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. In this paper the scientific evidence in support of why breast milk is beneficial for infants and children is summarised and the mechanisms whereby breastfeeding impacts on disease are explored.

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 breast milk 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 (Grulke C.G. et al., 1934; Grulke C.G et al., 1936). 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 Kobinsky, 1984), lower respiratory tract infections (Wright et al., 1989; Cesar et al., 1990), 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, 1953), urinary tract infections (Pisacane et al., 1992; Makild et al., 1990; Makild 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 (Faith-Magnussen et al., 1986), Crohn's disease (Peters et al., 2001) and ulcerative colitis (Corao 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, 1987; Bergstrom et al., 1996; Greene et al., 1996; Crane and Loganmann, 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 autimmunity) is reduced in breastfed children (Ellis and Atkinson, 1998; Boroh-Johnsen et al., 1984; Virtanen et al., 1993). The possibility that the early introduction of 'other milk' (Vasalva et al., 1996; 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, 1998) 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 Ferguson, 1998) experimental (Koletzkio et al., 1998) and neurodevelopmental studies (Wharton, 1992; Cladnin et al., 1980; Farquharson et al., 1992; Makrides et al., 1984, Harnsh and Salem, 1989; Jenson et al., 1992; Gibson and Makrides, 1988, Uauy and De Andrazca, 1996). 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, 1998). 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. Rogen and Gladen (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.
Oddy: Breastfeeding has long-term health benefits and the mechanisms for these effects are explored.

<table>
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<tr>
<th>Common illnesses</th>
<th>Reference</th>
<th>Feeding measure</th>
<th>Risk Ratio range*</th>
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<tbody>
<tr>
<td>Acute diarrhea</td>
<td>Victoria and Barros, 2000</td>
<td>Breastfed &lt; 3 months</td>
<td>8.10 (4.1-9.0)</td>
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<td>Lower respiratory tract infections</td>
<td>(Wright et al., 1989)</td>
<td>Breastfed &lt; 4 mo/ sharing bedroom</td>
<td>3.29 (1.8-6.0)</td>
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<td>Pneumonia</td>
<td>Cesar et al., 1999</td>
<td>No breastfeeding</td>
<td>1.67 (1.2-2.8)</td>
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<td>Ear infections (Recurring vs acute)</td>
<td>Duncan et al. 1993</td>
<td>Breastfed &lt; 6 months</td>
<td>1.61 (1.27-1.70)</td>
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<td>Asthma</td>
<td>Oddy et al., 1999</td>
<td>Breastfed &lt; 4 months</td>
<td>1.25 (1.02-1.52)</td>
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<td>Atepy</td>
<td>Oddy et al., 1999</td>
<td>Breastfed &lt; 4 months</td>
<td>1.30 (1.04-1.61)</td>
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<td>Less common illnesses</td>
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<td>Necrotising enterocolitis</td>
<td>Lucas and Cole 1990</td>
<td>39% formula fed/ 7% breastfed</td>
<td>4.50 (3.00-6.00)</td>
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<td>Urinary tract infections</td>
<td>Piscicine et al., 1982</td>
<td>Never breastfed</td>
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<td>Insulin dependent diabetes mellitus</td>
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<td>Current formula feeding</td>
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<td>Cholera</td>
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<td>Not breastfeeding</td>
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<td>Breastfed &lt; 3 months</td>
<td>1.63 (1.36-1.79)</td>
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<td>Lack of breastfeeding</td>
<td>1.90 (1.50-3.60)</td>
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<td>Ulcerative colitis</td>
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<td>Lack of breastfeeding</td>
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<td>Cardiovascular disease</td>
<td>Bergstrom et al., 1995</td>
<td>Lack of breastfeeding</td>
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<td>Metabolic disease</td>
<td>Bergstrom et al., 1995</td>
<td>Lack of breastfeeding</td>
<td>1 ApoB values</td>
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<td>Obesity</td>
<td>von Kries et al., 1999</td>
<td>Breastfed &lt; 6 months</td>
<td>1.26 (1.02-1.43)</td>
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* 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, 1986; Wold and Hanson, 1984; Xanthou et al., 1995; Hanson, 1988). 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 osmolality and pH change impacting on the physiology of the infant gut (Lawrence, 1989). 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 breastfeeding 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 pleotropic functionality (Garofalo and Goldman, 1990).

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 the 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 (Anasi et al., 1996) 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, 1996) 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
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; Garfalo et al., 1995). Anti-proteases in human milk such as α,- antitrypsin and α₁-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; Agnoud et al., 1969) and pancreatic secretion of chymotrypsin are very low in the neonatal period (Leibenhal and Lee, 1980; Soehm 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 newborn animals (Grosvenor et al., 1992), and are currently under investigation in human neonates (Garfalo 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., 1995) as demonstrated in animal studies (Jain et al., 1989).

