Prevention of Atopy and Allergic Disease: Type of Infant Formula

Hugh A. Sampson

Pediatric Allergy and Immunology, Elliot and Roslyn Jaffe Food Allergy Institute, Mount Sinai School of Medicine, New York, N.Y., USA

Introduction

The prevalence of allergy and atopic disorders has been increasing over the past several decades [1] and consequently investigators have sought to understand the reason for this increase and to develop strategies to reverse this trend. A great deal of attention has been focused on early intervention since most children afflicted with atopic disorders first develop symptoms during infancy and subsequently develop other atopic symptoms, i.e. the ‘atopic march’ [2]. About 70 years ago an article was published suggesting that breastfeeding could prevent eczema [3], and since then many studies have both supported and refuted this claim. Unfortunately, as discussed elsewhere in this symposium, most of these studies have serious methodological flaws making the arrival at firm conclusions impossible. Nevertheless, two recent meta-analyses of studies published between 1966 and 2000 indicate that exclusive breastfeeding in the first 4 months of life can reduce the prevalence of atopic dermatitis (AD) [4] and asthma [5] in children at risk of developing atopy, i.e. offspring of atopic parents. Given that not all women can or will breastfeed, alternative infant formulas also have been evaluated for their protective effect. On the basis of a retrospective study over 50 years ago [6], it has been suggested that soy-based formulas provide protection against allergic disease compared to milk-based formulas. However, a recent meta-analysis of studies done since the 1960s clearly demonstrated that soy- and milk-based formulas are no different in their ability to prevent food allergy or atopic disorders [7].
The first extensively hydrolyzed milk-based formula (Nutramigen®) was developed over 60 years ago for use in infants with cow’s milk allergy or intolerance. Since then a number of extensively and partially hydrolyzed infant formulas, and more recently amino acid-based formulas, have become available (Table 1). These extensively hydrolyzed formulas became known as ‘hypoallergenic’ since most infants and young children with cow’s milk allergy could tolerate these formulas without apparent symptoms. However, since the term ‘hypoallergenic’ was never clearly defined and in essence simply means ‘less allergenic’, a partially hydrolyzed formula was introduced in the United States in the late 1980s and was labeled ‘hypoallergenic’ (Goodstart HA®), which led to confusion among consumers and resulted in a number of severe reactions in cow’s milk-allergic infants [8]. Consequently the Committee on Nutrition of the American Academy of Pediatrics established a subcommittee which was asked to develop criteria for the labeling of infant formula as ‘hypoallergenic’ [9]. The subcommittee recommended that in order to label a formula ‘hypoallergenic for the treatment of cow’s milk-allergic infants’, the formula must fulfill a series of pre-clinical and clinical requirements, including the use of double-blind placebo-controlled oral food

Table 1. Hydrolyzed protein- and amino acid-based infant formulas

| ‘Non-allergenic’ infant formulas – amino acid-derived | Neocate, Neocate 1\textsuperscript{a,b} | EleCare\textsuperscript{a} | Nutri-Junior |
| Extensively hydrolyzed bovine casein-based formulas | Nutramigen\textsuperscript{a} | Pregestimil\textsuperscript{a} | Alimentum\textsuperscript{a} |
| Extensively hydrolyzed bovine whey-based formulas | Alfa-Re | Profylac\textsuperscript{b} | Pepti-Junior | Nutrion Pepti | Peptidi-Tutteli |
| Partially hydrolyzed whey-based formula | Nan HA/Bebe HA/Good Start/Nidina HA |
| Extensively hydrolyzed soy-based formula | Pregomin |

\textsuperscript{a}Available in the United States and fulfill the AAP ‘hypoallergenic for treatment’ criteria.

\textsuperscript{b}Not available in the United States but fulfills the AAP ‘hypoallergenic for treatment’ criteria.
challenges and subsequent open feeding for at least 7 days to demonstrate (with ≥95% confidence) that at least 90% of cow’s milk-allergic children could ingest the formula without developing allergic symptoms. In addition, the subcommittee recommended criteria for labeling a formula ‘hypoallergenic for the prevention of allergic disorders’. Prospective clinical trials were necessary to demonstrate that significantly fewer children at risk of allergy (based on family history), and given the study formula exclusively for at least the first 6 months of life, would experience significantly fewer allergic symptoms at 18 months or later compared to similar infants receiving a standard cow’s milk formula. If any allergic symptoms were reported due to either formula, they had to be confirmed by blinded oral food challenge. These recommendations were accepted by the American Academy of Pediatrics and reaffirmed more recently in an Academy position statement [10]. While several extensively hydrolyzed and amino acid-based formulas have fulfilled the American Academy of Pediatrics’ criteria ‘hypoallergenic for treatment’ of IgE-mediated cow’s milk allergy [11–13], no formula has been established as ‘hypoallergenic for prevention’.

