Concluding Remarks

So we are now coming to an end; the summary and concluding session. As the senior partner in this team of chairpersons, I would like to start by expressing my sincere thanks to the Nestlé Nutrition Institute, Ferdinand Haschke and Petra Klassen for taking the initiative for this conference. It’s more than a year since we met in Helsinki and started planning, and it has been a great pleasure all the way. This also refers to the excellent collaboration between the three chairpersons and also the enthusiastic acceptance which we received from all the speakers we invited. I would like to thank the speakers; it takes some effort to prepare these presentations and also to write the manuscripts for the symposium book, and that is an additional asset to this workshop – there will be solid documentation. I would also like to thank the moderators, and of course the local organizers. That team has really been something; they put everything together here locally and also the social program which was indeed tremendous, also for the accompanying guests. So thank you all for the organization. Now I finally come to the moderators who in a polite and structured way brought us through these 3 days. Of course, many of us like to speak and speak, it’s not so easy to stop some of us, but this was done very well so we had very lively discussions. Therefore, I would also thank the audience for contributing to this excellent workshop. I have been to many of this kind of meetings but I must say that the intensity and the interest in the discussion sessions have been quite remarkable. That is the way we learn: to listen to and confront different opinions. We need not agree on everything; if we did then we wouldn’t need to go to these workshops.

I am happy to say that the two keynote speakers really set the stage in a very nice way. Although Dennis Kasper could not come, the electronic transmission worked beautifully and he responded to our questions in a very clear manner; I was surprised, it was just like sitting with him. For me his topic really highlighted the title of this workshop. We all know now that microbial–host interaction is very complicated, but his work has dissected these things. We saw that a single carbohydrate, a single polysaccharide, can actually influence
the host’s immune system in a tremendous way, even controlling an inflammatory disease in an experimental animal, which shows that this is something we really should exploit in human medicine in the future. Tolerance induction as we know it now is very much dependent on the regulatory T cells. But this approach has not come into application in human therapy studies as much as we had hoped, although there are lots of experimental autoimmune and inflammatory disease models where the disease can actually be prevented or treated by oral tolerance induction with the right sort of antigens. In my opinion prevention is a much better option than treatment when trying to induce tolerance.

The next keynote speaker is sitting right here, Bengt Björkstén, my old friend. The way you put it, shows that the original hygiene hypothesis is no longer valid to explain the increase in allergy. We know too much about this now to really believe that all this can be ascribed to a lack of infection-driven balance between Th1 and Th2 cells. I also liked your first slide when you pointed out that the study of the indigenous Canadians done by Gerard in 1976 was the first glimpse at data showing that it’s not just genetics but actually an environmental drive of the immune system that is needed to avoid allergy. Moreover, parasites are now quite hot in this field, or components of parasites are important to induce regulatory T cells. This was probably the explanation why the indigenous population of Canada has much less allergy than Westernized Canadians. But why was this study forgotten? I think that’s a very important lesson to take home. In my opinion it was forgotten because these people, this indigenous population which had no asthma and allergy problems, or at least very little, had sky-high IgE levels in their blood. That didn’t fit with the current thinking that IgE was the only drive of allergy. So we don’t like to accept things which we don’t understand and which don’t fit with our current ideas. The beauty of this workshop was that here we dared to confront each other and challenge current ideas, and no one did that with Dr. Gerard. It took 13 years before we got the original hygiene hypothesis defined in 1989; and then it went on the bandwagon, everybody was jumping on this idea that an infectious drive is needed to keep the balance correct with the Th1 dominants, controlling the Th2 excess of IgE production leading to allergy. But then, after a while we also got regulatory T cells in the picture and perhaps you, Erika Isolauri, were the first to use the phrase ‘extended hygiene hypothesis’. It’s not just Th1 and Th2, it’s also regulatory T cells; and now we also know these funny cells which we just have learned about, Th17 cells, and ask what they mean in allergy. I am sure they play a role in asthma, but we don’t know enough about how they can be controlled by regulatory T cells and even turn into regulatory T cells with IL-10 production themselves.

