

# WHEY PROTEIN CONCENTRATE (WPC) AND GLUTATHIONE MODULATION IN CANCER TREATMENT

*Gustavo Bounous, M.D., F.R.C.S. (C)*

## **ABSTRACT**

The glutathione antioxidant system is foremost among the cellular protective mechanisms. Depletion of this small molecule is a common consequence of increased formation of reactive oxygen species during increased cellular activities. This phenomenon can occur in the lymphocytes during the development of the immune response and in the muscular cells during strenuous exercise. It is not surprising that so much research has been done, and is still being done on this small tripeptide molecule. Whey protein concentrate has been shown to represent an effective and safe cysteine donor for GSH replenishment during GSH depletion in immune deficiency states. Cysteine is the crucial limiting amino acid for intracellular GSH synthesis. Animal experiments showed that the concentrates of whey proteins also exhibit anti-carcinogenesis and anticancer activity. They do this via their effect on increasing GSH concentration in relevant tissues, and may have anti-tumor effect on low volume of tumor via stimulation of immunity through the GSH pathway. It is considered that oxygen radical generation is frequently a critical step in carcinogenesis, hence the effect of GSH on free radicals as well as carcinogen detoxification, could be important in inhibiting carcinogenesis induced by a number of different mechanisms. Case reports are presented which strongly suggest an anti-tumor effect of a whey protein dietary supplement in some urogenital cancers.

This non toxic dietary intervention, which is not based on the principles of current cancer chemotherapy, will hopefully attract the attention of laboratory and clinical oncologists.

**Correspondence to:** Gustavo Bounous, M.D., Research & Development Department, Immunotec Research Ltd., 292 Adrien-Patenaude, Vaudreuil-Dorion, Quebec, Canada, J7V 5V5

**Key words:** (whey protein), (glutathione), (cancer).

## Glutathione

Mammalian cells have evolved numerous mechanisms to prevent or treat injurious events that can result from normal oxidative by products 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 through the GSH peroxidase and maintains in reduced active form vitamins C and E, which also exert an antioxidant effect.<sup>1</sup> In addition, GSH detoxifies foreign compounds in a reaction catalyzed by GSH-transferases.<sup>2</sup> For these reasons, cellular GSH plays a central role in the body’s 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.<sup>3</sup>

The sulfhydryl (thiol) group (SH) of cysteine is responsible for the chemical properties of the whole GSH molecule (L-gamma-glutamyl-L-cysteinylglycine). As systemic availability of oral GSH is negligible in man<sup>4</sup> and because there is no evidence for transport of GSH into cells,<sup>2,3</sup> 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 toxic<sup>5</sup> and spontaneously oxidized.

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.<sup>6</sup>

Thus, cystine travels safely in the plasma and is promptly reduced to the two cysteine molecules on cell entry.<sup>7</sup>

### Glutathione and Immunity

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.<sup>8,9</sup>

### Whey Protein Concentrate and Immunity

In the early 1980's, it was discovered that normal mice fed a whey protein concentrate (WPC) as 20% of a formula diet exhibited a marked increase in antibody production in response to a T cell dependent antigen<sup>10,11</sup>. The immuno-sustaining effect of this WPC, unrelated to its nutritional efficiency, was confirmed by the protecting effect of this dietary treatment against pneumococcal infection<sup>12</sup>.

Growth, serum proteins, circulating lymphocytes<sup>10-13</sup> and more specifically, the genesis of B lymphocytes in the bone marrow<sup>14</sup> are not influenced by the WPC diet.

The cysteine content of the WPC appears to play a role in the bioactivity of the diet. In fact, optimization of the immune response in animals fed WPC is attributed to a

greater production of glutathione in the lymphocytes through dietary provision of supplementary doses of the GSH precursor cystine<sup>13</sup>.

The confirmation by Parker et al<sup>15</sup> of the immunenhancing effect of WPC was followed in 1995 by another independent study supporting this unique property of WPC. In this study, ingestion of bovine milk whey proteins, either as a supplement or as the only protein source in a balanced diet, consistently enhanced secondary humoral antibody responses following systemic immunization with ovalbumin when compared with other protein sources such as soybean protein isolate and ovine colostrum whey proteins. After 5-8 weeks of feeding, dietary milk whey proteins enhanced cell-mediated immune responses. These properties were unlikely to be related to the nutritional effect<sup>16</sup>.

#### Whey Protein Concentrate and Cancer

The search for the potential mechanism of immunoenhancement by WPC has revealed the provocative possibility that the GSH promoting activity of whey protein concentrate may contribute to a broader biological effect of a protective nature with regard to susceptibility to cancer as well as general detoxification of environmental agents.

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<sup>17</sup>. Conversely, a slightly higher GSH level in the colon, obtained by WPC feeding, is associated with a lower tumor burden in an experimental

model of human colon carcinoma (Fig. 1) again suggesting that tissue GSH levels modulate tumorigenesis.