Hydrolyzed Formulas for the Prevention of Atopic Disease and Allergy

The rationale for utilizing extensively hydrolyzed infant formulas for the prevention of milk allergy and atopic disease is based on the fact that these formulas are hypoimmunogenic as demonstrated in animal models as well as man, hypoallergenic for the treatment of milk allergy, and contain levels of milk proteins (β-lactoglobulin) [14] comparable to what is found in human breast milk. In the past 3 decades, at least 90 studies have been published comparing the utility of ‘hypoallergenic’ infant formulas to standard infant formulas for the prevention of allergy and atopic disease. However, as indicated in a recent meta-analysis [15], only 18 of these studies had <80% dropouts and fulfilled the Cochrane Neonatal Review Groups criteria for inclusion [16–33]. Studies were excluded from the analysis primarily because they had greater than a 20% dropout rate and/or lacked adequate randomization and allocation concealment, blinding of parents or caretakers and assessors to the intervention, and completeness of assessment in all randomized study subjects. In this review, a number of subgroup analyses were performed comparing the types of milk used in the control group, the length of supplementary feeding, the presence of co-interventions, the type of subject enrolled (high vs. low risk for atopic disease), the type of hydrolyzed formula used, and whether clinical allergy was confirmed by allergy testing. Primarily for ethical reasons, no randomized study has been conducted comparing the prolonged use of hydrolyzed infant formula to exclusive breastfeeding. Two studies evaluated short-term supplemental feeding (3 and
4 days) with extensively hydrolyzed formula and donor breast milk and found no difference between the two regimens [22, 27]. In addition, short-term feeding of hydrolyzed and standardized formulas followed by breastfeeding were compared and no significant differences were found. No study has compared the allergy-preventative effect of prolonged feedings with hydrolyzed formulas to standard infant formulas in children at low atopic risk. In the Cochrane Report [15], 12 studies compared prolonged hydrolyzed formula feeding to standard cow’s milk formula, but only seven of these studies did not incorporate other preventative interventions. Meta-analysis of seven studies, five of which included other interventions, found a significant reduction in ‘any allergic manifestations’ in infancy, and in 3 studies that evaluated a total of 333 children for a more prolonged period of time, a significant reduction in childhood allergy was also reported in infants who had received hydrolyzed formulas. Nine studies evaluated the development of AD in a total of 870 infants. Meta-analysis of these 9 studies revealed a significant reduction in AD during infancy in the infants receiving hydrolyzed formula (RR = 0.59; 95% CI = 0.40, 0.86). Similar findings were reported for 2 studies following a total of 198 children through early childhood [16, 24], and one study following 135 children through 5 years of age [19]. Six studies evaluated the incidence of asthma and meta-analysis of the six studies incorporating 945 infants found a significant reduction in asthma in those receiving the hydrolyzed formula (RR = 0.59; 95% CI = 0.40, 0.86). When meta-analyses were performed on the seven studies incorporating no co-interventions, infants receiving hydrolyzed formulas had reduced allergic symptoms (RR = 0.63; 95% CI = 0.47, 0.85) and AD (RR = 0.48; 95% CI = 0.34, 0.66) in infancy compared to infants receiving standard infant formulas. However, no difference was seen in the incidence of wheezing or asthma.

In the Cochrane Report [15], seven studies were analyzed that compared prolonged feeding of partially hydrolyzed formulas to standard cow’s milk formulas with no other preventative measures. Six of these seven studies were supported by industry. Meta-analysis of four studies containing 386 high-risk infants found a significant reduction in allergic manifestations in infancy (RR = 0.63; 95% CI = 0.47, 0.85) and meta-analysis of three studies with a total of 230 infants found a significant reduction in eczema in infancy (RR = 0.64; 95% CI = 0.42, 0.98). No significant difference in asthma symptoms in infancy was noted. Three studies compared the supplemental use of extensively hydrolyzed versus partially hydrolyzed formula in infants at high risk of atopic disease. Meta-analyses failed to demonstrate any significant difference in food allergy, any allergic manifestations, eczema or asthma between the two groups. One study compared the prophylactic effect of prolonged feeding with hydrolyzed soy formula to standard infant formula in high-risk infants, although other preventative interventions were employed [16]. While the authors found a significant difference in the incidence of infant (RR = 0.50; 95% CI = 0.32, 0.79) and childhood allergy (RR = 0.60;
95% CI = 0.39, 0.92), there was no significant difference in the incidence of infant or childhood eczema, asthma, rhinitis or food allergy.

