Neonatal Microbial Flora and Disease Outcome

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**Abstract**

The now outdated perception of microorganisms of the gastrointestinal tract as pathogens or at best commensals continues to undergo remodeling. It is now clear that the microbiome of the gut participates in many activities including: digestion, ecologic protection from pathogens, and an increasingly appreciated immunoregulatory role in vertebrates. Studies of the complex interactions of microbes and hosts point to a convergence of two well-supported (though imperfect) hypotheses: the ‘hygiene hypothesis’ and the ‘fetal programming hypothesis’ proposed by Strachan and Barker, respectively. Our current understanding is one in which factors that exist before conception, during gestation, or occur perinatally in the infant milieu, in addition to exposures to nutrients and microbes, have the potential for long-term effects in the development of healthy offsprings and adults. Epidemiology, basic science and clinical research in such previously diverse areas of study such as microbiology, allergy, gastroenterology, endocrinology, immunology, rheumatology, infectious disease, perinatology, and nutrition are providing evidence that appropriate development and tendency towards the development of certain diseases are directly affected by intestinal microbe–host interactions. It appears likely that perinatal colonization of the gastrointestinal tract is a particularly pivotal process in which microbe-host programming occurs. Intestinal microbes and hosts have co-evolved that, when in appropriate balance, they produce and propagate a life-long mutualism.

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**Introduction**

The ‘hygiene hypothesis’, originally proposed by Strachan, suggests that the relative sterilization of the modern world through health practices and improved sanitation has led to a decreased exposure to microbial antigens,
and that this in turn has had an adverse effect on the developing immune system with an increased tendency towards developing allergic conditions. It is increasingly clear that intestinal microbial flora plays an integral role in the relationship of microbial exposures, immunologic programming and when inappropriate, may lead to the development of allergy. Though in itself it is imperfect, there is a substantial support for the hygiene hypothesis and its fundamental prediction that host–microbe interactions that occur early in development have long-term consequence [for review see 1]. A caveat of the hypothesis is that the immune system can also be skewed towards an autoimmune predominant response by exposure to microbes. In multiple models and clinical conditions, exposure to viral or bacterial products promote the development of autoimmune and immune-mediated diseases such as the relationships of Coxsackie B4 virus to type 1 diabetes and Campylobacter jejuni to Guillain–Barré syndrome.

Barker [2] and colleagues are credited with the ‘developmental origins of adult disease’ hypothesis that predicts that events that occur in utero and conditions at birth have potential for long-term phenotypic effects in adulthood. Their initial epidemiologic observations of in utero and perinatal nutrition with sequelae leading to a predisposition for ischemic heart disease has been expanded to multiple other clinical entities including non-insulin-dependent diabetes, hypertension and stroke in adulthood [2]. It has become increasingly appreciated that the intestinal microbial community plays a major role in development of an appropriately balanced Th1/Th2 immune system. The most crude example being that animals born into germ-free conditions have a Th2 predominant immune response. Studies of the sequential (seemingly programmed) colonization of the gastrointestinal tract after birth, the relative stability of a host microbiome, and the influence of prebiotics and probiotics support the adaptation of the Barker hypothesis to a host-microbiome colonization corollary, e.g. that specific (though as yet incompletely defined) host–microbe interactions are necessary and interactions during gestation (with the mother’s immune system and microbiome) and particularly with the neonate are essential and have implications into adulthood.

Though the etiologies of many noninfectious clinical entities have been postulated to be associated with microbe–host interactions (see below), one group that continues to become inexplicably prevalent is allergic disease. Allergic disease is the result of an immune system imbalance, therefore it is a useful entity for evaluating the relationship of immunologic programming to the development of disease. The recent increase in allergic disease in the developed world is possibly related to altered microbiologic exposure and immune system programming at a critical window in development (application of both the hygiene and Barker hypotheses). In addition to epidemiologic and basic science research supporting this concept, clinical interventions with probiotics impressively demonstrate that altering the flora of both the mother and newborn modifies the offspring’s predisposition to disease [3].
Our understanding of factors that affect maternal health, gestation, programming of the immune system, perinatal microbial colonization, and microbial ecology, as a nexus of interrelated factors leading to the development of health and disease, increasingly point to the mutalistic relationship of the immune system and microbes within the gastrointestinal tract.

