended purpose as an antioxidant.

Clinical proof that dietary cysteine has a negligible effect upon immune response has been demonstrated by the Montreal researchers Drs. Gustavo Bounous and Gerry Batist. They compared specific protein precursors in the bioactive whey-protein Immunocal with a cysteine/casein combination. Animals fed oral cysteine showed no positive response.

METHIONINE (L-METHIONINE)

Methionine is an essential amino acid present in many foods and has been identified as a GSH precursor. It is also available from pharmacological supply outlets and health food stores. The metabolic transformation of methionine into GSH is a complex process, greatly affected by other factors. For example, methionine levels are very low when liver disease is present and non-existent in newborns. Above certain doses it can be toxic. Of great concern, methionine is also a precursor of homocysteine, recently identified as a
high risk factor in the development of atherosclerosis (hardening of the arteries).

MELATONIN

Melatonin is a naturally-occurring hormone manufactured by the pineal gland, which lies deep within the brain. Melatonin is a derivative of the amino acid tryptophan and the neurotransmitter serotonin. It has long been recognized for its role in the regulation of sleep and waking cycles and has gained popularity as a supplement for the treatment of jet lag, insomnia and other sleep disturbances.

Like most hormones, melatonin is rarely involved in just a single function. Recent research has led to a great number of papers describing the functions of melatonin, including potential anti-aging effects, application against Alzheimer‟s disease, cluster headaches, cancer prevention, cancer therapy, and as an immunostimulant. Melatonin is known to be a powerful antioxidant and plays a role in stimulating other antioxidants as well.

Apart from its ability to function independently as an antioxidant, melatonin has been shown to effectively raise glutathione levels in many tissues including the brain, liver, muscle and blood serum. Some of its positive benefits have been ascribed specifically to this ability.

An interesting scientific study measured melatonin levels against glutathione levels during sleep. A research team at the University of Texas showed that subjects given melatonin doubled their brain glutathione levels within 30 minutes. Like GSH anywhere in the body, it eliminates toxic hydroxyl radicals, but this brain GSH is more effective with sleep. It seems that melatonin may protect brain and nerve tissue because of its GSH-enhancing ability. Several European studies have supported these findings.

This same team in Texas led by R.J. Reiter has published many papers linking melatonin to GSH production. In a sports physiology experiment, muscle glutathione was measured before and after extended exercise. By using melatonin to pre-treat subjects before the stress of exercise, the usual, significant decreases in GSH levels due to oxidative stress were eliminated.

The long term safety of melatonin has not yet been established and response to it varies from person to person. This product should only be used in consultation with an appropriate health professional.

GLUTAMINE

Glutamine (GAM) is the most abundant free amino acid found in the body. It is common in both blood and muscle tissue, and is the second most common amino acid in the brain after glutamic acid (GA). The three semi-essential amino acids – glutamine, glutamic acid and gamma-amino butyric acid (GABA) – are closely related and are classified as glutamate amino acids. Glutamate is a salt of glutamic acid.

Described by Dr. Eric Braveman as "the brain‟s three musketeers," GAM, GA, and GABA are close in name and category but quite different in function. In the brain, GABA serves as an inhibiting (calming) neurotransmitter, GA as an excitatory neurotransmitter and GAM mainly as an energy source and mediator of both GA and GABA. Some proponents of glutamine have referred to it as "brain fuel".

These three amino acids usually fall into the same discussion because they have the ability to metabolize into one another. For example, if the brain senses a lack of glutamic acid it may draw glutamine from the muscles into the bloodstream, pass it through the blood-brain barrier and transform it into glutamic acid or glutamate.

Nitrogen is a critical component of all amino acids and is often released when they are broken down. Unfortunately this free nitrogen is easily converted to ammonia – especially toxic to nerve tissue and the brain. The liver must work hard to convert nitrogen into urea so it can be excreted in the urine. On the other hand, nitrogen may also attach itself to glutamic acid, forming glutamine. Because glutamine is unique among amino acids – the only one with two nitrogen molecules – glutamic acid serves as a "sink" to collect free nitrogen, protecting many tissues from harm.

Glutamine is crucial to the metabolism and maintenance of muscle. It is also the primary nutrient for cells lining the intestinal tract. In periods of stress or severe illness, glutamine levels may fall. That‟s why it is such a useful supplement for athletes, surgical patients, those suffering from the muscle wasting of AIDS or cancer and for various gastrointestinal disorders.

Glutamine can also boost the immune system, act as a cancer preventative and treatment, detoxify the body and support liver metabolism. Dr. Ronald Klatz of the American Academy of Anti-Aging Medicine (A^4M) describes glutamine as a „growth-hormone releaser‟ and an anti-aging agent. The overlap of the possible clinical applications of glutamine and glutathione is no coincidence. Glutamine supplies the body with glutamate (glutamic acid), the second most important component of GSH after cysteine.

Whether taken orally or intravenously, glutamine supplementation raises glutathione concentrations. T.R. Harward in Florida and M. Basoglu in Turkey conducted similar studies to measure the fortifying effect of glutamine on GSH levels in the gut. Levels of lipid peroxidation and oxidative stress both fell in these experiments. Y. Cao in Arkansas found a three-fold increase in intestinal GSH after glutamine supplementation.

R. Denno and J.D. Rounds of Harvard University conducted a study on parenteral nutrition – nutrients delivered by routes other than the stomach and gut. This is very important during long surgery and under other special circumstances. They showed that when glutamine was included,

plasma glutathione levels rose significantly and supported liver functions. R.W. Hong from the same team showed that glutamine supplementation improved survival odds against such toxic threats as acetaminophen overdose by preserving glutathione stores in the liver.

Glutamine also plays a role in cancer therapy. Tumor cells often act as a trap, stealing glutamine from other parts of the body and leading to muscle wasting and atrophy. For this reason, many cancer therapists avoided glutamine in the past, fearing they would be feeding the cancer. It is now known that just the opposite is true. Glutamine promotes GSH production, heightening the immune system‟s defense against tumor cells and making it easier for normal tissue to tolerate chemotherapy and radiotherapy.

Another University of Arkansas study led by Dr. K. Rouse showed how oral glutamine supplementation could lower glutathione in tumors – making them more susceptible to chemotherapy – and raise glutathione in healthy cells – making them more resistant to chemotherapy. S. Yoshida and A. Kaibara conducted similar experiments in Japan and concluded that glutamine supplementation prevents deficiencies of glutamine and glutathione and improves protein metabolism in cancer victims.

Glutamine is found in many plant and animal food sources but is easily destroyed by cooking. Raw spinach and parsley are good sources. Chicken, fish, pork and beef are high in glutamine. However, eating raw meats carries certain health risks. Braver individuals may eat sushi, carpaccio, kibbi, or steak tartar – all uncooked animal products.

Glutamine is being widely researched as a nutritional supplement for certain hospitalized patients. More research is still needed and the appropriate dosage for various scenarios is still unclear. The amount demanded by the body during periods of physical stress is still unknown. Store-bought tablets contain as little as 0.5 grams (500 mg). It also comes in powder form – often taken in daily doses of 4 or 5 grams. In extreme situations – following a bone marrow transplant, for example – doses as high as 40 grams per day have been given. Supplemental glutamine must be kept absolutely dry or it will degrade into ammonia.

Completely healthy individuals don‟t need supplemental glutamine. It can provoke such side effects as gastrointestinal upset. Older people and patients with impaired kidney and liver failure should be cautious. Any serious use of this supplement should be monitored by a health professional.

LIPOIC ACID

Also called alpha-lipoic acid or thioctic acid, lipoic acid is a disulfide compound that acts as an effective antioxidant, a neutralizer of various toxins including some heavy metals, and an important co-enzyme for recycling other antioxidants including vitamin C, vitamin E and glutathione. Lipoic acid occurs naturally in your body but has also recently appeared on the shelves of health food stores. It is being actively investigated by the scientific community for its medical merits.

Research has revealed the benefits of lipoic acid for such conditions as diabetes, HIV infection and AIDS, liver disease, lead and cadmium toxicities, cataracts, poisoning by amanita mushrooms, reperfusion injury (following stroke and heart attack) and vitamin E deficiencies. It also extends the endurance of body builders and their recovery time from injury. You may notice that its advantages entirely overlap those of glutathione. Lipoic acid is vital for converting glutathione back and forth from its oxidized (GSSG) to its reduced (GSH) form (see figure 6, chapter 1). It regenerates vitamin

C, vitamin E and coenzyme Q10. It can also provide reduction redox support to other sulfur groups and NADPH energy reactions.

Although lipoic acid has been described by many researchers as an antioxidant in its own right, scientists such as H. Bast and G.R. Haenen from the Department of Pharmacochemistry in the Netherlands believe that lipoic acid actually protects against lipid peroxidation by keeping GSH in its reduced (non-oxidized) state, and that GSH is the active antioxidant in this scenario. In fact, they showed that lipoic acid in the absence of glutathione actually promotes oxidation. One reason glutathione has been called the "master antioxidant" is because its critical enzyme glutathione-reductase maintains lipoic acid in its reduced (non-oxidative) state.

The ability of lipoic acid to enhance GSH function has been demonstrated by other scientists. E. Buses in Germany established that the protection offered by lipoic acid against radiation damage results from improved cell viability due to elevated glutathione levels.

Some leading American researchers in lipoic acid work at the University of California in Berkeley, led by L. Packer. They describe lipoic acid as providing intact cystine, which makes cysteine available to the cells. It is clinically significant that lipoic acid helps restore glutathione when it is deficient. Recommended dosages range from 100 to 200 mg per day.

SILYMARIN (MILK THISTLE)

The milk thistle plant, known scientifically as *Silybum marianum* has been used by herbalists for centuries to treat a variety of liver disorders, including hepatitis, alcoholic cirrhosis, jaundice and gallbladder disease, and to fight a number of toxins, including amanita poison mushrooms. The active ingredient of milk thistle is silymarin, a compound made up of the flavonoids silybin, silydianin, and silychristin and found in the seeds.

Many clinicians have studied this herbal extract and its use in toxicology and liver disease. It seems to stimulate the growth and regeneration of injured liver cells. However, its bioflavonoids seems to act primarily as free radical scavengers and to support detoxification enzyme pathways.

Further studies describing this action have demonstrated silymarin‟s impressive ability to promote glutathione production. It clearly prevents lipid peroxidation and maintains GSH levels. Silybin has a protective effect on acetaminophen overdoses – traditionally treated with the drug NAC. Silymarin can increase GSH by as much as 35% in certain glutathione – deficient states and accelerates detoxification of xenobiotics accordingly.

Recommended doses vary greatly, from 50 to 500 milligrams three times a day. Toxic reactions can include gas, cramps and diarrhea. Liver diseases should never be treated without the advice of a health professional.

WHEY PROTEINS

Whey, a large group of proteins, is a constituent of milk from all mammals, including human beings. The most commonly available whey comes from cow‟s milk. Raw milk contains 5 to 10% protein, of which 80% is casein and 20% whey. Casein is a mainstay of cheese production. For a long time whey was treated as an insignificant byproduct of the dairy industry but its advantages as a nutritional supplement are now creating a new surge of interest.

Many milk derivatives and whey products are marketed to health-conscious people. These products are extremely variable in their protein content, their concentration, the forms of proteins present, and other factors which determine the bio-effectiveness of the product, including the level of protein denaturation. Denaturation refers to a breakdown in the protein structure that may not affect its food value but that can affect is biological action (bioactivity) in the body. Many nutritionists point out that the fat or lactose content of milk products may still be high enough to cause concern. Others have reservations about the milk industry and its liberal use of antibiotics and steroids to boost product. And we cannot ignore the very real issue of fat-soluble and water-soluble environmental toxins passing into the milk.

Fresh milk whey contains potent GSH precursors such as lactoferrin, beta-lactalbumin, and serum albumin that are easily denatured. When consumed intact they are easily digestible and their constituent breakdown products pass readily into the bloodstream, serving as cysteine and cystine delivery systems. From there they are taken to individual cells, where these precursors are transported through the cell wall and metabolized into GSH.

Figure 14 – Whey protein variables
Concentration of total protein
Types of proteins
Degree of denaturization (breakdown)
Fat content
Lactose content
Bioavailability
Biological Activity
Contaminants, toxins

These precursors are fragile and easily denatured. They contain thermolabile components that are easily disturbed by heating and a mechanical shape that is quickly broken down by physical stresses such as shaking or churning. By the time most milk products reach your table their bioactivity is entirely lost, although their food value remains. Milk products are usually pasteurized several times to guard against bacterial contamination. This almost inevitably destroys their usefulness as glutathione precursors.

In order to maintain these precursors in a bioactive form, special means must be designed and used to extract whey proteins from milk and the process must be carefully monitored. Concentrations of protein in whey products range from as little as 20% to over 90%. They vary greatly in their make-up, as well as to the extent which GSH precursors are denatured or broken down. Some are bioactive. Most are not.

BIOACTIVE WHEY PROTEINS (IMMUNOCAL)

Bioactive whey proteins contain high levels of non-denatured protein. In scientific terms, they preserve the original bioactivity of the thermolabile components and mechanical shape of the proteins, guaranteeing the highest level of GSH-promoting activity.

Our knowledge of the GSH-sustaining effect of dietary whey proteins is the result of research begun at McGill University in Montreal in the early 1980‟s. Dr. Gustavo Bounous was studying protein

supplementation when by chance he discovered the bioactive potential of whey protein. He investigated this protein‟s effect on the immune system and published some exciting results. His findings encouraged many other scientific teams to study these GSH-enhancing qualities in tests on a wide variety of diseases. Dr. Bounous and his team went on to develop Immunocal – a whey protein made under conditions that maximize the protein‟s bioactivity.

Immunocal has been patented for its immuno-sustaining and GSH-enhancing effects. It is extracted exclusively from milk produced without antibiotics or steroids. The process produces 90%-pure whey protein and has received a patent for its method of use. It has also been recently granted a USA patent as a chemotherapeutic agent. It is the first natural supplement to receive such recognition.

Its history is backed up by phase I, II and III clinical trails including research into infectious disease (HIV/AIDS, hepatitis, Lyme disease, bacterial infections), cancer therapy, pulmonary disease, chronic fatigue syndrome and other disorders associated with high oxidative stress and low glutathione activity. It has been sold in Europe and the Orient by pharmaceutical distributors. In North America this all-natural product is available without prescription, although certain governmental agencies and insurance companies will reimburse patients with a physician‟s prescription.

Undenatured whey protein is a natural extract of milk and an ideal solution – a safe, dependable, effective way to raise and sustain GSH levels.

CO-FACTORS FOR GSH PRODUCTION

SELENIUM

Selenium is a trace element. It functions principally as an antioxidant but does other things too. It is involved in protein synthesis and other metabolic processes and acts synergistically (hand-in-hand) with other antioxidants – in particular vitamin E. Its clinical applications have received a great deal of attention and we are about to see an increase in the number of clinical trials using this mineral.

Plants absorb sodium selenite – an inorganic compound in the soil – and convert it into organic seleno-methionine. When we eat these plants the seleno-methionine is either used to make protein or converted once again, this time into seleno-cysteine. The cysteine portion of this molecule contributes to GSH production. The selenium portion is an essential component of the critically important enzyme glutathione peroxidase.

Browsing through a list of selenium research and clinical trials, one is reminded of GSH research and clinical trials. Both deal with the same types of disease, clinical symptoms and outcome. Selenium has been linked with heart disease and atherosclerosis, cancer treatment and prevention, liver and pancreatic function, detoxification of heavy metals, immune support, male infertility, AIDS, Crohn‟s disease, pancreatitis, cystic fibrosis and multiple sclerosis – a reflection of the contents of this book on GSH.

Most scientists agree that the principle way in which selenium fights these diseases is by elevating levels of glutathione peroxidase, the only known metabolically active form of selenium in the body.

A recent study sponsored by the National Cancer Institute (USA) caused quite a stir. Having examined favorable reports about selenium being cancer-preventive, it began a study on skin cancer.

Patients were given either selenium or a placebo, and monitored for eight years for any recurrence of their skin lesions. Initial results were disappointing – there was no evidence that selenium protects against skin cancer recurrences. However, they were startled to find that their test group suffered significantly lower rates of other cancers, including lung, prostate and colon cancers (see chapters 5, 14 and 15).
These unexpected findings rolled over into a host of new studies, some of which are still in progress.

Selenium is found abundantly in foods grown in selenium-rich soil and from the meat and dairy products of animals who have been raised on those plants. The suggested daily intake is 40 to 70 micrograms (mcg) – an amount found in normal diets and not requiring supplementation.

Be careful – too much selenium has a well-known toxicity and some individuals suffer ill effects at doses as low as 205 mcg/day. At 1,000 mcg/day, many symptoms become apparent. Selenium is usually sold in doses ranging from 25 to 200 mcg. It may be a natural food supplement but it must be approached with caution. People in good health with a reasonable diet should take no more than 25 to 50 mcg/day.

VITAMINS B1, B2
The water-soluble vitamins B1 (thiamine) and B2 (riboflavin) were two of the first vitamins discovered back in the 1920‟ and 30‟s. They each perform several important functions in our body. Vitamin B1 is essential for carbohydrate metabolism and energy production. It also helps conversion of fatty acids into steroid hormones. Vitamin B2 is just as involved in energy production and hormone regulation and helps combine individual amino acids into larger proteins, glutathione being one of them.

Vitamins B1 and B2 maintain glutathione and its related enzymes in their active forms, enabling GSH to function at its optimum capacity. They are integral constituents of coenzymes that product glutathione reductase and NADPH – essential for recycling oxidized glutathione (GSSG) back to reduced glutathione (GSH), the active form.

The currently recommended daily intake of these two vitamins is 1 to 2 milligrams. Most clinicians believe that these values are far too low and it‟s just a matter of time before they are raised. Doses of 50 to 150 mg are not uncommon and many feel that the optimum level lies between 25 and 300 mg/day. It is apparently not toxic – these higher doses have revealed no adverse effects. Nutritionists at times prescribe 500 mg/day for some conditions, but for most near-normal states 10 to 50 mg/day should suffice.

VITAMINS B6, B12, & FOLIC ACID
Like their cousins B1 and B2, vitamins B6 (pyridoxine) and B12 (cobalamin) are also water soluble. Both play an indirect but important role in glutathione metabolism. Vitamin B6 is one of the most widely used vitamins in our body and contributes to over sixty enzyme systems. It is crucial for the metabolism and function of many amino acids and essential fatty acids, so the majority of our tissues depend on it. Vitamin B12 acts as a coenzyme in the production and regulation of red blood cells, myelin and other neurological tissues. It is prone to depletion in various diseases including malabsorption, alcoholism, pernicious anemia and the complications of strict vegetarianism.

Folic acid – also known as folate or folacin – takes part in a number of various processes including DNA synthesis and neurotransmission. It works together with vitamin B12 in amino acid

metabolism and protein synthesis. Its role in cardiovascular disease has been recently highlighted – it lowers elevated homocysteine levels, a serious risk for cardiovascular disease. Folate tends to shunt cysteine preferentially towards glutathione production rather than homocysteine production.

North American recommended daily dietary allowances for vitamins B6, B12 and folate are 0.5 to 2 mg, 1 to 2 mcg, and 105 to 250 mcg respectively. Some nutritionists may recommend as much as 50 to 500 mg of vitamin B6, 100 to 500 mcg of vitamin B12, and 400 to 2,000 mcg of folic acid. Vitamin B12 has negligible toxicity but vitamin B6 can be neurotoxic at higher doses. Folic acid is relatively safe unless taken alone by someone deficient in certain B-vitamins, particularly B12. Under normal circumstances we recommend a maximum 10 to 50 mg of B5, 10 to 50 mc of B12, and 400 mcg of folic acid per day.

VITAMIN C

The water-soluble vitamin C has various names, including ascorbate and ascorbic acid. It has been a focus for antioxidant research longer than any other antioxidant. Linus Pauling, the foremost researcher in vitamin C is considered by many to be the grandfather of free radical biology. He blazed the trail along which this and many other books have evolved. Thousands of articles have been written about it and research is still going strong. Yet even after all this time the topic of vitamin C in health and disease is still fraught with controversy.

The classic disease of vitamin C deficiency is scurvy. More recently, the use of vitamin C has been studied in cancer, anti-aging medicine, cardiovascular disorders, emotional or physical stress, and of course in immunology and infectious disease. It is an antioxidant but performs many other functions in our body. It is involved in bone, cartilage and soft tissue repair, support of various biologic systems including the recycling of B-vitamins, folic acid and other antioxidants, iron storage and a list of other life-sustaining functions far too long and involved for us to discuss in this book.

It is mentioned here because of its important links with glutathione metabolism. It is intimately involved in the GSH-driven glutathione-transhydrogenase enzyme system which keeps GSH, vitamin C, vitamin E and other antioxidants in their reduced (nonoxidized) state.

Numerous studies have demonstrated the ability of vitamin C to support glutathione levels and activity. C.S. Johnston, C.G. Meyer and J.C. Srilakshmi from Arizona State University conducted a double blind study comparing the GSSH levels of three groups – one ate a low-vitamin C diet, another ate vitamin C at 500 mg/day, and the third received 2,000 mg/day. Those taking the vitamin had significantly higher GSH red blood cell counts than the no-vitamin C group. There was little difference in glutathione level between the two groups taking vitamin C.

The converse is equally true. Vitamin C is far les effective and rapidly depleted without adequate glutathione. When a vitamin C molecule mops up a free radical, it effectively neutralizes it. However, the vitamin C complex is now tied up. It is either ejected from the cell and eliminated by the body, or it is recycled to go back and do more work. In the latter case, glutathione is the recycling agent. GSH and GSH enzymes accept the free radical from the vitamin C complex and free it up to get back to work. This cycle drives antioxidant function in our bodies (see figure 6, chapter 1).

S. Mendiratta, J.M. May, and Z.C. Qu of Vanderbilt University in Nashville carried out a persuasive study demonstrating this phenomenon in human plasma and red blood cells. When GSH content

was intentionally depleted with the chemical diamide, vitamin C was either eventually lost from the plasma or severely functionally impaired in the red blood cells, remaining in its oxidized state (dehydro-ascorbate). Glutathione enabled its transformation back into the functional form, ascorbate.

There is still much dissent over the appropriate dosage of vitamin C. Although both the American and Canadian recommended daily allowances of vitamin are in the range of 30 to 60 mg/day, many scientists and nutritionists feel that this figure is far too low. Advocates of megadosing with vitamin C are not adverse to taking 10, 20, or 30 thousand mg/day.

It is well documented that supplies of vitamin C beyond a certain threshold are eliminated from the body, often accompanied by cramps and diarrhea. Other researchers feel that vitamin C is potentially harmful at high doses. It may serve as a pro-oxidant, and also strongly competes with other antioxidants, occasionally impairing their function. E.W. Flagg and her team at Emory University in Atlanta showed that high levels of vitamin C intake corresponded to lowered GSH levels.

If glutathione levels are adequate, no more than 200 to 1,000 mg/day of vitamin C is necessary.

VITAMIN E

The fat-soluble vitamin E is America‟s second most popular supplement next to vitamin C. Given the wealth of information and positive clinical studies done on this vitamin, its popularity will probably continue to grow. Some have estimated that if all North Americans took adequate vitamin E supplements, health-care costs could be reduced by billions of dollars.

Studies have shown benefits in cancer prevention and therapy, cardiovascular disease, diseases of aging, wound healing, neurodegenerative disease and many other states of health. Besides it clearly defined role as an antioxidant, it plays a part in detoxification of many compounds and in the immune system.

Like vitamin C, vitamin E has an important role in the GSH-driven glutathionetranshydrogenase enzyme system which keeps GSH, vitamin C, vitamin E and other antioxidants in their reduced (non-oxidized) state (see figure 6, chapter 1). Studies with GSH and vitamin E resemble those with GSH and vitamin C because these antioxidants depend on each other for proper function and recycling. The synergistic effect of vitamin E and glutathione can be attributed to vitamin E‟s ability to help GSH with antioxidation, and to its direct modulation of glutathione-related enzymes. Vitamin E comes in several forms, natural and synthetic. This vitamin actually represents different substances of which alpha-, beta-, delta-, and gamma-tocopherols are the most active. The natural form of tocopherol most often found is D-alpha-tocopherol, which is more potent and bioavailable than the synthetic DL-alpha-tocopherol.

The daily-recommended allowances range from 25 to 50 IU (international units), however studies hint that most of us would experience more benefit at much higher doses. Popular regimens use doses from 100 to 1200 IU/day. With adequate GSH levels, it is unlikely that one needs more than 400 IU/day. At excessive levels, vitamin E is toxic and can provoke gastrointestinal, cardiovascular and neurological side-effects.

OTHER MICRONUTRIENTS

Magnesium deficiency can lead to impairment of the enzyme gamma glutamyl transpeptidase, which is important in the synthesis of glutathione.

Vanadium is a trace element that depends on glutathione to remain in a reduced (nonoxidized) state and to increase its bioavailability. Under certain conditions, vanadium may recycle GSH. However, vanadium in high concentrations is toxic and may deplete glutathione.

Zinc deficiency is also detrimental to glutathione metabolism, reducing GSH concentration, especially in red blood cells. Zinc also carries a certain toxicity, and may reduce GSH at high levels.

CONCLUSION

For our bodies to sustain healthy glutathione levels, the limiting factor in our daily intake of food is usually the amino acid cysteine. It must be in a form that can survive the trip from our mouths to our cells. Unfortunately, merely eating either glutathione or the free amino acid cysteine does not give the cell what it needs to manufacture glutathione.

Several drugs and natural products can do this efficiently. NAC (N-acetyl-cysteine) is a powerful drug that is commonly used in critical care medicine, toxicology, and pulmonary medicine. It has been the most researched of all the GSH-promoting modalities, and newer clinical applications are being developed all the time.

Many natural products exert some of their positive effects by supporting or directly raising glutathione levels. Undenatured whey proteins are an exciting development. A whey protein isolate, Immunocal, has recently been patented to augment glutathione levels and enhance immune function. Ongoing clinical trials are underway to test it with a number of different medical conditions.

CANCER

Few words strike as much fear and loathing in a doctor"s office as „cancer". More than one hundred types are known, of varying levels of aggression. Many are treatable or even curable. Still, cancer is the second greatest cause of death in North America, after cardiovascular disease. One third of Americans will eventually die of some form of cancer. It must be emphasized that many cancers can be prevented through the threefold regimen of diet, avoidance of carcinogens and reinforced bodily defenses.

CARCINOGENESIS

Healthy cells have a built-in mechanism that only allows cellular replication for three purposes: normal growth, healing of injured tissue and replacement of cells lost in normal metabolism. But cells can lose their ability to regulate growth, replicating uncontrollably and eventually forming a clump of cancerous tissue. This tumor can grow sufficiently to crowd out normal tissue, sometimes releasing diseased cells that spread the cancer into other parts of the body by the process of metastasis. Symptoms develop when the growth begins to interfere with bodily functions or deplete energy resources.

It is not clear precisely how and why these cells lose their self-regulation, although many possible causes have been singled out. Certain environmental carcinogens will predictably initiate cancerous growth, including a variety of chemicals and high radiation levels. Other factors are less predictable. Differences in our genetic makeup or immune systems apparently protect some people better than others. We also know that susceptibility to certain cancers is sometimes inherited from the family or racial gene pool, but the triggering factors are still unknown.

Apart from genetic factors, we can identify the following casual factors: the pollution of cigarette smoke, fossil fuel exhaust, heavy metals, pesticides and others; the ionizing radiation of x-rays, nuclear waste, ultraviolet (UV) radiation from the sun intensified by a depleted ozone layer; poor diet is an important factor; finally, certain viruses can contribute to the development of cancer: AIDS, hepatitis C, Epstein-Bar disease and papilloma.

The American Cancer Society makes the following suggestions to minimize the risk of cancer: maintain appropriate body weight, eat a varied diet including daily fruits and vegetables, eat more high-fiber foods (whole grains, cereals, legumes, etc.), cut down on total fat intake and limit consumption of alcoholic beverages and salt-cured, smoked and nitrate-preserved foods.

Cancer starts with a mutation in the genetic code of the cell – a reprogramming of developmental patterns that results in uncontrolled growth. A combination of genetic and environmental factors including diet may contribute to this aberrant replication. One theory suggests that when free radicals form in the cell nucleus, its DNA code may be damaged. Another theory suggests that factors such as poor diet and cigarette smoke compromise the immune system and weaken bodily defenses which might otherwise destroy a newly cancerous cell at the outset, when it is still vulnerable. Regardless of theory, we owe it to ourselves to pay attention to all possible factors and take advantage of any way to minimize the danger of cancer. One of these is by maintaining GSH levels.

GSH AND CANCER

Hundreds of medical articles have been written describing the role of GSH in cancer prevention and cancer treatment. They fall into three main groups: 1) prevention, including detoxification of carcinogens, antioxidation and heightened immune response; 2) therapeutic possibilities, such as anti-tumor methodologies and the treatment and prevention of malnutrition and wasting, and 3) a special role for GSH in chemotherapy and radiotherapy whereby it enhances the effectiveness of these arduous treatments while minimizing their side effects.

CANCER PREVENTION

A 1996 article in the European Journal of Cancer actually suggested that free radicals be listed as an important class of carcinogens. Because of its great capacity as the cell‟s major antioxidant GSH can soak up oxyradicals and other free radicals as they form in the cell. This prevents subsequent damage to various parts of the cell, particularly to the DNA in its nucleus. GSH has the additional benefit of enhancing the effect of other antioxidants such as vitamin C, vitamin E and selenium. This further strengthens the body‟s ability to destroy free radicals. To top it off, GSH also plays an important role in the synthesis and repair of DNA.

There is no doubt that a well-functioning glutathione enzyme system wards of cancer. This is clearly illustrated by a study published in the Journal of the National Cancer Institute. It focused on people deficient in the enzyme glutathione-S transferase-mu-I (GSTM1). GSTM1 is an important antioxidant that also detoxified common bladder cancer carcinogens such as tobacco smoke. Approximately one person in two inherits two defective copies of the GSTM1 gene, impairing the function of this enzyme. It was found that 25% of all bladder cancers occurred in people missing this enzyme. Heavy smokers missing this gene were six times more likely to develop bladder cancer.

There is a link between the loss of glutathione activity and the development of prostate cancer. Another glutathione enzyme, glutathione-S-transferase-pi-1 (GSTP1) almost always disappears in both cancerous and precancerous prostate lesions. It seems that prostate cancer begins with the inactivation of this glutathione enzyme. Many studies have made the connection between GSTP1 loss and malignant transformation of prostatic tissues. Similar studies have linked GSH-defective genes to breast and lung cancer as well, especially in smokers. Several scientists have suggested that people should be screened for these genetic or enzymatic defects as a way to determine their risk level.

