

Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age

N.-I. M. KJELLMAN and S. G. O. JOHANSSON

*Department of Pediatrics, University Hospital, Linköping and
Blood Centre, University Hospital, Uppsala, Sweden*

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Summary

Forty-eight children with a biparental history of atopic disease were followed from birth to 4 years of age. One group was fed soy and the other cow's milk from weaning to 9 months of age. Two-thirds of the children developed symptoms of atopic disease with no significant difference between the groups. No difference was found in the serum immunoglobulins (IgE antibodies, IgA, IgG and IgM) during the observation period. The soy fed children showed transiently lower levels of IgG antibodies to cow's milk but higher levels of IgG antibodies to soy protein. Six children showed cow's milk intolerance and a further five had symptoms possibly related to the use of cow's milk. Withholding cow's milk during the first 9 months did not reduce the incidence of symptoms of cow's milk intolerance from birth to 4 years of age. Thus, no benefit was found from replacing cows' milk with soy. A prolonged breast feeding seems most rational for infants at risk of developing atopic disease, even if the present study did not show evidence of a prophylactic effect of breast milk against the development of atopic disease.

Introduction

The cumulative incidence of atopic disease (bronchial asthma, allergic rhinitis, atopic dermatitis as well as allergic urticaria and gastrointestinal allergy) in Swedish children is approximately 15% (Kjellman, 1977; Kornfält & Köhler, 1978), thus making this type of disease one of the most common health problems in childhood.

In accordance with the genetic background of atopic disease, probably multifactorial (van Arsdel & Motulsky, 1959), the highest incidence is found in children with a biparental history of such disease (Spain & Cooke, 1924). The possibility of preventing or postponing the development of atopic disease in such children by withholding foreign milk protein during early infancy has been studied with divergent results (Glaser & Johnstone, 1953; Brown *et al.*, 1969; Halpern *et al.*, 1973; Johnstone, 1977).

Correspondence: N.-I. M. Kjellman, Department of Pediatrics, University Hospital, S 581 85, Linköping, Sweden.

Serum IgE levels have been found to be elevated (Orgel *et al.*, 1975) and serum IgA levels depressed (Taylor *et al.*, 1973, Orgel *et al.*, 1975) in children who subsequently develop atopic disease.

The aims of the present study were to compare the development of atopic disease and serum immunoglobulins in two groups of infants with a biparental history of atopic disease, one receiving a soy formula and the other using cow's milk from weaning to 9 months of age and, furthermore, to evaluate the effect of the duration of breast feeding on the development of atopic symptoms and signs.

Materials and methods

All women who were delivered at the Linköping Obstetric Department during a period of 18 months received a questionnaire concerning their family history of atopic disease. When a biparental history of atopic disease was noted, the mother was interviewed further. In all, a biparental history of atopic disease was confirmed in fifty-one (2.8%) of 1827 newborns. Fifty of these families agreed to participate in the study and gave their full consent. All children were born at full term except one girl born during week 36. There were no major neonatal problems.

The children were randomized into two groups: group S was fed soy and group M cow's milk after the breast feeding period. Forty-eight children (Table 1) fulfilled the study (one in group S moved from the region and one in group M refused further participation after 6 months).

All mothers were encouraged to breast feed their infants as long as possible. Group S was supplied with a soy formula (Sojasemp®, Semper, Sweden) to be used as soon as the quantities of breast milk became insufficient. In this group no cows' milk whatsoever was allowed before 9 months of age. Cow's milk was introduced slowly after this age. Group M received a cow's milk formula after the breast feeding period. All other instructions were identical for both groups; all were instructed to avoid fish, egg, chocolate and strawberries before 9 months of age. Furthermore, general recommendations on allergen avoidance were given: no animal material in bed clothing, thorough vacuum cleaning of their homes and no new pets; no effort was made to make the families dispose of existing pets.

