

SCIENTIFIC AND MEDICAL RESEARCH

RELATED TO BOVINE COLOSTRUM

**ITS RELATIONSHIP AND USE
IN THE TREATMENT
OF
DISEASE
IN HUMANS**

**SELECTED
PUBLISHED ABSTRACTS**

By: Alfred Fox, Ph. D. & Anthony Kleinsmith, Ph.D.

TRUE BOVINE COLOSTRUM for the Practitioner

By: Alfred Fox, Ph. D. & Anthony Kleinsmith, Ph.D.

INTRODUCTION

Colostrum is the first milk-like fluid yielded from the mammary glands of mammals after parturition and is intended for ingestion by the newborn during the first hours of life. In most mammals, such as humans, many of the biologically active substances essential to development and survival, such as growth promoting substances and immunoglobulins, cross the placental barrier and are transferred to the fetus *in utero*. In sharp contrast, in ungulates, particularly bovines, essentially none of these biologically active substances cross the placental barrier and, thus, must be acquired by the offspring through suckling during the early hours of its life.

There is a considerable body of scientific evidence showing that if a calf fails to receive an adequate quantity of high quality complete colostrum, it will be more vulnerable to pathogens in its environment and will not develop a proper body mass.^{1,2,3,4,5,6,7,8} The impact of inadequate colostrum intake during the first hours of life on the survival and health of calves was studied in more than 2,200 animals over a five year period by the United Kingdom National Agricultural Center Calf Unit. As shown in the table below, they found that calves that received only a small amount of colostrum were six times more likely to die than those that received the required two quarts. If the animals that received a small amount of colostrum survived, they were ill almost three times as often as the calves that got enough colostrum. Getting enough high quality colostrum is essential to the health and well being of the calf and failure to do so will follow the animal for the rest of its life.

EFFECT OF COLOSTRUM INTAKE ON CALF HEALTH

<u>Colostrum Intake</u>	<u>% Died</u>	<u>% Ill</u>
Little	7.9	42.2
Some	3.0	24.2
Enough	1.3	15.4

In addition to containing a high concentration of maternally-derived immunoglobulins, first milking bovine colostrum is a complex resource of biologically active substances necessary to support the development and repair of cells and tissues; to assure the effective and efficient metabolism of nutrients; and to initiate and support the immune system. This is not completely surprising when we consider that it is intended for consumption by a newborn calf that has received none of the substances *in utero* that will be required for its proper development outside of the uterus and that its growth will occur at a very rapid rate, creating a huge demand for energy. The components of bovine colostrum are also compatible with almost any species and can readily convey its full

benefits to other mammals, including humans, by routine dietary supplementation.

COLOSTROGENESIS – THE FORMATION OF BOVINE COLOSTRUM

The formation of colostrum in the pregnant cow is initiated about 3-4 weeks before parturition when a limited amount of fluid containing small amounts of growth factors and other transforming substances is released into the developing mammary tissue.^{9,10} The process is regulated by a series of other hormones, one of the most important being progesterone, which attaches to special receptors on the cells lining the mammary gland and prevents them from secreting any fluid into the gland during most of pregnancy.^{11,12} About two weeks before birth, these substances influence the appearance of specific receptors on the surface of the cells lining the mammary gland that will facilitate the transfer of materials from the mother's blood into the gland, including the immunoglobulins (antibodies) necessary to convey passive immunity to the calf after birth and various hormones and growth promoters required to induce and support development of the newborn calf.¹³

About 2 days before birth, the hormonal balance begins to shift, initiating the production of copious secretions and switching on the ability of cells in the mammary tissue to synthesize various substances, including lactose.^{14,15} At birth, when the placenta is eliminated, progesterone levels fall dramatically in the mother and its inhibitory control of the secretions is removed.^{12,16,17} Simultaneously, a protein-based substance develops in the cells lining the mammary gland that essentially blocks any further transfer of substances from the mother's blood into the gland.¹³ The composition of the fluid in the mammary gland at birth is that of true colostrum and reflects the functional changes that have occurred in the gland up to that time; it a) has a high protein concentration, most of which is IgG; b) contains the highest concentration of growth promoters, other hormones and additional metabolically active substances; c) is low in lactose content; and d) is rich in milk fat.¹⁸

After birth, one of the most influential factors on the composition of subsequent secretions is physical removal of the fluid from the mammary gland. The removal of even small quantities of fluid triggers the production of copious amounts of secretion from the cells in the mammary gland.¹³ Since the transfer of biologically-active substances from the mother's blood is blocked, replacement fluid will contain primarily substances synthesized by cells in the mammary gland and, thus, will be of a different composition than the fluid originally contained in the mammary gland at birth. The fluid expressed at this time is known as “transitional milk”. This is further complicated by the fact that the basic composition of the colostrum changes after birth due to maternal reabsorption and does so rapidly beginning at six hours, as can be seen from the table below.¹⁸ Thus, the highest quality bovine colostrum, containing the maximum

concentration of biologically active substances, is collected in a single milking during the first six hours after parturition.

COMPOSITION OF LIQUID BOVINE COLOSTRUM

Hrs. After <u>Calving</u>	Total <u>Protein</u>	<u>Fat</u>	<u>Lactose</u>	Total <u>Solids</u>
0	17.57	5.10	2.19	26.99
6	10.00	6.85	2.71	20.46
12	6.05	3.80	3.71	14.53
24	4.52	3.40	3.98	12.77
36	3.98	3.55	3.97	12.22
48	3.74	2.80	3.97	11.46

COMPOSITION OF DRIED BOVINE COLOSTRUM

<u>Hours</u> <u>After</u> <u>Birth</u>	<u>Protein</u>	<u>Casein</u>	<u>Albumin</u>	<u>Fat</u>	<u>Lactose</u>
0	65.10	18.82	42.02	18.90	8.11
8	48.90	17.16	30.79	33.48	13.25
12	41.64	20.65	20.37	26.15	25.53
24	35.40	21.61	11.59	26.62	31.17
30	29.42	18.78	8.80	35.95	31.33
36	32.57	22.67	8.43	29.05	32.49
48	32.64	22.95	8.64	24.43	34.64
72	32.55	22.77	8.18	26.14	36.85
96	31.73	22.62	6.92	29.60	39.83

The rapidly changing composition of colostrum in the mammary gland of the mother fits together very well with events that happen in the body of the newborn calf. During the first six hours of life, the calf's stomach lining does not make any acid and there are very few, if any, enzymes present that can break down ingested proteins. Complete first milking colostrum also contains substances that inhibit the action of some enzymes. Therefore, these conditions work in favor of having the biologically active substances in complete colostrum pass through the calf's stomachs into the upper portion of the small intestine without being broken down. During the first 6-8 hours of life, an area in the upper duodenum has specialized sites where the biologically active substances can be absorbed and transported directly into the calf's bloodstream. After this period, the stomach begins to acidify, enzymes appear and the specialized absorption area in the small intestine changes dramatically so that most of the biologically active substances in colostrum are no longer absorbed. This process is aided by the fact that calves are born with a well-developed system of lymphoid tissue under their tongue and at the back of their throat that persists throughout their entire life. Many biologically active substances are absorbed through these tissues when the calf suckles its mother or a nursing bottle.^{19,20,21}

THE COMPOSITION OF BOVINE COLOSTRUM

From the chart above, it is very obvious how fast the relationship of the biologically active components in bovine colostrum changes after birth of the calf. Recognizing this changing relationship is extremely important in defining what bovine colostrum really is and in assuring that it contains the maximum amount of biologically active substances.²²

Protein.

Most of the biologically active substances in complete bovine colostrum that can convey significant health benefits are proteins. Since almost all of the beneficial proteins are conveyed from the mother's bloodstream into the colostrum before birth and the mother then begins to reabsorb them about 6-8 hours after birth, it is important to use colostrum that has been collected during a time period that will minimize the effect of the reabsorption process. Of real significance is the fact that by 24 hours after birth most of the proteins in the udder fluid can be accounted for by two individual proteins that are primarily only of nutritional value, casein and albumin.¹⁸

Colostrum Fat.

