Early Feeding Practices and Development of Food Allergies

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Abstract

Despite increasing efforts to prevent food allergies in children, IgE-mediated food allergies continue to rise in westernized countries. Previous preventive strategies such as prolonged exclusive breastfeeding and delayed weaning onto solid foods have more recently been called into question. The present review discusses possible risk factors and theories for the development of food allergy. An alternative hypothesis is proposed, suggesting that early cutaneous exposure to food protein through a disrupted skin barrier leads to allergic sensitization and that early oral exposure of food allergen induces tolerance. Novel interventional strategies to prevent the development of food allergies are also discussed.

Introduction

Recent epidemiological studies in the UK and North America have shown that prevalence rates of food allergy in children have increased. Food allergy prevention through allergen avoidance during pregnancy, breastfeeding, and infancy has been seen as an effective public health policy to prevent allergies. Nonetheless, there are little epidemiological data to support this recommendation. Intervventional trials on dietary elimination have failed to reduce IgE-mediated food allergies. Conversely, there are preclinical data and some clinical data to suggest that early oral exposure results in the induction of tolerance. New strategies to prevent food allergy in infants need to be put to test in randomized controlled interventional studies. In this review, we analyze potential risk factors and theories for the development of food allergy.
Rise in Food Allergies

Since the late 1950s, the incidence of allergy in developed countries has risen progressively. In the US, the prevalence of reported food allergy increased by 18% from 1997 through 2007 in children less than 18 years of age ($p < 0.01$) [1]. Ambulatory care visits due to allergy tripled between 1993 and 2006 ($p < 0.01$). In 2007, 3.9% of US children <18 years of age had reported food allergy [1]. In the UK, food hypersensitivity prevalence based on food challenges and appropriate clinical history is 5–6% by the age of 3 years [2]. Trends in hospital admissions in the UK show that admissions for food allergy in children rose nearly 7-fold from 16 to 107 per million for the time period 1990–1991 to 2003–2004 [3]. The increase in peanut allergy (PA) has been significant. In the US, the rate of self-reported PA increased from 0.6 to $1.4\%$ among children from 1997 to 2008 [4, 5]. In the UK, a recent study including 1,072 mothers and their children showed that the prevalence of peanut sensitization is $2.8\%$ and the prevalence of PA is $1.8\%$ among British children at school entry [6].

Epidemiologic Risks for Food Allergy

There are diverse theories that try to explain the presence and rise in allergies during the past few decades.

**Genetic and Molecular Risk Factors**

Some studies suggest a strong genetic contribution to PA. A child has a 7-fold increase in the risk of PA if he or she has a parent or sibling with this allergy [7]. In the case of monozygotic twins, a child has a $64\%$ likelihood of PA if his or her twin sibling has PA [8]. Although it is unlikely that genetic risk factors could account for the recent increase in food allergies, it is nevertheless likely that there are genetic predisposing factors for their development. The contribution of the HLA background and the development of individual food allergies to the rise of food allergies remains to be seen.

**Changes in Dietary Composition**

In the past 3 decades, there have been marked changes in diet, and it has been suggested by researchers that differences in macronutrient and micronutrient dietary content could explain the increase in allergies. There are 3 hypotheses that deserve discussion:

1. The vitamin D hypothesis is based on both epidemiological and immunologic data that suggest that either excessive vitamin D or conversely vitamin D deficiency has led to increased allergies. The first observations derived from farming communities in Germany where there was less vitamin D supplementation used in foods and a lower prevalence
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of allergies in children was found. Allergies increased coinciding with vitamin D supplementation intervention programs to prevent rickets in childhood [9]. Similarly, two independent cohort studies by Milner et al. [10] and Hyppönen et al. [11] showed that infants who had vitamin D supplementation were at increased risk of food allergy. On the other hand, the vitamin D deficiency hypothesis argues that inadequate vitamin D (mainly as a result of inadequate sunlight associated with more time indoors) is responsible for the increase in asthma and allergies. The study by Camargo et al. [12] found a strong north-south gradient for EpiPen (Dey, Napa, Calif., USA) prescriptions in the US. Northernmost states were prescribing 8–12 EpiPen self-injectors per 1,000 population, whereas the southern states were prescribing 3 per 1,000 population. This gradient persisted despite a multivariate analysis. There was an inverse association between EpiPen prescription and the incidence of melanoma in the population, suggesting that this north-south effect was due to sunlight exposure [12].

