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Why Breast Milk Has Health Benefits for Infants and Children: A Review

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Abstract: Breastfeeding is superior to formula feeding because it has specific and non-specific factors that have long term consequences for early metabolism and disease later in life. Human milk enhances the immature immunologic system of the neonate and strengthens host defense mechanisms against infective and other foreign agents. Mechanisms that explain active stimulation of the infant's immune system by breastfeeding are through bioactive factors in human milk such as hormones, growth factors, colony stimulating factors and specific nutrients. Human milk may show a reduced occurrence of disease because: 1) Mammalian evolution promotes survival advantage. 2) Factors that promote gastrointestinal mucosal maturation. 3) Factors that decrease the incidence of infection and alter the gut microflora. 4) Functional immunomodulatory and anti-inflammatory factors. 5) Hormones, growth factors and cytokines that may modulate the development of disease. 6) Reduced exposure to foreign dietary antigen. Following the termination of breastfeeding there is evidence of ongoing protection against illness due to influences on the immune system mediated via human milk. Industry continues to attempt to improve formula with the addition of compounds such as fatty acids, oligosaccharides, nucleotides and lactoferrin. However, human milk has such far reaching effects on the infant's immune response that normal development depends heavily on its provision. All mothers should be encouraged and supported to continue breastfeeding for six months and beyond in order to promote the good health of their infants.

Key words: Breastfeeding, infections, long-term effects, child health

Introduction

Breastfeeding is superior to formula feeding because it has specific and non-specific factors that have long term consequences for early metabolism and disease later in life. In this paper the scientific evidence in support of why breastmilk is beneficial for infants and children is summarised and the mechanisms whereby breastfeeding impacts on disease are explored.

The Epidemiological Evidence: The health hazards of bottle feeding were first reported in the early 20th century (Grulee C.G. *et al.*, 1934; Grulee C.G *et al.*, 1935). Mortality charts at that time showed a clear difference in risk of death between breastfed and bottle-fed babies. Since these earlier studies, evidence has emerged that breastfeeding may be directly responsible for reducing the incidence of many illnesses in infancy and childhood including acute diarrhea (Feachem and Koblinsky, 1984), lower respiratory tract infections (Wright *et al.*, 1989; César *et al.*, 1999), ear infections (Saarinen, 1982; Duncan, *et al.*, 1993) and asthma (Saarinen and Kajosaari, 1995; Oddy *et al.*, 1999). In addition, there is evidence that breastfeeding protects against less common illnesses such as necrotising enterocolitis (Lucas and Cole., 1990), botulism (Wigginton and Thill, 1993), urinary tract infections (Pisacane *et al.*,1992; Mårild *et al.*, 1990; Mårild *et al.*, 1989) sudden infant death syndrome (Ford *et al.*, 1993) insulin dependent diabetes mellitus (Gerstein, 1994) and childhood lymphoma (Davis, 1998).

There is also evidence that breastfeeding reduces the risk of immunologic disease including coeliac disease (Falth-Magnusson *et al.*, 1996), Crohn's disease [Peters *et al.*, 2001) and ulcerative colitis (Corrao *et al.*, 1998) although further confirmation of protection against these illnesses is required. In the longer term, breastfeeding appears to have beneficial consequences for metabolism, cognitive development and diseases later in life including cardiovascular disease, rheumatoid arthritis, multiple sclerosis and some cancers (Davis, 1998; Barker, 1997; Bergstrom *et al.*, 1995; Greene *et al.*, 1995; Drane and Logemann, 2000; Anderson *et al.*, 1999; Mason *et al.*, 1998; Pisacane *et al.*, 1994; Davis *et al.*, 1988).

Because breastfeeding stimulates the neonatal immune system, it may protect against autoimmune disease. Of interest is that breastfeeding enhances tolerance of maternal renal grafts (Campbell *et al.*, 1984), and that diabetes mellitus (an expression of autoimmunity) is reduced in breastfed children (Ellis and Atkinson, 1996; Borch-Johnsen *et al.*, 1984; Virtanen *et al.*, 1993). The possibility that the early introduction of 'other milk' (Vaarala *et al.*, 1998; Willems *et al.*, 1993) may increase the risk of type I and type II (Pettitt *et al.*, 1997) diabetes has been debated (Ellis and Atkinson, 1996) but the possible biological role of these observations is unknown (Mason *et al.*, 1998; Pisacane *et al.*, 1994; Fort *et al.*, 1990).

Compelling evidence for a relationship between breastfeeding and cognitive development now exists from longitudinal (Rogan and Gladen, 1993; Fergusson *et al.*, 1982; Rodgers, 1978; Lucas *et al.*, 1992; Horwood and Fergusson, 1998) experimental (Koletzko *et al.*, 1998) and neurodevelopmental studies (Wharton, 1992; Clandinin *et al.*, 1980; Farquharson *et al.*, 1992; Makrides *et al.*, 1994; Hamosh and Salem, 1998; Jenson *et al.*, 1992; Gibson and Makrides, 1998; Uauy and De Andraca, 1995).

It is biologically plausible that increased fatty acid exposure through breast milk may enhance brain development and learning ability. Epidemiological data do not allow certainty of knowledge that breast milk exposure does or does not enhance neurodevelopmental outcome (Feldman and Feldman, 1996). However, the effect of full breastfeeding to at least six months on the mean IQ of a population can be conceptualised as shifting the mean upward by 11 points for term infants and 8 points for preterm infants. Rogan and Gladden (Rogan and Gladen, 1993) noted that even minor changes in the mean IQ could significantly alter the number of children falling below a cut-off level.

Some of the levels of evidence in support of risk associated with lack of breastfeeding are summarised in Table 1.

Why Breastfeed? : Most women when asked why they want to breastfeed emphasise the bonding aspect. In fact, breast milk contains many substances that act as mediators between mother and child and establish a physiological and biochemical communication network, as an evolutionary extension of the intrauterine to extrauterine environment (Bernt and Walker, 1999). The extrauterine development of the human immune system is delayed (Goldman *et al.*, 1998) partly explaining why susceptibility of young infants to infections increases with prematurity. Immunologic agents are transmitted through amniotic fluid or the placenta during fetal life but the risk of infection to the newborn is lessened by breast milk feeding.

Table 1: Illness, disease and development feeding measure and risk ratio range.

Common illnesses	Reference	Feeding measure	Risk Ratio range*
Acute diarrhea	Victora and Barros, 2000	Breastfed < 3 months	6.10 (4.1-9.0)
Lower respiratory tract infections	(Wright *et al.*, 1989)	Breastfed < 4 mo/ sharing bedroom	3.29 (1.8-6.0)
Pneumonia	César *et al.*, 1999	No breastfeeding	16.7 (7.7, 36.0)
Ear infections (Recurring vs acute)	Duncan *et al.*, 1993	Breastfed < 6 months	1.61 (1.27, 1.79)*
Asthma	Oddy *et al.*, 1999	Breastfed < 4 months	1.25 (1.02, 1.52)
Atopy	Oddy *et al.*, 1999	Breastfed < 4 months	1.30 (1.04, 1.61)
Less common illnesses			
Necrotising enterocolitis	Lucas and Cole 1990	39% formula fed/ 7% breastfed	4.50 (3.00, 6.00)*
Urinary tract infections	Pisacane *et al.*, 1992	Never breastfed	1.62 (1.35, 1.78)*
Insulin dependent diabetes mellitus	Gerstein, 1994	Breastfed < 4 months	1.63 (1.22, 2.17)
Acute lymphobastic leukemia	Shu *et al.*, 1999	Never breastfed	1.21 (1.09, 1.30)*
Sudden infant death syndrome	Ford *et al.*, 1993	Current formula feeding	1.35 (1.09. 1.54)*
Cholera	Clemens *et al.*, 1990)	Not breastfeeding	1.70 p<.0001
Immunologic disease			
Coeliac disease	Falth-Magnusson *et al.*, 1996; Peters *et al.*, 2001	Breastfed < 3 months	1.63 (1.36, 1.79)*
Crohn's disease	Corrao *et al.*, 1998; Koletzko *et al.*, 1989a	Lack of breastfeeding	1.90 (1.50, 3.60)
Ulcerative colitis	Corrao *et al.*, 1998; Koletzko *et al.*, 1991b	Lack of breastfeeding	1.50 (1.10, 2.10)
Juvenile rheumatoid arthritis	Mason *et al.*, 1998	Lack of breastfeeding	1.60 (1.19, 1.80)
Multiple sclerosis	Pisacane *et al.*, 1994	Breastfed < 7 months	1.62 (1.26, 1.81)
Development			
Cognitive development in preterm	Lucas *et al.*, 1992	Lack of breastfeeding	↑ mean IQ of 8.3 pts
Cardiovascular disease	Bergstrom *et al.*, 1995	Lack of breastfeeding	↑ mean Tot Cholesterol
Metabolic development	Bergstrom *et al.*, 1995)	Lack of breastfeeding	↑ ApoB values
Obesity	von Kries *et al.*, 1999	Breastfed < 6 months	1.25 (1.02, 1.43)

* The risk ratios have been adjusted to reflect a level of risk of formula rather than protection of breast milk. This was done to ensure consistency of results.

Furthermore breastfeeding protects against infection well beyond the neonatal period (Clemens *et al.*, 1990).

The biochemistry of human milk encompasses a massive body of scientific literature most of which has been generated since the 1970's (Goldman and Goldblum, 1995; Wold and Hanson, 1994; Xanthou *et al.*, 1995; Hanson, 1998). Human milk changes composition from colostrum, to transitional, to mature milk and over time of day and as time goes by. Concentrations of protein, fat, carbohydrates, minerals and cells differ and physical properties such as osmolarity and pH change impacting on the physiology of the infant gut (Lawrence, 1999). More than 200 constituents have been discovered in human milk and the bioactivity and immunologic significance are yet to be explored in many. We now know that human milk contains an array of antimicrobial, anti-inflammatory, immunomodulating and bioactive molecules and compounds that are often multifunctional are adapted to mucosal sites and are not well represented in formula milks.

When human milk feeding is not practiced, reliable data on human milk constituents and their significance to infant health must be available for the preparation of formula by industry. However, there are myriads of factors that cannot be incorporated into formula. The adequacy of formula cannot be predicted from compositional analysis due to possible differences in compartmentalisation and the molecular form of nutrients (Picciano, 2001).

Industry continues to improve formula with the addition of compounds such as fatty acids, oligosaccharides, nucleotides and lactoferrin. It is clear however, that human milk has such far-reaching effects on the infant's immune response that normal immunologic development depends heavily on its provision.

Mechanisms Whereby Breastfeeding Could Impact On Disease: There are a number of reasons to expect that breastfed children may show a reduced occurrence of disease and illness (Table 2) (adapted from Chandra, 1991). The full sophistication of human milk has only recently become evident with many components exhibiting pleiotropic functionality (Garofalo and Goldman, 1999).

