Colostrum as a Dietary Supplement

Focus on Transfer Factor

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The possibility of stimulating immune function by natural means is a major focus of current interest among practitioners of both allopathic medicine and complementary medicine. Several herbal compounds, including Echinacea and Andrographis, are finding a role in the treatment of immunodeficiency or as agents to enhance immunity, to prevent infection and even contribute to longevity. The use of colostrum as a promoter of health and well-being has been recognized for centuries and its use is deeply rooted in the act of "filial piety' in Ancient Chinese Culture (Figure I).

The use of natural agents such as immune globulins or other products that are produced by the immune System of mammals has been the focus of intense research in recent times. The idea of providing passive immunity with immune globulin that is administered by injection is a well-defined medical intervention for the prevention of viral disease. A common example is the use of gamma globulin for the prevention of hepatitis A virus infection. Other products of the immune system that are candidates for use in medical treatment include interferon and molecules that can transfer "immune phenomena" from a donor to a recipient. An example of this latter process is the use of transfer factor (TF), an agent that can transfer cell-mediated immunity by the use of soluble factors that are produced by lymphocytes.

It is known that TF is contained within certain leukocyte fractions and such fractions have been used for the adoptive transfer of antigen-specific, cell-mediated immunity in animals and humans. Antigen-specific TF can also be obtained from colostrum or milk that is secreted by the mammary gland of a mammal that has been exposed to a variety of environmental antigens. The idea that a fraction of colostrum contains TF that can be administered to transfer cell-mediated immunity is very intriguing given the widespread availability of colostrum of bovine origin and the establishment of techniques for the collection of concentrates of TF and its purification for use as a dietary supplement.

Immunoglobulins in Cow’s Colostrum and Milk

A body of literature has appeared over the past 10 years that suggests that immunoglobulins (IgG) of various types have the potential for the treatment or prevention of infectious diarrhea in human clinical trials. Several studies have shown the protective effects of antibodies in cows milk against enteric infection in several different species of mammal. The use of IgG in colostrum as an immunoprophylactic or therapeutic agent is a very important issue for the standardization of colostrum used in dietary supplements. For example, high temperature sterilized milk has little if any measurable IgG. Companies that sell colostrum as a dietary supplement are obligated to provide evidence of the presence of IgG in colostrums if they are suggesting that their supplement has immune protective or enhancing effects. Few companies that make colostrum have provided evidence that they have retained IgG in their products.

Symbiotics, a corporation in Sedona, Arizona, has recently presented data on their product that was researched at the University of Osaka in New Zealand (Wyatt, D., personal communication). Symbiotics has shown that the product that they market under the brand 'New Life Colostrum' contains measurable antibody activity against Candida albicans, Bacillus cereus, Campylobacter jejuni, Escherichia coli (0157:H7), Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Propionibacterium acnes, Streptacoccus agalactiae, Staphylococcus aureus, Salmonella enteritidis, Staphylococcus epidermidis, Streptococcus mutans, Streptococcus pneumoniae, Staphylococcus pyogenes, Salmonella typhimurium, and Yersinia enterocolitica. These microorganisms cause a vast array of serious infectious diseases which can be life threatening.

Of particular interest in the Symbiotics study is the antibody activity against Candida albicans (the organism at the basis of the "yeast connection") and the impressive activity against the bacteria that cause enteric infections. We cannot lose sight of important studies that show that bovine colostrum is capable of treating diarrhea in human immunodeficiency virus-infected patients, with the immunoglobulins found in bovine colostrum. The focus of this article is primarily to discuss the implications of transfer factor, but these data show the potent and versatile potential of bovine colostrum in the treatment of disease. In the face of mounting concerns about resistance of pathogenic bacteria to antibiotics, natural therapies provide very interesting alternative and complementary treatment options. Other factors play a major role in the potential efficacy of colostrum and arguments prevail about the IgG content of various types of colostrum. The Symbiotics studies measured the immunoglobulin of G-type by ELISA, whereas other measurements have used different quantitative techniques. The antibacterial activity of any colostrum may not necessarily correlate with its immuno-lobulin content. With this in mind, researchers at Symbiotics have looked at the direct ability of the colostrum to inhibit the growth of various bacteria in culture and the results obtained overall mirror the observations of antibody activity against the various microorganisms.
Data show the potent and versatile potential of bovine colostrum in the treatment of disease