The milk fat in complete first milking colostrum is one of the most under-rated and misunderstood components by many companies that promote bovine colostrum for human consumption. There are all kinds of stories, none of which are ever substantiated with any scientific evidence, that the fat in colostrum doesn't serve any purpose and/or that having it there leads to faster deterioration of the product. Nothing could be further from the truth. In fact, one of the companies that removes the fat from what they call "colostrum" adds a component of the fat back to their dried products. They claim that this makes their "colostrum" more digestible, which was one of the functions of the fat in complete colostrum in the first place. Casein is a nutritionally valuable complete protein that is broken down in the stomach to small peptides and amino acids so that they can be absorbed and used to build new muscle protein by forming a cottage cheese-like curd in the stomach. This occurs enzymatically in the newborn and the adult and the basis for the curd that forms is the fat in the colostrum. So without it, in addition to losing some significant biologically active substances that are associated with the fat, one loses most of the nutritional value of the casein. That is part of the reason why the fat content of colostrum increases with time after birth as the amount of casein increases in the secreted fluid. Mother nature doesn't waste much and has organized the components of colostrum and their changing pattern in an efficient way to maximize the benefits to the offspring that is going to receive it.

High quality first milking bovine colostrum will contain 20-30% milk fat.¹⁸ The milk fat in colostrum is also a very important means to deliver some of its beneficial biologically active substances.^{22,23} Dissolved in or associated with the

fat in colostrum are vitamins A, D, E and K; steroid hormones; corticosteroids; some growth factors; and insulin.

Lactose (milk sugar).

Approximately 10-15% of all of the solid material in high quality complete first milking colostrum will be lactose.¹⁸ Lactose is extremely important to the calf as an immediate metabolic energy source when it is broken down to glucose and galactose by an enzyme (lactase) in the saliva and the stomach. Therefore, it makes good sense that the amount of lactose in transitional milk and mature milk increases as the calf develops rapidly during the early days of its life.

Since most people have the same enzyme (lactase) in their saliva and their digestive system, the lactose in the colostrum that they use as a dietary supplement can provide the same ready source of metabolic energy. However, there are "lactose intolerant" individuals who have problems digesting lactose because their body produces too little or none of the lactase enzyme. The amount of lactose in first milking colostrum collected within 6 hours after birth is about one-half of what it is at 12 hours after birth and one-third of what it becomes by 24 hours. Therefore, a high quality complete first milking colostrum collected within 6 hours after birth can be used as a dietary supplement by more people without potentially having them suffer the discomforts associated with lactose intolerance.

Other compositional considerations.

The following comparative facts about colostrum and milk further stress the value of a complete first milking colostrum in maximizing the health related benefits.²²

Colostrum contains 10 times more vitamin A than milk.

Colostrum contains 3 times more vitamin D than milk.

Colostrum contains at least 10 times more iron than milk.

Colostrum contains more calcium, phosphorous and magnesium than milk.

The biologically active components.

The biologically active components in complete first milking colostrum can be divided into categories based upon the health aspect where they exert their greatest influence. In some cases the functions of these components can be clearly separated into such categories, while, in many cases, the dividing line is clouded. The major categories are the **Immune Factors**, the **Growth Factors** and the **Metabolic Factors**. It is very important to recognize that most of the very broad claims made by many suppliers of colostrum for human consumption about what these substances do are based upon very specialized studies in experimental animals and represent **the company's** interpretation of the results and **not necessarily that of the original scientific investigator**.

The Immune Factors.

To comprehend what the Immune Factors are in high quality first milking colostrum and what they do, it is important to recognize that some of these components have one or more effects on the overall regulation and functioning of the immune system (immuno-regulating substances), while others are very restricted in what they can do and their benefits are usually very localized in the body, ordinarily exerting their effects primarily in the gut (gut protective substances).

Immuno-regulating substances.

Thymosin (alpha & beta chains). A hormone composed of two protein-based chains that are separately present in bovine colostrum. The chains act on the thymus gland independently or in concert with each other to stimulate activation, development and maintenance of the immune system.^{24,25,26}

Proline-rich peptide (PRP), a/k/a thymulin. A hormone-like small protein that acts upon the thymus and other organs associated with the immune system to keep them from over-reacting to an insult.²⁷

Cytokines. Small proteins produced by various cells in the body that induce the generation of specialized types of white blood cells, signal them to come to the site of an insult and help in their passage through tissues.^{27,28}

Lymphokines. Proteins of varying sizes that are produced by different types of white blood cells that tell related cells to transform themselves into more functional cell types that can release substances capable of destroying an invading microorganism.^{29,30}

Gut protective substances.

Immunoglobulins (IgG, IgM, IgA). Complex proteins, better known as antibodies, that make up a significant portion of the proteins found in complete first milking colostrum. These antibodies were produced by the mother's immune system in response to her exposure to many different microorganisms during her lifetime and then transferred into the colostrum prior to birth of the calf. There is no evidence that any of these antibodies are found intact in the blood of individuals who ingest colostrum by mouth. However, many of these antibodies are reactive against bacteria, viruses and fungi that infect the gastrointestinal tract of humans and there is scientific evidence that some of them can survive passage through the digestive system.^{31,32}

Transfer factors. Small proteins produced in response to the body's exposure to certain types of microorganisms, particularly those that reside in deep tissues for a long period of time, like *Mycobacterium tuberculosis*. They are specific for a

particular microorganism and are carried inside of certain types of specialized white blood cells. Transfer factors have limited effectiveness alone in defending the body against infection by such microorganisms, but, rather, act in concert with various white blood cells and other factors in an attempt to keep the microorganisms under control.^{33,34,35}

Lactoferrin. A mineral-binding carrier protein that attaches to available iron. Certain aerobic bacteria, like *E. coli*, require iron to reproduce and, therefore, lactoferrin is an effective substance, when operating in the presence of a specific antibody, to impede the growth of some microorganisms in the gut. A broad number of additional claims have been made by some providers of colostrum for human consumption regarding the application of lactoferrin as an immunoregulating substance with antiviral, antibacterial and anti-tumor properties. To date, none of these claims have been adequately substantiated through properly controlled studies.^{36,37}

Transferrin. Another mineral-binding carrier protein that attaches to available iron and can act independently or in concert with lactoferrin to impede the growth of certain aerobic bacteria, particularly in the gut.³⁶

Lysozyme. A very powerful enzyme that is capable of attaching itself to the cell wall of certain pathogenic bacteria and degrading selected proteins, leaving holes in the wall of the bacteria.³⁸

Lactoperoxidase. A mildly effective enzyme that can also attach to the wall of certain bacteria, degrade other selected proteins and interfere with the ability of the bacteria to replicate.³⁸

Xanthine Oxidase. Another mildly effective enzyme that can also attach to the wall of certain bacteria, degrade different proteins than those affected by lactoperoxidase and also interfere with the ability of the bacteria to replicate.³⁸

White blood cells (leukocytes). Primarily three types of functional white blood cells are present in colostrum, including neutrophils, macrophages and polymorphonuclear cells. Each has the ability to phagocytize microorganisms and other foreign bodies and apply substances carried internally to the destruction of the microorganisms. Their functions are dramatically enhanced when antibodies first attach to the microorganisms.²²

Oligosaccharides and glycoconjugates. Complex carbohydrates (sugars) that can adhere to specific sites on the inner surface of the gastrointestinal tract and prevent the attachment of microorganisms.³⁹

The Growth Factors.

Growth hormone. Very small quantities of growth hormone are found in complete first milking colostrum, but that is all that is required since this hormone is extremely potent. It has a direct effect on almost every cell type and significantly influences the proliferation of new cells, particularly their rate of generation. Scientific studies have shown that continued ingestion of small amounts of growth hormone are beneficial in limiting the ongoing deterioration of cells associated with the aging process.^{40,41}

Insulin-like growth factors (IGFs). Insulin-like growth factor-1 (IGF-1) and its closely related counterpart insulin-like growth factor-2 (IGF-2) are potent hormones that are found in association with almost all cells in the body. They are part of a group of more than 90 different proteins, called the "IGF Binding Protein (IGFBP) Superfamily", that is responsible for the processes by which cells grow and reproduce. These substances are also responsible for maintenance of the metabolic pathways by which cells convert glucose to glycogen, a primary metabolic energy resource, and assemble amino acids to create proteins. The key event that triggers the functions of the various proteins in the IGFBP Superfamily is the attachment of IGF-1 to a specific receptor site on the surface of a cell. Many of the growth factors found in colostrum and previously defined by their functions are now considered part of the IGFBP Superfamily. This includes the following substances, among others.^{42,43}

- **Transforming growth factors A & B.** Induces the transformation of cells from an immature form to a mature, functional status.
- **Epithelial growth factor.** Involved in the generation and maintenance of cells in the epithelial layers of the skin.
- **Fibroblast growth factor.** Associated with the regeneration of various types of tissue, including skin and other organs.
- **Platelet-derived growth factor.** Responsible for the generation of cells and functions associated with blood clotting.

