Personalizing Nutrient Intakes of Formula-Fed Infants: Breast Milk as a Model

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Abstract

The growth pattern of formula-fed infants is quite different from that of breastfed infants. There may be several reasons for this difference, ranging from different endocrine responses to feeding and the presence of growth factors in breast milk to different control of food intake, but it is highly likely that differences in nutrient composition of the food (breast milk or formula) have major effects on growth. In most countries infant formula is used more or less exclusively up to 6 months of age and as part of the diet up to 12 months of age and during this period its composition remains the same. In striking contrast, the nutrient composition of breast milk changes during lactation, most dramatically during early lactation, but with pronounced differences throughout lactation for many nutrients. It is a goal that the performance of formula-fed infants should be as similar to that of breastfed infants as possible, and attempts have been made to modify the composition of infant formula to achieve this goal. However, there has been no systematic attempt to gradually change the composition of infant formula in a manner similar to the changing pattern of breast milk. This represents a technical and nutritional challenge, but is now possible.

Introduction

The concept of individualizing the nutrient intake of infants originated from feeding regimens for preterm infants. It was realized that the breast milk produced by women delivering infants prematurely was often too low in energy and protein to meet their infants’ requirements. Consequently, some milk banks started analyzing breast milk samples from women of premature infants [1] with the intent of adding a human milk fortifier to make the concentrations of energy and protein commensurate with their estimated requirements at each age.
Several studies documented improved growth of infants fed such 'improved' breast milk [2]. The task of analyzing breast milk from individual women and 'personalizing' the nutrient density of the milk fed is intensive work, even if some instruments (e.g. IR analyzers) have been developed for this purpose.

The ‘personalized’ approach of feeding preterm infants was subsequently refined to measuring the metabolic response to feeding fortified breast milk (or preterm formula). By measuring blood urea nitrogen in the infants as an indicator of protein adequacy, the feeding regimes could be adjusted on an individual basis to keep protein intake at an adequate but not excessive level [3]. This approach has also been shown to improve the growth and development of preterm infants.

It is obvious that this kind of personalized feeding strategy is unrealistic for term infants. However, as described below, there are wide discrepancies in the nutrient intakes of formula-fed infants compared to breastfed infants and new approaches are needed to lessen these differences. This, in turn, may make the growth pattern of formula-fed infants more similar to that of breastfed infants which may have long-term consequences with regard to development and chronic diseases. Instead of analyzing clinical parameters in infants as a measure of the adequacy of their nutrient intake, it may be possible to develop formulas targeted to the individual’s age and consequently to his/her nutrient requirements.

The growth pattern of formula-fed infants is quite different from that of breastfed infants [4]. There may be several reasons for this difference, ranging from different endocrine responses to feeding and the presence of growth factors in breast milk to different control of food intake, but it is highly likely that differences in nutrient composition of the food (breast milk or formula) have a major effect on growth. Infant formula is in most countries used more or less exclusively up to 6 months of age and as part of the diet up to 12 months of age and during this period its composition remains the same (although some countries also use so-called ‘follow-on’ formula). In striking contrast, the nutrient composition of breast milk changes during the lactation period, most dramatically during early lactation, but with pronounced differences throughout lactation for many nutrients.

It has been stated as a goal that the performance of formula-fed infants should be as similar to that of breastfed infants as possible, and attempts have been made to modify the composition of infant formula to achieve this goal. However, although the concept of ‘individualizing’ the nutrient intake of premature infants fed their own mothers’ milk has been used, there has been no systematic attempt to gradually change the composition of infant formula in a manner similar to the changing pattern of breast milk. This represents a technical and nutritional challenge, but is now possible. Although many bioactive components are unique to breast milk, present dairy technology allows isolation of bovine milk fractions that may at least provide some of the bioactivities of breast milk components. Addition of such components at physiologically rel-
Protein

Colostrum and milk produced during early lactation are very high in protein concentration, up to 20–30 g/l [5, 6]. Partly this is due to the low volumes being produced, but mostly due to hormonal regulation of protein synthesis. During the first month of lactation, the milk protein concentration decreases considerably, reaching levels around 9–11 g/l. These levels are then largely maintained during the entire lactation period and even after 1–2 years of lactation, which is common in developing countries, protein concentrations are around 8–10 g/l [7]. Few factors appear to affect the protein concentration of breast milk and even malnourished women produce milk with a normal protein concentration [8], even if large differences in protein intake may have short-term effects on the milk protein concentration [9].

