Fifth Condensation
MONOGRAPH

Enhanced Transfer Factor

Dietary Supplement Containing Biologically Active Substances For Improved Immune Function

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Table of Contents

Introduction

AIDS, the very mention of the word causes visions of decimated persons, communities and even continents. The year 2000 estimates put the magnitude of the worldwide AIDS problem at 50 million infected, 6 million new cases a year, 16 million dead, 10 million orphans with a projection of 40 million AIDS orphans by 2010.[1] Sub-Saharan Africa was reported to account for 2.6 million AIDS deaths in 1999 in a population that by some estimates includes one-third of its 15-49 year olds as HIV infected.[2] These figures are especially disturbing when we remember that HIV was unknown only two decades ago. As serious as these statistics are the information on Hepatitis C is even more disturbing.

Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis, and liver cancer worldwide.[3] It is estimated that about 170 million people are chronically infected with HCV.[4] Hepatitis C virus (HCV)-related end-stage cirrhosis is currently the first cause of liver transplantation.[5] Hepatitis C was first identified in 1989.[6] The normal course of the disease runs 10-20 years.[7] As Hepatitis C infections mature in a greater number of infected persons will become candidates for liver transplants, far outstripping the available supply of transplantable livers. The spector of a black market in transplantable livers appears very real.

Not only are new and deadly diseases gaining power but antibiotics are beginning to fail us as antibiotic-resistant "superbugs" become a global problem."[8] Even the foods we eat are not safe. In fact, over a dozen new foodborne pathogens have been identified in the last twenty years.[9] The rapidity of air travel makes the most distant outbreak only hours away.

Our immune system—an intricate, interrelated defensive force made up of a trillion cells-- is our protection from this deadly and daily onslaught.[10] Our health, quality of life, and indeed our very survival, depend on the effectiveness of our immune response. Today many factors contribute to the general weakening of our body's defenses. We will examine the nature of the immune system and consider the recent research on natural agents that can potentially save lives, thereby enabling us to make choices that can improve our health and protect us in an increasingly dangerous environment.

The Immune System [11]

Many times, however, our innate immune ability is insufficient against the variety of microbes we encounter daily. In these cases, our immune system has the ability to learn new skills and construct new tools to deal with these microbial invaders. These immune responses are called *adaptive* or *acquired responses.*
"T cells" and "antibodies" are components of the immune system that are involved in adaptive responses. Once we are exposed to an infectious agent, our bodies destroy that agent by trying to identify it and react to it. This process takes about ten to fourteen days. After we have successfully dealt with an infection, our immune system retains a memory of what it has learned about this particular microbial culprit so that the body is prepared if attacked again. Typically, we are not even aware of subsequent exposures to the previously encountered microbe because our immune system responds so rapidly and with overwhelming force giving the microbe no opportunity to grow effectively. This adaptive response is the result of *acquired immunity.* This immune response is slow but normally very effective.

The Innate Immune System

The innate immune system is made up of various receptors, messenger molecules such as interferon, and natural killer (NK cells) which are our first-line defenders against cancer and infectious disease.[12] The innate immune response is characterized by the fact that it *does not* require prior exposure to an infectious agent."[13] Further, the intensity of an innate response does not change when the system is repeatedly exposed to the same agent. The innate response works instead by recognizing distinct patterns in microorganisms and reacting to them.[14, 15] Pattern recognition is innately coded into our immune system DNA and does not require us to have prior exposure to the microbial agent.

There are remarkable parallels in the innate immune systems of widely separated organisms, indicating that these ancient defense systems are essential to survival.[16] In the past, the innate immunity of vertebrates has been considered archaic and obsolete, but today the innate immune system is regarded as *essential* to the function of adaptive immunity.[17]

NATURAL ANTIBODIES

Natural antibodies are always present and do not require outside stimulus to appear. The main reason for their continual presence is their ability to target dangerous agents that are very common in the environment. These antibodies are not only produced by an effective immune system, but are also able to promote a more effective immune response. After the initial identification of the microbial invader, other antibodies are elicited as a part of the adaptive immune response.

THE COMPLEMENT SYSTEM [18]

The identification or tagging of the infected or malignant cell by an antibody is part of what's called the *complement tagging process.* The complement process is part of the innate immune system, and it provides the initial, if incomplete, antimicrobial defense. The complement system serves three main functions:

1. ***Opsonization.*** This involves tagging damaged or infected cells that need to be destroyed and cleared from the system.

2. ***Chemotactic response***. The complement system sends out signals that mobilize immune cells and draw them to the site of infection.

3. ***Membrane attack complex* (MAC).** MAC is formed to destroy tagged cells. Essentially, MAC is an assembly of complement proteins that punch a hole in the lipid (fat) membrane of the invader, allowing water to rush in and burst the membrane like an over inflated balloon. Some bacteria and cancer cells have an ability to destroy MAC if its formation is slow, so MAC speed is essential.[19]

It is important to note that the cell membranes of animals are made up of two layers of lipids. Animal cells appear as a minute drop of water inside a bubble made up of two layers of fat. Because of this, many viruses wrap themselves in a portion of the host's lipid membrane when they bud out from the infected host cell. By wrapping themselves in a portion of host membrane, viruses protect their fragile RNA or DNA fragments within the lipid envelope. The envelope also acts as a cloak, allowing the virus particle to evade the host immune system by masquerading as a normal, albeit small, cell. Viruses that wrap themselves in host membrane are called *enveloped viruses.* A partial list of enveloped and non-enveloped viruses is shown below. As you can see, the list of enveloped viruses reads like a "who's who" of the most notorious viruses emerging today.

ENVELOPED AND NONENVELOPED VIRUSES [20]

Enveloped

Hepatitis B	Herpes simplex	Varicella zoster
Epstein-Barr	Smallpox	Hepatitis C
HIV	Rubella	Yellow Fever
Ebola	Hanta	Influenza
Parainfluenza	Mumps	Measles
Rabies		

Nonenveloped

Human papillomavirus
Hepatitis A

Enveloped viruses, unlike cells, do not contain membrane repair machinery. This weakness can be exploited by the complement system. Even a tiny MAC prick will burst the viral bubble and destroy its infectivity.[21] Clearly then, the complement component of the innate immune system is critical in our ability to fight viral infections.

