Growth and Host–Pathogen Interactions

Andrew M. Prentice\textsuperscript{a,b}, Momodou K. Darboe\textsuperscript{b}

\textsuperscript{a}MRC International Nutrition Group, London School of Hygiene and Tropical Medicine, London, UK, and \textsuperscript{b}MRC Keneba, The Gambia

Abstract
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. We use data from contemporary societies that still suffer poor nutrition and high burdens of infectious disease to illustrate early growth patterns that have likely been typical of our evolutionary past. 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. Many infections are symptomatic (e.g. diarrhea, malaria, pneumonia, HIV), but others are subclinical (e.g. hepatitis B, cytomegalovirus, Epstein-Barr virus, herpes, \textit{Helicobacter pylori}). The great majority of young children become infected by multiple pathogens which initiate a downward cycle of infection $\rightarrow$ suppressed appetite and malabsorption $\rightarrow$ reduced growth $\rightarrow$ lowered immunity $\rightarrow$ repeated infection. Examination of the evolutionary ‘norm’ for early growth, and the external environmental factors that influenced it, may provide clues towards identifying the current day optimum for growth.

Introduction
There is now a substantial body of evidence linking the growth trajectories of infants and young children with later chronic disease [e.g. 1–5]. Nutritional interventions in premature babies suggest that an excess (forced) early growth has detrimental long-term sequelae [6], but most retrospective epidemiological studies indicate that poor growth in infancy is detrimental [1–5], especially if followed by positive centile crossing in later childhood [3]. Some studies suggest that the effects of these differing postnatal trajectories are independent of birthweight, and others reveal evidence of an interaction.
Postnatal growth is arguably more amenable to nutritional manipulation than fetal growth because the latter is buffered by maternal and placental physiological mechanisms. This raises new questions about defining the optimal rate and shape of growth in infancy and childhood. Over recent decades there has been a transition in thinking from the ‘biggest is best’ view held in the 1950–1970s (i.e. that the very high growth rates of infants fed high-solute, high-protein infant formulas were optimal), towards a more moderate view that holds the breastfed infant as the optimal model [7] and suggests that previous recommended intakes for energy represented a recipe overfeeding [8]. Further progress towards identifying optimal growth will require interrogation of longitudinal data from both observational and intervention studies. But perhaps we can also draw useful inferences from an understanding of the likely evolutionary norm of human growth, and the factors that impaired or stimulated growth.

Archeological data can inform us about final attained body size in ancient populations from which we can interpolate that child growth was usually very poor, but cannot contribute to a detailed knowledge of the trajectory of ancient growth rates. The best proxy for such information can probably be gleaned by studying contemporary populations in developing countries that are still affected by poor diet and a heavy burden of infections.

The struggle between the human host and pathogenic organisms, both enteric and systemic, has been the norm over most of evolutionary time and remains a major challenge for the majority of the world’s infants raised, as they are, in unhygienic conditions. This article uses our research from a rural population in The Gambia as a basis for describing the effects of such host–pathogen interactions on early child growth.

**The Burden of Infection in Poor Populations**

Using analysis of genetic variation, Linz et al. [9] have recently shown that the ubiquitous stomach pathogen *Helicobacter pylori*, spread from East Africa at the same time as humans around 58,000 years ago. Their results show that anatomically modern humans were already infected by *H. pylori* before their migrations from Africa and that the bacteria has remained associated with its human populations ever since, thus providing a graphic reminder of the longevity and intimacy of relationships between the human host and its multitudinous pathogens.

Table 1 shows data from a cohort of almost two hundred 21st century Gambian infants followed longitudinally from birth. It shows that by 9 months of age over two thirds have abnormally raised levels of the acute-phase marker, α1-acid glycoprotein. α1-Acid glycoprotein is marker of infection with a half-life of several days. Nasopharyngeal swabs taken from the infants and cultured for the presence of pneumococci indicate a very sharp rise from
almost zero carriage soon after birth to 78% carriage at 2 months and 88% at 5 months. Carriage indicates exposure rather than infection, but indicates that the infants are having to defend their respiratory tract from these potentially fatal organisms. *Helicobacter pylori* infection, assessed by the 14C-urea breath test, affected over half the infants by 9 months of age; a figure that is lower than previous studies in these communities [10].