Mammalian Evolution Promotes Survival Advantage: Paleontologic evidence suggests that vertebrates evolved gradually from deuterostome ancestors about 500-600 million years ago, where many innovations were retained in their evolutionary descendants (Smith and Davidson, 1994). The evolutionary innovation defining mammals was the mammary gland developed in evolution about 190 million years ago (Blackburn, 1993), as a consequence of newborn receiving nutrients from secretions of the maternal ventral thorax/abdomen favouring maternal infant interaction. Evolutionary success is determined by an ability to not only reproduce but to cope with the environment, reach the reproductive period and assure the long term survival of offspring (Goldman *et al.*, 1998). In an evolutionary context, milk allows the infant to mature to a sexually active adult better able to cope with the environment.

The mammary gland evolved prior to the placenta, evidenced by monotremes, mammals with no placenta (Griffiths, 1988). Milk from humans displays certain similarities of the immune system to these. Lysozyme, abundant in milk and produced by mammalian apocrine glands (Ansai *et al.*, 1995) is phylogenetically very ancient and found in both monotreme and human milks (Tehan *et al.*, 1991). So too are transferrins and difucosyl lactose, an oligosaccharide that interferes with attachment of common toxins to epithelial cells (C. jejuni, e coli) (Crane *et al.*, 1994). These primordial immunologic adaptations may have evolved to protect the recipient infant from maternal bacterial flora by secreting antimicrobial agents.

Homosapiens emerged at least 100 000 – 200 000 years ago (Ayala, 1995) with evolutionary relationships in the milk composition from various species evident. Part of the switch from immune factors provided in eggs to the immune system produced by the mammary gland, was suggested by the discovery of lysozyme in tortoise eggs (Aschaffenburg *et al.*, 1980). A further clue was the discovery that the human immune system including IgA type is most similar to that of the chimpanzee (Cole *et al.*, 1992). The immune activities of the mammary gland allowed newborns of primitive mammals who had evolved a slow rate of

Table 2 : Mechanisms whereby breastfeeding has long-term health benefits

Mammalian evolution promotes survival advantage
Factors that promote gastrointestinal mucosal maturation
Factors that decrease the incidence of infection and alter the gut microflora/ breast milk microbiology
Functional immunomodulatory and anti-inflammatory factors.
Hormones, growth factors and cytokines that may modulate the development of disease
Reduced exposure to foreign dietary antigen

immune development, to survive (Goldman *et al.*, 1998).

Defense factors in the milk of species that experience developmental delays exist reciprocally with the production of immune factors by the lactating mammary gland in all mammalian species investigated to date. Thus the evolution of infant protection interacts with the mother. Certain immunological components are highly conserved, others vary according to the species with variations evolving by genetic mutation and natural selection.

Evolutionary adaptations enhance the survival of specific defense factors in milk in the recipient infant. Defense factors such as lactoferrin, lysozyme and secretory IgA are inherently resistant to digestion (Brines and Brock, 1983; Lindh, 1985) whereas others are compartmentalised and are shielded from digestive enzymes or denaturing conditions (Rudloff *et al.*, 1992; Rudloff *et al.*, 1993; Garofalo *et al.*, 1995) Anti-proteases in human milk such as α_1-antichymotrypsin and α_1-antitrypsin protect immune agents composed of protein in milk from digestion (Lindberg *et al.*, 1982). Moreover, factors in milk are protected at least during the first month of life because gastric production of hydrochloric acid (Euler *et al.*, 1979; Agunod *et al.*, 1969) and pancreatic secretion of chymotrypsin are very low in the neonatal period (Lebenthal and Lee, 1980; Boehm *et al.*, 1995).

Factors that promote gastrointestinal mucosal maturation: Biologically active factors in the infant gut have profound effects beyond nutrition (Thorell *et al.*, 1996). During life in utero, the infant swallowed amniotic fluid and epidermal growth factor and gastric inhibitory peptide in the fluid influenced intestinal growth and function (Perin *et al.*, 1997). Following the first feed of mother's milk in many mammalian species the most striking interaction between diet and intestinal development immediately occurs. This interaction may be due to an expression of genes triggered by the constituents in the milk.

Unlike formula milk, human milk contains hormones and growth factors that promote gastrointestinal maturation (Sheard and Walker, 1988) and host defense (Xanthou *et al.*, 1995; Xanthou, 1998). The growth modulating effect of human milk has been ascribed to a range of growth factors, hormones and other similar biologically active substances, which act synergistically. Systemic absorption and subsequent biologic activity at distant sites of these factors have been reported in new-born animals (Grosvenor *et al.*, 1992), and are currently under investigation in human neonates (Garofalo and Goldman, 1999). By direct uptake into the infant's circulation, the bioactive components in human milk may significantly influence general long-term tissue development (Hasselbalch *et al.*, 1996) as demonstrated in animal studies (Jain *et al.*, 1989).

A large number of enzymes are present in human milk (Hamosh, 1995). Some of these enzymes provide potential protection against disease. Anti-proteases and proteases modulate the proteolytic breakdown of milk proteins, many which have specific functions in the neonate (Lindberg *et al.*, 1982; Lindberg, 1979). Milk bile-salt-dependent-lipase digests milk triglycerides (99% of milk fat) in the intestine to free fatty acids and monoglycerides, contributing indirectly to lytic activity through resistance to bacterial and viral growth in milk (Sbarra *et al.*, 1996). The addition of lipases to human milk or formula increases anti-viral and anti-gram-positive microbial activity. Platelet-activating factor acetylhydrolase, an enzyme in human milk, protects the intestine of the neonate (Furukawa *et al.*, 1993) from inflammatory diseases (Caplan and Hsueh, 1990).

Factors that decrease the incidence of infection and alter gut microflora:

Human milk cells: Human milk cells found in colostrum and mature milk are functional and active (Goldman, 1993) and include macrophages, polymorphoneutrophils and lymphocytes (Carlsson and Hanson, 1994) that have the ability to phagocytose and kill bacteria and fungi (Robinson *et al.*, 1978; Keeney *et al.*, 1993). As well as phagocytes, numerous other epithelial cells and cell fragments are present in human milk (Michie *et al.*, 1998).

The lymphocytes in human milk are mainly T-cell in origin (about 80%) and contain both CD4 (helper-inducer) and CD8 (suppressor-cytotoxic) cells with a ratio similar or less than in peripheral blood (Keller *et al.*, 1986; Slade and Schwartz, 1989). Selective colonisation of the mammary gland during lactation by memory T-cells could be one of the mechanisms through which a breastfeeding infant gains from the mother's own immunologic experience. Human milk lymphocytes like macrophages elaborate a wide number of lymphokines (chemical factors produced and released by T lymphocytes that attract macrophages to the site of infection or inflammation and prepare them for attack).

Milk immunocompetent cells have the ability to survive in the gastrointestinal tract, to secrete bioactive factors including hormones, growth factors and cytokines, and to migrate across the neonatal intestinal mucosa into the systemic circulation. Milk cells are able to traverse intact human fetal intestinal implants in mice and migrate into mice tissues (Xanthou, 1998; Xanthou, 1997). This bioactivity allows milk cells to potentiate not only the local response of the gastrointestinal tract but also systemic immune responses (Xanthou, 1998).

Recently, innovative studies have demonstrated that the primary immunological organ in infancy and early childhood, the thymus gland, is significantly larger in four-month-old babies exclusively or partially breastfed compared to those not breastfed (Hasselbalch *et al.*, 1996; Hasselbalch, 1999). By direct uptake into the infant's circulation, the bioactive components of human milk appear to significantly influence general long-term tissue development. Imprinting in the neonatal period may determine these apparent long-term health outcomes (Michie *et al.*, 1998) particularly in relation to endocrinological development (Phillips *et al.*, 1993) by traversing gut epithelium in the presence of milk (Michie *et al.*, 1998) and stimulating the growth and development of other organ systems (Hasselbalch *et al.*, 1996).

Protein: Because the gut mucosa is immature, the newborn infant has a high macromolecule absorption that leads to small amounts of foreign protein activating the immunological system (Delire *et al.*, 1978). Exposure to cow's milk in early infancy has long-lasting effects on the humoral antigen-specific responses, indicating less effective tolerance-inducing mechanisms in the intestinal mucosa during the first months of life (Jenmalm and Bjorksten, 1998). The immunomodulatory function of milk proteins (Xanthou, 1998) has been well documented elsewhere (Garofalo and Goldman, 1999). In summary, protein is an important determinant of immune responses (Chandra, 1997).

Immunoglobulins: Immunoglobulins (Ig) are a group of glycoproteins present in the serum and tissue fluids of all mammals and are often called antibodies because they have the ability to fight foreign proteins (Roitt and Brostoff, 1996). The main immunoglobulin in human milk is secretory IgA (sIgA) (Hanson *et al.*, 1978). The specificity's of sIgA antibodies in breast milk reflect the maternal enteric and respiratory antigens,

providing the immunologically immature infant with protection against environmental pathogens that the mother has come into contact with. The antibodies in human milk have specific functions and protect against numerous illnesses (Clemens *et al.*, 1990; Tsutsumi *et al.*, 1989; Bell *et al.*, 1988; Cravioto *et al.*, 1991; Cruz *et al.*, 1985; Kim *et al.*, 1984).

Enterobronchomammary pathway: Because the immune system of the human baby is not fully developed and functional at birth (Hanson, 1998) a unique system called the enterobronchomammary pathway has developed whereby maternal protection is passed to the infant through breast milk. During gestation, tissue defense is transferred across the placenta. After birth, sIgA antibodies in the mothers' milk provide defense to the newborn's gastrointestinal mucosal surfaces (Roux *et al.*, 1977).

Gut microflora and breast milk microbiology : The mucosal immune system's most important task is control of colonisation of mucosal surfaces by organisms. The commensal (normal, healthy) microbial flora of the gastrointestinal tract as well as respiratory microbial agents stimulate the functional maturation of the immune system (Holt *et al.*, 1997). This is accomplished through humoral and cellular mechanisms which control the growth of bacterial, viral and parasitic organisms and non-cellular elements. Microbial products of the gastrointestinal flora may activate the antigen presenting mechanism of dendritic cells, polarising towards a Th_1 memory (Heufler *et al.*, 1996; Ridge *et al.*, 1996). In early life Th_1 and Th_2 cell populations possess the potential of reversibility towards the alternate cytokine type but the reversibility is lost after long term stimulation by microbes (Murphey *et al.*, 1996). The microbiology of breast milk has a large impact on bowel development and gut microflora with breastfed babies having a more healthy microflora than formula-fed babies' (Orrhage and Nord, 1999). Formula-fed infants have higher numbers and isolation frequencies of enterococci and clostridia in their faecal biliary than breastfed infants.
Other defense agents are created after partial digestion in the gastrointestinal tract of the infant. For example, antiviral lipids and monoglycerides once freed from milk fat by in vivo lipolysis disrupt enveloped viruses (May, 1994), and lactoferricin created by partial hydolysis of lactoferrin kills Candida albicans (Bellamy *et al.*, 1993), some enteric bacteria (Yamauchi *et al.*, 1993) and Giardia (Turchany *et al.*, 1995) by damaging their outer cell membranes (Bellamy *et al.*, 1993; Yamauchi *et al.*, 1993; Turchany *et al.*, 1995).