KILLER CELLS

The main function of immune cells like cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells is destroying damaged or infected cells. CTLs receive their initial training in the thymus gland, which is part of the adaptive immune system and will be discussed later. However, NK cells, as mentioned earlier, are part of innate response. They target cells that are missing the self-marker that identifies a cell as one of our own.[22] Foreign cells do not have such self-markers, and cancer cells often have lost their self- markers. Cells without self-markers are attacked by NK cells, while normal cells with high levels of self-markers are intentionally spared from NK cell attack.[23] One could say that NK cells are like a National Guard battalion—they have roles in both defending against foreign invaders and maintaining domestic order against seditious cells in the body politic.

A number of conditions are associated with low NK cell activity—cancer, acquired or congenital immunodeficiencies, chronic illnesses and infections, autoimmune diseases and several genetic and behavioral disorders.[24] The young, the old and the stressed are more susceptible to immunological breakdown. Augmenting NK cell activity may be critical in strengthening immunity in members of these groups. Laboratory findings indicate that the young may have a reduced resistance toward cancer because of their diminished NK activity.[25] NK cells from elderly people show a decreased ability to multiply when stimulated and demonstrate an impaired killing capacity. [26]

Stress from a variety of sources such as poor nutrition, emotional strain, infectious assault, cancer or injury will weaken the immune system's ability to learn new healing strategies. Inappropriate psychological reactions to stress, fatigue associated with chronic stress, and physical injury can lead to a disruption of immunity and suppressed NK cell activity.[27] [28] [29] Continuous stress reduces NK activity and allows tumors to grow faster.[30] Individuals with low NK cell activity also tend to experience more frequent and severe forms of chronic fatigue immune dysfunction syndrome (CFIDS).[31] Without functionally efficient NK cells, other cells of the immune system are not optimally activated.[32] Dietary supplements that enhance NK cell activity may be critically important.

The Acquired Immune System

Acquired immunity is the result of immune system adaptation to new pathogens that have invaded the body. In order to adapt to these newly introduced threats, the immune system must first recognize the threat, then develop a set of specialized tools and finally, maintain a long-term memory of the organism to protect against possible re-infection. Four critical components of acquired immune response are essential to its proper function. They are (1) the thymus gland and T cell development, (2) antibodies, (3) cytokines and (4) transfer factor.

THE THYMUS AND T-CELL DEVELOPMENT

The education of immune cells can be compared to a school system having grammar school, prep school, college and graduate level training. The thymus gland is the grammar and prep school for three groups of immune cells. Because of the involvement of the thymus, these cells are called T-cells. They include helper T-cells, suppressor T cells and cytotoxic T-cells (most often called cytotoxic T-lymphocytes).

Each type of T-cell has its own particular function. Helper T-cells assist the other immune system cells in performing their important functions. Suppressor T-cells control immune response and keep the immune system from overreacting. Both helper and suppressor T-cells perform their function by working indirectly through other immune cells. Cytotoxic T-lymphocytes, however, act directly on offending cells. CTLs are programmed in the thymus to look for self-markers and foreign markers. A combination of markers on the same cell identifies it as one of the body's own cells that has been damaged.

The immune training functions of the thymus gland are weak in infants and increase in strength until puberty. After puberty, the thymus gland begins to shrink and continues to diminish in size and effectiveness throughout the

rest of our lives. The reduced training of T cells by the aging thymus is thought to be responsible for the immune deficiencies that develop during aging.[33] It is the job of the thymus to help us react against foreign cells and not against our own normal cells. As the thymus shrinks, the body's normal immune response to foreign cells weakens, while the autoimmune attacks on our own tissues becomes stronger. This situation is called the *aging paradox*.[34]

Incompetent thymic training produces T-cells that are unable to adequately interpret the immunological messages they receive from their environment. Dietary supplementation that supports the thymus and improves T-cell function results in a cascading improvement in the overall immune response.

ANTIBODIES

Antibodies are protein molecules produced by B-cells. Natural antibodies react against the most common features of the most common pathogens. Natural antibodies are so important that they are coded into our DNA and are part of our innate immune system. This is only a small portion of our total antibody repertoire. We acquire most of our antibodies as a result of a process of immune recognition and reaction. This process usually takes 10 to 14 days to mature. Structurally, antibodies have claw-like features that allow the antibody to seize unto foreign microbes or damaged cells. Once the antibody has attached itself to an offending cell, the rest of the immune system reacts by attacking the tagged cell and destroying it.

MACROPHAGES --"BIG EATERS"

Macrophages ("big eaters") are large immune cells that engulf and degrade foreign, dead or damaged cells. If the engulfed cell is infected or malignant, the macrophage retains intact any new foreign sequences that can be used as antigens. Antigens serve as recognition markers used by the immune system--to stimulate antibody production. Macrophages then act as *antigen-presenting cells,* which means that the macrophages present the newly discovered antigens in a form that T-cells can recognize. Once this has occurred the immune system can then initiate an adaptive immune response to eliminate any other foreign or cancerous cells.

Memory T-cells and B-cells are produced by the immune system as a means of storing the immunological information that has been gained by the host. Because of its memory capacity, the response of the immune system during the second exposure is usually so effective that we are not even aware that we have been re-exposed.

CYTOKINES

In addition to producing cells, the immune system produces a host of messenger and control molecules known as *cytokines*. Cytokines play important roles in all phases of immune response. Some cytokines act as mediators of innate immunity, while others are involved mainly in acquired immunity. In the latter case, cytokines control the activation, growth and differentiation of cells. Transfer factors may be among the most important cytokines.

Transfer Factor (TF)

INTRODUCTION: WHAT IS TRANSFER FACTOR?

While studying tuberculosis in the late 1940s, Dr. H. Sherwood Lawrence, discovered that the immune competence of a donor could be transferred to a naïve recipient by using low molecular weight extracts obtained from white blood cells.[35] Dr. Lawrence called these small molecule extracts transfer factor (TF). If the thymus gland can be compared to grammar school and prep school, transfer factor can be compared to collegiate and graduate level training for the immune system. The importance of a more sophisticated, immunological education should not be underestimated. Scientists later found transfer factors to be universally effective, regardless of the differences between the species of the donor and recipient. This aspect of transfer factors is partly explained by this core scientific belief: *the more essential a material or structure is to living organisms, the more common it is to see this material or structure throughout living systems.* Transfer factors are essential components of even the most primitive immune systems.[36]

One basic principle of the immune system is that it must be able to respond quickly and specifically, while not

exhausting itself by over responding and attacking normal tissue. Transfer factor preparations consist of three identifiable fractions named by their discovered effects on the immune system. They are *inducer, antigen specific* and *suppressor* fractions.[37] The TF inducer fraction triggers a general state of readiness in the immune system, and the antigen-specific fraction is an array of critical tags used by the immune system to identify a host of enemy microbes. Meanwhile, the suppressor fraction keeps the immune system from focusing all its strength on a defeated infection and ignoring new microbial threats; it is responsible for controlling immune overreactions that can cause autoimmune disorders. Each fraction (inducer, antigen specific, and suppressor) improves one or more aspects of the adaptive ability of the immune system.

