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It’s my job to summarize the first day and also to try and resolve some of the difficult areas and confusions that have arisen during that day of discussion.

You will recall that in my introductory piece I pointed out a new dimension in the field of early growth and that is it’s critical role in lifelong health, the idea that early growth was in a pivotal position in terms of the early origins of obesity, cardiovascular disease, cognitive development, cancer, and in animals lifespan and senescence. We identified that central to this idea that early growth has long-term effects is the broader biological process of programming. We also identified a number of programming agents such as visual inputs, hormones, drugs, nutrition and growth. Just taking two of these you can see that drugs and growth must have really quite fundamental effects on the organism to have so many and such diverse downstream effects including effects on the brain, metabolism, morbidity, of course cardiovascular disease and obesity, in this category cancer and lifespan. When it comes to programming by early nutrition and growth of later health, we considered in our session methodological approaches. In fact, the first studies in this field were in animals and animal research remains important because we can use an experimental design, we can do diverse interventions, some of which are impossible in humans, we can explore mechanisms and we can do lifetime studies. But when it comes to exploring programming effects of early nutrition and growth in humans, we have two basic approaches. We can do observational studies and, if these are retrospective, we get very rapid results, and we can study real endpoints like ischemic heart disease. The problem is that it is more difficult to prove causation with observational studies than with an experimental design. We can also do experimental studies in humans based on the pharmaceutical trial model, randomly assigning babies to diet and looking for efficacy and safety. Now the problem with experimental studies is that they are expensive, they take a long time to do and lifetime follow-up is obviously impossible and so we need surrogate markers. Still, the great advantage is that we can prove the cause and we can use the data to underpin practice, and as I pointed
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out in my introduction just in our center we have 27 trials now showing long-term programming of cardiovascular disease risk, brain development, bone health and allergy, some with prospective follow-up into adulthood, so those studies are actually feasible. But the consensus was that the way forward in programming research is to achieve the benefits of all of these approaches by a combination of animal experiments, human observations and randomized trials, and you'll have noticed that the selection of speakers on the first day was designed to reflect those different approaches. The main topic of the first day was the nutritional programming of cardiovascular disease and obesity. Underlying this was a constant theme, and that is that a high plane of nutrition resulted in faster growth that triggered the programming event that resulted downstream in increased cardiovascular risk and obesity. The idea that fast growth should have an adverse consequence is not a new one in biology. In fact, at least two of the speakers noted that fast early growth is of a long-term health cost in numerous other animal species. For the animal studies in this section, we had two speakers, Susan Ozanne and Sébastien Bouret, and I want to start with Susan Ozanne from Cambridge, UK. She presented us with evidence for adverse effects of rapid early growth or what we might call catch-up growth. She found that nutritionally induced intrauterine growth retardation followed by accelerated growth decreases longevity by as much as 50% in animal models. She also found that this nutritionally induced intrauterine growth retardation followed by accelerated growth resulted in diet-induced obesity in later life, perhaps through an appetite mechanism, in adiposity, in telomere shortening, which is a measure of aging or senescence, and oxidative damage. The other side of this was that she also demonstrated to us in animal models a beneficial effect of slower early postnatal growth. So nutritionally induced slow growth during lactation was found to increase longevity in laboratory rodents and this same intervention decreased later food intake again, probably through an appetite mechanism, decreased adiposity and decreased telomere shortening, in other words signs of senescence, and it increased favorably antioxidant defense capacity. So animal models showed that rapid early growth has deleterious effects and slow postnatal growth has a variety of beneficial effects. Sébastien Bouret provided us with perhaps part of the important mechanism involved here. What he did was to look at early growth, leptin and the development of parts of the brain related to appetite. What he pointed out was that what he called brain feeding circuits are still relatively immature at birth and that leptin promotes formation of brain circuits that will regulate feeding and appetite in later life. He noted that the neurodevelopmental actions of leptin appeared restricted to a brief critical neonatal period. He also pointed out to us that both postnatal under- and overnutrition influences postnatal leptin levels, and this has enduring consequences on hypothalamic neurodevelopment. And with regard to the postnatal growth acceleration concept, he noted that rapid early growth results in abnormal brain wiring which could increase
