Summary on Drivers of Growth

To summarize the day, we have had 6 outstanding presentations of a very diverse nature, ranging from the sophisticated molecular biology of some of this afternoon’s talks to the sophisticated analysis in nutrition as we saw in some of this morning’s talks, and again I want to acknowledge Nestlé for allowing us to have such a multidisciplinary discussion amongst people who are real experts. I can see 4 or 5 general points that have emerged from the day, and no doubt we will exemplify those in the next 2 days.

First, we have this question about what is normal and what is abnormal – it is very context specific, and it comes very much from the issues of how the different disciplines represented in this room study the human condition. We have groups that look at cohorts or look at normative people and investigate what is different in the range of phenotypes that such individuals have. We have on the other hand the molecular investigation of patients with a particular syndrome, in this case growth failure. I think that there is clearly a need to bridge mindsets between those who look at the issues of normality and those who look at the issues of abnormality. Anthropologists would look at it in a different way to those who use the tools of GWAS. But the kind of epigenetics that Keith Godfrey is involved in — now looking across the range of normative populations in the same way that Maria Makrides and Berthold Koletzko have been looking at normal populations — are focused very differently to what we saw of the work from Irène Netchine and from Vivian Hwa, where they were looking at abnormal populations. The discussion showed that there is some conceptual bridging yet to be achieved. I think that leads to a deeper question about what is normal, and the issue that I would like to emphasize is what is normal fetal development? How do we define that, and in what context? We danced around the issue this morning because the only measure we have generally in fetal development is birthweight and perhaps gestational length (although gestational length is something that we are not very good at assessing, particularly as we have got ourselves into the trap of using ultrasound
to date pregnancies and assume that everybody has normal first trimester growth, which is clearly not so).

Secondly, we were struggling this morning when considering what is normal fetal growth, what is normal birth, is birthweight meaningful, is there some other measure of birth size that is meaningful? And birth size needs to be taken within the context of that population; in that situation it might be very different for a person in rural India or in The Gambia to a person in the United States. And there was a workshop from the WHO some years ago focused on optimizing fetal development – a number of people in this room were at that workshop – and it suggested that we need to recognize that birth size is not a goal in itself, but what we are looking for is ensuring that the child is in optimal state at the time it is born to transition through the next phases of its development, and that will be highly context specific.

The third general theme that came out is about methodology. Here we are in the 21st century struggling with some relatively simple problems such as what is normality, how to feed mothers, and how to feed babies, and we are finding that it is very hard — simple questions turn out to be very complicated. In the final study of maternal nutrition, Maria Makrides gave us a brilliant exposition on the issues surrounding this. Berthold Koletzko did the same about infant nutrition, and you can see that here we are having to have some fundamental rethinking about what is as simple as the basic macronutrient content of food that a baby might be fed. We are uncertain and left with many unknowns because clearly there is something about breastfeeding which in at least an endocrine sense is very different to formula feeding. We have seen the complexities that surround GWAS studies, and I suspect that we are going to find much greater complexities when we consider epigenetics; Keith Godfrey was only giving a hint of the issues that will arise.

And all that leads to the next challenge, which I think everybody involved in developmental science from whatever perspective knows is the real problem. We are dealing with a genome, we are dealing with an epigenome, we are dealing with development — very different passages of development with different critical windows — and we are dealing with subtle changes in the environment which can turn out to have very major effects in the long-term. I don’t think we are anywhere near understanding the best ways to integrate all these different perspectives and to fill the knowledge gaps. This is going to be the big challenge to developmental scientists over coming decades, because what we keep on trying to do is reduce very complex systems to simplicity and expect that we will identify a simplistic intervention. Is that really what is going to happen? I doubt it. It is unlikely in my judgment that there will be a singular intervention which will address the problem of trying to give every child on the planet a healthier outcome – we will need more integrative approaches. We have seen some lovely holistic papers this morning, and we have seen some beautiful reductionist science in papers this afternoon. What
we see is that both dimensions are critical to advance our understanding. We are going to have to move to a much more interdisciplinary approach with collaborations across disciplines, and again that is why I am so delighted that there are so many different disciplines represented in this room today.

*Peter D. Gluckman*