Interaction of Early Infant Feeding, Heredity and Other Environmental Factors as Determinants in the Development of Allergy and Sensitization

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Abstract
The role of early infant nutrition in the development of allergic symptoms and allergic sensitization has been disputed for 70 years. Interaction between genetic factors and infant feeding has been limited to studies on parental heredity of allergy and length of breastfeeding, as well as the qualities of breast milk. In the 10 original studies comparing the development of allergic symptoms among children in whom breastfeeding duration was used as a risk factor separately among those with either positive or negative parental heredity for atopy, no definite answer could be found. The effect of early feeding was even changed in both heredity negative and positive groups when looking at symptoms at ages 2 and 5 years. Of 9 possible combinations, 6 were present in the studies, and none in more than 2 studies. For sensitization, long breastfeeding was a risk in 3 of 5 reports if the family history of allergy was positive, and in 2 if negative. Low levels of soluble CD14 and cow’s milk-specific IgA antibodies in breast milk may increase an infant’s risk of developing allergy.

Introduction
The role of early infant nutrition in the development of allergic symptoms and allergic sensitization has been disputed for 70 years, as cited in a review by Zeiger and Friedman [1] on the issue. Complex properties of breast milk (BM) have developed over thousands of generations to protect the newborn infant from a hostile environment. Major threats to the infant are infections, the weakest point of resistance being the gastrointestinal tract. The need for
effective absorption of nutrients makes mechanical defense impossible and
only a single epithelial layer separates the contents of the gastrointestinal
tract from a well-developed vascular bed in the intestine. The properties of
BM have developed in order to offer the newborn infant protection from path-
ogenic microorganisms in several ways [2]. BM contains factors which in non-
specific ways act as antimicrobial agents, and it contains IgA antibodies to
microorganisms the mother has contact with, which effectively reduces intes-
tinal infections even in developed countries [3]. BM also contains IgA antibod-
ies to food proteins and at the same time small amounts of food antigens, but
how these relate to the development of immune responses to food antigens is
poorly understood. BM contains large amounts of non-digestible oligosaccha-
rides, which are important in selecting the type of commensal microflora in
the gut. Intestinal commensal microflora prevents proliferation of pathogenic
bacteria and is the most important stimulus for innate immunity, the latter
directing the development of specific immune responses. Regulatory and
immunomodulatory substances in BM directly affect the development of gut-
associated lymphoid tissue, as well as morphologic development of the intest-
tine. Immunomodulation aims to advance non-inflammatory defense as local
inflammation in the intestine would weaken absorptive function.

**Early Infant Nutrition and Heredity for Allergy**

How a mother through this delicate system, in addition to providing com-
plete nutrition, contributes to an infant’s immunomodulation and the matura-
tion of its regulatory system and how this relates to the infant’s hereditary
predisposition for an allergic immune response are mostly unexplored.
Interactions between genes and environmental conditions for the develop-
ment of allergies have been explored since the 1990s and seem to be compli-
cated [4]. The same genotype may lead to either an increased or decreased
prevalence of asthma depending on environmental conditions, such as expo-
sure to a high endotoxin concentration during infancy. The interaction
between genetic factors and infant feeding has been limited to studies on
parental heredity for allergy and the length of breastfeeding (BF), as well as
the qualities of BM.

In a nutrition study we noted that allergic symptoms, mostly atopic der-
matitis, occurred during the first year of life more frequently among infants
who had received exclusive BF for longer than 9 months. According to a
questionnaire about symptoms to age 2, a similar number of new sympto-
matic cases developed in the group that was breastfed for <3.5 months and
those breastfed for >9 months. During the first 2 years, among those with a
positive family history of allergy (FHA), the length of exclusive BF did not
influence the prevalence of allergic symptoms (table 1); while among those
without FHA, those with short exclusive BF (<3.5 months) tended to have
**Table 1.** Allergic symptoms in a population-based cohort at ages 2, 5 and 20 years

