

## **GSH – ONE OF THE MOST POWERFUL THINGS MOST PEOPLE DO NOT KNOW ABOUT**

This will give you a nice overview about Immunocal®. Enclosed is an overview of the product as well as an introduction to Gustavo Bounous, MD, one of the inventors and currently the Director of Research for Immunotec Research. Additional information on the studies, patents, and ongoing research can be forwarded to you in the near future if you are ready and willing to receive it.

Immunocal® is a specially formulated whey protein isolate that has been clinically shown to raise glutathione levels in the maintenance and enhancement of the human immune response system. It was developed in Montreal at the Teaching Hospital of McGill University, the Montreal General Hospital by a team of researchers headed by Gustavo Bounous, MD. With its high concentration of essential amino acids it is accorded a high biological value. The protein content is approximately (90%) while the fat and lactose values are under 1%. The Clinical testing of Immunocal® is ongoing, with a number of protocols underway in the fields of AIDS, Cancer, Cystic Fibrosis, Asthma and Chronic Fatigue.

Unlike commercial whey concentrates, Immunocal® is produced using specially designed techniques aimed at preserving the bioactive cystine rich components in their undenatured form.

World-class athletes in a variety of sports and activity levels are exhibiting an increase in performance and are experiencing better recovery, both during and after workouts. A recent double blind clinical study on the effect of enhanced glutathione produced by Immunocal® on muscular performance at McGill University showed amazing results on the twenty healthy young adults who were involved with the test. Both peak power and 30-second workout resulted in an average 13% increase in performance with no change in the placebo group.

Recently cited articles, "Whey to Go" (Published in POZ, 2/97, Page 102) comment that whey, a component of milk, is a popular diet supplement because it improves weight gain and provides a protein-rich energy boost while containing no lactose. It pointed out that research studies have shown that a new whey protein concentrate, called *Immunocal®*, stimulates the production of glutathione. Trials of treatment with Immunocal® have demonstrated its benefit. James F. Balch, MD says in his recent book, *The Super Antioxidants*, that "people have thrown away money taking glutathione supplements that the body cannot use. Immunocal®...delivers effective quantities of cysteine. It is not a drug; it is...more like human milk...In addition, glutathione inhibits the replication of the HIV virus itself." **Immunocal® also meets the criteria for reimbursement.** 

I would welcome the opportunity to answer any questions you may have. Please feel free to call me at any time.

Sincerely,

## GregCropps 336-749-4249 www.immunotec.com/gcropps - www.goodhealthtoyou.synthasite.com



1. <u>THE COMPANY:</u> Solid financial base, principals are:

Chuck Roberts, President (former President and co-owner of Descente Skiwear, Canada) John Molson, Vice President, (Molson Brewery, Royal Bank of Canada) Dieter Beer, a world-renowned businessman and founder of Immunotec Research, Dieter has invested over \$10 million of his own money to further the research and marketing of Immunocal®!

**2.** <u>**RESEARCH:**</u> 20 years of research, Immunocal® is being used worldwide in hospitals. The research was first conducted by Gustavo Bounous, MD, FRCSC and his colleague Dr. Patricia Kongshavn.

**3.** <u>THE PRODUCT</u>: Immunocal® - A Bio-active Whey Protein Isolate, containing less than 1% fat and lactose. It is a white powder derived from natural sources and produces NO SIDE EFFECTS!

Immunocal® will optimize the level of glutathione intracellularly, thus optimizing the functioning of the Human Immune System. It is a produced from a natural food product, bovine milk, and provides your body with the raw materials necessary to replenish the cell's most important antioxidant, glutathione. Taking glutathione orally has been clinically shown to be a poor delivery system of cystine to the cell, drugs such as NAC or OTC are commonly and effectively used as an antidote for acetaminophen toxicity in humans when rapid restoration of glutathione level in the liver cells is needed. The effects however are short lived and may produce an adverse reaction. This can be attributed to the non-utilized cysteine either for glutathione synthesis or the sulfate pathway.

Immunocal® can be taken with juices, water, milk, cool puddings, applesauce, or yogurt. Immunocal® has a 30 DAY MONEY BACK GUARANTEE!

## 4. THE PATENTS: Currently Seven Method of Use Patents -

Method of Use patent differs from a manufacturing patent in that it verifies the products Effectiveness. (Typically given to drugs)

- 1 Canadian Method of Use Patent
- 5 US Method of Use Patents
- I Australian Method of Use Patent -

**5.** <u>**TIMING-BUSINESS:**</u> Immunocal® is marketed in South America through the pharmaceutical industry. However in North America, Australia, New Zealand, Japan, and Indonesia the product is marketed through the Direct-Tech system.

The US market is wide open---- we need key distributors in all states!! Ground Floor!!!! Tremendous support and tools are in place for rapid growth. Immunotec Research is committed to a major promotional campaign for Immunocal®.



# Available Now!

The CULMINATION OF 20 YEARS of Research at the Teaching Hospital of McGill University, Montreal Canada. Five U.S. & one Canadian <u>"METHOD OF USE"</u> <u>PATENTS</u>, Worldwide Patents Pending Documented Research with both in vitro and in vivo studies ONGOING STUDIES - U.S.A. & WORLDWIDE on numerous Illnesses RECOGNIZED in Leading Medical Journals 100 % naturally derived Protein Isolates

## **IMMUNE SYSTEM BOOSTER**

DETOXIFIES Pollutants and Carcinogens Nature's MOST POWERFUL Cellular Antioxidant

## WHAT EXPERTS ARE SAYING:

"Glutathione helps in preventing and battling weight gain, hyperactivity, alcohol, sugar and caffeine addictions, allergies, cataracts, lung and skin, and Prostate and bladder cancers." James F. Balch, MD, *The Super Antioxidants* 

"Of all antioxidant substances your body makes, the most important is glutathione." Dr. A.H. Pressman, *The GSH Phenomenon* 

"You must keep your levels of glutathione up if you want to keep your youth and live younger." Jean Carper, *Stop Aging Now!* 

# Immunocal®



## JUST RELEASED! IMMUNOCAL®

## 25 Years of Medical Research

## OPTIMIZES IMMUNE SYSTEM

Immunocal® is a patented milk serum (whey) protein concentrate. Its role in the effect on the immune system and its benefits similar to those of human milk, as well as its potential role in numerous illnesses, are well documented through research.