**Gestation**

Many variables including genetic, metabolic, nutritional, toxic and infectious factors affect maternal health and directly or indirectly the health of her offspring. Maternal health before conception can have a significant impact on the health of her offspring [2]. After conception, teratogenic programming can occur in utero either by exposure to a harmful factor (i.e. congenital cytomegalovirus infection) or by lack of exposure to an essential factor (i.e. the role of folate deficiency in the development of spina bifida). There is evidence that maternal immune health and exposure to microbial and dietary antigens play a role in the development of an appropriate immune response in her offspring. Ruiz et al. [4] have observed that maternal atopic dermatitis is a more significant risk factor than paternal atopy. The potential role of maternal consumption of dietary antigens and the risk of food allergy in her offspring has led to the recommendation by some to avoid and others specifically not to avoid certain foodstuffs during pregnancy. It is likely that the exchange of epigenetic programming, antigen and immunomodulatory molecules between a mother and her fetus contribute to appropriate immunologic development [5]. Lending support to this, as well as the likely role of the maternal immune system and microbiome, is the observation by Blumer et al. [6] that when a bacterial product (lipopolysaccharide) is administered to a pregnant mouse it modifies the immune response in her offspring. Together these and additional findings point to the likely role of the maternal microbiome in programming of the immune system during gestation. Figure 1 depicts several of the complex factors that determine the development of immune function and health through different life cycle stages.

**Gastrointestinal Immunology**

The gastrointestinal tract performs diverse functions including digestion, absorption, immunoregulation, and hormone production. The intestine plays a remarkable and essential (though as yet imperfectly understood) role in the development of immunologic tolerance. Multiple diverse cell populations inhabit the gastrointestinal tract and participate in host defense in addition to cells of the immune system. These include acid-producing parietal cells, mucus-producing goblet cells, defensin-producing Paneth cells, among oth-
ers, thereby creating distinct environmental niche conditions and selective pressures, and generating diverse microbial communities in the gastrointestinal tract. From birth the mature human intestinal tract is fully cable of responding appropriately to an array of antigens and pathogens while tolerating the colonization of the intestinal lumen with a plethora of potentially pathogenic, commensal and symbiotic bacteria. The intestine is home to the largest collection of lymphoid tissues in the body. Some are highly organized such as in Peyer's patches and mesenteric lymph nodes while others are diffusely localized dendritic cells and lymphocytes of the intestinal lamina propria and epithelium [7].

The lumen of the gastrointestinal tract needs to be selective in the molecules and signals it transfers. Two highly evolutionarily conserved components of the innate immune system are families of pattern recognition-sensing molecules: Toll-like receptors (TLRs) and Nod-like receptors (NODs). These receptors are able to bind ligands that the host has never encountered and perform an integral role in the interaction of luminal microbes with host

**Fig. 1.** Schema depicting positive and negative developmental factors which have implications for short- or long-term morbidity and/or mortality. Underlined items are known or hypothesized to affect/be affected by host–microbe interactions.
immune system defense, immune cell recruitment, and inflammation [8]. Lending support to the symbiotic nature between certain microbes and hosts is that TLRs participate in the maintenance of intestinal homeostasis through interaction with specific intestinal commensal bacteria [9].