The protein concentration of infant formula has always been considerably higher than in breast milk, in part due to the assumed lower digestibility and different amino acid composition of the formula protein source, in part to assure meeting the requirements of infants with high protein needs. During the past decades, however, there has been an overall tendency to reduce the protein level of infant formula, from the original levels of 18–20 to 15–16 g/l, and, more recently, to 12–14 g/l. Thus, the magnitude of the difference in protein level between breast milk and formula has diminished. However, combined with the higher daily volume of formula consumed by formula-fed infants (discussed below), the higher protein concentration of infant formula results in considerably higher protein intakes of formula-fed infants as compared with breastfed infants (fig. 1).

It should be noted that, with only a few exceptions, the protein level of infant formula is the same regardless whether it is fed to newborn or a 6-month-old infant. The assumed lower digestibility of infant formula proteins should be questioned; less excessive heat processing of formula and an increasing proportion of whey protein has most likely increased the digestibility of formula proteins [12]. Further, it has become more recognized that several breast milk proteins, such as lactoferrin and secretory IgA, are incompletely digested. Thus, breast milk proteins are not completely digested, in contrast to what was previously believed. Therefore, ‘digestible’ protein in infant formula is still considerably higher than that of breast milk, which is reflected by the fact that blood urea nitrogen levels of formula-fed infants are significantly higher than in breastfed infants, even when the protein level is reduced to 13 g/l [13].

The protein composition of breast milk also changes considerably during lactation [6]. In colostrum and early milk there is little or no casein, whereas
most milk-based infant formulas contain ~40% casein. Mammary gland synthesis of casein increases during early lactation so that the breast milk whey:casein ratio first reaches ~60:40 and then ~50:50 [14]. The major whey proteins in breast milk during early lactation are secretory IgA, lactoferrin and α-lactalbumin, and they are present in exceptionally high concentrations, but they remain in high concentrations throughout the lactation period. In contrast, there is very little lactoferrin and secretory IgA in infant formula, but bovine α-lactalbumin is a significant component of whey-predominant cow’s milk formula. Recently, some manufacturers have started to enrich infant formulas with bovine α-lactalbumin, primarily to achieve a more balanced amino acid composition.

Human milk is known to contain a multitude of bioactive proteins [15]. Some bioactive milk proteins may be obtained from cow’s milk and added to infant formula, provided that they can exert the same or partial bioactivity as their human milk counterparts. For example, it may be possible to isolate milk protein fractions with bovine secretory IgA, preferably from cows exposed to human pathogens, so that some immunoprotection may be achieved. Bovine lactoferrin is commercially available and even if it may not display all of the bioactivities of human lactoferrin, which in part are receptor-mediated, bacteriostatic/bactericidal activities may be similar. It has been shown that some bioactive proteins such as secretory IgA and lactoferrin can resist proteolytic digestion and be found in the stool of breastfed infants [16]. However, with increasing age, these proteins become digested and when added to infant formula it may only be worthwhile in products for younger infants. Further, such infants are also more likely to benefit from these bioactive components.
Carbohydrates