GSH also plays a specific role in the detoxification of numerous well-known carcinogens and mutagens in our environment. Some of the most important are:

Aflatoxin B1
N-acetyl-2-aminofluorine
Benzanthracene
Benzapyrene
Benzidine
Dimethylhydrazine
Dimethylnitrosamine
Ethyl methane sulfonate
N-methyl-4-aminoazobenzine
7-methyl-benzanthracene
3-methyl-cholanthracene
1-nitropyrene

These cancer-causing substances are conjugated or neutralized by GSH and rendered into a form the body can eliminate. The role of GSH in detoxification simply can‟t be overstated. Since the liver is the body‟s principal detoxifying organ it is not surprising that it carries the highest concentrations of GSH in the body.

The Chemoprevention Branch of the National Cancer Institute (USA) has for the last decade been developing drugs to diminish the incidence of this dreaded disease. Substances that raise GSH levels, such as NAC and the selenium derivative selenomethionine, are on their short list of useful therapies. One of the major successes of their research efforts is their statistical demonstration that selenium protects against prostate cancer. Other studies have identified selenium as protecting against colon, rectal and lung cancers as well as colonic polyps. R.B. Balansky, C.C. Conaway, H. Witschi, and other American and European researchers have successfully shown that NAC can slow the growth of cancers induced by toxins including urethane, nitrosamines, doxorubicin, ethylnitrosourea and other cancer-causing agents.

NAC apparently protects against the carcinogenic properties of cigarette smoke. N. VanZandwijk from the Cancer Institute of the Netherlands writes, "NAC has emerged as a most promising cancer chemopreventive agent." S. De Flora summarized a very large chemoprevention trial sponsored by Project Euroscan and described the many positive effects of NAC as a cancer prevention agent. It reviewed potential uses against lung, breast, bowel and skin cancers, and the actual mechanisms by which NAC and GSH exert these protective effects.

One of the glutathione‟s effects upon the immune system is to control and balance the growth of T-cell lymphocytes (a type of white blood cell), thereby strengthening the immune response. Immuno-depressed individuals are often more prone to cancer, a good example being Karposi‟s sarcoma, a cancer found mostly in AIDS patients. Cancer specialists have recently developed a strategy called immunotherapy – an attempt to optimize the body‟s natural defenses against the cancer. Immunotheraphy consists of tools to stimulate the immune system. A Japanese team from Kyoto University showed that adding NAC to cytokines – a class of immunotherapeutic agents – stimulated immune cells and their biochemical products. They suggest that this may be an effective compliment for the treatment of primary liver cancer.

Other anti-cancer substances produced naturally by the immune system include TNF (tumor necrosis factor) and IL-2 (inter-leukin 2). Glaxo Wellcome Research and Development scientists showed that NAC acts against tumors by elevating TNF. In the laboratory NAC halt4ed tumor growth in more than one third of mice injected with cancer cells. C.Y. Yim and J.B. Hibbs at the University of Utah had similar success in suppressing tumor growth by using NAC to stimulate IL-2 (a promoter of white blood cell activity) in lymphokine killer cells, a type of T-cell lymphocyte.

THERAPEUTIC POSSIBILITIES

Surgical removal of cancer is only feasible if the tumor is not widespread and its accessible. Radiation and/or chemical therapy can help, but both inflict great damage on normal as well as cancerous cells. A cornerstone of recent research has been the search for ways to limit the damage to normal cells by such anti-cancer treatments.

Chemotherapy is a controlled poisoning of the patient based on the idea that rapidly growing cancer cells are more sensitive to the poison than are normal cells. Many but not all chemotherapeutic agents produce particularly unpleasant side effects. Radiation therapy works in a similar way. The

cancerous area is targeted and bombarded with radiation. The tumor is theoretically more sensitive to the radiation than the surrounding healthy tissue, but this treatment can also produce severe side-effects.

Recent experiments show that the GSH content of both normal and cancerous cells makes them more or less susceptible to damage. High GSH levels clearly help protect cells from chemotherapy, low levels make them vulnerable. It would be ideal if GSH levels were high in normal cells and low in tumorous cells, but many human cancer cells have particularly high GSH levels. Cancer is the only known condition under which the otherwise tightly regulated GSH levels are exceeded. It is characteristic of cancer cells to bypass normal regulatory controls.

Tumor cells high in GSH often show resistance to chemotherapy, so there has been some effort to reduce GSH levels in cancerous cells with GSH-depleting drugs like BSO. The trouble is, BSO reduces GSH levels in healthy cells too, magnifying the already intolerable side-effects of chemotherapy. So this approach is impractical.

Nevertheless, there may be a way to diminish GSH in cancer cells alone. Paradoxically, the precursors that raise glutathione levels in normal cells trigger the opposite reaction in cancerous cells. When GSH production is overstimulated in cancer cells, they shut down glutathione production in a process called negative feedback inhibition, making them more susceptible to destruction. Meanwhile, normal tissue uses the precursors to make glutathione, leaving it with better defenses.

This paradox was described as early as 1986 by A. Russo‟s team in the journal Cancer Research. When the GSH-promoting drug OTZ was added to human lung cancer cells, their glutathione level did not increase even though GSH levels in surrounding normal cells did. McGill University researchers Sylvain Baruchel, Gerry Batist and their team in Montreal showed that OTZ could deplete GSH in breast cancer cells while enhancing it in normal cells. This team later worked with Dr. Gustavo Bounous and published similar results in the journal Cancer Research, using the whey protein isolate Immunocal to provide dietary GSH precursors.

Studies with the same product were also carried out on patients with metastatic carcinoma – cancer that is spreading through the body. They were fed Immunocal for six months. Although it did not cure the cancer, a significant proportion showed either tumor regression or stabilization. Most also experienced the advantage of normalized hemoglobin and white blood cell counts. The same researchers showed that elevated GSH levels may enhance the anti-cancer action of certain chemotherapeutic agents.

Another Canadian team – this one from the University of Saskatchewan – conducted trials on patients with advanced progressive cancer. They were given toxic doses of acetaminophen as chemotherapy, plus NAC to raise glutathione levels. They hoped that NAC would raise GSH in normal cells only, and their results bear them out. More than half the patients showed either improvement or stabilization.

Nevertheless, cancer specialists are still concerned that elevating GSH non-selectively might in certain cases diminish the advantages of chemotherapy. Any GSH therapy should be an integral part of the whole cancer treatment. Cancer patients should never initiate it on their own and must first talk to their treating physician.

Additional studies have investigated the effects of nutritional proteins on cancer-causing chemicals in animals. Researchers doing similar experiments in Canada and Australia subjected rodents to the powerful carcinogen Dimethylhydrazine – which causes colonic cancer similar to humans – and fed them a variety of proteins. Animals fed on undenatured whey protein concentrate showed fewer tumors and a reduced tumor load. The scientists found that this protein offered "considerable protection to the host," more so than any other protein.

It is accepted as a fact of life that the incidence and mortality rates of cancer increase with age. Certain cancers may in fact be considered diseases of aging, especially cancer of the prostate gland. Specific changes of aging render patients more susceptible to cancer. They also have less protection against oxidative damage, and diminished immune response. The protective effect of GSH diminishes with age. We generally lose from 20 to 40% of GSH after age 65.

A recent study convincingly showed that normal levels of androgens (male sex hormones) in older men lead to decreased GSH levels in the prostate gland. Antiandrogen therapy – also known as chemical castration – is a common treatment for prostate cancer. Androgens are known to act as oxidative stressors and can upset the prooxidant-antioxidant balance. Lowered GSH levels lead to loss of antioxidant function and may trigger the mechanism of prostatic carcinogenesis.

The prostate specific antigen (PSA) blood test is used to screen for prostate cancer and to track the progress of men suffering from this cancer. Higher PSA levels usually indicate progression of the disease, while falling levels show the success of treatment. Studies following PSA levels in patients taking GSH-promoting substances are in progress. GSH therapy has minimal toxic potential and one hopes it will become a standard treatment.

PREVENTION / TREATMENT OF SIDE-EFFECTS

Chemotherapy and radiotherapy lead to huge increases in free radical formation and a build-up of toxic metabolites. If the problem is not addressed, the side effects grow worse. Numerous studies have shown that when patients eat well – especially when their diets include vitamins and supplements – their tolerance of these unpleasant therapies improves. Patients with higher intracellular GSH levels experience far fewer chemotherapeutic side effects and cells with higher levels of GSH carry more protection against radiation damage, thereby lessening the side effects of radiotherapy.

Radiotherapists studying the protective role of GSH have correlated higher pretreatment glutathione levels with fewer subsequent radiation burns. Pre-treatment or simultaneous treatment with products that raise and maintain GSH levels gives patients greater tolerance to therapy.

Women with cancer were treated at the University of California (San Diego) with the standard chemotherapy cisplatin and supplemented with intravenous glutathione. This enabled them to take higher doses of chemotherapy while experiencing fewer sideeffects. A similar but much larger study was carried out at the Western General Hospital in Edinburgh, Scotland. Over one hundred and fifty patients being treated for ovarian cancer with cisplatin and glutathione were monitored for side effects, quality of life, and outcome. They were compared to another group receiving no glutathione. The first group showed statistically less depression, vomiting, hair loss, shortness of breath and

neurotoxicity. Their mental concentration and kidney function improved measurably and there was a distinct trend toward better outcome.

The hair loss that often results from chemotherapy may not be life-threatening but it can be extremely distressing to patients, especially at a time when they don‟t need additional stress. Hair loss may also suggest damage inflicted on other cells that regenerate quickly, like those lining the intestine. Researcher J.J. Jimenez at the University of Miami and others have demonstrated that NAC can protect from the baldness caused by common chemotherapy agents like cyclophosphamide.

Evidence suggests that glutathione-enhancing strategies may make certain chemotherapy agents more efficient. These include Adriamycin, cyclophosphamide, cisplatin and others. However, patients absolutely must talk to their treating physician before beginning any GSH-enhancing therapy. There are theoretical instances when nonspecific glutathione elevation may interfere with the anti-cancer treatment, although this is less of a risk after the course of chemotherapy or radiotherapy is complete.

MALNUTRITION / WASTING

Anti-cancer treatment is often accompanied by loss of weight, appetite, energy and strength. Good nutrition is critical and should include appropriate dietary supplements. The cancer itself, the anti-cancer treatment and the resulting state of nutritional compromise all decrease intracellular GSH levels. This greatly weakens antioxidant and immune defenses rendering patients more susceptible to other diseases and opportunistic infections. Well-known German immunologist and researcher Wulf Droge has studied weight and muscle loss in cancer, AIDS, sepsis and other diseases. He has noted the similarities among them and points to a common cause - GSH depletion. He and others have gone on to test the possibility that glutathione enhancing therapy may slow or halt this process of degeneration.

Increased GSH synthesis depends on the intake of cysteine-containing foods. Rich sources of this GSH-precursor are very hard to come by and often are not well tolerated by the patient. Cysteine is available as a free amino acid and may be taken, but it has toxic qualities and is not recommended. The drugs NAC and OTC can raise GSH levels but their effects are short-lived. These pharmaceutical drugs also have little nutritional value. Whey proteins have excellent nutritional value but usually lack GSH-precursors. The ideal source of dietary cysteine should be natural, nutritional, bioactive and undenatured. The patented whey protein Immunocal fits these criteria. It is biologically active, sustains elevated GSH levels and has great nutritional value.

CASE HISTORIES

Quebeccer Ivy-Marie is a very active thirty-seven year-old breast cancer survivor. After undergoing her initial surgery, the pathologist‟s report suggested she undergo a dozen sessions of chemotherapy and radiotherapy. She experienced many side-effects, including profound weakness and fatigue – a new experience for her. After ten sessions of therapy and many visits to her doctor to treat side-effects, she was put on 30 gm/day of the whey protein concentrate Immunocal. Her strength and sense of well-being improved within a week and she tolerated her last two sessions of chemotherapy with few sideeffects. She is back to her usual routine, and remains disease-free.

Complaining of abdominal pain, Louisa from Alberta was 54 when she found out she had ovarian cancer. While awaiting surgery, she fell ill with a persistent cough and malaise which turned out to

be a metastasis (spreading cancer) which had traveled to her lung. She ultimately needed pelvic surgery to relieve her discomfort, but decided not to undergo treatment for her lung metastasis. She started taking Immunocal and multivitamins daily and noticed a great improvement after several weeks. Four months later, repeat chest x-rays showed no increase in tumor size. Nine months later the radiographs revealed a decrease in tumor size. Louise continues to enjoy tending to her family and household.

CONCLUSION

There are many types of cancer, and perhaps hundreds of potential causes, but most cases are accompanied by poor antioxidant defenses. To make matters worse, most anti-cancer therapies place an enormous burden on the body and may deplete whatever natural defenses remain. Cancer sufferers must place themselves in best possible medical hands, but must also take special care of their nutrition. Patients are heavily dosed with pharmaceutical drugs and suffer from poor appetite and low energy, especially while undergoing chemical or radiation therapy. A natural source of energy that can also reinforce antioxidant defenses may make all the difference for people undergoing this distressing disease and its noxious treatment. Undenatured, bioactive whey proteins are an ideal way to increase GSH levels and simultaneously address protein requirements. Elevated glutathione replenishes antioxidant defenses, contributr4es to synthesis and repair of DNA and helps detoxify numerous carcinogens and mutagens.

AGING

The rules for aging are definitely being broken. In 1900 a North American's life expectancy was 49 years. As this chapter is being written it is 78 and climbing. With the advance of science and medicine a new breed of physicians is growing – longevity specialists. Doctors may now write certified board exams to obtain their specialty in antiaging. Dr. Ronald Klatz, founder and present of the American Academy of Anti-Aging Medicine (A^4M), representing over 8500 members in 1999, states, "These health professionals believe aging is not inevitable… Fifty years from now when millions of baby boomers start reaching the century mark, we will look back on the medical science of today as though it were the dark ages." Duke University demographer James Vaupel says, "There is no evidence that human life expectancy is anywhere close to its ultimate limit." Many believe that 100-120 years is an obtainable goal.

Over the twentieth century, improvements in sanitation, occupational health and life-style as well as advances in antibiotics, vaccines, and medical care have helped to extend the human life span. We all want to maintain our health during these senior years. A practical knowledge of GSH can help us ensure that our later years will bring us a good quality of life.

More than 12 percent of North Americans are over 65 and occupy a growing proportion of the population as baby boomers age. Most will suffer from heart disease, stroke, certain cancers, arthritis, Alzheimer's, Parkinson's, cataracts and other debilitating diseases. A common factor in these diseases is oxidative stress. In fact, the free-radical theory of aging based on oxidative damage underlies most anti-aging treatment.

GSH & AGING

The GSH antioxidant system is the body's powerhouse for diffusing and disposing of free radicals that threaten cell, tissue and organ damage, thus slowing the approach of aging. John T. Pinto of Sloan Kettering Cancer Center in New York proclaims GSH "The master antioxidant." Jean Carper in her bestseller Stop Aging Now! highlights the same point: "You must get your levels of GSH up if you want to keep your youth and live longer. High blood levels of GSH predict good health as you age and a long life. Low levels predict early disease and death."

These opinions result from convincing, fascinating research and experimentation. Agespecific decreases in GSH are seen in all tissues, including liver, kidney, lung, heart, spleen and the brain. Laboratory studies on the role of GSH in aging show GSH deficiency in all aging creatures, from mosquitoes and houseflies to rats and mice.

Similar findings in humans indicate that elderly subjects bear increased risk of disease and impairment. Blood-GSH concentrations in younger people (20-40 years) are 20 to 40% higher than in those aged 60-80 years. Studies by leading experts on aging (C.A. Lang, M. Julius and others) suggest that elevated GSH levels give elderly individuals a physical, psychological and sociological advantage over those with lower levels.

Researchers Mara Julius and Calvin Lang measured glutathione concentrations in community-based individuals over the age of 60 years. They mapped these values to their level of health, number of illnesses, and risk factors for chronic disease (tobacco, alcohol, cholesterol, blood pressure and obesity). Higher glutathione levels corresponded to lessened effects of aging and better general

health. Those with 20% greater blood GSH levels experience about one-third the rate of arthritis, high blood pressure, heart disease, circulatory difficulties and other maladies.

Dr. Lang also looked at glutathione levels in age groups: 20-40, 40-60, 60-80 and 80-100 years. The youngest group had acceptable levels but 14% of the 40-60 year olds and 53% of the 60-80 year olds had critically low levels. Interestingly, only 24% of the 80100 year olds had low levels, perhaps explaining how they reached such a ripe old age in the first place.

The Italians G. Paolisso and M.R. Tagliamonte went one step further, comparing adults under age 50 with those over 50. Both the GSH and antioxidant function were depressed in the older group. However, those over 100 years old had higher GSH levels than the other over-50 group. Again, this may explain their unusual longevity.

Several researchers over the years have also shown that life span can be extended by restricting diet and maintaining low body weight. No satisfactory explanation has emerged for this phenomenon, but some scientists have demonstrated that glutathione levels rise in these longer-living individuals. They suggest that glutathione may be involved in a molecular mechanism that contributes to longevity.

S.L. Nuttal and his British team published a revealing study in The Lancet, comparing GSH levels in individuals of different ages and states of health. The healthy young had the highest levels, ahead of the healthy elderly. The lowest levels were found in sick, elderly patients. The results clearly showed that GSH levels fall as we age and as we become ill. The more severe the illness, the more evident the decrease.

Back in the laboratory, scientists are trying to find out whether elevated GSH levels can actually extend the life span. Aging-expert John Richie Jr. thinks that glutathione deficiency may be a biochemical cause of the aging process. In some of his experiments MgTC – a GSH promoting drug similar to OTC – was fed to mosquitoes. GSH levels were found to be 50 to 100% higher, and life span was increased by almost 40%.

In another experiment, Diane Birt at the University of Nebraska fed hamsters the wheyprotein concentrate lactalbumin – a GSH-precursor. These animals also lived longer. Interestingly, control hamsters on a diet including casein and cysteine, or methionine did not benefit. In fact high cysteine loads proved harmful, showing how the bioactivity of these amino acids changes when part of a larger protein, rather than free amino acids.

Dr. Gustavo Bounous and other researchers at McGill University demonstrated this antiaging effect using a natural product to elevate GSH levels. They fed mice a specially developed whey protein isolate – later trademarked Immunocal – and compared their GSH levels and lifespan to mice on a standard diet. Not only were the tissue GSH levels found to be higher, the Immunocal-fed mice had an average life span of 27 months (corresponding to a human age of 80 years) as compared to the control diet average of 21 months (human equivalent of 55 years). This is an astonishing increase of 30%. Further experiments using both cysteine and caseine (another milk protein) neither increased longevity nor raised GSH levels.

AGING & DETOXIFICATION

As we age, GSH levels fall and we become increasingly susceptible to the toxic threats of many drugs and pollutants. Older people usually have quite enough health challenges without the additional load of drugs and toxins. Well-known again researchers T.S. Chen, J.P. Ritchie & C.A. Lang suggest that lower GSH levels in aging livers diminish the body's ability to detoxify poisons, including toxic doses of acetaminophen. Considering the widespread use of drugs in the geriatric population, this is highly significant.

AGING & EXERCISE

Increased physical activity as a way of life clearly corresponds to longevity and improved health. There are many reasons, and some researchers have focused on the role of antioxidants and GSH. H.M. Allessio and E.R. Blasi at the Department of Physical Education at Miami University, summed it up by saying that exercise can elevate antioxidant enzymes and cofactors and that antioxidant levels are inversely related to mortality.

The Germans M. Kretzschmar and D. Muller suggest in a series of reports that the elderly can compensate for the decline in glutathione levels through exercise. The resultant increase in GSH levels can protect against many of the disease processes common to older people. The Israelis A.Z. Reznick and E.H. Witt went one step further. They suggested that raised antioxidant function enables aging people to tolerate higher levels of exercise without the ill-effects of over-training.

Chapter 23 discusses Glutathione and athletic performance, explaining how glutathione levels increase with exercise and how it wards off some of the ill effects of excessive exercise. It has been suggested several times that physical activity promotes longevity by increasing glutathione levels.

IMMUNITY, AGING AND GSH

Aging is characterized by a decline in the immune system, accounting in part for increased incidence of cancer and other diseases, especially the infections common among aging individuals. R.K. Fidelius and M.F. Tsan from the Veterans Administration Research Service have linked low GSH levels with this increased susceptibility. By both raising and depleting glutathione levels they were able to significantly alter immune responsiveness.

As the immune system ages T-cell lymphocytes undergo the most significant changes, leaving us less able to respond to viruses, bacteria and other threats. The same T-cell insufficiency has also been identified in certain autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Separate study groups were able to enhance immune responsiveness in aging laboratory animals using GSH or GSH-promoting drugs like OTC (ornithine decarboxylase) or ^{2}ME (2-mercapto-ethanol), and these tests were carried into human studies. Tufts University researchers Drs. Simin Meydani & Dayang Wu showed that by adding GSH to the white blood cells of elderly people, immune activity approached the levels of much younger individuals. The same team went on to do an *in vitro* study in humans, feeding subjects supplements to raise GSH levels. These test had equally positive results in immune response. These leading researchers in aging and immunology conclude that increased oxidative stress and/or lower consumption of antioxidants contribute to the decline of white-blood cell function and weakened immune response in the aged.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a common chronic inflammatory joint disease that progresses with aging. Although its exact cause is unknown, several factors have been identified. Strong evidence shows that many of the changes in RA-affected joints are the consequence of oxidation and free radical damage. Some researchers have also implicated poor T-cell activity and overactive B-cell activity. Scientists have also demonstrated that T-cell GSH content in rheumatoid joints are significantly lower than in peripheral T-cells of the same patients. GSH modulation may play a role – a team of rheumatologists from Leiden University Medical Center in the Netherlands demonstrated clear improvement of inflammation at a cellular level by using NAC to raise glutathione in these tissues.

CONCLUSION

There is little doubt that cellular oxidative damage contributes to aging and the many diseases that accompany it. It has been documented that those who live for one hundred years or more have unusually high levels of glutathione. We also know that oxyradicals are highly destructive. So given that GSH is a powerful antioxidant, a connection between longevity and healthy GSH levels does not seem unreasonable. It may at least improve our immune defenses and quality of life at a time when many people experience one health problem after another. Although we are not mice, the extension of this rodent's life span by 30 to 50% suggests that GSH may reduce the wear and tear of aging on overall health. Quite apart from the process of aging, good health in general is associated with high GSH levels. And GSH helps the liver deal with the toxic side of many medications used by the elderly. It may also improve the usefulness of exercise, which in turn elevates the GSH system and contributes to overall better health and wellbeing. GSH can enhance our immune response at a time when it normally begins to decline, ward off age-related diseases, and especially improve T-cell function – a critical element of the immune system.

PARKINSON'S DISEASE

Also known as shaking palsy, Parkinson‟s disease is one of North America‟s most common debilitating illnesses. It is often thought of as a disease of old age – one person in a hundred will develop it by retirement age, but half of them may have it by age 40.

Parkinson‟s disease develops progressively. Nerve cells slowly degenerate in the part of the mid-brain that controls movement (the substantia nigra layer of the basal ganglia). In normal health, messages from the motor cortex to the reticular formation initiate free movement, and neurotransmitters released from the basal ganglia in response to the same messages slow or dampen movement, providing the suppleness and dexterity we take for granted. These two neurotransmitters are dopamine, which stimulates the damping effects, and acetylcholine, which inhibits it.

SYMPTOMS AND CAUSES

Its exact cause is usually unknown, but Parkinson‟s disease is characterized by cell damage in the basal ganglia. Production of dopamine slows down and the characteristic symptoms appear. It begins with weakness or stiffness accompanied by a slight tremor of the hands or head. Over time the shaking increases, muscles stiffen further and there is a visible deterioration in balance and coordination. In advanced stages, symptoms include generalized rigidity, drooling, loss of appetite, stooped posture, a shuffling walk and a fixed facial expression. Eventually, communication skills may be impaired. Dementia, depression and other emotional problems are common.

Genetic factors play a role too, but there are other contributing causes including certain medications, pesticides, carbon monoxide, cyanide, manganese, street heroin, specific viruses and the type of repetitive head trauma suffered by boxer Mohammed Ali (dementia pugilistica). Researchers at the National Institute of Health in Bethesda have recently identified a gene programmed for the production of a protein called alpha synuclein. There is hope that this clued will open the door to further discoveries about Parkinson‟s disease and innovative ways to treat it.

TREATMENT

There is so far no definite cure for Parkinson‟s disease but it is treatable – most effectively at its outset. Therefore, early diagnosis is best. For the time being, conventional treatments include medication that attempts to restore neurochemical balance by replacing or supplementing the body‟s production of dopamine. Neurosurgical techniques and fetal tissue implants have had some success. Some scientists are developing implantable electrodes into the brain to stimulate specific neural pathways. Drugs such as selegiline have shown promise. A team headed by researchers P. Jenner and C.W. Olanow from the Neurodegenerative Disease Research Centre in London have shown that selegiline may increase GSH activity. Recently, newer drugs like pramipexole and ropenerole have emerged as more effective treatments.

PARKINSON‟S DISEASE AND GLUTATHIONE

Recent research has revealed two important findings: first, biochemical analysis of the affected brain tissue shows damage consistent with extensive oxidative stress and the circulation of free radicals that follows it; second, GSH levels in these tissues are particularly low. A striking feature of Parkinson‟s is an approximate 40% decrease during the early stages of the disease. A group of researchers from the University of Southern California led by J.D. Adams Jr. were able to show that in advanced

Parkinson‟s Disease glutathione levels fall to a mere 2% of normal. Whether the drop in GSH is a cause or a symptom of this damage remains unclear. But there is good news – elevated GSH levels slow brain tissue damage. Some symptoms may even be reversed.

Since damage caused by free radicals is an invariable component of Parkinson‟s Disease, researchers have experimented with a variety of high-dose antioxidants. In addition to the more well-known antioxidants, glutathione therapy has also been used. Not only is GSH an exceptional antioxidant, the substantia nigra of Parkinson‟s patients is especially deficient in it, so their need is particularly great. M. Gabby‟s research team in Israel showed that elevated GSH levels more effectively reduce dopaminergic toxicity than the antioxidant vitamins C and E. Paradoxically, while brain cells need dopamine to function, dopamine at certain times is actually toxic to the same tissues. This may be why drugs which raise L-dopa levels, like Sinemet, only work for a few years before the effects wear off and the patient subsequently deteriorates.

Dr. P. Jenner and his team at the Parkinson‟s Disease Experimental Research Laboratories in London have extensively examined the role of GSH in the progression of this disease. They found that glutathione levels fall consistently at the onset of Parkinson‟s Disease and believe that elevated GSH levels can help prevent neural damage.

D. Offen‟s team at the Beilinson Medical Center in Israel experimented on the actual neurons involved in dopamine metabolism. They investigated the cell-death associated with the Parkinsonian decline in dopamine. To slow down this decline they used antioxidants, and found that the thiol (sulfur-containing) antioxidants GSH, NAC and dithioleitol worked well. In the cautious language of medical science, they described them as “markedly protective” of brain cells. This corroborated the findings of M. Gabby‟s work (above), further supporting the theory that GSH may prevent or delay dopamine-induced cell death.

G. Sechi and his team in Italy studied a group of untreated Parkinson‟s patients in the early stages of the disease who received intravenous GSH therapy twice a day for a month. All patients improved significantly with more than 40% decrease in their disability. The improvement faded away two to four months after the last GSH treatment.

“Other authors have drawn attention to the role of GSH-enhancing drugs in the treatment of this disease. There is much evidence to support the usefulness of elevated glutathione levels. Today, however, there are ways to raise GSH levels without the use of pharmaceutical drugs.

CASE STUDY

Glutathione is part of the body‟s defense system and protects us against the onset of many disease processes. It can also help to reverse certain conditions or symptoms, either temporarily or permanently. The following story illustrates the apparent helpfulness of GSH supplementation in one particular case.

Wally, a seventy-four year-old baseball fan, was diagnosed with Parkinson‟s disease in May 1997. His disease progressed quickly and his doctors placed him on Sinemet (carbidopa/levodopa). In November he began to experience severe headaches – presumably from the medication – and he discontinued it. Up to this point he had been a very active man, but now he deteriorated to the point where he could not get out of bed or even rise from a chair without help. He says movement felt like „walking in cement“. He was constantly fatigued and soon needed a

wheelchair to go outdoors. The doctors used other medications including Eldepryl (selegiline hydrochloride) and Requip (ropinirole hydrochloride). They helped slightly. In March 1998 he started taking Immunocal, a natural protein which raises GSH levels. After five days his headaches were gone. Within two weeks his fatigue had lessened. Two months later Wally was walking well again and was eventually able to visit the new Angels baseball stadium, Edison Field, and job around the block. There was no other therapeutic intervention and seven months later his active lifestyle continued.

62 year-old Carol maintained an active legal practice until 1990. After a diagnosis of Parkinson‟s disease in 1986, she was able for a while to continue her career as a lawyer, but eventually had to quit. The stress was aggravating her symptoms and the symptoms were in turn increasing her stress levels. She was treated with a number of different medications but her health continue to deteriorate until she eventually needed help at home to carry out day-to-day tasks. She quit driving her car and stopped taking her daily walks, which she loved. Then, within days of starting to take a bioactive whey protein isolate she noticed her strength returning. Weeks afterwards she was once more exploring her neighborhood and nine months later she was driving again.

CONCLUSION

Parkinson‟s disease is characterized by a loss of the brain cells that regulate dopamine. Significant evidence points to the role of oxidative stress and dramatically low GSH levels as critical contributing causes of this damage. Studies have demonstrated that protecting these cells from damage and death by raising GSH levels can succeed both in the laboratory and in patients and is a welcome addition to conventional medical treatments.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common form of dementia in North America and currently afflicts more than four million people. Studies estimate that as many as five to ten percent of adults over the age of 65 will be affected. Over age 80 this figure can rise to one in three. Given the change in our population demographics towards longer life spans, this represents an enormous future burden. Alzheimer's disease follows heart disease, cancer and stroke as the fourth most common cause of death.

Alzheimer's is a Neurodegenerative disease with progressive deterioration of memory, comprehension, intellectual function and behavior. It may have a subtle onset with a slow progression over twenty years or the patient may deteriorate rapidly with a devastating decline in mental capacity over a short period of time. The average duration is about seven years.

Not to be confused with the simple forgetfulness of normal aging, Alzheimer's leads to significant memory lapses, dramatic mood changes, emotional outbursts, childish behavior, inability to retain new information and general confusion or disorientation, particularly at night. Health and abilities decline until one is unable to care for oneself and eventually dies.

CAUSES

Alzheimer's disease is characterized by a degeneration of brain nerve cells and a shrinkage of brain mass. Although its exact cause has yet to be determined, certain changes in the brain have been well identified. Patients have decreased or altered levels of certain neurotransmitters such as ACh and GABA, which relay messages from neuron to neuron. Two other striking features or neurofibrillary tangles and neural plaque formation.

Several theories attempt to explain these changes. Alzheimer's was once thought to be a variant of the normal aging process. It used to be called 'senile dementia'. It is now clear that Alzheimer's is an abnormal condition but that a number of factors may at least delay or slow its progression. Recent research has identified a blood protein called ApoE which appears to be altered in Alzheimer's patients and leads to nerve cell damage. Other studies point towards the interaction of this protein with heavy metals such as aluminum and mercury, and other elements such as iron, zinc and calcium, leading to plaque formation. A strong argument has been made for the role of oxidative stress and free radical formation in promoting the damage in these tissues.