The children were submitted to a clinical examination, performed by the same pediatrician (N.-I.M.K.) throughout the study, at birth and at 1, 3, 6, 9, 12, 18 and 36 months of age. The oldest children ($n=6$) were also examined at 4.5 years of age before the final evaluation of the project in September 1977. The families had answered a

Table 1. Atopic disease after soy or cows' milk feeding. Cumulative diagnoses at 4.1 ± 0.5 years of age

Atopic disease	Soy			Cow's milk			Total	
	Boys	Girls	Total	Boys	Girls	Total	<i>n</i>	%
Obvious	8	5	13	3	5	8	21	43.8
Probable	3	1	4	2	5	7	11	22.9
Possible	2	2	4	1	4	5	9	18.7
None	1	1	2	3	2	5	7	14.6
Total	14	9	23	9	16	25	48	100.0

questionnaire before each medical visit concerning the period since the last attendance. At the time of the final evaluation the age of the children was 4.1 ± 0.5 years. All families except one were then interviewed by telephone.

Venous blood was drawn at birth (cord blood), 3, 9, 12, 18 and 36 months of age. Serum was separated and kept frozen at -20°C pending analyses. All samples were analysed simultaneously for IgE (Phadebas IgE PRIST®), and IgE antibodies (ab) to cow's milk and soy bean (Phadebas RAST®). IgG ab to cow's milk and soy bean were determined by the Sepharose-A technique as described in detail by Foucard & Johansson (1976). Serum IgE levels were expressed in ku/l and IgE ab in PRU (Phadebas RAST units; Pharmacia, Uppsala, Sweden): values above 0.2 PRU were regarded as significantly positive. IgG ab were given as ‰ of a reference serum and levels from 5‰ were regarded as positive.

Blood samples were also analysed for haemoglobin, cholesterol, albumin, IgG + IgA, using electroimmunoassay (Laurell, 1972) and IgM, using single radial immunodiffusion (Mancini, Carbonara & Heremans, 1965). For immunoglobulins, ± 2 s.d. from the mean were used as the limits of normality (Berg, 1969; Kjellman, Johansson & Roth, 1976).

Whenever needed for diagnostic purposes, a RAST test was performed using relevant food (egg, fish, soy, cereals) and/or inhalant (dust, animal dander, moulds, pollen) allergens; RAST class 1 or higher was regarded as a positive result. A skin prick test was performed when the children were 3 years of age using aqueous solutions (1:10 w/v of house dust, *Dermatophagoides pteronyssinus*, mixed moulds, horse epithelium and other suspected allergens. All wealing reactions were regarded as positive for the purpose of this study.

A diagnosis of the present state and a cumulative diagnosis were established at each medical visit and at the final interview. The children were divided into the following subgroups on the basis of the symptoms and signs presented up to that age:

Obvious atopic disease: atopic dermatitis (AD), bronchial asthma (BA), allergic rhinitis (AR) as well as allergic urticaria (U) and gastrointestinal allergy (GI). For a diagnosis of U and GI the same symptoms should have occurred repeatedly from the same food.

Probable atopic disease: either a disease not observed at the clinical examination, e.g. itching flexural eczema, or at least two episodes of urticaria and/or gastrointestinal allergy without identified aetiology. Also children with a wheezing chest in the absence of a respiratory tract infection (BA?) as well as those with a constant nasal discharge or stuffiness (AR?) were considered to suffer from a probable atopic disease (Johnstone, 1977).

Possible atopic disease was taken as the presence of the following symptoms or signs in which an allergic mechanism cannot be excluded (Johnstone, 1977): prolonged diarrhoea, non-itching eczema, skin rash after ingestion or direct contact with certain foods as well as wheezing during two respiratory tract infections or more.

Children without the symptoms enumerated above were regarded to be without atopic disease.

Results

The two randomized groups were nearly identical regarding background factors such as the family history of atopic disease (i.e. the type and intensity of atopic disease in the parents), the age of the mother and the birth weight of the children. There were slightly

more boys in group S but this difference was not statistically significant. Furthermore, the duration of complete and partial breast feeding was nearly the same in the soy group (group S: 1.5 ± 1.6 and 3.1 ± 2.9 months, respectively) as in the cows' milk group (group M: 1.5 ± 1.4 and 3.3 ± 2.8 months, respectively). There was no significant difference in the number of families with pets (in all, eleven decreasing to eight).