The major carbohydrate in breast milk is lactose which is synthesized in the mammary gland by lactose synthase, a complex between \( \alpha \)-lactalbumin and galactosyltransferase. In colostrum and during early lactation, the lactose concentration is relatively low, but it rapidly increases to a concentration of \( \sim 5-6 \) g/l of mature milk, and changes little thereafter. The significant remainder of the total carbohydrate content of breast milk consists of oligosaccharides, which are largely non-digestible and therefore pass through the gastrointestinal tract of infants in intact form [17]. A major part of the oligosaccharides has been found in the stool, but there is also some intestinal absorption as about 1% is found intact in the urine, as studied with stable isotopes [18]. There are numerous types of oligosaccharides in breast milk, varying from relatively simple structures like fucosyl- and sialyllactose to very complex structures [17, 19]. Many of these vary considerably in structure among individual women as they are affected by various glycosylation pathways, such as those determining the different blood groups (Lewis, ABO). Their concentrations have been shown to vary during lactation with most of them being higher in concentration during early lactation [20]. It has been estimated that there are several hundred different oligosaccharides in breast milk, and the structures of many of them have not yet been determined. Since many of these structures are similar to oligosaccharides present on the mucosal surface of the small intestine, it has been suggested that they act as soluble ‘decoys’ and bind pathogens, thereby preventing their attachment and possible invasion of the host [19]. They have also been suggested to have a prebiotic function by stimulating the growth of bacteria beneficial to the host, e.g. lactobacilli and bifidobacteria, but also discouraging the growth of pathogens [19].

It is obvious that it would be very difficult to mimic the oligosaccharide composition of breast milk when manufacturing infant formula, and very few and limited attempts have been made to add single oligosaccharides found in breast milk. An alternative approach that has been used by some manufacturers is based on the presumed prebiotic activity of breast milk oligosaccharides – by adding non-digestible carbohydrates such as fructo- and galacto-oligosaccharides (FOS and GOS, respectively) to infant formula, some of the perceived benefits of breast milk oligosaccharides, e.g. prebiotic activity, may be achieved [21].

Lipids

The triglyceride content of breast milk increases rapidly during the first week of lactation [5, 22]. Colostrum is usually very low in lipids (although the contents of fat-soluble vitamins such as vitamin A and carotenoids can be
high), early milk contains 1–2% lipids and when the milk has matured it is usually around 3.5–4.0% [5]. The individual fatty acids also change during lactation [5, 22], although this is affected by intake of lipids/fatty acids by the mothers and their energy balance. The major fatty acids in breast milk (C16, C18 and C18:1n-9) and the long-chain polyunsaturated fatty acids decrease during lactation, whereas the medium-chain fatty acids (C12 and C14) increase [5, 22]. Most infant formulas contain ~3.5% lipids and the fatty acid composition is usually tailored towards an ‘average’ breast milk composition.

Docosahexaenoic acid (DHA) and arachidonic acid (AA) have received special interest with regard to the addition of these fatty acids to infant formulas. DHA has been shown to be important for brain development (usually assessed by visual acuity) in preterm infants [23] and as breast milk from most women is substantially higher in DHA than infant formula, some manufacturers have supplemented their products for term infants with DHA. Whether DHA supplementation of infant formula is of benefit for visual acuity is still a matter of controversy, but a recent study on the increased DHA intake of infants leading to a lower BMI [24] may strengthen the argument for DHA supplementation, perhaps particularly to young term infants. The proper level of DHA to use is difficult to assess as few studies have evaluated the dose dependency of the beneficial effect of DHA and as the level of DHA in breast milk is highly variable and dependent upon maternal intake of DHA. Due to possible competition between metabolic pathways, the ratio of DHA to AA may also be an important consideration. Generally, an AA:DHA ratio of 1.5 is recommended, but there are few studies evaluating the ‘optimal’ ratio.

Most infant formulas use blends of vegetable oils in their lipid premix to achieve a fatty acid pattern similar to that of breast milk. Although there has been a trend towards avoiding milk fat in formulas due to its high content of saturated fatty acids, there may be a need to reconsider the possibility of using some milk fat. Conjugated linoleic acid has been shown to have some beneficial biological activities [25] and both breast milk and cow’s milk contain conjugated linoleic acids, whereas most infant formulas lack these fatty acids.