So the concepts are changing, and Dr. Björkstén suggested that we should now call the hygiene hypothesis, the microbial deprivation hypothesis. I wish you all the best Dr. Björkstén, but it’s not easy to change established
terminology, and in a way I don’t think the hygiene hypothesis is such a bad term. We really think that the environment influences our mucosal microbiota in the way you talked about. And as Dr. Kasper alluded to, we live as a sort of bacterial culture throughout life; there are perhaps 10–100 times as many bacterial cells in our gut as there are cells in the body, and the microbiome is defined as having 100 or perhaps 1,000 times as many genes as we have in the human genome. We also know now that the expression of the genes could be changed by methylation, and post-translational modification can take place for both endogenous and exogenous antigens coming into the body such as gluten. The gliadin peptides of gluten can be modified by deamidation giving enhanced induction of a T-cell response in celiac disease, and also our own proteins can be post-translationally modified. So it’s not just the genes as such, but the environment can influence the gene expression, so mucosal homeostasis is clearly determined both by the microbiota and by genes.

It has turned out that only half, or less than half, of all allergic patients have a family history, and Andrea von Berg said that family history is more reliable when the lady in the family fills in the form. The mothers are always cleverer in memorizing things about their children than the fathers, and we know that maternal history has a greater impact on later allergy presentation by the baby than paternal history. Another variable that was not mentioned was pointed out to me by my colleagues in forensic medicine back in Oslo; in their experience the father is not the father in almost 20% of the cases. That is remarkable, and I don’t think it’s unique for Norway to mess up the family history in this way, for I am sure there are also susceptibility genes in the paternal part of the allergic population. We still don’t know these genes and it will take a long time to define such polygenic diseases as allergy.

Coming to the gut barrier, it is clearly influenced by the microbiota; and as I alluded in my talk on the first day, I think it is a very important determinant of what is going on with regard to both productive induction of immunity, such as secretory IgA, and induction of regulatory T cells. We also heard about the importance of when we introduce new antigens, both before or after birth, and how these can influence tolerance induction. We have to distinguish between various mechanisms of tolerance induction, not just mucosally induced tolerance, and I think perhaps that we should avoid the term oral tolerance. However, it’s not too easy to get rid of such a convenient and long-lived term but it is really mucosally induced tolerance we are talking about after birth, and the epithelial barrier apparently needs to be somewhat open. Perhaps it makes sense that the epithelial barrier of the gut is to some extent permeable for a certain time after birth, because we need to take in more foreign antigens to drive the tolerance induction. So there are many things we cannot really define as yet and there are probably various mucosal routes we can use. We heard about the nasal route for tolerance induction and perhaps that’s more efficient to control allergy in the upper airways than the oral or enteric
route. I am not sure we know everything about this as yet. If we believe in the regulatory T cells, they seem to be more promiscuous in their homing properties than effector T cells. We know that the immune system of the mucous membranes is very compartmentalized with regard to homing molecules of effector B cells induced, for example, in Waldeyer’s lymphoid ring. The effector B cells have their homing molecules, and if you induce them in the tonsils or nasopharynx-associated lymphoid tissue, they have their special repertoire to find their way back to the airways. But as said, the regulatory T cells seem to be more promiscuous in their homing. So I think we have to work more on this. The nasal route is attractive and we know there are many studies on the sublingual route for tolerance induction. I think that important things are going on in the local lymph nodes which in a way are backup systems for the inductive mucosal lymphoid tissue. Thus, the mesenteric lymph nodes are a backup and amplification system for gut-associated lymphoid tissue, and these nodes seem to be essential for oral tolerance induction. When we come to the elimination and exposure of antigens, there is continuing discussion, so I am not going to give any more details on that. As was pointed out several times, we definitely need exposure for tolerance induction is an active adaptive immune response. It’s not a passive mechanism although it gives suppression. You need an adaptive immune system together with the innate immune system for antigen presentation, and a particular profile of antigen-presenting cells. Dendritic cells are very important in this area, and macrophages are also known to be able to induce suppressive responses; perhaps even better in the human gut than the dendritic cells. There is development from monocytes and macrophages to dendritic cells in the human gut, which makes it difficult to decide which cell type is more important.