The Metabolic Factors.

Leptin. A small hormone-like protein that can suppress appetite, enhance metabolic rate and lead to body weight reduction. Mature fat cells (adipocytes) release leptin in the presence of insulin, which is also found in colostrum. Insulin-producing pancreatic beta-cells have receptor sites for leptin and it is believed that the size of fat cells may be a major factor in determining the amount of leptin released. The binding of leptin to its receptors in the presence of insulin initiates a cascade of chemical signals to the hypothalamus resulting in appetite suppression and the triggering of fat metabolism in the liver. Leptin deficiency may be associated with obesity, particularly in diabetic individuals.^{44,45,46}

Insulin. A hormone required for the effective metabolic utilization of glucose. Insulin binds to specific receptor sites on cells, facilitating their interaction with IGF-1 and, thus, initiating the conversion of glucose to glycogen, a major source of metabolic energy.²²

Vitamin-binding proteins. Smaller proteins that act as carriers to deliver B-complex vitamins to the body. Carrier proteins and the associated vitamins folate (B6), B12 and orotic acid are found in colostrum.²²

Fat-associated vitamins. Significant quantities of vitamins A, D, E and K are dissolved in or associated with the fat in colostrum.²²

Mineral-binding proteins. In addition to interfering with the replication of certain microorganisms, the iron-binding proteins, lactoferrin and transferrin, also serve to capture iron from ingested sources and present it in a form that can be readily absorbed by the body. Lactoferrin can also bind copper and deliver it in a form suitable for absorption by the body. In addition, there are two carrier proteins in colostrum that assist in the absorption of calcium. They are casein, which is also an abundant source of amino acids to build new protein molecules, and alpha-lactalbumin, which is present in colostrum very soon after birth.²²

Cyclic adenosine monophosphate (cAMP). A phosphorylated nucleotide in a high-energy state that is applicable to energy transfer in metabolism. This is the lowest energy form of adenosine triphosphate (ATP), the primary energy transfer molecule in normal metabolism. AMP can be recycled to ATP through existent intracellular pathways and, thus, colostrum can serve as a resource for these energy transfer substances.²²

Enzyme inhibitors. These have been called "permeability factors" by other manufacturers, but are actually small proteins that slow down or inhibit the breakdown of proteins by certain enzymes. They provide limited protection to the immune, growth and metabolic factors as they pass through the digestive tract.²²

HEALTH-RELATED BENEFITS OF COLOSTRUM INGESTION

High quality first milking bovine colostrum is **not** a panacea that will cure every disease as claimed by many distributors of colostrum products. However, bovine colostrum is an amazing resource of substances necessary to support the development and repair of cells and tissues, assure the effective and efficient metabolism of nutrients and establish and maintain a healthy immune system. As such, it represents a very dynamic means to stabilize bodily functions that are frequently out of control in various disease states. In other circumstances, these bodily functions may just need the boost that colostrum can provide to ward off disease.

The use of colostrum for its health-related benefits is not a new concept. In India, where cows are sacred, colostrum is delivered to the home with the milk and is

used for medicinal purposes to treat everything from age-related symptoms to the common cold. This practice began several thousand years ago with Ayurvedic physicians and sacred healers known as Rishis. In the Scandinavian countries, the birth of a calf is celebrated by the making of a pudding for human consumption from the extra colostrum after the calf is fed. This practice has gone on for centuries and is intended to promote good health. Research conducted in these countries as early as the late 18th century showed the benefits of colostrum on the health and development of cattle and laid the groundwork for the early medicinal use of colostrum by humans. The early Amish farmers in America practiced this same ritual.

Gastrointestinal Diseases

Leaky gut syndrome is a very common condition wherein the mucosal lining of the small intestine becomes very inflamed and unusually large spaces develop between the cells that make up the mucosal lining. The large spaces between the cells allows bacteria, viruses, fungi and other potentially toxic material to enter the bloodstream and other parts of the body. In addition, undigested proteins, carbohydrates and fats can pass through the intestinal lining and can represent a serious health risk.

Medical research has shown that the inflammatory process responsible for leaky gut syndrome can be initiated in many different ways, including the following.

- Excess ingestion of alcohol and/or drinks containing caffeine.
- Continuous use of antibiotics resulting in destruction of the inherent bacterial flora in the intestine.
- Ingestion of foods contaminated by certain bacteria or parasites.
- Routine ingestion of corticosteroids, such as prednisone, and/or non-steroidal anti-inflammatory drugs like aspirin or ibuprofen.
- Consumption of large quantities of highly refined carbohydrates, such as the sugar found in candy, cookies, cakes and soft drinks.

Routine dietary supplementation with high quality bovine colostrum can be of substantial value when this condition occurs.^{47,48} In leaky gut syndrome, the individual's normal protective mechanisms against invading infectious bacteria, viruses, fungi and parasites are severely compromised. Colostrum contains a diversity of antibodies that can bind to invading microorganisms and hold them in check while they are engulfed and destroyed by white blood cells arriving in the area. The most important of these antibody molecules in colostrum are of the IgA class. They not only attach themselves to an invading microorganism, but are also able to stick to tissues, holding the pathogen in a fixed position and making it more susceptible to destruction by white blood cells. The lactoferrin transferrin, and enzymes in colostrum also significantly aid the entire process of destroying invading microorganisms.

The growth factors in colostrum, growth hormone (GH) and the insulin-like growth factors (IGFs), are also of substantial benefit. It is well documented in the scientific literature that the influence of growth hormone on the proliferation of new cells in the body operates primarily through what is known as the GH/IGF axis where the presence of growth hormone enhances the many effects of the insulin-like growth factors.⁴⁹ IGF-1 is like the captain of a ship. It directs the many activities of a multitude of specialized proteins found in every cell in the body, including the process by which the cell grows and reproduces itself. IGF-1 is also responsible for maintenance of the metabolic pathways by which the cell uses glucose to make energy and builds proteins from amino acids. Therefore, the presence of sufficient quantities of growth hormone and the insulin-like growth factors in the circulation will support the repair of damaged tissue.^{31,50,51}

Leaky gut syndrome also results in significant mineral deficiencies due to damage to the carrier proteins by the associated inflammatory process. Many essential minerals are not absorbed into the body unless they are attached to specialized carrier proteins. Two of the most important minerals, iron and copper, bind to the lactoferrin and transferrin found in colostrum, which function as effective carrier proteins. In addition, the casein in colostrum, which is an excellent source of the essential amino acids that the body cannot make, is also a highly functional carrier protein for calcium, allowing it to be effectively absorbed from the small intestine.²²

Individuals afflicted with ulcerative colitis or Crohn's disease also usually benefit significantly from routine dietary supplementation with high quality bovine colostrum.^{52,53} First, dairy cows are usually exposed during their lifetime to pathogenic forms of both *E. coli* and *Mycobacterium paratuberculosis*, infectious agents presumed to be associated with these conditions. Thus, the colostrum from these animals will contain immunoglobulins directed against both of these organisms. In addition, as for leaky gut syndrome, the broad diversity of antibodies against a multitude of potentially pathogenic microorganisms present in high quality colostrum will also be beneficial. Further, as also discussed above, the presence of sufficient quantities of growth hormone and the insulin-like growth factors found in bovine colostrum will support the repair of damaged tissue.

Enteric infections with potentially pathogenic bacteria, including coliforms, like *E. coli*, *Staphylococcus* species, *Streptococcus* species, and *Salmonella* species can also be abated. Antibodies to all of these pathogens are found in high quality colostrum.^{52,54,55,56} However, the antibodies are most beneficial when they are present early in an infection and, therefore, maximum protection is afforded against enteric infections by routine ingestion of high quality colostrum as a dietary supplement. In addition, as in leaky bowel syndrome, the lactoferrin, transferrin and enzymes present in colostrum will aid in destroying an invading pathogen once the antibody molecules immobilize it.