Figure 1 shows unpublished data, gathered from a number of separate studies in rural Gambia, on antibody positivity against a variety of other pathogens: hepatitis B virus, cytomegalovirus, Epstein-Barr virus and *Herpes simplex*. By their 3rd year, 100% of children have turned antibody positive to cytomegalovirus and Epstein-Barr virus, and 70–80% are positive to herpes and hepatitis B. Except in rare cases all of the acute infections leading to these immunological conversions will have passed clinically unrecognized, yet the children will have been expending their nutritional resources on mounting the humoral and cellular responses necessary to control the infections. These data provide a powerful reminder of the intensity of the battle between host and pathogen; one that is underestimated using simple clinical screening.

**Growth Failure**

The pattern of infant growth in rural Gambia is illustrated in figure 2. Babies are typically born small but then show rapid catch-up growth during the first 3 months of life when fully breastfed and generally free from infections. This catch-up is so successful that at 3 months of age the population average is close to Western growth norms. Thereafter there is a precipitate deterioration in growth so that by the end of infancy the population average

---

**Table 1.** Indicators of postnatal infections in Gambian infants (% affected)

<table>
<thead>
<tr>
<th>Marker of infection</th>
<th>Birth</th>
<th>2</th>
<th>5</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised α1-acid glycoprotein</td>
<td>0</td>
<td>18</td>
<td>43</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>Nasopharyngeal pneumococcal carriage</td>
<td>2</td>
<td>78</td>
<td>88</td>
<td>79</td>
<td>NM</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>NM</td>
<td>42</td>
<td>32</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>Chronic environmental enteropathy</td>
<td>NM</td>
<td>11</td>
<td>13</td>
<td>32</td>
<td>46</td>
</tr>
</tbody>
</table>

NM = Not measured. Normal cutoff for α1-acid glycoprotein ≤1 g/l. *H. 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].
**Fig. 1.** High prevalence of early infections in Gambian children. Results show antibody positivity. HBV = Hepatitis B virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus. Early high levels represent transplacental acquisition of maternal antibody that wanes during the first year. The subsequent rise represents postnatal exposure. Previously unpublished data kindly provided by Prof H.C. Whittle, MRC Laboratories, the Gambia.

**Fig. 2.** 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. [11].
z score is close to \(-2.0\) for weight, \(-1.2\) for length and \(-2.3\) for head circumference. This represents the average growth pattern across all calendar months and is strongly modulated by seasonal variation [12]. During the rainy season (July–October) growth virtually stops in many infants as a consequence of a sharp increase in infectious diseases including diarrhea [13], and a deterioration in maternal care practices due to the fact that mothers have to work long hours in the fields and frequently leave their infants with a young nursemaid or a grandmother who is no longer able to work. An audit of the number of severely malnourished infants referred by pediatricians to the local therapeutic feeding center revealed an average of 8 admissions per month in May to 29 per month in August.

**The ‘Weanling’s Dilemma’**

Weaning foods in sub-Saharan Africa typically have a very low energy and nutrient density, and frequently have high levels of bacterial contamination [14]. The issue of when to start introducing complementary foods has been described as the ‘weanling’s dilemma’ by Rowland et al. [15]. The dilemma is that if mothers introduce weaning foods too early they risk causing diarrhea and inhibiting their own lactational performance, but if they introduce them too late their infant’s energy needs may have started to exceed their milk energy supply. This dilemma is faced by all mothers but is much more acute in poor communities with few facilities for hygienic food preparation where weaning foods are likely to be contaminated. The hazards associated with this transition frequently result in the initiation of a downward cycle of infection → suppressed appetite and malabsorption → reduced growth → lowered immunity → repeated infection.

**Quantitative Effects of Infections on Growth**

The quantitative effects on early child growth of high levels of infectious disease in developing countries were first described in the late 1960s and early 1970s in Guatemala and The Gambia [13, 16–18]. These studies used clinical monitoring of the frequency and duration of infections in order to establish the levels of exposure together with stool analysis to search for enteric pathogens and blood films for malaria. Three decades later, and in spite of a 10-fold reduction in infant mortality, we find that infants in The Gambia still display these very high levels of infection (table 1; fig. 1).