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<tr>
<td></td>
<td>FHA pos. (n = 70)</td>
<td>FHA neg. (n = 108)</td>
<td>FHA pos. (n = 72)</td>
<td>FHA neg. (n = 88)</td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>3/12 (25%)</td>
<td>1/19* (5%)</td>
<td>&lt;2</td>
<td>5/14 (36%)</td>
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<td>3.5–6</td>
<td>3/15 (20%)</td>
<td>4/30 (13%)</td>
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<td>3/15 (20%)</td>
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<td>&gt;6</td>
<td>13/43 (30%)</td>
<td>12/59 (20%)</td>
<td>6–9</td>
<td>8/27 (30%)</td>
</tr>
<tr>
<td>&gt;9</td>
<td>4/13 (31%)</td>
<td>5/18* (28%)</td>
<td>&gt;9</td>
<td>9/16 (56%)</td>
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BF = Breastfeeding; FHA = family history of allergy.

*p = 0.06 by χ² test.
Table 2. Summary of the effect of long vs. short breastfeeding on allergic symptoms in children with or without a family history of allergy (FHA)

<table>
<thead>
<tr>
<th>FHA positive</th>
<th>FHA negative</th>
<th>Study</th>
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<tr>
<td>↔</td>
<td>↑</td>
<td>Savilahti et al. [3]</td>
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<td>Pesonen et al. [5]</td>
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<td>Wright et al. [7]</td>
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<td>Sears et al. [9]</td>
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<td>Oddy et al. [15]</td>
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<td>Kull et al. [11]</td>
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<td>Miyake et al. [12]</td>
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<td>Benn et al. [13]</td>
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<td>Obihara et al. [14]</td>
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↓ = Significant decrease in allergic symptoms in children who were breastfed long; ↑ = significant increase, ↔ = no significant change in allergic symptoms.

*Maternal asthma, paternal asthma did not have an effect.

allergic symptoms less often than those with long exclusive BF (>9 months) [3]. The same group was again studied at ages 5, 11 and 20 years [5]. At age 5 the prevalence of allergic symptoms was highest (41%) among the children who had received exclusive BF over 9 months. The risk for allergic symptoms among those with a positive FHA and exclusive BF for >9 months was 6.1 (95% CI 1.5–24.8; p = 0.01), compared to those with shorter BF (table 2). Among those with a negative FHA the same risk was nonsignificant (1.4; 95% CI 0.3–7.3). At age 20 years, the length of BF had no effect on the prevalence of allergic symptoms either in the whole group or in groups divided according to FHA [5]. Skin prick test (SPT) with 11 most common food and inhalant allergens was done at ages 5, 11 and 20 years. BF length did not have any effect on the prevalence of sensitization to the allergens at any age. In this population-based group, the length of exclusive BF showed different association with allergic symptoms during infancy and childhood. During infancy (to age 2 years) long exclusive BF was associated with an increased incidence of allergic symptoms among those with a negative FHA; it did not affect the incidence among those with a positive FHA [3], while at age 5 years long exclusive BF increased the risk atopic eczema among those with a positive FHA and the effect was nonsignificant among those without FHA. Milk feeding during infancy was not associated with allergic symptoms at age 20 years.

More recently, we looked at the effect of early feeding based on large population of 4,674 children born in 1994–1995, whose early feeding we recorded
carefully from birth. We selected 4 groups, 2 with the longest exclusive BF in the cohort with and without a FHA; everyone in these 2 groups had been exclusively breastfed for at least 4 (range 4–6.5) months. The 2 other groups had been given a cow’s milk (CM)-based adapted formula already during first 2 weeks of life; again one group with a positive and the other with a negative FHA [6]. These 285 children visited the outpatient clinic at age 4 years and were studied for allergic symptoms and sensitization both by SPT and specific IgE levels. Logistic regression analysis showed a significant interaction between FHA and length of BF to the effect on atopic eczema (p = 0.022) and symptomatic allergy (asthma, allergic rhinitis and atopic eczema; p = 0.006). When children were stratified by FHA, those with a positive FHA and long BF had a significantly lower risk of allergic rhinitis (OR = 0.41; 95% CI 0.18–0.95) for positive SPT to dog and cat and for a high level of cat-specific IgE than those with short BF. In contrast, among those with a negative FHA, long exclusive BF significantly increased the risk of atopic eczema (OR = 2.37; 95% CI 1.03–5.5), for any symptoms of allergy (OR = 2.6; 95% CI 1.2–5.7) and for high (>130 kU/l) total serum IgE. When children were stratified by early feeding pattern, the effect of FHA was a highly significant risk of several allergic symptoms among those with short exclusive BF. For any allergic symptom the OR for FHA-positive children was 6.4 (95% CI 2.9–14) and for any positive SPT 8.3 (95% CI 2.3–30). Among those with long BF, the effect of FHA was weaker and significant only for any positive SPT. We concluded that the interaction between BF and FHA was significant and resulted in a more distinct effect of FHA on children with short BF, whereas long exclusive BF seemed partly to protect children from the allergy-promoting effect of heredity [6].