Controlled studies in humans have shown that substances present in bovine colostrum inhibit the binding of *Helicobacter pylori*, the causative agent in ulcer lesions, to receptors on the intestinal wall.^{57,58}

Respiratory Diseases

In dealing with something as elusive as the common cold or as invasive as influenza, the best offense is a good defense. Coupling a nutritious diet with a program of exercise and routine supplementation with high quality bovine colostrum is the best possible defense. As we age, our immune system loses its ability to regulate itself and to respond to a challenge efficiently. This occurs primarily because the thymus, a glandular structure in the upper chest that is considered the seat of the immune system, begins to shrink after puberty and almost disappears by the time we are 50-60 years old.^{59,60,61} T-lymphocytes (T-cells) are generated from stem cells in the bone marrow and mature in the thymus. Some of these cells, called Killer T-lymphocytes, generate cell-mediated responses and directly destroy abnormal cells that have specific sites on their surface that are recognized by the Killer T- lymphocytes. Helper/Suppressor T-lymphocytes, a second type of cell, regulate the immune system by controlling the strength and quality of every immune response. It has been shown that the thymus can be restored to normal function by the growth factors in colostrum.^{62,63,64,65,66} In addition, colostrum contains specific hormones that regulate the functions of the thymus and other substances that help to keep the immune system under control and poised to respond to possible infections before they become established.^{35,36,37,67}

Cardiovascular Diseases

High quality first milking bovine colostrum does not contain any cholesterol and can be used safely by individuals with high serum cholesterol and high triglycerides. In fact, there are biologically active substances present in bovine colostrum that would be very beneficial to individuals at risk for atherosclerotic plaque formation. Bovine colostrum contains leptin, a hormone-like substance that not only suppresses appetite, but also orchestrates how the body uses and incorporates fat.

Growth hormone has been shown to work in concert with IGF-1 in the functioning and repair of heart muscle.⁶⁸ Receptors for both growth hormone and IGF-1 are found on all heart muscle cells and scientific evidence indicates that growth hormone may act directly on the heart, whereas the effects of IGF-1 may be indirect and operate through separate hormonal pathways.^{69,70} Research studies have also shown that both growth hormone and IGF-1 have stimulatory effects on heart muscle cells and it is believed that this occurs through the pathway by which the cells use calcium.⁷¹ It has also been shown that administration of growth hormone to patients with congestive heart failure can induce a marked improvement in heart function and clinical status.⁷²

Metabolic Diseases

Both Type I and II diabetes have an associated genetic component through which individuals appear to be predisposed. Diabetics also have low levels of IGF-1 in their circulation.^{49,73} Daily supplementation of the diet of the diabetic patient with a high quality first milking bovine colostrum will provide a functional source for the restoration of diminished levels of IGF-1, resulting in increased utilization of available glucose. This becomes extremely important for the Type I diabetic to assure effective and controlled utilization of available glucose once his/her insulin levels are restored. In the Type II diabetic, where sufficient insulin is available, it has been shown experimentally that restoration of reduced IGF-1 levels results in an enhancement of glucose utilization with a corresponding diminution of glucose levels in the blood and urine.⁷⁴

Autoimmune Diseases

Diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, among others, are complex clinical conditions with variable outcomes. All of these diseases represent an immune system that is out of control and could be restored and regulated through routine dietary supplementation with a high quality first milking colostrum. As indicated above (see Respiratory Diseases), as we age, our immune system loses its ability to regulate itself efficiently, primarily because the thymus begins to shrink after puberty and essentially disappears by the time we are 50-60 years old.^{59,60,61} Scientific studies have shown that the thymus can be restored to normal function by IGF-1^{62,63,64,65,66}, the levels of which diminish in the circulation with age. In addition, colostrum contains a) specific hormones, the alpha and beta chains of thymosin, that are known to regulate the functions of the thymus; and b) proline-rich peptide (PRP), a/k/a thymulin, that has been shown to keep the immune system under control.^{35,36,37,67}

It is also well documented that IGF-1 and the associated Superfamily of proteins found in colostrum operate in concert with growth hormone in the regeneration and repair of damaged cells.⁷⁵ Routine dietary supplementation with high quality bovine colostrum is, therefore, desirable for individuals afflicted with autoimmune diseases in order to assure that sufficient levels of IGF-1 and growth hormone are continuously available in the circulation. In addition, since IGF-1 is responsible for directing the conversion of glucose to glycogen and glycogen is a primary metabolic energy resource, such dietary supplementation could also help such individuals overcome the associated lethargy normally experienced with such diseases.

Acquired Immune Deficiency Syndrome (AIDS)

The primary site for maturation of T-lymphocytes and their release into the body in response to an insult is the thymus gland. Unfortunately, as we age this organ shrinks and loses its functions and valuable immune response capabilities are

diminished or lost. This is a serious consideration in the individual infected with the human immunodeficiency virus (HIV), since the immune system is the primary focus of attack by the virus. As indicated above, the IGF-1 found in colostrum has been shown to be capable of restoring the thymus to its normal functioning capacity. In addition, colostrum contains both the alpha and beta chains of thymosin, which are hormones that have been shown to operate independently and in concert to promote the functions of the thymus. Separate studies in experimental animals have also shown that daily ingestion of a high quality bovine colostrum results in a more expedient and effective response by the immune system when a potentially infectious microorganism challenges the body. In dealing with infectious diseases like AIDS, experts agree that the best offense is a good defense and that having the healthiest possible immune system, that is more capable of responding to a challenge, will likely assist in warding off infection and/or help in prolonging the development of the disease.

Other substances found in bovine colostrum may also prove beneficial to AIDS patients. In limited studies, lactoferrin, an iron-binding component of colostrum, has been shown to completely prevent infection with certain viruses to which the AIDS patient may become susceptible.^{36,76,77} Independent scientific studies have also shown that the lactoferrin found in bovine colostrum is at least twice as potent as that found naturally in humans.³⁷

The antibodies present in high quality bovine colostrum have also proven to be effective in helping to limit the severe diarrhea usually associated with the opportunistic enteric infections experienced by many AIDS patients. Actual studies conducted in persons suffering severe diarrhea in association with immune system deficiency evidenced that over half of the patients treated with bovine colostrum remained free of diarrhea for at least four weeks.^{78,79}

The wasting associated with the evolution of the disease in AIDS patients represents the destruction of muscle mass and is usually paralleled by the development of extreme fatigue and loss of energy. As described above, having a sufficient quantity of IGF-1 in the circulation, as would occur by routine dietary supplementation with high quality colostrum, assures the effective and efficient conversion of glucose to glycogen, supporting metabolic energy requirements to help overcome the developing lethargy and fatigue. In addition, having sufficient IGF-1 available also helps to assure proper utilization of amino acids in the building of proteins required to maintain muscle mass.

Body Composition and Performance

Supplementation with bovine colostrum has been shown to affect body composition in a study using a small group of trained athletes. After 8 weeks of daily supplementation with 20 grams of a powdered colostrum preparation, lean body mass increased significantly in the colostrum group compared to a placebo group given whey. There was no improvement in exercise performance in either group.⁸⁰ Other workers found increased levels of serum insulin, IGF-1 and

immunoglobulins in a group of athletes consuming a liquid colostrum drink daily for 8 training days, with no improvement in vertical jump ability.⁸¹

Other studies have found that supplementation with a “concentrated bovine colostrum protein powder” daily for 8 weeks did not increase serum IGF-1 levels, but appeared to improve recovery from a run to exhaustion test during the second half of the 8 week period. The placebo used was whey.⁸² A second study by the same research group using the same colostrum preparation and dosage and a whey placebo found that performance by trained young women rowers in the colostrum group improved by the ninth week of a 9 week training program, as compared to placebo.⁸³ In a separate study, routine daily supplementation with a colostrum powder was shown to increase the physical stamina of field hockey players.⁸⁴

In other studies, resistance-trained subjects received either bovine colostrum, a casein-whey placebo, colostrum + an additional supplement (containing creatine, carnitine, and taurine), or the supplement only, for 12 weeks. All subjects consumed the same amount of protein. The colostrum + supplement group showed a 5.7 lb increase in fat free mass (FFM), compared to 2.8 lbs in the colostrum group and 4.2 lbs in the supplement only group.⁸⁵ Measurements of training adaptations indicated that the colostrum + supplement group had the greatest improvements in bench press and leg press performance.⁸⁶

SAFETY

There appear to be no adverse effects due to the use of colostrum as a dietary supplement. However, the presence of IGF in colostrum and the reported increase in serum IGF levels following colostrum use has raised some concerns about its safety. Multiple studies have shown that there is an elevated level of IGF-1 in the circulation of patients with certain types of malignancies including, prostate cancer^{87,88}, breast cancer^{89,90}, colorectal cancer⁹¹ and acute lymphoblastic leukemia⁹². The fact that IGF-1 is a growth promoting substance led to the erroneous conclusion by some that it is a causative agent in malignant disease that would promote the growth of tumors. However, more recent studies have shown that tumor cells have poorly functioning or modified receptors for IGF-1 on their surface, and, since the binding of IGF-1 to a cell surface receptor triggers many functions in all cells, unbound, available IGF-1 will back-up in the circulation.^{93,94,95,96} Therefore, the higher levels of IGF-1 found in the circulation of cancer patients are a manifestation of their tumor and not a causative factor. A similar manifestation of receptor impairment and commensurate alteration in circulating levels of IGF-1 is seen in diabetic individuals.⁹⁷

COLLECTION AND PROCESSING OF COLOSTRUM

Source of Colostrum

The antibodies found in the blood of a pregnant cow that are eventually transferred into the colostrum were all derived by the immune system of that cow in response to foreign substances to which the cow had been exposed during its lifetime. These foreign substances include the various vaccines administered to protect the animal against different potential disease-causing microorganisms; clinical and non-clinical contagious infections experienced as a result of contact with other members of the herd, including microorganisms present in their excrement; and microorganisms vectored from handling and contact with equipment and other species.

