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Innovations in Infant Milk Feeding: From the Past to the Future

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Abstract

Innovation is important for life science and economy, but the value of innovation for public health depends on its impact on promoting health. Breastfeeding is not innovative but evolved slowly over 250–300 million years, yet its total benefits are not surpassed by more innovative ways of infant feeding. Until the 19th century, infants fed inadequate breast milk substitutes suffered from high mortality. In 1865 a major improvement was von Liebig's 'soup for infants', the first breast milk substitute based on chemical human milk analysis, soon followed by commercial applications. Other early innovations include whey protein-dominant formula, addition of specific carbohydrates to promote bifidobacteria ('prebiotic') and of live bacteria ('probiotic'), predecessors of apparently recent innovations. Opportunities for innovations exist since many outcomes in formula-fed infants do not match those in breastfed populations. Of concern, expected economic benefits through innovations may override scientific arguments. Business and marketing desires must be counterbalanced by independent pediatric and scientific evaluation. Developing innovations with relevant outcome effects is complex, costly and cannot be expected to occur every few years. Cooperation between academic investigators, small and medium enterprises with high innovative potential, and large industries promotes progress and should be facilitated, e.g. by public research funding.

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The term 'innovation' – derived from the Latin word *innovare* meaning to renew – refers to creating and implementing new ways of doing something. Innovation usually refers to making something better in thinking, research and development, products, services or processes, methods of production (e.g. more cost effective, or with lesser environmental burdens), or organizations. Innovation encompasses not only the creative development of new ideas but also implementing positive changes (diffusion). Interest in innovation is very

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much focused on its economic implications ever since Joseph A. Schumpeter one century ago described innovation as a key driver of the economy [1]. In particular, Schumpeter considered innovation leading to increased productivity (e.g. changing transporting goods from using stage coaches to railways) as the fundamental source of increasing wealth in an economy. Until today, public policy makers aim at boosting innovation which is considered critical to support sustainable economic growth, employment and prosperity, as reflected for example in the 'Strategy for American Innovation' recently published by the President of the USA [2].

Human Lactation – Slow Evolution rather than Rapid Innovation

Innovation is also of paramount importance for life science research and discovery, as well as for improving standards of healthcare and health promotion. However, for public health promotion generally, and for infant nutrition specifically, innovation is not a goal by itself but its value depends on the impact on maintaining and improving health and well-being of infants and their families. Breastfeeding, which is strongly recommended as the preferred mode of infant feeding [3], is not innovative at all from the perspective of a human lifetime. Nonetheless, breastfeeding is not only the natural way of feeding for countless generations of our species, but it also provides demonstrable benefits for both mother and child. For example, breastfeeding enhances regression of maternal fat deposits accumulated during pregnancy, and it reduces the child's risks of early infections, of immunologically mediated diseases in later life such as celiac disease or type 1 diabetes, and of later obesity and associated metabolic and health risks [3–6].

The evolution of lactation and milk feeding evolved very slowly over perhaps some 250–300 million years [7]. Mammalian ancestors apparently produced eggs that were not rigidly calcified but had a permeable shell and thus were prone to desiccation; they could absorb moisture and utilize supplemental sources of liquid water [8]. Early synapsid animals may have buried eggs in moist ground or incubated eggs in a pouch to minimize egg water loss, but these strategies would have exposed eggs to predators or would have limited maternal activity, respectively. Oftedal [8] concluded that mammary secretions originally evolved as an alternative means of supplying water to eggs from cutaneous glands and only later to also provide organic components that supplemented offspring nutrition. Blackburn and Murphy [9] described that these ancestral cutaneous gland secretions also provided antimicrobial properties which protected both the eggs and the hatchlings. During further evolution, the modification of ventral thoracic-abdominal epidermal glands to form the mammary gland was associated with large diversity in milk composition and function, related to factors such as conditions of reproduction, length of lactation and growth patterns of different species [10]. Based on studies of existing

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mammalian orders, Goldman [11] concluded that variation of anti-inflammatory and immunomodulating agents in milk such as immunoglobulins, iron-binding proteins, lysozyme, oligosaccharides, and leukocytes serves to compensate for different developmental delays in early postnatal production of antimicrobial factors among various species. The types or concentrations of immunological agents in milk appear to vary depending upon the type of placenta, lactation pattern, and environment of the species, and respective specific evolutionary strategies appear to have been followed. Similarly, the evolutionary development of highly nutritious milks shows a very variable pattern with regard to mammary gland anatomy, milk output, nutrient content, length of lactation, and relative contributions of lactation to offspring nutrition.