appetite and metabolic disregulation later in life. In other words, part of the mechanism by which early growth or rapid growth induces long-term effects could be through the leptin mechanism by changing the brain and regulating subsequent appetite. Matthew Gillman from the USA talked about the early origins of obesity in the West using observational study models. He pointed out that the current epidemic of obesity has affected even the youngest of children, even in the first months of life, and that human observational studies and randomized trial follow-ups have shown that rapid weight gain in the first 6 months predicts later adiposity in humans. In giving us examples, he pointed out that in one US study two upward centile crossings in the first 6 months predicts obesity at age 5 years, and he noted that SGA infants who gain weight rapidly have worse metabolic indices at follow-up. However, Prof. Gillman argued that to put this into public health practice needs data on the quality of growth, on the developing world, which I will come back to in a moment, and on modifiable determinants of adiposity as a basis for future intervention trials. Nevertheless, he pointed out that based on evidence to date babies born small should not receive enriched diets to promote rapid weight gain. Atul Singhal looked at the early origins of cardiovascular disease and obesity now based on randomized trials. He spent some time actually discussing the postnatal growth acceleration concept. Prof. Singhal was important in framing this concept which is implicit in the previous studies and presentations that I have been talking about, the idea that rapid early postnatal growth increases the risk of later cardiovascular disease and obesity. He presented data from randomized intervention trials in humans and pointed out that these were paralleled by equivalent studies in animals. He also noted that there are around 40 studies based on observations that now show greater cardiovascular disease and obesity risk after accelerated early growth in healthy full-term infants. In fact, we know here someone who has done a very detailed review of the literature and has actually found 50 studies showing this phenomenon. Prof. Singhal showed us as an example a trial in small but healthy full-term infants who were randomly assigned to a standard vs. an enriched formula with 30% more protein to stimulate catch-up growth, and at 8 years follow-up those fed the growth-promoting diet in infancy had a worse cardiovascular disease risk factor, particularly higher blood pressure at that time. Based on this, he came to a similar conclusion to Matthew Gillman that contrary to previous opinion rapid growth promotion in small but healthy full-term infants appears to be inadvisable. He also pointed out that environment is extremely important for the manifestation of programming effects. For instance, in the developing world with poor nutrient intake the programming effects that had occurred prior to this might not then manifest in adult life. We came to a consensus position then that fast early growth programmed a cascade of adverse effects including blood pressure, insulin resistance, fatness, raised LDL cholesterol and inflammatory markers with downstream effects on atherosclerosis and morbidity. This is only a model at the present
stage, but there is a lot of evidence now to support that construct. However, we also need to balance the long-term gain of slower earlier growth against any short-term risks, and because of that Linda Adair was invited from the US to talk to us about the short-term aspects of growth in developing countries. She pointed out that in developing countries poor growth as manifested by weight, height or weight-for-height, z scores remains highly prevalent. The associations with poor growth include impaired immune function, increased incidence, severity and duration of infectious diseases, especially diarrhea and pneumonia, and increased mortality in the under-5-year age group, particularly from infection. She noted that growth promotion to achieve recovery of a normal growth trajectory is critical in developing countries to promote short-term health and survival. Linda Adair recognized that there is a tradeoff between the long- and the short-term effects of rapid early growth and that different messages are needed for different groups of children. She also advised caution to avoid spillover of messages about slow growth for well-nourished children in optimal environment to those in suboptimal environment. So what is the best practice then, bearing in mind that slow early growth reduces later cardiovascular disease risk and obesity but in high-risk populations slow growth has adverse short-term effects. Our proposed plan of action that arose during our discussions on the first day was based on a balance of these risks. It was suggested that we should ignore programming and promote short-term growth in three groups, malnourished and at risk groups, preterm infants and extremely growth-retarded or sick infants. In malnourished and at risk groups, we agreed that short-term growth promotion, which reduces morbidity and mortality, is a priority. Premature babies also need good nutrition for short-term morbidity prevention, and also fast early growth in this group greatly improves or programs long-term cognitive function. In sick or extremely growth retarded babies, we also need to put in nutritional rescue because these babies may have poor brain growth, and they may have specific nutritional deficiencies. However, in well small term infants at low risk, there may be a disadvantage to rapid early growth, and so we have two potential recommendations here. Firstly, that we should feed them normally, that is breastfeed them or, if necessary, formula feed them with a regular formula and do not actively promote faster growth with specialized products, because this has been shown to increase later cardiovascular disease profile. The second point is that in these infants we should at the present time accept catch-up growth if it occurs spontaneously because although this is associated with adverse outcome there are no studies as yet to support suppressing catch-up growth. But it was recognized that there are grey areas, so balancing the long-term gain of slower earlier growth against any short-term risk really needs professional judgment. I would like to end up by saying that there are many unanswered questions in the sessions that we had in a very interesting first day, but I think there was some general agreement that early nutrition and postnatal growth are emerging as important factors for later cardiovascu-
lar disease and obesity risk that can potentially be manipulated in future clinical practice.