The acceptance of the soy formula was good. However, one group S child developed a malabsorption syndrome about 3 weeks after beginning the soy formula feeding; no IgE ab were found against soy protein but repeated challenge with the soy formula provoked the symptoms which all disappeared on a soy free diet. This diet could be abandoned when the child was 3 years of age. All other group S children continued the soy feeding to 9 months of age or more.

The patient compliance with regard to the special dietary restrictions was satisfactory. Two group S children are known to have once received cows' milk formula by mistake, one of these at the maternity ward; they were not excluded from the study as there was no laboratory evidence of sensitization to cow's milk afterwards.

The weight gain was normal in both groups and showed no significant group differences at any age.

Infections occurred with a similar frequency in both groups. *Otitis media* had been diagnosed one or more times in seventeen group S and in eighteen group M children, i.e. in 72.9% of all the children.

Obvious and probable atopic disease developed in thirty-two (66.7%) of the forty-eight children during the observation period (Table 1); in the majority (26/32) before 12 months of age. There were no sex differences. Neither were there any significant differences in this respect between the children fed soy or cow's milk (Fig. 1), nor in the time of appearance of the first symptoms of such disease (group S: 9.2 ± 11.3 months; group M: 9.3 ± 8.9 months).

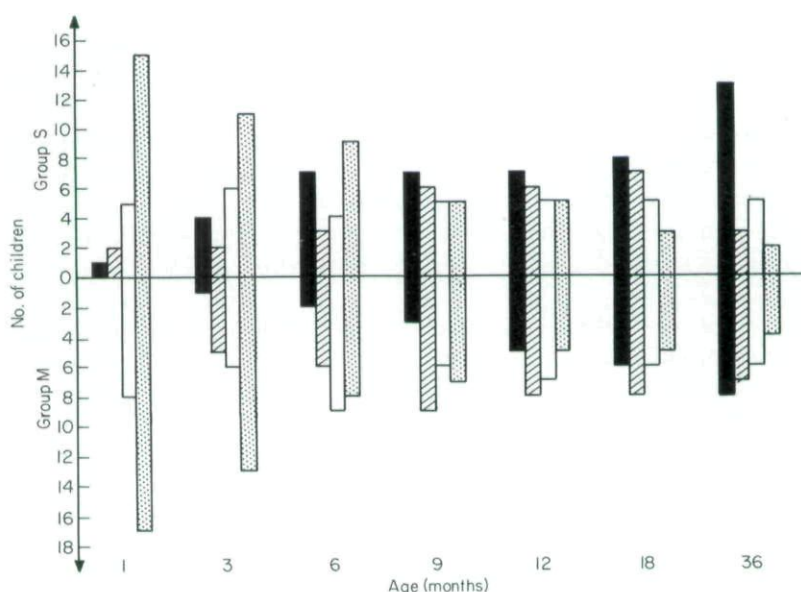


Fig. 1. Atopic disease from 1 to 36 months of age. ■, Obvious atopic disease; ▨, probable atopic disease; ▤, possible atopic disease; □, no atopic disease.

No significant group differences were found regarding the individual diagnoses of the children (Table 2). Atopic dermatitis was the most common ($19/48 = 39.6\%$) of the skin localized atopic symptoms (AD, U) and it was diagnosed at 9.0 months of age, on the average. Similarly, gastrointestinal allergy was found at 13.2 months and respiratory tract allergy (BA, AR) at 36.0 months of age, on the average.

In all, six children showed obvious intolerance symptoms after the ingestion of cow's milk, three from each group (Table 3). In a further five children symptoms occurred which may have been provoked by cow's milk, such as periods of diarrhoea and/or colic, possibly on the basis of allergic mechanisms. This latter group included three children with diarrhoea for a shorter or longer period at the start of cow's milk feeding (group S children); however, only one of these had to return to soy feeding.

Serum IgE levels occurred in the range from 0–480 ku/l. An IgE level above the $+2$ s.d. limit for age was found before the development of symptoms and signs of atopic disease in sixteen of the twenty-six children in whom IgE results were available at that period. There were no significant group differences in the serum IgE levels (Fig. 2).