- 7 North American Patents including Method of Use Patents
- Research with Phase I, II & III Studies
- Completed & Ongoing Worldwide Clinical Studies: Prostate Cancer – Mount Sinai &Royal Victoria Hospital Breast Cancer - Nova Scotia Cancer Center HIV - Royal Victoria Hospital Hepatitis B - University of Toyama Cystic Fibrosis – Montreal Children's Hospital
- Optimizes Immune System Validated by Clinical Research
- Gustavo Bounous, MD and Director of Research for Immunotec Research, developed Immunocal® along with a team of scientists at The Montreal General Hospital. The research began in 1978.
- FDA regulated as a food supplement, yet recognized in leading Medical Journals around the world because of its documented ability to optimize glutathione levels.
- Meets requirements for reimbursement. Listed in Physicians Desk Reference 2000 & 2001, and Pharmacists Red Book.

### SHARE THE GIFT OF HEALTH WITH A FRIEND!

Quality of Life is based on Health! Immunocal® is the product that has the potential to make a real and lasting contribution to your Quality of Life!

#### FOR MORE INFORMATION CALL: 336-749-4249

## LIST OF THE ON-GOING AND COMPLETED STUDIES WITH IMMUNOCAL®

## Cancer Studies:

- McGill Dept. Of Urology Clinical trial in cancer of the prostate
- Royal Victoria Hospital The effect of Immunocal® in patients with prostate cancer.

## AIDS Studies:

Phase III Canadian AIDS Network

 Montreal Chest Hospital (Montreal, Canada)
 Jewish General Hospital (Montreal, Canada)
 Montreal General Hospital (Montreal, Canada)
 (Directed by Dr. R. Lalonde, MD.)

## Hepatitis:

• Pharmaceutical (Hepatitis) Studies (Otsuka, Japan)

## **Prostate Cancer:**

- Mount Sinai Hospital, Dr. Roger Mazlen MD.
- Bladder, Kidney, Prostate, and Uterus. Dr. G. Bounous

## Cystic Fibrosis:

• Montreal Children's Hospital

## Chronic Fatigue Syndrome

• NY Chronic Fatigue Syndrome Clinic, Dr. Roger Mazlen MD

## <u>Overview</u>

## *IMMUNOCAL*®: A CLINICALLY TESTED IMMUNE SYSTEM OPTIMIZER DERIVED FROM NATURAL SOURCES

WHAT IS IMMUNOCAL®?	Immunocal <sup>®</sup> is derived from natural food sources that assists the body to maintain optimal concentrations of <i>glutathione, a vital cell constituent, and antioxidant</i> .
WHO DISCOVERED IMMUNOCAL®?	It was the discovery of the importance of <i>glutathione</i> in boosting the immune system that led to the development of Immunocal®. As a result of many years of research which began in the late 1970's, Gustavo Bounous, MD and his colleague, and Patricia Kongshavn, showed that immune function in experimental animals was enhanced when an isolate of milk serum was used as a protein source in their diet. This effect was seen in a variety of ways including a greater response to 'foreign antigens,' and heightened resistance to bacteria.
	Bounous and his colleagues were able to trace this immune-enhancing or 'bioactivity' of the protein mixture to its ability to provide a rich source of <i>glutathione</i> precursors which enabled the immune system to develop an optimum response when challenged with immune stimuli (foreign antigens), Since 1988, Immunocal® has been developed as a natural dietary supplement by Immunotec Research Ltd., under the scientific direction of Gustavo Bounous, MD.
WHERE DOES IMMUNOCAL® COME FROM?	<i>Glutathione</i> precursors, including the precursor <i>cysteine</i> , are crucial to the efficient function of <i>glutathione</i> , but are rare in edible proteins. A rich source of these precursors is found in several milk serum (whey) Proteins. 500 liters of raw milk is required to prepare I kilo of Immunocal®. Immunocal® is called HMS90 in Canada, to denote 'humanized milk serum' containing 90 percent protein* (and less than 1% fat and lactose, making it both suitable and desirable for all, even the most lactose-intolerant.
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	Immunocal®/HMS 90 is a highly refined protein powder that provides a rich natural source of <i>glutathione</i> precursors, especially <i>cystine</i> , <i>which</i> splits to become <i>cysteine on cell entry (cysteine is the rate limiting factor in the</i> ` <i>synthesis of glutathione</i> )
GLUTATHIONE:	<i>Glutathione</i> , a small molecule (L-gamma-glutamyl-L-cysteinyl-clycine) made up of three amino acids, has the potential to exist in almost every cell in the body.
GLUTATHIONE AS AS A MAJOR ANTIOXIDANT:	Oxiradicals, which are created as a result of normal cell metabolism, cause cell damage if they are left unchecked. For this reason, the body is equipped with a variety of antioxidants, including <i>glutathione</i> , which is one of the body's major antioxidant systems. Other well known antioxidants are vitamin C and vitamin E, both of which are kept in a functional state by the actions of <i>glutathione</i> .
GLUTATHIONE AND THE IMMUNE SYSTEM:	The presence of <i>glutathione</i> is required to maintain the normal functioning of the immune system in at least two ways. It is known to play a critical role in the multiplication of lymphocytes (the cells that mediate specific immunity) which occurs in the development of an immune response.
GLUTATHIONE AS A DETOXIFIER:	Supplements with detoxifying properties become necessary as our environment becomes increasingly polluted. Our food and water sources are contaminated with chemicals. Thinning of the ozone layer allows unsafe levels of ultraviolet radiation to reach the earth resulting in global warming, which in turn encourages the increased multiplication and spreading of disease producing micro-organisms.

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#### overview/page three

One of our main defenses against pollutants is *glutathione*, which is present in the liver in high concentrations. *Glutathione* acts as a detoxifying agent by combining with undesirable substances and ridding the body of them through urine and bile. There are at least one dozen known cancer-producing chemicals present in the environment that are detoxified by *glutathione*.