In 1988, it was reported that, after 24 weeks of dimethylhydrazine (DMH) treatment, the incidence of colon tumors in WPC-fed mice was substantially lower than that in mice fed either the equivalent casein or Purina diet. Similarly, the tumor area was less in the WPC group in comparison to either the casein or Purina groups. Body weight curves were similar in all dietary group<sup>18</sup>. In a subsequent similar study, all animals continuously fed the WPC diet were found to be alive at the end of the experiment whereas 32% of those on the casein or Purina diet had died. In this latter study, some animals were switched from Purina to a WPC diet only during the final 8 weeks of study. The marked difference in the number and size of tumors between these animals and those eating Purina throughout the entire 28 weeks experiment, indicate an effect following tumor initiation<sup>19</sup>. Almost identical results were subsequently obtained in rats by Australian investigators<sup>20</sup> (Fig. 1). Most recently, a study from Arkansas showed that diets formulated with whey protein provided significantly more protection than casein or soy-based diets against chemically induced mammary cancer in rats<sup>21</sup>. The immunoenhancing and anti-cancer properties of WPC have been defined as “bioactivity” of the product. In discussing the effects of milk proteins on tumors it is important to distinguish between anti-tumors effect and the anti-carcinogenesis effect. Our hypothesis is that (I) WPC may be important in both these effects; (II) it does this via its effect on increasing GSH concentration, in relevant tissues, probably by providing high levels of substrates for GSH synthesis; (III) that it may have an anti-tumor effect on low volumes of tumor via stimulation of immunity through the GSH pathway; (IV) that it may have

anti-carcinogenic effect by increasing GSH levels that could detoxify potential carcinogens in some cases by being conjugated to a known chemical like DMH. In spontaneous carcinogenesis models, GSH may also be playing a role. Since it is considered that oxygen radical generation is frequently a critical step in carcinogenesis<sup>22</sup> the effect of GSH on free radical detoxification<sup>2</sup> could be important in inhibiting carcinogenesis induced by a number of different mechanisms<sup>23</sup>. The prostate cancer hypothesis<sup>17</sup> could be a case in point.

In addition, an intriguing relationship has been discovered between cancer cell GSH and GSH precursors or cysteine pro-drugs. This phenomenon has been brought to light especially by *in vitro* studies. These observations indicate the strong possibility of a direct effect of cysteine delivery systems on tumor cells. In 1986, Russo et al observed that cellular GSH levels were 7-fold higher in a human lung adenocarcinoma cell line than in a normal human fibroblast line. In tumor cell line OTZ (oxothiazoline-4-carboxilate which yield cysteine for GSH synthesis) treatment *in vitro* had no effect; however, GSH levels of 140-170% of control were achieved in the normal fibroblast line<sup>24</sup>.

The same phenomenon was shown in an *in vivo* model of rat mammary carcinoma, where GSH concentration was increased in bone marrow and paradoxically reduced in tumor tissue<sup>25</sup>. A natural cysteine delivery system also exhibited on tumor cells *in vitro* the anti-GSH effect of the synthetic products. Thus an *in vitro* assay showed that, at concentrations that induce GSH synthesis and proliferation in normal cells, a WPC caused GSH depletion and inhibition of proliferation of cells in a rat mammary carcinoma and Jurkat T cells<sup>26</sup>. The selectivity demonstrated in these

experiments may be explained by the fact that GSH synthesis is lightly regulated and it is negatively inhibited by its own synthesis and since baseline intracellular GSH in tumor cells is much higher than in normal cells, it is easier to reach the level at which negative feedback inhibition occurs in this cellular system than in a non-tumor cellular system.

All these related observations may help understand the observed *in vitro* inhibition of tumor growth by WPC where involvement of systemic immuno-surveillance cannot be advocated. For example, the addition of bovine milk whey to the culture medium of human breast and prostate cancer cells results in a significant reduction of cells growth. It is noteworthy that the inhibitory effect of these proteins is manifest only after a 24-hour incubation<sup>27</sup>. What is particularly relevant is the fact that the proteins in WPC such as serum albumin, alpha-lactalbumin and lactoferrin with the largest concentration of cystine have been shown to exert individually inhibition of tumor cells. When undenatured, these proteins contain almost the same number of cystine residues per total amino acid<sup>28,29</sup>. Hence, in serum albumin, there are 17 cystine residues per 66,000 MW molecule, and six glutamylcystine (Glu-Cys) dipeptides<sup>28</sup>; in lactoferrin, 17 cystine residues per 77,000 MW, and four Glu-Cys dipeptides<sup>29</sup>, and in alpha-lactalbumin, four cystine residues per 14,000 MW molecule.<sup>28</sup> Conversely, beta-lactoglobulin has only two cystine residues per 18,400 MW molecule<sup>28</sup>, and IgG1, the predominant immunoglobulin in cow's milk serum, only four disulphide bridges (cystine) per 166,000 MW molecule. Bovine serum albumin inhibit *in vitro* the growth of the estrogen responsive human breast cancer cell line<sup>30</sup>. Selective apoptosis (cell death) of human cancer cells was obtained by incubation with  $\alpha$ -lactalbumin<sup>31</sup>. This article received great public recognition presumably because the title announced this effect of a

