The Window of Opportunity: Pre-Pregnancy to 24 Months of Age
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Foreword

The 61st Nestlé Nutrition Workshop – Pediatric Program, entitled ‘The Window of Opportunity: Pre-Pregnancy to 24 Months of Age’, was held in Bali, Indonesia, in early April 2007. The importance of proper nutrition during pregnancy, lactation, and infancy for later health has been addressed from a number of different angles right from the origins of this workshop series. Indeed the very first Nestlé Nutrition Workshop in 1980 ‘Maternal Nutrition in Pregnancy – Eating for Two’, chaired by John Dobbing, focussed on the role of nutrition of the mother-to-be in the determination of fetal growth. Some years later, the 36th Nestlé Nutrition Workshop ‘Long-Term Consequences of Early Feeding’, chaired by John Boulton, Zvi Laron and Jean Rey, dealt mainly with the impact of nutrition during early infancy on health outcomes in later life, including mental development, obesity, cardiovascular disease and immune response. One presentation by David Barker addressed the long-term consequences of fetal growth and also raised the question of the potential importance of nutrition during pre-pregnancy for fetal development.

In 2004–2005, three Nestlé Nutrition Workshops covered various aspects of longer term health effects of nutrition during pregnancy, infancy and childhood:

No. 55: The Impact of Maternal Nutrition on the Offspring
Chairpersons: Gerard Hornstra, Ricardo Uauy and Xiaoguang Yang

No. 56: Feeding during Late Infancy and Early Childhood: Impact on Health
Chairpersons: Olle Hernell and Jacques Schmitz

No. 57: Primary Prevention by Nutrition Intervention in Infancy and Childhood
Chairpersons: Alan Lucas and Hugh Sampson

In 2006, the United Nations Standing Committee on Nutrition, considering the double burden of undernutrition and obesity in many countries, proposed the intensification of efforts to improve nutrition at the local, national and global levels, with major ‘focus on the window of opportunity from pre-conception to around 24 months of age, the critical period when the foundation for life long health is set’. Thus
with the observed alarming increases in nutrition-related conditions such as obesity, cardiovascular disease, diabetes, osteoporosis, allergy and other disorders of immune function, we felt it was timely to review current knowledge on the influence of nutrition during the critical period of pre-pregnancy through infancy on such conditions. Against this background, the chairpersons of this workshop, David Barker, Renate Bergmann and Pearay Ogra, designed a workshop program focussing on this window of opportunity, looking not only at conditions such as heart disease, obesity and diabetes, but also addressing the effects of early nutrition and growth on the development of immune function. We warmly acknowledge the excellent scientific program conceived by the chairpersons. We are also indebted to all the renowned speakers and experts who came from across the globe to review and debate this important topic.

Finally, we wish to thank and congratulate Dr. Leilani Lestarina and her team from Nestlé Nutrition Institute – Indonesia for their first class logistic support, allowing the workshop to take place under ideal conditions and the participants to experience the wonderful culture and hospitality of the Balinese.

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

Dr. Denis Barclay, PhD
Scientific Advisor
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The Biology of Growth

Noël Cameron

The process of human growth is characterized by a set of phenomena that reflect the actions of biological control mechanisms. These mechanisms are subject to genetic and environmental influences and their expression is characterized by variation in timing, magnitude, and duration.

The recognition of these phenomena is dependent on our ability to detect the pattern of growth of the whole body and its various tissues and organ systems. The frequency with which we measure the process of growth dictates the observed pattern. If growth is assessed yearly it is characterized by a series of two or perhaps three curves that may be modeled by logistic functions. These curves divide the process into infant, childhood, and adolescent components from approximately birth to 3 years, 3–10 years, and 10–18 years, respectively (fig. 1).

**Fig. 1.** The pattern of growth in height when assessed at yearly and 6-monthly intervals. Redrawn from Tanner JM (Growth at Adolescence, ed 2. Oxford, Blackwell Scientific Publications, 1962).
Fetal growth in length also appears to be a smooth curve but when examined in terms of velocity demonstrates peaks in growth in length between 20 and 30 weeks of gestation and in weight between 30 and 40 weeks of gestation. If the frequency of assessment of postnatal growth is increased to daily or weekly measurements, as has been done by Lampl et al. [1], then growth in length corresponds to a series of aperiodic saltatory episodes separated by periods of stasis in which no growth occurs. This growth model of saltation and stasis implies that the controlling mechanisms are discontinuous and aperiodic.

Different tissues reflect different growth rates. In the first 5 years of life, for instance, the nervous system grows rapidly to the extent

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**Fig. 2.** Growth curves of different parts and tissues of the body, showing the four main types: lymphoid (thymus, lymph nodes, intestinal lymph masses); brain, neural tissue and head (brain and its parts, dura, spinal cord, optic system, cranial dimensions); general tissue (whole body linear dimensions, respiratory and digestive organs, kidneys, aortic and pulmonary trunks, musculature, blood volume), and reproductive tissue (testes, ovaries, epididymis, prostate, seminal vesicles, fallopian tubes. From Tanner JM (Growth at Adolescence. Oxford, Blackwell Scientific Publications, 1955).
that the brain reaches 95% of its adult size by about 7 years of age. Conversely tissues of the reproductive system, e.g., breasts and genitalia, do not demonstrate rapid growth until after 10 years of age. The tissues of the lymphatic system, e.g. thymus, grow rapidly in the first 10 years of life to achieve a size approximately 80% greater than they will be in adulthood but then recede during adolescence. These growth rates are in contrast to the curve of general linear growth that is represented by height (fig. 2).

Given these different growth patterns it is not surprising that the organism exhibits variation in the proportions of body segments at any particular age which change over time. These proportional changes in size, called allometric growth, are most marked during fetal growth (fig. 3).

Biological change involves two processes; growth and maturation. The former is structural and the latter functional. Rates of maturation, or tempo of growth, differ considerably within and between the sexes as figure 4 demonstrates. Here 3 boys and 3 girls exhibit dramatically different stages of growth and development in the peripubertal period. The differences between the sexes are a mark of sexual dimorphism which becomes more pronounced during adolescence as the functional requirements for successful reproduction become established.

Growth is a result of the interaction between genes and the environment. In the absence of constraint a child will grow to its ‘genetic

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**Fig. 3.** Proportional changes in fetal growth.
potential’ and demonstrate canalization in that its growth pattern tends to stay within a specific centile band. Insults to growth will cause growth faltering and the growth curve will fall through centiles as growth rate slows in response to the constraint. Once the constraint is removed or nullified growth rate increases rapidly to cause the child to ‘catch-up’ to its pre-insult centile.

The timing, intensity and duration of the insult affects the completeness of catch-up growth. Those children exhibiting a prolonged exposure to a severe insult will tend to show incomplete catch-up growth after removal of the insult.

Fig. 4. A child with growth hormone deficiency demonstrating catch-up growth following treatment with human growth hormone.
This apparent sensitivity to the timing, intensity and duration of insult has given rise to the recognition of ‘critical periods’ during which insult appears to have long-term effects in terms of health and wellbeing.

Reference

There is now clear evidence that the pace and pathway of early growth is a major risk factor for the development of a group of chronic diseases that includes coronary heart disease and type 2 diabetes, a disorder which predisposes to cardiovascular disease. This has led to a new ‘developmental’ model for the disease [1, 2]. The model proposes that nutrition during fetal life, infancy and early childhood changes gene expression and thereby establishes functional capacity, metabolic competence and responses to the later environment.

To explore the developmental origins of chronic disease required studies of a kind that had not hitherto been carried out. It was necessary to identify groups of men and women now in middle or late life whose size at birth had been recorded at the time [1]. Low birthweight is now known to be associated with increased rates of coronary heart disease and the related disorders, stroke, hypertension and type 2 diabetes. Associations between low birthweight and later disease have been extensively replicated in studies in different countries. They extend across the normal range of birthweight and depend on lower birthweights in relation to the duration of gestation rather than the effects of premature birth. The associations are thought to be consequences of developmental plasticity, the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development [3].

Research into the developmental origins of disease has focused on the nutrient supply to the baby, while recognizing that other influences, such as hypoxia, stress and maternal size also influence fetal growth. This focus on fetal nutrition was endorsed in a recent review [4]. The availability of nutrients to the fetus is influenced by the mother’s nutrient stores and metabolism, as well as by her diet during pregnancy.
Recent observations have shown that impaired growth in infancy and rapid childhood weight gain exacerbate the effects of impaired prenatal growth. Tables 1 and 2 are taken from studies of 8,760 men and women from the Helsinki birth cohort [5]. Table 1 shows the simultaneous effect of birthweight and body mass index at 2 years of age, divided into thirds, on hazard ratios for coronary heart disease. The highest hazard ratios were among subjects with birthweights of $<3.0$ kg and body mass indices at 2 years of age of $<17$ kg/m$^2$. Table 2 shows the simultaneous effects of body mass index at 2 and 11 years of age. The highest hazard ratios were among people with body mass indices of $<16$ kg/m$^2$ at 2 years of age and $>17.5$ kg/m$^2$ at 11 years of age. The hazard ratios in tables 1 and 2 were little changed if they were adjusted for socioeconomic status or income in adult life.