**Energy**

The energy density of infant formula has received little interest. Virtually all infant formulas have energy contents similar to the assumed energy density of breast milk, i.e., ~670 kcal/l. However, the energy content of breast milk changes during lactation and it has also been overestimated due to erroneous assumptions, such as all carbohydrates are digestible and breast milk proteins are efficiently digested and absorbed. Further, the volume of infant formula consumed by formula-fed infants considerably exceeds the intake of milk by breastfed infants; for example, by 3 months of age most breastfed infants consume ~800 ml/day whereas formula-fed infants have an intake of ~1,000 ml/day (with
considerable individual differences). It appears that most breastfed infants are able to regulate their intake [26], whereas formula-fed infants are less capable of doing this. With an energy density of formula higher than that of breast milk, and an intake much higher than that of breastfed infants, it is obvious that the energy intake of formula-fed infants exceeds that of breastfed infants. As shown in figure 2, the calculated (Atwater factors) energy intake of formula-fed infants exceeds that of breastfed infants by ~60–80 kcal/day. It is therefore not surprising that breastfed infants gain less weight during the first 6 months and are leaner than formula-fed infants by 1 year of age [27]. The possible long-term consequences of this difference in growth pattern and weight gain are a matter of controversy. There have been a few attempts to try to limit the intake of formula-fed infants but this has proven to be difficult. Studies on lower energy content of formula are sorely lacking and may have some difficulties with regard to ethical considerations due to the current consistency in energy content of infant formulas. However, several recent studies have shown that previous calculations of energy requirements of infants were overestimates and that ‘true’ energy requirements are ~10–30% lower than earlier believed [28]. Thus, an evaluation of the effects of lowering the energy density of formula appears logical and desirable.

**Micronutrients**

Several micronutrients which are important for infant development vary considerably in the concentration in breast milk during lactation. For example,
the zinc concentration of colostrum is ∼5–10 mg/l, whereas breast milk produced at 6 months of lactation only contains 0.3–0.5 mg/l [29]. Since infant formula contains ∼4–7 mg of zinc/l, formula-fed infants will receive about the same amount of zinc as breastfed infants during the neonatal period, but by 6 months of age they will consume more than 10 times as much. Although zinc is of particular importance during rapid growth, the prudence of such high intakes of zinc may be questioned. Similarly, the iron concentration of early milk is about 0.4–0.6 mg/l and at 6 months about 0.2 mg/l, whereas most infant formulas contain 4–12 mg of iron/l. The possibility of excessive intakes of these essential nutrients exists, particularly as they are known to compete with each other and other micronutrients for absorptive pathways. Further, in addition to iron, copper is considerably higher in infant formula than in breast milk (about 4 times), which means that the prooxidative potential of formula is much higher than that of breast milk. This may be of concern as even healthy term infants have shown evidence of oxidative stress during early infancy [30]. Since the human term infant is born with significant stores of iron and copper, and these are mobilized during early life, it may be advisable to limit the iron and copper content of formula for young infants. It is apparent that ‘individualizing’ infant formulas to specific age periods would make it possible to adjust the micronutrient concentrations to levels closer to those in breast milk at any given time during lactation, although they should always be somewhat higher than in breast milk due to their lower bioavailability from formula [31].

**Concept**

Every day, the mother/caregiver will prepare formula to feed the infant. To date, a single source of formula has been used from the early newborn period to late in infancy. If instead age-specific products were made available, it would be possible to provide the formula-fed infants with nutrient intakes corresponding to their needs at any given age. For example, there may be a ‘starter’ formula for the first 2 weeks, another one for the next month, one for 2–4 months, one for 4–6 months and one for infants older than 6 months. Not only could the nutrient composition of these formulas be tailored towards the requirements during each period, but there would be a possibility to add bioactive components during appropriate times – these components may be especially important during early life and, with regard to proteins, become digested/inactive in infants of older age. It should not be difficult to convince mothers about the biological ‘soundness’ of this approach; parents are acutely aware that their infants progress quickly through different developmental stages and will not be surprised that their nutrient needs also change.
References


Discussion

Dr. Vaarala: Are there differences in the breast milk of mothers living in a high-versus low-hygiene environment? You have done some studies in Peru, and together with Dr. Savilahti we have seen that probiotics may induce an increase in total IgA in serum and feces, and one could think that secretory IgA, for example in breast milk, may be higher in mothers living in a low-hygiene environment because the gut microbiota might stimulate IgA.