“human” milk protein with the concomitant awareness that breast-fed infant have lower incidence of infection and childhood cancers. Although it is true that  $\alpha$ -lactalbumin is a predominant protein in human milk (Table 1) it is also true that bovine WPC’s contain 22%-24% alpha-lactalbumin and that most of the non bovine milk proteins are homologous with the recognized families of those of bos taurus and this includes  $\alpha$ -lactalbumins that are coded for by a single gene<sup>32</sup>. Lactoferrin exhibit in tissue culture anti-tumor effect against human pancreatic cancer cell line<sup>33</sup>.

These three whey proteins have in common a similar relatively high content of cysteine. Because of the above-described anti-tumor effect of cysteine pro-drugs *in vitro*, it is reasonable to assume that the anti-tumor effect exhibited *in vitro* by cysteine-rich whey proteins is also related to their cysteine delivery potential. It appears thus, that cancer cells normally down regulate and loose their GSH when facing natural or synthetic cysteine delivery systems.

It was recently demonstrated that several sulfur-containing antioxidants such as NAC and OTZ selectively induce p53-dependent apoptosis in transformed but not in normal cells. In contrast, antioxidants whose action is limited to scavenging radicals do not seem to have this activity. This activity was found related to a 5-10 fold induction of p53 protein and not to GSH formation<sup>34</sup>. Therefore, a natural cysteine donor such a whey protein concentrate (WPC) could also inhibit tumors by directly increasing cellular thiol levels.

#### ***Acknowledgements***

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**REFERENCES:**

- 1 Meister A. *The antioxidant effects of glutathione and ascorbic acid.* In: Oxidative Stress, Cell Activation and Viral Infection. C. Pasquier et al (Eds.). Birkhauser Verlag, Basel, Switzerland, 101-11, 1994.
- 2 Meister A, Anderson ME. *Glutathione.* Ann Rev Biochem 52: 711-60, 1983.
- 3 Kaplowitz N, Aw TY, Ookhtens M. *The regulation of hepatic glutathione.* Ann Rev Pharmacol Toxicol 25: 715-44, 1985.
- 4 Witschi A, Reddy S, Stofer B, Lauterburg BH. *The systemic availability of oral glutathione.* Eur J Clin Pharmacol 43: 667-9, 1992.
- 5 Meister A. *New aspects of glutathione biochemistry and transport selective alteration of glutathione metabolism.* Nutr Rev 42: 397-410, 1984.
- 6 Bounous G, Gold P. *The biological activity of undenatured dietary whey proteins: role of glutathione.* Clin Invest Med 14: 296-309, 1991.
- 7 Dröege W, Eck HP, Mihm S, Galter D. *Abnormal redox regulation in HIV infection and other immunodeficiency diseases.* In: Oxidative Stress, Cell Activation and Viral Infection. C. Pasquier et al (Eds). Birkhauser Verlag, Basel, Switzerland, 285-99, 1994.
- 8 Noelle RJ, Lawrence DA. *Determination of glutathione in lymphocytes and possible association of redox state and proliferative capacity of lymphocytes.* Biochem J 198: 571-9, 1981.
- 9 Fidelus RK, Tsan MF. *Glutathione and lymphocyte activation: A function of aging and autoimmune disease.* Immunology 61: 503-8, 1987.
- 10 Bounous G, Stevenson MM, Kongshavn PAL. *Influence of dietary lactalbumin hydrolysate on the immune system of mice and resistance to Salmonellosis.* J Infect Dis 144: 281, 1981.
- 11 Bounous G, Letourneau L, Kongshavn PAL. *Influence of dietary protein type on the immune system of mice.* J Nutr 113: 1415-21, 1983.
- 12 Bounous G, Kongshavn PAL. *Influence of protein type in nutritionally adequate diets on the development of immunity.* In: Absorption and Utilization of Amino Acids. M. Friedman (Ed.). Boca Raton, Florida: CRC Press, Vol. 2, 219-32, 1989.
- 13 Bounous G., Batist G, Gold P. *Immunoenhancing property of dietary whey protein in mice: role of glutathione.* Clin Invest Med 12: 154-61, 1989.
- 14 Bounous G, Shenouda N, Kongshavn PAL, Osmond DG. *Mechanism of altered B-cell response induced by changes in dietary protein type in mice.* J Nutr 115: 1409-17, 1985.
- 15 Parker N.T., Goodrum K.J. *A comparison of casein, lactalbumin, and soy protein, effect on the immune response to a T-dependent antigen.* Nutrit Res 10: 781-792, 1990.
- 16 Wong C.W., Watson D.L. *Immunomodulatory effects of dietary whey proteins in mice.* J. of Dairy Res. 62: 350-368, 1995.
- 17 Ripple MO, Henry W, Rago R, Wilding G. *Prooxidant-antioxidant shift induced by androgen treatment of human prostate carcinoma cells.* J Nat Cancer Inst 89: 40-8, 1997.
- 18 Bounous G, Papenburg R, Kongshavn PAL, Gold P., Fleiszer D. *Dietary whey protein inhibits the development of dimethylhydrazine-induced malignancy.* Clin Invest Med 11: 213-7, 1988.
- 19 Papenburg R, Bounous G, Fleiszer D, Gold P. *Dietary milk proteins inhibit the development of dimethylhydrazine-induced malignancy.* Tumor Biol 11: 129-136, 1990.

