Concluding Remarks

This symposium focused on the window of opportunity for nutritional interventions to prevent chronic disease. Following a recommendation by the UN Standing Committee on Nutrition, 2006, the window of opportunity was defined as the period from conception to 2 years after birth. We discussed what is known and what needs to be known about (a) growth during this window, (b) critical periods of development, (c) the effects of nutrition, and (d) possible interventions to improve nutrition.

Growth

What Is Known. The window of opportunity is characterized by rapid growth. The brain and lymphatic tissue grow especially fast. Growth is episodic rather than continuous. Growth at this time may alter the path of later growth; becoming thin at 2 years, for example, may induce the adiposity rebound at an early age in childhood and thereby lead to childhood obesity. Chronic diseases, including cardiovascular disease and type 2 diabetes, are related to the path and tempo of growth during the window. The same disease may originate through more than one path of growth.

What Needs to Be Known. We need to define the optimal paths of growth between 6 months and 2 years. We know little about the costs of rapid growth during and after the critical window. We do not know how the growth of girls at this time affects the development and health of the next generation.

Critical Periods of Development

What Is Known. Sensitive, or critical, periods of development are those when a system or organ is plastic and can be changed by the environment. For most systems and organs the critical period occurs before birth: the brain, liver and immune system remain plastic after birth. An organ may have more than one critical period: the heart, for example, has critical periods in both early
and late gestation. During a critical period different environmental stimuli may have different effects on the same organ: for example, either the growth of the heart or its maturation may be affected. Gene expression is determined during critical periods: studies of osteoporosis and type 2 diabetes have shown that the effects of genes interact with those of early body size. Alternatively genes may be silenced during critical periods.

**What Needs to Be Known.** We need to know in more detail when the critical periods for each organ and major system in the body occur.

### Nutrition

**What Is Known.** Good nutrition is most effective if it begins before conception. The long-term consequences of the Dutch famine on people who were in utero at the time provide the clearest demonstration of the importance of nutrition during pregnancy. The baby is also nourished by the turnover of protein and fat in the mother’s body. It is influenced by the mother’s metabolism, as the effects of maternal obesity clearly demonstrate. Fetal IGF-1 concentrations are sensitive to nutrition and affect multiple organs and systems. Breast milk protects growth. Early initiation of breastfeeding protects against infections.

**What Needs to Be Known.** We do not know how early nutrition sets appetite or determines food preferences in later life. We know little about the differing needs of different babies. We need to know more about the role of the gut flora and the role of the microbes in breast milk.

### Interventions

**What Is Known.** There is an ongoing debate about the relative merits of single nutrient ‘magic bullet’ interventions, for example a single vitamin as opposed to interventions with foods. Interventions may need to be targeted to vulnerable people, for example, in Western societies those with low educational attainment. In the future interventions could be targeted to systems, for example to epigenetic systems.

**What Needs to Be Known.** We need more biomarkers to demonstrate the effects of interventions. We need to know more about ways of changing peoples food choices, especially those made by girls and young women.

### What Could Be Achieved

The Helsinki Birth Cohort is the best source of data in which growth during the critical window can be linked to chronic disease in later life. It has been estimated that if, within the cohort, each person had been in the highest third of
body size at birth (weight, length or ponderal index \((\text{birthweight/length}^3)\)) and had not increased their standard deviation scores for body mass index between 2 and 11 years, chronic disease would have been reduced as follows: (1) coronary heart disease by 25% in men and 63% in women; (2) type 2 diabetes by 57% in men and women, and (3) hypertension by 25% in men and women.

These estimates take no account of the additional effects of optimizing growth from birth to 2 years of age.

David J.P. Barker

This session provided a comprehensive overview on the interaction between nutrition and growth during critical periods of early development. Theresa Scholl demonstrated how specific nutrients may link maternal nutrition before and during pregnancy with the growth outcome of the fetus. During famine and starvation a low glucose stream from the mother to the fetus gives rise to a smaller size at birth. But even under normal conditions, a diet with a low glycemic index can alter maternal glucose production and consequently reduce fetal growth. Although a single micronutrient deficiency rarely occurs isolated in humans, it could be shown that iron deficiency anemia, even before conception, increases the risks of low birthweight and preterm delivery. A nutritionally or metabolically caused deficiency of circulating folate before and during pregnancy interferes with normal fetal growth and development. Many studies have demonstrated that micronutrient supplements before and during pregnancy improved pregnancy outcome.