IgE ab to cow's milk (≥ 0.2 PRU) were found in four children from each group (Table 3). Four of these children had shown symptoms evidently provoked by cow's milk. Three of the remaining four children had symptoms of other obvious or probable atopic disease. In all, a positive RAST was found in nine group S and seven group M children. Skin tests were positive at 3 years of age in five of twenty-two group S and in two of twenty group M children. In all, ten positive tests were found (house dust, five; animal dander, two; pollen, two; mite, one).

IgG ab to cow's milk were found in cord serum in all but three of the newborns (Fig. 3). Significant group differences occurred from 3 to 18 months of age with higher levels in group M but there was no significant difference in the levels at 3 years of age. The IgG ab values showed great individual variations with a trend towards higher levels in children in whom symptoms evidently were provoked by the ingestion of cows' milk (mean 968 ± 733): thus all four children above 1500 % showed symptoms of cow's milk intolerance. There was no significant difference at any age in the levels of IgG ab between children with subsequent obvious and probable atopic disease as compared to those without such disease during the observation period.

Low levels (0.2–0.5 PRU) of serum IgE ab to soy bean were found from 9 months of age in four children, three of whom belonged to the soy group. All these four children

Table 2. Cumulative diagnoses: obvious and probable atopic disease

Disease	Soy		Cow's milk		Total			
					Obvious		Probable	
	Obvious	Probable	Obvious	Probable	<i>n</i>	%	<i>n</i>	%
Atopic dermatitis	12	1	7	4	19	39.6	5	10.4
Bronchial asthma	3	0	0	0	3	6.3	0	0
Allergic rhinitis	4	3	1	2	5	10.4	5	10.4
Allergic urticaria	3	0	3	6	9	18.8	0	0
Gastrointestinal allergy	3	6	1	6	4	8.3	12	25.0

Table 3. Children with IgE antibodies against cow's milk and/or symptoms attributable to cow's milk

Group	Sex	Symptoms (in brackets if unrelated)	Age when symptoms (months)	Age at sampling (months)	IgE-ab PRU	IgG-ab (% of standard)
Soy	F	U*** + GI*** (AD)	9-18	9	4.5	500
	M	(Rash; AD, BA)	1-12	9	0.3	80
	F	U*** (AD)	9-12	12	0.6	1300
	F	GI? Lactase deficiency? (AD)	9-18	9	<0.2	130
	F	GI?*	6-12	9	<0.2	25
	M	GI?* (AD, GI?, AR, U)	9-10	12	<0.2	20
Cow's milk	M	GI** (AR?)	9-12	9	0.3	1900
	M	U** (AD)	3-9	3	0.4	60
	F	Repeated, nonurticarial rash*	1-12	36	0.3	180
	F	GI?* colics*	3-6	3	<0.2	650
	F	Repeated, nonurticarial rash; (AD)	1-12	36	0.4	260
	F	U** (AD?, GI?, U)	3-5	9	<0.2	450
	F	U** + GI? (U, AD?)	3-18	9	<0.2	1600
	M	GI?	6-12	36	0.2	450

*** Indicates obvious connection with cow's milk.

** Indicates probable connection with cow's milk.

* Indicates possible connection with cow's milk.

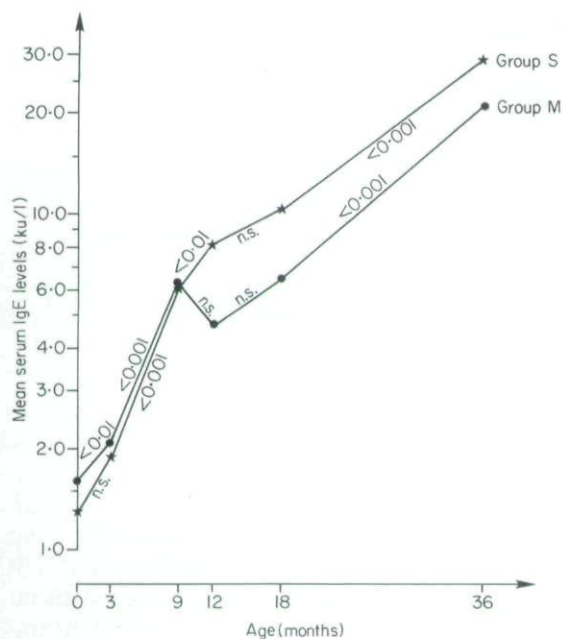


Fig. 2. Mean serum IgE levels (ku/l). The P -value for significant changes between two observation periods is given.

