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COMMON CAUSES OF
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INTRODUCTION

This publication is meant to provide a user-friendly yet fully documented overview of the role, relevance and effectiveness of our product, patented milk serum (whey) protein concentrate (WPC), in today's world.

Firstly, a brief review of common causes of glutathione (GSH) depletion and of GSH's role in increasing the body's resistance to these challenges will be presented: Secondly, an article by Dr. Gustavo Bounous will provide the reader with the opportunity to take a closer look at the following:

- how GSH is formed and its role in maintaining optimal function of the immune system;
- the role of the patented WPC including its effect on the immune system and its benefits similar to those of human milk, as well as its potential role in cancer prevention and the diseases of aging;
- the limits of other strategies aimed at increasing tissue concentration of GSH; and
- finally, the success of our milk serum protein concentrate in sustaining GSH levels, including discussion of its potency and bioactivity.

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COMMON CAUSES OF GLUTATHIONE (GSH) DEPLETION

A number of conditions may coexist, each of which places on the body a demand for GSH. Such conditions include:

- Production of endogenous oxyradicals during immune activity and strenuous muscular exercise;
- Detoxification of foreign pollutants; and
- Protection against radiation.

It is conceivable that during severe challenge, competition for GSH precursors may lead to single or multiple functional deficiencies. Global warming empowers microbes which are now expanding both in number and diversity. Thus, to make matters worse, the GSH-requiring immune system must now compete for GSH precursors with organs increasingly involved in the body's defense against pollutants and ultraviolet radiation resulting from ozone depletion.

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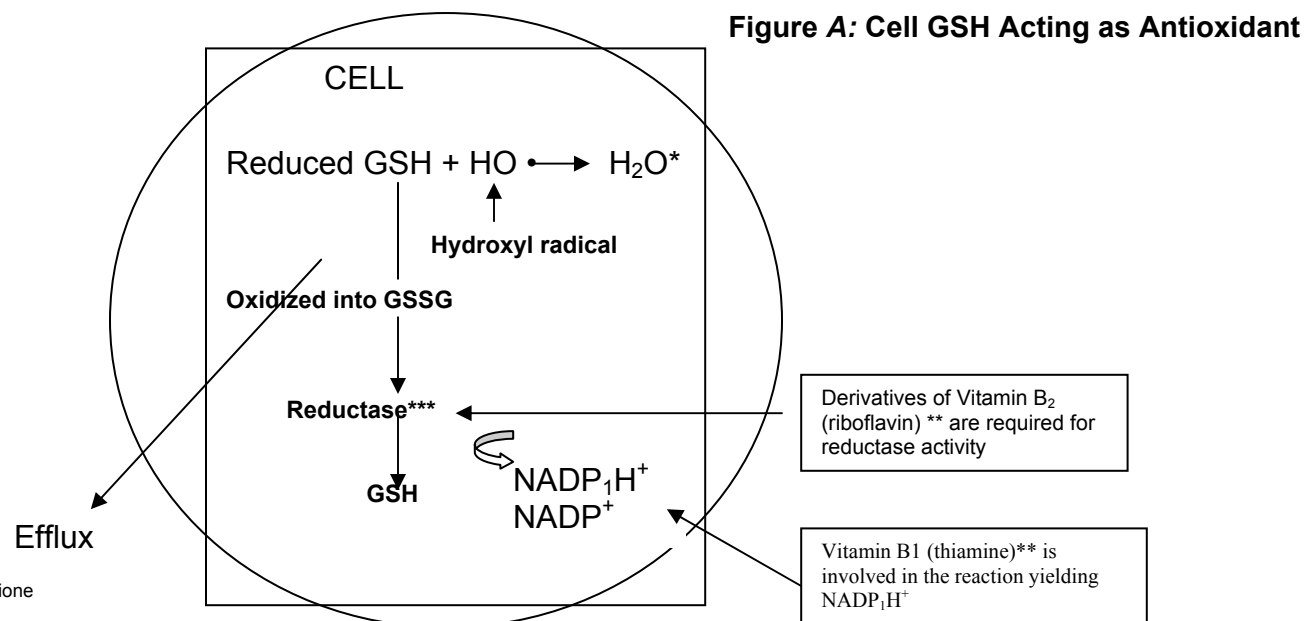
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CRUCIAL ROLE OF CELL GSH

Cell GSH is involved in increasing body resistance to challenges in many ways.