2 The dietary fat hypothesis argues that reduction in consumption of animal fats and corresponding increase in the use of margarine and vegetable oils has led to the increase in allergies. The argument is that there has been an increase in the consumption of ω-6 polyunsaturated fatty acids, such as linoleic acid, and similarly that through reduced consumption of oily fish, there has been a reduction in ω-3 polyunsaturated fatty acids, such as eicosapentaenoic acid. ω-6 fatty acids lead to the production of prostaglandin E2 (PGE2), whereas ω-3 fatty acids inhibit synthesis of PGE2. PGE2 reduces IFN-γ production by T lymphocytes, thus resulting in increased IgE production by B lymphocytes [13, 14].

3 The antioxidant hypothesis proposes that the decrease in consumption of fresh fruit and vegetables (containing antioxidants such as vitamin C, vitamin E, β-carotene, selenium and zinc) in the UK might account for allergies. However, dietary trends are conflicting; whilst the intake of some antioxidants has increased, for others intakes have decreased. Nevertheless, there is epidemiological, animal, molecular and immunological evidence suggesting associations between antioxidants and asthma and a reduced number of studies on atopic dermatitis and allergic rhinitis [15]. However, no such data are currently available for food allergies.

Hygiene Hypothesis

In general, allergies are associated with a western style of life. The hygiene hypothesis suggests that the lack of early childhood exposure to infectious agents, gut flora and parasites increases susceptibility to allergic diseases by modulating immune system development. Limited evidence for the hygiene hypothesis exists with respect to food allergy. A Norwegian birth cohort study found that birth through a cesarean section was associated with a 7-fold increased risk of parental perceived reactions to eggs, fish, or nuts [16]. A
recent meta-analysis found 6 studies that showed a mild effect of cesarean delivery, increasing the risk of food allergy or food atopy (OR: 1.32, 95% CI: 1.12–0.55) [17]. One explanation for these findings is that early colonization of the infant by colonic microflora protects against the development of allergic disease. Such observations have led to strategies to alter commensal gut flora either directly through the administration of probiotics or indirectly through the administration of prebiotics. Although some studies using probiotics have suggested some protective effect against development of eczema, they did not show any reduction in allergen sensitization [18]. There is no evidence that probiotics prevent the development of food allergies. However, cesarean section could appear to cause a higher rate of food allergy and atopy due to confounding factors that have not been analyzed in the published literature. Firstly, cesarean sections are associated with higher maternal age which in itself has been linked to atopy [19]. Secondly, cesarean section is associated with a higher number of first born infants which has been shown to be associated with food allergy [20]. Finally, cesarean sections are associated with a higher number of male births [21] and the prevalence of FA is higher in males than in females [22].

**Exposure to Food Allergens**

Important questions remain about exposure to food allergens both in the infant’s diet and in the maternal diet. The American Academy of Pediatrics recommended until very recently that families with an infant at increased risk of atopy based on family history should avoid peanuts in the infant’s diet during the first 3 years of life and common food allergens until the first (milk), 2nd (egg), or 3rd (tree nuts and fish) years of life [23]. According to these recommendations, mothers should avoid peanuts during pregnancy and breastfeeding and additional allergens during lactation. In the UK, similar recommendations are still in place with respect to peanut avoidance [24]. Recently, both the American Academy of Pediatrics and the section on Paediatrics of the European Academy of Allergology and Clinical Immunology have changed their position, acknowledging that we do not know whether certain aspects of avoidance prevent allergies, and recommendations about avoidance of specific food allergens have been withdrawn and replaced by comments about the lack of current evidence on these topics [25, 26].