One important determinant of the immunotherapeutic potential of certain types of colostrum is believed to be related to the source of the colostrum. The outstanding activity of one brand of colostrum is believed to be in part related to the large donor group of animals (more than one million) used as the source of colostrum. A further important issue is the acquisition of colostrums from pasture-fed animals who are exposed to more antigens (microorganisms) than nonpasture-fed cows. In addition, colostrum from New Zealand is harvested fresh, whereas the vast majority of colostrum produced in the United States is obtained from sources that have been frozen prior to processing as a dietary or nutritional supplement. I believe that standards are required in dietary supplements that contain colostrum and that disclosures should be made in product specifications by manufacturers.

Elegance and Simplicity

The versatility of viral organisms, such as HIV-1 virus, to change their antigenic structure and develop drug resistance has been a key problem in the treatment of viral disease. Viruses have been associated increasingly with the causation of a variety of diseases, including the acquired immunodeficiency syndrome (AIDS), cancer, autoimmune disease, and cardiovascular disease. Viruses are kept at bay in part by cell-mediated immunity which can be conveniently transferred from humans to animals or vice versa by TF. Some of the most exciting treatment concepts come from the obvious. Several -natural remedies have been used to enhance immunity in ancient medical systems but nature may hold the key in providing homeostasis for the human body (see Figure 1).

Mother-infant interactions provide examples of both passage of and protection against disease. Day-to-day living can provide circumstances for optimal homeostatic mechanisms but it may provide a circumstance for the transmission of disease. A simple example of this is the transference of viral infections between mother and infant and most notable in this regard is the transfer of Herpes simplex type-1 virus that causes the common cold sore. Maternal affection and kissing results in the transfer of infected saliva to an infant, who then carries the Herpes simplex type-I virus for the remainder of his or her life. Fortunately, maternal activity is often beneficial. The simple human act of breast feeding results in significant benefits to an infant to a major degree by the transfer of immune modulating or enhancing material in breast milk. One of the most important immune enhancing agents that is transmitted in the process of nurturing with breast milk is TF that is contained within colostrums. The objective of this overview is to describe the importance of TF in colostrum (early breast milk) as conferring immune advantages to infant and adult (animal or human). Milk of bovine origin is a principal source of nutrition in the world. The use of bovine colostrum containing TF as a dietary supplement has been proposed with a strong scientific platform to support a body structure function claim for enhancing wellness by several mechanisms and for promoting body defenses by mechanisms such as immune modulation.
One of the most important immune enhancing agents that is transmitted in the process of nurturing with breast milk is TF that is contained within colostrum

What is Transfer Factor?

In simple terms, TF is an RNA (ribonucleic acid) peptide that is responsible for the adoptive transfer of antigen-specific cell-mediated immunity in animals or humans. Cell-mediated immunity is a function of T-lymphocytes and it is termed delayed hypersensitivity. TF is capable of transferring cell-mediated immunity to specific antigens between animals. This adoptive transfer of cell-mediated immunity to specific antigens was first discovered by H.S. Lawrence, M.D., in 1949. Dr. Lawrence showed that when products of lymphocytes are taken from an individual who has cell-mediated immunity against Mycobacterium tuberculosis (they have a positive skin test against tuberculin [TBI]), and donated to a recipient who has no cell-mediated immunity to TB (i.e., has a negative skin test to Mycobacterium tuberculosis), then the skin-test positivity could be transferred to the recipient of the viable lymphocytes and their products.

The real significance of Dr. Lawrence’s findings was not recognized for several years. At the time that Dr. Lawrence performed his work on the adoptive transfer of antigen-specific cell-mediated immunity there was relatively little known about the importance of lymphocytes in immune function.

The Importance of Transfer Factor Emerges

Research in the 1970s, performed largely by Hugh Fudenberg, M.D., and his colleagues, showed that leukocyte extracts produced by dialysis could produce or initiate a variety of cell-mediated immune reactions. It has been shown that these leukocyte extracts could inhibit leukocyte macrophage migration and act in an antigen-specific fashion. Despite the very important observations of Dr. Fudenberg and his colleagues, the mechanisms of action of TF and its potential role as a therapeutic agent to modulate or enhance immune function remained poorly understood until the late 1980S. Dr. Fudenberg has indicated that this controversy about the importance of TF was due in part to unfortunate confusion of terminology.