Wright et al. [7] followed 1,246 children with questionnaires to the age of 13 years. They found that exclusive BF for >4 months was associated with a higher incidence of asthma to age 13 years among those whose mothers had asthma. Among those with short BF asthmatic symptoms were reported by 23.5%, and among those with long BF by 45.9%. Exclusive BF for >4 months in children whose mothers had asthma resulted in a significantly increased odds ratio for asthma (OR 8.7; 95% CI 3.4–22). Maternal asthma in the absence of exclusive BF was associated with a borderline increase in risk (OR 2.1; 95% CI 0.9–5.1). Among those with paternal asthma, the length of BF did not have an effect on the incidence of asthma. Children were classified to atopics and non-atopics on the basis of SPT at age 6 years, the effect of long BF on the incidence of asthma was seen among atopic children.

In the same group, Wright et al. [8] found that total serum IgE levels at ages 6 and 11 years depended on the IgE levels of the mothers and the length of BF. Children of mothers with high IgE levels, those in the highest IgE tertile, who had been exclusively breastfed for 4 months or longer had significantly higher IgE levels at age 6 years than those who had never been breastfed; the difference persisted at age 11 years, but was not significant. In contrast, BF of
any duration among those children with mothers in the 2 lower IgE tertiles resulted in lower total IgE levels at ages 6 and 11 years. No data are given on the association of IgE levels and the clinical status of children in the study.

Sears et al. [9] compared 504 children with a total BF of >4 weeks with 533 children with BF of <4 weeks, born in 1972–1973 in New Zealand. Children were assessed at ages 9, 11, 13, 15 and 21 years and sensitization with several allergens was studied by SPT at 13 and 21 years. At age 13 years sensitization to cat, house dust mite, grass and *Alternaria* were significantly more frequent among those with BF than those without BF; at age 21 years the finding was the same. When they looked separately children with and without FHA; BF increased the odds ratios for sensitization to the same degree. Asthma was significantly more frequent at all ages and at the time of the study (age 26 years) among those with longer BF than among those with short BF. The result was the same when only those with airway hyper-responsiveness were compared: risk of having asthma with airway hyper-responsiveness was greater at ages 9, 11, 13, 15, and 21 years among those with BF for >4 weeks than among those with short BF. The effect of BF on asthma was not affected by FHA at 9 years or after. Those with a positive FHA were more often sensitized at 13 and 21 years and more often had asthma at 9 years. BF significantly increased the risk for both sensitization and asthma among the FHA positive and negative groups of the cohort [9].

In a cohort of 1,980 children from western Australia, the risk of childhood asthma increased if exclusive BF was stopped before 4 months (OR 1.28; 95% CI 1.01–1.82). Maternal asthma status did not modify the effect. No evidence of a formal interaction in the logistic regression was found between BF and maternal asthma status for the child's asthma at age 6 years [10].

Kull et al. [11] followed a cohort of 4,089 newborns to age 4 years for the role of BF on the development of asthma and other allergic diseases. They found that BF, both exclusive and partial, was protective against the development of asthma. The prevalence of asthma at the age of 4 years was 9.1% among children who had been exclusively breastfed for <4 months, and 6.4% among those breastfed for >4 months (OR 0.72; 95% CI 0.53–0.97). The effect tended to be stronger in children without FHA; among those without FHA exclusive BF for 4 months or more was associated with an OR of 0.58 (95% CI 0.38–0.88 ) for asthma relative to those with exclusive BF for <2 months. Among those with FHA, the same OR was 0.73 (95% CI 0.43–1.2). Kull et al. [11] also studied sensitization to airborne allergens by measuring specific IgE antibodies with a multi-allergen test; sensitization was present in 15%. BF did not have any effect on the rate of sensitization; OR for sensitization of children with long exclusive BF was 0.93 (95% CI 0.7–1.22).