GSH AND ALZHEIMER'S DISEASE

How and where does GSH fit into this picture? If heavy metals are involved in the progression of Alzheimer's, GSH can play a critical role in their elimination and detoxification. Certain studies have demonstrated that when aluminum is 'pulled' out of the cells using chelators, the symptoms of Alzheimer's can be reduced or delayed. As we outlined in Chapter 2 one of our primary defenses against these toxins is an adequate GSH enzyme system. And as researchers further define how free radicals contribute to brain cell destruction, the role of GSH as the primary intracellular antioxidant will come to the forefront.

Much research has been focused on the role of antioxidants in alleviating Alzheimer's symptoms and its progression, especially vitamin E because of its availability and low price. But as we saw in Chapter 1 the interaction of these antioxidants is complex. Many are dependent on adequate GSH levels for their proper functioning. A large number of post-mortem studies have compared normal

with diseased brain tissue. They reveal significant changes in GSH and GSH peroxidase levels as well as elevated levels of the powerful oxidant lipid peroxide, against which GSH is a primary defense. Fibroblast cells cultured from brain tissue affected by Alzheimer's disease are more sensitive to damage by free radicals than normal tissue. The sites of this increased vulnerability likely occur at the mitochondrial level. Adams and his research team found GSH levels diminished in the area of the brain involved in short-term memory (hippocampus). Jenner and his co-workers found a similar decrease in the areas of the brain involved in higher intellectual functioning (the cerebral cortex).

Although Alzheimer's disease is certainly a multifactorial problem, certain aspects must be emphasized. It is unclear whether oxidative damage is the cause or just an effect of Alzheimer's. However, there is no doubt that diminished oxidative stress can retard or diminish disease progression. In addition, the part apparently played by toxins such as heavy metal needs to be addressed. In either case, elevated GSH levels can be a critical strategy against both of these dangers.

CASE STUDY

Despite excellent care at home, Max eventually had to be institutionalized for his Alzheimer's disease. His 78 year-old wife's arthritis and heart disease left her unable to give him the high-maintenance care he needed. Previously a gregarious salesman who loved to tell a joke, in his present condition he was even unaware of who was in the room. His previous history of smoking one to two packs a day left him with chronic bronchitis, requiring frequent inhalation therapy. To treat his ever-thickening secretions, the respiratory therapist started using Mucomyst (N-acetylcysteine – a GSH-promoting drug). After several weeks on the Mucomyst, Max began to smile when his wife entered his room and was visibly pleased by her visits.

CONCLUSION

In Alzheimer's disease certain proteins seem to react with heavy metals and other elements, leading to plaque formation. Oxidative stress and free radical formation definitely play a role in promoting this damage. When heavy metals are removed by chelators, the symptoms of Alzheimer's can be reduced or delayed.

It is unclear whether oxidative damage is the cause or just an effect of Alzheimer's. Nevertheless, antioxidants such as vitamin E may be useful. Their antioxidant function is maximized by maintaining adequate GSH levels. By diminishing oxidative stress disease the progression of this disease can be retarded or diminished.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common form of dementia in North America and currently afflicts more than four million people. Studies estimate that as many as five to ten percent of adults over the age of 65 will be affected. Over age 80 this figure can rise to one in three. Given the change in our population demographics towards longer life spans, this represents an enormous future burden. Alzheimer's disease follows heart disease, cancer and stroke as the fourth most common cause of death.

Alzheimer's is a Neurodegenerative disease with progressive deterioration of memory, comprehension, intellectual function and behavior. It may have a subtle onset with a slow progression over twenty years or the patient may deteriorate rapidly with a devastating decline in mental capacity over a short period of time. The average duration is about seven years.

Not to be confused with the simple forgetfulness of normal aging, Alzheimer's leads to significant memory lapses, dramatic mood changes, emotional outbursts, childish behavior, inability to retain new information and general confusion or disorientation, particularly at night. Health and abilities decline until one is unable to care for oneself and eventually dies.

CAUSES

Alzheimer's disease is characterized by a degeneration of brain nerve cells and a shrinkage of brain mass. Although its exact cause has yet to be determined, certain changes in the brain have been well identified. Patients have decreased or altered levels of certain neurotransmitters such as ACh and GABA, which relay messages from neuron to neuron. Two other striking features or neurofibrillary tangles and neural plaque formation.

Several theories attempt to explain these changes. Alzheimer's was once thought to be a variant of the normal aging process. It used to be called 'senile dementia'. It is now clear that Alzheimer's is an abnormal condition but that a number of factors may at least delay or slow its progression. Recent research has identified a blood protein called ApoE which appears to be altered in Alzheimer's patients and leads to nerve cell damage. Other studies point towards the interaction of this protein with heavy metals such as aluminum and mercury, and other elements such as iron, zinc and calcium, leading to plaque formation. A strong argument has been made for the role of oxidative stress and free radical formation in promoting the damage in these tissues.

GSH AND ALZHEIMER'S DISEASE

How and where does GSH fit into this picture? If heavy metals are involved in the progression of Alzheimer's, GSH can play a critical role in their elimination and detoxification. Certain studies have demonstrated that when aluminum is 'pulled' out of the cells using chelators, the symptoms of Alzheimer's can be reduced or delayed. As we outlined in Chapter 2 one of our primary defenses against these toxins is an adequate GSH enzyme system. And as researchers further define how free radicals contribute to brain cell destruction, the role of GSH as the primary intracellular antioxidant will come to the forefront.

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HEART DISEASE, STROKE AND CHOLESTEROL

ARTERIOSCLEROSIS

Heart disease and stroke are the main cause of death in North America. Both result from the same process - arteriosclerosis, also called atherosclerosis or hardening of the arteries. This is such a common disease in the developed world that it has been considered a normal part of the aging process. In fact, overwhelming evidence links it closely to diet and lifestyle issues such as smoking and lack of exercise, suggesting that this major cause of mortality and morbidity is preventable, or that its progress may be slowed down or even reversed.

Although it is more common in older people, the early stages of this disease is sometimes found in children, and people in their thirties can suffer significant damage.

The consequences of arteriosclerosis are disastrous – heart failure, heart attack, stroke, kidney failure, high blood pressure, impaired circulation and many other ailments. Additional contributing factors aggravate this condition and must be managed throughout our lives to ensure health and longevity. Some of the high risk factors are listed below and in figure 24, together with suggested ways to deal with them.

LOW FIBER

Dietary fiber adds bulk to the feces, which then pass through the intestines more easily, aiding normal bowel function. Low-fiber diets affect fat absorption and increase cholesterol levels. A high-fiber diet is critical. Adequate fiber can be found by eating a variety of fruits, vegetables, and grains every day.

To understand how GSH can help prevent and treat this disease, let's look at how arteriosclerosis develops. An artery wall has three layers – a tough epithelium, a thick muscular mesothelium and a delicate endothelium. The endothelial lining is especially prone to damage, and thin streaks of fatty deposits can build up there. In the healthy artery, this process is combated by several processes, including our natural antioxidant defenses. In arteries damaged by high blood pressure, stress or cigarette smoking, these fatty deposits accumulate. In an attempt to heal the damage, the body lays down platelets, calcium and scar tissue. Plaque thickens and makes the area stickier than normal, encouraging the accumulation of additional lipids. Slowly the artery becomes sufficiently clogged to inhibit blood flow, depriving organs and muscles of oxygen.

HEART DISEASE

Poor circulation affects all organ systems including the brain, kidneys, eyes and extremities, but its main burden is heart disease. When blood flow to areas of the heart through the coronary arteries is cut off, a heart attack results. The pain of angina comes from heart tissue that cannot get enough oxygen because of insufficient blood flow. A heart with poor blood flow weakens and leads to heart failure. Hardened arteries often lead to high blood pressure, which further compromises the heart.

Physicians try to prevent this downward spiral with medications that lower blood pressure, thin the blood, decrease cholesterol, strengthen heart muscle contractions and improve arterial blood flow. Surgery can provide a way around blockages. A coronary bypass operation consists of a grafted vein that bypasses the blockage. Angioplasty is a way to squash plaque against the artery wall and make more room for blood to pass through.

STROKE

A stroke is caused by blocked blood flow (ischemia) that deprives the brain of oxygen. All vital organs are prone to ischemia when arteries become narrow and hard. In these cases it is important to thin the blood and manage cholesterol levels. Occasionally, surgery is performed to remove the buildup of plaque in the arteries leading to the brain.

Both the deprivation of oxygen from brain tissue and its subsequent reintroduction cause significant damage. Neurologists from the University of California (San Francisco) showed the importance of glutathione in protecting the brain from such attack. Animals who glutathione levels were artificially lowered suffered significantly greater brain damage after a stroke. Neurosurgeons at the University of Washington went further, demonstrating that glutathione depletion also leads to further narrowing of the critical arteries serving those oxygen-starved areas.

CHOLESTEROL AND PLAQUE FORMATION

The process of plaque formation is complex and it takes years to reach the point of causing symptoms. However it is clear that certain types of fatty substances are more dangerous than others. LDL – bad cholesterol – leads to plaque formation, while HDL – good cholesterol – prevents it. Other factors increase the danger of these fats, especially oxidative stress.

Oxidation makes fat rancid. In our blood stream this chemical change is called lipid peroxidation and causes fatty deposits to stick to the artery walls. The corresponding formation of free radicals leads to further lipid peroxidation and subsequent hardening of the arteries. Cigarette smoke releases large amounts of free radicals into the blood stream, explaining why more smokers die of cardiovascular disease than of lung cancer. For similar reasons diabetics are also prone to vascular damage.

Researchers have identified many causes of cardiovascular disease. The biochemical changes that result in oxidation of fat, especially LDL-cholesterol, are important. But researchers are also studying the chemicals involved in the associated inflammatory response, platelet function and cardiac muscle aging. The new field of free-radical biology is revealing a greater than previously thought role for oxidative stress in cardiac disease. Thousands of published articles describe the role of oxidation in arteriosclerosis and huge studies are underway to establish the role of vitamin and mineral supplementation in treating and preventing this disease.

An excellent article published by a combined team of Canadian and Japanese heart researchers reviewed evidence for the role of oxidative stress in acute ischemic heart disease. They suggest that the use of antioxidant therapy prior to procedures such as angioplasty coronary bypass and thrombolysis may help prevent complications.

Without adequate protective mechanisms to combat free radicals and lipid peroxidation, vascular systems are quickly overcome by atherosclerosis. M.J. Kendall's team of Birmingham University examined over two thousand patients with confirmed coronary artery disease in a randomized clinical trial. Patients taking antioxidant supplements reduced their risk of cardiovascular disease by 47%. Some cardiologists argue that welldefined clinical trials have not yet proven beyond doubt that antioxidants are essential, but a poll of cardiologists published in the American Journal of Cardiology found that a full 44% of them take antioxidants themselves.

GSH AND ARTERIOSCLEROSIS

The principal antioxidant in our cells is GSH. This applies to the endothelial cells of the arteries as well as red blood cells and platelets. University of British Columbia researchers led by Kimberly Cheng showed the connection among cholesterol levels, GSH levels and plaque formation in the aorta. L.L. Ji, D. Dillon and E. Wu showed that decreasing GSH levels as we age contribute to the formation of atherosclerosis. Although antioxidants like vitamins C and E are increasingly considered important, the naturally occurring antioxidant in the cell is GSH. GSH also serves to recycle these other antioxidants into their functionally active form. This is described in chapter 1.

In determining cardiovascular risk factors, certain tests or markers can indicate the risk or existence of heart disease. Two of these are lipoprotein a (Lp[a]) and Homocysteine. D. Gavish, J.L. Breslow and other researchers have shown the GSH-promoting drug NAC to be very effective in lowering Lp[a] levels. They reported a 50 to 70% reduction using two to four grams of NAC per day – a considerable dose. Other researchers using more tolerable amounts were less successful at reducing Lp[a] but have suggested that NAC may influence atherosclerosis in other ways. They include reduction of bad cholesterol and inhibition of free radical formation by monocytes – white blood cells that are attracted to platelets.

The association between Homocysteine and GSH metabolism is still being elaborated but will clearly have important repercussions. In an influential review article J.S. Stamler and A. Slivka discuss the roles of GSH, its interaction with Homocysteine and the protective effect of GSH on the vascular system. The Swedes O. Wiklund, G. Fager and their group were able to lower Homocysteine levels with NAC.

An interesting article in the Japan Heart Journal described a study by A. Usal who measured the red blood cell glutathione of 21 patients with heart attacks and found evident glutathione depletion, indicating that this event presents a major demand for GSH.

GSH AND CHOLESTEROL

Undenatured whey proteins raise cellular GSH and some of them – including Immunocal – may contain unusually high levels of lactoferrin, an important protein known to prevent oxidation of LDL-cholesterol. In addition, increased GSH levels have been shown to improve reduction of overall cholesterol levels by raising the activity of the enzyme cholesterol hydroxylase. X. Zhang and A.C. Beynen compared various proteins that reduce cholesterol in the blood and liver. Their results showed that whey proteins were more effective than other milk proteins or amino acid mixtures. The authors suggest that the lower cholesterol levels result from the inhibition of cholesterol synthesis in the liver.

Researchers have shown that selenium levels correlate well with levels of HDL (good) cholesterol. In a double-blind study, P.V. Luoma's team was able to improve the ratio of good to bad cholesterol in healthy subjects by feeding them selenium supplements.
Selenium's only biological activity takes place in the formation of glutathione peroxidase and it is through this action that selenium exerts its positive effects. The Italians G. Franceschini and J.P. Werba had similar success altering HDL/LDL ratios using NAC (N-acetylcysteine).

GSH AND REPERFUSION INJURY

If a blood clot deprives tissue of blood and oxygen for more than a very brief period, its ability to produce life-giving energy is compromised. The immune system responds by building up neutrophils, a type of white blood cell, further compounding the damage by releasing even more products of oxidation. When bypass surgery or thrombolytic drugs break down the clot and re-

establish oxygen flow, the tissues are said to be “reperfused”. But when the fresh blood floods into the starved tissue, it responds with a surge of energy production that places exceptionally heavy oxidative stress on the tissue at the very time that its antioxidant resources have been depleted, paradoxically causing further damage. This condition is called reperfusion injury.

Pharmacologists such as K.S. Kilgore and B.R. Lucchesi from the University of Michigan long ago suggested the antioxidants should be administered alongside thromobolytic therapy. Cardiologists at the University of Brescia in Italy have shown significant glutathione depletion after cardiac ischemia, and the ability of ANC to combat this depletion.

GSH AND CIRCULATION

There are many other ways in which GSH protects blood vessels, but they exceed the scope of this book. They involved the role of GSH in maintaining smooth muscle tone in the vessel wall, the shifts and balance in substances including prostaglandins, leukotrienes, thromboxanes, and platelet factors. For more detailed information consult the references following this chapter.

CONCLUSION

Glutathione has been shown to diminish the oxidation of fats (lipid peroxidation), decrease circulating cholesterol, minimize the inflammatory response around arteriosclerotic plaque, stabilize platelets and protect the sensitive lining of the arteries. These are all important ways to combat hardening of the arteries and subsequent heart disease. Glutathione also diminishes damage to oxygen-deprived tissue during ischemia, and also during the subsequent complications of reperfusion.

Cardiovascular disease has had a huge impact on our population. It is to a great degree preventable, and strategies for raising GSH should go hand-in-hand with a responsible diet and life-style. Such measures can prevent and may even help reverse this all-too common illness.

DIABETES

Diabetes mellitus or 'sugar diabetes' is the most common glandular condition in North America. It affects 10 to 25 million people, most of whom have yet to be diagnosed. Diabetics run an above-average risk of developing heart disease and stroke, the leading causes of death in the USA and Canada. Given that most types of diabetes and its complications are related to life-style and environment, this is for the most part a preventable problem.

Diabetes mellitus is an insulin disorder that impairs the body's ability to metabolize sugar. The important hormone insulin is responsible for the absorption of sugar into cells for on-demand energy and into the liver and fat cells for energy storage. There are two principal types of diabetes mellitus.

In type 1 diabetes mellitus, insulin-producing cells in the pancreas are destroyed. With regular injections of insulin, the patient may lead a normal life. Without it, he or she may lapse into coma and die.

In type 2 diabetes mellitus, pancreatic production of insulin is diminished or the body gradually loses its ability to utilize it. This is by far the most common form of diabetes and is usually linked to bad eating habits, obesity and poor life-style.

Both type 1 and type 2 diabetes are generally characterized by high blood sugar (hyperglycemia) but in cases of overmedication or illness/stress during medication blood sugar levels can plummet (hypoglycemia). Both events are potentially serious.

Hyperglycemia produces excessive thirst and urination, fatigue, weight loss, and dehydration. Occasionally, life-threatening illnesses (hyper-os-molar coma or ketoacidosis) may result from excessive sugar levels. These are medical emergencies requiring immediate hospitalization.

Some diabetics take insulin injections or pills to lower sugar levels and are susceptible to the complications of low blood sugar levels. This may happen because they take too much medication, miss a meal, increase their energy expenditures, become sick or febrile, or suffer any sort of stress. This condition too must be treated immediately. Usually, a sweet drink or food is enough and produces rapid results.

Apart from the emergencies resulting from such blood sugar imbalances, most diabetics fall ill from complications of diabetes itself, of which there are two types: reduced ability to fight infection and damage to the circulatory system, including both small and large blood vessels. These complications can cause symptomatic problems with the eyes, muscle, kidneys and bladder. They can also reduce energy levels, promote thirst, and cause tingling in the extremities. Cardiovascular plaque buildup is another result of diabetic complications.

DIABETES AND THE IMMUNE SYSTEM

Diabetics should be considered immune-compromised because they are prone to many more infections than they can normally resist. Their immune systems may be overwhelmed by thrush and other fungal infections of the skin and even of the bloodstream. Bacterial infections are more

common and their consequences are serious – gangrene (especially of the toes and foot) and sepsis. Diabetics with any sort of infection must always be treated immediately and aggressively.

Most illness and death in diabetics is caused by circulatory damage. This can include heart disease, myocardial infarction, high blood pressure, atherosclerosis, stroke, renal failure, neuropathy, blindness and other effects of impaired blood circulation. In fact, diabetic complications are the major cause of blindness in the USA. Diabetics are also more prone to cataracts and glaucoma.

GLUTATHIONE'S ROLE IN DIABETES

GSH plays an important role in the fight against diabetes. We have seen that it can prevent circulatory problems such as arteriosclerosis and stroke – the main causes of diabetic death. GSH also enhances the immune system. Many visits to the doctor or hospital could be avoided if diabetics were less prone to infection. Elevated GSH levels may help by providing:

- Immune system support against infection
- Decrease of oxidative stress from hyperglycemia
- Decrease of platelet aggregation
- Prevention of vascular complications including:
- Atherosclerosis (including heart disease, stroke)
- Nephropathy (kidney damage)
- Retinopathy (retinal damage)
- Neuropathy (nerve damage)

In this way, GSH can help weakened immune system combat bacterial infection and fungal infection, support compromised circulation against hardening of the arteries (arteriosclerosis), kidney failure (nephropathy), visual loss (retinopathy) and neurological problems (neuropathy). It also retards oxidative stress and anemia in dialysis patients.

It is clear that the small blood vessels of diabetics are subject to accelerated degeneration, but the causes of this particular illness are still being identified. Recent studies demonstrate that diabetics are more prone than others to oxidative stress and free radical formation. In fact, the blood and tissues of diabetics are marked by critically low GSH levels.

R.K. Sundaram's studies suggest that this antioxidant deficiency precedes the subsequent complications of diabetes. K. Yoshida and his research group have shown that low or weak GSH synthesis leads to increased cellular damage and other complications. Going one step further, Thornalley's trials revealed a correspondence between low GSH levels and higher diabetic complications. S.K. Jain & R. McVie suggest that the low GSH levels characteristic of diabetes play a role in impaired insulin secretion in uncontrolled diabetic patients.

Many researchers have established a link between low GSH levels and a higher likelihood of endothelial damage, with increased platelet aggregation.

Other researchers have looked more specifically at the relationship of GSH to isolated complications such as hypertension, diabetic neuropathy and nephropathy, with favorable results. The role of GSH in protecting red blood cells from oxidative damage in the case of renal dialysis is also very promising.

CASE STUDY

Deana was a motivated, positive entrepreneur who developed a wellness health center even though she suffered from a serious case of diabetes. Increasingly fatigued, this 32 year-old Texan continued to run her center even after receiving and rejecting a kidney transplant, failing eyesight and dialysis treatments. Eventually she developed a chronic foot infection that required weekly debriding of dead tissue. Her doctor feared that amputation might prove necessary. She began taking high doses of the whey protein isolate Immunocal and found her energy levels increased over several weeks. Kidney function tests and hemoglobin levels improved. Medication doses for her anemia and hypertension were decreased or eliminated. Peripheral circulation was better. Five months later the foot was healed. Deana has since married and continues to run her clinic.

CONCLUSION

Circulatory damage contributes substantially to diabetic complications and GSH helps fight the oxidative damage that contributes to this damage. In fact, the blood and tissues of diabetics are marked by critically low GSH levels. These complications could be avoided or minimized if diabetics were less prone to infection, and elevated GSH levels may help accomplish that.

THE LIVER AND HEPATITIS

Hepatitis is an inflammation of the liver. The two major types of hepatitis in North America are alcoholic hepatitis (a type of toxic hepatitis) and infectious (viral) hepatitis, usually caused by virus types A, B, or C.

TOXIC HEPATITIS

Toxic hepatitis is a non-infectious condition caused by exposure to chemicals that damage the liver. The list of harmful agents is quite extensive, but simple alcohol abuse accounts for the vast majority of cases. Alcoholism tends to be a chronic disease, and this prolonged inflammation often leads to cirrhosis (scarring) of the liver.

INFECTIOUS HEPATITIS

Infectious hepatitis is the most common of all serious infectious diseases in North America. It is estimated that perhaps a half million Americans per year contract the disease. Given the growing prevalence of a relatively new hepatitis virus – type C – this number will likely increase. An accurate count is difficult because most cases of acuter hepatitis go undiagnosed or unreported – the illness often feels no more serious than the flue. Other viruses and pathogens can cause hepatitis, but less frequently than hepatitis virus types A, B and C.

The course of the disease is variable. It can range from being totally asymptomatic to causing death in a small percentage of cases. Most people with infectious hepatitis suffer a few weeks of a flue-like illness, consisting of fatigue, aches and pains, mild fever, loss of appetite, abdominal pain, nausea and vomiting. More serious cases exhibit jaundice, dark colored urine, light colored stools, itching, and altered mental states, lapsing occasionally into coma. Most patients experience full recovery, but some progress to chronic hepatitis and possibly cirrhosis.

The extent of liver inflammation determines how poorly the liver works. In hepatic dysfunction it cannot normally filter and eliminate toxins, help digestion, regulate the chemical composition of the blood, process and store nutrients, and other vital functions. The extent of dysfunction can be measured by liver function tests (LFT‟s), a measure of certain liver enzymes in the blood. LFT‟s are a sensitive indicator of liver well-being.

Treatment for acute hepatitis usually follows a conservative regimen – lots of rest, good nutrition and plenty of fluids. Special care must be taken to avoid spreading the disease.

CHRONIC HEPATITIS

Some cases of toxic or infectious hepatitis turn into chronic hepatitis, which poses a greater problem. Chronic cases are prescribed steroids or interferon. In both cases, benefits need to be weighed against side effects. In toxic hepatitis, the patient must be removed from the offending toxin. This may be challenging when the cause is alcohol.

PREVENTION

The best way to deal with all forms of hepatitis is prevention – proper sanitation and hygiene, screening of blood products, vaccination, avoidance of toxins such as alcohol and intravenous drugs, and avoiding contact with the bodily fluids of infected people.

GSH IN THE LIVER

Hepatologists know that GSH plays a critical role in the liver – it is that organ‟s most important abundant antioxidant enzyme. We have already said that GSH concentrations are higher in the liver than in any other organ. This is because it functions as a substance for key detoxification processes in the liver.

Phase I liver detoxification transforms toxins into water-soluble forms. GSH is essential in Phase II, which neutralizes or conjugates these products and helps the body eliminate them through the gut or the kidneys. If these two detoxification phases are impaired for any reason, toxins will accumulate in the body and lead to disease.

Medical science has long known that a GSH deficiency invariably accompanies liver damage. When hepatitis results from acute overdoses of hepatotoxic pharmaceutical drugs such as acetaminophen (Tylenol, Atasol, etc.), the GSH-enhancing drug NAC (Nacetylcysteine) is used to raise GSH levels rapidly. This eliminates the toxic breakdown products of the overdose. The GSH deficiency is critical because it further compounds the illness and can easily lead it on a downward spiral.

Decreased liver production of GSH is seen in alcoholic cirrhosis, sicknesses caused by exposure to hydrocarbons and other toxins, viral hepatitis, fatty livers and even aging individuals. Ongoing research aims to raise GSH levels in an attempt to support liver function in these patients. This approach is even being tried in the treatment of fulminant hepatic failure.

Alcoholic patients with lower GSH levels are more prone to liver damage. This has prompted researchers to try to treat alcoholic liver disease by raising GSH levels. Clinical symptoms and liver function tests have been shown to improve with this method.

GSH IN THE TREATMENT OF VIRAL HEPATITIS

N.S. Weiss and his team at the Max Planck Institute demonstrated the antiviral properties of NAC in human tissue cultures. C. Watanabe found that Immunocal, a natural GSH precursor, to be effective in improving liver function abnormalities and immunological parameters in hepatitis B patients. These improvements continued even after the treatment ended, reflecting the long-term benefits of such an approach.

Treatment options for chronic hepatitis C sufferers are far from ideal. G. Barbaro and his team in Italy eloquently described the systemic depletion of GSH in hepatitis C patients, suggesting that this deficiency could explain their resistance to interferon therapy. O. Beloqui‟s team confirms this in a controlled study of hepatitis C positive individuals. By successfully raising one group,,s GSH levels with NAC therapy, they showed that interferon therapy was enhanced.

CASE STUDY

When he was young, Roger required multiple blood transfusions for the bleeding disorder hemophilia. As a young adult his liver was tested for abnormal function and the results revealed that he had acquired hepatitis C, probably from contaminated blood. Worried about the side-effects of antiviral medications and their limited success rates, he preferred to undergo unconventional treatment. His protocol included milk thistle (silymarin), tumeric (curcuma), alpha lipoic acid, methionine, N-acetylcysteine, and intravenous glutathione as well as a low-meat diet and avoidance of alcohol, acetaminophen and cigarettes. His liver function tests have since normalized.

CONCLUSION

The liver is the largest and most complicated organ in your body. It is intimately linked to a myriad of factors effecting health and illness. GSH is a key constituent of proper liver function. Low GSH levels invite a host of toxicological and immunological diseases. High levels offer protection against these maladies.

AIDS

The spread of AIDS (acquired immune deficiency syndrome) is the most serious health crisis of our time and has reached epidemic proportions worldwide. In many American cities and other areas of the world it is the leading cause of death for 25 to 45 year-old. Because of widespread AIDS research, the scientific community has learned more about viruses and the immune system in the last few years than in the previous ninety.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

AIDS is linked to the human immunodeficiency virus (HIV), which is particularly destructive to the victim's T-cell lymphocytes – a type of white blood cell necessary for effective immune response. There are three types – killer T-cells, helper T-cells and suppressor T-cells. Helper cells – which signal the presence of antigens so the body can effectively counter them – are destroyed by HIV, preempting the build-up of killer cells that ordinarily combat viruses. The result is immune-deficiency. The AIDS virus does not kill directly, but leaves the victim defenseless against even the most innocuous disease organisms.

Long-term prospects for AIDS sufferers are slowly improving, and much can be done in the short-term. With good care the worst symptoms can be avoided for years and the patient can lead a productive life. As more is known about the disease and its spread, more effective treatments will emerge. There is widespread hope for a cure within the next decade.

Many pharmacological and naturopathic medications are promoted as possible AIDS therapies, both for treatment and prevention. These have varying levels of success but at a cost – many pharmacological drugs are toxic, and while they help in their own ways to fight the disease, they exact a heavy toll in other ways, both physical and financial.
There are certainly no miracle cures. Some therapies help, some are hazardous. Nevertheless, a combination of treatments is more effective than any one alone, so most AIDS patients adopt one of several regimens known as drug cocktails.

The worst aspects of the disease are secondary to HIV itself. Because the immune system has been compromised, it cannot respond adequately to most sorts of infection. These infections, not the HIV, cause disease.

THE ROLE OF GSH IN AIDS

Much attention is therefore paid to the role of GSH in AIDS patients. Among other things, the disease causes chronic inflammatory change and oxidative stress. These activities consume GSH and lead to dysfunction in CD_4 helper cells. Once T-cells lose their efficiency, the patient becomes susceptible to opportunistic infections, such as include certain types of pneumonia, diarrhea, candida and unusual cancers – diseases to which healthy individuals are immune. The immuno-deficiency becomes generalized and leads to malnutrition, wasting and death.

Researchers have discovered that, among other biochemical changes, AIDS patients experience unusually low GSH concentrations. Some have reported that GSH levels in the blood fall to about 30% of normal. They suggest that this deficiency contributes to the typical feature of HIV infection – progressive weakening of the immune system. Others assign GSH a proactive role, saying that the inflammatory cytokines that make HIV growth possible are inhibited by elevated GSH concentrations. They demonstrated this effect by raising GSH levels with drugs like NAC (N-acetyl-

cysteine). The same team in 1991 showed how the loss of $CD_4$and CD8 T-cell GSH corresponds to the progression of the disease.

In 1992, a team led by Dr. Gustavo Bounous investigated the properties of milk protein isolates at McGill University, Montreal. They developed a method of extraction that preserved the GSH-enhancing properties of the protein. The product was later patented and named Immunocal.

Dr. Bounous and his colleagues knew that heightened GSH levels seemed to enhance the human immune system. Learning of the correlation between HIV progression and low GSH levels, they studied its effects on AIDS patients. Their milk-protein isolate was given as a dietary supplement. The results were that it often diminished and sometimes reversed the wasting effects of AIDS. These patients also exhibited elevated CD_4 T-cell counts and decreased viral load.

The natural availability of GSH precursors was welcome news to the AIDS research community. Immunocal was presented at the Canadian Conference on HIV/AIDS Research in 1994 by Baruchel, Olivier and Mark Wainberg, the incumbent chairman of the International AIDS Research Association. Dr. Luc Montagnier, co-discoverer of the AIDS virus, drew attention to the promising effects of Immunocal in his opening address at the Tenth International AIDS conference in Japan in 1994.

Baruchel, Bounous and Gold's research with Immunocal was significant enough to receive funding from the Canadian HIV Trials Network, and a large multi-center study is in progress.

The Center for Disease Control (CDC), Atlanta reported in their AIDS web page, February 1997:

"...laboratory studies have shown that a new whey protein concentrate, called Immunocal, can inhibit HIV replication while also stimulating the production of GSH, an amino acid that helps control the virus."

