Concluding Remarks

It has been a very exciting meeting. Dr. Sampson is going to talk mainly about the second half of the presentations. So I would like to go through a number of the presentations and pick out a few points to remind you of some of the concepts that came across. Then I want to talk a little bit about some of the ideas and research issues that distill out of this.

At the beginning we discussed some thoughts and concepts on primary prevention in infancy and childhood nutrition. We agreed that primary prevention is both the prevention of disease before it occurs and the reduction of its incidence, but for this particular field we felt that this should be extended to prevent or reduce the risk of disease and prevent the impairment of cognitive potential because this a very important objective in pediatrics.

Now primary prevention includes education, what we do as clinical scientists (clinical and public health practice or intervention) and what governments do (policy, legislation and regulation), though as professionals we need to have an influence on the latter. Now the key issue of this workshop was research and primary prevention and, as we heard in the last few lectures, this may have a fundamental basis, but Dr. Sampson is going to focus on that. My point is that ultimately primary prevention requires outcome research to prove that nutrition has an impact on health risk. This can be short-term, it can be long-term programming effects or effects of nutrition throughout childhood; and nutrition is also a vehicle for factors that influence health such as pathogens, toxins, nutraceuticals and so forth. I gave some examples of these, such as the use of human milk in neonatal intensive care in the short-term which has a major impact on the life-threatening condition necrotizing enterocolitis, and in the longer term the use of pharmaceutical trials to demonstrate that early nutrition has long-term programming effects on the brain, on bone health and cardiovascular disease risk with huge prevention potential.

Dr. Fewtrell talked about bones, and I am going to come back to that later; Dr. Singhal talked about cardiovascular risk, and I focused a bit more on the brain. It is remarkable that in some groups such brief periods of dietary manipulation can have such profound effects on important outcomes like motor and
mental impairment, associated with major changes in the brain detected using sophisticated applications such as magnetic resonance imaging.

Dr. Singhal talked about the prevention of atherosclerosis and the metabolic syndrome. He pointed out that atherosclerosis begins in childhood, the risk factors are identifiable very early, and that the metabolic syndrome is really very common. He focused on the impact in human milk and pointed out that there is a wealth of observational studies showing that breastfeeding is associated with reduction of the key components of the metabolic syndrome, high blood pressure, raised LDL, obesity and insulin resistance. In preterm infants causation can be confirmed by dose-response relationships and more importantly randomized trials. He also pointed out the huge effect size here: the blood pressure effect size in some randomized trials is in the order of 3–4 mm whereas a 2-mm fold alone would produce 100,000 less cardiovascular events in the USA each year and 10% lowering of LDL cholesterol in adolescents previously fed breast milk, which would correspond in adults to a 25% reduction in cardiovascular disease risk. So there is a major potential here for prevention. He also talked about the importance of postnatal growth for cardiovascular programming, pointing out that in a wide variety of animal species fast early growth is at the cost of long-term health. He added humans to this list by giving us some very exciting data on the dangers of rapid growth in early life. So early growth and nutrition have become major factors for later health in all infants, not just small ones which have been the focus. These postnatal influences have a much larger effect than birth weight which has received so much attention recently. In fact birth weight may, to an extent, even be a proxy for postnatal growth and not prenatal growth. So favorable programming of cardiovascular disease is associated with breastfeeding and slow early growth. He pointed out that these were in fact unified in an early growth acceleration model, which has huge implications for prevention in terms of adjusting early growth rates to optimize long-term cardiovascular risk.

Dr. Maffeis talked about childhood obesity and considered the potential mechanisms for the prevention of an epidemic. Most of us were rather excited to discover that obesity is so strongly associated with inflammation because that gives us another route to prevention in this area. He also talked about the importance of signaling systems for appetite control and finished by considering the great importance of exercise and activity in the control of obesity.

Dr. Kroke rather disturbingly told us how much we didn’t know about the relationship between prenatal and postnatal factors in the development of obesity. In the first phase she talked about the complex relationship between birth weight and adult BMI, showing how difficult this was to relate to obesity. She felt in the end that birth weight, although much focused on, is actually not a very good indicator here, and pointed out that despite sound theoretical considerations and experimental findings the human data are not convincing in this area. Her second area related to perinatal factors. She
pointed out that there are many animal experiments and studies on maternal diet in relation to fetal growth, but in humans the evidence is really not there, except perhaps from the Dutch famine which gives us some important leads. The relationship between maternal diet and later weight in the offspring she felt was very difficult to interpret and the best route here is to exploit some of the trials that have been done in this area for long-term follow-up. She also pointed out this U-shaped curve where adequate nutrition, which might be defined as breastfeeding, was at the bottom of the curve as far as the risk for obesity is concerned, but undernutrition and overnutrition were risk factors, and potentially lead to prevention in that area. She summarized saying that the hypothesis on the early origins of obesity is well supported by physiological concepts and animal data but, due methodological constraints, the human data are really quite weak in this area. The one area that shone out was that breastfeeding appeared to be associated with an about 20% reduction in obesity risk. We argued whether this 20% was small or large as some of us felt that it was actually quite a large effect and could well amplify with time.

