Growth and Nutrition: The First Six Months

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\textbf{Abstract}

Today the WHO Growth Chart Standards, based on the growth of breastfed infants, are used. These growth curves solve the problem of the deviating observations for breastfed compared to non-breastfed infants using previous growth charts. Presently it is not clear how the mother’s diet, especially the fat intake, influences the growth of the offspring. Animal experiments indicate that a low intake of n-3 polyunsaturated fatty acids via the milk may have short- and long-term negative consequences. There is limited information in man. It has been suggested that the mammary glands may have phylogenetically originated from glands providing innate immunity, later developing capacities for providing nutrition. This would agree with the fact that human milk contains so many major components which do not primarily function as nutrients, but seem to protect nutrition and growth. Lactoferrin, oligosaccharides, glycoproteins, secretory IgA antibodies, \(\alpha\)-lactalbumin and the antisecretory factor have such functions.

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\textbf{Growth in Breastfed and Non-Breastfed Infants}

The usefulness of growth curves in the evaluation of the health status of infants and children has made them a basic instrument in clinical pediatrics and research. Growth curves are, for instance, most useful to show improvements...
in measures introduced to prevent impaired health and growth in underprivileged populations. This was illustrated in our long-term follow-up of children in different social groups in and around Lahore, Pakistan. Diarrheal illness was significantly reduced by measures such as starting to breastfeed within 3 instead of 47 h after birth, an increase in exclusive breastfeeding from 5 to 80% at 1 month of age, and a reduction in the use of pre-lacteal feeds from 100 to 34%. Within 10 years postnatal linear growth increased by about 3 cm at 24 months of age [1].

Today we use the WHO Child Growth Standards [2], which were set up to demonstrate optimal growth based on infants exclusively breastfed for the first 6 months, with complementary food added thereafter. Among those previously used, the Center for Disease Control reference tables showed the average growth of all infants, including those overfed, underfed and uncared for, as well as those well-fed. Using this standard, breastfed infants showed enhanced growth during the first 2 months and reduced growth during months 3–12 compared to formula-fed infants [3]. A very large observational cohort study analyzed the effects of different modes of feeding on growth, analyzing z scores of weight for age, length for age and weight for length [4]. The investigation showed a growth-accelerating effect of formula compared with human milk and other milks throughout infancy, but especially at the age of 3–6 months. This analysis confirmed several previous investigations. The study also brought out a strong negative association between cereal intake and length, weight and head circumference gains in the 3- to 6-month interval. This may be similar to the previously demonstrated effect of offering cereals and other solid foods during that critical time period [5]. The effect on final weight and length is not known from these studies. The normative growth in the WHO chart of weight as well as height is regarded as representative of infant growth and includes the additional growth previously seen in breastfed compared to non-breastfed infants during the first few months.

We studied the association of breastfeeding to linear growth using a non-linear model and followed the six phases, neonatal, infantile, early childhood, mid childhood, late childhood, and pubertal, introduced by Walker and Walker [6] in their model. Breastfeeding data and measurements of height were collected longitudinally for every Swedish infant born on the 15th day of any month in 1981. Data included measurements of height for 3,107 children. Information about breastfeeding was available for 2,773 of these (12.2% missing). There was a significant association between any breastfeeding and the growth rate of boys in the neonatal phase, i.e. up to 2–3 months of age [Silfverdal et al., unpublished]. The lowest growth rate was seen in those breastfed for less than 30 days. Next came the group with any breastfeeding for 30–150 days, illustrating a dose-response relationship (table 1). The same pattern could be seen for girls with a significant effect of the age at peak height velocity in the neonatal and infantile phases, which were delayed compared to those most breastfed (table 1). Further, among the girls, there was a
negative association with adult height for the group that was breastfed for less than 30 days compared to the group most breastfed. The reason for this is unknown, but we have previously noted that the body mass index was lower in breastfed girls [Silfverdal et al., unpublished]. Excluding infants with a low birthweight (<2,500 g), chronic disease, or of immigrant parents did not lead to any significant changes in the results. Moreover, separate analyses of groups based on birthweight categories (<2,500, 2,500–4,000, >4,000 g) did not change the conclusions as to the association with breastfeeding. A weakness is that no controls for confounding factors like smoking and socioeconomic status were included.