In a landmark 1997 paper Herzenberg and Herzenberg clearly stated that GS"H deficiency is associated with decreased survival in HIV disease. They improved survival rates by administering NAC (a GSH-promoting drug). Given the growing body of evidence demonstrating the benefits of raising GSH levels in AIDS patients, this represents a welcome addition to complementary therapy.

CASE STUDY

The first member of this family of three to be diagnosed with AIDS was the father Bob, who developed a pneumonia at age forty-four. His wife Joan who developed swollen glands (lymphadenopathy), tested positive shortly afterwards. Subsequently they discovered that their two-year old son Justin was also HIV-positive, although he was asymptomatic. Both Bob and Joan became progressively unwell and Bob quit his job due to fatigue. Both were started on the antiviral drug AZT, but both discontinued this therapy because of intolerable side-effects. Because of her vomiting and profound headaches on the drug, Joan decided not to allow her son to receive this therapy. Bob, Joan and Justin were started on Immunocal. Both husband and wife noticed significant increase in their energy levels within weeks. Monitoring the families' blood tests over the next nine months, 8iproveme4nts in viral load, lymphocyte (white blood cell) count and specific CD4 lymphocyte values were apparent. Bob's back at work. Justin is still symptom-free. Joan wanted another child, but has been convinced not to pursue this idea.

CONCLUSION

AIDS attacks the immune system and is characterized by decreased GSH levels and a general lack of resistance to pathogens. In fact, glutathione deficiency is associated with decreased survival in HIV disease. Scientific studies have shown that supplementation aimed at maintaining GSH levels can diminish and sometimes reverse the wasting effect of AIDS. The patients studied in these experiments often also exhibit elevated $CD\text{-}_4$ lymphocyte cell counts and decreased viral loads. As a result of these and many other AIDS trials, larger studies should establish glutathione supplementation as a mainstay of complimentary therapy.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) has in recent times been referred to as "the great crippler of young adults". It usually strikes victims in the prime of their life and is one of the most dreaded degenerative diseases of the nervous system. The symptoms of MS are quite variable, ranging from one or two attacks of weakness in a limb or blurred vision, to a relentless, progressive deterioration of speech, movement and other basic functions.

MS affects various parts of the nervous system by destroying myelin, a fatty sheath that insulates nerve fibers rather as a plastic sheath insulates electrical wire. This destruction leaves scars or plaques that short-circuit the electrical signals passing through the nerve fibers. The scarring process is called sclerosis.

Depending on the location of the nerves affected, patients may suffer localized weakness or stiffness, visual difficulties, diminished bladder or bowel control and other neurological dysfunctions. Attacks may be mild, lasting only days and followed by remission, but most sufferers relapse after months or years. A few experience rapid progression of the disease and are quickly disabled.

The causes of MS are still unclear. However, many theories have been put forward. Some point to environmental and/or genetic factors, and some researchers believe that certain viruses may be involved, or view MS as an autoimmune ailment (in which the immune system mistakenly attacks healthy tissue). Others are investigating dietary factors or exposure to toxins such as lead, mercury, pesticides and carbon monoxide. Yet another theory considers the role of allergies.

Conventional medicine treats the symptoms of MS but cannot cure it. However, some newer drugs show promise in diminishing the rate of relapse. Diets of all sorts have been widely tested without consistent results. Everything about this disease is difficult to study because symptoms vary so widely, patients often recover spontaneously and one can never be sure whether or not a treatment has been instrumental.

Multiple sclerosis is one of a group of nervous system diseases called neurodegenerative disorders. This group also includes Alzheimer's, Parkinson's and ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease). Although the specific causes of these diseases are unknown, a number of recent studies suggest that an important role is played by oxygen-derived free radical formation and/or lack of adequate antioxidant defenses.

OXIDATION AND MULTIPLE SCLEROSIS

The myelin sheaths destroyed by MS are made of lipids, fatty substances highly sensitive to damage by lipid peroxidation, a particularly aggressive type of oxidation. Our key metabolic defenses are GSH and SOD (super-oxide dismutase). It has been shown that elevating these natural defense systems reduces the damage of oxidative stress.

Investigations looking specifically at the breakdown products of oxidation have revealed significantly higher levels in MS patients. Pradlip Toshniwal and Edwin Zarling from Loyola University in Chicago went one step further in their studies. They were able to show that these levels of oxidative stress corresponded to the severity of the MS attack.

Some authors including S.M. LeVine from the University of Kansas suggest that the pathological process leading to the demyelination of nerves is possible because the immune system cooperates with a free radical generating system present within the myelin sheaths. This explanation combines the two hypotheses that describe MS – that it is an autoimmune disease, and is also caused by oxidative stress. He describes how during a demyelination episode, macrophages (cells of the immune system that are supposed to act protectively) seek out myelin and release powerful chemicals (lipases, proteinases, H_20_2 and others). These biochemicals result in tremendous levels of oxidative stress.

Such a hypothesis leads us to believe that either blunting the immune response or minimizing oxidative stress could help MS patients. Immunosuppressive drugs that blunt the immune response have had only limited success. This has driven researchers to find ways to improve antioxidant protection, glutathione modulation being one of the most promising areas.

GLUTATHIONE AND MULTIPLE SCLEROSIS

Many studies have compared groups of MS patients to healthy individuals. Among other things, they have measured levels of reactive metabolites (breakdown products of oxidation) and of protective enzymes, especially GSH.

An Italian group headed by Vince Calabrese drew samples of cerebrospinal fluid (CSF) through spinal taps. CSF analysis is a good indicator of brain metabolism. They found that GSH-peroxidase levels in the cerebrospinal fluid of MS patients were consistently low. Their conclusion was that in MS, the fundamental activity of anti-oxidation is abnormal and that oxidative stress plays a causative role.

Another study looking at CSF was performed by the Swedes G. Ronquist and G. Frithz who tested spinal taps from a large number of patients including those with stroke, seizures, brain tumors and MS. The cerebrospinal fluid of MS patients were found to be almost entirely lacking in GSH.

There is further evidence of the involvement of free radical elevation and GSH depletion in MS. Helen Langemann in Switzerland measured GSH levels within MS plaques themselves. Without exception, they were depleted.

Researchers led by I. Singh at the University of South Carolina examined the fundamental tissue abnormality in multiple sclerosis. The actual myelin breakdown occurs to a large part because of the release of strong inflammatory chemicals called cytokines. These cytokines generate huge numbers of free radicals. Pre-treating neurological tissues with NAC (N-acetylcysteine) to raise glutathione levels protected these tissues from demyelination. Conversely, when GSH was chemically depleted the demyelination grew worse.

Simpler studies demonstrating decreased blood levels by GSH peroxidase in MS patients have been repeated by many Scandinavian, Italian and North American researchers. These levels as well can be inversely correlated with the degree of severity of the attack.

SELENIUM AND MULTPLE SCLEROSIS

Some research suggests that low selenium levels are connected to the development of MS. Selenium is an essential part of the GSH peroxidase enzyme and low selenium levels certainly decrease GSH effectiveness. A Danish team led by J. Mai supplied highdose antioxidant supplements to MS

patients made up of 6 mg selenium, 2 g vitamin C, and 480 mg of vitamin E. These patients showed few side effects and glutathione peroxidase activity increased by a factor of five within five weeks.

CONCLUSION

MS is a difficult disease to study because its spontaneous remissions and relapses make it very unpredictable. It is therefore hard to correlate any sort of intervention with changes in a patient's condition. In order to be statistically significant, prospective trials would have to include hundreds of subjects.

However, certain findings have been demonstrated consistently in multiple sclerosis patients. The breakdown products of oxidative stress are present in large numbers, and the level of free radical formation corresponds to the severity of the MS attack. Furthermore, glutathione activity is clearly impaired in this disease.

Also, individual tissues suffer less free radical damage when antioxidants and glutathione therapy are used. Although not a cure, many authors have suggested that reduced oxidative damage would help MS patients, and suggest in particular the helpful role of elevated GSH levels.

LUNG DISEASE

One of the most distressing symptoms that anyone can experience is shortness of breath – dyspnea. Patients describe themselves as „not getting enough air". This triggers a series of physiological and behavioral reactions that include increased heart rate, blood pressure and hormonal secretions accompanied by a feeling of general panic. Shortness of breath is a common symptom of many respiratory illnesses.

Just as the gut separates and absorbs food from the outside world into the body, the lungs are a passage for the exchange of used air and fresh air. But there"s a crucial difference between food and oxygen – we can"t store oxygen. We must meet a second-by-second demand for the life-giving element or die within minutes. The body responds immediately to any interference with this exchange.

Over 30 million Americans are affected by chronic lung disease. Dozens of illnesses can affect the respiratory system. The study of pulmonary (lung-related) medicine is vast and complicated. It deals with congenital problems like cystic fibrosis, acquired diseases like bronchitis and self-inflicted problems like smoking. The importance of GSH in the respiratory system cannot be overstated. We can"t address every known respiratory problem but we will discuss a large number of common and not-so-common ailments, including:

Asthma
Bronchitis, acute and chronic
Chronic obstructive pulmonary disease (COPD)
Emphysema
Adult respiratory distress syndrome (ARDS)
Cystic fibrosis
Pulmonary fibrosis
Cancer
Pneumonia
Toxic exposures
Tobacco abuse

ANTIOXIDANTS AND THE LUNGS

As you will see in the following pages, inflammation of the lung is common to most pulmonary diseases, whether the disorder is acute – like toxic exposure – or chronic – like cystic fibrosis. The process of infection in asthma, bronchitis or pneumonia all lead to inflammation. Many traditional medications attempt to reduce this inflammation. The body"s inflammation response itself generates free radicals, and antioxidants are increasingly used to complement conventional treatments. The researchers P.E. Morris and G.R. Bernard drew attention to this complementary treatment in an article aptly called "Significance of glutathione in lung disease and implications for therapy", in which they reviewed the great weight of evidence that supports such research.

There is a fragile balance in the lungs between oxidants and antioxidants. Oxidative stress is high in the lungs for many reasons. For a start, this center of oxygen interchange produces very large numbers of oxyradicals. Secondly, white blood cells are highly active in the lining of the lungs, where they release huge quantities of oxidative products, both because of their high metabolic rates and the way they combat biological and chemical invaders. Finally, antioxidants in the fluid lining of the lungs play a large part in our front-line defense against airborne pollutants, many of which are powerful sources of free radicals.

When white blood cells encounter, for example, a bacteria, they release caustic substances like peroxides. This is biochemical warfare, and the white blood cell and the surrounding tissues use

GSH to defend themselves. When oxidant levels grow too high or GSH levels too low, the inevitable result is tissue damage. Remember that GSH is the most critical of all naturally-occurring antioxidants and that it effectively supports exogenous antioxidants such as vitamins C and E. Unlike glutathione, exogenous antioxidants are derived from the outside environment and are not native to the body, but together they soak up free radicals.

Generally, most tissues and organs must manufacture their own glutathione from dietary or drug-delivered precursors. However, the lining of the respiratory tree – which usually requires high levels of GSH – can absorb GSH directly. To take advantage of this unusual ability, a topical GSH aerosol has been developed and used successfully to treat a number of diseases, including adult respiratory distress syndrome (ARDS), pulmonary fibrosis and HIV infection. In addition, the topical form of NAC (Mucomist) – a potent GSH precursor – has long been used as a treatment for cystic fibrosis.

Oral and intravenous GSH precursors are receiving a lot of attention from researchers, and many papers have been published on the subject. Pulmonologists (lung doctors) are paying increasing attention to lung GSH content and learning a great deal about future applications. O. Ortolani and his team in Italy placed forty intensive care patients with respiratory difficulties on intravenous GSH. They compared their response to an equal number of patients not given the treatment and found significant reductions in oxidative stress levels.

An experiment in preventive medicine was conducted by S. De Flora and his research team at the Institute of Hygiene and Preventive Medicine, University of Genoa. Patients were placed on a course of oral NAC tablets or placebo during the months of the influenza season. Although the number of people infected by the virus was unchanged, subjects receiving NAC experienced significantly fewer and less virulent symptoms.

ASTHMA

Bronchial asthma causes constriction of the bronchioles (airway passages). Figure 34 shows the windpipe and lungs, and cross-sections of normal and narrowed air passages (bronchioles). Asthma is always unpleasant and sometimes even fatal. The intensity of asthma attacks vary, but all are characterized by a feeling of tightness in the chest, shortness of breath, restlessness, coughing and wheezing. Although asthma is reversible and intermittent, it tends to recur and is generally considered a chronic condition. It is one of the most common causes of absenteeism and hospital admission in school-age children, among whom it is most prevalent. It currently affects about 15 million Americans and is on the rise.

Asthma is variable in frequency and severity and can be triggered by a very wide variety of stimuli, including allergens (things that provoke an allergic response). These include dust, pollen, dander (tiny particles of animal skin, fur and feather), certain foods and drugs, viral infections, emotional stress, anxiety and even plain old exercise. Muscles within the walls of the bronchioles flex and go into spasm, the walls thicken, air passages become clogged by mucus, and air is trapped in the deepest airways (the alveoli). The wheezing sound is caused by air passing with difficulty through these narrowed passages. In its severest form, breathing become impossible and the patient suffocates.

Asthma sufferers should make an effort to identify and avoid the triggers that cause their attacks, whether allergic, infectious, toxic, or emotional. They can also take preventative medications – antihistamines and sodium cromoglycate. These minimize the effects of all allergic response. Once

an attack is in progress other drugs are needed to reopen (dilate) the walls of the bronchioles. These are called bronchodilators and are commonly used in inhalers such as salbutemol or albuterol. Inhaled or ingested steroids are also available. They minimize the swelling and inflammation of the bronchial walls. In any case, once an attack has begun, treatment must be immediate and aggressive. The longer an attack lasts, the more the symptoms advance and the longer they take to reverse. There is little time to waste.

It has been long thought that low levels of glutathione and glutathione peroxidase levels play a role in the onset and progression of asthma. Numerous studies in asthmatics have identified such abnormalities in their red-blood GSH, white-blood cell GSH, serum GSH, platelet GSH and lung-fluid GSH. There is a direct correspondence between low glutathione levels and the severity of the asthma attack.

Dietary, environmental, and genetic factors that diminish the potency of the antioxidant systems in the lung increase the risk of asthma. This relationship between antioxidant levels and asthma is seen in situations of elevated free-radical activity. Examples are lead poisoning, excessive iron stores and G6PD-deficiency, as well as low levels of vitamin C, vitamin E, and selenium (a component of glutathione peroxidase).

A recent presentation to the American Lung Association by pulmonologist Dr. Carol Trenga described an antioxidant cocktail that helped asthmatics who were particularly sensitive to air pollutants. European physicians have long used GSH precursors in the treatment of asthma, particularly as a mucolytic (phlegm thinner) to break down thick secretions. In a double-blind study, inhaled bronchodilators were used with and without NAC. The NAC (GSH-enhanced) group experienced greater improvement in pulmonary function than the control group.

CASE STUDY

Jean-Pierre, a financial analyst, suffered from allergies and asthma his whole life. Summers were particularly bad and he often had to leave his native Montreal for weeks in August to escape the ragweed allergy season. In early summer, he was started on a program of NAC (N-acetylcysteine), L-cysteine, selenium, alpha-lipoic acid, multivitamins and stinging nettle (Urtica dioici). That season, he reported having to use his Ventolin inhaler (salbutemol, a bronchodilators for asthma) only two or three times a week, rather than two or three times a day, and his use of antihistamine drugs was at a minimum. He‟s even ventured to go camping with his girlfriend.

BRONCHITIS, EMPHYSEMA, AND COPD

Bronchitis is an inflammation or obstruction of the bronchi, the larger airways that eventually branch out to become the bronchioles (the site of asthma). It resembles asthma in some ways, their common symptoms being shortness of breath, a phlegmproducing cough, chest discomfort and occasional wheezing. Bronchitis has two distinct forms – acute or chronic. They differ in important ways.

Acute bronchitis is almost always caused by infection, either viral or bacterial. Coughing, chest pains, fever and chills are common complaints. In the healthy individual, it is usually a short-lived illness that clears up once the infection is overcome. If the infection is bacterial or mycoplasmal, antibiotics may be required. Occasionally, some inflammation remains, leading to a post-inflammatory cough that may persist for weeks. Inhaled steroids are often prescribed for this condition.

Like emphysema (described below), chronic bronchitis is an ongoing illness requiring frequent medical attention. Although it may be exacerbated by infectious disease, chronic bronchitis is usually caused by long-term exposure to lung irritants – toxins, allergens or repeated bouts of acute bronchitis. The most common cause of chronic bronchitis is cigarette smoke.

Lungs exposed to tobacco smoke are subject to several pathological processes. One of the most critical is the dysfunction or loss of cilia lining the airways. Cilia are microscopic hair-like structures that trap and remove dust, mucus and other debris. A single puff of a cigarette can paralyze these hairs, increasing the chances of subsequent lung injury and infection.

As chronic bronchitis progresses, the lung‟s ability to exchange oxygen and carbon dioxide diminishes. In an attempt to compensate for the loss of pulmonary function, energy demands increase, the chest muscles work harder and the heart pumps faster. This in turn can lead to secondary diseases such as pulmonary hypertension, heart failure and emphysema.

Emphysema progresses slowly over time and is usually the result of prior lung disease. Chronic cough and shortness of breath are typical symptoms. Although it may occasionally be caused by hereditary factors, environmental exposures, chronic asthma or chronic bronchitis, emphysema most often results from years of heavy smoking. It is the most common cause of death from respiratory disease in North America.

Emphysema shares many symptoms with chronic bronchitis. In fact, the two diseases usually overlap to some degree. They are often classed together under the heading COPD (chronic obstructive pulmonary disease). However, they differ anatomically.
Emphysema results in irreversible damage to alveoli – tiny sac-like structures where the actual exchange of oxygen and carbon dioxide occurs. Alveoli are counted in the millions, like bubbles in a bubble bath. Emphysema causes them to burst one by one. They then coalesce into fewer, larger sacs. As a result, their total surface area dwindles, decreasing the amount of air that can be exchanged by each breath.

It is well known that most lung diseases are characterized by weak antioxidant activity and impaired glutathione-related enzyme systems. Taking advantage of this information, a group of French researchers tested to see whether GSH screening could predict a predisposition to pulmonary diseases. They tested subjects for the absence of a gene (GSTM1) responsible for a specific GSH enzyme. About 47% of the French population lacks this gene. They found that heavy smokers with moderate chronic bronchitis were missing this gene 66% of the time and that smokers with severe chronic bronchitis were deficient in 71% of cases. They concluded that factors diminishing GSH function – in this case a hereditary factor – put individuals at higher risk for respiratory problems.

Other studies determined that COPD patients were very sensitive to low GSH levels after even light exercise, demonstrating the precarious balance of glutathione in these patients and the great importance of maintaining adequate stores of GSH.

N.C. Hansen and his team at Odense University in Denmark conducted a double-blind study of the general well-being of patients with mild chronic bronchitis. They administered oral NAC during the winter months to these patients, and placebo to a similar group. Of the two groups, the GSH-enhanced group did much better on a GHQ (general health questionnaire). Several other research teams have studied the use of oral NAC as a preventative measure. Although it didn‟t significantly

reduce the number of chronic bronchitis attacks, their severity – measured by symptoms and days off work – was greatly reduced.

In a large open study of over two thousand patients, K.P. Volkl, B. Schneider from Hanover Medical School in Germany showed that the use of NAC led to clear improvements in symptoms and pulmonary function. The four-week study included patients with acute and chronic bronchitis, bronchial asthma and emphysema. All groups had similar improvement in their disease.

SMOKING AND GSH

There is no longer any doubt that cigarette smoking is a major risk factor for chronic bronchitis, emphysema, COPD, cancer and cardiovascular disease. One of the ways in which cigarette smoke damages the body is by profoundly raising the extent of oxidative stress in the lungs.

A single puff of cigarette smoke contains billions of free radicals and can literally "burn up" antioxidants. But this isn"t the worst of it. A still greater source of oxidative stress results from the lung inflammation resulting from smoking. The total oxidative damage caused by smoke corresponds directly to the degree of lung injury, respiratory compromise, morbidity and mortality found in individual patients.

Pharmacologists are investing the use of inhaled GSH to prevent the occurrence or progression of emphysema in smokers. As a GSH precursor, NAC is receiving equal attention. Double blind studies in smokers using NAC demonstrate the enhanced ability of their lungs to clear away thick secretions in their airways.

R.B. Balansky at the Institute of Hygiene and Preventive Medicine in Italy exposed rats to high levels of cigarette smoke. This led to decreased body weight, intense pathological damage of the terminal airways, inflammation of the bronchial and bronchiolar linings, alveolar damage, emphysema, white blood cell abnormalities and pre-cancerous lesions. Rats given daily NAC at the same time suffered significantly less damage, demonstrating the protective role of GSH against lung damage and the onset of cancer.

Smokers are also more prone to the development of infectious bronchitis and pneumonia. Chronic bronchitis in smokers results in increased bacterial colonization. Treatment with NAC has decreased both the frequency of infectious episodes and the virulence of the bacteria.

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is acute, life-threatening respiratory failure following pulmonary injury. It leads to profound dyspnea (shortness of breath), pulmonary edema (fluid accumulation in the lungs) and hypoxemia (oxygen starvation). This all-too-common medical emergency is caused by a number of different acute processes that directly or indirectly damage the lung. They include bacterial or viral pneumonias, inhalation of stomach contents or other toxins, direct trauma to the chest, sepsis (overwhelming generalized infection), profound circulatory shock, drowning and many other medical conditions. Even with appropriate therapy the survival rate is only about 50%. Long-term complications include the eventual development of pulmonary fibrosis.

ARDS is a very complicated inflammatory process of which edema is only one facet. In the past, physicians treated this disorder aggressively with corticosteroids, because of their well-known anti-

inflammatory properties. Unfortunately, randomized trials have shown that steroids are relatively ineffective against this disease. A hunt is on for useful treatments.

For several reasons, ARDS patients experience high levels of oxidative stress and subsequent depletion of antioxidants and glutathione. One cause may be the release of free radicals at the injury site by endotoxins. Endotoxins are produced by certain bacteria, though only released when the bacteria die. However, most of this oxidative stress probably comes from inflammation. Some white blood cells (neutrophils) are very active at sites of inflammation, producing very large amounts of reactive oxygen species, such as free oxygen radicals, hydrogen peroxide, „hot" oxygen, and others.

Recognizing the severe oxidant-antioxidant imbalance and GSH depletion that comes with this condition, many researchers have pt NAC under the spotlight. G.R. Bernard and his team at Vanderbilt University tested the usefulness of intravenous NAC for the lungs. Both in the lab and in clinical trials they found increased oxygen delivery, improved lung compliance (elasticity) and an improvement in the condition of pulmonary edema patients. Trials with another GSH precursor – OTZ (Procysteine) – led to similar results and reduced the duration of lung injury.

In a larger double-blind study, P.M. Suter"s group at the University of Geneva used intravenous NAC on intensive care patients. Compared to a control group, the NAC patients showed significant improvement in oxygenation and required less time on mechanical ventilators (life support).

PULMONARY FIBROSIS

Pulmonary fibrosis is also called fibrosing alveolitis or interstitial fibrosis, among other things. It is a non-specific condition in which the lungs respond to damage by the production of scar tissue (fibrosis). This leads to stiffness of the lungs and difficulties clearing secretions. It also interferes with gas exchange. Its causes include numerous bacterial, viral or fungal infections and inhaled toxins, dusts (organic and inorganic) and chemicals. Occasionally stomach contents can be inhaled to the detriment of the lungs. Other diseases are involved less often, such as certain autoimmune disorders (mistaken immune response to healthy processes), sarcoidosis (a multi-system inflammatory disorder), or collagen-vascular diseases (rheumatoid arthritis, lupus, polyarteritis nodosa, scleroderma and dermatomytosis). This disease is often an unwanted result of radiation therapy or chemotherapy. The standard treatments have limited success.

Oxidative stress plays an important role in the causes and conditions of many types of pulmonary fibrosis. J. Behr and his group of pulmonologists from the University of Munich studied this phenomenon both in laboratory cultures and in pulmonary fibrosis patients. Because pulmonary fibrosis is an inflammatory disorder, their treatment includes therapy to suppress the immune inflammatory response. With the help of NAC, patients" pulmonary function tests improved and the number of oxidative breakdown products fell. By using aerosolized NAC, Z. Borok from the NIH (National Institute of Health) revered the oxidant-antioxidant imbalance in pulmonary fibrosis patients. Both NAC and aerosol GSH have shown success in this situation. Clearly, both oral and inhaled NAC can successfully raise pulmonary GSH levels.

In patients with pulmonary fibrosis, fibroblasts – cells in part responsible for the fibrous scar tissue – grow excessively in both number and activity. When tissue cultures were made of these cells, it was found that the presence of GSH down-regulated their growth. This implies that GSH may slow the progress of pulmonary fibrosis.

CASE STUDY

With a background in law from her native France, Nona became actively involved with business and philanthropological pursuits in Canada. She was a 41 year-old mother of three suffering from Hodgkin‟s disease and requiring both chemotherapy and radiotherapy. Although these treatments cured her of Hodgkin‟s disease, the treatments left her lungs scarred – the condition of pulmonary fibrosis. Her interests had to be dropped as her breathing deteriorated. She ended up staying at home, using home oxygen and many medications. Despite all interventions, her pulmonary function tests (PFT‟s) continued to fall. After six weeks of Immunocal 20 grams/day she went back to her pulmonary doctor, claiming she could breath again. Thinking there might be a placebo effect; the physician repeated her pulmonary function tests, which showed her back at about 90% of normal values. To eliminate other possibilities, the Immunocal was withdrawn. She subsequently deteriorated again. Three weeks after reinstating the Immunocal, her PFT‟s went back up to 95% of normal values. She promised herself never to stop again.

CYSTIC FIBROSIS

Cystic fibrosis affects many organ systems, but particularly the lungs. It is also called mucoviscidosis because it secretes a sticky mucus which neither lubricates nor flows freely in the nose, throat, airways and intestines. Cystic fibrosis is one of the most common inherited diseases in North America and affects some 30,000 people. Survivors live to an age of about 28 years, depending on the extent of pulmonary involvement.

Cystic fibrosis is most often classified as a disorder of the exocrine glands, and primarily affects the pancreas in fibrocystic pancreatic disease, the sweat glands, and pulmonary mucus production in mucoviscidosis. The problem stems from an inherited defect in the gene responsible for secreting certain fluids from these glands.

The disease often becomes apparent early in life. As babies, cystic fibrosis patients have extremely frequent digestive difficulties. Their pancreas do not provide enough digestive juice. This leads to malabsorption (poor ability to use nutrients) and malnutrition. Their skin loses large amounts of salt and they may sweat profusely. The lungs secrete a very thick (viscous) mucus that can obstruct airways, causing coughing, wheezing, and recurrent lung infections. Comprehensive and intensive therapy with health workers specialized in nursing, nutrition, physical therapy ad respiratory therapy is essential for this problem.

Dr. Larry Lands, director of the cystic fibrosis clinic at McGill University in Montreal, aptly points out that inflammation is central to cystic fibrosis, that inflammation always precedes lung infection, and that lung infection almost inevitably follows severe inflammation. Continued inflammation depletes antioxidants and GSH even more and a vicious circle ensues.

The decrease of GSH in cystic fibrosis is noticeable in the fluid lining of the lungs (epithelial lining fluid), and also in blood serum, red blood cells and elsewhere. This points to whole-body depletion as a result of ongoing oxidative stress.

Cystic fibrosis patients are at even further risk of antioxidant depletion because of pancreatic involvement leading to digestive difficulties and poor absorption of essential nutrients. Many researchers are investigating the use of supplemental antioxidants in this disease, including Lands‟ team investigating Immunocal, the whey-based GSH precursor.

NAC as long been utilized in an aerosol form to break down mucus accumulation in cystic fibrosis patients. It can be used in the same way for asthma, bronchitis, COPD, emphysema, pneumonia and other situations where thick secretions impair pulmonary function.

CASE STUDY

Eight year-old Zach, a cystic fibrosis patient, loved baseball. He was smaller than the rest of the kids, but it was shortness of breath and recurrent respiratory problems, not height, that kept him off the team. He took more care of his nutritional needs and was good about taking his additional vitamin and antioxidant supplementation. His parents learned how to provide him with home aerosol treatments by mask. He has been using both oral and nebulized (by mask) Mucomyst (N-acetylcysteine). Although primarily used as a "bench-warmer," Zach is back on the team.

CONCLUSION

An impressive amount of research has made clear the critical importance of antioxidants and GSH in all these pulmonary diseases. Unlike most other tissues, the lungs can use GSH as-is – through direct contact – rather than having to first absorb its precursors and then manufacture it, s is the case elsewhere in the body. There are many ways to elevate pulmonary GSH, including oral, intravenous and inhaled therapies. In the next few years we will see increased use of these products to raise glutathione levels in acute, chronic and critical care patients.

DIGESTIVE DISEASES

The digestive tract is a string of connected organs stretching from the mouth to the bowels. We use it to eat food, digest nutrients and eliminate waste. There are many digestive disorders, caused by such factors as genetics, stress, toxins, infectious diseases and pharmaceutical drugs. This chapter discusses the latest research on glutathione in the digestive tract. GSH plays a role in protecting the mouth and salivary organs from periodontal disease, stomatitis and gingivitis. It must also protect the esophagus from inflammation. In the stomach, it protects against gastritis, peptic ulcer and cancer and in the liver, hepatitis and organ failure. GSH also protects the pancreas from inflammation and the large intestine (bowel) from colitis, inflammatory bowel disease, ulcerative colitis, Crohn‟s disease and cancer.

GASTRITIS

Gastritis is an inflammation of the stomach lining (gastric mucosa). Acute gastritis produces a short-lived inflammation with symptoms of pain, heartburn, occasional nausea, vomiting and loss of appetite. Chronic gastritis is more prolonged. It has fewer symptoms but more readily progresses to serious illnesses such as anemia, stomach ulcer and stomach cancer. As the population ages gastritis is becoming so common that some scientists consider it a part of the aging process.

One of the many possible causes of gastritis is generalized stress. It may be a psychological reaction to daily life or be physically induced by trauma – the result of major illness, head injury or burns. A long list of toxins has also been implicated with this ailment, the most common ones being coffee, alcohol, tobacco, over-spiced foods and certain infectious diseases. Some common pharmaceutical drugs may also induce gastritis, notably aspirin, corticosteroids, and anti-inflammatory medications. Mixing these drugs may be especially damaging. Consult your physician before you use them in combination.

STOMACH ULCERS

Stomach ulcers – also called peptic ulcers – are spots where the lining of stomach has been eroded leaving an open wound. This can vary in depth and may lead to an actual hole right through the stomach wall (a perforated ulcer). Most ulcers occur in the stomach or duodenum and are rarely found elsewhere along the digestive tract. About one in ten North Americans will suffer at some point in their life from an ulcer, leading to symptoms like those seen in gastritis – abdominal pain, heartburn, and even melena (black or maroon-colored stools caused by oxidized blood leaking into the digestive tract) and anemia (a low hemoglobin or red blood count) if the ulcer is bleeding.

