Drivers of Innovation in Pediatric Nutrition

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Drivers of Innovation in Pediatric Nutrition

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Preface

The 66th Nestlé Nutrition Institute Workshop was dedicated to an important but rather abstract topic analyzing potential drivers of innovation in pediatric nutrition. This topic clearly goes beyond the usual scope of academic pediatricians. The themes of other recent Nestlé Nutrition Institute Workshops such as nutritional challenges in emerging societies, personalized nutrition in pediatrics, or nutrition from before pregnancy to the age of 2 years relate closely to pediatric research, clinical practice, and public health. In contrast, this workshop aimed to address and to identify forces that potentially drive innovation in pediatric nutrition, a vision which surpasses research, clinical and academic thinking. While preparing this workshop, we came to appreciate that even if research comes up with the best innovative concepts, the likelihood of translational application of this knowledge will very much depend on a variety of other factors. Often, challenging preclinical and clinical studies must be performed to evaluate potential effects, effect sizes, suitability and safety. The commercial introduction of new or modified dietetic products for infants and children into markets depends on the regulatory standards and environments which differ considerably in various geographical regions and countries. In addition, policy and politics on child health and nutrition may be of considerable importance. The forces of marketing have become very influential, and these forces may not always agree with science and research. Economic considerations, intellectual property protection, adequate availability of safe and suitable raw materials, the state of food technology, as well as feasibility of production and distribution of a conceived new product are determinants of whether and how a product can be brought to the market. Expectations and response of both consumers and health care professionals, and many other factors also are of very high importance. As one might imagine, it was not easy for us to put a balanced program together on the variety and complexity of questions that are of relevance here, but it has been a truly enjoyable and informative experience. Given that this topic has more technological and commercial implications than other topics that are usually addressed by the Nestlé Nutrition Institute Workshops, we involved a slightly

higher proportion of expert speakers who are in one way or another related to the company, which we trust readers will understand.

It was a great pleasure and privilege to organize and co-chair this workshop. We wish to thank Dr. *Petra Klassen-Wigger*, Prof. *Ferdinand Haschke* and their colleagues at the Nestlé Nutrition Institute in Switzerland for the dedicated work and support, as well as *Lois Lin*, Dr. *Lawrence Li* and their colleagues at Nestlé Nutrition China who realized the symposium in China with cordial affection, meticulous attention to detail, and enormous enthusiasm. We also thank the speakers and discussants at the workshop who contributed to the intellectual content of this book.

Berthold Koletzko
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Foreword

'Drivers of Innovation in Pediatric Nutrition' was the topic of a unique workshop held in Sanya, China, on 1–5 November 2009. Innovation is defined in the dictionary as: 'the introduction of something new' or 'a new idea, method, or device: novelty'. When applying 'innovation' to pediatric nutrition, a large variety of different expertise needs to be taken into consideration in order to successfully develop new products from the idea to the shelf. These include: innovative ideas in research and development that are technically feasible, accepted by health care professionals and regulatory authorities and, last but not least, by the consumer.

In this context, the topics discussed in this workshop ranged from the history of infant feeding practices, novel insights into human lactation as a driver of infant formula development, to new approaches through modern analytical tools such as molecular biological assays, and finally the regulatory settings and consumer behavior. Altogether, the workshop was a rich source of information to paint the future of innovation in pediatric nutrition.

We would like to warmly thank the three chairpersons, Prof. Bert Koletzko and Prof. Sibylle Koletzko from Germany and Prof. Frank Ruemmele from France, who are very well-known experts in the area of pediatric nutrition and drivers of innovation themselves, for assembling the outstanding scientific program.

Our special thanks go to Mr. Lawrence Li and Ms. Lois Lin and their team for the superb logistical support of the workshop and the warm hospitality.

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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.

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

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

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.

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).

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].

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	+	?/(+)

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.

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

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,

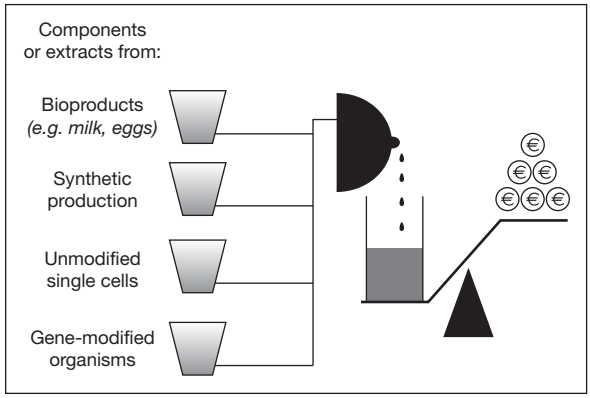

Fig. 1. Progress in food and biotechnology may make it feasible to potentially add a large number of components found in human milk to formulae, but such formulae could easily become extremely expensive. Hence, prioritization based on achievable benefits is essential. Modified from Koletzko [36].

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.

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].

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

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.

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

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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Novel Insights into Human Lactation as a Driver of Infant Formula Development

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Abstract

Progress in research on human lactation and breast milk has advanced our knowledge about the significance of breast milk for the recipient infant and the effects of various components on long-term outcomes. Recent findings have expanded our knowledge in this area. Several growth factors and cytokines are present in breast milk and their capacity to persist in the infant gut and exert their activities is likely to affect maturation of immune function, possibly affecting the development of oral tolerance. A proper balance of polyunsaturated fatty acids (n-3/n-6 ratio) may also be of significance for allergy prevention in children, emphasizing the need for the mother to achieve a balance of these fatty acids in her diet. The recent findings that specific strains of bacteria are present in breast milk and act as probiotics in the early colonization of the infant gut and that human milk oligosaccharides are specific substrates for these probiotic strains may not only affect the defense against pathogens, but also affect energy utilization and development of obesity. Previously neglected milk fat globule membranes contain several components involved in protection against infection and may be an additional arm in the multifaceted shield that breastfed infants have developed against bacterial and viral antagonists. All these findings have implications for development of improved infant formulae.

Introduction

Lactation is a complex and very dynamic physiological process. Initially, very small volumes of milk (colostrum) are being produced, which then rapidly increase up to some 600–1,000 ml per day, with large individual differences. Towards the end of lactation, involution starts to occur and volumes decrease. During these periods, concentrations of many individual milk components change considerably, whereas others change only modestly or not at all. While part of this is due to the changing metabolic activity of the

Table 1. Growth factors and cytokines in breast milk

Name	Action
Epidermal growth factor	Epithelial growth
Insulin-like growth factor-I	Epithelial growth
TGF-β	Immune function, IgA production
Tumor necrosis factor-α	Regulation of development, IgA production
Erythropoietin	Epithelial growth, growth and maturation
IL-1β	Immune function
IL-2	Immune function
IL-6	IgA production
IL-7	Immune function, thymus development
IL-10	Anti-inflammatory

mammary gland, it is highly likely that the alterations in milk volume and the changes in composition also meet the infants' changing requirements and maturing metabolism. Our knowledge about lactation as a process and the components of breast milk and their bioactivities has rapidly increased. The ability of breast milk to provide both passive protection and to affect development of the infant's mucosal and systemic immune responses is coupled to its contents of antimicrobial, anti-inflammatory and immunomodulatory activities. This knowledge now can be utilized as a guideline for improving the composition of infant formulae and their use, thereby hopefully improving nutrition, health and long-term outcomes of formula-fed infants.

Growth Factors and Cytokines

Human milk has been reported to contain several growth factors (epidermal growth factor, transforming growth factor-β – TGF-β, erythropoietin, insulin-like growth factors, etc.) and cytokines/adipokines (interleukin 1β – IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, etc.) [1–3]. In some cases, changes in concentrations during lactation have been described, but often only mean values for mature milk have been given. Recently, developmental patterns for some of these components have been characterized, but, more importantly, evidence for bioactivities in vivo has been provided. Cytokines work in networks and produce a cascade of effects that contribute to the regulation, development and function of the immune system (table 1). Several of these compounds are involved in immune responses of the intestinal epithelium. One example is TGF-β, which is present in high concentrations in colostrum and early milk, but also at biologically relevant concentrations in mature milk [1, 4]. TGF-β is known to affect cell growth and differentiation, but is also a potent immunoregulatory molecule [5]. It regulates differentiation, proliferation and

activation of macrophages, T cells, B cells, NK cells and dendritic cells, and thus plays important roles in tolerance, in prevention of autoimmunity and in anti-inflammatory processes. TGF-β knockout mice were shown to develop widespread tissue inflammation and die soon after weaning [6], demonstrating a critical role for TGF-β in immune modulation and inflammatory responses. It is likely that TGF-β in breast milk is particularly important at an early age, when production of endogenous TGF-β in the intestine is very low [4]. During this time, TGF-β can play an important role in instructing B cells to undergo class switching to IgA [7]. IgA, in turn, is important for protecting the epithelial surface of the intestine, and antigen-specific IgA can prevent adherence and penetration of bacterial and dietary antigens that can provoke inflammation. It is possible that TGF-β can promote IgA production in infants. Böttcher et al. [8] showed that IgA concentrations were correlated with TGF-β concentrations in breast milk, and may be important for induction of oral tolerance. This was supported by a study by Ogawa et al. [7] who showed that TGF-β in breast milk was associated with IgA production in infants. Further, a study by Rigotti et al. [9] suggests that TGF-β in breast milk is involved in the prevention of atopic disease in infants, which is supported by the finding of an inverse correlation between TGF-β in breast milk and wheezing in infants [10]. A recent systematic review of studies on the association between TGF-β in human milk and immunological outcomes in infants and young children showed that 67% of these studies showed a positive association between TGF-β and protection against allergy-related outcomes [5].

A role for TGF-β in neonatal immune function is supported by animal studies. Penttila et al. [11] showed that supplementation of rat milk formula with TGF-β resulted in downregulation of humoral and mast cell response to formula antigens and also directed the immune response away from inflammation even after weaning. Penttila [12] also showed that whey protein concentrate enriched in TGF-β added to formula could downregulate inflammatory responses in allergy-prone rats. Verhasselt et al. [13] showed in a lactating mouse model that airborne antigens are transferred into milk and that breastfeeding-induced tolerance relied on the presence of TGF-β during lactation. Thus, TGF-β may support immune priming to food antigens and induce oral tolerance.

We have investigated whether TGF-β2 in human milk and formula can resist proteolysis under conditions similar to those in the infant gut [14]. We found that the level of TGF-β2 in infant formula was variable and in some cases exceeded that of human milk samples. Digestion with pepsin at pH 2.0 or 3.5, followed by digestion with pancreatic enzymes substantially increased the immunodetectable TGF-β2 in human milk and formula. Additionally, the TGF-β2 in these digests was highly bioactive as measured in a cell-based assay. Thus, TGF-β2 present in some infant formulae and human milk continues to be immunodetectable and retains activity after in vitro digestion, strongly suggesting that TGF-β2 can survive in the infant gut and exert its biological activities.

Interestingly, growth factors/cytokines with proinflammatory activity, such as tumor necrosis factor-α, have soluble receptors in breast milk inhibiting their activity. It is possible that these factors may be of biological significance in the mammary gland, but need to be inactivated when reaching the developing infant gut.

Essential Fatty Acids in Human Milk and Development of Allergy

Addition of docosahexaenoic acid (DHA) and arachidonic acid to infant formulae has received special interest. DHA is important for brain development (usually assessed by visual acuity) in preterm infants, and as breast milk from most women is higher in DHA than infant formula, some manufacturers have supplemented their products for term infants with DHA. A recent study on increased DHA intake of infants leading to lower BMI [15] and a study showing a positive correlation between breast milk DHA and EPA levels with developmental scores [16] may strengthen the argument for DHA supplementation.

Recent findings on essential fatty acids in breast milk also suggest that a proper ratio of n-3 fatty acids to n-6 fatty acids may be important with regard to development of allergic disease. Levels of EPA (C20:5 n-3) and DHA (C22:4 n-3) as well as the total n-6/n-3 ratio were significantly lower in breast milk from mothers of allergic children as compared to those having non-allergic children [17]. In a follow-up study, women were supplemented with polyunsaturated fatty acids during pregnancy and lactation, and the prevalence of food allergy as well as IgE-mediated eczema was lower in the n-3-supplemented group compared to the placebo group [18]. Interestingly, Laiho et al. [19] found that women with allergic disease had lower concentrations of TGF-β2 in their milk. A positive association was found between polyunsaturated fatty acids and TGF-β2. It is therefore possible that the lower levels of TGF-β2 in the breast milk may interfere with the development of the mucosal immune system of the breastfed infant.

Probiotics in Human Milk

It has been well known that the gut microflora of breastfed infants is dominated by lactobacilli and bifidobacteria and is quite different from that of formula-fed infants. This has largely been believed to be due to fecal 'contamination' from the mother at delivery (which has made the differences less pronounced with increased sanitary measures) and to bioactive components stimulating the growth of beneficial bacteria and inhibiting the growth of pathogens. Recently, however, careful studies in which the breasts of lactating women have been cleaned rigorously have shown that live bifidobacteria

are found in breast milk [20–22] or that bacterial DNA signatures are present in breast milk cells [23]. Thus, the breastfed infant is essentially given oral doses of probiotics from birth on, and in every meal. This very early colonization may be very important, as it is known that it is difficult to alter a gut microflora that has already been established. Interestingly, lactating mothers with allergy had significantly lower concentrations of bifidobacteria in their breast milk than nonallergic mothers [24]. In addition, maternal allergy status had a significant effect on their infants' fecal bifidobacteria.

Recent findings also suggest that the subspecies of probiotic bacteria such as bifidobacteria may also be important. Sela et al. [25] completed the genome sequence of *Bifidobacterium longum* subsp. *infantis* and found that it reflects a competitive nutrient utilization strategy targeting milk-borne molecules that otherwise lack nutritive value to the neonate. Thus, this specific subspecies may be uniquely adapted to utilize milk oligosaccharides. Interestingly, *B. longum* subspecies *infantis* and *longum* were found in all breast milk samples in a study by Guiemonde et al. [22], whereas other biotypes were less abundant. Thus, it is possible that probiotics provided in breast milk are perfectly matched to the substrates (oligosaccharides) present in breast milk. This, in turn, may have important implications for infant formulae – what probiotic strain(s) should preferably be used, and what substrates (oligosaccharides) should be present? To date, the strains that are being used commercially in formula differ from those found in the feces of breastfed infants, and the prebiotic oligosaccharides differ considerably from the complex and dynamic mixture found in breast milk [22].

The establishment of an appropriate gut microflora, possibly initiated by the lactating mother through her milk, or by feeding formula with specific probiotic strains, may have significance beyond that of discouraging pathogens. The recent findings of 'crosstalk' between the microbiota and the host leading to effects on energy metabolism in the small intestine are very interesting and thought provoking. Bäckhed et al. [26] suggested that the gut microflora facilitates the hydrolysis of nondigestible oligosaccharides to easily absorbed monosaccharides and the activation of lipoprotein lipase by their interaction with the intestinal epithelium. Together, this leads to increased glucose absorption and storage of fatty acids as triglycerides, which increases weight gain. For example, increased numbers of *Bacteroides* in the gut microbiota were demonstrated to increase energy stores and obesity in experimental animals [27]. Interestingly, Kalliomäki et al. [28] recently found that bifidobacteria were present in higher numbers in children maintaining normal weight than in children becoming overweight. Being overweight was instead associated with a greater number of *Staphylococcus aureus*. The authors suggest that high numbers of bifidobacteria and low numbers of *S. aureus* protect against overweight and development of obesity, which may be supported by recent meta-analyses showing that breastfed infants are 13–22% less likely to become overweight or obese in childhood and that breastfeed-

ing is inversely associated with the risk of overweight [29, 30]. Thus, it is feasible that specific probiotic strains in breast milk not only facilitate colonization of the gut with beneficial bacteria and deter pathogens, but that they also modulate energy metabolism which in turn can affect development of obesity.

Milk Fat Globule Membrane Proteins and Defense against Infections

The protein fraction of the membranes surrounding the fat globules in human milk is quantitatively minor [31], but may be of significance in the defense against infections. Several of these proteins, such as lactadherin, butyrophilin, xanthine oxidase, alkaline phosphatase, etc., have been shown to have antimicrobial activity in vitro. Human milk mucin components were able to bind to various rotavirus strains and prevent replication and the ability was correlated to lactadherin [32]. Further, the content of lactadherin in breast milk was shown to be negatively correlated to symptomatic rotavirus infection in Mexican infants [33].

Infant milk formula, however, is made from skim milk powder and whey protein concentrate and consequently does not contain any milk fat globule membrane (MFGM). Recently, milk fractions enriched in MFGM have become available on a large scale commercially, and may therefore be added to infant formulae in the future. Some bovine proteins in the MFGM have been demonstrated to have broad activities against pathogens and a bovine whey protein concentrate enriched in MFGM may therefore help to prevent diarrhea of bacterial and viral origin [34]. This protein fraction contains several bioactive components including mucin (MUC1), lactadherin, folate-binding protein, lactoferrin, sialic acid, sphingomyelin, and gangliosides [34]. A bovine milk fraction containing MUC1 has been shown to inhibit hemagglutination of *Vibrio cholerae* and *Escherichia coli* [35]. In addition, purified mucin, a MFGM constituent, was demonstrated to decrease the adherence of *Yersinia enterolytica* to intestinal membranes [36]. The MFGM fraction has also been found to reduce rotavirus in vitro [37]. Sphingolipids, particularly gangliosides, have been shown to inhibit enterotoxins both in vitro and in vivo [38]. Infant formula with added sphingolipids (gangliosides) has been shown to reduce *E. coli* counts in the stool, and to increase beneficial bifidobacteria [39].

We have tested the concept of MFGM protein fractions having an effect on infectious diseases in Peruvian infants. The infants were given MFGM proteins in a milk-based meal twice daily for 6 months in a randomized controlled double-blind study [40]. Prevalence of diarrhea was significantly lower in the group given MFGM than in the group given the same type of meal with skim milk protein instead of MFGM. Although the exact constituents of MFGM having an inhibitory effect on diarrhea were not identified, it is quite possible

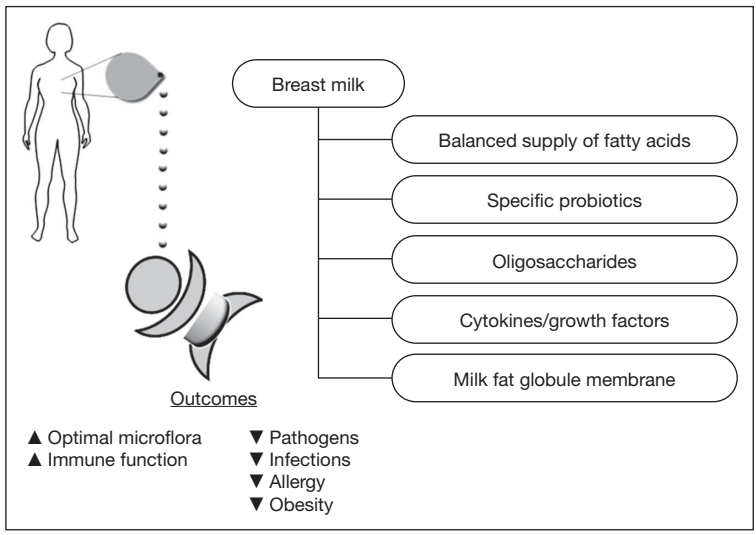

Fig. 1. Constituents of breast milk affecting infant outcomes.

that addition of the MFGM fraction to infant formula may have an effect on infectious disease.

Conclusions

The breast milk constituents described above are all likely to affect several outcomes in the recipient infant, either individually or, more likely, in a synergistic fashion (fig. 1). Long-term outcomes include an 'optimal' gut microflora, enhanced resistance against infection, improved immune function, reduced allergy, and decreased obesity. Our increased knowledge about these breast milk components is also likely to result in new and improved infant formulae.

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Discussion

Dr. B. Koletzko: You showed the fascinating results of your study on milk fat globule membrane effects on diarrhea, and you also showed the comparison of different components where mucins appeared to have beneficial effects. Would it not be easier to add just the active components to a dietetic product than the whole milk fat globule membrane? Secondly, I wish to voice my concerns as to what conclusions we can draw from association studies. The data of the Bäckhed study in mice, with very strong effects of bacterial colonization on body fat accumulation is impressive, but the physiology may be different from that in real humans. In germ-free mice, scavenging energy from undigested substrates reaching the colon by microbial fermentation is not achieved, which is considered a significant part of the overall energy balance. I am not sure we get the answer as to how important such effects on healthy humans are from association studies. If you find an association between the bacterial colonization patterns and obesity or non-obesity, one would not be sure whether this different bacterial colonization is the cause or consequence of differences in lifestyle and in diet in families who show obesity or no obesity. We clearly need other types of studies to address this question.

Dr. Lönnerdal: You bring up very good points. The first one is coming back to what we are addressing at this conference, which is what kind of drivers are behind the innovations that were taken. I agree with you that it would be very nice to study components of the MFGM. It's just that the entire MFGM fraction is the only one commercially available; that is, you can buy it in hundreds of kilograms and therefore you have the possibility to do human intervention studies. We have too many in vitro studies that give suggestions but not much more. I am not aware of any company that has mucins in a purer form, in commercially viable quantities. It's possible but I haven't

seen it, and I haven't seen human studies on such components, but I agree that it's most likely the crucial component for the outcomes we looked at. Unfortunately, we didn't have the resources to look at developmental outcomes where perhaps gangliosides and sphingomyelin could have an effect. Coming back to your other comment, I couldn't agree more with you when it comes to associations like in the Kalliomäki study. I think such observations are only suggestive. I think it's an area that needs more investigation; we need to look at the microbiota and its interaction with a lot of different factors. Mouse studies are easier because you can refine the hypotheses much more than you can in any type of observational human study. I think it is worthwhile coming back to where we started. We know today that the average daily intake of a formula-fed infant is about 1,000 ml per day, while the average intake of a breastfed infant is about 800 ml. Thus, you have an overabundance of energy intake in formula-fed infants. I think the Gordon group has a lot of things planned which at least would spur us into moving into that area. They have done studies on western style cafeteria diets where you also have an abundance of calories. How does that higher energy intake interact with the microbiota when it comes to development of obesity? This needs to be looked at from an energy point of view, and also from a lipid and carbohydrate perspective. I think that the subclasses of energy coming from various nutrients and the gut microbiota could be very interesting.

Dr. Gibson: To what degree can factors like TGF-β contribute to becoming obese or not?

Dr. Lönnerdal: Very difficult issue. When it comes to TGF-β, there may be clinical conditions that may shed some light on this. In the Verhasselt study, a knockout mouse model was used. There may be mutations in humans which haven't really been pursued that much. Sometimes you can find mutations and follow-up animal studies with human studies. When it comes to the obesity issue, it's a much more complex issue and we have to consider many things. Five years ago, we really didn't think that the gut microbiota had much to do with obesity and what they have shown at least is that it certainly can affect both energy reutilization in the gut but more importantly the crosstalk between the products of energy metabolism by the microbes in the gut with the mucosa. I think this is something which needs further studies.

Dr. Gibson: I am not disputing the bioactivity of TGF-β. I am wondering how we should design studies that compare formulas with different levels of TGF-β?

Dr. Lönnerdal: It is very difficult, but if we know that you can select a whey protein concentrate high in TGF-β which is commercially available, powdered infant formula with similar levels of TGF-β as you have in breast milk can be produced, and then you can have basically the identical product in liquid form with no TGF-β. This provides a possibility to do an intervention study.

Dr. Ivarsson: I have a comment about the possibilities of different study designs. The experimental design is the one that's often mentioned, and it is of course very useful. However, I want to emphasize that we also have several different observational study designs – so far underutilized – that can increase knowledge. Among these, the prospective cohort study with long-term follow-up is the most demanding; however, it is necessary to get the final evidence.

Dr. Lönnerdal: I agree totally.

Dr. Greer: How do the specific probiotic bacteria get into the breast milk that is secreted by the mammary gland? I can accept the fact that maybe this is a migration of the bacteria up the mammary ducts from the nipple. But if anaerobic probiotic bacteria are translocating across the GI tract and into the blood stream and then into the mammary gland, this would be a very hostile, aerobic environment and a complicated process. Are we just talking about PCR evidence of bacteria in human milk without any viable organisms?

Dr. Lönnerdal: That's not my area of expertise. I think we need both a bacteriologist and a lactation physiologist to resolve this. I have been fascinated by the transfer of various things into breast milk for a long time. We did some studies in which we looked at the transfer of dietary antigens into breast milk, and you actually can find β-lactoglobulin from cow's milk in intact form in breast milk. Thus, fairly large cow's milk protein can first be absorbed from the diet, pass through several biological membranes in the small intestine, be transported through the body, and then through several membranes in the mammary gland and finally be secreted in intact form. I am not sure how that happens, but it does. When it comes to bacteria, they are even larger. In this case, I believe the work of those scientists that performed the bacterial analyses in breast milk; they took all the care they could to clean the breasts, etc. I don't know how much more you can do unless you do some biopsies perhaps and see what is actually inside the mammary gland, but I wouldn't recommend that.

Dr. Bier: What were the intervention period and the primary end point of this study?

Dr. Lönnerdal: The study was a 6-month intervention. We started when they were between 6 and 8 months old and we followed them for 6 months. The evaluation was therefore between 12 and 14 months of age. Primary outcomes were diarrheal disease and morbidity. We also had a very complete evaluation of nutritional status, which was another part of the study.

Dr. Bier: You showed us several different ways to measure diarrheal disease.

Dr. Lönnerdal: I presented incidence and prevalence data. We also analyzed the pathogens in the stool, and in some cases saw a significant effect of specific pathogens

Dr. Bier: What was the primary variable?

Dr. Lönnerdal: Diarrhea prevalence.

Dr. Bodenstab: You mentioned rotavirus vaccination. There is a debate about its efficacy. Do you think it's important for future infant nutrition products to have anti-rotavirus functionality?

Dr. Lönnerdal: I can't respond to how efficient the vaccine is today, or how widely distributed it will be to the populations that we are looking at. I think both economic and social factors will determine this accessibility. I still think that during a transition period, dietary factors that can affect rotavirus may be important, but, like I said, in our study we had expected rotavirus to be a significant part, but it was not, so what we saw was a reduction in bacterial diarrhea and not rotaviral diarrhea.

Dr. Szajewska: I don't think there's been any debate regarding the use of the rotavirus vaccine. It's efficacious in preventing severe rotavirus gastroenteritis and hospitalization due to rotavirus gastroenteritis.

Dr. Haschke: I am coming back to the innovation process. You have shown a couple of molecules in relation to breast milk. What is your speculation, which components should formula milk include in 5–10 years from now?

Dr. Lönnerdal: There are certainly several components that I think are worthy exploring, TGF-β may be the easy one because it's not costly. It's there already, it has a physiological function like Dr. Gibson alluded to and therefore it can be tried. I think the right type of studies have not been done yet. I didn't talk today about lactoferrin which I think is very important and could be added, but there you have a significant economical factor, as it would be expensive. We have seen it in the past that if the formula is too expensive nobody will buy it, and then we haven't achieved much either. This needs to be looked at, and that's why I like this conference – we have an opportunity to discuss aspects that are driving innovation. It's not just about having an idea and trying to correlate things in vitro, we need to take it to the next step.

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The Clinical Challenge of Preventing and Treating Malnutrition

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Abstract

Malnutrition remains a major problem in children in large parts of the developing world. About 150 million young children in the developing world are either wasted or stunted, and it has been estimated that over half of childhood deaths are attributable to the potentiating effects of malnutrition. Thus, tackling both mild-moderate and severe malnutrition effectively is essential if the millennium development goals are to be achieved. Intervention strategies to promote exclusive breastfeeding for about 6 months in the absence of maternal HIV infection will result in significant improvements in nutrition, and are key to prevention strategies for malnutrition. Careful evaluation and effective counseling of HIV-positive mothers regarding feeding choices is essential. Evidence from a number of randomized controlled trials shows that ready to use foods have an important role to play in the prevention and treatment of both outpatient and inpatient malnutrition. Such foods were initially produced commercially, but it has been shown, particularly in Malawi, that such foods can be locally produced at low cost. In some parts of the world, HIV is a major underlying cause of malnutrition in children and is associated with high mortality rates in those with severe malnutrition. Strategies for the prevention and treatment of children with HIV need to be escalated.

Introduction

Interventions to improve child health over the past few decades have concentrated on issues such as immunization, oral rehydration and treatment of infections. Specific nutritional interventions have been relatively neglected.

Malnutrition affects a large proportion of the world's children. While malnutrition includes both under- and overnutrition, this chapter will deal with undernutrition. It has been estimated that about 150 million young children

in the developing world are either wasted or stunted. In highly affected countries, rates of children who are wasted may exceed 10%, while up to 40% of all children less than 5 years of age may be stunted [1]. Infectious diseases have been recognized as the leading cause of death in children under the age of 5 in developing countries for many years. However, it is only more recently that the potentiating effects of malnutrition on infectious diseases have been appreciated. Pelletier et al. [2] in a study on data from 53 developing countries estimated that 56% of child deaths were attributable to the potentiating effects of malnutrition. Somewhat surprisingly, over 80% of these deaths were attributable to mild-to-moderate malnutrition as opposed to severe malnutrition, reflecting the fact that the vast majority of undernourished children are in the former category. Black et al. [3] recently presented an updated analysis of the total burden of maternal and child undernutrition on childhood deaths. The main factors that they identified were stunting, severe wasting and intrauterine growth restriction combined, vitamin and trace element deficiencies, and suboptimal breastfeeding. All of these together, accounting for coexposure of these nutrition-related factors, were estimated to be responsible for 35% of childhood deaths and 11% of the global burden of disease.

Furthermore, children who survive the effects of undernutrition may have impaired cognitive development, reduced capacity for physical work and be at higher risk for some adult-onset chronic diseases [4]. Thus, the prevention and treatment of malnutrition are important for both child and adult health in large parts of the developing world.

Prevention of malnutrition is clearly a complex subject, and many factors responsible for malnutrition have their roots in the socioeconomic circumstances of communities and families. Poverty, poor quality food sources, overcrowding, and the lack of clean water and sanitation all contribute to a high burden of disease which in turn leads to inadequate food intake and increased energy requirements to combat disease. Thus, prevention of malnutrition requires a multi-layered approach, and this is reflected to some extent in the various components that make up the Millennium Development Goals.

Breastfeeding

The advantages of breastfeeding have been known for centuries and relate to a number of properties of breast milk. These include the appropriate composition of breast milk with respect to the growing term human infant, its many anti-infective properties and the important immune modulating effects. Numerous reports have indicated that the mortality of infants who are not breastfed is several times higher than that of breastfed infants in low-income countries, but it is often difficult to separate out the many

social factors that are associated with non-breastfed infants such as family disruption, alcohol and drug abuse, maternal and infant illness including prematurity, etc. However, in their comprehensive analysis, Black et al. [3] estimated that suboptimal breastfeeding was responsible for 1.4 million child deaths globally.

The full benefits of breastfeeding are obtained if exclusive breastfeeding continues from birth for about 6 months and then breastfeeding continues together with other foods up to the age of 12 months and beyond. While the rates of initiation of breastfeeding in most developing countries are high, the numbers of infants who are exclusively breastfed for 6 months is often unacceptably low. It was estimated that in Africa, Asia, and Latin America and the Caribbean, only about 50% of infants under the age of 2 months are exclusively breastfed, and this falls significantly over the next 4 months. The results of a Cochrane review on support for breastfeeding mothers that analyzed almost 30,000 mother infant-pairs from 14 countries showed that all forms of support increased the duration of breastfeeding: the relative risk for stopping breastfeeding before 6 months was 0.91 (95% CI: 0.86–0.96), admittedly a relatively small effect [5]. However, Coovadia et al. [6] were able to achieve excusive breastfeeding rates of 67% by 3 months of age and 40% by 6 months of age in those who initiated breastfeeding with an intensive intervention program that included frequent home visits by infant feeding counselors in a rural area of South Africa with a high HIV prevalence, showing that more intensive breastfeeding support programs can have a much greater impact. Thus, one of the priority areas for preventing malnutrition in the early months and years of life is to increase the rates of exclusive and prolonged breastfeeding by programs to support breastfeeding, and the more intensive the program, the more successful it is likely to be [7].

In many parts of the developing world, especially in sub-Saharan Africa, HIV is strongly associated with malnutrition. This in turn creates a major dilemma where breastfeeding increases the risk of HIV transmission from mother to infant which in turn may result in wasting and stunting, whereas in almost all other situations, breastfeeding results in optimal nutrition for young infants. A consensus statement by the World Health Organization (WHO) stated that where replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended; otherwise exclusive breastfeeding is recommended [8]. The challenge is to identify the infants of those families who can be fed safely with breast milk substitutes, and this requires intimate knowledge of the community on the part of the health worker. However, recent studies on providing breastfeeding mothers with antiretroviral drugs for the duration of breastfeeding show promising initial results. If these results are confirmed and provision of antiretroviral drugs is feasible on a large scale to breastfeeding HIV positive women, especially in those countries hardest hit by the HIV epidemic, this will be an enormous advance.

Table 1. Classification of malnutrition

	Moderate malnutrition	Severe malnutrition
Symmetrical edema	no	yes (edematous malnutrition)
Weight-for-height	–3 ≤SD score <–2 (70–79% expected)	SD score <–3 (<70% expected; severe wasting)
Height-for-age	–3 ≤SD score <–2 (85–89% expected)	SD score <–3 (<85%; severe stunting)

Stunting and Intrauterine Growth Restriction

Weight gain has been the focus of most assessments of nutrition programs, whereas stunting and linear growth retardation are considered to be more difficult to improve. Bhutta et al. [9] estimated that only one third of stunting could be averted with available short-term interventions. This was supported by data from Guatemala, where an intergenerational study showed that women who had received nutritional supplements in utero (given to their mothers) and as children up to the age of 7 years, produced offspring who had more rapid linear growth than they had as children [10]. Those who received additional protein as part of the food supplementation had children with the largest increments in linear growth. Thus, it would seem that several generations during which good nutrition is available would be required in those parts of the world where the rates of stunting are high before the full genetic potential of linear growth is obtained – this should be the longer term goal.

Assessing and Classifying Malnutrition

The measurements of weight and length/height have long been used in various classifications of malnutrition. However, more recently, the classification used by the WHO Manual on the Management of Severe Malnutrition has gained increasing acceptance [11]. This classification can be seen in table 1. However, in those areas where malnutrition is most common, the measurement of weight may not always be accurate, and length measurements are frequently inaccurate due to the limited availability of proper measuring equipment. In such areas, a simple method for detecting malnutrition by community health workers is needed, and the mid-upper arm circumference (MUAC) has been shown to be a good screening method for the detection of severe malnutrition. Using a cutoff for MUAC of <110 mm for children between 6 and 59 months, this method is simple and sufficiently accurate to detect severe malnutrition in children in this age range [12].

The clinical assessment of bipedal edema together with the MUAC, both of which can be done with staff that are not highly trained health workers, is sufficient to determine whether children fit the WHO category of severe malnutrition.

Advances in the Development of Ready to Use Foods

Based on formulae that had been developed in emergency and refugee settings [13], the WHO recommended the use of a high-energy formula, so-called F100 containing 100 kcal/100 ml, during the rehabilitation phase of children recovering from severe malnutrition [11]. This is a liquid formula prepared from dried skimmed milk, oil, sugar and a vitamin and mineral mix. However, these liquid formulae were susceptible to bacterial contamination and could thus be safely prepared only in settings where there could be close supervision and where there was access to clean water.

Subsequently Briend et al. [14] reported the successful results of a small study in Chad using a ready-to-use therapeutic food (RTUF) for treatment of marasmus. The nutritional composition was similar to F100 but was manufactured in the form of a paste with groundnuts as one of the main ingredients. It contained 543 kcal/100 g, tasted like peanut butter, was considered to be palatable by children and appeared to be resistant to bacterial contamination, thus giving it excellent storage properties. They speculated that it might be useful in centers where there was potential for bacterial contamination of liquid feeds and that it might also be useful for home treatment.

Several studies were performed on both moderately and severely malnourished children utilizing the WHO classification, which can be seen in table 1. Maleta et al. [15] supplemented moderately malnourished children in Malawi with either an RTUF or a locally produced supplement consisting of maize and soy flour. While both groups showed modest weight gain, the group receiving RTUF had better weight gain even after cessation of the supplement. Two studies, one in Senegal and the other in Malawi, evaluated the effects of RTUF supplements on severely malnourished children in non-hospital settings [16, 17]. In the Senegalese study, RTUF was compared with F100 and resulted in improved weight gain when compared with F100. The comparator in the Malawian study was again blended maize and soy flour. The RTUF group gained weight and height more quickly than those on maize/soy flour and was considered to warrant further work in operational settings.

In all of these studies, a commercially prepared RTUF produced in France was used. Concerns regarding these studies were expressed with regard to the cost of the product and the fact that this focused on technological interventions as a solution to what is fundamentally a geopolitical and socioeconomic problem. However, Manary [18] has demonstrated that

local production of RTUF similar to the commercially available product is possible using locally available milk powder, vegetable oil and peanuts. This locally produced RTUF could be produced in both small and large quantities in underresourced settings in Malawi, and this should be feasible in most settings in the world. However, further work needs to be done on alternative ingredients in areas where locally available foods may differ and modifications to the RTUF may be necessary. Further published studies have demonstrated the effectiveness of this locally produced RTUF in Malawi. Six-month-old infants were supplemented with RTUF for 1 year and compared with a second group randomly assigned to receive a micronutrient-fortified maize-soy flour supplement. The group receiving RTUF had similar weight gain to the maize-soy flour group, but showed significantly better linear growth which was maintained for a further 2 years after the supplement was stopped [19, 20].

Severe Acute Malnutrition

In addition to the definition of severe acute malnutrition (SAM) seen in table 1, it has been proposed that an MUAC <110 in children 1–5 years of age should be added as an alternative criterion when accurate measurements of weight and length/height are not feasible. The mortality rates for children admitted to hospital with SAM have remained at 20–30% for decades in spite of management protocols which, if properly implemented, should reduce these rates to <5% [21]. The WHO-published protocols for the management of SAM consisted of 10 steps that were divided into two phases: stabilization and rehabilitation [11]. However, these protocols required trained staff and admission to hospital in the initial stages to implement them fully and have not led to widespread decreases in case-fatality rates in developing countries. In a South African study in two poorly resourced rural hospitals with high HIV prevalence rates, following the introduction of the WHO protocols together with training of staff, case fatality rates of SAM fell from 46 to 21% in one hospital and 25 to 18% in the other. However, when new untrained staff took over in one of the hospitals, the improvement in case fatality rates was reversed [22].

While the programs for the treatment of SAM in the 1980s and 1990s met with limited success, more recent experience with RTUF have met with more success in non-hospital settings as discussed above. This has resulted in fewer children requiring initial hospital admission as only those with complications require hospital admission [21]. These complications include pitting edema, MUAC <110 mm, anorexia, lower respiratory tract infection, severe dehydration, etc. For those that do require hospital admission, a shorter hospital stay is possible, thus maximizing the use of hospital care for the sickest children.

HIV and Malnutrition

Attempts to achieve improvements in the prevention and treatment of malnutrition have been complicated in some countries, particularly those in Southern and East Africa, by the HIV pandemic. In South Africa, the prevalence of HIV-positive women attending antenatal clinics in South Africa rose from <1% in 1990 to close to 30% over the following 10–15 years depending on the region of the country. This has been largely responsible for the increase in under 5 mortality from 60 to 69 per thousand live births between 1990 and 2005, with over half of the deaths in 2005 being attributable to HIV as the underlying cause [23]. A similar trend has been seen in other Southern African countries, and the rates of severe malnutrition have also risen substantially over this period.

In a study of hospitalized children with severe malnutrition in a rural part of South Africa with a high prevalence rate of HIV, the traditional risk factors such as poor household food security, unhealthy feeding practices including low rates of exclusive breastfeeding and lack of adequate food diversity after the age of 6 months were still found to be important risk factors. However, of equal importance was the role of HIV either directly with respect to an infected child or indirectly where the child's parents were infected and ill or had died. The mortality rate in this study for those with severe malnutrition was 25% despite reasonable standards of hospital care, and it was felt that HIV infection played an important role in this high mortality rate [24].

In another study performed at three teaching hospitals in Johannesburg, South Africa, 51% of children admitted for severe malnutrition were infected with HIV [de Maayer, pers. commun.]. In those infected with HIV the mortality was 19%, whereas in the uninfected group the mortality rate was 3.6%. Thus, attaining a <5% mortality rate in children with severe malnutrition requiring hospital admission as proposed by the WHO would seem to be unrealistic in areas with high HIV prevalence.

The Future

Promotion of exclusive breastfeeding for about 6 months should be a priority, but careful consideration needs to be given to the circumstances of HIV-positive mothers when making feeding choices. RTUF has been shown to be extremely effective in the prevention and treatment of malnutrition, but is only available in a few countries. Development of RTUF made locally at low cost from locally available foods should be a priority so that widespread use of these products can be introduced in areas with high rates of malnutrition. In some parts of the world, HIV infection is a major contributor to childhood malnutrition, and interventions to prevent mother to child transmission of HIV and to treat those children infected with HIV should be rapidly escalated.

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Discussion

Dr. Hussain: Are the majority of malnourished children under or over 6 months old?

Dr. Cooper: In terms of the age we see both. Under 6 months of age is usually related to the lack of breastfeeding or HIV infection itself, and particularly those that are infected during pregnancy rather than at the time of delivery where they develop the illness very early on and become symptomatic within 6–8 weeks after birth and present with poor growth. But I would think that the majority of the children we see are over 6 months of age, as I am sure is the case in your country. That relates to either stopping breastfeeding or inadequate infant foods. In our country and in most parts of Southern Africa, maize is the staple food. Some children in many parts of the rural areas get very little else, and it has been calculated that in order to just get enough calories, let alone protein, micronutrients, etc., the amount that needs to be eaten by a young infant or child is huge, and so it's a lack of a varied and substantial diet.

Dr. Solomons: I would like to talk about pure microbiologically safe water. Much of the diseases which lead to severe malnutrition are caused by water-borne infections, and as the use of ready to use food is becoming more and more widespread, provision of safe water is a must.

Dr. Cooper: I agree with your comment. I think it sounds easy to say we should be providing safe water for everybody, but our country which is one of the better resourced ones in Africa is still battling with that, particularly in the rural areas. I think safe water is almost a sort of fundamental building block that will then determine so many other things.

Dr. Spieldenner: Do you have information on the financial sustainability of such programs and on the acceptance in the cultural environment?

Dr. Cooper: We haven't had experience except in one particular very small scale of study. But the group in Malawi, if one looks at their publications over the last 5 years, have taken this a long way. It's really developed from within a country rather than coming in from outside, although there obviously has been outside help. They seem to be highly successful in utilizing local products and being able to produce them relatively cheaply. But Malawi is a small country, and I think it's a relatively homogenous one in terms of the population, so it's really at the infancy of this particular type of ready to use food. I think we are going to have to look much more widely as to how widely applicable it is both financially as well as culturally from an acceptability point of view.

Dr. B. Koletzko: You referred to the enormous success of the ready to use foods. Perhaps this concept could be exploited to an even greater extent. The first foods used were rich in fats and based on peanuts; they were produced in France. Now, more and more locally made ready to use foods are made available. While there is already a lot of experience in using some lipid-rich foods for feeding undernourished children, there are questions that we might wish to have answered. For example, does it matter what the composition of the fats is in these ready to use foods, and which outcomes could be enhanced by modified compositions?

Dr. Cooper: I think most of the studies that have been done thus far have really been looking at a very limited composition or mix of foods. As I mentioned earlier, and it has pretty much been replicated in the local Malawi situation, I think there aren't any answers at this stage for what might be the optimal lipid source to use, what might

be a better mix of nutrients. So it's really, as I would see it, at the beginning of what might be a very long road ahead, but perhaps might be a very productive one in terms of managing and treating malnutrition. I think one can virtually ask any question at this stage because they are all unanswered as far as I am aware. The important thing to me would be to look at different parts of the world and see what food stuffs are available and if one could get the same results utilizing different sources.

Dr. Dhansay: A few comments, the first one is on information and data and the fact that we look at publications, for example the *Lancet* series, and then it becomes gospel. I just want to comment on South Africa, I don't think those stunting rates are great, similarly with clinical vitamin A deficiency. It was published that we have got clinical vitamin A deficiency but we do not have clinical vitamin A deficiency. I want to tell the audience that when one looks at publications, one should also look at the background. The second point is on the fact of social determinants. Context is all. In South Africa, although we are one physical country, we are not one nation as yet. There are large differences between population groups. The majority of our population is not privileged and most of them are HIV positive, so context, I just wanted to emphasize again, is extremely important. Somebody asked about malnutrition before/after 6 months of age. I can just say, and I think Dr. Solomons will back me up, we did a full country intervention study with multiple micronutrients and the study group was specifically selected. The infants were not malnourished; they did not have low birthweight, but at 6 months of age a good percentage of them were already stunted.

Dr. Thakre: I would like to ask how do we define ideal growth? Nutrition is influenced by numerous factors which operate before and after birth. Is there a gold standard for optimal growth?

Dr. Cooper: Very good question. I think the WHO growth charts which have come out very recently at least give us an idea of early growth and what the optimal pattern should be. But even there, they were based on healthy women who were breastfeeding successfully and excluded perhaps the outliers who would have problems. But I don't think there is any easy answer to that, and perhaps this is something that we will grappling with for the next 50 or 100 years as to what is optimal growth.

Dr. Ludan: Developing countries like the Philippines have high stunting rates. Stunting is associated with zinc deficiency. Among pregnant mothers, zinc deficiency has also been related to low birthweight and premature delivery. Some studies recommend zinc supplementation to pregnant mothers during the last 5 months of pregnancy to increase the duration of gestation and also while breastfeeding because we know that the level of zinc in breast milk is low [1]. So, in developing countries with high stunting rates, low birthweight and premature deliveries, would you recommend zinc supplementation to pregnant and lactating mothers?

Dr. Cooper: That's not really an area of expertise that I have, but I am sure it must depend on regional differences. This might be recommended in the areas of high zinc deficiency, but not necessarily everywhere.

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Progress of Enteral Feeding Practice over Time: Moving from Energy Supply to Patient- and Disease-Adapted Formulations

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Abstract

Enteral nutrition comprises the delivery of a liquid formula beyond the esophagus via a feeding tube in a patient with insufficient oral intake, as well as the provision of specialized nutritional formula irrespective of the route of delivery. Pediatric formulae have been designed for different age groups, and for children with certain diseases; examples are special formulations for regurgitating infants, metabolic diseases, cow's milk or multiple food allergies, intestinal, pancreatic, renal, and hepatic insufficiency. Exclusive enteral nutrition is a therapeutic concept to induce remission in children and adolescents with active Crohn's disease. A new area of nutritional research in pediatrics is potential immunonutrition in critically ill children. Formulae are enriched with single components or a combination of key substrates that might play a crucial role during intermediary metabolism in sepsis, inflammation, tissue healing, and growth. For pharmaconutrition, single components are investigated in a scientific stepwise procedure in order to identify effective disease-dedicated nutrition therapy. Any new formula needs to be evaluated, if possible in comparison to a normal diet or the reference formulation to demonstrate its safety and efficacy (equal or superior to standard formula).

Introduction

Enteral nutrition (EN) has traditionally been defined as delivery of a liquid formula beyond the esophagus via a feeding tube, either to the stomach or directly to the duodenum or jejunum in a patient with insufficient or inadequate oral intake. More recently, the term EN has been expanded [1] to the

provision of specialized oral nutritional formulation and includes the use of 'dietary foods for special medical purposes' as defined in the European legal regulation of the Commission Directive [2], irrespective of the route of delivery. This new definition already implies that formulations can be tailored not only to the age-dependent nutritional needs, but also to the individual patient depending on the underlying disease, residual digestive function and certain situations (i.e. pre- and postoperatively feeding).

Although it has been recognized for long that the nutritional needs of children differ from those of adults, it was only during the last 2–3 decades that liquid formulations for children have been developed. Tube-fed children beyond infancy had received either an infant formula or a liquid diet designed for adults. In pediatric hospitals, decisions on nutrition were often left to nurses, and tube-fed patients, e.g. with cerebral palsy, were fed with infant formula as the only source of nutrition until late adolescence. Similarly, elemental or whole-protein liquid diets designed for adults were fed to toddlers and young children. This resulted in inappropriately high nitrogen supplies in young children, who were exclusively fed with these formulations, since the protein/energy ratio reflecting physiologic needs drops from 3.5 g/100 kcal in young infants to 1.3 in toddlers and increases again to over 2 in adolescence and adulthood. The composition of formulae for preterm infants reflects their even higher protein requirements, and human milk fortifiers were designed to top up pumped breast milk to match the nutritional needs of very premature infants.

The first formulations for disease-specific use were developed for infants with intractable diarrhea which was often due to cow's milk protein allergy-induced enteropathy. Some of these infants were fed with home-made liquid diets based e.g. on chicken protein as nitrogen source, but failure to thrive was very common. The first formulae with hydrolyzed protein contained medium-chain triglycerides (MCTs) for infants with impaired digestive and absorptive capacity.

This chapter will focus on the development of specific pediatric formulations which have been designed for children with cow's milk or multiple food allergies and specific formulations which may benefit children with other diseases such as short bowel syndrome, pancreatic, renal and hepatic insufficiency. A new area of research in pediatrics is potential pharmaconutrition in critically ill children. Formulae are enriched with single components or a combination of key substrates that might play a crucial role during intermediary metabolism in sepsis, inflammation, tissue healing, and growth. Pharmaconutrition is an extended concept where single components are investigated in a stepwise scientific procedure in order to identify effective disease-dedicated nutrition therapy. Finally, nutrigenomics refers to the findings that nutrients directly or indirectly alter gene expression in enterocytes, cytokine release and modulate immune function within and outside the gut.