#### BENEFITS OF IMMUNOCAL®:

When used as a daily dietary supplement, Immunocal<sup>®</sup> can boost even a normally functioning immune system's ability to act as a preventive against tissue damage, which is the result of oxidation. However, it is particularly recommended for individuals who are likely to have low concentrations of *glutathione* in their tissues, as in immune-depressed patients or the elderly, or for those who place an increased demand for *glutathione* on their bodies, such as athletes.

It is well documented that AIDS patients (who are by definition immune deficient) with *Wasting Syndrome* have lower tissue *glutathione* concentrations, especially in the T lymphocytes. Recent studies showed that survival time was improved in AIDS patients who maintained higher *glutathione* levels in their CD4 T-cells (a particular subset of T lymphocytes targeted by the AIDS virus) than in those with low levels.

While the aging process is the result of a complex combination of degenerative factors, *glutathione* deficiency appears to be a common feature in the aging of tissue. In one study, half of a group of subjects over 40 years old had 25% lowered *glutathione* levels and in another study half of the 60+ age group had *glutathione* deficiency. Moreover, long-term feeding of Immunocal® to 21-month old mice (the corresponding age for human males in the industrialized world is 55 years) increased their life span by about 30%.

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#### overview/page four

*Glutathione* status is highly relevant in combating cancer. *Glutathione* detoxifies carcinogens and maintains effective immune function, which can promote anti-tumor activity in existing tumors, as well as discourage the development of new ones.

In athletes, *glutathione* delays the muscular fatigue induced by oxyradicals that accumulate in the muscles during the aerobic phase of strenuous muscular contraction. Preliminary results of a current study indicate that Immunocal® extends endurance, enhances performance and reduces recovery time.

ALTERNATIVE STRATEGIES TO RAISE GLUTATHIONE CONCENTRATION:	<i>Glutathione</i> cannot pass freely through the blood stream unless it is activated by <i>cysteine</i> . There are a number of synthetic drugs, like n acetyl-cysteine (used on patients with HIV) that can stimulate <i>cysteine</i> production, however, they result in side effects which limit their long-term use. Immunocal® encourages <i>cysteine</i> production with no known side effects.
CLINICAL TRIALS	Trials in Canada and Japan continue to point to the benefits of Immunocal®. As a result of favorable preliminary data, the Canadian government funded a study focusing on the use of HMS 90/Immunocal® as a specific treatment of AIDS patients with Wasting Syndrome. The Nova Scotia Cancer Center has undertaken a Phase II trial on the use of Immunocal® in the treatment of breast cancer.

Note: Additional articles published in scientific Journals are available upon request.

## BULLETIN For Immunotec Distributors

March 13,1998 USA Circulation Only

## AN AUSTRALIAN PATENT ISSUED TO IMMUNOTEC FOR METHOD OF USE IN CANCER TREATMENT

A patent abridgment has been issued by the Australian Patent Office to Immunotec Research Ltd. for the clinical application of Immunocal In the treatment of cancer. This is a tremendous addition to our growing lists of patents already acquired. Please keep In mind how difficult these method of use patents are to obtain, given the rigorous scrutiny applied by the patent bureaus. It is Important to note that this Australian patent takes us one step closer to procuring the USA patent for the same method of use. USA patents are considered the gold standard and enable us to secure world side patents with greater ease. This abridgment leads to the official Issue In approximately 6 months,

What this means to **yOU** as a distributor Is that the research on our product has been evaluated and been determined to perform what It claims that being an effective modality towards the treatment of cancer. No other whey protein may legally make that claim, even if In the future they were able to develop the technology to imitate our product.

Now, not only can we stand confident in front of our research, but we also have this critical patent to be proud of

AUSTRALIAN PATENT

AU-B-46937/93. acceptance # 687356

TITLE:

Anti-cancer Therapeutic Compositions Containing Whey Protein Concentrate

APPLICANT: INVENTORS:

Immunotec Research Ltd Phil Gold, Gustavo Bounous:

CLAIMS.1) A method of treating cancer In a patient in. need thereof Including the administration to said patient of a substantially undenatured whey protein concentrate which contains substantially all heat! labile whey proteins of the source milk with glutamylcysteine groups and disulfide Intramolecular bonds in an amount sufficient to replenish depleted Intracellular glutathione, enhance Immune response and exert anti-cancer effects.

2) The use of a substantially undenatured whey protein concentrate to replenish depleted Intracellular glutathione, enhance Immune response and exert anti-cancer effects In a patient having cancer, which concentrate contains substantially all heat labile whey proteins of the source milk with glutamylcysteine groups and disulfide Intramolecular bonds In an amount sufficient to replenish depleted intracellular glutathione, enhance immune response and exert anti-cancer effects in a patient having cancer.

March 13,1998

Immunonet Bulletin

GUSTAVO BOUNOUS, M.D., FRCSC Director, Research and Development



Gustavo Bounous, MD, FRCSC, has had a distinguished career in medical research and co-authored numerous articles in major professional journals worldwide. Born in Italy where he completed his studies (at the University of Turin) and his residency in surgery (at the University of Genoa), Dr. Bounous moved to the United States in 1956 and, until 1961, was a Research Fellow in surgery at the Indiana Medical Center, Indianapolis. With his work focusing on systemic and regional hemodynamics as well as renal hypertension, Dr. Bounous was responsible for elucidating the mechanism whereby normal blood pressure and blood flow are maintained in the kidney under pathological conditions.

In 1963, he moved to Canada and commenced an academic career that led him to become Professor of Surgery, firstly at the University of Sherbrooke (1973-1985), then at McGill University (1985-1993). Further to his discovery in 1964 of the primary role of pancreatic protease in the pathogenesis of intestinal hemorrhagic lesions associated with shock, which had important implications for pathophysiology and treatment of this condition, Dr. Bounous was awarded the 1965 medal of the Royal College of Physicians and Surgeons of Canada.