Ulcers develop when the stomach lining loses its ability to protect itself from the acids produced in the digestive juices. It was previously thought that this was caused by high acid levels, but it is now recognized that many ulcer patients have normal acid levels. We know that for various reasons, the lining‟s defense mechanism against these acids is insufficient, enabling ulcers to develop. Some of the risk factors for developing ulcers are:

Stress & anxiety	Alcohol
Trauma, burns	Vitamin C
Aspirin	Extreme foods
Anti-inflammatories	Tobacco
Corticosteroids	Blood type O
Caffeine	Heliobacter pylori

Several factors contribute to the protective nature of this lining. Mucus production, biochemical cellular barriers and adequate replacement of damaged mucosal cells all play a role in the maintenance of a healthy stomach. Immunological factors are only just now being understood. For example, they seem to explain why blood type „A" individuals are likely to develop stomach cancer whereas those with blood type „O" are more prone to duodenal ulcers.

Many factors can disrupt the protective lining. Over-secretion or over-production of stomach acids has already been mentioned. The same drugs that cause gastritis may also lead to ulcers, either by increasing acid production or by modifying the protective factors. These drugs include corticosteroids, aspirin, and dozens of anti-inflammatories known by various brand names.

As with gastritis, other risk factors include cigarette smoking, alcohol abuse, high caffeine intake, overindulgence in fatty foods and consumption of highly spiced foods like whole chili peppers. Even high-dose vitamin C (ascorbic acid) intake has been implicated with ulcers. Stress and anxiety have traditionally been identified as causes, but now seem less significant than previously thought.

Medical science has recently discovered an infectious agent involved with ulcer formation – the bacteria Heliobacter pylori. This is found in 70-90% of ulcer cases. A short course of antibiotics often but now always cures the infection. A significant portion of the population have H. pylori in their digestive tract yet never develop problems. Apparently, other immunological or physiological factors must come into play for this organism to become pathological.

CASE STUDY

Kurt was a 53 year-old vice-president of sales for a large manufacturing company. Among the seventy-hour weeks, two-martini lunches, coffees well into the night, a packand-a-half-a-day cigarette habit, and the stress of a poor sales quarter, he developed severe stomach pains. He was lucky. Medical investigation determined that he only had a gastritis (stomach inflammation) but that if his present lifestyle continued he would likely develop an ulcer. Unwilling to quit smoking or working so much, he agreed to a reduction in alcohol and coffee and also to visit a nutritionist. After three weeks on silymarin, melatonin, glutamine, chamomile, selenium, multiple vitamins including Bcomplex, C and E, he felt "infinitely better", even though sales were still down. He laughs about this now and is thinking of quitting smoking and starting regular exercise.
He now believes that if he feels better in his body, his performance at work will improve.

STOMACH CANCER

Stomach cancer – gastric carcinoma – often begins at the site of a stomach ulcer. It is generally believed that ulcers do not necessarily cause stomach cancer, but that this cancer is often preceded by a particular type of ulcer. In America, it is the seventh most common cause of cancer death. However, incidence of stomach cancer varies enormously around the world; in Japan, Chile, and Iceland, it is one of the most common causes of mortality. Scientists have suggested that this may be due to differences in diet or environment. The theory is supported by the fact that certain occupational hazards such as exposure to coal dust or heavy metals like mercury and lead increase one"s chances of contracting this disease.

Other risk factors include the consumption of certain types of prepared food and moulds. Foods preserved by smoking, pickling and curing contain added nitrates and other carcinogens. Barbecuing

also increase carcinogen levels. Moldy foods may include a type of carcinogen called aflatoxin. This byproduct of fungi can be found growing in nuts, seeds, corn and other dried foods.

The H. pylori bacteria has also been implicated in stomach cancer. Chronic gastritis (stomach inflammation) and polyps (abnormal protruding growth of tissue) may also become cancerous. Medical conditions such as stomach ulcer, chronic gastritis, stomach polyps, toxins like alcohol, tobacco, aflatoxins and foods that are barbecued, smoked, pickled and highly salted may all contribute to the development of cancer.

GSH AND THE STOMACH

Glutathione‟s ability to protect the stomach is being widely researched. Its therapeutic role is promising and it has been shown to protect the stomach in several different ways. It is a primary shield against oxidative stress, detoxifies potentially harmful or even carcinogenic substances and mediates the immune mechanisms, ensuring a more effective immune response.

ACUTE GASTRITIS

It has recently been shown that when the lining of the stomach faces a toxic challenge GSH levels rise. Several groups of researchers demonstrated this using alcohol to provoke an anti-toxic response by the body. Low to moderate levels of alcohol led to an adaptive elevation in GSH levels, but high levels of alcohol overwhelmed this system, causing subsequent damage. An even more direct clinical application of glutathione‟s protective role in the stomach was brought to light by G.A. Balint in Hungary. His team studied an all-too-common problem – the gastric side-effects of anti-inflammatory drugs such as indomethacin and piroxicam (Indocid, Feldene, etc.). Subjects given small amounts of glutathione or cysteine at the time of drug ingestion had significantly fewer side-effects. This is a great example of a natural therapy and traditional medicine being used to complement each other.

The increase in free-radical damage and GSH turnover is well known in patients suffering from chronic inflammation of the stomach lining (gastritis) and those carrying the bacteria Heliobacter Pylori. Both of these conditions may progress to ulcer disease and probably increase the risk of stomach cancer.

Ulcer disease may also be caused in part by high levels of lipid peroxidation and disruption of the antioxidant defense mechanisms in the lining of the stomach. There is certainly a close relationship between GSH-dependent enzymes and the progress of gastric ulcers. Glutathione and its related enzymes are found in very low concentrations within the ulcer, but often rise again when ulcerated tissues heal. When laboratory animals were given drugs to lower their GSH levels, oxidative damage to the stomach lining (gastric mucosa) was significantly higher.

Traditionally, Heliobacter pylori-related ulcers are treated with antibiotics (Amoxicillin, Biaxin, Flagyl, etc.) and proton-pump inhibitors (Losec, Pantoloc, etc.). This treatment is more effective when used in conjunction with antioxidants. A new medication called Rebamipide developed in Japan exerts some of its action by serving as a free radical scavenger. It also slows depletion of GSH. Studies using Rebamipide along with conventional drugs show improved healing.

A Swiss group from the University of Zurich recently studied smokers suffering from ulcers. They combined conventional treatment with the potent GSH precursor NAC (nacetylcysteine), with good results. This is understandable since smokers in general suffer from much higher levels of oxidative

stress than non-smokers and benefit more obviously from high antioxidant levels. Davydenko‟s team in the Ukraine believe that antioxidant therapy should continue even after conventional treatment has stopped.

When we look at cancer cells in the stomach as well as the immediately surrounding normal cells, we find several recurring characteristics – cells are heavily damaged by oxidative stress, their antioxidant defenses are diminished an the power-plants of each cell (the mitochondria) are defective – possibly due to free radical damage. Notably, GSH-related enzyme systems are impaired. There is little doubt that low glutathione levels go hand-in-hand with increased risk of cancer. The following research results speak for themselves.

T. Katoh at the National Institute of Environmental Health Sciences in North Carolina showed a particular relationship between GSH levels and the development of gastric cancer. For various reasons some people have inactive or inefficient sub-types of GSH enzymes. They are at greater risk for both stomach and bowel cancer.

A group from Italy studied glutathione levels in patients with stomach cancer and came to the unequivocal conclusion that the „decrease of this tripeptide‟ was „dramatical‟. Their work suggests that any therapeutic approach should include GSH precursors such as cysteine.

A Japanese team reached similar conclusions while investigating gastric ulcers. They found that levels of gastric mucosal GSH „are closely related to the etiology and course of gastric ulcer.‟ Various researchers and theorists have suggested that the antioxidant capacity of the cancerous tissues has been impaired and, even more significantly, that the body‟s entire antioxidant defense mechanism may be breaking down.

PANCREATITIS

The pancreas is an organ involved in several important functions, the two most crucial are to secrete digestive enzymes that help prepare food for intestinal absorption and to produce hormones such as insulin and glucagons that are critical to the metabolism of sugars and carbohydrates.

Pancreatitis is an inflammation of the pancreas that leads to pain (often severe), and digestive and metabolic abnormalities. It can be potentially life-threatening and if chronic may lead to other illnesses like diabetes. Acute pancreatitis is an abrupt onset of pancreatitis most commonly caused by blockage of the passage to the intestines. This usually happens when gallstones are lodged there, or sometimes at the site of a tumor. The pancreatic juices contain powerful digestive enzymes which may back up when blocked and start to dige4st the pancreas itself.

Other causes of acute pancreatitis include certain viral and bacterial infections, specific drugs, high fat levels in the blood including cholesterol or triglycerides (hyperlipidemia), abdominal trauma, and critically low blood pressure (severe hypotension). Chronic pancreatitis develops over months or years, usually after repeated bouts of acute pancreatitis. The most common trigger by far for this type is alcoholism. Chronic pancreatitis may impair normal functions such as insulin secretion and lead among other potential problems to secondary diabetes.

Many studies suggest that oxyradicals and free radicals are involved in the development of all types of pancreatitis. The importance of glutathione in the pancreas‟ antioxidant defense cannot be

overstated. J.M. Braganza and his team at the Royal Infirmary in Manchester, UK, have found GSH depletion in all early stages of acute pancreatitis.
They surmise that low levels may predict the vulnerability of other organs to pancreatitis. M.H. Schoenberg from the University of Ulm in Germany suggests that GSH supplementation may be a way to avoid extra-pancreatic complications.

Other researchers at the Royal Infirmary developed the „Manchester oxidant stress hypothesis" to describe the development of pancreatitis. They think that oxidant stress (caused mainly by toxins) opens the door to chronic pancreatitis because diminishing GSH levels allow the eventual breakdown of cells. This team developed a combination of antioxidants: methionine, vitamin C and selenium and tested them in placebo controlled and retrospective cross-sectional trials.

Oxothiazolidine carboxylate (OTC) – a potent GSH-enhancing drug – was successfully used by R. Luthen at the University of Dusseldorf in Germany to decrease the severity of pancreatitis. He found a critical loss of glutathione content in biliary pancreatitis (pancreatitis due to blockage by a gall stone). He and his researchers think that glutathione depletion has something to do with the early activation of auto-digestive enzymes, because the defense against oxidative stress is weakened. M.A. Walling says that GSH depletion is key to the evolution of chronic pancreatitis caused by external toxins.

The most common cause of chronic pancreatitis is alcoholic pancreatitis. Sufferers of this disease was found to be particularly deficient in levels of vitamins E and A, selenium, and glutathione peroxidase. Researchers have suggested that these patients required higher daily requirements to ward off this oxidative stress.

Another variety of this disease is known as hereditary pancreatitis, an inherited disease which was examined at the Cleveland Clinic Foundation. A correlation was found between the disease and diminished antioxidant defenses, most notably GSH, selenium and vitamin E. The relationships among these three antioxidants are described in chapters 1 and 4. The researchers at Cleveland propose supplementation therapy with natural products to decrease the frequency of attacks.

The major complication leading to death from pancreatitis is multiple organ failure. This is partly because the integrity of cell membranes breaks down, leading to leakages both in and out of these cells. X.D. Wang and his team at Lund University in Sweden successfully used N-acetylcysteine, a potent GSH-raising drug, to prevent damage to most tissues. I. Gukovsky at the University of California also found significant improvement in acute pancreatitis patients using NAC.

INFLAMMATORY BOWEL DISEASES

Inflammatory bowel disease occurs in several forms, including ulcerative colitis and Crohn"s Disease, both described here.

ULCERATIVE COLITIS

Colitis is a general term for inflammation of the bowel. Ulcerative colitis (UC) is a chronic inflammatory disease of the large bowel (colon) leading to the development of ulcers in the mucous membranes lining it. This causes pain, bloody diarrhea, gas, bloating and many other symptoms. Fever, weight loss, joint pains and even visual symptoms may accompany the digestive problems.

Most patients develop this disease early on in life, usually between the ages of 15 and 30. This disease ranges in severity from a single brief attack to a progressive course complicated by severe blood loss (hemorrhaging), perforated bowel or the spread of infection into the bloodstream (sepsis). Ulcerative colitis patients bear a higher risk of subsequent colon cancer. However, the ulcerative colitis is rarely fatal and the majority of those affected lead fairly normal lives.

The cause of this disease is still unclear but it has a small tendency to run in families. Various possible causes have been proposed, including infectious agents, immunological abnormalities, dietary factors, toxins, allergies and stress. However, these hypotheses remain unproven.

The large and small intestines are located in the lower abdomen like a loosely-folded fire hose that leads a long and winding patch from the stomach to the anus. Ulcerative colitis is marked by the formation of ulcers that eat away at the intestinal wall. Crohn‟s Disease is an inflammation that leads to swelling and tenderness in the intestinal wall. Figure 37 shows the location of these diseases and the different ways they affect the intestines.

CASE STUDY

28 year-old Debbie, a massage therapist, had ulcerative colitis but had so far managed to avoid any surgery. She maintained a sensible diet, continued the medications her doctor has prescribed, and avoided foods that disagreed with her. However, the previous few years had been fraught with repeated bouts of cramps, diarrhea and occasional bloody stool. Eventually, she could not make it through her workday without numerous visits to the washroom. A dietary consultant added to her diet a high-dose antioxidant mixture, selenium, L-glutamine, and – when her stool was firmer – psyllium husks. Her blood loss has abated, and she now visits the washroom at lunchtimes only.

CROHN‟S DISEASE

Crohn‟s disease (CD) is similar in many ways to ulcerative colitis (see above). Its differences, however, make this a potentially more severe disease. In ulcerative colitis small ulcers are scattered in the lining of the large bowel. Crohn‟s disease is less selective and may affect any part of the digestive system, from mouth to anus. It is most common in the ileum (the end of the small intestine where it joins the large intestine). The disease occurs in heavy patches, but areas between these diseased patches are also mildly affected. It is most common in the gut where the intestine wall may grow extremely thick following repeated inflammation. Deep ulcers may pass right through the lining and completely penetrate the gut tissues.

With repeated and prolonged inflammation of the intestine the entire thickness of the intestinal wall becomes affected. The thickening of the wall may narrow the intestinal passage and obstruct it. Symptoms can include spasms of abdominal pain, diarrhea, appetite loss, anemia and weight loss. The elderly are more prone to inflammation of the rectum. Young and old alike may suffer from chronic abscesses, deeps fissures (cracks) and fistulas (abnormal passageways) in the anus. Because the entire digestive system is susceptible, complications are more profound than those following ulcerative colitis. They include bowel obstruction, infection, malabsorption, and elevated cancer risk – as much as 20 times greater than healthy individuals.

Like ulcerative colitis, the exact cause of Crohn‟s disease is unknown, but there tends to be a stronger familial tendency. Some researchers think this may also be an autoimmune disease. Studies suggest that sufferers may benefit by avoiding certain food additives, allergens and cigarettes.

GSH IN INFLAMMATORY BOWEL DISEASE

It is clear from observing patients with inflammatory bowel disease that inflamed cells in the lining of the intestines are a hotbed of free radicals. However, there is still debate as to whether the free radicals cause or result from the damage characterizing these diseases.
Samples of tissue inflamed by ulcerative colitis and Crohn‟s disease show consistent evidence of severe oxidative stress. The degree of oxidative damage can even be correlated to the degree of inflammation. Of all the antioxidants that can prevent or retard this damage, GSH is the central one.

Researchers from all over the world – including L. Bhaskar from India and GD. Buffington from Australia have looked at tissues affected by inflammatory bowel disease and Crohn‟s disease. All have identified a significant depletion of glutathione and alteration of its enzymes. In the past, most researchers believed that GSSH depletion was more likely to be a consequence of ongoing inflammation and oxidative stress than a contributing cause of the problem. But today, opinions may be changing. More recent findings by B. Sido of the University of Heidelberg in Germany have found not only diminished GSH levels but also diminished activity of the enzymes involved with GSH production. This implies that declining GSH production may actually contribute to the development of the disease.

Antioxidant therapy has thus emerged as a treatment for inflammatory bowel disease. One of the more traditional groups of medications applied to these diseases are the aminosalicylates (sulfasalazine, Asacol, Dipentum, etc.). These are potent antioxidants, but are also pharmaceutical drugs, and the hunt for less toxic, more natural products is on.

T. Cruz and J. Galvez and their team from the University of Granada in Spain, were able to protect inflamed bowels with a flavonoid called rutoside – flavonoids are a variety of crystalline compounds found in plants. This worked with both acute and chronic disease. They explained their success by pointing to rutoside‟s tendency to maintain or increase GSH content in the gut.

Malnutrition results more often from Crohn‟s disease (CD) than from ulcerative colitis. The reasons are complex but are summarized by the fact that CD is more deeply involved in the bowel. The nutritional status of those suffering from this disease has been investigated at great length, and reveals a generalized GSH depletion throughout the body. These findings have also been reported in children with CD, possibly resulting from ongoing oxidative stress.

Numerous scientists have suggested oral GSH supplementation as a treatment for UC and CD. It is clear from the information we presented in chapters 1 and 4 that oral glutathione is not very effective in raising total body GSH. However, these digestive tissues seem able to make use of locally supplemented GSH. The tissues most positively affected by oral GSH are those in direct contact with it. The intestinal lining (mucosa) provides such an opportunity. In fact Alton Meister – often called the father of GSH research – suggests that both oral GSH and GSH excreted in the bile can protect the intestinal mucosa from injury. Experimental depletion of gut glutathione leads to severe damage of this sensitive lining.

CONCLUSIONS

GSH AND STOMACH DISEASE

Research evidence suggests that glutathione defends the stomach lining against various threats, including toxins, oxidative stress and carcinogenesis. Their results have prompted others to seek

ways to raise glutathione levels in humans, for both preventive and curative purposes. Elevated glutathione levels may protect against gastritis, ulcer and cancer and can certainly compliment conventional treatments for these diseases.

PANCREATITIS

The high levels of oxidative stress and the depletion of glutathione in pancreatitis is well documented and scientists are investigating the role of antioxidant therapy in the treatment of pancreatitis and prevention of recurrent bouts. Even though antioxidant therapy is a safe complementary treatment for chronic pancreatitis, its wider adoption as a standard healthcare tool will take time. The lynchpin of this new approach is the search for tools to enhance (modulate) intracellular glutathione levels. As these tools emerge, further research will be needed to use them effectively.

INFLAMMATORY BOWEL DISEASE

An imbalance in the formation of free radicals and a poor supply or availability of antioxidant micronutrients may cause or encourage tissue injury in inflammatory bowel disease. Levels of glutathione and its related compounds are significantly lower in these diseases. Different antioxidants including GSH, GSH monoesters, NAC (Nacetylcysteine), vitamin C (ascorbate), vitamin E (tocopherol), SOD (Superoxide dismutase) and others have been used with varying success. It may not be clear whether GSH loss is a cause or consequence of these inflammatory disorders, but in either case, they are positively affected by therapies that raise or sustain GSH levels. Recent research suggests that raising glutathione levels may be a novel approach to the treatment of ulcerative colitis and Crohn‟s disease.

KIDNEY FAILURE AND DIALYSIS

The kidney (renal) system controls the crucial urinary function of the body. It is responsible for filtering the blood and disposing of waste products, toxins and excess fluid in the form of urine. It also maintains water balance and regulates various chemical levels and blood pressure. If the kidneys cannot do their job, waste products and toxins accumulate in the blood. This affects other organ systems, often producing neurological symptoms and circulatory problems. Any sort of acute (sudden) or chronic
(gradual/prolonged) illnesses can interfere with kidney function and lead to long-term disease. Kidney disease may shorten life expectancy.

Acute kidney failure can be triggered by all sorts of conditions. For example, a massive hemorrhage, heart attack or overwhelming infection (sepsis) can severely and suddenly restrict blood flow, quickly injuring the sensitive kidney tissues. The most common medical conditions leading to chronic renal failure are hardening of the arteries
(atherosclerosis), high blood pressure and diabetes. These long-term diseases damage the circulation involved with the kidneys. Serious damage is also caused by organic and inorganic toxins, such as poisonous mushrooms, solvents, wood alcohol, antifreeze and heavy metals, either inhaled or ingested. There are many other causes of kidney failure, including chronic toxic exposure, inherited kidney diseases, vascular diseases and autoimmune disease.

Because kidney disease and renal failure are often triggered by other disorders it is important to identify the initial or potential cause. Diabetics must carefully control their sugar levels. Hypertensive patients must keep blood pressure down and all of us need to eliminate ongoing exposure to toxins. Some drugs can help manage chemical imbalances, circulatory problems and accumulation of waste products. Proper nutrition and dietary management are particularly important, and reduced protein intake is often advised in cases of renal failure.

If these measures do not sufficiently limit renal failure, a kidney transplant may be necessary. A less traumatic but very intrusive alternative is dialysis – the use of artificial devices to perform the kidney's functions. Two types of dialysis are commonly used today – hemodialysis and peritoneal dialysis.

Like chemical and radiation therapy for cancer patients, these procedures are life-saving but exact a heavy toll on the body's antioxidant defenses.

HEMODIALYSIS
In hemodialysis, blood is shunted out of the body to a mechanical filtering device, cleansed, chemically balanced, and shunted back into the person's circulatory system. The procedure is repeated several times a week. Each session takes several hours, during which the patient is physically attached to the machine.

PERITONEAL DIALYSIS
Peritoneal dialysis cleans blood without removing it from the body by using the peritoneal membrane (inner lining of the abdomen) as a filter. This membrane has many of the characteristics

of the kidney's filtering system. Once a plastic tube has been implanted in the abdominal wall, patients usually carry out the procedure for themselves.
A special dialysis solution (dialysate) is passed through the tube and into the abdomen. Waste material from the blood filters through the small vessels of the peritoneal membrane and is trapped by the fluid. After a few hours, the dialysate is drained and discarded. This procedure may be repeated several times a day.

GSH AND RENAL FAILURE

One cause of renal toxicity and kidney failure is exposure to heavy metals such as mercury, cadmium and lead. The body detoxifies these substances principally through GSH-related enzymes. Glutathione molecules bind themselves to these metals by the process of chelation, after which they are easily and safely removed from the body. The cells of the kidney are protected by high levels of GSH. In treatment for severe mercury toxicity, tests in laboratory trials and with kidney patients show that adding NAC (a GSH-enhancing drug) to the dialysate helps chelate inorganic mercury and remove it from the solution.

Acute renal failure occurs most commonly when the kidneys suffer inadequate blood flow (ischemia). Laboratory studies at the University of Texas and elsewhere have shown that damage suffered during ischemic renal failure is lessened by the infusion of NAC. This appears to result from an improved supply of antioxidants to the tissue, the detoxification of noxious metabolites like nitric oxide, or both.

Many pharmaceutical drugs have been implicated in kidney failure. Such common medications as ibuprofen, acetaminophen and even vitamin D put a high demand on the kidneys, and can damage them. Many of the anti-cancer agents used in chemotherapy do the same. Cyclosporin – an immuno-suppressant used after organ transplantation and in certain kidney diseases such as the nephrotic syndrome – can also damage the kidneys. Research indicates that elevated antioxidant defenses help protect the body from cyclosporin toxicity.

A rarer cause of kidney failure is polycystic kidney disease – the growth of cysts within the kidneys, eventually impairing their function. Experiments were carried out to artificially lower GSH levels with the drug BSO. This led to worsening of the disease and suggests that the presence of GSH plays a protective role.

The most common cause of poor blood flow is atherosclerosis – the build-up of plaque and other blockages in blood vessels. While GSH detoxifies pharmaceutical drugs and heavy metals, and fights such threats as polycystic kidney disease, it also fights plaque formation by inhibiting lipid peroxidation.

GSH AND DIALYSIS

Renal failure patients suffer from a profound imbalance of oxidants and antioxidants that grows worse as the kidney fails – and dialysis only compounds the problem. In spite of their life-saving action, peritoneal dialysis and especially hemodialysis worsen this aspect of kidney malfunction by increasing oxidative stress levels. Because dialysis is not optional for these patients, its side-effects must be addressed.

Some researchers think that dialysis damages the anti-oxidant system and leads to a dramatic fall in levels of the GSH enzymes that protect us from lipid peroxidation. The result is long-term complications such as accelerated atherosclerosis. In fact, cardiovascular disease is the major cause of morbidity and mortality in patients with endstage renal failure. There is plenty of evidence to show that antioxidant support might benefit these patients. A strong link between kidney function and glutathione availability has been identified. This has led some scientists to suggest that glutathione peroxidase levels may prove to be a yardstick of kidney function.

To test this hypothesis, elderly patients undergoing continuous peritoneal dialysis were studied to determine two things – nutritional status and oxidative stress levels. The former was measured by their ability to absorb and process certain nutrients, especially serum albumin and iron. Test results were well below normal. As for antioxidant defenses, glutathione peroxidase levels were even lower. It is clear that the ability of kidney patients to fight oxidation is profoundly and progressively compromised. Oxidative stress left unchallenged leads to untold damage.

To get a clearer picture of the process, the cells of the peritoneal membrane of peritoneal dialysis patients were examined. Researchers found that when the patients were exposed to the life-saving dialysate fluid, GSH levels fell significantly. To counteract this decline, OTZ (a pharmaceutical precursor of GSH) was added to the dialysate fluid. This helped restore GSH to protective levels in these tissues.

The link between GSH status and oxidative stress in dialysis patients is not only widely accepted, it is also considered highly significant. In patients with renal failure oxidative stress damages the circulating red blood cells (erythrocytes) causing low hemoglobin levels (anemia). This damage is normally kept to a minimum by glutathione – the principal antioxidant in this struggle. GSH acts on the surface of the wall of the red blood cell to preserve its integrity. Since hemodialysis causes significant oxidative changes and damages red blood cells, it is important that patients undergoing this procedure maintain high GSH levels. Drugs like NAC and OTZ effectively raise glutathione levels and improve the ability of patients to fight oxidative stress, but there are also safer, dietary ways to raise GSH levels.

Many dialysis patients are treated for their anemia (shortage of red blood cells) with erythropoietin. This drug is intended to stimulate the production of red blood cells, but provides an additional benefit. It turns out that younger cells have higher levels of GSH and are thus more resistant to lipid peroxidation and cell-wall breakdown. Studies have shown that antioxidants given to patients on erythropoietin may enhance the effectiveness of the drug, making it possible to lower dosage. This was demonstrated by giving patients intravenous GSH during dialysis sessions.

Another important study of hemodialysis patients was conducted by C. Costagliola's team in Italy. In this double-blind study some patients were given intravenous GSH while others received placebo. To test for anemia, doctors measured red blood cell, hemoglobin and hematocrit levels – all known to fall in dialysis patients. Those receiving GSH maintained higher levels than those on placebo. Their levels of oxidative stress also fell. Similar but separate Italian studies led by M. Usberti also resulted in lower levels of anemia. These findings show that elevated GSH levels help manage the anemia to which dialysis patients are particularly prone.

CASE STUDY

Since poor antioxidant and detoxification defenses are implicated in kidney disease and the complications of dialysis, there is reason to believe that GSH supplementation may help individuals like George, a 62-year-old former country and western singer.

George had struggled with diabetes for over thirty years. Following only moderate success controlling his sugar levels, he developed progressive kidney failure and subsequent anemia. In a few short years he went from an active, gregarious entertainer to a listless, sofa-ridden recluse. His energy level and concentration deteriorated more and more and the local hospital clinic inn Hawaii where he lived was obliged to monitor his condition closely. His levels of biliary urea nitrogen (BUN) and creatinine crept higher and higher – signs of diminishing kidney function – and his red blood cell (hemoglobin) value continued to fall. His physician placed him on a waiting list to undergo preparation for dialysis.

After hearing about GSH, George started taking 20 grams per day of a whey protein isolate high in GSH precursors. Within three weeks his BUN and creatinine levels started to fall – a sign of improving kidney function. After a further three weeks his hemoglobin climbed by one full gram per deciliter (g/dL) of blood and he was again singing at his friends' parties. His wife was uncomfortable about his exposure to alcohol and cigarettes but three months later his renal function tests and hemoglobin levels had improved so much his physician put plans for dialysis on hold.

PROTEIN INTAKE AND RENAL FAILURE

Diseased kidneys already have trouble clearing away breakdown products, many of which come from the digestion of dietary protein. Large quantities of protein leave high levels of urea-nitrogen in the blood, a condition called uremia that leads to further health problems. Therefore, protein intake is restricted and carefully monitored. Renal failure patients are encouraged to eat plenty of carbohydrates, but protein is an important nutrient and cannot be avoided. Since kidney failure patients often can consume it only in limited quantities, its quality is of great importance.

A measure of food protein quality is biological value (BV). It rates the usefulness and quantity of biochemicals made available to the body by a particular food protein. BV especially reflects the proportion of essential to non-essential amino acids. We must have a continuous supply of essential amino acids in our diet. We need non-essential amino acids too, but don't necessarily have to eat them – our body can manufacture them fro the essential ones. For dialysis patients, proteins rich in essential amino acids are preferable because of their higher biological value. Some patients undergoing dialysis become protein deficient (hypoalbuminemic). For them, the quality of dietary protein is even more important.

The natural protein with the highest biological value is whey protein, which is ideal for kidney patients. Also, the amino acids found in some whey proteins are GSH precursors (building blocks). Their presence depends principally on how the whey protein is prepared and stored.

CONCLUSION

GSH plays important roles in the prevention and treatment of renal failure, the anemia that often accompanies kidney failure and dialysis, and the cardiovascular complications of kidney disease. The use of GSH-modifying agents is a promising treatment for both short and long-term complications of kidney failure. GSH acts simultaneously as a detoxifier and as an antioxidant, preventing lipid peroxidation. Because some whey proteins contain additional nutritional benefits and act as glutathione precursors, they are a useful compliment to traditional therapy.

EYES, EARS, NOSE, THROAT AND TEETH

It‟s well known that glutathione is important for the normal functioning of the eye. Some of the earliest studies with GSH focused on its role in preventing cataracts, and GSH is relatively well known among ophthalmologists. Specialists in ear, nose and throat (ENT) and in dentistry have only recently become aware of the role of glutathione in the diseases they treat. Given the critical roles of GSH as the body‟s most important naturally occurring antioxidant, its ability to detoxify substances encountered in the environment and its immune-sustaining abilities, glutathione research is now finally picking up in these fields as well.

OPHTHALMOLOGY CATARACTS

Cataract is a clouding (opacification) that takes place in the lens of the eye. It is the leading cause of morbidity and functional impairment among the elderly and leads to more than one million operations per year in the United States.

The lens of the eye is composed of deceptively simple tissue. This completely transparent part of the eye has the job of focusing light on the retina, which it does by changing shape to adjust its focal length. Scientists believe that any damage to the lens, no matter how small, contributes to opacification. This usually results from physical injury, repeated exposure to ionizing radiation (such as sunlight) or any of a host of different illnesses. Over time the damage accumulates and the lens begins to cloud.