Diarrheal disease has for many years been considered the chief cause of growth faltering in young children. Early work in Guatemala focused intensively on identifying links between diarrhea and growth. Mata et al. [17, 19] 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 little later a quantitative regression analysis performed by Rowland et al. [13] in The Gambia confirmed that gastroenteritis was the main infection suppressing growth. Malaria actually had a larger effect per day of infection, but this was offset by the much higher prevalence of diarrhea with children suffering for up to 20% of the time in the wet seasons. These results were accepted for many years and still have currency, but there are some contradictory pieces of evidence in the literature. Briend [20] has questioned the direction of causality of the link between malnutrition and diarrhea and concludes that the evidence is strongest in the direction of malnutrition predisposing to diarrhea. In the same Gambian population in which Rowland et al. [13] first established the quantitative association, Poskitt et al. [21] later showed that a pronounced year-by-year reduction in the diagnoses of gastroenteritis in clinic records had not been accompanied by a secular improvement in growth.

**Gastrointestinal Infections**

Various bacterial and viral pathogens have been implicated as etiologic agents for diarrhea in The Gambia [22–24]. Some have been found to be significantly associated with diarrhea while others have been seen to be equally prevalent in asymptomatic children. Bacterial contamination of the jejunum was predominant in a small series of malnourished children with diarrhea [25].

In a longitudinal community study on giardiasis (measured by serology) and weight gain of rural Gambian infants, elevated titers of *Giardia*-specific IgM antibodies were associated with decreased weight gain in the 2-week period prior to serological conversion [26]. High *Giardia*-specific IgM was also associated with elevated intestinal permeability values and decreased mannitol absorption [27]. However, the mean IgM titers per child over the entire study period did not predict differences in long-term growth or intestinal permeability. In a community-based study it was also shown that although intestinal inflammation (as measured by fecal neopterin) was inversely associated with growth, the presence of giardiasis was neither associated with poor growth nor poor intestinal permeability [27]. It appears that in the Gambian setting, giardiasis is more prevalent in chronic diarrhea and malnutrition, but its role in modulating the acute growth of infants seems to be less clear.

An early study of *H. pylori* infection in severely malnourished Gambian children showed that close to half the children aged between 40 and 60 months had serologic evidence of infection [28]. Half of the children with chronic diarrhea and malnutrition were positive as compared to a quarter of
the healthy controls and undernourished children. In a later study using the \textsuperscript{13}C-urea breath test, it was shown that acquisition of \textit{H. pylori} infection may occur before 3 months of age as 20\% of the 3-month-old infants were positive [29]. An analysis of longitudinal growth data and serial breath tests demonstrated that children who acquired \textit{H. pylori} earlier ended up shorter, lighter and thinner than their uninfected peers [10]. It has been proposed that early \textit{H. pylori} causes a transient hypochlorhydria and thereby increases the likelihood of enteric infection thus compromising intestinal function and nutrition. \textit{H. pylori} infection may serve to reduce the mucosal defenses and allow further colonization of the small intestine with pathogens [10].

**Chronic Environmental Enteropathy as a Contributor to Growth Failure**

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 Gambian children [30, 31]. Early research established this inflammatory condition to be strongly associated with growth failure. First described in 1962, persistent enteropathy was found to affect individuals throughout the tropics, in Africa, Asia, South America and the Caribbean. For this reason it acquired the name ‘tropical enteropathy’. The condition was particularly observed in those living in less developed, or more contaminated, environments of the tropics. It was later shown that people living in temperate areas may develop similar histological and functional changes if living in environments with similarly high levels of microbiological pathogens. For these reasons the expression ‘chronic environmental enteropathy’ is now accepted as a more accurate description of the condition than ‘tropical enteropathy’.

Associated functional changes include subclinical malabsorption of fat and an increased mucosal permeability. The latter is demonstrated by markedly and consistently raised lactulose:mannitol ratios in the dual-sugar permeability test towards later infancy (table 1). Raised lactulose:mannitol ratios have also been described in children in several other parts of the developing world. The dual-sugar permeability test assesses both gut integrity and absorptive capacity, and has been used in numerous studies characterizing the etiology of growth failure in The Gambia [32] and elsewhere [33, 34].

Two sets of immunohistologic studies have been performed in The Gambia. These are consistent with past biopsy studies in marasmus and kwashiorkor done in other developing countries over the past four decades; in particular they describe a wide spectrum of crypt hyperplasia and villous atrophy across cases. In addition, immunohistology revealed intraepithelial lymphocyte infiltrates in the surface villi and crypt [30]. The most recent biopsies done in
The Gambia [31, 35] have demonstrated a generalized cellular hyper-responsiveness and a cytokine profile biased towards proinflammatory cytokines. These immunohistologic studies contradict the commonly held belief that malnutrition is associated with an immunosuppressed state, and instead suggest that both lymphocyte activation and ineffective enterocyte development play a significant role in chronic environmental enteropathy and malnutrition. These findings support the view that malnutrition is not necessarily accompanied by severe T lymphocyte deficiency, and that T lymphocyte dysregulation may be present [36].