Andreas Plagemann elaborated a fundamental concept for the fetal origins of obesity, diabetes mellitus, the metabolic syndrome, and subsequent cardiovascular diseases, launched by pre- and perinatal nutritional conditions and mediated by hormones. Hormones are organizers of the developing neuroendocrine-immune network. When present at nonphysiological concentrations during critical developmental periods, they can act as teratogens of the endocrine network, resulting in persistent functional and somatic alterations. Experimental results, clinical and observational studies demonstrated that elevated insulin concentrations in the fetus and newborn, induced by maternal diabetes and overweight, may program obesity and diabetes in the offspring. Screening and therapy of all types of diabetes during pregnancy, and avoidance of early postnatal overfeeding are recommended for a genuine primary prevention.

Renate Bergmann pointed out that it is problematic to use birth size for the assessment of poor fetal growth. The prevalence rates of intrauterine growth restriction are estimated to be highest in India and other Asian countries. The major determinant in developing countries is malnutrition before and during pregnancy, but in developed countries it is maternal cigarette smoking. While smoking cessation even before becoming pregnant is a sound
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recommendation, balanced nutritional supplements during pregnancy may come too late. The development and education of young women should be supported as early as possible. An epigenetic modification can already occur in the periconceptional period. A hormonal network regulates fetal growth and development in accordance with signals from the intrauterine environment. The fetus ‘predictively adapts’ to an unfavorable environment and develops a ‘thrifty phenotype’. Follow-up studies suggest that lean body mass rather than fat mass is programmed by intrauterine undernutrition. Catch-up growth is the consequence of intrauterine growth restriction. While catch-up in length is a favorable sign, an overshooting weight gain, mainly comprising adipose tissue, is accompanied by insulin resistance, a characteristic of the thrifty phenotype. Growth restriction in newborns therefore should be identified to avoid overfeeding. Increasing the muscle mass, e.g. by physical activity, may help to restrain this unfavorable development.

Lars Hanson described the role of human milk for growth, development and immune response of the young infant. Infants exclusively breastfed for the first 6 months are considered to demonstrate optimal growth. The new WHO growth standards are based on their growth data, which deviate from those of formula-fed infants even in later life. Breast milk contains growth-regulating hormones. Of importance is the maternal diet, e.g. in regard to LCPUFA, especially a balanced intake of n-3 and n-6 fatty acids. The immune defense provided by human milk includes the innate defense, e.g. by enzymes which additionally have nutritional functions, and components that can modulate toll-like receptors (TLRs) according to the microbial exposure of the newborn at delivery, and according to his own gut microflora. The dual function, i.e. protecting the infants from infection and promoting growth, is a feature of many nutrients and constituents of human milk, making it a unique food in infancy.

Dennis Bier demonstrated that postnatal growth is under different hormonal control than fetal growth. There is only a weak correlation between birth size and adult size, but the correlation between length at 3 years and adult height reaches 0.8. Genetic factors predominantly influence linear growth during the first 3 years, determining the growth velocity in order to compensate for intrauterine growth deviations. In early childhood, ponderal growth is different from linear growth. Although growth velocity and especially head growth is particularly rapid during the first 3 years, energy costs for growth decrease from 40% at 1 month to 3% and less at 1 year and later on. But the glucose consumption rates of the brain increase until about 4 years of age. Weight gain after a phase of slow growth, e.g. as an early adiposity rebound, is a risk for later obesity and its comorbidities. Cells and organs may remember their nutritional, and environmental experiences (e.g. maternal care) by permanent anatomic changes, epigenetic DNA imprinting, clonal selection, neuronal pruning or stable gut microbes.

Renate L. Bergmann
This session provided an in-depth discussion of the developmental aspects of Immune system in the neonate, nutrition and neonatal mucosal microflora relative to the impact of their interaction on subsequent disease outcome.

