

Carlo Agostoni, MD, and Kwang Sik Kim, MD, are the Guest Editors for this annual review issue on Nutrition and the Microbiome. Dr Agostoni is a Professor of Pediatrics at the Department of Clinical Sciences and Community Health, University of Milan, within the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan. Dr Kim is Professor of Pediatrics and Molecular Microbiology and Immunology, Johns Hopkins University School of Medicine and Bloomberg School of Public Health; and Director, Division of Pediatric Infectious Diseases, Johns Hopkins Children's Center, Baltimore, MD.

## Nutrition and the microbiome 2015

Carlo Agostoni<sup>1,2</sup> and Kwang Sik Kim<sup>3</sup>

### NUTRITION AND THE GUT MICROBIOME

In December 1999, a supplement of *The Lancet* was issued with the title, *Past, Present and Future*, indicating the three phases of medicine on the border between the second millennium and the third (1). The topic of nutrition was spearheaded by one of the most experienced nutritionists, Joseph Hautvast, who interpreted “The Potato Eaters,” painted by Vincent Van Gogh in 1885, as representative of the role of potatoes during the 18th century as bread for the poor in substitution for wheat products (2). Hautvast explained that potatoes provide energy, sufficient protein, and are a rich source of vitamin C. Unfortunately, the dependence of impoverished people on the potato as the main staple of their diet made them vulnerable to famine in the event of a serious crop failure. Fortunately, the 20th century ushered in the first renaissance in nutrition sciences, ranging from the introduction of “novel” foods to the first cases of food enriched with minerals and vitamins. These advances led to the nutritional sufficiency of food in Westernized countries but not for millions of people in other parts of the world.

Fifteen years have passed, and we are entering the new year, 2015, with plenty of food choices, as will be demonstrated in the 2015 Expo on nutrition in Milan, Italy, named “Feeding the Planet, Energy for Life” (3). Accordingly, this timely issue of *Pediatric Research* includes narrative reviews, comments, and new perspectives of nutrient effects.

### NUTRITION SCIENCE: PAST AND FUTURE

The main concepts that have come from the past 15 y are as follows: first, a good start in nutrition and growth may have lifelong lasting consequences, for all infants. Second, early growth spurts may affect the expression of noncommunicable disorders. This phenomenon may affect premature, low-birth-weight infants on an individual basis, as well as infants and children in developing countries (4,5). In both cases, an excess

of nutrients in selected stages of early years may overwhelm the biologically planned functional reserve of splanchnic organs, resulting in type 2 diabetes, high blood pressure, dyslipidemic conditions, and hepatic steatosis in later ages (4,5).

A third discovery is that individual nutrition status may affect the clinical expression of infectious and immune disorders through the life span. Fourth, we do not live and eat alone but with billions of commensal microorganisms in the gut (as well as the respiratory tract and the mouth), which potentially influence the three previously mentioned conditions (early nutrition status and growth, energy balance and growth acceleration, and the response to infections and allergy- and immune-mediated disorders). This relatively recent discovery, for which the origin lies in observations on the possible effects of yogurt by Metchnikoff at the end of the 19th century (6), has the potential to change our approach to health and disease, as well as decision making, when considering the consequences of the types of delivery (7).

This Supplemental Issue of *Pediatric Research* is devoted to the roles of nutrition and gut flora on infants' and children's health and disease. In putting together the issue, our goal was to obtain review articles covering the cutting-edge topics summarized above. Similar to *The Lancet* comment on nutrition in 1999, we chose to represent on this issue's cover the concept of nutrition through a child's painting of a fruit bowl, representing both the topic of nutrition and the ultimate beneficiaries of pediatric research.

Fruits are natural, sweet, low-energy dietary components, rich in antioxidants and helping to decrease the energy density of meals. They are one of the richest sources of fibers (pectin, amylopectin, hemicelluloses, etc.) and nondigestible oligosaccharides (trioses and others) that are metabolized by the intestinal flora while balancing the absorption of pro-energetic compounds (8). Fruit intake and other positive dietary habits of pregnant women can prevent or solve some gastrointestinal

<sup>1</sup>Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; <sup>2</sup>Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; <sup>3</sup>Division of Pediatric Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland. Correspondence: Carlo Agostoni ([agostoc2@gmail.com](mailto:agostoc2@gmail.com)) and Kwang Sik Kim ([kwangkim@jhmi.edu](mailto:kwangkim@jhmi.edu))

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symptoms and have positive overall effects on the composition of intestinal flora (better defined as the gut microbial ecosystem), not just on the mother, but also on infants and children during growth, to the point of modulating their energy expenditure in health and disease.