Overall the authors of the Cochrane Report on the use of hydrolyzed formulas for the prevention of allergy [15] concluded that there is no evidence to support the use of hydrolyzed infant formulas in place of exclusive breastfeeding in the prevention of allergic disease. However, in infants who are unable to receive exclusive breastfeeding for at least the first 4 months of life, use of hydrolyzed formulas can reduce the incidence of allergy, especially atopic eczema, through the first 5 years of life, but further studies are necessary to determine whether the benefit persists beyond this age. While the use of meta-analysis provides a powerful tool to assess the validity of clinical trials addressing a similar medical question, its outcomes remain subject to a number of limitations including publication bias, inconsistent quality of trial design, and potential inconsistency of study conduct.

In the late 1990s, a government-sponsored multicenter study was initiated in Germany to compare the efficacy of three hydrolyzed infant formulas to standard cow's milk formula in the prevention of milk allergy and atopic disorders [34]. Between 1995 and 1998, 2,252 infants at high risk of developing atopic disease were enrolled in a multicenter, prospective, randomized, double-blind interventional trial to compare the efficacy of three different hydrolyzed infant formulas to standard cow's milk formula for the prevention of milk allergy and atopic disorders (German Infant Nutritional Intervention Study – GINI Study). To be included in the study, infants had to be healthy, ≥2.5 kg at birth, ≥ than 37 weeks gestation and born to a family with at least one atopic family member (mother, father, and/or sibling). At the time of enrollment, infants were randomized to one of four study formulas, standard cow's milk-based formula (CMF; Nutrilon Premium®, Nutricia/Numico), partially hydrolyzed whey formula (p-HWF; Beba HA®, Nestlé), extensively hydrolyzed whey formula (e-HWF; Hipp HA®, Hipp/NutrilonPepti®, Nutricia/Numico) or extensively hydrolyzed casein formula (e-HCF; Nutramigen®, Mead Johnson), and stratified by an independent person for single or double parental history of atopy and region. All mothers were encouraged to breastfeed exclusively for at least 4 months, and preferably 6 months. However, if this was not possible, supplementation or exclusive use of the study formula was initiated and continued through the first 6 months of life. Solid foods were excluded for the first 6 months of life and then added in a standardized fashion. Parents were asked to record the type of feeding (breast milk or study formula), the time of first introduction of study drug, kind of solid foods introduced, health problems, and any ‘allergic manifestation,’ e.g. AD, allergic urticaria, food allergy with manifestation in the gastrointestinal tract, or asthma.

A total of 1,249 infants received study formula and, as shown in table 2, similar numbers of infants received each of the study formulas. A total of 304 infants dropped out or were excluded, so 945 of 1,249 (76%) infants receiving formula were evaluable at 12 months. Of note, significantly more infants
dropped out or had to be excluded for ‘non-compliance’ from the e-HCF group (18%) than from the other study formula groups (10–12%). At the 1-year evaluation, the incidence of ‘allergic manifestations’ in each group was the following: CMF = 16%; p-HWF = 11%; e-HWF = 14%; e-HCF = 9%, and BF = 11%. Only infants fed the e-HCF had significantly less ‘allergic manifestations’ at 1 year compared to infants receiving the standard milk formula (adjusted for AD in family history, sex, and maternal smoking (adj) OR = 0.51 (0.28–0.92)). The incidence of ‘AD’ in each group was the following: CMF = 15%; p-HWF = 9%; e-HWF = 13%; e-HCF = 7%, and BF = 9.5%. Infants fed the e-HCF and p-HWF had significantly less ‘AD’ at 1 year compared to infants receiving the standard milk formula (adj OR = 0.42 (0.22–0.79) and adj OR = 0.56 (0.32–0.99), respectively) [34]. The cumulative incidence of ‘allergic manifestations’ at 3-year follow-up was the following: CMF = 31.4%; p-HWF = 25.8%; e-HWF = 32.2%, and e-HCF = 26.5%. There was no significant reduction in ‘allergic manifestations’ in infants receiving hydrolyzed formula compared to standard milk formula. As depicted in table 3, the cumulative incidence of AD at 3 years was the following: CMF = 22.5%; p-HWF = 14.9%; e-HWF = 20.9%; e-HCF = 14.0%, and BF = 19.2%. Only infants receiving p-HWF or e-HCF had significantly less AD over the 3-year period and at the 3rd year evaluation, i.e. period prevalence. No difference in the incidence of asthma was noted during the first 3 years of evaluation. Interestingly, the p-HWF appeared to be more protective for AD in infants who came from families without a history of AD while e-HCF appeared more protective for infants from families with a history of AD. Since the BF infants were not randomized to treatment and therefore represent an observational cohort, their incidence of atopic disorders cannot accurately be compared to that of the formula-fed groups.