Role as Antioxidant

Figure A illustrates the antioxidant properties of cell GSH. As shown in the figure, reduced GSH is oxidized into GSSG in the process of destroying oxyradicals. GSSG is then reduced back to GSH by the action of GSH reductase.



* Water

** Both vitamins naturally occurring in whey

*** An enzyme involved in reducing oxidized glutathione (GSSG) into reduced glutathione (GSH)

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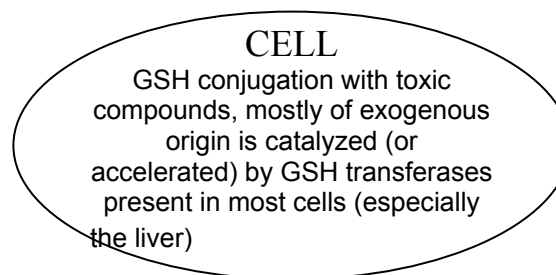
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Role as Detoxifying Agent

Figure B summarizes the role of GSH in detoxification. This process requires resynthesis of GSH, as indicated in the figure.



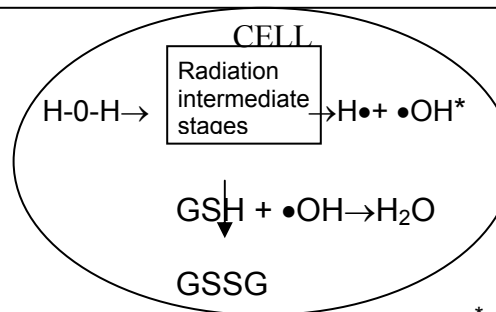
Process Requiring Stimulation Of GSH Resynthesis

Extracellular degradation of GSH conjugates and elimination into bile or urine

Role as Protection against Ultraviolet Radiation

Figure C illustrates the role of GSH in fighting increased ultraviolet radiation resulting from ozone depletion. Here again, GSH reductase reconstitute oxidized GSH to its functional status.

Figure C: Cell GSH Acting as Protection against Ultraviolet Radiation



Increased ultraviolet radiation resulting from ozone depletion

*•OH is the most reactive radical known to chemistry

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A Closer Look at the Central Protective Role of Glutathione (GSH) against Free Radicals Infections and Chemical Pollutants, and at Milk Serum (Whey Protein Concentrate, a Natural Source of GSH Precursors

Gustavo Bounous, MD

Mammalian cells have evolved numerous mechanisms to prevent or treat injurious events that can result from normal oxidative byproducts of cellular metabolism. **The “glutathione (GSH) antioxidant system” is foremost among these endogenous protective systems because GSH participates directly in the destruction of reactive oxygen compounds and maintains in reduced active form vitamins C and E, which also exert an antioxidant effect.¹ In addition, GSH detoxifies foreign compounds.²** For these reasons, cellular GSH plays a central role in body defense against infection, free radicals and carcinogens. It is not surprising that the liver, which is the major organ involved in the detoxification and elimination of toxic materials, has the greatest concentration of GSH.³

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How GSH is Formed

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The sulfhydryl (thiol) group (SH) of cysteine is responsible for the chemical properties of the whole GSH molecule (L-gamma-glutamyl-Lcysteinylglycine). As systemic availability of oral GSH is negligible in man⁴ and because there is no evidence for transport of GSH into cells,^{2,3} **GSH has to be synthesized intracellularly.** Though the inflow of cysteine, glutamate, and glycine (components of GSH) may prove somewhat limiting under selected circumstances, **numerous observations have shown that cysteine tends to be the rate limiting event in GSH synthesis.**

However, free cysteine does not represent an ideal delivery system: it is toxic⁵ and spontaneously oxidized.