Dr. Lönnerdal: It’s quite possible but I am not aware of any such studies. What we looked at in Peru was the common belief that women who had infections produced breast milk of inferior quality and therefore should not nurse. We questioned the factual basis for that, and did studies in Peruvian women who had infections during early lactation and looked at the composition of their milk as compared to milk from women who had no infection [1]. We repeated the study in another cohort during mid-lactation when milk production was more established and found no differences in composition [2]. Their pathogen load certainly was very different, and did not affect milk composition, but that does not exclude the possibility you are referring to.

Dr. Björkstén: There is a study from the 1980s comparing milk from Swedish and Pakistani mothers and, if I recall correctly, there were surprisingly small differences in IgA levels between the two rather extreme environments.

Dr. Lönnerdal: I think there was no difference in total secretory IgA but in the specific secretory IgA levels towards certain antigens.

Dr. Björkstén: Yes, because obviously the Swedish and Pakistani mothers had been exposed to different microbes, but the total levels were similar.

Dr. Walker: The advantage of sIgA in breast milk is that it provides antibodies against microorganisms in the maternal environment which is also the infants’ environment. As you mentioned, what you see is a difference in the actual type of sIgA compared to total.

Dr. Koletzko: We have actually been discussing the staged approach in Europe for many years but so far have not found a manufacturer willing to do that. Obviously there is not a huge volume that could be used but the concept is very convincing. You pointed out the effect of heat treatment on lowering bioavailability, and you showed the data for protein and copper. Jacques Rigo has also found very similar effects in his studies of nitrogen balance on mineral bioavailability. These heat-treated products are used due to the fear of enterobacter contamination, particularly in newborn and pre-mature infants where obviously the concern about lowering bioavailability would be greatest. Should we be more careful in using heat-treated products and could UHT products play a role? I would assume they would have less of a problem.
Dr. Lönnerdal: Certainly extensive heat treatment would affect protein digestibility and as you indicated this has indirect effects on the bioavailability of several minerals. I think it is a good idea because as far as I know UHT is as efficient with regard to bacteriological quality. I don't know what it would take to change manufacturing into this direction, but we have done clinical studies on that aspect and found much better utilization of amino acids [3]. We therefore may be able to lower the protein level in formula and therefore avoid the high levels of BUN found in formula-fed infants. I think that any heat treatment that would maintain bacterial quality while minimizing heat exposure would be beneficial.

Dr. Haschke: We continuously talk about the microbiota and whether there are differences or not. I would like to mention that we tend to forget the godfather of this idea, Willy Heine from Rostock. He attended several of these workshops in the 1980s showing that the same microbiota can be achieved with a formula in which there is lactalbumin and a low protein and high whey fraction. Unfortunately he was working in the Eastern German environment and was not able to publish in proper journals. Only when he went to Houston did he finally have access to good journals in which he could show his findings. The second comment is from the industrial perspective. At present there is a push situation from science to industry to add lactoferrin and secretory IgA because science shows advantages. On the other hand I would like to point out that there must be some understanding that there is a long development process for this kind of formula because these are ingredients which need to be approved by regulatory agencies, the Food and Drug Administration or European Food Safety Association (EFSA), and that requires long-term clinical trials, even from two centers, on safety and then on efficacy, and then come the regulatory hurdles. Even if a company could be convinced that these ingredients should be in, it will take time. I already had the same reaction when we discussed this one year ago in Vietnam at another workshop. You showed a difference between breastfeeding and formula feeding in terms of intake. Do you really think it is only the formula? There are so many variables: the attitude; the mode of breastfeeding; if the baby cries then it is taken to the breast which only takes few seconds, whereas if the baby starts to cry the mother has to prepare the formula fresh if the rules are followed, she has to get up in the night and go to the kitchen. Has anybody looked at these factors which provide so much inconvenience. If formula-fed infants are fed more often, really on demand, couldn't the same pattern be achieved?

Dr. Lönnerdal: It is a very complex issue and we have also done some studies showing self-regulation by the breastfed infant [4]. Thus, even if the breastfed infant has more milk available it will not take it. We don't know why; it is most likely some neuroendocrine regulation that is occurring. I think that for a formula-fed infant part of it is parental control, part of it may even be easy access. There are preliminary studies showing that when smaller holes in the nipple of the bottle are used, the infant is forced to fight for the content and intake will be reduced.

