Personalized Nutrition for the Diverse Needs of Infants and Children
Personalized Nutrition for the Diverse Needs of Infants and Children

Editors

Dennis M. Bier, Houston, TX, USA
J. Bruce German, Davis, CA, USA
Bo Lönnerdal, Davis, CA, USA
Contents

VII  Preface

XIII  Foreword

XVII  Contributors

Biological Diversity in Human Infants

1  Developmental Perspectives on Individual Variation: Implications for Understanding Nutritional Needs
Gluckman, P.D.; Beedle, A.S. (New Zealand); Hanson, M.A. (UK); Yap, E.P. (Singapore)

13  Factors Influencing the Establishment of the Intestinal Microbiota in Infancy
Adlerberth, I. (Sweden)

35  Genetically Determined Variation in Polyunsaturated Fatty Acid Metabolism May Result in Different Dietary Requirements
Koletzko, B.; Demmelmair, H.; Schaeffer, L.; Illig, T.; Heinrich, J. (Germany)

Assessment Technologies for Human Infant Health

51  Discussion on ‘(Molecular) Imaging: Developments Enabling Evidence-Based Medicine’
Hofstraat, H. (The Netherlands)

55  Metabolic Profiling
Berry, G.T. (USA)

81  Newborn Screening of Metabolic Disorders: Recent Progress and Future Developments
Contents

Health Challenges of Human Infants

97 The Phenotype of Human Obesity: The Scope of the Problem
   Bier, D.M. (USA)

111 Intestinal Immune Health
   Conroy, M.E.; Walker, W.A. (USA)

127 Gut Decontamination with Norfloxacin and Ampicillin Enhances Insulin Sensitivity in Mice
   Chou, C.J.; Membrez, M.; Blancher, F., (Switzerland)

141 Individual Epigenetic Variation: When, Why, and So What?
   Gomes, M.V.; Waterland, R.A. (USA)

157 Interaction of Early Infant Feeding, Heredity and Other Environmental Factors as Determinants in the Development of Allergy and Sensitization
   Savilahti, E. (Finland)

173 Personalized Care of Pediatric Cancer Patients
   Rabin, K.; Man, T.-K.; Lau, C.C. (USA)

Opportunities for Improving Human Infant Nutrition and Health

189 Personalizing Nutrient Intakes of Formula-Fed Infants: Breast Milk as a Model
   Lönnerdal, B. (USA)

205 Human Milk Oligosaccharides: Evolution, Structures and Bioselectivity as Substrates for Intestinal Bacteria
   German, J.B.; Freeman, S.L.; Lebrilla, C.B.; Mills, D.A. (USA)

223 Opportunities for Improving the Health and Nutrition of the Human Infant by Probiotics
   Salminen, S.; Isolauri, E. (Finland)

239 Do We Need Personalized Recommendations for Infants at Risk of Developing Disease?
   Hernell, O.; West, C. (Sweden)

253 Concluding Remarks

257 Subject Index
Preface

The field of nutrition is building the basic science necessary to produce a revolutionary shift in agriculture and public health, moving from dietary guidelines for populations to foods and diets for individuals. Considerable epidemiologic and mechanistic research has documented that humans respond differently to diets and display varying predispositions to many diet-dependent metabolic and degenerative diseases. The field of nutrigenomics is emerging with the goal of assigning this human diversity in nutritional response to diet and the subsequent consequences to human health to specific genetic elements. At the same time, breakthroughs in our understanding of developmental biology and the importance of diet to early human maturation and lifelong health have emphasized that diet is itself a critical determinant of human diversity. These two major emerging trends in nutrition converge on one life stage and one issue: how different are humans as infants and children with respect to nutritional needs and responses to diet? International experts in various fields whose research work interfaces with the nutrition of infants and children came together in Helsinki, Finland, for a workshop to address this critical subject to human health. The workshop focused on 4 clear questions.

How do children differ?