The WHO growth curve does not take the diet of the breastfeeding mother into consideration. Based on studies in experimental animals, as well as in man, there is evidence that the quality of the mother’s fat intake plays a role in the fat content of the milk with possible consequences for the offspring. This was obvious in our investigations in rats during pregnancy, lactation and adulthood. Thus a deficiency in essential fatty acids in the maternal diet during late pregnancy and lactation caused significantly low serum leptin levels in the offspring [7]. The effect was due both to the regulation of the amount of adipose tissue and leptin mRNA expression [8]. A perinatal deficiency in essential fatty acids was also associated with increased body weight and significant changes in the trabecular and cortical bones of adult male offspring [9]. Dams eating a diet with a low ratio of 0.4 of n-6/n-3 polyunsaturated fatty acids (PUFAs), compared to those given a high ratio of 9, had offspring with lower leptin levels and body weight, length, inguinal fat pads and adipocyte size [10]. In adult age the male offspring of the mothers given the high ratio n-6/n-3 diet compared to those given the low ratio showed increased systolic blood pressure and serum triacylglycerol levels [11]. The females in that diet

Table 1. Parameter estimates and 95% confidence intervals for the Walker and Walker model with the first of the five phases of growth in girls

<table>
<thead>
<tr>
<th>Parameter estimate (95% CI) for reference group (breastfed &gt;150 days)</th>
<th>Estimated difference (95% CI) compared to reference group for children breastfed 30–150 days</th>
<th>&lt;30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult height</td>
<td>167.6 (167.1; 168.2)</td>
<td>-0.35 (-1.15; 0.43)</td>
</tr>
<tr>
<td>Growth phase I (neonatal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at peak</td>
<td>-0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Height velocity</td>
<td>(-0.14; -0.11)</td>
<td>(-0.02; 0.03)</td>
</tr>
<tr>
<td>Growth rate</td>
<td>5.97 (5.76; 6.20)</td>
<td>-0.66 (-0.93; -0.40)</td>
</tr>
</tbody>
</table>

Significant group differences are printed in bold type.
group had increased cortical bone thickness and significantly longer femurs with larger cortical cross-sectional bone area, as well as bone mineral content [12].

In humans the fat content in milk varies much and can provide up to 50% of the energy intake of the infant [13]. Colostrum contains a higher percentage of long-chain fatty acids, whereas the n-6 and n-3 series PUFAs decrease during the first month. The milk fat content varies between breasts and women. In a small group of infants such variations could not be shown to affect growth [14]. Chinese mothers with a high carbohydrate but low fat, protein and energy intake had high concentrations of PUFAs in milk with a n-6/n-3 ratio of 21.6. The ratio between arachidonic and docosahexaenoic acid was as high as in vegans. The concentration of these two fatty acids correlated positively with the breastfed infants’ weight gain at month 1 and length gain at 1 and 3 months [15]. Supplementing the diet of lactating women with fish oil during 0–4 months of lactation did not change the growth of their infants with regard to weight or length during the first 9 months, but had effects on body composition at 2.5 years of age. A preferential transfer of n-3 PUFA via breast milk to the infant’s erythrocytes was suggested [16]. Supplementation with fish or corn oil for 3 weeks during pregnancy did not have any effect on infantile growth during the first year [17].

Breastfeeding compared to formula-feeding was found to give higher leptin but lower grehlin and insulin-like growth factor-1 serum levels in the infant [18]. Decreased milk leptin levels were related to rapid growth in small for gestational age infants; large infants instead received milk with increased leptin levels seemingly adjusting the appetite of the infants [19]. Milk leptin levels at 1 month of lactation were related to maternal plasma leptin and inversely to the maternal body mass index [20].