Some distributors of colostrum state that colostrum should only come from cows that are pasture-fed since that provides more antibody diversity. Although it is theoretically possible that some pathogens may be present in the soil and be vectored to the cow, this is highly unlikely since microorganisms that would ordinarily be found in clean soil and on grasses suitable for grazing would not be pathogenic to mammals - otherwise all of the animals in the herd would be sick most of the time. Pathogens found in a pasture or any other environment would most likely be present as a result of animal excrement.

In the United States, it was recognized many years ago that open pasturing of dairy cows, including breeding and unsupported calf delivery in the pasture environment, was not conducive to good herd management practices and led to a higher incidence of disease; affected milk production volumes and the quality of milk. It also failed to provide the support necessary to assure that calves received adequate volumes of colostrum of sufficient quality to promote their proper development. A large number of dairy farms in the United States have shifted to the use of so-called "dry lot" techniques that restrict the cows to little or no pasture grazing. The animals are kept either inside of a structure or outside within clean, non-grass, fenced environments and fed a well-defined diet containing the required nutrients to assure effective development and maintenance of their health status. These areas can be cleaned routinely, either manually or automatically, to assure removal of excrement. The animals in such environments are frequently divided into groups reflecting the number of lactation cycles they have experienced and their average milk production capabilities. This approach allows the dairy producer to more effectively control disease development and to recognize and separate animals with problems, regulate milking schedules, and control the quality and flavor of the milk.

It has also become a dairy industry standard in the United States that all pregnant cows due to deliver are monitored every 1-2 hours around the clock. For this purpose, most dairy farms have a "maternity ward" away from the main herd that allows for the required monitoring and facilitates calf handling and colostrum collection within the first six hours after birth. It is also very common for producers to prevent newborn calves from suckling as they receive better care and better colostrum delivery if they are nursed by hand. In addition, when calves are removed from their mothers at birth, they have less exposure to the

maternity area, decreasing disease transmission through contact with fecal material and the mother's teats.

Companies marketing the highest quality bovine colostrum usually have access to at least 500 dairy herds averaging about 300 cows each. Since cows are biological creatures and, thus, will not all have the same levels of biologically active components in their individual colostrum, collecting from a large number of animals in different herds and manufacturing from large pools of colostrum supports the control of product uniformity and assures a maximum level of all of the beneficial components in each production lot.

Collection and Processing

True colostrum must be obtained in the first milking taken during the 6 hours after birth of the calf. Many years ago the United States Department of Health defined colostrum as the "milk" collected in the first six milkings after birth. This was done to keep colostrum out of milk intended for human consumption since it was believed then that it was only suitable for consumption by the calf. However, science has now significantly advanced our understanding of what colostrum really is, how it is formed and the many benefits that it can convey to humans as well as calves. We now know that, in the pregnant cow, colostrum formation ceases at birth and that the mother begins to reabsorb the active components about 6-8 hours after birth if the colostrum is not collected. We also know that the colostrum should be collected in one unit since, as soon as a small volume of colostrum is removed, a much larger volume of transitional milk will enter the udder and dilute the residual colostrum.

Apparently, the scientific facts have not reached every manufacturer of colostrum since some of them still market "colostrum" that is collected from multiple milkings after the birth of the calf. This obviously results in much more "product" per cow, but the resulting colostrum powders are deficient in many of the most beneficial components and the remaining constituents have been significantly diluted. Thus, they will never provide the same range of benefits that can be realized with high quality first milking colostrum.

High quality colostrum must be collected under very stringent conditions. These conditions require that a) colostrum be included only from cows that have experienced three or more live births to maximize the quality of bioactives and assure antibody diversity; b) no colostrum be collected from any animal evidencing any form of inflammation of the udder; and c) no colostrum evidencing blood, mucus, somatic cell clumps or strings, other foreign matter or discoloration be included.

Colostrum should be frozen immediately after it is collected and then transferred as quickly as possible, in the frozen state, to the processing facility. This is very important since no milk product is completely free of bacteria when it is collected and leaving the colostrum in the liquid state would encourage some bacteria to

reproduce, spoiling the colostrum and, perhaps, generating large numbers of disease-causing bacteria.

Some colostrum manufacturers claim that freezing will destroy the biologically active components and make them insoluble and impossible to absorb in the body. Freezing, in itself, does not alter the water-soluble nature of organic substances such as those found in colostrum. For this to occur in colostrum would require that the configuration of the many protein molecules be changed, such as occurs when they are heat-denatured at excessive temperatures, often causing them to precipitate from solution. In fact, freezing of protein solutions is the principal means of storage by laboratories to maintain the integrity and biological activity of molecules. It is well established in scientific practice that the method used for thawing frozen specimens, rather than freezing, can denature proteins and, to avoid this, the protein solution must be thawed slowly at a temperature that does not exceed 98.6° F/37° C.

When the individual colostrum units arrive at the processing facility, they must be thawed very gently and then examined and tested thoroughly to assure their quality. They can then be pooled together and processed by specialized methods that maintain the integrity of all of the biologically-active components to a) destroy bacteria that may have been present; and b) remove at least 98% of the water to yield a dry powder with good storage capabilities. These are complex and costly procedures and if a manufacturer cannot provide assurances that they have been carefully followed, it is highly likely that the resulting "colostrum" powder will yield few, if any, benefits no matter when or how it was collected.

Complete Colostrum

To maximize the benefits from a colostrum powder, it must not only meet the above criteria, but it must also be derived from complete colostrum that is unadulterated and contains everything found in true colostrum as it is generated in the cow. In addition, it should contain only complete colostrum and no additives or supplements that might change the characteristics of the biologically active components or interfere with their effectiveness.

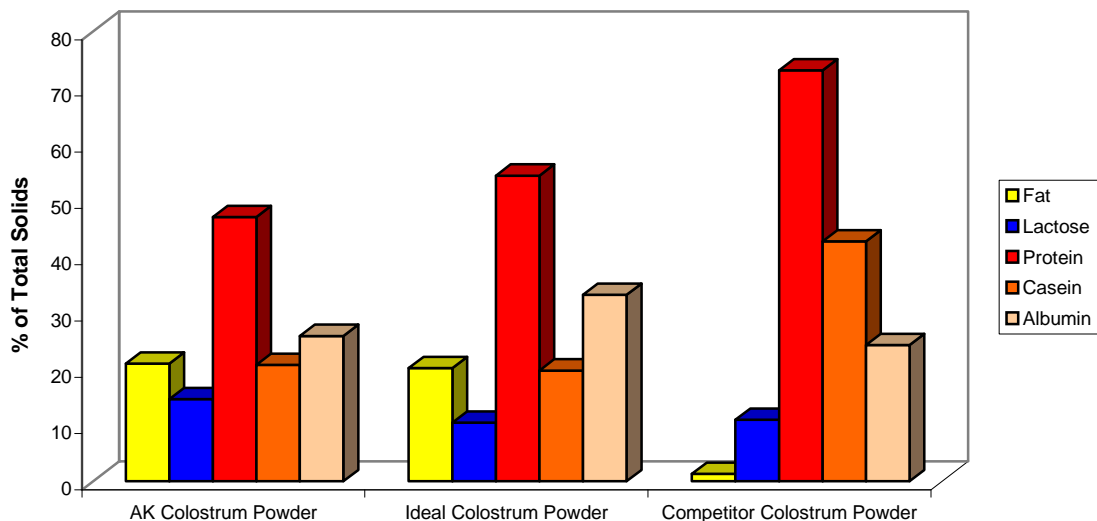
Some companies that market so-called "colostrum" physically or chemically remove some of the components, like the fat, claiming that it avoids the development of rancidity and increases the shelf-life of the powder. This approach not only changes the composition of the colostrum and the relationship of the active components, but also removes some very valuable constituents, like the fat-soluble vitamins and a portion of the growth factors. The argument that removing the fat increases the shelf life is, in itself, completely without scientific merit since rancidity in dairy products is associated with fluid materials and is not a consideration for a properly dried colostrum powder.