Based on questionnaire, Miyake et al. [12] found that atopic eczema at age 12–15 years was associated with feeding in infancy. The prevalence of wheeze during past 12 months was 6.7%, that of rhinoconjunctivitis 23.9%, and atopic eczema 14.5%. BF in comparison to artificial feeding increased the incidence
of eczema significantly (OR 1.56; 95% CI 1.13–2.22). When children were divided according to FHA, only among those with a negative FHA did BF during first 3 months significantly increase the risk when compared to those fed artificially (OR 1.9; 95% CI 1.1–3.6). Among those with positive FHA the OR was 1.4 (95% CI 0.97–2.2).

According to telephone interviews, 1,770 of 15,430 full-term Danish infants (11.5%) had atopic dermatitis at age 18 months [13]. Exclusive BF for at least 4 months did not have an overall effect on the risk of atopic dermatitis occurring between ages 4 and 18 months, but the effect depended on the FHA. If neither parent had allergy, exclusive BF at 4 months of age increased the risk for atopic dermatitis (RR 1.3; 95% CI 1.1–1.6) appearing between ages 4 and 18 months; in contrast if the FHA was strong, both parents and a sibling had allergy, BF was protective (RR 0.7; 95% CI 0.5–1.0).

Among poor urban children in South Africa, Obihara et al. [14] found that long exclusive BF had a protective effect on the development of allergic diseases at age 6–14 years. Among 884 children, altogether 213 had symptoms of allergic diseases. BF protected from allergic symptoms if neither mother nor father had had allergic symptoms, An inverse linear association existed between the prevalence of allergic symptoms and the duration of BF in these groups and the association was significant for hay fever; for asthma or eczema the association was not significant. No association between allergic symptoms and length BF was found among those children with positive FHA [14].

Wegienka et al. [16] examined the prevalence and risk factors for sensitization to inhalant allergens at 6–7 years among 484 children. Children who were breastfed only, regardless of the length of BF, had higher risk (RR 1.5; 95% CI 1.1–2.1) of allergic sensitization than those fed formula only. The risk was greater for children with a mother reporting a history of allergy than for those with a mother without an allergic history, though the confidence intervals overlapped. The effect of infant feeding was effected also by the presence or absence of pets: among those with multiple pets in the household, an elevated risk was not found for any level of BF. Also the birth order modified the risk. Table 3 gives a summary of studies on the association of infant feeding and sensitization in children with and without FHA.

**Interaction between Early Infant Nutrition and Other Environmental Factors**

Among 7,766 children the prevalence of physician diagnosed asthma between ages 2 months and 6 years was 5.9% [17]. Children breastfed for >4 months regardless of exclusivity, were less likely to be diagnosed with asthma than those fed the shorter duration (hazard ratio 0.61; 95% CI 0.4–0.9). If the household had one or more smoker, the protective effect was striking: the hazard ratio among those breastfed exclusively compared to those never...
breastfed was 0.27 (95% CI 0.1–0.99). The authors speculate that BF may reduce the tobacco smoke-related asthma by interfering with the gene–environmental interaction [17].

Interaction between the effect of BF and the level of dichorodiphenyl dichloroethylene (DDE) was described in 338 children studied at age 7–8 years [18]. BF longer than 12 weeks was protective against asthma; OR 0.3 (95% CI 0.11–0.9) for ever having had asthma. The protective effect became stronger in children with a DDE blood level below the median value, and among those with higher values the protective effect was lost.

Immunologic Factors in Breast Milk and Development of Allergies

Several studies [5, 8, 10] have shown that maternal heredity is a stronger determinant for the development of allergy than paternal heredity. This has given rise to the assumption that BM properties account for this difference. Further, higher concentrations of IL-4, IL-8 and RANTES were found in milks from allergic than non-allergic mothers [19, 20]. The findings of the associations between immunologic factors in BM and the development of allergic symptoms in infants and children are presented in table 4. Findings on both total and antigen-specific IgA antibodies on the development of CM allergy are contradictory. Our recent study shows associations between low IgA CM-specific antibodies and the development of allergies by age 4 years [21].