There is a lack of evidence in which to base advice for weaning infants. We have little evidence-based guidance about when to introduce allergens in the diet and whether to introduce these foods in large or small quantities, and what the frequency should be. The World Health Organization strategy to prevent allergy is to promote exclusive breastfeeding during the first 6 months of the infant’s life and thus delay weaning onto solids and milk for-
mulae [27]. However, there is no convincing evidence that exclusive breast-
feeding beyond 4 months of age has any effect on reducing atopic disease. 
Indeed, more recently, observational cohort studies showed that breastfeed-
ing [28] and prolonged breastfeeding [29] are associated with an increased 
risk of asthma and eczema. Although such studies do not eliminate the pos-
sibility of reverse causality as an explanation for this finding (high-risk infants 
with eczema are deliberately breastfed longer), they raise the question as to 
whether exposure to solids in infancy might have a role in preventing allergic 
disease.

**Food Allergen Exposure Revisited**

It is surprising that studies eliminating food allergens during preg-
nancy, lactation, and infancy have consistently failed to reduce long-term 
IgE-mediated food allergy in children [30]. There are four possible expla-
nations for this failure. First, exposure to allergens is irrelevant for the 
development of food allergy. This explanation can be immediately ruled 
out because food allergy is an antigen-specific immunologic disease, and 
antigen exposure is necessary for T cell maturation, affinity maturation, 
and isotype switching. Second, allergen reduction measures have not been 
sufficient in previous studies, and dietary elimination was not sufficiently 
stringent. This is certainly plausible. However, it seems very unlikely that 
‘complete’ allergen avoidance could successfully prevent food allergies as 
a public health measure, given that careful elimination studies have failed, 
despite rigorous dietary supervision, to achieve a reduction in food aller-
gies [30, 31]. Third, sensitization to food allergens does not occur as a 
result of consumption, but can occur through other routes of exposure. 
This is supported by a number of murine studies that show that allergic 
sensitization to antigen occurs after cutaneous exposure and also this has 
been suggested in recent clinical studies. Finally, the paradigm of allergen 
avoidance is flawed, there are animal data and some observational clinical 
data supporting that early oral exposure can be required to prevent the 
development of allergy. These last two explanations are discussed further 
below.

**Dual Allergen Exposure Hypothesis**

The established view that allergic sensitization to food occurs through oral 
exposure and prevention of food allergies is best accomplished through elimi-
nation diets has been challenged. It is proposed instead that allergic sensiti-
ization to food can occur through low-dose cutaneous sensitization and that 
early consumption of food protein induces oral tolerance [32]. The timing and 
balance of cutaneous and oral exposure determine whether a child will have 
allergy or tolerance (fig. 1).
Data Suggesting Cutaneous Sensitization

Current knowledge suggests that atopic dermatitis is the result of a combination of an altered skin barrier function, abnormal immune reactivity and environmental factors such as allergens and microbes [33]. There is indeed a molecular basis for the increased skin permeability in eczema; this is the loss of function or missense mutations in the gene encoding for filaggrin. This protein is important for epidermal differentiation, desquamation and barrier function and has been recognized as the strongest genetic contributor to eczema [33–36]. In the positive studies, it has been shown that 14–56% of cases of eczema carry one or more filaggrin null mutations, and the presence of a filaggrin null allele represents a 1.2- to 13-fold increased risk of developing atopic eczema [37]. Furthermore, there is evidence that TH2 inflammation in the skin of patients with eczema reduces filaggrin gene expression [38]. It has been suggested that low-dose exposure to environmental foods (on tabletops, hands, and dust) [39], penetrates the disrupted skin barrier and is taken up by Langerhan’s cells. This leads to TH2 responses and IgE production by B cells [33]. This hypothesis can explain the association between the presence of early severe eczema in infancy and the subsequent development of food
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**Table 1.** Food allergies among allergy clinic patients

<table>
<thead>
<tr>
<th>Country</th>
<th>PA, %</th>
<th>Dietary practice recommendations (infant peanut consumption)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (n = 191)</td>
<td>25</td>
<td>avoidance</td>
</tr>
<tr>
<td>US (n = 300)</td>
<td>69</td>
<td>avoidance</td>
</tr>
<tr>
<td>Israel (n = 992)</td>
<td>2.1</td>
<td>high infant consumption</td>
</tr>
<tr>
<td>Philippines (n = 184)</td>
<td>0</td>
<td>high infant consumption</td>
</tr>
</tbody>
</table>

From Lack [32], with permission.