Formulae for Treatment of Infants and Children with Intolerance to One or More Nutritional Components

Treating food allergy and other food intolerances is based on dietary elimination of causative food ingredients [3]. Therefore, formulations which exclude certain ingredients not only serve a nutritive purpose, but also serve as dietary treatment for a specific disease or condition. In older children, the exclusion of certain components may be possible by giving alternative foodstuffs which do not contain the non-tolerated nutrient. However, in infants or tube-fed older children, who fully or to a major part depend on a liquid formula, balanced formulations must be used in order to avoid under- and malnutrition. Intolerance may occur to one or more components in the food, such as carbohydrates, proteins, fats, or to selected amino acids or micronutrients due to allergic diseases, digestive disorders or inborn errors of metabolism.

Carbohydrate intolerance in young infants is rare. Lactose, the main carbohydrate in human milk and infant formula must be strictly avoided in infants with inherited galactosemia, and be largely removed in cases with the infantile form of lactase deficiency or with glucose-galactose malabsorption. These infants require a formulation largely (lactase deficiency) or completely (galactosemia) free of lactose or in the case of glucose-galactose malabsorption a glucose-free formula with fructose or inulin as the only carbohydrate. The genetic late-onset form of hypolactasia which becomes clinically relevant after 5–6 years hardly plays a role in EN since formulations designed for children beyond infancy are lactose free, with glucose polymers (maltodextrin) or occasionally starch as carbohydrates.

Glucose polymers have a low osmotic load and are well tolerated by most patients, except in the rare cases of inherited isomaltase or maltase deficiency. If carbohydrates reach the colon, they are metabolized by the colonic flora to short-chain fatty acids, which serve as energy fuel to the colonozytes or may be absorbed and contribute to the energy pool. However, if this rescue mechanism is overwhelmed, carbohydrate malabsorption results in osmotic diarrhea with acidic watery stools and bloating. In children with intestinal insufficiency, in particular severe enteropathy or short gut syndrome, the amount of carbohydrates is often the limiting factor to increase enteral feeding. This had been already recognized during the early balance studies with hydrolyzed infant formulations [4]. In these situations, special module feeding with a carbohydrate concentration of 2–3 g per 100 ml or per 70 kcal is recommended.

Protein intolerance is much more common and requires specific formulae. Normal infant formulae and formulations for enteral feeding in older children are based on cow's milk protein, with casein and/or whey. Formula-fed infants with an immunologically mediated intolerance to certain proteins or peptides of cow's milk (cow's milk protein allergy) need either an extensively hydrolyzed protein or an amino acid-based formula. For infants, human milk

or infant formula is the only source of nutrition during the first 4 months of life and continues to be a major source throughout the 1st year. Therapeutic formulae that can replace a regular formula in these disease situations are required for adequate nutrition. Infant formula based on soy protein or other animal's protein or formulae designed for adults are not recommended in infants who receive formula as the major nutritional intake [5, 6].

Formulae based on extensively hydrolyzed casein or whey have been used for more than 30 years. Due to amino acid imbalances, metabolic problems occurred with the old formulation [7]. The hydrolyzed formulae have been constantly adapted and improved, and fulfill a high safety profile with respect to growth pattern and plasma amino acid concentrations [8]. New formulations have been designed with highly purified lactose substituting part of the glucose polymer [9]. Lactose is beneficial for the infant's gut flora and improves calcium absorption compared to a lactose-free formulation of otherwise the same composition [10].

In infants with rare amino acid disorders such as phenylkentonuria or glutaraciduria, specific formulations depleted of specific amino acids (phenylalanine or lysine, respectively) have been developed.

Formulae for Infants and Children with Chronic Diseases and Special Nutritional Needs

Formulations for specific chronic diseases or situations have been commercialized for pediatric patients with specific needs (table 1). For most of these specialized formulations, randomized controlled trials in children are not available due to the low number of patients or for ethical reasons in severely ill infants. Therefore, the superiority to standard formulae has not been proven for most formulations, although safety data are available.

For infants with faltering growth, it has been widespread practice to add energy supplements (fat and carbohydrates) to standard infant formula. Whilst increasing the energy density, the protein-to-energy ratio is changed. Consequently, nutrient-dense infant formulae have been developed to overcome these problems. In infants with bronchopulmonary dysplasia, a nutrient-dense formula resulted in significantly greater length ($p < 0.05$), radial bone mineral content ($p < 0.01$) and lean mass ($p < 0.01$) at 3 months corrected age compared to a supplemented standard formula [11]. Male infants in the nutrient-enriched group had significantly greater whole body bone mineral content ($p = 0.02$). In another open, parallel, randomized study, 49 infants with faltering growth were randomized to receive a nutrient-dense formula or an energy supplemented normal infant formula for 6 weeks. Both formulae provided 1 kcal/ml [12]. No significant differences in tolerance, feed volumes or energy intakes were recorded but the nutrient-dense formula group received 42% more protein and 15–40% more vitamins and minerals. Blood

Table 1. Examples for special formulae for infants and children with certain diseases and situations

Disease or condition	Energy density	Modification of macronutrients	Modification of electrolytes, trace elements and vitamins per 100 kcal energy
Cow's milk protein allergy	⇔	Protein: extensively hydrolyzed or amino acids only	⇔
Phenyketonuria	⇔	Phe free	⇔
Glutaraciduria	⇔	Lysin free	⇔
Galactosemia	⇔	Lactose free	⇔
Infant with frequent regurgitation	⇔	Addition of starch or carob bean gum	⇔
Infants with failure to thrive, poor intake, heart disease	⇑	Normal relation of P: L:CH, but higher concentration, polyglucose to reduce osmolality	⇔
Cholestasis	⇑	Lipids, but MCT ⇑	Fat-soluble vitamins ⇑
Cystic fibrosis	⇑	Protein: hydrolyzed lipids ⇔, but MCT ⇑	Na ⇑, Se ⇑ Fat-soluble vitamins ⇑
Renal insufficiency	⇔	Protein: ⇓	K ⇓, P ⇓
Short bowel syndrome	⇔	Protein: extensively hydrolyzed Lipids ⇔ but MCT ⇑	⇔
Oxidation of long-chain fatty acids, lymphatic loss	⇔	Lipids: ⇓, but MCT ⇑	⇔
Intractable epilepsy, GLUT1 transporter defect, PDH deficiency	⇔	Lipids ⇑⇑⇑	⇔

PDH = Pyruvate-dehydrogenase; ⇔ = Unchanged, ⇑ = increased, ⇓ = decreased compared to standard formula for age.

urea concentration in the control group fell by 50% over the trial period, suggesting a suboptimal protein-to-energy ratio in the energy-supplemented feed.

For infants with frequent regurgitation, formulae with added thickening agents such as carob bean gum, starch or fibers have been developed. A recent meta-analysis including 14 RCTs concluded that thickening of the

feeding decreased episodes of regurgitation compared to controls, but not acid exposure to the esophageal mucosa [13]. In spite of the beneficial effect on the frequency of regurgitation, a switch to a so-called 'reflux formula' is not indicated in healthy and thriving infants who are not bothered by the symptom [14].

Fiber supplementation of enteral feeds for children and adults has been proposed to reduce gastrointestinal side effects of enteral feeding such as diarrhea or constipation [15, 16]. A recent meta-analysis of controlled studies in adults or children compared fiber-supplemented vs. fiber-free formulae given as the sole source of nutrition [17]. The analysis included 51 studies (43 randomized controlled trials) with a total of 1,762 subjects, but only few pediatric patients. In 13 randomized controlled trials, the incidence of diarrhea was reduced with fiber administration (OR 0.68, 95% CI: 0.48–0.96). In both patients and healthy subjects, fiber significantly reduced bowel frequency when baseline frequency was high and increased it when it was low, revealing a significant clinical benefit on bowel functioning.

Exclusive Enteral Nutrition as Therapy for Active Crohn's Disease

Crohn's disease (CD) and ulcerative colitis, the two major forms of inflammatory bowel disease, are characterized by a chronic relapsing course of destructing inflammation of the affected bowel. Recent studies have demonstrated rising incidences of pediatric CD [18]. It is generally accepted that environmental factors together with bacterial antigens cause a dysregulation of the immune system in genetically predisposed persons. Epidemiological studies identified several environmental risk factors for childhood onset inflammatory bowel disease. Dietary factors showed a shift towards high intake of the n-6 fatty acid linoleic acid and a high n-6/n-3 fatty acid ratio [19]. Following the concept of the hygiene hypothesis, a cleaner environment, lack of infections and exposure to certain microbes and an urban place of living, all predispose to inflammatory bowel disease [20].

At time of diagnosis, malnutrition and/or growth failure, a decreased muscle mass and bone mineral density are commonly present and may persist in spite of intensive therapy [21]. A therapy that leads to resolution of gut inflammation, whilst improving nutrition and growth could therefore be seen as an ideal therapy for the management of CD in children. Exclusive EN (EEN) provides optimal supply of energy, macro- and micronutrients and corrects malnutrition and its complications. EEN is as effective as systemic corticosteroids in decreasing inflammation, symptoms and inducing remission [22, 23], and even superior in achieving mucosal healing [24].

EEN is defined as exclusive intake of an elemental or polymeric formula given orally or via nasogastric tube feeding for at least 6–8 weeks instead of a

normal diet. The discovery that EEN is effective in decreasing bowel inflammation and inducing remission was found by chance in the late 60ies in adult CD patients who were fed with elemental diets to improve their nutritional status before surgery. After the first successful studies, it was already speculated that the diet may be effective because it provides nutritional support, is hypoallergenic, acts as a medical bypass around the affected area, or alters bowel flora [25]. The exact mechanism of how EEN leads to downregulation of the inflammatory process and mucosal healing in CD is still unclear.

Studies on EEN have focused on single components in the formulations such as nitrogen source and lipid composition. An updated Cochrane review of comparative studies confirmed that whole-protein formulae are as effective in inducing remission as amino acid-based formulae [26]. Several RCTs tried to identify the optimal lipid concentration (low versus high) and fat composition (MCTs versus long-chain triglycerides, n-6 polyunsaturated versus monounsaturated fatty acids, and n-3 polyunsaturated fatty acid) [27]. However, results are conflicting, with a nonsignificant trend for a better performance of a very low fat and/or very low long-chain triglyceride content in the formulations [26].

Only EEN, but not partially EN decreases inflammation in children with CD in spite of similar weight gain [28]. Close monitoring of CD patients demonstrated a rapid fall of c-reactive protein, the erythrocyte sedimentation rate, and immune markers such as IL-6 within 3 days of starting EEN, before any nutritional changes could be noticed [29]. Therefore, it is not a change in nutritional body status that induces remission in CD, but most likely a mechanism within the intestine itself. EEN leads to a rapid alteration of the luminal content and the gut flora [30], which in itself is modulating the cytokine response [31]. Leach et al. [32] investigated the changes to key intestinal bacterial groups of eubacteria, *Bacteroides*, *Clostridium coccoides*, *Clostridium leptum* and bifidobacteria, during and after EEN in CD children compared to controls, and correlated these changes to disease activity and intestinal inflammation. EEN had a significant effect on the composition of the predominant intestinal flora, which remained altered until 4 months after the dietary intervention. Changes of the gut flora have major effects on the bacterial fermentation in the intestine resulting in different levels of short-chain fatty acids, particularly butyrate. In animal models, butyrate was shown to have a strong effect on the epithelial cell signaling genes and alter in a concentration-dependent manner the secretion of IL-8 and IGF binding protein [33].

The mucosal immune system of the intestine and tissue gene expression may respond directly to nutrients or their metabolites or indirectly to alterations in the luminal environment, particularly the gut flora [33, 34]. The altered expression of signaling genes in enterocytes influences the mucosal immune response via release of different chemokines. The term nutrigenetics implies the (beneficial) effect of nutrients on gene expression and cytokine

response. However, the effect may not be due to a single dietary item or even a group of nutrients and may act differently in different patients.

Some beneficial cytokines such as transforming growth factor-β (TGF-β) may be delivered with the formula as a natural component of cow's milk. A casein-based formula for EN with appreciable contents of TGF-β was claimed to have additional benefits for EEN in CD patients [35]. TGF-β has a broad spectrum of activities including mucosal regulation of tolerance induction, anti-inflammatory action, secretory IgA expression and downregulation of major histocompatibility complex class expression; all effects may be beneficial in the treatment of CD [36, 37]. However, so far an RCT is lacking to prove that the TGF-β-rich formulae are superior over other formulations for mucosal healing. In fact, elemental formulae apparently free of cytokines including TGF-β are as effective as whole-protein formulations.

Immunonutrition and Pharmaconutrition

Nutritional pharmacology is defined as the use of specific substances for effects beyond their nutritional role. The term pharmaconutrition seems more appropriate compared to the term immunonutrition, which refers to feeds including a mixture of 'immune-enhancing' substrates with beneficial effects such as improved immune parameters and clinical outcomes.

Particularly four nutrients have been the subject of recent research: glutamine, arginine, nucleic acids, and essential fatty acids, particularly n-3 fatty acids. Glutamine has been classified as conditionally essential amino acid, with special usefulness in critically ill patients. Immunomodulation, gut protection, and prevention of protein depletion are mentioned among its positive effects in such circumstances. In newborn rats, glutamine administration partially prevented the sepsis-induced fall in plasma glutamine levels and reduced the concentration of both proinflammatory and anti-inflammatory cytokines [38]. Most RCTs have been performed in adult patients with trauma, burns, cancer or in critically ill patients on intensive care units. A recent meta-analysis of studies in adults showed no significant benefit of immunomodulating diets on mortality, but lower acquisition rates of new infections compared to control [39]. This effect was evident in patients in intensive care units and with burns, but less so in trauma patients.

Several clinical trials have been performed in adult perioperative cancer patients evaluating nutritional pharmacologic interventions using an enteral formula with a mixture of 'immune-enhancing' substrates including arginine, nucleotide, and n-3 fatty acids. The methodology of these studies was very diverse, which limits the ability to determine the best timing for initiation of immune-enhancing EN. The 2009 guidelines of the American Society of Parenteral and Enteral Nutrition recommended that individuals undergoing gastrointestinal or major head and neck surgery in whom there is preexisting

Table 2. RCTs of immunonutrition in critically ill children

Author	Intervention	Subjects	Clinical outcome and results	Comments
Briassoulis et al. [41]	Immune-enhanced formula for adults vs. pediatric standard formula	50 critically ill ventilated children on PICU 25 in each group	No change in mortality Decreased nosocomial infection rates and positive gastric aspirate culture rates More diarrhea in immune-enhanced formula	Immune-enhanced formula was not adapted to children
Briassoulis et al. [42]	Immune-enhanced formula for adults vs. pediatric standard formula	40 critically ill ventilated children with severe traumatic head injury, 20 in each group	No change in mortality, time on ventilator or PICU, decreased Il8 level and gastric colonization with immune-enhanced formula	Immune-enhanced formula was not adapted to children, most patients are included in 2005 study (not stated)
Barbosa et al. [43]	0.3 g/kg glutamine vs. 0.3 g/kg casein for 5 days	9 children <2 years on PICU 5 glutamine 4 controls	Bacterial infection 75% (3/4) in placebo vs. 20% in verum group Deaths 2/4 vs. 0/5	Sample too small for conclusions
Ward et al. [44]	0.65 g/kg enteral glutamine for 7 days vs. no intervention	55 children, chemotherapy, randomized cross-over trial	Symptoms of mucositis n.s., with glutamine: fewer patients needed parenteral nutrition (7 vs. 15) with a shorter duration	No toxicity, poor taste of glutamine, possible bias due to no blinding

malnutrition would benefit from 5–7 days of preoperative supplementation [40]. Fewer studies have examined supplementation with single nutrients. The data on the use of formulae with supplementation of a single nutrient such as arginine or glutamine are too limited to make recommendations.

Only a few RCTs have been performed with immune-enhancing EN in children (table 2). Briassoulis et al. [41] reported their results of a blinded RCT in children admitted to the pediatric intensive care unit because of sepsis, respiratory failure, and severe head injury and a need for mechanical ventilation of ≥5 days. EN was started within 12 h of admission. Fifty critically ill children were randomized to receive either an immune-enhancing formulation designed for adults containing glutamine, arginine, n-3 fatty acids, and antioxidants, or

standard age-appropriate pediatric formulation. Both formulae were isocaloric. Enteral caloric intake with predicted energy expenditure was reached by day 4. The study did not show any differences in the main outcome parameters, although the authors report a decrease in nosocomial infection rates and positive gastric aspirate culture rates in the intervention group compared to standard formula group. The immunologically active formula was less well tolerated with more diarrheal episodes, which may be due to the higher osmolarity compared to the control formula (420 vs. 206 mosm/l). The same investigators reported their results of an RCT in 40 children with severe head injury using the same formulae and study design [42]. Although not particularly stated in the paper, this recent study seems to include a proportion of the previous study. Again, no difference with respect to mortality and length on ventilator or intensive care unit was noticed. Il8 levels were reduced and significantly less positive gastric cultures were noticed with the immune-enhanced formula. RCTs using enteral glutamine supplementation were performed in a pilot study including 9 seriously ill infants [43]. Improved outcomes were reported in the glutamine-supplemented group, but the numbers are too small for meaningful conclusions.

Glutamine supplementation has also been used in a randomized crossover study in 50 children who received at least two cycles of identical chemotherapy. Although the main outcome parameters, symptoms of mucositis, did not differ in relation to enteral glutamine application, parenteral nutrition was significantly less often required compared to the non-intervention, and in those who needed parenteral feeding, the duration was shorter. This could be an indirect sign that glutamine supplementation improved gut and barrier function during chemotherapy.

In conclusion, a normal functioning immune system is crucial to our health, and diet is one of the major exogenous factors modulating immune regulation and competence. Recently, nutrition research has focused on the role of foods or specific food components in enhancing immune response, improving health, reducing disease risks and even treating diseases and inflammatory processes. EN has a greater potential than providing optimal nutrition, since changes in luminal contents directly affects molecular pathways, cytokine expression resulting in decreased inflammation and expression of class II major histocompatibility complex.

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Discussion

Dr. Greer: What is Modulen exactly and does anyone have any idea how it really works?

Dr. S. Koletzko: Modulen is a casein-based formulation which has been used in most studies in pediatric Crohn's patients. It contains high levels of TGF-β; however, we don't know whether this has any effect since we have no comparison between the same formulation without or with TGF-β. Modulen is – at least in Europe – the preferred and most commonly used formula for children with Crohn's disease. This may have historical reasons.

Dr. Ruemmele: We know roughly where the idea comes from. Unfortunately, in the past these patients, adult patients in the beginning, required surgery for Crohn's disease and as part of the preparation for surgery you had to improve their nutritional

status and use parenteral nutrition or in those who tolerated it enteral nutrition. Surprisingly, after the preparation phase some of these patients did not require any surgery anymore, at least temporarily, and that was the beginning of this enteral nutrition story for Crohn's disease. So it was a surprise, it was not intended to improve the disease, just to improve the nutritional status.

Dr. S. Koletzko: The first studies were conducted back in the 1960s in Ireland by O'Morain and some surgeons [1, 2]. They used an elemental diet based on amino acids only. I can't answer why Nestlé came up with an exclusively casein-based whole-protein formula for this purpose.

Dr. Haschke: There was a whole Nestlé Nutrition Workshop on this at the end of 1995 when this TGF-β-enriched formula was launched. The company made a lactose-free product based on casein which worked very well against diarrhea, and the idea came from the pediatricians to enrich it with TGF-β which they thought could be beneficial.

Dr. S. Koletzko: But the question remains, does the TGF-β content matter? Since we see the same remissions rates with elemental diets which do not contain TGF-β, I just wonder if this has any additional benefit or not? We just don't know.

Dr. Lentze: I wanted to come back to Crohn's disease and to nutrition. When I talk to my colleagues from adult gastroenterology, they are always astonished that we do this in children because they have studied this in detail and the number of adult patients studied in gastroenterology is much higher than the number of children. My question is what is the difference between the two groups, and could it be that we haven't studied enough children?

Dr. S. Koletzko: First of all it also works in adults. The per protocol analyses in these old studies show almost the same efficacy. However, many adults in the nutritional treatment arm dropped out and as a consequence, the intention to treat analysis was in favor of steroids. Children have less choice; they are more compliant with the treatment. This is part of the answer. With respect to adults, there are recent results from Japan reporting the successful treatment of Crohn's patients with exclusive enteral nutrition. Unfortunately, nutritional therapy is – as a medical treatment – more effective in newly diagnosed patients compared to patients with longer disease duration. At the pediatric IBD meeting in Paris in September 2009, Annemarie Griffiths presented the original data from the Canadian nutritional trial which unfortunately have never been published. The results showed that enteral nutrition is less effective in patients with longer disease duration. Therefore, to compare the efficacy in adults and children, they should be matched for disease duration.

Dr. Singhi: My question is about nutrition in critically ill children. Do we have any scientific basis for using enteral nutrition as we've done it until now, because there are no randomized trials available, except in immunonutrition. Are there any studies that deal with energy-dense enteral nutrition in these children? And have we attempted in any way to define the components of the increased catabolism or weight loss in these patients, and tried to incorporate them in the formula that we give in enteral nutrition?

Dr. S. Koletzko: The benefit of energy-dense formulations in critically ill children depends on the underlying disease. The beneficial effect has been shown in randomized controlled trials in infants with failure to thrive but a normal gut function. The situation may be different in infants with enteropathy or short gut. Increasing energy density means increasing osmolarity which is often not tolerated. Carbohydrate concentration is the limiting factor in most of these patients. However, if you have a normal gut function, energy-dense formulations are preferable compared to supplementation of a standard infant formula with polyglucose and fat.

Dr. Singhi: Do you have any studies to support all this?

Dr. S. Koletzko: Yes, I showed you two studies, one in infants with bronchopulmonary dysplasia which showed a significantly greater length, bone mineral content and

lean mass at 3 months with the energy-dense formula compared to a supplemented standard formula. Both formulae provided 1 kcal/ml [3]. The other randomized study was performed in infants with faltering growth; most of them had congenital heart disease [4]. Again, there was better weight gain and growth in the children with the energy-dense formula.

Dr. Shenoi: In our country, we don't have special formulas for children with inborn errors of metabolism. Are there any studies on nutritional supplementation for these children?

Dr. S. Koletzko: Sorry, I am not the right person to answer this question. We give part of the protein as human milk and then supplement it with special amino acid mixtures, for example free of phenylalanine for phenylketonuria. Do you want to add anything, Dr. Koletzko?

Dr. B. Koletzko: This depends, of course, on the type of underlying metabolic disease. If the problem is protein restriction, then it is our standard practice to combine human milk with a disease-specific amino acid formulation. In infants with phenylketonuria, for example, we can usually provide half of the meals by breastfeeding and half of the meals by a phenylalanine-free infant formulation during the first months of life. If you have a more restricted tolerance to some amino acids than in phenylketonuria, or if you have critical reactions like in some children with organic acidemias or hyperammonemia, the dietary management becomes more complicated, and sometimes breast milk can only be given by bottle in strictly defined amounts. There are also disorders where no breastfeeding is possible, for example galactosemia and some forms of long-chain fatty acid β-oxidation disorders.

Dr. S. Koletzko: And is there an ideal human milk fortifier?

Dr. B. Koletzko: We have good human milk fortifiers for preterm babies, but I would not qualify any of them as ideal. There may be considerable room for improvement.

Dr. Klassen: My question is related to the use of extensively hydrolyzed formulas and the development of the gut. Since proteins are absorbed in the gut mainly as peptides and only in part as free amino acids, would you suspect that providing only very small peptides to the infant's digestive tract could potentially have a long-term effect on gut development?

Dr. S. Koletzko: My preference is a formula based on hydrolyzed protein rather an amino acid based formulation, because peptides may have a beneficial effect on gut barrier function and absorptive capacity and even on the gut flora. We also use hydrolyzed formulae in children with short gut because peptides have a better effect on the adaptation process compared to amino acids. In addition, the osmolarity is lower. However, with respect to maturation and long-term effect I think nobody looked at that.

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Molecular Mechanisms of Pediatric Nutrition

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Abstract

Over the last years, major scientific advances allowed to decrypt the human genome with over 22,000 protein-coding genes. We do know some of these genes, but yet only few of their functions and even less of their control and regulation as well as the complex interplay between different genes and their products. Genotyping allows to analyze particular genes, but it cannot predict phenotypes. What can we expect from the recent scientific advances with regard to the needs of the developing child or adult and the intention to prevent disease and/or to improve life quality? We address two particular points in this review: the (direct/indirect) interaction of nutrition with genes of the host and the impact of genetic variations (polymorphisms) on requirements, tolerance or metabolism of nutrition. Over the last 5 years, major research efforts were made to address the potential interaction of nutrition and genes, now named nutrigenomics (interaction of nutrition and genes) and nutrigenetics (impact of gene variants on nutrition and/or their metabolism). We give in this review examples of molecular approaches in the understanding of this bidirectional interaction between nutrition and genes, focusing also on epigenetic imprinting.

Introducing Remarks

At the reference center for disease prevention, year 2039 somewhere in Europe: The parents, both suffering from inflammatory bowel disease (IBD), bring their two healthy children (2 and 5 years old) in your office and ask for advice how to prevent them from developing IBD. They emphasize that several family members are affected by Crohn's disease, indicating the familial nature of their disease. After a complete physical exam, you check their chip card for their individual genetic and

microbial data. You enter additional key data in the computer which prints out the recommendation for an individual lifestyle and nutritional disease prevention program. Fiction or clinical practice of tomorrow?

Introduction

The scientific progress in various biomedical fields over the last 10 years is impressive. A major breakthrough in this evolution is related to the outstanding progresses in genetics allowing to uncover the human genome with over 22,000 protein-coding genes. However, as often in science, advances open new questions and knowledge becomes more and more complex and difficult. We now have the (very expensive) techniques to analyze the over three billion of base pairs across our 23 pairs of chromosomes. And we do know some of these genes, but yet only few of their functions and even less of their control and regulation as well as the complex interplay between different genes and even more important their products. Genotyping allows to analyze particular genes, but it cannot predict phenotypes.

What can we expect from the recent scientific advances with regard to the needs of the developing child or adult and the intention to prevent disease and/or to improve life quality? One might expect that this new genetic knowledge will help us to better understand the interactions between external, environmental factors, such as nutrition, and the host.

There are two major questions, which we intend to address in the following review:

1 Does nutrition interact (directly/indirectly) with genes of the host?
2 Do genetic variations (polymorphisms) impact on requirements, tolerance or metabolism of nutrition?

If this new biomedical and genetic knowledge (enabling the development of new analytic tools) might help us to elucidate at least one of these questions, we can expect a real 'revolution' in the field of nutrition in the near future. In fact, over the last 5 years major research efforts were made to address the potential interaction of nutrition and genes, now named nutrigenomics (interaction of nutrition and genes) and nutrigenetics (impact of gene variants on nutrition and/or their metabolism).

However, the dualistic view of the interaction between nutrition and genes of the host is oversimplistic. At least one third player has to be introduced to complete the picture: the intestinal microflora and the effect of nutrition on the commensal bacteria which in a subsequent step impact on the host. However, this aspect will not be detailed in this review.

That the interaction of nutrition and genetics has an important effect on human well-being and disease development is a quite well established concept [1]. For instance, a particular and specific genetic background is required to develop celiac disease, an immune-mediated inflammatory disease of the

gastrointestinal tract related to the oral intake of gliadin. It is now well established that the DQ2 or DQ8 structure is indispensible for gliadin to bind to the T cell receptor, starting a long and chronic cascade of T cell-mediated inflammation [2, 3]. This means that a precise and single genetic factor decides if a host cell can bind and recognize an alimentary antigen, i.e. gliadin, responsible for disease development.

Nutrient–Gene Interaction

Theoretically, different ways of nutrient–gene interaction are possible.

Nutrients can interact directly with a nuclear receptor and behave like transcription factors, able to induce or repress genes. A good example is the interaction of vitamin A derivates with the retinoic acid (RA) receptor proteins, which can potently control gene expression via so-called RA response elements in the promoter region of distinct genes [4]. This interaction can have extremely important functions, since behavior and biological functions of antigen-presenting cells, such as dendritic cells, is markedly influenced by the availability of RA. In the presence of RA, a tolerogenic DC response is obtained within the intestinal mucosa, whereas the absence of RA will cause a potent upregulation of inflammatory responses [5]. Other examples are dietary fatty acids or vitamin D which via peroxisome proliferator activate receptors (PPAR) or the vitamin D receptor, respectively, bind directly to the DNA, thereby controlling gene expression. These are examples of short-term signals that directly alter gene transcription. But the effect stops immediately as soon as the specific nutrient is removed.

In contrast to these short lasting and highly specific effects via response elements on gene expression, there is also the possibility to interfere in a long-lasting, sometimes lifelong manner. These sustained effects can be mediated by direct modification of the DNA in form of methylation of CpG motifs or via methylation, acetylation or eventually biotinylation of histones [6–8]. Histones are nuclear proteins on which the DNA is wrapped in a very dense manner. This tightly packed DNA is largely inaccessible to transcription; however, after histone modification (methylation or acetylation) these molecules change their tertiary structure. They uncoil or unfold, thereby giving access of transcription factors to previously hidden promoter regions inducing gene expression. Most often histone modification goes along with DNA methylation which occurs at cytosine bases (CpG islands), a mechanism indispensible for genomic stability [9]. In the human genome, between 60 and close to 90% of CpG islands are methylated.

Usually, DNA methylation reduces gene expression (gene silencing). We now know the precise mechanism of this gene silencing in that the methylated 5′-CpG-3′ attract capping proteins that hinder the access to the gene for transcription factors (fig. 1). This mechanism of DNA methylation or histone acetylation/methylation is an only recently discovered, but extremely important

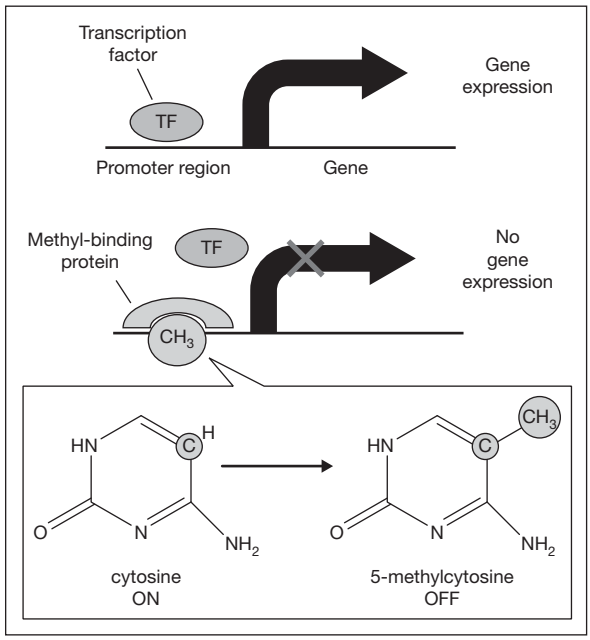

Fig. 1. Epigenetic mechanism of DNA methylation resulting in gene silencing, modified from [8].

mechanism to control gene expression. The knowledge and research in this area which is now called epigenetics is dramatically advancing. The plasticity of the human genome via epigenetic modulation (resulting in the so-called epigenome) is amazing [10]. There are good experimental data to believe that fundamental processes such as cell differentiation, X chromosome inactivation and genetic imprinting are all consequences of epigenetic regulation. Epigenetic modulation does not only result in a postgenetic modification of an individual, but these epigenetic modifications can also be transmitted over generations.

One might ask if alimentation can impact or influence epigenetic phenomena. The clear answer is yes! Via alteration of the levels of alimentary available methyl groups, epigenetic modulation can cause subtle and important, sometimes even lifelong consequences.

One of the nicest examples of epigenetic regulation and the impact of nutrition on this process comes from honeybees *(Apis mellifera)*. The *queens* of honeybees are characterized by fertility, a markedly larger phenotype with a considerably longer life span (2 years) compared to the majority of bees which are sterile, show the smaller 'worker' phenotype and live only a few weeks (fig. 2). What is responsible for the fact that genetically identical larvae end up with so contrasting phenotypes and functions? The only difference between these two is that a few female larvae are fed the so-called 'royal jelly', a poorly

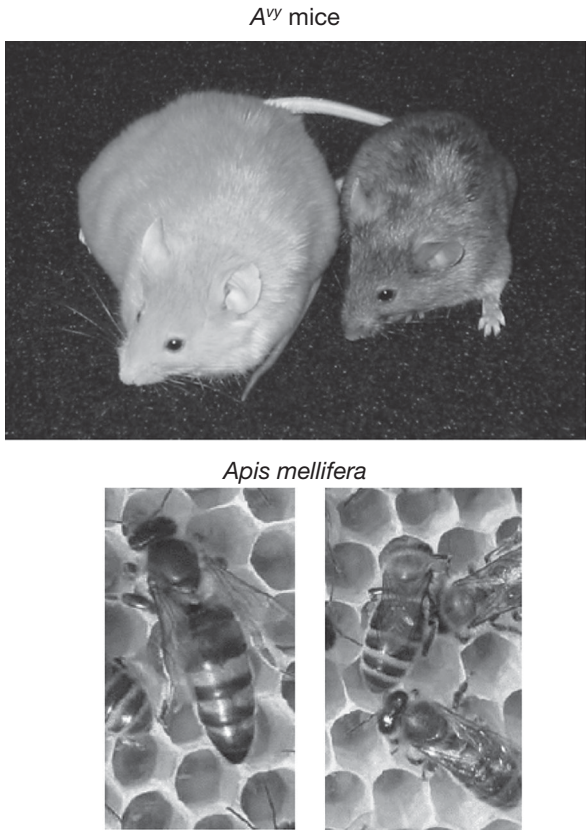

Fig. 2. Difference of phenotypes (while identical genotypes) due to epigenetic modification in A^{vy} mice and honeybees. A^{vy} mice: left, low DNA methylation status; right, high methylation status. *Apis mellifera:* left, queen (higher DNA methylation); right, working honeybee (lower DNA methylation).

defined aliment. These larvae end up with the 'royal' phenotype of queens. Very recently, it could be confirmed that the differing nutritional input (royal jelly) results in a higher degree of DNA methylation modifying the expression of genes, such as Apis, implicated in the modulation of epigenetic regulation [11]. One key element seems the activity of DNA methyltransferase Dnmt3 in honeybees. Suppression of Dnmt3 in larvae results in a queen-like phenotype, further emphasizing the importance, but also the plasticity of the system. This observation clearly confirms that environmental factors via epigenetic modification have a major impact on the final adult phenotype.

Another interesting and well-studied observation is the impact of maternal nutrition (before and during pregnancy as well as during suckling) on the phenotype of the pups of so-called *agouti* mice. The agouti gene is expressed in hair

follicles of mice during a brief stage of hair development and growth. It encodes a paracrine signaling molecule which is responsible for the production of a yellow pigment by specialized pigment-producing cells. In wild-type mice, a yellow band appears on the otherwise brownish hair. In the viable yellow agouti (A^{vy}) mice however, an intracisternal A partial (IAP), a retrotransposon common in the mouse genome, has spontaneously inserted into the *agouti* gene [12]. The result is a constitutive and permanent expression of agouti in all tissues, due to a cryptic promoter within IAP. Therefore, A^{vy} mice show a yellow coat and they are markedly obese. This can be explained by the ectopic agouti expression and ability of agouti protein to bind antagonistically to the melanocortin-4 receptor in the hypothalamus, thereby causing hyperphagia. For a still unknown reason, insertion of IAP into the agouti gene also causes epigenetic dysregulation, resulting in spontaneous interindividual variability in CpG methylation at the A^{vy} locus. Therefore, within a single litter of genetically identical A^{vy}/a mice, some have a very low level of methylation resulting in a yellow and obese phenotype, whereas those with a high methylation level, repressing agouti, display the normal 'agouti' phenotype. This interesting model opened the door for nutritional intervention studies in supplementing high or low levels of methyl donors. Indeed, a supplementation with choline, vitamin B_{12} and folic acid before and during pregnancy clearly shifted the coat color from yellow to brown, along with body fat mass differences (fig. 2). Indeed, Waterland et al. [13] demonstrated that the differences in maternal food supplementation cause a differing methylation status at A^{vy}, which clearly correlated with the definite adult phenotype of the offspring.

These data provide clear evidence that specific and targeted nutritional intervention at a critical time point of development causes a permanent phenotypic change by epigenetic gene regulatory mechanisms.

The interaction of nutrition with genes is not unidirectional, it should also be analyzed the other way round. There are excellent data indicating that genetic variations (polymorphisms) have a major impact on nutritional requirement as well as functions. One well-studied interaction is the requirement and metabolism of folate. The enzyme 5,10 methylenetetrahydrofolate reductase (MHTFR) is a key enzyme in folate metabolism [14, 15]. MHTFR has an important role in supplying methionine, which is important in many metabolic pathways, such as the production of neurotransmitters and the regulation of gene expression. Folate is essential to the efficient functions of this enzyme. MHTFR has a common single nucleotide polymorphism (SNP) at position 677 with a C to T transition, resulting in the conversion of an alanine to a valine (MTHFR Ala 222Val); this SNP results in a thermal labile version of the protein which has a markedly reduced enzyme activity. People with one or two C copies have normal folate metabolisms, whereas homozygous persons (TT) with reduced enzyme activity have elevated plasma homocysteine levels, unless they have an increased folate intake. This allows to compensate the slow enzyme activity by an increased substrate supply. The link between increased homocysteine levels and increased risk for cardiovascular diseases, one of the main causes of mor-

tality in our society, is well established. In addition, various efforts are underway to control or lower homocysteine levels in view of disease prevention. On the other hand, the observation that approx. 15–30% of the European population has the TT genotype raises the question why this polymorphism persisted over generations and if there is not a distinct evolutionary advantage.

Another important aspect of this gene-nutrition interaction in the folate metabolism is the observation that the risk of having a child with a neural tube defect (spina bifida, etc.) is several times increased in pregnant women with another very common SNP (MTHFD1-G1958A). This risk clearly differed between mothers with the highest choline intake and mothers with the lowest choline intake, with the former having a lowered risk for a baby with a neural tube defect [15].

The list of examples how genetic factors may impact and influence nutritional requirements is getting longer with at least 20 genes that have a polymorphism that may confer a specific disadvantage in the view of disease development, but which may be overcome with a specific dietary modification. Other well-studied interactions are the effect of mutations in the apolipoprotein E protein (e4/e4) or polymorphisms of APOA1 or PPARA and the intake of lipids or cholesterol and the risk of the development of cardiovascular diseases [16, 17]. To increase this knowledge and to create a research network, the European Nutrigenomics Organisation was built up (www.nugo.org) in 2004.

Conclusions

We are at the starting point to integrate the growing knowledge of genetic variations and the postgenetic (epigenetic) modulation and plasticity in the field of the interaction of environment and the host. This is particularly important for the understanding of developing organisms, prenatally as well as postnatally. One major environmental factor is nutrition, especially for the developing child. Research in the field of nutrigenetics and nutrigenomics is at the starting point, and I am sure that it will 'explode' over the next two decades. However, there are major limitations and key questions that have to be addressed and solved on a common ground. Who are the drivers of the development of nutrigenomics and its applications to disease prevention or healthy living and aging? Is it the private sector or health professionals? How are ethical or confidential aspects defined and controlled (for example, are life insurances allowed to consider the risk of persons with an MTHFR 'TT' polymorphism, etc.)? The main drivers should be on one side the societies themselves and on the other side strong international science foundations elaborating on the clinical value of genetic risk factors and the effects of specific nutritional targeting in individuals with a particular (genetic) susceptibility or risks factors. Therefore, in the near future, individual nutrition advice will enter into clinical routine and will be part of everyday practice for healthy persons, as well as in the cure of some diseases.

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Discussion

Dr. Cai: Could you comment about the relationship between diabetes and genetics?

Dr. Ruemmele: As in many diseases, there is also a genetic background in diabetes. But it's not a monogenetic background which means there is one or a couple of single genes which are responsible for the development of the phenotype which can be seen in some very rare monogenetic causes of congenital diabetes, no the cause of diabetes is multigenetic. Over one or two generations, the genes do not change completely. If you look at the incidence of these diseases over the last 50 years, our genes did not change considerably, however many environmental factors did change.. So with regard to genetic aspects for the disease development, you are in the heart of epigenetic modification. It's some type of lifestyle which changed considerably which impacts on different levels.

Dr. Yang: My question concerns intrauterine growth retardation. As we know, a baby with IUGR is at higher risk to suffer from metabolic diseases in adulthood than a normal baby. Do you think it is because early nutrition has an effect on epigenetic and genetic information?

Dr. Ruemmele: It's extremely difficult to give a clear answer to this question because I think we would have to redo a huge bench of studies we did in the past

looking on the genetic information and the epigenetic modulation in these high risk group of newborn children. At this time point, we can only speculate on the molecular events. But I think Dr. Koletzko can comment on this.

Dr. B. Koletzko: Please allow me to come back to the question is it genetics or is it substrate supply that matters? In my view it is an interaction of both. A very good example is the effects of the polymorphisms of the fatty acid desaturase 1 and 2 (FADS1 and FADS2) that we first described in 2006 [1]. We found about one quarter of the European population studied to have a low activity of the desaturating enzymes and therefore a low level of essential fatty acid conversion into the long-chain metabolites. This effect has been confirmed in several other studies [2–4]. If one finds effects of these polymorphisms of PUFA metabolism on outcomes such as IQ in breastfed and non-breast-fed populations or as we have described before on the prevalence of atopic dermatitis and rhinitis [1], this represents pretty convincing evidence for an effect of PUFA on these outcomes. George David Smith in Bristol has coined the term Mendelian randomization, proposing that polymorphisms are distributed in the population at random, and unless there is a mechanism that the polymorphisms are directly affecting the end point, then you really can consider effects of polymorphisms on end points as evidence that it's as close to a randomized clinical trial as you could imagine. Thus, it is justified to conclude from the available observations that PUFA provided with breast milk affect later cognitive development, because breastfeeding has an effect on IQ development if subjects have a certain genotype of PUFA metabolism, whereas breastfeeding has no effect on IQ if subjects have another genotype of PUFA metabolism, assuming that the choice to breastfeed is not related to the FADS polymorphisms. I think the real exciting story here is that we may have infants who have a higher requirement for long-chain PUFA than others, depending on their genotype, to achieve the very same cognitive development outcome or to achieve the same allergy risk. Thus, some people may need different intakes than others. Is that an academic discussion or is it of practical relevance? With respect to folic acid supply perhaps it is of academic interest only. Given that folic acid is so cheap, one could easily provide a sufficient amount of folic acid to every woman of childbearing age, rather than doing genotype testing. With respect to PUFA supply, however, it could be a practically very relevant question, for example if you think of the intensive care situation where today some interventions are made using omega-3 fatty acids enterally or parenterally to downregulate the inflammatory response. Here, one could imagine doing genotype testing before dosing such a targeted clinical intervention.

Dr. Shenoi: I was just wondering whether anybody has studied the genetics of the bacteria in certain disease like Crohn's disease because there is an interaction between food bacteria and the illness.

Dr. Ruemmele: There is a huge literature on the composition of the bacteria and the change in the gut. There are few papers analyzing the genetic variance between the bacteria because at the moment the question is to identify the different bacteria which are normally implanted in the GI tract and what are the quantitative and perhaps more important qualitative changes that occurre in IBD patients. So I think the answer will come in the next years, but at the moment there is no particular genotyping of a single strain or different groups of strains which look different, if this was your question, in Crohn's disease patients. But we know a lot on the genotyping of patients. On the host side, there are susceptibility factors which are clearly defined and which contribute to the risk to develop the disease, good examples are mutations in nod2, IL23 receptor polymorphisms, autophagy genes etc.

Dr. Cooper: I was just wondering whether identical twins might be a fertile ground for the hypotheses generated in this field. Has any work been done in this area?

Dr. Ruemmele: There is literature on epigenetic analysis in identical twins. The risk to develop Crohn's disease from a genetic point of view between identical twins is 50%, it's not 100 or close to 100; but between brothers or non-identical twins this risks is lower with 5–10%. So genetic factors contribute to a high degree to the risk of disease development But there is a lot of space for other modifications, which impact on disease develioment,. These factors are considered to be environemental, or exogenous factors, opposed to the endogenous genetic factors. An indeed there are good theoretical arguments to believe that epigenetic modifications can contribute to disease onset or perpetuation. So indeed it's an ideal situation to compare the impact of the environment between two individuals who have the same genotype. The genetic studies on twins and epigenetic studies are of major interest to track down some effects.

Dr. S. Koletzko: A polymorphism which is involved in the metabolism of fatty acids with potential beneficial functional effects may cluster over generations in certain populations. One example is the lactase persistence gene in north-eastern Europe. Since a low socioeconomic status is related to a low breastfeeding rate, it could be that in the group with the lowest socioeconomic status there is an enrichment of certain polymorphism and not a random distribution.

Dr. B. Koletzko: As far as I recall, the investigators found a direct effect on the association of polymorphisms with IQ. They found no association of the polymorphism with breastfeeding, and they found an interaction between breastfeeding, polymorphism and IQ.

Dr. Dhansay: You said that vitamin A may be pro- or anti-inflammatory. Based on that statement can you make any recommendations for vitamin A supplementation especially in developing countries?

Dr. Ruemmele: Vitamin A is very interesting to look at. The local concentration of Vitamine A such as in the intestinal mucosa predefines the way dendritic cells drive T cell responses. However, it is important to strengthen that this very powerful effect of Vitamin A on T cell responses reflects is dependent on local, ie tissue concentration of the vitamin, it does not necessarily reflect the intake, or the total concentration of vitamin A or stocks in your organism, it's a local effect, it's very local. It is interesting to underline that vitamin A orients immune responses towards tolerogenic or anti-inflammatory responses and thereby avoids proinflammatory responses. If under the same condition experimental conditions you induce a T cell response, now vitamin A levels are low, you can shift towards a proinflammatory answer. I am not sure that based on this fundamental observation for inflammation and regulation of inflammation we should make any recommendations on the level of supplementation of vitamin A, particularly in developing countries or under special conditions. Before we can do this, we need further analyses on the tissue level, and I do not want to make any new recommendation on vitamin A intake other than those existing today.

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Epidemiological Research Drives a Paradigm Shift in Complementary Feeding – The Celiac Disease Story and Lessons Learnt

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Abstract

Breast milk is the initial natural food for infants, but already during the second half year complementary feeding is essential. Epidemiological research, first on celiac disease and later on atopic diseases, has driven a paradigm shift with respect to most favorable age to introduce complementary feeding. Simplified, this implies a shift from later to earlier introduction, which is now taken into account in recommendations on infant feeding. Complementary feeding, including all foods, should not be initiated for any infant before 4 months of age, and not later than around 6 months, including infants with elevated disease risk (e.g. for celiac disease or atopic diseases). Motivating reasons could be that ongoing breastfeeding provides an 'immunological umbrella' and/or a different age interval gives a 'window of opportunity' for developing oral tolerance towards gluten and other food antigens. This will for some infants be in conflict with recent WHO recommendations on exclusive breastfeeding for 6 months. Epidemiology has evolved over time and could, if increasingly used, contribute even more to innovations in pediatric nutrition and other phenomena related to population health.

Introduction

Maternal and infant food habits deserve attention, since early nutrition, during intrauterine and infant life, is important not only for a child's health, but also throughout adult life [1, 2]. Flavors experienced early in life, including amniotic fluid, breast milk and complementary foods, are likely to guide lifelong food preferences and choices [3].

Breast milk offers nutritional, antimicrobial, and immune-modulating advantages over infant formula to the recipient infant [4–6]. The World Health Organization (WHO) recommends that infants should be exclusively breastfed for the first 6 months of life, and thereafter receive nutritionally adequate and safe complementary feeding while breastfeeding continues for up to 2 years or beyond [4]. Introduction of foods and liquids in conjunction with breast milk or infant formula – referred to here as complementary feeding – is essential for the nutritional needs of the infant, fostering normal growth and development and enabling the transition to family food [7]. Evidence-based knowledge on how best to feed infants is growing, although many unknowns remain. Dissemination of this knowledge and implementation in daily practice is occurring at a slow pace. Across the globe, complementary feeding practices vary according to culture and available resources, and there is potential for improvement in many settings.

Celiac disease (CD), also called gluten intolerance, has emerged as a global public health problem, from previous perceptions as a rare disease only affecting European children [8]. Classically, the disease presents during the first years of life with diarrhea and failure to thrive, but nowadays atypical presentations at any age are increasingly recognized. Symptoms and signs are often misinterpreted, leading to delayed or missed diagnosis, with extensive short- and long-term negative health consequences. CD is effectively treated with life-long exclusion of foods containing any gluten-bearing cereals (wheat, rye, or barley). Epidemiological research has revealed that infant food habits play a role in development of autoimmune diseases, such as CD [9], and also influence the risk of atopic disease, another increasingly common health problem [10]. Such findings have been taken into account in recent revisions of European and American infant feeding recommendations [6, 7, 10], and are also likely to be relevant for infant health in other parts of the world.

In this chapter, we show how epidemiological research has driven a paradigm shift in complementary feeding. We describe this paradigm shift and the reasoning behind it with illustrations from epidemiological research on CD and also partly from research on atopic disease. We give a brief overview of epidemiology from a methodological perspective again using CD research as the example. We hope that this will inspire other researchers to embark on multidisciplinary research involving epidemiological approaches, for example in pediatric nutrition.

A Paradigm Shift Concerning Complementary Feeding

The Prevailing Thinking Was 'Later Is Better'

During the 1920s and following decades, it became normal to introduce solid foods to infants only a few months old, which is still the practice in many low- and middle income countries. During the 1970s, concerns were

raised about possible adverse effects arising from the early introduction of solids, which thereafter were reflected in several guidelines on infant feeding. European infant feeding recommendations in 1982 stated that: (a) solid foods should not be introduced earlier than 3 months or later than 6 months; (b) gluten-containing foods (wheat, rye and barley) should not be introduced before 4 months and postponement until 6 months may be advisable, and (c) certain foods known to be highly allergenic such as eggs and fish are probably best deferred until 5–6 months [11]. When WHO in 2001 launched their recommendation of exclusive breastfeeding for 6 months, this influenced infant feeding habits in many countries towards further delay in introducing solids [4]. Over the same period, other guidelines were launched that recommended avoiding food allergens such as peanuts, fish, and eggs up to 1 year of age, or even longer, as this was expected to reduce the risk for atopic diseases [12]. The postponed introduction of gluten was expected to delay the onset of CD, or even possibly to reduce the risk of the disease. The prevailing thinking about introducing solids seemed to be 'later is better'.