The placenta is likely to play a central role in programming the baby, but little is known about this. Coronary heart disease and the disorders related to it arise through a series of interactions between environmental influences and the pathways of growth and development that precede them. We are beginning to understand the processes through which different paths of development initiate cardiovascular

### Table 1. Hazard ratios (95% confidence intervals) for coronary heart disease according to birthweight and body mass index (BMI) at 2 years of age for boys and girls combined

<table>
<thead>
<tr>
<th>Birthweight, kg</th>
<th>BMI at age 2, kg/m$^2$</th>
<th>BMI at age 2, kg/m$^2$</th>
<th>BMI at age 2, kg/m$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;16</td>
<td>16–17</td>
<td>&gt;17</td>
</tr>
<tr>
<td>&lt;3.0</td>
<td>1.9 (1.3–2.8)</td>
<td>1.9 (1.2–3.0)</td>
<td>1.3 (0.7–2.2)</td>
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<tr>
<td>3.0–3.5</td>
<td>1.5 (1.0–2.1)</td>
<td>1.6 (1.1–2.2)</td>
<td>1.2 (0.8–1.8)</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>1.7 (1.2–2.5)</td>
<td>1.5 (1.1–2.2)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### Table 2. Hazard ratios (95% confidence intervals) for coronary heart disease according to body mass index (BMI) at 2 and 11 years of age for boys and girls combined

<table>
<thead>
<tr>
<th>BMI at age 2, kg/m$^2$</th>
<th>BMI at age 11, kg/m$^2$</th>
<th>BMI at age 11, kg/m$^2$</th>
<th>BMI at age 11, kg/m$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td>1.6 (0.8–3.3)</td>
<td>2.4 (1.2–4.9)</td>
<td>3.0 (1.4–6.3)</td>
</tr>
<tr>
<td>16–17</td>
<td>1.4 (0.7–3.1)</td>
<td>1.6 (0.8–3.3)</td>
<td>1.9 (0.9–3.9)</td>
</tr>
<tr>
<td>&gt;17</td>
<td>1.0</td>
<td>1.3 (0.6–2.7)</td>
<td>1.1 (0.5–2.3)</td>
</tr>
</tbody>
</table>
disease. The changes occur at different levels and include allocation of stem cells and alteration in gene expression in the embryo, changes in organ growth, and alteration in metabolic and endocrine set-points. These changes can make the affected systems more vulnerable to disruptive influences in postnatal life.

References

The Role of Growth in Heart Development

Kent L. Thornburg, Samantha Louey and George D. Giraud

Barker et al. [1] showed in one English population that the risk of mortality from ischemic coronary heart disease is more than twofold higher in babies born at the 2.26-kg end of the birthweight scale than those born at the 4.1-kg end of the scale. Subsequent studies have shown that the growth trajectory of the baby before birth is dependent upon the nutrient environment during the peri-conceptional period and the nutrient flow into the fetus during gestation. It is now well recognized that babies born small at birth are vulnerable for a host of chronic disease conditions in adult life, including coronary artery disease, hypertension, type 2 diabetes and osteoporosis.

The heart has several developmental windows of time when it is affected by environmental stressors. One period is during the last half of gestation when cardiomyocytes stop dividing and become terminally differentiated so that they cannot divide further. These cells change from being mononucleated to being binucleated. If the heart is nutrient-deprived when these processes are normally occurring, proliferation and maturation of the cardiomyocytes may be suppressed. This process appears to be nutrient-dependent.

The fetus acquires all nutrients including oxygen via the placenta. Thus, if the placenta is poorly constructed or lacks appropriate numbers of nutrient transporters, the flow of nutrients to the fetus will be impaired. When the exchange area of the placenta is experimentally reduced by infusing 50 μm microspheres into the placenta of a mid-gestation sheep fetus, the fetus becomes hypoxemic and its growth is dramatically slowed as in human intrauterine growth retardation [2]. However, unlike conditions of fetal hypertension or chronic hypoxemia at altitude, the growth of the heart in the embolized fetus slows to nearly a standstill. Indices of cardiomyocyte proliferation and binucleation show that the fetal myocardium is growing and maturing little. Because it is well known that insulin-like growth hormone-1 (IGF-1)
levels are reduced under conditions of placental insufficiency, it appears that depressed nutrient transport lowers IGF-1 levels. While the regulation of growth of the myocardium is under the control of chemical signals including angiotensin II, cortisol, thyroid hormone and insulin-like molecules, IGF-1 is especially important in regulating the proliferation of cardiomyocytes. When an IGF-1 analog is administered to the fetus over a period of several days, the heart grows out of proportion to other organs [3].

The experiments of Davis et al. [4] demonstrated the enormous capacity of the coronary tree to remodel itself under conditions of anemia. When the hematocrit of the fetal heart is reduced over several days, the coronary arteries are able to carry greater and greater flow rates during dilation with adenosine. In fact, at the normal fetal blood pressure of 40 mm Hg, the heart muscle receives more than 1 liter per minute for every 100 g of tissue in a fetus that has been anemic over several days. This is more than 3 times the flow rate for a normal fetus that has never been anemic (fig. 1). Thus, it is clear that growth of the fetal coronary tree is highly plastic before birth and that an increase in coronary architecture lasts into adulthood. It is likely that other

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**Fig. 1.** Maximal coronary blood flow at normal arterial pressures for the fetus and the adult sheep. Maximal flow was obtained during continuous adenosine infusion. For the fetus, flow data are shown in the same near-term fetus at two hematocrits (Hct): normal 32%, and following 6 days of anemia with Hct at 16%. Both fetal flows were measured when arterial pressure was 40 mm Hg and the coronary vessels were maximally dilated. For the adult, flow data were obtained from a 6-month-old adult sheep after having been made anemic as a fetus for only 6 days (expt; prepartum blood transfusion returned Hct to normal levels) compared to its normal twin that was never anemic. Arterial pressure was 100 mm Hg and the coronary vessels were maximally dilated.
stressors including nutritional insults will alter the coronary tree for life in ways that impart vulnerability for coronary artery disease.

In summary, the fetal heart is highly plastic and subject to abnormal deviations from its optimal growth patterns by nutritional insults. These include abnormal numbers of cardiomyocytes and abnormal architecture and function of the coronary tree.

References

Osteoporosis is a skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The cumulative incidence of fracture from age 50 years is estimated at around 50% among white women and 20% among white men. Although most effort in fracture prevention has been directed at retarding the rate of age-related bone loss, and reducing the frequency and severity of trauma among elderly people, evidence is growing that peak bone mass is an important contributor to bone strength during later life. The normal patterns of skeletal growth have been well characterized in cross-sectional and longitudinal studies. It has been confirmed that boys have higher bone mineral content, but not volumetric bone density, than girls. Furthermore, there is a dissociation between the peak velocities for height gain and bone mineral accrual in both genders. Puberty is the period during which volumetric density appears to increase in both axial and appendicular sites. Many factors influence the accumulation of bone mineral during childhood and adolescence, including heredity, gender, diet, physical activity, endocrine status and sporadic risk factors such as cigarette smoking. Measures to maximize bone mineral acquisition, particularly through encouraging physical activity and adequate dietary calcium intake, are likely to impact upon fracture risk in later generations.

Although there is evidence to suggest that peak bone mass is inherited, current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk. Evidence has also begun to accrue that fracture risk might be modified by environmental influences during intrauterine or early postnatal life, which modify the trajectory of skeletal growth and mineral accrual. The relatively rapid rate of mineral gain during this period, coupled with the plasticity of skeletal development in utero, offer the possibility of profound interactions between the genome and early environment in this stage of the life course; it is one example of a ubiquitous
phenomenon (developmental plasticity) which enables one genotype to give rise to a range of different physiological or morphological states in response to different prevailing environmental conditions during development. Its essence lies in the critical period during which a system is plastic and sensitive to the environment, followed by a loss of that plasticity and a fixed functional capacity.

The evidence that osteoporosis risk might be modified in this way stems from four groups of studies: (1) epidemiological studies which confirm that subjects who are born light and whose growth falters in the first year of postnatal life have significantly lower bone size and mineral content, at age 60–75 years; (2) cohort studies demonstrating that subsequent lower trajectories of childhood growth are associated with an increased risk of hip fracture among such men and women; (3) detailed physiological studies of candidate endocrine systems which might be programmed have shown that birthweight and growth in infancy alter the functional settings of the GH/IGF-1, and hypothalamic pituitary adrenal axes, and (4) studies characterizing the nutrition, body build and lifestyle of pregnant women and relating these to the bone mass of their newborn offspring, have identified a number of important determinants of reduced fetal mineral accrual (maternal smoking, low maternal fat stores and maternal vitamin D deficiency, intense levels of weight-bearing physical activity in late pregnancy). Follow-up studies of randomized controlled trials of vitamin D supplementation in infancy suggest persisting benefits in adolescence and

![Fig. 1. Relationship between maternal 25(OH)-vitamin D status, cord calcium and childhood WBBMC.](image-url)
young adulthood. These data suggest that undernutrition and other adverse influences arising in fetal life or immediately after birth have a permanent effect on body structure, physiology and metabolism, which might independently influence the later risk of osteoporotic fracture.