Allergies. Furthermore, this hypothesis can explain different rates of food allergies in different parts of the world and changes in food allergy over time. Thus, in societies in which a food is not consumed, there is no environmental exposure, and therefore allergy to that food will not occur. Allergy to kiwi was not a problem in the UK before it was introduced into the market in the 1970s through 1980s. In countries where consumption of peanut is high and peanut is therefore present in the environment but infants are avoiding peanuts, one would expect to see allergic sensitization (UK, US, Canada and Australia). In countries where consumption and consequently environmental exposure are high but infants are eating peanut regularly, one would not expect to see PA (southern/western Africa/Asia) [32] (table 1).

In animal models, it has been shown that exposure of mice to ovalbumin or peanut on abraded skin led to significant specific IgE responses [40, 41]. There are human studies in which food allergen-specific T cells have been isolated from lesional skin in patients with eczema [42]. In a prospective birth cohort study, it was found that low-dose exposure to peanut in the form of arachis oil applied to inflamed skin on infants was associated with increased risk of PA at age 5 years [43]. Similarly, transcutaneous sensitization to oat used in emollients or moisturizers was suggested in a study assessing children with atopic dermatitis. Thirty-two percent of children using creams containing oat had oat-positive patch test compared with 0% in the children who did not use them [44]. In a recent cross-sectional study [45], the relevant route of peanut exposure in the development of allergy was evaluated. Maternal peanut consumption during pregnancy, breastfeeding, and the first year of life was recorded by using a questionnaire; additionally, peanut consumption among all household members was quantified. The median weekly household peanut consumption in the peanut allergic cases was significantly elevated (18.8 g, n = 133) compared with controls without allergy (6.9 g, n = 150) and high-risk controls (1.9 g, n = 160; p < 0.0001). A dose-response relationship was observed between environmental (non-oral) peanut exposure and the development of PA. These findings suggest that high levels of environmental exposure to peanut during infancy may promote sensitization, whereas low levels appear to be protective.
in atopic children. Early oral exposure to peanut in infants with high environmental peanut exposure may have had a protective effect against the development of PA. No effect of maternal peanut consumption during pregnancy or lactation is observed, supporting the hypothesis that peanut sensitization occurs as a result of environmental exposure (fig. 2).

**Data Suggesting Oral Tolerance**

Oral tolerance is well recognized in murine models. Numerous studies have demonstrated that early high-dose oral exposure confers both immunologic and clinical tolerance to food allergens. A single oral dose of allergen (β-lactoglobulin, ovalbumin, or peanut) is sufficient to achieve tolerance and prevent subsequent allergic sensitization [46–48]. In a murine model, a single high dose of peanut flour (100 mg) was sufficient to promote oral tolerance and prevent subsequent IgE sensitization and T cell proliferation [48]. In human subjects, cutaneous exposure to nickel during childhood leads to sensitization and nickel allergy, but oral exposure to nickel through orthodontic braces before ear piercing protects against nickel allergy [49, 50]. Similarly, subjects exposed to pancreatic extract by means of inhalation or contact have IgE-mediated allergic reactions, whereas subjects exposed orally do not [51].

Regular fish consumption before the age of one year appeared to be associated with a reduced risk of allergic disease [OR: 0.76, 95% CI: 0.61–0.94] and sensitization to food and inhalant allergens [OR: 0.76, 95% CI: 0.58–1.0] during

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**Fig. 2.** PA among children with food allergy (n = 293) as a function of environmental exposure depending on whether child first ate peanuts by 12 months. Reprinted with permission from Fox et al. [45].
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the first 4 years of life in a cohort of 4,089 newborn infants [52]. On the other hand, a recent study showed that delaying initial exposure to cereal grain after 6 months of life was associated with an increased risk of IgE-mediated food allergy [53].