Insights from recent genome studies support the concept that lactation has evolved to minimize the energy cost to the dam while maximizing survival of the neonate, thus promoting survival of the maternal-offspring pair. The analysis of the bovine and six other mammalian genomes [human, dog, mouse and rat (eutherians), opossum (marsupial) and platypus (monotreme)] showed that milk and mammary genes were more conserved and seemed to evolve more slowly than others in the bovine genome, despite selective breeding for milk production [12]. The most divergent proteins in the lactome were those with nutritional or immunological attributes. Thus, continued selection of these genes seems to have occurred, presumably to meet nutritional and pathogen challenges in diverse environments and reflecting different conditions of reproduction. The most conserved genes were those for proteins of the milk fat globule membrane, supporting a key role for milk fat secretion.

It is tempting to speculate that the evolutionary success of mammals compared to other species, in spite of the high metabolic costs of lactation, may have resulted not only from the nutritional and antimicrobial properties of milk, but also from the extended period of contact between mothers and their young [13]. The regular and frequent transfer of milk that is particularly characteristic for primates affords the offspring the opportunity for more learning and the eventual development of the levels of intelligence present in higher primates such as humans. Thus, lactation provides for enhanced prospects for maternal stimulating effects on development and on the eventual phenotype of the offspring, in addition to those that occur during pregnancy or from other behavioral interactions.

In conclusion, the preferred mode of early feeding for our species is not the result of rapid innovation but of slow and continuous evolutionary processes adapted to the conditions of reproduction, growth and environment. While new areas of vulnerability may arise from the discordance between the slow evolutionary adaption of human genome and related biological characteristics such as human lactation, relative to the rapid change of our environment and conditions of life within the last century [14, 15], there are no indications that the totality of benefits of breastfeeding would be surpassed by any more innovative ways of infant feeding.

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Development of Breast Milk Substitutes: Some Early Innovations and Their Commercial Application

Until at least the late 19th century, breastfeeding was the only reasonable choice for infant feeding. If infants could not be breastfed by their mothers the only good alternative was a wet nurse, as promoted already by the Persian philosopher and medicus Avicenna (985–1036): 'Breast milk is the best for the child... Is the mother prevented from breastfeeding, the wet nurse should be between 25 and 35 years of age, healthy, of good and honorable manners, and having given birth 1 1/2 to 2 months before' [16]. Some centuries later, wet nursing had become very popular in populations who could afford to pay for it. Of the 21,000 infants born in Paris, France in the year 1780, some 17,000 are said to have been fed by wet nurses, and around the same time some 4,000–5,000 wet nurses were employed in the city of Hamburg, Germany [17].

Industrialization during the 19th century led to a rapidly growing urban working class in many European countries, which was associated with a marked decline of breastfeeding because many mothers had to accept paid work to support their families. Infants not breastfed were fed goats' milk or milks of other animals, or a large variety of different preparations made with cereals, sugars, honey or other sources [18]. In 1853, not less than 68 different formulations for infant feeding were recommended in Germany [18]. This large variety suggests that none of them was satisfactory. In fact, infants fed according to such concepts suffered from an extremely high mortality that was about sevenfold higher than in breastfed infants (table 1). These deaths were frequently caused by gastrointestinal infection with severe dehydration, following the feeding of inadequate preparations with high renal molar load reducing the tolerance to water loss.