Cysteine present as cystine—a natural delivery system

On the other hand, **cysteine present as cystine** (two cysteines linked by a disulfide bond) released during digestion in the gastrointestinal tract is more stable than the free amino acid: the disulfide bond is pepsin- and trypsin-resistant, but may be split by heat and mechanical stress.⁶

Thus, cystine travels safely in the body and is promptly reduced to the two cysteine molecules on cell entry.⁷

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GSH and the Immune System

It has been demonstrated that **the ability of lymphocytes to offset oxidative damage (during their oxygen-requiring clonal expansion and following that expansion in the production of antibodies, and helper-CD4 and cytolytic-CD8 T lymphocytes) is measured by determining the capacity of these cells to regenerate intracellular stores of GSH, therefore allowing them to respond more fully to the antigenic stimulus.**^{8,9}

Evidence from studies related to HIV infection

More evidence for the involvement of GSH in the modulation of immune function comes from studies related to HIV infection. Staal et al showed that HIV-infected individuals have lower GSH concentrations in their blood lymphocytes.¹⁰ Moreover, a recent study indicates that the more GSH the patients carry in their CD4 helper T-cells—the cells primarily targeted by the HIV virus—the longer these patients are likely to survive.¹¹

Conditions which facilitate cellular GSH replenishment or maintenance are thus expected to optimize the activity of the immune system.

Milk Serum (Whey) Protein Concentrate

In the early 1980s,¹²⁻¹⁴ it was discovered that normal mice fed a **whey protein concentrate (WPC), especially prepared under mild non-denaturing conditions, exhibited a marked increase in antibody production in response to a T cell dependent antigen.** This product (hereafter designated as “the patented WPC”) was patented in recognition of its immunosustaining and GSH promoting activity. The immunosustaining effect of the protein mixture, unrelated to its nutritional efficiency, was further confirmed by the demonstration of the protective effect of this dietary treatment against pneumococcal infection.¹⁵ This unique property has been defined as the “bioactivity” of the product.

Cellular GSH is a tightly regulated system; hence, substantially increased values are not anticipated in normal animals. There is, however, an increased demand for GSH during the proliferation of lymphocytes in the development of an immune response and, following that expansion, in the production of antibodies, and helper and cytolytic T lymphocytes.

When GSH stores are “used up,” or depleted, the bioactive proteins present in the patented WPC help maintain GSH levels, thus supporting an optimal immune response.

Effect on the immune response

The patented WPC differs from other proteins, including most commercial WPCs, in the following way.

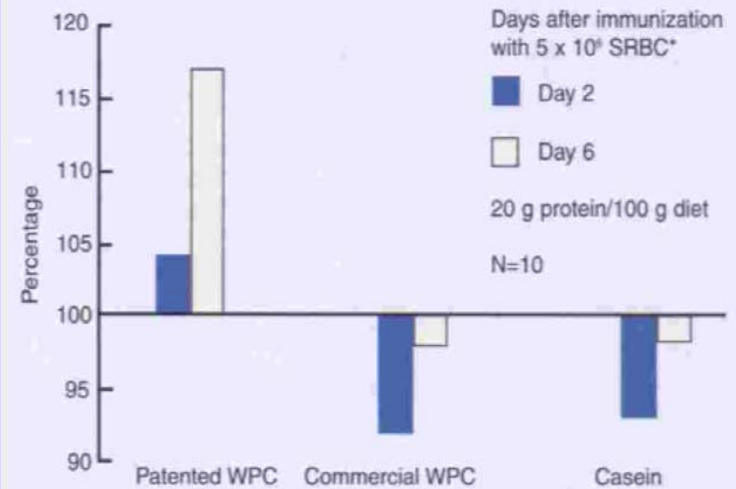
Under normal conditions, at a 20% concentration in the diet, all proteins have been found to exhibit similar nutritional efficiency as measured by body weight, serum protein, circulating lymphocytes¹²⁻¹⁶ and, more specifically, genesis of B lymphocytes in bone marrow.¹⁷ **However, our milk serum (whey) protein concentrate was shown to differ from other proteins in its effect upon the immune response.**

As illustrated in Figure¹, optimization of the immune response in animals fed the patented WPC is attributed to a greater production of GSH in their lymphocytes through continuous dietary provision of supplementary doses of GSH precursors.¹⁶ In addition, when lymphocytes are taken from normal animals which have been fed the patented WPC for a long period of time and cultured in vitro, these cells retain the ability to provide an increased response to an immune stimulus. Thus, this product not only increases intracellular levels of GSH or GSH precursors at the time of ingestion, but also builds up a store of these substances inside the cells, which lasts for considerable periods thereafter.¹⁸