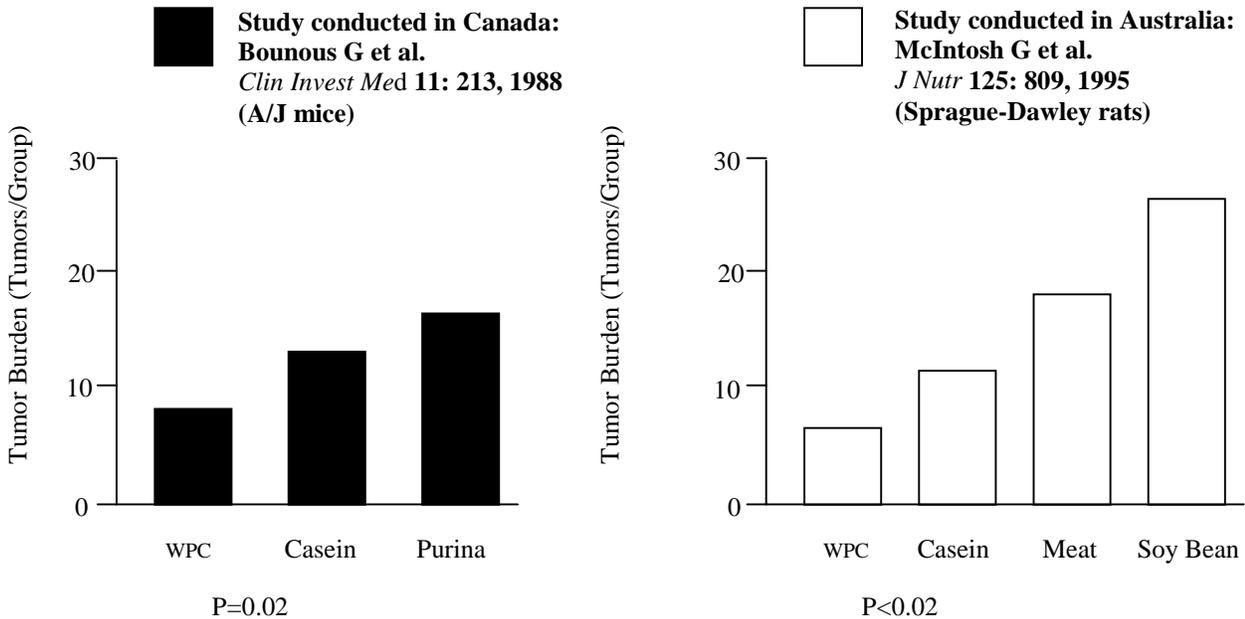
**REFERENCES:** (cont'd)