There were enormous challenges in developing breast milk substitutes (BMS) of reasonable safety and nutritional quality. A major innovative step towards this goal was the 'soup for infants' created in 1865 by Justus von Liebig (1803–1873), Professor of chemistry at the universities of Giessen and later Munich, Germany [19]. In his attempts to find a feeding option for two of his grandchildren who were not breastfed, he developed for the first time a BMS based on the chemical analysis of human milk composition performed in his laboratory. The formulation based on cows' milk, wheat flour, malt and potash (potassium carbonate) proved to be a major step forward, worked well, became popular, and very soon led to commercial applications. Already in 1867, Heinrich Nestle who was born and trained as a pharmacist in Frankfurt/Main (close to Giessen) marketed his *'Kindermehl'* ('children's flour') in Vevey, Switzerland [18]. It followed a similar concept as von Liebig's preparation, but achieved much wider popularity and was a great commercial success, which built the foundations of what later developed into a successful global enterprise (now Nestlé Nutrition).

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Table 1. Deaths per 10,000 infants up to the age of 10 months in 1885 in Germany by mode of feeding and maternal marital status (a marker of socioeconomic status)

Age months	Mother married		Mother unmarried	
	breastfed	animal milk	breastfed	animal milk
0	196	1,028	267	1,252
1	76	580	143	915
2	64	544	63	887
3	58	478	75	801
4	49	441	46	720
5	44	424	31	525
6	42	444	80	417
7	47	325	26	389
8	50	282	38	363
9	47	259	45	260
10	59	218	81	276
Total mortality, %	7.3	46.4	8.5	68.1

The high morbidity and mortality in infants not breastfed was a strong drive to improve BMS. Compiled by Prof. Arthur Schlossmann; from the collection of the Children's Hospital, University of Düsseldorf, Germany.

A few further examples of innovations and commercial applications in this area are summarized here (table 2). The author chose a number of examples from Germany because these are familiar to him, but analogous developments also occurred in other parts of the world [20, 21].

In the 1880s, attempts were made to decrease the poorly tolerated casein in cow's milk, for example by treatment with pancreatic extracts. Twenty years after von Liebig's development, in 1885 Alexander Backhaus, Professor of agriculture at Göttingen, Germany, introduced a further major innovation. In his formulation, casein was digested, and remaining casein precipitated and removed to produce a whey protein-dominant formula, which was well tolerated [18]. Apparently, he was not only a scientist but also a talented entrepreneur. In Berlin, he opened a laboratory to analyze milks made according to his recipe, the *'Nutricia-Zentrale'*. In 1896, he sold the rights both for this formulation and for the name 'Nutricia' to Martinus van der Hagen in the Netherlands, who opened his company Nutricia (now Danone Baby Nutrition) in 1901 and produced products following the 'Backhaus method' [22].

In the 19th and early 20th centuries, infant formulations acidified by bacterial fermentation became popular with the aim to enhance tolerance and to reduce infectious risk, such as the widely used *Eiweissmilch* developed by the pediatricians Finkelstein and Meyer in Berlin in 1910 [23]. These formulations were predecessors of the fermented formulae in use today [24].

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Table 2. Examples of nutritional innovations in infant formulae introduced in the 19th and 20th centuries

Innovation	Key goals/endpoints	Documented effects on biochemical or other biomarkers	Documented effects on clinical endpoints
'Soup for infants', formula composition based on chemical analysis of human milk composition [18]	Improved tolerance, support of adequate growth, reduction in morbidity and mortality	+	+
Reduced casein, increased whey-to-casein ratio [18]	Improved tolerance, adequate amino acid supply	+	?
Addition of micronutrients (e.g. vitamins) [43; 46]	Nutrient supply securing metabolic requirements, prevention of deficiency	+	+/?
Fermented, acidified milks [23; 24]	Improved tolerance, reduced infection risks	+	(+)/?
Addition of lactose [25; 26] and oligosaccharides	Softer stools, enhanced growth of bifidobacteria, modulation of infection risk and immune response	+	+/(+)
Addition of lactic acid-producing bacteria later various probiotic bacteria [29]	Benefits for digestion, modulation of infection risk and immune response	+	(+)
Replacement of butterfat by vegetable oils [43]	Improved fat and calcium absorption, softer stools	+	+
Infant and follow-on formula [43]	Supply adapted to different age-related needs	+	+/(?)
Formula content of various substances found in human milk (e.g. taurine, nucleotides, lutein, gangliosides, TGF-β, and others) [43]	Formula closer to human milk	+	?/(+)