Functional immunomodulatory and antiinflammatory factors: Specific cell-mediated immunity and humoral response tests to antigen suggest that breastfeeding may have an immunoregulatory purpose (Garofalo and Goldman, 1999). Breastfed infants appear to have more effective immune function, reflected by an ability to mount a targeted response to a potential pathogen (Pabst *et al.*, 1997; Pabst, 1997).
Immunomodulating factors in human milk include α-tocopherol, β-casomorphins, prolactin and anti-inflammatory components. These direct-acting agents protect by non-inflammatory mechanisms, including enzymatic activity that degrades inflammatory mediators.

Anti-inflammatory components: Generally the anti-inflammatory components in human milk include vitamins A, C and E, enzymes, E prostaglandins, enzyme inhibitors, protease inhibitors, growth factors (eg. Epidermal growth factor and transforming growth factor alpha (TGFα) that promote gut maturation); anti-inflammatory cytokines and specific receptors for inflammatory cytokines (Hamosh, 2001).

Antioxidant defense system: Mammalian cells have developed an elaborate antioxidant defense system that includes both non-enzymatic antioxidants (e.g. glutathione, vitamins C and E {α-tocopherol} and β-carotene) and lactoferrin as well as enzymatic activities (e.g. glutathione peroxidase, catalase, and other hemoprotein peroxidases) both of which play a significant part in the anti-inflammatory system of human milk. As by-products of reactive oxygen species, oxidative stress (which is an excess production of reactive oxygen species) can damage cells by lipid peroxidation and alteration of protein and nucleic acid structures. The antioxidants, α-tocopherol and β-carotene are readily absorbed into the systemic circulation (Ostrea *et al.*, 1986) and are potent scavengers of oxygen radicals that may be produced at the mucosal sites of the infant. Lactoferrin in human milk may also act as an important antioxidant (Nuijens *et al.*, 1996).

Vaccine responsiveness: An infant's active immune response to specific antigens during the first year of life may be different in breastfed and formula-fed babies (Hahn-Zoric *et al.*, 1990). Evidence for this is that breastfed infants had enhanced vaccine responses (Hahn-Zoric *et al.*, 1990; Pabst *et al.*, 1989; Pickering *et al.*, 1998) when tested between nine and 20 months of age. Breastfed babies given BCG vaccination (Pabst *et al.*, 1989) either at birth or later had a significantly higher lymphocyte blast transformation response to purified protein derivative than those who were never breastfed. Following these findings a trial was conducted with Haemophilus influenzae B conjugate vaccine in breastfed versus formula fed infants (Pabst and Spady, 1990). Antibody response to foreign protein at seven and 12 months was significantly higher in breastfed compared to formula fed infants. Similarly at 21 to 40 months breastfed children had higher serum neutralising antibody titers and higher concentrations of salivary secretory IgA antibodies to polio, tetanus and diptheria toxoid (Hahn-Zoric *et al.*, 1990). Furthermore by in vivo measures, breastfed infants had a T-helper 1 type response to measles, mumps and rubella (MMR) vaccination, a response that enables division, differentiation and production of antibodies. Breastfed infants may have a clinical advantage over formula fed infants, due to their enhanced immune response (Pabst *et al.*, 1997).

Hormones, growth factors and cytokines that may modulate the development of disease: Milk provides essential nutrients for infant growth and development but also serves as transport from mother to infant of molecules that regulate development. Recent clinical and experimental observations suggest that, unlike formula milk, human milk not only provides passive protection but can also directly modulate the recipient infants developing immune system. The study of human milk is difficult due to the number of biochemically active substances and their biochemical complexity, the small concentration of some bioactive components, the compartmentalisation of some agents, the dynamic quantitative and qualitative changes of milk during lactation, and the lack of specific reagents to quantify the components. In spite of these difficulties hormones, growth factors and cytokines have been identified in human milk (Table 3) (Garofalo and Goldman, 1999; Goldman and Rudloff, 1991; Garofalo and Goldman, 1998; Srivastava *et al.*, 1996). It is likely that some of these substances are important for control and maturation of the neonatal immune system and gastrointestinal mucosa (Sheard and Walker, 1988).

Hormones: Milk hormones may be the product of local mammary synthesis, maternal transfer or mammary modification of blood borne- hormones. Many of these hormones are transferred from maternal blood to milk. They affect various aspects of growth, differentiation and functional maturation of specific organs in the infant. Resistance to digestion in the infant's digestive tract is increased by post transcriptional modification of peptide hormones in the mammary gland before secretion into milk (Hamosh, 2001). During critical periods of development the infant may be conditioned by the transfer of milk borne hormones (Ellis *et al.*, 1997). The effects of hormones may be immediate in the newborn, or delayed.

Table 3: Some of the biochemically active substances in human milk

Hormones		Cytokines	
Hypothalamic	GRH	Interleukins	IL-1αβ
	Somatostatin		IL-2
	TSH		IL-4
	Dopamine		IL-6
Pituitary	Growth hormone		IL-8
	ACTH		IL-10
	TSH		
	FSH/LH	Other cytokines	TNF-α
	Prolactin		IFN-γ
Thyroid	Triiodothyronin		TGF-β
	Thyroxin		RANTES
	Calcitonin		GROα
Parathyroid	PTH and PTH related peptides		MCP-1
Adrenal	Cortisol		MIP-1α
	Progesterone		
	Estradiol/Estriol	Colonystimulating factors	
	Testosterone		GM-CSF
Gastrointestinal	Gastrin		G-CSF
	Cholecystokinin		M-CSF
	GIP		
	VIP	Nutrients	
	Peptide YY		Protein
	Erythropoietin (EPO)		Nucleotides
			Glutamine
Growth factors	IGF		Lactoferrin
	EGF		Lipids
	NGF		Oligosaccharides
	MGF		
	bFGF		

Adapted with permission of the authors (Bernt and Walker, 1999)

Adrenocorticotropic hormone (ACTH) and cortisol have both been isolated in human milk. While ACTH modulates cortisol level, cortisol exhibits multiple functions including gene regulation. An example of this is the glycosylation pattern of the intestinal microvillus membrane favouring colonisation of the gut by non-pathogenic bacteria thereby providing protection against infection (Mahmood and Torres-Pinedo, 1985). Because the primary cause of necrotising enterocolitis is intestinal barrier immaturity cortisol's influence on intestinal barrier maturation is of particular interest. Cortisol also has immunomodulatory effects, increasing leukocyte counts while selectively suppressing B and T cell activation and lymphocyte counts, and inhibiting prostaglandin and leukotriene generation depending on conditions. Finally cortisol is involved in the regulation of intermediate metabolism and activation of energy in response to stress, a model for the transmission of environmental information through a biochemical message.

Prolactin (PRL) in milk is biologically active in the neonate and may regulate differentiation and maturation of neonatal neuroendocrine, reproductive and immune systems (Ellis *et al.*, 1997). This early conditioning may regulate neuroendocrine function later in life (Grosvenor *et al.*, 1992; Kacsoh *et al.*, 1991).

A wide array of gastrointestinal hormones has been isolated from milk. Gastrointestinal hormones constitute important components of epithelial host defense helping to prevent or delay gastrointestinal allergy and playing a role in gastrointestinal tract function as well as growth and maturation (Berseth *et al.*, 1990.

Growth hormone (GH) and growth hormone releasing hormone (GRH) have been isolated from human milk. There is good evidence that maternal GRH is involved in neonatal stimulation of pituitary GH synthesis in suckling rats (Kuhn *et al.*, 1978).

Erythropoietin (EPO) another hormone found in milk stimulates erythropoiesis in suckling rats (Carmichael *et al.*, 1992). Physiologically active EPO may be transferred to the infant from the mother or increased if a supplement is added to formula.

Other hormones have been found in milk including thyroid-releasing hormone, thyroid stimulating hormone, triiodothyronin and thyroxin, somatostatin and the estrogens, progesterone, androgens, calcitonin and parathyroid hormone. Interactions of these hormones with the infant endocrine system can be demonstrated but their clinical relevance for the infant's development remains unclear (Grosvenor *et al.*, 1992).

Growth factors: Human milk contains several known growth factors including Insulin like Growth Factor (IGF), Epidermal Growth Factor (EGF) and Transforming Growth Factor (TGF) (Koldovsky and Goldman, 1998). These factors promote the maturation of gastrointestinal mucosa restricting the penetration of harmful antigenic material indirectly contributing to the anti-inflammatory effect of human milk. In general IGF is a comprehensive mediator of growth and development and some animal studies have detected a positive effect of IGF supplementation to formula fed infants (Houle *et al.*, 1997)

Transforming Growth Factor Beta (TGF-β) in human milk has important immunomodulatory properties (Cummins and Thompson, 1997) and directly affects immunity and inflammation by suppressing the proliferation and modulating the activity of leukocytes. TGF-β inhibits the production of cytokines such as IL-1, IL-6, and TNF; reduces the expression of the human leukocyte antigen (HLA)-DR on antigen-presenting cells; and inhibits the synthesis of nitric oxide by IFN-γ-activated macrophages (Ding *et al.*, 1990).

Nerve growth factor (NGF) found in milk triggered speculation about its role in neuronal development and cognitive function. It's uptake in a newborn rat model ileum has been shown (Siminoski *et al.*, 1986) and although there is no evidence yet that NGF stimulates cerebral growth or function some studies have reported a statistically improved outcome for cerebral dysfunction in premature infants fed breast milk (Morley and Lucas, 1994) and better school results in breastfed 'normal' children (Rogan and Gladen, 1993).

The presence of growth factors in milk provides a fascinating model for the developmental benefit of breastfeeding. However, even though numerous factors including mammary-derived growth factor and basic fibroblast factor have been isolated from milk many of their roles are unresolved.

Cytokines: Cytokines are pluripotent polypeptides that act in autocrine/paracrine fashions by binding to specific cellular receptors. They operate in networks and orchestrate the development and functions of the immune system. Cytokines influence the development and immunologic function of the mammary gland and the neonate. The cytokines IL1, IL6, IL10, G-CSF, MCSF, TNFα, interferon gamma, have all been found in human milk (Goldman *et al.*, 1996).
Mononuclear cells of human milk have a potential for production of many different cytokines and when nitrogen stimulated in vitro (Skansen-Saphir *et al.*, 1993) mononuclear cells are potent producers of cytokines. However in vivo implications of these findings remain to be investigated.

Colony-stimulating factors: Unlike hormones that act as systemic messengers, Colony-stimulating factors (CSF) stimulate cell growth and are synthesised in the bone marrow. Granulocyte (G)-CSF stimulates the proliferation of granulocyte progenitor cells and leads to their increase in circulation.

Nutrients: Besides mediators such as protein, hormones, growth factors and cytokines some other simple nutrients are able to transmit biochemical messages to the developing infant.

Nucleotides: Nucleotides in milk have multiple functions (Thorell *et al.*, 1996; Moya, 1991; Ebrahim, 1998), which include effects on gut microflora (Gil *et al.*, 1986), effects on intestinal growth and development (Uauy *et al.*, 1990) and effects on the response to immunisation (Pickering *et al.*, 1998). Nucleotides are involved in a wide variety of biological processes that include serving as precursors of RNA and DNA and comprising bases for the high energy source ATP, regulatory signals (cyclic AMP and cyclic GMP), coenzyme components and methyl donors.
The effects of nucleotides support the hypothesis that human milk is a potentially potent biological food, which serves to fine-tune the growth and maturity of function in a number of physiological systems as well as providing nutrition. Infant formulae supplemented with nucleotides have been developed by industry and are on the market although the full implications of such additions are not properly understood or biologically tested.