Independent confirmation of the adverse effect of pancreatic protease in several intestinal disorders inspired Dr. Bounous to study possible reduction of pancreatic secretions by dietary means, His first step consisted in developing and pioneering the use of "elemental" diets in the prophylaxis and treatment of intestinal lesions associated with shock, intestinal ischemia, radiation, cancer chemotherapy, and Crohn's disease. In 1968, he was named Career Investigator of the Medical Research Council, an award that was reconfirmed until 1993, the year of his retirement from McGill University.

In 1978, Dr. Bounous initiated a novel research program to search for a dietary protein source that would boost the immune system, in conjunction with a colleague from the McGill University Faculty of Medicine, Studies led to the discovery of an undenatured serum mild concentrate that sustains normal glutathione levels and promotes immumoenhancing and anticarcinogenic activity. Subsequent identification of the active ingredients present in this protein mixture brought on, in 1993, the production of a high-quality bioactive material given the name and trademark Immunocal®.

#### Title

The use of a whey protein concentrate in the treatment of patients with metastatic carcinoma: a phase I-II clinical study.

#### Author

Kennedy RS; Konok GP; Bounous G; Baruchel S; Lee TD

#### Address

Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada.

Source Anticancer Res, 15(6B):2643-9 1995 Nov-Dec

#### Abstract

Glutathione (GSH) concentration is high in most tumour cells and this may be an important factor in resistance to chemotherapy. Previous in-vitro and animal experiments have shown a differential response of tumour versus normal cells to various cysteine delivery systems. More specifically, an in-vitro assay showed that at concentrations that induce GSH synthesis in normal human cells, a specially prepared whey protein concentrate, Immunocal, caused GSH depletion and inhibition of proliferation in human breast cancer cells. On the basis of this information five patients with metastatic carcinoma of the breast, one of the pancreas and one of the liver were fed 30 grams of this whey protein concentrate daily for six months. In six patients the blood lymphocyte GSH levels were substantially above normal at the outset, reflecting high tumour GSH levels. Two patients (#1, #3) exhibited signs of tumour regression, normalization of haemoglobin and peripheral lymphocyte counts and a sustained drop of lymphocyte GSH levels towards normal. Two patients (#2, #7) showed stabilisation of the tumour, increased haemoglobin levels. In three patients (#4, #5, #6,) the disease progressed with a trend toward higher lymphocyte GSH levels. These results indicate that whey protein concentrate might deplete tumour cells of GSH and render them more vulnerable to chemotherapy.

Language Eng Unique Identifier 96271380

#### **MESH Headings**

Adenocarcinoma DT/IM/ME/SC ; Adult ; Aged ; Breast Neoplasms DT/IM/\*PA ; Carcinoma DT/IM/ME/PA ; Carcinoma, Infiltrating Duct DT/IM/PA/\*SC ; Case Report ; Comparative Study ; Cysteine PH ; Female ; Glutathione \*ME ; Hemoglobins AN ; Human ; Lactalbumin AD/PD ; Lactoferrin AD/PD ; Liver Neoplasms DT/IM/SC ; Lymphocyte Count DE ; Lymphocytes ME ; Middle Age ; Milk Proteins CH/PD/\*TU ; Neoplasm Metastasis ; Neoplasm Proteins \*AI/ME ; Neoplasms, Unknown Primary ; Pancreatic Neoplasms DT/IM/ME/PA ; Quality of Life ; Serum Albumin, Bovine AD/PD

#### **Publication Type**

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#### ISSN 0250-7005

Country of Publication GREECE

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0 (whey protein); 0 (Hemoglobins); 0 (Lactoferrin); 0 (Milk Proteins); 0 (Neoplasm Proteins); 0 (Serum Albumin, Bovine); 4371-52-2 (Cysteine); 70-18-8 (Glutathione); 9013-90-5 (Lactalbumin)

## INFOTRIEVE ONLINE - MEDLINE ® Document

#### Title

Modulation of glutathione by a cysteine pro-drug enhances in vivo tumor response.

#### Author

Wang T; Chen X; Schecter RL; Baruchel S; Alaoui-Jamali M; Melnychuk D; Batist G

#### Address

Department of Oncology and Experimental Pharmacology Program, Lady Davis Research Institute, McGill University, Montreal, Canada.

#### Source

J Pharmacol Exp Ther, 276(3):1169-73 1996 Mar

#### Abstract

Glutathione (GSH) is known to play a role in cellular sensitivity to some chemotherapeutic agents and to radiation. Depletion of cellular glutathione increases toxicity of these drugs, and this approach is being explored in the clinic as a form of biochemical modulation using the drug buthionine sulfoximine. The fact that some drug-resistant cell lines have increased GSH levels, and that enhancing glutathione concentrations in animal tissues protects against a variety of xenobiotic agents, suggests a different potential approach to improve anticancer therapy. We previously showed a selective enhancement by the cysteine "pro-drug," L-2-oxothiazolidine-4-carboxylate (OTZ), of GSH concentration in some normal tissues of tumor-bearing rats, whereas there is a paradoxic GSH depletion in tumor. OTZ has been shown to protect animals from a variety of toxins, and in vitro studies showed a selective increase in GSH in normal cells that results in reduced sensitivity to some chemotherapy drugs. This report describes evidence that OTZ provides this effect in an in vivo rat mammary tumor model. We have examined the OTZ "activating" enzyme, 5-oxoprolinase, in these tumors and found it to be 4-fold lower than that of normal rat liver. This may explain at least the lack of increased GSH in tumor in response to OTZ. A limited number of human breast cancer samples show similar activity.

Language Eng Unique Identifier 96184101

#### **MESH Headings**

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#### **Publication Type**

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ISSN 0022-3565

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0 (Prodrugs); 4371-52-2 (Cysteine); 70-18-8 (Glutathione)

INFOTRIEVE ONLINE - MEDLINE ® Document

#### Title

In vitro selective modulation of cellular glutathione by a humanized native milk protein isolate in normal cells and rat mammary carcinoma model.

#### Author

Baruchel S; Viau G

#### Address

Department of Pediatrics and Oncology, McGill University, Montreal, Quebec, Canada.