**Recommendations**

A number of other large prospective studies not fulfilling the Cochrane Report inclusion criteria for evaluation of hydrolyzed formulas also suggest a
The protective effect of e-HCF for the prevention of AD in infants up to the 4th year of life [35–38]. While the ideal study to evaluate the protective effects of hydrolyzed formulas is yet to be performed (i.e. a randomized trial comparing exclusive breastfeeding to exclusive use of hydrolyzed infant formula for at least the first 4 months of life, and therefore a trial that is very unlikely to be performed for ethical reasons), the weight of the evidence appears to support a number of conclusions. First, there is no evidence to support the use of any hydrolyzed infant formula over exclusive breastfeeding for the prevention of atopic disorders. At this time there is no evidence that breastfeeding beyond 4–6 months provides further benefit with respect to prevention of atopic disease. Second, if exclusive breastfeeding is not possible, infants from ‘high-risk’ families, i.e. those with one or two parents and/or a sibling with food allergy, AD, asthma or allergic rhinitis, should be given a p-HWF or e-HCF for the first 6 months of life. Evidence from one large, prospective multicenter trial (GINI Study) suggests that infants from atopic families without a history of AD in a primary relative will receive the protective effect from the less expensive partial whey hydrolysate formula whereas those infants

### Table 3. Cumulative incidence and period prevalence of AD and asthma in the first 3 years according to study formula and adjusted odds ratios (OR)* in comparison to cow’s milk feeding (assigned OR = 1)

<table>
<thead>
<tr>
<th></th>
<th>CMF (n = 245)</th>
<th>p-HWF (n = 229)</th>
<th>e-HWF (n = 230)</th>
<th>e-HCF (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cumulative incidence of AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in the 1st 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No AD in FH</td>
<td>32/158</td>
<td>1</td>
<td>0.45 (0.24–0.87)</td>
<td>0.60 (0.37–0.97)</td>
</tr>
<tr>
<td>AD in FA</td>
<td>23/87</td>
<td>1</td>
<td>0.88 (0.43–1.81)</td>
<td>0.34–1.18</td>
</tr>
<tr>
<td>Contribution to incidence in 2nd and 3rd years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>17 (6.9%)</td>
<td>1</td>
<td>15 (6.6%)</td>
<td>17 (7.4%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.95 (0.46–2.0)</td>
<td>1.1</td>
<td>1.0 (0.52–2.1)</td>
<td>1.1 (0.53–2.2)</td>
</tr>
<tr>
<td><strong>Contribution to incidence in the 1st year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>38 (15.5%)</td>
<td>1</td>
<td>19 (8.3%)</td>
<td>31 (13.5%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.49 (0.27–0.88)</td>
<td>0.81 (0.48–1.4)</td>
<td>0.33 (0.17–0.66)</td>
<td></td>
</tr>
<tr>
<td><strong>Period prevalence of AD in 2nd year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>27 (11.0%)</td>
<td>1</td>
<td>16 (7.0%)</td>
<td>24 (10.4%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.62 (0.32–1.2)</td>
<td>0.88 (0.49–1.69)</td>
<td>0.44 (0.21–0.91)</td>
<td></td>
</tr>
<tr>
<td><strong>Period prevalence of AD in 3rd year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>29 (11.8%)</td>
<td>1</td>
<td>13 (5.7%)</td>
<td>20 (8.7%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.46 (0.23–0.90)</td>
<td>0.68 (0.37–1.2)</td>
<td>0.46 (0.23–0.93)</td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative incidence of asthma in 3rd year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>25 (10.2%)</td>
<td>1</td>
<td>28 (12.2%)</td>
<td>29 (12.6%)</td>
</tr>
<tr>
<td>Crude OR (95% CI)</td>
<td>1.2 (0.69–2.2)</td>
<td>1.3 (0.72–2.2)</td>
<td>0.92 (0.49–1.7)</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for gender, maternal smoking in the first year, family history of AD.
Adapted from von Berg et al. for the GINI Study Group, with permission.
Significant effects are underlined.
who have first-degree relatives with AD should receive the e-HCF. Third, while some studies suggest that the use of hydrolyzed infant formulas in high-risk infants also may prevent the development of allergic rhinitis or asthma [19, 29, 33], there are insufficient data at this time to demonstrate any prophylactic benefit. Finally, there are no data to demonstrate that the use of hydrolyzed formulas in the first 4–6 months of life will prevent atopic disease in infants from low-risk families. Given that the majority of children diagnosed with atopic disease come from ‘low-risk’ families, it may be beneficial to evaluate the effect of partial hydrolysate formulas, which are palatable and no more expensive than standard cow’s milk infant formulas (in the US), for their potential prophylactic effect on the development of atopy in this population.