Epidemiological Research Drives a Paradigm Shift towards 'Earlier Is Better'

Many were surprised when Sweden, in the mid 1980s, was struck by an abrupt fourfold increase in CD occurrence among children under 2 years of age, leading to levels higher than ever previously reported [13, 14] (fig. 1). This unusual cumulation of newly diagnosed CD cases was observed by most pediatricians in their clinical practice. Strict diagnostic criteria involving small intestinal biopsies were followed throughout the epidemic [15] (fig. 2).

The start of the epidemic followed nationally launched recommendations to delay the introduction of all gluten-containing foods to infants until 6 months of age, in line with changes at that time in many European countries [13]. This was the starting point for extensive epidemiological research with findings that initially were met with skepticism [9], but later accepted and often referred to as a benchmark in CD research.

Our findings about this CD epidemic, in a genetically stable population, illustrated that the disease must have a multifactorial etiology going beyond genetic disposition and exposure to gluten in the diet. In studying 12-year-old children born during the peak of the epidemic (in 1993) as part of a CD screening program (using serological markers, followed by evaluation of the small intestinal biopsy in suspected cases), who as infants had been introduced quite abruptly to gluten often without ongoing breastfeeding, we revealed a CD prevalence of 3% (95% CI: 2.5–3.3) [16]. This should be seen alongside the often assumed universal prevalence of around 1%. The highest recorded prevalence, 5.6%, was reported among Saharawi children in Algeria (95% CI: 4.2–7.1) [17]. It is worth noting that CD cases have been reported from all continents, with rising incidence in many places.

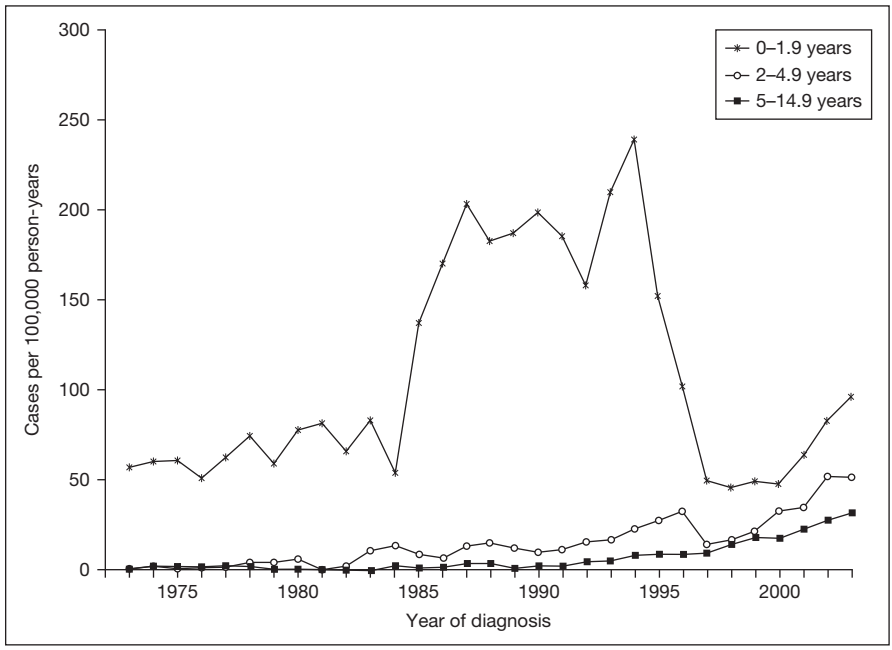

Fig. 1. Annual incidence rates of CD in children from 1973 to 2003. From Olsson et al. [14], with permission.

This has stimulated us and others to pursue research for identifying strategies for primary prevention, thus avoiding disease development at least for some people [9, 18, 19]. Most importantly, we showed that CD risk is lower if breastfeeding is still ongoing when gluten-containing foods are introduced, and if gluten is given in small to medium amounts (as compared to large amounts) during the introductory period [13, 20]. We also showed that further prolonged breastfeeding reduced CD risks even more. This is in line with the theoretical thinking that breast milk with its immunological properties is likely to promote oral tolerance [21]. Notably, almost half of the CD cases that occurred during the Swedish epidemic would have been avoided if infant feeding practices had been as favorable as possible (table 1) [20].

Our findings did not pinpoint a certain age interval associated with increased or reduced risk of developing the disease, but subsequent studies suggested the optimal age for introducing gluten as being 4–6 months [22]. By the mid-1990s, Swedish national infant feeding recommendations changed in line with these findings, and at that time the CD epidemic also abated [13]. Thus, the message from CD research regarding introduction of gluten is that ‘earlier is better’, as long as the mother is still breastfeeding, possibly provid-

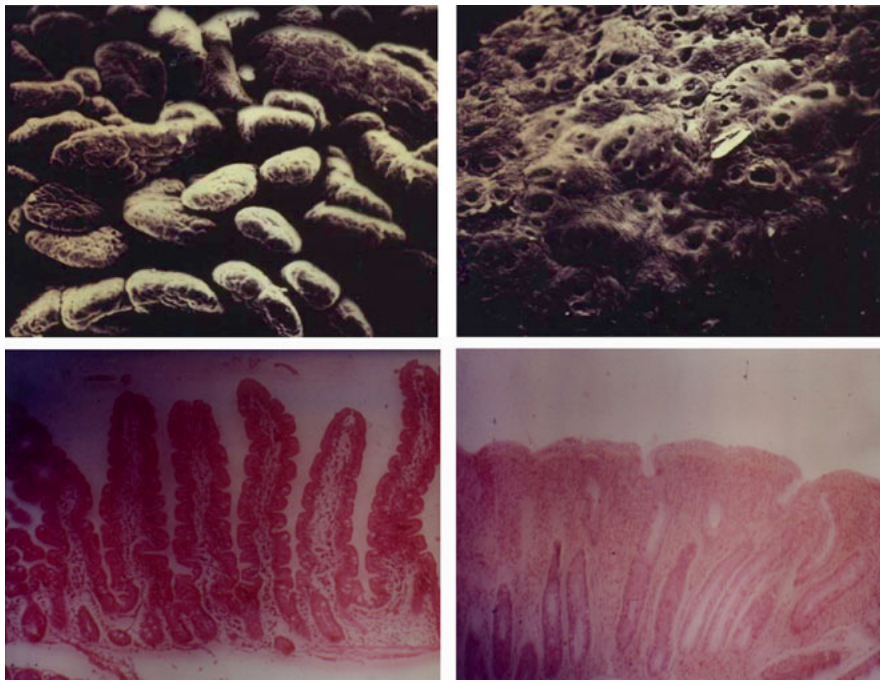

Fig. 2. The intestinal mucosa of a healthy child (left column) and one with active CD (right column). Top row shows scanning electron micrographs and bottom row histological sections.

Table 1. Dietary patterns during infancy and risk for CD before 2 years of age, and an estimate of public health impact

Dietary pattern[a]		Relative risk[b]	Prevalence of exposure %		AF_p[c] %
breastfeeding at introduction of flour	amount of flour at introduction		cases (n = 392)	referents (n = 626)	
Continuing	Small-medium	1.0	28	81	
Continuing	Large	2.0 (1.4–3.0)	18	16	9
Discontinued	Small-medium	2.8 (1.9–4.0)	24	16	15
Discontinued	Large	3.3 (2.3–4.8)	30	7	21

Adapted from Ivarsson et al. [20].

[a] Breastfeeding status (continued or discontinued) at the time gluten-containing flour was introduced into their diets, and amount of flour given (small to medium or large amounts).

[b] Relative risk estimates were based on odds ratios with 95% CIs from conditional logistic regression with 392 matched sets of cases and referents.

[c] Public health impact was estimated by the population attributable fraction $AF_p = p_c (OR - 1)/OR$, where p_c is the prevalence of the studied exposure among the cases.

ing an 'immunological umbrella' and/or a different age interval gives a 'window of opportunity' for developing oral tolerance.

However, the evidence can still be challenged, and we are now continuing our research along two main lines within a European collaborative project (www.preventcd.com): (a) a CD screening program for Swedish 12-year-olds born when the epidemic had abated (in 1997), during a period when gluten was usually introduced gradually from 4 months of age, with ongoing breastfeeding (to compare the prevalence in the 1993 and 1997 cohorts), and (b) a randomized, blinded field trial among pregnant women carrying potentially high-risk infants, who are allocated either to careful introduction of gluten at 4 months of age, or to infant feeding according to country and family practices (carefully recorded for both groups) [19].

Recently, the same shift in thinking to 'earlier is better' for infant feeding practices has been reflected in publications on atopic disease risk. This thinking also includes solids that are considered highly allergenic such as fish, eggs, and foods containing peanut protein. A systematic review of available evidence up to 2005 concluded that there was little evidence supporting an association between early solid feeding and allergic conditions, other than eczema [12]. In a recent birth cohort study (LISA) with follow-up to 6 years of age, delayed introduction of solids (beyond 4–6 months) was *not* associated with a decreased risk for asthma, allergic rhinitis, or sensitization against food or inhaled allergens [23]. However, with respect to eczema there are still conflicting results [12, 23, 24]. Now, this research field calls for epidemiological studies addressing the role of early exposure to allergenic foods, rather than avoidance, and their role in atopic disease expression.

A Change in Infant Feeding Recommendations

As evident from the Swedish experience of a CD epidemic, changes in national infant feeding recommendations can have far-reaching consequences. Our experience also illustrates the value of epidemiological surveillance – as in the Swedish Prospective Incidence Register of Celiac Disease in Children [14] – that allows long-term follow-up of consequences for health and disease after changes in exposure, either on purpose or unintentionally.

Recently, current evidence on the benefits of breastfeeding, and on when and how to introduce complementary feeding, resulted in revised European recommendations [6, 7]. It was concluded, as advocated by WHO [4], that exclusive breastfeeding for around 6 months is desirable but partial breastfeeding, even for a shorter duration, is also valuable. In addition, continuation of breastfeeding after introducing complementary feeding should be encouraged. Complementary feeding should not be initiated for any infant before 4 months of age, and not later than around 6 months. This recommendation was given for all foods, including gluten-containing foods and potent food allergens such as fish and eggs. Recommendations with similar messages

have followed from the American Academy of Pediatrics [10]. Further revisions will be required as evidence evolves.

There is a notable conflict between the WHO recommendation of exclusive breastfeeding for at least 6 months [4], and other guidelines that recommend introduction of complementary feeding within the age interval of 4–6 months [6, 7, 10]. It has been discussed that delaying introduction of solids until 6 months of age is difficult to justify in richer parts of the world, in the face of emerging evidence that this may be detrimental [6, 21]. There are also other reasons for adapting the WHO recommendations to specific country situations or individual needs, such as maternal infection with the human immunodeficiency virus, where mixed feeding confers the greatest risk of maternal to child transmission after birth [6]. The changing, and potentially confusing, recommendations pose challenges for health care personnel, parents and other caregivers, and some efforts have been made to also give guidance in this respect [25].

Current Epidemiological Research

It is evident that epidemiological research has contributed to an improved understanding of the role infant feeding habits have on the development of CD and atopic disease, and on many other phenomena related to health in populations. In our opinion, epidemiology should be more appreciated and utilized, also within the field of pediatric nutrition, because of its potential to contribute to future innovations. We therefore briefly describe how this discipline has evolved over time, and share our experience of epidemiological research applied to CD from a methodological perspective.

In the past, epidemiology was mainly concerned with communicable disease epidemics, but nowadays contributes to increased understanding of many phenomena related to health in populations. A commonly used definition is *'The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems'* [26]. The emphasis is on taking advantage of the often underutilized potential of observational studies, but experimental study designs for complex community interventions are also being developed in parallel. Importantly, it is becoming increasingly evident that the highly valued experimental randomized controlled trial (RCT) is not a sufficient method for many research questions related to human health. Consequently, taking advantage of optimized observational designs is also important. Supporting guidelines are, for example, TREND (Transparent Reporting of Evaluations in Nonrandomized Designs) [27], and GRADE [28], which can help when grading quality of evidence and strength of recommendations both for observational and experimental studies.

In approaching a certain phenomenon, a step-wise use of different epidemiological research designs is often advisable, moving from observational

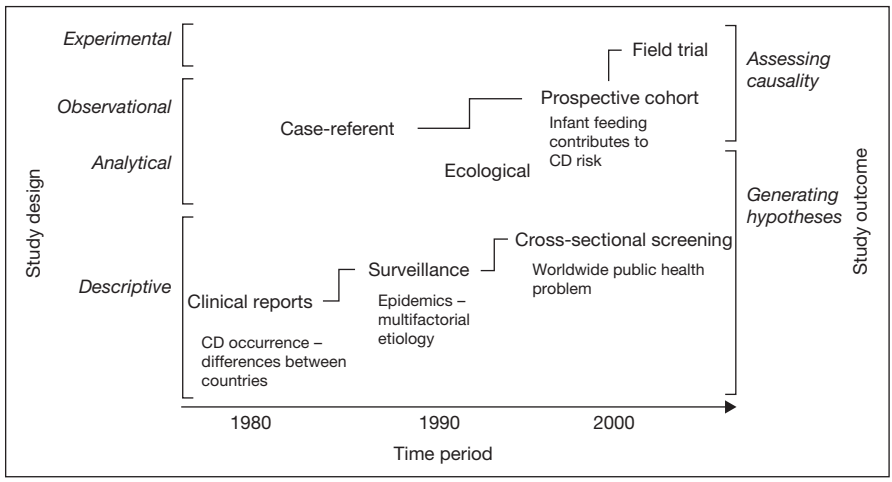

Fig. 3. An epidemiological approach to CD research. Adapted from Ivarsson et al. [18], with permission.

descriptive and analytical studies towards experimental designs when feasible. This is illustrated by the epidemiological approach to CD research from the early 1980s until now [18] (fig. 3). Clinical case reports, followed by observational surveillance studies and cross-sectional screening studies, revealed complex epidemiological patterns relating to person, time and place. Based on these findings, and with ecological studies added (also called correlation studies), hypotheses on causality were generated. Thereafter observational analytical studies, such as case-referent and cohort designs, were used to assess causality. Recently, further steps have been taken to field trials, basically RCTs involving healthy persons.

It is important to recognize that multidisciplinary research teams are needed, encompassing epidemiological and statistical skills as well as knowledge in other sciences. Different study designs are listed and briefly described below, with some strengths and weaknesses. Further details can be found in epidemiology textbooks [29].

Observational Descriptive and Analytical Studies

Observational studies, also called non-experimental, imply that the researcher does not intervene except to collect information for statistical analyses. Thus, the researcher observes and takes advantage of natural courses of health and disease to learn more about the studied phenomena.

Observational descriptive studies report the occurrence of diseases and other health-related characteristics in population, often under the headings of person, time and place. Such studies are useful for disease surveillance and

dimensioning for health care services, and for generating hypotheses about disease causality. A next step can be ecological study designs where data on exposure and disease are compared for populations or groups of people (but not for single individuals), which can give valuable insights even though causality cannot be proven. The cross-sectional design, with data on individuals at one particular time, can further increase our understanding, but cannot be used to prove causality as information about the temporal sequence of cause and effect is lacking.

In contrast, the purpose of observational analytical studies is to evaluate putative associations or hypothesized causal relationships. The prospective cohort study, often considered to provide the best basis for assessing causality, encompasses a large number of subjects followed over a long period (often years), comparing occurrence of the phenomena under study in groups that differ in exposure. The retrospective cohort design can be as reliable if it is possible to take advantage of exposure data collected and documented far back in time. Importantly, the case-referent study design and interlinked methods for analyses have been extensively developed over the years, and now represent a valuable and cost-effective option for consideration. Persons with the disease or other outcome of interest (cases) are compared with referents (also sometimes called controls) with respect to the exposures of interest, also taking potential confounding factors into account. For valid results, the selection of referents is crucial and careful thought needs to be given as to how referents represent the population giving rise to the cases.

Experimental Studies

In most experimental studies, the exposure is intentionally altered in order to study the outcome. Sometimes, however, the intervention is beyond control of the researcher, for example in the case of naturally occurring events, or impositions following societal decisions. Such quasi-experiments have their limitations as the allocation is not random. Attempts to draw conclusions on causality can still be done, as analyses across different groups can be made and potential confounders taken into account.

In modern usage, the term experimental epidemiology is synonymous with RCTs, i.e. with subjects randomly allocated to the study group receiving the exposure, and the control group usually receiving 'standard care'. Some suggest the term *RCT* be saved for studies on patients, with the term *field trial* being used when a study involves healthy persons, and the term *community trial* being used when whole groups of people are involved. Many interventions, especially community interventions, are highly complex. Developing and evaluating such interventions poses many additional challenges. Guidelines have recently been launched [30], but standards for such evaluations are still lacking.

For some time, the RCT has been considered the best, or even the only, study design that can link cause and effect. However, this is now increasingly

questioned. The RCT is limited to highly standardized conditions and often by restricted follow-up times. In the field of infant nutrition, such studies are likely to be unrealistic or even impossible to conduct for evaluating the effects of infant dietary exposures on long-term health outcomes.

Conclusions

Breast milk is the initial natural food for infants, but already during the second half year complementary feeding is essential. Epidemiological research has driven a paradigm shift with respect to most favorable age to introduce complementary feeding, that simplified implies a shift from later to earlier introduction, which has been taken into account in recent recommendation changes. Complementary feeding, including all foods, should not be initiated for any infant before 4 months of age and no later than around 6 months, also for those with elevated disease risk (e.g. for CD or atopic diseases). Epidemiology has evolved over time and could, if increasingly used, contribute even more to innovations in pediatric nutrition, and other phenomena related to population health.

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Discussion

Dr. Greer: Do you have any data from 2003 to 2009? It would appear that the incidence of celiac disease was starting to rise again in 2003?

Dr. Ivarsson: The incidence curve I showed is based on our National Swedish Childhood Celiac Disease Register with prospectively collected data from 1991 and onwards. Thus, we also have information from 2003 to 2009, but data from the most recent years need more quality checks before being presented. But even when only including data up to 2003, it is correct that the incidence rate is increasing year by year in all age groups [1].

Dr. Hernell: You discussed the possibility that there is an immunological window, perhaps between 4 and 6 months, explaining the advantage of early rather than late introduction of strong food allergens. I think that such a window is easily shown in mice and perhaps other experimental animals, but it's not that easy to show it in humans. This raises an interesting question. Take celiac disease as the example. We have shown that breastfeeding has a preventive effect, or rather, as you mentioned, introducing gluten during breastfeeding reduces the risk for celiac disease. It has never been studied whether introducing other food antigens under the immunologic umbrella of breastfeeding has a similar preventive effect against allergy. So maybe the important thing is to introduce strong food antigens while the mother is still breastfeeding. What we as pediatricians have caused with the recommendations with respect to allergy is to actually postpone the introduction of allergens, so that most mothers, particularly those with allergy in the family, have stopped breastfeeding before the introduction, that is if they have followed the recommendations. The question now is what will happen if we start to introduce those antigens while the mother is still breastfeeding? Is it an important concept to introduce them during breastfeeding, or is there indeed an immunological window in humans? I think that's still an open question.

Dr. Ivarsson: True, I agree. There are many unanswered questions.

Dr. Mittal: I think I can take your argument for the introduction of complementary feeding further. We need to look at the WHO guidelines again because in poor countries like ours growth of the infants cannot be sustained with exclusive breastfeeding for 6 months. So, it is not only from an allergic point of view or a celiac point of view but also the nutritional point of view. Secondly, the process of weaning cannot be done in one day, it is a gradual introduction. Thirdly, and this is more of an observation, if you start introducing something new after 6 months, many babies are very reluctant to leave the breast. I will call it breast addiction. So I think we need to look back at these recommendations of exclusive breastfeeding for 6 months.

Dr. Cooper: In my part of the world, Southern Africa, the staple foods that are first introduced are all maize based and it would be uncommon for children, particularly in the rural areas, to be exposed to wheat before a year of age. Have you any data on how that might affect celiac disease?

Dr. Ivarsson: I am surprised about your comment on wheat consumption in South Africa as it isn't that low according to the official statistics, but of course it might still be low for the infants.

Dr. Cooper: The adults eat it.

Dr. Ivarsson: What we know for sure is that as long as gluten-containing foods haven't been introduced into the diet the disease will not develop as the gluten proteins – present in wheat, rye and barley – are the triggers and maintainers of the immunological processes of the disease. However, according to our incident case-referent study the overlap between breastfeeding and introduction of gluten reduced the risk for celiac disease, at least for the first 2 years of life [2]. Delaying introduction of

gluten up to 1 year of age or later, as you tell is common in South Africa, would according to this reasoning increase the long-term risk for celiac disease. However, more studies are needed to clarify if this is the case or not.

Dr. Thakre: Would you suggest any intervention for the huge majority of patients with subclinical celiac disease?

Dr. Ivarsson: It is evident from clinical experiences that celiac disease cases, also those with vague symptoms, benefit from being diagnosed and treated with a gluten-free diet. In your country, and many other parts of the world, I am quite sure that you could find the celiac disease children among those with chronic diarrhea and among those that are malnourished, for example those stunted. Thus, it is important to increase awareness of the disease, and encourage active case finding by generously testing for celiac disease serological markers. If these diagnostic tools are not available, also a trial period with gluten-free diet could be worth considering. Although most celiac disease cases still remain undiagnosed, there is not yet sufficient evidence for suggesting mass screening of populations. However, through our present studies we will be able to increase knowledge on the consequences of having subclinical celiac disease. In our ongoing population-based screening studies of 12-year-olds, the families are asked to respond to comprehensive questionnaires (well-being, health, etc.) before getting the result of the serological marker analyses [3], which increases reliability of their responses. Thus, this study will enable us to clarify self-reported consequences of having undiagnosed celiac disease up to this age. Other comparable studies on the consequences of this disease in adults are underway.

Dr. S. Koletzko: We just finished a study in Germany in 17,000 randomly selected children in all age groups up to 17 years. They were screened for celiac disease with tTG antibodies. Children with positive antibodies were significantly smaller compared to age- and sex-matched controls and the BMI was also lower. We know from undiagnosed celiac adults that their bone mineral density is decreased and other health problems may occur in spite of absence of GI symptoms. Particularly in countries with a higher prevalence of undernutrition, the effect on length and BMI may even be stronger compared to countries with an 'overfed' population like in Germany.

Dr. Ivarsson: Irrespective of clinical signs and symptoms, celiac disease cases have an ongoing inflammatory process in their small intestinal mucosa, as illustrated by some of the slides I showed. Also, today we know that the celiac disease processes are not restricted to the gastrointestinal tract, but can affect any organ in the body. Thus, I would be surprised if the subclinical cases haven't suffered from long-term negative health consequences. However, further scientific evidence is needed.

Dr. Wang: We are very interested in the research results of the celiac disease. We don't know what happened in China, because we've never done an investigation into the disease before. Still, it has always been believed that celiac disease was not very common in China. But I think that this may not be true. I think perhaps we should do the same investigation as you did in China. My question is what is the protocol and method to be used; do you use a commercial package for the screening?

Dr. Ivarsson: There are several commercially available kits for measuring celiac disease serological markers, and most of them measure anti-human tissue transglutaminase antibodies. However, many laboratories use in-house-developed methods to keep down the costs. In our celiac disease screening studies, we use Celikey (Phadia, GmbH, Freiburg, Germany), which is a test that in our experience performs well [3]. Among the about 7,200 tested children, only 192 had elevated markers, and out of the 180 that accepted a small intestinal biopsy, the celiac disease diagnosis was confirmed in 145. Thus, only few unnecessary small intestinal biopsies were performed. Also, children with elevated markers, but a normal intestinal mucosa, will be checked repeatedly as they might be in the process of developing the disease.

Dr. Wang: This means that if you get a positive result of the screening test, you should do the biopsy.

Dr. Ivarsson: Yes, so far the diagnosis of celiac disease has been based on evaluation of the small intestinal mucosa, even though the serological markers have shown increasing reliability over time. If the celiac disease prevalence in a population is unknown, a first step could be to determine the prevalence of elevated markers, which also without follow-up biopsies would give an estimate of the celiac disease prevalence. However, for involved individuals a follow-up biopsy is important as it will confirm the diagnosis for most, but also out rule the disease for some.

Dr. Wang: You just mentioned that you have done an investigation about the timing of solid food introduction in young children. What kind of solid food have you investigated?

Dr. Ivarsson: In our incident case-referent study we asked the parents to report at what age different solids (and liquids) were introduced and in what amount, and then 2 weeks later about both frequency and amount. Thus, our study asked for the introduction pattern of all foods, but we restricted the analyses to gluten-containing foods [2].

Dr. B. Koletzko: Are there data on the prevalence of celiac disease in Asian populations outside of Asia, for example in Europe or the US?

Dr. Ivarsson: The only such population I am aware of are Indian immigrants in Great Britain, who have about the same prevalence as those originally British. Globally, the prevalence nowadays is assumed to be about 1% in the general population; however, in reality it varies between different countries, and within a certain country with respect to age and sex. In Sweden, we recently revealed a prevalence of 3% among 12-year-olds [3], while in an adult screening study in the mid-1990s the determined prevalence was 0.5% [4]. The highest prevalence reported so far is 5.6% among Saharawi children in Algeria [5].

Dr. Mittal: We have adequate data from India to say that celiac disease now is almost as prevalent, at least in the northern part, as in the developed countries, and we also share the same HLA antigen.

Dr. Ivarsson: The only parts of the world from which I haven't seen any prevalence estimates, or even case reports in the native population, are from Sub-Saharan Africa and South-East Asia. Thus, screening studies are needed there.

Dr. De Curtis: I would like to ask two questions. What is the most appropriate age to give complementary food and gluten to premature infants? Is there a difference in the prevalence of celiac disease between premature and term infants?

Dr. Ivarsson: I am not aware of any studies that specifically have addressed these issues in prematurely born children, neither with respect to the celiac disease prevalence nor suitable age for introducing gluten. However, as for all other children introducing gluten while still breastfeeding seems preferable [2], which implies not delaying introduction too much.

Dr. Shenoi: I would like to ask a question and make a comment. The question is: would the gluten intake in a breastfeeding mother be a confounder in your studies, because there are certain communities in South India which restrict gluten intake in lactating mothers. The comment is: I concur with Dr. Mittal's comments about North India. We do find celiac disease in South India, but this is in a segment of children who are failing to thrive and have resistant iron deficiency anemia, resistant to iron therapy. In that subgroup, we find a high incidence of celiac disease.

Dr. Ivarsson: There are a few studies clearly showing that breast milk contains both small amounts of gluten and antigliadin antibodies, but the clinical significance of that is unclear. Perhaps Dr. Hernell would like to give a comment?

Dr. Hernell: It's more likely that the small amounts of gliadin peptides or gliadin in breast milk would induce tolerance rather than celiac disease, and I am not aware of a single case of celiac disease that has been diagnosed before you have introduced gluten as complementary food into the infant's diet.

Dr. Ivarsson: It is likely that this question can be further clarified by the ongoing European collaborative celiac disease study (www.preventcd.com). More than 1,000 pregnant mothers from high-risk families are recruited with a planned follow-up at least until the child is 2 years of age. Among many things, the breast milk content will be analyzed, and could be put in relation to the risk for celiac development in the child.

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Technological Progress as a Driver of Innovation in Infant Foods

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Abstract

Advances in nutrition and food sciences are interrelated components of the innovative framework for infant formula and foods. While nutrition science continues to define the composition and functionality of human milk as a reference, food ingredient, formulation and processing technologies facilitate the design and delivery of nutritional and functional concepts to infant products. Expanding knowledge of both nutritive and non-nutritive components of human milk and their functionality guides selection and development of novel ingredient, formulation and processing methods to generate enhanced infant products targeting benefits including healthy growth, development as well as protection of health through the life cycle. In this chapter, identification and application of select novel ingredients/technologies will be discussed in the context of how these technological advancements have stimulated innovation in infant foods. Special focus will be given to advancements in protein technologies, as well as bioactive long-chain polyunsaturated fatty acids, prebiotics, probiotics that have allowed infant formula composition, and more critically functionality, to more closely align with that of human milk.

Introduction

Innovation is critical to continually improve the quality and accessibility of infant foods worldwide. As these products are designed to support the health and development of the infants who consume them as a primary or sole source of nutrition, innovation in infant foods must be a continuous process involving improvement in product nutritional quality, functionality and/or the delivery of a quality product to consumers for enhanced value. Apart from non-technical factors such as market and economic forces, food

science and nutritional technologies are often considered primary drivers of innovation in the food industry. Both groundbreaking as well as incremental technological innovations are critical in the infant food industry. These innovations arise primarily from (1) scientific advancement in infant/child nutrition, (2) development of novel ingredient technologies, (3) advancements in food safety technology (processing, packaging, etc.), and (4) the science of consumer insight and behavior as it relates to infant feeding. While each area is critical to continuous innovation of infant foods, parallel advancements in nutritional and food sciences play a central role in driving infant food innovation. This is largely due to continuous research on both nutritional and functional properties of human milk, and subsequent translation of this knowledge into formula through creation and application of novel food ingredients, compositions and food processes [1]. This chapter specifically focuses on how the fundamental understanding of the composition of human milk has expanded to include both nutritive and non-nutritive components with important biological activity, and on how these findings have driven recent innovations in infant formula. The application of select ingredients and technologies will be discussed in the context of how these advancements have enabled the industry to more closely align infant formula functionality with that of human milk.

Exploring Human Milk Composition and Functionality as a Source of Innovation

The characterization of human milk composition and function, in relation to infant nutrition, has resulted in the definition of an adaptable and evolving 'gold standard' for infant formulae [2]. Human milk contains components, both nutritive and non-nutritive, that support healthy growth, development, proper immune function, and provide many other functional benefits to the infant [3]. As the body of knowledge regarding human milk composition and functionality matures, manufacturers strive to innovate by applying novel nutritional or functional ingredients or concepts to adapt infant formula profiles in an effort to better emulate the benefits of human milk and breastfeeding [1] (fig. 1). This approach requires the translation of nutrition science through food and ingredient technology to generate innovative impactful products of high quality, stability, safety and value for consumers (fig. 2). This is particularly true in cases where functional components of human milk may not be commercially available in a fashion matching the naturally occurring components. For example, improved understanding of human milk protein composition has led to adjustments in total protein content and the ratio of bovine whey to casein in infant formula to better mimic human milk composition and nutritional value [4]. Characterization of long-chain polyunsaturated fatty acids (LC-PUFAs) in human milk and their association with infant eye

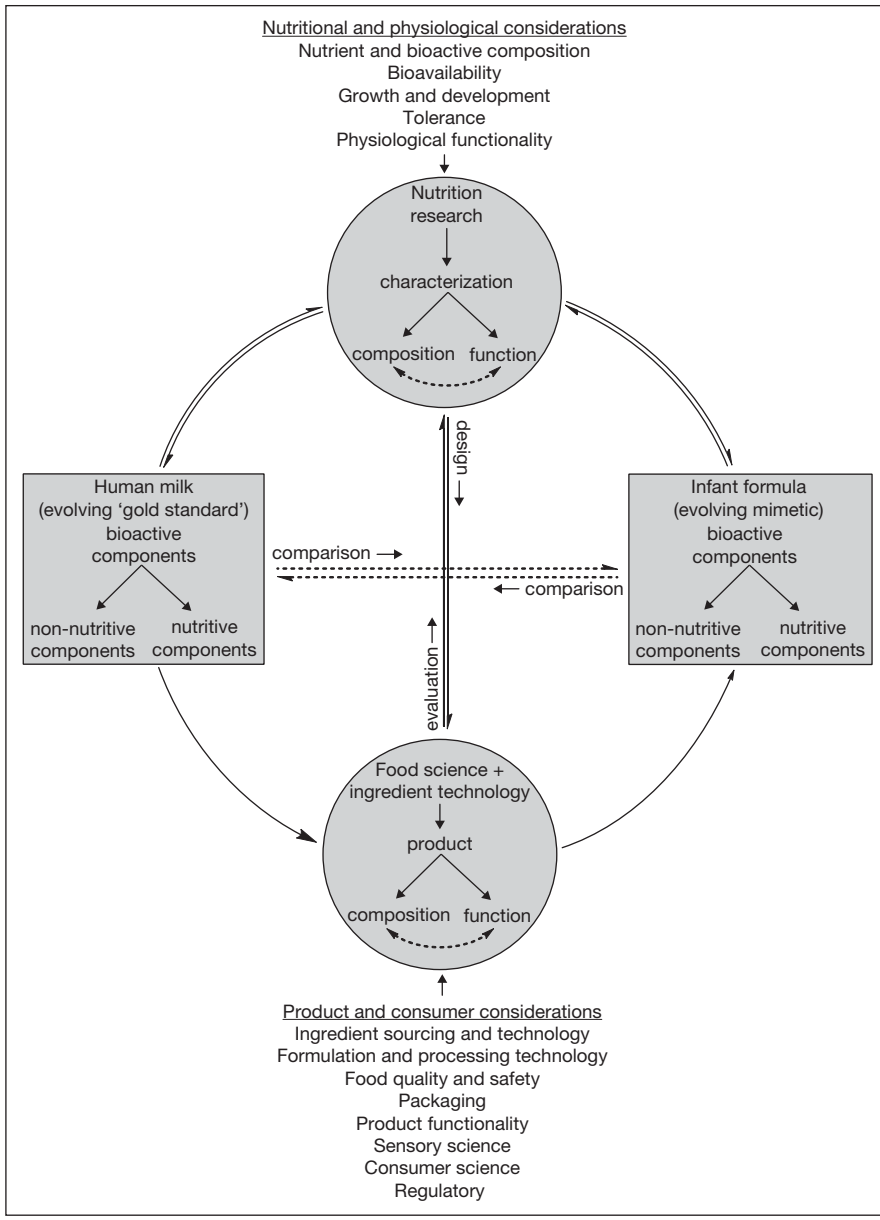

Fig. 1. Technological advancement drives innovation in infant foods. Technological advancements in nutrition science provide critical information on composition and functionality of human milk. Advances in food science, ingredient technology and consumer insight allow for translation of nutrition science into infant formula and foods.

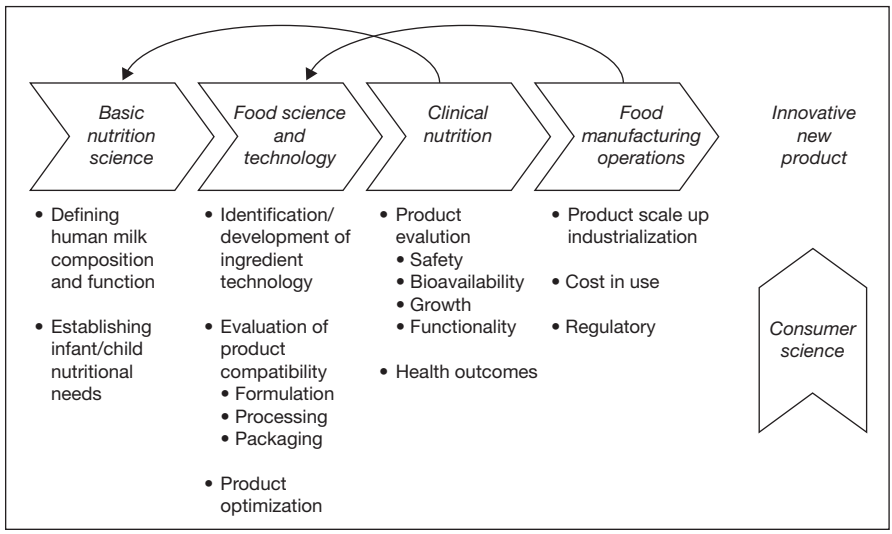

Fig. 2. Translation of innovations in nutrition science research into infant products is incrementally achieved through technological advancements in food technology. Design and development of infant products with novel ingredient technology is followed by rigorous assessment of quality, safety and ultimate efficacy through well-designed clinical trials prior to industrialization and commercialization. Consideration of ingredient/technology scalability, cost in use and regulatory compliance is critical to successful development. Additional consideration of consumer needs and expectations may enhance the acceptability of nutritionally and technologically innovative products.

and brain development has led to development of algal- and fungal-derived lipids suitable for enrichment of these fatty acids in infant foods [5]. More recently, the carotenoid pigment lutein has been added to select infant formulae in the US as a biological antioxidant, supported primarily by the carotenoid content of human milk and proposed but not fully demonstrated roles in eye development [6]. Examples illustrating how characterization of nutritive and non-nutritive components of human milk and their function has driven innovative adaptation of infant formula are discussed below.

Nutritive Components of Human Milk as a Source of Innovation in Infant Foods

The macro- and micronutrient profile of human milk is highly variable, and depends on several factors including the nutritional status of the mother and the extent and duration of nursing. Human milk composition also changes along with the needs of the growing infant. Despite this variability, the key

nutritive components of human milk appear to be carbohydrates, lipids, proteins, vitamins, minerals, and several other growth factors [3]. Additionally, knowledge of the differences between human and bovine or goat milks (from which infant formula is typically made), have provided opportunities for innovation in the design of macro- and micronutrient profiles in infant formula in order to better mimic human milk. The following examples illustrate how knowledge of the composition and functionality of select nutritive components of human milk has driven innovation in infant formula.

Protein Sources, Composition and Fractions

The source, composition and nutritional value of protein utilized in infant formula should mimic human milk protein with regards to nutritional quality and tolerance. This is particularly challenging with standard protein-based ingredients, considering the highly variable nature of the protein and amino acid content of human milk [3]. Infant formula is largely produced using bovine milk or soy protein isolates, with defined minimum and maximum values for optimal infant growth and development [4]. This reliance on bovine and soy ingredients has required innovation in protein technology, to generate protein ingredients and/or compositions that better mimic human milk quality and tolerance. Specifically, technological advancements in base protein ingredients include the generation of enriched whey protein fractions, expanded availability of partially and highly hydrolyzed bovine milk proteins, and development/application of specific soy protein isolates. These improved proteins have facilitated development of products with improved digestibility and lessened potential for allergenicity from bovine or soy products [7]. These technological advances have resulted in innovative products that more closely resemble the nutritional quality and function of human milk and provide consumers additional flexibility in selection of infant formulae.

Beyond protein composition, identification of specific functional proteins and bioactive peptides in human milk has provided an additional source of product innovation. For example, lactoferrin is a significant component of the whey fraction of human milk. Several associations have been identified between lactoferrin and infant growth and development, including improvement of iron absorption and immune enhancement through modulation of GI flora [8, 9]. While present in human and bovine milk, the concentration of lactoferrin is 5-fold to 10-fold higher in human milk. The high concentration in human milk, combined with the potential activity of lactoferrin (particularly as an immune-enhancing agent), has stimulated interest in the role of lactoferrin in infant growth and development and, by extension, has led to interest in the enhancement of lactoferrin levels of infant formula to more closely approximate levels in human milk.

Significant efforts have focused on development and assessment of bovine lactoferrin isolates for targeted enrichment of infant formula. Specific

challenges associated with the development of lactoferrin ingredients include stabilization of protein functionality through thermal processing common to infant formula, as well as assessment of its impact on product quality markers (oxidative stability, etc.) [8, 10]. Following the successful development and safety assessment of bovine lactoferrin ingredients, GRAS status was achieved in 2003. Lactoferrin is now commercially available and is used in infant formulae globally. More recently, the characterization of bioactive peptides derived from hydrolytic lactoferrin digestion (lactoferricin) has drawn additional attention due to the potential antimicrobial and immune stimulatory activities of this hydrolysate [8] as well as its potential for enhanced product functionality and stability. Future innovation in protein ingredient technology for infant formula will likely involve characterization of specific bioactive peptides present in the infant gut and development of strategies to optimize delivery and stability of these bioactive peptides to the infant.

Long-Chain Polyunsaturated Fatty Acids

Another example of how advancements in infant nutrition have directly translated to innovations in infant foods involves LC-PUFAs. LC-PUFAs (including docosahexaenoic acid, DHA, and arachidonic acid, ARA) are relatively minor components of human milk, representing ~0.1–4% of the total fatty acid content of milk from healthy mothers. Levels of LC-PUFAs in human milk vary by geographical region and dietary patterns; higher levels are often associated with higher intakes of fatty fish [11]. While LC-PUFAs are minor components of human milk, evidence of functional roles for DHA and ARA in brain and eye development have been identified through significant research efforts, resulting in recommendations for DHA and ARA addition to infant formula at levels between 0.2 and 0.5% of the total fat [12].

A critical technological hurdle for inclusion of DHA and ARA into infant foods was the need to identify a sustainable, high-quality source of these bioactive lipids. While fatty fish represent the primary dietary source of LC-PUFAs, several challenges exist with marine sources of these lipids, including sustainability and variability in fatty acid composition including higher levels of eicosapentaenoic acid. Development of sustainable algal *(Crypthecodinium cohnii)* and fungal *(Mortierella alpina)* sources of DHA and ARA which provide high-quality, consistent lipid composition has facilitated the progression of DHA and ARA functionality beyond the science and into practical product application [13]. The application of DHA and ARA in infant foods remains an example of how functionality, rather than a rationale based purely upon composition, was effectively utilized as a driver of innovation. Expansion of DHA and ARA into products such as follow-up formula, children's products and mother's supplements further highlights the importance and success of these ingredients.

Non-Nutritive Components of Human Milk as a Source of Innovation in Infant Foods

In addition to nutritive components, characterization of non-nutritive constituents in human milk, such as prebiotic oligosaccharides, probiotic microorganisms and phytochemicals, are a source of innovation for infant foods. Advancement of our understanding of the functional roles these components may play in support of infant health and well-being has stimulated interest in the development of relevant ingredients and strategies for their application in infant foods. A few key examples of how non-nutritive human milk components have driven recent innovation in infant formula are described below.

Milk Oligosaccharides

More than 130 human milk oligosaccharides (HMOs) have been characterized. The majority of known HMOs are primarily composed of five monosaccharides: D-glucose, D-galactose, N-acetylglucosamine, L-fucose, and sialic acid [14]. HMOs are significant components of human milk (present at ~5–10 g/l). HMOs are believed to possess a broad array of functional properties including prevention of intestinal infections, inhibition of pathogenic bacterial adhesion, prebiotic functions, prevention of allergies, and immune enhancement [15]. Commercial sources of natural oligosaccharides similar to those in human milk do not currently exist. The general absence of a natural or synthetic compositional mimic to the complexity of HMO remains a significant technological hurdle to fully leveraging this scientific knowledge. However, innovation in this area has proceeded through advances in ingredient technology centered on natural and synthetic prebiotic oligosaccharides which mimic HMO functionality but differ in composition from natural HMOs [16].

Use of enzymatically generated and/or naturally occurring plant sources of fructo-oligosaccharides, lactose-derived galacto-oligosaccharides and combinations of these fibers have provided a source of innovation in infant formula [15]. While these non-HMO prebiotic fibers appear to be somewhat less effective than human milk rich in natural HMOs, some potential benefits do exist with regard to prevention of atopic disease. Ongoing research is beginning to address how formulae containing these non-human prebiotic oligosaccharides mimic human milk functionality by promoting growth of infant intestinal flora and infant growth [16]. While promising, application of these non-human ingredients is a good example of an ‘innovative bridge’ to a potentially larger breakthrough. Ultimately, more detailed functional characterization of specific bioactive HMO constituents or mixtures would provide the framework for the synthesis or isolation of bioactive oligosaccharides from other species suitable for inclusion into infant formula and foods [14].

Probiotics

Probiotics are live bacteria that, when consumed, illicit a beneficial effect on the host by improving intestinal microbial balance [17]. Benefits associated with consumption of probiotics include improvement in lactose malabsorption and tolerance, enhanced gastric motility, reduced constipation, prevention/treatment of diarrhea, improved immunity and amelioration of atopic diseases and food allergies [18]. Infant formulae with probiotic bacterial strains have existed for over a decade. Several bacterial strains have been identified for addition to infant formula including several *Lactobacillus* and *Bifidobacterium* species [19]. Basic research efforts have also characterized bacterial species endogenous in human milk including *Lactobacillus*, *Lactococcus*, *Enterococcus* and *Staphylococcus* species. These endogenous bacteria are believed to contribute to development of the infant gut microflora [20], and by extension are believed to impart functional benefits to the growing infant, including enhanced immunity. This research has strengthened the notion that addition of beneficial probiotic strains to infant formula is consistent with the goal of mimicking both the form and functionality of human milk. Specific research efforts have further stimulated interest in development and commercialization of unique endogenous probiotic strains isolated specifically from human milk [21]. This evolution from existing exogenous probiotic strains to human milk-specific strains will require significant safety and efficacy testing, but would more closely align infant foods in composition and potential function to human milk. Additional innovation may arise from symbiotic strategies (pro- and prebiotic combinations) and/or characterization of endogenous microbial ecologies specific to regional populations.

Carotenoids

Plant-based phytochemicals such as carotenoids also offer a potential source of innovation for infant foods. While the provitamin A and antioxidant activities of carotenoids are well known, the association of specific oxy-carotenoids (lutein and zeaxanthin) with prevention of oxidative retinopathy in infants and age-related macular degeneration in adults [6, 22], has increased interest in these pigments as critical non-nutritive components of human milk. Carotenoid content of human milk is generally proportional to the carotenoid profile of the mother's diet [23, 24]. Although highly variable, research has identified both provitamin A (α- and β-carotene, and β-cryptoxanthin) as well as non-provitamin A (lutein, zeaxanthin and lycopene) carotenoid species in human milk. Lutein and zeaxanthin selectively accumulate in the macula pigment of the retina and have been directly associated with prevention of associated ocular disorders [22]. Unless specially included by formulation, carotenoid content of standard infant formulae is generally variable and low compared to human milk [25], providing opportunities for innovation. As a result, several natural and synthetic carotenoid

ingredients have since been added to commercial infant formula in the US. While definitive clinical evidence justifying their inclusion is lacking to date, this emerging science has created additional opportunities for innovation in ingredient technology and product concepts. This includes development of concepts focused on synergies between carotenoids and other bioactive ingredients such as DHA to improve infant antioxidant status and support vision and eye health [26].

Infant Feeding Practices Influence Behavior and Chronic Disease Risk in Adulthood

While ingredient technology has served as a rich source of innovation, opportunities will also evolve from our expanding knowledge of how infant nutrition and feeding practices may impact chronic disease risk in adulthood. For example, improved cardiovascular disease markers including BMI, lipoprotein profiles and blood pressure in adulthood have been associated with infants fed human milk compared to formula [27, 28]. While the factors responsible for these apparent benefits are not fully understood, both nutritional and behavioral components may be an additional focus area for innovation. Recent evidence suggests that the type of milk (human, bovine or hydrolysate) may have an impact on subsequent food preferences [29], indicating a technological link to future behavior and potential disease risk. Understanding how infant milk/formula composition may influence perceived taste and subsequent food preferences and/or ingestive behavior in adulthood will be critical to development of improved infant products with flavor profiles and delivery systems that favorably impact eating habits and dietary selection in adulthood. Considering the potential impact these outcomes may exert through the lifecycle, this area will likely be a future driver of innovation in infant foods as research elucidating underlying mechanisms may be applied to development of specific formulation and process strategies for infant foods that can positively influence diet-related disease risk and outcomes in adulthood.

Future Opportunities for Innovation in Infant Foods

While food and nutrition sciences continue to evolve and converge on health-related end points, future innovations in infant foods will include a focus on identification of novel, bioactive ingredients, preparations and/or delivery systems through the continued study of human milk composition, functionality and feeding practices. Efforts to better mimic human milk will depend on our understanding of this ‘gold standard’, which constantly evolves along with improved technology and investigative approaches. It is believed

that future innovation in infant foods must consider how to best mimic the differences in human milk composition and functionality that occur as a function of lactation stage, region, and mother's diet [2]. This should include a consideration of the complexity of physical, chemical and biochemical interactions between individual nutritive and non-nutritive components and how these interactions influence bioavailability and functionality of bioactive compounds from human milk. With a detailed understanding of composition, interactions and adaptability of human milk, a conceptual framework for development of strategies leading to personalized infant foods as described by Lönnerdal [30] would be facilitated. While food and nutrition sciences continue to converge in an effort to understand and then mimic the complexity of human milk composition to match the nutritional and functional needs of the infant, it is also critical to consider changing consumer demands and perception of product quality attributes (such as demand for organic infant products) when designing infant foods. Continued technological advancement is required in ingredient technology, processing and packaging strategies to better mimic human milk composition, bioavailability of bioactive components and ultimate functionality of infant formula and foods. In all cases, innovation will continue to require a balance between technological progress and assessment of both efficacy and safety of novel ingredients, platforms and finished product concepts.

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Discussion

Dr. Gibson: I want to ask you a little bit about your connection to clinical trials and randomized trials to demonstrate clinical efficacy rather than just identifying compounds and assuming that X plus X equals to Y and therefore this is a good thing to be adding. You'll be well aware of the systematic review and meta-analysis that was done on antioxidants and published in *JAMA* a couple of years ago. They showed quite dramatically that most of those antioxidants were actually harmful and caused more deaths than they did save in people. So we have never been able to find the roles of vitamin E and a number of other so-called antioxidants. I think that putting them in food is quite dangerous. Could you comment on that?

Dr. Ferruzzi: I think those are excellent points and critical issues to address the food science, nutrition science and of course the clinical side. Establish efficacy in large randomized trials would be the ultimate goal. The challenge may be in establishing enough evidence leading up to a large trial. I don't think we should be adding ingredients based only on in vitro activity. Secondly, and I think your point on toxicity is important, understanding the importance of dose of many of those bioactive compounds such as phytochemicals is critical. Are they better to be consumed as foods? Are they better to be consumed as dietary supplements? Speaking in regard to the infant foods, I think obviously we have to be much more conservative when we are looking for bioactive compounds to innovate from. We have to understand much more about the individual component and its potential interactions before we begin to include these into products and assess outcomes and of course before communication on that.