As the product of a competent immune system, transfer factor can teach a less competent immune system how to better respond. For example, mammalian mothers transfer immunity to their offspring through the colostrum in their milk. A mother's gift of transfer factor greatly improves the immunity of her offspring and many times means the difference between life and death for the newborn. The modern dairy cow is in intimate microbial contact with her environment., Because of this and because she produces so much colostrums, she also produces far more transfer factor than her calf needs. Harvesting the excess colostrum and isolating its transfer factor provides an abundant and beneficial source of transfer factor for human consumption.[38]

Unlike antibodies that are large molecules, transfer factors are quite small.[39] In fact, their small size helps to make them nonallergenic.[40] And while antibodies are used up when they attach themselves to the offending cell or protein, transfer factors perform a different role. They are immune messenger molecules that educate and alert naive immune cells to an impending danger. In this regard, transfer factors perform a catalytic role in the immune system—triggering the effect without being consumed.[41]

Originally, transfer factor preparations were administered by injection.[42] However, later studies showed that transfer factor was equally effective when taken orally.[43] The nonspecific inducer and suppressor fractions of transfer factors are fully compatible between different species. The antigen-specific transfer factors are each specific to a particular pathogen and these pathogens vary from species to species. An example might help illustrate the potential benefit of antigen specific transfer factors in recipients of a different species than the donor.

Although the highly contagious and often fatal disease of smallpox devastated many European and American communities in the 1700s, one subset of individuals seemed to survive the epidemics—milkmaids. Milkmaids often contracted cowpox from infected animals during milking through a cut or break in the skin. Milkmaids infected with cowpox usually followed a mild course of the disease that was resolved without much difficulty. It was then found that milkmaids who had contracted cowpox were immune to smallpox. In a classic, early inoculation experiment, Edward Jenner vaccinated a young boy with cowpox and then demonstrated that the child was protected from contracting smallpox. The relationship between smallpox and cowpox is a case of antigen crossover where the immune system recognizes two different pathogens after being exposed to either one. Antigen crossover between the of human and bovine pathogens is highly likely. (Appendix 1 contains a more complete list of human pathogens and their related bovine pathogens). The antigen-specific, bovine transfer factors should therefore provide protection to humans against the corresponding human pathogens, resulting in a milder course of disease.

BENEFITS OF TRANSFER FACTOR

The exciting benefits of transfer factors—the essence of the immunological message, could spark a revolution in medicine. The need for such a new weapon in our immune defense arsenal is clear. "Transfer factor [has] an important role to play in modern medicine which, from AIDS to Ebola, faces the emergence of new viruses or the resurfacing of old pathologies such as tuberculosis."[44] Nevertheless, there are always many who resist new ideas, regardless of the their benefits. In a recent international symposium on transfer factors, Dr. D. Viza summarized this conventional resistance:

> At the end of the 20th century, the triumph of biology is indisputable… However, the triumph of biological science is far from being complete. The toll of several diseases, such as cancer, continues to rise and the pathogenesis of AIDS remains elusive.
>
> In the realm of inductive science, the dominant paradigm can seldom be challenged in a frontal attack, especially when it is apparently successful, and only what Kuhn calls 'scientific revolutions' can overthrow it. Thus, it is hardly surprising that the concept of transfer factor is considered with contempt . . . [since] its putative mode of action contravenes dogmas of both immunology and molecular biology. And when facts challenge established dogmas, be [it] in

> religion, philosophy or science, they must be suppressed. …because they challenge the prevalent paradigm. However, when observations pertain to lethal disorders, their suppression in the name of dogmas may become criminal. Because of the failure of medical science to manage the AIDS pandemic, transfer factor, which has been successfully used for or treating or preventing viral infections, may today overcome *a priori* prejudice and rejection more swiftly.[45]

The benefits of transfer factor have been reviewed and the proceedings of the Tenth International Symposium on Transfer Factor have been published.[46] [47] [48] These reports cover the successful use of transfer factor in addressing viral, parasitic, fungal, malignant, neurological and autoimmune diseases. Transfer factor has been shown to be beneficial to all age groups, from children to the elderly. The benefits from human use of animal-derived transfer factors have been repeatedly illustrated. In like manner the efficacy of the oral administration of transfer factor has been demonstrated. In most of the published research on the use of transfer factor, disease and malaise were present, but the real power of transfer factor is actually in prevention. *The use of transfer factor in the prevention of illness and the maintenance of health is its greatest potential benefit, and its safety when used chronically has been well established.* The future financial burden of medical care could be curbed significantly by the general use of transfer factor.

SAFETY OF TRANSFER FACTOR

Transfer factor has an excellent safety record, and no adverse side effects have been reported. This has been shown even when TF administered in extreme excess or over several years.[49] Infants and the elderly are two groups most at risk for infection. The naturally high levels of transfer factor in colostrum clearly indicate its intended use and safety for infants. In particular, oral administration of transfer factor is convenient and easily accepted by all age groups.[50]

In addition, over 3,000 papers have been written on transfer factor since it was first reported in 1949. Studies on the human use of transfer factor have shown how it can relieve unnecessary suffering simply and safely. For a more complete examination of transfer factor and its benefits to human health, interested readers are referred to the booklet *Transfer Factor: Natural Immune Booster.*

Innate and Adaptive Immunity Working Together

Recent research has significantly advanced our understanding of the interplay between the innate and adaptive immune systems.[51] We now know that the innate immune system initiates and improves the slower, but more specific, acquired immune response.[22] The complement system is where the early innate immune reaction and the later acquired immune reaction merge, providing a continuous immune response.[52] Natural Killer (NK) cells are normally considered part of the innate immune system. Nevertheless, NK cells produce a number of cytokines (messenger molecules) that are potent immune regulators of the adaptive immune response.[53]

Microbial and Malignant Immune Evasion

Most pathogens invading the human body are actively attacked by the immune system. In order to protect themselves, some pathogens have developed "cloak and dagger" immune evasion techniques. "Cloaking" strategies include a continuous changing of surface antigens in a process called antigenic drift or interfering with antigen presentation. This strategy makes the infected cell invisible to certain parts of the immune system.[54] "Dagger" strategies include the infection and destruction of immune cells themselves, as in the case of the Human Immunodeficiency Virus (HIV).