- 20 McIntosh GH, Regester GQ, Le Leu RK, Royle PJ. *Dairy proteins protect against dimethylhydrazine-induced intestinal cancers in rats.* J Nutr 125: 809-16, 1995.
- 21 Hakkak R., Korourian S., Ronis M., Irby D., Kechclaua S., Rowland C., Benson J., Weatherford C., Lensing S., Badgber T. *Dietary prevention of mammary cancer in multiparous female rats by whey protein, but not soy protein isolate.* Proc American Ass for Cancer Res 40: 2010, March 1999.
- 22 Cerutti P.A. *Prooxidant state and tumor protection.* Science 227: 375-381, 1985.
- 23 Bounous G., Batist G., Gold P. *Whey proteins in cancer prevention.* Cancer letters 57, 91-94, 1991.
- 24 Russo A., DeGraff W., Friedman N., Mitchell J.B. *Selective modulation of glutathione levels in human normal versus tumor cells and subsequent differential response to chemotherapy drugs.* Cancer Research 26: 2845-2848, 1986.
- 25 Baruchel S., Wang T., Farah R., Alaoui-Jamali M., Batist G. *In vivo selective modulation of tissue glutathione in a rat mammary carcinoma model.* Biochem Pharmacol 50: 1499-1502, 1995.
- 26 Baruchel S., Viau G. *In Vitro Selective Modulation of Cellular Glutathione by a Humanized Native Milk Protein Isolate in Mammal Cells and Rat Mammary Carcinoma Model.* Anticancer Res. 15: 1095-1100, 1996.
- 27 Bourtourault M., Buleon R., Samperez S., Jouan P. *Effet des protéines du lactosérum bovin sur la multiplication de cellules cancéreuses humaines.* C.R. Soc. Biol 185, 319-323, 1991.
- 28 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.
- 29 Goodman RE, Schanbacher FL. *Bovine lactoferrin in RNA: Sequence, analysis, and expression in the mammary gland.* Biochem Biophys Res Commun 180: 75-84, 1991.
- 30 Laursen I., Briand P., Lyekesfeldt A.E. *Serum albumin as a modulator on growth of the human breast cancer cell line, MCF-7.* Anticancer Res 10: 343-352, 1990.
- 31 Hakanson A., Zhivotovsky BI, Orrenius S., Sabharwal H., Svanborg C. *Apoptosis induced by a human milk protein.* Proc Natl Acad Sci USA 92: 8064-8068, 1995.
- 32 Jennes R. *Comparative aspects of milk proteins.* J. of Dairy Res 46: 197-210, 1979.
- 33 Sakamoto N. *Antitumor effect of human lactoferrin against newly established human pancreatic cancer cell line SPA.* Gan to Kagako Ryoho 10: 1557-63, 1998.
- 34 Liu M., Pelling J.G., Ju J., Chu E., Brash D.E. – *Antioxidant action via p53-mediated apoptosis.* Cancer Res. 48: 1723-29, 1998.

**FIGURE 1**

**Results of Studies Demonstrating the Role of Specially Prepared Dietary WPCs on Tumor Growth**

Carcinogen was dimethylhydrazine-dihydrochloride (DMH), which induces colon tumors similar to those found in humans (with regard to type of lesions<sup>1</sup> and response to chemotherapy<sup>2</sup>). The diets were fed before and throughout the 24-weeks 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.”

1. Enker WE, Jacobitz 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 agents in mouse colon carcinogenesis. Cancer 40 : 2650, 1977.  
Rodent chow (purina) containing varying amounts of beef, fish, corn, and whey proteins.

**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)	$8.19 \times 10^{-4}$	$13.87 \times 10^{-4}$	
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.). ASP NY : 87, 1982; and Eigel WN, Butler JE, Ernstrom CA, Farrell HM et al. Nomenclature of proteins of cow's milk. *J Dairy Sci* 67 : 1599-631, 1984 - Fifth revision.

## CASE REPORTS

Showing the Effect of Whey Protein Concentrate (WPC)<sup>1</sup>  
on urogenital malignancies

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<sup>1</sup> *The whey protein concentrate, specifically an isolate defined by protein grade, in non-instantized native form, marketed as Immunocal/HMS90, was obtained from IMMUNOTEC RESEARCH LTD.*

**TREATMENT OF UTERINE CARCINOMA IN SITU: A CASE REPORT**

DANIEL MOREAU, M.D. F.R.C.S. (C) - (OBSTETRICS AND GYNECOLOGY)

*Ottawa Civic Hospital - Canada*

M.A. DOB - SEPTEMBER 13, 1962

On May 15, 1997, the specialist was consulted because the cytology done by the family physician had revealed moderate dysplasia compatible with human papilloma viral infection. An endocervical curettage showed, on May 15, 1997, severe cellular dysplasia. On February 9, 1998, the Pap test showed severe dysplasia. On April 30, 1998, severe dysplasia was still present on the Pap test. A cervical curettage performed the same day, exhibited epithelial fragments with severe dysplasia. On August 7, 1998, a curettage of the neck demonstrated carcinoma in situ. The same procedure repeated on September 10, 1998, confirmed the presence of carcinoma in situ. The patient was advised of the possibility of a hysterectomy.

Instead, beginning November 1998, she took 20 g daily of a specially prepared whey protein concentrate. On March 8, 1999, the cytology showed "possibly atypical cells" and a biopsy of the neck and endocervical curettage on April 9, 1999 showed only a light dysplasia. On July 13, 1999, and again on December 22, 1999, the cytology was completely normal.

**WHEY PROTEINS IN THE TREATMENT OF METASTASIS OF RENAL CARCINOMA**

ROBERT BENDER, M.D., MEDICAL DIRECTOR

*Community Medical Group of Corona – Corona, CA*

DOB: 1-7-48

Patient is a 52-year-old Caucasian female who developed vaginal bleeding in November, 1996. Pelvic examination revealed a large strawberry-like lesion at the urethral opening onto the vaginal introitus.