The first scientific issue addressed by the workshop was the most fundamental and yet the most bold: how do children differ? Just how much diversity is there in the human population as infants and what is the nature of important differences with respect to dietary needs? This question was separated into various determinants of biological variation: genetic diversity; environmental inputs; prior imprinting, and resident microflora. Unquestionably there are important genetic variations among humans that lead to unique nutritional requirements. The issue is how many children in the population experience deleterious consequences in their immediate and long-term health due to diets unmatched to their genetic makeup? Surprisingly with the tools of modern genomics it can be seen that many infants and children are distinguishable as genetically at risk for particular diets. From the well-known disease phenylketonuria to inborn errors of metabolism and genetic predispositions for allergies, although the absolute proportion of the population is small, the numbers of children affected are significant.
The environments into which infants arrive and within which infants grow and develop are improving throughout the world, yet discouragingly in much of the world environmental conditions are threatening the optimal health of young children. Pathogen and allergen exposure, nutrient quality of indigenous diets and the presence and timing of vaccination are now recognized to be environmental variables that can translate into diverse outcomes in children’s health. The implications of these environmental variables are profound. The tools of genomics are enabling scientists to understand the regulation of developmental patterning in biology and with this understanding has come the means to document the mechanisms by which early environments imprint individual organisms. From a nutritional perspective, it is becoming increasingly clear that early dietary effects prior to and immediately after birth can persist throughout the lives of individual humans.

The largest reservoir of genes in humans are not their own genome but the genomes of the thousands of bacteria that co-habit the human intestine and body surfaces. For the infant, birth is the emergence from a sterile environment into this cacophony of microbial colonizers. During the first few hours and days, the infant must become reconciled to peaceful coexistence with an ecological population of microorganisms numbering ten times its own cell numbers. Science still does not understand how this process takes place, nor all of the consequences of the varying success that different infants achieve. Remarkably, for each of us, these bacterial ecosystems once established in infancy remain relatively constant throughout life. In a strictly cellular sense, our environment is largely defined by these bacteria.

What are the consequences of these differences?

The workshop then addressed the critical pragmatic question: what are the immediate and long-term consequences of these various sources of individual difference? Are some children faced with important negative consequences of diets that are designed for the average or population mean and further, are some children limited in their future potential by diets that are considered appropriate for the average? Perhaps the most important and yet least understood of the bodily processes is the successful development of immunity. The rapid establishment of innate immunity is more variable than previously thought, with clear differences in the ability of different individuals to mount an immediate protective response to pathogens. Further, the timing and diversity of acquired immunity is not solely the consequence of diversity of exposure, but varies with genotypic determinants and with critical environmental cues, not the least of which are the colonizing bacteria in and on the developing infant. In addition to varying susceptibilities to pathogen invasion, intestinal disease and the success of its resolution, many infants are now recognized to carry genetic predispositions to the immunological failures that lead to allergy. Genetics, however, cannot account for the astonishing rise in allergic and autoimmune diseases throughout the world.
during the past 50 years. These increases must be assigned to changes in environmental factors acting upon a background of genetic susceptibilities. Varying outcomes in immune protection and autoimmune diseases are not the only aspects of health that are being documented to be on the rise in the world’s infants and children. Metabolic dysregulation and its most visible sign—post obesity has been frustrating health researchers around the world as it is seen to be moving inexorably into younger and younger children. Scientific mechanisms and epidemiological data together point to the conclusion that early diets in some infants are both promoting excess weight gain as children, but establishing a phenotype that persists throughout adult life. The most recent research has even more disturbing implications. Obesity in this generation’s children carries greater risk of other metabolic consequences than the same apparent ‘level’ of obesity in previous generations. The progression in children and adolescents towards a broad range of metabolic disturbances is unprecedented in recorded human history. If these trends continue, a substantial number of adults will transition to type-2 diabetes as young adults. The potential for early diets to alter the basic mechanisms of infant and childhood development through several mechanisms ranging from methylation of chromosomal DNA to alteration of endogenous microflora has many other implications than metabolic regulation. Many cellular processes of immunity, protection, tissue proliferation and cellular elimination are known in simpler biological systems to be modified during development. If these basic processes are acting similarly in humans, early infant diets and their effects on these persistent developmental mechanisms could alter many diseases of late adulthood including heart disease, neurodegeneration and cancer. Interestingly, the implications of these developmental changes would even extend to altering the responses of individuals to standard therapeutic approaches for these diseases once established.

Can we accurately assess differences?