Dr. Yang: As we know, in breast milk there are many kinds of growth factors such as EGF or IGF. What is your comment on this kind of growth factors in infant formula?

Dr. Ferruzzi: This is beyond my area of expertise, but it goes back to looking at the fundamental paradigm, which is understanding the human milk composition and function as initial target for innovation. Growth factors added to any formula should strive to emulate function of those from human milk components. So again, this should consider function, safety assessment, understanding really the intended outcomes and intended improvement to a formula.

Dr. Ludan: I want to ask a question about the bioavailability of trace minerals. You mentioned that lactoferrin is a cotransporter of iron. Is there a specific cotransporter of zinc, and is this affected by the type of zinc compounds given because we know there are several zinc compounds available, like zinc gluconate, zinc sulfate, etc.

Dr. Ferruzzi: Sure, there are specific factors associated with zinc absorption and assessment of zinc absorption. Dr. Lönnerdal is in fact the expert in this area and we could discuss it in more detail afterwards.

Dr. Bier: This is a little bit aside from the actual point of the talk but I find the slide of the lutein formula astonishing. I would be amazed if you try to get through an IRB in the US an experiment on who knows how many children providing lutein without any evidence at all in an uncontrolled human experiment. I can imagine this would get through any university IRB in the US.

Dr. Ferruzzi: I don't think you would find much disagreement, at least in this room. I think that was a premature addition to formula considering the evidence. It goes back to justifying addition of bioactive compounds. Is it important just because it's there rather than why is it there and what is its function and establishing that before moving on to innovation in these specific products, I absolutely agree with that.

Dr. Solomons: It seems that innovation in pediatric nutrition could have two additional suffixes for products and benefits of child nutrition and then the decisions we make regarding how we balance those two would change their context.

Dr. Ferruzzi: I think what's interesting is to understand the market push to innovation rather than just the technological push, and I think it's important especially in this area to really stay more on the understanding of the technological push towards innovation rather than exclusively proceeding by market-driven ideas. In the food industry, you see a trend to more market-driven innovation; so it's a lot of window dressing of products. Back to the antioxidant comment: Sometimes people are advertising antioxidant content, enhanced vitamin and mineral content. It typically has nothing to do with nutrition, rather it's what is going to process well and not make a product taste bad and sale. So it's always important to understand that market push. From the infant food perspective, it should clearly be less a market push but rather the context of what the market needs from the standpoint of communication on the

product, how do we better translate the science for the consumer to understand that this is a new and improved product, a better product, providing that we have the science to substantiate that. That not only drives innovation but can drive outcomes, and I think it is important to work with marketing rather than for them.

Dr. Haschke: Coming back to bioavailability, there has been a paradigm for the last two decades that highly bioavailable components are better absorbed, are kept in the body and should be used for fortification. So, the industry was looking for these bioavailable components, let's say iron, which is easily absorbed, and had a lot of problems in terms of solubility, taste perception. In the more recent literature, it turns out that this might not be so important because if the body has a deficiency, the body takes what it needs. In his population outcome studies, Richard Harrell said that the final outcome is what is in the population, no matter whether you give a salt with low bioavailability or high bioavailability. This is very important, for example for micronutrient fortification of food in the whole world, not looking for the high-fly component, looking for a component which is affordable.

Dr. Ferruzzi: I agree, and I think one of the interesting things from the bioavailability perspective relates to understanding what the product is delivering. But also it offers some opportunities in terms of innovation by synergizing concepts back to food. One of the reasons there is, for example, if rather than looking at blood levels or any specific compound you look at the specific metabolic effect as a marker of bioavailability, you may find you need dose X. That dose may be exceedingly high in food product, and it may cause instability in the food product. The final strategy is to reduce the amount in food to deliver the same benefit, not so much to overfortify, but actually to deliver on the promise of the benefit, bioavailability may be more useful to control cost. If you can use significantly less of an ingredient because you have better bioavailability, you may significantly impact the cost. So there are some opportunities, but I fully agree with you, I don't think that we should just 'optimize' it.

Dr. B. Koletzko: Please allow me to come back to the topic that Dr. Haschke raised on the impact on production technology. We heard a very impressive example by Dr. Lönnerdal demonstrating that a change from powder formula to ready to use liquid formula can basically eliminate all bioactive TGF-β. We have seen other examples that liquid formulas have lower protein quality and poorer absorption of micronutrients. Most clinicians probably aren't quite aware of the powerful effects of the methodology of production on product quality. You showed an insightful scheme of how the innovative process might work while you develop a product idea. Oftentimes, manufacturers would produce a product in a pilot plant in a small amount and then perform a clinical evaluation with that product. If the study outcomes are satisfactory, one might scale up production and do production on an industrial scale. During that process, product qualities might change. For example, I would assume that the detailed conditions on how one produces a protein hydrolysate really matter for the allergenic properties, and if one thinks about a probiotic product obviously it's very important how those probiotic bacteria are treated and in which environment they are maintained for their biological activity. Thus, one wonders if formula products produced by a large company in, say, three different plants around the world are truly equivalent, if the conditions of production in those three plants are not exactly the same, for example they use different milk to start with, they have different machines and different technology, and perhaps even different other raw materials added. Also, one would assume that production technology will be modified and improved over time, for example new machines come in, new mineral and vitamin mixes are used, other factors will change, and steps may be taken to reduce costs. Thus, do we really know to which extent this might affect the relevant qualities of the product? What is the degree of quality assurance that can be implemented here to make sure we know what is happening?

Dr. Ferruzzi: I have several points to those questions. First, it is important to understand that quality parameters need to be very stringent for a product like infant formula, so whether you are producing it in factory A or factory B or factory C you should see very tight quality parameters. I think we have to understand that from a food processor's perspective the process more often is related to the 'first objective', which is always safety. Usually, that means excessively overprocessing to ensure you have a microbiologically safe product. You additionally want to control spoilage, and then you think about other parameters. How those processes synergize with delivering of the eventual functionalities and clinical outcomes has to be defined. So, it could be that if we are measuring at the standpoint of the standard nutrition labeling and everything else we may not see a difference, but that process may have destroyed other functional factors which were important and may have consequences on functionality. The second point relates to the heterogeneity in ingredient supply. It is important to understand, the source and the quality of the ingredients. It's up to you, the processor, to specify what you want in terms of quality parameters and ingredients in the finished product and then hold it to that. There are obviously regulatory aspects for some of this, but it is extremely important to understand that the processing strategy and especially the current ones are not always designed; actually, they are almost never designed from a standpoint of the nutritional end point per se, again safety first. Also, scale-up is a real issue. Ensuring that the product that comes out of the factory meets the target you established as a new gold standard which is out of your pilot plant or lab bench is extremely difficult but important. Scaling the process is important but so is scale-up of the ingredient, especially if you have a little-volume high-quality very expensive ingredient. For example, if you have to go from making 10 kg of a bioactive protein to making 10 tons, it may not be quite the same. The best is to be intimately involved throughout that process with the manufacturer of the ingredient and product. These are tremendous challenges, it's not so much just for infant formula, but food in general.

Dr. Gibson: One of the challenges for developing countries is actually meeting their nutritional requirements through better foods. I recently attended the International Congress in Nutrition in Bangkok, and there was a general agreement that this was very hard to do through technology alone, that supplementing foods is very expensive, and that there was a better need. To what degree is there a driver from your point of view in terms of finding better plants or better sources of foods to put into the pipeline?

Dr. Ferruzzi: I guess there are two ways to approach that. One is to define better plants, better sources and better ingredients. When dealing with processed food, you have to additionally conform to current processing technology, especially in some of the developing world, rather than trying to bring in something extremely high-tech to do. So, trying to understand what is available locally, what can be used, what can be enhanced to the current techniques. You can use new products, new plants and new sources, but it comes down to integration into the current processing and distribution technology. Not only developing countries are concerned; even in the US we have a difficult time rolling out advanced technologies in food processing due to cost. We hear that a lot, it's something that is definitely not unique, but it has really been about finding ways to readapt current technologies to some new and novel ingredient sources. It's interesting because it relates back to the biofortification approach for some of the staple foods/grains such as the golden rice. You may have added ten times more β-carotene to a product, but what if consumers do not want the product?

Dr. Bodenstab: I want to add two comments to Dr. Koletzko's questions about clinical trials. If you produce a product for clinical trials on a pilot plant scale, the later product on the industrial scale may look different. In our company, we frequently do

productions for clinical trials in our factories, on the industrial scale. Or product can be produced in one of our so-called Product Technology Centers where our pilot plant actually is on the industrial scale.

Dr. Ferruzzi: That is required actually, that it is actually on the finished product that your evaluation is done, not on the pilot product in some markets.

Dr. Bodenstab: Absolutely.

Dr. B. Koletzko: But is that a standard generally applied in the industry, or are there variable standards in different companies?

Dr. Bodenstab: I am talking about Nestlé. I don't know about other companies, but we do certainly use industrial scale production methods, not only for clinical trials but also for regular consumer trials. The second comment I would like to make concerns technology. Do all factories perform the same way? Nestlé has around 500 factories globally. In the last 10 years, a huge effort has been made to improve safety and regulatory compliance in what we do. Our standards in Nestlé are global; whether it has been produced in China or in Europe or in the US, we have the same quality and safety standards. It's not exactly the same at any point in time because a new technology may go into one factory first wherever that may be, but then if it works successfully it goes into other factories. This also has an impact on our understanding of raw materials, in terms of geography and also season; we start to use databases that give us information which allows us to better understand the composition of the raw material and later on the finished product. When talking about innovation, the question that's very often asked is what is important for consumers. There is another question: What is important for our operations and our factories? This question is much less prominent in the discussion; however, I believe it's a very important question.

Dr. Singhi: I think that one of the issues concerning technology is that we are not giving importance to what is variable, what nature is doing as part of adaptability. We are saying this is infant milk, this is the standard formula for every baby, but nature's variability, how do you think technology can put that in practice. Also, how can we see that we are not adding too much of the different micronutrients that we have lately learned about into the formula? How do we know that we are not making an imbalance in what is existing, can technology answer that?

Dr. Ferruzzi: I have been speaking mostly from the food technology side. I think we also have to understand the technological advances, analytical techniques and experimental techniques. We heard yesterday about the advances in scientific techniques that will allow us to learn significantly more about what the gold standard, human milk, is 'doing'. The more we learn about the composition of human milk, the more we can begin to probe the questions of interactions, and so we can also do that using similar techniques in the formulas and the products you make. Do we see positive or negative interactions when we combine different micronutrients? The question of adaptability is an excellent one. I think you need someone significantly smarter than me that can tell you how to create a product that I can put on the shelf but it adapts and is personalized during use. Technology gets to the point of being able to tell us maybe what one individual needs over another. Do we create three or four different categories of formulas? Do we further fractionate that into people that need slightly different things? So, it's not quite personalized but it is slightly modified. But the question is how do you change formulas in terms of adaptation not so much over months and periods of lactation but day to day, hour to hour? Those are very good questions, and I think there is a lot of opportunities to think of creative ways to innovate in these areas.

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Health Economic Perspectives of Pediatric Malnutrition: Determinants of Innovative Progress

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Abstract

Despite some improvements in recent years, extreme poverty and malnutrition remain a critical concern for developing countries. Malnutrition, and more specifically pediatric malnutrition, is a reality affecting millions of children, particularly in South Asia and Africa. It causes increased mortality and morbidity, decreased physical and intellectual development, poor productivity and a number of negative economic outcomes. Health economics data clearly demonstrate that interventions are effective and efficient, but more data are needed to measure that efficiency. Initiatives to address microdeficiencies have focused on vitamin A, iodine, zinc, iron and folate. Iodine is often used as a best practice example. Two main institutions lead the efforts to address malnutrition throughout the world: the UN with its UN Millennium Development Goal project, and the Copenhagen Consensus. We consider micronutrient deficiencies, particularly in iodine, corresponding interventions, their effects and health economic data. We discuss how developing public/private partnership could boost the effectiveness of interventions by combining the competencies of both sides: credibility, national and international buy-in, experience of public institutions, commercial competencies, high penetration rate, and product knowledge of private industry.

Introduction

Despite some reductions in world income poverty in recent years, malnutrition remains widespread. Recent estimates [1] suggest that 'maternal and child malnutrition is the underlying cause of 3.5 million deaths annually, 35% of the disease burden in children younger than 5 years, and 11% of the total global DALYs' (disability-adjusted life years). Malnutrition is a critical parameter to understand when trying to evaluate the overall state or

Table 1. List of interventions ranked by the Copenhagen Consensus 2008 [4]

	Solution	Challenge
1	Micronutrient supplements for children (vitamin A and zinc)	malnutrition
2	The Doha development agenda	trade
3	Micronutrient fortification (iron and salt iodization)	malnutrition
4	Expanded immunization coverage for children	diseases
5	Biofortification	malnutrition
6	Deworming, other nutrition programs in school	malnutrition
7	Lowering the price of schooling	education
8	Increase and improve girl's schooling	women
9	Community-based nutrition promotion	malnutrition
10	Provide support for women's reproductive role	women

progress of a society in health and well-being because malnutrition is often the origin of a series of negative downfalls at human, health and economic levels.

Malnutrition, the underlying cause of death for at least 30% of children in the world, is a problem of such magnitude that the UN included it in the UN Millennium Development Goal project. In 2000, world leaders came together at UN Headquarters in New York to adopt the United Nations Millennium Declaration, committing their nations to a new global partnership to reduce extreme poverty and setting out a series of time-bound targets – with a deadline of 2015 – that have become known as the Millennium Development Goals [2]. Two of the eight goals are to eradicate extreme poverty and malnutrition, and reduce child mortality. Other goals, such as cure major diseases or improve maternal health, heavily depend on improvement of the malnutrition situation. So far, child deaths declined from 12.6 million in 1990 to around 9 million in 2007 and the percentage of underweight children declined from 31% in 1990 to 26% in 2007. However, rising food prices and the state of the global economy might erode these results, and it is highly questionable whether the targets to halve between 1990 and 2015 the proportion of people who suffer from hunger and to reduce by two thirds the mortality of children under 5 years of age will be met [3].

The Copenhagen Consensus 2008, is a group of 8 world-renowned economists, including 5 Nobel Laureates who were asked to assign a fictive amount of USD 75 billion over a period of 4 years to the ten most pressing challenges facing the world today. The criteria used included the cost-benefit ratio, as well as feasibility and sustainability of the interventions. Table 1 shows the interventions mentioned, and table 2 shows the attribution of the financial resources. They ranked micronutrient supplements (vitamin A, zinc, iodine, iron and folate) for children as the top international development priority [4].

Table 2. How to spend USD 75 billion over 4 years [4]

	Solution	Yearly cost in million USD
1	Micronutrient supplements for children (vitamin A and zinc)	60
2	The Doha development agenda	0
3	Micronutrient fortification (iron and salt iodization)	286
4	Expanded immunization coverage for children	1,000
5	Biofortification	60
6	Deworming and other nutrition programs at school	27
7	Lowering the price of schooling	5,400
8	Increase and improve girls' schooling	6,000
9	Community-based nutrition promotion	798
10	Provide support for women's reproductive role	4,000
11	Heart attack acute management	200
12	Malaria prevention and treatment	500
13	Tuberculosis case finding and treatment	419
	Total	18,750

The objectives of this article are first to demonstrate that malnutrition is a problem of great magnitude and that in particular micronutrient deficiencies can be effectively addressed. Second, we will discuss the role of public/private partnerships. And third, we will discuss the criteria for such interventions, their outcome, and whether there are some innovative approaches.

Macro-/Micronutrient Deficiencies

For a long time, hunger in the world was principally addressed by shipping food to developing countries. In 1990, some analyses revealed that some of these interventions had a poor efficacy in decreasing malnutrition. Addressing hunger does not necessarily resolve nutrient deficiencies: large volumes of bulky foods do not necessarily bring the density of nutrients, particularly vitamins and minerals, required for the normal growth and development of children.

Natural sources of food and diversity in diet provide most bio-available forms of nutrients but they are also higher cost items, and most poor people cannot afford them and have limited opportunities to diversify their meals. In addition, during periods of increased needs or acute vulnerability, everyday foods simply do not offer the necessary density of nutrients, including vitamins and minerals. Children under 5 are particularly vulnerable because of their physiological needs and susceptibility to infections.

According to the WHO definition, macronutrient deficiencies, also referred to as protein-energy malnutrition (PEM), are a nutritional deficiency resulting from either inadequate energy (caloric) or protein intake and manifesting

in underweight and slow growth. These two parameters are the most widely used indicators of nutritional status in children less than 5 years of age [5]. Pediatric malnutrition affects first and foremost children under the age of 2, but young children less than 5 years of age, adolescents, and children with HIV/AIDS and TB are also vulnerable.

Malnutrition may be followed by developmental disability of varying degree, including reduced physical and/or mental ability, often associated with reduced strength, impaired cognitive function, reduced occupational activity [6]. In developing countries – mainly in Asia and sub-Saharan Africa – 146 million children under the age of 5 are underweight (1 in 4 children) and 60 million children under the age of 5 are wasted (almost 1 in 10 children). Most recent estimates for India suggest that nearly one half of all children aged 0–3 years are underweight and about 40% are stunted [7, 8].

Although severe malnutrition is associated with higher risk of death in children under 5, mild and moderate malnutrition accounts for the heaviest public health burden. Interventions to address malnutrition and the associated loss in economic productivity have demonstrated the effectiveness of breastfeeding in addressing a large part of the PEM issue. Following these results, WHO and UNICEF recommend exclusive breastfeeding during the first 6 months of life and continuation of breastfeeding beyond this age.

It is reported that the most critical micronutrients missing in developing countries are vitamin A, zinc, iodine, iron, and folate [5]. The Copenhagen Consensus placed interventions addressing these deficiencies on top of the list in particular due to their low cost of intervention (tables 1 and 2).

UNICEF estimates that 100–140 million children (mainly in South Asia and sub-Saharan Africa) are still deficient in vitamin A, despite supplementation efforts in many countries. Vitamin A deficiency in newborn babies, infants, and children accounts for about 6% of deaths of the children under 5 years, 5% of the under the age of 5 years DALYs and 1.7% of total DALYs lost [1].

An estimated 2 billion individuals worldwide suffer from iron deficiency, of whom more than half live in South Asia. Progress has been very difficult, although policy efforts are intensifying considerably. Iron fortification has a very high benefit-cost ratio, estimated as 8.7:1 [9]. The cost of iron fortification varies according to the iron compound used and the food vehicle but can be USD 0.10–0.12 per person per year. Fortification, however, requires that there exists a product that is purchased by a target population regularly and in sufficient quantities to convey the iron requirement [5].

Zinc deficiency is hard to measure, but tends to be correlated with iron deficiency and low animal food intake. IZiNCG [10] estimates that 20% of the world's population is at risk of deficiency based on food intake patterns. Zinc deficiency accounts for about 4% of under the age of 5 years DALYs and 1% of total DALYs lost [7]. Cost-effectiveness results for zinc supplementation suggest that its therapeutic use in diarrhea is highly cost-effective. A study [11] suggests that the incremental cost of zinc as part of case management is USD

0.47 per course of treatment, leading to an average cost of USD 73 per DALY gained, and USD 2,100 per death averted.

Concern over folate is relatively new. Although diets based on unrefined grains and beans (such as those in many rural areas of developing countries) tend to have good folate content, small studies from India and China find high incidence of birth defects, perhaps related to refined rice as the main staple. There are approximately USD 8 billion lifetime costs associated with birth defects related to births in a single year in the US alone [12].

Iodine deficiency affects mainly the development of the brain, and causes major losses in cognitive development, having significant economic impact in the affected regions. Prior to 1993, an estimated 633 million individuals suffered from iodine deficiency [13]. In 1993, the WHO and UNICEF recommended universal iodization of the salt to achieve elimination of iodine deficiency disorders. Salt iodization costs around USD 0.05/person per year, with a benefit:cost ratio in the order of 30:1 [5].

There is an increased dissociation between micro- and macronutrient deficiencies, and possibly an emerging bias in favor of programs that address micronutrient deficiencies relative to those that address PEM [14, 15]. One wonders whether this is driven by the cost-effectiveness of micronutrient interventions or whether it is determined by the technical nature and ease of implementation of micronutrient deficiencies (relative to PEM). Interventions that address PEM are complicated to plan and implement, and require community and household participation in order to be successful – unlike micronutrient interventions that can often be implemented top-down, e.g. via food fortification at source [16, 17]. Indeed, relatively little is known about which interventions reduce PEM among children and what the costs of these interventions are. In contrast, there is a good deal of evidence on interventions that address micronutrient deficiencies [5].

However, it is not always clear what the best way to address micronutrient deficiencies is, and there is an ongoing debate to choose between fortification and supplementation. Fortification refers to the addition of extra nutrient(s) to staple foods (e.g. cereal, milk, salt, condiments, etc.) in an industrial or manual fashion. Double and triple fortification is sometimes possible, meaning that to a single staple two or three nutrients are added. Supplementation, on the other hand, refers to the enrichment of a diet with extra nutrient(s) isolated from the staples. It can be in the form of a tablet, fluid, or other.

Fortification requires central production facilities with adequate safety standards, good distribution and that the components used do not affect the stability, color, taste or smell of the product aimed to be fortified. Fortification tends to have a lower unit cost than supplementation and hence is preferable if feasible, particularly if the deficiency is of importance across a wide range of population groups and if the fortification has no undesired negative effects for the nondeficient population – such as fortification with iron in malaria-endemic regions. Such undesired effects need to be taken into account in

cost-effectiveness and cost-benefit analyses as this has been neglected in the past, e.g. in iodine. Fortification can be more effective in reaching hard-to-reach populations, especially when using staple foods with high penetration rates.

Supplementation, on the other hand, usually requires a specific infrastructure such as field workers and health centers, for a wide distribution. Supplementation can be more complex to put in place for financial reasons, and because it involves a change in food intake habit. Supplementation tends to be used if a subpopulation is of particular interest and if the micronutrient is more costly and needs only to be taken twice a year (e.g. vitamin A).

For many if not all nutrients, one needs to consider the region, the target population and their cultural preferences and the cost-effectiveness. The resulting strategy will then be the most favorable mix of fortification and supplementation [18].

Macroeconomics

Beyond the ethical factor, malnutrition has a number of negative effects on economic growth. It leads to higher mortality and morbidity, higher health care costs, lower levels of education for children, causing a loss of economic output and an overall lower productivity. A number of studies concur to prove the importance of addressing malnutrition from an economic point of view [4, 8] and estimate the economic losses for societies attributable to malnutrition to be in the order of billions of dollars.

Horten [19] reports a productivity loss of children of mothers with goiter to be on average 10.3% and productivity loss associated with anemia to be 5%. A recent review confirms the association between malnutrition and reduced economic productivity [20].

There is a strong relationship between economic growth and nutritional factors, as revealed by the results of econometric procedures, despite some criticism expressed concerning methodology. The growth rate figures vary from 0.4 to 5% [8], which can partly be explained by varying nutritional status of countries. Fogel and Robert [21] go further and believe that the approximate contribution of nutrition to economic growth probably errs on the low side. The impact of nutrition on economic growth would appear to operate directly, through nutrition's effect on labor productivity, as well as indirectly, through improvements in life expectancy.

Nutrition is widely accepted as a critical contributor to physical and mental health, well-being of a society, and economic productivity and growth. It is also recognized that factors to be taken into account to address malnutrition include nutrition itself, as well as economic growth and poverty alleviation. It might even be argued that, in the medium to long run, non-nutritional interventions, such as improving agricultural productivity, expanding female

schooling, and bringing piped water and electricity to rural areas, have larger effects on the reduction of child malnutrition than nutritional supplementation or fortification programs [7]. A study [22] estimated the contribution of various factors to reducing child malnutrition (between 1970 and 95) to be as follows:

- 43.0% women's education
- 19.3% health environment
- 26.1% national food availability
- 11.6% women's status

These findings have been reported in similar results, but a problem with nearly all of the studies is that the unit costs of the non-nutritional interventions (such as sanitation or electricity coverage) are not compiled, so it is not possible to know whether improved sanitation access or electricity coverage delivers more nutritional improvements per dollar of investment than community nutrition programs [7].

However, the income-malnutrition relationship is modest. When gross national product per capita in developing countries doubles, nutrition does improve, but the changes in underweight rates are much more modest decreasing from 32 to 23% [8]. A possible explanation is that the growth indicator GDP does not adequately reflect the income distribution within a given population.

But even if economic productivity and growth contribute substantially to addressing malnutrition, there is a danger of losing sight of explicit nutrition goals by driving towards broader economic goals, whose effects on malnutrition are complex to measure. Because of the belief that interventions focused on non-nutrition will also address malnutrition, the resources allocated for malnutrition remain insufficient: the direct nutrition allocations in the global funds account for less than 1% of the other global funds [23]. Another issue is the composition of 61 Millennium Development Goal indicators, whereby only two are measuring nutrition, and this being only quantitative data [2]. Micronutrient deficiencies and their impact may not be evaluated with these tools despite their very positive cost-benefit ratio (see also table 3) [24].

Despite the striking evidence, it remains questionable whether more political attention and more substantial resources will be dedicated to specific malnutrition interventions.

Public-Private Partnership

Fortification of salt with iodine has been one of the longest-standing micronutrient interventions, and is often quoted as a model to follow for other micronutrient fortification programs. A worldwide effort has dramatically raised the proportion of people consuming iodized salt from less than 20% in 1990 to about 70% in 2000. Experience over the past two decades shows

Table 3. Summary of health economic impact: if 1 DALY = USD 1,000 [24]

Intervention	Benefit:cost	Cost-effectiveness
Fortification of staples		
Salt iodization	30:1	
Flour fortification – iron	8:1	
Flour fortification – folic acid	46:1	
Sugar/oil fortification – vitamin A	50:1	USD 17–22/DALY saved
Double-fortified salt (additional benefit for iron)	2:1 to 5:1	
Home fortification		
'Sprinkles' – effect of iron	37:1	
'Sprinkles' – effect of zinc		USD 12.20–73/DALY
Food-based approach		
Fortified complementary food	2:1 to 1:1[1]	USD 500–1,000/DALY
Ready-to-use therapeutic food	25:1	USD 41/DALY

[1] Estimates for complementary food underestimates: exclude productivity gains.

that the success of the Universal Salt Iodization program is based on [adapted from 25]:

- A supportive political and regulatory environment
- The formation of multi-sector coalitions and transparent partnerships involving international organizations, private producers, national governments and civil society
- Financial sustainability
- Communication efforts with the target populations
- Technical improvements
- Monitoring and evaluation

However, currently 31% of developing-world households still do not consume iodized salt and are therefore not protected [26]. Still, 38 million children are born every year at risk of lifelong brain damage associated with iodine deficiency [13]. Low coverage remains a problem particularly in South Asia (India, Pakistan, and Bangladesh) and some sub-Saharan African countries [26, 27]. It appears that more data are needed to understand the reasons for the lack of penetration of the iodized salt programs, and how to remedy it. One aspect to consider is the food staple used for supplementation, so far limited to salt for iodine supplementation. Condiments may be attractive alternative food vehicles to deliver micronutrients to populations in countries where rice is the dietary staple, and in countries where centrally processed rice is not consumed by rural populations who produce their own rice. Certain condiments e.g. Maggi cubes have a penetration rate of up to 90% in urban areas and 70% in rural areas in Central and Western Africa and reaching out to 50–90% of the hard to reach groups.

In order to address these 31% of households not consuming iodized salt, some critical competencies can be coordinated and put at play:

- In-depth knowledge of specific populations' eating habits and cultural preferences
- Identification of minimal possible nutritional changes to add iodine in diet –intelligent fortification taking into account the fact that behavioral changes in habits are less likely to be long-term successes
- Experience in various food vehicles (salt, flour, condiments, etc.)
- Manufacturing inventiveness and strength: quality control on new products, volume production
- Market insight driving adapted pricing, distribution and communication strategy

Such competencies reside predominantly in the private food industry. Public-private partnerships could combine and leverage the long-term experience of public institutions in malnutrition interventions with the industry's competencies in market knowledge, food vehicle and local implementation. Such partnerships could increase the efficiency of malnutrition intervention programs considerably.

Interventions with rather immediate effects have a higher chance of adoption than measures that demonstrate their effects beyond a political term (iodine interventions produce effects within a rather short period of time). However, more research is needed for the result evaluation of concise intervention programs including health economics analysis in order to demonstrate clear clinical outcome data, cost structure and finally the benefits for public health [28]. To develop pediatric malnutrition initiatives and support private/public collaborative programs, there is clearly a need to better analyze and quantify the efficiency of nutritional and non-nutritional interventions.

Conclusions

Innovative fortification (double or triple fortifications, home or biofortification) with several micronutrients (e.g. iron and iodine) should lower current malnutrition intervention costs and most probably be even more cost-effective than current single fortifications.

The iodine fortification case is a success story with improvement possibilities addressing pediatric malnutrition. Lessons learnt may be transferred for optimal intervention design not only for other micronutrients but also for other forms of malnutrition, and here in particular for lowering the high infant mortality rate due to unsuitable breast milk substitutes. As public-private partnership is crucial in the implementation of iodine deficiencies and other micronutrient deficiencies, this model may also be valid for breast milk promotion in order to achieve the highest public health benefit and best possible cost-benefit results.

Health economics data (the proven cost-effectiveness and the extraordinary cost-benefit ratio) are strong arguments complementing the burden of disease and other arguments in favor of investment in malnutrition and further recognition of this challenge by all actors involved including governments, NGO's, international organizations and the food industry.

More coordinated effectiveness research needs to be undertaken in the area, in particular on the effectiveness and costs of interventions or programs and their outcome on costs and on the health burden in a given region and country [29].

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Discussion

Dr. Mao: We talked about nutrition, now we are discussing malnutrition or undernutrition, and nutrition deficiency, including macro- or micronutrition. We have already learned that every 3 s a child under 5 dies due to malnutrition. In terms of health economics, if you picked two top actions which today could prevent or decrease malnutrition, what would they be?

Dr. Spieldenner: This is exactly the question governments ask, and they often hear that it needs more research and investment provide an answer. Looking at the presented evidence I would chose a nutritional intervention and a non-nutritional intervention, the latter being female education. It has been shown that this measure is very effective in improving the nutritional status of children. The nutritional intervention is more complex as macronutrient deficiencies are the bigger problem, but micronutrient deficiencies can be addressed very cost effectively.

This is why I would choose triple fortification (iron, iodine, vitamin A) in a common and accessible product that is distributed all over a country.

Dr. Cai: I have one comment and one question. The comment: you mentioned that China is very successful in supplementing iodine. I have to say that in some areas we are supplementing too much, and we find thyroid disease may be related to that, but so far has been no evidence and we are trying to do a study right now. My question is: how much GDP can reduce malnutrition significantly?

Dr. Spieldenner: Exactly, in China iodine deficiency is most probably not so much of a problem on a national level but probably more so on a regional level such as in the North and in the mountain regions. The same may apply to malnutrition in general, and research into this is very valuable in order to develop the appropriate responses. The higher the relative household expenditure on nutrition, the more likely it is that GDP growth helps to address the issue of malnutrition. Zimbabwe has a GDP per capita of USD 286, which makes it one of the poorest countries in the world, and people have to spend up to 90% of their household income on food. In such a context, GDP growth would have a considerable impact on malnutrition.

China has a GDP per capita of USD 9,000, but this does not essentially reflect the problem of malnutrition as the family income distribution measured by the GINI index is a better indicator. Therefore, tailor-made programs to address malnutrition in rural areas with very low income will be beneficial in addressing malnutrition overall, most probably more than a rise in the overall GDP growth. It would be helpful to know the household expenditure on nutrition in poor and rural areas in China to develop targeted programs.

Dr. Akbar: My first question is: do you think that only GDP growth can solve the problem of malnutrition in a developing country like Bangladesh, because even if there is a GDP growth, without a mechanism of equal distribution the resources will not reach the poor rural population. And my second question is: how far has the developed world contributed to reach the MDG goals so far?

Dr. Spieldenner: To answer your second question, it is not up to me to judge or to evaluate the work of international organizations in that field, but going through the literature and the different websites of the international organizations it did not become clear to me where all the efforts were put together for each individual country. And I do not believe that the Millennium Development Goals will not all be reached by all countries. I am doubtful about some goals in India and in Bangladesh. And to your first question on GDP growth in Bangladesh, I think that you are right and that family income distribution is the better indicator for a relationship between malnutrition and economic development. But every measurement on a national or international scale has its limitations, and this is one of the reasons why more regional and local studies are needed.

Dr. Cooper: Perhaps just to follow on from my colleague in Bangladesh, in South Africa we have had a democratic government for the last 15 years. We have had quite impressive economic growth, around about 2–3% a year as opposed to the higher rate in India and China. But although there has been a growth particularly in the black middle class, the numbers of people living in poverty haven't changed, the levels of unemployment have if anything increased, compensated to some extent by a better social net in terms of child support grants, but the question is are there macroeconomic policies that perhaps one should be pushing at a national and international level that would ensure some reduction in the GINI coefficient because South Africa certainly has one of the highest in the world.

Dr. Spieldenner: There may be a particular situation in South Africa. The very high GINI index may partly be due to the millions of refugees coming from Zimbabwe and other neighboring countries and immediately falling below the poverty line. This is more an epidemiological point of view rather than a macroeconomic point of view, but it may explain some of the disparities.

Dr. Cooper: It's a bit complicated, but it is still a major problem within what one might call the South African population.

Dr. Spieldenner: It really depends on what indicators you look at. Macroeconomic policy success is measured with its own indicators, and these indicators are not essentially the best indicators to measure and to monitor what they were not originally made for. Why should a government change its macroeconomic policy if the country has a good GDP growth, although other indicators such as schooling and education rates are most probably better indirect indicators for macroeconomic policies to address malnutrition.

Dr. Haschke: I think it's relevant to talk about famine. There are factors which you cannot predict, for example flooding, earthquake or war, in which case you can't do anything in terms of prevention. But there are other areas in the world where problem of famine comes at regular intervals. Our measures usually are to intervene and help, and we know that these measures are very ineffective, a lot of money is wasted, and

after a certain while everything returns to normality, malnutrition stays. Is there any model or are you aware of any population-based or even community-based activity where this is done in a preventive way? What would it cost to prevent through certain measures a population from famine versus helping once it has happened.

Dr. Spieldenner: Engaging in a behavioral change for prevention is very difficult, in particular for people who are poor and have to struggle every day. Only a system with clear direct incentives such as assistance with profitable farming while preserving the environment and producing the healthiest products possible is a possible pathway, and here the food industry plays a crucial role in engaging in such incentives ideally together with governments.

Dr. Singhi: You presented your argument as to convince politicians that if you improve the health you improve wealth and the availability of more resources, but I think that we really do not have a direct evidence for this yet. Is there any model which has clearly shown that investing money in nutritional intervention has resulted in increased GDP or personal income?

Dr. Spieldenner: Yes, there is evidence. Micronutrient deficiencies are rather well researched. However, not many longitudinal studies with a long-term follow-up of nutritional interventions have been carried out.

Dr. Singhi: I think most of these are estimates and extrapolations, that's why I am asking if we have any direct measures.

Dr. Spieldenner: Of course, one part is economic modeling, but there are also interventional data supporting the modeling, particularly in micronutrient deficiencies.

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Economic Perspectives on Pediatric Obesity: Impact on Health Care Expenditures and Cost-Effectiveness of Preventive Interventions

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Abstract

This chapter surveys two segments of the economic literature on pediatric obesity: first, research regarding the impact of childhood obesity on health care expenditure, and second, research evaluating the cost-effectiveness of programs to prevent pediatric obesity. Evidence in support of the hypothesis that obese children and adolescents have higher health care costs than their otherwise similar healthy-weight peers has been found for female adolescents. Studies trying to calculate the complete lifetime health care costs attributable to childhood obesity are missing. Only a small number of studies assessing the cost-effectiveness of preventive obesity interventions among children have been published until now. The results call for the inclusion of nutrition behavior as an intervention target. There is some evidence that childhood obesity prevention might be successful in combining health gains with cost savings. However, it is not possible to rank the interventions according to their cost-effectiveness or to assess the generalizability of their results. Cost-effectiveness increasingly will be a major consideration in public reimbursement decisions. Therefore, evaluation research has to pay more attention to the economic aspects of new health technologies. Without providing good value for money, those technologies probably will not turn from inventions to innovations in health care. Moreover, future research should address various methodological and conceptual challenges and limitations which economic evaluations of preventive interventions into childhood obesity are faced with.

Introduction

Obesity is not only a health but also an economic phenomenon. There are underlying economic causes, such as technological developments and associated changes in the prices of goods and commodities, behind the obesity epidemic. Obesity has serious economic consequences such as lower skill attainment and academic outcomes, worse labor market outcomes, and increasing obesity-related health care expenditures. Because of the high societal costs of obesity, and the fact that the majority of these costs are compulsorily financed by taxpayers or payers of contributions to public health insurance, there is a strong motivation for governments to intervene into the obesity epidemic and to reduce the costs related to it. This raises questions about the economic rationales for public interventions to control obesity. Given the assumption that, from an economic perspective, public intervention to reduce obesity is justified either on efficiency or on equity grounds, the question follows how policy makers should choose between the potentially many possible ways to prevent or treat obesity. There is a rapidly increasing economic literature on all these issues, regarding obesity in general as well as childhood obesity in particular. The purpose of this chapter is to present a short survey on two selected segments of this literature: first, research on the economic consequences of childhood obesity in terms of its impact on health care expenditure, and second, research evaluating the cost-effectiveness of interventions to prevent pediatric obesity. Economic research on the causes of rising childhood obesity is completely out of the scope of this chapter; the interested reader is referred to Anderson et al. [1] as an informative review of this issue.

Impact of Rising Pediatric Obesity on Health Care Expenditures

Economists have studied various potential non-health consequences of childhood obesity, including, e.g., lower skill attainment and academic outcomes, and worse labor market outcomes in terms of earnings and probability of employment. In this chapter, the focus is exclusively on how rising pediatric obesity affects health care expenditure.

Using different methodologies, previous empirical research has demonstrated that obesity is associated with a substantial economic burden in terms of health care costs. For example, for Germany a recent study has shown that in 2003, total health care expenditure attributable to obesity added up to EUR 11.3 billion, corresponding to about 6% of total health expenditure [2]. Furthermore, it has been shown for the adult population in the KORA study region (Augsburg, Germany) that in 1999/2001 severe obesity (BMI ≥35) was associated with incremental health care costs of EUR 1,720 per person per year compared with normal weight [3].

Comparable data for children and adolescents are few. There are some studies focusing on the impact of childhood obesity on hospital care costs. These studies demonstrate that in the US and in Ireland the annual costs of children's and adolescents' hospital stays with obesity listed as a principal or secondary diagnosis increased much more than total expenditure for hospital care over time [4–6]. However, it remains unclear to what extent this increase reflects a growing awareness of childhood obesity being a clinically relevant condition and/or changes in coding behavior or a real increase in the proportion of obesity-attributable health care costs.

Pediatric obesity can lead to various adverse health outcomes already in childhood. Therefore, it is plausible to assume that obese children concurrently have more health care utilization and higher health care costs than their otherwise similar healthy-weight peers. However, the evidence resulting from studies applying this incremental or excess cost approach is mixed:

- There are three US studies examining health care expenditure for special child populations (HMO members [7]; utilizers of a primary care clinic for well-child care visits [8], Medicaid insurees [9]) and reporting higher costs for obese children than for normal-weight children. However, not all findings were statistically significant, and their generalizability to the total child population remains an open question.
- There are four studies using data from the nationally representative US Medical Expenditure Panel Surveys (MEPS). Johnson et al. [10] used data from the 1998 MEPS on children between 4 and 17 years. They found that being obese increased the probability of obtaining medical care, but had no effect on the level of expenditure conditional on the expenditure being positive. Skinner et al. [11] examined 2002 MEPS data of children aged 6–17 years; they did not find any differences in expenditures between obese and healthy-weight children, neither for the probability of having any expenditure nor for average expenditures among those with any expenditure. Finkelstein and Trogdon [12] used pooled data from the 2001–2003 MEPS for children aged 8–19 years; they found a higher level of expenditures for obese children only in the age group of 14–19 years. Monheit et al. [13], who examined only adolescents and used also pooled data from the 2001–2003 MEPS, found statistically significant differences across bodyweight class not for male, but for female persons. Female obese and overweight adolescents were found to have expenditures that exceeded those of normal-weight females by nearly USD 800 per year with a substantial part of the differences in mental health expenditures.

In sum, there is only limited evidence that childhood obesity is associated with increased concurrent health care costs. However, children and adolescents who are overweight or obese tend to remain so over time, and therefore are confronted with increased risks of morbidity during adult-

hood. As there is compelling evidence that in adulthood obese individuals compared with normal-weight individuals have higher health care costs, in a lifetime perspective economic costs of childhood obesity might add up to a substantial amount. Only a few papers have attempted to quantify lifetime costs of obesity (see, e.g. [14] for the US, and [15] for The Netherlands). Unfortunately, these studies start in early adulthood and therefore are not suitable to calculate the health care costs attributable to obesity in childhood and adolescence. However, the studies provide some, but no definite, evidence that although obesity in adulthood results in higher annual medical spending, it may actually reduce lifetime medical spending due to a shorter life expectancy of obese persons. Therefore, it cannot be excluded that successful obesity prevention cannot stem the tide of increasing health care expenditures.

Economic Evaluations of Interventions to Prevent Pediatric Obesity

There are probably many possible ways to prevent childhood obesity. Economists propose that policy makers should look at the results of economic evaluation studies and choose those interventions that provide the most 'bang for the buck'. Until now, only a small number of studies assessing the cost-effectiveness of preventive obesity interventions among children have been published. Based on a PubMed search conducted in July 2009 in the literature published since 2001, economic evaluations of totally twelve preventive interventions could be identified. The major contribution to this research has been made by the ACE-Obesity (Assessing Cost-Effectiveness in Obesity) project which, in addition to five interventions targeted at overweight or obese children and adolescents, comprises the economic evaluation of eight obesity prevention programs [16, 17]. Furthermore, four more evaluations of several school-based programs were found [18–21]. The studies differ in a large number of methodological aspects such as study type, intervention target, target population, outcome measure, follow-up time horizon, costs included, and alternatives against which the interventions are assessed. Table 1 provides some information on these differences.

The results show with some degree of confidence that in order to reach acceptable cost-effectiveness values, interventions should include nutrition as an intervention target. In addition, there is some evidence in support of the expectation that childhood obesity prevention may be successful in combining health gains with cost savings. However, it is not possible to rank the interventions according to their comparative cost-effectiveness. This holds even for the interventions examined in the ACE-Obesity project, although a common evaluation methodology has been applied in this project. But priority to be included in the project was given not only to interventions with

sufficient evidence of effectiveness, but to interventions with high relevance to current policy-making, as well. Therefore, the quality of best available evidence actually used in the models was very different; in the worst case, there was almost no empirical evidence of effectiveness at all. In the framework of lifetime modeling, there was a serious lack of evidence, above all, concerning children's BMI development after the end of the intervention or follow-up period. The ACE-Obesity approach assumed that the mean BMI change due to the intervention would be maintained over the life of the child, without specifying the basis for this questionable assumption. Furthermore, this approach did capture only those health benefits which where linked to changes in BMI. However, there are good reasons to assume that the examined interventions may generate health outcomes that are independent of changes in BMI [22].

It is even more difficult to assess the generalizability of the reported results. This finding supports the observation of Wolfenden et al. [23] noting a general lack of reporting of contextual factors in intervention trials that are critical in judging the relevance and applicability of findings in practice. Information on those elements is needed to make more confident conclusions about the potential effectiveness and successful dissemination of intervention evidence into practice settings.

Given the present state of knowledge, it is neither clear whether the most cost-effective solution to the problem of obesity is prevention or treatment, nor is it clear what the most cost-effective point of time for preventive interventions would be. Although a focus on obesity prevention in childhood may seem plausible, it might be that early interventions are not the most cost-effective way to attack obesity. Preventing obesity in adulthood may be more cost-effective, due to the more immediately occurring benefits of avoiding the otherwise high prevalence of obesity-related comorbidities that develop during adulthood. Unfortunately, those comparative studies are lacking. Therefore, the best strategy for the short run – while such cost-effectiveness data are still lacking – is not clear [24].

Despite all limitations, there is a clear message to be derived from the available findings on the cost-effectiveness of preventive child obesity interventions. The large variation in the incremental cost-effectiveness ratios even among studies based on the same methodological approach impressively underscores the urgent need for analyzing not only the effectiveness, but the efficiency of those interventions as well, in order to ensure the most economical use of the limited financial resources available for improving the young population's health.

However, it is not sufficient to simply increase research on the efficiency of child obesity interventions. Economic evaluations of those interventions face a number of challenges and limitations, which are to be considered carefully when using the study results in the process of decision-making. They include the following issues:

Table 1. Cost-effectiveness studies of preventive obesity interventions in children and adolescents

Reference	Intervention and setting	Intervention target	Target population	Study approach	Time horizon	Health gain measure	Cost per unit of health gain
ACE-Obesity [16, 17]	Walking School Bus	PA	children aged 5–7 years	model	lifetime	DALY	AUD 760,000
ACE-Obesity [16, 17]	TravelSMART	PA	children aged 10–11 years	model	lifetime	DALY	AUD 260,000
ACE-Obesity [16, 17]	Active after School Community Program	PA	children aged 5–11 years	model	lifetime	DALY	AUD 80,000
ACE-Obesity [16, 17]	multi-faceted SBP without active PE component	N, PA	children aged 6 years	model	lifetime	DALY	AUD 6,000
ACE-Obesity [16, 17]	multi-faceted SBP with active PE component	N, PA	children aged 6 years	model	lifetime	DALY	cost saving
ACE-Obesity [16, 17]	SBP to reduce the consumption of sweetened carbonated drinks	N	children aged 7–11 years	model	lifetime	DALY	cost saving
ACE-Obesity [16, 17]	SBEP to reduce TV viewing	(N, PA)	children aged 8–10 years	model	lifetime	DALY	cost saving
ACE-Obesity [16, 17]	reduction in TV advertising of high fat/high sugar foods and drinks directed at children ≤14 years	(N)	children aged 5–14 years	model	lifetime	DALY	cost saving
Wang [18]	SBP Planet Health	N, PA	middle school children	model	lifetime	QALY	USD 4,305 (girls only)
Brown [19]	SBP CATCH	N, PA	children 8–11 years	model	lifetime	QALY	USD 900

Wang [20]	SBP FitKid	N, PA	elementary school children	trial	1 year	% body fat reduction	USD 417
McAuley [21]	SBP APPLE	N, PA	children aged 5–13 years	trial	4 years	kg weight gain prevented	NZD 664–1,708 (depending on age)

PA = Physical activity; N = nutrition; SBP = school-based program; SBEP = school-based education program; PE = physical education; DALY = disability-adjusted life year; QALY = quality-adjusted life year. Parentheses signify indirect impact of intervention on behavior expected.

- *Outcome identification and measurement.* A major problem in the conduct of economic evaluations of preventive interventions is the appropriate identification and measurement of their benefits. Looking only at the changes in body mass and the health gains to be expected from reduced risk of obesity might too narrowly define health benefits to be expected from improvement of eating and physical activity behavior. In addition, community-based programs may have social diffusion effects into other population groups.
- *Measuring quality of life.* Including all health outcomes of obesity interventions in only one measure of effectiveness requires to apply a generic measure of health benefits. Economists prefer to use QALYs which are derived from preference-based evaluations of states of health, as they are described in generic measures of health-related quality of life. However, until now there is no consensus on how health-related quality of life should be defined and measured in pediatric populations [25]. Moreover, proxy rating for measuring quality of life and, above all, for valuing states of health, is unavoidable, which may compromise the validity and reliability of those data.
- *Attributing outcomes to interventions.* Interventions may reduce future ill health over a very long time period. Estimating such consequences obviously raises considerable study design and measurement problems. In general, some sort of modelling is needed to estimate these effects to be expected to occur beyond the end of the trial. In modelling, all relevant evidence is used, including the synthesis of evidence from studies of different experimental and non-experimental design. However, the use of non-experimental data always bears the risk of biased estimates of the impact of an intervention on the target variable. In the end, to accurately calculate the lifetime health gains produced by specific interventions, studies with longer follow-up are urgently needed to determine the persistence of changes observed in a short-term perspective.
- *Unrelated health care costs in life years gained.* A further issue is whether any potential saving in costs from one disease needs to be adjusted for the higher health care costs that may arise from extendings people's lives. While preventive interventions may reduce diseases and expenditures related to the risk factors, they will increase diseases and expenditures unrelated to those risk factors primarily in gained life years. For obesity, the costs of these unrelated diseases have been demonstrated to potentially outweigh the savings on related diseases [14, 15]. Following the highly questionable recommendations of many national guidelines, current health economic evaluations usually exclude the costs of unrelated diseases in life years gained. This may result in too favorable estimations of cost-effectiveness, feeding the unfounded optimism among policymakers who tend to regard effective lifestyle interventions as a cost-saving option [26].

– *Discounting future costs and benefits.* In order to adjust for the individuals' positive time preference, future costs and benefits are discounted in economic evaluations to their present value. Typically, discounting is done at a time-constant discount rate, equal for costs and benefits. The choice of the discount rate can profoundly affect the result of an economic evaluation, especially if there is a large time distance between the cost of the intervention and its health outcomes. Therefore, the cost-effectiveness of a childhood obesity prevention program critically depends on the discount rate applied. There is not only an ongoing debate on how the appropriate discount rate should be determined. If an increasing value is attached to health over time, a discount rate for health benefits should be used, which is lower than the rate applied to costs [27]. Furthermore, uncertainty about the future economic development of society may require time-declining discount rates [28]. Finally, there is some evidence that people devaluate future health gains of their children less than their own future health benefits [29]. This finding would require to apply a discount rate for child health gains lower than the rate for adult health gains.
– *The maximization rule.* Economic evaluation of health care programs is based the decision rule of maximum benefit, i.e. it is endorsing the ethical position that it is the total sum of health gains produced what matters, no matter how that sum is distributed among people. However, evidence about the public's perspective on the allocation of health care resources convincingly demonstrates that people consistently articulate views that conflict with health gain maximization [30] by taking into account, in addition to efficiency, a broad range of fairness and equity principles. As prevention activities frequently are motivated by the intention to tackle socioeconomic health inequalities, prioritizing according to the maximization criterion without considering the equity issue may be particularly inappropriate.