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Figure 1: Lymphocyte GSH as Percentage of Values in Unimmunized C3H/HeN Mice Fed the Corresponding Diet (Patented WPC, Commercial WPC or Casein) for Three Weeks



*Sheep red blood cells

Cysteine/cystine, crucial GSH-promoting components

In the early years of our studies, this newly discovered property was found on a sporadic basis, varying from batch to batch of whey (milk serum) protein concentrates. **It was subsequently realized that the product's bioactivity was dependent upon a critical concentration of three bioactive proteins contained in the milk serum: i.e., the thermolabiles—serum albumin, alpha lactalbumin and lactoferrin.**

When undenatured, these proteins contain almost the same number of cystine residues per total amino acid.^{19,20} Hence, in serum albumin, there are 17 cystine residues per 66,000 MW molecule, and six glutamylcystine (Glu-Cys) dipeptides;¹⁹ in lactoferrin, 17 cystine residues per 77,000 MW, and four Glu-Cys dipeptides;²⁰ and in alpha-lactalbumin, four cystine residues per 14,000 MW molecule.¹⁹ Conversely, beta-lactoglobulin has only two cystine residues per 18,400 MW molecule¹⁹, and IgG1, the predominant immunoglobulin in cow's milk serum, only four disulphide bridges (cystine) per 166,000 MW molecule. In addition, it has been demonstrated that the Glu-Cys precursors of GSH can easily enter the cell to be synthesized into GSH. Interestingly, the Glu-Cys dipeptide is an exclusive feature of the only obligatory foods in the early life of mammals and oviparous species, i.e., milk and egg white respectively.⁶

Throughout the digestive-absorptive process, the other coexisting protein fractions of whey (milk serum) influence the rate of release of the GSH precursors to the blood, thus affecting the bioavailability of these crucial ingredients. Figure 2 (page 8) summarizes results obtained in studies serving to clarify the role of cysteine/cystine as GSH precursors in the immunosustaining activity of specially prepared dietary WPCs, and illustrates the higher potency of our product, the patented WPC. As shown in the figure, peak antibody production by spleen lymphocytes (number of plaque-forming cells) is measured after challenge with sheep red blood cells in C3H mice fed different protein-type diets of similar nutritional efficiency. **A higher immune response is exhibited in animals fed WPC, the response being highest with WPC containing more cystine (the patented WPC).**

Benefits similar to those of human milk

Using modern technology; we have succeeded in obtaining and consistently preserving, in their native form, the specific cow's milk proteins which share with the predominant human milk proteins the same extremely rare GSH-promoting components, as illustrated in Table 1 (page 8).

The patented WPC may thus be considered as a humanized native milk serum protein isolate; the natural benefits of mother's milk for the human baby are now available to the adult population by the oral administration of this health-promoting protein mixture. Breast-feeding is known to be superior to cow's milk-based formulas of similar nutritional efficiency with regard to the health of human babies; for example, it protects against otitis media and pneumonia.^{21,22} Mother's milk also has a protective effect on the incidence of several types of childhood cancers including leukemia, lymphomas, bone tumors and brain tumors.²³ Children who are artificially fed or breast-fed for only a short time are at increasing risk for developing several types of cancers before age 15 as compared to long-term breastfeeders.²⁴

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The search for the potential mechanism of immuno-enhancement by milk serum (whey) protein dietary supplementation has revealed the provocative possibility that whey protein may contribute to a broader biological effect of a protective nature with regard to susceptibility to cancer and diseases of aging, as well as general detoxification of environmental agents. Cancer and diseases of aging all appear to be somehow related to a drop in GSH—an ubiquitous element exerting a protective action against oxyradicals and other toxic agents.

The two major theories on the origin of cancer both implicate GSH as a putative protective factor owing to its dual function as antioxidant and detoxifying agent. It has been suggested that the underlying mechanisms of aging and carcinogenesis are closely related, since the incidence of cancer increases progressively with age in humans and experimental animals. Indeed, theories of aging based on the accumulation of nonrepairable lesions over time—such as the free radical theory—are similar to theories explaining the origin of certain tumors. Others attribute the aging-associated increase in cancers to accumulation of carcinogens and increased exposure to the action of carcinogens with time.²⁵ In fact, at least 12 carcinogens have been shown to be detoxified by GSH conjugation. These are: aflatoxin B₁, N-acetyl-2-aminofluorene, benz-(a) anthracene, benz (a)pyrene, benzidine, dimethylhydrazine, dimethylnitrosamine, ethylmethane sulfonate, N-methyl-4-aminoazobenzene, 7-methylben-zanthracene, 3-methyl-cholanthracene, and 1-nitropyrene³³⁸