References

The Role of Genes in Growth and Later Health

Johan G. Eriksson

Epidemiological studies have shown that there is a strong association between birth size and later health. It has repeatedly been shown that, e.g., an increased coronary heart disease risk associated with a small body size at birth is a consequence of growth restriction during fetal life – not prematurity. These findings support the view that maternal and fetal undernutrition are important underlying risk factors for cardiovascular disease. The ‘fetal insulin hypothesis’ proposed that one genotype could be the common denominator altering intrauterine growth as well as influencing adult health outcomes [1]. Today, there is no strong evidence suggesting that any single common gene or gene variant would explain the common association observed in epidemiological settings between birth size and later health outcomes. It is important to keep in mind that there might be gene–environment interactions not easily identified in genetic studies with little or no information on early growth.

The Helsinki Birth Cohort Study (HBCS) comprises two study cohorts consisting of 15,846 individuals. The older cohort includes 7,086 individuals born 1924–1933, with information on birth characteristics as well as growth data between 7 and 15 years of age. Clinical examinations of 500 individuals from the cohort at the age of ~70 years have provided more detailed information on metabolic and genetic aspects and their associations with growth and adult health outcomes.

The peroxisome proliferator-activated receptor (PPAR) genes play a major role in the regulation of glucose, lipid and energy metabolism. A common missense mutation in the functional domain of the human PPARγ-2 gene resulting in a substitution of proline by alanine in codon 12 modulates the transcriptional activity of the gene. In the HBCS elderly carriers of the Ala allele had lower fasting insulin and glucose concentrations compared to the carriers of the Pro12Pro genotype. There were no differences between the groups in body size at birth or during childhood. The association between a small body
size at birth and insulin resistance was observed only in individuals with the high risk Pro12Pro genotype (table 1). In other words, the Ala allele was protective against the negative effect of a small body size at birth. There was a strong interaction between birth size and the PPAR-γ2 genotype (p = 0.03) [2]. The Pro12Pro genotype was also associated with a higher cumulative incidence of type 2 diabetes (p = 0.08). This association was however confined to people who were ≤49 cm in length at birth, among whom the cumulative incidence of type 2 diabetes was 24.5%, compared with those >49 cm in length at birth, whose cumulative incidence was 14.3% (p = 0.02) [3].

The plasma cell glycoprotein (PC-1) gene regulates the insulin signaling pathway. PC-1 inhibits the autophosphorylation of the insulin receptor and impairs post-receptor insulin signaling. The 121Q variant of the PC-1 gene has a greater inhibitory action on the insulin receptor

Table 1. Mean fasting insulin concentrations (pmol/l) according to PPAR-γ gene polymorphism and birthweight

<table>
<thead>
<tr>
<th>Birthweight, g</th>
<th>&lt;3,000</th>
<th>3,500</th>
<th>&gt;3,500</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro12Pro</td>
<td>84</td>
<td>71</td>
<td>65</td>
<td>0.003</td>
</tr>
<tr>
<td>Pro12Ala/Ala12Ala</td>
<td>60</td>
<td>60</td>
<td>65</td>
<td>0.31</td>
</tr>
<tr>
<td>p value#</td>
<td>0.008</td>
<td>0.02</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

*p value for the difference among birthweight groups.
*p value for the difference between the Pro12Pro and Pro12Ala/Ala12Ala genotypes.
*p value for interaction 0.03 (birthweight and genotype).

Fig. 1. Prevalence of type 2 diabetes according to length at birth and the PC-1 gene polymorphism. *p = 0.005. p for interaction (genotype and birth length) <0.05.
than the 121K variant. Carriers of the 121Q allele had a significantly higher prevalence of type 2 diabetes and hypertension combined, but only in the presence of a small body size at birth. Figure 1 shows the prevalence of type 2 diabetes in relation to birth size and K121Q polymorphism of the PC-1 gene. Only the carriers of the high risk 121Q variant had a higher diabetes prevalence in association with a small body size at birth [4].

These findings could be interpreted as manifestations of gene early environmental interactions and illustrate the importance of the early environment in relation to risk factors for type 2 diabetes and related disorders. Acknowledging the interactions between early growth and genotypes might help us to design individual therapies as well as to plan lifestyle interventions.

References

Maternal Nutrition Before and During Pregnancy

Theresa O. Scholl

Apart from exceptional circumstances such as famine, the influence of the maternal diet on fetal growth and gestation duration is controversial. Many signs consistent with poor maternal nutritional status are present in women who deliver preterm. These include a low pregravid body mass index, inadequate weight gain for gestation and faltering fetal growth. Apart from food shortages, periods of extended maternal fasting are associated with increased production of corticotropin-releasing hormone and an increased risk of preterm delivery [1]. In animals a short interval of food deprivation around the time of conception – from 2 months before to the first month after conception – increases risk of preterm birth [1]. And, in the classic study of wartime famine in Holland, a first trimester exposure at the peak of the famine, in combination with another factor, possibly infection, was linked to an excess of preterm births, and to an increase in infants weighing <2,000 g. There was also a rise in the frequency of malformations of the central nervous system including spina bifida [2].

The Dutch famine is best known for its effects on fetal growth and third trimester exposure to intense famine resulted in decreased maternal postpartum weight and reduced infant birth weight [2]. During the famine, reduced maternal intake following small, infrequent meals would have resulted in lower circulating levels of maternal glucose that would have given rise to slower fetal growth, smaller birth size and an increased risk of fetal growth restriction. Maternal glucose production is also influenced by the type of carbohydrate in the diet. A low dietary glycemic index will alter maternal blood glucose production and give rise to reductions in fetal growth and infant weight at birth [3].

Reduced food intake during famine would also reduce the concentration of micronutrients in the maternal diet. Emerging evidence suggests that the use of micronutrients containing prenatal vitamins before and during pregnancy is associated with reductions in adverse
pregnancy outcomes [1]. Two micronutrients (iron, folate) have effects on pregnancy outcome that have been shown with some consistency. Iron is essential for the formation of hemoglobin to transport oxygen and for the synthesis of enzymes that use oxygen to provide cellular energy. Maternal anemia is linked to an increased risk in adverse outcomes during pregnancy; randomized trials now suggest that poor outcomes such as preterm delivery and low birthweight (LBW) can be reduced with iron supplementation [1].

Fortification of flour and cereal products in the United States with folic acid since 1998 has been associated with a 19% decline in risk of live-born infants with neural tube defects, along with changes in biomarkers of folate status, including increases in serum and red cell folate and a decline in homocysteine levels. An absolute deficiency of folate – from a diet inadequate to meet the needs of pregnancy – will interfere with the growth of the conceptus and increase the risk of preterm delivery and LBW. A metabolic effect of folate deficiency is an elevation in homocysteine. Women with high homocysteine levels are likely to have current or past reproductive histories that include increased risks of preeclampsia, preterm delivery, LBW, and fetal growth restriction [4]. Thus, maternal nutrition and nutritional status before and during pregnancy are associated with decreased birthweight and an increased risk of LBW, measured either as preterm delivery or restricted fetal growth. This is particularly germane in the developing world where much of the LBW that occurs is related to the mother’s past and present nutritional status. By affecting fetal growth and gestation, it is plausible that maternal nutrition may have a long-term influence on the risk of chronic disease in later life [5].

References

Health and diseases are generally perceived to be caused genetically. It is meanwhile accepted, however, that alterations to the intrauterine and early postnatal nutritional, metabolic, and hormonal environment may also predispose to disorders and diseases throughout later life. Studies in the offspring of diabetic mothers (ODM) have decisively contributed to this perception [1–4]. Alterations in the fetal and neonatal environment ‘experienced’ by ODM may epi-genetically ‘program’ the development of, e.g., obesity, diabetes mellitus and metabolic syndrome in later life. Low birth weight is also accompanied by increased later risk [5]. The pathophysiological mechanisms responsible for perinatally acquired ‘malprogramming’ are still unclear.

It has long been known, however, that hormones are environment-dependent organizers of the developing ‘neuroendocrine-immune network’, which regulates all fundamental processes of life. When present in non-physiological concentrations during ‘critical periods’ of development, induced by an altered intrauterine and/or neonatal environment, hormones can therefore also act as ‘endogenous functional teratogens’ [1]. This means that, during cybernetogenic ‘self-organization’ of neuroendocrine regulatory systems, abnormal concentrations of the respective hormones may induce a lasting ‘malprogramming’ and ‘malfunction’ throughout life [4].