Dr. Fudenberg and his colleague Dr. Giancario Pizza have proposed that the term Transfer Factor should be used to describe the components of lymphocyte extracts that result in the transfer of T-lymphocyte responses in an antigen-specific manner. The precise mechanisms of action of transfer factor are not completely understood but it appears to have some actions at the molecular level by influencing DNA (deoxyribonucleic acid) polymerization.

Terminology "Trips Up" Understanding

It is known that fractions of leukocyte extracts and colostrum contain a vast array of transfer factors which represent the sum of antigen stimuli and corresponding, immune responses of the animal species in question. In other words, a human or an animal, such as a cow, can be exposed to a variety of antigenic stimuli, such as infectious agents, and the dialyzable leukocyte extract from the white cells of the individual in question (or the colostrum secreted in breast milk) contains polyvalent transfer factor which is a function of the overall sum of the immune experience of the individual in question. To distinguish between antigen-specific transfer factor and more complicated mixtures of polyvalent transfer factor, certain terminology has arisen. The notation TF, is used to describe components of leukocyte extracts that transfer T-lymphocyte responses in an antigen-specific fashion and the notation DLETFas is used for dialyzable leukocyte extract that is known to be specific for a desired antigen.

The use of these terms has helped to clarify the understanding of the importance and distinction between various types of transfer factors. However, some individuals use the term TF to describe all of the components of dialyzable leukocyte extract. Of course, there is much confusion by just using the general term TF because the simple dialysis of extracts of leukocytes contain different moieties that have immunologic activity or adjuvant effects. For simplicity, the author uses the generic term TF but acknowledges the importance of specific terminology that has been proposed.
Studies have shown that the oral route of administration of TF is effective in the adoptive transfer of cell-mediated immunity.

Defining Types of TF

The nomenclature of the different forms of TF is highly complex and has evolved as a consequence of in vitro and in vivo observations on the biologic activity of TF derived from leukocytes and TF derived from colostrum. Studies in humans and in several animal species indicate that there are at least three different structural forms of TF for each antigen specificity. Immunology of the delayed hypersensitivity type can be conferred in humans and animals by an effective dose of TF obtained from bovine colostrum. The TF can be administered in a variety of ways and effective immunity can be conferred between species of animals. The characterization and structure of different forms of TF are beyond the scope of the present discussion and readers are referred to the work of Chase, Fudenberg and Pizza, and Kirkpatrick for a fuller discussion of this topic.

TF Is Active When Given Orally

A number of studies have shown that the oral route of administration of TF is effective in the adoptive transfer of cell-mediated immunity's Charles Kirkpatrick, M.D., has described recently the components of an extensive research program on TF. In the face of some skepticism about the bioavailability of TF when administered orally, Dr. Kirkpatrick has conducted dose response studies of the delayed hypersensitivity reaction in animals that were administered TF by the oral or systemic route. These findings confirm that TF is active when given orally and it is not destroyed substantially by gastric acid or enzymes in the gastrointestinal tract.

Focus on Transfer Factor as a Dietary Supplement

Transfer factors derived from human, murine, and bovine sources have been extensively studied. The most accessible source of TF is in the colostrum of breast milk and the most widely available form of TF is derived from cow's milk. Transfer factor is composed of a group of small molecules with molecular weights between 3500 and 6000 daltons. It is known that TF is quite stable when stored at low temperature but TF may be heat labile. The exact components and structure of TF remain to be determined but there is general agreement that TF has an oligoribonucleotide-peptide structure.

One of the most interesting aspects of the characterization of polyvalent TF is that it is freely available from colostrum that is collected from dairy cattle. In addition, milk is part of the normal human food chain and, therefore, transfer factor prepared from cow's milk (colostrum) can be made available as a dietary supplement. Whilst it is possible to produce antigen-specific transfer factor in cows, there is potential gain from using polyvalent transfer factor that will be available in bovine colostrum as a consequence of a variety of antigenic stimuli that a dairy cow will experience in its normal lifetime. In addition, TF stimulates immunity in a more general but nonspecific manner.