As well, a University of Wisconsin study convincingly showed that physiological levels of androgens are capable of decreasing the GSH content in human prostatic androgen-responsive cells, which could provide a mechanism by which androgen exposure promotes prostate carcinogenesis.³⁹ Conversely, a slightly higher GSH level in the colon, obtained, by whey protein feeding, is associated with a lower tumor burden in an experimental model of human colon carcinoma (see Figure), again suggesting that tissue GSH levels modulate tumorigenesis.

A further argument supporting the preventive role of GSH with regard to tumor development is the fact that GSH decreases in aging humans and experimental animals.⁴⁰⁻⁴⁸ Figure 3 summarizes results of studies conducted to illustrate the potential role of WPCs in cancer prevention.

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Figure 2: Results of Studies Demonstrating the Immunosustaining Role of Specially Prepared Dietary WPCs

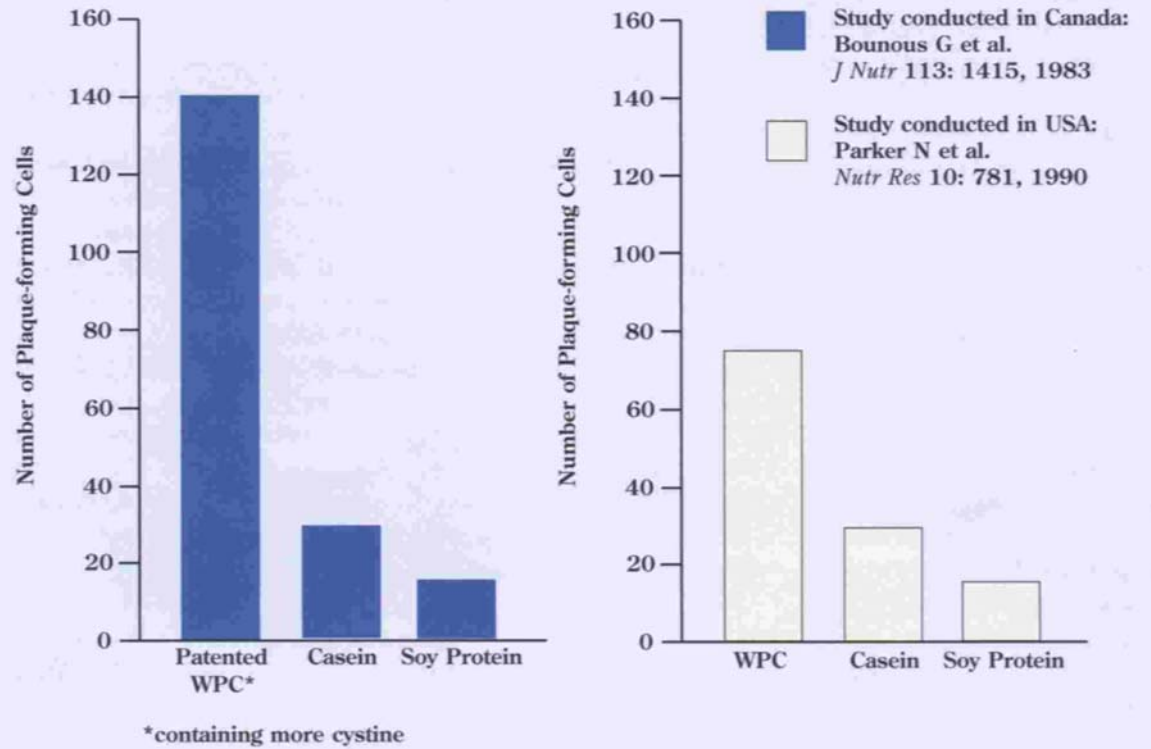


Table 1: Protein Composition of Cow's and Human Milk

Protein	Composition (g/L)		
	Cow's Milk	Human Milk	Cystine/Molecule
Casein	26	3.2	0*
Beta-lactoglobulin	3.2	Negligible	2
Alpha-lactalbumin	1.2	2.8	4
Serum albumin	0.4	0.6	17
Lactoferrin	0.14	2.0	17
Total cystine (mol/L)	8.19 x 10 ⁻⁴	13.87 x 10 ⁻⁴	
Total cystine (mg/g of proteins)	6.4	38.7	

*Casein has 0 to 2 cysteine/molecule.