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Protein hydrolysates [47; 48]	Prevention of eczema, improved formula tolerance	+	+
Addition of LC-PUFA [49]	Benefits for visual function, cognitive outcomes, immune response	+	+/(+)
Reduction of formula protein content [50]	Normal weight gain (relative to breastfed populations), potential risk reduction for later overweight/diseases	+	(+)

LC-PUFA = Long-chain polyunsaturated fatty acid.

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The driver of a commercial innovation was the inability of the wife of the Bavarian gingerbread baker Joseph Hipp in Pfaffenhofen, Germany, to breastfeed her twin babies. This prompted her husband in 1899 to produce in his pastry shop a rusk flour that was mixed with cows' milk to feed the infants. Some 20 years later, his son sold 'Hipp's rusk flour' successfully to customers in the nearby city of Munich, which laid the basis for the Hipp baby food company. Following the same concept, the rusk baker Emil Pauly produced 'Pauly's nourishment' since 1930 under the company name Milupa (an acronym developed from letters of his name) in Friedrichsdorf, Germany (now part of Danone Baby Nutrition).

The concept of prebiotic effects of infant feeding was developed by the pediatrician Günther Malyoth from the Hauner Children's Hospital at the University of Munich in the 1930s. He achieved enhanced growth of bifidobacteria in infant stools by providing a lactose-based sugar preparation [25, 26], a predecessor of later products with added prebiotic oligosaccharides [27]. Malyoth's sugar preparation and a matching infant formula were produced commercially under the brand name *Alete*, that he had also created, by Allgäuer Alpenmilch (now part of Nestlé Nutrition).

As a further early innovation, Johann Baptist Mayer proposed in 1948 the concept of benefits of live bacteria in infant feeds, and he developed an infant formula with added lactic acid producing bacteria that achieved modification of the infant stool flora [28], a predecessor of current probiotic formula concepts [29].

This brief review of some early concepts indicates that a number of apparently recent innovations in infant feeding are actually following concepts that were developed already many decades ago. Translation of a number of innovative concepts arising from academia occurred in commercial applications, and some of the key factors that drive innovation in this area today (table 3) are detectable also throughout the last 150 years.

Innovations in Infant Formula – Lessons Learnt

Infant formula – like breast milk – must be suitable to serve as the sole source of nutrients for several months during a critical phase of rapid growth and development, and thus must meet very high quality standards. Over the last 1 1/2 centuries, a large number of major and minor modifications of infant formulae have been implemented, which have led to the current availability of high-quality BMS providing good nutrition to healthy babies. In addition to some of the nutritional innovations (table 2), perhaps refinements in securing the quality of raw materials used and in production technology may have been at least of equal importance in improving the quality and safety of products.

Nutritional innovations appear to have been driven by a variety of factors, including the identification of an apparent problem or deficit, the current state

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Table 3. Some driving factors for innovation of BMS (BMS/infant formulae)

Progress in scientific knowledge on human milk composition
Progress in scientific knowledge on human lactation and infant physiology
Achieving a composition of BMS that is closer to breast milk
Achieving a BMS composition with effects in recipient infants considered closer to populations of breastfed babies
Availability, relative effects and cost of dietary versus non-dietary approaches to achieve effects in infants that are considered beneficial
Expectations and needs of recipient infants' families and society
Expectations and needs of the scientific community and of health care practitioners
State of the art of preclinical evaluation of novel BMS
State of the art of clinical trials on novel BMS
Availability and validation of suitable biomarkers
Conditions of the regulatory environment
Conditions and costs of development, including the evaluation of suitability, benefits and safety
Cost of raw materials, production, packaging and distribution
Progress in technology of food and ingredient production
Competitive advantages, in particular if protected by patents
Competitive environment, strategies and success of competitors
Opportunities for securing nutrition and health claims
Marketing decisions
Business decisions (e.g. capability for long-term investments, time expected for return of investment into research and development)

of scientific knowledge and technology, the desire to achieve a composition that is closer to the composition of human milk, the aim to achieve functional or health benefits in the recipient infants which may attenuate the gap in outcomes between breastfed and formula-fed populations, and others (table 3).