Conclusions

To design effective public policies to curb the obesity epidemic, a more detailed and more precise knowledge is necessary on the long-term costs associated with overweight and obese children as a first step in determining cost-effective treatment and prevention interventions. However, until now a large part of our empirical knowledge on the potential health and non-health consequences of rising obesity is based on survey methods representing short-term measures of calorie intake and consumption, health status, and health care utilization and costs. Calculating more precise estimates of the lifetime health care costs attributable to obesity and its overall societal

costs requires longitudinal data about diet quality and physical activity for better understanding the links between overweight and obesity and chronic disease risks as well as longitudinal data about health care consumption and costs.

Systematic cost-effectiveness analyses are not widespread in studies on childhood obesity interventions. Remarkably, there are no studies at all evaluating the efficiency of interventions aiming at influencing gestational weight gain or preventing pre-school obesity, nor are there studies analyzing the cost-effectiveness of interventions based on the use of typical economic incentives such as taxes on less healthy foods and/or subsidies for relatively healthy foods. The reasons for this lack of economic evaluations are unknown, but it highlights the need to design intervention trials with translation and dissemination in mind. There is little doubt that cost-effectiveness increasingly will be a major consideration in decision-making by health politicians and third-party payers. Therefore, evaluation research has to pay more attention to the economic aspects of new health technologies. Without providing good value for money, those technologies probably will not turn from inventions to innovations in health care.

However, the economic evaluation of preventive interventions into childhood obesity faces various methodological and conceptual challenges including the definition and measurement of intervention outcomes, the definition and measurement of health-related quality of life in pediatric populations, the attribution of outcomes to interventions if RCTs are not feasible to test causal relations, how to deal with unrelated health care costs in life years gained, how to value future costs and benefits, and finally, how to integrate considerations of equity and fairness into economic evaluations. These challenges are to be addressed in future research if the full potential of economic evaluation as an aid to decision-making is to be exhausted.

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Discussion

Dr. Bier: I don't quite know how to frame it because I don't know the economic terms but what is the cost of being thin. I am really talking about personal economics because people have obviously voted on cost. If it was cheaper to a person to be thin than fat we would all be thin. People are fat, so on a personal level they have decided it cost them less to be fat than thin, and the costs of being thin involve your spouse being unhappy because you are not home with the children when you are at the club doing exercise and all the other things of this sort. So how do we determine that?

Dr. John: You are describing the choice between being thin and being fat in terms of economics, where individuals are assumed to compare the costs and benefits of alternative courses of action and to choose the option with the largest net benefit. The cost-of-illness perspective on obesity is much narrower: it looks at obesity's economic impact in terms of its 'direct costs', the costs of resources consumed because of the associated illnesses (including medical care, travel costs, etc.), and 'indirect costs', the value of lost production due to reduced working time [for a critical review of cost of illness methodology, see 1]. Of course, cost-of-illness methodology could be applied to the problem of underweight as well. In the same way as we have calculated the costs of overweight and obesity, one can measure the costs of underweight by calculating the cost differences between underweight and normal-weight children. However, this is only a descriptive analysis of the magnitude of the two health problems. Comparing the costs of overweight and the costs of underweight neither guides the individual in her or his decision between being fat or being thin, nor provides enough information in order to decide whether and how health policy should intervene in these health problems. In both cases, a comparison of costs and benefits of the available options is required for a rational decision.

Dr. Ivarsson: I am involved in health economic studies exploring celiac disease screening in Sweden, and I increasingly appreciate that scientific field. I find health economic studies extremely helpful when trying to motivate politicians and health care decision makers to take action against public health threats. However, in your example of teenagers and obesity, you don't show us the full potential of such studies. Firstly, in my opinion, you need to use a life course approach also taking the long-term consequences of obesity into account, even though that would involve modeling and thereby introducing a larger extent of uncertainty. Secondly, when taking only health care expenditures into account you may not see the whole picture, as future decreased productivity also needs to be considered, as well as the estimated value of decreased health and well-being. Thirdly, I agree that health economic studies can't tell us how to design the interventions needed to prevent or treat obesity. However, such studies can help us by estimating how much the individual and society would save economically if we succeeded in developing an effective intervention, and could thus guide priority setting. Thus, in my opinion the discipline of health economics has an even larger role to play in the future than you bring forward in your lecture.

Dr. John: I agree with all you have said, especially with your statement that health economics can and should play a larger role in supporting policy decisions. However, looking at the various unsolved methodological challenges of health economic evaluation, it seems to me that health economics can and should inform, but not guide policy decisions. Regarding your comment on modeling, I would like to underscore that modeling of course is an 'unavoidable fact of life' [2]. Moreover, and perhaps more important, we should be aware of the fact that decisions will always be taken under conditions of uncertainty, and decision-analytic modeling provides strong instruments

to deal with uncertainty in decision-making in a rational way. However, economic evaluation using decision-analytic modeling in order to identify the preferred option should be based on the decision-maker's value function, and I have some doubt whether the decision rules incorporated in standard economic evaluation can always be regarded as valid representations of this value function.

Dr. Hussain: I just want to add that it is an established fact that childhood obesity or increased BMI leads to a high risk of coronary artery disease and atherosclerosis in adulthood, that's another economic pattern. Having said that, there is not much data as yet from developing countries, only data from Delhi by Sachdev et al. [3]. They say that although it is not an established indicator, increased BMI is a risk factor in developing countries, but in the countries with a rapid economic growth the affluent class of population definitely has a high risk of coronary heart disease. Do you have any comment on this?

Dr. John: It's not really in my competence to comment on the issue of increasing BMI in the perspective of low-income and lower-middle-income countries. Meanwhile, it is well known that in those countries there is very often a coincidence of malnutrition and obesity in the course of rapid economic development. The question how to solve this problem under the economic constraints of these countries is a difficult one, and it needs special knowledge and experience, which unfortunately is beyond my expertise.

Dr. Greer: On your early slide, you showed that in the US it is very difficult to show the cost of pediatric obesity, particularly in the young children between the ages of 0 and 12. I hear this every day from the 55,000 members of the Academy of Pediatrics, that basically nobody thinks these kids are ill. The parents don't think these kids are ill, most of the pediatricians don't think these kids are ill, the private insurance companies don't think these kids have a problem and even the government-sponsored insurance programs don't think these kids are ill. If a pediatrician should become interested in trying to do something about obesity in this age group, there is absolutely no reimbursement for this activity. The reason given for the lack or reimbursement is that there is no cost-effective treatment for this age group. Is the situation in Western Europe similar? The real problem in our country is that nobody wants to pay for obesity treatment for children.

Dr. John: Yes, we have similar problems in Germany. For example, take the case of weight-reducing drugs, which are not covered by Germany's National Health Insurance (NHI). However, the exclusion of those drugs from the list of reimbursed drugs is not based on effectiveness or cost-effectiveness considerations. The key issue is that these drugs are regarded as primarily lifestyle medications, and according to the current legal regulations, they are thus excluded from the benefit basket of NHI. I have some doubts about the cost-effectiveness of designing the health care benefit basket the way we've done it until now in Germany. However, as I have already mentioned, health politicians' and third party payers' willingness to pay for interventions into obesity is a slowly changing landscape, and in the near future we might expect some regulatory changes in Germany as well.

Dr. Spieldenner: It is right that programs addressing behavioral change and environmental factors at the same time, e.g. the EPODE program in France, are cost effective. Policy makers, however, often prefer projects that are behavioral projects for school children as they transmit a good image, but often they are not effective. From the perspective of health economics, the society as such has to assume most of the health care costs.

Dr. Bier: The society is made up of the people, so imposing society is not always the same as the society coming to that solution I think.

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Sustainable Clinical Research, Health Economic Aspects and Medical Marketing: Drivers of Product Innovation

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Abstract

Marketing-driven innovation in the field of pediatric nutrition, in particular in the infant formula segment is not sustainable. New benefits of products must be scientifically proven and safety and efficacy of new formulae established in clinical trials. The scientific innovation process of three infant formulae is described. Improvement in protein quality allowed to reduce the protein concentration in whey-based infant formula. Weight gain and BMI of infants fed those formulae corresponds to breastfed infants and is lower than in infants fed traditional formulae with higher protein concentration. A meta-analysis indicates associations between rapid weight gain in infancy and obesity later in life. If infants cannot be exclusively breastfed until 4–6 months of age, feeding low-protein formulae may contribute to positive long-term health outcome with potentially important health economic effects. A partially hydrolyzed whey based formula for prevention of allergic symptoms in children with hereditary risk for allergic diseases was developed more than 25 years ago. The most recent meta-analysis which included 15 randomized clinical trials indicates that the risk of all allergic diseases and atopic dermatitis/eczema is significantly reduced in infants at risk when the partially hydrolyzed formula is fed. The partially hydrolyzed formula had the same protective effect as casein-based high-degree extensively hydrolyzed formula. Because of substantial price differences between the two formulae, feeding the partially hydrolyzed whey formula is cost saving. Hypoallergenic claims can be made in many countries, and international nutrition committees have positively commented the preventive effect of those formulae. Acidified formulae have been widely used during the last decade in replacement feeding programs for infants whose mothers are HIV positive. The formula was innovated by improving whey protein quality and lowering protein concentration. The bacteriostatic properties of the new formula were proven in in vitro tests. Meta-analysis indicated that feeding the formula to immunocompromised infants resulted in growth similar to breastfeeding. The bacteriostatic effects of the acidified formula need to be

communicated to health care professionals, but also the risks if replacement feeding is not acceptable, feasible, affordable, sustainable, and safe for mother and infant.

Introduction

Prenatal, early postnatal, and early childhood nutrition plays an important role for short- and long-term health. The short-term effects of inadequate nutrition are well documented both in developed and developing societies. In addition, there is a growing body of evidence showing that nutrition during the early life cycle may program endocrine, cardiovascular, and central nervous systems and induce epigenetic phenomenons with long-term effects on health. Industry must continuously learn from research and try to add sustainable innovation to products once new health benefit areas have been clearly identified [1].

Innovation in the field of dietetic foods for infants and small children is a cumbersome process. In order to launch new products, in particular formulae for premature and term infants, safety and efficacy has to be established. Therefore, new product development in that segment requires a pharmaceutical project management which starts with preclinical evaluation and ends with clinical trials in the target group. The innovation process can take 5–10 years and is expensive. In the pharmaceutical industry, patent protection generally allows to market new drugs for several years, whereas in the baby food industry patent protection is poor and can be easily circumvented. Small and medium-sized companies have difficulties to compete in the innovation process and consolidation in the industry occurs. Finally, the extremely conservative regulatory environment in the field of formulae for low-birthweight and term infants [2–5] requires a novel food approach to add new ingredients and make product-related claims.

Marketing, on the other hand, would like to quickly push new products with nutritional benefits to the market. One typical example was the addition of DHA to infant formula. More than 15 years after introduction of the first formulae with DHA, science has evidence for benefits for low-birthweight infants [6]. The debate on benefits for term infants continues [7, 8]. However, companies put pressure on regulatory agencies to allow the addition of DHA and to make claims. Marketing in the meantime had done an ‘excellent’ job and convinced mothers via TV advertising, in particular in Asian countries that DHA in formula is important for long-term better brain performance, which is a typical example of ‘over-claiming’. Formulae with added DHA have a substantial price premium which parents have to pay. Therefore, mainly non-breastfed infants from higher social classes receive formulae fortified with DHA. With very limited scientific data, the baby food industry now also adds DHA to weaning food in jars, cereals and formulae for infants and children between 6–36 months of age. Key opinion leaders in pediatric nutrition

and pediatricians who carefully follow the relevant literature should make up their mind if formulae and baby food with DHA are important for long-term health and performance and should be recommended.

Long-term development projects of three infant formulae, which have been available during the last 5 years, will be presented. One formula is a product mainly used in developing countries. Sustainable research has resulted in product development with short- and long-term health benefits for the infant. Furthermore, health economic aspects and responsible medical marketing of those products will be addressed.

Low-Protein Formula with Improved Protein Quality

There are three factors which stimulated the development of a new infant formula generation in the 1990s:

- First, new insights into the composition of breast milk: during the first months of lactation, the protein concentration in breast milk decreases considerably, reaching levels of around 9–11 g/l [9]. If the lactation period persists until 1–2 years of age, protein concentrations are still around 8–10 g/l [10]. Protein concentrations in infant formula were in the range of 15–20 g/l until the end of the last decade, and therefore substantially higher than in breast milk. This was due to differences in amino acid composition and the assumed lower digestibility. In addition, infants fed infant formulae which were on the market before 2000 had higher volumes of intake than breastfed infants, which resulted in protein intakes which were >50% higher than in breastfed infants [11].
- Second, detailed insights into early nutrition and growth: several cohort studies had indicated [12, 13] that formula-fed infants show higher weight gain than breastfed infants during the first months of life, and the discussion on potential associations between rapid weight gain during infancy and later risk of obesity started up.
- Third, studies on metabolic outcome in breast- and formula-fed infants: already in 1988, Axelsson et al. [14] published that a high level of protein intake during early infancy influences plasma amino acid concentrations, insulin secretion, and growth. Stimulation of insulin-like growth factor-1 could result in rapid weight gain and increase in adipose tissue [15].

In view of the insights on breast milk concentration and after intensive discussion with the authors of the studies which had indicated faster growth [12] and unfavorable metabolic outcome [14] in infants fed 'high-protein' formulae, it was decided in 1995 to develop a low-protein formula with improved protein quality [16]. Modification of the protein whey fraction resulted in lower threonine and higher concentrations of tryptophan, cysteine, arginine and histidine. An amino acid profile closer to breast milk and improved levels

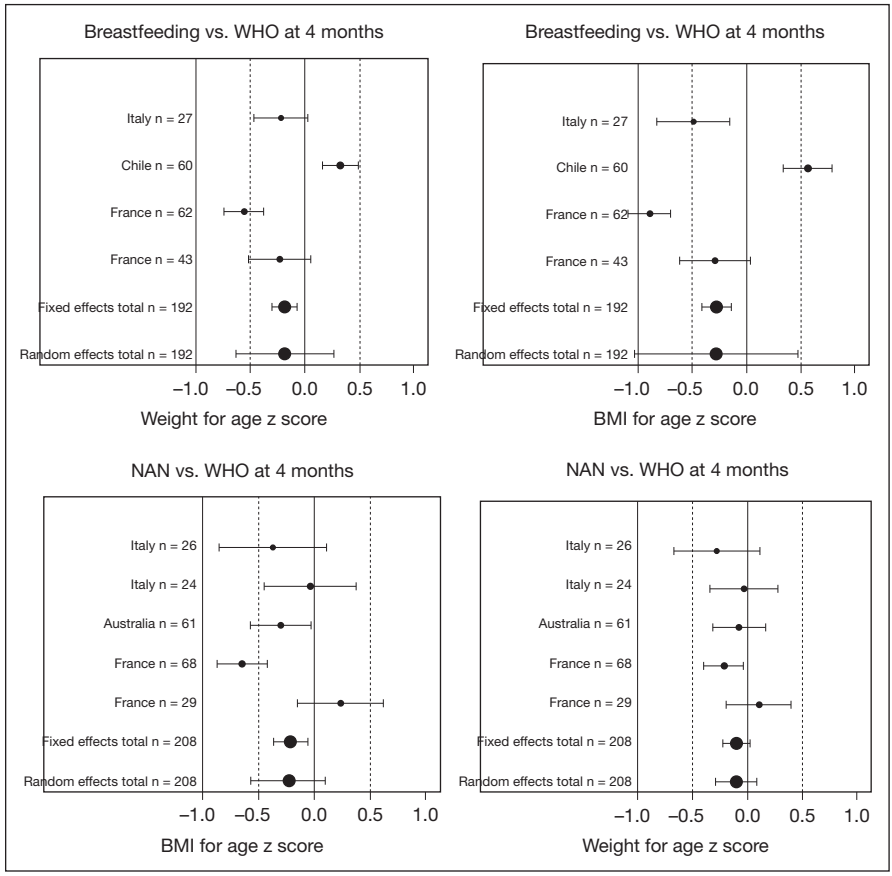

Fig. 1. Weight-for-age and BMI at 4 months of age (z scores, WHO growth curves). Breastfeeding vs. low-protein formula. ANCOVA correcting by birth z score and gender (means, 95% CI). Adapted from Steenhout et al. [17.]

of limiting indispensable amino acids allowed to reduce total protein quantity in the formula. After animal trials had indicated safety of the new formula, randomized clinical trials with the new whey-based 'low-protein' formula (casein:whey ratio 30:70) with 12 g protein per liter (1.8 g/100 kcal) were done in different parts of the world. Longitudinal growth studies indicated that weight and length gain of infants who were exclusively fed the 'low-protein formula' until 4 months of age were similar to breastfed infants. Two recent meta-analyses included the results of all randomized clinical trials and growth studies and confirmed the findings (fig. 1) [17]. Metabolic outcome, in particular plasma amino concentrations were close to breastfed infants [16], and insulin-like growth factor-1 concentrations were lower than in the infants

who were on 'high-protein' formulae [18]. The 'low-protein' formula was introduced in the years 2000 as starter (NAN 1®) and 2009 as follow-up formula (NAN 2®). In 2005 and 2009, a 'low-protein' hypoallergenic (NAN HA®) and acidified formulae (NAN Pelargon®, BIONAN®) were launched, respectively. Other formula companies have launched similar products during the last years.

At the end of the first decade of the 21st century, evidence-based medicine is strongly indicating that early infant feeding, weight gain during infancy and recently, protein intake with infant formulae are important for later health outcome. Meta-analyses and systematic reviews indicate that in comparison with breastfeeding, the consumption of high-protein formulae (only high-protein formulae were on the market when the studies were done) was associated with a 3–25% higher prevalence of obesity during childhood and adolescence [18–23]. Systemic reviews have also confirmed that high weight gain during infancy is associated with higher risk for later obesity [19, 24–26]. A recent randomized controlled clinical trial [27] compared weight for age, length for age, weight for length and BMI of infants fed 'low-protein' or 'high-protein' formulae between birth and 12 months of age. Growth of exclusively (at least until 3 months of age) breastfed infants was also presented. Infants fed the low-protein formulae at 6 and 12 months of age had lower weight for age, BMI and weight-for-length. At 24 months of age – i.e. 12 months after the formulae were discontinued – BMI and weight-for-length were still significantly lower in the children who had been on the 'low-protein' formulae. No significant differences between the infants fed the low-protein formulae and the breastfed control group were observed at any age. The authors speculated that lower protein intake in infancy might diminish the later risk of overweight and obesity.

We have only just began to look at health economic aspects of the impact of infant feeding practices – in particular breastfeeding and feeding formulae with 'high' – and 'low-protein' concentrations – on childhood, adolescent, and adult obesity. As indicated, breastfeeding is associated with lower risk, and duration of breastfeeding seems to play a role [21, 19]. Koletzko et al. [27] recently calculated that feeding low-protein formula compared with high-protein formula could be associated with a 13% lower risk of obesity in adolescence. The lifetime medical cost burden of obesity and implications for obesity prevention have been recently published by Finkelstein et al. [28]: the average lifetime attributable medical costs to obesity in the US (BMI >30) for 20-year-old adults is approximately USD 19,600, if degree of obesity, sex and ethnic differences are considered. Calculations of savings are presented (table 1) for two hypothetical scenarios. Adult obesity (rate in the US is 35% [29]) would be 1 or 13% lower in non-breastfed infants born in the US (4.3 millions [30]) if 'low-protein' formulae were provided. The annual economic burden would be reduced by USD 205 million and 2.67 billion, if obesity rates were 1 or 13% lower, respectively. This scenario is based on the assumption

Table 1. Avoidable costs if 'low-protein' formulae protect from adult obesity

	Risk reduction[1]	
	–1%	–13%
Avoided cases/year	10,490	136,370
Avoided cost/year, USD	205 million	2.67 billion

[1] This scenario is based upon the assumption that all formula-fed infants would receive low-protein formula and the results are nondiscounted for the purpose of discussion. Calculated from Koletzko et al. [27] and Finkelstein et al. [28].

that all infants on formula would receive low-protein formula and the results are nondiscounted for the purpose of discussion. Therefore, health authorities need to carefully analyze new incoming data on potential risk reduction of obesity through early infant feeding measures.

With the exception of the US, infant formula-producing companies are not allowed to communicate infant formulae directly to parents. Medical marketing should be very careful when already communicating 'anti-obesity' effects of low-protein formulae to healthcare professionals. However, the fact that low-protein formulae are closer to the reference breast milk and feeding of those formulae results in growth similar to breastfed infants can be communicated to all pediatricians who are interested in the long-term consequences of rapid infant weight gain.

Hypoallergenic Infant Formula

It is well documented in the literature that formula-fed infants with a documented hereditary risk for allergy are suffering more often from allergic disease than breastfed infants, in particular during the first years of life [31–33]. Early exposure to foreign protein, in particular cow's milk protein can play an important role. In order to make infant formula hypoallergenic, it was necessary to test the technologic treatments which result in substantial reduction in the allergenicity of cow's milk protein. Hydrolysis with proteases followed by heat treatment as well as hydrolysis followed by fractionation turned out to be practical ways of reducing milk protein antigenicity [34]. The taste of hypoallergenic formulae improved by further adapting the technology. Animal [35] and infant studies which are presented in a meta-analysis [33] then proved safety and efficacy of a 100% whey-based partially hydrolyzed formula (phF NAN HA®). Recently, safety of that whey-based phF with reduced protein content was confirmed by randomized controlled growth and metabolic outcome studies [18].

More than 25 years ago, the first cohort studies indicated that formula-fed infants with a documented hereditary risk of allergy (i.e. having an affected parent and/or sibling) might benefit from receiving a partially or extensively hydrolyzed formula (ehF). There are now 84 studies in the literature, among them 44 (15 randomized clinical trials) which involved one phF. There must be certainty regarding the choice of a hydrolyzed formula for allergy prevention as well as safety and efficacy of a particular hydrolyzed formula. Factors such as protein sources and method and degree of hydrolysis are important for clinical outcome.

Using clearly defined criteria, Szajewska and Horvat [36] included fifteen randomized clinical trials into their recent meta-analysis that compared the use of one phF with use of standard infant formula or extensively hydrolyzed bovine proteins (whey or casein). Incidence of all allergic diseases and atopic dermatitis/atopic eczema was the primary outcome variable.

This recent meta-analysis indicates reduced risk of all allergic diseases in favor of the phF compared with standard formula. At 3–6 months and at 12 months, administration of the phF compared with standard formula was associated with approximately 50 and 38% risk reduction, respectively. Seven and 12 infants needed to receive the phF to save one infant from allergic disease (NNT) at corresponding ages. The pooled results of data (5 trials) at 0–36 months of age indicated a significantly lower cumulative incidence of all allergic diseases.

Data from 5 trials [36] reported the effect of the phF on the cumulative incidence of eczema within a given period (0–3, 0–6, 0–18, 0–24 months, and 0 to 5–6 years). A consistent significant reduction in the risk of eczema in favor of the phF was shown in both fixed and random effects meta-analyses.

Five trials (table 2) [36] compared the effect of use of the phF versus an extensively hydrolyzed casein formula, and found no significant difference between the two groups for all allergic diseases and atopic dermatitis/eczema.

The preventive effect of feeding partially hydrolyzed whey-based formula is well documented, but health economic aspects have not been published so far. However, they are needed in order to be able to discuss reimbursement with health insurances. Cost of feeding the whey-based phF is easy to calculate – i.e. the price premium over regular formula is about 20–30%, but cost estimates for treatment of atopic dermatitis/eczema are needed to calculate a cost/benefit ratio.

Cost comparison between feeding (0–4 months) a partially hydrolyzed whey-based or an extensively hydrolyzed casein-based formula to non-breastfed or short-term (<3 month) breastfed infants at risk for development of allergy are presented for one European country (table 3). Meta-analysis had indicated that the two formulae are similar in their ability to prevent allergic manifestations and atopic dermatitis/eczema. The assumptions were

Table 2. Whey phF vs. casein ehF preventive effect outcome

	Cases	Effect	Difference
All allergic diseases (cumulative incidence)			
0–12 months	1,137	0.98 (0.72–1.35)	NS
0–18/24 months	164	0.90 (0.60–1.35)	NS
0–36 months	1,137	1.03 (0.81–1.27)	NS
0–5/6 years	1,137	1.05 (0.90–1.23)	NS
Eczema (cumulative incidence)			
0–12 months	1,137	1.06 (0.74–1.53)	NS
18 months	164	1.12 (0.67–1.85)	NS
36 months	1,137	1.13 (0.87–1.47)	NS
5/6 years	1,137	1.17 (0.94–1.45)	NS

Adapted from Szajewska and Horvarth [36].

Table 3. Population-based cost comparison of non-breastfed infants at risk (France) receiving either whey phF or casein ehF (similar protective effects)

	Whey-based phF	Δ	Casein-based ehF
Cost of formula/kg, EUR[1]	24	33	57
Annual costs/year, millions of EUR	25	34	59

[1] Pharma retail price 2009.

made based upon the number of births in France in 2007 [8], a breastfeeding rate of 53% in the first 3 months and percentage of infants at risk for allergy (23%) [37] who are not breastfed or breastfed <3 months and are therefore fed hypoallergenic formula, volumes of formula intake [38], and retail pharma prices per kilogram of the two formulae. The calculated cost length was 4 months with exclusive formula feeding. Even with these rather conservative assumptions, the cost difference between the two formulae can be estimated at EUR 34 million per year. Taking into consideration less conservative assumptions and that one fifth of the infants on ehF switch to amino acid-based formula with a much higher price, the cost difference can be estimated to be up to EUR 80 million per year.

Already in 1999, the EU regulation allowed to make a hypoallergenic claim for infant formula if clinical trials prove safety and efficacy of the formula. This claim was confirmed in the most recent EU directive on infant formulae. ESPGHAN/ESPACI [32] and more recently, the American Academy of Pediatrics [39] have made comments on hypoallergenic formulae. Therefore, medical marketing can communicate that the partially hydrolyzed whey-

based formula can prevent allergic disease in children at risk and has a cost-benefit and taste advantage when compared with high-degree hydrolyzed casein-based formulae.

Feeding Infants of HIV-Positive Mothers

In non-breastfed infant populations exposed to suboptimal or compromised hygienic conditions, the risks to acquire gastrointestinal infections are substantially higher than in breastfed infants. Therefore, promotion of exclusive breastfeeding until 6 months of age and continuing breastfeeding beyond that age is key to reduce infant morbidity and mortality [40]. The WHO recommendations are embraced by almost all countries as well as by infant formula manufacturers. However, infant feeding choices are under discussion in a population of mothers, where HIV can be transmitted to the infant through breastfeeding. In such cases, WHO recommends [41] that HIV-infected mothers breastfeed exclusively for the first 6 months unless replacement feeding is acceptable, feasible, affordable, sustainable, and safe (AFASS) for mother and infants, and if replacement feeding is AFASS, avoidance of all breastfeeding by HIV-infected mothers should be recommended. In relation to feeding the infant at risk for transmission, particularly in the developing world, a setting associated with a much higher mother-to-child transmission (as high as 40%) than in developed world (<2%) [42], the implementation of current feeding recommendations, even when understood, may be hampered by ignorance and/or poor implementation of the recommendations [43–45]. Available evidence indicates that mixed feeding is the cultural norm, especially in Africa. In fact, exclusive breastfeeding is rarely practiced for 6 months, and is often discontinued much sooner. At best, more than half of the infants are exclusively breastfed for 6 months in only 28 countries in the world [46]. Even under study conditions, in most African countries duration of exclusive breastfeeding ranged only between 0.4 and 4.9 months of age [47, 48]. Best prevalence estimates of exclusive breastfeeding at 6 months of HIV-infected mothers under maximal support are reported to be up to 40% [48, 47]. Prophylaxis of mother-to-child transmission by giving the mother antiretroviral medications which are proven to be efficient [49, 50] has the potential to reduce transmission through breast milk. Antiretroviral prophylaxis to the breastfed infant is under evaluation, but the long-term effects for the children are not known [51, 52].

Botswana, which has remarkable success in reducing mother-to-child transmission, has introduced replacement feeding (formula) in its preventive strategy [53]. Available evidence indicates that with adequate support, safe replacement feeding which meet the AFASS criteria can be successfully implemented in resource-limited settings [54]. Therefore, providing a formula with the highest possible safety margin during replacement feeding pro-

grams is a challenge for the industry. Already during the mid 1990s it became clear that a cow milk-based formula which was chemically acidified (NAN Pelargon®) became the preferred product in governmental and NGO-driven replacement feeding programs.

Before the introduction of modern infant formulae in the 1970s and 1980s, acidified formulae were very popular both in developing and developed countries. In countries where fermented milk products are part of the eating culture such as in Sub-Saharan Africa, acidified infant formulae are still very popular. Early clinical trials with the chemically acidified formula (pH <5) had resulted in lower gastric pH and a faster gastric transit time [55]. Randomized controlled clinical trials in Chile and France indicated lower incidence of gastrointestinal infections [56] and shorter duration of diarrhea [57]. Safety and efficacy of acidified formulae with and without the addition of the probiotic strain *Bifidobacterium lactis* have been documented [58, 59].

The acidified formula was never promoted by the company for replacement feeding programs. The widespread use and increasing demand since the mid-1990s prompted us to start a project to upgrade the formula according to the latest EU standards (e.g. low-protein whey protein formula similar to the formula described above) [4] and proof safety and efficacy in randomized clinical trials.

In the case of contamination due to poor hygienic settings, in a bottle of regular infant formula at 37°C in just 2 h the number of *Escherichia coli* germs can grow rapidly. The new acidified whey-based formula is characterized by an acidic pH value of 4.6–4.9, which ensures sufficient bacteriostatic activity of the formula without disturbing the organoleptic properties. Joosten and Lardeau [60, 61] confirmed the growth-restraining effect of the new acidified formula on pathogenic and putrefactive bacteria (fig. 2). In an in vitro study, three regular (soy-, whey-, and casein-based) and one acidified infant formula were artificially contaminated with eight different bacteria, including *Enterobacter sakazakii*, *Salmonella dysenteria*, *Salmonella typhimurium* and *E. coli* 0157:H7. The initial concentration of the bacterial strains was about 10^3 CFU/ml of reconstituted formula. Growth of the different bacteria was monitored through counting before and after 3- to 6-hour incubation at 37°C. Most bacteria were growing rapidly in all non-acidified formulae, but growth was strongly suppressed in the acidified formula (fig. 2). Safety of the low-protein whey-based acidified formula was confirmed in three randomized controlled growth studies [17, 58, 59], which included both healthy and immunocompromised infants. The infants grew according to the WHO growth charts. The addition of the probiotic strain *B. lactis* to the formula resulted in better weight gain in the immunocompromised infants. The new formula now continues to be the preferred product for replacement feeding programs.

Comparing costs between two feeding methods in any given clinical setting (including HIV) is difficult, since actual costs, treatment delivery and

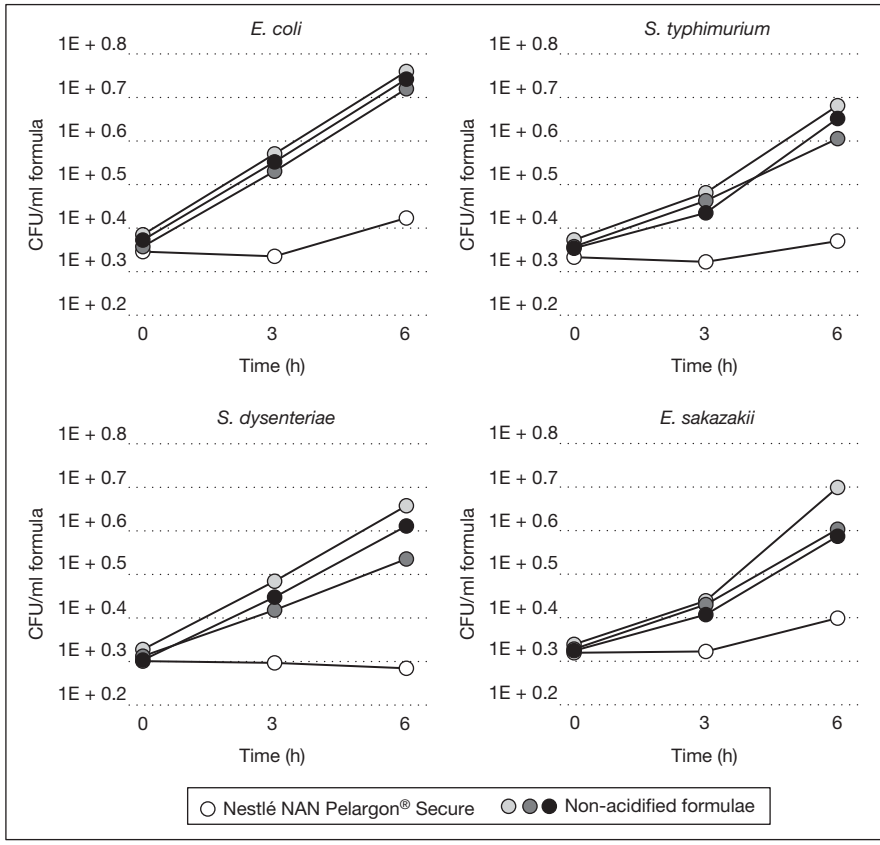

Fig. 2. Growth behavior of pathogenic micro-organisms in various commercially available infant formulae. Dehydrated infant formulae were reconstituted with demineralized water and deliberately contaminated with micro-organisms at a level of approximately 1,000 CFU/ml. Micro-organisms were counted after 3- and 6-hour incubation. Adapted from Joosten and Lardeau [61].

approaches, and other factors vary from country to country. Despite the hypothetical and real advantages of any feeding method, moral and ethical considerations mitigate against cost comparisons. Today, only a minority of eligible infants in most developing countries have access to antiretroviral medications. In order to change this, large investments are needed in infrastructure and personnel.

It is worthwhile to communicate the safety (bacteriostatic) aspects of the new acidified formula to governmental authorities and the medical community. Any other medical marketing of the formula in such sensitive environment would be inappropriate.

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Discussion

Dr. B. Koletzko: You showed us in two studies the effects of formula acidified with fermentation on reducing diarrhea. I wonder whether you can really compare the effects of fermented formula to those of formula that is chemically acidified. Thus, allow me to ask whether the three studies that you performed in collaboration with Dr. Cooper and others have shown significant effects of the chemically acidified formula on diarrhea.

Dr. Haschke: In the growth studies with Dr. Cooper, we had infants during the first 4 months. We had both biologically acidified formulas and chemically acidified formulas in the study, and there was no difference between the two types of acidification.

Dr. B. Koletzko: In growth.

Dr. Haschke: In growth but also in disease outcome, so there is no difference.

Dr. B. Koletzko: So you found an effect of chemical acidification on diarrhea, that's my question.

Dr. Haschke: The study which I showed is a study after 6 months of age when the diarrhea time is starting up, one was in Chile and one was in France.

Dr. B. Koletzko: Allow me to add a comment regarding DHA. I fully agree with you that marketing of DHA formula, and also perhaps pricing of DHA-containing formula is hardly acceptable in many instances, but I would like to challenge your conclusion that we have no evidence for any effects of DHA in term formula. I want to cite the conclusions of the European Food Safety Authority who found that there is conclusive evidence for a cause-effect relationship between DHA intake in term infants and visual function development. The EFSA also concluded that the adequate DHA intake for infants and young children is 100 mg/day. Thus, while we do have a number of open questions and the IQ effects are overemphasized and not well based, we do have evidence for benefits of a DHA supply.

Dr. Haschke: I agree with you, I was just showing the meta-analysis. After so many years of research, this is the outcome. When health claims related to DHA will be submitted to EFSA they will be turned down. You are mentioning a transient effect on visual acuity; all other effects were rejected by EFSA. The European Food Safety Agency is very critical about DHA, but I agree with you that this one claim went through.

Dr. B. Koletzko: In their document concerning the requested claim on an effect of early DHA supply on cognitive development at 3 years, the EFSA pointed out that the evidence for the 3-year end point was not sufficient, but that they find a role of DHA in brain development and cognitive development.

Dr. Haschke: For me the main thing is that EFSA has rejected the claims. If they hadn't, the companies would have been trying to go over board, also in Europe. You must consider that due to the price positioning of these formulas in Asia, only children from the upper class have access. So there is a segmentation of the population which should not be there.

Dr. Cooper: Just to comment further on our studies. In each of the studies, there was a non-acidified standard formula, and we could show no difference in terms of incidence of diarrhea or any other morbidity as was shown in some of the other studies. Although, I don't think those were starter formulas. But I think there are two points to be made. The one is the studies were not powered for that outcome, and secondly because it was under study conditions, there was very close and ongoing education of the mothers in terms of preparation of the formula, and so from our studies we could not say that that had any effect on gastrointestinal infections, but whether it would happen in the field I don't think we would know in an unmonitored environment. However, our Health Department provides free milk for babies of HIV-positive mothers who elect not to breastfeed and have chosen the acidified formula. What Dr. Haschke didn't mention was perhaps the biggest advantage of the acidified formula, and that is that it doesn't taste good, it doesn't mix well in coffee and it's more likely to end up in the baby's tummy than in the parents' tummies.

Dr. Gibson: You were talking about the balance between economic evaluation research and marketing. In the *Economist* this past week there has been a big article about Nestlé's commitment to R&D in health and wellness, trying to make it a health and wellness company. How does a company, given the marketing people are the main drivers from your perspective, take on board more research, how do you do that?

Dr. Haschke: I was part of the panel that was interviewed by *The Economist*. One of the factors we have clearly indicated is investing in research and development. Nestlé could show that during the last 10 years the effort dedicated to research for the whole company has been increased by 100%. There are certain segments of the company which are dedicated to nutrition like the Nestlé Nutrition company or the pet food company. Pet food is much more advanced in terms of health food than any other food. In the weight management for example, we have increased our research efforts by 400%. I am not giving you the absolute figures, investing in research means that

more scientific serious output can be expected. We have more resources to look at benefits which we have identified and we have more resources for long-term research. Similar approaches apply to pharma companies. We are not going in all fields of the area of nutrition. We have product segments like chocolate, but even here we look that the composition adheres to the standards. We have a clear policy in the company, and you can see that our company is in fact a producer of a lot of health products. If you look at micronutrient fortification, we are one of the biggest distributors of micronutrients. Yearly, 200 billion servings of fortified food are delivered to people, and among them there are 90 billion Maggi cubes. Maggi is a culinary product, but in many countries it's a source of iodine.

Dr. Gibson: You made a big point here that the marketers are big drivers here. Has that been taken into consideration? How is the company going to get a reward out of this?

Dr. Haschke: In the western countries you have the phenomenon of the discounters, where the food prices are low. If the consumer believes in the added value and if the food is recommended by health care professionals, this is a different story. We are heavily investing in our medical field force which is responsible worldwide for communicating medical or scientific product messages, and this is our main marketing drive in many countries. In most Asian countries you cannot go on TV and advertise.

Dr. Ganguly: I have a comment on the meta-analysis. We should view the meta-analysis results with respect to the population as there is a tendency to overestimate the results and extrapolate them to populations where the situation may be very different. For example, in India, where the majority of the population are vegetarian, there may be a role for DHA in term formulas as often the maternal diets are deficient in DHA. Studies that have been carried out in India have shown a benefit of adding fish oil to the maternal diet to decrease the incidence of low birthweight [1]. Therefore, adding DHA to term formulas in situations where maternal DHA intake is low may be justified.

Dr. Solomons: I would like to back that statement because what we have done so often is to use meta-analyses as universal truths. I always said that if you take the individual meta-analysis cases and their various positionings and overlap with zero, if they were well done they would be reproducible, that's to say doing them again in the same setting you would find the same effect, and those with other effect doing them in the same place again you would find the same effect. For me, the meta-analysis weakness is that it seeks a worldwide mean for situational truths, and the situational truths are going to be more relevant to those situations than the worldwide average mean, so that's why I applaud the kind of comment my colleague made.

Dr. Haschke: There is no gold standard. Meta-analysis is just another way to interpret studies which have a certain quality. I would like to pass this question onto either Dr. Makrides or Dr. Szajewska who have done many meta-analyses.

Dr. Szajewska: I fully agree with that, and very often the results of a meta-analysis are overinterpreted. People do not look into the details such as the population, interventions, comparisons, and outcome measures. In particular, they do not determine whether the outcome measures were similar and measured in the same way. I don't think that it's a problem with the meta-analysis. I think that very often it's an overinterpretation of the results of the meta-analysis. Some people jump to conclusions without reading the details. As you said it Dr. Haschke, it's not the gold standard; it's one way of looking at the evidence, that's it.

Dr. B. Koletzko: So, perhaps we should not draw the conclusion that a meta-analysis gives us the true answer, but a meta-analysis simply summarizes the available evidence in a systematic way.

Dr. Szajewska: A meta-analysis is not the way to make recommendations. It helps you like any systematic review in formulating recommendations, but that is not equal to making recommendations.

Dr. Solomons: The debate has to do with not seeing one's country or oneself in the meta-analysis, and yet having to confront interpretations whatever they be of the meta-analysis. Now, there are arguments for why Bangladesh or Pakistan or Nepal or India are not represented in the meta-analysis. It has to do with cost, it has to do with placements, skilled people to do them. But to see that one is excluded for whatever reason from the meta-analysis profile, not seeing oneself there, is very likely to make one wary of any influence that they would make on one's own possible policies in one's own country. That's what I think is the counter-interpretive argument of this tool.

Dr. Makrides: Just a couple of further comments to add to those made by Dr. Szajewska about meta-analyses. The conclusion of a meta-analysis is only as robust as the quality of the studies within the meta-analysis. It is important to have sensitivity analysis within meta-analyses to be able to understand the heterogeneity and the way things may be combined. For example, in meta-analyses involving LC-PUFA interventions it is legitimate to combine different sources because the biochemistry reacts in the same way, but it might not be appropriate to combine different sources of probiotics. Regarding the comment about generalizability to different population settings, that comes back to the nature of the individual studies that make up the meta-analysis. For example, the meta-analyses of LC-PUFA supplementation of infant formulas are largely extrapolable to industrialized societies, while other meta-analyses in the area of iron nutrition apply to both industrialized and semi-industrialized societies. So it is possible to tease out differential responses based on the characteristics of the population or the class of treatment through sensitivity analysis, and yes meta-analysis is a good tool to try to come as close to the truth as possible but there are issues with interpretation.

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Evaluation of Dietetic Product Innovations: The Relative Role of Preclinical and Clinical Studies

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Abstract

A variety of systems are used to establish efficacy of food ingredients. Immortal human cell lines have the advantage of rapid throughput and often have the ability to point to mechanisms of action. Transgenic and natural variants of animals (usually rats and mice) have proven to be extremely useful in elucidating effects in vivo, although extrapolation of results to humans has risks. Animal models are also useful in establishing safety and toxic levels of ingredients. Human trials have the most relevance to society. Types of evidence for efficacy rise from improved status level in subjects as a result of eating food (long-chain polyunsaturated fatty acid, levels in erythrocytes), change in surrogate markers as a result of eating food (plasma cholesterol or glutathione peroxidase activity), change in a physiological outcome (such as visual evoked potential acuity or heart rate variability) through to the highest level of evidence, a change in a clinical outcome (improved global development, reduction in infections) established in randomized controlled trials. Ultimately, there is a need for tests of pragmatic interventions that can easily be incorporated into usual dietary practices of the culture in which it is tested.

There is great potential for nutritional interventions in early life to result in improved health outcomes. This is based on the large body of evidence of both experimental and epidemiological studies showing that good nutrition during pregnancy and early life may enhance neurodevelopmental outcomes, reduce the prevalence of allergies, improve body composition and may ultimately reduce the prevalence of chronic diseases [1–3]. With such promise, the evaluation of nutritional interventions, which often take the form of specialized products or food innovations, is of paramount

importance. The scope of this paper is to review the relative role of preclinical and clinical studies in the assessment of both safety and efficacy for new food innovations.

Role of Preclinical Studies

There is a range of preclinical studies that are relevant to the assessment of food innovations, and these extend from cellular studies to studies with experimental animals. There are immortal cell lines available to screen bioactive molecules or fractions that are dietary components. Such assays can happen quickly, and it is possible to investigate or screen multiple bioactive compounds in specific cell types and gain insight into possible mechanisms of action. However, if it difficult to assess the relevance of such studies to women and children when the putative bioactive compounds are included as part of a dietary regimen. Such cellular studies provide an important first-pass evaluation to select bioactive molecules (for example, protein or lipid fractions) worthy of further investigation.

Animal models offer greater diversity and specificity of effect than is possible in cell studies, although they are more time consuming and resource intensive. Numerous models are available to assess the effects of dietary components in situations relevant to the human target group. For example, the (rat) pup-in-a-cup model aligns well with the neural and gastrointestinal maturity of a very preterm infant [4]. The intricacies and complexities of the model in many ways are not surprising as the rat pup requires some of the extra supports (thermoregulation) that would also be required in a neonatal intensive care unit. More commonly, however, animal models are based on genetic predisposition, such as Brown Norway rats, which are allergy prone, and offer a model of an allergy-sensitive human [5]. Animal models are useful in identifying target outcomes for human trials. It is possible to harvest organs, and so provide information about how nutrients or bioactive ingredients are acting. There are, however, some dangers in over-extrapolation to humans as effects in animal models are not always translated to the human situation. For example, conjugated linolenic acid has a long history of improving growth and body composition in animal studies and is widely used in the pig industry for this reason. However, human studies have not consistently demonstrated the positive effects observed in other animals [6, 7].

One of the most important roles of animal studies is safety evaluation. Safety in experimental animals is commonly assessed using a toxicological approach where the innovative ingredient is fed at concentrations well beyond what would normally be expected in typical dietary patterns. This allows the determination of tolerable safe levels and gives an indication of the safety buffer in relation to usual dietary intake.

Role of Clinical Studies

The ultimate evaluation of safety and efficacy of new food innovations is through well-designed and appropriately powered randomized controlled trials (RCTs). Such trials are complex and expensive and involve a large investment from all involved including the participants, the researchers and the industry. RCTs are therefore the final studies in the pathway to new, innovative products with proven clinical efficacy. However, before arriving at large-scale RCTs, different types of clinical studies are often undertaken to answer questions of bioavailability or tolerance in order to ensure that the product tested in the large-scale RCTs has an optimized composition and a maximum chance of resulting in the desired clinical benefit. The following section uses the addition of long-chain polyunsaturated fatty acids (LC-PUFA) to infant formula as a case study of the pathway from small, focused biochemical human studies to large-scale RCTs.

Bioavailability and Biochemical Status Studies

The earliest intervention studies to show that adding the LC-PUFA, docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3) as fish oil, to infant formula resulted in increased plasma and erythrocyte DHA and EPA concentrations were reported in the late 1980s [8]. This change in biochemical status was evidence of bioavailability, although more intricate studies of absorption [9] and dose response using different LC-PUFA sources followed [10, 11]. The value of these studies was the demonstration that the key LC-PUFA are efficiently absorbed from triglyceride and phospholipid sources even by preterm infants with an immature gastrointestinal tract [9]. In addition, the biochemical response in plasma and erythrocytes was dependent on the concentration in the diet/product, and the degree of response was equivalent between different sources [12].

Safety and Tolerance Studies

Although measures of tolerance and safety are often included in many study designs, it is also considered mandatory to conduct clinical studies with the aim of demonstrating that the new product containing the innovation is equivalent to the standard product. For studies involving infants and young children, growth is most often used as a surrogate for safety. As nutrition and growth are inextricably linked, nutritional interventions that have a negative influence on growth represent an undesirable change that in many cases is associated with negative shorter or longer term clinical outcomes. It was for this reason that significant concern was raised in the LC-PUFA field when the results of some of the earliest intervention studies involving preterm infants suggested that supplementation of infant formula with n-3 LC-PUFA was related to poorer weight and length gains compared with unsupplemented formulae [13], while conversely resulting in improved visual function [14, 15].

It was this paradox that was of concern as poor growth of premature infants is well known to be associated with poor neurodevelopmental outcomes [16], the very domains that LC-PUFA supplementation was postulated to support. Nevertheless, the published intervention trials currently available suggest little or no effect of LC-PUFA supplementation of infant formula on growth of preterm infants [17–19]. However, it should be noted that the majority of studies that have investigated the effect of LC-PUFA supplementation on infant growth were not designed as trials of equivalence, that is, clinical trials specifically designed and powered to demonstrate equivalence of growth between the supplemented and unsupplemented, control infant formula [20]. Such trials require the investigators to decide on the smallest difference that would be considered clinically significant and set the confidence interval that would include the mean of groups, treatment and control, to claim equivalence. It is therefore not uncommon for equivalence trials to require larger sample sizes than trials which are designed to test hypotheses of difference.

Studies Designed to Show Changes in Surrogate Markers or Physiological Responses

Surrogate markers or physiological responses are used as outcomes in clinical intervention trials to provide an indication of a likely effect in an associated clinical outcome. Trials with surrogate or physiological outcomes are often smaller (fewer participants) and have a faster turnaround time than trials with clinical outcomes. In the LC-PUFA field, different measures of infant visual acuity have been used as short-term assessments that may be indicative of longer term neurological maturity [21]. The visual acuity studies in the LC-PUFA field have been useful in clarifying the dose-response for preterm infants [22] and have also helped to elucidate the more subtle response of term infants [23]. However, such surrogate or intermediate outcomes are often less complex and focus on specific developmental domains and therefore do not consistently predict global neurodevelopmental outcome.