Considerable therapeutic benefit has been obtained with antigen-specific TF. Transfer factor has been used to treat a variety of specific diseases (see box entitled "Conditions in which Various Antigen-Specific Transfer Factors Have Been Used With Variable Success"). In most reported circumstances, antigen-specific TF has been used and prepared by a variety of techniques, most notably, extracts of leukocytes. Transfer factor has been given by injection in many clinical studies. However, it is apparent that TF is freely bioavailable when given orally. It is not destroyed by gastric acid, and it resists peptic digestion when given by the oral route. The molecular weight of TF (3500-6000 daltons) is such that it will freely cross the intestinal mucosal barrier. The mechanism of absorption of TF and the pharmacokinetics of orally administered TF remain to be explored. However, in experiments where transfer factor has been given orally, clearly demonstrable and potentially favorable immunologic effects have been noted in animals and humans.

Immunotherapeutic Potential of Transfer Factor

Overall, it is apparent that TF can be considered as a valuable option in circumstances in which there are defects in cell-mediated immunity. Transfer factor is useful in individuals who had selected defects in cell-mediated immunity. Defects in cell-mediated immunity are the hallmark of AIDS and it may be important in the pathophysiology of certain types of cancer's. The therapeutic benefit of TF is debated. The problem is that TF is considered to be experimental by many physicians and its use has been restricted to circumstances where conventional medication has failed to produce results. This has led to a circumstance where clinical studies have been performed in patients who have already received medication which may have compromised immune function. For example, in patients with cancer in whom TF has been used, there has been a frequent circumstance of irreparable damage to the immune system by the preceding administration of chemotherapy and/or radiation. This situation provides a "setup" for failure of TF and other natural medical options. Natural therapies are often only able to be evaluated in patients who are far advanced in their disease status.

It could be argued that the use of natural agents, such as TF, is a much better option for people with incurable diseases than the application of a clinical trial where a double-blind placebo study is undertaken, especially in the absence of any known effective treatment for the disease that is being studied. Double-blind controlled clinical trials are very important in determining safety and
efficacy of drugs but such studies may not be universally relevant in circumstances where there is no effective treatment for a condition. This situation has not been recognized by regulatory agencies that continue to be obsessed with the supremacy of the placebo-controlled trial. This is an ethical dilemma that dictates the need to consider trials of therapeutic equivalence.

**Is Transfer Factor Safe?**

Many studies have been undertaken where leukocyte extracts have been administered by injection without untoward effect. There is less documented information on the administration of TF by the oral route, by suppository, or by incorporation into novel drug delivery systems, such as liposomes. Overall, it can be stated with confidence that dialyzable leukocyte extracts have been shown to be remarkably free from adverse effects. Furthermore, there are no real significant adverse effects that can be ascribed to the oral administration of colostrum of bovine origin which contains TF. Bovine colostrum probably should not be taken by an individual with milk protein allergy.

In experiments where TF has been injected, low grade fever has been noted but there have been no reports of serious hypersensitivity reactions or long-term adverse effects with the use of transfer factor. Clearly, if TF contained within colostrum derived from cows is administered by the oral route, then this activity must be assumed to be as safe as drinking milk! There are some risks with drinking milk or taking products from any animal source but these are quite acceptable risks in societies where an omnivorous diet is the rule.

**Clinical Applications of Transfer Factor**

Transfer factor both in an antigen-specific format and a polyvalent format has a variety of potential uses in health promotion (see sidebar). An obvious application of the use of specific TF is to transfer antigen-specific cell-mediated immunity in conditions where a single agent is the cause of the disorder. An example of such a condition is chronic Candidiasis. The "Yeast Syndrome" has increasingly been recognized as a problem underlying a variety of symptoms and illnesses.

Dr. Fudenberg, and his colleagues have produced antigen-specific transfer factor to a number of viruses, including Herpes simplex virus-1 (cause of oral herpes), Herpes simplex virus-2 (cause of genital herpes), and Herpes simplex, zoster, virus-3 (cause of shingles). Antigen-specific transfer factor has also been prepared and used with success against coccidiomycosis, cryptosporidiosis, and cytomegalovirus (CMV) infection.