It was a major step forward when human milk analysis was first used as guidance for designing macronutrient composition of BMS by von Liebig in 1865 [19], which has been adopted by many others thereafter. Until today, better understanding of the composition and functional properties of human milk of healthy, well-nourished women and of the physiology of lactation can provide valuable guidance for the development of modified infant formulae and follow-on formulae. However, compositional similarity of BMS to human milk composition by itself is not an adequate determinant or indicator of the suitability, nutritional adequacy and safety for infants [30, 31]. One important limitation for simply copying human milk is that breast milk composition is highly variable, because contents of many nutrients change during lactation,

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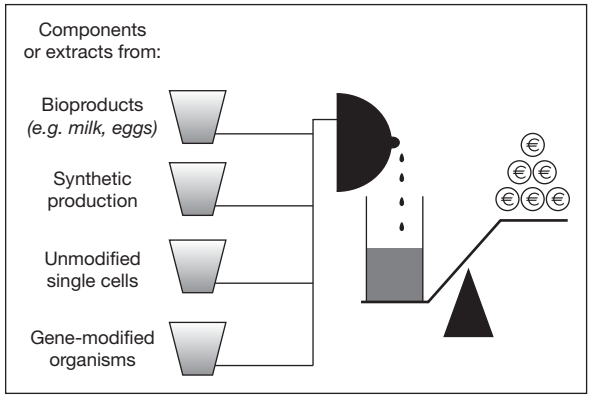

Fig. 1. Progress in food and biotechnology may make it feasible to potentially add a large number of components found in human milk to formulae, but such formulae could easily become extremely expensive. Hence, prioritization based on achievable benefits is essential. Modified from Koletzko [36].

throughout the day, within each feeding, and among women [32–35]. In addition, the bioavailability and metabolic effects of similar contents of many specific nutrients in human milk and in BMS, respectively, are rather different. Therefore, the similarity of some compositional aspects of infant formula to samples of human milk on its own does not allow conclusions on the suitability and safety for infant feeding. Moreover, in some cases clear deviation from the compositional model of human milk can provide benefits to the recipient infants, for example a far higher iron content in formula to compensate for lower absorption and improve infant iron status, or the use of protein hydrolysates to reduce the risk of atopic eczema.

In the 21st century, progress in food and biotechnology may make it feasible to potentially add a large number of components found in human milk to infant formulae, but such formulae could easily become so expensive that they would need to be weighed in gold, and hence be unaffordable [36] (fig. 1). Therefore, prioritization of promising innovations is essential. Moreover, the occurrence of a substance in human milk alone is not considered a satisfactory justification for adding it to infant formula. For example, taurine has been added to infant formula for many decades because it was found in human milk, there were some physiologic concepts that made an addition appear potentially beneficial, and because the existing patent protection made the addition profitable to some. Many decades later we are confident that taurine addition to formula is safe but we really still do not know what clinical benefits it might provide to healthy infants. Similarly, for other components such as nucleotides, lutein, gangliosides and others, the extent of relevant benefits on clinical endpoints have not been demonstrated.