Participants at the workshop explored the next logical steps in bringing scientific knowledge to effective practice and intervention. Is it possible with currently available diagnostic and measurement technologies to assess the differences between infants and children that are the basis of these health outcomes prior to the deterioration of their health? The possibilities for measuring human diversity are quite broad ranging from cellular, tissue and whole body imaging to detailed analysis of constituent molecules in biofluids even to genotyping. The technologies of medical imaging have reached remarkable capabilities in providing spatial information on biological structures and processes. The attendees at the workshop were treated to a literal view of the visual future that imaging of humans will provide medical sciences for the treatment of disease. The workshop participants then considered the question: can these imaging approaches, so successful in delivering diagnostic accuracy to disease management, provide equally valuable insights into the
personal variations that anticipate disease? The key issues that must be resolved include not only spatial precision but chemical accuracy. The variations among healthy infants and children are subtle and it is still not known which of the differences that are measurable are indeed associated with important variations in subsequent health. The tools necessary for genotyping individuals are moving forward rapidly and only time stands in the way of being able to genotype every individual. However, knowing an individual’s genome does not translate immediately into the knowledge of what the variations mean for the multiple interactions between diet and health. The field of nutrigenomics is building this knowledge and there is much knowledge to build but relatively few scientists engaged. The difficulties posed by sequencing of entire genomes unfortunately do not end there. With the new knowledge that during development each individual’s DNA is specifically methylated and that the pattern of methylation is both sensitive to diet and influences subsequent response to diet poses a dilemma for human assessment. If the pattern of methylation of an individual’s DNA is important to their diet and health, can these methylation patterns be measured? The workshop explored the technologies that have emerged that are capable of such analyses and, indeed, it is possible to accurately measure DNA methylation at a research level. Only time will be required to translate these techniques into routine tools of human measurement. However, once again, interpreting patterns into accurate predictions of future health is a massive research challenge. The more direct evaluations of genetic variation include gene expression profiling or transcriptomics, protein expression, proteomics or metabolite distributions, metabolomics. Transcriptomic analyses are capable of becoming a routine component of disease management and the example of stratifying cancer patients for therapeutics based on straightforward expression patterns provides a vivid proof of principle. Proteomic technologies are not as well developed, nonetheless their application to disease is equally appropriate. It is not yet clear whether either technology is capable of providing the accuracy and precision necessary to resolve the subtle differences between healthy infants. This basic question has indeed been answered for metabolic profiling, albeit for a small proportion of children and a small number of metabolites. The principle of measuring concentrations of metabolites in infant blood as a means of distinguishing those with diet-dependent metabolic dysregulation is already a worldwide system of blood spot analyses. Currently used for genetically based inborn errors of metabolism whose phenotype makes certain diets toxic such as phenylketonuria, the potential of this simple technology to revolutionize the management of infant and childhood diet management is apparent.

Can we act on these differences?

The workshop finally addressed the most central and defining question for nutrition as a science: knowing that infants and children differ in their
responses to diet and that these differences imply that diets delivered during infancy and childhood could improve the lives of these individuals, do we know what diets they should be guided to? The participants took the various nutrient classes in turn to examine where we stand, what we know and what we still need to know. The simple abundance of protein in the early diets of infants has emerged as a focus of considerable attention in the search for factors that could explain imprinting to predisposition of obesity. With the massive variations in protein sequence and the ability of proteins to interact biologically with different intestinal targets, with the tendency of this same sequence variation to lead to diversity of subsequent peptide fragments released during digestion and with the capability of proteins and peptides to conjugate with and bind virtually all other nutrient classes, it is clear that we have just begun to explore proteins as components capable of influencing development. Lipids have been the subject of intensive research due to the potential of polyunsaturated fatty acids to influence the development of infant neurological tissues and the obvious implications for long-term cognitive functions. While the simple presence of the different families of polyunsaturated fatty acids was long thought to be sufficient, breakthrough research on variations in humans are suggesting that differences in requirements can be traced to infant genetics, maternal phenotype during pregnancy and even infant microflora. Nutrition scientists have invested in decades of research to establish quantitative recommendations for the various micronutrients required by infants and children. Underpinning this global mandate was the assumption that all infants have the same quantitative requirements for all of these micronutrients. Groundbreaking research is beginning to cast doubt on this basic assumption. In fact, iron supplements in particular at the same dose may be highly beneficial to some children in one circumstance and yet deleterious to other children in other circumstances. Examining the consequences of evolution on the components of human milk produced by mammary biosynthesis during lactation has revealed a remarkable class of biologically active compounds, oligosaccharides. What is remarkable about this class of molecules is that they are apparently most biologically active not to the human infant that cannot digest them but to the bacteria inhabiting the intestine of the infant for whom they are astonishingly selective as a fermentation source. With the realization that human milk is highly concentrated in a class of molecules whose principle purpose is to nourish the endogenous microflora of infants, the implications of the bacteria themselves is becoming inescapable. Should all children be inoculated with the same bacteria, with different bacteria at different life stages, or should each individual’s microflora be considered a personal choice?