On January 29, 1997 the lesion was excised. Cystoscopy was negative. Pathological report demonstrated metastatic renal cell carcinoma. Chest x-ray was unremarkable. Pelvic ultrasound did not reveal any pathology other than evidence of a previous hysterectomy.

CT scan of the abdomen on February 7, 1997 revealed a 10 x 8.6 x 10 cm mass of the left kidney involving the upper pole with central necrosis extending into the perirenal fat and lateral fascia. CT of the pelvis was normal. Bone scan was normal.

On March 11, 1997 the patient underwent a left radical nephrectomy. The mass was found to adhere to the psoas muscle superiorly, but did not involve the spleen or colon. No significant lymph adenopathy was noted in the periaortic chain. The liver was noted to be unremarkable and there was no pelvic mass noted. Renal vein was free. Nuclear Grade was 2+4. Adrenal gland was benign. Lymph nodes were negative.

The vaginal wall tumor recurred following the initial excision. When the patient underwent staging in August, 1997 a CT scan of the chest demonstrated multiple scattered tiny peripheral pulmonary nodules mainly seated in the lung bases with associated pretracheal and right paratracheal adenopathy, most typical of pulmonary

metastasis. Also, two low density lesions involving both the right and left lobes of the liver were suspicious for metastasis. Bone scan also revealed an area in the right pelvis in the iliac bone medially near the SI joint that was suspicious for metastatic disease.

The patient declined the recommendation for pelvic external beam radiation and also declined the chemotherapy recommendation of Interferon, Interleukin and 5-FU.

Repeat evaluation performed October 1997 and repeated in December 1997 for CT scan of the abdomen demonstrated liver metastasis increasing in number. CT scan of the thorax demonstrated extensive mediastinal adenopathy and lung parenchyma with multiple small nodules throughout both lung fields.

This patient was again evaluated in April 1998 and the result was progressive disease with enlarging size and number of nodules in the liver and persistent extensive mediastinal adenopathy and pulmonary nodules.

Because this patient was experiencing increasing metastatic disease and a treatment plan could not be offered with any kind of satisfactory prognosis this patient sought out other possible treatment methods.

Therefore, in June, 1998 “a specifically prepared whey protein concentrate treatment” was instituted. The patient took one pouch (10 g) in the Am and two pouches in the PM. Within the first two weeks of taking the whey protein concentrate the patient’s nausea had resolved. Also, the patient reported improved appetite and a great improvement in her energy level.

The CT scans of the abdomen and thorax, in August, 1998, demonstrated no significant changes in the lungs and liver. Overall, the patient continued to improve clinically.

In November 1998, a chest film demonstrated a decrease in the lung nodularity and no further progression of the mediastinal adenopathy.

In January 1999, a chest film was performed and the lungs were free of opacities.

In March 1999, the patient experienced projectile vomiting and further studies were undertaken. A CT scan of the abdomen demonstrated no bowel obstruction and the metastatic lesions to the liver were diminished in size with increased central necrosis. A CT scan of the pelvis was unremarkable, except for status post left nephrectomy. An upper GI demonstrated absence of disease except the suggestion of duodenitis. No further vomiting was experienced.

CT scan studies of the abdomen, thorax, pelvis and chest in July 1999 continued to demonstrate resolution of pulmonary nodules and almost total resolution of peritracheal and subcarinal adenopathy. The liver appeared stable with no evidence of additional abnormality.

The November 1999 CT of the abdomen compared to the July 1999 report demonstrates a probable slight decrease in the appearance of the area of the low density within the liver presumed to be sites of metastatic disease. There were no new areas of metastatic disease noted.

The CT of the pelvis was unremarkable and the follow up CT of the chest remains clear of nodularity in the lung fields and no new evidence of disease.

To date, this patient continues to live a full, active life and her only treatment continues to be the “specifically prepared whey protein concentrate”.

**A PROSPECTIVE STUDY OF THE EFFECT OF SPECIALLY PREPARED WHEY PROTEIN  
CONCENTRATE ON THE PROGRESSION OF CANCER OF THE PROSTATE**

JOHN M. ZABOROWSKI, M.D.

*Physicians Care Center – Chicago, IL*

**Objective:** to test the hypothesis that by manipulating GSH levels thorough oral supplementation of specially prepared whey protein concentrate, thus causing the conjugation of electrophylic carcinogen(s) involved in the genesis of cancer of the prostate that such manipulation may lead to the remission and/or destruction (apoptosis) of the cancer cell(s) in the patient with prostate cancer.

**Methods:** Otherwise healthy patients with elevated PSA and cancer of the prostate were given specially prepared whey protein concentrate 10 grams twice a day. Each patient had an initial PSA and PSA while under treatment. These patients were not on any drugs that would interfere with PSA levels.