**Phylogenetically, Milk Glands May Initially Have Provided Innate Defense, Later Adding Nutrients**

According to a recent review [21], mammary glands providing nutrition and host defense may have originated from skin glands initially involved in innate immunity. Such host defense, providing broad nonspecific protection, may also have developed the capacity to provide energy for the growing offspring in incremental steps, in man primarily as lactose and fat. This seems obvious in man where the protein content is low compared to many other species and where most of the major milk proteins do not seem to be available for nutrition, but rather function in defense. The evolution of two enzymes, xanthine oxidoreductase and lysozyme, which are both expressed in and secreted from the lactating mammary epithelium, was used as examples of this development. These enzymes are thought to be involved in the evolution of the nutritional capacity of human milk and are antimicrobial [22].
Factors Affecting Growth in the Neonate and Young Infant

Early Microbial Colonization and Host Factors that May Protect/Enhance Growth

The newborn meets a very complex microflora from delivery on. Already from birth the infant is equipped with receptors on mucosal membranes and leukocytes belonging to the toll-like receptor (TLR) family. These receptors activate an inflammatory response based on the production of nuclear factor (NF-κB). This is the transcription factor which initiates the production of proinflammatory cytokines such as interleukin-1β, tumor necrosis factor-α and interleukin-6, which among many other effects induce increased levels of leptin, decreasing appetite.

In a recent study of mice, it was found that already in the birth canal neonates meet with microbes which seem to tolerize their innate immune system so that TLR4 on the intestinal epithelium was inactivated. Those born by cesarean section were not similarly tolerized [23]. In contrast the TLR4 on submucosal leukocytes remained capable of activation to defend against any Gram-negative microbes entering tissues. But there was a 1- to 3-log lesser response of monocytes from cord blood with regard to the production of tumor necrosis factor-α compared to adult blood monocytes to a ligand activating many TLRs, including TLR4, suggesting a less strong proinflammatory response in the neonate [24].

Human milk, but not formula, also contains a proteinaceous component, which can modulate TLR-mediated responses specifically and differentially. This may be a milk-mediated mechanism helping the neonate to finely tune its response to microbial exposure from delivery on, especially in the extensive gut mucosa [25]. By activation of TLRs, inflammation with subsequent symptoms like anorexia might otherwise be induced via the proinflammatory cytokines produced. These authors also showed that human milk contains soluble TLR2 which may downregulate the responsiveness via cellular TLR, which are activated by Gram-positive bacteria [26].

The microflora of the gut is extremely complex and only part of it has been defined and described. Obviously the neonate starts to become colonized by microbes from the mother already in the birth canal, and especially by being exposed to maternal stool flora by being born next to the mother’s anus. In early life the aerobic microflora is more prevalent than after the anaerobic flora has expanded and, by competition, reduced the number of aerobes which contain many potential pathogens. Breastfeeding supports this form of protection by presumably promoting the strict anaerobes. A recent study demonstrated that infants delivered vaginally at home and exclusively breastfed mostly had a ‘beneficial’ microflora with the highest number of bifidobacteria and lowest of *Clostridium difficile* and *Escherichia coli* [27]. A study from The Gambia showed that colonization with *Helicobacter pylori* in early infancy predisposed to malnutrition and growth faltering [28]. Actually, the
weight loss caused by colonization with *H. pylori* showed a significant relation to the absence of secretory IgA antibodies in their mothers’ milk against the *H. pylori*-vacuolating cytotoxin A of these bacteria [29].

**Factors which May Promote or Protect Growth**

**Human Lactoferrin**

Lactoferrin is a major milk protein present in concentrations of 5–7 g/l in colostrum and 1–2 g/l in mature milk. It is not only an antimicrobial protecting against experimental urinary tract infection in mice given lactoferrin orally [30], it is also an anti-inflammatory. It downregulated inflammation in a model of dextran-sulfate-induced colitis in mice [31]. This effect could be further defined, showing that lactoferrin downregulated the production of the proinflammatory cytokines by reducing the activation of NFκB [32].

Further studies demonstrated the additional effects of human lactoferrin which is potentially favorable to the growth of the breastfed infant. Thus we find that it seems to function like a heat shock protein [33], suggesting that it may protect the integrity of proteins during synthesis and afterwards; it may have carrier functions and aid in the uptake of proteins in the gut. We also noted that, similar to heat shock proteins, lactoferrin unsaturated with iron binds ATP and has ATPase activity. ATP may become available when milk lactoferrin and the peptides thereof, like lactoferricin, exert their antibacterial activities on the bacteria in the gut. Furthermore, a complex is formed by lactoferrin and casein kinase protecting CK-2 [Moisei et al., unpublished], which results in phosphorylation of lactoferrin [34]. Since CK-2 phosphorylates a number of cellular enzymes and functional proteins such as transcriptional and translational factors, it can be suggested that lactoferrin may stimulate protein synthesis at the cellular level. All this indicates that human milk lactoferrin may have additional effects in the breastfed infant by the lactoferrin-CK2 complex influencing the intracellular phosphorylation process and signal transduction. Actually the phosphorylation sites for CK2 on human lactoferrin are about twice those of bovine lactoferrin [34]. The availability of some phosphorylated components or nucleotides for the infant may be enhanced by human milk lactoferrin.

