Concluding Remarks

I am going to summarize very briefly what I understood from the talks in the session which I shared with Bhaskar Raju. The first one was given by Andrew Prentice. It was a brilliant lecture, and he spoke of a number of things which I had always tried to understand, but I had never understood them before. Today I don't have much difficulty actually putting this together.

His talk was the evolutionary origins of obesity and the contribution of rapid nutritional transition. He stressed that the rapid increase in obesity has only been over the last few decades. Then he raised the question, ‘Are developing populations more susceptible? Do we have any indications in the evolutionary analysis?’ He discussed the thrifty gene hypothesis which proposes that the thrifty genes deposit more fat during food availability. These are positively selected when food is not available because these people are able to use their energy stores. He then raised the issue that all populations have faced, famine which is episodic rather than a long-term supply problem. By definition everyone alive today must carry the thrifty genes. He challenged the original description that selection is related to viability and showed evidence that selection is more related to fertility. He quoted recent work from Cambridge on genetic syndromes of obesity. Almost all of them are related to the control of appetite in the hypothalamus, there is hardly any genetic syndrome related to an energy expenditure problem. We don't have any experimental support for the thrifty genes. The recently describe FTO gene polymorphism has been replicated in the majority of European populations, but not in Africans. In Indians it is strongly related to diabetes, but weakly or not related to obesity. So in Indians it remains a diabetes gene but not an obesity gene. I interpret this to indicate a basic difference in Indians and Europeans about how obesity is related to diabetes. I think the geneticists have provided us with an exciting marker whose epigenetic regulation may reveal fundamental processes in this pathway. Dr. Prentice also thought that with the genome-wide search clever statisticians are going to provide us with some answers very soon.
Concluding Remarks

*Parul Christian* spoke on the prenatal origins of undernutrition and made the important point that the high prevalence of childhood stunting and wasting occurs in parts of the world where low birthweight is common. She showed that low birthweight increases the risk of stunting by 2–5 times. She then highlighted that IUGR rather than prematurity contributes to subsequent stunting. She discussed factors which determine birthweight and IUGR. Intervention is possible for pre-gestational factors, e.g. maternal age, parity, inter-pregnancy interval, maternal size at the time of pregnancy and maternal education, and a number of gestational factors, such as weight gain, diet, physical activity, stress, toxins including tobacco. Clearly more research is needed and we had a lot of discussion on this. During the discussion I think we all agreed that rather than weight we need more refined measurements of size and body composition so that we can dissect these problems further. Animal models could be useful, and we discussed some of these models.

*Marc-André Prost* told us about postnatal origins and he showed us that, despite a lot of interest in obesity, nutritional deficiencies are still among the top 15 causes of mortality in the world. Nutritional problems lead to impaired physical growth, cognitive development, reduced economic productivity, and increased morbidity and mortality. He also discussed the UNICEF scheme of undernutrition. He showed a graph, which I found very interesting, that length faltering starts much earlier than weight faltering. He stressed 3 factors which affect postnatal nutrition and postnatal growth, i.e. inadequate nutrition, infections, and problems related to care. He pointed out that mothers’ nutrition is important for the quality of the breast milk and that problems could arise by relatively early complementary feeding at the cost of breastfeeding. Iron and zinc are important for growth between 6 and 23 months of age. He finally stressed the issue of societal care and its components including the GDP of the country, safe water supply, sanitation and healthcare facilities.

Finally *Anne-Lydia Sawaya* made a brilliant presentation. She said that stunting in the slums of Brazil reflects both malnutrition and poverty which are inseparable, therefore any approach and intervention must tackle both. In her experience 70% of stunted children had low birthweight. She shared with us her experience with these children and stressed the team approach which makes a lot of difference to the results. The comprehensive approach includes dietary, educational, social support, and treatment of associated conditions. She also talked of her research on risks of stunting, which is associated with adiposity and metabolic risk factors. In her studies successful height recovery reverses the majority of these changes except blood pressure. Further intervention studies are needed in this population.

*Chittaranjan S. Yajnik*
We had a session on the mechanisms of metabolic damage or what we should be calling the mechanisms of injury. We started with an outstanding summary of genomic methylation and epigenetics from a geneticist perspective. It was important to learn that there is only a small group of genes that have been identified so far, so-called metastable epialleles which are sensitive to environmental influences, and they undergo molecular changes such as methylation, acetylation, and that these changes remain permanent and for a lifetime. There was an important lesson to be learned from that. The second lesson was that the lifestyle of one generation can significantly influence the health of the next generation. The best example is that the intrauterine environment can influence growth of the embryo at multiple developmental stages.