TGFβs, both 1 and 2, are plentiful in BM. Associations between their levels and the development of allergic symptoms is again contradictory (table 4). TGFβ1 was lower in samples of mothers of infants with IgE-mediated CM allergy than in those from mother of infants with non-IgE-mediated CM

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**Table 3.** Summary of the effect of long vs. short breastfeeding on sensitization in children with or without a family history of allergy (FHA)

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<th>FHA positive</th>
<th>FHA negative</th>
<th>Study</th>
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<td>Pesonen et al. [5]</td>
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<td>Sears et al. [9]</td>
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<td>Wegienka et al. [16]</td>
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↓ = Significant decrease in sensitization in children who were breastfed long; ↑ = significant increase; ↔ = no significant change in sensitization.

*aOn total IgE level.*
allergy; the levels of controls were between the patient groups and did not differ significantly from either group [22]. Oddy et al. [23] found an inverse relationship between the dose of TGFβ1 infants received in the BM and the percentage of infants with wheezing during first years of life. Böttcher et al. [20] looked for a relation between allergic symptoms and sensitization at age 2 years and the BM content of IgA antibodies, several cytokines, including TGFβ1 and TGFβ2, as well as some chemokines, but found no significant associations. We also did not find any difference between the levels of TGFβ1 or TGFβ2 in colostrum samples of mothers of infants who at age 4 years either had allergic symptoms, were sensitized to common allergens or both, compared to those of mothers of non-allergic children [21]. Soluble CD14, a co-receptor with a Toll-like receptor-4, is also plentiful in BM and colostrum. Its low concentration is associated with the development of eczema by age 6 months [24]. Rothenbacher et al. [25] found an interaction between the length

<table>
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<tr>
<th>Breast milk component</th>
<th>Observed effect</th>
<th>No effect</th>
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<tr>
<td>Total IgA</td>
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<td>Appearance of cow’s milk allergy [22]</td>
</tr>
<tr>
<td>Specific IgA antibodies</td>
<td>Low Symptoms suggestive of cow’s milk allergy [28]</td>
<td>Appearance of cow’s milk allergy [22]</td>
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<td></td>
<td>Development of cow’s milk allergy [27]</td>
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<td></td>
<td>Sensitization and allergic symptoms at age 4 [21]</td>
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<tr>
<td>TGFβ1</td>
<td>Low Development of IgE-mediated cow’s milk allergy [22]</td>
<td>Allergic symptoms and sensitization at age 2 [20]</td>
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<td></td>
<td>More frequent wheezing during 1 year [23]</td>
<td>Allergic symptoms or sensitization at age 4 [21]</td>
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<td>TGFβ2</td>
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<td></td>
<td>Asthma by age 2 among long BF and mothers without atopy [25]</td>
<td>Allergic symptoms and sensitization at age 4 [21]</td>
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<td>Verified atopy at age 4 [21]</td>
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Table 4. Immunologic properties of breast milk and the development of allergies
of BF, a maternal history of atopic disease, and concentrations of soluble CD14 in BM at 6 weeks postpartum and the cumulative incidence of asthma at age 2 years. Among mothers without atopic diseases, a significant negative trend ($p = 0.02$) existed between the length of BF and the cumulative incidence of asthma by age 2 years. In this group those with mothers with soluble CD14 concentrations below the median tended to have a higher incidence of asthma (21.6%) than those with a higher content (14%; $p = 0.07$). Rothenbacher et al. [25] concluded that the protective effect of BF seems to be synergistic with soluble CD14 concentrations in BM. We also found that children without atopy at age 4 years who had long BF received BM with a significantly higher soluble CD14 concentration than children with allergic symptoms and sensitization (fig. 1) [21].

