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Dietary manipulations in infants and their mothers and the natural course of atopic disease

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Overview of allergy prevention

A particular urgency exists today to identify actions that promote allergy prevention due to the formidable increase in prevalence and morbidity of atopic disease that is occurring throughout the world. Manipulation of the genetic and immunologic constitution of the atopic-prone subject provides targets for future allergy prevention. At this time, environmental engineering, which attempts to lower both the allergenic and adjuvant load, exists as the principal target. Discussion here will focus on primary prevention (prevention of sensitization, primarily IgE) of atopic disease by combined maternal and infant food allergen avoidance. Secondary prevention (deterrence of disease expression despite prior sensitization) and tertiary prevention (suppression of symptoms despite disease occurrence) could be approached by implementing methods found effective in primary prevention. One must anticipate great obstacles to environmental engineering due to limitations in scientific knowledge and societal compliance/resources.

Studies have suggested that infancy represents an especially vulnerable period in which the genetically programmed atopic-prone infant may be at an increased risk to become sensitized to allergens under certain environmental conditions. Perinatal identification of such at-risk neonates would allow directed allergy prevention should preventive efforts prove efficacious, safe, and cost effective. Though several genetic and immunologic factors/markers have significantly associated with the subsequent development of allergic disease, none possess adequate sensitivity or specificity for universal neonatal screening (1). Atopic family history and elevated cord blood IgE level provide practical identification of high-risk infants for prospective prevention studies. To best appreciate the effect of combined maternal and infant food allergen avoidance on the development of allergy, one must first evaluate the results of studies which instituted either maternal or infant food allergen avoidance regimens.

Abbreviations
CM: cow milk; CMA: cow milk allergy; IgG BLG: immunoglobulin G beta-lactoglobulin level; IgG OVA: immunoglobulin G ovalbumen/ovomucoid level; SPT: skin puncture test.

Prevention of food allergy: isolated maternal or infant food allergen avoidance

Grulee and Sanford reported almost 60 years ago in a non-randomized prospective study of over 20,000 unselected newborns that breastfeeding compared with boiled cow milk (CM) feeding lowered the incidence of eczema seven fold (Fig. 1) (2). Many disparate studies followed. The failure to appreciate the various potential routes of food exposure: placenta (probably insignificant, see below), breast, formula, solids, airborne droplets/floor dusts, and errors in the nursery, may be responsible for some of these studies conflicting findings. Hen's egg, CM, and peanut are the foods in Western society which most often induce food-specific-IgE sensitization in infancy; their avoidance during infancy are essential to reduce food allergy. The relative importance of these routes to the development of food allergy and the successes/failures of preventive efforts to interfere with these exposures and their relevance to combined maternal and infancy avoidance regimens will be critically summarized in this discussion.

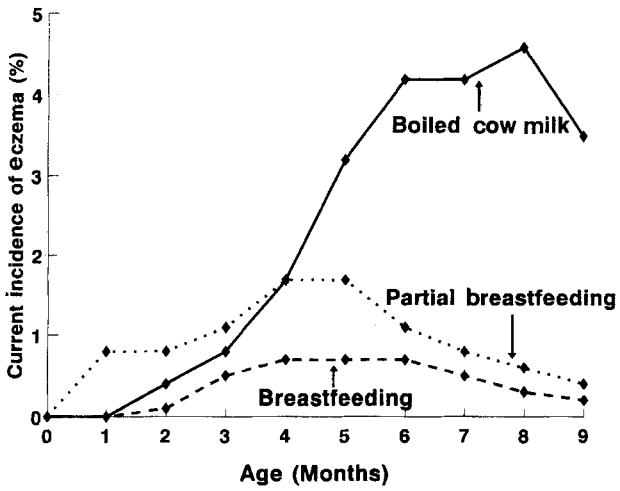

Fig. 1. Current incidence of eczema from birth to 9 months related to type of feeding from birth to 9 months in unselected non-randomized prospectively followed infants: breastfeeding (n=9,749), partial breastfeeding (n=8,605), boiled CM (n=1,707). Comparisons between groups: breast feeding vs boiled CM 4–9 months ($p<0.01$), breast feeding vs partial breast feeding 1–9 months ($p<0.01$). (Modified from Grulee CG, Sanford HN. J Pediatr 1936: 9: 223–225).

Avoidance of allergenic foods during pregnancy

Specific IgE sensitization to foods *in utero* represents a rather rare event (possibly denoting false positives assays), since such occurrences have been detected in less than 0.3% of monitored pregnancies (1). Three prospective randomized studies have demonstrated unequivocally that maternal allergen food avoidance diets (no CM or egg) or increased food allergen intake during the third trimester of pregnancy fail to affect atopic disease, serum IgE levels, and food sensitization from birth to up to 5 years of age in offspring at high-risk for atopy (3–7) (Table 1). As such, it is inappropriate and nutritionally potentially harmful to mother and fetus (demonstrated reductions in maternal 3rd trimester weight gain and infant birth weights) (3–8), to implement, except for investigational purposes, such food avoidance regimens during pregnancy with the intent of preventing food allergy.

Breast feeding

Protective effect of breast milk on food allergen exposure and absorption – Breast milk may decrease allergic sensitization by reducing both exposure to and intestinal absorption of food allergens. The breast milk factor(s) responsible for these effects remain speculative but include the protective capacity of human immunoglobulins, especially sIgA, to inhibit intestinal absorption of food antigens (9), although conflicting data exist (10), and mucosal growth factors which facilitate early maturation of the gut (closure) (11).