In Western industrialized societies where peanuts are avoided in pregnancy and infancy, the rate of PA is higher [54]. In regions where peanut is consumed in high amounts during infancy (Middle East, Southeast Asia, and Africa), PA is reportedly rare [55–57]. However, different rates of food allergies in the UK compared with those in Asia and Africa might be due to genetic differences or the generally lower rates of atopic disease in developing countries, possibly resulting from differences in microbial exposure [58, 59]. In a recent cross-sectional study among Israeli (n = 5,615) and UK (n = 5,171) Jewish children [60], the prevalence of PA was 10-fold higher in the UK (1.85%) than in Israel (0.17%; p < 0.001; fig. 3). This study also found that peanut is introduced earlier and is eaten more frequently and in larger quantities in Israel than in the UK. The median monthly consumption of peanut in Israeli infants aged 8–14 months is 7.1 g of peanut protein, and it is 0 g in the UK (p < 0.001). The median number of times peanut is eaten per month was 8 in Israel and 0 in the

Fig. 3. Early consumption of peanuts in infancy is associated with a low prevalence of PA. Adapted from Du Toit et al. [60].
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UK (p < 0.0001). This difference is not accounted for by differences in atopy, social class, genetic background, or peanut allergenicity. These findings raise the question of whether early introduction of peanut during infancy, rather than avoidance, will prevent the development of PA.

**Randomized Controlled Trials Using Oral Tolerance Induction to Prevent Food Allergies**

Indeed, it has been argued that early introduction of foods such as peanut may lead to tolerance and protect against the development of food allergy. These theories are currently being tested in two randomized controlled trials (RCTs).

The LEAP Study [61] (www.leapstudy.co.uk) involves 640 such high-risk children who were enrolled in the study when aged 4–10 months. Each child was randomly assigned to follow one of the two approaches – avoidance or consumption. Children in the avoidance group avoid eating peanut-containing foods until they reach the age of 3. In the consumption group, parents are asked to feed their child an age-appropriate peanut snack three times per week (equivalent to about 6 g of peanut protein per week). All participants receive allergy testing, dietary counseling, physical examinations and will be asked to provide occasional blood samples that will be used to examine differences in immune system development in each of the study groups. The proportion of each group that develops PA by 5 years of age will be used to determine which approach – avoidance or consumption – works best for preventing PA. We anticipate that the study will reach completion in 2013, at which time the results will be analyzed and published.

The EAT study [62] (www.eatstudy.co.uk) is an RCT investigating the effect of early introduction of complimentary foods together with breastfeeding. Infants taking part in the study (n = 1,400) are being recruited from the general population and randomized to one of two groups: one group (n = 700) introduces six allergenic foods from 3 months of age alongside continued breastfeeding, having been screened to check for pre-existing food allergy (early introduction group). The other group (n = 700) follows present UK government weaning advice, i.e. aim for exclusive breastfeeding for 6 months (standard weaning group). The children will be monitored until 3 years of age to see whether early diet has an effect on reducing the prevalence of food allergy determined by double-blind, placebo-controlled food challenges.

**Pitfalls in the Interpretation of Randomized Controlled Trials to Prevent Food Allergy (Necessary and Sufficient Causes)**

Interventional studies clearly represent an advantage over observational studies in the determination of the role of early food and micronutrient
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exposure in the development of allergies. RCTs represent the gold standard of clinical medicine, especially when findings are replicated and shown to be consistent in further meta-analyses. However, we should bear in mind that positive RCTs are easier to interpret than negative studies. The pathogenesis of food allergies is likely to be multifactorial, and it is also likely that the induction of oral tolerance is dependent on several conditions being met. Thus, we need to differentiate between necessary and sufficient causality.