Adapted from : Jenness R. Inter-species comparison of milk proteins. In : *Developments in Dairy Chemistry-1*. Fox W. (Ed.). 4 ASP NY : 87, 1982; and Eigel WN, Butler JE, Ernstrom CA, Farrell HM et al. Nomenclature of proteins of cow's Milk. Fifth revision. *J Dairy Sci* 67 : 1599-631, 1984

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GSH and the Diseases of Aging

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The free radical theory of aging⁴⁹ hypothesizes that degenerative changes associated with aging result from toxic effects of free radicals produced during cellular metabolism. Aging is thus considered to be caused by the products of the normal physiological metabolic processes of life. One approach taken to verify the free radical theory of aging has been to determine whether any age-related changes occur in cellular antioxidative protective mechanisms.

One such principal mechanism is GSH, an ubiquitous cellular constituent and the most abundant thiol-reducing agent in mammalian tissues. It appears that, whereas data on age-related changes in tissue vitamin E and other antioxidants are, at best, contradictory,⁴⁹ reports that tissue GSH levels decline with old age are more consistent. Thus, GSH contents of the liver, kidney,⁴⁰ heart and brain⁴¹ were found to be respectively 30%, 34%, 20% and 30% lower in very old mice as compared to mature mice. Recently, an increased incidence of low blood GSH levels in apparently healthy elderly subjects as reported.⁴² More specifically, some characteristic age-related diseases, such as Alzheimer's disease⁴³, cataracts,⁴⁴ Parkinson's disease,^{45,46} and arteriosclerosis,⁴⁷ appear to be preceded by or associated with a drop in GSH content in the organ or systems involved.

Our experimental studies have shown that long-term administration of the patented milk serum protein concentrate diet in old mice slightly increases their heart GSH content; it also increases their life span by about 30%⁴⁸ when administered to 21-month-old mice. (The corresponding human age from the survival curves for males in the industrialized world would be 55 years). These data are consistent with two previous studies in hamsters investigating the effect on longevity of dietary milk serum protein in nutritionally adequate and similar diets. In lifetime-feeding studies, survival was reported to be better in hamsters fed 10, 20 or 40 g milk serum protein/100 g diet in comparison with those fed a commercial laboratory diet containing an estimated 24% protein from various sources: hamsters fed the 20% level of milk serum protein survived the longest.⁵⁰ In another study, survival of hamsters during the first 20 weeks was better in animals fed the 20 g milk serum protein/100 g diet than in those fed a corresponding methionine- and cysteine-enriched casein diet.⁵¹