Then Emma Whitelaw left us with the challenge: what the true transgenerational genetic inheritance of these traits is, is the embryo affected by the maternal environment or nutrient environment or whatever the other components of the environment are. So far there is not a very good evidence to confirm the transgenerational inheritance of these traits in humans, and it will require a definitive confirmation with improved modern and newer technologies. I am not sure that we will find the answer because as we learned that the blastocyst goes through massive demethylation and all the methyls are lost, and the fertilized embryo becomes a pleuripotent stem cell from where all the tissue’s specific genes are expressed, and for example the liver cells become the liver and the brain cells become the brain. Then the question arises: what are these inheritable traits that are affecting the genome, and why they are surviving through that demethylation stage? This question has not been answered and is a challenge for the future.

In my own talk I tried to convey that methionine along with folate are the key methyl donors for a large number of methyltransferase reactions, there are a lot of methylation processes occurring on throughout the organism/and that every cell expresses the methionine cycle. Because methionine metabolism requires several vitamins, B₁₂, folate, pyridoxine, etc., and cofactors, it is regulated by a number of hormones, nutrient and environment changes can easily influence methionine metabolism and therefore the methylation status of the developing organism, and possibly cause permanent effects and programming. The last part is a speculation which needs to be confirmed. There is experimental evidence showing that alteration in folate metabolism does cause some changes in the methylation status of the genome and this can be reversed by appropriate nutrient supplementation and interventions.

Then we heard from Eric Ravussin, and the highlight of his talk was the issue of calorie restriction. As we know from a lot of animal studies, calorie restriction has a favorable effect on a number of physiological, hormonal and biochemical parameters and biomarkers of longevity. The interest in the biomarkers of longevity has to do with the changes in mitochondrial biogenesis particularly in the skeletal muscle, the change in the core temperature and
in overall energy metabolism. He discussed at length that, in the presence of increased mitochondrial biogenesis, the changes in energy metabolism were going somewhat in the opposite direction, which is a very interesting and challenging issue to address in the future.

**Vidya Subramanian** next convinced us that obesity induces a complex inflammatory state by both inter- as well as intracellular signaling pathways. There is infiltration of macrophages in the adipose tissue associated with systemic metabolic responses such as the development of insulin resistance in the skeletal muscle, in the liver, through various cytokines and other molecular mechanisms. There is a whole corollary to this phenomena and she showed us evidence to support these concepts.

Finally **Arthur McCullough** introduced us to the consequences of atopic fat in the liver and non-alcoholic fatty liver disease, a rapidly emerging disease worldwide. We recognize it in Western societies with a rapidly increasing obesity, insulin resistance and inflammation. Ultimately it leads to hepatocellular degeneration, cirrhosis and other consequences. He showed us a number of intervention strategies, described the molecular mechanisms of fibrosis. Thus far the success of many of these interventions has been low. This particular syndrome is not necessarily confined to Western societies, it is rapidly increasing in emerging societies too.

**Satish C. Kalhan**

It is the end of a long day and a very fruitful meeting, so I will try to be rapid. We started our meeting by setting the scene for the later discussions. **Barry Popkin** gave us a lot of information that actually we are very well aware of, and we are well aware of it mostly due to Barry's work and his writing about this and the infiltration into the mass media. Congratulations. He addressed the global juggernaut in terms of food policies, changes in the dietary supply, changes in transportation and all the issues that are associated with this enormous global transformation. This is the first time that any species has so radically changed its own environment in such a way as to profoundly change its pattern of lifestyle and ultimately its physiology. We want to use that to perhaps amend some of the changes that we can predict are going to occur in the emerging nations. We got a picture of that for China from **Shi-an Yin**, for India from **Srinath Reddy** and for Africa. What we saw was that although these regions are at very different stages of change, in fact if the underlying themes are examined there is a very strong unified story as to where we come from and where we are going. I guess the overall message is that because some continents, and I am thinking particularly of the US and then Europe, have gone there first, surely those of us who are later behind the malnutrition-demographic transition should be able to learn something from the mistakes that have gone before. Whether we are able to do that or not remains to be seen.
Concluding Remarks

In summarizing Session 4, there is again an underlying theme to all of the talks. I think it is possible to take away from any one of these talks something that we in the audience can do about the problem because that is ultimately what we are here for: to try to design interventions, be they in our pediatric clinic, be they in our special care baby unit, or wherever we work whether that is perhaps as a director of an institute of medical research or someone working in the private sector. We want to do something about this problem.