All mammals can to some extent synthesize nucleotides, i.e., the essential building stones in DNA and RNA. The mere fact that all milks, including human milk, contain substantial amounts of nucleotides strengthens the assumption that nucleotides are semi-essential for newborns. As exogenous nucleotides may derive either from the diet or from the gastrointestinal microflora we performed the following experiment. At weaning, young conventional and germfree rats were put on either a nucleotide-free diet or the same diet enriched with nucleotides. After 2 weeks on these diets the rate of enterocyte mitosis was investigated [35]. No effect was found in conventional...
rats, whereas an increase in the rate of mitosis was found in germfree rats (27/11, 19/18, 23/12 and 12/15% increase in the duodenum, jejunum, ileum, colon of male/female rats, respectively). In short, the results demonstrate that young animals can utilize microflora-related as well as dietary-related supplementation of nucleotide.

Milk Oligosaccharides and Glycoconjugates, Secretory IgA and α-Lactalbumin

These major milk components are, like lactoferrin, better known for their roles in host defense and protection of the host’s integrity than for nutrition, again stressing the complex role of human milk in supporting the infant. For secretory IgA an additional function has just been described: after binding to the antigen in the gut it attaches to the M cells over Peyer’s patches and is taken up together with the antigen potentiating the breastfed infant’s defense by an immune response to an additional microbe or toxin [36]. Milk antibodies have also been found to be able to hydrolyze nucleotides [37]. α-Lactalbumin has the capacity to transform into a complex with oleic acid that makes it lethal to tumor cells (HAMLET = α-lactalbumin made lethal to human tumor cells) [38].

Anti-Secretory Factor Protects against Mastitis in the Mother and Diarrhea in the Infant

The peptide anti-secretory factor (AF) appears in body fluids including human milk, presumably in response to exposure to bacterial enterotoxins. It can also be induced by eating a specially treated cereal [39]. We were able to show that clinical mastitis was prevented by inducing this peptide in milk after intake of the special cereal by lactating mothers [40]. Presumably the effect is due to decreased secretion in the inflamed area, making the intense pain subside.

In a double-blind randomized study of diarrhea in 240 children, 6–24 months of age, in Lahore, Pakistan, in addition to oral rehydration we gave either egg yolk from hens fed the AF-inducing cereal, thus containing preformed AF in high concentrations, or ordinary egg yolk without AF [41]. Of those 120 who had been sick for <7 days 60 received the AF and 60 did not. Within 3 days we noted a striking reduction in the number of stools among the treated compared to the controls (p = 0.0054). The consistency of stools also normalized significantly faster (p < 0.05). Those 120 who had been sick for >7 days were similarly studied. The number of stools did not differ from the controls, but the stool consistency normalized faster in the active treatment group (p < 0.008). Since AF can easily be induced in human milk by intake of a special cereal diet and also may result from oral exposure to enterotoxin-producing V. cholera and E. coli [42], it is likely that AF provides a further explanation as to how breastfeeding may protect against diarrhea.
References


Discussion

Dr. Bier: The last slide you showed us about infections and birthweight, was that corrected for the small infants, the number of days they might have spent in a neonatal ICU or a neonatal facility in the hospital?

Dr. Hanson: No, such details were not available. 1.7 million children is quite a large number, such details were not there. On the other hand, and what I am stressing, is that it was an increased problem also above 1,500 g.

Dr. Björkstén: Thank you for a very interesting and nice presentation. I have a question regarding exclusive breastfeeding starting very early. To my knowledge there
is no traditional society in which some sort of Beikost is not given in addition to breast-
feeding. We usually discuss exclusive breastfeeding meaning no formulas, but mothers 
have always been giving something in addition to breastfeeding. As you know there 
are numerous bacteria present in breast milk, including almost any pathogens, but 
they do not cause any harm, as long as the breast milk is fresh. However if you pas-
teurize it, then the microbes can cause disease as when present in any food. So my 
question is whether addition of food proteins and microbes under the umbrella of 
breastfeeding is actually important for tolerance induction. Going through the litera-
ture, we did not find a single example of an infection epidemic caused by banked 
breast milk, provided the milk was fresh and not pasteurized. All examples of breast 
milk spreading disease have been related to pasteurized milk.