**Catch-Up Growth Following Acute Infections**

It is well recognized that there is a strong innate drive towards catch-up growth in the period immediately after acute weight loss caused by infections [37, 38]. To achieve its full potential the child must be cleared from infections and then provided with a regular supply of energy and nutrient-dense feeds. Under such conditions children can achieve short-term growth rates many times above the norm. It is sometimes stated that there is a window within which this catch-up must be achieved and that failure to do so will reset the growth trajectory, but appropriate studies to test this thesis have not been done, and there is considerable counterevidence.

**Possible Implications for the Developmental Origins of Disease Theory**

We have described above some of the interactions between infections and growth in poor children in developing country settings on the principle that these probably represent close to the norm for early human growth over most of evolutionary time. Can these further inform our understanding of how early growth patterns influence later health? At one level the immunological responses illustrated by the antibody positivity shown in figure 1 represent a perfect example of the ‘predictive adaptive response’ proposed by Gluckman et al. [39], and we have shown that an apparent failure to mount such a response by babies born in the Gambian hungry season is a very strong predictor of later survival [40]. We believe that there may be, as yet undetected, links between early programming of the immune system and the chronic disease outcomes that have dominated the field of developmental origins of adult disease. The question of whether the growth repression caused by infections represents an intentional response with later adaptive value or whether it is simply an unavoidable result of the infection–malnutrition cycle seems to have a clearer resolution. Even though being a small adult in an
energy-restricted environment has survival advantages, the fact that there is a strong drive towards catch-up growth in children as soon as infections resolve would suggest that growth suppression is physiologically undesirable. This would support the bulk of the epidemiological evidence in Western populations that suggests that growth restriction in infancy represents an undesirable exposure that predisposes to later ill health.

References

Discussion

Dr. Walker: That was a very provocative talk which allows a lot of room for thought about growth in general, as well as specifically in your setting. The period of nursing seems to be the most positive time period for these infants when they are born small, they grow well transiently, and then they fall off. Is it possible to control how long mothers nurse their babies; can they nurse them for a year for example?

Dr. Prentice: Mothers certainly cannot nurse them for a year. Of course the WHO now recommends exclusive breastfeeding to 6 months, which has been something that I, as many in this audience, have had to battle with because, physiologically speaking, I am not sure that the majority of mothers can really sustain that. In the early years of our work we brought all children in Keneba to a community supplementation center at 3 months of age where we were then able to randomize every alternate child and bring them back to that center at 6 months of age instead. We showed
very clearly, as Dewey et al. [1] have shown in Honduras, that milk production does increase substantially if alternative feeding is delayed, so mothers can produce more milk. Unfortunately the babies don't grow any better. They grow just as well but they don't grow any better, and I think that again reflects the high pathogenicity of the environment. We really have got to get rid of the bugs before we are going to really impact on that. But remember that there is a constant battle between the mother and her infant. The mother has to think about her total reproductive output. She is not so much interested in the individual child, she has to defend herself and her nutritional resources at some stage for future offspring, and that is the very important compromise.

**Dr. Walker:** The slide you showed of the intestine and the corresponding drawing suggest that you are dealing more with infection than with malnutrition for two reasons. One, there are a lot of lymphoid cells which frequently is not the case with severe malnutrition. But more importantly if that drawing is accurate, then there is a large proliferation of crypt cells which usually does not occur in malnutrition but does occur as a compensatory response to insult to the epithelium.

**Dr. Prentice:** Absolutely the case, and the other proof is that we have tried everything we can think of in terms of interventions: glutamine, zinc, protein, vitamin A, multiple micronutrients, etc., and they do not benefit growth. Incidentally, there was an enormous effect on survival in our population. The mortality rates are now less than one tenth of what they were when we started working there, but there is still no impact on growth failure.

**Dr. Björkstén:** Thank you for this beautiful presentation. Aaby et al. [2] have an intriguing and provocative story about certain vaccines in Guinea Bissau increasing childhood mortality. They suggest that it has to do with Th1 Th2 stimulatory vaccines and at what stage they are given. Do you have any comments in the light of your extensive studies?