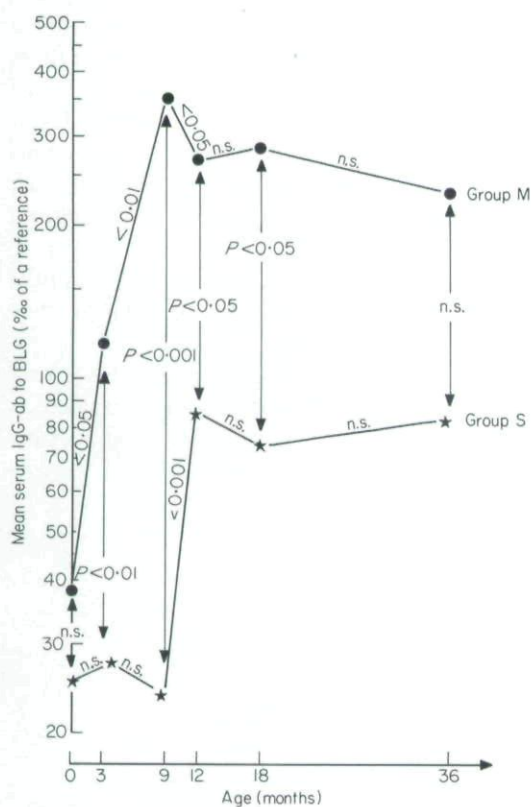


Fig. 3. Mean IgG antibody levels to cow's milk (Betalactoglobulin=BLG). For P -values, see legend to Fig. 2.

Table 4. Serum IgG antibodies to soy bean protein (% of a reference serum)

Age (months)	Soy			Cow's milk			<i>P</i>
	<i>n</i>	$\bar{x}$	$\pm$ s.d.	<i>n</i>	$\bar{x}$	$\pm$ s.d.	
Newborns	13	23.7	25.3	8	25.5	31.6	n.s.
3	20	30.2	49.5	17	14.1	12.1	n.s.
9	23	65.7	164.1	19	9.5	2.0	<0.01
12	23	63.3	104.5	24	24.5	52.5	<0.05
18	24	796.4	2361.1	22	943.3	2587.5	n.s.
36	22	1848.0	2362.0	19	2421.9	3038.9	n.s.

had symptoms of atopic disease during the observation period but there was no indication of any clinical significance of the antibodies. IgG ab to soy bean (Table 4) were transiently higher in the soy group at 9 and 12 months of age but there was no significant difference in the levels of such antibodies between the healthy children and children with atopic symptoms.

No significant group differences were found regarding haemoglobin concentrations, or in the levels of serum albumin (all within normal limits), IgG, IgA and IgM. No child had a serum IgA or IgM level below the -2 s.d. limit at any age but three in group S and four in group M had one serum IgG level or more below this limit; in three of the children such a low IgG level was found before and in the remaining four it was found after the development of atopic disease. Serum IgA (Table 5) or IgM levels showed no significant differences at any age between children with subsequent obvious or probable atopic disease as compared to children who remained free from such disease, nor were such differences found when the interest was focused on children developing gastrointestinal allergy or skin allergy.

Serum cholesterol levels showed significant group differences from 3 to 12 months of age with lower levels in group S (Fig. 4). These differences were significant also when the somewhat skewed sex distribution was taken into account.

Finally, it was found (Table 6) that there was no significant difference in the period of complete and/or partial breast feeding between children ultimately classified as having obvious and probable atopic disease as compared with those showing possible atopic disease and/or no atopic disease during the observation period.