Effect of breast milk compared to CM feeding on allergic sensitization and allergic disease – Debate exists today regarding the capacity of breastfeeding to prevent, reduce, or delay the development of allergic disease owing to disparate data derived from studies differing in design, quality, size, and duration as summarized recently (1, 12, 13). Prospective studies which compared the effect of breast to CM feeding on the development of atopy have been non-randomized and generally weak due to lack of immunologic and food challenge confirmation of food allergy, unmasking, inadequate sample size, and a too brief period of exclusive breastfeeding. Lack of randomization creates confounding which especially affects personal characteristics and raised health consciousness observed in breast feeding families: reduced smoking and day care attendance, delayed solid food introduction, higher socioeconomic status, and greater parental atopy (14). These behaviors potentially could affect atopy development since they reduce food allergen exposure, decrease viral exposure, and reduce second-hand smoke inhalation (1). These design limitations frustrate reaching definitive conclusions regarding the potential benefits of breastfeeding in preventing food allergy and other allergic disorders. The detection of dietary allergens in breast milk and the early sensitization of exclusively breast fed infants to egg and CM (15–17) add complexity to this situation.

The absence of a definitive study to resolve this issue does not dissaude this author from recommending exclusive breast feeding for at least 6 months in atopic-prone infants with the intent to prevent atopy. A recent prospective longitudinal study by Høst, et al. involving almost 1800 unselected Danish neonates followed to 1 year of age for the development of CMA provides support for the above recommendation (18). Høst, et al. noted a significantly lower incidence of CMA in exclusively breastfed (excluding the few with CM in the nursery) (0.5%) compared to CM formula supplemented infants (2.2%). Inadvertent exposure to up to 4 oz. of CM formula in the nursery was possibly responsible for sensitization of those in the exclusive breastfed group developing CMA (18). The quantity of CM protein present in 4 oz. of CM formula approaches 1 to 3 g of BLG. It would require approximately 17 years consuming 1 l of breast milk daily to consume similar quantities of BLG (18).

Maternal avoidance of allergenic food during lactation – Sensitization to food allergens in human breast milk have been implicated in part in food sensitization and food allergy. About 6% of atopic-prone infants presumably exclusively breastfed have experienced atopic symptoms with their presumed initial direct food exposure (17). Moreover, egg and

Table 1. Prospective randomized controlled studies of hypoallergenic dietary regimens on the development of atopic disease in infants of atopic parents

Study (Reference)	Subjects (n)	Mom pregnancy diet	Mom lactation diet	Infant diet	Follow-up	SPT/RAST	DBPCFC	Atopic disease	Comments
Magnusson, et al. (1987)[3] (1988)[4] (1992)[5]	197	3rd trimester (No egg, CM) vs No restrictions	None	Breast +/or casein hydrolysate (3 Mo); Solids (>4 Mo); CM (>6 Mo); egg/fish (>9 Mo)	5 Yr	Not significant	No	Not significant	Pregnancy diet had no effect on infant atopy, SPT, or IgE
Lilja, et al. (1989)[6] (1991)[7]	162	3rd trimester (No egg, CM) vs No restrictions	None	Breast +/or soy (6 Mo); Solids (>3 Mo); CM (>6 Mo, most); egg/fish (>9 Mo)	1.5 Yr	Not significant	No	Not significant	Pregnancy diet had no effect on infant atopy, SPT, or IgE
Chandra, et al. (1986)[55]	71	Entire pregnancy (No egg, CM, fish, peanut, beef) vs No restrictions	Entire lactation (Same as pregnancy) vs No restrictions	Exclusive breast (5–6 Mo) vs No restrictions	1 Yr	Not determined	No	Reduced severity of AD by 1 Yr*	No immunologic or food challenge confirmation. Benefit probably derives from infant diet and/or maternal lactation diet and not pregnancy diet
Zeiger, et al. (1989)[6] (1992)[41]	288	3rd trimester (No egg, CM, peanut) vs No restrictions	Entire lactation (same as pregnancy) vs No restrictions	Breast +/or casein hydrolysate (12 Mo); Solids (>6 Mo); CM, soy, corn (>12 Mo); egg, fish, peanut (>24 Mo) vs AAP guidelines	4 Yr	Reduced CM-IgE prevalence at 1* and 2 Yr**	Yes	Reduced current prevalence of AD* and food allergy** at 1 Yr. Asthma, AR unaffected	Benefits probably derive from infant diet and/or maternal lactation diet and not pregnancy diet (see Magnusson and Lilja above)
Hattevig, et al. (1989)[29] (1990)[30] (1992)[31]	115	None	1st 3 Mo of lactation (no egg, CM, fish) vs No restrictions	Breast +/or casein hydrolysate (6 Mo); CM/ solids (>6 Mo); egg/fish (>9 Mo)	4 Yr	Reduced # of CM +/or egg-IgE tests at 3 Mo**	No	Reduced AD at 3**, 6*, and 48** Mo	Groups assigned by hospital rather than by randomization
Chandra, et al. (1989)[32]	97	None	Entire lactation (No egg, CM, peanuts, soy, fish) vs No restrictions	Exclusive breast (~6 Mo), Solids (~6 Mo)	1.5 Yr	Not determined	No	Reduced AD by 1.5 Yr*	No immunologic or food challenge confirmation
Chandra, et al. (1989)[32]	124 (3 groups)	None	None	Exclusive casein hydrolysate vs soy or CM. No breastfeeding	1.5 Yr	Not determined	No	Reduced AD* by 1.5 Yr with casein hydrolysate	No immunologic or food challenge confirmation
Chandra, et al. (1989)[44] (1991)[45]	288 (4 groups)	None	None	Exclusive partial whey hydrolysate (6 Mo) vs CM, soy formula, or breastfeeding (6 Mo)	1.5 Yr	No difference in CM-IgE at 2 and 6 Mo	No	Reduced 6 & 12 Mo AD cumulative prevalence	No immunologic or food challenge confirmation; Cord blood + RASTs to CM/soy unaccountably high
Vanderplas, et al. (1992)[46]	67	None	None	Partial whey hydrolysate (6 Mo) vs CM formula	1 Yr	Only determined on symptomatic	(?)	Reduced current CMA at 6 Mo*	6 Mo prevalence of AD (77%) and CMA (34%) unaccountably high in Controls; CMA during hydrolysate feeding (n = 1) and after hydrolysate D/C'd (n = 3)
Arshad, et al. (1992)[57]	120	None	Entire lactation (No egg, CM, fish, nuts) vs No restrictions	Breast +/or soy hydrolysate (9 Mo); CM/soy (9 Mo); egg (11 Mo); all others (12 Mo) plus Mite avoidance (acaracide and encasings) vs No restrictions	1 Yr	Not significant	No	Reduced AD* and asthma* by 1 Yr	Control group with more smoking mothers ($p = 0.11$) and dual family atopy ($p < 0.05$)

