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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.