Glutamine: The amino acid glutamine, rich in human milk, has important influences on the metabolism and function of enterocytes and cells of the lymphatic system (Newsholme and Calder, 1997). In an experimental animal model of gut-derived sepsis, oral glutamine demonstrated an ability to decrease bacterial translocation through the intestinal wall and to enhance the destruction of bacteria following infection with E coli, an effect that improved considerably when the animals were substituted with glutamine (Gianotti *et al.*, 1995).

Lactoferrin: Lactoferrin, the major milk protein is lymphostimulatory, anti-inflammatory, bactericidal, viricidal and fungicidal. The protective function of lactoferrin was initially ascribed to its iron binding capacity, but its low iron saturation (6% - 9%) and high iron affinity suggests that it could act as a bacteriostatic agent in human milk (Peterson *et al.*, 1998). Indeed, a broad spectrum bactericidal peptide has been isolated following gastric cleavage of lactoferrin (Bellamy *et al.*, 1992; Tomita *et al.*, 1994).
The immunomodulating activity of lactoferrin is due to specific binding of lactoferrin receptors on monocytes or macrophages (Miyazawa *et al.*, 1991) that appear to inhibit cytokine production (Misra *et al.*, 1994). Lactoferrin inhibits the discharge of interleukins 1,2 & 6 and TNF-α from monocytes and of prostaglandin E_2 from macrophages protecting against inflammation (Mattsby-Baltzer *et al.*, 1996; Bartal *et al.*, 1987; Mechnicki *et al.*, 1993).

Lipids: Afte proteins milk fat globules are the second most abundant component of human milk. The fat in human milk is contained within these globules, the core of which is made up of fatty acids and triglycerides. Unsaturated fatty acid chains have been shown to inhibit parasite adherence (Crouch *et al.*, 1991) and disrupt enveloped viruses (Thormar *et al.*, 1987; Isaacs and Thormar, 1991). Although lipolysis generates similar products for formula-fed and breastfed infants, breastfed infants have higher rates of lypolysis associated with the fat structure and the presence of the enzyme, milk-salt-dependent-lipase.
Lipids in human milk are a source of the "nutritionally essential" fatty acids, linoleic (18:2 n-6) and linolenic (18:3 n-3). Breast milk also contains other very long chain polyunsaturated fatty acids such as docosahexanoic acid (DHA) and arachidonic acid (AA) that have been linked to visual and cognitive function in human infants through randomised controlled trials. As a result of these trials some formulas for preterm and term infants are now supplemented with DHA and AA (Gibson *et al.*, 2001).
Human milk contains a wide range of long chain polyunsaturated fatty acids (LCFUFA) most importantly DHA (22:6ω3), whereas conventional formulas contain only a small amount although there is no convincing evidence concerning the effects of long-chain PUFA supplementation on long-term cognitive development (Jenson *et al.*, 1992). Lipids also act as carriers of fat-soluble vitamins and hormones (Gibson and Makrides, 1998; Makrides *et al.*, 1996), as precursors of biologically potent mediators (eg prostaglandins, thromboxanes, leukotrienes) and as vital structural components of membrane systems in all tissues (Innis, 1994; Calder, 1997). In particular the long chain fatty acids (Calder, 1997) in breast milk have been implicated as potential modulators of the immune system (Hasselbalch *et al.*, 1996; Goldman, 1993; Pabst *et al.*, 1997; Miles and Calder, 1998; Wold and Adlerberth, 1998; Howie *et al.*, 1990). For the possible influence of DHA and AA on the developing immune system a lower proportion of CD45RO+ cells and deficient Interleukin-10 production by formula-fed infants, compared with human-fed was corrected with supplementation of long-chain polyunsaturated fatty acids (Field *et al.*, 2000).

Oligosaccharides and glycoconjugates: Human milk is unique because of its high concentration of complex oligosaccharides compared with milk from other species (Pabst, 1997). The oligosaccharides are quantitatively one of the three main components of human milk in addition to protein and fat with more than 100 structures described (Peterson *et al.*, 1998; Newburg, 1996). The structure of oligosaccharide mimics that of bacterial receptors on intestinal cells, blocking bacterial attachment to intestinal cell membranes (Goldman *et al.*, 1986). They can function as receptor analogs for bacteria and viruses and inhibit the adhesion of microbes (including pneumococci) (Andersson *et al.*, 1986). Oligosaccharides also influence intestinal flora growth by the provision of substrate for lactobacillus bifidus, the healthy bacteria, while limiting the growth of potentially pathogenic bacteria (Carlson, 1985).

Reduced exposure to foreign dietary antigen: Although a breastfed infant is less exposed to foreign dietary antigen in cow's milk (Höst, 1994), there are also antigens in maternal milk. More than 70 years ago it was hypothesised that infants might react to foods in the mother's diet, such as egg or cow's milk protein, transmitted through her milk (Shannon, 1921; Vandenplas, 1997). Some exclusively breastfed infants develop allergic reactions to cow's milk protein (β-lactoglobulin) (Lifschitz *et al.*, 1988) but the incidence of this is very low (0.5-1.7%) in comparison to the incidence in unselected populations of infants (2%-3%) (Businco *et al.*, 1993).
In most lactating women (50-95%) the cow's milk protein, β-lactoglobulin can be detected in small concentrations about eight hours after ingestion with continuous testing of breast milk (Sorva *et al.*, 1994). Given the low frequency of cow's milk allergy in breastfed infants, the small measure of β-lactoglobulin found in

Table 4: Ten steps to successful breastfeeding (World Health Organisation, 1989)

Have a written breastfeeding policy that is routinely communicated to all health care staff.
Train all health care staff in skills necessary to implement this policy.
Inform all pregnant women about the benefits and management of breastfeeding.
Help mothers initiate breastfeeding within a half-hour of birth.
Show mothers how to breastfeed, and how to maintain lactation even if they should be separated from their infants.
Give newborn infants no food or drink other than breastmilk, unless medically indicated.
Practice rooming-in - allow mothers and infants to remain together 24 hours a day.
Encourage breastfeeding on demand.
Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants.
Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

breast milk may induce tolerance rather than allergic sensitisation (Vandenplas, 1997) and may help to explain the almost constant presence of β-lactoglobulin in mother's milk (Host *et al.*, 1995; Stuart *et al.*, 1984). Furthermore, dietary proteins other than cow's milk antigens (such as egg proteins) are transferred to breast milk and can induce adverse reactions in hypersensitive infants (De Boissieu *et al.*, 1994; De Boissieu *et al.*, 1997).

On the other hand, a maternal diet low in allergens in a lactating mother until the infant is six-months-of-age may be the most relevant factor in protecting the infant from the development of atopic disease (Zeiger and Heller, 1995; Zeiger, 1994; Hide and Guyer, 1981; Bruno *et al.*, 1993) . Family history however, may be one of the confounding factors for allergy independent of breastfeeding (Lucas *et al.*, 1990). Although evidence is conflicting, current advice from the European Society of Paediatrics is that if a family history of asthma is present it is best to breastfeed, and cow's milk and eggs should be avoided by the mother (Host *et al.*, 1999). Many children *do* receive cow's milk proteins in the first days of life (Höst, 1994; Saarinen, 1997) that may initiate sensitisation in susceptible individuals, and subsequent exposure even to minute quantities of β-lactoglobulin in breast milk may elicit an allergic manifestation that may be associated with IgE mediated adverse reactions.

The young infant's gut is immature, and may poorly exclude multiple allergens or large quantities of allergens that can react with the system of sensitisation. The benefits of exclusive breastfeeding derive not only from elimination of cow's milk protein but from local protection of human milk in the bowel. For example secretory IgA coats the mucosa and blocks entrance of antigens (Taylor, 1973). Because of this, recommendations to exclusively breastfeed and to withhold infants from solid food until after six months of age may be well founded.

Contraindications to breastfeeding : A balanced discussion of the contraindications to breastfeeding is credible only when the enormous benefits of breastfeeding to infants and to mothers are considered together with the risks for any possible contraindication (Lawrence and Lawrence, 2001).

Poor maternal diet is not a contraindication to breastfeeding and all mothers should be counseled to eat appropriately. Even in apparently well nourished women milk vitamins D and K may not always provide adequate amounts for infants. Therefore, it is recommended that all infants receive vitamin K at birth to prevent hemorrhagic disease of the newborn caused by vitamin K deficiency in the first few days of life (Lawrence, 1999).

If and when a medical situation arises in the mother that poses a threat to the breastfeeding infant, the theoretic risk needs to be measured against the projected benefits of breastfeeding (Lawrence, 1997). Maternal infectious disease is not a contraindication to breastfeeding in most cases (Beaudry *et al.*, 1995). The most infectious disease that is a contraindication to breastfeeding however, is Human Immunodeficiency Virus (HIV). HIV type 1 can be transmitted through human milk, and detailed suggestions for implementation of the WHO current policy are available (World Health Organisation, 1998). The policy states that in most countries policy must cover a range of socioeconomic conditions, and the aim should be to promote and protect breastfeeding for the majority of women while offering as many choices as possible to women who are HIV positive, enabling them to decide what is most appropriate for their circumstance and supporting them in their choice. Human T-cell Lymphotropic Virus (HTLV-1) is another distinct retrovirus, epidemic in parts of the world and the only other infectious disease that is an absolute contraindication to breastfeeding (Lawrence and Howard, 1999).

Certain maternal diseases may be a contraindication to breastfeeding because of the treatments that may cross into the mother's milk. An example is penacillamine because it binds minerals and the effect on the infant's microminerals may present a significant risk.

In rare cases an infant has unique nutritional needs for example if the infant has a metabolic enzyme deficiency disease such as galactosemia, phenylketonuria or maple syrup urine disease. These infants may be partially breastfed, supplemented with special formula and monitored closely (Lawrence, 1999).

Chemicals in the environment may pose a risk to breast milk where unusual exposure does occur. A massive exposure of polybrominated biphenyls entered the food chain in the 1970's exposing women in the immediate geographic area (Poland and Cohen, 1980). The exposure of the general public to herbicides and dioxins is generally minimal and the WHO does not consider DDT a major cause for concern. Breastfeeding is not contraindicated in association with environmental hazards under ordinary circumstances with excessive exposure assessed on an individual basis.

In face of any potential contraindication to breastfeeding the benefits to the infant of being breastfed must be compared with the theoretic risk for the determined hazard and a decision made on an individual basis.

Effects of breast milk in premature infants: The American Academy of Paediatrics in 1997 acknowledged that human milk is beneficial in the care and management of premature infants. The special needs of premature infants that arise due to metabolic and gastrointestinal immaturity, immunologic compromise and associated medical conditions must be considered in order for adequate nutrition to be provided to meet the needs for intrauterine rates of growth and nutrient accretion (Ziegler *et al.*, 1976).

Although the optimum nutrition of premature infants is not known, recent data suggest that human milk fortified with additional nutrients is more appropriate for tube fed infants than unfortified human milk (Schanler, 2001). Such manipulation of milk may affect milk's intrinsic host defense properties but fortified human milk may provide significant protection from infection and necrotising enterocolitis (NEC). Furthermore skin to skin contact provides species specific anti-microbial protection. Additional investigation is required but neonatal centers should encourage the feeding of fortified human milk in addition to skin to skin contact as methods to enhance maternal milk production and the development of the enteromammary response.