Oxidative stress plays a role in the aging of the lens, so antioxidants are an important defense against cataracts. The researcher M.A. Babizhaev in Russia measured the breakdown products of lipid peroxidation as cataracts developed. He found that as the cataract worsened, oxidative stress increased. An Italian team at the University of Bari went a step further and demonstrated that in people with cataracts the loss of GSH paralleled the increase in oxidative breakdown products.

It is known that cataract in humans usually shows significant, extensive oxidation of lens proteins. With this in mind, researchers experimented on cataracts by stimulating them with various chemicals. They showed that cataract formation could be delayed or prevented by elevated GSH levels. Clearly, the key defense in the lens against oxidation is glutathione.

The legendary GSH expert, Alton Meister and a team at Cornell University in New York, used the drug BSO to deplete glutathione levels in the eyes of laboratory animals. The animals subsequently developed cataracts. Meister‟s team was then able to prevent cataract formation by reestablishing glutathione levels with GSH-monoester and suggested that this strategy may be effective in delaying cataract formation.

Diabetics are more prone to cataract than non-diabetics. E. Altomare‟s team in Italy measured glutathione status in the lenses of four groups of patients: diabetics with and without cataracts and non-diabetics with and without cataracts. As expected, both cataract groups showed impaired glutathione defenses, but the diabetic groups fared worse in all cases.

CASE STUDY

Edgar loved to paint. Now retired, he could pursue this hobby fulltime if he so pleased. Over the previous few years, his wife had commented that the color in his landscapes was too loud. At first he did not believe he had changed his techniques, but a side-by-side comparison with earlier works proved him wrong. Still, he felt the colors in previous paintings were "weak". A routine check revealed cataracts. One eye required surgery, the other was "not yet ripe". After surgery he eventually recovered excellent vision, but post-operative complications left him hesitant about having the same treatment on the other eye. His wife did some homework, learning about glutathione and cataracts. She started him on Immunocal. One year later, his ophthalmologist was baffled by the unusual observation that the cataract was less dense.

MACULAR DEGENERATION

Macular degeneration is a progressive loss of sight due to breakdown of the macula – the portion of the retina responsible for fine vision. Age-related macular degeneration (ARMD) is a leading cause of visual loss in people over 65. Although susceptibility to this disease may be predominantly genetic, contributing factors such as smoking and atherosclerosis can make it worse. This disease is thought to result from the cumulative damage of free radicals primarily released by exposure to ultraviolet (UV) sunlight, but other sources of oxidative stress may play a role.

Because elderly people generally have low GSH levels, they are predisposed to oxidative damage. Researchers have shown that low GSH levels go along with poor eye health in ARMD patients compared to normal control groups. Experiments have been conducted to test glutathione‟s antioxidant function in the whole body and in the eyes of patients suffering from macular degeneration. S.M. Cohen and his team at the University of California (Davis) found significantly altered GSH activity in blood samples of macular degeneration patients. It appears that high GSH levels correspond to healthy eyes and suggests a possible role for GSH in the protection against or delay of this disease.

GLAUCOMA

Glaucoma is a serious condition in which fluid pressure within the eye rises. A certain amount of pressure is necessary to maintain the shape of the eyeball. Too much pressure compresses and obstructs the small blood vessels within the eye. This damages the surrounding areas, most importantly the optic nerve. Glaucoma is one of the leading causes of visual loss.

It becomes more common as we age, runs in certain families, and is often seen in conjunction with diabetes, hypertension (high blood pressure) and severe myopia (nearsightedness). Traditional therapy aims to relieve the pressure in the eye either surgically or with drugs.

The Russians A.I. Bunin, A.A. Filina and V.P. Erichev measured GSH levels in the eyes of hundreds of patients undergoing surgery for all sorts of reasons. The lowest GSH levels were found among cataracts patients and in patients with open angle glaucoma. They noticed this fall even at the earliest stages of the disease and suggested that reestablished glutathione levels would help prevent or delay this process, and used the nutritional supplement lipoic acid to do so.

A Harvard University group investigated different GSH-related compounds to increase the outflow of fluid from the eye and reduce pressure within it. In combination with the topical form of

ethacrynic acid (a diuretic) they found that cysteine, glutathione and Nacetylcysteine all benefited eye pressure and even lessened the side effects of the drug.

EAR, NOSE & THROAT

GLUTATHIONE IN THE UPPER RESPIRATORY TRACT

The nose, mouth and throat make up the upper respiratory tract. All the food we eat, fluids we drink and air we breathe pass through it. The importance of GSH in the lower respiratory tract (lungs) is well known. Since the upper tract is our front-line contact with the external environment, it seems fitting that glutathione would protect us here against xenobiotics (infections and toxins).

The respiratory tract is lined with a fluid made up of a complicated mixture of biochemicals and cells of the immune system, called the respiratory tract lining fluid (RTLF). Glutathione is the main antioxidant in this fluid and provides our initial defense against inhaled toxins. Institutions like the Inhalation and Toxicology Research Institute in Albuquerque, New Mexico started researching the role of antioxidant enzyme activities in RTLF in the early 1990‟s. More recent work at the University of California (Davis) elaborates further on the role of antioxidants in this fluid.

This research project is only one of several focusing on the importance of glutathione in the respiratory tract lining fluids, where it protects us from xenobiotics and infection. In severe or prolonged illnesses, these GSH levels may become depleted and enable the disease to progress and cause further complications. Furthermore, N.S. Krishna and his team at the University of Kentucky showed that this glutathione defense system weakens with aging, and more quickly in men than women.

B. Testa and M. Mesolella from the Institute of Otolaryngology, University of Naples, used a GSH nasal aerosol spray in their studies. Statistics from the experiments show that this treatment significantly improved nasal obstruction, rhinorrhea (runny nose) and ear fullness. The lining of the nose is one of few human tissues that readily absorb glutathione. Most other tissue can only use the glutathione it manufactures for itself from GSH precursors.

SINUSITIS

Infection or inflammation of the sinus cavities in the bones of the face is one of the most common reasons people go to the doctor. As many as 50 million Americans are affected each year. The most common causes of sinusitis include bacterial or viral infection, allergies and impaired mucus flow. Most treatments are designed to either destroy the infection or improve drainage of mucus from the sinuses. The sinus cavities are near the front of the head, behind the forehead, nose region and cheeks.

Physicians have long used the drug NAC for the treatment of disorders involving thickened lung secretions (cystic fibrosis, chronic bronchitis). It is now being used for upper airway problems such as sinusitis. NAC breaks down mucus and raises glutathione levels at the same time. American, French, Italian, Korean and Scandinavian research teams have all studied the efficacy of NAC and other antioxidants in the treatment of sinusitis.

The Amsterdam group led by G.J. Westerveld showed the glutathione levels fall during chronic sinusitis. They concluded that this drop is part of a generally decreased antioxidant defense, which subsequently worsens the disorder.

EAR INFECTION

Infection of the middle ear is an extremely common cause of illness, especially among children. It is caused mostly by a combination of fluid buildup in the middle ear and infection. The triggering event often is a viral infection, but the site is commonly superinfected (one infection on top of another) by bacteria. Treatment for many years was with antibiotics, but doctors are increasingly reluctant to over-prescribe these drugs nowadays, especially for ear infection. Decongestants can help drain fluid from the middle ear, through the Eustachian canal and into the throat.

More and more evidence shows that free radicals play a large part in the development of inflammation leading to middle-ear infections. Studies examining GSH levels in these tissues show that they fluctuate according to how infected or inflamed the site is. Scientists have examined the effects of both ways of raising glutathione levels – topical and ingested, and have found both to be effective ways to address oxidative stress in these tissues.

Patients with middle-ear infections are sometimes treated by placing tubes through the eardrum to drain accumulated fluid and prevent subsequent infection. This does the job but has its downside. In response to this intrusion by a foreign object the body sets up an inflammatory process. The procedure also encourages a high oxygen state in the middle ear. Both of these factors lead to free radical and oxyradicals formation, causing changes in the cells lining the middle ear that lead to scarring and fibrosis. T. Ovesen and his team of ENT researchers at the Aarhus University in Denmark instilled liquid NAC through these small tubes. The drug reduced inflammation and prevented the long-term scarring that normally follows this condition.

DEAFNESS AND HEARING LOSS

Almost 30 million North Americans experience sufficient hearing loss to interfere with their ability to converse. This is almost one person in ten. One percent of our population cannot hear at all and is considered deaf. Almost a third of individuals over the age of 65 have some form of hearing loss and this figure increases with age.

There are many causes of impaired hearing, all of which broadly fit into two categories: conductive hearing loss caused by a mechanical problem in the middle ear or external ear canal and sensorineural hearing loss, a problem of the inner ear or auditory nerve. In the latter category the problem may be sensory – in the cochlea, the essential organ of hearing – or neural – affecting the auditory nerve itself. Causes of hearing loss include physical trauma, exposure to repeated loud noise, infection, tumors and malignancies, obstruction of the ear canal, genetic defects, toxins and drugs, various neurological diseases and the aging process in general.

NOISE EXPOSURE

Exposure to noise accounts for about one third of all hearing loss cases. It‟s particularly unfortunate because most cases are avoidable. All it takes is appropriate caution. Teenagers often enjoy and are fed damaging levels of noise. Preventive aids such as earplugs can help. So can turning down the volume.

People working in noisy environments and those with noisy hobbies all risk their hearing. Most of us have experienced that buzzing, ringing or hissing in our ears after leaving a concert or

construction site. Hearing is sometimes diminished temporarily. This can last minutes or days and is generally followed by a return to normal. This is a „temporary threshold shift" and is caused by injury to the sensitive hair cells in the cochlea – the spiral shaped organ in the middle ear. Severe, repeated or prolonged exposure to excessive noise can destroy these neurological hair cells and lead to permanent hearing damage.

Interestingly enough, the cochlea can be trained to withstand greater noise levels and suffer less damage. This is known as „sound conditioning" or „toughening". Priming the ear to low level noise before the higher levels seems to protect from hearing loss. Researchers at the Albert Einstein College of Medicine in New York examined the biochemical changes found in sound conditioning. They saw that certain enzymes which raise GSH levels or keep glutathione in a reduced (non-oxidized) state were stimulated by low noise exposure. This suggests that whatever protects or increases the glutathione system in the cochlea also protects against noise-induced hearing loss.

Other studies in the area of glutathione and noise exposure lend support to this model. A team at the Kresge Hearing Research Institute at the University of Michigan chemically depleted glutathione levels using the drug BSO, with the result that noise-induced hearing loss was more profound. The same team went on to raise GSH levels with OTC, with the result that hearing loss was minimized. Dr. Denis McBride, from the Office of Naval Research in Arlington, Virginia, found that delivering antioxidants directly to the cochlea through a small tube could prevent permanent damage following noise exposure. This treatment must be delivered within six hours of exposure. Other researcher suggest that workers with prolonged noise exposure would gain long-term benefits from elevated glutathione levels.

HEARING LOSS INDUCED BY DRUGS OR TOXINS

Exposure to all sorts of pharmaceutical chemicals may lead to sensorineural hearing loss. They include high doses of aspirin, several different antibiotics, a number of diuretics (high blood pressure medication), quinine, and several chemotherapy agents.

One of these chemotherapy drugs is cisplatin. It is a common cancer treatment that can also damage auditory neurons (hearing nerve cells). Researchers have shown that this damage is caused by free radicals in the tissue. Studies lowering GSH levels show increased damage, those raising GSH decreased the damage. It seems that raising glutathione levels could protect patients from both the hearing and the kidney damage that may result from this treatment.

Similar studies have been conducted in relation to aminoglycoside antibiotics (gentamycin, kanamycin, amikacin, others) and loop diuretics (lasix, furosemide, ethacrynic acid, others). Research teams from the USA (University of Michigan, Southern Illinois University), Japan (Hiroshima General Hospital), and Germany (Universitats HNO) all found that substances used to raise glutathione activity have a protective effect against the hearing loss than can be provoked by these drugs. Dr. C.P. Maruzi from the Houston Medical Center even suggests that deafness following acute meningitis may be caused by free radicals in the inflamed tissue, and that antioxidants preventing lipid peroxidation in the auditory nerve would protect the patient.

DENTISTRY

A fact little known by doctors but common knowledge to dentists is that dental and periodontal (gum) disease is the most common illness in America. Even more importantly, periodontal disease has recently been linked to more serious systemic diseases that may be encouraged by poor oral hygiene. Robert Genco, editor-in-chief of the Journal of Periodontology has said, "It seems clear that gum disease, far from being just a oral health problem, actually represents a significant health risk to millions of people."

It goes beyond unsightly smiles and bad breath. The infections and toxins harbored in the mouth have been linked with heart disease, stroke, bacteremia, prosthetic device infection, diabetes, pulmonary disease, impairment of fetal growth and other systemic disease. Dr. Charles Mayo, founder of the Mayo Clinic is purported to have said,
"preventive dentistry can extend your life expectancy 10 years."
One of the most impressive of all studies is the Veteran Administration‟s Normative Aging Study in Boston. They followed the medical history of over one thousand outwardly healthy men, starting in the 1960‟s. Those who started out with any sign of gum disease suffered about twice the death rate – mostly from cardiovascular disease – than those with healthy gums. At a recent conference on the subject, Dr. Raul Garcia, one of the researchers, stated, "Gum disease kills. Floss or die!"

Many links have been made between the infective and inflammatory processes of periodontitis and the generation of free radicals. Research is required to see whether elevated glutathione levels will combat the formation of free radicals and bolster the immune system‟s defenses. Immunotec Research has developed a toothpaste with glutathione precursors. Direct application to these tissues may combat the disease.

CONCLUSION

Scientists studying the eye have long recognized the critical importance of glutathione as an ocular antioxidant. Practical applications are now available for the prevention and treatment of disorders like cataract and macular degeneration.

GSH has a triple role in the upper respiratory tract. Its ability to suppress free radical formation, detoxify environmental xenobiotics and reinforce the immune system gives us a tool against airway irritation from pollution, sinusitis, otitis and other infections and inflammations of our ears, nose and throat. Having long utilized NAC in pulmonary disease, the medical profession is now pursuing its use in ear nose and throat diseases. An interesting clinical application of elevated GSH is the treatment and prevention of noise-induced hearing loss as well as that caused by certain ototoxic drugs.

The importance of dentistry in total health care is only recently being fully acknowledged. Periodontal disease has been identified as a risk factor for heart disease, stroke and other systemic disease. Enhanced glutathione levels should be part of a good oral hygiene program.

PREGNANCY, LACTATION AND CHILDBIRTH

Women undergo drastic physiological changes during pregnancy. More so, in fact, than at any other time except for their own birth. Pregnancy is challenging at the best of times. It is fraught with hazards and potential complications. The mother and child are at the mercy of their genetic makeup, which may be the main cause of some of these challenges. However, they are also susceptible to the environment – mainly the air, food and liquids they consume. It is especially important to void or limit exposure to toxins and teratogens (substances causing birth defects). Good general health and nutrition are important for both mother and child. Vitamins and antioxidants naturally have an important role to play. GSH wears several hats in this scenario and proves itself indispensable.

The list of pregnancy-related illnesses is very long. We cannot describe them all in this chapter but will cover those in which the role of GSH has particular relevance. Since the newborn‟s GSH levels greatly depend on the mothers‟ glutathione status, we will also discuss the brief but eventful stages of childbirth and the neonatal period (from birth to six weeks).

PRE-ECLAMPSIA, ECLAMPSIA & HYPERTENSION OF PREGNANCY

Many pregnant women are susceptible to hypertension (high blood pressure). This is caused by hormonal shifts and changes in blood volume and circulation. Some women are always Hypertensive and some experience this problem only during pregnancy. About one in twenty have a more serious condition called preeclampsia.

Symptoms of preeclampsia are hypertension, proteinurea (protein in the urine) and edema – accumulation of water in the tissues leading to swelling, particularly of the hands, feet and face. It usually occurs between the 20^{th} week of gestation and the week following birth. Its exact cause is unknown but most obstetricians (pregnancy and delivery doctors) consider it a vascular disease. It occurs most often in first-time pregnancies and in women who already have high blood pressure.

If left unchecked, one in 200 cases of preeclampsia progresses to eclampsia, a very serious condition featuring convulsive seizures and coma. If not dealt with promptly eclampsia is usually fatal, so it must be treated aggressively. Another major complication of preeclampsia is the HELLP syndrome: Hemolysis (red blood cell breakdown), Elevated Liver enzymes (indicator of liver damage), and Low Platelet count (impaired blood clotting).

Treatment for a mild case of eclampsia includes bed rest, increased fluid intake and nutritional support. Attempts to stimulate urination and stabilize fluid levels with diuretics and salt restriction have no effect. Blood pressure and neurological symptoms are best controlled with intravenous magnesium sulfate and hydralazine. The definitive solution for eclampsia patients is childbirth, which is often induced or cesarean.

PRE-ECLAMPSIA AND GSH

Many scientists have noticed that when pregnancy is complicated by preeclampsia, there is a precipitous drop in the patient‟s antioxidant function. This has been linked to the oxidation of circulating fats (lipid peroxidation) which damages the sensitive endothelium (lining of the blood vessels). Subsequent constriction of the muscles in the artery wall leads to narrowing of the passageways and decreased blood flow. Combined with the demands of gestation, this triggers a complex cascade of events that can lead to full-blown eclampsia.

Researchers have consistently found glutathione levels of Hypertensive pregnant mothers to be very low. G. Chen and his team at the University of Glasgow believe this depletion might account for some of the important features of pregnancy-induced hypertension – elevated intracellular calcium, decreased red blood cell deformability and endothelial damage. D.W. Branch‟s team at the University of Utah think the lipid peroxidation that follows may be part of the pathological process in cells of preeclamptic placentas – the foam-cell formation of deciduas. It also seems that measuring GSH levels may be a good way to determine the severity of this disease.

The HELLP syndrome is a serious complication of preeclampsia. Patients suffer liver damage, breakdown of red blood cells and loss of blood-clotting cells. GSH loss is particularly pronounced. Researchers have established a threefold correlation – severity of the preeclampsia, cell fragility and the level of GSH-oxidation.

C. Lee‟s obstetrical team in London, England attempted to control symptoms in a testgroup of preeclampsia patients. Women with severe cases not responding to traditional therapy were given S-nitroso-glutathione. Arterial pressure, platelet activation, and uterine artery resistance all improved without further compromise of fetal well-being. In other words, it slowed or reversed the symptoms of the disorder.

GESTATIONAL DIABETES AND DIABETES IN PREGNANCY

Some women enter pregnancy with a long history of diabetes while others only suffer the disease‟s high blood-sugar levels when they become pregnant. This is called „gestational diabetes‟ and occurs in one to three percent of pregnancies. A number of gestational diabetics will develop true diabetes later in life.

The main cause of death among newborn children of diabetic pregnancies is abnormality of the child in the uterus (congenital malformation). The causes can be traced to inadequate control of the mother‟s diabetes during pregnancy. Diabetic mothers run the risk of larger babies and tougher deliveries. As a result, births are usually induced if they haven‟t occurred by the forty-second week of pregnancy. Aside from developmental defects these babies are also at higher risk for developing jaundice, respiratory difficulties, blood sugar abnormalities, low blood calcium and other metabolic abnormalities.

GSH AND DIABETES IN PREGNANCY

All diabetic patients are subject to higher levels of free radical production and lipid peroxidation. In a diabetic environment, embryos develop a higher incidence of malformations and developmental problems. This phenomenon is called „embryotoxicity‟. The exact mechanism of embryotoxicity in diabetes has yet to be elaborated, but it is clear that oxidative damage to cells plays an important role. Low GSH levels in these patients‟ embryos place the fetus at risk from the ravages of free radicals.

A Japanese study confirmed that restoring GSH status in embryo cultures normalized the growth retardation and embryo malformations seen with untreated mothers. A Swedish group had similarly positive results treating embryo cultures with NAC (Nacetylcysteine), a potent GSH-enhancing precursor.

TOXINS AND TERATOGENS IN PREGNANCY

We are all exposed to toxins from our environment. They come from the food we eat, the water we drink, the air we breathe, the medications we take, the jobs we hold and bad habits like drinking and smoking. The embryo is exposed to the same toxins as its pregnant mother, but is at much higher risk because they affect its fundamental growth and development.

The consequences range from low birth weight to malformations or even fetal death. Sometimes the consequences are so subtle that they may not appear for years – such as diminished IQ scores in later childhood. The mother is the only one who can keep these risks to a minimum. Above all, she must ensure that her built-in detoxification processes are working well.

GSH AND TOXICOLOGY IN PREGNANCY

According to recent research, the fetus seems to be low in antioxidant defenses. Perhaps it depends on its mother‟s good health, in which case anything that further depresses these levels could compromise fetal development. After all, the fetus grew from the embryo, and GSH levels are very high in the embryo‟s conceptual tissue. Conceptual tissue is the extraordinary mass of cells that differentiates and grows into the organs and systems of a human fetus. The process of organ development (organogenesis) is extremely sensitive, but at this stage is especially well protected by higher GSH levels. Researchers in toxicology are studying the possibility that elevated GSH levels may protect unborn children from foreign substances (xenobiotics). If this proves so, measuring GSH in early pregnancy may also be a way to identify possible risks of toxicity.

Some pediatric researchers have tried to match levels of antioxidant defense systems to the frequency and severity of birth defects. W.D. Graf and his associates at the University of Washington compared the frequency of neural tube defects with GSH enzyme levels and established just such a connection. In a very significant Ukrainian study, scientists collected the placentas of women from around the country. All lived in areas affected to a greater or lesser extent by radioactive pollution. As expected, the placentas from the most polluted areas had the lowest GSH levels. They were simply depleted by the overwhelming demands of an ongoing radiation threat. This group was able to show that placentas with low GSH levels were associated with more difficult pregnancies, harder deliveries and poor postnatal health. They concluded that “glutathione status [is] a prerequisite of the detoxifying activity of the feto-placental barrier.” In other words, without placental GSH the fetus is largely unprotected from toxins and other xenobiotics.

The two most common toxins found in pregnancy are alcohol and tobacco. Although most pregnant women can and do choose to avoid them, abuse of these drugs is not uncommon. The mother may have a habitual dependence on these drugs or may simply be exposed to secondhand smoke. In either case, GSH plays an important role in protecting mother and child against such toxic threats.

ALCOHOL AND TOBACCO

Most drug-induced malformations of the fetus result from alcohol abuse during pregnancy. Fetal alcohol syndrome is a clinical condition leading to a long list of possible abnormalities, the most serious being severe mental retardation. In tests on laboratory mammals, the presence of alcohol drained GSH from the liver much more quickly in the fetus than in the mother. Other studies combined alcohol with cocaine, which further magnified the fall in GSH. At the University of New Mexico researchers gave test animals GSH-depleting drugs. This increased the severity of fetal alcohol syndrome. On a more positive note, G.I. Henderson and his team at the University of Texas used antioxidants on their test animals and showed that much of the damage of fetal alcohol exposure could be avoided by maintaining adequate GSH levels.

Women who smoke during pregnancy risk many complications, including early labor, premature rupture of membranes and premature delivery. A possible cause was identified by researchers who demonstrated that cigarette smoke interferes with signals between certain white blood cells and blood platelets, thus interfering with normal blood clotting. The same researchers were able to stop this interference by raising GSH levels.

OTHER TOXINS

Many other studies have shown that antioxidant defense systems – notably the GSH system – play an indispensable role in detoxifying the newborn of numerous xenobiotics, including heavy metals such as mercury, lead, cadmium and arsenic, drugs such as hydantoin, phenytoin, and various poisons. In the lab, GSH-enhancing drugs like NAC actually diminish the toxic effects of mercury on congenital abnormalities and death. NAC is in fact recommended as an emergency measure for pregnant women who have overdosed on acetaminophen.

GSH, CHILDBIRTH, AND THE PERINATAL PERIOD

One of the major complications around childbirth (the perinatal period) is inadequate oxygen supply to the baby (hypoxia). Before the separation, the baby is dependent for its oxygen on umbilical supplies, but this can be compromised during difficulties. For a number of reasons the baby might also suffer respiratory difficulties. In either case, the consequences of hypoxia are problematic and every effort is made to avoid it.

When the baby does not get enough oxygen individual cells are unable to maintain energy levels. This results in hypoxic damage. One molecule – adenosine triphosphate (ATP) – is responsible for carrying energy from the power generators (mitochondria) of individual cells. Because GSH stimulates ATP-production it can be considered antihypoxic. Another complication of the hypoxic child is lipid peroxidation, which is also addressed by GSH. And there is every reason to believe it would also help infants suffering from diminished liver function (jaundice).

OXYGEN – SOURCE OF LIFE AND OXIDATIVE STRESS

Premature infants often need oxygen therapy. This brings energy production up but also increases oxidative stress, explaining why visual problems are often encountered by premature infants. Excessive oxygenation causes immature tissue such as that at the margin of the retina to shut down their blood vessels. This condition is called retrolental fibroplasias or retinopathy of prematurity, and has such serious consequences as retinal detachment. Antioxidants may be a potential antidote to this side effect of oxygen therapy. A. Papp from Hungary suggests that giving mothers sulfur-containing amino acids sustains GSH levels and helps prevent this problem.

Other problems relating to high oxygen levels include developmental changes to the nervous system and oxidative lung injury. Newborn animals depleted of glutathione with BSO (a GSH inhibitor) experienced a dramatic increase in these types of damage. J. Sastre and his group from Spain conducted laboratory tests to demonstrate NAC‟s ability to lessen oxidative stress in newborns. The NAC was administered to the mothers. L.A. Brown of Emory University in Atlanta was able to prevent oxygen-induced lung injury in mammals with GSH supplementation. There is every reason to believe that elevated GSH levels in the mother will counteract the negative effects of many perinatal complications.

GSH AND LACTATION

Lactation and breast-feeding are usually discussed alongside pregnancy and childbirth. In this context, GSH is particularly interesting. One could say it plays a starring role.

It is impossible to overestimate the benefits of mother‟s milk on the health and development of newborns, especially considering its long-term effects on the immune system. Compared with bottle-fed children, those who are breast-fed suffer from fewer infectious diseases, especially ear infections and pneumonia, fewer problems with allergies, and fewer cases of childhood cancer, including leukemia, lymphoma and bone and brain tumors.

Compared to the milk of other mammals, human milk has the lowest proportion of protein. But the protein make-up is also very different. The two major protein constituents of milk are whey and casein. The whey to casein ratio is much higher in human milk, and these predominant whey proteins contain the critical precursors of glutathione, including beta-lactoglobulin, alpha-lactalbumin, serum albumin, and lactoferrin. These proteins are high in sulfur-containing amino acids such as cysteine and cysteine. The structure of these proteins as well as their content is very important.
Because the cysteine and cysteine are integrated into these larger proteins, they can survive the rigors of digestion and arrive intact in the cells of the infant. There, they are subsequently used to manufacture GSH. Breast-feeding therefore profoundly affects the baby‟s immune function by giving it high levels of glutathione precursors.

It is possible to extract these proteins intact from cow‟s milk. The extraction of whey must be carried out carefully, because these proteins are extremely fragile. Their structure easily changes to a form that is biologically inactive. In spite of its unchanged food value, denatured protein loses its capacity to delivery GSH precursors. New technologies have been developed to extract these proteins from mammalian milk without denaturization. In a sense, this is mother‟s milk protein for adults – a natural way to raise GSH levels. Immunocal is one such whey protein.

CONCLUSION
Glutathione‟s role in embryonic, fetal and placental development is crucial. It is constantly at work as a scavenger of free radicals and as a detoxifying enzyme of dozens of foreign substances and toxins. Without GSH, these substances can push the child towards an unnerving variety of developmental and health problems. Once past the stage of organogenesis, the unborn child‟s principal GSH protection comes from outside its own body – the placenta. There is an interesting similarity between the placenta and the liver. Among their many other functions, both act as filters for toxins and both have high levels of GSH within their tissues. It is no coincidence.

Many common complications of pregnancy including high blood pressure, preeclampsia and gestational diabetes coincide with low glutathione levels. Decreased GSH can cause many difficulties in pregnancy. A great deal of research is being carried out using GSH enhancing strategies to combat these problems. There is already some success and much optimism.

TRAUMA AND BURNS

Trauma is any sort of injury, including the emotional trauma of divorce or the physical trauma of a broken hip. In this chapter, we will talk mostly of physical trauma even though emotional trauma is also known to deplete glutathione. Motor vehicle accidents, work injuries and falls are common examples of accidental trauma. Intentional trauma includes everything from gunshot wounds to surgical procedures. Burns may be caused by heat, chemicals or radiation. Radiation burns are discussed in chapter 2, and sunburn and UV (ultraviolet) burns in chapter 21.

Glutathione, antioxidant protection, immune defenses, and oxidative stress play an important role in all of these conditions. High or low levels of GSH have a significant effect on the susceptibility, tolerance and degree of injury, as well as the recovery time and outcome.

PHYSICAL TRAUMA

Until this century, traumatic injury was the major cause of death in human beings. In North America today, trauma has fallen to third place behind heart disease/stroke and cancer, but in some economic groups – especially poor urban male populations – trauma remains at the forefront.

Any critical illness depletes glutathione reserves. In a recent article from the journal Critical Care Medicine, F. Hammarqvist shows that intensive care patients suffered an approximate 40% loss of glutathione compared with healthy individuals. M.
Kretzschmar from Germany followed patients with multiple injuries in an intensive care unit, from admission to discharge or death. He found the more severe the injuries, the higher the degree of oxidative stress and depletion of glutathione defenses. An Irish team led by C. Kilty suggests the measurement of glutathione S-transferases could be a useful indicator of general organ damage.

A Harvard Medical School team led by M.K. Robinson showed that lab animals artificially depleted of glutathione were dramatically more prone to death and complications of blood loss (hemorrhagic shock). Their results suggest that treatment of trauma should include some way to maintain glutathione levels. This would decrease the likelihood of multi-system organ failure in the event of shock.

The role of oxidative stress and glutathione metabolism in brain and neurological tissue injuries has been the focus of much research. Head injuries often damage the crucial blood-brain barrier, and subsequent circulatory problems lead to swelling and fluid buildup in the brain. Free radicals mediate some of the complex “secondary injuries” seen in this type of trauma. Efforts to prevent post-injury complications are a crucial part of treatment in emergency and critical care management.

Glutathione metabolism counteracts the damage caused by these oxyradicals. Increases in glutathione peroxidase activity following neurological trauma have been well documented. If injury is severe or complicated, these resources may become eventually depleted. Canadians B.H. Juurlink and P.G. Paterson of the University of Saskatchewan suggest that nutritional interventions with GSH-precursors can maximize antioxidant defenses, and that such strategies should be pursued aggressively.

E.F. Ellis’s team at the Department of Pharmacology and Toxicology with the Medical College of Virginia, tested the use of NAC against concussion after trauma to the brain. They discovered that NAC given prior to or shortly after the brain injury could prevent some of the consequences of

oxidative circulatory compromise. At Ohio State University, J.H. Lucas and D.G. Wheeler showed a similar protective effect of glutathione on spinal cord injury. Using the GSH-precursors gamma-glutamyl-cysteine and OTZ elevated glutathione levels increased spinal neuron survival after physical trauma.