Dr. Salminen: I just wanted to comment on the idea knowing a little bit about the EFSA side: it really is a long process and we are dealing with the most well-regulated and safeguarded part in our food supply when we talk about infant formula. As I look at the process once you are ready with your scientific discovery, it will probably still take 2 years to get on the ingredient list, to have the scientific opinions of the EFSA panel, and to have the commission approve your ingredients. So we are really talking about a long-term process unless you have something that is immediately lifesaving and could actually go faster.

Dr. Lönnerdal: You are correct and I believe formulas should be tightly regulated. However, we should not give up. It is a long process and we have to set our goals which I think have been fairly modest previously; we need to raise that barrier a little bit higher.
Dr. Bier: I wanted to come back to the stepwise issue. Putting aside the study Dr. Koletzko told us about the other day about the effect on weight, what should be measured to know that this makes any difference at all and how long is it going to take us to find that out? I don't have an immediate end point at which I will know whether that is going to make a difference or not. By enlarge for the formula-fed infants you may be showing us a mean or average intake; for the breastfed infant we take that as a requirement level but really it is not a generous requirement, it is a marginal requirement level. So if we look at populations and there is a child whose protein requirements are on the high end and we start stepping down, what is the public health perspective of that? How do we even know? What do we use to tell us that this has any human beneficial effect?

Dr. Lönnerdal: That's why I think this workshop has been very stimulating. We have to use new approaches to measure outcomes which I did not have time to discuss here. What you are saying may be correct but what happens if you have a breastfed infant who has a high protein requirement and a mother producing a low protein breast milk – what is the consequence for that infant? There have been very few studies on individual infants who were followed by analyzing the diet of that particular infant. This could now be combined with some metabolomic approaches to study how each infant responds metabolically. It has always been thought that the breastfed infant just meets its requirements but not much more. How much evidence do we have for that? I believe that if breastfed infants are that close to meeting their requirements, wouldn't we see a whole lot of breastfed infants having nutritional problems?

Dr. Bier: I guess some people would say we really don't know that answer either. Let's look at this from the other perspective of requirements. If someone came into the nutrition community and said, I am going to make all my nutrition recommendations on the basis of the estimated average requirement for all the other nutrients at age 15, we would have 10,000 nutrition scientists stand up and say, what are you crazy. So here we are saying this in some ways for the newborn. I don't know the answer to this but it just seems to me that there are inconsistencies here, that we have great unknowns about that.

Dr. Hernell: I was actually thinking along the same lines. In Sweden we used to have two and even three formulas during the first 6 months, and the change in breast milk is of course a continuum. So what would you envision if we turned back and again had more formulas; how many would you suggest during the first 6 months?

Dr. Lönnerdal: More than two perhaps. I have talked to many formula manufacturers and it has always been said that the mother is not ready for such an 'educated' message. I don't think that it is true because any mother knows that a newborn baby is not the same as a 1-month-old baby, or as a 3-month-old baby, and it would not be difficult to understand the nutrient requirements and physiological needs do change with age and that you need to change the infant's diet. How many products that are practically possible will be up to the formula industry, but I still think that any step to make them more diversified and more fit to their needs would be a step forward. We actually did a study in Taiwan in which we used a staged approach and in our publications we documented benefits with regard to metabolic responses [5, 6].

Dr. Isolauri: Going back to the discussion on microbes and probiotics we had at the beginning, our early data in diarrhea patients, rotavirus diarrhea patients, and vaccine studies as well as in milk-allergic children showed that the enhancement of IgA as assessed by the Elispot method was also antigen-specific and transient. Interestingly then the experimental data showed that the effect was also related to the formula we were using. So we do not achieve the same effects on immunostimulation in formula-fed children that we see in breastfed babies, and also there are differences in the effects if we give children hydrolyzed protein or unmodified milk protein. Therefore
these effects are strain-specific but depend on the host and the food matrix as well. Finally, in your slide two breast milk oligosaccharides are listed: galacto-oligosaccharides and fructo-oligosaccharides. Is it correct, or what is the justification for listing fructo-oligosaccharides as breast milk oligosaccharides?