#### Source

Anticancer Res, 16(3A):1095-9 1996 May-Jun

#### Abstract

We report the in vitro selective inhibitory activity of a humanized whey protein concentrate IMMUNOCAL on growth of mammary carcinoma cells and Jurkat T cells in comparison to normal peripheral blood mononuclear cells. We relate this inhibitory activity to a selective depletion of intracellular glutathione synthesis. The use of humanized whey protein concentrate as a food supplementation may have direct implication in clinical trial with adjuvant chemotherapy.

#### Language

Eng

#### **Unique Identifier**

96273130

#### **MESH Headings**

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The following excerpt is from Chapter IX of. "What You Should Know About The Super Antioxidant Miracle" by Dr. Earl Mindell published by Keats Publishing Inc. 1995.

Dr. Mindell is also the author of the bestsellers: "Earl Mindell's Vitamin Bible",

"Earl Mindell's Herb Bible" and "Food as Medicine".

• • •

## **GLUTATHIONE AND L-CYSTEINE: The Anti-aging and Healthy Eyes Antioxidants**

This humble little protein is found in the cells of nearly all-living organisms on earth, and its primary job is waste disposal.

GSH (Glutathione) has three main detoxifying jobs in the body:

- 1) When there are free radicals lurking about, threatening to start an oxidation reaction, GSH catches them, neutralizes them, passes them on (often to another antioxidant such as Vitamin E and begins the cycle anew;
- 2) In the liver, GSH latches on to toxic substances and binds to them, so the liver can excrete them without being damaged; and
- 3) GSH prevents red blood cells from being damaged by neutralizing unstable forms of oxygen.

We literally cannot survive without this miraculous antioxidant. GSH also plays a role in fighting cancer, stabilizing blood sugar, and cellular repair after a stroke.

## GLUTATHIONE WORKS HARD EVERYWHERE IN THE BODY

Glutathione's antioxidant work is the front-line defense for preventing oxidation of LDL cholesterol, which damages the arteries. It maintains the integrity of red blood cells, and prevents damage to them. If glutathione levels drop anywhere in the body, the burden of toxic stress goes up. Cells with decreased levels of glutathione are more susceptible to the harmful effects of radiation, free radicals and many pharmaceutical drugs.

In addition to the many benefits of glutathione listed below, supplementing it may be useful in modulating blood sugar in diabetics and in boosting performance in athletes.

## HOW WE DEPLETE GLUTATHIONE

GSH levels drop as we age; and can also be depleted by:

- Chronic diseases such as cancer and arthritis
- An overload of rancid oils (such as Polyunsaturated and partially hydrogenated vegetable oils).
- Overexposure to poisons such as pesticides.
- Pharmaceutical drugs that stress the liver such a acetaminophen (Tylenol) and aspirin
- Since glutathione often passes off its neutralized waste products to antioxidants such as vitamin C and vitamin E, and needs the minerals selenium, copper and zinc to do its cleanup work, a deficiency of these impair its function.
- Birth control pills and hormone replacement therapy.

## **GLUTATHIONE KEEPS THE ELDERLY HEALTHY**

Glutathione levels drop as we age which no doubt contributes greatly to the aging process and diseases of aging. Many elderly people suffer from malnutrition. This leads to a depletion of antioxidants in the tissue setting the stage for cancer to take hold.

### **GLUTATHIONE/CYSTEINE BOOST THE IMMUNE SYSTEM**

An important study done in Germany showed that HIV-infected humans and SIV-infected monkeys had low levels of cysteine\_and glutathione. Raising the levels of these substances increased the T cells, a key marker of good immune system function. In the published study the authors hypothesized that part of the mechanism that switches those who are HIV-positive into AIDS is very low cysteine and glutathione levels. I have heard a number of anecdotal reports that cysteine supplements are helping dramatically in HIV-infected people.

### **GLUTATHIONE/CYSTEINE PROTECTS THE DIGESTIVE SYSTEM**

Glutathione also works hard to keep the digestive system healthy, neutralizing free radicals, particularly those caused by unstable fats and oils. It indirectly keeps the digestion healthy by being a key part of the liver's ability to detoxify the body.

## **GLUTATHIONE/CYSTEINE IS CRUCIAL FOR EYE HEALTH**

We've known since the early 1900's that all people with cataracts have low levels of glutathione in the lens of the eye. In a study from the National Cataract Study Group it was reported that there was approximately a 35 percent reduction in cataract formation in the study group with the higher antioxidant levels.

## **GLUTATHIONE/CYSTEINE PROMOTES HEART HEALTH**

Glutathione is the body's first line of defense against oxidation and cholesterol. An Italian animal study even suggests that giving cysteine supplements after a heart attack could greatly reduce damage done to the heart.

## **MOST FREQUENTLY ASKED PRODUCT QUESTIONS**

1) Q. What is the difference between Immunocal® and other whey proteins?

A. Immunocal® was shown to differ from other proteins in its effect upon the immune response. Immunocal®, studies, have shown it not only increases intracellular levels of GSH or glutathione precursors following ingestion, but also builds up the store of these substances inside the cells. This lasts for considerable periods thereafter.

### 2) Q. What is the Product's bioactivity dependant upon?

A. Concentrations of 3 bioactive proteins contained in the milk serum: thermolabiles serum albumin alpha lactalbumin and lactoferin. These are rich in known precursors of glutathione.

### 3) Q. If someone was able to duplicate our technology, could they make the same claims?

A. No. The power of our patents is not in manufacturing. Immunocal® patents relate to methods of use. That is, no other whey protein can state; stimulates the immune system raises glutathione levels and positive effects on HIV. This provided the greatest protection for the company against potential "knock-off" and imitators.

# 4) Q. What is the difference in products or pills that people use as supplements that are stated to be glutathione or cystine?

A. Glutathione is produced intracellularly. When taking a pill, little, if any is absorbed. Immunocal® is a natural delivery system from the cystine to the cell. Cystine, found in Immunnocal®, is a natural precursor for the body's production of glutathione.