**Dr. Prentice:** Yes and no. Earlier this morning I might have been tempted to give you my particular view on that. I think I would now prefer to hold back because there are people in the audience who are much greater experts than myself, and I imagine that you have your own answer and it would be much more informative than mine. But let me make the point that of course I am persuaded that there are windows of opportunity, particularly with regard to the data presented by Dr. Marchant with the timing of BCG. There are windows of opportunity which may be critical to directing and sign posting the immune system. I am well aware of the data of Aaby et al.; I am also very aware that it is highly controversial and that I should be cautious making other comments.

**Dr. Haschke:** I have a question related to the high z score. You showed very nice tracking, it is \(-1\) from birth and they finally end up with \(-1\), which contradicts a little bit what we discussed yesterday in non-tracking, but here it is very clear in this selected population. Did I understand you correctly when you interpret their genetic potential as starting at \(-1\) and end up at \(-1\), or is the \(-1\) at birth already the modified genetic potential which is due to intrauterine factors, which we don't know, or even factors before conception?

**Dr. Prentice:** I think the latter is the case. I would imagine that the genetic potential is pretty much around zero. I think the genetic potential in Gambia is pretty much the same as anyone else, and it is intriguing that that has held itself within the genome in spite of the fact that for millions of years no one has been growing anywhere near that? We have evidence that there would be positive selection in terms of birthweight. What we know from birthweight is that the optimal survival birthweight is always to the right hand side of the mean birthweight of any population that has been studied. So we know that there is always a selective favor in terms of bigger
birthweight. I am quoting some rather old data so I am not sure that it would necessarily still be true now that we have probably got pretty much towards maximal types of birthweights, but in the old days certainly it was true that optimal birthweight was always bigger than mean birthweight in any population. It may be true that optimal survival is slightly bigger than the mean size of children. Certainly that would be true in The Gambia, bigger children are going to survive better. So something is holding it in the genome, but I think it is intriguing in terms of our thoughts as to what is the optimal.

*Dr. Scholl:* I want to ask you about preterm birth or shortened gestation and thymic size because I recall from some of your publications that during the hungry season, when women lose weight, their gestation duration is shortened. When they have these babies that are born before term or preterm perhaps, are their thymuses smaller?

*Dr. Prentice:* We don't know that from The Gambia because we haven't got a large enough data set. But from the huge data set in Bangladesh we are starting to tease that out, and particularly because we also have serial ultrasound measurements in pregnancy and last menstrual period for all those 1,700–1,800 children, so that will give us excellent data.

*Dr. Hanson:* What do you know about the milk content of fat components when comparing mothers during the hungry and the non-hungry season? Also would it matter if they had been born during the hungry season or not with regard to the fat content or energy content of the milk?

*Dr. Prentice:* It is a struggle to look at that because seasonality is both a wonderful opportunity and a hazard. Any particular child, dependent on its day of conception, is going to go through a completely different pattern of exposure and remarkably they seem to cancel each other out. In the survival curve I showed at the beginning, the children were really remarkably similar in the early years of life, so they tend to cancel each other out in terms of many of these phenomena and in fact survival, so that the latent mortality effect was one of the first things that we were really able to show very strongly. Of course we are chasing this down in terms of other effects, in terms of other immune effects, we are trying to look at it specifically in terms of milk. What we can show is that there are some changes in the composition of the milk throughout the seasons of the year and, as I described, changes in immunological factors and also the recent IL-7 work of Ngom et al. [3] show that there are certainly seasonal changes which we think have effects on the infants.

*Dr. Boev:* With regard to Dr. Walker's comment that he thinks that small bowel atrophy has mainly nutritional and infectious causation, do you think this is direct damage by infection or is it an immunological response to infection, and secondly, what kind of infection, generalized systemic infection or localized gut infection? Is there any evidence of a particular widespread organism causing this?

*Dr. Prentice:* We would love to know the answers to your questions which clearly have been going through our research for some 20 years, and I am ashamed to say that we still haven't got the bottom of it. One line of research was that this is perhaps a food-related antigen that is creating the problem. I stress straight away that I am not a gastroenterologist, so my comments are perhaps rather naive. We do think it is infectious in origin, and we have tried to look at particular infectious agents both viral and bacteriological. As you know the general story there is, of course, that children get many diarrheal episodes where you can't even find the pathogenic organism; perhaps we find the specific pathogen in 30% of the cases, those are a very mixed bag of organisms (apart from the rotavirus epidemics that occur in January in the dry season). But one thing that does seem to be coming out pretty strongly is *H. pylori*, and Dr. Solon will soon be publishing data showing that even if you take biopsy tissue from the small

208
intestine then those do respond to *H. pylori* CAG and VAC antigens, and so it would seem that perhaps the *H. pylori* infection is having a particular aggravatory effect further down the intestine but we are not sure yet.