Dr. Hanson: This is quite an important question. What is given to the neonate is 
often given without realizing how small the neonate’s stomach is. It is tiny and it 
expands only a little in the next 2 days. As far as possible the newborn should only 
receive the early milk, the colostrum, which has very high levels of secretory IgA anti-
bodies, between 7 and 15 g/l (mature milk contains 0.5–1.0 g/l). These antibodies are 
mainly directed against the mother's intestinal microflora, which normally is the main 
colonizer of the newborn. When the bacteria expand in numbers they provide ‘colo-
nization resistance’ against other microbes, limiting their numbers. I would assume 
that tolerance induction in early life is a less relevant mechanism than build up of 
defense.

Dr. Björkstén: My question is related to host defense mechanisms, and the idea is 
that you would not only induce tolerance but a regulated immune response also to 
pathogens. Thus it may actually be an advantage to be exposed to the antigens 
together with breast milk. We have an instructive example from Sweden when we 
changed feeding practice and introduced high doses of wheat flour rather suddenly at 
6 months. The incidence of celiac disease increased rapidly to about 1 in 200 until we 
realized that gluten should be introduced gradually and preferably under the umbrella 
of breastfeeding. So my question relates not only to tolerance, but also to the actual 
development of a good immune response to the bacteria you are being exposed to 
under the umbrella of breast milk.

Dr. Hanson: It’s an interesting point but I would also add that the immune system 
is tiny in a newborn. What makes it grow is primarily the exposure to microbes. 
Therefore I would regard microbial colonization, as this happens normally by being 
delivered next to the mother's anus, to be the most efficient way to expand the 
immune system and possibly also the capacity to develop tolerance. In many settings 
the material given instead of mother's milk is more or less contaminated with microbes 
other than from the mother and thus potentially risky. The role of such microbes for 
development of the immune system is, as far as I know, not defined.

Dr. Walker: Celiac disease is an autoimmune disease, and unless you are talking 
about a very rare form of celiac disease, which is allergy to wheat, it doesn't matter. The 
reason that wheat is not introduced early is that it creates growth failure in infants. It is 
a genetic disease; I don't think it has anything to do with breast milk. There is a condi-
tion called ‘breast milk colitis’. The mothers drink cow's milk and other allergens that go 
into the breast milk, and an infant has only small quantities that cause inflammation. So 
it is very controversial whether providing foreign antigens with breast milk is a good 
thing early on in life. The other point I wanted to make is first of all you continue to 
underscore the quality of breast milk, but there is something that perhaps should be 
pointed out: the protective factors are highest in concentration early in nursing, when 
the baby needs it, and then they fall off. This is a very important area.

Dr. Ogra: There are several new pieces of information which you alluded to in 
your elegant talk. I would like to pursue a couple of those issues with you. One relates
to the phylogenetic concept that the breast started as a skin tissue. If that is the case, are there any data to suggest that the macrophages in the milk are homologous to the Langerhans cells in the skin? Second, is there a defined process of antigen presentation or processing by these cells, similar to the skin?

Dr. Hanson: I do not know of any data that would help me answer your question. Rather little has been done on milk cells recently. There was quite an interest many years ago, but it has not been followed up.

Dr. Ogra: The second question relates to the issue of transmission of infections via breastfeeding. What you outlined in your presentation is absolutely correct. However, there are data to suggest that milk does transmit infections with the development of disease. One of them would be the HTLV and there are some data on HIV, although soft, but it is still possible to transmit infections via breastfeeding. Milk does carry a lot of infectious agents and antigens. Is there any evidence to suggest that such feeding-associated transmission of infectious agents and their antigens is protective in the long run against disease or contributes to the induction of tolerance against allergy and hypersensitivity?