Dr. Lönnerdal: I think that’s a mistake, I did not show that fructo- and galacto-oligosaccharides are in breast milk. Those are the ones being used in formula in an attempt to achieve the prebiotic effect of the human milk oligosaccharides. As far as I know those are not in breast milk.

Dr. Brandtzaeg: I would like to come back to the possibility of adding secretory IgA to the formulas as you mentioned. In my opinion, it can never be achieved with the broad range of antibodies that occur in breast milk, reflecting both the antigen exposure of the mother’s mucous membranes in the airways and the gut. There were many attempts to elicit secretory IgA antibodies in cow’s milk 20 years ago. Of course that was against a selective antigen used for local immunization, a special bacteria or pathogen. In the end it was deemed to be unethical because of the need for complete Freund’s adjuvant with oil and mycobacteria which gave rise to terrible abscesses in the cow’s udder. So that was stopped for ethical reasons. Perhaps you could use serum IgG instead of secretory IgA antibodies. But as you mentioned, IgG is easily degraded in the gut lumen. However, perhaps it is not so much of a problem at the beginning, in the first postnatal weeks, so that is one realistic option. But, nevertheless, I think there is a lot of information coming up now that the individualized spectrum antibodies provided by breast milk are needed because there are receptors for IgA on the lymphoid tissue in the gut which will guide the mother’s IgA back to the baby’s immune system and thus actually introduce the right antigens to the developing immune system to stimulate a homeostatic immune response as part of the tolerance mechanisms. So in this way secretory IgA in breast milk actually is a sort of link between the mother and the developing infant’s immune system to direct the immune responses in the gut-associated lymphoid tissue.

Dr. Lönnerdal: I have never believed that any type of produced secretory IgA would have the functions of the breast milk secretory IgA, but I have heard that there are companies producing bovine secretory IgA which they obtained by exposing the cows to a cocktail of pathogens that many human infants are exposed to. I don’t know how far they have come, but serious attempts are going on and it may be possible that a small part of the functional secretory IgA in breast milk could be copied by that approach.

Dr. Brandtzaeg: As you mentioned, this disappeared from the literature for ethical reasons.

Dr. Isolauri: This kind of hyper-immune milk is used for instance in intensive care to reduce the risk of clostridium infections.

Dr. Brandtzaeg: But that is mainly based on IgG.

Dr. Venter: Why isn’t any eicosapentaenoic acid (EPA) added to infant formulas? They all contain arachidonic acid (AA) and docosahexaenoic acid but there is no EPA.

Dr. Koletzko: In fact the EPA content in formula is limited both in the European legislation and in the guidance provided by the Codex Alimentarius Commission that was adopted this summer. The guidance is given that a formula should not contain high amounts of EPA because EPA is not found in breast milk in appreciable amounts, only in very small amounts, and it is not found in infant tissues. There is some concern that EPA acts as a metabolic competitor with AA, and as Dr. Isolauri raised the other day AA is not only bad but it has important biological functions. Some of the early studies in preterm infants have reported that formula with a high EPA content was associated with reduced infant growth. So unless that is resolved there is caution about adding high amounts of EPA.
Dr. Michaelsen: Dr. Bier asked about what to measure and I would suggest that IGF1 would be interesting to measure, at least at the group level. We have data where we looked at IGF1 during the first year compared to IGF1 at 7 years of age and there is a reverse relation. It seems that there is a programming of the IGF1 axis where breastfed infants have low values while they are breastfed and then higher values later on. There are a few studies suggesting that breastfed infants are taller as adults and somehow this fits to the whole hypothesis of the relation between early growth velocity and later disease. We could not get immediate responses on what it means in the long-term, but I think it is fascinating to look at this programming of IGF1 as well.

Dr. Lönnerdal: I think it is a very good idea. Clinical studies evaluating changes in infant formula composition should look at response factors. IGF1 is certainly one, and if we use proteomic or genomic approaches we could follow a wider array because to date most clinical studies have followed very few parameters. It will be nice when a much wider array of biomarkers can be used in clinical studies.