The interaction of microbes and immune cells in the gastrointestinal tract participates in maturation of the adaptive immune system. The homing of T cell populations to the intestine is associated with the developmental colonization with microbes perinatally (fig. 2). Hooper et al. [10] have shown that a specific product of the commensal bacterium *Bacteroides thetaiotaomicron* participates by directly stimulating host defense mechanisms. In addition the greatest exposure to antigens that the immune system encounters is through ingested antigens and bacterial products. Proper maturation of the immune system has been linked to the colonization of the gastrointestinal tract with specific flora [11]. It is becoming increasingly clear that bidirectional communication

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**Fig. 2.** Cartoon outlining the development of mucosal immunity. Each component (1–4) is affected after delivery and initial colonization, and continually thereafter by interactions with microorganisms.
promotes the symbiosis between the host and its intestinal flora. As an example, germ-free animals are known to have an impaired tolerance mechanism. Continuous immunologic vigilance permits and promotes symbiosis and peaceful coexistence with intraluminal microbial communities [12].

Colonization and the Peripartum Period

At birth, animals pass from a sterile environment to one filled with bacteria, fungi and viruses. It has been shown that the method of delivery, vaginal versus cesarean section, has a significant effect on the colonization of humans. It has also been observed that the progression of bacterial species during colonization is altered by the route of nutrition, either breast milk or formula [13]. Indicating that the relationship of gut maturity may need to be coordinated with microbiota, findings suggest that formula-fed infants acquire ‘mature’ colonization sooner than babies fed breast milk [14]. Immunoreactive factors that are transferred from mother to child in breast milk include immunocompetent cells, immunoglobulins, antimicrobial peptides, growth factors, cytokines, lysozyme, lactoferrin and complement. A recent stimulating observation is that a component in breast milk binds to a TLR [15].

The neonatal immune system is initially characterized by a Th2 response but, as the immune system develops and is exposed to microbes and greater antigenic diversity, this becomes more Th2/Th1 balanced. An additional association is that infants behave clinically as moderately immunocompromised until they reach an age associated with more adult gastrointestinal flora (personal observation). Gronlund et al. [16] have observed that the patterns of colonization of the newborn may affect the development of the naïve immune system.

Ultimately, the human gastrointestinal tract is colonized with greater than 500 species of bacteria. The communities of microorganisms differ along the length of the gastrointestinal tract and across the three dimensions of the lumen and mucous layer. It is calculated that the total number of genes possible by the microbial community colonizing a single human intestine exceeds by more than 100-fold that of a human genome, and only with the recent advance in large scale sequencing have investigators been able to generate profiles of many previously unidentifiable non-culturable species [17]. The known activities of the microbial factory in the intestinal lumen includes digestion, production of nutrients, detoxification/toxification, defense from pathogens, gut motility, angiogenesis, and immunomodulation. Turnbaugh et al. [18] have recently reported a transmissible phenotype of increased capacity for energy harvest and total body fat by inoculation with flora from obese mice to thin mice, thereby identifying a novel effect on physiology by the microbiome–host relationship to the area of energy metabolism. Though populated by a dynamic and complex (and currently ill-defined) ecosystem, it
appears that there is a relative stability of an individual's microbiome. This is borne out by multiple lines of evidence including that antibiotic use or probiotic use have significant but not permanent effects on gastrointestinal microbial ecology.

**Immunologic Programming and Allergy**

It has been hypothesized that appropriate stimulation by environmental antigens (microbial and dietary) is a stimulus for the neonate to shift from Th2 to Th1 predominant immunologic responses. It is not clear whether these effects occur in utero and/or perinatally. It is likely that the development of allergic disease (and likely some autoimmune disease) is secondary to inappropriate immunomodulation (or lack thereof) by microbial exposures during critical periods. Within the gastrointestinal tract, co-stimulatory signals and nutrition promote (or inhibit) the origin of an organismal tendency towards the allergic state. The study of allergic disease contributes to our understanding of the relationship of microbiology and immunologic dysregulation [19]. The role of exposure to environmental antigens in the etiology of immune system dysregulation has been supportive positive evidence of the hygiene hypothesis proposed by Strachan. Additional understanding is necessary to account for the fact that there has been a concomitant increase in Th1-associated autoimmune disease with the increase in allergic Th2-predominant allergic disease.