Dr. Laron talked about childhood diabetes with an emphasis on perinatal factors, and noted the really steep rise in both type-1 and type-2 diabetes and the importance of environmental factors, focusing on viral and nutritional factors for type-1 and changes in nutrition and lifestyle for type-2. He put forward the hypothesis that the onset of both types of childhood diabetes occurs in the perinatal period, the autoimmune process being triggered as early as in utero or postnatally by cow’s milk proteins. This was an extremely important route into prevention after having made the point that secondary and tertiary prevention failed rather miserably and that primary prevention now must be a priority.

Dr. Fewtrell talked about osteoporosis and whether primary prevention possible. For instance she noted adequate vitamin D and calcium intake in mothers, and breastfeeding was beneficial in babies and preterm infants. She presented the results of randomized trials showing that nutrition actually increases bone formation and therefore might be an important risk factor for later bone disease. This needs to be followed up. She pointed out that calcium and vitamin D as intervention were somewhat disappointing, but physical activity and optimizing linear growth might be more promising solutions. Her ideas for future research were to follow up existing trials particularly to determine adult outcomes and the effects of interventions on bone structure and geometry, looking at sensitive periods, site specificity and optimal interventions, and gave us some very good clues as to where we might go with gene interactions and potential mechanisms. But the really important issue was whether there was going to be a useful quantitative effect here. She tried to estimate this pointing out that the effects observed on bone mass with calcium supplementation were in the region of 1–5% and with physical activity in the region of 3–5%; and that could delay the onset of osteoporosis by
6 years and reduce fracture risk by 10–20%. I think if those were feasible they would be very worthwhile aspects of prevention.

Dr. Hursting gave us a really inspiring talk on nutrition and cancer protection, and pointed out that in the transition from normal to neoplastic cells there are a number of factors: anti-initiation strategies which he listed and anti-promotion progression strategies which involve steps that were all theoretically influenced by early nutrition, thus leading to cancer. To be more specific about this he pointed out that nutrition has been identified as one of the key influences on cancer, that prior active food components can affect many aspects that are relevant to cancer, including DNA repair, hormonal regulation, inflammation, immunity, apoptosis, cell cycle carcinogen metabolism, and that we should eat more fruits. He pointed out the areas in which nutrition interfaced with cancer, IGF-1, leptin, obesity, inflammation, LCP-UFA and prostaglandins. The IGF-1 story is really interesting in the way that early growth and nutrition could actually, through IGF-1, form a link between both cancer risk and cardiovascular disease outcome risk.

The huge association between cancer and obesity is surprising to many of us here, at least raising the possibility that one of the ways of preventing cancer would be to attack obesity. With regard to real interventions that could be done, Dr. Hursting pointed out that human studies were really quite rudimentary but that there are a number of animal studies and animal models for effects on cancer that give us some important leads for future human research.

Against that background I want to remind you of some of the things that I discussed in my introduction which have become rather more relevant now that we have had 3 days of discussion. I want to consider some of the research issues in primary prevention for the future. I identified critical interactions which could be genetic, environmental, relating to subject characteristics, and the interaction between early diet and our subsequent Western environment, the importance of the timing of the window, the emergence of the effect which could be late, the quality of evidence required in this area, risk-benefits analysis and mechanisms. Just to focus on those points I have taken out of my lecture, some of the research messages that I put forward, and I thought it would be useful to review them again: Genetic characterization and family history may well be needed in some primary prevention studies to identify the best target groups for intervention. We identified a few areas overall where quite specific genetic groups would be affected by nutrition interventions. Then we pointed out that the effect of an intervention might be quite different in opposing subgroups, like males and females and small-for-gestational age babies and appropriate-for-gestational age babies. So looking at interactions overall, the impact of a health intervention can be highly influenced by genes, subject characteristics, and current and subsequent environment, and that clearly needs to be thought about when planning new studies. Another important message is that the
efficacy of a prevention strategy may be highly influenced by its timing, and we talked about the timing of intervention to reduce the incidence of cardiovascular disease; in the examples we discussed it could be more effective and practical to intervene in the postnatal period rather than in the fetal period.