### 5) Q. What Is the difference between colostrum and whey protein?

A. The proteins in colostrum have almost no cystine and cystine is what we are looking for. Colostrum is mainly made of immuoglobulin and some Lactoferin at least during the first 26 hours of production. As far as we know from experiments and clinical trials done in Germany it has shown no effect on the immune system. Since the mechanism of action on the immune system is via stimulation of the synthesis of glutathione in the near absence of glutathione precursors in the immunoglobulin fraction explains the lack of effect. On the other hand, Immunocal® contains substantial amounts of thermolabile proteins, which are rich in cystine and glutamylcystine known precursors of glutathione. The replenishment of the glutathione in the lymphocytes determines the intensity of the immune response. It optimizes the proliferation and antibody production by lymphocytes destroying oxiradicals.

### 6) Q. How does the manufacturing of our product differ from other whey proteins?

A. In the manufacturing of other whey proteins several things happen: in the process of heating and pasteurization critical bonds holding the cystine together get broken down and the exact type of proteins that serve to raise glutathione most effectively are often lost or diminished. We've developed a process by which these delicate proteins remain intact in their natural form to serve us most effectively.

### 7) Q. What are some additional benefits that are exhibited in whey proteins?

A. In-vitro studies in Japan show that whey can stimulate the bone cell to produce more bone, hence increasing more bone density. Glutathione from whey protein lowers the cholesterol by stimulating

bile synthesis in the liver. In addition, glutathione is a powerful antioxidant, which will prevent lipid peroxidation, an initial step in arteriosclerosis, better known as hardening of the arteries.

### 8) Q. Can a person who is lactose intolerant take the product?

A. Yes, Immunocal® has less than 1% lactose which will not create any ill effect even in the most severe case of lactose deficiency.

### 9) Q. Who should not take the product?

A. People with an allergy to milk protein, which is rare. Be sure to realize that lactose intolerant is not a milk allergy. Also, someone who has had an organ transplant and is receiving immuno-suppressant therapy should not take this product.

### 10) Q. What are some of the critical ingredients in a daily amount of Immunocal®?

A. 9 Grams of 90% protein, 0 fat, Less than 1% Lactose, Calcium 60 Mg. Selenium 4 micrograms, Potassium 30 mg. Iron 4%, Approx. 40 Calories

### 11) Q. What is the recommended intake of protein for an average adult a day?

A. 50-60 grams of protein.

#### 12) Q. What is the difference in taking Immunocal® as opposed to taking other antioxidants?

A. Immunocal® as such, is not an antioxidant, but provides the building block for the synthesis of glutathione, which is the principal intracellular antioxidant. More importantly, it serves as a detoxifying agent for multiple toxins that we encounter on a daily basis through the environment and medications we're exposed to. It has been well demonstrated to act as an effective protectant against ultraviolet radiation. We mention this because of the continued loss of the ozone layer.

#### 13) Q. What is the best way to mix Immunocal®?

A. Use any juice or liquid that is not above lukewarm temperature. Mix the packet with the liquid in some kind or small container with a lid so that you can shake it. It is then ready to drink. It can also be mixed in applesauce, yogurt, or sprinkled over cereal. DO NOT, mix in blender, place in any liquid that is above lukewarm temperature or let it remain mixed over one hour before drinking. This effects the bio-activity of the product. Immunotec Research has available some small personal blenders that use a plastic spindle and also spin at a slower rate of speed. These work well to blend Immunocal® with liquids.

### 14) Q. Is the milk used in the production of Immunocal® free of steroids, hormones, etc.?

A. Yes, the milk used for all products is supplied from farmers who are under contract with the dairy used by Immunotec. The cows are not given growth hormones and/or steroids. A full

range of tests is carried out prior to milk reception at the plant, as well as random inhibitor screening. In addition to a very vigorous internal testing protocol, as part of its regular duties the FDA performs random screening for all families of drug residues.

#### 15) Can children take Immunocal® and how much should they take?

A.Yes, children can take Immunocal<sup>®</sup>. They should take approximately 1/4 tsp. For every 3 lbs. Of body weight mixed with their favorite juice, etc., as long as it is not mixed in anything warmer than lukewarm.

### 16) Does Immunotec Research Ltd. have product liability?

A.Yes, Immunotec Research Ltd. has product liability on all of its fine products.

#### 17) Is Immunocal® certified kosher?

A.Yes, this product is kosher when identified with a label bearing the MK Kosher Dairy symbol. Kashrut Certificate KosherThis is to certify that the following product, distributed by the above mentioned Company, is under the supervision of the Jewish Community Council of Montreal/Vaad Ha'ier and is kosher DAIRY not Cholov Yisroel for year-round use EXCLUDING PASSOVER.

# "I don't have health problems, I feel fine!"*REESER* "Why Should I Take Immunocal®?"

Answer: Based on the amount of pollution in the air we breathe, acceptable contamination and chemicals in the food and water we consume, and the thoughtless exposure to other people's contagious ailments we encounter on a daily basis, everyone should be taking Immunocal®. Your immune system is the only natural defense your body has against these harmful intruders. Immunocal® helps keep your immune system at its optimum level so it can effectively combat these constant threats to your body.

- If you are middle-age or older, you've probably witnessed changes in your body's appearance when stepping out of the shower and in front of a mirror. Most of the changes you see in your reflection are actually originating from the changes taking place inside your body. It's nature's way of letting you know your body is gradually losing the ability to maintain itself. Many people, who witness changes in their appearance, will run out and buy vitamins, minerals and other nutritional supplements in hopes of regaining their youth. Others will begin diets or exercise and jogging routines in an effort to improve their body's appearance and perhaps their overall health.
- Unfortunately, few people ever consider their immune system. Very few really know anything about their immune system and how it's supposed to function. Most take it for granted. The truth is, even the healthiest immune system fluctuates on a daily basis.
- Strenuous exercise, dieting and fatigue from working can all reduce the efficiency of your immune system. The lower your immune system drops, the more vulnerable you become when exposed to virus or flu bacteria and other contagious ailments.
- Every part of your body competes for the antibodies produced by your immune system. Your liver is the filter system for your body so it demands a majority of the available antibodies to combat chemicals, pollution and toxic substances that enter your body.
- Each organ within your body has a specific and dedicated function. Your immune system is a guardian to protect the health of each organ and your entire body. Nothing can do more to protect your overall health than the maintaining your immune system at its optimum level. In fact, researchers have found that a low immune system drastically reduces the benefits a person can receive from vitamins, minerals and other supplements. This finding holds true with many treatment medications. The lower the immune system, the less effective they are. So, if you want to get your money's worth from the medications and supplements you take, you should elevate your immune system first. Immunocal® is patented and supported by clinical studies to perform according to its manufacturer's claims.
- Research has determined that once a person passes the age of fifty, the efficiency of their immune system can drop as much as 34%. Perhaps this explains why so many seniors are making more frequent trips to their doctors. A daily dose of Immunocal® will maintain the immune system at its optimum level, which can allow the body to provide a natural defense for combating aging and many of those age-related ailments.
- More and more healthcare professionals are in agreement. Based on the lack of natural nutrients in the food groups, people should be taking nutritional supplements to ensure their own better health. The most recommended are vitamins, minerals and antioxidants. Immunocal® is not only an antioxidant but it provides the body with the ability to take full advantage of any other vitamin, mineral or antioxidant supplements.
- Of all the supplements available on the market today, Immunocal® is the only natural product that's specifically produced to elevate your body's immune response system.