Exposure to food proteins in the GI tract may require an optimal microenvironment, if the necessary conditions for the induction of tolerance are to be met (e.g. immune factors such as cytokines, antibodies, regulatory T cells whose function may depend on vitamin D, as well as bacterial colonization). For example, in animal models, oral tolerance induction with a single dose of food protein protects against the development of allergies. However, oral tolerance cannot be induced in germ-free mice – tolerance requires the presence of both intestinal microflora and food antigen [63]. Each factor is necessary but neither is sufficient for the development of tolerance. The consequence is that we may intervene with a single factor which in itself is necessary but may not be sufficient to induce tolerance. For example, if foods or micronutrients are introduced into the diet of young western infants with reduced microbial exposure, no effect may be seen, but we may be wrong to interpret this lack of effect as evidence of causal irrelevance. A western urban lifestyle is associated with numerous changes in the way foods are presented to young infants. For example, it may be important that food allergens be presented to the GI tract in the context of breast milk which contains numerous immunomodulatory factors [64]. Recent practices in infant weaning have had the consequence of separating exposure to breast milk from allergenic food proteins. Thus, a 6-month period of exclusive breastfeeding followed by a slow introduction of hypoallergenic foods followed in turn by the delayed introduction of food allergens means that in practice infants are rarely exposed to peanut or egg in the presence of breast milk. Similarly, the decline in the practice of premastication (see below) means that the infant may be deprived of numerous immunomodulatory factors that shape its response to food proteins.

**Premastication May Be Important in the Development of Oral Tolerance Induction**

Premastication occurs when mothers or child’s caregivers chew up solid foods and feed the resulting mash to their infants. In a cohort study conducted in Thailand, it was shown that up to 17% of infants received premasticated foods as early as their 2nd week of age and 81% by 6 weeks of age [65]. In the US, Fein et al. [66] estimated from a nationally distributed sample of predominantly Caucasian infants an overall prevalence of premastication of
14%. Recently, in an extensive anthropological review of 119 cultures, it was shown that at least 30% of them practiced premastication [67].

Adult human saliva contains an array of cytokines, chemokines, antibodies and elements that includes IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TGF-β, IFN-γ, TNF-α and TNF-β, MIP-1α and MIP-1β, RANTES, vitamin D, iron, IgA, IgG4 and IgM [68]. Saliva contained in prechewed foods could transfer passively IL-10, TGF-β, vitamin D, secretory IgA, and IgG. Thus, premastication may provide antigen in an immunologically favorable milieu that promotes the development of oral tolerance to specific dietary antigens that prevents the development of allergies in the infant.

Premastication has declined worldwide over the past decades with transition from a traditional to modern lifestyle. Interestingly, over the same time period, there has been an emerging epidemic of allergies and autoimmune diseases, especially in the developed world [69]. Thus, this practice may have an important role in the development of oral tolerance mechanisms and the prevention of atopic and autoimmune diseases. Currently however, there is no evidence that premastication prevents the development of allergies and indeed no justification to recommend this practice which may increase the risk of infectious transmission however small from mother/caregiver to infant [70].

Conclusions

It is argued that antigen exposure through a disrupted skin barrier or through the gastrointestinal mucosa might be involved in the establishment of allergy and tolerance. Immune responses to such allergen exposures are likely to be modulated by nonspecific factors, such as gastrointestinal microflora, infectious exposure, dietary factors, immunomodulatory factors passively transferred and possibly sunlight exposure. It is hoped that interventional trials in progress and those to be conducted in the next few years will help to determine the relative contribution of these different factors and allow us to reduce the burden caused by food allergies.

References

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Discussion

**Dr. Jones:** Checking early vitamin D exposure is quite difficult unless you have got serum, so are there any data on the prevalence of sensitization in babies who have had phototherapy?

**Dr. Lack:** Not to my knowledge. I asked myself the same question a while ago and haven’t found anything on that, but I think that’s a great question. You might expect them to be very different, yes.

**Dr. Papadopoulou:** Children born with C-section are at increased risk for IgE sensitization. I wonder whether in the frame of the EAT study it would be useful to separate the group of children who are at highest risk for atopy by those with a genetic predisposition and those who were born with C-section to see whether there is a difference.