Dr. Hanson: It is certainly true that normally there is a very wide variety of microbes in milk and at times pathogens pass through; HIV being a very sad example. Since HIV transfer via the milk is linked to the presence of subclinical mastitis, we thought we might possibly prevent this by using the peptide antisercretory factor which reduces the secretion of fluids over membranes, for instance preventing clinical mastitis in a controlled study [1]. However, the peptide had no effect on subclinical mastitis according to the preliminary outcome of our controlled study in Pakistan.

Dr. Ogra: The final question relates to the fascinating data on TLRs in milk. It would be interesting to see whether soluble TLRs in milk adhere to the mucosa of the breastfeeding infant. Is it possible that such TLRs in milk function as a bypassing mechanism by directly binding to the pathogen-associated molecular patterns of infectious agents and thus affect their elimination from the neonate?

Dr. Hanson: The answer is not known but it is a really interesting point you made, because it turns out that the tolerance induced in a mouse model included only the TLR on the mucosal epithelium, the submucosal sets kept the TLR. This seems to be a very interesting, well-adapted defense system. These are very new data and I am sure we will hear more about it.

Dr. Giovannini: Could exclusively breastfed infants need more nutrients in the 4- to 5-month period, and does the z score on the new WHO charts progressively decrease in exclusively breastfed infants after 4 months? In your opinion should complementary food be started before 6 months? DHA is not used for growth, but perhaps for neurobehavioral development. The kind of fish the mother eats is also very important because for instance sole has no n-3 but salmon and cod do. When speaking of allergy, it is very important that weaning be complementary, not supplementary. In southeast of Asia 78% of the mothers throw away the colostrum because the color is different, and it is very important to educate these women against throwing away the colostrum because it is the first protection against infection and disease.

Dr. Hanson: As to the colostrum, I consider that nature has after long development come up with a very specialized milk for the newborn with its very tiny stomach and a rather empty gut, which is very quickly colonized with bacteria that reach high numbers quite fast. It is an urgent matter for the baby to get as much protection as fast as possible over its large mucosal membrane surfaces, especially in the gut. I mentioned previously the very high content of the secretory antibodies in the colostrum which will likely cover the mucosa. Thus they prevent the microbes that are invading the baby’s gut from reaching the mucosa, where they could potentially cause inflammation and infection. Thus I believe that colostrum is very important. One might add
its very high content of lactoferrin with its many positive functions. It seems to have been developed to try to support the baby in a critical period when aerobic bacteria, including potentially dangerous ones, reach high numbers in the gut during the first week of life. Therefore I would avoid anything other than breast milk that might bring unknown microbes: from hospitals, their staff or contaminated foods. In many traditional societies various symbolic, often heavily contaminated foods and fluids are given to the newborn early after delivery, before anything else is given.

As to breastfeeding, as you all know 6 months is indicated as the optimal period of exclusive breastfeeding. There are good reasons for that goal, and I am aware that there are many factors that can make this difficult, for instance some mothers have to go back to work much too early. Sweden has a system which permits the mother to stay home for an extended period of time so that does not become a problem. We have to put our hope into the next generation, with better support for the mother and baby during this very important period of life. If it is possible to continue to breastfeed exclusively for 6 months, then this is favorable.

Of course I am a bit sided in this because I spent the last 45 years working on components in human milk and we just keep finding new, remarkable ones, presumably energy-expensive ones for the mother. So why are they there; for nothing? I think that human milk and especially colostrum is a very elaborate and elegant system for protection of growth and development of the human offspring. Presumably we still only understand part of it. Yet I think we can conclude that human milk really gives the baby the best chance to develop and grow optimally. So in my mind the answer to your question is easy, but I am sided although based on facts.

Dr. K. Bergmann: You mentioned something very interesting, namely that there is some protection from infections up to the age of 10, but you said most of this occurs during the first 6 months. Do you also have data on the incidence of infection beyond 1 year?

Dr. Hanson: Firstly, for certain vaccines the immune responses are enhanced by breastfeeding, for other vaccines this is not seen. Secondly, there seems to be long-term protection against certain tumors in breastfed children, as against breast cancer in mothers who have breastfed. There is also evidence to suggest protection against certain immunological diseases, like celiac disease. In addition there are reports on enhanced protection against certain infections. It should be added that such long-term studies are difficult to do and control perfectly. Still there are data to suggest that there are in some instances long-term protective effects. One could consider that many of the growth factors and multiple other signals present in human milk may be involved in such long-term effects. Clearly more research is needed.

References