Abbreviations: CM (Cow Milk), AD (Atopic Dermatitis), CMA (Cow Milk Allergy), DBPCFC (Double-blind, placebo-controlled, food challenge), Mo (Month), Yr (Year), D/C'd (Discontinued), *$p < 0.05$; **$p < 0.01$

Table 2. Immunologic and allergenic properties of several commercial protein hydrolysates

Brand	Nutramigen	Alimentum	Good Start	Pregomin
Year introduced in USA	1942	1989	1989	Not available
Hydrolysate protein	CM Casein	CM Casein	CM Whey	Beef Collagen/Soy
Oil	Corn	Safflower	Coconut/palm	Vegetable Mix
Carbohydrate	Corn syrup solids	Sucrose tapioca	Lactose-14%	Glucose Polymers
Molecular weight (% > 1.5 kD)	None	< 1%	> 20%	All < 5.0 kD
Whey antigen (μg/ml)*	0.4 ± 0.1	1.3 ± 0.3	752 ± 124	Not determined
Casein antigen (μg/ml)*	0.07 ± 0.03	0.19 ± 0.06	24.2 ± 7.0	Not determined
BLG (μg/g)**	0.006	0.03	200	Not determined
% + RAST disc (45 CMA pts)**	8.9%	6.6%	24%	Frequent[1]
USP guinea pig assay	Negative	Negative	Negative	Negative
+ SPT in CM + SPT pts*,**,***,&	25/143 (17.5%)	21/104 (20.2%)	73/134 (54.5%)	4/17 (23.5%)
+ DBPCFC in IgE-CMA (series)	1/54 (1.9%)*,**,1,&	1/34 (2.9%)*,**	10/13 (76.9%)*,1	1/8 (12.5%)[1]
+ DBPCFC in CMA (single reports)	Yes*,5	Yes@	Yes@	Not reported
Recommended for CMA	Yes with caution	Yes with caution	No	To be determined

*Sampson HA, et al. J Pediatrics 1991: 118: 520, **Oldaeus G, et al. Pediatr Allergy Immunol 1991: 4: 156 & J All Clin Immunol 1992: 90: 133, ***Scwartz RH, et al. Pediatr Asthma Allergy Immunol 1989: 4:207, +Businco L, et al. Ann Allergy 1989: 62:333, #Saylor JD, Bahna SL. J Ped 1991: 118:71, [5]Lifschitz CH, et al. J Pediatr Gastroenter Nutr 1988: 7:141, @Amonette MS, et al. Pediatr Asthma Allergy Immunol 1991: 5:245, [1]Rugo E, et al. Clin Exp Allergy 1992: 22:635, &Sampson HA, et al. Pediatr 1992: 90:463.

CM-specific IgE have been reported commonly in and even sometimes more often in breastfed than formula-fed infants (19–20). Nanogram concentrations of beta-lactoglobulin (BLG), casein, bovine IgG egg ovalbumin (OVA), and gliadin in molecular size adequate for sensitization have been detected in samples of breast milk from the majority of mothers consuming these foods (21–27). After maternal ingestion of 4 oz. of CM, 1 raw egg, or 1 slice of bread, these food allergens appear in breast milk within 2 to 6 h and may persist for days (21, 23, 24, 26, 27). It is unknown whether such quantities can *prime* the infant's immune system to produce food-specific IgE; though the levels of food allergens in breast milk exist in sufficient quantity to trigger allergic reactions in sensitized infants.

Two controlled prospective studies, and one with group allocation determined by hospital attendance (29–31), and the other randomized (32) have evaluated the effect of maternal diets during lactation on the development of atopy in high-risk newboms (Table 1). In the non-randomized study eczema was significantly reduced at 3, 6, and 48 months but food and respiratory allergy were unaffected by maternal lactation diet. Less infants developed egg or CM RASTs at 3 months, but egg and CM skin prick tests (SPT), serum IgE levels, and IgG/IgA BLG and OVA antibodies were unaffected (29–31).

In the randomized study, eczema was reduced 50% by 18 months in the maternal lactation diet group (32). Both studies failed to document food allergy by food challenge and the latter study omitted immunologic confirmation. More definitive randomized studies with both food challenges and immunologic confirmation are mandatory before maternal lactation diets can be recommended as effective in the prevention of atopic disease.

Effect of soy feeding on development of atopy

Soy formula feeding was extolled for its food allergy preventive capacity in retrospective and non-randomized studies. One prospective randomized study by the same group as above (33) reported that soy feeding reduced asthma and perennial rhinitis by 3 years without affecting the development of atopic dermatitis in infancy or hay fever during childhood. The failure of soy feeding to affect atopic dermatitis (the atopic condition most associated with food allergy) led to subsequent prospective randomized investigations which failed to demonstrate any reduction in the development of atopy in infancy and childhood from soy compared to CM formula feeding (32, 34–37). These findings are consistent with studies that verified the immunogenic and allergenic capacity of soybean protein (38, 39). These results suggest that intact soybean protein formulas should not be considered hypoallergenic nor used in attempts to prevent food allergy in infancy.