Fetal and neonatal hyperinsulinism is the pathognomic feature in ODM. Hyperinsulinism also occurs as a result of neonatal overfeeding. Epidemiological, clinical, as well as experimental data obtained by our group indicate that insulin itself, when occurring in elevated concentrations during perinatal life, may ‘program’ the development of obesity and diabetes [3, 4]. Similarly this may occur due to maternal overweight accompanied by increased fetal food supply and neonatal overfeeding. Moreover, a modified neural coding causally involved and
the resultant adipogenic and diabetogenic disposition can even be passed on to succeeding generations materno-fetally in a non-hereditary way, because of the resulting metabolic and hormonal alterations in the affected female offspring during their own gestation.

These aspects exemplarily reveal that our general view on the principles of etiopathogenesis should be extended. Health and disease are not only caused by genes and exposures to environmental risk factors but also result from the nutritional, metabolic, and hormonal conditions during critical periods in early life. For instance, maternal overweight, gestational diabetes, and neonatal overfeeding may lead to a perinatally acquired epigenetic disposition for obesity, diabetes, metabolic syndrome and subsequent cardiovascular diseases (fig. 1).

From a clinical point of view, general screening and therapy of all types of diabetes during pregnancy as well as avoidance of early postnatal overfeeding and, hence, fetal or neonatal hyperinsulinism are therefore recommended. These measures might serve as causal approaches to a genuine primary prevention, exemplarily revealing
critical new implications for chances and challenges of perinatal preventive medicine in the future [4].

References


Newborn size is the result of intrauterine growth. In clinical practice, fetal growth patterns, and intrauterine growth velocities are analyzed by serial sonographic measurements. But empirical follow-up studies have relied on anthropometric measurements of the neonate. Premature neonates are often intrauterine growth restricted (IUGR). When gestational age is unknown, low birthweight (LBW; <2,500 g) is used as a proxy for IUGR. Small for gestational age (SGA), defined as a birth weight <10th percentile for gestational age, is the preferred substitute for IUGR. Customized antenatal growth charts allow adjustment for constitutional variables, and are better predictors for neonatal outcome.

The prevalence of premature births is increasing in developed countries. However, in developing countries LBW and IUGR are more prevalent. Worldwide, at least 20.5 million newborns per year were calculated to be LBW, approximately 30 million or 24% were IUGR [1]. The major determinant for IUGR in developed countries is smoking during pregnancy. Of major importance in developing countries are low energy intake and poor nutritional status of the mother (table 1) [2].

The mean birthweights were higher when undernourished mothers received calorie or balanced protein/calorie supplements. High protein supplements may increase the risk of IUGR. Micronutrient supplements in malnourished women, e.g. iodine, iron, zinc and folic acid, reduced the occurrence of IUGR. Giving up smoking in pregnancy increased newborn birthweight. Preventive measures are most efficient when started before pregnancy.

SGA newborns have about the same percentage of lean body mass as appropriately grown (AGA) and large for gestational age (LGA) infants, but a lower fat mass (table 2) [3]. Follow-up studies of persons born SGA have consistently shown a positive association between
birthweight and lean body mass, whereas associations with adiposity were more variable.

Although most SGA infants catch-up in length, even in developed countries more than 10% remain short adults. With catch-up weight (but not height) a transition towards central adiposity developed, concomitantly with insulin resistance, increased triglyceride, and decreased high density lipoprotein-cholesterol values. The risk of obesity in the offspring of mothers who had suffered from hunger or who had

Table 1. Determinants of intrauterine growth restricted newborns in developing and developed countries, listed in decreasing order of importance

<table>
<thead>
<tr>
<th>Developed country</th>
<th>Developing country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Low energy intake, low gestational weight gain</td>
</tr>
<tr>
<td>Low energy intake, low gestational weight gain</td>
<td>Low pre-pregnancy BMI</td>
</tr>
<tr>
<td>Low pre-pregnancy BMI</td>
<td>Short stature</td>
</tr>
<tr>
<td>Primiparity</td>
<td>Malaria</td>
</tr>
<tr>
<td>Low stature</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>Primiparity</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>Pregnancy-induced hypertension</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Other genetic factors</td>
<td>Other genetic factors</td>
</tr>
<tr>
<td>Alcohol, drugs</td>
<td></td>
</tr>
</tbody>
</table>

BMI = Body mass index. Adapted from Kramer [2].

Table 2. Body composition of small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA) German and Swiss newborns, measured by DXA

<table>
<thead>
<tr>
<th>SGA (n = 26)</th>
<th>AGA (n = 118)</th>
<th>LGA (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks</td>
<td>38.2 ± 2.7</td>
<td>38.3 ± 3.0</td>
</tr>
<tr>
<td>Age at study, days</td>
<td>5.0 ± 2.4</td>
<td>4 ± 2.2</td>
</tr>
<tr>
<td>Birthweight, g</td>
<td>2,320 ± 660</td>
<td>3,150 ± 680</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>46.1 ± 4.8</td>
<td>49.7 ± 3.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>10.4 ± 1.4</td>
<td>12.2 ± 1.5</td>
</tr>
<tr>
<td>Fat mass, g (% BW)</td>
<td>210 ± 100</td>
<td>430 ± 190</td>
</tr>
<tr>
<td>Lean body mass, g</td>
<td>2,080 ± 520</td>
<td>2,650 ± 520</td>
</tr>
<tr>
<td>Bone mineral content, g</td>
<td>39.2 ± 16.0</td>
<td>54.5 ± 15.8</td>
</tr>
</tbody>
</table>

BMI = Body mass index; BW = birthweight.
smoked during pregnancy was higher if the insult had occurred in the first trimester. In adults the cortisol concentration fell with increasing birthweight. A meta-analysis of 14 studies found a U-shaped relation between birthweight and later life risk of type 2 diabetes.

The term ‘thrifty phenotype’ was proposed by Hales and Barker [4] to describe the metabolic adaptation of a malnourished fetus that allows him to survive in a deprived environment. Gluckman and Hanson [5] elaborated the concept of the ‘predictive adaptive response’. Adult diseases develop when the SGA subject succumbs to abundance instead of the anticipated deprivation.

Epigenetic modification controls the placental supply to fetal demands of nutrients from the earliest stage of feto-placental development. Hormones play a central role in regulating fetal growth and development [6]. The glucocorticoids are key regulators, they act directly on genes and indirectly through changes in the bioavailability of hormones. Nutritional or hormonal exposure during fetal or early neonatal life may be important in the subsequent development of the appetite regulatory system, e.g. by prenatal undernutrition and postnatal hypercaloric nutrition.

Of main importance in the prevention of adult diseases induced by disadvantageous environments in fetal and early life is to propagate personal and social resources, especially of females, for a good start to a bright future.

References

Growth and Nutrition the First Six Months

L.Å. Hanson, S. Zaman, B. Werner, L. Håversen, C. Motas, M. Moisei, I. Mattsby-Baltzer, S. Lange, M. Banasaz, T. Midtvedt, E. Norin and S.-A. Sifverdal

Growth Curves and Infant Feeding

Using previous reference tables (CDC, USA), breastfeeding resulted in enhanced growth during the first 2 months but reduced growth during months 3–12 compared to infants fed formula throughout infancy. The new WHO growth curve gives the normative growth including the effects of breastfeeding on growth.

In a study of 3,107 Swedish children born in 1981, we found the lowest growth rate appearing among those breastfed <30 days, thereafter those breastfed for 30–150 days, indicating a dose relationship of human milk (table 1). Girls breastfed for <30 days showed a negative association with adult height.

The WHO growth curve does not take into consideration the diet of the breastfeeding mother. In rats we investigated the effect of variations in essential fatty acids in the maternal diet during late pregnancy and lactation. Using an intake of n-6/n-3 fatty acids with the ratio of 9 or a low ratio of 0.4, the low ratio was shown to be linked to lower leptin levels and body weight, length, inguinal fat pads and adipocyte size in the offspring [1]. In adult age, the male offspring in the high n-6/n-3 ratio group showed increased systolic blood pressure and serum triacylglycerol levels [2]. A diet causing a perinatal deficiency in essential fatty acids was linked to increased body weight and changes in bone structure in adult male rats [3].