Ranjan Yajnik in his usual manner displayed his innovative thinking in the way that his research here in India has really lead the field. Obviously we have to give David Barker a great deal of credit for this, but I think Ranjan Yajnik is the one who is pushing the boundaries now and I think it is an immense credit that it is happening here in India, and congratulations to you and all your colleagues. What he told us was that diabetes is going to show a 300% predicted increase and we will have 18 million diabetics in India by 2025. He told us very clearly that the preventative efforts are starting too late and they are far too costly; we already cannot afford them and if you project those numbers forward, then we definitely cannot afford to be treating these people who have already got all these obesity-related comorbidities. He also made the important point that it only postpones the problem anyway, and in fact a very interesting cost-effectiveness analysis was published a couple of months ago [1] showing that actually the aggregated costs of keeping people alive and treating their obesity and diabetes are in the end going to cost us more. The sad fact is that people who die are very cheap. Keeping people alive is going to cost a lot more if those people have the associated obesity and metabolic defects. It is not an argument that he actually used but I think it strengthens very strongly the argument that Ranjan Yajnik was making, that we have got to stop trying to look at these things in the post-reproduction phase because that brings no benefit to the offspring and therefore is really not investing in the future. We are just trying to put out fires as they exist at the moment. And so there is a very strong imperative to look at the life-course approach. That was the real essence of Ranjan Yajnik's message. The situation is still confusing, a lot of it is an unfinished agenda, we don't understand yet how best to tackle this, but work is in progress. Disharmonious growth was obviously a very important part of the problem, and we find ourselves in a sort of intellectual trap: if we can’t affect growth at any stage of the lifecycle without having problems downstream, then how can we do anything, and that is something that Ranjan Yajnik has written and talked about. The core of his interest at the moment relates to B₁₂ and folate and the intriguing imbalances between those and the fact that we really need to be very careful how we intervene, and there will be issues of course for discussions as to how extrapolatable that is.

Staffan Polberger gave us a micro example of interventions and what we could do. He described the necessity of dealing with very low birthweight babies and how in his particular special care baby unit they are trying to
individualize that. Very impressive work within that setting, there were controversy and arguments later as to whether that is affordable even in a Swedish special care baby setting. But clearly it points the way forward and ultimately this kind of individualized approach to nutrition is going to be something that will be affordable in many populations. We can add to that the possibility that we will know every individual’s genetic profile which will help form that argument also.

_Dewan Alam_ gave us a wide ranging review of the factors that affect low birthweight, and the fact that some of these are modifiable, some of them are not. Most of his talk was really about supplementation. He warned us that there are many reasons why there may be limited effectiveness of supplementation, and then he gave us a summary of the effects of those supplements as we know them so far. He talked about balanced protein energy supplementation, really very modest effects. I totally accept the points that were made later about the fact that our Gambian trial really has major weighting in the Cochrane analysis and that if you take that out then there is a very minor effect altogether, and the cost-effectiveness of that is very dubious. Single micronutrient interventions showed surprisingly little evidence of positive effects. Many multiple micronutrient trials have been published recently. We are starting to get a much more informed evidence based on this, some of them showing benefits, some of them showing benefits over and above iron and folate, and some of them not. I guess if you came down and said what is interesting about the issue you would say actually it is difficult to shift birthweight by more than 50 g, and that is a very small effect on birthweight. So then we talk about increasing the left hand side of the birthweight distribution, and a lot of these programs are quite effective at reducing low birthweight, so that is good news.