Effect of hypoallergenic protein hydrolysate formula feeding on development of allergic disease

Allergenicity/immunogenicity – Hydrolysates of CM, soy, or beef collagen have been developed in an attempt to reduce the immunogenicity and allergenicity of the parent proteins while maintaining nutritional completeness and acceptance. A comparison of several commercial protein hydrolysates appears in Table 2. The two extensively hydrolyzed casein hydrolysates, Nutramigen and Alimentum, have been shown to be hypoallergenic [95% confidence of tolerance in 90% of CM allergic (CMA) subjects] (40), in contrast to the partial CM whey hydrolysate (Good Start), which frequently leads to

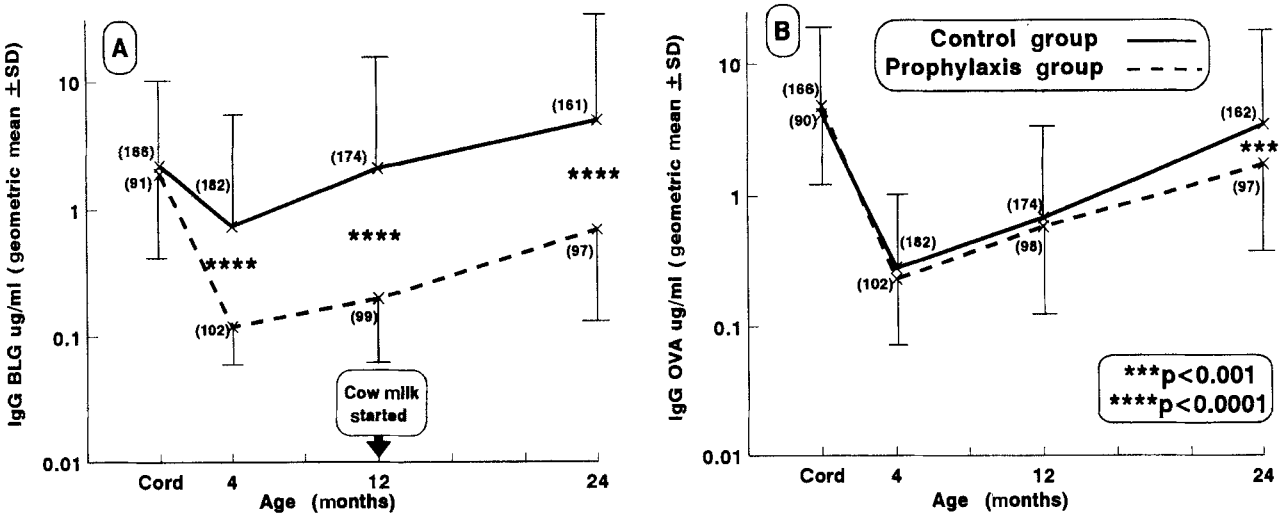

Fig. 2. IgG BLG (A) and IgG OVA (B) response from birth to 2 years in combined maternal/infant prophylactic-treated and control groups. Numbers in parentheses refer to number of subjects. (Reprinted with permission from Zeiger RS, et al. Pediatr Allergy Immunol 1992: 3: 110–127).

symptoms in CMA. These findings should dissuade clinicians from using partial hydrolyzed CM protein formulas in CMA, but since even the extensively hydrolyzed hydrolysates have led to reactions in CMA, all such formulas should be introduced with caution in CMA.

Prevention of atopy – Nutramigen (as part of a hypoallergenic dietary regimen) compared to CM feeding from birth in non-breastfed infants or as a supplement to breastfeeding was associated with a lower prevalence of formula allergy and specific-CM IgE by 1 year in infants at-risk for atopy (8). In addition, the hypoimmunogenicity of Nutramigen was documented by its capacity compared to CM formula to inhibit the IgG BLG response prior to and following CM introduction (Fig. 2A) (41), confirming an earlier preliminary study of Eastham, et al. (42). Casein hydrolysate fed infants in the former study exhibited a decreased BLG IgG response similar to that observed in infants solely breast fed until 1 year, whether or not a maternal lactation diet free of CM was adopted (41), extending findings of Kletter, et al. (43). These findings reveal reduced immunogenicity of casein hydrolysate formula (Nutramigen) and exclusive breastfeeding in unselected infants (42, 43) and also in at-risk atopic neonates (41), those most expected to mount strong immunologic responses.

Three subsequent prospective randomized studies of high-risk newborns suggested that protein hydrolysate feedings were beneficial in reducing atopic dermatitis, atopy, or CMA (32, 44–46) (Table 1). Comments concerning the lack of definitiveness of these studies are noted in Table 2. These studies require confirmation with additional prospective, randomized, masked, food challenged confirmed studies of CMA prevention by 18 months before protein hydrolysate formulas are proclaimed effective and safe for the prevention of atopy in high-atopic risk infants when breastfeeding is not a choice or formula supplementation is desired. The extensively hydrolyzed casein hydrolysates may be preferable (40, 48) to the partial whey hydrolysates for purposes of allergy prevention, since they have been determined both hypoallergenic (40, 47) and hypoimmunogenic (Fig. 2A), while the partial whey hydrolysates may induce CM-specific IgE (46) and are more likely to cause anaphylaxis in an infant who has become sensitized to CM from other sources (Table 2).