Other evasive techniques used by pathogens involve tactics such as shedding antigenic markers. These antigenic markers are the handles the immune system uses to grab onto infected cells. By putting out numerous unattached handles, the immune cells have their hands so full that they are unable to effectively attach themselves to real pathogens. Meanwhile, other pathogens disrupt the complement system in order to evade detection. For instance, an elegant pathogenic technique involves the production of imitation complement inhibitory proteins (molecular

mimicry) that block complement activation.[55] Another evasive technique used by pathogens involves disruption of cytokine production, which creates a false sense of security in the immune system.[56]

The evasion of the immune system by cancer cells is an instructive example of how invaders can circumvent immunity. Cancer cells are derived from our own cells. This complicates the immune surveillance process since they look so much like our normal cells.[57] Initially, cells that become transformed into cancer cells retain all of the normal self-markers that define them as our own cells. However, these cancer cells also display markers that should not be present on our own cells. These markers indicate that the cell is damaged, and their presence signals the Cytotoxic T-lymphocytes (CTLs) to destroy the cell before it has a chance to multiply. But if immune response is slow, for whatever reason, the cancer cell has a chance to multiply. When the immune system does respond, those cells that are most susceptible to CTL attack will be selectively killed.

Occasionally a cancer cell will mutate further and yield offspring without self-markers. This situation is critical for two reasons. First, the loss of a self-marker increases the ability of the cancer to metastasize. Second, the CTLs can no longer recognize the cancer cell and destroy it. At this point, the NK cells that target foreign cells take over. In fact, both natural and elicited antibodies are commonly present in the serum of cancer patients. Unfortunately, the responses of these antibodies to many cancers are ineffective in stopping tumor growth.[58]

This weak antibody response however, is often sufficient to launch the complement system. Antibody involvement restricts deposition of the complement-generated iC3b tag to tumor cells, and normal tissue surrounding the malignant cells should be spared. Activation of the membrane attack complex (MAC) is often blocked by inhibitory/regulatory proteins that are normally present on our cells. These same inhibitory/regulatory proteins are also present on cancer cells. Because of this cancer cells are also able to reject the developing MAC if its formation is slow.[59] Tumors seem to be able to develop several other immune-escape mechanisms that either inactivate specific immune cells or prevent the activation of anti-tumor mechanisms.[60]

Dietary Supplements

If an infection or cell abnormality is too complex, the inadequately trained immune cells may not be able to develop skills fast enough, causing us to get sick. When this happens, additional outside support may be needed. Conventionally, we have employed drugs such as antibiotics when we are sick. The function of most drugs is to replace rather than strengthen the immune system. Oftentimes the toxicity of a drug toward its target microbe or cancer cell will also have a negative effect on other cells or systems of the body.[61] On the other hand, the role of a supplement is to strengthen the body from within by working with the body rather than circumventing its natural functions. This approach reduces the risk of toxic side effects. Before recorded history, man used dietary supplements to improve his health. Most of these supplements were derived from plants containing peculiar healing properties. Two of the oldest recorded medicinal supplementation codes are the Chinese codex from the Shang dynasty (ca. 1766-1122 BC) and the Indian medical system Ayurveda, first recorded in the seventh century BC. In ancient America, echinacea was used from Texas to Saskatchewan. The whole discipline of *ethno-pharmacology* developed in order to capture and substantiate the folk medicine of cultures throughout the world.

Many of the oldest and most revered supplements have been found to strengthen the immune system. Interestingly plants may not be the most ancient source of immune system supplements used by man. The oldest immunological supplement may in fact be found in the colostrum provided by every mammalian mother who nurses her offspring.

IMMUNOLOGICAL AGENTS FOUND IN COLOSTRUM

Transfer Factor. The first milk of every mammalian mother naturally contains transfer factors that reflect her rich immunological experience.[62] If the baby is allowed to nurse, initial immunity is rapidly established. This is nature's way of quickly educating a naive infant in the hazards of a microbe-infested world.[63] On the other hand, infants who are not breast-fed show a greater susceptibility to infections, allergies and childhood cancer.[64]

The nature of the modern dairy cow is such that she is in intimate microbial contact with her environment and produces far more colostrum—and therefore more transfer factor—than her calf needs. Since transfer factors are universally effective regardless of the differences between the species of the donor and the recipient, harvesting the excess colostrum and isolating the transfer factor provides a commercial source of transfer factor for human consumption.

Originally transfer factor preparations were administered by injection.[65] However, later studies clearly established that transfer factor is also effective when taken orally. It is obvious that nature intended colostral transfer factors to be taken orally.

Transfer factor, as an extract of colostrum, is *generally recognized as safe (GRAS)* and is considered to have a safety profile similar to milk. Although lactose intolerance due to milk ingestion is present to a degree in many populations, even persons who are clinically lactose sensitive can tolerate between two and six grams of lactose, as a result of colonic bacterial degradation of lactose.[66] Unlike large-molecule antibodies, transfer factors are quite small.[67] As stated earlier the small size of transfer factors helps to make them non-allergenic. In fact, it is actually the immunoglobulins (antibodies) found in bovine colostrum that are the source of most cow-milk allergies in humans.[68]

Antibody (Immunoglobulin) Supplements. Absorption of maternal immunoglobulins ceases after the first 30 hours of life for a human.[69] Beyond the first 30 hours of life, no absorption of intact antibodies has been shown in humans.[70] Oral administration of antibodies to adults leads to rapid degradation of the antibodies both due to the acidity of the stomach and the action of intestinal enzymes. This led to the recommendation that both stomach acid and intestinal enzymes be neutralized to obtain maximum benefit from orally administered antibodies.[71]

Rapid transit and incomplete digestion are the hallmarks of diarrhea. It is in just such a condition that oral ingestion of antibodies is most effective.[72] No absorption of the intact antibodies is required since the troublesome agent is in the intestines.