### THE MICROBIOME

The microbiome (repertoire of microbial genes) of a single human is made up of an estimated 100 trillion microbes, or more microbes than all the humans who have ever lived, with the bulk of the microbiome existing in our gut. The human genome carries ~22,000 protein-encoding genes, while the microbiome is estimated to carry more than 3 million unique protein-encoding genes. Unlike the host genome, the microbiome can change rapidly, resulting in modified transcriptomic, proteomic, and metabolic profiles. Thus, human development and physiology as well as disease can be featured as a blend of human and microbial traits. This special edition of *Pediatric Research* addresses selective topics regarding the microbiome, with particular illustration of maternal influences on fetal microbiota and disease risk.

Microbial exposure during pregnancy has important developmental and physiological implications on fetuses and children. A traditional concept is that babies are born “germ-free,” getting their first exposure to the microbiome through the mother’s birth canal, but this concept has been disproven with demonstration of microbes in the intrauterine environment and tissues, as shown by the presence of bacterial DNA in the placenta, amniotic fluid, and meconium. These findings suggest that the fetal gut may be colonized within the intrauterine milieu and that the window of opportunity of intervention begins prior to birth, likely within the fetal period.

The infant gut microbiota has been shown to be affected by gestational age (e.g., full-term vs. premature), diet (e.g., breastfeeding vs. formula feeding), mode of delivery (cesarean section vs. vaginal delivery), maternal nutritional status (e.g., maternal malnutrition and obesity), and exposure to antibiotics. By the age of 3 y, infants have established the majority of the microbiome that will endure for life.

The early-life development of the neonatal gut microbiota plays an important role in human physiology (e.g., nutrient processing), development, and disease (e.g., immune education, stimulation of angiogenesis, regulation of host fat storage, protection against pathogens, and development and homeostasis of other host tissues including the bone). The conditions that have been linked to the microbiome include inflammatory bowel disease, obesity, diabetes, rheumatoid arthritis, food allergies, asthma, infection, animal models of multiple sclerosis, and microbiome–brain connection, e.g., autism via microbial metabolites.

Microbial translocation from the maternal gut to the mammary gland and breast milk was demonstrated (9–11) in human lactating mothers via macrophages or dendritic cells, suggesting the presence of a microbial enteromammary circulation during lactation.

Microbial production of vitamins and amino acids is important during human infant development. Vitamin K is the classic example. Routine vitamin K prophylaxis of healthy newborns

is required to prevent hemorrhagic disease because of minimal placental transfer of the vitamin and low concentrations of vitamin K–producing bacteria in the gut at birth.

The microbial diversity decreases in low-birth-weight infants who develop sepsis compared with healthy premature infants. One of the beneficial properties of a balanced gut microbiota is to provide nutrition for the host. Bacteria in the gut are involved in metabolizing otherwise indigestible food components, such as dietary fiber. The mechanisms that link the gut-associated microbial communities to immune education, nutrition, and protection against pathogens point to microbiota-derived metabolites, e.g., short-chain fatty acids, breakdown products of dietary fiber, mainly comprised of acetate, propionate, and butyrate, as key players during microbe–host interactions.

It is important to remember that antibiotics can disrupt immune homeostasis by disrupting the community of short-chain fatty acid products, in turn increasing the inflammatory tone of the intestinal mucosa. The bacterial composition of feces for most part reverted to the pretreated state 4 wk after antibiotic treatment, but repeated treatment generated even bigger changes to the composition of the gut microbiota.

The gut microbial ecosystem is transmissible, with demonstration of potential host–microbiota co-metabolism as shown with fecal transfer experiments in germ-free mice from individuals with obesity as well as with kwashiorkor. Food insecurity alone does not explain the incidence of malnutrition in various populations. Identification of uncultured human fecal microbiota samples that transmit physiologic, metabolic, and immune phenotypes to germ-free mice (so-called effector strains) will be the next challenge.

This Supplemental Issue of *Pediatric Research* is devoted to the roles of nutrition and the microbiome on infants’ and children’s health and disease.

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