Dr. Saavedra: This was a great presentation of the multiple things that we obviously need to start thinking about. From a historical perspective we have improved these alternatives to breast milk substitutes principally by a process of trial and error. For example, we found that cow casein caused problems in formula, so it was decreased because even though there is a lot of casein in human milk casein, the cow casein is very different. We knew that we needed to given iron and found that if we gave the same amount of iron in breast milk this led to many anemic babies, so we had to increase the levels. Then we recognized the antigenecity of cow's milk, so we tried to bring it down. In the end, what we are really doing is finding ways to decrease the complications that come from not exclusive breastfeeding. I think a better paradigm would probably be to try to get compositionally ‘closer’ to breast milk, but rather, we should work on getting functionally closer to breast milk, that is, causing less complications in children who aren’t exclusively breastfed. For example, we need to decrease the metabolic and immunologic complications that come from not exclusively breastfeeding, and if we focus on understanding those implications, both the metabolic and immunologic ones which are the bigger ones, then we have something to fix. We then have a reason to go after all these interesting potential ingredients, but not simply adding ingredients because they happen to be in breast milk. We would be adding things like EPA and cholesterol if that was the case (just because ‘they are in breast milk’). Does that make sense?

Dr. Lönnerdal: It makes sense but I am not sure I like it. It seems more to be a reactive approach than a proactive approach and to kind of find out when something is wrong we need to fix it. I would like to reemphasize that we cannot use breast milk as a perfect model, but I still think we can use it as a goal for several nutrients, but not all of them.

Dr. Saavedra: The only answer I would have is that until we know what the issues are, it is just going to be very hard to try to copy.

Dr. Gluckman: We know increasingly from experimental work in rats that short periods of changes in nutrition during lactation can have enormous effects on the offspring in the long-term. The issue that does crop up is that of fine tuning the match between nutritional requirements at different stages during what is a very long lactation cycle in relationship to the time of human development and the need of the organism. I don’t know how we address that because this is limited to what you clinical people can do in terms of studying human beings and making interpretations. Do you have a view as to which if any of the various animal species is useful for studying these questions? Whether epigenetics or other biomarkers are used to address these questions, animal models could play a large role if there was an animal model that could be found useful.
**Dr. Lönnerdal:** Excellent question, and I think my response would be that for each individual nutrient or group of nutrients and for each developmental stage there may be a good animal model. For example, we have documented that when it comes to iron we have been able to replicate findings from human infants in rat pups. For example, we have done radioisotope studies in rat pups and found very similar results to those obtained from stable isotope studies in human infants at corresponding developmental stages. I think that animal models, such as piglets or rat pups, can be very valuable, but they need to be validated.

**Dr. Gluckman:** You focused largely on micronutrients and immune-related substances. There is increasing interest in hormones and other factors in milk. To what extent has it been looked at systematically in human versus other milk? Formula has very low levels of IGF1 and IGF2 and human milk has quite significant levels of IGF1 and IGF2, and there are the issues of leptin and prolactin, particularly in early milk.

**Dr. Lönnerdal:** It is possible that rodent models may be less valid for studying hormones and growth factors. However, Park et al. [7] have done very interesting studies on IGF1, and IGF-binding proteins in the piglet model and for those the piglet seems to be a valid model. As I stated before, for each group of compounds or nutrients, the appropriateness of the animal model chosen must be taken into consideration.

**Dr. Gluckman:** I really wasn’t asking a question in relation to animal models, I wanted to know to what extent are those of you who are interested in human formula design thinking about the issues of the small bioactive? For example there is literature on IGF1 and IGF2 in terms of gut maturation in particular. The other point I would like to raise is the one about bottle-fed babies drinking more than breastfed babies; this intrigues me because the issue of what creates satiety in an infant is something we do need to understand more about. There is growing comparative literature on the ratio or sources of energy in setting satiety, in other words whether it is from protein or carbohydrates or from lipids. It would be interesting to know whether the ratios of energy sources are different between breastfed and formula-fed infants because it could be anticipated that if there is an altered ratio favoring the non-protein energy sources as a ratio, not as an absolute amount, the food volume intake would tend to be greater.

**Dr. Haschke:** We know that during the breastfeeding protein is initially high; at the end fat is higher, so this probably answers your question.

**References**