Antibodies from one species are not effective in other species. No positive systemic effects can be expected after oral administration of foreign antibodies to humans.[73]

Lactoferrin. Lactoferrin is a protein that binds iron.[74] Because of its iron-binding properties, lactoferrin has been proposed to act as a *bacteriostatic agent* by withholding iron from iron-requiring bacteria. Lactoferrin is found in high concentrations in human colostrum, but the level of lactoferrin in bovine colostrum is very low. Thus, consuming bovine colostrum as a lactoferrin source is not effective.

ZINC AND THYMUS SUPPORT

Zinc. Zinc is an essential element for growth, nervous system function and especially the immune system response. The relevance of zinc for immune efficiency has been well established.[75] Zinc-deficient persons experience increased susceptibility to a variety of pathogens.[76] The regulation of innate immunity, as well as the function and maturation of lymphocytes and monocytes, is critically dependent on zinc concentration.[77]

With advancing age, humans undergo a progressive reduction in their zinc levels. Studies suggest that the age-related thymic involution (regression) and peripheral, immunological dysfunctions are not intrinsic and irreversible events but are largely dependent on the altered zinc pool.[78] Interestingly, melatonin helps restore zinc balance from negative to positive values which further demonstrates the interdependence the neuroendocrine, digestive and immune systems.[79] As little as ten milligrams of supplemental zinc improved cell-mediated immune response in an older population.[80] Similarly, only five milligrams of zinc per day reduced morbidity and improved immune function, as well as growth, in low birth weight, full-term infants.[81]

Thymulin. Thymulin is a thymus hormone. Diminished levels of thymulin occur in immunodeficiency and autoimmune diseases. It has been demonstrated that thymulin plays a role in immune and neuroendocrine system interactions.[82] Thymulin has also been shown to reduce inflammatory pain.[83] Thymulin is not active by itself. Thymulin requires an equal amount of zinc for it to be biologically active.[84] In one set of tests, the highest degree of vaccine effectiveness was achieved when a mixture of thymulin and zinc was administered concurrently.[85] In the case of AIDS, levels of total thymulin are not diminished, but the amounts of active thymulin are reduced to nearly undetectable levels.[86] By adding zinc, all of the missing thymulin activity was recovered.

Plasma levels of active thymulin are also reduced in cervical cancer due to low zinc bioavailability. Thus, zinc supplementation may restore impaired central and peripheral immune efficiency in cervical carcinoma.[87] A recent examination of the importance of zinc indicated that it "significantly determines development of diseases".[88]

Carbohydrate Adjuvants

AGARICUS BLAZEI (Sen Su Take)

Agaricus blazei is considered by many to be the king of medicinal mushrooms. Reported health benefits of *Agaricus blazei* span millennia and application of modern scientific methods have validated the traditional use and benefits of *Agaricus blazei*. Dr. Fujimiya and his colleagues have studied the effects of *Agaricus blazei* extracts on solid tumors. They found that when a solid tumor is injected with *Agaricus blazei* extracts, the tumor begins to shrink. Most interestingly other tumors present in the host also shrink. Such a distant response is a clear indication of an immune system reaction.[89] Dr. Fujimiya was able to show that the body's natural killer (NK) cells were able to recognize and actively attack the local and distant tumors.[90] Dr. Fujimiya found the cytotoxicity or cell killing activity of *Agaricus blazei* was selective for the tumor cells.

Dr. Mizuno, et al. clearly demonstrated that both the helper T-cell (CD4+), and cytotoxic T-cell (CD8+) populations were significantly increased after oral administration of *Agaricus blazei* extract.[91] 5-Fluorouracil, a common anticancer drug, is known to suppress the immune system.[92] By including *Agaricus blazei* polysaccharide extracts in a 5-Fluorouracil drug program, the antitumor effects of 5-Fluorouracil were enhanced.[93] These results, along with the work of Dr. Ito, clearly indicate that *Agaricus blazei's* antitumor effect occurs through strengthening the host's immune system.[94]

CORDYCEPS SINENSIS

Cordyceps sinensis is a fungus that is highly valued in China as a tonic food and herbal medicine. The use of in Chinese medicine is now centuries old. In ancient China, *cordyceps sinensis* was used to hasten recovery from exhaustion, an effect that has recently been scientifically validated. *Cordyceps sinensis* has been tested in trials involving over two thousand patients. Researchers were unable to establish a toxic dosing level, which shows that it is very safe. The only side effects of chronic ingestion *cordyceps sinensis* have been an increase in sperm count and testes weight. A recent exhaustive two-part review of the Chinese and English literature provides a wealth of historical and scientific validation for the safety and benefits of *cordyceps sinensis*.[95]

Immune System Effects. *Cordyceps sinensis* extract greatly increased the very low levels of interferon-gamma, tumor necrosis factor-alpha, and interleukin-1 in cell cultures of leukemic cells. *Cordyceps sinensis* also increased the production of interleukin 2 and its absorbency by immune cells. Each of these cytokines is associated with increased antiviral and/or antitumor activity as well as overall immune responsiveness.

A preparation of cordyceps caused significant elevation in the number of helper T-cells and increased the helper to suppressor T-cell ratio. Cordyceps augments the NK cell activity. The importance of these effects should not be underestimated (For example see previous discussion on natural killer cells).

Antitumor/Cancer. As discussed earlier, tumors use a myriad of methods to escape immune surveillance. Two of these techniques are down-regulation of self-markers on tumor cell surfaces and reduction of the macrophage migration toward and engulfment of tumor cells. This latter technique is often dramatically seen in lymphomic tumors.

The antitumor effect of *Cordyceps sinensis* is mediated through its immunomodulating action rather than through any direct toxicity toward the cancer cells. *Cordyceps sinensis* extracts caused an increased appearance of self-markers, making the host immune surveillance more effective against tumor cells that down-regulated self-markers as a means of immune evasion. Oral administration of *cordyceps sinensis* also induced an above normal level of macrophage activity, resulting in reduced lymphoma tumor size and increasing the murine survival rate.