The introductory talk by Pearay Ogra suggested that immune response in the neonatal mucosal surfaces is a complex interplay of innate and adaptive immunity and available external environment, including the microflora. Changes in the mucosal microflora significantly influence the development and regulation of neonatal immune responses. Expression of autoimmune or immunologically mediated disease processes may be a reflection of a lack of immunological tolerance or altered mucosal immune responses. It was proposed that the underlying neonatal immune status may program for subsequent disease outcome later in life. Christopher Wilson discussed key features of antigen-specific immunity in the neonatal period. It is now clear that T-cell-independent antibody responses to polysaccharide antigens are absent and not amenable to intervention in the early neonatal period. However, T-cell-dependent antibody responses are present even prior to birth. Interestingly, the slow pace with which such responses develop during the neonatal period may allow microbes to induce infection before the expression of effective T-cell responses can contain such infections. It was also proposed that, in the absence of effective microbial TLR agonists, protective Th1 and other T-cell-dependent responses to vaccines reach protective levels somewhat slowly. It should however be emphasized that the extent to which these deficits are T-cell intrinsic or result from impaired neonatal dendritic cell response to TLR agonists is not known. Field studies on the relation of nutrition-immunity and mucosal homeostasis discussed by Andrew Prentice have shown that infections with pathogenic microorganisms are a major suppressor of growth. Of these, infectious gastroenteritis was considered to be an important cause of growth retardation in Africa. Catch-up growth seems to occur during recovery or convalescence from such infections. These studies have also suggested that unique windows of opportunity, if missed, can result in permanent growth suppression until puberty, at which time there may be another opportunity for growth catch-up. Allan Walker discussed the role of perinatal microflora and mucosal disease. As pointed out earlier, initial mucosal colonization appears to be very important to the nature and development of neonatal host defenses. Furthermore, mucosal colonization with probiotics and other commensal agents can affect disease expression. Yvonne Maldonado provided an extensive overview of microbial infections in the global setting and their role in disease outcome. It is clear that global mortality related to infectious diseases continues to remain very high especially in neonates and young children, with over 12 million deaths per year. The pathogenesis of perinatal viral infections appears to be related to primary maternal infections with common organisms. Postnatal and possibly breastfeeding-related HIV infections have become a major challenge in global perinatal HIV prevention. On the other hand, It is interesting to note that with the exception of malaria, most perinatal parasitic infections are generally
benign and may even contribute to the disease outcome especially in the prevention of allergic and/or autoimmune diseases. This concept of the hygiene hypothesis was discussed in detail by Bengt Bjorksten. His field studies have shown that allergy as a disease entity is on the increase in affluent societies especially in the young. However, rural farm life, and possibly hepatitis virus infection appear to be associated with protection. Recent investigations carried out in Estonia have suggested that infants are born with lower Th1 and Th2 responses, rapid development of secretory IgA responses, and a lower frequency of positive allergic skin tests. These changes may be related to significant changes in the composition of neonatal mucosal flora, especially for probiotics, other commensal and other anaerobes (clostridium) in the mucosa, and between allergic and nonallergic subjects. Nonallergic children seemed to be selectively colonized with lactobacilli and other bifidobacteria, while allergic subjects were more often colonized with clostridia. Other studies have shown that certain lactobacilli improve infantile eczema especially if given early. It was also suggested that mucosal microflora is essential for the postnatal maturation of the immune system and a prerequisite for the development of oral tolerance, the principal immunologic mechanism underlying the concept of the hygiene hypothesis.

It is clear that mammalian hosts especially the human neonate exhibit a delicate and a complex interaction with the mucosal environment (mucosal flora, nutrition), and the developing innate and adaptive immune functions. From a evolutionary perspective, it is important to recognize that mammalian host–microbial interactions have evolved over billions of years of coexistence. Virtually all human microbial agents, both pathogens and commensal, have been acquired from other animal species and all microbes must be considered pathogenic. However, some organisms over millions of years of cohabitation with human and other life forms have been attenuated by pathogenesis and continue to live in a delicate balance with the host, often favoring the host. However, that balance can shift in favor of the microorganism to render it pathogenic. Factors which can shift the balance include a variety of host as well as microbial functions. There is strong interest and some evidence for a protective role of some probiotic organisms in prevention and/or treatment of infectious, allergic or autoimmune disease processes. However, additional information must be acquired about the dynamics of the natural microbial ecosystem before these agents can be used for large scale therapeutic purposes.

To date, the single most important success story in the history of mankind has been the prevention of childhood infection through the use of vaccines. There is no evidence to suggest that the global introduction of vaccines against infectious diseases has adversely affected the development of the human immune system or the acquisition of mucosal or external environmental microflora.

Pearay L. Ogra