Premature infants fed their own mothers milk have fewer episodes of NEC, diarrhea and urinary tract infection than premature infants fed formula suggesting that human milk may enhance premature infants host defenses. Because di*et al*so affects fecal flora, the flora of human milk-fed babies is less pathogenic than those fed formula.

International support for breastfeeding: Universal breastfeeding has been the goal of the World Health Organisation; American Academy of Pediatrics and many other organisations for nearly a quarter of a century. The World Health Organisation International Code Of Marketing Of Breastmilk Substitutes was developed in 1981 (World Health Organisation, 1981). The aim of the Code was to contribute to the provision of safe and adequate nutrition for infants, by the protection and promotion of breastfeeding and by the proper use of breast-milk substitutes, when these are necessary, on the basis of adequate information and through appropriate marketing and distribution. The Code also forbid inducements to health workers (Taylor, 1998) to promote specific breast-milk substitutes (Chren and Landefeld, 1994).

There is enough evidence to support maternity facilities and the ten steps to successful breastfeeding (Table 4). This will ensure that hospitals become 'baby friendly', that mothers are encouraged and supported to commence breastfeeding and that there is adequate community support for the continuation of full breastfeeding for at least the first six months of an infants life and beyond.

In conclusion, breastfeeding has numerous factors such as hormones, cytokines and other bioactive compounds that protect against disease in infancy and promote optimum development. The current level of knowledge about breast milk and the mechanisms whereby breastfeeding impacts on infant health and development provides evidence that breastfeeding should be promoted to the public. The aim must be to increase the duration of full breastfeeding for all infants to at least six months and beyond up to two years.

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References

Agunod M., N.Yamaguchi, R. Lopez, A.L. Luhby and G.B. Glass, 1969. Correlative study of hydochloric acid, pepsin, and intrinsin factor secretion in newborns and infants. Am. J. Dig. Dis., 14:400-414

American Academy of Paediatrics, 1997. Work Group on Breastfeeding: Breastfeeding and the use of human milk. Pediatrics, 100: 1035.

Anderson J.W., B.M. Johnstone and D.T. Remley, 1999. Breast-feeding and cognitive development: a meta-analysis. Am. J. Clin. Nutr., 70:525-535.

Andersson B., O. Porras, L.A. Hanson, T. Lagergard and C.Svanborg-Eden,1986.Inhibition of attachment of Streptococcus pneumoniae and Haemophilus influenzae by human milk and receptor oligosaccharides. J. Infect. Dis., 153: 232-237.

Ansai S., S. Koseki, Y. Hozumi and S. Kondo,1995. An immunohistochemical study of lysozyme, CD-15 (Leu M1) and gross cystic disease fluid protein-15 in various skin tumors. Assessment of the specificity and sensitivity of markers of apocrine differentiation. Am. J. Dermatopathol., 17: 249-255.

Aschaffenburg R., C.C. Blake, H.M. Dickie, S.K. Gayen, R. Keegan and A. Sen,1980. The crystal structure of tortoise egg-white lysozyme at 6 Å resolution. Biochim. Biophys. Acta., 625: 64-71 .

Ayala F.J., 1995. The myth of Eve: molecular biology and human origins. Science, 270: 1930-1936.

Barker D.J.P., 1997. Fetal nutrition and cardiovascular disease in later life. Br. Med. Bull., 53: 96-108.

Bartal L., S. Padeh and J.H. Passwell,1987. Lactoferrin inhibits prostaglandin E2 secretion by breastmilk macrophages. Pediatr. Res., 21: 54-57.

Beaudry M., R. Dufour and S. Marcoux, 1995. Relation between infant feeding and infections during the first six months of life. J. Pediatr., 126: 191-197.

Bell L.M., H.F. Clark, P.A. Offit, P.H. Slight, A.M. Arbeter and S.A. Plotkin, 1988. Rotavirus serotype-specific neutralizing activity in human milk. Am. J. Dis. Child., 142:275-278.

Bellamy W., H. Wakabayashi, M. Takase, K. Kawase, S. Shimamura and M. Tomita,1993 Killing of Candida albicans by lactoferricin B, a potent antimicrobial peptide derived from the N-terminal region of bovine lactoferrin. Med. Microbiol. Immunol., 182: 97-105.

Bellamy W., M. Takase, K. Yamauchi, H. Wakabayashi, K. Kawase and M. Tomita, 1992. Identification of the bactericidal domain of lactoferrin. Biochimica. et Biophysica. Acta., 1121:130-136.

Bergstrom E., O. Hernell, L.A. Persson and B. Vessby, 1995. Serum lipid values in adolescents are related to family history, infant feeding and physical growth. Atherosclerosis, 117: 1-13.

Bernt KM. and W.A. Walker, 1999. Human milk as a carrier of biochemical messages. Acta Paediatr., 430, S27-S41.

Berseth C.L., S.R. Michener, C.K. Nordyke and V.L. Go Postpartum, 1990. changes in pattern of gastrointestinal regulatory peptides in human milk. Am. J. Clin. Nutr., 51: 985-990.

Blackburn D.G., 1993. Lactation: historical patterns and potential for manipulation. J. Dairy Sci., 76: 3195-3212.

Boehm G., U. Bierbach, A. DelSanto, G. Moro and I. Minoli, 1995. Activities of trypsin and lipase in duodenal aspirates of healthy preterm infants: effects of gestational and postnatal age. Biol. Neonate., 67: 248-253.

Borch-Johnsen K., G. Joner, T. Mandrup-Poulsen, M. Christy, B. Zachau-Christiansen, K. Kastrup and J. Nerup, 1984. Relation between breastfeeding and incidence rates of insulin-dependent diabetes mellitus: a hypothesis. Lancet., 2: 1083-1086.

Brines R.D. and J.H. Brock, 1983. The effect of trypsin and chymotrypsin on the in vitro antimicrobial and iron-binding properties of lactoferrin in human milk and bovine colostrum. Biochim. Biophys. Acta., 795: 229-235.

Bruno G., O. Milita, M. Ferrara, R. Nisini, A. Cantani and L. Businco, 1993. Prevention of atopic diseases in high risk babies (long-term follow-up). Allergy Proceedings, 14: 181-187.

Businco L., S. Dreborg, R. Einarsson, P.G. Giampietro, A. Host, K.M. Keller, S. Strobel, U. Wahn, B. Bjorksten and M.N. Kjellman, 1993. Hydrolysed cow's milk formulae. Allergenicity and use in treatment and prevention. An ESPACI position paper. Pediatr. Allergy Immunol., 4: 101-111.

Calder PC., 1997. n-3 Polyunsaturated fatty acids and cytokine production in health and disease. Ann. Nutr. Metab., 41: 203-234.

Campbell, D.A., M.I. Lorber, J.C. Sweeton, J.G. Turcotte, J.E. Niederhuber and A.E. Beer, 1984. Breastfeeding and maternal-donor renal allografts. Transplantation., 340-344.

Caplan M.S. and W. Hsueh, 1990. Necrotizing enterocolitis: role of platelet activating factor, endotoxin, and tumor necrosis factor. J. Pediatr., 117:47-51.

Carlson S.E., 1985. N-acetylneuraminic acid concentrations in human milk oligosaccharides and glycoproteins during lactation. Am. J. Clin. Nutr., 41:720-726.

Carlsson B. and L. Hanson, 1994. Immunologic effects of breastfeeding on the infant, in Handbook of Mucosal Immunology, P.L. Ogra, *et al.*, Editors. Academic Press: San Diego., p: 653-660.

Carmichael, R.D., J. LoBue and A.S. Gordon, 1992. Neonatal erythropoiesis. II. Bone marrow and splenic erythropoietic activity: data suggest erythropoietin transfer via maternal milk. Endo. Reg., 26: 143-149.

César J.A., G.C. Victora, F.C. Barros, I.S. Santos and J.A. Flores, 1999. Impact of breastfeeding on admission for pneumonia during postneonatal period in Brazil: nested case-control study. BMJ., 318: 1316-1320.

Chandra R.K., 1997. Nutrition and the immune system: An introduction. Am. J. Clin. Nutr., 66: 460S-463S.

Chandra R.K., 1991. Interactions between early nutrition and the immune system, in The childhood environment and adult disease. Wiley: Chichester.

Chren M.M. and C.S. Landefeld, 1994. Physicians' behaviour and their interactions with drug companies: a controlled study of physicians who requested additions to a hospital drug formulary. JAMA., 271: 684-689.

Clandinin, M.T. J.E. Chappell, S. Leong, T. Heim, P.R. Swyer and G.W. Chance, 1980. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. Early Hum. Dev., 4: 121-129.

Clemens J.D., D.A. Sack, J.R. Harris, M.R. Khan, J. Chakraborty, S. Chowdhury, M.R. Rao, F.P. van Loon, B.F. Stanton and M. Yunus, 1990. Breast feeding and the risk of severe cholera in rural Bangladeshi children. Am. J. Epid., 131:400-11.

Cole M.F., C.A. Hale and S. Shurzenegger, 1992. Identification of two subclasses of IgA in the chimpanzee (Pan troglodytes). J. Med. Primatol., 21: 275-278.

Corrao G., A. Tragnone, R. Caprilli, G. Trallori, C. Papi, A. Andreoli, M. Di Paolo, G. Riegler, G.P. Rigo, O. Ferrau C. Mansi, M. Ingrosso and D. Valpiani,1998. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC). Int. J. Epidemiol., 27:397-404.

Crane J.K., S.S. Azar, S. Annick and D.S. Newburg,1994. Oligosaccharides from human milk block binding and activity of the Escherichia coli heat-stable enterotoxin (Sta) in T84 intestinal cells. J. Nutr., 124: 2358-2364.

Cravioto A., A. Tello, H. Villafan, J. Ruiz, S. del Vedovo and J.R. Neeser, 1991. Inhibition of localized adhesion of enteropathogenic Escherichia coli to HEp-2 cells by immunoglobulin and oligosaccharide fractions of human colostrum and breast milk. J. Infect. Dis., 163:1247-1255

Crouch, A.A., W.K. Seow, L.M. Whitman and Y.H. Thong,1991. Effect of human milk and infant milk formulae on adherence of Giardia intestinalis. Trans. R. Soc. Trop. Med. Hyg., 85: 617-619.

Cruz, J.R., B.V. Carlsson, Y. Hofvander, D.T. Holme and L.A. Hanson, 1985. Studies of human milk. II. Concentration of antibodies against Salmonella and Shigella in milk of women from different populations and the daily intake by their breast-fed infants. Acta Paediatr. Scand., 74: 338-341.

Cummins, A.G. and F.M. Thompson, 1997. Postnatal changes in mucosal immune response: a physiological perspectiveof breast feeding and weaning. Immunology & Cell Biology, 75: 419-429

Davis, M.K., 1998. Review of the evidence for an association between infant feeding and childhood cancer. Int. J. Cancer, 11: (Suppl) 29-33

Davis, M.K., D.A. Savitz and B. Grauford, 1988. Infant feeding and childhood cancer. Lancet. ii, 365-368.