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The promise of economic benefit from innovations, exploitation of protected intellectual property and potential marketing advantages over competitors, with direct or indirect messages indicating 'now closer to human milk', may sometimes be much more powerful in driving decisions on formulations of infant formula than scientific or medical arguments [37]. Applbaum [38] recently proposed – with respect to the pharmaceutical industry – that marketing has become an enemy of true innovation due to its ascendancy throughout the pharmaceutical industry, and in particular due to the integration of marketing efforts with the formerly semiautonomous research and development divisions. The classical concept that marketing follows the process of research and development appears not to hold true any more. Rather, marketers often seem to have a strong influence on decision making in research and development [38]. While this may be quite legitimate from a business perspective, it is also problematic because what is meaningful to marketers may be meaningless to science and public health. Medical and scientific value relates to being able to explain biological phenomena and then apply this knowledge to improving human health and well-being, whereas marketing value is measured by its ability to achieve product differentiation, making a product appear unique in the marketplace and superior to those of one's competitors [38]. Therefore, business and marketing desires with regard to modifications of infant feeding need to be tested and counterbalanced by independent pediatric and scientific evaluation. Direct consumer marketing of any foods serving as a partial or total replacement for breast milk, such as public advertising, is not accepted by the World Health Organisation Code of Marketing [39] and should be rejected by the pediatric community and other health care professionals.

Evaluating the Suitability, Benefits and Safety of Infant Formula Innovations

While innovation typically adds value, innovation may also have negative effects such as increasing price and making a product such as infant formula less affordable to some populations. Moreover, any change from an established and well-proven practice may carry risk. For example, in 1978 and 1979 two infant formulae were introduced into the market in the USA which were deficient in chloride and led to development of hypochloremic metabolic alkalosis and growth faltering in a number of recipient children, as well as some degree of impairment in mathematical and language skills in later childhood [40]. In 2003, a soy protein formula produced specifically for the Israeli market to meet Kosher specifications was thiamine deficient, which led to lactate acidosis and encephalopathy in a number of infants and two deaths [41]. Twenty children who were exposed to the thiamine-deficient formula in infancy were examined at a mean age of 32 months and showed abnormalities in language and mental development [42].

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These examples show that apparently minor changes in formula design can have severe short- and long-term consequences. Therefore, there is agreement in the international scientific and pediatric community that formulation of dietary products for infants must be based on sound medical and nutritional principles, and infant and follow-on formulae must by demonstrated by scientific evidence to be safe and beneficial in meeting the particular nutritional requirements of the target group and to promote their normal growth and development [30, 31, 43, 44].

While human milk composition may provide some general guidance, gross compositional similarity of formulae with human milk samples do not indicate suitability or safety. Rather, infant formula should be evaluated based on the comparison of physiological (e.g. growth patterns), biochemical (e.g. plasma markers) and functional (e.g. immune response) outcomes in infants fed formulae with those in infant populations fully breastfed for 4 to 6 months [30, 31, 43, 44].

Infant formulae and follow-on formulae generally should only contain components in amounts that serve a nutritional purpose or other benefit. Documented safety of ingredients in specific amounts in adults or older children does not by itself establish safety in infants. Guidance on the recommended approach to evaluating suitability and safety has been published, and it is agreed among the international scientific community that premarketing authorization of modified infant and follow-on formulae by an independent scientific panel is required [30, 31, 43, 44].

Future Challenges and Opportunities

Current infant formulae and follow-on formulae appear generally adequate and safe, but many outcomes of formula-fed infants are not equal to those of breastfed populations. Therefore, opportunity to further improve formula feeding of infants exists. The development of modifications with documented effects on outcomes – according to current scientific and ethical standards – is a complex and difficult task that requires a long time period of research as well as preclinical and clinical evaluation, with a considerable risk of failure with each novel approach. Therefore, it is unreasonable to expect that innovations of relevance for infants and their families will occur again and again in intervals of just a few years. Of concern, the level of complexity reached for both development of innovations and for their evaluation according to current standards now typically requires very high investments, which usually can only be absorbed by large, multinational companies. Such large amounts may only be invested by a company that has an opportunity for patent protection of the particular modification, but this limits the innovative potential for child health. In contrast, academic organizations or small and medium-scale companies with a high innovative potential may hardly have a chance today to