Studies Designed to Show Changes in Clinical Outcome

Although often complex, time consuming and expensive, RCTs with clinical outcomes provide the most robust and directly relevant answers regarding the efficacy (and safety) of new food or supplement innovations. It is for this reason that major RCTs are not generally undertaken without a body of congruent evidence from preclinical studies and other human biochemical or physiological studies that all point towards a safe and efficacious dietary intervention. It has been relatively uncommon for large scale RCTs to be undertaken in early life nutrition, and the cases of successful large-scale RCTs have best been achieved with a combination of government and industry funding. This underscores the large investment required. The coinvestment by government is particularly noteworthy because it highlights the acceptance that nutritional interventions during early life have the potential to change longer term outcomes that are

important to the functioning of the individual as well as to the community more generally. The most recent and relevant example from the LC-PUFA field is the DINO (DHA for the Improvement in Neurodevelopmental Outcome) trial in preterm infants born before 33 weeks' gestation [24].

The significance of the DINO trial comes from the fact that the developmental quotient of children born preterm is 11 points (95% CI: 9–13) lower than term-born controls [25]. In addition, preterm children have a higher incidence of attentional problems [26], impaired executive functioning [27], reduced memory and learning capacity [28], and visual-spatial perceptual deficits [29]. Collectively, these cognitive impairments compound so that preterm children have higher rates of learning disability, a greater need for integration assistance, and an increased likelihood of repeating a grade at school compared with their term-born counterparts [30, 31]. Therefore, any intervention with potential to enhance cognitive development for preterm children, and hence improve quality of life and decrease the burden on families and society, is considered a priority and worthy of investment.

The DINO trial included all preterm infants born less than 33 weeks' gestation regardless of whether infants were fed expressed breast milk or infant formula. DINO demonstrated that DHA given at a dose designed to approximate the in utero accumulation rate (three times the standard dietary dose) resulted in fewer preterm children with significant cognitive delay at 18 months corrected age compared with control (5.2 vs. 10.5%; $p = 0.03$), although there was no overall difference in the mean developmental quotient [24]. This was explained by two significant interactions (diet by sex and diet by birthweight strata). The effect of DHA supplementation was most pronounced in girls born <33 weeks' gestation and in infants born weighing <1,250 g [24]. Despite the complex results, the importance of the DINO trial is that of all the neonatal interventions tested in children born preterm (drugs, nutrients, environmental) only caffeine and increased dietary DHA have shown promise as strategies to improve cognitive outcomes [24, 32].

Three key lessons to come from the DINO trial that are important for other large-scale nutrition interventions are, first, the importance of having a pragmatic intervention that can be easily incorporated into usual dietary practices, second, the need for an appropriate (often large) sample size with minimal attrition to underscore the robustness of the outcomes, and finally the role of the independent scientific researcher is vital to ensure potential outcomes of true public health importance and secure the funding relationship between industry and the competitive government funding.

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Discussion

Dr. S. Koletzko: Dr. Makrides, did you find in the reviewed studies and also in your own DINO study any hints concerning other beneficial outcomes for LC-PUFA supplementation like immunological or infectious parameters, immune response to vaccination, or incidence of atopic diseases?

Dr. Makrides: We did measure many other clinical outcomes [1]. There were no differences except for chronic lung disease. Fewer babies in the high DHA group required oxygen therapy at 36 weeks postmenstrual age, and again there was an interaction. The effect was driven by the smallest babies and the boys, so neonatal clinicians that are interested in respiratory outcomes have been more focused on this result rather than the developmental results, which was the primary reason for doing the trial. We have also measured parental report of allergies through to 18 months. There were no differences in the medical diagnosis of asthma, which you would expect at such a young age, eczema, food allergy, but there was a lower prevalence of doctor diagnosis or medication for hay fever in children in the high DHA group. Allergy outcomes are part of the 7-year follow-up.

Dr. B. Koletzko: I greatly appreciated your presentation and particularly the conclusions that you have drawn. I couldn't agree more with your recommendation to do clinical trials properly with adequate power. You described very nicely the systematic review of the trials on PUFA and visual acuity. You concluded that in term infants half of the trials describe a benefit, others describe no difference. Based on this analysis, you conclude that only a trial in preterm infants is justified. I must admit I do not understand the basis for the conclusion. There are differences in results, heterogeneous studies, different interventions, different outcomes, outcome measures, so further studies may well be justified to add clarity.

Dr. Makrides: I was actually saying that when you stand back and consider all the data as a researcher you focus on the research question that is likely to have an important public health impact and be worthy of a large financial and human resource investment. For this reason, we focussed on preterm infants. Regarding term infants, I think there are different issues here. The issue of LC-PUFA and term infants implies infant formula, whereas for preterm infants we are considering both breastfed and formula-fed babies.

Dr. B. Koletzko: I would fully agree then if you reword the conclusion to say it is more likely to find something in preterms. The second question I have relates to your categorization of visual acuity measures as a surrogate marker and the DQ measure as an end point marker. I am just wondering how you define a surrogate marker and an end point marker. Is DQ really an endpoint or are not both markers of function, even though potentially of different predictive value? If we count the number of deaths or the number of patients that have a remission of leukemia then we have an endpoint. Is DQ really an endpoint?

Dr. Makrides: In the LC-PUFA field, visual function has been used largely as a surrogate or physiological outcome rather than a clinical outcome. For example, VEP is largely a physiological measure. It is possible to be blind and still have a very normal VEP response. The LC-PUFA studies using VEP as an outcome were designed to exclude children with visual abnormalities so that the VEP response could be used as a marker of the maturity of the visual pathway and what that might tell us about neural maturation because it's easy to measure during early life. The issue of DQ is a more complex one. When children are less than 2 years of age, tests like the Bayley Scales give a good indication of global developmental delay indicated by whether children are falling 1 or 2 standard deviations below the mean. For more subtle, clinically relevant changes, testing at older ages is needed. The clinical relevance of VEP function is debatable as we do not know of robust or consistent associations between VEP acuity and later outcome. This is why I said that DQ was more clinically relevant than VEP acuity.

Dr. B. Koletzko: Well that's debatable. If you would take the same effect size, for example your intervention changes visual acuity by 3 standard deviations, I would predict that has effects on the perception of the environment and learning. But let me move to my last and third question with respect to the really outstanding DINO trial that you have performed. You said the follow-up, which is admirable, will tell us whether there are important effects, in other words you regard effects only as important if they persist until 7 years of age. As a pediatrician I find that a rather unfair assessment. For example, would you consider iron supply in infancy as irrelevant if it improves iron status in early childhood but not permanently into school age and later? Or if you take Anneli's example, do you consider it irrelevant to diagnose celiac disease at 1 year rather than 3 years, which will reduce suffering of the child during 2 years, but it's a transient effect and probably will not change outcomes in adulthood. So why is an effect irrelevant if it is transient?

Dr. Makrides: With regard to the DINO trial, the 7-year follow-up will actually give us the conclusive outcome data in terms of impact into adulthood because what we can measure at 7 is much more likely to be predictive of adult IQ than what we can measure at 18 months. I am not denigrating the 18 months data, I think it's incredibly important, but the 7-year outcome data will be more robust in terms of understanding the full public health impact.

Dr. Solomons: It's a comment directly related to the last example. I want to point out that Dr. B. Koletzko probably is unaware of the studies by Betsy Lozof published in *Pediatrics* which show the transient situation. Anemia in infancy related to iron deficiency has a permanent long-term effect on cognition. They have studied the children until their adolescence, so transiency of the syndrome has nothing to do with long-term outcome of a dependent functional outcome, and I think you should apologize to everyone for forgetting that you knew that.

Dr. Greer: I was just going to comment on the visual acuity versus the IQ. Personally, I would be much more in favor of using the IQ as a primary outcome. If you look at what I consider the best studies in visual acuity with infants randomized to LC-PUFAs or control, the difference between groups amounts to one line on the standard Snelling eye chart. Does it really make a difference if your visual acuity is 20-20 rather than 20-15? It is a quantitative assessment, but still it's not really as important as an IQ difference.

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Regulatory Environment and Claims – Limits and Opportunities

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Abstract

During the past decade, the use of claims became more and more important in many countries in relation to the increased awareness of consumer about the link between foods and health, offering to industry a valuable opportunity to differentiate and valorize their products and to promote innovation. However, more and more stringent regulations are developed, all based on the general principles adopted by the Codex Alimentarius Commission. In addition to the different regulatory processes and administrative requirements according to the country, the high level (and cost) of scientific substantiation of claims, the constraints introduced by nutrient profiles and the poor knowledge of the impact on consumer depending on the cultural contexts may limit these opportunities or, at least complicate their use. All these issues are briefly analyzed, highlighting some striking convergences and differences between countries.

Since more than a decade, there has been a sharp increase in the use of nutrition and health claims not only on the food labels, but also in industry communication and advertising. At a worldwide level, food products claiming a nutrition or health effect represented one third of the new food products put on the market in the mid-1990s, and currently could represent about three quarters. In most of the countries, the progression rate is larger for this food segment than for traditional foods: as an example, in Japan, which was a pioneering country in this field, the authorizations for FOSHU products grow linearly from some units in the mid-1990s to around 100 per year in 2006 [1], and the annual value of this market has increased from around one billion USD in 1997 to more than 5 billions in 2005 [2].

The reasons for such an increase are certainly diverse and probably rely on the convergent, though diverse, interests of the four major stakeholders: consumers, industry, researchers and public health authorities:

- Consumers are more and more aware of the links between nutrition and health. Though skeptical, they are influenced by claims in their food purchases [3].
- For industry, especially in Europe, after the food crises occurring in the last decade of the 20th century, it was also an opportunity to claim that food does not constitute only a risk. In addition, using nutrition and health claims constitutes an opportunity for product differentiation and valorization in a mature and saturated food market, and to promote innovation, allowing in many cases an increase in profit margins.
- For researchers, unraveling the health effects of food and nutrients was always the final challenge; since public funding is limited or decreasing in many countries, funding by industry for research supporting claim substantiation became a growing alternative source of financial support. This cooperation between industry and academic research is encouraged by public authorities in many parts of the world.
- For public health managers, it could represent a tool for decreasing the growing health costs. In some countries, medical societies also support some products or claim types.

The major issues limiting such an attractive opportunity relate to the regulatory environment for the different types of claims, the scientific substantiation of claims, the conditions of use for claims (especially the nutrient profile issue), and finally the consumer perception of claims on which depends their economic and health impact.

Regulatory Environment

Many countries regulate claims, with more or less specific regulations. However, they are all based on the initial principles agreed upon at the international level by the Codex Alimentarius Commission as early as 1979 [4]. Claims are defined as 'any representation which states, suggests or implies that a food has particular characteristics'. The general principle was to not mislead the consumer, completed by specific mentions: prohibiting claims stating that a food can provide all essential nutrients, claims stating that a balanced diet cannot supply adequate amounts of nutrients, claims that cannot be substantiated or could raise doubt about the safety of similar food products. These characteristics were detailed in a following Codex guidelines adopted in 1997 [5] which may relate to nutrient content (nutrient content claims and nutrient comparative claims) or to a health relationship, comprising nutrient function claims, other function claims and reduction of disease risk claims. In addition to the claim, additional information is required: nutritional labeling, the target group, warnings and/or maximum safe intakes, and a general statement on the importance of maintaining a healthy diet. These texts should be read also in the context of the general

standards for the labeling of prepackaged foods [6] or foods for specific medical purposes [7].

Due to the long time needed for the adoption of Codex standards, many national authorities have developed their own regulations [review in 8]. No systematic comparisons of the different systems have been published, with the exception of the comparison between China and Japan [9] for the whole process, and a comparison of USA, Canada and Europe for the scientific substantiation [10, 11]. A systematic review is outside the scope of this paper, but some striking differences are highlighted in the following sections.

Different Types of Claims

In Japan [1, 2], a specific category was created in 1991 for regulating claims, the FOSHU (Food for Specified Health Use); the regulation evolved in 2001 and 2005, to consist now in several categories of FHC (foods with health claims), including FNFC (food with nutrient function claims), ordinary FOSHU and new type FOSHU (standardized, qualified and disease risk reduction). In Europe [12], there is a very general regulation (regulation 1924/2006/CE), covering all the products falling into the field of food law, including dietetic products and dietary supplements, but distinguished different procedures for generic claims (Article 13.1 claims), newly emerging or proprietary claims (Article 13.5 claims), and claims on children growth and development and disease risk reduction (Article 14 claims). In the USA [13], the Nutrition labeling and education Act (NLEA), implemented in 1994, regulates health claims made on foods; in parallel, the Dietary Supplement and Health Education Act (DSHEA, adopted in 1994) regulates claims on nutrient functions. Additional information on the regulatory environment can be found elsewhere for Australia New Zealand [14], China [15], and Korea [16].

In line with these differences in the regulatory status, there are also differences in the requirements for different types of claims. In the USA under the DSHEA regulation [13], nutrient function claims do not require preapproval by the FDA before being used on labels, but must be accompanied by a disclaimer. In Europe, such claims will be used only after scientific evaluation by the European Food safety Authority (EFSA), authorization by the Standing Committee of the Food Chain and Animal Health (SCFCAH), and inscription in the European register of claims. More than 44,000 claims have been collected at the European level, which, after elimination of redundancies, of claims not conform to the legislation, such as medicinal claims, led to a consolidated list of 4,185 entries corresponding to around 10,000 claims for around a thousand of substances. A first series of opinions on these generic nutrient function claims has been released in October 2009.

Since a food which would prevent, treat or cure a disease would be classified as a drug everywhere, the concept of ‘disease risk reduction claim’ has

been developed and agreed upon at the international level in the Codex guidelines [5]. These claims are always considered as high-level claims and require preapproval before use. The extent to which such claims are approved or used largely varies between countries. Today, there are fifteen claims authorized in USA [13], five proposed in Australia-New Zealand [14], four in China [15] and only two in Japan [1]; two disease risk reduction claims have been approved in Europe, but more applications are still currently under scrutiny. The regulation in Europe (and China) focuses not on disease risk reduction per se, but on the reduction of a disease risk factor, although what is a risk factor is not clearly defined in the European regulation. This has led to an apparently paradoxical situation, where claims on phytosterols were accepted despite the fact that there is no actual demonstration of the efficacy in decreasing the risk of cardiovascular disease but only serum LDL cholesterol, whereas claims on xylitol, for which EFSA recognized the efficacy in decreasing the risk of dental caries, could not be legally accepted, since no clear risk factor was identified.

Scientific Substantiation of Claims

If there is a general agreement on the need for scientific substantiation, the exact interpretation on what constitutes substantiation has given rise to many debates, and different wordings, reflecting different approaches, are included in regulations. The Codex recommendations for the substantiation of health claims have been adopted only in 2009 [17]. Originally, in the USA, there was a request for a 'significant scientific agreement', some experts choosing the word 'consensus'. Since this was contested in justice courts, as opposed to the First Amendment of the US Constitution [8], the concept of 'qualified claims' has now been adopted in this country: the wordings of claims should reflect the scientific evidence, from level A claims (the strongest) to level D ('there is little scientific evidence supporting this claim'). This approach has partly been adopted by Japan, with the category of 'qualified FOSHU', but not in Europe. However, all the regulations require the strongest scientific evidence to support disease risk reduction claims. All the regulations, including Codex guidelines, favor well-designed human intervention studies, but may accept less stringent study types on a case-by-case basis, the assessment being based on the consideration and weighing of the totality of the available evidence. China and Japan request that some of the submitted studies are performed on Chinese or Japanese populations [1, 15]. Like in Europe, 'generally accepted scientific evidence' can be used. In some countries, and especially in the USA, authoritative statements from public scientific authorities can be used; by contrast, in Europe and other countries, specific assessment made by the competent authority is required. Guidelines for the preparation and submission of the dossiers are available on the websites of these authorities.

The European regulation has introduced the concept of proprietary data, covering the studies funded by the applicant. If the EFSA positive opinion could not have been reached without the use of such proprietary data, then these data cannot be used by another applicant (unless the first one agrees with this use). This form of protection of claims was laid down in the regulation 'in order to stimulate research and development within the agri-food industry'; this protection is limited in time (5 years from the official approval) 'in order to avoid the unnecessary repetition of studies and trials, and to facilitate access to claims by small and medium-sized enterprises'. Today, only one dossier received a favorable opinion from EFSA.

Nutrient Profiles

The Codex guidelines of 1997 [5] require that claims 'should have a clear regulatory framework for qualifying and/or disqualifying conditions for eligibility to use the specific claim, including the ability of competent national authorities to prohibit claims made for foods that contain nutrients or constituents in amounts that increase the risk of disease or an adverse health-related condition'. This possibility has been implemented in the USA in 2002: it is a threshold scheme with an 'across the board' approach. FDA takes into account ten nutrients, four considered as 'disqualifying' (total fat, saturated fatty acids, cholesterol and sodium: no more than 20% of the daily value per serving) and one out of six as 'qualifying' (vitamin A, vitamin C, iron, calcium, protein, or fiber prior to any fortification: at least 10% of the daily value per serving). The introduction of such nutrient profiles in the European regulation is also in line with the Codex recommendation and led to many research works and debates at the European level [18, 19] in order to answer the questions laid down in the regulation: system 'across the board' or by food category, choice of nutrients, reference basis, calculation (threshold or score) and validity testing. In European Member States, the first system was proposed and implemented in the UK [20] and is known as the 'traffic light' scheme; this system has been slightly modified for use in Australia-New Zealand. Comparative testing has been published [21, 22]. Though the different systems reach agreement for 'extreme' foods' (such as fruits and vegetables or 'junk foods' at the two ends of the continuum), very large differences in results are obvious for 'intermediate' foods, with important practical consequences for industry. Therefore, the validity of the results of a system should be assessed by more objective techniques than the comparison with expert consensus, the only method used so far [23]: comparison with dietary surveys [21], with the Healthy Eating Index or food-based dietary guidelines [24]; more recently, we proposed to use linear programming to verify whether a balanced diet can be built by using only foods eligible to bear claims [25]. In Europe, the issue is complicated by the fact that the regulation requires that

the various dietary habits across Europe should be taken into account. The initial proposal of the European Commission was a mixed system (across the board, with a few number of specific categories), consisting in thresholds for three nutrients (sodium, fat, sugars). Today, what should have been a technical issue, managed by the traditional European Comitology procedure at the level of the SCFCAH, has become a very sensitive political issue, having led to debates in some national Parliaments and to a direct management by the President of the European Commission, and for which the final result cannot be predicted.

Conclusion

Though science is universal, claim perception, acceptance and impact on individual and public health vary considerably according to the cultural context of the country where a food is sold, constituting an important limit to the success of a claim [26]. Much less research works have been devoted to these issues [27]. Claims do not stand alone, but are inserted into a complex network of information, linking in the consumer's mind, according to the prominent model used by social scientists, values (for health), attitudes (toward functional foods, including hedonic expectations and perception of the food healthiness) and behavior (intention to purchase). Some (still rare) works suggest that there could be a negative impact of health claims on consumers [13] and especially children [28, 29] for whom health and pleasure could be mutually exclusive. Some experimental research with actual foods also shows the relatively low acceptance of disease risk reduction claims for foods as compared to other claim types, which questions the industry interest to fund high-cost research necessary to substantiate this type of claims in the context of more and more stringent regulations [28].

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Discussion

Dr. Spieldenner: If industry has to prove that a product acts on a risk factor and contributes to disease reduction, how can an animal model be sufficient to prove this?

Dr. Martin: Clearly in China, as you know, it's an issue of risk factor, but in my opinion it's not mandatory that the risk factor should be clearly identified and demonstrated in human. In human, you can demonstrate, for example, that Xylitol reduces

the disease (caries) itself and you can provide supportive animal studies demonstrating what the risk factor could be. So it's the totality of the evidence which is taken into account and not only one type of study; thus, if you cannot demonstrate what could be the risk factor in human and you have only supportive studies in animal, it can be accepted.

Dr. Greer: You had a number of slides about the US where the situation I would describe it is schizophrenic, and I don't think a lot of people in the audience appreciate that. We have two sets of regulations, one is for qualified health care claims on food and the other is for dietary supplements. Essentially, the one for dietary supplements is uncontrolled. Take something like DHA; if you want to market DHA for pregnant women and put it into food marketed to pregnant women or even encourage pregnant women to eat more fish with DHA in it you have a problem with the FDA. However, if you put it into a pill and market it as a dietary supplement with no control of how much is in there and no control of how you are supposed to take it, that's not a problem. I assume you don't have the situation in Europe, is that correct?

Dr. Martin: We don't, since the regulation is the same for staple food and dietary supplements.

Dr. Greer: The other interesting thing is nutrient profiling, just to take a nutrient like calcium. It is possible to add calcium to foods in the US and claim that it builds stronger bones. You can add it to cookies for children, you can add it to sugar-coated breakfast cereals for children, and even add it to sweetened fruit drinks for children and claim that it builds stronger bones. This is how schizophrenic the system is as none of these products is in the best interest of children. More recently, the dairy industry in the US tried to get a qualified health-care claim for milk (a good source of calcium and vitamin D in the US), that it prevents osteoporosis and builds stronger bones. It took them almost 3 years to get the FDA to approve the qualified health care claim for a whole food like milk. You mentioned that the US has nutrient profiling. This is a schizophrenic process as well as we have at least four different systems. The systems are not government regulated. You can take an unhealthy food product like sugar-coated cereals. Add multiple vitamins and minerals to it and raise its nutrient profile score to the 'smart choice' product. So it's really driven by the marketing process and is not in the best interest of children.

Dr. Martin: Of course, it was not my intention to give a very exhaustive picture: there are public regulations but there are also private logos which complexify this issue too, but as far as I understood, here we were concerned with public regulation of the access to the authorization of claims linked to an innovation. Of course, I am aware of the problem with dietary supplements. In one of my papers 10 years ago, we were asked for 1,000 reprints by a small enterprise in the US which sold the type of sugars we were studying in humans, and clearly it was used to support the claims for dietary supplement in which these sugars were introduced, so it's clear. But the only point I wanted to emphasize for you is the fact that depending on the market you target you have to take all these issues into account. For big companies like Nestlé who work all around the world, of course it's additional work for each region of the world.

Dr. B. Koletzko: I am rather puzzled by the list of Article 14 health claims that the EU has published in October and I wonder whether you could enlighten us on the underlying wisdom. The Commission has decided to approve claims that linoleic, α-linolenic acid, calcium, vitamin D and protein are needed for a normal growth and development of children. Clearly that is scientifically correct. However, if you consider the practical implications, it may be beneficial to enhance the average intake of calcium and vitamin D if a large part of the European population has a low intake of these nutrients. With regard to protein, I cannot image any benefit of a health claim on protein-rich foods in the European population which already has a protein intake clearly far above

the requirements. Thus, consumers will be misled into thinking that increasing protein intake even further would benefit bone health, for which we have no evidence whatsoever. If the Commission has accepted these claims, one would logically expect that they should accept claims for any single essential nutrient. There is scientific evidence that, like protein, also salt is essential for growth and development of children, and energy, which can be provided by sugar and fat, is essential for growth and development of children. Do we really want a health claim that indicates salt is needed for the growth and development of children, and hence encourage people to buy more salty foods?

Dr. Martin: I fully agree. We have discussed that endlessly, but it's a policy decision and not a scientific decision. In terms of reference we received from the commission, it was clearly indicated that the fact that there is no public health concern about a nutrient should not be taken into account and cannot be an argument to reject a claim. Of course, for protein we cannot not say anything else, but claims are useful for commercial reasons; it's not a nutritional health policy. So, for me, claims could be very dangerous if there is no national or European nutrition policy in order to give clear references to consumers. If a consumer is hesitant about claims that are true but useless, he should consider also this public, official information into account when he analyzes that claim to decide if he purchases a product or not.

Dr. Ferruzzi: I want to follow up on Dr. Greer's comment because what I think is also interesting is that the multiple 'claims' systems that are in place in the US are in some ways providing a disincentive to true innovation. On one hand you see 'calcium builds strong bones'. This is not a health claim, these are in fact structure/function claims, and it's clearly important to differentiate those tools from the standpoint of innovation. However the consumer does not differentiate those tools. In fact, structure/function claims for the most part require no pre-market approval from the FDA and all you have to do is have your studies in a dossier put together in a case, so when you see a barrier to entry to this health market as a company you are more likely to take the structural function side because you can communicate on it in a way that the consumer understands. The shorter simpler message is preferred by marketing. What has that done to the state of innovative science? It's an interesting debate.

Dr. Martin: If you say calcium is needed for bone it's a nutrient function claim which requires no approval in the US, but which requires approval in Europe; it's on a list of claims on which we are working now. If you say calcium strengthens your bones, it's quite different, it's a health claim which requires a specific dossier.

Dr. Ferruzzi: Not in the US. In the US, a health claim relates to a disease state, but 'strong bones' is not; it has to say osteoporosis.

Dr. Martin: Strengthened bones is a health benefit.

Dr. Ferruzzi: In the US, it's a structure/function claim. You are right, it's a benefit, but not in the US legally.

Dr. Martin: The last point, I saw this paper which was published some time ago that indicates that claim perception clearly is culturally related and depends on the country in which you perform the study [1].

Dr. Haschke: My question is related to intellectual property, which is normally regulated by patents. In Europe, as you have mentioned, there's a 5-year protection of so-called proprietary data. This has caused fundamental confusion in the associations and companies because let's say you have a patent protection and 12 years later you publish a clinical study with some data which can result in a claim, you have an extension of the patent which is not justified. This probably has to go to court and has to be clarified. The European Commission is not so clear on whether this 5-year protection proposal is illegal or not. Could you comment on this?

Dr. Martin: It's clearly an innovation in the regulation, and I remember I gave a talk at the European Commission with the Head of the Units in 2001, and I talked about

the possibility to have some form of protection of claims. At that time, the answer was: no, it's not possible, it would create a distinction and inequalities in the food sectors, but some years later they have accepted the issue. For the moment, only one claim has been accepted in this condition, so we'll have to wait and see what the actual interpretation and management of this issue could be. For us, the only thing we have to do as scientists is to say if without the studies which are identified by the applicant as proprietary, the claim could have been justified. I am very much in favor of that, even if there are some difficulties in implementation and interpretation, because as scientists we can expect that this type of protection could lead to more investment in higher quality studies. But I agree, at the moment it's just a beginning of a new process, of an innovative regulatory issue and, we have to wait for clearer indications because we don't know exactly if a published study can be considered as proprietary. For some people, the best result of this regulation will be to give a huge amount of work to lawyers.

Dr. Solomons: I just want to get back to what Dr. Greer discussed earlier as smart choices. In Europe, we have the Choices International Foundation. This is a new concept that I think many people here in the room are just getting their heads round of front labeling as opposed to back labeling, and the back label is mostly about the adequacy of nutrients in a serving. Front labeling, which Dr. Greer partially characterized, is a formula for the lack of damage or overconsumption of risky elements from a serving of a food, that's what it's about. In your data about how consumers feel, I think there is a very interesting thing we need to begin to look at which is: they seem to be skeptical. They first want pleasure, second they don't want to be harmed, and third they want that a product is healthy or nutritious. If the consumer is skeptical about it because it might cause harm, it puts in a way a priority for the front label over the back label. I think we need to understand what front labeling is about because in terms of driving innovation as soon as front labeling is understood it can be optimally exploited in issues relevant to product, production, marketing and so forth.

Dr. Martin: I agree with that, there is little consumer research studies on these types, and unfortunately they are generally published in journals which are not read by nutritionists, i.e. *Journal of Consumer Research* or *Journal of Marketing Research*. As an example, there has been some indication in consumer studies [2] that the existence of a claim on the front label can divert the consumer to read the true information on the back, the nutrition information; so, it's necessary to regulate the correspondence between front labeling and back information.

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The Role of Consumers

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Abstract

It is particularly important that in areas of strategic public health significance, e.g. infant feeding, the processes used to extract robust scientific findings are timely, rigorous and transparent. Low rates of breastfeeding, poor weaning practices and variability within and between countries have been reported by many authors and resulted in a call for more consistency of recommendations across regions. The adoption of consumer behaviors in line with recommendations is of course not guaranteed. The consumers in this instance are both the infant and their mother or other carers. As infants completely depend on their carers to make food choices for them, it is important that they understand nutrition, and the importance of food choices for health of the baby and in future life. Parents obtain information from a variety of sources, the quality of which may vary, and is not necessarily evidence-based. Although carers decide what is offered or withheld, the infant may contribute to this decision by expressing dissatisfaction or refusing food. At the heart of all feeding choices lies this interplay between carer and child, influenced by the environment at household, community and societal level.

Scientific expertise underpins policy making to ensure that the decisions reached are reasonable, justifiable and effective, and to provide accountability and value for money, possibly also facilitating greater public acceptance, and thus a valuable tool in policy makers' efforts to manage accountability and justify value-based decisions [e.g. 1–2]. As a result of extensive research, there is widespread endorsement of breastfeeding as the gold standard [3]. However, recent unpublished data comparing infant feeding policies for breastfeeding in five European countries (England, Germany, Finland, Hungary and Spain) have highlighted the varied nature of such documents possibly reflecting variations in the structure of health services, resources, history and culture. Interestingly, these results were to some extent mirrored in the food-related content of the most popular parenting magazines and infant feeding leaflets

available in the same five countries. It has been recognized that the wide diversity in the progress towards a coherent public health nutrition policy across Europe is due to diverse public health nutrition policy traditions as well as the diverse scientific bases used to inform policy [4].

Health care professionals provide advice and information to consumers, and promote health-enhancing behaviors within a framework provided by policy documents and guidelines. Although policy documents are of course not the only influences on practice, their contents is likely to be related to how health professionals transmit recommendations. Lack of consistency between documents and countries in the representation of the health benefits of breastfeeding should be a cause for concern for policy makers [5] but could be explained by lack of agreement amongst experts [3, 6], with some arguing that there is no evidence that introducing complementary feeding before 6 months is harmful [7]. It is thus not surprising that policy makers might be cautious in adopting certain evidence. The evidence base on the link between infant nutrition and lifelong health is incomplete and sometimes inconsistent.

The way in which in scientific research finds its way into policy documents to provide recommendations for professionals and guidance for practice is important, but often opaque. The preferred approach to producing guidelines is through consensus amongst stakeholders, including practitioners, commissioners, and service user representatives around the available evidence [8], with the final decisions about the health effects of breastfeeding that are included depending on the influence of a variety of contextual factors such as the local interest groups and the balance of committee membership. It is, however, particularly important that in areas of strategic public health significance, e.g. infant feeding, the processes used to extract robust scientific findings are timely, rigorous and transparent.

Low rates of breastfeeding, poor weaning practices and variability within and between countries have been reported by many authors and resulted in a call for more consistency across regions such as Europe [e.g. 9]. The Social Ecological Framework [e.g. 10, 11] (see also fig. 1) offers a means for understanding the levels through which people's behavior can be influenced and the following levels can be distinguished:

- intrapersonal (e.g. an individual's knowledge, skills, attitudes, values, preferences, emotions, values, behavior),
- interpersonal (e.g. an individual's social networks, social supports, families, peers, and neighbors)
- community (e.g. community resources, neighborhood organizations, social and health services),
- organizational (e.g. businesses, public agencies, churches, service organizations), and
- public policy levels (e.g. legislation, policies, taxes, and regulatory agencies, health system, social care system, political/geographic environment).

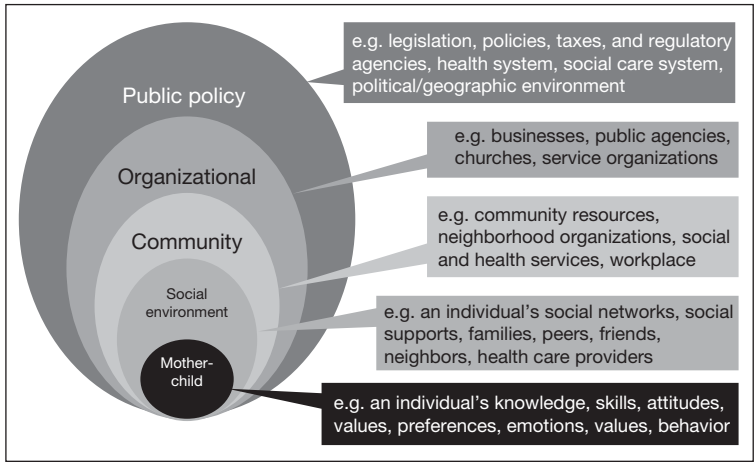

Fig. 1. Influences on infant feeding. Adapted from McLeroy et al. [10], and Bentley et al. [11].

The adoption of consumer behaviors in line with recommendations is of course not guaranteed. Consumers in this instance are both the infant and their mother or other carers. Infants are born with a set of behavioral predispositions that allow them to learn to accept the foods made available to them, which in turn is modulated by the sociocultural environment that they are born into [12]. As infants completely depend on their carers to make food choices for them, it is important that they understand nutrition, and the importance of food choices for health of the baby and in future life. Parents obtain information from a variety of sources, the quality of which may vary, and is not necessarily evidence based. Health care professionals may have gaps in their knowledge [e.g. 13]. Even knowledge may not be sufficient, however, and pragmatic factors such as convenience and cost may override health considerations [14].

When critically reflecting on the evidence base collated in a recent systematic review [15] of intervention studies that promote and support the duration of breastfeeding, the authors [16] found it to be very limited due methodologically weak studies, small sample sizes, inconsistent definitions of breastfeeding, lack of appropriate outcomes, and little use of appropriate theory. The authors highlighted the following areas as being in need of further research: the impacts of health and welfare policies, mass media promotion and social marketing, interventions targeting subgroups of disadvantaged women, 'insufficient milk' syndrome, painful feeding, specific baby and maternal problems, the education and training of health professionals, and ways of changing practice. The authors [16] noted the lack of focus on the psychosociobiological

nature of breastfeeding in the studies reviewed. The effects of women's views and feelings, and the social and cultural context of breastfeeding were not considered in most studies.

MacInnes and Chambers' [17] synthesis of qualitative research on mothers' and healthcare professionals' (mainly midwives, nurses, health visitors/community child health nurses and lactation consultants) experiences and perceptions of breastfeeding support in westernized countries published between 1990 and 2007 helps to fill the above-mentioned gap. With regard to health service support of breastfeeding, six themes were identified: the mother-health professional relationship, skilled help, pressures of time, medicalization of breastfeeding, the ward as a public place and health professional relationships. Overall findings included that mothers were not receiving the desired support from health professionals. There were two themes with regard to social support, compatible and incompatible. The former was either practical (e.g. help with housework or older children, or problem-solving), informational (e.g. from someone with knowledge of breastfeeding) or emotional (e.g. empathy, approval, praise, feeling nurtured or cared for or being replenished for 'giving out'). When coming from someone with personal experience, the source of support was potentially considered to be as important as the actual support received. Where mothers did not have a supportive network, pressure to change, confusion and self-doubt were experienced. Social support was particularly important where health professional support was lacking. The authors [17] stressed the importance of including mothers in the development and delivery of optimal services.

Women usually already receive information about infant feeding during pregnancy from different sources, including formal sources such as health care providers and prenatal health education classes, and informally from family and friends, as well as audiovisual and reading materials [18]. A recent systematic review of decision support needs of parents making child health decisions [19] suggests a parental need: (a) for timely, consistent, up-to-date, evidence-based information tailored to the individual, delivered in a variety of formats from trustworthy sources; (b) to talk with others in the same situation to share information, experiences and ideas, and (c) to be in control of one's level of preferred involvement in the decision-making process (see also fig. 2). These themes highlight the complexity of the health decision-making process and are consistent with previous research across a range of health decisions including those made on behalf of a child. Health professionals often do not address these themes very well, a finding in even the most recent papers reviewed [19]. This is consistent with a recent systematic review, of information in decision aids, across a variety of health decisions including those made on behalf of a child [20]. The increasing policy emphasis on patient-centered care [e.g. 21] and developments in shared and informed decision-making theories [e.g. 22] seem rarely to have been translated into practice, or at least, are not reflected in research on decision support needs conducted with parents.

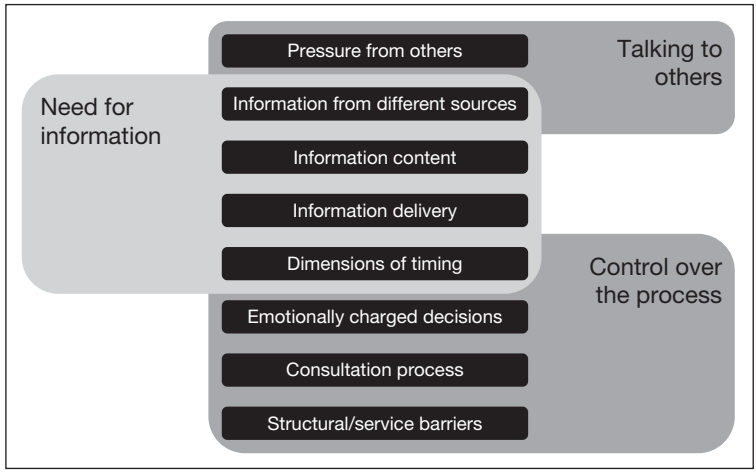

Fig. 2. Child health decisions: parents' decision support needs. Based on Jackson et al. [19].

An area of infant feeding that has received less attention is that of bottle-feeding. A recent review [23] identified evidence relating to five main themes: experiences of bottle-feeding, sources of information and support, feed preparation, quantity of feeds and formula milk changes. The qualitative studies for the most part explored experiences of bottle-feeding found that mothers who bottle-fed experienced a range of negative emotions including guilt, anger, uncertainty and a sense of failure. Whilst mothers were found to be relatively well informed as to the benefits of breastfeeding, they often felt the pressure to breastfeed unreasonable. Another important finding of the review [23] was mothers reporting not receiving sufficient information about bottle-feeding. It should be noted that this review [23], striving for consistency of context, excluded studies carried out in developing countries; the findings may thus not apply to such settings. The authors [23] concluded that as the vast majority of babies receive at least some formula milk during the 1st year of life, it is important that this is prepared and administered safely and correctly. They stressed that whilst increasing the levels of initiation and duration of breastfeeding is important, minimizing the risks associated with bottle-feeding through providing adequate information and support sensitively and non-judgmentally to parents who choose to bottle-feed their infants is also necessary.

The shift from milk feeding to the introduction of solid foods is of course complex and also influenced by a wide range of social and psychological factors, particularly for a mother providing solid food to an infant for the first time [24]. The evidence base with regard to complementary (weaning)

feeding practices is very limited [25, 26]. As with all aspects of infant feeding, decisions around weaning are made after taking a number of factors into account, and future health outcomes are by no means the sole driver of this decision [e.g. 27]. Murphy et al. [28, 29] have shown how mothers balance their babies' needs against their other obligations and own personal needs and priorities, with hunger-related behavioral changes being the main rationale for commencing weaning, including behaviors such as the infant needing more frequent feeds, crying after a feed, and changes in sleeping patterns. In some instances, particularly in public settings, food is used to control or distract babies [28, 29]. The types of foods and way in which food is consumed (e.g. self-feeding, use of a spoon) are in some cases regarded as measures of a child's progress and/or intelligence, and mothers are thus often eager to encourage their babies to move on to 'the next stage' of feeding [28, 29].

Although carers decide what is offered or withheld, the infant may contribute to this decision by expressing dissatisfaction or refusing food. At the heart of all feeding choices lies this interplay between carer and child, influenced by the decisions and practices at the household, community and societal level. In making infant feeding decisions, carers are likely to benefit from:

- having access to timely, consistent, up-to-date, evidence-based information tailored to the individual, delivered in a variety of formats from trustworthy sources,
- being able to talk with others in the same situation to share information, experiences and ideas, and
- being in control of one's level of preferred involvement in the decision-making process (i.e. the extent to which one wants to take on board advice from health professionals, family friends, etc.).

Infant feeding decisions are shaped and constrained by the existing social and cultural norms (e.g. regarding breastfeeding in public, expectations of 'motherhood', culinary traditions), and there are policies (e.g. legislation governing maternity leave, parental support initiatives) in place that support healthy infant feeding practices and influence the extent to which healthy choices are easily and readily made.

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Discussion

Dr. Cooper: On the one slide you had about who would influence the most, there seemed to be a follow-up at 8 months. Is that correct?

Dr. Raats: Yes.

Dr. Cooper: You had a slide about intentions to breastfeed for how long, but do you have any idea from that follow-up as to what they actually did?

Dr. Raats: Yes we do, but I haven't brought a slide along with that. We do see some changes, and we are looking at the data to try to determine what some of the influences might be.

Dr. S. Koletzko: I have two questions. Is there a difference in the perception of the mother whether the information leaflets were provided by health care professionals or the government or from industry? Did you look at this?

Dr. Raats: We didn't look at that in this study because it was on a very general level comparing different sources of information. But I know that that is something that is looked at in some other studies where people do have different views in a lot of areas, work around the areas of food, that there are certain sources that are trusted. But again, this is different in different countries depending on the information system that is in place. If you look at a lot of materials, it's not always clear what the sources of information are, that's again something I haven't presented. When you analyze materials, they are very variable in how explicit they are, with regard to their source, and people have views on what they might regard as better or less good information.

Dr. S. Koletzko: My second point is related to mixed feeding; I completely agree with you, this is not clearly communicated both to health professionals and to the consumers. Even the top scientific studies often do not differentiate whether the absence of breastfeeding is harmful or the presence of formula feeding. If this has been analyzed it was mostly the absence of breastfeeding which was associated with a negative outcome and not the presence of formula feeding. This indicates that as long as the mother continues to breastfeed – even not exclusively – there may be benefits. This is not communicated especially in countries where mothers have to go back to work after 3 months and can not exclusively breastfeed. This may result in a terrible conflict for these mothers.

Dr. Raats: Yes, and I think that's where you get a non-alignment of policies thus giving people a very conflicted environment within which to operate, and that I think leads to the stress that many people are experiencing. There is data from many countries that shows that, and it's also recognizing that the decisions aren't just being made on the behalf of the child. You also need to consider the mother's interest in that, and not recognizing those making the policies can lead to a lot of problems. There is a very interesting qualitative paper done in China which reflects on mothers decisions, and again it has very much to do with when does one go back to work, the relationship with the husband. There are many pressures which stop people doing what they might think is the right thing to do in terms of being a good mother, but it's in conflict with what's the right thing to do with making the other decisions and meeting the other obligations in their lives.

Dr. Akbar: In your presentation, you found that the reading materials, leaflets or magazines, are the most important instrument that the mothers use. But where the literacy rate is not high, how do you think the messages could be propagated to the mothers? And also don't you think that the contribution of professionals is underestimated because medical professionals or paramedical professionals can increase mothers' awareness during prenatal check-ups.

Dr. Raats: There is a real need for doing work within the areas and with the populations that you want to work with and really to understand the world that people live

in and where they draw their information from. So, you need to do work before actually getting out there and changing things. There is a whole range of methods that you can use which are both qualitative and quantitative, but you need to study the reality of the world within which people operate and what decisions they make, where they get their information from. Then, if you want to think about changing that you also need to understand the totality of the environment, not just how the mothers view the world but also how the world in which they live views them. That's another important thing to consider because you can come in and change things and that might meet the way that mothers would accept and take messages. But you might also have to create changes in the system and the way it treats and works with parents. So you also need to do a lot of work to understand the systems within which you want to create the changes.

Dr. Singhi: I think that what our colleague from Bangladesh said is to some extent true for us in India. Do you think that the leaflet has a big impact? Are these leaflets prepared by health professionals or non-health professionals? And if this is not a working mother, would these perceptions change?

Dr. Raats: I think you have highlighted important points. This is just a reflection on what people say, it isn't even necessarily what they do because even if we ask ourselves to reflect on what influences the decisions that we make it's still only a reflection of what we think is influencing ourselves, not necessarily what is the case. And so in some sense studies are needed to be done where you implement interventions where you use some of these materials and you look at what the effects are rather than just asking people like we have done. There is a need for studies to better look at that, and I think what will work and how that happens and how you study that in one country might be very different. That's partly the big problem we have in this area of evaluating interventions. You can't within even a very small region like Europe just take the learnings from one country and introduce them somewhere else. What works in one part of the world and what consists of an intervention will be different in different areas, so they need to be put together differently, but we can very easily build up this standardized evidence base which will suggest what works and why.

Dr. Singhi: Behavior is influenced by culture, and we have something similar in the way parents perceive their children and their illness. Europe differs completely from Asia and Asia differs completely from Latin America.

Dr. Raats: I think one of the things that we probably didn't look into as much is the interrelationships between people. People especially at this time in life draw information, as you do with most topics, from people around them. How to measure and quantify and actually even get explicit what it is that you draw in terms of the information from your peers and from the world within which you live is very difficult, and because again it's very complex, it's not as controllable as a leaflet or the communication from a health professional, and it's actually what is more likely to be influencing people. So again, how do you study that, how do you control for that and how do you create a change by having to change whole communities within infant feeding. It's not just the parent who is doing the feeding who makes the decisions, they are being influenced by the decisions made within the family.

Dr. Ivarsson: I find this area of promoting behavior change challenging, but at the same time extremely important from a public health perspective. I am responsible for developing and implementing a child health promotion program, beginning with antenatal care, continuing within the child health care arena, into preschool, and up through school years. In my experience, one problem is that professionals give conflicting messages which confuse parents and children. From your experience, do you have any advice on how to handle this?

Dr. Raats: I think at one level we need to reflect back on ourselves as scientists and say that we have great difficulty into coming to conclusions about certain things and then finding ways to imbed that in the system. I think there is a lot of pressure that you come up with unique results and so quite often we don't see the efforts going into trying to get the consistency of message and decisions around consistency, and where that has to happen and where that agreement needs to lie, who is it that has to come to these decisions. It's difficult in an area where there is relatively strong emphasis on coming up with consensus view on things. That's maybe not the case in some other countries. I think it comes back to really understanding your country and how it works in your environment as to how some of those decisions and what would work and what would be the suggestions in one place might be different somewhere else because of the traditions that you have of formulation of advice and ways of doing things.

Dr. Ruemmele: Do you have experience with targeted intervention just after birth? We have a program in France to improve the rate of breastfeeding which has been very low over the last years. There is very good evidence that if you have targeted intervention in the maternities the day of delivery and the days after, you markedly improve the rate of breastfeeding over a prolonged period. Can you give us some advice on how to push this in the countries like in the North?

Dr. Raats: I think there it's important to understand the health care system and whether you have the things in place to be able to do that. I know that in the UK we have a lot of pressure on our health system and there isn't the staff to have the time to spend necessarily with people, and so it could be that what works on paper and looks to work in some places might not be that transferable unless you have a system in place which would allow for that to operate.

Dr. Thakre: It was interesting to hear the western perspective. My question is how would this be in a country like India with numerous culturally driven practices that significantly influence the decision to breastfeed, to wean and also the healing of a child?

Dr. Raats: The starting point is to really understand and do the work to understand why people do what they do, and that will be different for the exact reason that you say that there are different culture practices. To have an in-depth understanding of why decisions have been made and behaviors exist is very much the starting point that one needs to do. The methods that you would use to do that in one country are not necessarily that different than in another country, but it is a different set of data and a different starting point and it's only then that you can start to think about how you might make changes to the system. So, it's not understanding the practices at the individual level but it's also understanding all the layers up to the level of a nation in terms of how it's organized that you need to first have in place before you can think about how best to make some of those changes. I think you probably do in many countries have data on that, and it's really the starting points and then you can reflect on and learn from other places. I think what we in western countries often don't do is realize that there is a lot that we can learn from developing countries where I think you have had a lot of experience in introducing changes in ways that we haven't been able to do because we have so-called free markets, but there is data out there and learnings to be had. At the moment, I am working in another project looking at policies around micronutrient intakes, and there is probably more interesting work being done in developing countries to be learned from because programs have been implemented and created to introduce behavior changes in ways that wouldn't have been possible in some of the western countries.

Dr. Solomons: Your studies projected to me a sort of neuroticism, it sounded so neurotic, all these people are neurotic, and I wonder whether or not that is true and if it is true whether or not the scarcity of having a child in both of the settings that you

mentioned, China and the UK, people do it later in life in the UK and maybe only once or twice in China and have to have a good outcome, bills on neuroticism which is not seen in the country where I live or where Dr. Cooper lives, where first of all girls are always around feeding children, this from birth onward. They know about it, they have lots of siblings, they expect to have lots of children, and unfortunately when a child dies it's not an unusual catastrophic event because it happens often, so that somewhat reduces the pressures all around. I just wonder whether the situation in the UK and China and the situation in Guatemala, where the median age for the first child is 17, it's sort of as natural as rolling out a tortilla.

Dr. Raats: I think you're making an interesting point, and I think it's an interesting comparison. In the countries in which choices are not made that frequently, decisions are made in a different way, and I think that translates to other behaviors in life.

Dr. Bier: I have listened to the discussions dealing with the US and western countries now for more than 40 years, I have watched the initiation of breastfeeding, and then 6 months or 1 year later the 6-month rate is downward, it has always been. Are we doing something wrong, I mean I am sitting and listening to the same conversations I had in 1960 with the same kind of numbers. Can you give me five things that I know if I do now I'll have an infant who is exclusively breastfed at 6 months?

Dr. Raats: Change things at top level, don't focus on the individual. I think structural changes that make some of the decisions easy will make the biggest difference. These are some of the interventions I think that we have not been able to study. I think there has been a lot of focus on pushing the decisions down to the level of the individual, and the thought is that the focus on getting it right, getting the wording right might be the means to which change will happen. I think that's why it has been difficult to change things because you have to change things quite deep within people and within practices in the way society operates, and until we change some of those things I think we won't see the changes we'd ideally like to see because there are somewhat tougher decisions to make than changing the wording or the format of a leaflet or a booklet.

Dr. Haschke: I would like to address a point which is unique. It's the week program in the US. This program to give a free supply of infant formulas to almost 50% of the population doesn't exist in any other country of the world. I am not saying this is good or bad because the intentions are good to help and support good nutrition of the mother and the child, but the way in which it is executed and how it might interfere with breastfeeding, especially in the duration of breastfeeding, could be an issue.