In humans, supplementing the mother’s intake of n-3 fatty acid-containing fish or corn oil did not have any effect on infantile growth. Breastfeeding seems to induce higher leptin, but lower ghrelin and IGF-1 levels in infants. Milk leptin levels after 1 month of breastfeeding were related to maternal blood plasma leptin and inversely to maternal body mass index [4].
**Table 1.** Parameter estimates and 95% confidence intervals for the Walker and Walker model with the first of the five phases of growth in girls

<table>
<thead>
<tr>
<th>Parameter estimate (95% CI) for reference group (breastfed &gt;150 days)</th>
<th>Estimated difference (95% CI) compared to reference group for children breastfed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30–150 days</td>
</tr>
<tr>
<td>Adult height</td>
<td>167.6 (167.1; 168.2)</td>
</tr>
<tr>
<td>Growth phase I (neonatal)</td>
<td></td>
</tr>
<tr>
<td>Age at peak height velocity</td>
<td>−0.12 (−0.14; −0.11)</td>
</tr>
<tr>
<td>Growth rate coefficient</td>
<td>5.97 (5.76; 6.20)</td>
</tr>
</tbody>
</table>

Significant group differences are printed in bold type.
Factors Influencing Growth in the Neonate

There are many threats to nutrient uptake, especially in the neonatal phase. Adaptations from birth prevent the catabolic effects of mucosal exposure to colonizing microbes activating Toll-like receptors (TLRs) which, when recognizing microbes, induce production of proinflammatory cytokines which increase leptin, and decrease appetite. In newborn mice exposure to microbes in the birth canal tolerized the gut mucosal TLRs. This did not occur among mice delivered by cesarean section. Human milk modulates TLRs and contains soluble TLR2, blocking microbial binding to mucosal TLR.

Milk lactoferrin kills microbes, blocks inflammatory responses and acts like a heat shock protein, possibly supporting protein uptake. Lactoferrin may enhance phosphorylation and the uptake of nucleotides. This agrees with germ-free animals using gut microbes as a source of nucleotides.

We found that the peptide had an antisecretory factor which is inducible in human milk and prevents mastitis [5]. It also has anti-diarrheal effects in infants and children, which supports growth.

References
Growth in the First Two Years of Life

Dennis M. Bier

Growth has been defined variously and the issue of definition is not merely academic when evaluating the relationships between growth, healthy development and pathological consequences later in life, as nutritionists often define growth in the context of increasing body weight, while pediatric endocrinologists view growth primarily in the context of increasing stature. Compared to other periods of life, infancy is a period of rapid growth, but the relative relationships among rates of linear growth, body mass accretion and brain growth vary dramatically during the first 2 years of life. The large genetic contributions to growth in length and weight are extensively documented. Presumably, there are similar genetic contributions to brain growth, but these are less well studied.

Pediatricians have long appreciated the nutritional, parental, and social environmental contributions to CNS development (environment × gene interactions) and have long recognized that the observed secular increase in height is due to environmental factors, even though genetic contributions to height are greater than for all other adult indices of successful growth. Until recently, however, environmental contributions to weight accretion have almost always been addressed in the context of failure to thrive. This situation has changed due to extensive data suggesting that rapid postnatal growth may come at the ‘cost’ of increasing risks for the development of chronic diseases in adult life.

Traditional biochemical pathways provide the means by which an infant can read his or her current environment. Recently, specific molecular and cellular mechanisms have been identified that describe how the infant can retain into adult life the ‘memory’ of an environment × gene interaction that took place during a critical period of development. Among others, these include epigenetic silencing of gene expression via DNA methylation, clonal selection, and permanent anatomic alterations in hypothalamic dendrite formation, growth and
pruning. What remains unanswered is how a developing infant makes the decisions about its future environment, if it does. Does the infant, during development, try to ‘predict the future’ and alter developmental pathways to accommodate the prediction, or are adult consequences of developmental events merely set by the environmental conditions present during the critical developmental period? One parsimonious hypothesis is that the infants only read their current environment and do so with a range of accuracy similar to that observed for all other biological processes. Thus, a defined fraction of infants misinterpret to some degree the true state of their current environment and this misinterpretation persists into adult life. A second parsimonious hypothesis is that genotypes determine both the distribution of current and future population responses and position an individual infant within that distribution. In this scenario, both current and future environmental conditions merely shift the population distribution to the left or right of the original population center. A third theory postulates that the developing organism does, in fact, make predictions about the future and that these are based on the evolutionary principle of Darwinian fitness. Thus, during the course of human evolution when environmental conditions during development have been largely marginal or inadequate, the population distribution of genes shifted toward those that are ‘thrifty’ and, likewise, thrifty phenotypic adaptations were selected for because they conferred advantages for survival and reproduction. Thus, in the past, those who predicted poorly were selected against and the chronic disease consequences of large size and weight were not readily observed. However, the modern environment has led to human life spans far beyond those anticipated by a prediction model based on reproductive fitness. Thus, current poor predictions during development are unmasked as individuals age beyond the reproductive age, resulting in the consequences of chronic disease. Delineation of the validity of these hypotheses is crucial to understanding the fundamental biological principles of now well-observed events; however, it is difficult to see precisely how these individual hypotheses can be tested in human beings.
Effects of Early Environment on Mucosal Immunologic Homeostasis, Subsequent Immune Responses and Disease Outcome

Pearay L. Ogra and Robert C. Welliver Sr.

The human neonate, having lived in a relatively sterile uterine environment during its gestation, is suddenly forced into the outside world and exposed continuously to a plethora of microbial agents and other environmental influences. The mucosal surfaces constitute the primary portals of exposure and possible entry for virtually all pathogenic organisms, dietary macromolecules and other soluble and cellular elements in the external environment. These surfaces also function as the first line of defense and the principal sites of initial interaction between the mammalian host and the external environment. The mucosal mechanisms of defense have continued to evolve and are repeatedly shaped by past learning from the changing conditions of the environment in a manner similar to the evolution of life itself.

Although the evolution of man and its hominid ancestors are relatively recent events in evolutionary biology, their appearance has had a remarkable impact on the overall biologic ecosystem. For example, the introduction of man-made products such as vaccines, chemotherapy and immunotherapy for many serious and fatal infectious processes, and improvements in human nutrition and societal hygiene have contributed immensely to the elimination of many infectious diseases, prolongation of life, and exponential growth in the human global population. However, human interventions have also been accompanied by many unanticipated untoward effects. These include the acquisition of pathogenicity for otherwise benign microorganisms, the emergence of new pathogens, the re-emergence of previously controlled diseases, and the emergence of several new pathologic states, including allergic and autoimmune disease processes.

The mechanism of mucosal defenses which have evolved to date include the innate and adaptive immunity. The external environmental
factors which contribute significantly to the mechanisms of mucosal
defense include mammalian lactational products, and the environmental
microbial flora available to the developing neonate and infant.

Innate immune mechanisms develop before the acquisition of
adaptive immunity by natural selection, with defined specificity for
infectious agents, more specifically for the pathogen-associated mole-
cule patterns. These are pathogen (and not host) generated determin-
ants which are essential for the survival and pathogenicity of the
organisms. They are highly conserved and are present in an entire
class of organisms. These include bacterial lipoproteins, lipopolysac-
charide (LPS), peptidoglycan, lipoteichoic acid, mannans, bacterial
DNA, double-strand DNA, and glucans.

The recognition of pathogen-associated molecule patterns is medi-
ated through specific pathogen recognition receptors (PRRs) in the
mucosal surfaces. These receptors are germ line-coded, and the speci-
ficity for each receptor is genetically predetermined. Several classes of
PRRs have been identified during the past decade. These include
secreted, endocytic, and signaling classes. The PRRs function in
opsonic-phagocytic activity, uptake and delivery to lysosomes and anti-
gen presentation, signal transduction, activation of immune response
genes, NF-κB induction and expression of a variety of immunoregula-
tory or inflammatory gene products. Other pathogen recognition recep-
tors identified to date include C-reactive protein, serum amyloid
protein, LPS-binding protein, macrophage receptors with collagenous
structures, double-stranded RNA-activated protein kinase, the caspase-
recruitment, and nucleotide-binding oligomerization domains of the
signaling PRRs. The toll-like receptors (TLRs) have been studied most
extensively. At least 10 forms of TLRs have been identified in man.
Different TLRs are expressed on different tissue surfaces and mucosal
cells including dendritic cells, intraepithelial cells, macrophages, B and
T lymphocytes and natural killer cells. Most TLRs function as essential
receptors for pathogen-associated molecule patterns, and modulate
development of proinflammatory or immunoregulatory cytokine
responses, and thus impact significantly on the final outcome of spe-
cific adaptive immune responses. The cellular responses induced by
TLRs include increased surface expression of important co-stimulatory
molecules, production of defensins and other antimicrobial peptides
and microbicidal components, and apoptosis of phagocytic cells. The
TLR-signaling mechanisms involve activation of NF-κB nucleic trans-
scription factors which regulate many genes including those involved
in the expression of proinflammatory cytokines.

The role of TLRs in the pathogenesis of immunologically medi-
atated disease remains to be determined. However, many TLRs have
been linked to the evolution of such diseases as arteriosclerosis and heart diseases (TLR-1/2, TLR-4), allergy (TLR-4), HIV infection (TLR-2), interleukin 1 receptor-associated kinase 4 deficiency (involving signaling for TLR-2/1, 2/6, 5, 7, 8, 9), defects of NF-κB essential modalities associated with incontinentia pigmenti in females and IκB defects associated with partial blockage of NF-κB-signaling process. Furthermore, many single nucleotide polymorphisms have been noted in several TLR genes, although their role in any functional carcinogenesis has not been clearly established.