Table 5. Serum IgA levels (g/l) from birth to 18 months of age in the children with and without atopic disease (obvious and probable)

	Newborns			3 months			9 months			12 months			18 months		
	<i>n</i>	Mean	$\pm$ s.d.	<i>n</i>	Mean	$\pm$ s.d.	<i>n</i>	Mean	$\pm$ s.d.	<i>n</i>	Mean	$\pm$ s.d.	<i>n</i>	Mean	$\pm$ s.d.
Atopic disease															
Present	0	—	—	8	0.15	0.13	15	0.29	0.12	18	0.29	0.09	18	0.31	0.12
Subsequent	21	0.06	0.06	19	0.19	0.12	13	0.33	0.18	9	0.30	0.07	6	0.33	0.07
None	6	0.04	0.01	6	0.19	0.08	6	0.42	0.24	6	0.40	0.14	5	0.37	0.14

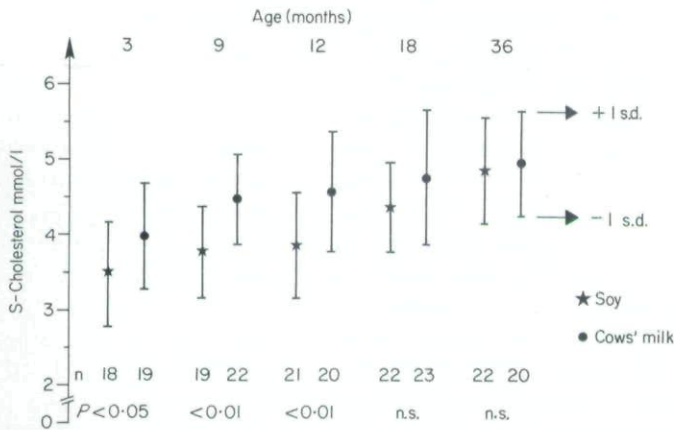


Fig. 4. S-cholesterol levels and no. of children examined at different ages.

Table 6. Atopic disease and period of breast feeding

Atopic disease	n	Period of breast feeding (months)			
		Complete		Partial	
		$\bar{x}$	$\pm$ s.d.	$\bar{x}$	$\pm$ s.d.
Obvious	21	1.6	1.4	3.8	3.0
Probable	11	1.3	1.6	2.3	2.1
Possible	9	1.0	0.6	1.7	1.2
None	7	1.9	2.6	4.1	3.9

Discussion

Infants with a biparental history of atopic disease constitute an ideal group for the study of the possible preventive effect of dietary and/or environmental measures during early infancy for many reasons:

(1) The total incidence of atopic disease (obvious and probable) was high ($32/48 = 66.7\%$). This incidence agrees well with findings of others in children with the same genetic background (van Arsdel & Motulsky, 1959; Kaufman & Frick, 1976; Dannaeus, Johansson & Foucard 1978).

(2) The first symptoms of the disease appeared at an early age (mean 9.1 ± 0.5 months) and only a slight increase in the incidence occurred between 36 and 49 months of age. This is what could be expected from the findings of others (Spain & Cooke, 1924; Halpern *et al.*, 1973; Kaufman & Frick, 1976; Johnstone, 1977; Dannaeus *et al.*, 1978).

(3) Parents, both of whom have atopic disease cooperate exceptionally well in a prospective study of this type. The drop-out rate was low (Fig. 4). Furthermore, dietary restrictions seem to have been followed well.

Soy-bean protein like cow's milk is foreign for human beings. It is therefore not surprising that there was no significant difference in atopic manifestations between the children fed soy and those fed cow's milk from weaning. Thus, the total incidence of

atopic disease, the incidence of any particular atopic disease, and the number of children experiencing symptoms of food intolerance during the observation period were all nearly the same in both groups. Indeed, the incidence of atopic disease seems somewhat higher in the soy group, but this difference does not reach the limit of statistical significance. Thus, we were not able to confirm the observations of the first study by Glaser and Johnstone in 1953, who reported a marked reduction in the incidence of atopic disease (mainly atopic dermatitis, as in our study) by giving a soy-bean formula instead of cow's milk. However, in a later study (Johnstone & Dutton, 1966) less spectacular but still significant effects were obtained upon withholding cows' milk; remarkably few cases of atopic dermatitis were found in this study. Others have failed to reproduce these findings in similarly designed studies with large numbers of participants (Brown *et al.*, 1969; Halpern *et al.*, 1973). In the study of Halpern *et al.*, the children fed cow's milk showed symptoms of allergy earlier than a breast fed control group, but no significant difference was found in the total incidence of atopic disease between children fed breast, soy or cow's milk.