Multiple observations support the thesis of the pivotal role played by the colonization of the gastrointestinal tract and immunologic programming including: (1) intervention with probiotics prenatally and in infancy can have a prolonged effect on the prevention of allergic disease [3, 20]; (2) differences in the bacterial composition of the intestinal flora in infants precedes the manifestation of atopy [21]; (3) bacterial colonization in the neonatal period can promote immunologic tolerance [22]; (4) an association between atopy with polymorphisms in NOD genes; (5) microbial flora is necessary in the neonatal period for the development of tolerance [23], and (6) a ubiquitous bacterium promotes anti-inflammatory responses in the intestine [24].

**Prebiotics and Probiotics**

Probiotics have been well studied and have been demonstrated to have beneficial immunologic effects that influence both systemic and gut-associated immune responses; they likely function by having both direct and indirect (immune system) effects on the microbial community in the intestine [25]. Some of the strongest supportive data thus far for use of probiotics is that they are most effective during the development of the immune system and initial colonization. It is tempting to speculate that these findings support a
theory that these two processes are themselves linked. Clinical entities that have been shown to be ameliorated by the ingestion of probiotics include: childhood infectious gastroenteritis and antibiotic-associated diarrhea, with potential efficacy of probiotic strains in better growth of infants; atopic eczema; inflammatory bowel disease; *Helicobacter pylori* gastritis; neonatal necrotizing enterocolitis; prevention of Candidal colonization in very low birthweight infants, and as a substitute for inadequate initial neonatal colonization through as yet unclear mechanisms [25–27]. The immature intestine is particularly susceptible to the inflammatory entity of NEC which has substantial mortality and morbidity in primarily preterm newborns. The administration of probiotics to preterm infants has been shown to confer a degree of protection from the development of NEC [27]. We have identified an intriguing mechanism by which probiotics downregulate the intestinal innate immune response (unpublished data). In addition, ingestion of probiotics prenatally and in infancy has been shown to have immune effects beyond the mucosa such as skin immune homeostasis in a mouse model [28], as well as affect the transfer of antibiotic resistance genes in mice [29].

Prebiotics are indigestible (to the host) food ingredients that have a beneficial effect by selectively stimulating the growth, activity or both of one or a restricted number of bacteria in the colon [30]. The utilization of prebiotics in addition to probiotics in support of intestinal ecology and prevention of disease is showing positive results [30].

**Conclusions**

The gastrointestinal tract performs a multiplicity of functions and plays a central role in the development of the immune system as well as immunologic tolerance. The dynamics of microbiome–host interactions are just beginning to be elucidated. There appears to exist a ‘founder’ immunologic effect on the microbiota associated with colonization in the perinatal period and that microbes play a role in programming of the immune system even before birth. It is our understanding of the interaction of the host immune system with microbial communities pre- and perinatally that permits us to make the observation of the merging of the Barker and hygiene hypotheses. Many questions are yet to be answered including; why and how is an individual’s microbiome maintained; are specific species or bacterial molecules associated with specific clinical conditions; how is the complex action (or inaction) of immune tolerance carried out, and why is there a simultaneous rise in autoimmune disease which is traditionally though of as Th1 with the increase in Th2 conditions in the developed world?

Therapeutic strategies are beginning to include our most current understanding of microbiome–host interactions such as the ingestion of polymicrobial probiotic cocktails and prebiotic molecules or immunostimulatory
molecules such as DNA or helminthes. Technological means now exist to begin to address the interactions of entire bacterial communities and their role in immune system function spanning from gestation through adulthood. Ultimately we will continue to generate new models and interventions of microbial–host interactions to promote health and prevent disease.

References


Discussion

**Dr. Malka:** What do you personally suggest by the hygiene hypothesis? In the first year of life, do we have to live with 2 dogs, 2 cats, under dirty conditions?