References


19 Chandra R: Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. J Pediatr Gastroenterol Nutr 1997;24:380–388.


37 Host A, Halken S: Hypoallergenic formulas – when, to whom and how long: after more than 15 years we know the right indication! Allergy 2004;59:45–52.

Discussion

Dr. Chad: As you all know soy and peanut are both in the legume families and to a certain degree do share some antigens. I was wondering if early use of soy formula can actually be a sensitizer for the development of peanut allergy later on? In other words is that the hidden exposure we are looking for in some of these children?

Dr. Sampson: That is a very good question. Certainly the study published by Lack et al. [1] in the New England Journal of Medicine a couple of years ago looked at the utilization of soy formula in those infants who did develop peanut allergy and found a correlation between soy formula ingestion and the development of peanut allergy. I think the problem that we have again, it being an observational study, is possible sampling bias. We know that if you have a child who develops milk allergy or is suspected of having milk allergy, one of the first formulas these infants go onto is going to be a soy-based formula. The other thing we know is that if you look at an infant who has cow's milk allergy and also has atopic dermatitis, which many of them do, a higher rate of those children will go on to develop peanut allergy and that may be as high as 25%. So I am not sure whether the association that Lack et al. saw in their study was more related to the fact that these are children who are at high risk of developing food allergy and were given soy. Also, it is not clear how long these infants received soy, so whether or not it would really have a particularly sensitizing effect is not known. On the other hand, when we look at the actual allergenic epitope recognition, or where the IgE binds the peanut compared to where IgE binds the soy, the places where children who are peanut-allergic generate IgE antibody to epitopes that are in areas which are different than those on the soy protein. In other words, the areas that are non-homologous or non-identical are the areas that seem to distinguish those children who develop peanut allergy from those who develop soy allergy, and we know that about 90% of peanut-allergic children eat soy without any problem. Whether or not there still could be some potential T-cell cross-reactivity and T-cell promotion, we don't know, but my feeling is that we don't have the evidence to say that the ingestion of soy promotes the development of peanut allergy at this point.

Dr. Kerner: I have a couple of clarifications and questions and these relate to the pediatricians who are attempting to get family history for allergy. The first question is if you have a history, I mean you define very clearly what atopic history should be, but if you have a history for example of an allergic colitis which is supposed to be a non-IgE-mediated reaction, would you classify that as an allergic; is that part of the family history of allergy or not?

Dr. Sampson: No, I would not classify that as atopic. Most of the studies that have been done, especially those that have evaluated hydrolyzed formulas, such as the GINI study, would not consider that as an atopy.

Dr. Kerner: Because when a history of bleeding is found in allergic colitis some pediatricians may think that. This may be more controversial, when families are screened and an allergic reaction to a drug is found, should that be considered as part of the family history of allergy?

Dr. Sampson: No, I would not consider that either.

Dr. Cohen: As a pediatrician I was wondering if there is a potential future rapid diagnostic test in the newborn period, other than cord blood IgE, that might help us identify those children that might be predisposed to atopy?

Dr. Sampson: I am sure we would all like to develop one but right now I am not aware of any. At the moment, family history is still our best indicator of those at high risk. But as I said, we are still going to miss at least half of the children that develop atopic disease because that history is not going to be present.