De Boissieu, D. P. Matarazzo, F. Rocchiccioli and C. Dupont,1997. Multiple food allergy: a possible diagnosis in breastfed infants. Acta Paediatr., 86: 1042-1046

De Boissieu, D., C. Dupont and J. Badoual, 1994. Allergy to non-dairy proteins in mother's milk as assessed by intestinal permeability tests. European J. Allergy and Clin. Immunol., 49: 882-884

Delire, M., C.L. Cambiaso and P.L. Masson, 1978. Circulating immune complexes in infants fed on cow's milk. Nature, 272(5654), 632.

Ding, A., C.F. Nathan, J. Graycar, R. Derynck, D.J. Stuehr and S. Srimal, 1990. Macrophage deactivating factor and transforming growth factors-beta 1, -beta 2 and -beta 3 inhibit induction of macrophage nitrogen oxide synthesis by IFN-gamma. J. Immunol., 145: 940-944.

Drane, D.L. and J.A. Logemann, 2000. A critical evaluation of the evidence on the association between type of infant feeding and cognitive development. Paediatr. Perinat. Epidemiol., 14, 349-356

Duncan, B., J. Ey C.J. Holberg, A.L. Wright, F.D. Martinez and L.M. Taussig, 1993. Exclusive Breast-Feeding for at Least 4 Months Protects Against Otitis Media. Pediatrics, 91: 867-872

Ebrahim, G.J. 1998. Breastmilk nucleotides. J. Tropical Paediatrics., 44: 318-319.

Ellis, T.M. and M.A Atkinson, 1996. Early infant diets and insulin-dependent diabetes. Lancet., 347: 1464-1465.

Ellis, L.A., A.M. Mastro and M.F. Picciano, 1997. Do milk-borne cytokines and hormones influence neonatal immune cell function? J. Nutr., 127:(5 Suppl) 985S-988S.

Euler, A.R., W.J. Byrne, P.J. Meis, R.D. Leake and M.E. Ament, 1979. Basal and pentagastrin-stimulated acid secretion in newborn human infants. Pediatr. Res., 13, 36-37

Falth-Magnusson, K., L. Franzen, G. Jansson, P. Laurin and L. Stenhammar, 1996. Infant feeding history shows distinct differences between Swedish celiac and reference children. Pediatr. Allergy Immunol., 7: 1-5.

Farquharson, J., F. Cockburn, W.A. Patrick, E.C. Jamieson and R.W. Logan, 1992. Infant cerebral cortex phosholipid fatty-acid composition and diet. Lancet., 340: 810-813

Feachem, R.G. and M.A. Koblinsky, 1984. Interventions for the control of diarrhoeal diseases among young children: promotion of breast-feeding. Bull World Health Organ., 62: 271-291.

Feldman, W. and M.E. Feldman, 1996. The intelligence on infant feeding. Lancet. 347(9008): 1057.

Fergusson, D.M., A.L. Beautrais and P.A. Silva, 1982. Breast-feeding and cognitive development in the first seven years of life. Soc. Sci. Med., 16: 1705-1708

Field, C.J., C.A. Thomson, J.E. Van Aerde, A. Parrott, A. Euler, E. Lien and M.T. Clandinin, 2000. Lower proportion of CD45RO+ cells and deficient Interleukin-10 production by formula-fed infants, compared with human-fed, is corrected with supplementation of long-chain polyunsaturated fatty acids. J. Paediat. Gastroenterol. Nutr., 31: 291-9

Ford, R.P., B.J. Taylor, E.A. Mitchell, S.A. Enright, A.W. Stewart, D.M. Becroft, R. Scragg, I.B. Hassall, D.M. Barry and E.M. Allen, 1993. Breastfeeding and the risk of sudden infant death syndrome. Int. J. Epidemiol., 22: 885-890.

Fort, P., N. Moses, M. Fasano, T. Goldberg and F. Lifshitz, 1990. Breast and soy-formula feedings in early infancy and the prevalence of autoimmune thyroid disease in children. J. Am. Coll. Nutr., 9:164-167

Furukawa, M., H. Narahara and J.M. Johnston, 1993. The presence of platelet-activating factor acetyl hydrolase in milk. J. Lipid Res., 34: 1603-1609

Garofalo, R., S. Chheda, F. Mei, K.H. Palkowetz, H.E. Rudloff, F.C. Schmalstieg, D.K. Rassin and A.S. Goldman, 1995. Interleukin-10 in human milk. Pediatr. Res., 37:(4 Pt 1), 444-449.

Garofalo, R.P. and A.S. Goldman, 1999. Expression of functional immunomodulatory and anti-inflammatory factors in human milk. Clin. Perinatol., 26: 361-378.

Garofalo, R.P. and A.S. Goldman, 1998. Cytokines, chemokines and colony-stimulating factors in human milk: the 1997 update. Biol. Neonate., 74: 134-142.

Gerstein, H.C., 1994. Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature. Diabetes Care, 17:13-19.

Gianotti, L., J.W. Alexander, R. Gennari, T. Pyles and G.F. Babcock, 1995. Oral glutamine decreases bacterial translocation and improves survival in experimental gut-origin sepsis. J.Parenteral and Enteral Nutr.,19: 69-74.

Gibson, R.A., W. Chen and M. Makrides, 2001. Randomisation trials with polyunsaturated fatty acids interventions in preterm and term infants: functional and clinical outcomes. Lipids, 36: 873-883

Gibson, R.A. and M. Makrides, 1998. The role of long chain polyunsaturated fatty acids (LCPUFA) in neonatal nutrition. Acta Paediatr., 87: 1017-1022

Gil, A., M. Pita, A. Martinez, J.A. Molina and F. Sanchez Medina, 1986. Effect of dietary nucleotides on the plasma fatty acids in at-term neonates. Human Nutr. - Clin. Nutr., 40: 185-195

Goldman, A.S., S. Chheda, R. Garofalo and F.C. Schmalstieg, 1996.Cytokines in human milk: properties and potential effects upon the mammary gland and the neonate. J. Mammary Gland Biology and Neoplasia, 1:251-258

Goldman, A.S. and H.E. Rudloff, 1991. Are cytoklines in human milk? Adv. Exp. Med. Biol., 310: 93-97

Goldman, A.S., S. Chheda and R. Garofalo, 1998. Evolution of immunologic functions of the mammary gland and the postnatal development of immunity. Pediatr. Res., 43: 155-162

Goldman, A.S., L.W. Thorpe, R.M. Goldblum and L.A. Hanson, 1986 Anti-inflammatory properties of human milk. Acta Paediatr. Scand., 75: 689-695.

Goldman, A.S., 1993. The immune system of human milk: antimicrobial, antiinflammatory and immunomodulating properties. Pediatr. Infect. Dis. J., 12: 664-672.

Goldman, A.S. and R.M. Goldblum, 1995, Defense Agents in Milk, in Handbook of Milk Composition, R.G. Jenson, Editor. Academic Press: San Diego., p: 727-745.

Greene, L.C., A. Lucas, M.B. Livingstone, P.S. Harland and B.A. Baker, 1995. Relationship between early diet and subsequent cognitive performance during adolescence. Biochem. Soc. Trans., 23: 376S.

Griffiths, M., 1988. The platypus. Sci. Am., 258: 84-91.

Grosvenor, C.E., M.F. Picciano and C.R. Baumrucker, 1992. Hormones and growth factors in milk. Endoc. Rev., 14:710-728

Grulee, C.G., H.N. Sanford and P.H. Herron, 1934. Breast and artificial feeding. JAMA.,103: 735

Grulee, C.G., H.N. Sanford and H. Schwartz, 1935. Breast and artificially fed infants. JAMA., 104: 1986

Hahn-Zoric, M., F. Fulconis, I. Minoli, G. Moro, B. Carlsson, M. Bottiger, N. Raiha and L.A. Hanson, 1990. Antibody responses to parenteral and oral vaccines are impaired by conventional and low protein formulas as compared to breastfeeding. Acta Paediatr. Scand., 79: 1137-1142

Hamosh, M. and N.J. Salem, 1998. Long-chain polyunsaturated fatty acids [Review]. Biol. Neonate., 74: 106-120

Hamosh, M., 1995. Enzymes in human milk, in Handbook of Milk Composition, R.G. Jenson, Editor., San Diego Academic Press: San Diego. p: 288-427.

Hamosh, M., 2001. Bioactive factors in human milk. Pediatr. Clin. N. Am., 48: 69-86.

Hanson, L.A., S. Ahlstedt, B. Carlsson, S.P. Fallstrom, B. Kaijser, B.S. Lindblad, A.S. Akerlund and C.S. Eden, 1978. New knowledge in human milk immunoglobulin. Acta Paediatr. Scand., 67: 577-582

Hanson, L.Å., 1998. Breastfeeding provides passive and likely longlasting active immunity [Review]. Ann. Allergy Asthma Immunol., 81: 523-537

Hasselbalch, H., M.D. Engelmann, A.K. Ersboll, D.L. Jeppesen and K. Fleischer-Michaelsen, 1999. Breast-feeding influences thymic size in late infancy. Eur. J. Pediatr., 158: 964-967

Hasselbalch, H., D.L. Jeppesen, M.D. Engelmann, K.F. Michaelsen and M.B.Nielsen, 1996. Decreased thymus size in formula-fed infants compared with breastfed infants. Acta Paediatr., 85: 1029-1032

Heufler, C., F. Koch, U. Stanzl, G. Topar, M. Wysocka, G. Trinchieri, A. Enk, R.M. Steinman, N. Romani and G. Schuler, 1996. Interleukin-12 is produced by dendritic cells and mediates T helper 1 development as well as interferon-gamma production by T helper 1 cells. Eur. J. Immunol., 26: 659-668

Hide, D.W. and B.M. Guyer, 1981. Clinical manifestations of allergy related to breast and cows' milk feeding. Arch. Dis. Child., 56: 172-175

Holt, P.G., P.D. Sly and B. Björksten, 1997. Atopic versus infectious diseases in childhood: a question of balance? Pediatr. Allergy Immunol., 8: 53-58

Horwood, L.J. and D.M. Fergusson, 1998. Breastfeeding and later cognitive and academic outcomes. Pediatrics., 101: E91-E97

Host, A., B. Koletzko, S. Dreborg, A. Muraro, U. Wahn, P. Aggett, J.L. Bresson, O. Hernell, H. Lafeber, K.F. Michaelsen, J.L. Micheli, J. Rigo, L. Weaver, H. Heymans, S. Strobel and Y.Vandenplas, 1999. Dietary products used in infants for treatment and prevention of food allergy. Joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. Arch. Dis. Child., 81: 80-84

Host, A., H.P. Jacobsen, S. Halken and D. Holmenlund, 1995. The natural history of cow's milk protein allergy/intolerance. Eur. J. Clin. Nutr., 49:(Suppl 1), S13-S18.