**Recommendations for future research**

After 3 days of intensive discussion, the workshop participants arrived at the obvious point of decision: what recommendations should be made for
scientists and for the industries whose products feed infants and children? Research and epidemiological data are quite convincing, waiting until adulthood to attempt to resolve metabolic and immunologic problems of disease progression is not appropriate. It is critical to act as early as possible to improve the health in each individual. Scientists studying the nutritional implications of diets for infants need to be brought together with all the tools of modern life sciences. Also, nutrition scientists need to guide and validate the technologies of human assessment for infants and children. These technologies can then be brought to clinical trials to build accurate databases of infant and childhood health. Within those trials, scientists should include the perspective that differences between children, not just their common biological processes, are critical to the ability to discriminate endpoints. Finally, the ongoing issue of the nutrition field needs to be reconciled for studies on children every bit as much as for all ages. Nutrition desperately needs to gain control of its independent variable: food. Studies need to measure and report in detail the ingredients used as input variables.

For the Industries that are actively involved in developing foods for infants and children, the recommendations are equally compelling. Their ability to provide standardized and compositionally defined diets for multiple clinical trials should be advanced as one of the most immediate and yet powerful and unifying principles for nutrition research. For the near future, however, as assessment technologies provide the means to distinguish differences among infants and children, industries must be able to provide parallel technologies capable of metering distinct diets to each individual with compositions and concentrations appropriate to their metabolic, physiological or nutritional needs.

D.M. Bier  
J.B. German  
B. Lönnnerdal
Foreword

With the completion of the human genome sequence just a few years ago, it is most interesting to note that 99.9% of the genetic information is similar in all humans; it is the remaining 0.1% that varies and which makes each of us individual. Epigenetic studies have demonstrated that variation in nutrient requirements depends upon individual variations in genes which can affect nutrient metabolism. It was in this context, that the 62nd Nestlé Nutrition Workshop was dedicated to ‘Personalized Nutrition for the Diverse Needs of Infants and Children’ and took place in Helsinki, Finland, on September 2–6, 2007.

This was the first workshop within the 27-year history of the Nestlé Nutrition Workshops – Pediatric Program that addressed personalized nutrition in infants and young children. Individuality was discussed at the genetic, biochemical, environmental, metabolic and nutritional levels. The first food in life, breast milk, has been reported to dynamically vary between mothers, between feeds and during the lactation period. This natural individualized nutritional concept can explain in part the differences of growth pattern between breastfed and formula-fed infants. By gradually changing the composition of infant formula in a manner similar to that of breast milk, it may be possible to come closer to the goal of achieving similar growth and development of formula-fed infants relative to those which are breastfed. Bioactive factors, such as prebiotics and probiotics were discussed in the context of mimicking nature’s example, breast milk. Additionally, factors that distort ‘healthy’ development, such as gene defects leading to inherited diseases, or epigenetic factors that can influence individual susceptibility to obesity and type-2 diabetes/insulin resistance were emphasized. Key questions during the workshop were during which time window modification of the effects can be possible, and to which extent nutrition and its personalization can contribute to optimal growth and development.

We wish to warmly thank the three chairpersons of this workshop, Dennis M. Bier, J. Bruce German and Bo Lönnerdal for establishing an exciting scientific workshop program. Many thanks also to Annette Järvi and her team from Nestlé Nutrition Nordics for the excellent logistic support and for enabling the workshop participants to enjoy the charm of Finnish culture.
Our special thanks go to Denis Barclay who has coordinated the last five Nestlé Nutrition Workshops. He will move as scientific advisor for adult nutrition and enrich the Nestlé Nutrition Institute activities.