Currently there is intense interest in the use of TLRs in developing therapeutic modalities to treat a variety of diseases in man. These include the use of imiquimod and isatoribine as TLR-7 agonists. The administration of oligodeoxynucleotides containing CpG motifs possibly via binding to TLR-9 have been employed to enhance Th1 response in cancer therapy or allergen immunotherapy.

Because of their unique location and their interaction with the external environment, the mucosal surfaces have developed complex barriers of adaptive immunity in addition to the natural barrier of innate immunity. The mucosal surfaces of the respiratory, intestinal and genital tracts must discriminate benign antigens, food protein, inhaled antigen and sexually transmitted sperm protein and cellular products from infections and other potentially pathogenic or toxic agents. In addition to the components of innate immunity, such functions are mediated through many nonspecific, but highly effective barriers in mucosal epithelium, mucins, a variety of other protective factors, and specific adaptive immunity.

The adaptive mucosal immune mechanisms consist of antigen-induced B and T lymphocyte products. These products are designed to respond by antigen-presenting cells (APC) such as dendritic cells in association with major histocompatibility complex (MHC) molecules. The antigen-mediated effects on B cells result in the expression of specific secretory IgA, and to a smaller extent IgM and IgG. The cellular immune responses are mediated by diverse sets of T lymphocytes. These include CD4+ helper (Th1, Th2) cells, CD8+ (suppressor-cytotoxic), and regulatory T cells (T reg). These T cell subsets respond to antigens processed on the APC-MHC complex described above.

CD4+ T cells respond to processed antigens in association with MHC class II molecules. CD4+ Th1 cells secrete predominantly IFN-γ, tumor necrosis factor-α (TNF-α), IL-2, and IL-12. The Th2 subset of CD4+ T cells regulates B cell differentiation by secreting IL-4, IL-5, and IL-13. The CD8+ T cells respond to processed antigens in association with the MHC class I molecule and mediate suppression and antigen-specific cytotoxic activity against infected cells. The regulatory
T cell (Tr1, Th3B) cells include CD4+ CD25+ T cells, which can inhibit or downregulate Th1 or Th2 responses via cell to cell contact or by production of specific cytokines, such as IL-10, TGF-β.

The ultimate expression of the innate and adaptive immune responses are greatly influenced by the external environment, in particular by the microbial flora during the neonatal period and early infancy. It is estimated that there are over 100 trillion microbes living in or on a normal human being. The intestinal mucosal lumen is estimated to be the home of over 10^{12} organisms/g of intestinal contents. The nature of the mucosal immune response is significantly influenced by a variety of environmental factors including diet, breastfeeding, use of antimicrobial agents, and prevailing socioeconomic conditions.

Studies carried out during the past 2 decades have clearly demonstrated the importance of innate immunity and microbial flora in the eventual outcome of adaptive immune responses to specific pathogens or dietary proteins or autoantigens.

It has been shown that LPS, lipoprotein, peptidoglycans, zymosan, and lipoteichoic acid are the natural ligands for TLR-1, 2, and 6. Such ligand and TLR interaction results in expression of precursor Th1, Th2 and Trg cellular responses through the production of IL-12, and IL-10.

Other studies have suggested that different organisms serve as specific ligands for different TLRs, such as Escherichia coli LPS, HSP60/70, or RSV for TLR-4; bacterial flagellen for TLR-5; Toxoplasma gondii profilin for TLR-11; dsRNA for TLR-3, SSRNA for TLR-7, 8, and cpG DNA for TLR-9. These ligand-TLR interactions result in the development of the Th1 type of helper cell responses largely through the expression of IFN-α and IL-12.

In general the Th1 profile development is fostered by normal commensal flora in the early neonatal period and infancy, release of inflammatory cytokines, breastfeeding and several infectious processes. Several diseases have been associated with increased Th1 cytokine profile. These include autoimmune allergic encephalitis, multiple sclerosis, insulin-dependent diabetes mellitus, Crohn’s disease, allograft rejection and autoimmune thyroiditis. On the other hand, Th2 profile development is fostered by the extensive use of antibiotics and a change in the ‘normal commensal flora’, processed foods, diet in developed world, the introduction of cow’s milk in the neonatal dietary regime, and several infectious disease processes. The diseases associated with increased Th2 cytokine profile include many cell-associated infections like Leishmania major, Mycobacterium leprae, candidiasis, toxoplasmosis, infections with human immunodeficiency virus, bronchial asthma, atopic dermatitis, allergic rhinitis, and conjunctivitis.
Based on the information available to date, it appears that alterations in the mechanisms of interaction between the innate immunity and microbial environment in the early neonatal period may ultimately determine the outcome of specific immune responses to other infectious agents and environmental macromolecules. Mucosal microflora can either induce protection against or contribute to the pathogenesis of infection-associated autoimmune or allergic diseases. Some organisms may have a different impact on the development of autoimmunity vs. allergy.

Thus mucosal inflammation may reflect a dysregulation of normal immune responses against mucosal microflora or their metabolic products, and the expression of certain immunologically mediated diseases appears to be in part a reflection of a breakdown in tolerance or altered mucosal responses to antigens which normally do not induce any immune response.

References
2 Schnare M, Rollinghoff M, Qureshi A: Toll-like receptors: sentinels of host defence against bacterial infection. Int Arch Allergy Immunol 2006;139:75–85.
Induction of Antigen-Specific Immunity in Human Neonates and Infants

Christopher B. Wilson and Tobias R. Kollmann

The first months of life represent a period of heightened susceptibility to infection, but the immunological differences involved are as yet incompletely understood [1]. T cell-independent B cell (antibody) responses are clearly and markedly compromised in the first year of life and do not reach adult competence until 4–5 years of age [2, 3]. By contrast, T cell-dependent B cell responses are evident at birth, but neonates and young infants may require multiple immunizations to achieve or sustain titers comparable to those in older individuals (fig. 1).

Fig. 1. Ontogeny of T cell-independent (a) and T cell-dependent (b) antigen-specific antibody responses in humans. a T cell-independent antibody responses are mediated by marginal zone B cells in response to cross-linking of surface Ig

Bacterial polysacch
Ag

PAMP
TLR

Marginal zone B cell

Plasma cell

Bacterial polysacch
Ag

PAMP
TLR

Marginal zone B cell

Plasma cell

TLR
BAFF
APRIL

Plasma cell

TLR
BAFF
APRIL

Plasma cell

CD4+ Th effector

APRIL

BAFF

TLR

PAMP

APC

CD4+ H11001

Th effector

APC

APC

APC

APC

APC

APC
Fig. 2. Ontogeny of antigen-specific T cell responses in humans. Naïve CD4 and CD8 T cells are activated by binding of their T cell receptor (TCR, shown as a Y shape) to peptide-antigen-major histocompatibility complexes displayed on dendritic cells (DCs). DCs are activated in response to binding of pathogen-associated molecule patterns (PAMPs) to their toll-like receptors (TLRs), causing them to express CD80 and CD86 on their surfaces that bind to CD28 on the naïve T cell (not shown in this figure) and to secrete cytokines, thus providing essential second and third signals, respectively, needed to stimulate naïve T cells to proliferate and differentiate into effector cells. CD4 T cells can differentiate into specialized Th17, Th2 or Th1 effector and memory cells depending on the cytokines secreted by DCs, while CD8 T cells differentiate preferentially into cytotoxic CTL, which produce IFN-γ. Age-dependent maturation of responses is illustrated by the timeline at the bottom.

by multivalent antigen along with the cytokines BAFF and APRIL secreted by antigen-presenting cells (APCs) in response to binding of pathogen-associated molecule patterns (PAMPs) to toll-like receptors (TLRs) on these APCs. T cell-dependent antibody responses are mediated by follicular B cells in response to engagement of surface Ig (shown as a Y shape) by antigen in concert with an obligatory second signal provided by CD40 ligand on follicular helper (Th) CD4 T cells, which have been activated by peptide antigen-major histocompatibility complexes displayed on the B cell; cytokines produced by T cells and BAFF and APRIL produced by APCs influence the Ig isotype and facilitate T cell-dependent antibody responses, respectively. Age-dependent maturation of responses is illustrated by the timelines at the bottom.
Consistent with the latter finding, neonates can mount effective T cell responses, but CD4 T cell responses are often slower to develop, less readily sustained, and in general more easily biased towards a Th2 type response (fig. 2) [2–4]. The last observation likely reflects in part the less efficient capacity of neonatal dendritic cells (DCs) to secrete cytokines, including IL-12p70 and type I interferons, which establish a milieu that favors a Th1 CD4 T cell response. However, given appropriate stimuli, as occurs in neonates immunized with bacillus Calmette-Guérin, it seems that neonatal DCs are capable of promoting a strong and sustained Th1 CD4 T cell response, suggesting that this limitation is not immutable. Unfortunately, we currently lack a clear mechanistic understanding of the molecular basis for these immunological differences between adults and neonates. The goal of ongoing and future studies is to generate the mechanistic insights needed to enable the rational design of vaccines and adjuvants for use in neonates and young infants, since neonatal vaccination is by far the most effective measure by which to reduce the morbidity and mortality of infections early in life.