Delayed introduction of solid foods

The beneficial role of delaying solid food feeding in the prevention of atopy has been addressed elsewhere in this symposia and will be briefly commented upon here. A non-randomized prospective prevention study noted increased atopy by 1 year (49, 50) while a longitudinal non-randomized birth cohort study observed an increased risk for eczema but not asthma in infants fed multiple foods in infancy (51–54). These studies must be considered only suggestive until a definitive randomized study confirms such findings.

Prevention of atopy by combined maternal and infant avoidance of allergenic foods

The existence of multiple potential sources of food exposure in infancy led to two prospective randomized studies which attempted to interfere with the ingestion of food allergens by mother and her infant from all of these potential sources in an attempt to

Table 3. Design of Kaiser Permanente/UCSD combined maternal/infant food allergen avoidance study

	Atopic parents randomized prenatally	
	Prophylactic-treated (n = 103)	Controls (n = 185)
Maternal diet		
3rd trimester and lactation	No egg, milk, peanut	No restrictions
Infant diet		
Breastfeeding	Encouraged	Encouraged
Formula	Casein hydrolysate	Whey-based cow milk
Solid foods	> 6 Months: low allergenic foods >12 Months: milk, soy, wheat, corn >24 Months: egg >36 Months: peanut, fish	American Academy of Pediatrics Guidelines
Outcomes		
Birth/yearly	Atopy, SPT, DBPCFC, serum IgE, IgG BLG and IgG OVA levels	

(Reprinted with permission from Zeiger RS, et al. Pediatr Allergy Immunol 1992: 3: 110–127)

reduce the development of atopy; knowing full well of the inability to determine which of the interventions would be responsible for the preventive effect. Moreover, these studies were intitiated before definitive studies demonstrated the failure of 3rd trimester maternal food allergen avoidance to affect atopy. Three studies have examined the effect of such combined maternal and infant food allergen

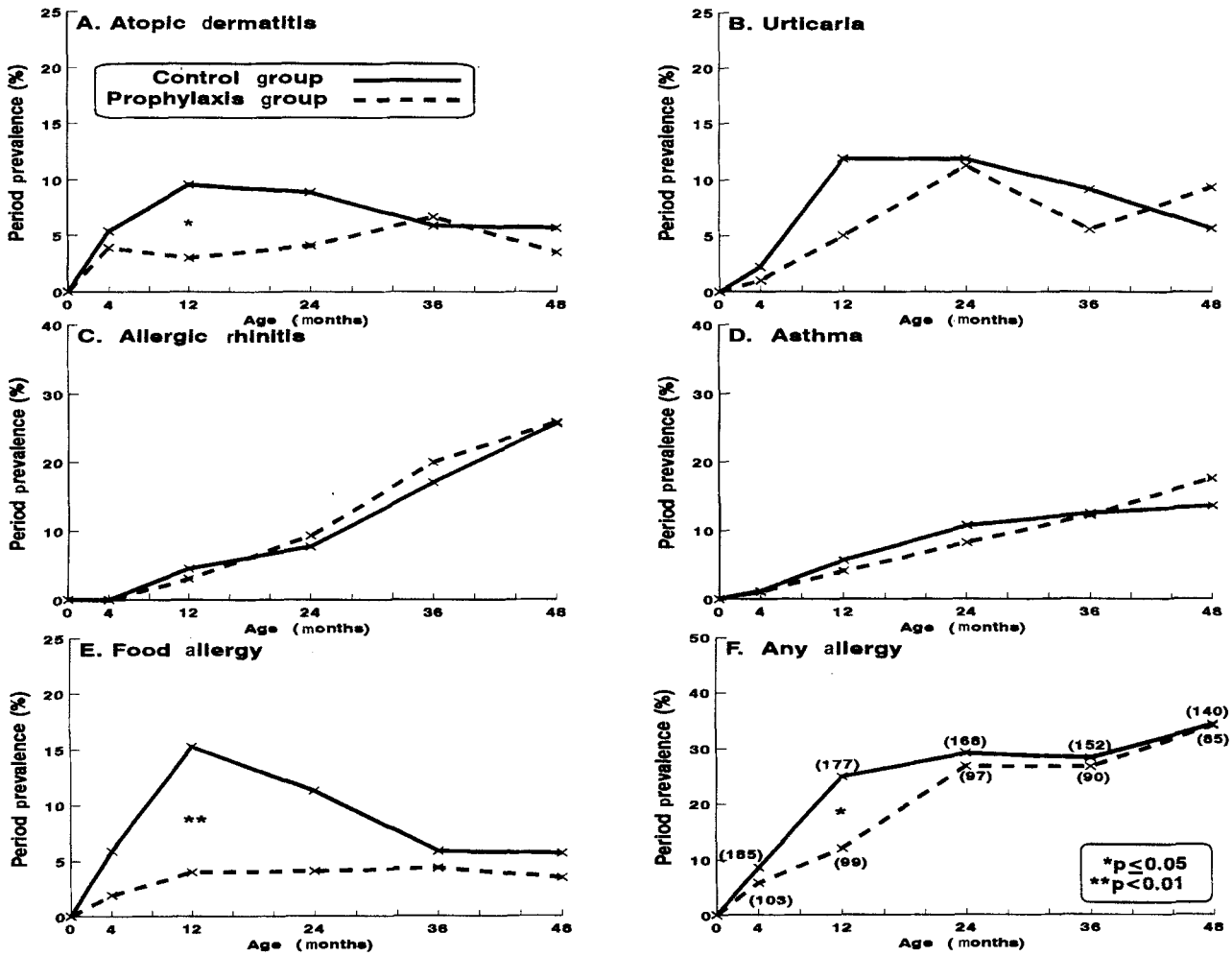

Fig. 3. Period (current) prevalences of atopic disorders from birth to 4 years in combined maternal/infant prophylactic-treated and control groups. Numbers in parentheses refer to number of subjects. (Reprinted with permission from Zeiger RS, et al. Pediatr Allergy Immunol 1992: 3: 110–127).