**Conclusions**

Upon examination, the results of the original studies cited do not allow any straightforward conclusions. My idea was that within a single study definitions for BF, for heredity as well as allergic symptoms and sensitization are the same, and the interaction between the factors should not depend on the variability of definitions, ways of diagnosing the diseases and sensitization. If any interaction exists, such studies might be the answer. The cited studies show all types of combinations on the interaction: long vs. short BF being either beneficial, having no effect or being detrimental for the development of allergies or sensitization when combined with the knowledge of parental heredity for allergy. None of the possible 9 combinations is found in more
than 2 studies. Complexities of genetic and environmental interactions, together with epigenetic influences, make one think that it is not possible that such a simplified association would exist and as such the above analysis is valid. Further, the content of immunologically active substances in BM varies widely. They again have an independent influence on the development of a child’s allergies. Analysis concerning infant nutrition as an environmental factor interacting with the genes needs to be much more focused than the studies published so far. Both the nutrition parameters and the disease endpoints need to be carefully defined, and great care should be taken to have in all other aspects a similar environment for the study population to allow analysis of an interaction with genetic factors.

References

Discussion

Dr. Nassar: We did similar work in Egypt and found that maternal diet is the most determinant factor in early infant sensitization since the mothers who received cow's milk were the ones who had sensitized children regardless of the family history of allergy [1]. In your study and in the other studies you mentioned, was maternal nutrition taken into consideration as a risk factor for early sensitization?

Dr. Savilahti: There are several Swedish studies looking at this question of eliminating certain factors from the mother's diet. I think that Dr. Björkstén may be better able to comment on these studies which did not find any effect when eliminating at least certain factors from the mother's diet. I don't have any personal experience on this matter but the general opinion is that it doesn't have an effect on the development of allergy.

Dr. Björkstén: Could I comment on that since we studied this in Sweden. Elimination of all fish, egg and milk products from the maternal diet during the last trimester of pregnancy had no protective effect. In contrast, there were 5 of about 200 children who still retained their clinically relevant cow's milk allergy at the age of 5 years. As fetuses all these 5 children had been subject to the maternal avoidance diet and not been exposed to milk. In another study we actually looked at the same elimination diet but starting after birth and continuing through the first 3 months of lactation. Babies in the avoidance diet group were not sensitized at 3 months, but when milk was then introduced the first positive skin prick test appeared within 2 weeks and there was no maternal effect on the clinical outcome with time. So we concluded that it is clearly not worthwhile to manipulate the diet either during pregnancy or lactation.

Dr. Prescott: I agree that there is certainly no doubt about the benefits of breastfeeding but it seems, as Dr. Björkstén pointed out, that there is increasing controversy
over whether this should be exclusive and when solids should be introduced. Certainly based on animal studies there is a growing school of thought that in fact earlier and regular exposure to allergens may actually be protective as this may promote tolerance and prevent sensitization. The fact that we have been recommending avoidance and delayed feeding for many years may actually be doing our patients a disservice. Would you care to comment on that?

Dr. Savilahti: I quite agree that it might be the right direction. Breastfeeding is good and the best nutrition for the newborn but I don't think that allergy as such should be used as an argument to promote breastfeeding because, as you said, we don't actually know how it should be done, whether certain nutrients should be introduced earlier and at what age. There is a lot of work to be done before we will know this.

Dr. Walker: My question is similar to what Dr. Prescott asked. Have you compared infants exposed to formula versus breast milk as opposed to hydrolysate? How would it stand up if you compared hydrolyzed formula in allergy-prone infants initially versus breastfeeding?

Dr. Savilahti: Yes, many intervention studies have been done and work on much the same level, as has been summarized for instance in the review by Zeiger et al. [2]. It is an effective intervention but I don't think it could be used on a population basis, only in selective cases. But again, we don't really know what happens in the long run in those children who have been on the hydrolyzed formula because, as Dr. Prescott pointed out, we also need stimulation of the immune system by foreign antigens, which might be important for the development and balance of the immune system. There are so many unknown questions, and there may be some danger if we eliminate everything for a very long time from the intestine, we don't really know what happens, and that is the difficulty.