In our study, we found no definite evidence of a protective effect of breast milk. This is in contrast to the findings of many others (e.g. Grulee & Sanford, 1936; Fomon, 1967; Matthew *et al.* 1977). Matthew *et al.* reported fewer ($P < 0.05$) children with atopic dermatitis at 6 and 12 months of age in children fed breast milk (or soy) to at least 6 months of age as compared to children fed cow's milk. No relationship between the development of atopic disease and the time for the onset of artificial feeding could be demonstrated in another study on this subject (Dannaeus *et al.*, 1978). Nevertheless, there are many other reasons which favour the use of breast milk (Gerrard, 1974; Matthew *et al.*, 1977), such as the rather high incidence of cow's milk intolerance during infancy reported by Gerrard *et al.* (1973) and confirmed by our study. Indeed, in our selected group of forty-eight children six had major and five minor symptoms of cow's milk intolerance (Goldman & Heiner, 1977), a total incidence of 11/48 (22.9%). Of the children with reactions an equal number belonged to the soy and cow's milk groups indicating that withholding cow's milk to 9 months of age does not prevent the subsequent development of intolerance to cow's milk. If the cow's milk had been introduced after 18 or 36 months of age, the results may have been different.

We were unable to confirm the observation that a transient serum IgA deficiency is often found at 3 months of age in children with subsequent atopic disease (Taylor *et al.*, 1973; Soothill *et al.*, 1976). However, others (Dannaeus *et al.*, 1978, Brasher & Bourland, 1975) have also failed to find low serum IgA levels before the onset of atopic disease. Recently, the London group (Matthew *et al.*, 1977) was unable to reproduce their initial results when using a more sensitive technique for the analysis of serum IgA. Even if our results do not exclude the possibility that a subpopulation of atopic individuals may have a (possibly transient) deficiency in the production of IgA and/or of secretory IgA, we do not believe that such an immune deficiency is of any major importance in the aetiology of atopic disease.

The withholding of cow's milk did not reduce the incidence of high IgE levels, positive RAST tests or positive skin tests and it resulted in only transiently lower serum levels of IgG ab to cow's milk. We could not confirm the finding (Kletter *et al.*, 1971a, b) that a later introduction of cow's milk reduces significantly the level of the IgG antibody peak. Nor could we reproduce recent findings (Dannaeus *et al.*, 1978) that a high level of transplacentally received anti-cow's milk antibody (=IgG) protects against the development of atopic disease. On the other hand, the use of a soy formula

instead of cow's milk gave few side effects—only one case of probable soy allergy was found. The IgE and IgG ab against soy bean did not parallel the obvious allergic symptoms, but seem to indicate that a contact with soy antigen had taken place. The weight gain was equally good in both groups as expected from the studies of others (Bates *et al.*, 1968, Cherry *et al.*, 1968).

The lower serum cholesterol levels on the soy diet confirm earlier findings (Cherry *et al.*, 1968). As expected (Fomon, 1971) girls showed higher serum cholesterol levels than boys. Even when the skewed sex distribution was taken into account we still found lower serum cholesterol levels in soy fed children. The long-term effect on serum cholesterol is under study.

Also in the present study serum IgE levels above the +2 s.d. limit for age were frequently (16/26 children) found before the development of symptoms of atopic disease. One-third of the children with subsequent atopic disease (obvious and/or probable) during the first 4 years of life could be identified by means of an elevated serum IgE level in cord blood. A screening of serum IgE in about 1800 newborns followed up to 3 years of age is under progress.

In conclusion, soy instead of cow's milk from weaning to 9 months of age, given to infants with a biparental history of atopic disease did not lower the incidence of atopic symptoms, or postpone the development of such symptoms, or reduce the development of laboratory findings indicative of atopy. Two-thirds of the children showed atopic disease at 4 years of age, most of them already before one year of age. Hence, substitution of cow's milk with a soy formula for the prevention of allergy does not seem warranted. A prolonged breast feeding remains the most rational prophylaxis in such children and in addition it has many other advantages.

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