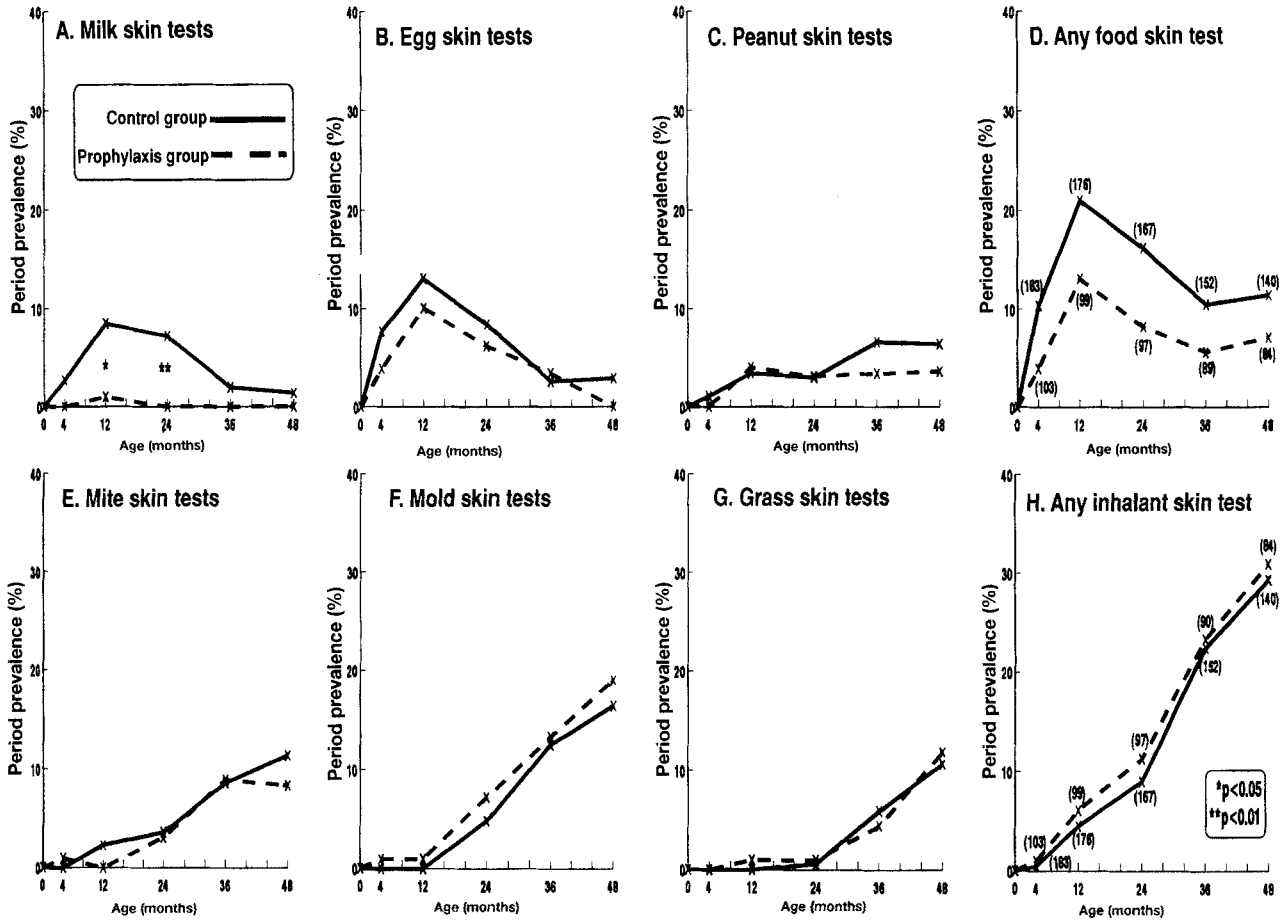

Fig. 4. Period prevalences of food SPT (upper half, A–D) and aeroallergen skin sensitization (lower half, E–H) from birth to 4 years in combined maternal/infant prophylactic-treated and control subjects. Numbers in parentheses refer to number of subjects. (Reprinted with permission from Zeiger RS, et al. Pediatr Allergy Immunol 1992: 3: 110–127).

avoidance regimens on atopy (Table 1) (8, 41, 55, 57).

Maternal avoidance diet during entire pregnancy and lactation with 6 months exclusive breast feeding

Chandra, et al. (55) reported less severe eczema by 1 year in infants whose mothers excluded CM, egg, peanut, fish, and beef throughout *pregnancy and lactation* compared to a group whose mothers maintained an unrestricted diet, in a prospective, randomized, controlled study of atopic-prone infants exclusively breastfed for 6 months. BLG, casein, or OVA were rarely detected in the breast milk of mothers practicing dietary restriction compared to control mothers ($p < 0.01$), confirming relative compliance in the restricted diet group. The absence of food challenge and immunologic confirmation of food as causative of the eczema are shortcomings of the study (55).

Combined maternal and infant food allergen avoidance during the perinatal period during 2 years

Over the past two decades our group has examined both the natural history of allergy in infancy and its potential for prevention (8, 15, 41). During the course of a prospective, randomized study of the effect of combined maternal/infant food allergen avoidance on atopy (study design summarized in Table 3), these investigations have led to a further understanding of the interaction of genetic and environmental factors in the development of atopy through age 4 in 288 children of atopic parents, of which 78% were evaluated at age 4 years (8, 41).