In addition to acting as a carrier vehicle for certain components, the fat in colostrum plays a very significant role in assuring that the maximum benefits are

available from ingested colostrum powder. High quality colostrum also contains a significant amount of casein, a complex, complete protein that contains beneficial essential amino acids. When complete colostrum enters the stomach, an enzyme (rennin) naturally present there acts upon the casein and fat to form a soft cottage cheese-like curd that entrains the active components and protects them from exposure to stomach acid and digestive enzymes. This helps to assure that as much of each biologically active component as possible reaches the small intestine, where absorption into the blood stream occurs.

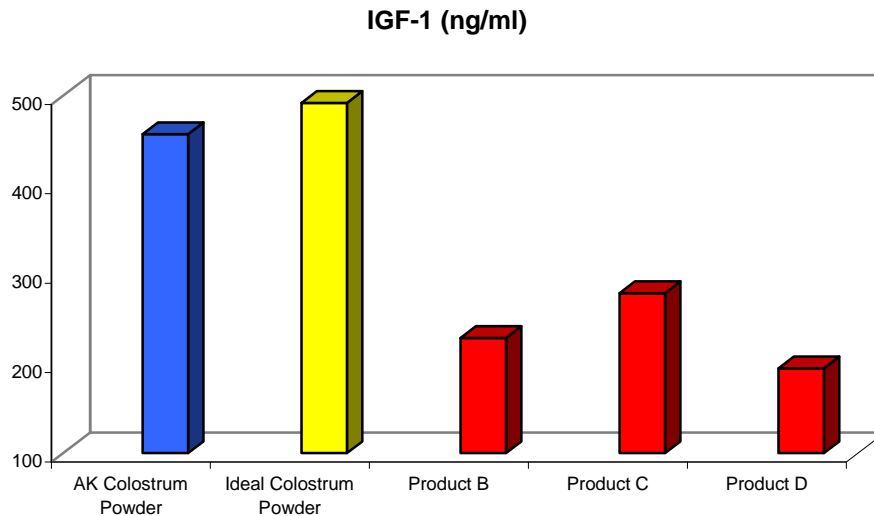
Chemical Composition

The following is a graphic representation of the actual findings from studies done at a major dairy product testing laboratory to characterize the amount of key ingredients in bovine colostrum in comparison to what is present in products offered for human consumption. The material in the middle set of bars, identified as *Ideal Colostrum Powder* was a carefully prepared powder made from a large pool of colostrum that was all definitely collected within six hours after birth. Comparison of these results with each of the tested products shown clearly demonstrates the differences between these products. The colostrum powder from AK is virtually identical in chemical composition to the Ideal Colostrum Powder. In sharp contrast, the Competitor Colostrum Powder has most of the fat removed and the relationship between the remaining components has been dramatically altered.



Does this really mean that the competitor product would provide less health benefits than the AK colostrum powder? The answer to that question becomes evident based upon the comparative amount of one of the most important biologically active components in colostrum, insulin-like growth factor-1 (IGF-1). The Endocrinology Laboratory of a major US college of veterinary medicine performed these studies. The results are shown in the graph below. It is obvious

that the colostrum powder from AK contains almost the same amount of IGF-1 as the Ideal Colostrum Powder. Three production lots of the Competitor Colostrum Powder were tested to verify the findings and none of them contained more than 60% of the IGF-1 found in the Ideal Colostrum Powder. Less IGF-1 means less benefit and it can be presumed that the amount of the other key components is similarly reduced.



Summary & Conclusions

Colostrum is an amazing material that, like many other things in nature, reflects the evolutionary development of a unique composition that will serve the needs of the offspring for which it is intended. The most unique of the colostrums from mammalian species occurs in bovine species where everything required for the development of a healthy, productive offspring is provided in the colostrum. As such, it provides a specialized resource that offers the broadest possible spectrum of biologically active substances that can promote the development of a sound body mass, assure effective and efficient metabolism and support the activation and maintenance of a fully functional immune system capable of combating potential insults from microorganisms and other deleterious sources. Bovine colostrum is also compatible with almost any species and can readily convey its full benefits to humans by routine dietary supplementation without any significant adverse effects.

However, it is very important to recognize that all colostrum products are not the same and, despite the claims made by their manufacturers, they do not all contain every beneficial component at an optimum concentration and, in many cases, they have been manipulated and may be missing some of the essential components. When choosing a colostrum product, one should be certain that it is made from only first milking bovine colostrum collected within 6 hours after birth

of the calf and that the colostrum is "complete" and that none of the components have been removed, including the fat.

REFERENCES

1. Blum JW, Baumrucker CR; Colostral and milk insulin-like growth factors and related substances: mammary gland and neonatal (intestinal and systemic) targets, *Domest Anim Endocrinol* 2002; 23(1-2):101-10.
2. Buhler C, Hammon R; Small intestinal morphology in eight day old calves fed colostrum for different durations or only milk replacer and treated with insulin-like growth factor and growth hormone, *J Anim Sci* 1998; 76(3):758-65.
3. Hammon HM, Blum JW; Feeding different amounts of colostrum or only milk replacer modifies receptors of intestinal insulin-like growth factors and insulin in calves, *Domest Anim Endocrinol* 2002; 22(3):155-68.
4. Nocek JE, et al; Influence of neonatal colostrum administration, immunoglobulin, and continued feeding of colostrum on calf gain, health and serum protein, *J Dairy Sci* 1984; 67(2):319-33.
5. Nussbaum A, et al; Growth performance and metabolic and endocrine traits in calves pair-fed by bucket or by automate starting in the neonatal period, *J Anim Sci* 2002; 80(6):1545-55.
6. Korhonen H, et al; Bovine milk antibodies for health, *Brit J Nutr* 2000; 84(Suppl1):S135-46.
7. McGuire TC, et al; Failure of colostral immunoglobulin transfer in calves dying from infectious disease, *J Am Vet Med Assoc* 1976; 169:713-8.
8. Quigley JD, et al; Formulation of colostrum supplements, colostrum replacers and acquisition of passive immunity in neonatal calves, *J Dairy Sci* 2001; 84:2059-65.
9. Plaut K; Role of epidermal growth factor and transforming growth factors in mammary development and lactation, *J Dairy Sci* 1993; 76(6):1526-38.
10. Plath A, et al; Expression of transforming growth factors alpha and beta-1 messenger RNA in the bovine mammary gland during different stages of development and lactation, *J Endocrinol* 1997; 155(3):501-11.
11. Delouis C; Physiology of colostrum production, *Ann Vet Res* 1978; 9(2):193-203.
12. Forsyth IA; *The Endocrinology of Lactation*, T.B. Mepham, ed.; Elsevier Science Publishers 1983; pp 309-49.
13. Barrington GM, et al; Regulation of immunoglobulin G1 receptor: effect of prolactin on in vivo expression of the bovine mammary gland receptor, *J Endocrinol* 1999; 163(1):25-31.