Dr. Koletzko: A comment in response to the point that Dr. Prescott raised: I could not agree more with your conclusion. The Committee of Nutrition of ESPGAN has recently reviewed the evidence on complementary feeding, time of introduction and choice of products, and has written a comment which is to be published in the Journal of Pediatric Gastroenterology and Nutrition. It is looking not only at allergy but also many other aspects, also considering the data available on allergy. The conclusion was that the interaction of complementary feeding in the European setting, where there is little risk of infections from early introduction, should occur between 17 and 26 weeks and not only from the first day of the 7th month onward. With respect to your review of these numerous data in which you point out that apparently there is an effect of family history and genetics, even though it is difficult to interpret exactly, the question is what information is available on infection as a confounder? Obviously we are all impressed by the hygiene hypothesis identifying early infections and the exposure to infectious agents as a strong predictor of later allergy risk. There are numerous data showing that breastfeeding reduces the risk particularly of gastrointestinal infections. The recent reviews of WHO, the Dutch State Institute of Population Health and the US Agency of Healthcare and Quality have shown a very strong reduction in diarrhea with breastfeeding, but it is not the same in all populations. Is there any information to identify to which extent that might be a relevant interaction for allergy?

Dr. Savilahti: There are very extensive data available on that question. I am not an expert, but certainly infections cannot be taken as one entity. There are several specific infections which increase the rate of allergies, some are viral infections, and then there are some viral infections which are associated with a decreased prevalence of allergies. This is a very complicated question and I am not really an expert, but certainly it is an important cofactor, probably more important than feeding itself.
Dr. Koletzko: Couldn’t one assume that this interaction would be different in various populations? For instance in a country like Finland where the risk of early infection is rather low, one might assume that the interaction between breastfeeding, infection and allergy is different than in a country where infection reduction by breastfeeding is very strong?

Dr. Savilahti: Yes, you are quite right; it is really what I was trying to look at in these papers, but it is usually not taken as a confounding factor in the studies. This neglect is one reason why these studies are so conflicting; so much data and knowledge are missing on the other environmental factors which might be important in this development. I am saying that diet per se is not important, but it might be associated with some factors that haven’t been described in these studies.

Dr. Björkstén: We heard yesterday that the gut flora is not that different between breastfed babies and babies fed a modern formula. As some of you might remember, in the 1950s and 1960s when the first-born infants received formula, their stools looked and smelled like adult feces. This may explain why we do not see any differences in allergy development between breastfed babies and infants fed a modern formula. You have a point regarding the gut microbiota in that way. On the other hand, I question that respiratory infections could play any significant role in this context because they do cause wheezing and they do not affect allergy atopy or sensitization. I suggest that one should look along your lines, but rather at the gut microbiota.

Dr. Strandvik: It is perhaps a little dangerous for me to disagree with two authorities like Dr. Savilahti and Dr. Björkstén, but I am very surprised that they say that the diet has no influence. I am sure it has, but we have not yet studied all the components which could be of importance. Is there a difference in parity; is allergy more common in siblings or in the first child? Has anyone looked at that?

Dr. Savilahti: To answer your first question it was actually the basis for the hygiene hypothesis by Strachan [3] in 1989. In one of the first studies, he found that allergies were more common in older siblings, in the first child. Dr. Björkstén has published data on that.

Dr. Strandvik: One very important thing is that we haven’t looked at the ratio of the essential fatty acids in breast milk and it varies a lot, and with time. In long-term breastfeeding, the ratio between n-6 and n-3 changes remarkably in the infants [4]. We have also done studies in rats [5, 6] showing that both the amount of essential fatty acids in the rat mothers’ diet and the ratio between n-6 and n-3 have a profound influence on the development of oral tolerance and also the development of IgE antibodies in the pups. So I would say that when we study the diet and say how much fish we eat, we don’t take into consideration how much vegetable oil is ingested at the same time, because this ratio is probably more important for the immunological system, i.e. whether it will have Th1 or Th2 dominance. Please don’t say that this has no influence. We need to study the relation between the fatty acid content of the mothers’ breast milk and the development of allergy before we can say this.

Dr. Björkstén: We have shown that a low n-3 to n-6 ratio in colostrum and early milk is associated with an increased risk of allergy in children. The same person who did these studies in my laboratory is now doing a placebo-controlled intervention study with PUFA. The data are not available yet but the 6-month data are extremely encouraging.