Dr. Bowen: Given that no difference has yet been shown in the outcome of rhinitis or asthma, is there any reason to suspect we shouldn't wait for the development of
atopic dermatitis first and then switch to a fully hydrolyzed formula? Would that have any different outcome from fully hydrolyzed from day 1?

**Dr. Sampson:** Number one, I don’t know the answer to that because I am not aware of anybody who has looked at that question. I think the biggest problem though is that we don’t have long enough observation studies to really make any comment on what the effect is on allergic rhinitis or asthma. If we are in some way altering the atopic predisposition, which is demonstrated by a decrease in atopic dermatitis early on, there is a potential that it may have some beneficial effect, but at this point in time, I don’t think anybody has really adequately followed these patients long enough to be able to tell us that.

**Dr. Moukarzel:** Can you speculate on why hydrolyzed casein will not work but hydrolyzed whey protein will work? Is it because the hydrolyzation process is different?

**Dr. Sampson:** It is actually the other way around. It was the extensively hydrolyzed whey formula that didn’t work whereas the extensively hydrolyzed casein did. One of the things that I think we have to be aware of is that there are significant differences in the outcome of different hydrolysate processes. We have evaluated a number of hydrolyzed formulas for use in the treatment of children who have cow’s milk allergy, and I was quite surprised by the number that didn’t work, i.e., were not hypoallergenic. Yet when you looked at their preclinical profile, they actually looked to be comparable to what we saw in Nutramigen and Alimentum. I think the difference reflects where exactly these breaks in the protein took place relative to the relevant epitopes that account for the generation of sensitization or to reactivity. So all hydrolysates are not going to be comparable and I think that each hydrolysate is going to have to be looked at individually to really know whether or not it is going to have the beneficial effect that we want, and I think that is going to be especially true in the partial hydrolysates.

**Dr. Greeff:** The role of the hydrolyzed formulas in the over 6-month-old infants, could you comment on that, please?

**Dr. Sampson:** As far as prevention I don’t think we have any good data. The AAP recommends that we continue these hydrolyzed formulas for the first year of life but I am not aware of any data to support that practice. As far as the infants who have cow’s milk allergy, we either have to put them on a different type of protein so that they are not going to react to or continue to keep them on hydrolyzed formula.

**Dr. Hamburger:** Were there any other restraints in the GINI study and in the German study that you reported that might be relevant to the results that we saw?

**Dr. Sampson:** I am not sure what you mean by restraints.

**Dr. Hamburger:** Dietary restrictions, changes in the home environment, anything at all, were there instructions given that I don’t know about?

**Dr. Sampson:** Dr. von Berg will comment on that.

**Dr. von Berg:** Yes, I think I should comment on that. First of all we gave the advice to avoid solid foods for the first 4 months and thereafter to avoid certain foods, but asked the parents to record all solids that the child was given in diaries. We looked at that and I am going to talk about it afterwards. In addition we had questionnaires about almost everything. So we looked at houses and pets and other environmental factors and adjusted for them in the analysis.

**Dr. Zeiger:** You or Dr. von Berg could also speculate on the potential reasons for the differential effect of the hydrolysates on the development of atopic dermatitis with respect to a family history of atopic dermatitis?

**Dr. Sampson:** That is a great question. I would speculate that we are seeing a genetically different population and consequently the response to the size of the protein or the particular protein presented is going to be different. In those individuals with atopic dermatitis in the family, you might say they have a more robust atopic
predisposition and therefore are going to require a greater alteration of the protein to be able to have a protective effect.

**Dr. Zeiger:** When you examine the GINI data at both 1 and 3 years, one observes that extensive casein hydrolysates reduced atopic dermatitis more than the partial whey hydrolysate regardless of stratification by family history of atopic dermatitis.

**Dr. Sampson:** I think that when we look at these atopic individuals, we are going to have to subdivide patients into different populations, e.g., there is a population that has a more severe, more persistent atopic predisposition compared to those individuals that are going to have a transient predisposition. Certainly in food allergy, we see the majority of children who react to milk and egg have a transient effect, and it doesn’t seem to matter too much how we do the initial feeding, whereas with those individuals that have this more persistent form, again whether they were breastfed or whether they got formula, it doesn’t seem to alter the fact that they are going to stay sensitized. For example, most of the children who develop milk or egg allergy while they are being breastfed are the ones who almost never tend to outgrow their allergy.