References

Growth and Host–Pathogen Interactions

Andrew M. Prentice, Momodou K. Darboe and M.R.C. Keneba

Numerous studies have now demonstrated that differing trajectories of infant and child growth are associated with different patterns of disease and mortality in adulthood. Since postnatal growth patterns are partially modifiable by diet, these associations raise fresh questions about what constitutes an optimal growth rate. Examination of the evolutionary ‘norm’ for early growth, and of the external environmental factors that influence it, may help in identifying the current day optimum. Here the data from contemporary societies that still suffer a combination of poor nutrition and a very high burden of infectious disease are used to illustrate the consequences on early growth patterns that have likely affected most of humankind’s evolution. We show that pathogenic assault is a major suppressor of growth; populations frequently average $-1.0$ to $-1.5$ Z-scores (standard deviations relative to standard growth curves) for height, and $-2.0$ to $-2.5$ Z-scores for weight, body mass index and head circumference (fig. 1).

Many of the infections leading to growth faltering are symptomatic (e.g. diarrhea, malaria, respiratory infections, HIV), but others are subclinical (e.g. hepatitis B, cytomegalovirus, Epstein-Barr virus, herpes, Helicobacter pylori) and their silent imprint is detected only by antibody testing. Table 1 lists several markers of infection in young Gambian children. This pathogen load initiates a downward cycle of infection→suppressed appetite and malabsorption→reduced growth→lowered immunity→repeated infection, and so on.

Diarrheal disease has for many years been considered the chief cause of growth faltering in young children. Mata et al. [1] were among the first to review the detailed host alterations seen with specific enteric infections that lead to malnutrition. These include: mucosal dysfunction; cytokine-mediated systemic metabolic responses; impaired intake, digestion and absorption; nutrient losses; altered immune responses, and ultimately, impaired growth and development.
A quantitative regression analysis performed by Rowland et al. [2] in the Gambia confirmed that gastroenteritis was the main infection suppressing growth. These results were accepted for many years and still have currency, but there are some contradictory pieces of evidence in the literature, for instance challenging the direction of causality between diarrhea and malnutrition [3].

Persistent gastroenteropathy, as characterized histologically by small intestine mucosal villous shortening and broadening, crypt hyperplasia, increased crypt depth, and lymphocyte infiltration into the lamina propria and epithelium, is displayed by many if not most children in developing countries [4] and is strongly associated with growth failure.

A key element in a child’s growth trajectory under these conditions is its ability to ‘catch-up’ with its previous (genetically endowed) growth centile during the recovery phase from an infection. There is generally a strong drive towards catch-up but there may be windows of opportunity which, if not exploited, close up and leave the child with permanently suppressed growth until puberty when there is a fresh opportunity for catch-up. The growth rates of contemporary healthy and well-nourished populations have probably been rarely seen in our evolutionary past but, judging by the catch-up drive, have always been the organism’s ‘desired’ rate indicating that they represent the physiological optimum.

Fig. 1. Early growth faltering in Gambian infants. Data from 138 Gambian infants assessed longitudinally and expressed as Z-scores relative to the UK 1990 standards. Reproduced with permission from Collinson et al. [5].
Table 1. Indicators of postnatal infections in Gambian infants

<table>
<thead>
<tr>
<th>Marker of infection</th>
<th>Birth Age, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Raised α1-acid glycoprotein</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngeal pneumococcal carriage</td>
<td>2</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>NM</td>
</tr>
<tr>
<td>Chronic environmental enteropathy</td>
<td>NM</td>
</tr>
<tr>
<td>HBV antibody positive</td>
<td>100</td>
</tr>
<tr>
<td>EBV antibody positive</td>
<td>100</td>
</tr>
<tr>
<td>CMV antibody positive</td>
<td>100</td>
</tr>
<tr>
<td>Herpes antibody positive</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| NM = Not measured. Normal cutoff for α1-acid glycoprotein ≤1 g/L. *Helicobacter pylori* infection assessed by the 14C-urea breath test. Chronic environmental enteropathy determined as abnormal values for the lactulose:mannitol ratio in the dual-sugar permeability test. Data from 197 infants participating in a randomized controlled trial high vs. low-dose vitamin A [Darboe et al., unpublished data]. Data on antibody positivity use previously unpublished data kindly provided by Prof H.C. Whittle, MRC Laboratories, The Gambia. HBV = Hepatitis B virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus.

References

Neonatal Microbial Flora and Disease Outcome

Milo F. Vassallo and W. Allan Walker

The now outdated perception of microorganisms of the gastrointestinal tract as pathogens or at best commensals continues to undergo remodeling. It is now clear that the microbiome of the gut participates in many activities including: digestion, ecologic protection from pathogens, and an increasingly appreciated immunoregulatory role in vertebrates. Studies of the complex interactions of microbes and hosts point to a convergence of two well-supported (though imperfect) hypotheses: the ‘hygiene hypothesis’ and the ‘fetal programming hypothesis’ proposed by Strachnan [for review see 1] and Barker [2] respectively. Our current understanding is one in which factors that exist before conception, during gestation, occur perinatally, and in the infant milieu, in addition to exposures to nutrients and microbes have the potential for long-term effects in the development of healthy offspring and adults [3–5] (fig. 1). Epidemiology, basic science and clinical research in such previously diverse areas of study such as microbiology, allergy, gastroenterology, endocrinology, immunology, rheumatology, infectious disease, perinatology, and nutrition are providing evidence that appropriate development and tendency towards the development of certain diseases are directly affected by intestinal microbe–host interactions [3, 4] (fig. 2). It appears likely that perinatal colonization of the gastrointestinal tract is a particularly pivotal process in which microbe–host programming occurs. Intestinal microbes and hosts have co-evolved so that, when in appropriate balance, they produce and propagate a life-long mutualism.

Probiotics have been well studied and have been demonstrated to have beneficial immunologic effects that influence both systemic and gut-associated immune responses; they likely function by having both direct and indirect (immune system) effects on the microbial community in the intestine [5]. Some of the strongest supportive data thus far for the use of probiotics is that they are most effective during the development of the immune system and initial colonization. It is
tempting to speculate that these findings support a theory that these two processes are themselves linked. Clinical entities that have been shown to be ameliorated by the ingestion of probiotics include: childhood infectious gastroenteritis and antibiotic-associated diarrhea, with potential efficacy of probiotic strains in better growth of infants; atopic eczema; inflammatory bowel disease; *Helicobacter pylori* gastritis; neonatal necrotizing enterocolitis (NEC); prevention of candidal colonization in very low birthweight infants, and as a substitute for inadequate initial neonatal colonization through as yet unclear mechanisms [5]. The immature intestine is particularly susceptible to the inflammatory entity of NEC which has substantial mortality and morbidity in primarily preterm newborns. The administration of probiotics to preterm infants has been shown to confer a degree of protection from the development of NEC. We have identified an intriguing mechanism by which probiotics downregulate the intestinal innate immune

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**Fig. 1.** Schema depicting positive and negative developmental factors which have implications for short-term or long-term morbidity and/or mortality. Underlined items are known or hypothesized to affect/be affected by host–microbe interactions.
response (unpublished data). In addition, ingestion of probiotics prenatally and in infancy has been shown to have immune effects beyond the mucosa such as skin immune homeostasis in a mouse model, as well as affect the transfer of antibiotic resistance genes in mice.

Prebiotics are indigestible (to host) food ingredients that have a beneficial effect by selectively stimulating the growth or activity of one or a restricted number of bacteria in the colon. The utilization of prebiotics in addition to probiotics in support of intestinal ecology and prevention of disease is showing positive results.

Therapeutic strategies are beginning to include our most current understanding of microbiome–host interactions such as the ingestion of polymicrobial probiotic cocktails and prebiotic molecules or immunostimulatory molecules such as DNA or helminthes. Technological means

**Fig. 2.** Picture outlining the development of mucosal immunity. Each component (1–4) is affected after delivery and initial colonization and continually thereafter by interactions with microorganisms.
now exist to begin to address the interactions of entire bacterial communities and their role in immune system function spanning from gestation through adulthood. Ultimately we will continue to generate new models and interventions of microbial-host interactions in to promote health and prevent disease.

References

Impact of Fetal and Neonatal Viral (and Parasitic) Infections on Later Development and Disease Outcome

Yvonne A. Maldonado

Introduction – the Global Impact of Fetal and Neonatal Infections

It is estimated that there are 4 million neonatal deaths and an equal number of stillbirths annually, the majority in the developing world [1]. Neonatal deaths account for one third of deaths in children under 5 years of age, and at least one third of neonatal deaths are related to infections. Infections also account for 80% of deaths in the post-neonatal period through 5 years of age. There are several viral and parasitic infections which produce fetal and neonatal morbidity and mortality. This brief report will provide an overview of the pathogenesis, general outcomes, and known pathogens associated with perinatal viral and parasitic infections. It is beyond the scope of this review to discuss diagnosis and treatment.