**Results:**

Patient	Age	Start Date	Finish Date	Initial PSA	Date	Last PSA	Date
JR	65	3-5-2000	Still on	6.7	3-5-2000	4.4	4-8-2000
ZR	63	7-7-1999	1-18-2000	11.5	7-8-1999	1.6	12-29-1999
LD	67	6-7-1999	10-4-1999	7.9	6-25-1999	7.6	10-5-1999
SK	69	5-5-1999	8-31-1999	17.5	5-4-1999	15.9	8-31-1999
HS	70	1-20-1999	6-9-1999	7.3	9-16-1998	6.7	6-9-1999
--	--	1-19-2000	Still on	8.7	1-19-2000	7.5	4-5-2000

Of the 10 patients that I was able to isolate from my practice, 5 patients opted for surgical intervention.

3 showed initial improvement i.e. a lowering of the PSA then dropped out of the study for various reasons.

The 2 remaining patients both responded positively. One had an elevation of PSA higher than the initial PSA after stopping supplementation for 2 months. After restarting supplementation, he had a lower PSA than initial PSA after only 2 months of treatment.

**Conclusion:** further research on a larger population should be conducted to validate these findings. All the patients had lower PSA's with the administration of whey protein isolate supplementation.

The fear of reliance of treatment by a natural product and pressure to conform to the present standard treatment of CA of the Prostate may have been the reason for the high drop out rate and poor compliance in my patient population.

\* \* \* \* \*

### **WHEY PROTEIN IN THE TREATMENT OF METASTATIC PROSTATE CANCER**

ROGER G. MAZLEN, M.D., F.A.C.N.

*Mount Sinai Medical School and Medical Center – New York*

Case Study of a 77 year old male (J.) with metastatic carcinoma of the prostate with extensive bone metastases and localized spread to the rectal area.

**1) Prior to entry into study**

	<b>PSA</b>	<b>Free PSA</b>
8/9/98	205.3 (<4.01 mg/ml)	--

Treatment failure on standard therapies and treatment chemotherapy discontinued due to cardiac toxicity. Only on prednisone 10 mg po daily, 10/98. Multiple bone metastases present on CT scan on 10/02/98.

**2) Began on WPC 10 gm OD 10/29/98**

	<b>PSA</b>	<b>Free PSA</b>
11/20/98	11.35	11% ("Feels good")
01/99	15	--

Increased WPC dosage (20 gm a day)

**3) Began on WPC 20 gm OD 3/01/99**

	<b>PSA</b>	<b>Free PSA</b>
3/99	26.8	--
4/99	27.7	-- (Lupren IM)
5/99	36.4	-- (Cytosan)
6/99	52	--
7/99	37	--
8/99	53	-- (good energy)
11/29-12/10/99		"misuse" of WPC Nov/Dec (in hot denaturing water) Local radiation therapy to bone metastases A total of 10 treatments
1/10/00	68	
1/18/00	102.4	Resumed WPC in prescribed condition
3/14/00	66	Feels improved

**WHEY PROTEIN IN THE TREATMENT OF BLADDER CANCER**

Patient: A.G. Male Age 74 years

**I Medical History**

BPH 1987

Prostate Cancer diagnosed 1993. Treated with radiotherapy, with a left renal artery stent. Recent PSA 0.9

Renal Vascular Hypertension 1997

Atrophic Right Kidney 1997

Coronary Artery Disease/Angina Pectoris

## II Social History

Significant for a history of 50 packs per year smoking habit which he discontinued in 1989

- III A) Bladder Cancer 1995 Multiple recurrences. Since that initial diagnosis. Multifocal grade I bladder tumors were resected on 6/10/99 (papillary transitional cell carcinomas) at 5 sites. Previously he had BCG treatment. Has cystoscopic examination of the bladder every 3 months.
- B) Placed on WPC at his office visit of 7/8/99 at a dosage of one (1) (10 g) packet daily. At his cystoscopies of 8/99 and 2/2000 there were no recurrences of the papillary transitional cell carcinoma.

**A PROSPECTIVE STUDY OF THE EFFECT OF SPECIALLY PREPARED WHEY PROTEIN  
CONCENTRATE ON THE PROGRESSION OF CANCER OF THE PROSTATE**

BELA S. DENES, M.D., FACS – DIRECTOR

*The Prostate Center of Greater St-Louis - Missouri*

We present our early experience in the treatment of 8 patients with biopsy proven carcinoma of the prostate with whey protein nutritional supplementation alone. Response to treatment was monitored by serial PSA levels. PSA is a highly sensitive tumor marker for prostate cancer and is widely used as a measure of response to therapy. Spontaneous regression has not been described.

**Patient Demographics**

The patients were men in our regular urologic practice who underwent endorectal biopsies of the prostate in an office setting. All men had elevated PSA levels with or without palpable induration in the prostate. None of the patients had any previous treatment for prostate cancer.