14. Akers RM; Lactogenic hormones: binding sites, mammary growth, secretory cell differentiation and milk biosynthesis in ruminants, *J Dairy Sci* 1985; 68(2):501-19.
15. Barrington GM, et al; Regulation of colostrogenesis in cattle, *Livest Prod Sci* 2000; 70(1-2):95-104.
16. Guy MA, et al; Regulation of colostrum formation in beef and dairy cows, *J Dairy Sci* 1994; 77(10):3002-7.
17. Tucker HA, Lactation and its Hormonal Control, *in* The Physiology of Reproduction, 2nd edition, E. Knobil & J. Neill eds.; Raven Press Ltd. 1994; pp 1065-110.
18. Fundamentals of Dairy Chemistry, 2nd Ed, B.H. Webb, A.H. Johnson, J.A. Alford eds; The AVI Publishing Co., Westport, CT, 1978.
19. Quigley JD, Kost CJ, Wolfe TM; Absorption of protein and IgG in calves fed a colostrum supplement or replacer, *J Dairy Sci* 2002; 85(5): 1243-8.
20. Schams D; Einspanier R; Growth hormone, IGF-1 and insulin in mammary gland secretions before and after parturition and possibility of their transfer into a calf, *Endocrine Regulation* 1991; 25(1-2): 139-143.
21. Xu R; Development of newborn GI tract and its relationship to colostrum/milk intake: a review, *Reprod Fertil Devel* 1996; 8(11):35-48.
22. Hurley WL; Animal Science 308 (on-line): The Neonate and Colostrum, University of Illinois Urbana-Champaign; 2000, 11 pgs. [<http://classes.aces.uiuc.edu/AnSci308>].
23. Kuhn NJ; The Biochemistry of Lactogenesis. In *Biochemistry of Lactation*, T.B. Mepham, ed.; Elseviers Science Publishers 1983; pp 309-49.
24. Ancell CD, et al; Thymosin alpha-1, *Am J Health Syst Pharm* 2001; 58(10):879-85.
25. Li QY, et al; Thymosin beta-4 regulation, expression and function in aortic valve interstitial cells, *J Heart Valve Dis* 2002; 11(5):726-35.
26. Yarmola M, et al; Formation and implications of ternary complex of profilin, thymosin beta-4, and actin, *J Biol Chem* 2001; 276(49):455-63.
27. Kanaan SA, et al; Thymulin reduces the hyperalgesia and cytokine upregulation induced by leishmaniasis in mice, *Brain Behav Immunol* 2002; 16(4):450-60.
28. Solomons NW; Modulation of the immune system and the response against pathogens with bovine colostrum concentrates, *Eur J Clin Nutr* 2002; 56(S3):S24-8.
29. Pido-Lopez J, et al; Molecular quantitation of thymic output in mice and the effect of IL-7, *Eur J Immunol* 2002; 32(10):2827-36.
30. Saito H, et al; Topical antigen provocation increases the number of immunoreactive IL-4, IL-5 and IL-6 positive cells in the nasal mucosa of

patients with perennial allergic rhinitis, *Int Arch Allergy Immunol* 1997; 114(1):81-5.

31. Nord J, et al; Treatment with bovine hyperimmune colostrum of cryptosporidial diarrhea in AIDS patients, *AIDS* 1990; 4(6):581-4.

32. Rump JA, et al; Treatment of diarrhea in human immunodeficiency virus-infected patients with immunoglobulins from bovine colostrum, *Clin Investig* 1992; 70(7):588-94.

33. Kirkpatrick, CH; Activities and characteristics of transfer factors; *Biotherapy* 1996; 9(1-3): 13-16.

34. Kirkpatrick, CH; Transfer factors: identification of conserved sequences in transfer factor molecules; *Mol. Med.* 2000 Apr.; 6(4): 332-41.

35. Lawrence, HS, Borkowsky, W; Transfer factor - current status and future prospects; *Biotherapy* 1996; 9(1-3):1-5.

36. Lonnerdal B, Iyer S; Lactoferrin: molecular structure and biological function, *Ann Rev Nutrition* 1995; 13:93-110.

37. Brock J; Lactoferrin: a multifunctional immunoregulatory protein. *Immunol Today* 1995; 16(9):417-19.

38. Kussendrager KD, van Hooijdonk AC; Lactoperoxidase: physico-chemical properties, occurrence, mechanism of action and applications, *Brit J Nutr* 2000; 84(Suppl 1):S19-25.

39. Gopal PK, Gill HS; Oligosaccharides and glycoconjugates in bovine milk and colostrum, *Brit J Nutr* 2000; 84(Suppl 1):S69-74.

40. Cameron CM, et al; The acute effects of growth hormone on amino acid transport and protein synthesis are due to its insulin-like action, *Endocrinol* 1988; 122(2):471-4.

41. Shing Y, Elagabrun M; Purification and characteristics of a bovine colostrum-derived growth factor, *Molec Endocrinol* 1987; 25(3):335-40.

42. Hwa V, et al; The insulin-like growth factor binding protein (IGFBP) superfamily, *Endocrin Rev* 1999; 20(6):761-87.

43. LeRoith D; Insulin-like growth factor receptors and binding proteins, *Clin Endocrinol Metab* 1996; 10(1):49-73.

44. Baratta M; Leptin – from a signal of adiposity to a hormonal mediator in peripheral tissues, *Med Sci Monit* 2002; 8(12):282-92.

45. Guerre-Millo M; Adipose tissue hormones, *J Endocrinol Invest* 2002; 25(10):855-61.

46. Bjorback C, Hollenberg AN; Leptin and melanocortin signaling in the hypothalamus, *Vita Horm* 2002; 65:281-311.

47. Playford RJ, et al; Bovine colostrum is a health food supplement which prevents NSAID induced gut damage, *Gut* 1999; 44:653-8.

48. Playford RJ, et al; Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability, *Clin Sci* 2001; 100:627-33.

49. Bereket A, Lang CH, Wilson TA; Alterations in the growth hormone-insulin-like growth factor axis in insulin dependent diabetes mellitus, *Horm Metab Res* 1999; 31(2-3): 172-81.

50. Kelly KM, Oh Y, Gargosky SE, Gucev Z, Matsumoto T, Hwa V, Ng L, Simpson DM, Rosenfeld RG; Insulin-like growth factor-binding proteins (IGFBPs) and their regulatory dynamics, *Int J Biochem Cell Biol* 1996; 28(6): 619-37.

51. Pankov YA; Growth hormone and a partial mediator of its biological action, insulin-like growth factor-1, *Biochemistry* 1999; 64(1): 1-7.

52. Hosseini S, et al; Colostrum and milk in the treatment of disease, *Adv Nutr Res* 2001; 10:201-12.

53. Khan Z, et al; Use of the 'neutraceutical' bovine colostrum for the treatment of distal colitis; results from an initial study, *Aliment Pharmacol Ther* 2002; 16(11):1917-22.

54. Funatogawa K, et al; Use of immunoglobulin enriched bovine colostrum against oral challenge with enterohemorrhagic *Escherichia coli* O157:h7 in mice, *Microbiol Immunol* 2002; 46(11):761-6.

55. Huppertz HI, et al; Bovine colostrum ameliorates diarrhea in infection with diarrheagenic *Escherichia coli*, shiga toxin-producing *E. coli* and *E. coli* expressing hemolysin, *J Pediatr Gastroenterol Nutr* 1999; 29(4):452-6.

56. Lissner R, et al; A standard immunoglobulin preparation produced from bovine colostrum shows antibody reactivity and neutralization activity against Shiga-like toxins and EHEC-hemolysin of *Escherichia coli* O157:h7, *Infection* 1996; 24(5):378-83.

57. Bitzan MM, et al; Inhibition of *Helicobacter pylori* and *Helicobacter mustelae* binding to lipid receptors by bovine colostrum, *J Infect Dis* 1998; 17(4):955-61.

58. Korhonen H, Syvaaja EL; Bactericidal effect of normal and immune serum, colostrum and milk against *Helicobacter pylori*, *J Appl Bacteriol* 1995; 78(6):655-62.

59. Andrew D, Aspinall R; Age-associated thymic atrophy is linked to a decline in IL-7 production, *Exp Gerontol* 2002; 37(2-3):455-63.

60. Aspinall R, et al; Age-associated changes in thymopoiesis, *Springer Semin Immunopathol* 2002; 24(1): 87-101.

61. Fry TJ, Mackall CL; Current concepts of thymic aging, *Springer Semin Immunopathol* 2002; 24(1):7-22.

62. Binz K, et al; Repopulation of the atrophied thymus in diabetic rats by insulin-like growth factor-1, *Proc Nat Acad Sci* 1990; 87(10):3690-4.

63. Burgess W, et al; The immune-endocrine loop during aging: role of growth hormone and insulin-like growth factor-1, *Neuroimmunomodulation* 1999; 6(1-2):56-68.

64. Clark R, et al; Insulin-like growth factor-1 stimulation of lymphopoiesis, *J Clin Invest* 1993; 92(2):540-8.

65. Geffner M; Effects of growth hormone and insulin-like growth factor-1 on T- and B-lymphocytes and immune function, *Acta Paediatr* 1997; 423:76-9.