A large number of enzymes are present in human milk (Hamosh, 1996). Some of these enzymes provide potential protection against disease. Anti-proteases and proteases modulate the proteolytic breakdown of milk proteins, many with specific functions in the neonate (Lindberg et al., 1982; Lindberg, 1979). Milk bile-salt-dependent-lipase digests milk triglycerides (59% of milk fat) in the intestines 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 acetyhydrolase, an enzyme in human milk, protects the intestine of the neonate (Farukova et al., 1993) from inflammatory diseases (Caplan and Huseh, 1960).

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, polymorphonuclears 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 90%) 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 relationship 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 (Jennmalm and Bjorksten, 1998).

The immunomodulatory function of milk proteins (Xanthou, 1998) has been well documented elsewhere (Garfalo 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 (Roll and Brostoff, 1988). The main immunoglobulin in human milk is secretory IgA (sigA) (Hanson et al., 1978). The specificity of sigA antibodies in breast milk reflect the maternal enteric and respiratory antigens.
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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, 1989) 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, s.IgA antibodies in the mother's 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 Th1 memory (Heufler et al., 1986; Ridge et al., 1986). In early life Th2 and Th1 cell populations possess the potential of reversibility towards the alternate cytokine type but the reversibility is lost after long term stimulation by microbes (Murphy 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 (Onhage 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, 1984), and lactoferrin created by partial hydrolysis of lactoferrin kills Candida albicans (Bellamy et al., 1995), some enteric bacteria (Yamauchi et al., 1993) and Gardia (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 anti-inflammatory 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-carotene, vitamin D and retinoids. 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 (e.g. 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., 1988) 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 polo, tatumus 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, 1996; Golden and Rudloff, 1991; Garofalo and Goldman, 1988; 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 transcripational modification of peptide hormones in the mammary gland before secretion into milk (Hahn, 2001). During critical periods of development the infant may be conditioned by the transfer of milk hormones (Eills et al., 1987). The effects of hormones may be immediate in the newborn, or delayed.
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<td>Hypothalamic</td>
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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, 1988). 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 leucocyte 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 (Grosvener 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., 1982). 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 (Grosvener 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., 1998).

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 (Sinioski et al., 1990) 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 Giad, 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 IL.1, L6, IL.10, G-CSF, M-CSF, 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., 1988). 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 bacterioclastic agent in human milk (Peterson et al., 1998). Indeed, a broad spectrum bactericidal peptide has been isolated following gastric digestion 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 (Miyazawva et al., 1991) that appear to inhibit cytokine production (Misra et al., 1994). Lactoferrin inhibits the discharge of interleukins 1, 2 & 6 and TNF-c from monocytes and of prostaglandin E2 from macrophages protecting against inflammation (Matsuy-Baltzer et al., 1996; Bantel et al., 1987; Miechuicki et al., 1993).

Lipids: After 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 (Grouillard et al., 1991) and disrupt enveloped viruses (Thormar et al., 1987; Issacs and Thorner, 1991). Although lipolysis generates similar products for formula-fed and breastfed infants, breastfed infants have higher rates of lipolysis 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 docosahexaenoic 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 (LCUFA) most importantly DHA (22:6n-3), 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, 1984; Calder, 1997). In particular the long chain fatty acids (Calder, 1997) in breast milk have been implicated as potential modulators of the immune system (Hasselbach et al., 1998; Goldman, 1993; Pabst et al., 1997; Milles and Calder, 1998; Wold and Adlerberth, 1998; Hoekje et al., 1990). For the possible influence of DHA and AA on the developing immune system a lower proportion of CD45R0+ 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, 1986). The structure of oligosaccharide mimics that of bacterial receptors on intestinal cells, blocking bacterial attachment to intestinal cell membranes (Goldman et al., 1988). They can function as receptor analogs for bacteria and viruses and inhibit the adhesion of microbes (including pneumococci) (Anderson et al., 1988). 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, 1986).

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; Vandenberg, 1997). Some exclusively breastfed infants develop allergic reactions to cow's milk protein (β-lactoglobulin) (Lüschtz 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%) (Bussino et al., 1993).

In most lactating women (60-96%) 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., 1984). Given the low frequency of cow's milk allergy in breastfed infants, the small measure of β-lactoglobulin found in
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., 1996; 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 Gruer, 1981; Blom 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., 1996). Many children do receive cow’s milk proteins in the first days of life (Hill, 1994; Saarinan, 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 counselled 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., 1986). 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, 1996). 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 penicillamine 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 galactosaemia, 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 defence 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. Methods that enhance maternal milk production and the development of the enteronomimary response. Premature infants fed their own mothers milk have fewer episodes of NEC, diarrhoea and urinary tract infection than premature infants fed formula suggesting that human milk may enhance premature infants host defenses. Because diet also affects fecal flora, the flora of human milk-fed babies is less pathogenic than those fed formula.
Oddy: Breastfeeding has long-term health benefits and the mechanisms for these effects are explored

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
Oddy: Breastfeeding has long-term health benefits and the mechanisms for these effects are explored


Oddly: Breastfeeding has long-term health benefits and the mechanisms for these effects are explored.


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