Dr. Venter: Some of the children in your study were exclusively breastfed for longer than 9 months. How did you define exclusive breastfeeding?

Dr. Savilahti: They were allowed to have water and vitamin D supplementation. There were also some infants who had extended exclusive breastfeeding up to 12 months of age.

Dr. Venter: Does that actually mean that there were some infants who had no solids introduced into their diets up to the age of 12 months, or was that breastfeeding plus solid food?
Dr. Savilahti: No, only breastfeeding.

Dr. Lönnерdal: I am not an expert on allergy but I would like to share an observation with you because I think that breastfed groups may not be as homogenous as many believe. We did a study a few years ago which unfortunately has not yet been published. For those of you in the allergy field I am sure you remember the publications on cow’s milk proteins appearing in breast milk. We followed up on those observations and developed sensitive assays for bovine β-lactoglobulin and bovine α-casein. We followed 30 women and looked at the penetrance of the cow’s milk antigens into the breast milk. There were ‘penetrators’ or ‘non-penetrators’, and there was no correlation between the two proteins. Of these 30 women, 15 had the cow’s milk antigens in their breast milk, and 15 had not. When we put the women with antigens in their milk on a cow’s milk elimination diet, the concentrations of antigens went down but the rate of that varied a lot individually. As a biochemist and biologist, I have a hard time understanding how these antigens penetrate into the breast milk but there was no doubt that cow’s milk proteins were in the breast milk of some women but not all and, depending on the exclusively breastfed population, some breastfed infants may be exposed to cow’s milk proteins which may be a confounder in the interpretation of the results.

Dr. Savilahti: Certainly it is a well-known phenomenon that breast milk contains these antigens and it is probably also very important for the development of the response to food antigens that they are there because they are complexed IgA antibodies. It may be that nature has thought that they should be in connection with the mother’s breast milk antibodies. This is a phenomenon which we probably see for all antigens. More recently there has been much data importantly showing that these food antigens might penetrate the skin or may be inhaled. There are many ways in which infants can probably come in contact with these foreign antigens; not only the food eaten. But I think that in breast milk they are meant to be there for the development of the immune response of the infants.

Dr. Björkstén: Breast milk was designed by evolution for very particular reasons. Allergy and diabetes were not among those. Mothers are extremely prone to guilt feelings. If the child develops an allergy, the mother will blame herself for not having breastfed or for not doing it long enough. We have an obligation to be very careful with advice that would add to those guilt feelings. The fact is that breastfeeding does not prevent allergy, although it modestly reduces infant wheezing.

Dr. Salminen: I couldn’t agree more with your statement on the fat side because it is also very important to look at the microbiota in early colonization. The mother’s breast milk fatty acid composition has a profound effect on what kind of microbes actually enter and adhere to the newborn intestine and you see very quickly that the diet is reflected in the breast milk fatty acid composition. I think it is one of the important factors that has been neglected.

Dr. Adlerberth: I would like to come back to the role of the intestinal flora and I want to point out that, although the differences in the intestinal microbiota between breastfed and bottle-fed infants are not so big today, there is a tremendous difference with regard to how these bacteria are encountered by breastfed and bottle-fed infants. If an infant is breastfed, it will have enormous amounts of secretory IgA present in the gut which will prevent bacteria from translocating over the epithelium and coming in contact with the immune system. That is a main function of breast milk, to protect the infant from microbes, and breastfeeding efficiently protects from septicemia and other infections. However, according to the hygiene hypothesis, microbial stimulation might protect from allergy, and then breastfeeding could actually be a risk factor for allergy as it prevents translocation of intestinal bacteria. At the same time breast milk contain numerous factors which could possibly influence maturation of the immune system and in that way breastfeeding could be protective.
Dr. Savilahti: I quite agree that it is really important for the defense against these pathogens in the intestine, that is the main function of these protective factors, it is not against allergy.

Dr. Björkstén: As one of the few allergy-trained people here, there are two things that our fellow allergists may be saying. One is that sensitization is a risk factor because when there is an immune response then tolerance is induced. A positive prick test in early infancy is only showing an immune response, and from that point, avoidance is not always necessary.

References