Pathogenesis of Fetal and Neonatal Infections

Neonatal infections occur during one or more perinatal periods: in utero (congenital), intrapartum (during labor and delivery), and early or late postpartum. Here the term perinatal refers to all these stages of fetal or neonatal infections. The mechanisms of perinatal viral and parasitic infections vary depending on the specific pathogen; however, all begin with maternal infection. Following maternal infection, organisms may produce indirect placental infection with or without fetal infection, direct fetal or neonatal infection, or primary maternal infection and subsequent perinatal sequelae without either placental or fetal infection. Some pathogens may produce infections by more than one mechanism. A list of the most common viral and parasitic infections affecting the fetus and neonate are outlined in table 1.

The most common mechanism of fetal infection is transplacental passage of the organism after maternal infection and bloodstream.
Table 1. Viruses and parasites associated with perinatal infections

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>American trypanosomiasis (Chagas’ disease)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>African trypanosomiasis (African sleeping sickness)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Ascaris</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Giardiasis</td>
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<tr>
<td>Human herpesvirus 6 and 7</td>
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<tr>
<td>Human papillomavirus</td>
<td>Malaria</td>
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<tr>
<td>Herpes simplex virus</td>
<td>Schistosomiasis (bilharziasis)</td>
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<tr>
<td>Influenza</td>
<td>Toxoplasmosis</td>
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<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td>Trichinosis</td>
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<tr>
<td>Mumps</td>
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<tr>
<td>Parvovirus</td>
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<tr>
<td>Respiratory syncytial virus</td>
<td></td>
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<tr>
<td>Rubella</td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
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<tr>
<td>West Nile virus</td>
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invasion, with or without placental infection. Transplacental fetal infection is most commonly seen in congenital infections with cytomegalovirus, enterovirus, parvovirus, rubella and toxoplasmosis. Transplacental infections with herpes simplex virus and varicella-zoster virus are rare. Intrapartum infections are most commonly seen with human immunodeficiency virus, herpes simplex virus, human papillomavirus, and varicella-zoster virus, and early postpartum infections occur with human immunodeficiency virus and are most common with cytomegalovirus and hepatitis B. Some pathogens cause fetal or neonatal disease secondary only to maternal infection. Severe systemic maternal symptoms with these organisms may lead to abortion, stillbirth or preterm delivery. This is most likely to occur after maternal infections with malaria.

General Outcomes of Perinatal Viral and Parasitic Infections

Fetal and neonatal outcomes due to perinatal viral and parasitic infections range from asymptomatic disease to death. These outcomes include embryonic death and resorption, abortion or stillbirth, prematurity, intrauterine growth retardation, developmental anomalies and teratogenesis, congenital disease, persistent postnatal infection with progressive disease, or asymptomatic infection. The range of outcomes is depicted in table 2 [2].
**Table 2.** Effects of transplacental viral and parasitic infection on the fetus and newborn infants

<table>
<thead>
<tr>
<th>Organisms or disease</th>
<th>Prematurity</th>
<th>Intrauterine growth retardation/low birthweight</th>
<th>Developmental anomalies</th>
<th>Congenital disease</th>
<th>Persistent postal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
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<tr>
<td>Rubella virus</td>
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<td>+</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Herpes simplex</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Varicella-zoster virus</td>
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<td>(+)</td>
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<td>Mumps virus</td>
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<td>Rubeola virus</td>
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<td>Vaccinia virus</td>
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<td>+</td>
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<tr>
<td>Coxsackie virus B</td>
<td>+</td>
<td>–</td>
<td>(+)</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Echoviruses</td>
<td>–</td>
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<tr>
<td>Polioviruses</td>
<td>–</td>
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<tr>
<td>Influenza virus</td>
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<tr>
<td>Hepatitis B virus</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Human immunodeficiency virus</td>
<td>(+)</td>
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<tr>
<td>Lymphocytic choriomeningitis virus</td>
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<tr>
<td>Parvovirus</td>
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<tr>
<td><strong>Protozoa</strong></td>
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<tr>
<td><em>Toxoplasma gondii</em></td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>Plasmodium</em></td>
<td>(+)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

+ = Evidence for effect; – = no evidence for effect; (+) = association of effect with infection has been suggested and is under consideration. Reprinted from Remington et al. [2], permission pending.
Congenital TORCH Infections and Infections with Other Viruses [3, 4]

There is a large body of literature regarding the congenital TORCH infections (TOxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus, Enterovirus). The TORCH syndromes frequently include nonspecific findings such as hepatosplenomegaly, jaundice, adenopathy and pneumonitis. However, clinical findings specific to each pathogen are frequently identified, such as skin or mucous membrane involvement, central nervous system findings, cardiac lesions, and eye lesions. Other perinatal viral infections outlined in table 1 may produce clinical findings similar to those found with TORCH infections.

Congenital Infections with Other Parasites [5]

Parasitic infections are highly prevalent in most of the world. The placenta serves as an effective barrier, even in infections with malaria and schistosomiasis in which systemic involvement and hematogenous spread are common. Although transplacental infections of the fetus are uncommon, in developing countries the prevalence of parasitic infections among infants younger than 1 month of age is high, primarily through transmission during or shortly after birth. Among these, malaria and toxoplasmosis produce the highest disease burden and fetal and neonatal morbidity and mortality worldwide.

References

Environmental Influences on the Development of the Immune System: Consequences for Disease Outcome

Bengt Björkstén

The prevalence of allergies, diabetes, inflammatory bowel disease and other ‘immunologically mediated diseases of affluence’ has increased progressively, particularly over the last 50 years. There is a strong global correlation between childhood wheezing and diabetes [1]. A unifying environmental link between the increase in both Th1-dependent autoimmune disease and Th2-linked atopic allergy would be a disturbed immune regulation involving T regulatory cells. This has prompted an interest in finding protective factors operating in low prevalence countries, which have been lost in countries with a high recent increase in disease prevalence.

Early T cell responses to external antigens and autoantigens are subject to a variety of regulatory mechanisms. A broad range of regulatory mechanisms are involved, which are dictated by the concentration, frequency and route(s) of antigen (allergen) exposure, and the developmental status of the individual at the time of exposure. The relevant immunoregulatory mechanisms involved are likely to span the full range from classical low zone tolerance to high zone tolerance phenomena and will include subsets of T regulatory cells. In atopic children, consolidation of Th2-polarized immunity against inhalant allergens is initiated in early infancy [2, 3] and may be completed within a few years in children who do not develop clinically manifest allergy [3]. In contrast, in infants who develop allergic manifestations, low level Th1 responses are established.

As the normal microbial flora of the intestinal tract is the principal environmental signal for postnatal maturation of T cell function (in particular the Th1 component), it is increasingly recognized that microbial colonization of the gastrointestinal tract, linked with lifestyle and/or geographic factors, may be important determinants of the global heterogeneity in disease prevalence [4]. Recognition of the
signals is mediated by a series of toll-like receptors expressed on cells of the innate immune system [5].

The potential effects of environmental stimuli on immune function are greatest in early life including fetal life, when systems and responses are developing and the maternal influences during fetal life could be particularly important for the development of immune regulation and tolerance induction [6].

Intestinal microbiota are arguably the most abundant source of early immune stimulation, and contribute significantly to ‘microbial burden’ in early life. A number of studies have suggested differences in colonization patterns of infants who go on to develop allergic disease. Similar studies have not been published in relation to diabetes, but from the outcome of experimental and animal experiments it appears reasonable to suggest that the findings would be similar. These differences were already apparent at one week of age, suggesting that early colonization can influence subsequent patterns of immune development [4]. Studies in germ-free animals confirm that a microbial gut flora is essential for the development of oral tolerance and for the induction of normal immune regulation. The controversy regarding the role of gut bacteria in allergy development thus lies in the clinical consequences of these findings and not as much to what extent they affect the immune system.

In recent years, focus has switched from searching environmental risk factors towards an interest in factors that could induce and maintain immune regulation and tolerance to allergens and autoantigens. Currently evaluated strategies include the use of immunomodulatory factors, such as probiotics, prebiotics, and dietary nutrients, although data are still insufficient to make specific recommendations. There are now at least three studies trying to prevent infantile eczema and one to prevent diabetes with various probiotic strains of lactobacilli. In the study with a negative outcome on infantile eczema the bacteria were given only to the babies, while in the two studies with some protective effect they were also given to the mothers during the last month of gestation. This suggests a significant influence by the mother during gestation on the development of immune regulation. Similarly, other environmental exposures during fetal life, such as maternal tobacco smoking, reduces lung function in later childhood.

References

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