Alan Lucas

It’s my pleasure to summarize the second session, which was focused on growth and neurological development. We were amiably moderated by Dr. Hussain and Dr. Cheah yesterday and Dr. Zulkifli this morning. Dr. Martorell summarized very nicely for us the interrelationship between growth and development in disadvantaged countries and developing communities. Dr. Richard Cooke focused mostly on premature babies and Dr. Hüppi extended that to consider the more high-tech aspects of growth and development of the brain. Dr. Domellöf and I talked about the specifics of micronutrient supplements. Dr. Martorell clearly identified gestation and the first 2 years of life as the window of vulnerability and showed us studies that related low birthweight, low weight gain in the first 2 years of life as well as stunting to all be associated with fewer years of schooling, the increased likelihood of failing a grade at school and reduced annual income even after adjustment for confounding variables like socioeconomic status and maternal education. He summarized by showing the interrelationship between stunting as a measure of cumulative growth failure and poverty. He described the cyclical nature of the relationship and highlighted that cumulative growth failure really has a true impact on societies in developing countries in terms of economic outcome, and postulated that achieving good growth will be important in breaking the poverty cycle. Indeed the Copenhagen consensus has recognized this, and of the ten most important solutions for improving global outcomes prevention of malnutrition is noted in three of them. Moving to growth and development in the preterm infants, Dr. Cooke suggested that a critical period of brain growth for preterm infants occurs between day 28 of life and the first 2–3 months of age. He showed that dietary intervention after hospital discharge might improve growth, but this was not paralleled by better development. However, neurocognitive development was poor in boys fed a term infant formula compared with girls. Dr. Cooke also showed us that accelerated growth in preterm infants fed a nutrient-enriched discharge formula was not associated with increases in adiposity but in fact was associated with increased linear growth and lean body mass, which was considered to be a good outcome for these children. Dr. Hüppi used state-of-the-art imaging techniques to help us further understand brain growth and development, and showed that brain volume and cortical volume were both related to neurodevelopmental outcomes and that brain volume was not only influenced by postnatal factors but was also influenced by the volume of the brain at birth. The two examples of postnatal factors were nutrition in terms of protein having a positive impact and the use of glucocorticoids having a negative impact. She also noted that
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IUGR babies are the ones that are most at risk. Moving to the more specific supplementation, Dr. Domellöf presented a very balanced review about iron supplementation and its effects on growth development. He showed that in regions where iron deficiency is prevalent, widespread supplementation is useful for the prevention of iron deficiency anemia, enhancing neurodevelopment and possibly enhancing growth. However, in regions where iron is replete, there were possible reductions in neurodevelopment, poorer growth and increased infection, and widespread supplementation was not recommended. In regions with malaria, widespread iron supplementation has been shown to cause increased morbidity and mortality and there was a vigorous discussion as to the approach forward. Supplementation of formulas with LCPUFA for both term and preterm infants does not appear to affect growth in the 1st year of life at the doses that have been used and tested. The potential benefit of LCPUFA supplementation in infants born healthy and at term is likely to be limited, whereas supplementation for preterm infants is likely to have a modest positive effect on neural development; however, the dose and timing require further investigation. There is an emerging area of research with regard to pregnancy supplementation.

Maria Makrides

Stef van Buuren gave us a very nice review of the study that led to the new WHO growth standards. He presented some details I wasn't aware of, and using data from a large growth study in Holland that he analyzed with regard to the effects of selective dropout, he made the plausible case that selective dropout explains at least part of the high weight that we see in the WHO growth standards during the first 6 months of life. I and others try to understand what the cause is and to understand the implications. The argument that at least part of it is due to selective dropout convinces me, so I am grateful for his careful work.

Dr. Ogden from the CDC gave us a detailed description of the sample on which the CDC charts are based. She also told us about plans to add or to replace some data in order to correct some shortcomings of the CDC charts. But the CDC charts have obvious strengths, the biggest of which is that they are clearly nationally representative of the US. She showed us that the better data in the 1st year of life will lead to an increase in weight on average of about 0.5 kg, which is quite substantial, and in length of 0.5–1 cm.

I want to thank Dr. Li and congratulate her on this monumental accomplishment of generating growth charts for China. Obviously, the sample size is enormously high, even though it represents only Chinese living in urban centers, and maybe the next step will be to include some urban areas to make the charts more representative of the entire Chinese population. It’s a little bit difficult to judge how the Chinese reference compares to WHO and CDC because, as you all are now aware, by just superimposing charts it is difficult
to appreciate how big the differences are, and whether they are important. But anyway, congratulations on this accomplishment.

Dr. Ellis reviewed with us the methods that we have for measurement of body composition in infants and children, and he reminded us that the methods are complex, most of them require expensive machinery and expertise that are usually not available in the field. Therefore, the frequently heard call to take body composition into account in assessing nutritional interventions meets the reality that those methods are only available at some select centers such as Dr. Ellis’. He also reminded us that BMI is a poor predictor of body fat and that BMI was never designed for infants, which we tend to forget. The body volume measurements that are now available with PEA POD are very accurate but subject to errors due to the degree of hydration. The PEA POD is currently very popular and the company that makes the PEA POD is very aggressively marketing the machine. I am glad you didn’t talk more about BIA because I think the method as far as assessing body composition is far too inaccurate. But, as Dr. Ellis said, for measurement of body water it would be an appropriate method. It has the big advantage of being simple and cheap but that doesn’t make up for the inaccuracy and the lack of specificity.

Finally, Dr. Rosenfeld gave us a splendid overview of the genetics of IGF and growth hormone and their receptors; that was just wonderful. I think the most important message that I take away from his talk is that we can never easily separate normal from abnormal. I think this point was very well made, and we all know that there is never a sharp line between normal and abnormal. That point was illustrated very well and I thank him for this very elegant talk. On behalf of my co-chairs I would like to thank all the speakers for their very excellent and informative presentations. I would like to thank the discussants and the entire audience for their lively participation.

Ekhard E. Ziegler