*Dr. R. Bergmann:* As I understood, one of the great hazards is weaning food. Why is it not possible to teach people to prepare the supplement from the dry and the fluid ingredient (or the water) just before feeding?

*Dr. Prentice:* Yes, but it is so very difficult. We have gone down all sorts of lines, for instance fermented weaning foods, acidification, all sorts of lines. The basic problem is the conditions. The quality of the water is not good and it is full of pathogens. One of the problems is that when the mothers cook the weaning foods, they then have to leave it with the nursemaid. A powdered corn flour acts as a thickening agent so if too much of this is used and it is brought to the boil, it creates a glutinous gruel which the children can't eat. So two things are done. One they don't put very much powder in (resulting in a very low nutrient density), and secondly they don't bring it to the boil, and that combination is a real problem. We have been doing a lot in terms of education.

*Dr. Ogra:* That was a very elegant look at nature, perhaps at its best or its worst, depending on how we look at it. The last picture which you showed was of these beautiful children: the picture of perfect health. Perhaps we should think of this as the positive outcome of benign neglect in nature. These children are from the same environment, yet they have grown, they have survived the whole environment and have become very 'healthy' children. Perhaps this is how nature fosters survival relative to the environment.

In the context of your elegant studies in this setting, is there any relationship between any of the functional alterations you see in the children related to the size of the thymus? Are there any direct correlations between pathogens and weaning foods, the development of asymptomatic infections and mortality or morbidity in the long run?

*Dr. Prentice:* Let me start with the last question because I can quickly say that I can't contribute any answer to that. It is an intriguing question but we simply don't have the data which would allow us to address it. Going back to your first point, you may be right, that would be one view. We are vaccinating children, we are trying to make optimal survival; in fact evolution has really come almost to an end because we are saving premature babies at 28 or well before 28 weeks, and we are aiding people through IVF to have children when they normally would not have them. That is the way we have chosen to go as a world. Under those conditions then Dr. Barker's theories are important because we do want to have optimal survival. Now it is a real conundrum and problem because, taking hemoglobin for instance, iron deficiency, is something we are really struggling with. In the West we want to optimize iron nutrition. Why do we want to do that? Because we believe that it affects cognitive function, motor development, etc., in children. But in the developing countries (I have to thread a very careful line here) I actually think that a little bit of mild anemia is protective, almost as you are suggesting in terms of growth. One interferes with that at one's own peril, and the recent data from the Pemba trial with an increased mortality in the groups receiving iron are really a manifestation of that concern. There are lots of times when growing small, having a low hemoglobin, etc., have been adaptive and protective, but we have changed the goalposts now and that is what the challenge is. Those children, as you say, look very healthy but if you measured them you would see that they look healthy because their weight for height is actually relatively good. If they are put side by side with a European child, you would see that they are profoundly smaller than the European child. That is what we are really struggling with: what is the optimal rate of growth in terms of optimizing these later outcomes.
Dr. Malka: About 83% of these malnutrition-related deaths were attributed to mild to moderate malnutrition and immune function. My question regards malnutrition among girls, does it affect them later in life like iodine deficiency, cretinism etc.?

Dr. Prentice: Of course it affects the girls. We are just doing some DEXA measurements of pelvic size in relation to total height and size in the girls, and we will shortly publish a paper showing that pelvic size is inappropriately small even given their height. So yes, it would have effects and we would imagine that it would have effects in terms of uterine constraint and other things which would be passed on to future generations; the affect of their early life growth. So that is precisely in line with the sorts of theories that we are addressing at this meeting.

Dr. Cameron: Just to add to Dr. Prentice’s comments about the cost of poor growth. It is not just a structural cost, because you have been malnourished as an infant child, you are not just stunted for life. There is also work from Guatemala which clearly demonstrates that there is a functional cost of early malnutrition [4]. Individuals who were stunted between the ages of 3 and 6 showed in early adulthood, at 18 upwards, significantly worse scores on tests of functional ability, mental and physical functional ability. So there is a real cost involved, it is both structural and functional, and clearly that is why we need good growth.

References