**Dr. Zeiger:** In clarification to the question that was asked relative to hydrolysates and weaning, there was one study that looked at a weaning diet at about 6 months with hydrolysates, and no difference in the subsequent development of atopic disease was found when such feedings were started after weaning [2].

**Dr. Saavedra:** A question with regard to the population study. You pointed out very well that, as might be expected, most of the studies that show these differences are in at-risk populations and, as discussed earlier, each one of those studies identified risk in their own particular way. In many instances, as far as we know there is no true standardized way of getting a family history, and in real practice pediatricians don’t go through an extensive questionnaire before making decisions on the kind of feeding recommendations. How good are the tools that we currently use to identify a family history, if any, and what would you recommend from a practical point of view?

**Dr. Sampson:** To begin with, I am not aware of any validated history for diagnosing atopic dermatitis. There certainly are standardized questionnaires that are available but, as far as I know, there is nothing that has really been validated.

**Dr. Björkstén:** Benn et al. [3] in Denmark actually did a big study evaluating a simple questionnaire which was validated by dermatologists. Unfortunately, coming back to Dr. Saavedra, no single question had the specificity and sensitivity that would make it useful. And if I may just continue, there is one word of caution again regarding the family history, and as I said, probably at least half of the population has the genetics for allergic disease and the fact that you don’t have it may be the fact that you became tolerant early in life. So the value of a family history is very different in different populations. We cannot use the family history for example in Estonia for the very simple reason that the phenotype is not expressed.

**Dr. Sampson:** I think one of the other problems you run into is that most of these studies have different definitions of positive family history. Some of the questions would ask things such as itchy rash, which may very well not be atopic dermatitis, and have similar vague symptoms for asthma and allergic rhinitis. I think it would be really useful to have a well-validated, standardized questionnaire that we could use but even when we get that, as you point out, the specificity is still unlikely to be very good.

**Dr. von Berg:** The problem with the questionnaires also is that they normally ask for present or past diseases, and actually to diagnose the past disease is very difficult. Another point is that there is atopic and non-atopic asthma or atopic and non-atopic dermatitis, and that these are different phenotypes, which is not considered in these questionnaires.

**Dr. Lake:** A question about tolerance. In studies that go back probably 20 years or more in animal models of immunologically intact rodents, when we attempted to induce tolerance to an intact protein we found that extensively hydrolyzed protein
was not capable of inducing tolerance and partially hydrolyzed protein could [4]. Do you have any concerns about altering tolerance development by raising babies on extensively hydrolyzed products from early on?

**Dr. Sampson:** One of the things we have to look at is the age at which we do these studies in rodents; the rodent is highly tolerizable so that giving them almost any protein will generate oral tolerance. What we do in our animal models when we generate cow's milk-allergic mice, i.e., mice that will develop anaphylaxis with ingestion of cow's milk, we give them cow's milk plus cholera toxin which will cause them to develop allergy to that particular protein. If you give it to them in a hydrolyzed formula, they are not going to develop that particular sensitivity. So the question remains is the atopic group or the predisposed group more like the mouse that we give the cholera toxin or is it more like the mouse that has a normal tolerogenic capability. I think the data at this point would suggest that in those high-risk infants, the infants that are likely to develop the sensitization, are probably more like the mouse with cholera toxin; they are not capable of developing that normal tolerance. I think this is analogous to different types of atopic individuals in the sense that some individuals are going to develop transient problems and probably are better off getting the partial hydrolysate that may in fact cause them to tolerize more efficiently whereas the group not destined to have the transient form is going to become reactive regardless.

**Dr. Björksten:** Perhaps the discussion is becoming slightly confused because I think what you are showing here is less atopic dermatitis. If you don't see an antigen, then you are not sensitized. However I think at this stage there is very little evidence, if any, that the atopic march would be prevented because an early positive skin prick test and early exposure to inhalant antigens is actually associated with a significantly decreased risk for having allergy as at the age of 11. So I am wondering whether the best we can hope from these hypoallergenic formulas is actually that we could prevent atopic dermatitis in infants.

**Dr. Sampson:** I think that with the data that we have right now, all we can say is that we can prevent the development of some atopic dermatitis. We know that many children outgrow their atopic dermatitis and the two-point prevalence rates come together over the course of time as Dr. Zeiger showed in his study. However, I think the jury is still out on the issue of asthma and allergic rhinitis. One of the problems with the study by Hattevig et al. [5] was that it was done in two different cities and so was not really randomized, which introduces other potential causative effects. One of the things we have to do is to make sure Dr. von Berg keeps going with her study and follows these children for the next 15 years. Perhaps then we will get an answer, but I think right now the answer is not there.