Höst, A., 1994. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. Pediatr. Allergy Immunol., 5: Suppl, 5-36

Houle, V.M. E.A. Schroeder, J. Odle and S.M. Donovan,1997. Small intestinal disaccharidase activity and ileal villus height are increased in piglets consuming formula containing recombinant human insulin-like growth factor-I. Pediatr. Res., 42: 78-86

Howie, P.W., J.S. Forsyth, S.A. Ogston, A. Clark and C.D. Florey, 1990. Protective effect of breastfeeding against infection. BMJ., 300: 11-16

Innis, S.M., 1994. The 1993 Borden Award Lecture. Fatty acid requirements of the newborn. Can. J. Physiol. Pharmacol., 72: 1483-1492

Isaacs, C.E. and H. Thormar, 1991. The role of milk-derived antimicrobial lipids as antiviral and antibacterial agents. Adv. Exp. Med. Biol., 310: 159-165

Jain, L. D. Vidyasagar, M. Xanthou, V. Ghai, S. Shimada and M. Blend, 1989. In vivo distribution of human milk leukocytes after ingestion by newborn baboons. Arch. Dis. Child., 64: 930-933

Jenmalm, M.C. and B. Bjorksten, 1998. Exposure to cow's milk during the first 3 months of life is associated with increased levels of IgG subclass antibodies to beta-lactoglobulin to 8 years. J. Allergy Clin. Immunol., 102(4 Pt 1): 671-678

Jenson, R.G., A.M. Ferris and C.J. Lammi-Keefe, 1992. Lipids in human milk and infant formulas. Ann. Rev. Nutr., 12: 417-441

Kacsoh, B., B.E. Toth, L.M. Avery, Y. Yamamuro and C.E. Grosvenor, 1991. Molecular heterogeneity of prolactin in lactating rats and their pups: biological and immunological activities in pituitary gland, serum and milk. Endo. Reg., 25: 98-110

Keeney, S.E., F.C. Schmalstieg, K.H. Palkowetz, H.E. Rudloff, B.M. Le and A.S. Goldman, 1993. Activated neutrophils and neutrophil activators in human milk:Increased expression of CD11b and decreased expression of L-selectin. J. Leukocyte. Biol., 54: 97-104.

Keller, M.A., J. Faust, L.J. Rolewic and D.D. Stewart, 1986. T cell subsets in human colostrum. J. Paediat. Gastroenterol. Nutr., 5: 439-443

Kim, K., L.K. Pickering, H.L. DuPont, N. Sullivan and T. Wilkins, 1984. In vitro and in vivo neutralizing activity of human colostrum and milk against purified toxins A and B of Clostridium difficile. J. Infect. Dis., 150: 57-62

Koldovsky, O. and A. Goldman,1998. Growth factors in human milk, in Mucosal Immunology, P. Ogra, *et al.*, Editors., Academic Press: Orlando.

Koletzko, S., A. Griffiths, M. Corey, C. Smith and P. Sherman,1991b. Infant feeding practices and ulcerative colitis in childhood. BMJ., 302:1580-1581

Koletzko, S., P. Sherman, M. Corey, A. Griffiths and C. Smith,1989a. Role of infant feeding practices in development of Crohn's disease in childhood. BMJ., 298: 1617-1618

Koletzko, B., P.J. Aggett, J.G. Bindels, P. Bung, P. Ferre, A. Gil, M.J. Lentze, M. Roberfroid and S. Strobel, 1998. Growth, development and differentiation: a functional food science approach. Br. J. Nutr., 80:(Suppl 1), S5-S45

Kuhn, C.M. S.R. Butler and S.M. Schanberg, 1978. Selective depression of growth hormone during maternal deprivation in rat pups. Science, 201: 1034-1036

Lawrence, R.M. and R.A. Lawrence, 2001. Given the benefits of breastfeeding, what contraindications exist? Pediatr. Clin. N. Am., 48:235-251

Lawrence, R.A., 1997. A Review of the Medical Benefits and Contraindications to Breastfeeding in the United States. National Center for Education in Maternal and Child Health: Arlington, Virginia.

Lawrence, R., 1999. Breastfeeding: a Guide for the Medical Profession. 5th edition. 5th ed. St. Louis: CV Mosby.

Lawrence, R.A. and C.R. Howard, 1999. Given the benefits of breastfeeding, are there any contraindications? Clin. Perinatol., 26:479-490

Lebenthal, E. and P.C. Lee, 1980. Development of functional response in human exocrine pancreas. Pediatrics., 66: 556-560

Lifschitz, C.H., H.K. Hawkins, C. Guerra and N. Byrd, 1988. Anaphylactic shock due to cow's milk protein hypersensitivity in a breast-fed infant. J. Paediat. Gastroenterol. Nutr., 7: 141-144

Lindberg, T., 1979. Protease inhibitors in human milk. Pediatr Res., 13:969-972

Lindberg, T., K. Ohlsson and B. Westrom, 1982. Protease inhibitors and their relation to protease activity in human milk. Pediatr. Res., 16:479-483

Lindh, E., 1985. Increased resistance of immunoglobulin dimers to proteolytic degradation after binding of secretory component. J. Immunol., 113: 284-286

Lucas, A., O.G. Brooke and R. Morley, 1990. Early diet of preterm infants and development of allergic or atopic disease: randomised prospective study. BMJ., 300:837-840

Lucas, A., R. Morley, T.J. Cole, G. Lister and C. Leeson-Payne, 1992. Breast milk and subsequent intelligence quotient in children born preterm. Lancet., 339: 261-264

Lucas, A. and T.J. Cole, 1990. Breastmilk and neonatal necrotizing enterocolitis. Lancet., 336:1519-1523

Mahmood, A. and R. Torres-Pinedo, 1985. Effect of hormone administration on the sialylation and fucosylation of intestinal microvillus membranes of suckling rats. Pediatr. Res., 19, 899-902

Makrides, M., M.A. Neumann, R.W. Byard, K. Simmer and R.A. Gibson, 1994. Fatty acid composition of brain, retinea and erythrocytes in breast- and formula- fed infants. Am. J. Clin. Nutr., 60: 189- 194

Makrides, M., M.A. Neumann and R.A. Gibson, 1996. Is dietary docosahexaenoic acid essential for term infants?. Lipids, 31: 115-119

Mårild, S., U. Jodal and L.A. Hanson, 1990. Breastfeeding and urinary-tract infection [letter; comment]. Lancet., 336: 942

Mårild, S., U. Jodal and L. Mangelus, 1989. Medical histories of children with acute pyelonephritis compared with controls. Pediatr Infect. Dis. J., 8: 511-515

Mason, T., C.E. Rabinovich, D.D. Fredrickson, K. Amoroso, A.M. Reed, L.D. Stein and D.W. Kredich, 1998. Breast feeding and the development of juvenile rheumatoid arthritis. J. Rheumatology, 22:1166-70

Mattsby-Baltzer, I., A. Roseanu, C. Motas, J. Elverfors, I. Engberg, and L.A. Hanson, 1996. Lactoferrin or a fragment thereof inhibits endotoxin-induced interleukin-6 response in human monocyte cells. Pediatr. Res., 40, 257-262.

May, J.T., 1994. Antimicrobial factors and microbial contaminants in human milk: recent studies. J. Pediatrics and Child Health, 30: 470-475

Mechnicki, M., M. Zimecki and T. Zaguski, 1993. Lactoferrin regulates the release of tumor necrosis factor alpha and interleukin-6 in vivo. International J. Experimental Pathology, 74: 433-439

Michie, C.A., E. Tantscher and A. Rot, 1998. The long term effects of breastfeeding: A role for the cells in breast milk? J. Tropical Pediatrics, 44: 2-3.

Miles, E.A. and P.C. Calder, 1998. Modulation of immune function by dietary fatty acids. Proceedings of the Nutrition Society, 57: 277-292

Misra, U.K., C.T. Chu, G. Gawdi and S.V. Pizzo, 1994. The relationship between low density lipoprotein-related protein/alpha-2-macroglobulin (alpha 2M) receptors and the newly described alpha 2M signaling receptor. J. Biol. and Chem., 269: 18303-18306

Miyazawa, K., C. Mantel, L. Lu, D.C. Morrison and H.E. Broxmeyer, 1991. Lactoferrin-lipopolysaccharide interactions. Effect on lactoferrin binding to monocyte/macrophage-differentiated HL-60 cells. J. Immunol., 146: 723-729

Morley, R. and A. Lucas, 1994. Influence of early diet on outcome in preterm infants. Acta Paediatr. Suppl., 405: 123-126

Moya, F.R., 1991. In Textbook in Neonatal Nutrition, R. Suskind and L. Suskind, Editors., Raven: New York.

Murphey, E., K. Shibuya and N. Hosken, 1996. Reversibility of T-helper 1 and 2 populations is lost after long term stimulation. J. Exp. Med., 183: 901-913

Newburg, D.S., 1996. Oligosaccharides and glycoconjugates in human milk: Their role in host defense. J. Mamm. Gland Biol. Neoplasia., 1: 271-283

Newsholme, E.A. and P.C. Calder, 1997. The proposed role of glutamine in some cells of the immune system and speculative consequences for the whole animal. Nutr., 13: 728-730 .

Nuijens, J.H., P.H. van Berkel and F.L. Schanbacher, 1996. Structure and biological action of lactoferrin. J. Mamm. Gland Biol. Neoplasia., 1: 285-295

Oddy, W.H., P.G. Holt, P.D. Sly, A.W. Read, L.I. Landau, F.J. Stanley, G.E. Kendall and P.R. Burton, 1999. Association between breastfeeding and asthma in 6 year old children: findings of a prospective birth cohort study. BMJ., 319: 815-819

Orrhage, K. and C.E. Nord, 1999. Factors controlling the bacterial colonization of the intestine in breastfed infants. Acta Paediatr., 430: S47-S57.

Ostrea, E.M., J.E. Balun, R. Winkler and T. Porter, 1986. Influence of breast-feeding on the restoration of the low serum concentration of vitamin E and beta-carotene in the newborn infant. Am. J. Obstet. Gynecol., 154:1014-1017

Pabst, H.F., 1997 Immunomodulation by breast-feeding. Pediatr. Infect. Dis. J., 16: 991-995.

Pabst, H.F. and D.W. Spady, 1990. Effect of breast-feeding on antibody response to conjugate vaccine. Lancet., 2: 269-270

Pabst, H.F., D.W. Spady, L.M. Pilarski, M.M. Carson, J.A. Beeler and M.P. Krezolek, 1997. Differential modulation of the immune response by breast- or formula-feeding of infants. Acta Paediatr., 86: 1291-1297

Pabst, H.F., J. Godel, M. Grace, H. Cho and D.W. Spady, 1989. Effect of breast-feeding on immune response to BCG vaccination. Lancet., 1: 295-297

Perin, N.M. and M.T. Clandinin, 1997. Thomson ABR. Importance of milk and diet on the ontogeny and adaptation of the intestine. J. Paediat. Gastroenterol. Nutr., 24: 419-425

Peters, U., S. Schneeweiss, E.A. Trautwein and H.F. Erbersdobler, 2001. A case-control study of the effect of infant feeding on celiac disease. Annals of Nutr. and Metabolism, 45:134-142

Peterson, J.A., M. Hamosh, C.D. Scallan, R.L. Ceriani, T.R. Henderson, N.R. Mehta, M. Armand and P. Hamosh, 1998. Milk fat globule glycoproteins in human milk and in gastric aspirates of mother's milk-fed preterm infants. Pediatr Res., 44:499-506

Peterson, J.A., S. Patton and M. Hamosh, 1998. Glycoproteins of the human milk fat globule in the protection of the breast-fed infant against infections. Biol. Neonate., 74: 143-162

Pettitt, D.J., M.R. Forman, R.L. Hanson, W.C. Knowler and P.H. Bennett, 1997. Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians. Lancet., 350: 166-168.