**Dr. Lack:** We intend to do that by the way, but I don’t think that’ll work in the LEAP study because they are all highly atopic, but in the EAT study, where we have a mixture of atopic and non-atopic, you may find differences. I personally think that there are so many confounding factors for C-section, one of them being high rate of
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first-born infants, which we know is associated with the high rates of allergy, so it's very difficult to separate those apart, but we will be looking for that.

Dr. Rings: I have a question related to one of your comments on the anaphylaxis and the low incidence. You made the observation that a lot of children and young adults, are walking around with an EpiPen these days, which also gives a certain burden knowing that that's related to severe anaphylaxis. So I was wondering, if you are taking that observation into account in your EAT and LEAP studies – the risk of anaphylaxis related to food allergen. That might be something that can be lowered with the early introduction of food allergen.

Dr. Lack: The only place I alluded to carrying an EpiPen was in the vitamin D study, where that was used as a surrogate marker of food allergy in a population. In the EAT and LEAP studies we were defining food allergy by double-blind placebo-controlled food challenges at the end of the study, not by the number of children who have been prescribed an EpiPen. Obviously, if children developed allergies along the way, we gave them all the standard allergy advice, which includes carrying injectable epinephrine.

Dr. Rings: Yes, but lowering that amount of prescribed EpiPens would be a very nice end point, because it gives a certain burden, walking around with an EpiPen.

Dr. Lack: I agree, getting rid of the EpiPens, getting rid of the food allergy in the first place would be a nice end point. It's something we hope to achieve, but we will have to see what the final outcome is because of all these other factors that may come into play to induce tolerance. If we are deficient in microbes, bugs, if we are deficient in vitamin D, if we are deficient in other factors that we may even ignore at the moment, the necessary conditions for oral tolerance induction may not be there. We hope that they will, and we hope to see an effect.

Dr. Fasano: I was really impressed to see the skin barrier business, and I don't know if you are familiar with Barbara Becks's work. She just made this observation, I believe it's already been published, that apart from the stratus corneum barrier defects she also found defects in tight junction. One of the components of tight junction is downregulated, and she claimed that this is a key element to lose barrier function in atopic dermatitis, making this trafficking a key element in terms of this yin and yang between tolerance and immune response. What would you think that this would entail? And how important is indeed the route of exposure, with the skin being the one where you have to develop an immune response that leads to allergy compared to the mucosal route where you have a chance of tolerogenic response?

Dr. Lack: I think it's OK to have cutaneous exposure even if you have an inflamed skin. The theory goes that so long as you have got oral tolerance occurring at the same time, you get a balance in these two routes, and the outcome will be tolerance. I haven't presented the work that Susan Chan in our group has done, which is to look at the origin of lymphocyte, T cell responses, in allergic and tolerant children, and we have been following sensitization based on different T cell compartments in the T cell circulation. So what Susan did is she isolated skin-homing lymphocytes at the CLA-positive cutaneous lymphocyte antigen-positive lymphocytes and got very high purity, and then she isolated from the same or different patients the α4β7, those T cells that home to the gut. What is interesting is we find in the allergic children that proliferative response to peanut is derived almost entirely from the CLA population. Now our hypothesis was that in the tolerant children it would all be in the α4β7 but it's not, you see a mix, so you see T cells that respond, there is about a 1:1 ratio in the response rate. I think in the children with eczema who are tolerant, both routes are occurring, and there is a balance. As far as the mechanisms of decreasing skin permeability are concerned, I think it's important, but I think there are numerous others we don't know much about. Donnelly, Yung and others have shown that as eczema worsens, even in
the wild type where you have normal filaggrin expression, IL-4 and IL-5 switch off filaggrin expression in the skin. So, I think there are other mechanisms, and of course we know that IL-5 and other cytokines induce apoptosis of keratinocytes, which is why when you look microscopically at the skin in atopic dermatitis you see spongiosis, these empty gaps in the skin. So, there is a lot of things contributing to that.