## Help Your Body Heal Itself...Take Immunocal® Every Day.

## **Press Release** Cysteine supplement may help lung patients

SAN DIEGO, Apr 30 (Reuters Health) -- A nutritional supplement may be useful for patients with lung disorders, such as chronic obstructive pulmonary disease or cystic fibrosis, according to a Toronto researcher.

The supplement, called Immunocal, increases body levels of glutathione, a protein that can improve muscle performance and help fight oxidative stress. The product is a specially pasteurized form of cow's milk whey protein that is rich in cysteine, an amino acid that the body uses to produce glutathione, said Dr. Larry C. Lands, of McGill University Health Centre in Montreal, Quebec, Canada, in an interview with Reuters Health.

Unlike other cysteine sources, the cysteine found in Immunocal is both biologically active and in a form that is readily available for cellular uptake, said Lands, who presented study findings on the supplement recently at the American Lung Association/American Thoracic Society International Conference here.

In the study, 20 healthy, young volunteers were randomly assigned to take either Immunocal daily or a casein placebo, which is low in cysteine. After 3 months, there was a 13% increase in work capacity and peak power in leg muscles during cycle testing among those taking Immunocal, but no similar improvement was found in the placebo group. The concentration of glutathione increased in white blood cells by 35%.

"In situations of ongoing stress, like chronic obstructive pulmonary disease, like cystic fibrosis, there is an even greater demand (for glutathione)," Lands said. The researchers are currently beginning a clinical trial of Immunocal in which they expect to enroll approximately 30 patients with cystic fibrosis.

# **IMMUNOCAL®** Nutritional Information

Per Pouch (10g)

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TOTAL FAT (mg)	13
SATURATED FAT (mg)	8
POLYUNSATURATED FAT (mg)	1
MONOUNSATURATED FAT (mg)	4
CHOLESTEROL (mg)	.037
SODIUM (mg)	25
POTASSIUM (Mg)	45
TOTAL CARBOHYDRATE (mg)	100
DIETARY FIBER (mg)	-
SUGARS(mg)	120
PROTEIN (g)	9
VITAMIN A (µg RE)	<1
VITAMIN C (mg)	-
CALCIUM (mg)	35
MAGNESIUM (mg)	5.8
CHLORIDE (mg)	.35
IRON (mg)	.93
THIAMIN g)	.05
RIBOFLAVIN (mg)	.02
NIACIN (mg)	
PHOSPHORUS (mg)	21
CALORIES	40
CALORIES FROM FAT	.10



## As listed in the Physicians' Desk Reference (PDR) IMMUNOCAL® PDR® 2006 NUTRACEUTICAL (Bonded cysteine supplement) Powder Sachets DESCRIPTION and CLINICAL PHARMACOLOGY IMMUNOCAL® is a U.S. patented natural food protein

IMMUNOCAL® is a U.S. patented natural food protein concentrate in the FDA category of GRAS (generally recognized as safe) which assists the body in maintaining optimal concentrations of glutathione (GSH) by supplying the precursors required for intracellular glutathione synthesis. It is clinically proven to raise glutathione values (Lands et al, 1999).

Glutathione is a tripeptide made intracellularly from its constituent amino acids L-glutamate, L-cysteine and glycine. The sulfhydryl (thiol) group (SH) of cysteine is responsible for the biological activity of glutathione. Provision of this amino acid is the rate-limiting factor in glutathione synthesis by the cells since cysteine is relatively rare in foodstuffs.

Immunocal<sup>®</sup> is a bovine whey protein isolate specially prepared so as to provide a rich source of bioavailable cysteine. Immunocal<sup>®</sup> can thus be viewed as a cysteine delivery system.

The disulphide bond in cystine is pepsin and trypsin resistant but may be split by heat, low pH or mechanical stress releasing free cysteine.

When subject to heat or shearing forces (inherent in most extraction processes), the fragile disulfide bonds within the peptides are broken and the bioavailability of cysteine is greatly diminished.

Glutathione is a tightly regulated intracellular constituent and is limited in its production by negative feedback inhibition of its own synthesis

through the enzyme gamma-glutamylcysteine synthetase, thus greatly minimizing any possibility of overdosage.

Glutathione has multiple functions:

1. It is the major endogenous antioxidant produced by the cells, participating directly in the neutralization of free radicals and reactive oxygen compounds, as well as maintaining exogenous antioxidants such as vitamins C and E in their reduced (active) forms.

2. Through direct conjugation, it detoxifies many xenobiotics (foreign compounds) and carcinogens, both organic and inorganic.

3. It is essential for the immune system to exert its full potential, e.g. (1) modulating antigen presentation to lymphocytes, thereby influencing cytokine production and type of response (cellular or humoral) that develops, (2) enhancing proliferation of lymphocytes thereby increasing

magnitude of response, (3) enhancing killing activity of cytotoxic T cells and NK cells, and (4) regulating apoptosis, thereby maintaining control of the immune response.