Cytomegalovirus (CMV) infection is common in the terminal stages of AIDS and accounts for blindness and occasional, terminal, fulminating disease in patients with AIDS. CMV has also been implicated as a cause of restenosis in patients who have undergone coronary artery bi-pass surgery and it is believed to played an important role in the rejection of renal transplants. The mechanism whereby CMV induces these effects is not entirely understood. It may be due to some "mimacy" of human tissue antigens on the part of the virus or due to intracellular events as a consequence of the viral infection per se.

Transfer factor may have considerable benefits in the treatment of a variety of other conditions, including autoimmune disorders and malignant disease. It has been estimated that one of the most important applications of TF is in the treatment of nasopharyngeal cancer that may affect as many as 100 million people in Eastern Asia. This type of nasopharyngeal cancer is believed to be related to viral infection with the Epstein-Barr agent.

The role of transfer factor in the amelioration of super-infection or opportunistic infection of patients with immunodeficiency, such as is common in patients with AIDS, is quite obvious. There have been a number of recent successful anecdotal reports of the use of transfer factor in patients with AIDS. These experiences have involved the use of antigen-specific TF to combat a variety of opportunistic infections in AIDS patients.

**Bovine Colostrum Has Real Potential Benefits**

On one hand, it is clear that antigen specific TF can be used in a specific clinical instance, but there are benefits of using polyvalent (nonspecific) TF as a dietary supplement. Transfer factor can enhance cell-mediated immunity in a nonspecific manner by a factor of up to 15 percent. Overall, TF seems to act as an immune modulator. When there is "too much" or "too little" in terms of an immunologic response, the TF appears to upregulate or down-regulate immune functions.

It should be recognized that colostrum of a general source, such as regular bovine colostrum, contains a variety of other immune-enhancing agents. These agents include lysozyme, secretory IgA, and other Proteins such as lactoferrin. The nonspecific immune enhancing effect of transfer factor can be readily demonstrated in studies of T-cell function. Such changes have been noted by Dr. Fudenberg and his colleagues in leukocyte migration inhibition testing.

Exciting information has come from experiments in animals where TF has been used beneficially in several viral diseases, such as Newcastle disease and Meyrick's disease (chronic lymphoma) in chickens and equine encephalitis. Some of the experiments on the use of transfer factor in the treatment of cancer have produced conflicting results. This situation may be due, in part, to uncertainty about the constituents administered immunologic agents or uncertainty about the role of cell-mediated immunity in fighting the spread of certain types of cancer. However, cancer therapy is a very promising area for further research with TF.
Transfer Factor in Bovine Colostrum

Several companies have developed dietary supplements that are based on colostrum. Gregson, B. Wilson, M.D., and Gary V. Paddoci, Ph.D., received a patent (U.S. Patent No. 4,816,563) for a process to obtain TF from colostrum and use it for the prevention and treatment of disease. These investigators have described a method for concentrating and sterilizing TF from bovine colostrum and the potency of the concentrate can be determined in an assay described in a patent (U.S. Patent No. 4,610,578) that they had filed in 1983, but subsequently abandoned. These investigators described the ability of colostral-whey associated TF to be lyophilized and stored in a dry format for subsequent use by reconstitution with water, for injection or oral administration. In their patent, these investigators have provided many examples of the application of TF in the treatment or prevention of infection in animal models and by inference in humans.

Daniel G. Clark, M.D., and Kaye Wyatt have drawn attention to the potentially versatile and potent health benefits of specially prepared bovine colostrum, in their new book titled *Colostrum, Life's First Food.* These authors have provided a very useful account of research related to the use of colostrum and its fractions in the therapy of a variety of disorders. They point out the importance of a variety of potentially health giving components of colostrum including immunoglobulins, lactoferrin, proline-rich polypeptide, insulin-like growth factors, transforming growth factors, lactoperoxidase-thiocyanate, peroxidase or xanthine oxidase enzymes, lysozyme, cytokines, interleukin-10, glycoproteins and trypsin inhibitors, lymphokines, oligopolysaccharides and glycoconjugates, orotic acid, and other immune factors. It is clear that colostrum is a treasure chest of natural substances which have important implications for the promotion of immune function and health.