Cordyceps sinensis has been tested against other cancer cell lines as well. Extracts of *Cordyceps sinensis* increased the median survival time of mice bearing either Ehrlich ascites carcinoma or Meth A fibrosarcoina by over 300 percent. *Cordyceps sinensis* extract, in combination with blood mononuclear cells, inhibited the proliferation of human leukemic U937 cells by 78 to 83 percent. Cancer cells are often immature cells, and maturation of the cancer cells diminishes their cancerous characteristics. Examination of the U937 cells after treatment with *Cordyceps sinensis* extract showed that about 50 percent of the leukemic cells had become mature monocytes and macrophages. *Cordyceps sinensis* also reduced colony formation of B16 melanoma and helped to maintain NK cell activity in spite of the presence of the immunosuppressive drug cyclophosphamide, suggesting its potential usefulness in treating cancer in immunodeficient patients. Helper T cells were also protected from the deleterious effects of the

immunosuppressive drug prednisolone acetate. These results further substantiate the potential utility of cordyceps in immunodeficient or immunosuppressed patients.

Cordyceps sinensis appears to evoke a balanced immune response. In experimental transplants, high doses of *cordyceps sinensis* (4 g/kg/day) significantly prolonged the survival time of unmatched skin grafts. It has also been suggested that cordyceps may have great potential for the management of human systemic lupus erythematosus (SLE), which is a serious autoimmune disease with multiple organ system involvement. The immunosuppressive ingredients contained in *cordyceps sinensis* are not cytotoxic to human mononuclear cells.

Anti-infective. Oral administration of *cordyceps sinensis* was tested against systemic infection by salmonella. The protective effects were probably due to the observed increase in antibody response. *Cordyceps sinensis* also improves liver function and positively adjusts body immunocompetence in chronic hepatitis B patients.

Summary. *Cordyceps sinensis* has both immunostimulating and immunosuppressive effects. Cordyceps stimulates significant protective effects in both the liver and kidney, and it has a very safe profile even during chronic ingestion of large doses.

GLUCANS

Defense against fungi such as yeast is one of the most primitive functions of the immune system. This is accomplished through recognition of molecular patterns found only in the cell walls of microorganisms. One of the main molecular recognition patterns is poly-1,3-beta-glucose or beta-glucan. Hundreds of papers have been published on various aspects of beta-glucan's ability to modify biological responses.[96]

The natural killer cells require dual signals before they unleash their violence. When a cancer cell is tagged with complement system proteins, the natural killer (NK) cells can attach themselves to the cancer cell. If a second confirmatory signal molecule is present on the cancer cell, the NK cells are activated and the cancer cell is destroyed. If the second signal is absent or if the cancer cell has developed a blocking protein, the tumor cell will survive.

Beta-glucans were first reported to stimulate tumor rejection in 1963.[97] Beta-glucan appears to supply the second signal that completes the activation of NK cells. Having received both recognition and activation signals, the NK cells are authorized to destroy their malignant target.[98] This may be the same mechanism that is responsible for the frequently observed tumor regression that follows an infection.[99]

Bacteria like *Escherichia coli* and *Staphylococcus aureus* can produce lethal septic infections in animals. Treating the animals with beta-glucan prior to bacterial infection prevented death.[100] [101] In humans, preoperative administration of glucan reduced serious postoperative infections and death by 39 percent after high-risk operations.[102]

Beta-glucan has been administered by intramuscular and intravenous injection, and is also bioactive when administered orally.[103] Sources of beta-glucan include yeast, mushrooms,[104] including Shiitake[105] and the Maitake D-fraction[106] and certain higher plants.[107]

MANNANS

Acemannan is the major carbohydrate fraction obtained from the gel of the *Aloe vera* leaf.[108] Most if not all of the immunological benefits of aloe gel appear to come from the acemannan fraction of the gel.

The use of aloe vera gel as a skin treatment is centuries old. Recently acemannan was shown to reduce the effects of radiation damage to skin if applied immediately and continuously for two weeks after radiation exposure.[109] Radiation is also extremely damaging to immune cells. Acemannan appears to be an effective adjunct to surgery and radiation.[110] The benefit of acemannan is probably due to its support of the immune cell populations during and after irradiation.[111]

At least two immune cell types can be strongly affected by acemannan. Acemannan enhanced the number and killing capacity of cytotoxic T-lymphocytes (CTLs) by almost *50* percent.[112] Macrophages incubated with acemannan for ten minutes demonstrated a ten-fold increase in their ability to kill the yeast *Candida albicaus.* After sixty minutes of exposure to acemannan, the ability of macrophages to kill candida rose another three-fold, resulting in a nearly complete destruction of all the fungi.[113] This occurs in spite of the fact that no dose of acemannan was found to be cytotoxic to the target pathogens.[193] Clearly then, acemannan operates throughout the immune system

rather than independent of this system. The antitumor activity of acemannan in tumors is believed to result from macrophage activation and the release of antitumor cytokines.[114 115 116]

Viruses use a variety of mechanisms to avoid destruction by the immune system. One of these mechanisms is the inhibition of T-cells. Pretreatment with acemannan reduced the virus-induced inhibition of T-cells,[117] and acemannan therapy was significantly beneficial for cats exhibiting clinical signs of feline immunodeficiency virus (FIV) infection.[118] Acemannan is one of only a very few plant-derived, anti-HIV products that have been used in a limited number of patients suffering from AIDS.[119] To date, the benefit of acemannan on HIV patient health has been limited in cases of advanced HIV.[120]

Acemannan has shown benefit in other areas as well. Acemannan inhibited adherence of the bacteria *Pseudomonas aeruginosa* to lung cells.[121] In addition its use as a vaccine adjuvant was shown to be beneficial either in raising or sustaining the immune response.[122] Acemannan increased the primary response to the heartworm antigen ten-fold over control levels.[123] A combination of melatonin and aloe extract has been reported to arrest, though not reverse, brain carcinoma.[124] Also, the safety of acemannan at high dosages has been clearly demonstrated.[125] Further, acemannan does not potentiate HIV-1 or herpes simplex virus type 1 (HSV-1) replication.[126]

PHYTIC ACID, INOSITOL HEXAPHOSPHATE, OR IP6

Inositol hexaphosphate, also known as phytic acid (IP6), its lower phosphorylated forms (IP 1-5), and inositol are important in regulating vital cellular functions.[127 128 129 130] IP6 is found in cereal brans and legumes, and it has been shown to be the agent responsible for much of the anticancer activity of high fiber diets.[131] The anticancer action of IP6 has been demonstrated both *in vivo* and *in vitro* against cancers of the liver, breast, prostate, large intestine and colon. The effectiveness of IP6 against human mammary cancers is independent of the estrogen receptor status of the cells.