Effect on food allergy and other atopic disorders (Fig. 3). a. Food allergy – The current (period) prevalence of food allergy peak at 1 year declining to about 5% by 3 and 4 years (Fig. 3E). The cumulative prevalence of food allergy (41) was significantly lower in the prophylactic-treated group from ages 1 to 4 years, owing to the initial lower current (period) prevalence of food allergy (Fig. 3E) observed at 1 year. Current prevalences of food

allergy were similar among groups at 3 and 4 years. These findings suggest that the combined maternal/infant food allergen avoidance reduced food allergy primarily in the first year of life and that current prevalences may represent a more appropriate measure to assess the impact of intervention measures on the development of atopic disease after 1–2 years of age.

b. Skin allergy – The current prevalences of atopic dermatitis paralleled food allergy, peaking at 1 to 2 years and then declining at 3 and 4 years (Fig. 3A). Only at 1 year was there a significant reduction in the current prevalence of atopic dermatitis in the prophylactic-treated compared to the control group (Fig. 3A). Urticaria which included food, viral, drug, and unknown causes was unaffected by the dietary regimen (Fig. 3B).

c. Respiratory allergy – In contrast to food allergy prevalences, the current (period) and cumulative prevalences of respiratory allergy paralleled each other by increasing steadily from birth to 4 years (Figs 3C, D). The current (Figs 3C, D) and cumulative (not shown) prevalences of allergic rhinitis and asthma from age 4 months to 4 years were similar in both groups, attesting to the failure of the dietary intervention to affect respiratory allergy. Children with food allergy evidenced somewhat higher 4-year cumulative prevalences of allergic rhinitis and asthma ($p < 0.05$).

Effect on immunologic parameters. a. Serum IgE level – Serum IgE levels increased steadily in both groups from birth to 2 years and from 2 years to 4 years. Newborns evidencing elevated IgE levels at birth (>0.5 IU/ml) maintained significantly higher IgE levels from 4 months to 4 years compared to those with normal IgE levels at birth (41). Combined maternal and infant diets marginally lowered serum IgE levels ($p = 0.07$) at 4 months, while not affecting levels from 1 to 4 years. In the control group, CM formula feeding was associated with higher serum IgE levels at 4 months ($p < 0.05$). Significantly higher serum IgE levels occurred from 4 months to 4 years in those subjects developing food allergy, atopic dermatitis, allergic rhinitis, and asthma as well as egg and CM sensitization, compared respectively to those without atopy or positive egg or CM SPTs (41).

b. Food sensitization (Fig. 4A–D) – The current prevalences of SPT sensitization to foods in both groups paralleled prevalences of food allergy, peaking at one year, only to ebb by 3 and 4 years. CM was the only food in which SPT prevalence was reduced at 1 and 2 years with combined dietary avoidance; by 3 and 4 years CM, egg, peanut, or any positive food SPT declined in prevalence and were similar among groups.

c. Inhalant sensitization (Fig. 4E–H) – Paralleling the development of allergic rhinitis, aeroallergen SPT sensitization nearly increased linearly from birth to 4 years, and similarly was unaffected by food allergen avoidance from age 4 months to 4 years.

d. Nasal eosinophils and nasal basophilic cells – Combined food allergen avoidance had no effect on these nasal inflammatory cells, which were affected predominately by inhalant sensitization and allergic rhinitis, and only marginally by food allergy and food sensitization (56). Nasal basophilic cells developed in both atopic and non-atopic high-risk infants but occurred in significantly increased frequency and quantity in those with atopy from ages 4 months to 4 years. Nasal eosinophils, rare at 4 months in all infants, increased in atopic children from 1 to 4 years, remaining infrequent and nominal in the nonatopic. Both cellular types correlated significantly with one each other from 4 months to 4 years, reaching an $R_s = 0.84$ at 4 years. These cells also correlated with the log serum IgE levels of the children at 3 and 4 years, reaching $R_s = 0.40$.

e. IgG BLG and IgG OVA responses (Fig. 2) – As noted above, the IgG response to foods represents a normal immunologic response mounted by infants during natural food exposure, decreasing from birth to 4 months and then increasing thereafter to 2 years. Prophylactic-treated children developed lower levels of IgG BLG from 4 months to 2 years (Fig. 2A), but lower IgG OVA levels only at 2 years (Fig. 2B), attesting to the marked difference in CM and marginal difference in egg exposure among the groups. The AAP guidelines suggest delay in introducing egg white during infancy, which may be responsible for the similarity of responses of the groups during year one.

Significantly higher levels of IgG BLG and OVA occurred from 4 months to 2 years in infants developing food allergy and also subsequently developing respiratory allergy by 4 years, suggesting that these higher levels of antibodies do not protect against food allergy, but may represent heightened immunologic responses by especially atopic or atopic-prone subjects.

Risk factors for allergic disease and sensitization – Both retrospective and prospective studies have identified various risk factors for the development of atopic disease in both unselected and atopic-prone infants. The present combined maternal and infant food allergen avoidance study provided the opportunity to prospectively evaluate the relative strength

Table 4. Summary of genetic/environmental factors increasing atopy prevalence and serum IgE levels from birth to 4 years in offspring of atopic parents

Atopic measure	Genetic/familial	Environmental
Food allergy	Elevated cord IgE	Food allergens early
Eczema	Elevated cord IgE Non-whites	Birth month (Jan-Aug)
Rhinitis	Non-whites	Birth month (Jan-Aug)
Asthma	Males	Less schooling
Any disease	Elevated cord IgE Males	
Serum IgE	Elevated cord IgE High parental IgE Males Non-whites	Parental smoking Early cow milk intake Early egg intake Lower job level

Derived from univariate, multivariate, and logistic analyses ($p < 0.05$) of data from Zeiger, RS. Pediatr Allergy Immunol 1992: 3: 110–127

of these risk factors as well as the modulating effect of the dietary regimen on atopy and serum IgE levels. The reader is referred elsewhere (41) for specific relative risks and contributions to serum IgE levels from birth to 4 years; Table 4 summarizes these findings.