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move major developments forward on their own. Thus, it is highly important to facilitate cooperation between academic investigators, small and medium enterprises, and large industries to promote progress towards enhancing child health and well-being. For example, the European Community research funding schemes puts particular emphasis on such collaborative research and development to enhance the likelihood that creative ideas can transformed into application. An example of such a successful multidisciplinary research collaboration is the European Early Nutrition Programming Project which develops new physiological insights and strategies, performs clinical evaluation of dietary interventions in pregnancy and infancy, and explores new concepts and ingredients including the use of recombinant proteins in infant feeding [45]. Such programs supporting collaborative research under public guidance on priorities and standards should be continued and enhanced to promote child health and well-being, to attenuate the gap in relevant clinical outcomes of breastfed and formula-fed infants, and to also produce affordable quality products for infant feeding that are accessible to less privileged populations.

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Discussion

Dr. Haschke: You stated in your presentation that public health is not related to innovation. I would address this in particular because I think it is related to innovation; it's not always the product innovation, it's innovation between the things, it's innovation in communication and product innovation.

Dr. B. Koletzko: I couldn't agree more with you. Clearly, yes, innovation is important to secure and enhance the quality of health care and of public health, and to make it affordable for broad populations. Perhaps I was not clear enough in what I was trying to say. The comment I was trying to make was that innovation is not a value in itself; but when it comes to health care or public health promotion, the key goal is the end point, the key goal is supporting in the best possible way the health and well-being of infants and not simply the most innovative product. We need to strive to achieve the key goal of optimizing outcomes in children. I absolutely agree with you that we do need innovative strategies; but the point I was trying to make is we should always put innovations to the test whether they actually reach the goals that we want to achieve.

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Dr. Lönnerdal: I have a question regarding formula development. There was a change from milk fat to vegetable oils quite some time ago. The reason you gave was low calcium absorption. I believe that this happened about the same time as it was found that the adult diet was too high in saturated fats, and that we should switch to more polyunsaturated fats. The reason I am bringing this up is that the risks are high when translating adult nutrition findings to infants. That is what happened with the low-sodium formula disaster. I think that the recommendation to lower salt intake for adults was extrapolated to infants, which is incorrect, and turned out to be disastrous. Another example is in the US, where you have some 30–40% of all formula-fed infants consuming soy formula. I don't think this is a specific nutritional need of the US infant population, I think it's again an implication – if soy products are healthy for adults, they are also good for infants. I think we have to be very careful when it comes to translating issues of adult nutrition into issues of infant nutrition.

Dr. B. Koletzko: Thank you, that is an excellent point. Problems were caused by full butter fat formulations which were reported already over a century ago by Czerny and Keller, who described in great detail the constipation that arose from calcium soaps. Replacement of part of the butter fat by vegetable fat was an innovation to improve that problem of constipation, and it worked. There are also well-documented effects on fat absorption and calcium absorption. But of course there are also other factors that have played a role, including the perception in the population that vegetable oils and polyunsaturated fatty acids are good for people, therefore one should put them in formula, and perhaps the more you put in the better. Also, vegetable oils were cheaper for producers than butter fat. In evaluating effects, oftentimes people have focused on the percentage fat absorption rather than evaluating growth or other clinical outcomes. This has led to a widespread use of coconut oil and medium-chain triglycerides in term infant formula without any documented benefit for outcome. Perhaps we do have an opportunity here to look at this question in more detail in the future and explore the potential for further improvements.

Dr. Gibson: You highlighted things that we have learnt from breast milk and how that knowledge has been used in the development of infant formula. Could you comment on microorganisms and protein allergens which have been scientifically proven to be present in breast milk?