Finally _Prakash Shetty_ gave us a really comprehensive analysis of community-based intervention trials. There is evidence to suggest that interventions to improve maternal nutrition and health are the most successful, which comes back to Ranjan Yajnik’s point about lifecycle approaches. Again if there is a theme coming out of this meeting, it is the huge importance of early intervention and lifecycle approaches. The nutrition transition definitely places new challenges and the need for a modification of programs. We have discussed the fact that we need to be looking at both ends of the spectrum of undernutrition and overnutrition. The new interventions need to be integrated and joined up. They must start very early in life and must concentrate on both ends of the burden. It is very important that evaluation is conducted. A lot of programs must be scaled up if they are available, and sustainability requires political will, resources in terms of both money and people, and community involvement. When invited to give us other additional slides, he made some very pertinent comments about not just the community-based interventions but what we should be aiming for at the national level, and gave us examples of where there has been success.
There are some final cross-cutting conclusions. It is critical to tackle the issues very early in the lifecycle. I think that has come out loud and clear from our meeting here. The evidence base on how to intervene is growing but there remain huge research questions. I know scientists are always saying we need more research money and there is more research to be done, and I genuinely think this is the case. In whom should we intervene, when, at what stages in the lifecycle should we intervene, and how do those interact with each other? How do we balance the short- and long-term benefits and risks? It seems that if we benefit one short-term endpoint, we may be harming a longer term endpoint, so we have to learn a lot about that. How do we disentangle the very complex matrix of possibly conflicting effects of interventions? The material we heard from Satish Kalhan in terms of the complexities of the methionine cycle and a rather overlapping complexity from Ranjan Yajnik in terms of the folate-B12 angle, just give us a little glimpse at some of the enormous complexities of this. And finally, in the meantime how do we guide health professionals and governments; what as pediatricians can we do, and what do we tell our colleagues as a result of this meeting?

Andrew M. Prentice

Discussion

Dr. Prentice: I had a specific request from the audience for a final discussion: can we please talk about what messages we take back to our pediatric clinics and our colleagues? I think it would be especially useful if we could just spend a few minutes discussing that.

Anonymous: To me the topics that have been discussed during these 3 days have been very diverse. From the very depth of the presentations from the biomedical level to the community level, it is difficult to think who will take what kind of message home. Probably it depends on individual interests. As a pediatrician the message that I have taken from these presentations is that we should look into the totality of the matters, as far as the children are concerned, undernutrition is concerned, and obesity is concerned. Unless and until we take it as a total message, as a package and not in piecemeal fashion, and until we have sifted through the opportunities from the top to the bottom, it will be difficult to solve the problem.

Anonymous: The message that I as a pediatrician will take back would be first in all certainly prevent obesity in the child who was born low birthweight or SGA. We don't know what is catch-up growth is, but we certainly must not allow them to become obese at any time during their lifecycle. The second message would be that in all these babies, regardless the diets we give them or what growth monitoring we do, they must be monitored for the metabolic syndrome early in their lives because that will really show us what is harmful or beneficial to the baby.

Anonymous: From my understanding of all that we have discussed today, I think we are actually looking at supervisory nutrition for everyone, from childhood to adulthood, and even in the case of the obese child. During supervisory nutrition, when the child is catching up it gets to the point where you know that at this age there should be some control of the child’s diet. With this supervisory nutrition you do not stop certain types of intervention and begin another type, and that is what I see in the
issue of catch-up growth in the young child. Then for the general population at large, I think we need to begin to look at the situation of population intervention, whereby the government is responsible for making some policies as we heard yesterday; policies to ensure that globally nutrition is apt in our countries, support for the resources available in each nation as far as agricultural products are concerned, and in the light of research, I think preventive measures are something that a bigger authority ought to be looking at. I find it very sad that, within the same household, some people are undernourished and some people are overnourished. We have to ensure supervisory nutrition for all with education for the household, knowing what is needed for the household. That is one of the message I would like to take home as a community nutritionist. Individuals in the household should know what is right to eat; adequate nutrition is the key in every household. At the government level, the authorities have control over the resources of the country, and they are responsible for supporting food agriculture, the nutrition of the people, and also to make information available to the people. With regard to catch-up growth, the child must be observed so that it will not suffer all the disease outcomes in adulthood.

**Dr. Singhal:** Can I just go back to an important point for pediatricians, the monitoring of follow-up of SGA babies in terms of the metabolic syndrome. There was a consensus statement published last year on the management of the SGA baby which states that you should not be monitoring for the metabolic syndrome [2] because programming is based on populations an not on individuals. The positive predictive value of all programming factors is small for the individual. There is a difference between populations and individuals. Pediatricians are concerned with the individual for whom there is very little evidence of benefits of surveillance. Now regarding the question whether we promote growth fin SGA babies, I come back to the answer I gave early. It depends on the population you are interested in. The same consensus statement argues that in the West there is no indication for the promotion of catch-up growth in these babies [2].