Comparison with other studies – The effectiveness of the prolonged combined maternal and infant dietary avoidance regimen practiced in the above study (8, 41), contrasts with that of Lilja, et al. (7) which did not observe a reduction in food atopy when maternal and infant food avoidance were practiced for less than 6 months postnatally. Lilja, et al. (7) reported that both the restricted and non-restricted diet groups developed similar IgG responses to BLG and OVA from birth to 18 months of life. In contrast, Zeiger, et al. (41) documented significantly suppressed IgG BLG responses from 4 to 24 months (8) and IgG OVA by 24 months with prolonged food allergy avoidance by mother and her infant (Fig. 2). Such findings suggest that a prolonged avoidance of allergenic foods may be necessary to optimally prevent/reduce the development of food allergy. The optimal duration of dietary avoidance remains speculative, but between 6 and 12 months is suggested by previous studies (1).

Summary – Intense and prolonged maternal/infant food allergen avoidance perinatally (1) reduced food allergy and IgE food sensitization (particularly to CM) during early infancy, (2) lowered serum IgE levels marginally at 4 months, and (3) suppressed the IgG BLG response to CM from 4 months to 2 years and the IgG OVA response to egg at age 2 years. This combined maternal/infant regimen *failed* to reduce (1) current food allergy or food sensitization at 3 and 4 years of age, (2) allergic rhinitis, asthma, or inhalant sensitization from birth to 4 years of age, or (3) serum IgE levels from ages 1 to 4 years (41).

Combined maternal/infant food avoidance postnatally and household mite avoidance

Recently, Arshad, et al. (presented elsewhere in this symposium) noted that a maternal lactation food avoidance regimen combined with breastfeeding and/or soy hydrolysate feeding and delayed solid food introduction and house-dust mite avoidance (encasings and acaricide treatments) led to a reduction in atopy by 1 year of age in atopic-prone offspring (57). Unrestricted infancy diet, parental smoking, maternal atopy, and lower SES were identified risk factors for the development of atopy by 1 year. Odds ratios for asthma and eczema were about 4-fold higher in those infants on unrestricted diets.

Implications and recommendations

These studies suggest but do not prove that strict prolonged food avoidance by mother and infant for more than 6 months reduces the development of food allergy in early infancy, but not thereafter, and absolutely has no effect on allergic respiratory disorders during infancy and early childhood. The reduction in food allergy was brief and limited to the first year of life due to the frequent remissions in food allergy by 2 years and the elimination of the responsible foods from the diets of the food allergic infant. The benefits attained by the combined maternal and infant avoidance regimens cannot be attributed to the pregnancy diet since, as discussed above, prenatal sensitization to foods is rare and prenatal maternal dietary restrictions when examined separately in prospective randomized studies failed to prevent food allergy in infancy (1, 3–7). The addition of mite elimination to the above food avoidance may provide hope for prevention/amelioration of respiratory allergy.

Parental compliance, motivation, and resources will present major obstacles to the success of these preventive efforts. Specifically, the well controlled studies discussed above emphasized that parental compliance was far from optimal despite apparent motivation and resources provided (8, 57). One can anticipate less success when preventive efforts are implemented in uncontrolled, unstructured settings such as seen in clinical practice. Given the multiple obstacles encountered during environmental engineering, dietary and inhalant avoidance efforts can only serve, at best, as interim measures until more effective and universally acceptable genetic or cellular engineering methods are developed. Only provisional recommendations can be offerred at this time for the prevention of allergic disease, demanding updating with new findings. These recommenda-

Table 5. Provisional recommendations for the prevention of food and other allergic disorders in neonates at high-risk for atopy

Strategy	Method or measure
1. Identify high risk infant prenatally or early postnatally	Atopic family (biparental, parent and sibling) or elevated cord IgE
2. Avoid infant exposure to:	
a. Food Allergens	
In breast milk	Maternal lactation diet with no egg, CM, peanut (consider?) Supplement maternal diet with 1500 mg calcium daily
In infant diet	Breast feed for at least 4–6 mo, longer if possible Supplement/wean with hypoallergenic protein hydrolysate Begin solid foods >6 mo adding least allergenic first After 1 year, add biweekly or monthly, if tolerated: CM, wheat soy, citrus, egg, peanut, fish. Delay egg, peanut, and fish in food atopic infants
b. Aeroallergens	Reduce household dust mite, mold, pet concentrations Use air conditioners, air purifiers, acaricides, denaturants
c. Non-apecific environmental adjuvants	No smoking prenatally or postnatally by caretakers/subject reduce pollution Minimize infections (breast feed, avoid early daycare)

tions should be directed at high risk neonates with highly motivated parents and not proselytized universally (Table 5).

Alternatively, one can argue that a more efficient and cost effective approach for allergy prevention would involve periodic prospective surveillance of high-risk infants both clinically and immunologically for atopic expresssion or sensitization (SPT or RAST/ELISA screening of specific-IgE for foods such as egg, milk, and peanut at 3, 6, and 12 months and aeroallergens such as dust mite, cat, grass and mold mix, yearly). Allergy preventive regimens shown effective for primary prevention would be expected to be effective for secondary/tertiary prevention and could be instituted when IgE sensitization/disease are recognized during prospective follow-up of these high-risk infants. Such an approach would direct intensive preventive efforts only to those high-risk infants who develop sensitization/disease, increasing the likelihood of compliance and success.

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