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Bioethics and Innovation in Pediatric Nutrition Research

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Abstract

Advances in technology and understanding of fundamental human biology allow for an increasingly innovative research agenda in pediatric nutrition. All human research is governed by the norms of bioethics, which are in turn based on four primary principles: free will in participation, freedom from harm, opportunity to benefit, and non-discrimination in access. Legally, if not essentially, juveniles do not have free will to affirm their participation as research subjects. They have an absolute right, in nontherapeutic research, however, to decline. Pivotal in the discussion in nontherapeutic research in healthy children is the tolerance for risky procedures. Complicated situations include: multi-national protocols, choice of developing country sites, the inclusion of placebo treatment arms, analysis of genetic biomarkers, and research for commercial enterprises. The overly stringent interpretation of bioethical principles, as adapted to children, would stifle innovation in research. A relaxed bioethical attitude in pursuit of advancing science, by contrast, could violate essential human rights and expose a population worthy of special protection to undue risk and harm. By following the course of utility, seeking the steepest benefit-to-risk ratios, weighted toward safety and child welfare, the divergent nature of the considerations should be brought into convergence for the sake of continuing innovation.

When you reach the fork in the road, take it.
G.T. Keusch [1]

We live in a world of growing population, shrinking natural resources, a stable – but precarious – food supply, unstable climate, and differentially shifting demographics in developed and developing countries. The current world population is estimated to be 6.8 billion, with 27% under 15 years of age, and 10% below 5 years. Pediatric nutrition research could potentially affect the lives of billions of individuals.

Table 1. Glossary of terms related to the social compact and the principles of bioethics

Key definitions
Values are conditions or characteristics that members of the society consider important.
Morals are concerned with the judgment of what is right or wrong in human conduct.
Ethics are rules or standards governing the conduct of people in general, or specifically the members of a profession.
Major principles of bioethics
Autonomy: The principle that everyone has a free will, and this will must be respected with a person's voluntary compliance and consent in all interactions.
Nonmaleficence: The principle of not causing harm to an individual – consciously or unintentionally – in any clinical or investigational interaction.
Beneficence: The principle of endeavoring to provide positive benefits to those with whom one engages in the healing process (or in research).
Justice: The principle that no discrimination of any sort (e.g. gender, ethnic, religious, social class, etc.) should be exercised in providing access to benefits (or risks) in clinical medicine or biomedical investigation.

Today, we also have unprecedented communication capacity, with interconnection among all regions and societies of the world derived from rapid air travel, massive oceanic shipping and trade capacity, informatics, and a shift away from the regional hegemonies of the Cold War era. The situation is a two-edged sword. It brings awareness of ideas and norms from one part of the world to another, but these may clash with the values in the other part. Moreover, despite our means and media to communicate, the degree of understanding and trust across regions and cultures, across nations within regions, and among classes within societies, may actually be in retreat.

Values, Morals, and Ethics: The Governing Principles of the Social Compact

Values, morals and ethics are elements of the social compact that holds societies together and allows for cordial and just relations among the members. Despite the semantic confusion and recognized interrelationships, the three terms are not synonyms and must be understood in their appropriate connotations and contexts.

The Definitions and Distinctions

The definitions of the terms of reference are provided in the upper panel of table 1. In the broadest sense, each deals with good and bad, right and wrong. Social *values* are collective judgments as to what is important to and in a

society. What is appropriate interpersonal behavior derives from these judgments. Therefore, what constitutes 'good' and 'bad' treatment of one's fellow man or woman is based on the values adopted in the society. Morals are the values that directly express right and wrong. Morality constitutes the convictions that are held to be authoritative in matters of right and wrong. Ethics is a code of conduct for approved relations among persons, one that is dictated by the social norms of the society.

The Ethical Principles of Bioethics

Biological and medical sciences represent professions in which an ethical code is an obvious necessity. Biomedical ethics or bioethics is the domain of the ethical code of conduct in issues of medical practice or research. The four hallmark principles of bioethics are: autonomy, nonmaleficence, beneficence and justice; they are defined in the lower panel of table 1, and have been expanded upon elsewhere [2, 3]. The basic general principles and considerations of bioethics have contributed directly to the formulation of treatises dealing with diagnostic and therapeutic issues in the clinical context [4], preventive issues of the public health [2, 5, 6], and investigations involving human subjects [7].

According to Graber [8], ethical theory has two tasks: '(1) for those situations in which we already know what is right and what is wrong, it should help us explain why the one choice is right, and the other wrong; (2) for those situations in which it is not obvious, what is right and what is wrong, it should guide us to discover what is the right thing to do'. For instance, the principles of beneficence and nonmaleficence could be seen in absolutist terms, such that neither can be violated. This is akin to requiring all diagnostic screening tests to be both 100% sensitive and 100% specific at the same time. The probability of perfection for either situation is remote. Thus, we are inevitably faced with ethical dilemmas, and the issue of finding an acceptable balance. The exigency of dilemmas has given rise to a *(relativistic)* fifth principle, which is not ranked among the *big four*, but is importantly operative for the present discussion. This refers to what Beauchamp and Childress [3] call the *principle of utility*, which emphasizes the 'benefit-to-risk' ratio as the final governing arbiter in bioethical dilemmas at the interface of benefiting the participants and doing them no harm.

The Bioethical Principles Applied to Biomedical Research

The original motivation for concern about human investigation was moral and ethical atrocities committed by the Axis allies during World War II, and later uncovered in US institutions. Table 2 provides a chronology of important historical landmarks in research bioethics. As of 1978 in the US, a legal framework of regulation of human research has been codified. Among its requirements is the approval and supervision of studies on human subjects by oversight bodies known variously as institutional review boards, and independent ethics committees or ethical review boards. These are to assure protection of subjects'

Table 2. Important landmark documents and declarations in the history of the ethical protection of human subjects in research

General and universal statements
Nuremberg Code – 1949.
– 10 point code from Nuremberg Military Tribunals of 1945–1947
Declaration of Helsinki – 1964.
– Original version. 18th Meeting of the World Medical Association, Helsinki, 1964.
Belmont Declaration: Ethical Principles and Guidelines for the Protection of Human Subjects of Research – 1978.
– U.S. Department of Health, Education and Welfare
Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Geneva 1982–2002.
'Common Rule': Federal Policy for the Protection of Human Subjects – 1991.
– Uniform set of regulations covering 14 US Federal departments and agencies
Declaration of Helsinki – 2008.
– Sixth version. 59th Meeting of the World Medical Association, Seoul, 2008.
Related to child research
The National Human Research Protections Advisory Committee (NHRPAC) (Washington, DC) – 2000.
Ethics Working Group, Confederation of European Specialists in Paediatrics (CESP). Research in children. A report of the Ethics Working Group of the CESP – 2002.
Ethics Working Group of the Confederation of European Specialists in Paediatrics. Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP) – 2004.
The Institute of Medicine (IOM) Committee on the Ethical Conduct of Clinical Research Involving Children (Washington, DC) – 2004.
The United States Department of Health and Human Services Secretary's Advisory Committee for Human Research Protections (SACHRP) (Washington, DC) – 2005–2007.

welfare and ethical conduct of human research, including respect for autonomy with informed consent for individual participation. As an example from North America, the fundamental elements of informed consent under US Federal regulations [9] are outlined in table 3. Specific bioethical regulations regarding supervision of human investigation vary from nation to nation.

Social Values and Innovation in Investigation in Children

The theme term of our workshop, 'innovation', can be defined as the *process of introducing something new*. It has multiple and interacting connotations in the context of bioethics and pediatric nutritional investigation. The first is the wide gamut of emerging and novel research questions surrounding diet, nutrition and physical activity, which represent innovative inquiry. The

Table 3. A description of the elements of informed consent for participation in medical and health investigations according to the US Federal Regulations Codes

1	A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental
2	A description of any reasonably foreseeable risks or discomforts to the subject
3	A description of any benefits to the subject or to others which may reasonably be expected from the research
4	A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
5	A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
6	For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained
7	An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
8	A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

From Title 45 Public Welfare [9].

challenge for safety and efficacy – but more for containment of health costs – brought the term 'evidence-based' practice into vogue at the close of the 20th century. The best investment in health and nutrition for the individual citizen's money or with the public funds was seen to be the one demonstrated by rigorous scientific evidence. To the extent these inquiries respond to the needs of the world's juvenile population and provide solutions to problems, they are essential.

At least in Guatemala, a more colloquial connation comes from the National Council on Science and Technology (CONCYT) of Guatemala which sees its mission in the promotion of Research, Technology and *Innovation* in the national interest; for them, the latter term signifies applications that can be patented or turned to restricted uses in a commercial sense, eventually to contribute revenue.

Social values and financial prowess influence the pediatric research agenda, and this lies upstream of the research ethics. Regarding innovation in complementary feeding and its timing, for example, the World Breastfeeding Alliance (WABA) laments that 'amongst the many stakeholders in malnutrition, there is no well-resourced breastfeeding champion' [10]. As a consequence, public-

Table 4. Five considerations related to priorities for research investment in the basic questionnaire of the CHIRI survey series

• That the new or improved health intervention is likely to indeed be developed through proposed research investment
• That, if developed, it is likely to have a real and true effect against the disease that it aims to tackle
• That, if developed, it is likely to be delivered to most of those who are in need for it
• That, if developed, it is likely to influence the majority of affected individuals
• That, if developed, it is likely to become available to all segments of the society equally

Modified after Kapiriri et al. [11]. Reproduced with permission.

private funders ignore indigenous, traditional complementary feeding options. An informal international consortium of public health nutrition investigators, the Child Health and Nutrition Research Initiative (CHNRI), performed a unique triple survey among diverse stakeholders in health research and their representatives. Two were conducted in an international context and one within the confines of South Africa [11]. The queries related to prioritizing five basic considerations in research planning. The phrasing in one of the questionnaires is show as an example in table 4. CHNRI found: 'At the global level, the wide and diverse group of respondents placed the greatest importance (weight) to the criterion of maximum potential for disease burden reduction, while the most stringent threshold was placed on the criterion of answerability in an ethical way' [11]. By contrast, those surveyed in South Africa found the predicted impact on equity to be the most important. These researchers argue for the ideal of a broader consultation on setting research priorities, beyond the investigators themselves.

Prof. Jerry Keusch, renowned leader in Global Health, has developed an evolutionary argument in his publication 'When you reach the fork in the road, take it: science and product development as linked paths' [1]. For him, scientific inquiry has emerged from the pure animus to know how nature operates, through the obligation to publish and disseminate new knowledge, to a contemporary imperative to make applied use of the findings. His new motto for scientific inquiry becomes: 'if it is not used, it is not done'. He focuses on research education and career development as an often ignored element in the discussion. Keusch's synthesis is a convoluted and interactive one. He argues that the: 'education and research system must ensure that the scientific workforce will understand public needs, that the public health workforce will understand the contributions of science, and that the financial and organizational mechanisms that create the private good of products for better health care can address the global public health requirements for global

development' [10]. In light of such contrasting – if conflicting – social values considerations, there may be need for finding innovative application of ethical theory to inform us about the ethical dilemmas that the innovation in the research agenda generates.

The Constraints of Assent, Risk and Child Welfare in Pediatric Research: The Judgments in the Ethicists' Literature

The four bioethical principles are operative in pediatric research, but the tender age of the population brings out three correlative issues: power relations, informed consent and confidentiality [12]. There is an extensive debate in the pediatrics literature over the meaning and application of autonomy for children's participation in research. The law generally sees minors as legally incapable of giving consent. As the wards of parents and guardians, the responsible adults must provide the informed consent (or, in effect, 'permission' for participation) or not. However, there is a requirement for the child subject's 'assent'. Maturation of decision-making among adolescents is heterogeneous, but one noted ethicist suggests that 14 years is an age one when 'become(s) able to understand the research in question' [13]. There is general consensus, however, that respect for a child to dissent (refuse participation even if parents have consented) should be absolute. The current fulcrum of controversy is whether parents and the law should respect the positive assent decision of a child, short of legal age of maturity [14]. Adult guardians, however, can sign their children up for investigations that are unsafe or harmful. One reaches the conclusion that autonomy and nonmaleficence are more intimately intertwined for this group, since, no matter who makes the positive decision for a child's participation in research, the protection from harm for this vulnerable population emerges as paramount.

Despite the nuances, as stated by many commentators, it is unethical *not* to involve children in investigative research. To the extent that drug efficacy for children is generally extrapolated from adult experience, the US government has encouraged the conduct of ethical drug trials in and for children [15, 16]. Drug studies are the point of departure for discussion of beneficence and justice by Rowell and Zlotkin [17]. They call above all for the mobilization of advocates for the children's well-being, while finding merit in empowering children, without discrimination, to safely ensure that medications are secure and effective for pediatric use.

The Geographic and Cultural Encounters

Multinational research in pediatric nutrition is clearly one of the avenues of innovation, since resources and technology in one location must

be merged with the existence of the problem in another. Here, issues of relative power and sophistication merge with those of cultural values and national sovereignty. At one level are arrangements within a single region, such as the EU. Indeed, there have been murmurings from British professionals about loss of UK ethics sovereignty from EU-wide directives. In actuality, the collaborators in the Healthy Lifestyle by Nutrition in Europe in Adolescence (HELENA) Study [18], which involved European children (adolescents), documented the diverse and persistent efforts needed to achieve all of the legal and ethical board approvals across the ten nations of the network, with all of their different norms and the different considerations raised. The optimistic moral of their tale is, however, that it proved able to be done [18].

North–South collaborations in research financing and investigation raise both similar and different issues. If indeed there is mistrust across the English Channel and inconsistency with the EU, the bases for mistrust and power differentials with affluent collaborators joining with colleagues in middle- and low-income countries are more profound. As related by Pitler [19], one of the legendary international clashes of culture related to the inclusion of a placebo arm in a study of prevention of maternal to child transmission of HIV, in which the editor of the *New England Journal of Medicine*, the venue of publication, took the ethics of such a design to task in a stinging Editorial, alleging that the participants should be offered 'state-of-the-art' treatment. She meant state-of-the-art for the US, the funding nation. A counter argument relates to the sustainability of the most advanced therapy if declared a standard of care in a resource-poor country. Innovation requires both the most advanced – but also the most practical and appropriate – technology when resolving problems in low-income settings.

Hyder et al. [20] openly recognize the diverse weaknesses and limitations for conducting ethical research in less-developed societies, and propose a solution in a *Lancet* review entitled: 'Moving from research ethics review to research ethics systems in low-income and middle-income countries'. This system approach looks to deepen the bases for an ethical research environment through issues of: development, enabling conditions, national/regional strategy, institutional commitment, and investigators' conduct, in addition to the research ethics review process itself. It is pertinent to consider their entire treatise, but just the list of the 'enabling conditions' considered by Hyder et al. [20] is highly illustrative. These conditions include: values, strong civil society, cadres of trained people, healthy working population, public accountability, trust in basic transactional processes, and freedom of people to determine boundaries of personal risk. These requisites set the bar high, with criteria that would be utopian even for the most advanced societies. They inform and guide emerging societies, while raising the question of how ethical research can be conducted in the countries of the South *before* the consolidation of the ethical system conditions.

Ethical Flash Points in Pediatric Research

Beyond the training, infrastructure and commitment to protection of subjects, are a host of sensitive 'flash points' of ethical dilemmas in the design of some of the most innovative and high-value research. Among the points of contention are the enrollment of children for nontherapeutic inquiry with no direct benefits, the inclusion of placebo (nonintervention) controls in the research protocol, and the obtaining and divulging of genetic information gathered in pediatric research.

The Role of Children in Nontherapeutic Research

There are more ethical certainties in research on children affected with a disease or condition, as they might benefit directly from a successful new therapeutic approach; this is in contrast to research in healthy children with no major benefits to be reaped. The degree of risk in the privations, exposures or procedures acceptable in this population needs to be better understood. In the US, Federal regulations call for no more than 'minimal risk' in child research, or alternatively 'no more than a minor increase over minimal risk'. Fisher et al. [21] identified: 'the ethical issues posed by ambiguities in regulatory language', and call for 'a national consensus on recommended criteria'. Ross [22] calls the current language a 'double standard' and calls for the unification of criteria. Failure to arrive at a robust resolution of nontherapeutic research dilemma regarding 'risk' threatens innovation research for preventive nutrition.

The Role of Placebos in Controlling for Positive and Negative Effects of Intervention Studies in Children

As discussed, the use of placebos is controversial in HIV research [20]. In pediatric research, this has extended over into relatively benign conditions, such as mild hypertension, in which a controversy concerning leaving children untreated for even a short period has been debated [23]. US Federal regulations permit placebos in pediatric clinical trial protocols under stringent conditions, but again related to the ambiguous 'minimal' and 'no more than a minor increase over minimal' risk criteria [24]. For healthy children and nontherapeutic research, the US government is somewhat 'agnostic' on the subject of placebos.

In childhood nutrition, addressing endemic nutrient deficiencies and imbalances sets the scene for a dispute over placebo-containing study designs. In situations in which spontaneous improvement of a condition or developmental changes with age, such as hematological status, it is difficult to discern what effects on anemia prevalence could be attributable to an iron intervention without a situation of control reference. On the safety side of the ledger, there are examples in which interventions were found not only to be nonefficacious but even to be *harmful*, but only by virtue of a no-treat-

ment arm included in the design [25]. Safety is a higher essential priority than efficacy for nutrition innovations. Appropriate control comparisons are indispensable for detecting any adverse effects or damage in intervention research.

Collection of Genetic Information in Children

The issues of nontherapeutic research and placebo interventions in healthy children are not the only sensitive issue in pediatric nutrition research. An even more sensitive issue surrounds obtaining consent for and maintaining anonymity of identification in the collection of genetic information in children [27, 28]. When it comes to screening for genes associated with adult-onset disease, for example, it was a consensus that: 'If there were no urgent medical reasons, all guidelines recommend postponing testing until the child could consent to testing as a competent adolescent or as an adult' [27]. Writing from Malawi, Ndebele and Musesengwa [28] fret, beyond resolution of the ethical pitfalls, about what tangible fruits application of genetic techniques might hold for developing countries; their perspective and concerns deserve serious consideration.

One of the recognized foibles of randomized clinical trials is that they involved representative – but unselected – populations, in which the vulnerability to disease development and susceptibility to benefit are heterogeneous and not synonymous [29]. A more valid test of efficacy would come from enrolling and randomization *only* of those with susceptibility to an affliction, if this could be identified. Conversely, universal en masse application of preventive measures will have uneven and inefficient effects if the exposed individuals do not all have a substantial chance to receive benefit from the efforts. As far back as the 1980s, Holtzman [30] argued to the nutrition community that 'selective policies should be considered when discernible differences in risk exist...' Within today's armamentarium of genetic biomarkers, a contorted interface of innovation and ethical complexity arises in the domain of pediatric genetics and genomics research. Hang-ups on the ethical dilemmas surrounding genetic profiling of minors could seriously stifle innovation in preventive nutrition.

The Footprint of the Investigative Enterprise on Participating Communities

Not on the flash point list, but important for those of us who live in low- and middle-income countries, is the issue of the 'footprint' a research study may leave in the participating communities. What we call 'developing' societies are, by definition, susceptible to rapid evolution and change. Inducing changes in behavior, for the purposes of a research investigation, may contribute to social evolution and change with unintended consequences.

Box 1

Case study
Effects of Routine Iron Supplementation on Anemia and Health of Children in a Malaria Area in Tanzania

A consultancy conducted in 1998 by the World Health Organization (WHO) and the International Nutritional Anemia Consultative Group concluded that, when the population of children aged 6–24 months in a given locality had an anemia prevalence of >40%, universal supplementation of the target group with 12.5 mg of iron and 25 µg of folic acid should be instituted as a public health measure [32]. In an area holoendemic for malaria on Pemba in the Zanzibar Islands of Tanzania, involving 24,076 children, randomized to iron, folic acid and zinc, iron and folic acid, zinc alone, and no-treatment (placebo) [33], an interim analysis by the Data Safety Monitoring Board detected a trend towards increased adverse outcomes in the groups randomized to iron, as compared to a placebo (no treatment group). The iron supplementation intervention was suspended. A formal analysis of the accumulated findings before cessation of the iron trial found a 15% increased risk of death, an 11% increased risk of hospitalization (statistically significant, $p = 0.03$), and a 12% increased risk between the combined adverse outcomes (statistically significant, $p = 0.02$). A consultancy group, convened by the WHO in Lyon, France, subsequently recommended a moratorium on universal iron interventions in malaria holoendemic areas.

A pivotal point in ethical theory for innovation research is around the issues of how to restore the participating individuals and families to their *prestudy* community norms if the tested intervention proves to be either inefficacious, unsafe or both. In a Guatemalan case in point, a permanent loss of 'market share' for agriculturists who were retired from the maize commerce to participate in an *improved* corn variety intervention became a concern [31]. There is the related concern of avoiding 'contamination' of the traditional behaviors among nonparticipant neighbors who might mimic or emulate a course advocated by the investigators to the selected few enrolled in a study.

Finally, the scope of the beneficence principle intercedes with respect to sustaining any beneficial effects found in a study. How are they continued in the treatment arm sample, and for how long? When and how are they extended to the control group, who did not benefit during the trial? What is the obligation to bring the benefit to the community as a whole? The region? The nation? Often, the low-income country values and policies feel that sustained subsidizing of the benefit, with funds from the investigation, is a moral obligation of involving the population in the research. The other side of this coin would be any obligation for compensation to families, community, etc., for adverse effects discovered during interim data monitoring or at the conclusion of a full intervention trial, as exemplified in the Pemba study [32, 33] (box 1).

Conclusions

The imperative for innovation research is driven by the interests of those who can benefit from the new knowledge and its application. At times, the dilemma can be posed as a conflict between the compromise of the welfare of the young individuals, who are enrolled or otherwise included, and the greater good for their peers in society. Ethical quandaries can prove to be a damper to innovation at one level and a stimulus to innovation at another. A case study summary of the now notorious iron supplementation innovation in a high-incidence malarial population [33] is presented in box 1. The international reaction to the occurrence was a recoiling and retreat from universal iron supplementation for children in such areas. However, it has also stimulated the quest for innovations to overcome the barriers. This includes such ideas as noninvasive (bloodless) screening of hematological and iron status to target therapy to the truly deficient or develop alternative ways of providing iron with compounds less provocative of adverse outcomes [34].

The advance in scientific knowledge and applicable technology in basic laboratory science is inexorable. It will be funded by public funds and corporate investment. By limiting the application in children, bioethical principles may appear at times to stifle innovation in pediatric nutrition. The prospects for certain lines of pediatric research will inevitably come to *forks in the road* [1]. By following the course of utility [3] to seek the steepest benefit-to-risk ratios [17] with a profound weighting toward safety and child welfare while always respecting an absolute right to subjects' dissent [13], the divergent nature of the considerations should be able to be brought into convergence for the sake of continuing innovation.

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Discussion

Dr. Gibson: I personally have never been restricted in any of our research in terms of ethics. Everyone that I know who conducts ethical research sits quite comfortably within the context of the ethical rules in our hospital, and further we ask ourselves another question: would I let this be done to my child, and that's a question we have asked ourselves repeatedly and then turned our backs on some tests. The thing that really bedevils us is one of the steps that you brought forward, and that is what I would call the translation. The public gives us enormous amounts of money, we do these studies, and then it sits comfortably on somebody's shelf I don't know how long. Then it gets published in *JAMA* or *BMJ* or any other journal, and it just sits there unless there is some organism that has got the money, the energy and the time to see that the findings are translated either into a product on a supermarket shelf or in clinical practice guidelines or a number of other things. We need creation of translation mechanisms, I am a nutritionist, somebody else is a translational person, and unless they pick it up and provide dollars nothing happens, I think it's almost immoral, and it's certainly frustrating.

Dr. Solomons: I think it's moral. I've often said to my post-docs and graduate students it's immoral for you not to get that paper off to the journal, whether it was a negative or a positive study. I have a very close friend at Stanford University, who said that there's an intersection between health care efficacy and its just distribution in society, and he said: here's where I take off, I make sure the studies are as good as possible, and when they show a significant benefit, it's my job to find out how we move that translation from a significant benefit demonstrated to those who need it as quickly as possible. Yesterday we had a discussion about the issue of meta-analysis, size effects 11% significant, 20% significant. I was cheering all over the place because I think 18 lives saved out of a 100 is a significant issue. But there are some people who operate from an abundance of caution and clamor to see a study redone and confirmed and viewed in the context of meta-analysis; this is an overabundance of caution perhaps. What happens in our ethics, and I think you have probably seen this, is that once an intervention measure has a powerful lobby behind its efficacy it's no longer ethically acceptable to use a placebo, so we can't really confirm it. This is another argument to design it right the first time because if you get a sort of a rumor out there and the rumor is wrong but placebo research is constrained for ever, you have done the worst of all evil to the situation. That's my response to that. Really get it right the first time, because once the moral ethicist will say 'no longer placebo here', the repeat study is totally proscribed from ever being done.

Dr. Cooper: I just have to take you up further on that. I think the end points become very important and particularly looking at the nitric oxide study that in itself I think was a very good study, but going back a little further in the neonatal research steroids given to premature babies to either prevent or modify the development of chronic lung disease came in a very few relatively small studies, became very widely used, and it took probably more than a decade to realize that it was having harmful long-term effects in terms of an increase in the rate of cerebral palsy. So, I think if we go back to Dr. Makrides' studies, a 7-year follow-up, is clearly very important, and a longer follow-up is necessary to be sure that there are no long-term harmful effects, and I think that's where the importance of publication, discussion, presentation at meetings becomes very important to explore these areas.

Dr. Solomons: Let me mention just two key words, thalidomide and ethylstilbestrol. That's an intrinsic and sad aspect of research, that is, that it is always easier to develop an efficacy statistical profile faster and with a smaller sample size than to see the long-term safety. So, in fact ethylstilbestrol did preserve fetal implantation and

allowed for birth. It did it very powerfully. It was only later, 20 years later, that vaginal malignancy was found to be an awful consequence. Thalidomide was a little closer, it did provide sleep and antinausea for women who were pregnant, but at the same time, it did produce children without limbs. It takes a while from efficacy to safety because safety requires a much larger sample size than efficacy.

Dr. Cooper: I think one of your last slides was on profit, public good versus private profit. I think there the dividing line is not clear at all. As an example, one of the major studies on pneumococcal vaccine was done in Soweto in South Africa. At the time, I was in the ethics committee, and one of the questions asked was this is never going to be affordable in the countries where it matters most. Yet, the study went ahead, and we have seen major changes in global players such as the Gates Foundation, and now it is becoming available very widely in the poorest of countries. So what might have been going to benefit the company 15 years ago has now become an enormous benefit to the whole population of children worldwide.

Dr. Solomons: That's a wonderful case study, and I think you are right, the same thing happened with antiretroviruses.

Dr. Ruemmele: I completely agree with what you've mentioned, that children are particularly vulnerable and have to be protected, so there are major issues and controls if you want to perform trials in children, mainly drug trials. But now I think the picture is moving on because in pediatrics we have to treat diseases and a lot of drugs we use for various indications are off label, there is no approval, they are not tested. The agencies in North America and in Europe now urge us to do these trials, so I think this overprotection of children is now moving to 'now you have to test and to reassure that what you've been doing over the years is appropriate'.

Dr. Solomons: They started saying that in 1991.

Dr. Ruemmele: Yes, but my feeling is that protection of children limits a little bit very useful and beneficial research with this regard. What is your comment on that?

Dr. Solomons: My comment is what I commented during the talk: that there are some situations in innovation in which the ethical practices would be road blocks and will act as road blocks. My answer to the question is that there are ways through it in an ethical manner, I rely back on Graber and ethical theory, it's a very positive aspect that if you understand it and talk it through you can come to a decision which moves things forward, even for children.

Dr. Bier: As far as the pharmacologic studies are concerned, in pediatrics there is a pediatric pharmacological research unit network which exists throughout the major medical schools. We do some very large number of pharmacologic studies in children precisely for this reason. In fact, it was a government priority and they established the units for that purpose. These are studies in which there is an indication of the drug.

Dr. Solomons: That's right, that's a step up. As you know, safety studies in adults for drugs start with safety studies, and I submit that during that kind of safety study just finding some healthy kids to see if anything goes wrong is not done, cannot be done, should not be done.

Dr. Bier: As you pointed out in your talk, there is essentially no way to prove safety except from massive numbers and long experience, so small studies for safety don't work.

Dr. Solomons: But we do large studies for safety in adults, that's the point.

Dr. Ivarsson: I agree that publishing research findings is crucial; however, our responsibility doesn't end there. In my opinion, we as researchers also have a responsibility to explain the findings in a way that makes them understandable and useful for the society. If the findings are from pharmaceutical research, the drug companies support this process. However, in the field of public health, for example, with respect to the need

for behavioral changes in the population, there is not a strong driving force that supports the move from evidence to practice. Do you have any comment about this?

Dr. Solomons: It's much more likely that a promising finding that was financed by industry money and is patented and has intellectual property rights is going to be used, not necessarily gain access to those most needing, than something which comes out of the public domain. Now, I have two men both of whom I know both well, one has recently deceased, Guillermo Arroyave of Guatemala and Al Sommer, both who worked in vitamin A, and both who found, reported and published important interventions that were successful against vitamin A deficiency. Dr. Arroyave was in Guatemala and did the studies in Guatemala, he published the studies in *The American Journal of Clinical Nutrition,* and then the government of Guatemala would not move. So what he did, he took the blind children from the school for the blind into the galleries of the legislature on the day they were going to vote on it, and it passed. But he took that initiative in conjunction with the woman who ran the school for the blind; he used some guerrilla theater and he got it across. I often criticized that, I said there should be a non-me (external) evaluation of what I publish to translate it. Now, let's move to Al Sommer who had a bigger study with bigger findings (34% reduction in mortality), in a bigger population (the whole island of Sumatra). He went to the US Congress and received financial support to do what you now see as vitamin A supplementation all over the world for prevention of child death. If we are looking now, as every intervention seems to weaken over time, there may have been too much of an 'I am the investigator, I have to be the advocate' attitude in both instances. There needs to be break on direct transfer to policy and program and translators between the finder and that person's own advocacy. I am inclined to think that there should be an agency somewhere upon which investigators can call for translators who can make external and independent judgments.

Dr. B. Koletzko: You as well as Dr. Cooper discussed potential conflicts between private companies and public agencies regarding values or priorities. Is there not a potential problem sometimes with public agencies as well? The design of clinical trials on drugs and on pediatric nutrition products is often very much influenced by the requirements for registration of products or ingredients. There are many examples where these requirements formulated by public agencies are not at all shared by the scientific community. For example, oftentimes growth studies or absorption studies with balance studies are requested where most experts in the field would say: 'We really don't have a reasonable hypothesis on which to base that requirement. Why should we burden infants with such absorption studies?' There are other examples where studies are requested to be repeated merely in a different country, to show results in the country where a product should be registered. Even the US are not an exception to that concept. Is that not also a concern?

Dr. Solomons: Yes, but that's a complex question. I am glad you mentioned Dr. Cooper and me in the same place because while I was praising the organizers of this meeting initially for all the bilingual, multilingual people around the table, all the globalization in the room, I also want to point out that there are only two people among the speakers who are from countries other than the countries of the North. Dr. B. Koletzko is not responsible for the distribution of published research on fetal programming at the moment, you are not, but I think you should be part of an advocacy to see that resources have flowed in some way to the better researchers in *developing* countries. In this way, Denmark, UK, Germany, etc. would not be the only countries having invited speakers. So I think there is a justice issue. Yesterday, Dr. Spieldenner said something wonderful, he said that in any given year 7% of the Chinese population of children constitutes the number born in all of the European states. So, why is Europe getting more investment? They have more money to start with to invest

among themselves, they have better researchers. So justice, which I made the center piece of my talk, begins to respond to all the parsing of your statements. Now, what we have surpassed is the attitude 'let's go to a poor country because it has a lesser ethical regulation and we can do something there we can't do here', we have gone beyond that. The most interesting one, 'we have papilloma in Soweto, we have papilloma in Paris, and we do the papilloma research in Soweto to get rid of the papilloma in Paris', we are getting beyond that as well. So once you've identified the dilemma, you talk honestly and openly about it, you point it out to try to find a way forward. I think we are doing well. Most people are not complaining about the way ethics works. I think there is a tremendous positive feeling among these stakeholders that basically we are trying to do ethical good work and that we basically succeed more often than getting meta-analysis in order.

Dr. Haschke: One comment on the South-African situation and the antiretroviral drugs. It was not the issue of knocking at the door of pharma companies to get the drug. After it had been realized that the drugs are efficient, it was in the 1990s, of course the pharma companies tried to sell them in the southern part of Africa at prices which were not affordable. What was then done, generic drugs were imported from India, and they bypassed all the license fees. I remember quite well in 2001, at the World Health Economic Forum in Durban the heads of states met the heads of the companies. There was agreement that there would be some substantial decrease in the license fees, making all these drugs available to the population. What was done, the political leadership of South Africa denied the efficacy of these measures until 2005, and the population suffered from this. In South Africa the issue is very complex, it's not related to intellectual property on the one side and to not having access to the drug on the other, it's more complex, politics here played a very negative role.

Dr. Solomons: I will accept that history because I did know the former Minister of Health of South Africa, but I think that you overcomplicated the ethical point about when there is no access. The ethical point is when there is no access to those who most need it because of intellectual property times market price. I think what you are saying is that you also, given the position you have in industry, are in favor of generic non-license copying, pirating if you will, bring on the pirate competition and we won't sue in the Hague, we will just applaud the initiative of bringing it to the people who need it. Am I interpreting you right?

Dr. Haschke: I am not giving you a legal view because I am not allowed to do this, but negotiations in that case are the best thing you can do with the companies. The companies showed the understanding of what the situation was, they realized what had happened, and they found an agreement; this was finally the best way to go.

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The Role of Pediatricians as Innovators in Pediatric Nutrition

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Abstract

Innovation is about making changes. When it comes to health care, innovations, though they may be something 'new', may not be beneficial if not demonstrated to be an improvement over what is current practice. Innovations in pediatric nutrition sometimes fall into this category. The establishment of safe water and milk supplies at the end of the 19th and beginning of the 20th centuries is viewed as one of the greatest advances in preventative medicine and truly was an 'innovation', with its dramatic impact on infant mortality. Other innovations in pediatric nutrition included the development of the caloric method of infant feeding which led to the large-scale adoption of a single infant formula. This required cooperation with industry and ultimately led to the development of life-saving specialty formulas for various disease states including inborn errors of metabolism. Over the last 50 years there have been further modifications of term infant formula that have included taurine, carnitine, nucleotides, whey proteins, PUFAs including decosahexenoic acid (DHA) and arachidonic acid, probiotics, and prebiotics. Many of these additions are of questionable benefit and are questioned as true innovations. Though the addition of novel nutrients to infant formula has been an area of great interest, more basic research (including randomized controlled trial) is needed to determine many pediatric nutrient requirements including the lower and upper limits of nutrients added to infant formula. Such research could be facilitated by institutions such as the US National Institute of Child Health whose establishment in 1962 was a significant 'innovation' as it led to advances in pediatric nutritional research. Much more research is needed to determine basic pediatric nutritional requirements and pediatricians should strive for such true innovations.

Innovation is about making changes. According to *Webster's Ninth New Collegiate Dictionary*, innovation can be defined as the 'introduction of something new' or 'a new idea, method, or device'. Innovations are often incremental over time, with no 'Eureka' moment. However, when it comes to health care,

innovations, though they may be something 'new', may not be beneficial if not demonstrated to be an improvement over what is current practice. In fact, in this case, 'innovation' unnecessarily increases the burden of the cost of health care for society. It is these kinds of 'innovations', whether an advancement in medical technology or the introduction of a new drug, that are a major contributor to the unsustainability of the health care system in the US at the present time [1]. Innovations in pediatric nutrition sometimes fall into this category.

Physicians who have chosen to pursue careers in the field of pediatric nutrition cut across a multitude of pediatric subspecialties. However, we have one unifying goal: to advance child health through pediatric nutrition by guiding pediatric health care providers to optimize the nutritional status of infants and children. Such advancements are made with innovations both large and small. These innovations may result from advances in pediatric nutritional research or technology, or from new cooperative efforts with government health agencies and other professional societies to develop and implement new public policy that improves the nutritional status of children. However, to achieve our ultimate goals, partnership with the food industry is often needed to implement the innovations. Industry has the wherewithal to sponsor nutritional research, but more importantly, to translate research and technological advances into practice that improve the nutritional status of children. A primary example of this is the cooperation between pediatricians and industry that resulted in the addition of iron to infant formula or iron sprinkles to infant foods.

From 10 years of service as a member of the American Academy of Pediatrics Committee on Nutrition, I have been made more aware of the importance of industry in another important role in making nutritional innovations.

Thus, groups like the Committee on Nutrition can develop new pediatric nutritional guidelines, but it lacks the resources to promote and implement these nutritional guidelines even to the American Academy of Pediatrics (AAP) membership. This includes the educational component of new guidelines that is often necessary. The 55,000 members of the Academy are also inundated with new guidelines and policy from more than 100 other groups within the AAP that impact on health care, frequently with the expectation that they all be implemented in a 20-min office visit. For example, though the Committee on Nutrition can increase the recommended vitamin D intake for children in a published guideline [2], the driving force behind its implementation may be the mother who asks about the need for increasing the vitamin D intake of her child. How does the mother know to ask this question? Frequently, the source of information is the food industry working with the media to highlight the new AAP guidelines as well as promoting their products containing added vitamin D. Thus, industry may play an important part in the implementation of guidelines developed to improve the nutritional status of children.

Since establishing itself as a subspecialty in the mid-19th century, pediatrics has a long history of making innovations in the field of nutrition [3, 4]. By 1900, 64 out 119 US medical schools had a special chair for pediatrics

and there was a proliferation of textbooks that dealt with the 'Diseases of Children'. These early textbooks contained an abundance of pediatric literature on rickets and infantile scurvy. Their authors also noted that the first 2 years of a child's life were the most treacherous. Horrendous infant mortality rates were identified and attributed to diarrheal diseases secondary to unsafe bottle-feeding as infants were weaned from the breast. In fact, the mortality rate was observed to be 80–90% among non-breastfed infants in the immigrant populations in large cities along the east coast of the US [3, 4]. Overcoming this formidable cause of infant mortality became the prime mission of pediatrics from 1870 to 1930. Therefore, the solution of the 'milk problem' became of pivotal significance as a vital element in the history of infant feeding. With the common goal of preventing mortality, pediatricians took the lead in learning to work together with public health officials on this issue [3, 4].

As pediatric nutrition entered the 20th century, emphasis was placed on the sterilization or pasteurization of milk, and the growing need for refrigeration was recognized. Indeed, the establishment of safe water and milk supplies was viewed as one of the greatest advances in preventative medicine, and in my opinion, the greatest 'innovation' in the history of pediatric nutrition. This began to change the empiricism and dogmatism that had dominated infant feeding during the 19th century, which included disbelief in the germ theory of disease and that raw, unpasteurized milk was best for infants. However, more than 100 years later, this greatest of pediatric nutritional innovations, has still not been implemented in many parts of the developing world.

After 1920, a great deal of pediatric practice was devoted to the feeding of infants during the first year of life and the prevention of malnutrition (defined as undernutrition). Key to this was the development of infant formula as a 'safe' alternative to breastfeeding. This was probably the second greatest innovation in pediatric nutrition, though there are many breastfeeding advocates who would argue against this for obvious reasons. This innovation also required the cooperation of pediatricians and private industry.

Before the large-scale adoption of a single infant formula occurred, it was first necessary for the widespread acceptance of the caloric method of infant feeding based on the work of Rubner and Huebner [3, 5, 6]. This had occurred by 1920 in the US, and led to the development of evaporated milk formula by W.K. Marriott in 1927. Key to the development of this product was the preparation of the dried milk powder from cow's milk with the addition of lactose and water to make it more like human breast milk (table 1). Its use spread rapidly across the US in the 1930s and 1940s. In fact, by 1960, 80% of bottle-fed infants were fed this formula [3, 4]. However, even before the 1920s, the search had begun for a single formula that would more closely resemble human milk. In the US, the first of these so-called 'humanized milk formulae', was introduced by H.J. Gerstenberger at a meeting of the American Pediatric Society in 1915 [3, 7]. Gerstenberger imitated the fat of human milk by using a combination of various homogenized animal and vegetable fats (table 1). This mixture contained 4.6%

Table 1. 'Innovations' for infant formula

Lactose, water	Used to make cow milk more appropriate for human infants (evaporated milk formula)
Vegetable oils	Saturated and unsaturated – replaced animal fat and cholesterol
Iron, vitamin D, vitamin K	Prevents disease – iron deficiency anemia, rickets, hemorrhagic disease of the newborn
Taurine, carnitine, nucleotides, whey proteins, DHA, arachidonic acid, probiotics, prebiotics	Of questionable benefit for term healthy infants
Partially hydrolyzed proteins	May be of benefit in preventing atopic disease

fat, 6.5% sugar, and 0.9% protein to simulate the caloric distribution of human milk. By 1919, Gerstenberger and Ruh had described the successful use of this food in the feeding of 300 infants [8]. This led to the first commercially available single formula in the US, Synthetic Milk Adapted, which contained nonfat cow's milk, lactose, oleo, and vegetable oils. Largely due to the cost differential, the commercially available formulae that preceded those we use today, had limited use until after 1960. However by 1972, 70% of the infants in the US were fed this 'humanized' milk formula by 3 months of age [3, 4].

Unfortunately, there were missteps along the way, which pointed out the pitfalls of some 'innovations' to infant formula. In 1978, a major manufacturer of infant formula reformulated two of its soy products without the addition of salt. Inadequate chloride, an essential nutrient for growth and development in infants, resulted in severe hypochloremic metabolic acidosis in a substantial number of infants [9]. This resulted in the passage of the US Formula Act of 1980 which amended earlier legislation to ensure the adequacy of the nutrient composition of infant formulae [10]. Subsequent amendments to this legislation in 1986 gave the US Food and Drug Administration broader regulatory authority over infant formulae [11]. Other missteps that occurred in the infant formula industry included the absence of vitamin K in meat-based formulae [12], the absence of thiamine in kosher soy formulae prepared in Israel [13], *Cronobacter sakazakii* sepsis in formula-fed infants [14], and more recently the contamination of infant formulae with melamine in the People's Republic of China [15].

Other significant innovations followed in the second half of the 20th century. These included the development of specialty formulae for various disease states including inborn errors of metabolism, again with the help of private industry. Efforts by pediatricians coupled with technological resources from private industry led to the development of appropriate pediatric total parenteral solutions after 1969, truly a life-saving innovation [16]. Also special attention was paid to the nutritional needs of low birthweight infants, especially those born prematurely [17]. Ironically, however, as the 20th century came to an end, the focus shifted to the problem of 'overnutrition' and obe-

sity throughout the developed and more recently in the transitioning worlds. Indeed, in the transitioning world today the problems of malnutrition and obesity exist simultaneously. At present, the whole world is anxiously waiting for the 'innovations' to solve the pediatric obesity problem.

Over the last 50 years, there have been further modifications of term infant formulae to make them more like human milk (table 1). These typically have been heralded as 'innovations' and include the addition of taurine, carnitine, nucleotides, whey proteins, PUFAs including docosahexaenoic acid (DHA) and arachidonic acid, probiotics, and prebiotics. If one looks closely at these new additives to infant formula, however, they are all of questionable benefit for the term healthy infant [18], and one would question them as true innovations. Though there is some evidence supporting their addition, consistently demonstrated positive functional outcomes from randomized controlled trials showing appropriate benefits (short-term and long-term) are lacking. Take the example of the addition of whey proteins to cow milk-based formulae. The whey proteins of cow milk are quite different from those of human milk, and even today there is slim evidence that cow milk-based formula with added whey proteins resulted in a product that is superior to a standard cow milk-based formula [19].

In contrast, there have been additions to infant formulae that have not 'humanized' them. These include vegetable oils and partially hydrolyzed proteins, as well as Fe, vitamin K and vitamin D. The latter three nutrients have been shown to eliminate diseases in children and are truly innovative. The addition of iron dramatically eliminated iron deficiency anemia in US infants. The additions of vitamin K and vitamin D have prevented late hemorrhagic disease and rickets in formula-fed infants, respectively.

Though today there is great interest in introducing novel nutrients to the diets of infants and children, there are still fundamental areas of pediatric nutrition that are in need of innovative research and development. These include an understanding of the true nutrient requirements for intakes. In 1996, the United States Food and Drug Administration requested the Life Sciences Research Office of the American Society for Nutrition to prepare a state-of-the-art analysis of the scientific and medical literature on the nutritional needs of infants since 1985 [18]. This was done in consultation with nutritional scientists and various professional groups including pediatricians involved in the field of infant nutrition. It was largely driven by the new interest, at that time, in adding fatty acids of the n-3 family (DHA) to infant formulae, which was following the course of the addition of other novel ingredients to infant formulae to make them more like human milk. The committee reviewed the nutrient requirements for protein, carbohydrates, fats, minerals, vitamins and other additives (nucleotides, carnitine, taurine, urea, cholesterol, glutathione, oligosaccharides). The committee also examined the upper and lower limits of concentrations of these nutrients in infant formulae [20].

The committee's report was published in 1998, and is now known as the LSRO Report for term infant formulae [20]. What was most notable in the con-

Table 2. Recommendations for the assessment of the addition of new substances to infant formulae

Documented statement of potential efficacy of a new substance
Complete and reproducible characterization of the physical and chemical properties of the new substance
The biological/metabolic activity of the agent, including interactions with other formula components
Standards of purity and good manufacturing practices
Source and availability of appropriate amounts to be used in infant formulae
Safety evaluations based in part on exposure
Feeding trials in adults to determine safety and pharmacokinetics of the substance
If adult trials are conclusive and positive, feeding trials in healthy older infants (> 6 months) to determine safety and pharmacokinetics
Adverse events should be identified, collated, and reported for consideration; particular attention should be paid to immunological responses, inflammatory responses and potential interactions resulting in a compromised response to other therapeutic agents
In the absence of clinically significant adverse effects, long-term trials should be conducted to assess the impact of the substance on growth and development
Efficacy of the agent could be confirmed based on biological activity and functional measures of growth and development, and advantages to the infant as predicted from prior studies documented in the original statement of efficacy

Adapted from [18, 20].

clusions of this report was the absence of the necessary data for establishing nutrient requirements. This included more fundamental nutrients as well as trace minerals. It was also true for the novel ingredients added to formulae since 1980. In addition, there was almost no data to characterize the potential risks associated with high intakes of specific nutrients and iron nutrition remained unresolved and contentious. Methods used for assessing protein quality in infants, were again found to be inadequate. The LSRO strongly endorsed further nutritional research to deal with these deficiencies. Strong recommendations for justifying the additions of new ingredients to infant formula were also made. These recommendations for the assessment of addition of new ingredients to infant formula are summarized in table 2. Unfortunately, little has been achieved on the issues identified in this report since its publication in 1998, and much of the report appears to have been ignored. Yet, additional nutrients continue to be added to infant formulae in which the nutritional requirements and the data establishing upper and lower limits remain inadequate.

A disturbing trend in the modern formula industry is to use a single branded name to cover an entire ‘family’ of related formulae, many with subtle differences that are not readily obvious to the consumer or the pediatrician without reading the fine print on the labels. Members of these formula families are

modified frequently with both additions and subtractions resulting often in only minor changes. In addition, they vary dramatically in price. Individual members of the 'family' include those with prebiotics, probiotics, partially hydrolyzed protein, extensively hydrolyzed protein, rice, as well as LC-PUFAs and those that are lactose free. There is also a family member that is labeled 'organic'. Indeed, this has become the era of the 'boutique formula' which makes selection of any one product by the consumer or the single recommendations of a single produce by the pediatrician, very difficult. Most of the additives to these boutique formulae remain of questionable benefit for the term healthy infant, and consistently demonstrated functional outcomes from the results of randomized controlled trials proving both short- and long-term benefits are lacking. In the case of many of these formulae, it is more about marketing, which is often the enemy of innovation.

Finally, a significant incremental innovation has been the promotion of pediatric research to advance nutrition. In 1962, President John F. Kennedy of the United States signed legislation creating the National Institute of Child Health and Development as the 9th Institute of the US National Institute of Health in Bethesda, Md. [21]. President Kennedy noted at the time that: 'The future health of our Nation rest on the care of our children and the development of our knowledge of the medical and biological sciences... Research in recent years has established beyond question that adult behavior, intelligence, and motivation are established by the experience and patterns of response developed in the formative years of life...' It is noted that President Kennedy even at this time acknowledged the idea behind the present widespread interest in the importance of metabolic programming early in life. There was a great deal of opposition to the establishment of the NICHD, especially from the other 8 institutes who did not want to share the US tax payers largess, though there are about 30 institutes making up the NIH in 2009. This was the first institute acknowledging the complete organism and more importantly, pointing out to the eyes of the medical research establishment, that children were not 'little adults'. The creation of the NICHD would not have been possible without two other individuals, notably Dr. James E. Cooke and Eunice Kennedy Shriver, the sister of President Kennedy. It was Dr. Cooke who conceived the idea of the NICHD, but it would not have been possible without the assistance of his friend and collaborator Eunice Kennedy Shriver who had the ear of the President. As noted above, change is incremental, and perhaps the idea behind this legislation led subsequently to the establishment of the US Department of Agriculture's Agricultural Research Service Children's Nutrition Research Center in Houston, Tex., in 1978. Of the six such Nutrition Research Centers in the US, one of two devoted to the nutrition of infants and children, it was created largely by the persistence of one individual, Dr. Buford Nichols, a pediatric gastroenterologist at Baylor University Medical School in Houston [22]. It was Dr. Nichols who marshaled the resources and influence of the Texas Congressional delegation to create a publicly funded research institution for advancing pediatric nutrition.

In the 21st century, the role of pediatricians as continued innovators in pediatric nutrition will be determined by their efforts in research, education, and advocacy to effect improvement of patient care. As in the past, pediatricians do not do this in isolation but will continue to work with other health care professionals, government agencies, the media and private industry. At present, there is an alarming decrease in the efforts of pediatricians both in basic and hypothesis-driven clinical research, particularly in those completing pediatric training in recent years. This is despite many attempts by various professional groups and government agencies to reverse this trend with various incentive programs [23]. On the other hand, there are increased efforts in education, advocacy, and quality improvement in patient care. However, with less of a research component to their activities, one wonders whether pediatricians will be innovators or merely effectors of innovation in nutrition in the future.