In a recent book entitled *Colostrum: Nature’s Gift to the Immune System,* Beth M. Ley traces the knowledge that colostrum (mother's milk) provides an individualized food that is perfectly engineered to promote and transfer passive immunity to the infant. Ms. Ley has provided evidence that adults with immune deficiency (e.g., AIDS), cancer, and autoimmune problems (e.g., multiple sclerosis, arthritis, etc.) may benefit from the administration of colostrum. In particular, benefits are to be expected in the prevention or treatment of opportunistic infections in AIDS, such as diarrhea caused by *Cryptosporidium parvum* and *Escherichia coli.* The book by Ms. Ley analyzes scientific literature that reveals the immune enhancing, digestive, anti-infective, and anti-inflammatory benefits of colostrum.

In my opinion, many of these benefits of colostrum on immune function could be ascribed to its content of TF. The potential health giving, properties of colostrum seem to extend beyond immune enhancement by providing benefits to body builders, athletes, and convalescent patients. The mechanisms whereby colostrum may speed recovery time from illnesses are not fully understood but colostrum is known to contain several natural growth factors.

Processing, and Source of Colostrum

The safety and effectiveness of colostrum will vary in a manner dependent on its source and the manner in which it is processed. Several scientists have drawn attention to the heterogeneity of TF and methods for its preparation vary considerably. There are many other components of colostrum that exert diverse biologic actions and these components can be present to a variable degree depending upon processing techniques. It is known that heat can denature components of colostrum and processes that use heat can result in loss of biologic activity of colostrum. The most obvious source of colostrum is the mammary gland of the cow. The cow becomes a "factory" for producing colostrum and this factory should not be contaminated with harmful chemicals or drugs. Therefore, pasture-fed cows that are reared on organic farms are preferable. A cow is exposed to a vast array of antigens in its natural habitat and this exposure will result in the development of natural immunity that may be passed via colostrum in the process of adoptive transfer of immunity.

Arguments prevail among manufacturers of various types of colostrum about the relative benefit of specific processing techniques, sources of colostrum, and modes of delivery. These companies produce colostrum for use in dietary supplements with various claims about the health giving constituents of their respective colostrum products. It is known that some colostrum that is marketed for human consumption is a veterinary grade colostrum that has been repackaged for human use. It is proposed that this may not be harmful, but the safety and efficacy of these products remain in question. In addition, much of the available colostrum is frozen prior to transportation. Frozen products have limitations in the manner in which they can be processed and they may not be water soluble.

It is known that organic herds in the United States that comes from "organic," pasture-fed cows. It is known that organic herds in the United States are often not pasture-fed and it is suggested that the use of dried, processed food for these cows may not provide an optimal diet that will result in a cow’s ability to produce colostrum with versatile health benefits. For these reasons, some manufacturers have sourced colostrum from New Zealand and Australia where pasture feeding is common and “mad cow disease” is not present.
It is not easy to find a U.S. domestic source of colostrum that comes from "organic pasture-fed cows.

Conclusion

There is much further research required before our understanding of the overall benefit of TF is clear. TF appears to contain many moieties. There has been a reluctance in certain scientific sectors to acknowledge that transfer factor may have clinical efficacy.16 The reluctance to accept the potential clinical efficacy of transfer factor may be more related to the fact that the mechanism of its action remains poorly understood.11 Some scientists will not accept a phenomenon without a well understood "mechanism" of action.16

TF has been used widely in several countries, including Japan, China, The Czech Republic, and many other Eastern European countries.2,3 Much contemporary information has accrued from the use of TF in studies in Japan and mainland China.3 In these countries, TF has been prepared from lymphocytes of normal healthy donors, and from porcine, bovine, and other sources. The key issue is that TF administered to humans appears to be quite safe, even though the optimum dose of TF is not known.2,3,15 There is great interindividual variation in response to this administration of TF.2,3 The approach of using polyvalent, nonspecific TF as a dietary supplement is of great interest with much potential benefit for the immuno-suppressed individual.13,14

Indeed, current evidence indicates that TF may be very useful in many of the diseases that affect patients with immunodeficiency and it appears to have potential benefit for the treatment of patients with AIDS.13,14 It would appear that bovine TF, even when given in a nonspecific format, can be useful in at least the nonspecific enhancement of immune function. When given in a more specific format, it can be targeted at certain infectious disease states and play a role in the treatment of cancer and a variety of other diseases.13,14

References