Another important issue was that long-term follow-up is essential in nutritional intervention trials. Quite a number of effects of our interventions do not emerge until late. Remembering the LCPUFA example we discussed earlier today, when they do emerge they may be the opposite to what was expected, raising a safety concern. Therefore long-term issues really need to be addressed in our studies. That came out in many of the speakers’ work. In terms of the quality of evidence whenever they are possible, experimental studies are a more sound basis for practice than observational ones, and quite a number of the speakers, including myself, pointed out the difficulty of proving causation and the dangers of basing practice with observational data. Of course it is not always possible to have experimental studies but it should be a goal. I also pointed out that it may not be safe to devise primary prevention policies based only on the outcome of interest to the investigator. The same intervention can have beneficial effects on one system, such as cardiovascular health and detrimental effects on another, such as the brain, so that performing a balance of risks is a critical exercise in actually producing the best compromise for infants and children.

Dr. Bier and myself pointed out that multilevel mechanistic research may provide the best underpinning for prevention strategies, and we should not just think of mechanistic research at a genetic or molecular cell biological level but also at the physiological level. We talked about mechanism at a structural, behavioral, and social level; the latter being very important in the area of obesity. Finally we stepped outside the human species and considered evolutionary modeling to generate hypotheses for future human studies. In terms of assessing the prevention potential of a new area we considered the quality of evidence and noticed that in some areas this is very good and in other areas it is really poor, and set out a task list of areas that we need to be working on in the future. The size of the effect when we looked at it critically was trivial in some areas and probably not worth achieving, and extremely important in others. The feasibility of application varied hugely for different areas of prevention strategy and I think we would all agree if it depends on public education then this is often hard to achieve.

In an overview, primary prevention by infant and child nutrition was an area that we identified collectively as having immense potential and which could not have beed contemplated 20 years ago. But the research in this area is highly complex with many pitfalls. Perhaps a really important overarching point, and this came out very much today in the discussions, is that primary prevention practice cannot be based safely on theory, politics, and uncontrolled observations. We as a profession have to resist political decisions that
are not evidence-based. It is really a sound evidence basis that we need to optimize health and development.

Alan Lucas

I would like to thank the organizers at Nestlé again for inviting us and supporting this conference. What I would like to do then is to go ahead and review the allergy section that was done yesterday and then some of the later slides today. As you may have noticed I have been over here trying to make slides as people were giving their presentations. Dr. Lucas was much wiser; he picked the early speakers.

Yesterday we talked about the potential prevention of atopy and allergic diseases and 4 speakers addressed various topics in that area: Dr. Björkstén spoke about gut microbiota; Dr. Zeiger looked at studies that have been done related to breastfeeding; I took on the task of looking at what we know about the use of various modified formulas, and then Dr. von Berg talked about the introduction of solids. Just to review why we are so interested in this topic, this slide depicts the increasing prevalence of atopic disease, although I think one of the things I have learned in the course of this conference is that obesity or cardiovascular disease could be depicted in a similar way, so we are all attempting to prevent some fairly serious outcomes.

Dr. Björkstén started it off by giving us quite a bit of information about the gut microbiota; we all know now it is not flora, it is microbiota. We were thrilled to learn that we are all carrying around 1kg of bacteria in our gut, which consists of over 500 species. However, at this point in time, fewer than 50% of the strains in there are known. He emphasized the fact that this is really a very vibrant environment that, as he called it, is an ecosystem characterized by stable chaos, and I would add that it basically is living under controlled inflammation. So this is a very dynamic area that Dr. Bier also pointed out as a very exciting area of future research. There clearly have been demonstrations of interaction between the microbes in the host and between components of the microbiota and the host. This is a very dynamic and open ecosystem that maintains some functional stability, but it does have many factors which can affect it including nutrition, which we were talking about, drugs and infection, etc. Dr. Björkstén also introduced his new theory on the TH1/TH2 paradigm, which is probably much more on the mark than what we used to believe was the potential role of microbiota in the development of the immune response. So what are the potential health effects of early intervention, assuming that gut microbiota early in life are a major driving force for immunologic maturation and function? He gave us some examples including the changes over time, which may in fact underlie some of the increases that we are seeing in allergy, autoimmunity, inflammatory bowel disease and perhaps even obesity. The gut microbiota may offer
a potential for disease prevention and treatment if we learn more about it, but what bugs we need, which show the most important effects, and can we really make alterations, I think remain up in the air. If we are going to take advantage of alterations in the gut microbiota to improve health, this probably will have to be done early in life.