4. It plays a fundamental role in numerous metabolic and biochemical reactions such as DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport and enzyme activation. Thus, every system in the body can be affected by the state of the glutathione system, especially the immune system, the nervous system, the gastrointestinal system and the lungs.

## **INDICATIONS AND USAGE**

IMMUNOCAL® is a natural food supplement and as such is limited from stating medical claims per se. Statements have not been evaluated by the FDA. As such, this product is thus not intended to diagnose, cure, prevent or treat any disease.

Glutathione augmentation is a strategy developed to address states of glutathione deficiency, high oxidative stress, immune deficiency, and xenobiotic overload in which glutathione plays a part in the detoxification of the xenobiotic in question. Glutathione deficiency states include, but are not limited to: HIV/AIDS, infectious hepatitis, certain types of cancers, cataracts, Alzheimer's Disease, Parkinsons, chronic obstructive pulmonary disease, asthma, radiation, poisoning by paracetamonol and related agents, malnutritive states, arduous physical stress, aging, and has been associated with sub-optimal immune response. Many clinical pathologies are associated with oxidative stress and are elaborated upon in numerous medical references.

Low glutathione is also strongly implicated in wasting and negative nitrogen balance (Droge and Holm, 1997), notably as seen in cancer, AIDS, sepsis, trauma, burns and even athletic overtraining. Glutathione supplementation can oppose this process and in AIDS, for example, result in improved survival rates (Herzenberg et al, 1997).

## CONTRAINDICATIONS

IMMUNOCAL® is contraindicated in individuals who develop or have known hypersensitivity to specific milk proteins.

## PRECAUTIONS

Each sachet of IMMUNOCAL® contains nine grams of protein. Patients on a protein-restricted diet need to take this into account when calculating their daily protein load. Although a bovine milk derivative, IMMUNOCAL® contains less than 1% lactose and therefore is generally well tolerated by lactose-intolerant individuals.

## WARNINGS

Patients undergoing immunosuppressive therapy should discuss the use of this product with their health professional.

## **ADVERSE REACTIONS**

Gastrointestinal bloating and cramps if not sufficiently rehydrated. Transient urticarial-like rash in rare individuals undergoing severe detoxification reaction. Rash abates when product intake stopped or reduced.

## **OVERDOSAGE**

Overdosing on IMMUNOCAL® has not been reported.

### **DOSAGE AND ADMINISTRATION**

For mild to moderate health challenges, 20 grams per day is recommended. Clinical trials in patients with AIDS, COPD, cancer and chronic fatigue syndrome have used 30-40 grams per day without ill effect. IMMUNOCAL® is best administered on an empty stomach or with a light meal. Concomitant intake of another high protein load may adversely affect absorption.

## RECONSTITUTION

IMMUNOCAL® is a dehydrated powdered protein isolate. It must be appropriately rehydrated before use. Remains bioactive up to 12 hours after mixing. DO NOT heat or use a hot liquid to rehydrate the product. DO NOT use a high-speed blender for reconstitution. These methods will decrease the activity of the product. Proper mixing is imperative. Consult instructions included in packaging.

## HOW SUPPLIED

10 grams of bovine milk protein isolate powder per sachet. 30 sachets per box.

## STORAGE

Store in a cool dry environment. Refrigeration is not necessary. Patent no.'s: 5,230,902 - 5,290,571 - 5,456,924 - 5,451,412 - 5,888,552

## REFERENCES

1. Baruchel S, Viau G, Olivier R. et al. Nutraceutical modulation of glutathione with a humanized native milk serum protein isolate, Immunocal®: application in AIDS and cancer. In: Oxidative Stress in Cancer, AIDS and Neurodegenerative Diseases. Ed.; Montagnier L, Olivier R, Pasquier C. Marcel Dekker Inc. New York, 447-461, 1998 2. Bounous G, Kongshavn P. Influence of protein type in nutritionally adequate diets on the development of immunity. In Absorption and Utilization of Amino Acids Vol.II. Ed. M. Friedman. CRC Press, Inc., Fla. 2:219-32, 1989 3. Bounous G, Gold P. The biological activity of undenatured whey proteins: role of glutathione. Clin Invest Med 14:296-309, 1991 4. Bounous G, Baruchel S, Falutz J. Gold P. Whey proteins as a food supplement in HIV-seropositive individuals. Clin Invest Med. 16:3; 204-209, 1992 5. Bounous G. Whey protein concentrate (WPC) and glutathione modulation in cancer treatment. Anticancer Res. 20:4785-4792,2000 6. Bounous G. Immunoenhancing properties of undenatured milk serum protein isolate in HIV patients. Int. Diary Fed: Whey: 293-305, 1998 7. Droge W, Holm E. Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction. FASEB J: 11(13):1077-1089, 1997 8. Herzenberg LA, De Rosa SC, Dubs JG et al. Glutathione deficiency is associated with impaired survival in HIV disease. Proc Natl Acad Sci 94:1967-72,1997 9. Kennedy R, Konok G, Bounous G et al.. The use of a whey protein concentrate in the treatment of patients with metastatic carcinoma: A phase 1-II clinical study. Anticancer Res. 15:2643-50,1995 10. Lands LC, Grey VL, Smountas AA. Effect of supplementation with a cysteine donor on muscular performance. J. Appl. Physiol. 87:1381-1385, 1999 11. Locigno R, Castronovo V. Reduced glutathione system: Role in cancer development, prevention and treatment. International Journal of Oncology 19:221-236, 2001

 Lomaestro B, Malone M. Glutathione in health and disease: pharmacotherapeutic issues. Ann Pharmacother 29: 1263-73,1995
 Lothian B, Grey V, Kimoff RJ, Lands. Treatment of obstructive airway disease with a cysteine donor protein supplement: a case report. Chest 117:914-916, 2000
 Meister A. Glutathione. Ann Rev Biochem 52:711-60,1983
 Peterson JD, Herzenberg LA, Vasquez KK, Waltenbaugh C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. Proc.Natl. Acad. Sci. 95:3071-3076, 1998
 Watanabe A, Higachi K, Yasumura S. et al. Nutritional modulation of glutathione level and cellular immunity in chronic hepatitis B and C. Hepatology. 24:597A, 1996

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