Phillips, D.I., D.J.P. Barker and C. Osmond, 1993. Infant feeding, fetal growth and adult thyroid function. Acta Endocrinologica, 129:134-8

Picciano, M.F., 2001. Nutrient composition of human milk. Pediatr. Clin. N. Am., 48:53-67

Pickering, L.K., D.M. Granoff, J.R. Erickson, M.L. Masor, C.T. Cordle, J.P. Schaller, T.R. Winship, C.L. Paule and M.D. Hilty, 1998. Modulation of the immune system by human milk and infant formula containing nucleotides. Pediatrics, 101: 242-249

Pisacane, A., N. Impagliazzo, M. Russo, R. Valiani, A. Mandarini, C. Florio and P.Vivo, 1994. Breast feeding and multiple sclerosis. BMJ., 308:1411-1412

Pisacane, A., L. Graziano, G. Mazzarella, B. Scarpellino and G. Zona, 1992. Breast-feeding and urinary tract infection. J. Pediatr., 120:87-89

Poland, R.L. and S.N. Cohen, 1980. The contamination of the food chain in Michigan with PPB: The breastfeeding question., in Drugs and Chemical Risks to the Fetus and Newborn, A.R. Liss, Editor. Alan R. Liss: New York. p: 129-137.

Ridge, J.P., E.J. Fuchs and P. Matzinger, 1996. Neonatal tolerance revisited: turning on newborn T cells with dendritic cells. Science, 271: 1723-1726

Robinson, J.E., B.A.M. Harvey and J.F. Soothill, 1978. Phagocytosis and killing of bacteria and yeast by human milk cells after opsonisation in aqueous phase of milk. BMJ., i: 1443-1445

Rodgers, B., 1978. Feeding in infancy and later ability and attainment: a longitudinal study. Dev Med Child Neurol., 20: 421-426

Rogan, W.J. and B.C. Gladen, 1993. Breast-feeding and cognitive development. Early Hum. Dev., 24:S21-S26.

Roitt, I. and J. Brostoff, 1996. Immunology. 4th ed. Barcelona: Mosby.

Roux, M.E., M. McWilliams, J.M. Phillips-Quagliata, P. Weisz-Carrington and M.E. Lamm, 1977. Origin of IgA secretory plasma cells in the mammary gland. J. Exp. Med., 146: 1311-1322

Rudloff, H.E., F.C. Schmalstieg, A.A. Mushtaha, K.H. Palkowetz, S.K. Liu and A.S. Goldman, 1992. Tumor necrosis factor-alpha in human milk. Pediatr. Res., 31: 29-33

Rudloff, H.E., F.C. Schmalstieg, K.H. Palkowetz, E.J. Paszkiewicz and A.S. Goldman, 1993. Interleukin-6 in human milk. J. Reproductive Immunol., 23: 13-20

Saarinen, U.M. and M. Kajosaari,1995. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. Lancet., 346: 1065-9

Saarinen, K., 1997. Early feeding of cow's milk formula - a risk for cow's milk allergy. J. Pediatric Gastroenterology and Nutr., 24: 461(A)

Saarinen, U.M., 1982. Prolonged breastfeeding as prophylaxis for recurrent otitis media. Acta Paediatr. Scand., 71: 567-571

Sbarra, V., E. Mas, T.R. Henderson, M. Hamosh, D. Lombardo and P. Hamosh, 1996. Digestive lipases of the newborn ferret: compensatory role of milk bile-salt-dependent-lipase. Pediatr Res., 40: 263-268

Schanler, R., 2001. The use of human milk for premature infants. Pediatr. Clin. N. Am., 48: 207-219

Shannon, W.R., 1921. Demonstration of food proteins in human breast milk. Am. J. Dis. Child., 22: 223

Sheard, N.F. and W.A. Walker, 1988. The role of breast milk in the development of the gastrointestinal tract. Nutr. Rev., 46: 1-8

Shu, X.O., M.S. Linet, M. Steinbuch, W.Q. Wen, J.D. Buckley, J.P. Neglia, J.D. Potter, G.H. Reaman and L.L Robison,1999. Breastfeeding and risk of childhood acute leukemia. J. National Cancer Institute, 91:1765-1772

Siminoski, K., P. Gonnella, J. Bernanke, L. Owen, M. Neutra and R.A. Murphy, 1986. Uptake and transepithelial transport of nerve growth factor in suckling rat ileum. J. Cell Biol., 103, 179-190

Skansen-Saphir, V., A. Lindfors and U. Andersson, 1993. Cytokine production in mononuclear cells of human milk studies at the single-cell level. Pediatr Res., 34: 213-216

Slade, H.B. and S.A. Schwartz, 1989. Antigen-driven immunoglobulin production by human colostral lymphocytes. Pediatr. Res., 23: 295-299

Smith, L.C. and E.H. Davidson, 1994. The echinoderm immune system. Characters shared with vertebrate immune systems and characters arising later in deuterostome phylogeny. Annals of New York Academy of Science, 712: 213-226

Sorva, R., S. Makinen-Kiljunen and K. Juntunen-Backman, 1994. Beta-lactoglobulin secretion in human milk varies widely after cow's milk ingestion in mothers of infants with cow's milk allergy. J. Allergy Clin. Immunol., 93:787-792

Srivastava, M.D., A. Srivastava, B. Brouhard, R. Saneto, S. Groh-Wargo and J. Kubit, 1996. Cytokines in human milk. Res, Commun. Mol. Pathol. Pharmacol., 93:263-287

Stuart, C.A., R. Twiselton, M.K. Nicholas and D.W. Hide, 1984. Passage of cows' milk protein in breast milk. Clinical Allergy, 14:533-535

Taylor, B., 1973. Transient IgA deficiency and pathogenesis of infantile atopy. Lancet., ii: 111-113

Taylor, A., 1998. Violations of the international code of marketing of breast milk substitutes: prevalence in four countries. BMJ., 316: 1117-1122.

Tehan, C.G., H.A. McKenzie and M. Griffiths, 1991. Some monotreme milk "whey" and blood proteins. Comp. Biochem. Physiol., 99B: 99-118

Thorell, L., L.B. Sjoberg and O. Hernell, 1996. Nucleotides in human milk: sources and metabolism by the newborn infant. Pediatr. Res., 40: 845-852

Thormar, H., C.E. Isaacs, H.R. Brown, M.R. Barshatzky and T. Pessolano, 1987. Inactivation of Enveloped Viruses and Killing of Cells by Fatty Acids and Monoglycerides. Antimicrob Agents Chemother., 31:27-31

Tomita, M., M. Takase, H. Wakabayashi and W. Bellamy, 1994. Antimicrobial peptides of lactoferrin. Adv. Exp. Med. Biol., 357: 209-218

Tsutsumi, H., T. Honjo, K. Nagai, Y. Chiba, S. Chiba and S. Tsugawa, 1989. Immunoglobulin A antibody response to respiratory syncytial virus structural proteins in colostrum and milk. J. Clin. Microbiol., 27:1949-1951

Turchany, J.M., S.B. Aley and F.D. Gillin, 1995. Giardicidal activity of lactoferrin and N-terminal peptides. Inf Immunol., 63: 4550-4552

Uauy, R. and I. De Andraca, 1995. Human milk and breast feeding for optimal mental development. J. Nutr., 125:(8 Suppl), 2278S-2280S

Uauy, R., G. Stringel, R. Thomas and R. Quan, 1990. Effect of dietary nucleosides on growth and maturation of the developing gut in the rat. J. Paediat. Gastroenterol. Nutr. 10: 497-503

Vaarala, O., J. Paronen, T. Otonkoski and H.K. Akerblom, 1998. Cow milk feeding induces antibodies to insulin in children - a link between cow milk and insulin-dependent diabetes mellitus? Scand. J. Immunol., 47:131-135

Vandenplas, Y., 1997. Myths and facts about breastfeeding: does it prevent later atopic disease? Acta Paediatr., 86: 1283-87

Victora, CG. and A.J.D. Barros, 2000. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Lancet., 355:451-455

Virtanen, S.M., L. Rasanen, K. Ylonen, A. Aro, D. Clayton B. Langholz, J. Pitkaniemi, E. Savilahti, R. Lounamaa and J. Tuomilehto, 1993. Early introduction of dairy products associated with increased risk of IDDM in Finnish children. Diabetes, 42: 1786-90

von Kries, R., B. Koletzko, T. Sauerwald, E. von Mutius, D. Barnert, V. Grunert and H. von Voss, 1999. Breastfeeding and obesity: cross sectional study. BMJ., 319:147-150

Wharton, B.A., 1992. Food for the brain. Proc. R. Coll. Phys., 22: 336-346

Wigginton, J.M. and P. Thill, 1993. Infant botulism: A review of the literature. Clin. Pediatr., 32: 669-674

Willems, R., J. Duchateau, P. Magrez, R. Denis and G. Casimir, 1993. Influence of hypoallergenic milk formula on the incidence of early allergic manifestations in infants predisposed to atopic diseases. Ann. Allergy, 71:147-150

Wold, A,E. and L.Å. Hanson, 1994. Defense factors in human milk. Curr Opin Gastroenterol., 10: 652-658

Wold, A.E. and I. Adlerberth, 1998. Does breastfeeding affect the infant's immune responsiveness? Acta Paediatr., 87: 19-22

World Health Organisation, 1981. International Code of Marketing of Breast-Milk Substitutes. World Health Organisation: Geneva.

World Health Organisation, 1998. HIV and infant feeding: Guidelines for health care management and supervisors. World Health Organisation: Geneva.

World Health Organisation,1989. Protecting, Promoting and Supporting Breastfeeding: The special role of maternity services, a joint WHO/UNICEF statement. World Health Organisation: Geneva.

Wright, A.L., C.J. Holberg, F.D. Martinez, W.J. Morgan and L.M. Taussig, 1989. Breast feeding and lower respiratory tract illness in the first year of life. BMJ., 299: 946-9

Xanthou, M., J. Bines and W.A. Walker, 1995. Human milk and intestinal host defense in newborns: an update. Advances in Pediatrics, 42:171-208

Xanthou, M., 1997. Human milk cells. Acta Paediatr., 86: 1288-1290

Xanthou, M., 1998. Immune protection of human milk. Biol. Neonate., 74: 121-133

Yamauchi, K., M. Tomita, T.J. Giehl and R.T. Ellison, 1993. 3rd., Antibacterial activity of lactoferrin and a pepsin-derived lactoferrin peptide fragment. Infection & Immunity, 61: 719-728

Zeiger, R.S. and S. Heller, 1995. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomised study of combined maternal and infant food allergen avoidance. J. Allergy Clin. Immunol., 95: 1179-1190

Zeiger, R.S., 1994. Dietary manipulations in infants and their mothers and the natural course of atopic disease. Pediatr. Allergy Immunol., 5: (Suppl 1) 33-43

Ziegler, E.E., A.M. O'Donnell and S.E. Nelson, 1976. Body composition of the reference fetus. Growth, 40: 329