R. Wagner and R.R. Myers of the University of California developed an interesting therapy for nerve injury and sciatic inflammation and presented it in the journal "Pain". They were able to decrease the pathological consequences of sciatic nerve injury by using the drug NAC to raise GSH levels. Pre-treated subjects responded best. The longer the delay in administering NAC after injury, the less effective was the treatment.

Surgery is intrusive and disrupts a patient's anatomy. It leads to a host of physiological adjustments. Although from the surgeon's pint of view this is a controlled procedure with end-point objectives, from the body's point of view, it is traumatic. Just like recovery from accidental trauma, the outcome of the operation depends on the patient's prior defenses, fitness, and immune status.

Surgery releases billions of free radicals into the body. These severely tax the patient's antioxidant defenses and poor surgical outcomes seem to go hand-in-hand with low antioxidant levels. As the cell's primary intracellular antioxidant, glutathione is drawn from stores in the liver and skeletal muscles and dispersed to reduce the damage. The result of major surgery may be whole-body glutathione depletion. Articles from the American Journal of Physiology as well as the Annals of Surgery describe a fall in glutathione levels of 40% after abdominal surgery. This may increase the patient's susceptibility to cellular oxidative injury.

A relatively new surgical device – the laparoscope – is a tube with a fiberoptic cable through which the surgeon can see into and work within a body cavity. Tools are attached to the end of the laparoscope and procedures are performed through small surgical holes in the patient's body. This reduces cutting, recovery time and hospital stays for many patients. The difference in trauma induced by conventional surgery and laparoscopic surgery is measurable. A team of Hungarian surgeons noted oxidative stress and GSH levels in two such groups of patients undergoing gall-bladder removal. The laparoscopic group showed significantly lower values of oxidation and less depletion of GSH-systems than the open-surgery group.

Glutathione not only protects us from oxidative stress, it also bolsters immune response, controls and balances the inflammatory response and helps synthesize and repair proteins involved in the healing process. This knowledge has stimulated research into the use of GSH enhancing strategies to improve and accelerate wound repair.

Plastic surgeons from the University of Michigan, Ann Arbor showed that depleted glutathione levels lead to delayed wound healing and poor repair. Biochemists from the Max Plank Institute in Germany showed that while healing, skin wounds initially increase their production of glutathione peroxidase in order to fight free radical formation. As healing progresses GSH levels fall. Pharmacologists from the Central Drug Research Institute in India demonstrated a 60-70% depletion of glutathione peroxidase and glutathione S-transferase levels in skin wounds after several days healing. Understanding these mechanisms at play, Van der Laan described in an article in the Journal of Surgical Research how NAC infusion could reduce tissue injury and shorten the repair period of crush injuries.

An important consideration in all surgery is disruption of blood flow to tissues (ischemia). When blood flow is re-established (reperfusion) there is a burst of free radical formation in the affected region that may affect the survival of those tissues. The Australians K.R. Knight and K. MacPhadden found that NAC, the glutathione precursor was able to decrease the amount of reperfusion injury in skin flaps. Potential applications are being investigated in cardiac surgery to avoid reperfusion injury.

BURNS

Heat or thermal burns consist of a complex series of events involving initial injury, physiological adjustments to circulatory and fluid changes, hematological and immunological responses, and an elaborate healing process. Death from heat burns is often delayed. Days after a burn, patients may die from circulatory shock, a result of loss of fluids from the burn. Weeks after a burn, patients may succumb to overwhelming infection (sepsis) because of the breakdown in their immune defenses.

Burn specialists have long known that oxidative stress can be dramatic in severe burn patients. Lipid peroxide levels, a good measure of free radical damage, are consistently high. Glutathione and its related enzyme activities are impaired. This has initiated research into the use of antioxidants to protect the cell from further damage.

A German team of pediatric surgeons conducted a two-year study on children with burns and severe inflammatory diseases. They managed to correct parameters of oxidative stress in these patients using selenium substitution, which raised glutathione peroxidase. They found this a valid supportive therapy for such conditions. Other nutritionists have increased selenium delivery through TPN (Total Parenteral Nutrition or intravenous nutrition) or through tube feeding, where food is supplied directly to the stomach or intestines.

One phenomenon of the early post-burn period is a drop in hemoglobin (red blood cell count). Scientists have questioned why. A team from Varna Medical University showed that burns depleted the glutathione and antioxidant defenses of the red blood cell itself. Oxidative byproducts accumulated, leading to destruction of these cells. They suggest that adequate antioxidant therapy might prevent this complication, as long as it is begun early enough.

A Japanese team led by Y. Kasanuma from the Environmental Health Sciences Division of Tohuku University of Medicine investigated the effects of mild heat injury on oxidative stress. Rather than burning tissue, they exposed animals to mild chronic heat exposure (35^0C, 95^0F). They showed that chronic exposure to high temperatures causes oxidative damage and that GSH-related anti-oxidative systems play an important role in defending against this damage.

A recent study published in the journal “Burns” by D. Konukoglu was aimed at the use of NAC to treat burns. Researchers were able to decrease levels of lipid peroxidation and increase GSH levels. Using antioxidant supplementation (GSH, vitamin C and NAC) to raise glutathione levels, several Boston studies published in the Journal of Burn Care Rehabilitation and in Shock, showed that they could reduce mortality from 60% to zero in animals suffering third degree burns. This is strong evidence that oxidation contributes to post-burn mortality.

CONCLUSION

Surgery, burns, trauma and shock are all complex events, consisting of a series of biochemical, anatomical, physiological and immunological responses. Oxidative stress and the release of free

radicals is an inevitable part of the initial injury, the subsequent inflammatory reactions and the healing processes. Glutathione is an integral part of our body's mechanism to minimize damage and promote healing. It acts both as an antioxidant and as a support for the immune system.

The value of antioxidant supplementation and nutritional support has historically been underestimated, but new approaches to this problem are under development and attitudes are changing. Strategies to maintain or increase glutathione enzyme systems have been beneficial in preliminary trials and show much promise in the treatment of major trauma, surgery and burn management protocols.

PSYCHONEUROBIOLOGY

As our understanding of the brain has evolved, we have begun to appreciate the intricate interweave of psychiatry, neurology and biochemistry. These fields have overlapped and melded into psychoneurobiology, an integrated medical science that has already yielded important advances in the recognition and treatment of many brain disorders.

Free radicals and oxyradicals have been recognized by psychoneuro-biologists 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 dealt with here and in other chapters.

Psychosocial stress has also been shown to increase oxidative stress. An interesting experiment studying lipid peroxidation levels in older people, some of whom practiced transcendental meditation, showed that meditators suffered less stress and suffered significantly lower levels of lipid peroxidation.

SCHIZOPHRENIA

The Greek translation of schizophrenia is “split mind”, and may be misleading. The disorder should not be confused with split personality or multiple personality disorder. It is a different illness characterized by psychosis – a severe disturbance of normal thought, perception, speech and behavior. In mood disorders like anxiety and depression, the ability to discern the real from the imagined is relatively intact. A schizophrenic patient on the other hand often suffers from delusions, auditory or visual hallucinations and paranoid thoughts not based on reality.

Although there is no consensus as to the causes of schizophrenia, most specialists will agree that the symptoms stem from a disturbance of normal brain chemistry. The tendency seems to run in families, but no single schizophrenia gene has been identified. Psychotherapy by itself is of little value but antipsychotic drugs have been able to reduce relapses by 50% and considerably shorten periods of hospitalization. However, these drugs have significant side effects and long-term complications.

It has long been known that glutathione levels are lower in schizophrenic patients. Researchers have consistently demonstrated an increase in their oxidative stress and a decrease in their glutathione status. GSH levels even correspond to the severity of the disease. The Russians N.V. and A.V. Govorin further demonstrated that schizophrenics undergoing an acute phase of their disease had higher levels of lipid peroxidation than when in remission. Research scientists such as J.K. Yao and R.D. Reddy of the Veteran‟s Administration Healthcare System, University of Pittsburgh suggest that oxidative stress plays an important pathophysiological role in schizophrenia.

A group of neurochemicals called catecholamines are products normally by the body. They seem to be over-produced in both schizophrenia and Parkinson‟s disease. The catecholamines break down into ortho-quinones – a group of powerful oxidants. S. Baez‟s team at the Department of

Biochemical Toxicology in Stockholm University examined glutathione‟s ability to detoxify these metabolites. They concluded that GSH enzymes provided critical protection against the neurodegenerative diseases that are caused or conditioned by these dangerous oxyradicals.

T.D. Buckman and A.S. Kling at UCLA School of Medicine conducted a fascinating study. CT-scans of schizophrenic patients revealed brain atrophy (shrinkage), suggesting damage to nerve tissue. They linked the extent of atrophy to the degree of glutathione peroxidase deficiency. This suggests a unique function of GSH in preserving the brain from tissue damage in schizophrenics. These findings are corroborated by other centers such as Hahnemann University in Philadelphia.

Antipsychotic drugs require long term use and cause a number of side-effects. Haldol, Thorazine and other neuroleptics cause a movement disorder called tardive dyskinesia. This results in involuntary puckering of the lips and writhing of the arms and legs and disfigures a large number of patients. It is possible that lipid peroxidation accounts for neuronal damage in this disorder, and scientists have put this theory to the test.

The Scottish team led by K. Brown and A. Reid measured oxidative breakdown products and antioxidant depletion in diskenetic patients and confirmed the relationship between lipid peroxidation and tardive dyskinesia. Other researchers have shown that lipid peroxidation and GSH depletion are aggravated by antipsychotic drugs. Y. Sagara at the Salk Institute in La Jolla California said that treatments resulting in decreased intracellular GSH would aggravate haloperidol (a neuroleptics antipsychotic) toxicity and may increase a tendency towards tardive dyskinesia.

Researchers J.L. Cadet and L.A. Kahler from the National Institute of Health in Baltimore, S.P. Mahadik and R.E. Scheffer from the Department of Health Behavior, Medical College of Georgia and others have suggested that antioxidants should be used to prevent side effects in patients taking antipsychotics. The Georgia team also showed that oxidative injury increases and GSH peroxidase levels fall even at the earliest stages of psychosis, and that antioxidants may prevent or slow deterioration.

It appears that sustained GSH levels may slow the progress of schizophrenia and decrease the side effects of some of the drugs used against this disease.

DOWN SYNDROME

Down syndrome is also known as trisomy 21, and inappropriately as mongoloidism because of the distinctive facial characteristics. Ironically, certain areas in the Far East refer to it as „caucausianism“. This congenital disorder occurs during fetal development, when chromosomes divide mistakenly, producing a third 21st chromosome when there should only be two. It is not an inherited trait and is found more frequently in pregnancies of older women. It is relatively common, occurring once in about every 700 births.

Down syndrome leads to several easily recognizable traits including moderate to severe mental retardation, typically flattened facial features, slanted eyes, low-set ears and a large tongue. Les obvious is a tendency toward congenital heart defects, poor vision, leukemia and susceptibility to infectious disease. In a proper environmental setting, Down syndrome patients may lead happy, productive, but generally shorter lives.

Oxidative stress and free radical formation have been studied in Down syndrome. Although there is still debate, certain factors are clear. The gene for an enzyme involved in oxidation/antioxidation reactions called „superoxide dismutase“ (SOD) is located on chromosome 21. Increased SOD activity may overproduce hydrogen peroxide and thus release free radicals. Researchers have observed the heightened demand this places on antioxidant defenses.

Down syndrome patients that make it to an older age seem more prone to the development of Alzheimer‟s dementia, another neurodegenerative disease. Scientists including those working at the University of California (San Diego) think this is due to changes in free radical metabolism, causing increased destruction of nerve cells. Simple experiments measuring blood serum levels of glutathione reveal significant alterations in GSH activity. More elaborate studies compare GSH activity in Down patients with and without Alzheimer‟s disease, and demonstrate that the already abnormal glutathione defense is further impaired in Down syndrome patients who also suffer from Alzheimer‟s disease.

An interesting animal experiment was published in the August 1997 issue of Brain Research. It showed that in brain cells affected by Down syndrome, those with lowered GSH died more quickly. By chemically lowering GSH even further, cell death rates increased. There is no doubt that low GSH levels accelerate brain cell death and that elevated levels slow the progression of neurodegeneration. Intervention with glutathioneenhancing therapies seem helpful.

GSH AND SLEEP

Certain tissues are more susceptible to GSH depletion than others. Measuring glutathione levels in specific areas of the brain of sleep-deprived animals reveals that the thalamus and hypothalamus are particularly susceptible. The vulnerability of these tissues may contribute to some of the functional effects of sleep deprivation.

Oxidized glutathione (GSSG) is an active component of a neurochemical called SPS (sleep promoting substance). Researchers at the Tokyo Medical University showed that high levels of oxidized glutathione promote sleep and affect other hypothalamic functions, such as temperature control. The same team also suggests that GSH detoxifies neuronal tissues more actively during certain periods of sleep. This may explain why those taking GSH-enhancing products like Immunocal often report lessened for sleep yet feel more energetic.

CASE STUDY

Benjamin, a 44 year-old physician, always wished for a 36-hour day so he‟d have time to see his patients, do his research, practice his music, keep in shape, and spend more time with his wife and children. Like many other professionals, time and energy were at a premium. Aware of the effects of GSH on the immune system, he took a course of vitamins, selenium and amino acids in the hope of more easily fighting off the viral illnesses to which he was exposed daily. He incorporated Immunocal in to his regimen, wishing to take advantage of its GSH precursors. He soon noticed he was waking up from 30 to 60 minutes before his alarm went off, and he felt just as refreshed. Now he regularly works later into the evening.

HUNTINGTON‟S DISEASE

Huntington‟s disease, also known as Huntington‟s chorea, hereditary chorea, or chronic progressive chorea, is an inherited neurodegenerative movement disorder with progressive intellectual deterioration. It strikes people between the ages of 35 and 50 and advances relentlessly, leading

eventually to a physical and mental inability to look after oneself. The term “chorea” refers to the rapid, complex, jerky motions of the face, trunk, and limbs. The associated dementia is accompanied by psychiatric disturbances as well. Traditional treatments are symptomatic and only minimally effective.

These patients seem to be less able than others to deal with oxidative stress. They suffer from increased free radical generation and decreased GSH defenses. Studies depleting glutathione from affected tissue show increased damage to and death of these cells. In the laboratory, antioxidants help cells survive. The neurochemical 3-hydroxykynurenine (3-HK) is found in excessive levels in the brains of Huntington‟s patients and strongly promotes oxidation. Lab experiments using the GSH-enhancing drug NAC seem to reduce the damage done by 3-HK.

O. Bandmann and a team of neurobiologists at the Institute of Neurology in London, think that an inherent defect in the brain‟s ability to detoxify neurotoxins may be at the root of Huntington‟s and Parkinson‟s diseases. Given the importance of glutathione as an antioxidant, its deficiency in these patients will stimulate many more studies.

CONCLUSION

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. Even mental stress has been shown to destabilize oxidant/antioxidant balance in the brain.

Both schizophrenia and the drugs used to treat it lead to GSH abnormalities. Supporting and sustaining glutathione levels may prevent or slow the damage to brain cells typical of this disease. Tardive diskinesia, a long-term side-effect of antipsychotic drug usage, has also been linked to free radical production and depletion of glutathione defense mechanisms. Researchers have proposed that elevated GSH levels may slow the progression of schizophrenia and erase the side effects of medications used to treat it.

Down syndrome patients have an inherent chromosomal abnormality that causes overproduction of abnormal SOD (superoxide dismutase). This leads to high levels of oxidative stress that may compound the death of brain cells typical of this congenital disease. The increased rates of Alzheimer‟s disease in older Down syndrome patients seem to support this theory. Glutathione is the major naturally-occurring antioxidant in the brain and serves to combat these oxyradicals.

Other applications of GSH in neurodegenerative disease are discussed elsewhere in this book.

Chapter 21

SEIZURES

Seizures are a group of neurological disorders typified by muscle contractions, twitching and partial or complete loss of consciousness. Specific symptoms depend on the precise location in the brain of chaotic bursts of electrical activity. Seizures range from violent, uncontrollable contractions of the whole body to a subtle and momentary "loss of contact" that may appear to be little more than daydreaming.

Seizures have been referred to as convulsions, fits and epilepsy, as well as by other names that do not accurately reflect the various disorders. Types of seizures include tonic-clonic (gland mal), absence (perit mal), complex-partial (psychomotor, temporal lobe), focal (Jacksonian), and status epilepticus (intractable fits). Not all seizures are epileptic. The most common type of seizure in very young children are called febrile seizures, caused by the rapid onset of fever. Other causes of seizures include stroke or may be a result of injury, tumors, meningitis, hypoglycemia, alcohol withdrawal or other health complications.

Epilepsy – a specific type of seizure with recurrent, unprovoked attacks – is however the most common type, affecting close to three mullion North Americans – about one in a hundred people, half of them children or adolescents. Of these, one-half fortunately grows out of the disorder.

Treatment

Recurrent seizures usually require medication with such oral anticonvulsants as Phenobarbital, valproic acid, phenytoin and carbamazine. Patients may need to take these drugs indefinitely. Unfortunately they are not a cure and can have many side effects, some severe.

Nutritional supplements are used in both conventional and complementary medicine. B-vitamins, particularly B6 (pyridoxine), are effective against certain seizures. Magnesium is also useful, especially in seizures related to high blood pressure. Selenium is used in epileptics, since deficiency of this mineral may intensify the frequency and severity of seizures.

FREE RADICAL DAMAGE IN SEIZURES

Seizures are typified by tremendous bioelectrical activity in the affected area of the brain that generates free radicals in large numbers. Convulsions that provoke loss of consciousness may be accompanied by breathing abnormalities and subsequent oxidative stress. When frequent and/or prolonged, this oxidative stress can damage brain cells. May studies show that lipid peroxidation (a result of free radical formation) can lead to neuronal damage of destruction of these neurological cells. Moreover, the higher the level of oxidative stress in these tissues, the harder it is to treat. Patients respond less effectively to medication when the ongoing injury and nerve damage provokes further epileptic activity. Canadian researchers at the University of Calgary have even suggested that this continual free radical damage may even result in certain brain tumors.

GLUTATHIONE LEVELS IN SEIZURES

Considerable research has demonstrated that glutathione levels fall significantly in seizure conditions. What is less clear is whether this glutathione deficiency causes seizures, results from

them, or both. Nevertheless, the total body glutathione levels of seizure patients are measurable lower than those of normal individuals, and this GSH deficiency is even more noticeable in the affected areas of the brain.

Swiss scientists led by S.G. Mueller studied three groups: patients with active epilepsy, those with controlled epilepsy and non-epileptics. They determined that low glutathione levels more often lead to seizures than result from them. Other research supports this theory by showing how seizures are more frequent or severe when glutathione levels are experimentally lowered. Whatever the specific mechanism, the overall picture shows that glutathione levels fall lower and lower as seizures progress. Worse still, not only are glutathione levels lowered by seizure activity, the drugs used to treat seizures themselves reduce glutathione levels even further. Japanese researchers H. Ono, A. Sakamoto and N. Sakura showed that both cabamazepine and phenytoin-popular anti-seizure medications-diminish glutathione and leave cells even more susceptible to oxidative damage. Turkish physiologists found the same of valproic acid, another anti-seizure drug. However, scientists studying childhood seizures at Harvard University found that glutathione levels improved after anticonvulsants were halted and patients were given selenium.

GLUTATHIONE PROTECTS FROM SEIZURES

Since glutathione directly affects the activity of brain cells, it is called neuromodulator, Japanese scientists K. Abe, K. Nakanishi and H. Saito protected animals from drug-induced seizures by injecting glutathione directly into the fluid of the brain and spinal cord. Canadians at Toronto Western Hospital showed that combined vitamin E and glutathione reduced the number of brain cells damaged after seizure activity. In Texas S.G. Jenkinson, J.M. Jordan and C.A. Duncan were able to protect laboratory animals from seizures and death by injecting them with glutathione and Italians at the University of Milan successfully prevented seizures caused by isoniazid-a tuberculosis medication-by administering patients with glutathione beforehand.

Several scientists have used n-acetylcysteine (NAC, see chapter 4), a powerful glutathione precursor, to treat seizures, and Swedish researchers led by E. BenManachem applied it to patients suffering from progressive myoclonic epilepsy-a particularly hard to treat disease that gradually destroys the nervous system. Patients given a daily dose of 6 grams showed marked improvements, and an American team from Gainesville, Florida used NAC, vitamin E, B2, zinc and selenium to treat this type of seizure, obtaining similar improvements.

CONCLUSION

Free radical formation and oxidative stress can be seen as both a cause and a result of seizures, and conditions that diminish glutathione levels-including the use of anti-seizure drugs themselves-may well lower glutathione levels as well. Since glutathione is also itself an anticonvulsant, it may be used as a complementary therapy to both treat and prevent seizures as well as to lessen the adverse effects of conventional drugs.

SKIN DISORDERS

What is the largest organ in the body? Most people think it‟s the liver on even the intestine, but in fact it‟s the skin. Besides providing a protective barrier against the environment, the skin performs a large number of important functions, endocrinological, thermoregulatory, immunological, toxicological and circulatory.

The skin can host a huge variety of diseases and disorders and about one third of North Americas will experience some sort of skin problem. Skin disorders also affect patients differently, especially in their psychological reaction to the disease. Firstly, the fact that they can actually see the problem makes it hard to forget; secondly they are often nervous about the actual or perceived reaction of others, and the social or interpersonal consequences.

GSH AND SKIN DISEASE

Given the number of functions served by the skin, it is no surprise that glutathione is involved in many skin problems. The role of GSH in detoxification and prevention of radiation damage in other tissues is well-known. It plays just as vital a role here. Low levels of GSH have been documented in many types of skin disease, including:

Psoriasis	Atopic dermatitis
Eczema	Seborrheic dermatitis
Vasculitis	Contact dermatitis
Mycosis fungoides	Dermatitis herpetiformis
Polymyositis	Pemphigoid
Scleroderma	Acne conglobata
SLE (lupus)	Acne vulgaris

In this chapter we will focus on psoriasis, dermatitis and ultra-violet radiation damage.

PSORIASIS

Psoriasis is a common, chronic recurrent skin condition characterized by scaly white or red patches of skin on the legs, knees, arms, elbows, ears, scalp or back. The rash may consist of one or two inconspicuous small patches or cover the whole body. This can affect the joints and occasionally even lead to disabling arthritis. However, such extreme cases are rare and general health for most psoriatic patients is good. Lesions are typified by an overgrowth of skin cells which multiply up to ten times faster than normal skin cells. This overgrowth continues and leads to the classic raised, silvery, flaky appearance of the condition.

The actual cause of psoriasis remains unknown. It may be triggered by different factors in different people. Fair-skinned individuals in particular may have a genetic predisposition to it. It certainly has something to do with the immune response itself. Attacks or flare-ups can be triggered by emotional or physical stress, illness, injury, infection, drug and alcohol abuse, obesity, and many different chemicals. The other chapters of this book describe the critical role of glutathione in many of these processes.

One source of relief for psoriatic patients is travel to a healing environment. The Dead Sea in Israel is particularly popular. A medical facility – The Dead-Sea Psoriasis Treatment Center – has been set up specifically for this purpose. Researchers have tried to understand why this

particular area seems to help. High levels of sunlight seem to affect psoriasis positively. Most interestingly, the drinking water in the area is very high in selenium. A local research team explains that the best indicator of selenium bioactivity is patients‟ glutathione peroxidase levels. Compared to a control group and to their own initial GSH levels, patients spending weeks in this treatment center increased GSH peroxidase levels, often as much as 50%.

Psoriasis patients suffer from abnormal glutathione enzyme activities, and researchers have inked the disease to high levels of free radicals. Lowered GSH activity results in greater damage. The clinical results of raising GSH in this disease are promising and more studies are underway.

CASE STUDY

Roland is a 44 year-old energetic and sociable business entrepreneur who suffered from psoriasis for ten years. Itchy, scaly eruptions often covered his entire body, and aggressive scratching led to bleeding and scabbing. His dermatologist tried many different treatments including strong topical corticosteroids and methotrexate tablets, which he had to discontinue due to side-effects. Ultraviolet light therapy was suggested, but having the financial means, Roland preferred frequent trips to Mexico and the Caribbean to sitting in artificial light. Having done significant homework on his condition, he concluded that the psoriasis was caused by an immune dysfunction. He started taking 40 grams/day of Immunocal to raise his glutathione levels. Within two weeks he was free of bleeding and scabs and described his scaling as 75% improved.

DERMATITIS

Dermatitis is a general term meaning inflammation of the skin. It is caused by a wide range of different ailments. Toxins or irritants can lead to contact dermatitis. Allergies can lead to allergic or atopic dermatitis. Many intestinal or immunological diseases can lead to such forms as dermatitis herpetiformis. Overproduction of oils in the skin can lead to Seborrheic dermatitis. Dermatitis can be triggered by stress or illness. Overly hot, dry, cold or wet environments also promote dermatitis. All are characterized by red itchy skin and in extreme cases blistering, crusty or oozing lesions. Almost all of these conditions have been linked to abnormal glutathione activity.

In both irritant contact dermatitis and allergic contact dermatitis, glutathione levels fall both in the skin and the whole body. A group of Japanese dermatologists inhibited GSH production with BSO. They found that both allergic and irritant contact dermatitis rashes were subsequently more severe. They link this both to the detoxification abilities of GSH, and to the effect of GSH on the immune system.

Several research teams have shown that GSH-precursors help the immune system respond to contact sensitivity. A Swedish team using the GSH enhancing drugs NAC and DiNAC demonstrated significant results with contact and delayed-hypersensitivity reactions. G. Senaldi of the University of Geneva successfully used both topical and oral NAC to experimentally treat contact and irritant dermatitis. His team suggested that a similar approach may benefit cancer patients suffering from skin inflammation secondary to TNF-alpha (tumor necrosis factor-alpha), an inflammatory side-effect of cancer.

Contact dermatitis often arises from the use of cosmetics, including make-up, skin creams, eyeliners and other products. One particular culprit is a group of preservatives/sanitizers known as MCI-MI (methyl-chloro-isothiazolinone/methylisothiolinone). A group of Swedish occupational and

environmental dermatologists found that the addition of as little as 2% GSH to these emollients deactivates the MCI/MI.

Thimerosol is another popular preservative used in toiletries, including contact lens solutions. It is known to cause skin and eye reactions, probably because of its organomercury content. At Rome‟s Dermatological Institute, B. Santucci showed that adding I-cysteine or glutathione to solutions containing Thimerosol reduced or prevented reactions to this chemical.

AIDS patients are more prone to skin disease than others. These conditions include Karposi‟s sarcoma, Seborrheic dermatitis and others. As we discussed in chapter 12, most AIDS patients are glutathione-deficient, a factor that contributes to these skin conditions. S. Passi and A. Morrone in Italy and other teams have shown a deficiency of glutathione peroxidase activity both in HIV-positive patients and in otherwise healthy individuals with Seborrheic dermatitis.

An interesting experiment was carried out at the Welsh School of Pharmacy. They examined the dermatitis-inducing chemicals of plants such as poison ivy and poison oak and found that most inflammation was due to free radicals. Using the GSH-precursor OTZ they were able to reduce the irritation and sensitizing effect of these noxious compounds.

SUN AND ULTRAVIOLET RADIATION SKIN DAMAGE

By far the most common cause of abnormal aging, wrinkling and cancer of the skin is sun exposure and ultraviolet radiation. We may pay later in life for the „healthy‟ bronzed glow of our youth. The skin-aging consequences of tanning lead many people to plastic surgery. But most facelifts would be unnecessary if these patients had avoided tanning when they were younger. Many skin cancers that appear in adult life may actually be initiated by severe sunburn as a child.

The well-known ozone layer in the atmosphere blunts the damaging effects of ultraviolet. A and B radiation found in sunlight. The ozone depletion which has so concerned scientists in recent years has already increased the number of skin cancer patients. We may yet witness an even more dramatic increase in the years to come. Physicians are treating sunburn in more and more patients who claim they have never before been so dramatically affected by sun exposure.

Radiation releases high levels of hydroxyl-radicals in the skin. These are the most toxic free radicals known to man. Such radiation comes from sunlight UV-A and UV-B, sun lamps, radiotherapy treatment and X-rays. The damaging radicals are normally neutralized by glutathione, but overexposure overwhelms this protective system and GSH levels can fall, resulting in even more damage. For this reason, doctors have considered using antioxidant supplementation to protect the skin. Studies using various antioxidants have had mixed results. Research into elevated GSH levels has been much more encouraging.

P. Baas and his team at The Netherlands Cancer Institute used halogen lamps to sensitize their patients to light, and showed that sensitivity decreased when the patients were pretreated with NAC to raise glutathione levels. Another Dutch team at the Department of Medicinal Photochemistry, Leiden University looked at various oral and topical products and their capacity to decrease UV skin damage. They found that NAC, whether ingested or applied to the skin was a practical means of protecting from UV-B radiation damage.

French researchers at Joseph Fourier University in Grenoble examined how effectively various GSH precursors could limit UV-A radiation damage. These products included NAC, OTZ, CIT, and selenium. Most are described in detail in chapter 4. To various degrees, all GSH-enhancing substances inhibited the deleterious effects of UV-A radiation. The researchers conclude that elevated GSH levels protect against UV-A damage.

Similar studies at Harvard University and Hirosaki University in Japan investigated the way UV-B radiation causes sunburn. Using animal subjects they first showed that glutathione depletion resulted in significantly greater sunburn damage. Further studies with orally administered esterified glutathione raised GSH levels and resulted in less damage. Other Japanese experiments using higher doses of UV-radiation on their animals showed that pre-treatment with glutathione esters could actually decrease the number of skin tumors that developed much later on.

A German team at the University of Berlin studied the effect of UV-B damage on people with an inherited defect in a glutathione enzyme called GSH S-transferase. The GSHimpaired group suffered significantly more intense damage than the control group, so it seems that inherited GSH-transferase deficiencies determine how sensitive an individual is to sunlight.

UV-B exposure not only damages skin, at high doses it can affect the immune system itself by suppressing the local and general functioning of T-cell lymphocytes. Substances that deplete GSH levels decrease this response even more, and substances that elevate glutathione levels protect it. D.P. Steenvoorden and his team at the Amsterdam Center for Drug Research used BSO to lower glutathione levels and NAC or GSH-esters to raise them, demonstrating that elevated GSH levels provide protection against UV-B immunosuppression.

CASE STUDY

The 61 year-old Canadian Charles loved boating. His dream was to retire and spend most of his time on the water, traveling the coasts. Tall, handsome and fair-skinned, he was unfortunately prone to sunburn. Despite sunscreens and hats, being on the water often left him unprotected and his complexion grew ruddy and inflamed. His physician was worried about the possible development of pre-cancerous sun-induced lesions on his face. Charles had already started taking Immunocal for a potential prostate problem. After several weeks he noticed that his tendency to burn was significantly decreased, despite some “accidental” exposures. In two months his in-the-sun complexion was no longer so different from his winter complexion.