Prof. Ferdinand Haschke, MD, PhD
Chairman
Nestlé Nutrition Institute
Vevey, Switzerland

Dr. Petra Klassen, PhD
Scientific Advisor
Nestlé Nutrition Institute
Vevey, Switzerland
Contributors

Chairpersons & Speakers

**Dr. Ingegerd Adlerberth**
Department of Clinical Bacteriology
Göteborg University
Gudhedsqatan 10
SE–413 46 Göteborg
Sweden
E-Mail ia@microbio.gu.se

**Prof. Gerard Berry**
Children's Hospital
Division of Genetics and Program in Genomics
Harvard Medical School
300 Longwood Avenue
Boston, MA 02115
USA
E-Mail gerard.berry@childrens.harvard.edu

**Prof. Dennis M. Bier**
Children's Nutrition Research Center
Baylor College of Medicine
1100 Bates Street
Houston, TX 77030
USA
E-Mail dbier@bcm.tmc.edu

**Prof. Jason Chou Chieh**
Nutrition and Health Department
Nestlé Research Center
PO Box 44
CH–1000 Lausanne 26
Switzerland
E-Mail chieh-jason.chou@rdls.nestle.com

**Prof. Bruce German**
Department of Nutrition
University of California
One Shields Ave
Davis, CA 95616
USA
E-Mail jbgerman@ucdavis.edu

**Prof. Peter Gluckman**
Liggins Institute
University of Auckland
Private Bag 92019
1023 Auckland
New Zealand
E-Mail pd.gluckman@auckland.ac.nz

**Prof. Olle Hernell**
Department of Clinical Sciences, Pediatrics
Umeå University
SE–901 85 Umeå
Sweden
E-Mail olle.hernell@pediatri.umu.se

**Prof. Dr. J.W. (Hans) Hofstraat**
Healthcare Strategic Partnerships
Philips Research Laboratories/CTMM
High Tech Campus 11 (HTC 11 P 2.41)
NL–5656 AE Eindhoven
The Netherlands
E-Mail hans.Hofstraat@philips.com
Contributors

**Prof. Berthold Koletzko**
Division of Metabolic Diseases and Nutritional Medicine
Dr. von Hauner Children’s Hospital
Ludwig Maximilians University of Munich
Lindwurmstrasse 4
D–80337 Munich
Germany
E-Mail berthold.koletzko@med.uni-muenchen.de

**Prof. Ching Lau**
Baylor College of Medicine
Texas Children’s Cancer Center
6621 Fannin Stret, MC 3-3320
Houston, TX 77030
USA
E-Mail cclau@txccc.org

**Prof. Bo Lönnerdal**
Department of Nutrition
University of California
One Shields Ave
Davis, CA 95616
USA
E-Mail bllonnerdal@ucdavis.edu

**Prof. Piero Rinaldo**
Biochemical Genetics Laboratory – Hilton 360C
Department of Laboratory Medicine and Pathology
Mayo Clinic College of Medicine
200 First Street SW
Rochester, MN 55905
USA
E-Mail rinaldo@mayo.edu

**Prof. Seppo Salminen**
Functional Foods Forum
University of Turku
FI–20100 Turku
Finland
E-Mail seppo.salminen@utu.fi

**Prof. Erkki Savilahti**
Pediatric Gastroenterology and Immunology Department
Helsinki University Central Hospital
Hospital for Children and Adolescents
POB 281
FI–0029 Hus
Finland
E-Mail erkki.savilahti@hus.fi

**Prof. W. Allan Walker**
Developmental Gastroenterology Laboratory
Massachusetts General Hospital for Children
Department of Pediatrics
Harvard Medical School
114 16th Street (114–35 03)
Charleston, MA 02129–4404
USA
E-Mail wwalker@partners.org

**Prof. Robert A. Waterland**
Department of Pediatrics and Molecular and Human Genetics
Baylor College of Medicine
USDA Children’s Nutrition Research Center
1100 Bates Street
Houston, TX 77030
USA
E-Mail waterland@bcm.edu
Contributors

Moderators

Prof. Bengt Björkstén
Allergy Prevention and Pediatrics
Institute of Environmental Medicine
Karolinska Institute
SE–17177 Stockholm
Sweden
E-Mail bengt.bjorksten@ki.se