If we talk about inflammatory processes in the gut which cannot be stopped by normal regulatory mechanisms – I refer to them as a point of no return. We have examples of that in inflammatory bowel diseases where the epithelial membrane is so damaged that you cannot expect regulatory T cells or whatever mechanism to suppress the disease, so medicines and even surgery are needed. There is, in fact, no cure for inflammatory bowel disease to date, so we try not to get to this point of no return, and that’s what we have been talking about: can we exploit the host–microbial interaction to stop this vicious circle?

Per Brandtzæg

It has been really nice during this meeting to have the opportunity to critically evaluate the management and prevention strategies in allergy to create new ideas. This is how the science in nutrition has developed: we see that the role of diet in health is changing as scientific knowledge is accumulating. The basis lies of course in providing sufficient nutrition for growth and development in children; as a next level we have the balanced diet which frequently
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is not achieved in allergic children or children at risk of allergy because of this old strategy to eliminate important energy nutrients from their diet, which has created problems. Then we have the dietary management of specific disease with specific food products, like hydrolyzed infant formulas for cow’s milk allergy and probably now a very specific tailored product for prevention. Finally, current research activities are directed towards specific compounds in diet which could have a very specific scientifically proven effect to reduce the risk of disease. We have discussed how the proteins can be degraded to a certain extent to induce tolerance and lipids, with immunomodulatory effects, and also vitamins were mentioned as well as probiotics and prebiotics. There are protective nutrients we know very little about. There was a discussion on diet and autoimmunity in which vitamin A was mentioned, glutamine is important for gut health and also fatty acids. Therefore I think that the future in this kind of research is multidisciplinary, we need to collaborate. Therefore I am happy to see dieticians and nutritionists at this meeting. I am privileged to work in the NAMI group where Seppo Salminen represents microbiology and Kirsi Laitinen nutrition. With this kind of approach I think we can plan more complete studies in the future.

Erika Isolauri

I only have a few comments about the allergy autoimmunity context versus tolerance, and I will just pick out a few of the recurring themes that I think are apparent to us all from our discussions. We have talked about ‘the window of opportunity’; I am not sure how accurate that term is because there are probably many windows, where different exposures will have different effects. In utero there are many different factors which might influence immune programming; in the early postnatal period obviously colonization is a major factor and the timing of that is probably very important, and then we have other incremental exposures such as the introduction of diet and so forth.

I think in utero programming is a very important theme that has continued throughout this meeting. We talked about epigenetics which was a major theme at the NNW meeting in Helsinki in 2008 and it certainly continues through at this meeting as well. Some very interesting new data are coming out in the field of allergy and immune programming and epigenetics because our field has really lagged somewhat behind many of the other areas such as nutrition and growth, cardiovascular disease, and many of the others.

The other clear and recurring theme is the multifactorial nature of these modern diseases and the fact that there are very complex interactions. In that context, interactions that we might have traditionally thought were negative, we now know are perhaps not. Twenty years ago we thought about microbial exposure in quite a different light; we have now come around to understanding that there is a harmonious balance between the microbial environment
and the host. Now we are also beginning to understand that allergens are not bad either, and we have been hearing about how allergen exposure at a critical time may be important for allergy prevention and now also in the treatment of sensitized individuals as well. We also know that avoidance is actually very difficult to achieve; we can't avoid everything, clearly anything in the environment is a potential antigen or allergen, and it's not possible or probably even desirable to avoid allergens.