CONCLUSION

Low glutathione levels characterize many skin diseases. Practical applications with GSH-raising substances have been studied in the treatment of several diseases. There has been success in some but not all cases of psoriasis. This may reflect the multiple and various causes of this disease. Many of the diseases that fall under the very general definition of dermatitis may be positively affected by raised glutathione levels. GSH is of extreme imp9ortance as a protective agent against ultraviolet radiation of the sun.

GLUTATHIONE IN THE HUMAN MALE

PROSTATE PROBLEMS

Of the hundreds of animal species with a prostate gland, only humans and dogs are known to suffer from prostate cancer and prostatic hyperplasia (an overgrowth of prostate tissue). The prostate is a walnut-sized gland that surrounds the urethra, the tube that drains the bladder through the penis. It is responsible for the production of fluid that carries the sperm when ejaculating. Other prostate problems include infection – both acute and chronic prostatitis. The majority of men will have some sort of prostate problem in their lifetimes.

PROSTATIC HYPERTROPHY (ENLARGED PROSTATE GLAND)

Not all prostate enlargement is cancerous. In fact most enlarged prostates are benign. Hypertrophy of the prostate is caused by an enlargement of the cells in the gland, unlike cancer, which is enlargement caused by an increase in the number of cells. This condition is age related and increases from an incidence of 8% in 30 to 40 year olds, to over 80% in men over 80. Enlargement of the gland often leads to impaired flow from the bladder. Symptoms are frequent and difficult urination, a weak urinary stream, straining, dribbling, incomplete emptying and recurrent urine infections.

Traditional treatments include surgical removal of all or part of the prostate, widening of the urethral passage by such means as scraping or laser surgery, and a number of drugs that either relax the muscles at the neck of the bladder or actually shrink the prostate. Saw palmetto is an herbal therapy that is greatly valued by alternative practitioners and is now also gaining acceptance by conve3ntional doctors as an adjunct to shrink prostate tissues.

In prostatic hypertrophy and prostate cancer the prostate overgrows for several reasons. Male hormones (androgens) have considerable influence on this growth. Physicians may prescribe anti-androgens as an antidote.

Researchers have found that abnormal growth in these tissues often corresponds to deficiencies in glutathione enzymes. One is glutathione S-transferase, which has several sub-types. The balance of these sub-types varies from normal prostate tissue to hypertrophic prostates to cancerous prostates. Several researchers propose that deficiencies in this GSH enzyme system increase the likelihood of developing both an enlarged prostate and prostate cancer.

PROSTATE CANCER

Well-known nutritional specialist Bonnie Liebman writes about “Death, taxes…and prostate cancer…,” a poignant comment on the prevalence of prostate cancer in our population. When researchers include in their statistics individuals with pre-cancerous cells, they claim that more than three-quarters of men over the age of 80 show evidence of cancer in their prostate glands. Some scientists are of the opinion that if a man lives long enough, he will eventually get prostate cancer. By this definition, prostate cancer would certainly be a disease of aging.

Nevertheless, the vast majority of men easily outlive prostate cancer. Many may not even suffer significant symptoms. Although the average age at which men are diagnosed is 72, it is usually with a slow-growing tumor that may even have begun thirty or forty years earlier. It is by far the most common type of cancer to occur in men, but death by prostate cancer is less frequent than death by either lung cancer or cancer of the colon, the two most frequent cancer killers.

Screening for prostate cancer is pursued aggressively, usually by digital rectal exam or a blood test called a PSA (prostate specific antigen). Rectal exams are a simple way to check for swelling and sensitivity. PSA levels rise in the presence of prostate cancer and are a good screening tool for this cancer. They may also indicate the effectiveness of anti-cancer treatment.

Traditional treatments include surgical removal, heat therapy, laser therapy, radiotherapy, chemotherapy, hormonal therapy and benign neglect.

Alternative therapy focuses more on slowing down the process than on curing it. Diet is important since prostatic cancer has been linked with high-fat, low-fiber diets. The use of antioxidants such as vitamin A or selenium is popular for reasons we describe below. Recently, a carotenoid called lycopene that gives certain fruits and vegetables their rich color has been linked to the prevention of prostate cancer. It seems that men who eat lycopene-rich foods (tomato sauces, dark grapes) have lower rates of prostatic disease. This theory is still under investigation.

One of the more significant series of papers to be published on glutathione and prostate cancer comes from the University of Wisconsin. Researchers there describe male hormones (androgens) as a source of oxidative stress, particularly in cancerous prostate cells. An article in the Journal of the National Cancer Institute claims that androgens stimulate free radical damage and also deplete glutathione. Give the natural decline of glutathione levels in males as they age, the article suggests that "unopposed androgen pro-oxidant stress" contributes to prostate cancer. Natural defense against oxidative stress is weakened by the decline of GSH enzymes. This is an interesting model for the development of prostate cancer.

Another finding links the loss of glutathione activity to prostate cancer. The function of a particular glutathione enzyme – glutathione S-transferase-pi-1 (GSTP1) – is almost universally lost in both cancerous and pre-cancerous prostate cells. The inactivation of this glutathione enzyme is an early event in the development of prostate cancer. Many studies have linked the loss of GSTP1 to malignant transformation of prostatic tissues.

Medical discoveries are often a matter of chance. A very large study was undertaken by the National Cancer Institute (USA) to determine whether selenium could bring down the rate of skin cancer, notoriously caused by strong exposure to sunlight. Researchers L.C. Clarke and G.F. Combs from Cornell University and the University of Arizona already knew of selenium‟s ability to raise glutathione levels and to oppose cancer-causing free radical damage from ultraviolet light. As it turned out, selenium supplementation did not affect the incidence of skin cancer, but did surprisingly and dramatically diminish the incidence of prostate cancer in the selenium supplementation group.

A more recent study from Harvard University confirms that higher selenium levels go hand-in-hand with a decreased risk of prostate cancer. It measured selenium levels in the toenail clippings of over 51,000 male health professionals between 40 and 75 years of age. Those with the highest selenium levels had the lowest chance of developing advanced prostate cancer. Note that selenium is only biologically active – and only has health benefits – when it is part of the enzyme glutathione peroxidase, through which selenium expresses its positive health benefits.

Studies using whey protein isolates such as Immunocal to raise glutathione levels are underway at several research centers including McGill and Harvard Universities, where its usefulness in the treatment of prostate cancer is being weighed.

CASE STUDY

Franklin was a semi-retired general practitioner who at age 68 scored a PSA reading of over 8 micrograms/liter on a routine screening exam, suggesting a high possibility of prostate cancer. In continued tests, an urologist took a cystoscopic biopsy and confirmed the diagnosis. Four out of Franklin‟s six biopsy sites tested positive for high-grade tumor. For personal and practical reasons, Franklin delayed aggressive treatment and opted to take 30 grams/day of Immunocal, a protein isolate that raises glutathione levels. Bimonthly PSA levels showed a gradual decline, his latest reading being 3.8 u/L. He is still being closely followed by his urologist, and his decision to undergo chemotherapy, radiotherapy or surgery will be deferred unless his PSA levels rise again.

MALE INFERTILITY

Many complicated factors play a part in the infertility that affects about one fifth of American couples. Ovulatory dysfunction accounts for 20%, tubal dysfunction for 30% and abnormal cervical mucus for 5%. These are all female problems. But male sperm disorders account for 35% of cases. The problem may be low sperm count or another abnormality of the sperm, such as impaired swimming ability.

A growing body of evidence implies that oxidative stress may cause loss of sperm function. Sperm generate an excess amount of oxyradicals and these reactive oxygen molecules may lead to lipid peroxidation (oxidation of fatty substances) in the cell wall of the sperm itself. This leads to poor movement characteristics of the sperm and their impaired ability to fuse with the female‟s ova or egg. This understanding has opened doors for the development of innovative techniques in the treatment of male infertility.

Patients with idiopathic male infertility were compared to fertile volunteers by measuring oxidative stress, antioxidant activity and glutathione levels. Urologist I. Alkan and his team found significant differences among all parameters of both groups, suggesting that oxidation may cause infertility. Similar studies conducted by F.R. Ochsendorf at the Center of Dermatology and Andrology in Germany support these findings.

A group of reproductive biology scientists led by D.S. Irvine in Edinburgh, Scotland, is raising GSH contents in male infertility patients. In a paper entitled „Glutathione for male infertility,“ he showed that GSH seems to act at the epididymis and during sperm formation as well as improving the function of ejaculated spermatozoa. Another German team headed by T. Oeda experimented with NAC (N-acetylcysteine) and showed that it reduced oxidative stress and improved impaired sperm function.

A. Lenzi‟s team at the University Laboratory of Seminology and Reproduction in Rome has published many papers on the use of injectable GSH in a variety of infertile males. These studies were human double-blind, cross-over studies and the therapy had consistently positive effects on sperm motility, morphology (structure), and semen quality.

BALDING & HAIR LOSS

Human hair varies widely in texture, color, thickness and distribution. It is a sensitive tissue, prone to loss or balding (alopecia). Alopecia universalis is a rare condition of total body hair loss. Alopecia areata is loss of hair in patches. Toxic alopecia is a common cause of hair loss, usually temporary and following serious illness, fever, pregnancy, various drugs (especially those used in chemotherapy) or overdoses of vitamin A. The most common cause of hair loss is androgenic alopecia or male-pattern baldness, which varies in pattern and severity.

Normal hair grows in cycles. Anagen is the active growing phase, catagen is a brief phase when growth slows down, and telogen is a resting dormant phase, where hair falls out, hopefully to be replaced in the next anagen phase. Research shows a positive correlation between GSH content and the percentage of anagen hairs present in a scalp sample, concluding that glutathione helps maintain the hair growth cycle. Researchers theorize that free radical formation plays a role in male pattern baldness. It is possible to measure the breakdown products of oxidative stress in bald and hairy areas of the scalp. The values are doubled in the balding areas. And correspondingly, hairy areas have almost three times as much glutathione.

In male-pattern baldness, androgens (male hormones) target hair follicles, which convert them into even stronger hormones. The unfortunate result is that hair growth slows or stops. M.E. Sawaya at the University of Miami showed that the conversion of these hormones can be influenced by glutathione, suggesting that GSH plays a protective role.

Age-related GSH losses in human hair follicles is part of the total body glutathione depletion described in chapter 6 on aging. Working at the L‟Oreal research lab, M. Kermici measured follicular GSH activity in men and women ranging in age from 19 to 102 years and found a significant decline up until about age seventy, then a slower second decline.

For many patients one of the more distressing side effects of cancer chemotherapy is hair loss. Rapidly growing cells such as hair cells and intestinal lining cells are the most sensitive to chemo-toxins, which quickly lead to temporary hair loss, and also cause diarrhea and cramps. Elevated GSH levels help protect these cells from chemotherapeutic agents and diminish their unfortunate side-effects.

The GSH precursor NAC enhances the tumor-killing effect of the drug doxorubicin on skin cancer in the lab, but also completely prevents the hair loss that normally accompanies this treatment. Other researchers have produced similar hair protective effects using NAC in cyclophosphamide and cytarabine chemotherapy.

CONCLUSION

Oxidative damage and low glutathione levels has been implicated in the onset and development of many prostate problems, including cancer. GSH supplementation may provide protection against carcinogenesis in this gland, or at least slow the development of the disease. Male infertility is associated with increased oxidative stress and low GSH levels. Elevated GSH levels may enhance the quality of sperm and increase fertility. And GSH also feeds hair follicles and may prevent or delay hair loss, especially that suffered as a side-effect of chemotherapy.

[24] AUTISM

Autism is an abnormal neurological development syndrome seen and recognized increasingly in children during the last two decades of the twentieth century. Whether the number of cases is truly on the rise or we‟re getting better at diagnosing it is debatable. In either case, most estimates suggest that from two to six of every 1,000 children is at risk, and these numbers are on the rise.

Also called autistic spectrum disorder, autism is diagnosed relatively early, usually before the age of three. One initial sign is the child‟s resistance to cuddling and affection, which may initiate a pattern of difficulty in forming interpersonal relationships. Over time, autistic children tend to withdraw into their own world and show minimal interest in family, friends and their surroundings. Language, communication skills, eye contact, physical contact and relationships never quite develop normally.

Aside from social difficulties, autistic children often exhibit repetitive body movements – such as rocking, hand flapping or finger flipping. Common symptoms include the repetition of words or phrases (echolalia) and dependence on familiar or rigid routines. Autistic children may also be unusually preoccupied with lights or moving objects. A particularly disturbing effect can be self-inflicted mutilation or other injury.

Causes of Autism

The cause for autism remains unknown. Several theories have become credible and most researchers now agree that more than one mechanism is at work. Forms of autism have been shown to run in families, so there seems to be a genetic component. Other evidence points to environmental factors. Conventional wisdom marries these two theories – a genetic predisposition towards autism that is triggered by exposure to certain environmental substances. It seems that several different forms of autism may exist. What‟s clear that older psycho-dynamic theories linking autism to parental neglect or behavior are mistaken.

Autism is associated with several diseases, including congenital rubella (German measles), Fragile X syndrome, abnormal purine metabolism, William‟s syndrome, tuberous sclerosis, Down syndrome and others.

Researchers have long sought „biomarkers‟ or specific genes that lead to autism and dozens of potential candidates have been identified – but none of them are found in every single case. For this reason autism is called a „complex disorder‟, not meaning that it‟s complicated but that it‟s not the simple result of a simple cause. Research into the causes of autism have pointed to such various factors as autoimmunity, chronic inflammatory state, exposure to teratogens in early pregnancy, viral infection, phospholipid abnormalities, oxytocin administration during birth, and exposure to toxins – notably mercury.

Any identifiable feature of autism presents scientists with a potential avenue to either prevent or treat it. Since environmental toxins – a potentially controllable circumstance – seem to be a contributing factor in the development of this disease, scientists are hard at work trying to identify the culprits.

Mercury-Thimerosal Link

In sufficient concentrations, the heavy metal mercury is a potent neurotixin. Most of the heavy metals we are exposed to come from fish, but other sources include the mercury amalgams of dental fillings, industrial pollution and some preservatives. The effects of mercury and heavy metal poisoning are discussed in Chapter 2 [GSH & Detoxification].

Mercury exposure in adults can lead to recognizable changes in nervous and mental function. Its effects on newborn and young children is less well known. Studies at the National Center for Health

Statistics, Center for Disease Control and Prevention suggest that heavy metal concentrations in about eight percent of American women of childbearing age exceeded the US Environmental Protection Agency‟s recommended exposure. Several public advocacy agencies have subsequently challenged the FDA (Food and Drug Administration), pushing for stricter guidelines for fish consumption in women and children.

Thimerosal, consisting of about 50% ethyl mercury, is an effective preservative used by the pharmaceutical industry for a range of products from contact lens solutions to immunizations. From 1988 to 2002 American children had been routinely exposed to Thimerosal during their first six months of life – and even before. Unborn children (in utero) of Rh-negative mothers were exposed when their mothers were given their „RhoGAM‟ shot. The influenza vaccination was another source of potential mercury exposure. Routine immunizations including the MMV vaccine (measles, mumps and varicella) also once contained Thimerosal. Most state governments are removing Thimerosal from many immunizations and other states seem ready to ban this preservative outright.

The question of whether Thimerosal causes autism remains hotly debated. Those who think it does point to epidemiological studies (population statistics) showing that increased use of immunizations in the United States was matched by increased rates of autism. Opponents believe that the increased numbers are due to more effectively diagnosing autism. While the debate continues and no clear answer is apparent, the conservative approach would suggest avoiding any substance with potentially devastating results. This doesn‟t mean avoiding immunizations, but avoiding the mercury-based preservatives they may contain.

Glutathione and Autism

The first easily-to-locate article on glutathione and autism dates back a quarter century to France. A team in Paris tried to identify various scenarios in which autism occurs, and were perhaps the first to discover that glutathione activity was lower in this group of patients. Other than some rare reports, also of French origin, the association between glutathione and autism was not noted in other major centers.

The work was picked up in Turkey at the dawn of the twentieth century by two groups, one of child psychiatrists and one of biochemists. Both demonstrated a statistically significant decrease in glutathione activity in autistic children as compared to healthy controls. They proposed that oxidative stress was at work, causing neurological damage.

Meanwhile, North American scientists were hard at work looking for a “cause” (etiology) for autism, but with increasing evidence that such a finding was unlikely. Back in 2003 Eigsti and Shapiro from Columbia University (NY) looked at all the work being done examining the genetic, biochemical and anatomical differences described in this disease, and bluntly stated that, “autism is a heterogeneous disorder and is likely to have multiple possible etiologies.” It seemed that answers might come by finding some pathways common to different circumstances, and perhaps intervening in these events.

Researchers attempt to intervene through dietary changes by eliminating such potential causes as gluten and casein, with some promising outcomes. Some teams focused on environmental toxins while others looked to allergens as potential culprits.

Recently, a research team led by Jill James from University of Arkansas, has started assembling the various pieces of this puzzle. Since previous studies indicated a higher load of oxidative stress in autistic children, and implicated mercury toxicity in the development of this disease, it seemed possible that glutathione played a greater role than previously thought.

The idea arose that many autistic children were unable to protect themselves from neurotoxic heavy metals. This team from Arkansas demonstrated a significant glutathione deficiency in up to four out of five cases. It was also noted that several genes normally associated with normal

glutathione metabolism were often faulty in autistic children. They went one step further and attempted to address this deficiency with dietary supplementations, with reasonable success.

Janet Kern and her associates at University of Texas Southwestern Medical Center were interested in using a dietary supplement to raise glutathione. They initiated a pilot study using the bioactive whey protein isolate Immunocal on autistic children to ensure its tolerability, since many of these children appear highly sensitive to a wide variety of foods. The bioactive isolate was well tolerated, and although not statistically relevant because of the small numbers of patients, a definite trend was observed in improvement of behavioral parameters. A much larger study is underway at the time of writing this chapter, with many researchers anxiously awaiting the results.

Although it is early to consider raising glutathione as an accepted treatment, many clinicians anticipate that further research in this direction will bear fruit. Anecdotally, several clinicians have related success stories. E. Memper, an associate professor of clinical pediatrics at the University of Virginia has been quoted as saying that many of the patients she has been involved with have shown marked improvement using this approach. Other studies are underway using intravenous glutathione.

Conclusion

Autism is a multi-factorial disease involving a combination of genetics and environmental triggers. No single “cause” for autism is likely to be found, but one notable problem identified is a deficiency in normal glutathione activity. Early trials suggest that raising glutathione has potential, and research efforts to establish this strategy are currently being investigated.

CHAPTER 25
EXERCISE & ATHLETIC PERFORMANCE

EXERCISE AND HEALTH

Statistics tell us that a sedentary lifestyle without exercise is as bad for health and longevity as smoking a pack of cigarettes a day. Countless studies show the health benefits of regular physical activity. Recent research suggests that moderate but consistent exercise may actually be more beneficial than intense workouts. The trouble is, most North Americans are not even doing enough to reach this plateau. The U. S. Surgeon General reports that 75% of American adults are physically inactive, and 25% get virtually no exercise at all. Such people are at increased risk for the most common ailments and causes of death of our times. Inactivity as a lifestyle leads to heart disease, obesity, high blood pressure, diabetes, osteoporosis, stroke, depression and certain cancers.
Fortunately, in the last decade interest in preventative health care has skyrocketed. Many people are discovering the benefits of exercise: weight control, muscle strength, bone mass and strength, increased energy, reduced stress, greater endurance, more self esteem and longevity. The fitness industry is growing quickly. Enrollment in gyms and aerobic classes, and sales of fitness supplements, bicycles, skates and blades have all reached new heights. This raises new questions, especially about how much exercise is enough and whether there is such a thing as too much. How far can we push the limits of exercise? And of course amateur and professional athletes want to know how to enhance their performance.
Even moderate exercise has a measurable impact on health and longevity. The Norwegian researcher G. Erikssen followed patients over a 22-year period and found that middle-aged men benefited from moderate fitness improvements and experienced lower risks of mortality from all causes. And it doesn‟t take extreme exertion to improve fitness. University of Washington doctor Rozenn Lemaitre recently showed that walking for at least one hour per week reduces the risk of heart attacks as much as high-intensity physical activity.
An hour three to five times per week of light, moderate or vigorous effort is all that‟s needed. A light workout can provide the same benefits as a strenuous one if it lasts longer. An hour of light walking, volleyball, easy gardening, stretching and baseball, thirty to sixty minutes of brisk walking, biking, raking leaves, swimming and dancing, or twenty to thirty minutes of jogging, aerobics, hockey, basketball or fast dancing provide similar health benefits.

AGING AND EXERCISE

Aging is associated with major alterations in body composition and exercise tolerance. Muscle mass, immune defense, antioxidant function and GSH levels all decrease. As our immune system ages, exercise workouts tax us more and more. Performance suffers. So does our ability to recover. Older women and men who participate in regular exercise therefore require more antioxidants in general and GSH in particular. Chapter 1 discusses the antioxidant role of GSH. Chapter 6 discusses GSH and aging.

EXERCISE AND THE IMMUNE SYSTEM

Exercise appears to strengthen the immune system, but too much may have just the opposite effect. Many elite athletes come down with viral illnesses when they train intensely. A widespread virus ravaged the athletic community prior to the 1996 Atlanta Olympic Games, upsetting years of hard work. However, few of us will push our immune resources to the limit. By using it in good measure, exercise can bolster our defenses against disease.
Statistical studies show that adults who exercise are ill less often than non-exercisers. The mechanisms of this increased resistance are very revealing. Many studies have found enhanced

activity of various white blood cells-our frontline defense against infection. Fit people have a greater count of natural killer cells, macrophages and T-cell lymphocytes-crucial workers in the immune system-and higher levels of virus-fighting immune factors in their blood. Some studies have shown that the saliva of athletes contains higher levels of viral antibodies, offering greater resistance to disease. This is particularly relevant since many upper respiratory infections enter through the mouth.

After several well-designed studies D.C. Nieman‟s team of exercise physiologists at the Department of Health and Exercise, Appalachian State University have said that people who exercise can double resistance to viral illness.

Although it is clear that the immune system responds positively to moderate activity, it has been repeatedly shown that too much leads to a winding down of the immune systemimmunosuppression. After a certain time the increase in immune factors and white cell activity initiated by exercise becomes blunted. This period depends on the intensity of the activity and the condition of the athlete‟s defenses. Dozens of articles have documented a temporary immune deficiency following exhaustive training. Tests conducted on marathon runners revealed that those running over 60 miles per week were twice as likely to catch a cold than those running 20. Some of these effects can be avoided by balancing and regulating nutrition and training levels.

OVER-TRAINING SYNDROME

Besides the obvious possibility of physical injury, serious athletes run the risk of contracting all sorts of sickness. Their weakened immune response following exhaustive training is only one aspect of „over-training syndrome.“

Adjectives like „burn-out“, „staleness“ and „plateauing“ are used by athletes to describe the physical sensation. Some respond stubbornly by pushing even harder, with increasingly negative effects. Some exercise scientists have shown that decreasing the intensity of workouts may actually improve performance.

The over-trained athlete experiences a host of physiological effects that contribute to poor performance and illness. They include fluctuations in insulin secretion, alterations in glucocorticoid and hormone levels, inhibition of glucose uptake to tissues, catabolic (breakdown) effects on protein and nitrogen excretion and lactic acid over-production.

OXIDATIVE STRESS

While working out, athletes may consume ten to fifteen times more oxygen than usual, so oxidative stress is a major factor in exercise. Physical activity increases oxygen consumption and intensifies numerous metabolic processes. The result is the creation and circulation of liberated oxidative breakdown products, free radicals (see chapter 1).

Some scientists believe that free radicals might play a significant role in the events leading up to muscle inflammation and damage. More and more evidence supports this theory. When cells need more energy their mitochondria (power plants) work harder. In addition to increasing energy, this also boosts production of unhealthy by-products and results in lipid peroxidation-the harmful oxidation of fats. Bad cholesterol and fats, for example, are rendered even more harmful by peroxidation. Another consequence of increased mitochondrial activity is electron transport flux-the chain reaction of atoms snatching each other‟s electrons and gradually destabilizing cellular structure (see chapter 1). These two threats can be countered both by exogenous antioxidants-derived like vitamins C and E from food sources-and endogenous ones-those produced within the body. The most critical of these in-house antioxidants is GSH.

The body is not entirely defenseless. Exercise also increases the level and activity of many antioxidants. A well-trained body will adapt to increased oxidative stress by developing improved

physiological mechanisms, but the drive for better performance can overtake these adaptations and lead to increased muscular fatigue, injury and recovery time. And antioxidants can easily be depleted by over-training. We therefore strongly encourage the use of oral antioxidant supplements.

GSH AND ATHLETIC PERFORMANCE

Because antioxidants are especially critical to those who exercise, researchers have spent considerable time observing and testing them. This research has two possible goals. To avoid the negative potential of over-training and to explore the possibility of improving performance. A great deal has been written about the role of antioxidants in sports physiology. As you might imagine, much of this research is focused on the body‟s most important endogenous antioxidant-glutathione. Elevated glutathione levels provide better immune defenses and reduced susceptibility to infectious disease. They also help decrease recovery time from workouts, reduce muscle fatigue and soreness and increase performance.

L.L. Ji, C. Leeuwenburgh and a group of researchers at the University of Illinois carried out a series of studies on muscle injury influenced by free radical formation. Their objective was to measure the usefulness of GSH in cellular damage control. It is not easy to test the body‟s adaptive response to exercise. Two metabolic processes in particular are somewhat unpredictable. One is the variability of GSH levels at any particular site. The other relates to the transport of GSH between tissues. Never-theless, GSH levels were seen to vary in proportion to the level of exertion, the individual‟s fitness, and his/her nutritional status.

Measuring GSH levels before, immediately afterward, hours after, and days after subjects completed a long-distance run, B. Dufaux‟s experiments revealed a significant drain of glutathione. Recovery of GSH levels was quite variable, taking from hours to days. Subjects remained susceptible to subsequent illness or injury. Similar studies were conducted on cyclists and other athletes. In all cases, GSH levels in muscle tissue were found to fall with exercise.

Researchers have shown that glutathione levels are more efficiently restored in the elite athlete than in the less well trained. General bodily fitness encourages the manufacture of GSH and its more efficient release from tissues. Some scientists have gone one step further, suggesting the exercise slows the aging process by increasing one‟s ability to produce and distribute GSH on demand.

It is known that diabetics in particular can benefit from exercise. This is believed to result in part from the enhanced GSH metabolism of a fit body. It helps diabetics deal with the intense oxidative stress from which they characteristically suffer (see chapter 10). Training in good measure stimulates greater GSH reserves and enhances one‟s ability to detoxify foreign substances. Tests have shown that well-exercised animals suffer less from acetaminophen toxicity than non-active ones. Some theorists even believe that the enhanced glutathione metabolism following exercise explains why the physically fit suffer less from cancer.

Given all this, it seems useful to take antioxidant or GSH-enhancing supplements prior to intensive exercise. J. Sastre and his group from the University of Valencia in Spain tested this idea using vitamin C, NAC (see chapter 4) and GSH on animal subjects. The result was to successfully reduce oxidative damage and maintain reduced glutathione in blood reserves. Another group at the University of California (Berkley) headed by C.K. Sen proved the corollary-that if greater levels improved antioxidant response, lower levels would worsen it. They forced GSH levels down with the drug BSO and the ability of their subjects to endure exhaustive exercise fell by 50%.

Psychologists investigating the role of GSH in the immune response to exhaustive exercise have shown raised GSH levels to increase the number and activity of white blood cells. Other studies show that taking NAC before a workout diminishes oxidative stress within these white blood cells. Further studies conducted at Baylor College of Medicine in Texas, first on rodents and later on

humans, showed that intravenous NACwhich raises GSH levels-enables subjects to perform longer and harder in exhaustive muscle tests.
A dramatic example of increased muscle strength comes from Dr. Larry Lands of McGill University, Montreal. Thinking that oxidative stress contributes to muscular fatigue, his team gave young adults the whey-based GSH precursor Immunocal for three months. During this time they measured peak power and work capacity as indicators of strength and endurance. They found that performance values could be enhanced by a remarkable ten to fifteen percent.
A team at the Peak Wellness Lab in Connecticut examined the effects of whey isolate protein on athletes. They showed that dietary supplementation of this protein could maintain white blood cell levels (CD4 T-lymphocytes and neutrophils) that otherwise fall during extremely intense workouts. Whey proteins have an extraordinarily high „protein biological value" and are extremely effective in meeting the higher protein demands of athletes, who may require as much as two or three times as much as the average person. For this reason, whey protein is used widely in weight training to increase body mass. Another study was carried out on AIDS and cancer patients in an attempt to counter the muscle loss (catabolism) they often suffer. This resembles the muscle decline resulting from heavy exercise protein breakdown. A German group led by R. Kinscherf found that NAC-supplemented group undergoing anaerobic exertion lost less body cell mass and interestingly carried less total body fat. The shift of body fat to body muscle is a strong focus in weight training.

CASE STUDY

Susan, a 35 year-old fashion merchandiser and mother of two, was a great fitness advocate. Free weights, aerobics, step and spinning classes-over fifteen years she had done them all. She was persistently dissatisfied about "the ten pounds of fat" that prevented her from achieving the muscular definition she wanted. Nutritionally conscious, she also knew that merely restricting her calories would probably just leave her feeling washed out. She started taking 40 grams/day of whey protein isolate in combination with minimal adjustments in fat and carbohydrate intake. In three weeks she noticed better endurance during her cardiovascular workouts and was able to lift heavier weights with greater intensity. Recuperation between workouts improved, enabling her to continue without the usual soreness. Her weight remained unchanged. Despite not having made any great changes to her routine, six weeks after the dietary supplement, people at the gym commented on how "well cut" she was.
John, a national champion cyclist, understood the phenomenon of over-training and its consequences on the immune system. He and his training partners were quite aware of their tendency to get sick before big events if they pushed too hard. Having two children in day-care certainly exposed him to viral illnesses. Hearing that the product Immunocal had potential immune-boosting effects, he incorporated it into his daily diet. The frequency of viral illnesses decreased and when he did get sick, it was for only a day or two, rather that three or four. To his surprise, his performance times were improved as well as his ability to recover faster from grueling competitions. After some initial hesitancy, he shared the advantages of this product with his teammates.

CONCLUSION

The health benefits of exercise cannot be overstated. Simply put, physically fit individuals are statistically more resistant to illness and live longer. They also show increased antioxidative abilities. This is visibly reflected in glutathione metabolism. However, moderation is crucial. Exercise is not without risk. Over-training may lead to immune deficiency states, prolonged fatigue and depletion of antioxidants, especially GSH.

Research into exercise physiology shows raised GSH levels to increase immune function, help resist infection, decrease muscle damage, reduce recovery time, increase strength and endurance and shift metabolism from fat production to muscular development.

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THE AUTHOR

Dr. Jimmy Gutman is a world-wide expert on the role of glutathione in health and sickness. He is often heard on radio and television and lectures regularly to medical specialists and the general public all over North America.

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