The next series of discussions were about the results of breastfeeding, various formulas and solid foods, and one of the common themes in these three talks was the fact that there are divergent findings in many of the studies. This was due to several reasons including the differences in design, deficiency in many of the designs, confounding factors, some of which were not adequately controlled, sample size, factors that we just don't know about at this point, and the fact that most are observational studies, the influence of reverse causation, and then other factors that haven't really been looked into but have been alluded to throughout this conference. For example, the variations that do occur in breast milk from different mothers and the variation in the content of various hydrolysate formulas may lead to very different results.

Looking at some of Dr. Zeiger's conclusions in evaluating the effects of breastfeeding, there is evidence to suggest that it does promote less wheeze, less asthma and less eczema. The effect size is about 30%, which makes breastfeeding one of the most effective things that we can do for infants, similar to the effect of eliminating tobacco smoke from the environment of an infant. The data support exclusive breastfeeding through the first 3–4 months of life, and the beneficial effect occurs without altering the maternal lactation diet. In other words, we should not be imposing any kind of restriction on the maternal diet, and the effect is not lost if in fact the mother herself is atopic or asthmatic. At this point in time, as is apparent with many of the studies we have heard about at this conference, the effect of breastfeeding on atopy beyond 6 years of life is really not known, and like many of the areas, the studies are of too short a duration. Looking at infant formula feeding, it was my conclusion that there is certainly no evidence to support the use of any hydrolyzed formula in place of exclusive breastfeeding as long as exclusive breastfeeding can be done. In situations where that is not possible, where supplementation is needed, infants from high-risk families should be given hydrolyzed infant formulas for at least the first 6 months of life. There is some suggestion in the literature that this will prevent some cases of atopic dermatitis. Evidence from the GINI study would suggest that if there is no atopic dermatitis in the family, the partial whey hydrolysate formula appears to be as effective, but if there is atopic dermatitis in the family suggesting a more robust atopic predisposition, then the use of extensively hydrolyzed casein formula is probably necessary. At this point there is insufficient evidence to demonstrate any preventive effect for asthma or allergic rhinitis but this may be due in part to the fact that the studies have all been of short duration. Finally there is no evidence at this point for the benefit of hydrolyzed formula
in low-risk infants and this is primarily because the long-term studies have not been done.

Looking at the timing of introduction of solid foods, Dr. von Berg concluded that the earlier studies showing an increased risk of atopic dermatitis with early introduction of solid foods have not been confirmed by more recent studies and that in fact some of the previous information may have been due to reverse causality. She also indicated that early nutritional antigen exposure does not necessarily parallel early sensitization. She looked at early hen’s egg sensitization and gave us fairly striking evidence that this was a good marker for atopic disease, especially when combined with an atopic family history. She also presented some data from the GINI study related to the introduction of solid foods, which I think has really improved our understanding of this area. She concluded that the early introduction of solid foods seems to be less harmful than we previously thought and therefore many of the recommendations out there, especially those of the American Academy of Pediatrics should be far less rigid.

Today then we had some very interesting discussion on LCPUFAs, something I have to admit I know little about and hadn’t really thought much about, but it is clearly a very interesting and exciting area for future research to investigate its multiple effects on health of young infants.

Dr. Fewtrell started off with a critical review and current knowledge in the area of the LCPUFAs, Dr. Hanson looked at the impact on the immune system and Dr. Massiera looked at the possible impact on body fat mass. So starting out, it appears that it is a fairly contentious area with lots of emotion behind it. However, I believe that the presentations gave us the impression that theoretically it seems to make sense that LCPUFA supplementation should be beneficial, but as pointed out, at this time the evidence is really all biochemical and the clinical efficacy may in fact be quite difficult to establish. One of the strong pleas was for good long-term follow-up studies to evaluate the effect of the n-6/n-3 ratio as opposed to just looking specifically at levels of these specific LCPUFAs. One of the other things that was pointed out was the fact that when we are doing these studies, just as we see in the hydrolysate studies for prevention of allergy, there are considerable variations in the different formula preparations. These differences may lead to potential pitfalls when we are just considering the generic effect of these particular formulas. It also was pointed out that minor differences can certainly affect these outcomes, again stressing the point that Dr. Lucas made in his opening remarks, i.e., there is a major need for long-term studies here because we may see differences as the studies are carried out longer term.