**Dr. Walker:** It is a very good suggestion, I am not sure I could make a clinical recommendation at this point other than to encourage vaginal delivery with hopefully the standard development of colonization and to try to reduce the use of antibiotics during that period of time. I can give you a personal experience. In the last 4 years both my daughter-in-law and my daughter have delivered by cesarean section. I had them put their babies on lactobacillus GG for a period of time, just based on what I know about this. I can’t say that I would recommend this to everyone, but it seems to me in the absence of appropriate colonization, they might have a greater risk of developing some of the diseases we talked about.

**Dr. Wilson:** On your last slide on epigenetic programming, unfortunately I didn’t see which genes and which cells you were talking about and what the nature of the evidence was. Could you elaborate please?

**Dr. Walker:** That whole section is to provoke discussion, it’s very provocative. I was just quoting the authors’ suggestion that allergens in a fetal environment could through epigenetic mechanisms affect methylation of DNA, deacetylation of histone, etc., a persistence in genes that are normally downregulated as the infants are moving towards development. That is total speculation; just a hypothesis.

**Dr. Ogra:** I am not sure whether bringing together the hygiene hypothesis with fetal programming is a good marriage because there are issues which might not blend in the long run. One of them relates to the corum sensing in the gut in terms of microbiotal cross-talk and the lack of neonatal exposure. Perhaps it is not simply a lack of neonatal exposure but a lack of appropriate exposure to appropriate organisms regardless of how they are born.
**Dr. Walker:** I raised this not because I necessarily believe it but mostly because it is the topic of the conference and I would like to provoke some discussion. There is evidence that mothers who are allergic during pregnancy are more likely to produce allergic children, that allergen exposure is likely to produce an allergic reaction. Earlier we talked a little bit about cord cells and it has been shown that there must be some stimulus in utero for the cord cells to produce some of the cytokines they do. This is speculative and I only raised it as a possibility.

**Dr. Ogra:** Obviously there is fascinating evidence of the cross-talk between the microbes and the mucosa, but I think there is also cross-talk between the organisms themselves which is probably as important, a critical mass of appropriate organisms which might provide either protection or result in the development of disease.

**Dr. Walker:** You are absolutely right and that is really a topic for another symposium, that microorganisms can communicate with each other. That is one of the criticisms of a probiotic being given to change gut flora, because it is an artificial situation and it doesn't necessarily create a problem, except when it has been shown to have some effect. The other thing that we don't know very much about, and needs to be looked at, is what is going on with the mother during her pregnancy that influences the infant, not necessarily bacteria getting into the amniotic fluid but certain responses the mother might have to microorganisms that are transplacentally passed onto the infant that modulates the infant's response.

**Dr. Ogra:** Do you have any thoughts about the types or species of probiotics that will be more appropriate for the induction of oral tolerance? Not all probiotics are alike.

**Dr. Walker:** That is another very good point; probiotics have different functions. But the problem is that only a few probiotics have been looked at extensively. The probiotic, used by the Finnish group in mothers in late pregnancy to affect atopic dermatitis, was lactobacillus GG. Lactobacillus GG is the most studied probiotic. That doesn't necessarily mean that it is better than others, it is just the others haven't been studied.

**Dr. Smith:** Why don't hygiene and fetal programming explain everything on allergy? There is a report in the UK suggesting a 7-fold increase in acute admissions for food anaphylaxis in the last 12 years, and a 5-fold increase in food allergy admission to hospital [1]. Eczema is increasing in milk studies in the same population, same survey, over 500% in a 30-year period. There was a 500% increase in food allergy in Australia over 10 years [2]. The telephone survey on peanut allergy by Sicherer et al. [3] also showed a doubling within 5 years in North America between 1997 and 2002. We haven't got that much cleaner, we are not using so many antibiotics, and there is still a lot more that we need to know about this. Have you any thoughts where this goes beyond these two conditions?