IP6 is rapidly absorbed and metabolized by human malignant cells in vitro. IP6 up-regulates the expression of tumor suppressor genes and also blocks incitement of tumor activator proteins.These discoveries help in part to explain the decreased tumor aggression and diminished tumor size prompted by IP6.

Olives and Olive Leaf Extracts

OLEUROPEIN, HYDROXYTYROSOL AND ELENOIC ACID

Studies of oleuropein provide a new link between the Mediterranean diet and prevention of coronary heart disease (CHD) and cancer.[132] Indeed many of the beneficial effects of the Mediterranean diet may be derived from oleuropein and its hydrolysis products hydroxytyrosol and elenoic acid.

Oxidatively modified low-density lipoproteins (LDL) contribute to the onset of the atherosclerotic disease. Natural antioxidants abound in the Mediterranean diet and may contribute to the observed protection from coronary heart disease (CHD) by retarding the formation of the atherosclerotic plaque. Not only is LDL oxidation inhibited by oleuropein[133] and hydroxytyrosol[134] but also the blood levels of both total and free cholesterol are significantly reduced.[135]

The olive tree, *Olea europaea*, is a potential source of promising antimicrobial agents for treatment of intestinal or respiratory tract infections in man.[136] The recent discovery that microbial infection and heart disease are correlated[137] provides an additional dimension to the protective features of olive and olive leaf extract consumption in CHD.[138] The addition of oleuropein significantly and immediately decreased outgrowth of Bacillus cereus T spores.[139] Low concentrations of oleuropein also delayed the growth of Staphylococcus aureus.[140] In addition oleuropein improves the macrophage-mediated response during endotoxin challenge leading to an increased cellular and organismal protection.[141]

Elenolic acid has been repeatedly demonstrated to exert antiviral activity. Calcium elenolate reduced influenza viral infectivity and was also demonstrated to be both preventive and therapeutic in the case of parinfluenza 3 virus.[142] More than ten years before HIV was identified, calcium elenolate was shown to inhibit a viral reverse transcriptase enzyme.[143] In the case of myxoviruses, Calcium elenolate was found to be as effective as the anti-viral drug virazole against influenza virus.[144] The safety of oral ingestion was demonstrated in rabbits, rats, mice, dogs and humans in both acute and chronic toxicity models.[145]

Olive and olive leaf extracts provide an array of anti-inflammatory benefits.[146] Hydroxytyrosol was the best

anti-inflammatory component found in olives.[147] Inhibition of inflammation may reduce damage to arterial linings. Hydroxytyrosol was also highly protective against DNA damage which is involved in the pathology of several chronic diseases.[148] There is growing evidence that reactive oxygen species are involved in the aetiology of fat-related neoplasms such as cancer of the breast and colorectum.[149] Hydroxytyrosol is a potent inhibitor of free radical generation in the feces providing a clear mechanism for prevention of colorectal carcinogenesis.[150]

The bioavailability and safety of oleuropein and hydroxytyrosol are excellent. Kinetic data demonstrate that hydroxytyrosol can be quantitatively absorbed at the intestinal level with the majority of the absorbed material excreted in the urine.[151] Neither oleuropein nor hydroxytyrosol were toxic to leukocytes at the concentrations tested.[152]

Phytosterols

Phytosterols are important constituents of healthful diets.[153] Legumes, long known for their healthful properties, are one of the best sources of phytosterols.[154] Peanuts have also been found to be an excellent source of phytosterols.[155] Beta-sitosterol is the major phytosterol in higher plants. Western processed diets contain only 20-25% of the beta-sitosterol present in vegetarian and Oriental diets.[156] Like Vitamin C, humans do not produce any beta-sitosterol. In nature beta-sistosterol is bound to plant fiber, making it difficult to absorb. Concentration procedures break down much of the plant fiber matrix, which should improve the bioavailability of beta-sitosterol.

Phytosterols have been shown to modulate the immune system, inhibit colon cancer development, and normalize cholesterol levels.[157] Beta-sistosterol as an immune-modulator is involved in normalizing T-cell function, dampening overactive antibody responses, and rebalancing DHEA:cortisol ratios.[158] Proliferation of T-cells, increased secretion of IL-2 and gamma interferon, and increased NK-cell activity are some of the immune parameters that are enhanced during immune challenge when phytosterols are present.[159]

Epidemiologic and experimental studies suggest that dietary phytosterols may offer protection from the most common cancers in Western societies, such as colon, breast and prostate cancer.[160] Early work demonstrated that phytosterols including beta sitosterol were protective against chemically induced colon cancers.[161] Rao and Janezic have proposed that the interaction of phytosterols with gut microflora protects the colon from toxic metabolites of cholesterol.[162] High intakes of phytosterols also explained most of the gastric and esophageal cancer protection that results from high vegetable and fruit intakes.[163] Other studies concluded that dietary phytosterols retard the growth and spread of breast cancer cells.[164] Mechanistic studies by Awad, et al. are elucidating the mechanisms whereby phytosterols inhibit prostate cancer cell growth.[165]

Beta-sitosterol has also been identified as the antimicrobial and antifungal constituent of many medicinal plants.[166] When patients suffering from pulmonary tuberculosis added sitosterols to their diet, in addition to an efficacious anti-tuberculosis regimen, the patients' immune parameters and overall quality of life improved.[167]

Phytosterols including beta-sistosterol have been identified as the active anti-inflammatory principles in cactus and other medicinal plants.[168] Beta-sitosterol was found to be nearly as potent as indomethacin in inhibiting ear inflammation.[169] A decrease in the cortisol: DHEAs ratio may in part explain this diminished inflammation.[170]