Prof. Mikko Hallman
Department of Pediatrics
Faculty of Medicine
Kajanintie 50
Oulu University Hospital
FI–902 20 Oulu
Finland
E-Mail mikko.hallman@oulu.fi

Prof. Erika Isolauri
Department of Pediatrics
Turku University Central Hospital
Kiinamyllynkatu 4–8
FI–205 20 Turku
Finland
E-Mail eriiso@utu.fi

Prof. Olli Simell
Department of Pediatrics
Turku University Central Hospital
Kiinamyllynkatu 4–8
FI–205 20 Turku
Finland
E-Mail olli.simell@utu.fi

Prof. Outi Vaarala
Laboratory for Immunobiology
Department of Viral Diseases and Immunology
National Public Health Institute
Mannerheimintie 166
FI–003 00 Helsinki
Finland
E-Mail outi.vaarala@ktl.fi

Invited Attendees

Susan Prescott/Australia
Nadja Haiden/Austria
Karl Zwiauer/Austria
Bosco Paes/Canada
Simon Lam/China
Rosanna Ming Sum Wong/China
Kim Fleischer Michaelsen/Denmark
Rafael Aulestia/Ecuador
May Nassar/Egypt
Anne Ormission/Estonia
Merle Palust/Estonia
Heli Kuusipalo/Finland
Kirs Laitinen/Finland
Harri Niinikoski/Finland
Anneli Pouta/Finland
Tuula Simell/Finland
Suvi Virtanen/Finland
Agnés Guiseppi/France
Clemens Kunz/Germany
Axel Von der Wense/Germany
Iraklis Salvanos/Greece
Maria Trigka/Greece
Diane Devy Sondakh/Indonesia
Dr. Wistiani/Indonesia
Luca Bernardo/Italy
Giovanni Corsello/Italy
Mario De Curtis/Italy
Ieve Eglite/Latvia
Ruta Kuciskien/Lithuania
Vaidotas Urbanos/Lithuania
Sigita Zindziuvi/Lithuania
Yael Enricas Bravo/Mexico
Ulises Leal/Mexico
Victoria Lima/Mexico

XIX
Contributors

Ignacio Ortiz/Mexico
Francis H. Bloomfield/New Zealand
Steve Hodgkinson/New Zealand
Per Brandtzaeg/Norway
Per H. Finne/Norway
Janusz Ksiazyk/Poland
Hania Szajewska/Poland
Abdurrachid Nuramod/Portugal
Susanna M. Saraiva Pissarra da Silva/Portugal
Tatiana Loskuchervaja/Russia
Bengt Björkstén/Sweden
Hugo Lagercrantz/Sweden
Inger Öhlund/Sweden
Staffan Polberger/Sweden
Niels Räihä/Sweden
Birgitta Strandvik/Sweden
Anan Alhaffar/Syria
Pimol Srisuparp/Thailand
Deniz Ertrem/Turkey
Ayşe Mkkadder Selimoglu/Turkey
Carina Venter/UK

Nestlé Participants

Mr. Xavier Payrard/Australia
Ms. Lisa Beausoleil/Canada
Dr. Louis-Dominque Van Egroo/France
Mr. Mike Possner/Germany
Mr. Panagotis Bagkas/Greece
Dr. Inguna Berzina/Latvia
Dr. Darius Praninskas/Lithuania
Dr. Fernando Carvalho/Portugal
Prof. Olga Netrebenko/Russia
Dr. Sergey Ukraintsev/Russia
Mr. Robert Aderbauer/Sweden
Dr. Anette Järvi/Sweden
Dr. Denis Barclay/Switzerland
Mrs. Elisabeth Chappuis/Switzerland
Dr. Irene Corthésy/Switzerland
Mrs. Ulrike Deland/Switzerland
Dr. Marie-Claire Fichot/Switzerland
Prof. Ferdinand Haschke/Switzerland
Dr. Petra Klassen/Switzerland
Dr. Françoise Maynard/Switzerland
Dr. Bruce McConnell/Switzerland
Mr. Giovanni Pascalicchio/Switzerland
Dr. Evelyn Spivey-Krobath/Switzerland
Dr. Thierry Von der Weid/Switzerland
Mrs. Zelda Wilson/UK
Prof. Jose Saavedra/USA