**Dr. Walker:** I couldn't agree with you more. I am not saying that the answer to the entire question of increased allergy is because of the hygiene hypothesis. I think peanut allergy and anaphylaxis are probably a different category of allergy that probably represents the more genetically based response. Why there has been an extensive increase over the last few years, I don't know. I am not an allergist so I can't say. Perhaps Dr. Björkstén could talk a little bit to that effect.

**Dr. Smith:** If it is genetically based are you suggesting epigenetic causes because there is a massive increase? In Malaysia for example peanut allergy is not seen in the native Malay population. I know roasting increases the allergenicity but it might also be the timing at which it is presented. As you suggested timing of bacteria is incredibly important to the types of responses that we get. Perhaps we are controlling things a bit too much with the way that we eat.

**Dr. Walker:** It is hard to explain the striking increase in specific allergies in a very short period of time. Under those circumstances there should be some environmental
factors perhaps with some genetic predisposition as opposed to a finite genetic defect. It could be an epigenetic response but again this is all speculation.

Dr. Giovannini: There is problem regarding the difference in microflora between natural birth and the cesarean section. Do you have any data on what will happen in the future? We know very little about probiotic strains. We know about Lactobacillus casei and bifidus, and we know that there are many problems with probiotics. Why have only two been studied and hardly anything is known about the others?

Dr. Walker: Your point is extremely well taken. This is an area that needs to be looked at much more carefully. Coming back to what Dr. Ogra and Dr. Wilson have pointed out, the gut is filled with many organisms that are not only communicating with the host but communicating with each other, and understanding what exactly is happening by the reductionist approach of using a single probiotic makes it very difficult. It might be better to look at the indigenous flora, for example prebiotics stimulate indigenous bifidobacteria and lactobacilli, and that may be a way to more naturally look at this process in vivo.

Dr. Björkstén: I would like to call attention to microbial diversity. I think that we may be on a dangerous track if we limit our thoughts to a traditional reductionist approach, thinking that one bacteria or one molecule would solve all problems. Less microbial diversity seems to be the only consistent difference in microbial ecology between allergic and non-allergic children. You can have basically the same bacterial species and numbers, for example E. coli or lactobacilli, or whatever, but the diversity is larger in healthy children than in atopic children. I would like in particular to ask the immunologists whether perhaps the gut microbial stimulation is a question of having enough hits on the immune system. If you continuously change E. coli and other strains of the various species in the gut as a consequence of a continuous exchange with the environment, rather than retaining the same strains for a long time, you get many more events that stimulate the immune system. The search for a single probiotic would thus not solve any problems. The microbial diversity is larger in rural than in urban areas and in children with an anthroposophic compared to a conventional life style.

Dr. Walker: The problem clinically with this whole area is taking observations made in an in vitro situation to a clinical study. So few clinical studies have been done that it is very hard to come back to your suggestion with a clinical recommendation; we haven't enough information. We just need to work more carefully.

Dr. Barker: Can I comment on the rather modest increase in the hygiene hypothesis. The intellectual model for the hygiene hypothesis, when we were thinking about appendicitis in the 1980s, was the polio epidemics which came about as there were improvements in hygiene in Europe. The first country that was hit was Sweden in the 19th century, and then the epidemics spread to different European countries. I don't know of any opposition to the idea that these were triggered by delays in encounters with the polio virus which attended improved hygiene. There must have been quite modest improvements but my goodness they killed a lot of people. The appendicitis epidemics, if they followed the same general model, attended relatively modest standard improvements in hygiene. The polio epidemics came to an end because we introduced vaccines, but the appendicitis epidemics came to an end just spontaneously. By what process could the kind of things that you have been describing induce an epidemic which then goes away?