**Anonymous:** I was actually very amazed by Finland where food habits changed and there was a major decrease in ischemic heart disease and diabetes by behavioral change. There the women definitely took the step. But what about the Third World; how do we communicate these things to our governments? It is difficult. I don't see epidemiologists trying to communicate this to the government. What they did in Finland is an excellent thing, simply taking skim milk instead of a lot of soft drinks. About the food habits, this is also a matter of mass media. Mass media can also help us to spread this message especially in underdeveloped countries where education is another problem.

**Dr. Prentice:** In relation to your question, I think this comes back to what Dr. Shetty was saying that money speaks and governments listen when it is going to hurt them, when it is going to hurt their pockets or going to hurt them being reelected. One of the problems is that it is mostly going to hurt the pockets of governments five governments ahead, so it is difficult to concentrate the mind of governments of today. In the UK our Prime Minister actually called in the head of National Westminster Bank to do a future analysis on this, and he made reports which really did paint a very gloomy picture of the future if we didn't do anything about it, and now I think the UK is really moving and trying to do things and certainly it is suddenly taking the issue seriously. So I think this comes back to the point Dr. Shetty was saying about the necessity of cost analysis.

**Dr. Chittal:** This has been a wonderful experience, like standing in front of the Mona Lisa painting or the Taj Mahal. I am admiring, I am appreciative, but I am also baffled and I don't know what I am admiring and I don't know what I am taking back home. I can't change government, I can't even change the government's opinion, but I
Concluding Remarks

need to take something home for my patients. I look after small IUGR preterm babies, I encourage them to put on weight, but yet I need to warn them somewhere. Dr. Singhal says there is no point monitoring individual babies for the risk of type 2 diabetes; I need some marker, I need to monitor that. Is HOMA the marker or is insulin resistance the marker? I need one biochemical marker with which I can predict that this baby is going the wrong way. If I take that home, then yes, I have learned something.

Dr. Prentice: Let’s not lose sight of the certainties that we do have and one of those certainties was articulated in the very first point in this discussion which is, avoid obesity. Now how you measure that as a pediatrician is another issue, but I think let’s hang on to at least some of the things that we do know and then we know other things which Dr. Sawaya has been articulating about balanced diet and common sense, not losing sight of common sense. It may sound boring when related to the complexities of the methionine cycle, but we must not lose sight of those things as well.

Dr. Pandit: The last two and a half days have been like a movie which played in the Western world, in the developed world, at the end of the 19th century and early 20th century, which exposed itself as diabetes and cardiovascular disease; in the mid 1950s, it kind of slowed down in the West. Now this same movie is being shown in the East, in the developing countries. Only the characters have changed, there is a new character called affluence, otherwise it is the same movie. The West had an infant mortality of 200 per 1,000 at the end of 19th century which was also here some years ago and that resulted in diabetes hybridization in the 1950s in the West, and today we are facing the same. So it is a movie replayed with a new character, affluence.

Dr. Prentice: It is a movie, and when they do screen tests in Hollywood they ask the audience to chose between different endings. What we have got to do is to try and chose a happy ending.

Dr. Pandit: There is no micro-message that comes from this. I think we should get sensitized to the fact that government programs are basically research to be conducted not on an individual child basis but looking at the associations, not a cause and effect relationship. What we have discussed for the last two and half days are association paradigms, they are not cause and effect. Pediatricians like us came here to look at cause and effect, and it is not possible in two and half days.

Dr. Kikafunda: My message is to Africa. As was reported on the first day, there are limited data on the problem of obesity and its consequences in most African countries, particularly Sub-Saharan Africa. When there are no data, you believe there is no problem. But the problem is huge. Every 5 years demographic and health surveys are carried out. On nutrition, they only report on stunting, underweight, wasting and micronutrient deficiencies. The columns for overweight and obesity are left blank! So let us get data, and then we can face the problem.

Dr. Prentice: Because I was presenting the last session, it is only by accident that I am standing up here. Dr. Kalhan and Dr. Yajnik, do you want to make any closing comments before we the conference is closed.

Dr. Kalhan: My only comment is to look at the big picture. Biology has to move and we have to investigate all aspects of it. All these things that we have heard over the last two days, from basic sciences to genetics, to epidemiology, these are not mutually exclusive, they complement each other, we learn from these and create new paradigms and we tackle the problems.

Dr. Yajnik: I have to say that I enjoyed the last 3 days. Thanks to Nestlé for organizing this and thanks to everyone for your very active participation. I am taking home a number of new ideas to test in our studies. Thank you everybody.
Concluding Remarks

References