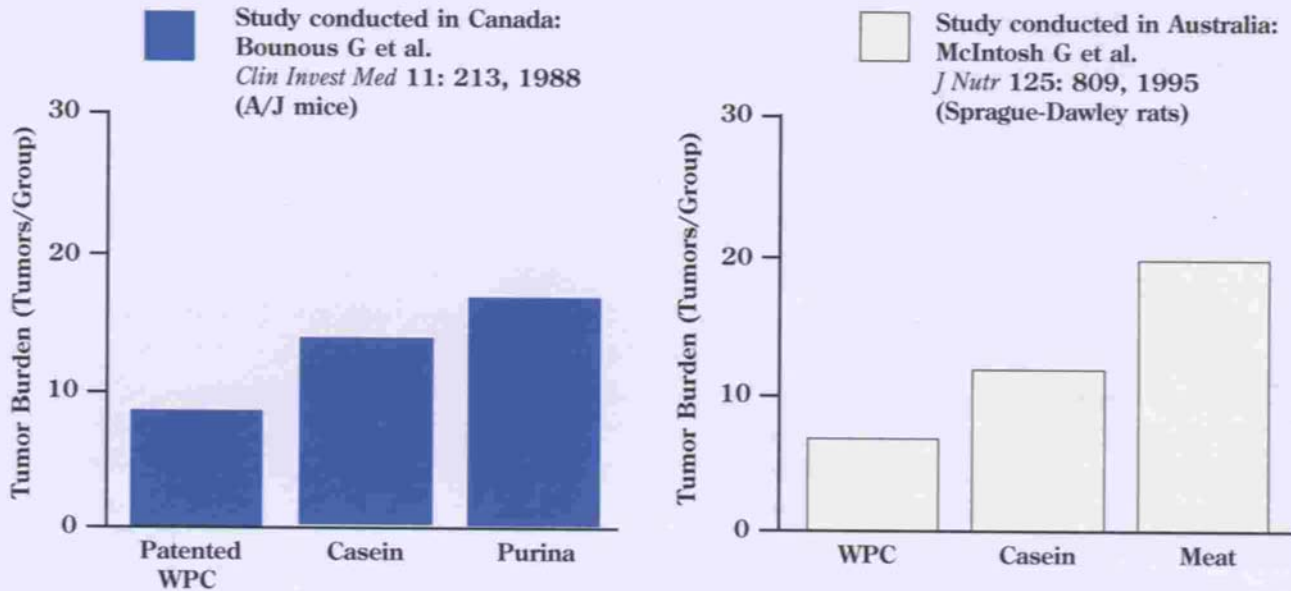
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1. Enker WE, Jacobits JL. Experimental carcinogenesis of the colon induced by 1,2-dimethylhydrazine-dl HCL : Value as a model of human disease. *J.Surg Res* 21 : 291, 1976.
2. Corbett TH, Griswold DP, roberts GJ, Peckham JC et al. Evaluation of single agents and combinations of chemotherapeutic

Figure 3: Results of Studies Demonstrating the Role of Specially Prepared Dietary WPCs in Cancer Prevention

Carcinogen was dimethylhydrazine-dihydrochloride (DMH), which induces colon tumors similar to those found in humans (with regard to type of lesions¹ and response to chemotherapy²). The diets were fed before and throughout the 24-week DMH-treatment period. No differential effect of diet on body weight was seen.



Colon GSH

WPC	casein	meat
1.01	0.92	0.92

“...These findings confirmed and extended earlier observations of a Canadian research group [Bounous et al, 1991] that also identified dairy proteins, and whey protein in particular, as being protective against the development of intestinal cancers induced by DMH.”

Tumor mass was lower in mice fed patented WPC than in mice fed casein or purina.³

No significant difference in tumor mass was noted among the treatment groups.

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Although cellular GSH is decreased in old age, conditions known to favor GSH replenishment or sustainment—such as feeding of milk serum protein concentrate—are shown to prolong life expectancy. This strongly suggests that aging cells are able to synthesize sufficient amounts of GSH when provided with an increased supply of its natural precursors.

As mentioned in the section on GSH synthesis (see page 5), administration of GSH by oral or intravenous routes does not have a sustained effect in increasing tissue GSH concentration even in GSH depleted cells.⁵² GSH monoethyl ester was found to lead to an approximate doubling of the kidney and liver GSH levels two hours after injection to normal mice, with return to preinjection values eight hours later.⁵³ However, metabolism of GSH monoethyl ester will release ethanol;⁵⁴ ethanol is metabolized to acetaldehyde which, in high concentration, can conjugate and deplete GSH.

Oral supplementation of sulfur amino acids can replete tissue GSH,⁵² but cysteine and methionine are toxic at high doses;⁵⁵ in addition, cystine is readily catabolized.⁵² The limitations of sulfur amino acid administration can be overcome by cysteine pro-drugs that are converted intracellularly to cysteine.

N-acetylcysteine administered to patients by the oral or intravenous routes transiently increases GSH concentrations in plasma and erythrocytes⁵⁶, and is used as an antidote for acetaminophen toxicity in humans.⁵⁷ Oral N-acetylcysteine may however result in nausea and diarrhea; with intravenous administration, some patients may experience anaphylactic reactions⁵⁸ and other unacceptable side effects.⁵⁹

Another cysteine pro-drug, oxothiazolidine-4-carboxylate (OTC), was found to restore GSH levels in the liver of mice that had previously been depleted of GSH.⁶⁰ OTC supplementation, however, does not escape factors such as feedback inhibition and nutritional regulation of GSH synthesis.⁵²

Basically, these methods offer an interesting possibility for short-term intervention—as, for example, in acute liver failure—but their long-term effectiveness in producing sustained elevation of cellular GSH has not been confirmed, nor has the potential toxicity of their long-term use been disproved.