Then Dr. Hanson gave us some information about the potential effect of LCPUFAs on the immune system, showing that a deficiency of the n-6 and n-3 essential fatty acids in the maternal diet was able to decrease leptin in offspring and also the amount of inguinal white adipose tissue and its leptin messenger RNA. He also showed that essential fatty acid deficiency gave
increased milk leptin, and then discussed the potential outcome in offspring from these animals. He also discussed the effects of tolerance induction, showing that a low ratio of n-6/n-3 in the maternal diet resulted in neonatal tolerance in the pups following ovalbumin exposure via the milk and speculated that this tolerance was possibly due to an effect on regulatory T cells and the production of TGF-β. He also showed that there was no tolerance in the group that had the high ratio of n-6/n-3 and in the very high ratio group there was evidence of tolerance but apparently due to a different mechanism, that of T cell anergy, thus suggesting a major interaction between diet and tolerance induction. Dr. Hanson then gave us some information on the potential effects of maternal diet on gestational immunity. He first showed data on IL-10 messenger RNA content in the decidua of Swedish mothers who had infants with intrauterine growth retardation, and then showed us data from his large cohort of Pakistani patients who had a significant decrease in IL-10 and increase in TGF-β in both decidua and trophoblast in those with intrauterine growth retardation. He suggested that this reduced IL-10 in the placenta may be involved in the pathogenesis of intrauterine growth retardation.

Then Dr. Massiéra went on to give us information about the potential effects of diet on body adipose tissue and showed us a comparison between animals that received a high n-6 diet compared to a standard diet and pointed out the fact that this group had much higher adipose levels. This was probably mediated through the IPR promoter since this phenomenon was not seen in IPR knockout mice. She then gave us some tentative conclusions on the effects of LCPUFAs on body fat indicating that dramatic changes in the fatty acid composition of the dietary fats probably have gone largely unnoticed over the years and that this may be leading to changes in white adipose tissue development of newborns and infants and potentially accounting for some of the increase in obesity that we are seeing. Whether or not the prevention of childhood obesity is the key issue, the fatty acid composition of dietary fat should be reconsidered and provided in a more balanced manner with the supplementation by n-3 polyunsaturated fatty acids being accompanied by a simultaneous reduction of the n-6 polyunsaturated fatty acids in formula, as well as other foods. She noted that this was a recommendation that was made previously by a NIH panel as well.

Then in the last series of discussions we heard presentations on the impact of nutrition from a more mechanistic aspect, Dr. Kussmann giving us a really excellent lecture on the different ‘-omics’ and encouraging us to use ‘-omics’ in everything, and then Dr. Bier followed it up with future prospects and even ‘wholomics’; I think we are now getting a whole new vocabulary. I think Dr. Kussmann's presentation on the different aspects and the different ways to use genomics, proteomics and metabolomics was really one of the nicest presentations bringing all this together and giving us a unified concept. He stressed the complexity of this area, making us aware of the fact that where
at one point we thought genomics was such a complex area, it really is pretty simple when we start looking into some of the other areas such as the proteomics and metabolomics. Looking at how these different approaches will be useful in the future will hopefully help us get to the bottom of many of the nutritional issues and other medical issues that are confounding us.

Then finally Dr. Bier gave us an outstanding final summary of some of the major issues that are coming up and need to be dealt with in the area of research, especially research in children. I think this whole area of ethical standards related to experimentation in children really has to be addressed face on, that as he pointed out, we are all experiencing more and more difficulty doing research on children. I definitely would agree with one of the statements in his slides, that it may be unethical for us not to be doing research in normal children. He also wants us to think about the field of epigenomics, and I was not aware of the two studies he presented demonstrating the major effect that environment can have on the expression of our genome. He then reviewed a number of the new technologies of the 21st century, again encouraging us to shift our way of thinking about these traditional approaches that we have taken in the past, something he has labeled the small science, and really start to think much more about the big picture. He indicated that the mathematics of this area may be somewhat of a limiting factor in the near future but hopefully this is something that we will be able to overcome. When it comes to the point where we will be able to apply some of these principles, human behavior may serve as a limiting factor.

So in wrapping up, I will take away from this meeting many common interests in all our areas of research. There is certainly a major need for well-designed, prospective multicenter trials in many areas of infant nutrition. Everyone has said there is this need for long-term studies and this is something that seems to be an area that is very difficult to get funded. It is not so difficult to get the first 5 years of a large study funded, it is trying to keep the cohort going beyond that. It looks to me, from what we have seen here, that this may be the most important information that we need to disseminate, and somehow we have to get the funding agencies to help with this.

Finally I would like to thank all the speakers who came and for their excellent presentations, and thank the audience for the great questions; I think many of them were quite stimulating and kept all the speakers thinking. I believe that this has been a good experience for all of us. Thank you.

Hugh A. Sampson