**Dr. Moukarzel:** What is the role of elemental formula, free amino acid formula as prevention? Do you have any comments on non-inducing tolerance in the long term? A free amino acid formula may not induce tolerance as partially hydrolyzed formula.

**Dr. Sampson:** Right now we have no evidence on the use of the amino acid-based formula for prevention. However, if there is concern about the extensively hydrolyzed formulas having insufficient tolerizing effects, then the amino acid formulas would likely be worse. Right now we do not have any data to support the use of amino acid-based formulas for prevention, only for treatment.

**Dr. Sorensen:** You mentioned two interesting aspects of the GINI study and I don't know if you or Dr. von Berg could help us with this. One was that there was a higher attrition rate in the extensively hydrolyzed casein group, another one that only the extensively hydrolyzed casein seemed to be protective against atopic dermatitis in children born to mothers who had active atopic dermatitis. Is that correct?

**Dr. Sampson:** No, it is atopic dermatitis in the parents.

**Dr. Sorensen:** Now I wonder if the attrition rate may have been higher in that group, and that is why it seems to have a better effect.
Dr. von Berg: It was slightly higher in the extensively hydrolyzed casein group, but the group was restocked.

Dr. Seidman: You began your lecture discussing the fact that the majority of patients who are going to develop atopic disease in fact don’t have a positive family history and then very quickly concluded that there is no evidence that any intervention helps, but I wonder if you would comment on the ZUFF study from Switzerland?

Dr. Sampson: I am not aware of that.

Dr. Seidman: This is a population-based study in two villages, Zug and Frauenfeld, where one city had an intervention and the other didn’t. I don’t know if there is anybody here who is associated with that study and would like to comment.

Dr. Exl-Preysch: We conducted that study. It is a study in a non-selected normal newborn infant population with the aim of finding out if an allergen-reduced nutrition will lead to better health outcome than a regular high allergenic infant nutrition. For very obvious reasons this was not a truly randomized study because feeding recommendations cannot be randomized in normal surroundings. However, it was a prospective study in two cities, 50 km apart, that we compared independently before we started the study. All possible confounding factors were finally included in the evaluation via a logistic regression analysis and worst case evaluation. The nutrition recommendations were the same as in the GINI study only that we had an unselected infant population. There were 566 infants in the regularly fed control group and 564 newborns in the allergen-reduced (NAN HA) prevention group [6–8]. However, it is important to make clear that we didn’t only look into allergy, because we were interested in the overall health of the infants. Would they grow healthier on a partially hydrolyzed formula than on a normal formula, would they grow as well? After 2 years we could finally show that the infants in the partially hydrolyzed group (NAN HA) were having less skin problems, only half of the amount of those who got regular infant formula and grew the same.

Dr. Sampson: I think you have the same problem as the study by Hattevig et al. [5]; you are doing two different techniques in two different cities. You have different observers in each of the cities and I think there are a lot of potential problems with that.

Dr. Exl-Preysch: We knew and discussed the problem of randomization a long time before we started that study. It is just not possible in a normal population to try to randomize feeding recommendations. Finally you will end up in a mess, because people are communicating with each other and will change their views and finally their feeding behavior. That is why we decided with the help of internationally renowned people to choose the ‘randomization of two cities’ version. To make sure they were comparable, we asked before starting this study an independent institute to make a survey of those two cities that are 50 km apart. We looked into all important parameters in terms of possible confounding factors. Most of them were comparable, those that were not spoke in favor of the control group – ergo against our hypothesis – and secondly in the final analysis that was intention to treat inclusive worst case analysis, we took all of those potentially confounding factors into account. So I don’t think that finally this sort of randomization that we did would or could be taken into account for any differences. We analyzed everything that we could, in the end we individually analyzed each doctor’s own sort of analysis of the results as confounding factors against the others. Altogether, we had 80 study doctors all coming from that region. They were all trained in several training sectors, and they were again taken into account in the final analysis with the logistic regression. I don’t think they will count for any differences between the two cities. So, our final result seems to be very clear: allergen-reduced infant nutrition for all non- or partially breastfed infants seems to be the best state-of-the-art at the moment that we know of.
References