The median age was 82.5 years (range 77 to 89 years)

The median PSA at diagnosis was 14.2 ng/ml (range 5.0 to 44 ng/ml). All PSA serum specimens were run by the Smith-Kline-Beecham Labs., hyrbertech assay.

The median testosterone level was 391 ng/ml (range 253 to 619 ng/ml).

The median Gleason score was 5.5 (range 4 to 7).

Performance status in all patients was excellent, all were living independently. None of the patients had symptoms of clinically active disease (e.g. bone pain, hematuria, B.O.O., peripheral adenopathy, renal insufficiency) and in our practice would have been

treated with “watchful waiting” until there was significant PSA progression or signs of clinically active disease.

### **Treatment Protocol**

After review of the biopsy material and with informed consent, patients were enrolled into the study. The specially prepared whey protein supplements was provided to the patients. The prescribed dose administered was three 10 gm packs per day (30 gm total). No other prescription or OTC treatment was prescribed. Patients were specifically instructed not to use saw palmetto or any of its derivatives.

Serum levels for PSA were drawn at 0, 6 and 12 weeks. Serum testosterone levels were repeated at 12 weeks. Patients were given the option of withdrawing at any time from the study.

### **Results**

Of 10 patients enrolled, 8 have completed 3 months of therapy. Six of the eight patients (76%) have demonstrated a decline in PSA at 6 and 12 weeks. One patient (12%) has had PSA stabilization and one patient (12%) demonstrated a slow but continuous rise in PSA at 6 and 12 weeks. No patient has become clinically symptomatic to date.

One patient (T.M.) has now completed 24 weeks of therapy. His initial PSA was 44. At 12 weeks it had declined to 37 and has continued to decline to 28.

The median decline in PSA at 3 months was 1.8 ng/ml (range 0.2 to 7.0 ng/ml). This represents a 12.8% decrease in the median PSA for the group.

### **Summary**

These preliminary results with a whey protein concentrate for the treatment of prostate cancer are encouraging. This cohort of elderly patients with biopsy proven CaP without any previous treatment demonstrated a significant decline in serum PSA at 3 months. All patients tolerated the specially prepared protein concentrate.

Whey protein dietary supplementation appears to exert clinical efficacy in elderly men without previously treated CaP, based on PSA response. Further studies to evaluate its role as primary or adjuvant treatment are anticipated.

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### **IMPROVEMENT IN PSA VALUES USING ORAL GLUTATHIONE PRECURSORS OBTAINED FROM SPECIALLY PREPARED WHEY PROTEIN CONCENTRATE (SWPC).**

JIMMY GUTMAN, M.D., FACEP

Assistant Professor, McGill University - Canada

*Department of Family Medicine, Emergency Medicine – April 2000*

PSA levels are traditionally used both for the diagnosis of prostate cancer and to monitor success of treatment modalities. The basis of these case reports was to follow the PSA levels in established cases of prostate cancer in patients whose glutathione levels were enhanced using SPWC.

**Methods:**

Two patients with biopsy-proven carcinoma of the prostate were followed with regular physical examinations, routine blood-work and PSA levels. Both expressed an interest in commencing oral SPWC as a proactive measure to combat their disease process. The patients were started on whey protein concentrate at 10 grams per day, and PSA levels subsequently documented.

**Case histories and results:**

CASE #1 – This gentleman of Italian descent was suspected of having prostatic cancer based on an elevated PSA value at age 66. Subsequent biopsy confirmed a high grade intraepithelial neoplasm. History, physical exam and laboratory studies did not suggest any metastatic process. His medications included ranitidine (Zantac) for a remote gastric ulcer, and terazosin (Hytrin) both for hypertension and symptoms of prostatism. He was in otherwise good health and was very attentive to keeping a good lifestyle and diet. His PSA levels are found in figure 1, and show a significant drop in values after commencing SPWC.

CASE #2 – This patient of Haitian descent with mild untreated hypertension, was diagnosed as having prostatic cancer at age 54. Biopsies revealed high-grade tumor and he underwent radiotherapy and treatment with the anti-androgens bicalutamide (Casodex) and goserelin acetate (Zoladex). PSA levels showed an initial positive response to the hormonal therapy, but then levels began to rise again and his urologist suggested another course of anti-androgen treatment. Having had very poor reaction to the side effects of

the first session, the patient declined further chemotherapy. He elected instead to initiate SPWC. His PSA levels improved as documented in figure 2.

**Discussion:**

These two cases show significant improvement in PSA levels in patients with biopsy-confirmed prostate cancer using oral glutathione-precursors found in specially-prepared whey-protein concentrate. No concurrent therapy could explain the drop in values. Larger, blinded studies using this therapeutic strategy are warranted.

# CASE REPORTS