Another comment that has been made is that this is a lifelong process, that just as we have programming, we also have reprogramming and deprogramming. This may in the first instance help us to explain how we get emergence of disease later in life. But on the flip side the good news is that this does give us a chance to reprogram and induce tolerance. There was another point that was brought up in one of the discussions but perhaps lost slightly, and that was that the really new mystery, if you like, of the ‘second wave’ of the allergy epidemic, and I think it was Mimi Tang who actually raised this, is particularly noted in English-speaking countries. I don’t know why that is but at the moment in Australia, New Zealand, the UK and the USA we are seeing an epidemic of food allergy, and it’s quite different from the food allergy that we have been hearing described in continental Europe and Scandinavia. In English speaking countries we seem to be seeing an epidemic of anaphylaxis at very high rates, we are seeing a 5- to 10-fold rise in recent years, and this is obviously a changing phenotype of allergy – very interesting, very mysterious. It is obviously these children are declaring themselves much earlier in life and it is interesting that this lag in food allergy has occurred 25 years after the ‘first wave’ of the allergy epidemic which was respiratory allergy. I may be wrong but I think the same countries may have led the way there as well, and we have no idea why this is occurring. These patients we see now are of course the children of the ‘first wave’; so if this has anything to do with it, we don’t know. Is this something to do with maternal programming? Again, we don’t know. So this is just a point of great interest and great mystery that I really wanted to emphasize as an important factor to ponder because the environmental changes may be different now than 20 years ago. So these are the main points that I wanted to make. Are there any other points or that you in the audience feel were key take-home messages which we can discuss further?

Susan L. Prescott

Discussion

Dr. Isolauri: I could raise a question that was discussed earlier, combining different clinical studies with different probiotic strains. We could take the GINI study as a model, a large multicentric study with defined intervention is a much better approach than to do a systematic review of existing studies.
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with very little methodological similarities in terms of strains, population and food matrix. Dr. Szajewska, you are an expert in systematic reviews, shouldn’t we be doing these clinical studies?

Dr. Szajewska: I can just comment that not all probiotics are equal, not all meta-analyses are equal, as their quality really varies. It is very important to look at the methodological issues of each of these meta-analyses and then you reduce their number. But in general, of course I do agree, it would be wonderful to do one big randomized multicenter study with different probiotic strains. However, it’s very often an organizational or financial problem that prohibits such study.

Dr. Brandtzaeg: In my opinion we also need to think about geographic variations, both in the commensal flora in that region and also with regard to the IgA response in the breast milk. I am a bit surprised that no one really has looked at the probiotics, how they respond to breast milk in vitro by IgA coating for instance. How coated would the bacteria be by secretory IgA? Could that be tested easily with all the strains?

Dr. Isolauri: The early experimental studies document stimulation of IgA with the probiotic, and then in breastfed children an IgA response could be promoted with two specific probiotics.

Dr. Brandtzaeg: I would like to see some studies in Australia and, for example, some studies in Finland where these bacteria are just mixed with breast milk from that region, obtained from a large range of mothers, and flow cytometry is done to see the extent to which the IgA will bind.

Dr. Isolauri: I called that the multicentric approach earlier.

Dr. Brandtzaeg: But in that way the extent of the natural response to these bacteria can be seen in that area because IgA is largely cross-reactive in the secretions. It will be expected that these probiotic bacteria are actually coated with IgA to variable degrees which will influence their adhesion and uptake properties in the gut.

Dr. Isolauri: IgA and the breast milk composition are not only affected by geography but also by the diet.

Dr. Prescott: Going back to our original topic of host–microbial interaction and I have extended this to obviously include the entire environment, and as the host we don’t contribute a whole lot, apart from perhaps our genes if we break it down into real basics, and it is the environment that then influences and helps determine the expression of our genes to determine our ultimate phenotype. Many modern diseases, we are not talking about single or mutational diseases, we are talking about modern diseases which have emerged as a result of environmental changes, so this model is clearly very important. The good news of course is that the fact that the environment plays such a great role in the determination of the phenotype and disease predisposition means of course that we have the opportunity to change this interaction to prevent disease, to treat disease. So that was my take on the whole workshop, if I am allowed to put it in a simple way.
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That moves us to some final words of thanks. Dr. Brandtzaeg has already done so, but I would just like to echo the thanks to the Nestlé Nutrition Institute for making this meeting so stimulating, enjoyable and really possible. We have already thanked the moderators and the speakers but I would like again to thank the audience because you and your stimulating questions, I think you will all agree, really made the discussions most rewarding and most stimulating thing that we got out of this meeting. I think the structure of having half an hour presentation and half an hour discussion is absolutely wonderful and this should be a model for other meetings. So thanks to everybody, particularly the local organizing committee for making a such successful, stimulating and enjoyable workshop.

Susan Prescott