Conversely, oral administration of natural GSH precursors found in the patented WPC has been shown to produce significant, rapid GSH replenishment in lymphocytes during the GSH-depleting immune response in mice,¹⁶ as well as a moderate but sustained increase in organ GSH of old mice (following long-term administration).⁴⁸

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Moreover, a Canadian clinical trial with the patented WPC was conducted in children with AIDS and Wasting Syndrome over a six-month period. Patients who started the study with low blood-lymphocyte GSH exhibited a substantial increase in GSH content.⁶¹ A most recent clinical trial showed that a three-month administration of the patented WPC to patients with hepatitis B restores GSH concentrations in lymphocytes to normal values.⁶²

Finally, the success of this form of dietary treatment, using natural GSH precursors and by the previously mentioned methods, clearly indicates that, in most experimental or clinical conditions characterized by GSH depletion, the capacity of the cell to synthesize GSH is maintained. **Hence, optimal concentration of GSH can be obtained through an adequate “cysteine delivery system,” such as the one provided by our patented milk serum protein concentrate.**

Potency and bioactivity of the patented milk serum (whey) protein concentrate (WPC), a key characteristic

In animal studies, WPCs constitute the only protein component of the diet. This is of course not feasible for humans, for whom a protein-free diet is impractical even in a hospital setting. Therefore, WPCs must be taken by humans as a protein supplement.

Here is where the important question of potency comes into play. For example, in a comparative *in vivo* study, we found that commercial WPCs containing substantially less cystine rich proteins exhibit a marginal bioactivity, or none at all.⁶ Recently, similar results were obtained using an *in vitro* assay of GSH synthesis by normal human lymphocytes.⁶¹ **It is therefore essential to provide a milk serum isolate such as our product in which the ratio of active ingredients—such as cystine—to other amino acids allows biological activity to be obtained without overloading the system with nitrogen.**

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This article has addressed the central role of GSH in providing protection against endogenous oxyradicals and foreign pollutants. As an antioxidant, GSH is essential for allowing the lymphocyte to express its full potential, without being hampered by oxyradical accumulation during the oxygen-requiring development of the immune response. In a similar fashion, GSH delays the muscular fatigue induced by oxyradicals during the aerobic phase of strenuous muscular contraction.

It is, however, the second function of GSH – that of detoxification of chemical pollutants, carcinogens and ultraviolet radiation – that may well be of greater concern to medical science today, because of the ever-increasing demand on GSH as the major detoxifying agent. Under normal circumstances, a nutritionally balanced diet should provide sufficient precursors of GSH to allow for intracellular synthesis of adequate amounts of GSH. But in our current polluted environment, trace amounts of precursors found in an otherwise adequate diet may not be sufficient to allow for full GSH replenishment. This results in highly undesirable competition for GSH precursors developing amongst different systems. Cysteine prodrugs have helped clarify the essential role of GSH in athletic performance, immune function, AIDS, etc., but their effect is short-lived and their long-term use is not without adverse effects.

Using modern technology, it has been possible to obtain and consistently preserve, in their native form, the specific cow's milk proteins which share with predominant human milk proteins the same extremely rare GSH promoting components. This product—the patented WPC—differs from most commercial WPCs in that it contains the active ingredients—notably cystine and glutamylcystine—in undenatured form and an amount sufficient to exhibit its potency when given as a dietary supplement, without overloading the system with excessive nitrogen intake.

It is therefore possible to obtain, with the patented milk serum protein concentrate, long-term moderate but sustained intracellular elevation of GSH and GSH precursors so that, when the challenge occurs, an efficient cellular response can be achieved.

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References

CRUCIAL ROLE OF CELL GSH

Role a Detoxifying Agent
Role as Protection against Ultraviolet
radiation

EVIDENCE

- [How GSH is Formed](#)
- [GSH and the Immune System](#)
- [GSH in Cancer Prevention](#)
- [GSH and the Diseases of Aging](#)
- [Limits of Other Strategies to Increase Tissue GSH Concentration](#)
- [Success of the Patented WPC in Sustaining GSH Levels](#)
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