Benign Prostate Hypertrophy (BPH) is a non-cancerous enlargement of the prostate that affects the quality of life for most men as they enter their fifth and subsequent decades of life. In a rigorous and matched study, the efficacy of phytosterols was validated as an effective approach to BPH.[171] Beta-sitosterol improves urological symptoms and flow measures in BPH.[172] A German multi-center study of 177 BPH patients showed that beta-sitosterol is an effective option in the treatment of BPH.[173] These results were supported by the results of a three month Japanese study employing a low dose of phytosterol containing 180 mg of sitosterol per day. Significant improvement in the patients' International Prostate Symptom Scores (IPSS) and their quality-of-life (QOL) scores were recorded.[174] In a critical review of sitosterol effectiveness in controlling BPH, Lowe and Ku noted that it was sitosterol not its glycoside that has shown the greatest benefit in relieving BPH.[175] Four placebo-controlled studies involving 519 men support this conclusion that the non-glucosidic B-sistosterols improve urinary symptoms and flow measures.[176] The beneficial effects of beta-sistosterol treatment for BPH were maintained for 18 months.[177]

Lowering total and especially LDL cholesterol levels is strongly recommended for the prevention of coronary heart disease. Since the 1950's dietary phytosterols have been considered beneficial in regulating cholesterol levels.[178] Phytosterols have been shown to lower serum cholesterol in approximately 88% of mildly hypercholesterolemic subjects.[179] Physicians and researchers have stated that the addition of sitosterol and the other phytosterols to the diet may be the preferred method for controlling hypercholesterolemia in both adults and children.[180] [181] Sitosterol is incorporated into the intestine plasma membranes and significantly decreased the amounts of cholesterol absorbed from the intestinal tract.[182] [183] Beta-sitosterol interrupts the recirculation of bile

acids and selectively increases LDL receptor expression resulting in a drop in LDL cholesterol levels.[184] Beta-sistosterol had inhibitory effects on 3T3-L1 fat cell growth which may play a role in controlling obesity and cholesterol levels.[185] Becker and Von Bergmann recommended phytosterols as the "treatment of choice" for severe familial hypercholesterolemia in childhood.[186]

Consumption of phytosterols has been shown to be safe and non-toxic.[187] Nevertheless Sitosterolemia is a very rare recessive genetic disease.[188] These rare individuals born with sitosterolemia are advised to limit their intake of virgin oils, fruits and vegetables.

Summary

The immune system is an elegant and sophisticated network of cells and molecules that strive constantly to maintain our health and physical integrity against an onslaught of increasingly resistant microbial invaders. These microbes and our own cancer cells use an array of techniques to evade or subvert our immune responses. Dietary supplementation discussed in this booklet may help us attain an immunological advantage over invading microbes and invasive cancers.

Zinc is involved in over two hundred critical biochemical functions including immunity. Adequate zinc absorption diminishes with age. Maintenance of the body's zinc levels through dietary supplementation helps reduce or stop the age related decline in immune function. Reactivation of thymulin by dietary zinc supplementation has been used to recover immune competence in immune compromised individuals.

Rediscovery and scientific validation of the ancient benefits of Sen-su-take, maitake, and shiitake mushrooms as well as *cordyceps sinensis* provide a valuable basis for the use of these products and their extracts in strengthening the immune response. Some of the ingredients of these plants that provide the immunological benefits have been identified. Many other minor components may also play signigicant roles in supporting the immune system

The beneficial effects of acemannan depend on the presence of the immune system. Beta-glucan has an extensively documented immunological benefit. Recent research has clarified much of the earlier therapeutic confusion and has led to a rational basis for the effective use of beta-glucan as a biological agent. The combination of acemannan and beta-glucan appears to provide a greater immunological impact than what occurs when either agent is used alone.

The phytosterols are important elements of healthful diets. They help modulate the immune response, inhibit cancer growth, and normalize cholesterol levels. Phytosterols are the active principles in many medicinal plants exerting antimicrobial, antifungal, and anti-inflammatory activity.

Oleuropein, hydroxytyrosol, and elenoic acid from olive leaf extracts have been shown to be antibacterial, antiviral, as well as being anti-inflammatory. All of these characteristics help protect the body and reduce the strain on the immune system. In addition these natural products are good anti-oxidants and this may in part explain their ability to protect cells from DNA damage that is associated with cancer and other chronic diseases. Inositol hexaphosphate (IP6) appears to act by a different mechanism that results in improved intracellular control of malignant cell.

The combination of these agents has demonstrated a synergistic impact on NK cell activity with no measurable toxicity, even at excessively high concentrations. These facts open up the potential for enhanced nutritional support for an optimally functioning immune system.

APPENDIX 1. HUMAN AND BOVINE PATHOGENS: POTENTIAL CROSS REACTIVITY

Human Pathogen or Disease	Commonality	Bovine Pathogen
BACTERIA		Travelers Diarrhea *(E.coli)*
	very	Toxigenic *E.coli*
	very	*Campylobacter jejuni*
Bloody diarrhea/hemolytic uremia	increasing	*E.coli* 0157:H7 Verotoxic
Salmonellosisi/Typhoid Fever	common	*Salmonella thyphimurium, Salmonella typhosa dublin*
Diarrhea, from food and water	very	*Campylobacter jejuni*
Clostridial Infection	common	Clostridia (many species)
(non tetanus)		C. *dificil*
Mycobacterium Infections		Mycobacterium species
johnei, Crohn's Disease	common	common in Jersey cattle
Staphylococcal super infections	common	*Staph. aureus*
Streptococcal Infections	common	Streptococcus
Endocarditis	common	Beta Strep.
Superinfection	increasing	*S. pyogenes*
Enterococci	common	Enterococci (most spp. & VRE)
hospital/VRE strains serious	common	*Helicobacter pylon* (ulcers)
	common	Bovine/Porcine association
VIRUS		
Influenza	common	Influenza virus
Pneumonia Resp. Syncytial Virus	common	Bovine Resp. Sync. Virus
Papilloma, Condylomaya	common	Bovine Papilloma Virus
Virus Diarrhea	common	Bovine Virus Diarrhea
Rotavirus		Rotavirus
		Coronavirus
Cytomegalovirus	common	Bovine CMV and IBR
Herpes Infections	common	Bovine Rhinotracheitis
HIV (Retrovirus) common	Bovine Immune Deficiency	Virus
Rhinoviurs (common cold)	very	Bovine Rhinovirus
YEAST, FUNGI and PROTOZOA		
Candidiasis	common	Candida exp. common
Cryptosporidiosis	very	Calf diarrhea, *C. parvum*
Giardiasis	common	Calf diarrhea, G. *lamblia*
OTHER		
Mycoplasma pneumonia, arthritis	common	Bvn. Mycopl. Pneumonia

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