66. Burgess W, Liu Q, Zhou J, Tang Q, Ozawa A, Van Hoy R, Arkins S, Dantzer R, Kelly KW; The immune-endocrine loop during aging: role of growth hormone and insulin-like growth factor-1, *Neuroimmunomodulation* 1999; 6(1-2): 56-68.

67. He F, et al; Modulation of human humoral immune response through orally administered bovine colostrum, *FEMS Immunol & Med Microbiol* 2001; 31:93-6.

68. Anwar A, Gaspz JM, Pampallona S, Zahid AA, Sigaud P, Pichard C, Brink M; Effect of congestive heart failure on the insulin-like growth factor-1 system, *Am J Cardiol* 2002; 90(12): 1402-5.

69. Granata R, Gauna C, Arnolfo E, Atragine D, Broglio F, Ponti R, Ricotti E, Ghigo E; H9c2 cardiac muscle cells express insulin-like growth factor binding protein-3 (IGFBP-3), *J Endocrinol Invest* 2002 25(S10): 44-6.

70. Li H, Dimayuga P, Yamashita M, Yano J, Fournier M, Lewis M, Cercek B; Arterial injury in mice with severe insulin-like growth factor-1 (IGF-1) deficiency, *J Cardiovasc Pharmacol Ther* 2002; 7(4): 227-33.

71. Van Den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE; Endogenous hormones and carotid atherosclerosis in elderly men, *Am J Epidemiol* 2003; 157(1): 25-31.

72. Hosseini S, Inserra P, Araghi-Niknam M, Watson RR; Colostrum and milk in the treatment of disease, *Adv Nutr Res* 2001; 10: 201-12.

73. Spagnoli A, Chiarelli F, Vorwerk P, Boscherini B, Rosenfeld RG; Evaluation of the components of insulin-like growth factor (IGF) and IGF binding protein (IGFBP) system in adolescents with type 1 diabetes and persistent microalbuminuria: relationship with increased excretion of IGFBP-3 18 kD N-terminal fragment, *Clin Endocrinol* 1999; 51(5): 587-96.

74. Thomas F; Increased weight gain, nitrogen retention and muscle protein synthesis following treatment of diabetic rats with IGF-1, *Biochem J* 1991; 276(3): 547-54.

75. Skotiner V; Anabolic and tissue repair functions of recombinant insulin-like growth factors, *Acta Paediat Scand* 1990; 376: S63-6.

76. Steijns JM, van Hooijdonk AC; Occurrence, structure, biochemical properties and technological characteristics of lactoferrin, *Brit J Nutr* 2000; 84(Suppl 1):S11-7.

77. Moddoveanu Z; Antibacterial properties of milk: IgA, peroxidase-lactoferrin interactions, *Ann NY Acad Sci* 1983; 409:848-50.
78. Nord J, Ma P, DiJohn D, Tzipori S, Tacket CO; Treatment with bovine hyperimmune colostrum of cryptosporidial diarrhea in AIDS patients, *AIDS* 1990; 4(6): 581-4.
79. Rump JA, Arndt K, Arnold A, Benedick C, Diehtelmuller H, Franke M, Heim EB, Jager H, Kampmann B, Kolb P; Treatment of diarrhea in human immunodeficiency virus-infected patients with immunoglobulins from bovine colostrum, *Clin Investig* 1992; 70(7): 588-94.
80. Antonio J, et al; The effects of bovine colostrum supplementation on body composition and exercise performance in active men and women, *Nutrition* 2001; 17:243-7.
81. Mero A, et al; Effects of bovine colostrum supplementation on serum IGF-1, IgG, hormone and saliva IgA during training, *J Appl Physiol* 1997, 83:1144-51.
82. Buckley JD, et al; Bovine colostrum supplementation during endurance running training improves recovery, but not performance, *J Sci Sport Med* 2002; 5(2):65-79.
83. Buckley JD, et al; Oral supplementation with bovine colostrum improves rowing performance in elite female rowers. Presented at 5th IOC World Congress on Sport Sciences, Sydney 1999 (Abstract: www.ausport.gov.au/fulltext/1999/iocwc/abs246c.htm).
84. Hofman Z, et al; The effect of bovine colostrum supplementation of exercise performance in elite field hockey players, *J Sport Nutr Exerc Metab* 2002; 12(4):461-9.
85. Kreider RB, et al; Effects of bovine colostrum supplementation in training adaptations I: Body composition, *Med Sci Sports Exerc* 2001; 33(Suppl 5):Abstract LB316.
86. Kerksick C, et al; Effects of bovine colostrum supplementation in training adaptations II: Performance, *Med Sci Sports Exerc* 2001; 33(Suppl 5):Abstract LB317
87. Chan JM, et al; Plasma insulin-like growth factor-1 and prostate cancer risk: a prospective study, *Science* 1998; 279(5350):563-6.
88. Wolk A, et al; Insulin-like growth factor-1 and prostate cancer risk: a population-based, case-controlled study, *J Nat cancer Inst* 1998; 90(12):911-5.
89. Bohlke K, et al; Insulin-like growth factor-1 in relation to premenopausal ductal carcinoma in situ of the breast, *Epidemiology* 1998; 9(5):570-3.
90. Sachdev D, Yee D; The IGF system and breast cancer, *Endocrine Related Cancer* 2001; 8:197-209.

91.Ma J, et al; Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3, J Natl Cancer Inst 1999; 91(7):620-5.

92.How HK, et al; Insulin-like growth factor binding proteins (IGFBPs) and IGFBP-related protein-1 levels in cerebrospinal fluid of children with acute lymphoblastic leukemia, J Clin Metab 1999; 84(4):1283-7.

93.Sprenger CC, et al; Insulin-like growth factor binding protein-related protein-1 (IGFBP-rP1) is a potent tumor suppressor protein for prostate cancer, Cancer Res 1999; 59(10):2370-5.

94.Yang DH, et al; Identification of glycosylated 38-kDa connective tissue growth factor (IGFBP related protein 2) and proteolytic fragments in human biological fluids, and up-regulation of IGFBP-rP2 expression by TGF-beta in Hs578T human breast cancer cells, J Clin Endocrinol Metab 1998; 83(7):2593-6.

95.Yamanaka Y, et al; Characterization of insulin-like growth factor binding protein-3 (IGFBP-3) binding to human breast cancer cells: kinetics of IGFBP-3 binding and identification of receptor binding domains of the IGFBP-3 molecule, Endocrinology 1999; 140(3):1319-28.

96.Vorweck P, et al; CTFG (IGFBP-rP2) is specifically expressed in malignant lymphoblasts of patients with acute lymphoblastic leukemia (ALL), Brit J Cancer 2000; 83(6):756-60.

97.Travers SH, et al; Insulin-like growth factor binding protein-1 levels are strongly associated with insulin sensitivity and obesity in early pubertal children, J Clin Endocrinol Metab 1998; 83(6):1935-9.

Dr. Alfred E. Fox holds a Ph.D. in Microbiology (Immunochemistry) from Rutgers University and has more than 25 years of senior management experience at Carter-Wallace, Baxter Dade Division and Warner-Lambert, where he was responsible for research and development and regulatory affairs. He was also the founder and president of two biotechnology companies focused on agribusiness and environmental monitoring, respectively. For the past 15 years, Dr. Fox has been the President of Fox Associates, a business and technology consulting firm serving small- to mid-size companies in the human and animal healthcare fields. He focuses primarily on marketing and regulatory issues and for the past 10 years has continuously consulted to bovine colostrum manufacturers, where he has gained regulatory approval for their products, been a technical advisor, helped design and develop marketing strategies and served as an expert witness in legal matters.

Dr. Anthony Kleinsmith holds a Ph.D. in Nutrition and is a board certified Naturopath from Chatworth College of Natural Health & Nutritional Sciences with more than 15 years of nutritional research and formulating for company's around the world. He has formulated and been involved with research for human and animal health and product development. His specialty and focus has been on Anti-Aging, Immune Enhancement/Regulation and Weight Loss. His work with recombinant

forms of Growth Hormones led him to solidify research on natural forms of the IGF-1/GH Super Family. Dr. Kleinsmith has written several books, made appearances on TV, Radio and toured the world as a public speaker primarily on Anti-Aging, Immune Enhancement/Regulation and Weight Loss. He has also established a very unique contract manufacturing facility that has the ability to maintain the integrity of natural substances without the use of excipients or fillers.