Today, pediatricians work together with other health care professionals in many settings. Pediatricians are involved in both primary and subspecialty care in the US, unlike Western Europe where pediatricians do not deliver primary care. Typically, group practices are allied with large medical centers which often include academic departments of pediatrics with many pediatrics subspecialists in many different disciplines. In turn, pediatricians and pediatric subspecialists have organized into professional societies throughout the world, with the largest being the AAP. There are relatively few pediatricians whose primary focus is nutrition, though for many, nutrition in daily practice has expanded beyond the period of infancy given the current obesity epidemic. Many of the pediatric professional societies, such as the AAP, ESPGHAN, the SPR, and ESPR provide resources for basic and clinical nutrition research, nutritional education, and nutrition advocacy. Many of these organizations have close working relationships with larger professional groups such as the American Medical Association and the American Dietetic Association. Thus, pediatricians are good at working with other professionals to make nutrition recommendations. However, in many instances, these recommendations are based more on expert opinion rather than evidence from research including randomized controlled trials. Such research is needed to determine many pediatric nutrient requirements including the lower and upper limits of nutrients added to infant formulae. Pediatricians should strive for the true innovations that would result from accomplishing this goal.

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Discussion

Dr. Lentze: Pediatricians could be multipliers of knowledge in pediatrics, particularly in nutrition. A question I would have is how is it in the US? Are pediatricians listening to the Academy of Pediatrics and follow recommendations, because a survey in Germany has shown they don't.

Dr. Greer: We know that the recommendations of the Committee on Nutrition and the ESPGAN are not getting through to pediatricians, and there are lots of reasons for this. The number one reason that anybody joins the American Academy of Pediatrics (we know this from surveys) is for the published recommendations, believe it or not. There are a hundred different groups in the American Academy of Pediatrics making recommendations, with over four hundred statements published by the American Academy

containing recommendations. The poor pediatrician who has only a 20-min office visit with each patient cannot possibly advise his patients about all of the recommendations. To be familiar with all of the recommendations is an impossible task as well. And I also tried to make this point in my talk, that industry working through the consumer through its marketing process can get the message about specific recommendations to the parents of children. Thus, if industry supports the nutritional recommendations made by the AAP, they will get the message to the parents who will then follow the recommendations and very likely ask their pediatrician about it at the next office visit. We have seen this with vitamin D, that mother gets the recommendation from the lay press supported by private industry, and begins supplemental vitamin D for her infant.

Dr. Hernell: In Sweden, we have an ongoing discussion about clinical research and the declining trend in clinical research. Fewer clinicians are interested in research and particularly in basic science. I learn from you that the same trend exists in the US. Which solution would you suggest to that problem?

Dr. Greer: Dr. Bier has all the answers in the next talk, so I don't have to answer this one.

Dr. S. Koletzko: One short question related to Dr. Lentze's comment. Do you think that guidelines for nutritional problems are followed and respected any better than guidelines for treatment of gastrointestinal disorders?

Dr. Greer: You know that we are overwhelmed by the obesity epidemic in the US, and pediatricians keep asking me what we can do to treat obesity. We don't really have any good clinical guidelines for treating obesity, and because of this pediatricians have a great difficulty getting reimbursed for the services they render to patients regarding obesity treatment. I would like to think that the issue of nutrition is important to pediatricians, but when I look at surveys that are done by the AAP on the compliance with AAP recommendations, if 25–30% of the pediatricians follow the recommendations, that's exceptional. I would say the answer to your question is that pediatricians have trouble prioritizing recommendations, and recommendations that deal with a specific disease may have a higher priority than nutritional recommendations in patients who otherwise seem healthy.

Dr. Makrides: Can you comment on the role of general practitioners because in many countries they would be the front line health care professionals that would see most of the children.

Dr. Greer: We don't necessarily have the same system you have in Australia and Europe. Pediatricians in the US are considered primary care providers, believe it or not, and they provide primary care (not necessarily subspecialty care) to the majority of children in the US. In the US, general practitioners have their own professional organization and care for a relatively few children compared to other developed countries. In Australia and Europe, pediatricians are specialists and not primary practitioners, so are not on the front line of routine pediatric care.

Dr. Ivarsson: You really bring up an important issue here! There is a long delay before research becomes visible in guidelines (if it ever in fact does), and then a further delay before many of our colleagues are aware of these guidelines and move them into practice. You suggest going through media and the public, and I agree that might be a good strategy, but aren't there also other options?

Dr. Greer: Very few professional physician groups have the resources to promote their recommendations – hence their frequent partnering with private industry. The AAP only has the resources to publish the recommendations, but does not have the resources to promote them to the general public or further educate their members on what to do with the recommendations as a rule.

Dr. Ivarsson: I agree, there is no easy solution to the problem. However, I think lessons learnt from research on how to promote behavioral change in parents and

their children, as highlighted in a previous lecture, could partly be applicable. Also, more research on how to move from evidence to practice is needed.

Dr. Greer: As I heard this morning in another lecture, it is supposed to start at the top and I assume that's right, but I am not sure how to do that, I have been at the top for a while now, so maybe I am a failure.

Dr. Mittal: You have been associated with *Pediatrics*, so I would like to remind you about a paper on infant feeding that appeared in *Pediatrics* somewhere in the early 1970s. It said that infants continue to grow whatever the innovations. We have many innovations, but are they really of so much value to infant nutrition? I think that from a developing country point of view the very first innovation of giving enough milk and safe water might be the best innovation of all, and if the consumers, that is infants, were to have a meeting or a conference like this, they would probably all laugh at us and say what are you discussing, just give us milk and we will be happy.

Dr. Greer: Thank you very much, you heard me, that's very clear.

Dr. Gibson: I don't know whether I am pushing your argument to the extreme or not, but are you making the case that maybe a lot of these dozens of different brains are creating so much confusion that in fact we are going backwards rather than forwards, and that a little bit of common sense is required here? Are you also suggesting that maybe we should all get to work in various governments and their agencies and make a list of the nutrients that are in breast milk, and allow a certain window for each of those nutrients and just say that's infant formula, and unless we hear something different then that's what it has got to be. There is a minimum requirement there, sort of like on the line of Codex, but if we simplified it then would it destroy the infant formula industry, would it stop us moving forwards, would it be improving or worsening the health of children?

Dr. Greer: I don't know the answer to your question, I don't know how formula companies see a benefit from all these formula variations. It's hard for me personally to understand how you can make more money by making more formulas that differ very little from one another. There must be some rationale behind this because it's just absolutely explosive, as you note. I would agree that most of these new ingredients don't do any harm, so why not simply put all the new ingredients in relatively few formulas and be done with it. This proliferation of products with minor differences is confusing to the pediatrician and to the public.

Dr. Akbar: The whole world is divided into one spectrum that is obesity and another spectrum – malnutrition. How do you bring the two together and work out a uniform policy that would help reduce obesity and at the same time address nutritional deficiency disorders in children. Are there any guidelines you can suggest?

Dr. Greer: I don't have any answer to that question. Can anybody else answer? I don't know how to bring the two together to be truthful. Many developing countries now have the unique problem of dealing with obesity and malnutrition in the same population, as you point out.

Dr. Islam: I would like to know what the present status of breastfeeding in the US is and what formula the majority of people are using in the US.

Dr. Greer: So, you ask two questions. What is the status of breastfeeding in the US and what formulas do we use or recommend. The answer to the second question is easy. There is no formula that has captured the whole of the US market or anything close to it. Pediatricians are somewhat at loss with what to recommend given the broad range of choices. When I am asked by a family to recommend a formula, I tell them it really doesn't make that much difference. We have this whole industry of generic formulas in the US now which are available in large department stores like Wall-Mart and Target. Most of these less expensive formulas are also made by the major formula companies, the same formula companies who have the 'boutique', higher priced formulas.

And to your second question, I can tell you that according to the latest government CDC survey, 80% of infants in the US are on complementary feeding by 5 months of age; so, between 4 and 5 months of age 80% of the infants stop exclusive breastfeeding. No more than 20% are exclusively breastfed at 6 months. Breastfeeding rates in the US whether it's exclusive breastfeeding or not, are greatly influenced by employment practices that limit maternity leave to 6 weeks. Initiation of breastfeeding is about 75%, but once the mother goes back to work at 6 weeks we see a dramatic fall not only the in rate of exclusive breastfeeding but the rate of any breastfeeding at all.

Dr. Hernell: Just another comment on the implementation; in my opinion, in Sweden we have at least in theory, an almost ideal organization with a shared expert committee for pediatric nutrition between the Swedish Pediatric Association and the National Food Administration. That makes it easy to join efforts and implement new recommendations. Someone mentioned that media can help, but media can also be a serious problem because in many respects they are much more interested in controversial recommendations than in the 'right' recommendations. So, if they start to question the action and recommendations of, for instance, the National Food Administration, you are lost because the population at large listens more to the media than to the experts.

Dr. Greer: There is no question that there are some missteps by the infant formula industry. I can tell you that the melamine scandal in China was on the television news night after night after night. On the other hand, all of our national TV networks and most of our regional TV networks have programming for a 'medical minute' which allows for daily broadcast of general information on nutrition and health and disease; that didn't exist 20 years ago. This shows that today there is a lot of emphasis on communicating medical and nutritional information to the public which, for the most part, is good information.

Dr. Solomons: The AAP has recently suggested doubling the daily intake of vitamin D to 400 U or 10 µg. Does that represent in your mind an innovation in pediatric nutrition?

Dr. Greer: There is nothing innovative about that recommendation, nothing at all.

Dr. Solomons: But it represents a change in recommendations.

Dr. Greer: Yes it's a change, but it goes back to what we have always done even before the 1997 IOM report recommending 200 U. It should be understood that it is difficult to give just 200 U of vitamin D in the US; all the preparations for children conveniently supply 400 U. The 2003 AAP recommendation for 200 U of vitamin D was a result of compromises between the various groups within the Academy of Pediatrics some of whom did not want vitamin D to be given. But 400 U is what you find in a teaspoon of cod liver oil. The late Sam Fomon said in 1963, that 400 U of vitamin D a day will prevent rickets, and 400 U a day will treat rickets if you give it long enough, so the new recommendation does not qualify as an innovation. We do have a new IOM committee reviewing the 1997 recommendation, and there are members of the AAP in this committee to determine if new recommendations for calcium and vitamin D are needed.

Dr. Raats: A study of not just consumers' but of scientists' behavior, of all the processes for coming to agreements about things might give us insight into why things aren't changing, and what processes we have in place. Now, just a brief comment about the media. I have a little bit of evidence from some work on the folic acid campaign that was run in the UK, where we looked at the media reporting of that campaign. There was actually a distinction between two forms of media. In the UK, we have a very sensationalized press which is interested in the stories that are sensational, and we also have the local press, that is the free newspapers that come out maybe once a week and are more about lifestyle. So there are different parts in the press that portray messages in different ways.

Dr. Greer: Yes, the media loves the vitamin D story – what else prevents cancer, obesity and even rheumatic disease? The media are promoting vitamin D almost to the extreme, but the AAP has had good support from the media in promoting its vitamin D and calcium recommendations for kids.

Dr. Haschke: We all agree that the functional outcome of the breastfed and the formula-fed infant should be similar. We are still away from that, but we are working on it, and I give two examples where I don't think that 1998 is the last really scientific end point. One is the growth of infants where we can probably achieve success if we modify, for example, formulas, and the other one concerns iron and how much iron should be given to infants. Indeed, in the year 2000 there were two surveys in Europe and in the US. In the US, you had 12, in Europe we had 6–8 mg iron per liter, and the prevalence of biochemical iron deficiency and anemia in Europe and in the US at 1 year of age was exactly the same. Later, and I think this is something which we have to consider, clear indications that too much iron might be bad for growth came from Sweden, from Olle Hernell's group. Markus Dömellof has recently published this; it needs to be confirmed, but we always have to bear in mind that even though functional outcome should be the same, the composition might be different to achieve the goal.

Dr. Greer: I think the regulations for the WIC program dictate that you can have no less than 10 mg/l of Fe in infant formula in the US. This has prevented the formula industry in the US from decreasing the Fe content of infant formulas. Such a change would require legislation and you know how hard that is in the US at the present time. I appreciate the controversy but the issue of iron deficiency is really problematic. We don't really have a practical way to diagnose iron deficiency. The current laboratory tests utilized for this in most children are unsatisfactory, which has been recognized by the AAP, ESPGAN, and the WHO. Until we get a handle on diagnosing and the follow-up treatment of iron deficiency without anemia, I do not see any reason for changing the amount of Fe recommended for formulas in the US.

Dr. Klassen: From your presentation it became very clear that the major achievement in infant nutrition was prevention of death in infants that could not be breastfed.

Dr. Greer: That was achieved by safe milk and water supplies.

Dr. Klassen: And I think this is an enormous achievement. I wanted to comment on a different topic. You mentioned the use of evaporated milk as a breast milk substitute which, if I recall well, was given in the 1950s to around 50% of the infants in the US, whereas in the 1970s the number went down to maybe 5%, clearly demonstrating that the pediatric community did not consider this as a suitable substitute for breast milk. However, what has been achieved in the US a few decades ago is still a major issue in other parts of the world, i.e. the use of non-suitable breast milk substitutes is still very high even in the 21st century. When it comes to innovation driven by research, I would like to refer to Dr. Ruemmele's talk demonstrating the potential that may come with the discovery of new markers. New markers and new research hypothesis may allow to further clarify the role that early nutrition plays in long-term health. The question I have is related to malnutrition which in many countries coexists with obesity. Do you think that recommendations and legislations will be able to take into consideration a personalized approach to account for both problems? I assume that the scientific data are being established right now, so we cannot make recommendations yet.

Dr. Greer: You certainly need a lot more information. Just one final comment: there are about 2.5 million births a year in the US, of which 55% are in the WIC program and receive nutritional supplements including infant formula. Most of these infants are not breastfed by 2 months of age; thus, most of them are getting the iron-fortified formula, and almost all of them are started on complementary food before 5 months of age.

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Promoting Innovation in Pediatric Nutrition

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Abstract

Truly impactful innovation can only be recognized in retrospect. Moreover, almost by definition, developing algorithmic paths on roadmaps for innovation are likely to be unsuccessful because innovators do not generally follow established routes. Nonetheless, environments can be established within Departments of Pediatrics that promote innovating thinking. The environmental factors necessary to do so include: (1) demand that academic Pediatrics Departments function in an aggressively scholarly mode; (2) capture the most fundamental science in postnatal developmental biology; (3) focus education and training on the boundaries of our knowledge, rather than the almost exclusive attention to what we think we already know; (4) devote mentoring, time and resources to only the most compelling unanswered questions in the pediatric sciences, including nutrition; (5) accept only systematic, evidence-based answers to clinical questions; (6) if systematic, evidence-based data are not available, design the proper studies to get them; (7) prize questioning the answers to further move beyond the knowledge limit; (8) support the principle that experiments *in children* will be required to convincingly answer clinical questions important *to children*, and (9) establish the multicenter resources in pediatric scientist training, clinical study design and implementation, and laboratory and instrument technologies required to answer today's questions with tomorrow's methods.

Arguably, truly impactful innovation can only be recognized in retrospect. Further, allowing for the most expansive meaning of innovation, developing algorithmic paths on roadmaps meant to lead to innovation are unlikely to be successful because true innovators do not generally follow established routes. Nonetheless, I will take the position that academic Pediatric Departments can provide the conditions necessary to foster environments where innovation will flourish. Possible options include the following.

Correct Common Misperceptions about Pediatrics. In many areas of medical science, pediatrics is viewed as an inadequately compensated subspecialty that feeds babies, promoting breastfeeding practices and magical unproven rituals for the introduction of complimentary postweaning foods. Pediatricians are also seen as spending their time giving infants immunizations against classical childhood illnesses and providing antibiotics for largely self-limiting viral infections. Later in childhood and adolescence, they are perceived as the mediators (and medicators) of learning problems among mother, child and teacher and as the medical professional providing some psychosocial counseling to teens. These are critically necessary and highly commendable functions, and training programs would be remiss if they did not adequately prepare pediatricians for delivering these essential services. Nonetheless, I might argue that these perceptions diminish the choice of pediatrics as a career by many medical students who want to be at the aggressive, leading-edge 21st Century science. To be sure, the perception is not the reality, but we pediatricians have, apparently, not adequately communicated the opportunities of pediatric sciences to medical students. Moreover, the constraints placed on the structure of pediatric training programs by credentialing and licensing requirements (at least in the United States) are now such that the vast bulk of residency training is devoted to the practical aspects of what we 'know' (or think we know). Little time is left for development of investigative minds. Arthur C. Clarke's Second Law reads 'The only way of discovering the limits of the possible is to venture a little way past them into the impossible' [1]. To encourage the thinking that will promote young scientists' discovering innovative ways beyond the boundaries, we need to spend more time teaching the limits of our knowledge, focusing on what we do not know rather than on what we 'know'.

Pediatrics Needs to Be the Dominant Force in Human Developmental Biology. For a significant part of the 20th Century, pediatrics was the focal point for research in human developmental biology. Further, pediatricians have long appreciated that development does not end at birth, but continues throughout childhood both at the organ and system levels and in the realms of neurodevelopment and psychosocial maturation. More recently, however, the field of developmental biology has largely focused on embryonic and fetal development following dramatic advances in the fundamental molecular regulation of the developmental processes in these areas. Most of the work takes place outside of pediatrics. Further, Departments of Pediatrics have been slow in capturing a dominant position in uncovering the basic processes of postnatal development and investigating the direct consequences of aberrant developmental regulation on the pathobiology of adult diseases, a now well-recognized phenomenon [2–7]. Thus, pediatric scientists need to take the lead in promoting recognition of the fact that development does not end at birth and in developing the investigative tools that will allow us to discriminate real developmental programming effects from the pari passu changes in

age and size, etc. Furthermore, since the development of behaviors in childhood has profound consequences on attempts to modify behaviors both during childhood and later in adult life, pediatric scientists must (a) promote the growth of the developmental behavioral field in pediatrics and (b) apply the same level of fundamental science and scientific methods within the field of childhood behavioral development. From the perspective of pediatric nutrition and in the context of the Worldwide prevalence of obesity, basic scientific data on how appetite, satiety and food preferences develop in childhood and are modified (or not) as the child progresses into adulthood are woefully limited.

Ask Compelling Questions. Jacob Bronowski said 'that is the essence of science: ask an impertinent question, and you are on the way to a pertinent answer' [8]. Steve Butler likewise said that 'behind every great answer is a greater question' [9], a proposition that I firmly believe. As a complement, I also argue that mediocre questions attract mediocre scientists. The quality of the question drives both the quality of the scientist as well as the quality of the innovation. Furthermore, it is likewise the obligation of senior mentors to foster the development of great questions by trainees. In an New York Times interview [10], Tim Brown, Chief Executive Officer of IDEO is quoted as saying '... you don't know where the best ideas are going to come from... so you'd better do a good job of promoting them when they come and spotting them when they emerge... I've gone to great lengths to encourage what I call an emergent culture... where people understand that it's essentially their responsibility to have good ideas... If you're focusing on the wrong questions, you're not really providing the leadership you should... the great leaders... somehow had the ability to frame the question in a way nobody else would have thought about' [10].

Question the Answers. Limit complacency with one's findings, especially if they agree with one's preconceived notions. Philip K. Dick addressed this issue when he wrote 'Reality is that which, when you stop believing in it, does not go away' [11].

Incisive answers always lead to new compelling questions. Bernard Haisch said 'Advances are made by answering questions. Discoveries are made by questioning answers' [12].

Question the Experts. Expert opinion is at the lowest level of an evidence-based hierarchy. Almost all expert committee reports and narrative reviews currently fall into this category. In 1931, during the rise of Nazi Germany, Albert Einstein was criticized in a tract entitled 'One hundred authors against Einstein' [13]. In his now classical response, Einstein replied 'If I had been wrong, one author would have been enough' [13].

Provide an Environment That Allows for Mistakes at the Cutting Edge. One cannot expect to extend the limits of current knowledge without making mistakes while trying to push through the boundaries. Innovation requires risky hypotheses. In turn, taking risks will surely lead to some mistakes.

These should be viewed as learning opportunities rather than failures. Niels Bohr said that 'An expert is a man who has made all the mistakes that can be made, in a very narrow field' [14].

Don't Settle for Maybe. Follow Mark Twain's dictum 'Supposing is good. Finding out is better' [15]. It is difficult to do research in children for both ethical and practical reasons. For those reasons, one should be committed to convincingly answering the questions asked in any pediatric clinical research study. In the era of evidence-based medicine, it is neither adequate nor ethical to conduct underpowered studies with inadequate primary end point variables. Similarly, one should exercise caution about underpinning theory or driving practice with observational data. Associations uncovered in such studies cannot prove cause and effect, but only suggest 'maybe'. As Werner Heisenberg stated '...since the measuring device has been constructed by the observer... we have to remember that what we observe is not nature in itself but nature exposed to our method of questioning' [16]. C-reactive protein (CRP) provides an example of how the method of questioning exposes different views of Nature. The literature is filled with observational studies showing the association of elevated CRP, a marker of inflammation, with an increased risk of heart disease, cancer and other pathological end points. Causation is often implied. When, following Mendelian randomization that takes advantage of common single-nucleotide polymorphisms that result in elevated CRP levels, cardiovascular and cancer risk data are observed from the different perspective, it becomes clear that elevation of CRP per se is not associated with ischemic heart disease or cancer [17, 18]. Thus, it is highly unlikely that elevated CRP levels themselves are causal agents in the increased risk observed in traditional observational studies. The fundamental principles of scientific evidence are the same in all the sciences. Among these are an explicit question, an explicit end point variable, isolation from confounding variables, randomization, intervention, replication and prediction. Pediatric clinical studies should be devoted to providing the highest grade evidence possible from every experiment conducted in children. Often, randomized controlled trials or meta-analyses unmask results that are contrary to conventional 'wisdom' and are heavily critiqued as not being too narrowly defined for decisions in related clinical circumstances. However, if a randomized controlled trial or meta-analysis is properly designed and conducted, the answer is correct *for the specific question asked.* If clinicians want the answer to a different question, they should design a similar study that is specifically directed at the question they want answered, providing new data for integration rather than merely critique of properly collected data that does not address their question.

Provide an Environment That Supports Research in Children. Based on the scientific hierarchy of evidence, it should be obvious that one can not be convincingly sure of answers to clinical questions in children without doing experiments *on children*. Why should our standard for evidence in children

be less than that in adults? I am not suggesting that children be subject to unnecessary risk, but, in my opinion, there is a current prevailing atmosphere that has set the bar of 'minimal risk' so low that it is almost impossible to conduct many safe experiments, or obtain the minimally invasive samples, necessary to convincingly answer important questions.

Improve the Quality of the Methods Used in Nutrition Research. Arthur C. Clarke's Third Law states that 'any sufficiently advanced technology is indistinguishable from magic' [1]. Few nutrition methods are magical and few fields of fundamental biology today use methods as old as many that are routinely used in nutrition research. 20th Century methods lead to 20th Century answers. While many tried and true methods remain appropriate for certain questions, old methods often address a level of what was once mechanism but is now only upgraded phenomenology, providing now new insight at the current level of mechanism. Furthermore, few, if any, cutting edge fields in biology propose 'validating' demonstrably inaccurate and imprecise methods against other demonstrably inaccurate and imprecise methods, a practice common with, for instance, various dietary intake instruments used in nutrition research.

Since most of the 'action' in biology occurs within cells rather than in readily accessible compartments like the vascular system, focus should be on methods that interrogate inaccessible compartments noninvasively. These include magnetic resonance spectroscopy and functional imaging methods such fMRI, along with corresponding stable isotope tracer approaches that employ compartmental modeling [19]. Additional investment should be made in nutrigenetics, nutrigenomics, metabolomics and epigenomics [20], all new approaches that will help clarify the basic systems biology of nutritional regulation of metabolism and function. One goal of nutrigenetics is to use information on DNA sequence variation to elucidate nutrient gene interactions and permit better identification of variable individual responses to diets. Nutrigenomics and epigenomics will allow dissection of how environmental signals (i.e. food, in the case of nutrition) are transduced to alter gene expression [20]. One ultimate goal is individualized nutrition, although one must be only cautiously optimistic. For example, the promoter region of a single gene, the phosphoenolpyruvate carboxykinase gene, contains an exceedingly complex number of regulatory elements [21, 22]. It is difficult to fathom, then, how one might untangle the unimaginably immense complexity of regulatory interactions that might occur among all nutrients and all genes of the human body to arrive at individualized solutions.

Unfortunately, many Departments of Pediatrics and Departments of Nutrition do not have the financial resources necessary to upgrade the technologies available within the Departments. In 2008, only 23 Departments of Pediatrics in the US received more than USD 10 millions in research grants from the NIH, and 20 received less than USD 1 million. [23] Similarly, only two university Departments of Nutrition received more than USD 10 millions

in research funding from the NIH in 2008, and most were awarded less than USD 5 millions [23].

Invest in Multicenter Resources. Given the tools necessary to answer 21st Century questions with 21st Century methods and the limited instrumentation, intellectual capital, and subjects available within most individual Nutrition or Pediatrics Departments, it is imperative that such departments invest in the development of multicenter resources that complete and complement the resources available within a department. First, these investments should be directed at developing resources to train pediatric nutrition scientists, since very few individual Departments of Pediatrics have the basic science intellectual capital resources necessary to train such scientists at state-of-the-art levels. Secondly, shared investments should be made to develop or support technology resources that include the instrumentation for the technologies mentioned above, as well as high throughput sequencing, bioinformatics, nutrient biomarkers, and related new methods for answering fundamental questions in nutrition. Third, since few individual Departments of Pediatrics have access to the number of subjects/patients necessary to convincingly answer most outstanding clinical nutrition questions, it is also imperative that multicenter clinical subject resources be promoted, along with the necessary statistical, bioinformatics, core laboratory, safety monitoring and compliance resources required to conduct the large-scale clinical studies that must be done to confidently settle nutritional questions important to the healthy growth and development of children.

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Discussion

Dr. Ivarsson: I want to come back to the question you raised about different study designs. I agree that experimental studies as randomized control trials are terribly important. However, it is required that all studies, regardless of design type, are carried out with a high quality in every step, which is not always the case. In the field of pediatric nutrition, a lot of knowledge could still be gained by using an observational study design. I am thinking of both observational analytical studies as the case-referent and cohort designs, as well as the ecological design with aggregated data. I agree that the ecological design can never prove causality, but it can be used to generate hypotheses and thereby push research areas forward. In my opinion, observational studies in general are underutilized, and that is especially true for the case-referent and cohort designs. Observational study designs take advantage of the heterogeneity within and between populations both with respect to exposures and outcomes, and through collaborative studies across several countries, and even continents, we could increase knowledge in several different research fields, and also within pediatric nutrition.

Dr. Bier: I don't disagree with that, but at the end of all of those kinds of studies what you have is a hypothesis, and that's great. So you don't get causality, and if you sell it as associations and a reasonable and highly plausible hypothesis, that's fine; but what is done pretty much by the press to a great extent but also among a very large number of serious epidemiology departments, for example, is to say 'it's only an association, of course it's not causal', but you wouldn't be interested in associations unless you thought it was causal, otherwise who would care? So it's sold frequently as causal.

Dr. Ivarsson: I don't completely agree. Epidemiological observational studies, especially with the cohort design, can also allow for causal inferences provided they are analyzed with advanced biostatistics and taking knowledge about biology into account. Then, it is possible to draw causal inferences. I would argue strongly for that.

Dr. Bier: Causal inferences, yes, the key word there is inferences, I agree with that. And, by the way, advanced statistics to me may have a different meaning than to you. It means I need complicated mathematics to make a more complicated model to fit what I found the associations to be.

Dr. Singhi: I think you raised the very important issue of how to get young pediatricians into the research. I fully agree with you that we should let them ask questions, and even if they are absurd sometimes they would raise some very pertinent researchable issues. The question that I have is how in a particular department of pediatrics you would involve young pediatricians to get into the research in a concrete way. Would you give them a direction in a particular field of research or you would let them develop their ideas, because first you have to start with one department and then probably move on to network training, you have to have this trend to have that network absorbed into that research.

Dr. Bier: Thirty years ago, in American departments of pediatrics the house staff trainees had time to connect with a particular specialty mentor to undertake small research projects, and it was very common to have residents leave their residency with a publication or things of this sort. The way the boards have been restructured now, they require almost every minute of the resident's time to be taken up by the necessary clinical care activities, so there is no time anymore for that. The residents who do it, and there are some, do it on their own time. But that's what has been missing, we have lost this, so it's very hard now to get fellows who have had some exposure. It seems to me that the main job of the pediatric faculty member is to identify the resident who seems to be interested in his/her specialty, who is interested in how he/she works and then start discussing together what some of the really compelling questions are and the possibility to design a fellowship for that purpose. You have to get them interested.

Dr. Singhi: Would you say that there are grants given for doing research?

Dr. Bier: Again, I can only speak for the US. I haven't been on the subspecialty board, but my former department chairman who is one of the most aggressive research chairmen in the country, told me repeatedly that he could not get a change in this when we needed some residents to be more engaged in doing research. Now if he was unable to do that, it has to be very hard to do, Dr. Greer do you want to comment on that?

Dr. Greer: The fellowship training programs in the US are a miserable failure right now in getting young investigators into research. We stress during their training that they have to produce a significant publication, which almost never happens even though it is a requirement. It's similar with residency training programs; the residents have little to no time to participate in a significant research experience given the limitations in the time they can actually work. Their clinical training consumes all of their time. It's pathetic, and yet the regulations and requirements for training keep increasing; at the same time the total number of work hours continues to decrease.

Dr. Bier: The way this has been happening over the last two decades or so has created a level of junior faculty in many departments who have no research funding because they went through the system so they can no longer support the fellows who are coming to do the new research. We have already a serious research gap in pediatrics, and unless it's changed we are going to be in big trouble, and if we are already in trouble we are going to be in real trouble in a little while. I don't know if other people in other parts of the world would speak on this because my experience is only limited to the US.

Dr. Gibson: The NIH grants in the US are way smaller than I thought they were, and if you did a quick calculation you could see that each project was probably in the order of USD 200,000 or 300,000 which you can do very little with, we have had experience with that. The other thing you have highlighted that I was really impressed with is the sort of the mythology about nutritional research. You can't randomize breastfed babies for example; you can within breastfeeding of course, and you can do things to give the mother supplements, which we have done, and do that sort of randomization. There is a general laziness that I find in nutrition research, where people say you can't do that because this is nutrition, it has to be an open study, and then you end up with the sort of data that you are talking about. Finally, you have highlighted the very real gap that's opening up between the clinician and the scientist, and we've had a hard time trying to attract clinicians into our projects for the very reasons that you have outlined. I know that clinicians who are actively working in research have the same trouble attracting scientists, but the marriage is absolutely essential, that we have both arms going, and I always despair when I start hearing about research institutes wanting their own buildings; I want to see them embedded in hospitals where you can see where the need is.

Dr. Spieldenner: Taking the role of a policy advisor, I would be puzzled after the last two presentations as hardly any recommendations and guidelines got through to those who have to implement them, that the research done in the last 20 years did not lead to any real innovation and that not enough money was put into this field. In conclusion, it would be hard for a policy advisor to recommend to put resources into a science that does not create real innovation and communicate its results to the people.

Dr. Bier: I think that we have done a little bit of that. Frankly, I think it's potentially important to have these micro-manipulations of infant formulas and all of that sort of stuff, but that's not going to drive the cutting edge of pediatric research. Several people in this room are doing longitudinal studies which will give us answers to things that will happen over time, but we are left with all sorts of hypotheses in pediatrics for which there are no hard end point variables. We now have the whole issue of developmental programming, where we had initially no clearly plausible mechanistic data. Then, in animals we got a variety of really good mechanistic data that have you believing that these things are possible. Now we have to determine whether these mechanisms apply in humans. But how are we going to do those experiments? We are not going to find out by association.

Dr. Solomons: You have made some both on the record/off the record comments about the certainty of findings which has to do with reproducibility that are provocative, and as a matter of fact I very much support that statement. However, I want to question the motivations and the reward system that we have. Publishing the same findings twice has certain probabilities in the reward system we use for publications, so if we use the standard it should be published twice, the first time was outstanding news and discoveries, but who is going to publish the paper the second time, especially if it's a negative finding on both occasions? That's the publication issue, where will we find that mechanism for the reproducibility that adds the confirmation that needs us to go forward.

Dr. Bier: I think it depends on the nature of the question and how important the answer is to society. Some of the negative homocysteine trials were published in *The New England Journal of Medicine*, *JAMA*. Reproducibility of a relatively minor observation may be important ultimately to science so that we know it, but that is not going to necessarily compel getting the second paper published. However, there are lots of observations that are so important to human society or nutrition or health that they will.

Dr. Solomons: Let's go to the second part, which has to do with motivation for how we give rewards both in commercial innovation, industry let's say, and how we

give rewards in what you and I do, which is academics, and there we have your recommendations for science which costs more than the aggregate NIH for instrumentation. That's where I think it runs into big trouble. We need to have the investment from capitalism's wealth and a socialist ethos for the distribution of its access. I am often frustrated with my close friends from one industry or another who say we have got to get more market share rather than their collaborating with their resources to something which I think is compelling. The academic side has to do with asking the question that gets you promotion, recognition and otherwise, and sometimes the question is tied to the use of, for example, the MRI. My suggestion there, the socialist ethos, is that if there are people in Bangladesh or Philippines who have a compelling question and you have the MRI, what's the access of their to use it since it is a very expensive apparatus that could be very useful when they've come across the compelling question but certainly could not have the access to this technology?

Dr. Bier: If the study can be done by having samples of something run in the US, I say that there is access. Having run resources where we have people from all over the world using these things, I don't think that's an issue. Again, the people who run the resources are interested in the quality of the question. They get requests all the time to use their instruments, and they say 'why do I want to use it for this, this isn't worth the answer'. If the answer is worth it, people find a way to do the samples. But there are a lot of MRI studies where you have to find a way to get the instrumentation and the resources in the place where the study can be done. Most big medical schools realize that having instrument resources brings in grant money. Bringing grant money pays salaries, pays overhead. The more grants you have, irrespective of what else you do for the university, that makes university happy, they build the resources. It's not any different than other kinds of businesses.

Dr. Cooper: Certainly, part of the problem is almost a complete lack of funding within countries for research in many developing countries. Speaking from South Africa which is, I think, by far the best resourced country in sub-Saharan Africa, the amount of funding we can get from our equivalent of the NIH is absolute peanuts. To do proper research, it has really become necessary to depend on collaboration with funders from outside of the country and from the developed countries, and only a few researches have really got to the point where their research profile is good enough to be able to attract that sort of funding. Although we have been talking about whether the study done in North America is applicable to China and so on, my experience in a fairly multiethnic country is that there are far more similarities than differences. Therefore, I would urge people in this room and beyond to look for partners in developing countries because I think there are very important questions that can be asked in those countries that will still have major relevance to all parts of the world.

Dr. Bier: I think that it works both ways though. I think that many investigators in the US would not be aware that there is a population available in a developing country that would answer a question that might interest them. They are generally not going to go out searching, but suppose that there is a unique set of populations and nutritional circumstances in South Africa that will tell us for sure the answer to X or Y. Bring that to the people who may be interested in the answer, it works both ways.

Dr. Lönnerdal: I would like to bring up one issue which I am sure you are aware of but I would like to emphasize here since we have been talking about the age period of 0–6 months. I have been on NIH grant review panels, program project reviews, the USDA human nutrient requirements grant panel, etc., and it is very difficult to get any funding for that age bracket because in most of the studies what we would like to compare is breastfeeding, which has basically no commercial interest behind it, and the alternative is formula feeding, and that is of commercial interest. Therefore, colleagues of mine on all these review panels basically would downgrade the priority and

say this should be funded by the formula industry. So very little of this funding would go to that particular age bracket. I think that in the US one of the dilemmas is that we don't yet have these partnerships that we see in some of the European Community countries, and in Australia. There, you have partnerships between industry and non-profit organizations or governmental institutions. I think we need larger initiatives and better funding to do this.

Dr. Bier: There are areas of all sciences that are harder or less hard to get funded. In the case of those issues, it's a question of how important the answer is that we need to know, that we need to spend the money on, and that's a value judgment by the people who give out the money.

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Conclusions on Innovation in Pediatric Nutrition

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Also on behalf of *Sibylle Koletzko* and *Frank Ruemmele*, I would like to give you a summary of some of the thoughts, and messages that we have understood during this workshop. Over the 3 days, we have discussed innovation, creating new ways in doing pediatric nutrition, improving pediatric nutrition, promoting through nutritional intervention health and well-being of infants and their families at affordable cost, and we tried to look at a variety of factors that modify innovation or may modify innovation with respect to infant feeding and clinical nutrition. For some of us whose hearts are really in pediatrics, it may have been sometimes a bit of an abstract and dry process because much of the discussion was not as close to our usual excitement about patient care, about clinical research that we see at other meetings, but still it was really stimulating and worthwhile.

We started with some thoughts on where we come from and where we are heading. We thought that breastfeeding is still the most recommended way of feeding babies even though it's not an innovative approach to feeding babies. We have looked at some innovations since the 19th century. We identified some major driving forces here, the understanding of human milk composition, the description of a clinical problem, the use of current food technology and the evaluation of effects. We concluded that for a number of innovations that have occurred, there is a very good description of safety of biomarker effects, but sometimes not a fully satisfactory description of effects on relevant end points. We also noted that some innovations that appeared to be relatively recent had in fact already been introduced many decades ago. Closer to breast milk appears not to be sufficient anymore as a guiding motive. Innovation in infant feeding should rather look at beneficial effects on outcomes, child health, well-being, or otherwise the benefit and safety of innovation should be evaluated independently by thorough process and preferably

prior to its introduction on the market. If we want to achieve good progress in innovative steps forward, we probably need good collaboration of academia, small and medium enterprises that often have more innovative potential and large industries. This would probably also benefit a lot from public research funding. And again, one important goal of innovation is not only to produce better and more expensive products but also affordable quality products that are also accessible to less privileged populations.

Bo Lonnerdal gave us a wonderful overview of opportunities for improving formula based on understanding of human milk physiology. He looked at balanced supply of fatty acids, the use of certain probiotics or certain prebiotic oligosaccharides, he looked at cytokines and growth factors and the potential role of milk fat globule membranes or components thereof, and again he emphasized the importance of looking at infant outcomes, for example microflora, immune function, occurrence of infections, allergy and obesity. He also emphasized that it is not only nutritional science that matters but also food science and technology, and presented to us his very impressive arguments that the form of formula, whether it's a powdered or liquid ready to use formula, makes a dramatic difference in the bioactivity of some components.

Sibylle Koletzko addressed enteral nutrition and emphasized that enteral nutrition should be understood both as tube feeding of sick children and as oral feeding of special formulations of food for special medical purposes. She gave us a number of examples of such special formulas and their potential use. She told us that most patients are adequately fed with standard formula with age-adapted composition, generally with fiber, and only a minority of patients – those with food intolerance, chronic diseases and special nutritional needs – require specialty formula. *Sibylle* looked at pharmaconutrition and immunonutrition, and concluded that benefits have been shown in selected adult populations, but there is no conclusive evidence of benefits in children as yet. She looked at exclusive enteral nutrition in Crohn's disease and told us this is really the first choice of treatment in pediatric Crohn's disease. It achieves remission equal to steroid treatment but with mucosal healing, improves growth and bone development, and she concluded that from the data available we have no basis to conclude that one formula is better than another.

Frank Ruemmele gave us a stimulating insight into the area of nutrition and genes, looking at nutrigenomics, that is how nutrition affects short- and long-term function health through modulation of gene expression, nutritional epigenetics modifying gene expression particularly by nutrition in the perinatal period, switching genes on and off for long periods of time, and finally nutrigenetics where genetic variation between individuals modifies required or desirable dietary intakes. He gave us a few examples, the example of folate metabolism where polymorphisms of the MTHFR enzyme change the metabolism of folate, the risk of neural tube defects and folate requirements, and

he also talked about the polymorphisms in fatty acid desaturate genes which have a strong effect on PUFA metabolism and have been associated with the cognitive effects of breastfeeding and with allergy end points and appeared to modulate PUFA requirements in different people. One in 4 Europeans has a single nucleotide polymorphism profile that provides a low activity of conversion. That might lead us to personalized nutrition. Could we imagine that in the future we take a blood sample before we enter the supermarket and then chose our food?

Anneli Ivarsson has shown us the data on the celiac disease epidemic where changes in recommendations with introducing gluten later at higher doses led to a dramatic threefold increase in celiac disease incidence, and reversal of the recommendations was associated with a decrease in the incidence again. She showed us other data also associating timing of introduction with the health end points celiac disease risk, diabetes risk, and wheat allergy risk, and this along with similar data on allergy risk has led to a changing paradigm in complementary feeding recommendations in affluent populations. There are now clear recommendations in Europe and the US that complementary feeding should be introduced between the age of 17 and 26 weeks in all infants, including those at increased risk for celiac and allergic disease risk. We have discussed that here there may be room for considering that the same recommendations are not always appropriate for the whole population in the world. In populations with high diarrhea risk, there is clearly a need to promote long exclusive breastfeeding to reduce significant morbidity and mortality risk, whereas different recommendations should be considered for other populations.

Mario Ferruzzi gave us some insights into food technology. Those of us who look at nutrition science perhaps often underestimate its role. Food technology is extremely important for translating the nutritional research idea into products using ingredient technology, formulation strategies, technologies of processing and also packaging. We have discussed that quality assurance and quality control, shelf stability, ingredient safety and regulatory aspects are of key importance. Here, questions such as process and storage behavior, delivery characteristics affecting bioavailability and metabolism and costs are critically important to achieve benefits of new and innovative products.

We had two papers looking at malnutrition. *Peter Cooper* showed us the dimension of the problem and that was picked up again by *Jörg Spieldenner*, and we were shocked to hear that every 6 s one child dies from hunger-related causes, it's a dramatic figure. You have seen the figures around the world with particularly high numbers in sub-Saharan Africa but also very high numbers in Southeast Asia. Even in China, 5% or more of the childhood population is malnourished, so a large number of children are affected. *Peter Cooper* told us that some simple strategies appear to be effective in preventing and treating malnutrition: exclusive or predominant breastfeeding unless there are contraindications, appropriate foods for infants and young children. He

told us about the success of the ready to use foods that are now also increasingly produced locally and addressed some of the open questions that exist here. He addressed the vicious cycle of HIV infection resulting in malnutrition and then malnutrition further impairing immunity and aggravating malnutrition even more. Prevention of mother to child transmission of HIV can be achieved using antiviral treatment, and a particular challenge in some poor parts of the world is to have adequately trained staff ensuring implementation of such measures. *Jörg Spieldenner* addressed particularly the health economic impact and the questions how do we translate thoughts into practice. He emphasized that a number of interventions such as fortification of foods or the use of ready to use foods are extremely cost-effective; it's a very small amount of money that is needed to gain one disability-adjusted life year, so it's one of the really worthwhile investments to do. He addressed success factors for food based on nutritional supplement strategies, political will and commitment, embedded in the cultural preferences (we've heard about examples of failed attempts to implement western concepts in other parts of the world), partnership with the food industry as well as governments, production, distribution, the right economic aspects, monitoring and evaluation. He addressed sustainability, public and political attention and critical subgroups that are hard to reach.

Jürgen John discussed the economic aspects of the other extreme – overweight and obesity. He told us that there are quite good data now showing that adult obesity, especially the more extreme forms of obesity, have a cost tag attached to it, both direct medical costs and loss of productivity. However, it is unclear whether the lifetime cost of obese people is actually higher because obesity is associated with shorter life expectancy. For pediatrics, that question is not as easily answered. He told us the strongest evidence for incremental cost of obesity exists in older children above 14 years, particularly in girls. If one assumes that most obese children will remain obese in adulthood, then one would assume they have also higher health care costs in adulthood than normal-weight peers. So, one would expect that there is an increased cost over lifetime, but we have a number of open questions and more work is clearly needed. He also emphasized that paying for obesity is a changing landscape and the ensuing costs influenced by a lot of modifying factors.

Ferdinand Haschke looked at health and cost implications of dietary products and conditions of marketing. He looked at lower protein content in infant formula which was shown to normalize early growth and perhaps might reduce later obesity risk. This still needs to be shown. If it does, then major cost savings are possible. He calculated the savings for the US to be in the order of USD 2.7 billion per year. He also looked at the relative cost of moderately hydrolyzed versus extensively hydrolyzed protein for preventing atopic eczema, and since the preventive effects of both products are comparable, there would be considerable cost savings if one used the cheaper product. He gave us a shocking example of misleading direct consumer formula market-

ing and emphasized that in line with WHO code of infant formula marketing, direct formula marketing to consumers should not be tolerated. I think it is also the responsibility of health care professionals and pediatricians to move this goal forward. He looked at the relative roles of economic impact and business decisions, marketing and research development, gave us examples of companies where marketing is the dominant strategy and research and development is not very relevant, and gave us hope that other companies are trying to place more emphasis on research and development. He presented some figures from his own company where there has been a fourfold increase in the budget for research and development in a few years time only. We anticipate with interest the progress over the years to come in different companies around the world.

Maria Makrides gave us a wonderful review of the history of scientific evaluation of long-chain polyunsaturated fatty acids from observation of effects on electroretinograms in rats to visual acuity in primates, electroretinograms and later visual acuity first in preterm infants, then in term infants. Then, moving on to developmental outcomes such as cognitive development, motor development and also immunity, she described early concerns of growth effects which were later dismissed based on better data with different interventions as well. She described the importance of doing animal and human studies in tandem and of moving from biochemistry to function and from small underpowered studies that were done in the beginning to large and conclusive randomized clinical trials. I think the story of LC-PUFA evaluation has told us a lot about the evaluation of formula innovations overall. Maria told us that preclinical studies provide indication of likely effects, mechanisms and preliminary safety, and that they inform us whether investment in large-scale trials is worthwhile. Large-scale trials may be best achieved through a nationally competitive government funding, or in the European context through international and European funding as well, with industry partnership, which has the advantage of preserving independence and focusing on the clinically relevant main questions and giving the clinical researcher the driving role. This approach also increases the chances of publication in a high-impact journal and achieving credibility. She also stated that too many resources are spent on biochemical and physiological studies, which I believe could be further debated.

Ambroise Martin gave us a wonderful review of the somewhat foreign territority of claims, regulations and the complex issues that exist there. He showed us data demonstrating that claims actually may influence consumer behavior, purchasing intention, information on ingredients and nutrition labeling. They are probably efficient marketing tools, but the real impact is not very well known, particularly with regard to children. He described the different types of claims on food, nutrition claims, function claims, health claims, disease reduction claims, and showed us some examples of recent health claims accepted for children where these nutrients were accepted to be needed for normal growth and development.

Monique Raats examined variables modulating infant feeding choices, the influencing factors which are important for the mother in making her choice for this or that concept of infant feeding. She looked at some studies on breastfeeding and formula feeding, and told us that in some studies mothers reported that they are not receiving the desired support on breastfeeding from health professionals, that there is a need to improve the situation here, and also added that this is also true for formula feeding. While increasing breastfeeding rates and duration is important, it is also important to minimize risks associated with bottle feeding by providing adequate information and support on safe preparation and handling.

Noel Solomons looked at ethical aspects. He told us, innovation and progress are driven by technology and by societal rules, including bioethics, where a set of society principles for ethical conduct and their operational system is needed with international review boards or ethics committees, informed consent, data safety and monitoring, and clinical trial registries. He told us that we are of course particularly concerned about vulnerable groups including pregnant women and children. He addressed values, conditions and characteristics that members of the society consider important (not always is there consensus on these values in one and the same society, let alone across societies), justice and interest among different stakeholders. He raised the question whether infant feeding as well as drug science may be distorted by commercial investments and by regulatory requirements. He said that legitimacy and fairness are important in setting priorities, and showed that intellectual property is used to promote development of and access to products to address global health disparities.

Frank Greer gave us a rather critical presentation on the role of pediatricians and health care professionals. He told us that innovations must be beneficial so that we have an improvement in what is current practice. However, a number of so-called new innovations are a major factor in inducing unsustainability of health care and also increasing the cost of dietary products. A major progress in pediatric nutrition over the last century in the US has been the provision of safe and adequate infant feeding. But innovations are usually incremental and not evolutionary, often achieved by collaboration between pediatricians and industries, and he challenged most new additives to infant formulas since 1980 as being of questionable benefit to healthy babies. He said that while some indications or theoretical arguments support benefits of these additions, there is no consistent demonstration of short-term and long-term functional outcome benefits while these formulas are of course on the market today. Regarding the future role of pediatricians, he wondered whether pediatricians would continue to act as innovators in nutrition determined by research and education to improve the nutritional state of children; will they be in the position to work with all the health care professionals, government agencies, the industry and the media or will they have a declining interest in basic science and clinical research and only be followers rather than drivers of innovations?

Dennis Bier gave us a wonderful and stimulating talk on ways to strengthen pediatric nutrition research, make pediatrics a more aggressive academic specialty, take it back to basic physiology, developmental biology, fundamental scientific questions, teach the boundaries of knowledge and focus on what we don't know rather than what we know, ask compelling questions, and improve the quality of the methods. He also emphasized that many pediatric and nutrition departments do not have resources to upgrade technologies, and perhaps the solution would be strengthened collaboration.

I should like to thank you all for your attention, the thoughts and comments that all of you had and many of you introduced into the discussion, the speakers for the presentations and even more importantly for their manuscripts. We would like to thank the Nestlé Nutrition Institute, *Ferdinand Haschke*, *Petra Klassen Wigger* and their team for making this all happen, and of course Nestlé and the Nestlé Nutrition Institute in China with *Patrick Levieil*, *Lois Lin*, *Lawrence Li*, *Spring Li* and the whole team who have done an absolutely fantastic job in getting this workshop going.

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