**Dr. Simmer:** Thank you for your interesting talk. As I understand it, you allergists have come up with one recommendation for prevention which is exclusive breastfeeding for 6 months. Whereas everyone here would promote breastfeeding for 6 months for lots of reasons, you are saying that you believe breastfeeding per se reduces atopy compared with partially hydrolyzed formulas. Are you recommending breastfeeding because you are a pediatrician or are you recommending breastfeeding because you really think it reduces allergy?

**Dr. Lack:** There are several strands to that question. First of all, the 6 months recommendation obviously didn’t come out of allergy, it came for other beneficial health effects which I think few allergists or pediatricians in their right mind would deny. So, the issue really is exclusive breastfeeding versus feeding with solids. Do I believe that breastfeeding has a protective effect? Yes, I do, but I could also cite you, and it would be very dishonest of me to do so, but I could cite you studies that show the deleterious effects of prolonged breastfeeding on the development of allergies. The problem is those studies aren’t possible to interpret, especially those after the late 1970s and early 1980s. Why? Early in the 1970s, we had some studies showing protective effects of breast milk, not huge protective effects but I do believe there were some protective effects, then along came the public health message that this was a good thing to do in atopic families. What you find now in all the atopic populations, and these are observational studies, prolonged exclusive breastfeeding is practiced but that’s reverse causality. That has been done because the population is advised by their GPs and pediatricians to do so because there is a family risk and you can’t interpret those studies. So, I think there has been a C change in the effect we see before the late 1970s and from the mid-1980s onwards. I think it’s impossible to interpret without doing randomized controlled trials, which is why we are doing particularly the EAT study to try and disentangle these effects. But I think that breastfeeding, and I am not advocating premastication either, but it was until very recently practiced very widely and still is, including the US. There are surveys showing a significant percentage of population practicing it, and in parts of Asia it’s practiced as of 2 months of age, so those may be factors, breast milk, colostrum, some of the factors we see may be very important. Obviously, we feel and the ethics committee felt it was ethical to do the study we are doing, but it would be completely unethical to randomize children to breastfeeding or not breastfeeding as a randomized control study, so that study will never be done.

**Dr. Klish:** A few years ago, when I first met Wesley Burks he had just identified the peanut epitope and the gene that produced it. That got me thinking about the chemistry of allergic epitopes. At the time, I recall a paper that looked at a myriad of allergic epitopes and showed that there was some commonality within their chemical structure. They seemed to fall into groups based on not only their chemical structure but their tertiary structure as well. It always seemed to me that if that science was true, it would be possible to develop treatment for allergies through vaccines, etc. Since I haven’t followed that science, has it moved forward?

**Dr. Lack:** I think probably both of us should answer that one. That sort of links in with the question which is one of the holy grails of allergy: what makes a protein an allergen? I think we are still a long way from answering that question. There are certain properties of protein allergens that have been identified, they’re more stable to heat they’re more stable to digestion, they fall within a certain molecular weight, but there are numerous exceptions to this, and there are some proteins you would predict
to be allergens that very rarely cause allergies and vice versa. I think that component-resolved diagnostics, as it’s now known, where you look for IgE to different allergens within peanut, are proving to be very helpful. So, there is a recent publication showing that the specificity of IgE to arah2, one of the major peanut allergens, is extremely high. If you have a level of 0.3 something, the specificity is 97%. So, if you have IgE to arah2 you nearly always have peanut allergy. So what are the properties of arah2 that make it an allergen? I don’t really think we have advanced much on that front but Dr. Shreffler, you may have some observations from some of your work.

Dr. Shreffler: I think what Gideon said is on the money; that is that basic structural properties of the allergens such as the stability, size, etc., are repeatedly observed but with many exceptions. It’s true that among all protein families or structural motifs, allergens are overrepresented by relative few. But if you look specifically at the epitopes on those allergens, there have not been consistent structures that emerge as being more likely to produce an IgE response versus an IgG response, to my knowledge. Where there is a lot of interest, however, and that’s relatively new, is discovery of the innate immune stimulatory properties of allergens. Examples of both respiratory allergens and dietary allergens have emerged in which the allergens themselves or intimately associated molecules have the capacity to directly stimulate the innate immune system.