Dr. B. Koletzko: The finding that there are 10^2 to 10^3 bifidobacteria in human milk has created quite some excitement in the pediatric and scientific community. Clearly, even if you have relatively small numbers of bifidobacteria in breast milk but put them in an environment that promotes growth of bifidobacteria, which obviously is the case in breastfed babies, then even small amounts may have an important role for inoculation. But who would be surprised that there are bacteria in milk? Dairy farmers have known that for a long time, and therefore it is standard practice in dairy farming to reduce bacterial contamination of milk, and to pasteurize milk. You would not drink raw cows' milk because you know it's full of pathogens. It is not much different in human milk. For example, Krist and coworkers published in 2008 a great study on Swedish breast milk donors, more than 400 women, where milk was collected under very clean conditions, after cleaning the breast with saline and usage of surgical gloves by the mothers. Milk was collected into sterile containers, and bacterial counts showed 10^6 to 10^7 of all kinds of pathogens, coagulase-negative *staphylococcus*, *Staphylococcus aureus* streptococci of all sorts, *Pseudomonas*, *Klebsiella* and many other pathogens. Thus, the content of bifidobacteria in breast milk makes up only 1% or so of the total bacteria. If you were to follow the concept to add bacteria to infant formula based on the human milk model, you would probably have to add a lot of serious pathogens to formula, which would be considered dangerous and would not meet the expectations of regulatory authorities. The simple concept that anything that occurs

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in breast milk should be put it into formula is just not a sufficient basis. Dr. Bier has very nicely emphasized that point before. We need to try to strengthen our ability to look at effects on relevant outcomes in the infant and child. With respect to the foreign proteins such as ovalbumin in milk, I trust we will hear more about that question from Dr. Ivarsson in her paper. There is a lot of exciting thoughts now that exposing infants to foreign proteins together with human milk and its immunological properties might have different effects than first exposing the infant to the same protein after weaning from breastfeeding. Dosage and timing might be important here as well.

Dr. Solomons: You stated that the end point of the standard for feeding replacement should be as safe as and as good as with breastfeeding. Our challenge in innovation is thinking beyond the evolutionary aspect of feeding to promote a lifespan of 30 years. The challenge would be, can we have end points in which replacement feeding has a better outcome than breastfeeding in the context of a lifespan of 60–90 years in a population with a new pattern of lifestyle.

Dr. B. Koletzko: Thank you for that comment. It relates to what I tried to address with the term evolutionary discordance. Breastfeeding has considerable advantages and appears to be safe and adequate under most conditions. But if you look at breastfeeding from an evolutionary perspective, an evolutionary drive would not only be the benefit for babies, but rather the benefit for both mothers and babies and also for future reproduction. For example, if we consider the relatively low iron content in breast milk, one might wish to explain this by a compromise between meeting the iron needs of the infant and maintaining reasonable iron stores of the mother. One cannot generally exclude that some forms of breast milk substitutes might even be superior to breastfeeding with respect to some specific end points, but before we jump into that conclusion we really want to have firm evidence. If one wanted to demonstrate the promotion of lifespan by some form of infant feeding, then the challenge in documenting that by adequate science would be enormous.

Dr. Mao: It seems that formula milk is more and more in fashion. But human milk is the best food for our babies. Do you think we can produce a formula from animal milk that is better than human milk?

Dr. B. Koletzko: Thank you, that's almost a philosophical question, isn't it? Perhaps we might be able to have better effects than breastfeeding on specific endpoints, that is conceivable. For example, if you try to secure iron nutrition and to prevent iron deficiency, then perhaps some formula would be superior in that specific end point to exclusive breastfeeding for long periods of time, but that doesn't mean that the totality of benefits of breastfeeding would be surpassed by infant formula. Personally, I cannot imagine that one could reach or even surpass the totality of benefits from breastfeeding by any breast milk substitute in the foreseeable future, not the least because we cannot match the mode of delivery by breastfeeding. The specific effects, such as the skin contact, the stimulation, the interaction between mother and child is something we should not neglect as a potentially important factor either.

Dr. Bodenstab: I would like to hear your comments on the importance of the complementary feeding and innovation in complementary feeding to the development of the child.

Dr. B. Koletzko: We know much less about complementary feeding and its effects than we know about milk feeding, and much less research has been done on this aspect of infant feeding. However, we do know that complementary feeding has very important effects on health end points. For example, in this workshop the story of effects of complementary feeding on celiac disease manifestation is presented. We also know about the major importance of quality of complementary feeding for micronutrient supply, particularly in populations that are less privileged. I think there is enormous opportunity and potential, and it's worth to invest in research in this area.

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