Dr. Walker: I can only speculate and would suggest, as you pointed out, that using hot water allows for different milieus in which the bacteria will proliferate, and that is probably what caused the inflammation of the appendix. It doesn't take much to disrupt the balance between huge numbers of bacteria, some of which are potential pathogens, some of which are protective, to cause that to occur. The term 'hygiene hypothesis', you are right, is a misnomer, but from the original observation, which was
published in the late 1980s, there has been a lot of revision. What I tried to point out is that, as research has moved from pathogens to commensal or symbiotic bacteria, we are beginning to recognize that just general communication with colonizing bacteria may be what prevents these things rather than a child having to have infections such as hepatitis or influenza or whatever.

Dr. Haschke: In response to Dr. Giovannini’s question about whether children born by a cesarean section are more frequently sick; yes, there are data clearly indicating this. They have more upper respiratory tract infections and more asthma. The question I have is, when you look at the different microbiota in infants born by cesarean section or vaginal delivery, and in view of what we have heard from Dr. Hanson that material from bacteria might be transferred through breast milk, could it not be an effect of the later start of breastfeeding in infants born by cesarean section and not only the mode of delivery?

Dr. Walker: It could be and your point is well taken, but this is a very new area. Until a recent paper, which I think Dr. Hanson mentioned, suggesting the mechanisms by which probiotics can get into the breast milk, the feeling was that it was contamination from the skin of mothers who were breastfeeding. It is a possibility that this is also a factor, and I think it is a combination of a number of factors. Children born by cesarean section who lack the initial normal colonization need an additional protective function to prevent them from having allergies, infections, etc. Not all of them get that so obviously there are some factors, and breast milk could be one. But at this point based on what has been reported, I can’t say that it is bacteria in breast milk. That has to studied further.

Dr. Maldonado: With reference to the issue of appearing and disappearing epidemics, from the microbiologic standpoint there are a couple of examples of modern phenomena which may be related to bacterial pathogenesis and sanitation. One is rheumatic fever which we know from years of careful observation increased over many decades and actually began to decline before the advent of the penicillin use. In fact we know that the organism itself mutated and became less trophic for heart tissue, and of course as we know now it is much more trophic for skin and soft tissue. Some of these events may actually be related to organisms in the environment as well, and have adapted to something spontaneously or to other influences in the environment. The other example is that neonatal infections seen over the last several decades have also changed in terms of the types of predominant organisms that affect newborns; going from gram-positive infections, then moving along to gram-negatives and changing back to gram-positives again. Those of course have been stimulated by the effects of antibiotic use. Is that perhaps something you have evidence for?

Dr. Walker: There is something that I should have brought up before and that is genetic polymorphisms. It is very likely that some of these are conditions we are seeing in children who have a polymorphism. For example a study was done on children raised in a farm community with exposure to endotoxin; they actually developed allergy and had a fairly high percentage of the TLR4 polymorphisms. I think that confuses the observations we are making in the context of specific association, colonization, no colonization, what type of organisms exist, and so on. This is going to have to be worked out very carefully.

Dr. Malka: The infant born and raised in an inner city like New York has a higher endotoxin level than in the non-inner city infant. In the inner city household the endotoxin level was associated with less atopic dermatitis. At the age of 2 years the non-inner city children started to wheeze, similar to the inner city, metropolitan cohort. How can that be explained?

Dr. Walker: I can't. The child born in New York, in an inner city, could have a high exposure because they live in a low socioeconomic, less clean state. Urban versus
rural is not the answer; it must be looked at very carefully. One also has to look individually at the patient to see what is happening. I don’t believe we can make generalizations on these observations, and that is one of the downsides to epidemiologic studies where an observation of one thing is compared with another. In my view that does not tell the whole story.

Dr. Björkstén: I think endotoxin is a marker for something else. In Sweden, we can confirm what has been shown in other places that endotoxin levels are inversely related to skin prick test positivity. In Estonia, however, which has a different environment, the endotoxin levels are much higher and there is zero relationship with skin prick test reactivity or allergic disease. So it seems that the relationship is limited to Western affluent societies. My other comment is that inner city wheezing to a large extent is not IgE-mediated allergic disease but has other causes.

References