

The effect of maternal avoidance of eggs, cow's milk, and fish during lactation on the development of IgE, IgG, and IgA antibodies in infants

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Serum levels of IgE, IgE antibodies to egg white (EW) and cow's milk (CM), IgG, and IgA antibodies to ovalbumin (OA) and β -lactoglobulin (BLG) were measured in a group of 115 infants with a family history of atopy/allergy at birth and at 3, 6, 9, 12, and 18 months of age. The mothers of 65 infants avoided eggs, CM, and fish during the first 3 months of lactation (maternal antigen avoidance diet, D group), whereas the remaining 50 mothers had no diet restrictions (no maternal antigen avoidance diet, ND group). CM was introduced after 6 months of age and EW after 9 months. The only statistically significant difference between the D and ND group infants was a lower rate of specimens with IgE antibodies to EW and/or CM in the infants at 3 months of age ($p = 0.008$). IgE antibodies to EW and/or CM appeared in 62 infants during the study period and often during complete breast-feeding. In 40 of the infants, IgE antibodies appeared before the introduction of EW and CM into the diet. The IgE concentrations of the D and the ND group infants were similar. Cord-blood IgE was a poor predictor of atopy/allergy; for example, only seven of 103 infants with double heredity for atopy/allergy had values above the 90th percentile of our normal reference. The concentrations of IgG antibodies to OA and BLG were similar in the two groups. The levels decreased significantly ($p < 0.001$) from birth to 6 months of age, indicating a passive placental transfer. From 6 months of age after the introduction of CM formulas, but not eggs, there was a rise in the IgG concentrations of antibodies to both OA and BLG, indicating that low doses of EW antigen in breast milk can evoke an IgG antibody response. Babies with high IgE responses to EW also had high IgG responses to OA. (J ALLERGY CLIN IMMUNOL 1990;85:108-15.)

In a previous study, we demonstrated that sensitization to EW and CM occurs early during infancy and even in exclusively breast-fed infants.^{1, 2} The most likely source of the sensitization would be passage of

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Received for publication Nov. 7, 1988.

Revised Oct. 3, 1989.

Accepted for publication Oct. 4, 1989.

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*Supported by First of May Flower Annual Campaign for Children's Health and from Lions Foundation for Medical Research, Gunnar Hattevig, and by the Council of Skaraborg and Department of Pediatrics Foundation, Skövde, Gunnar Hattevig and Bengt Kjellman.

****Supported by Swedish Medical Research Council Grant 19X-07510.

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Abbreviations used

EW:	Egg white
CM:	Cow's milk
AD:	Atopic dermatitis
D:	Maternal antigen avoidance diet
ND:	No maternal antigen avoidance diet
PRU:	Phadebas RAST Units, Pharmacia
OA:	Ovalbumin
BLG:	β -Lactoglobulin
PBS:	Phosphate-buffered saline
HSA:	Human serum albumin

small doses of antigen into the breast milk, since a diet free from eggs and CM during pregnancy did not diminish the incidence of atopy in the offspring.^{1, 3}

We therefore evaluated the effect of maternal avoidance of eggs, CM, and fish (hypoallergenic diet) during the first 3 months post partum on the development

of atopic symptoms in the infants.⁴ We found a significantly lower incidence of AD during the first 6 months of life in infants of mothers adhering to a hypoallergenic diet, compared to a matched group of infants of mothers without dietary restrictions. However, no effect was observed on the sensitization to EW, CM, and fish, as judged by skin prick tests performed at 9 months of age.

In the present study we report the results of determinations of IgE, IgG, and IgA antibodies in the two groups of infants.

MATERIAL AND METHODS

Subjects

The two groups comprised 103 infants from families with atopic disease in at least two close relatives, that is, parents and siblings, and 12 infants with single heredity and cord-blood IgE ≥ 0.9 kU/L (high-risk infants). Only nonsmoking families without indoor pets were admitted.

During the first 6 months, infants received only breast milk, or if the volumes were insufficient, a formula based on casein hydrolysate (Nutramigen; Birstol-Myers, Stockholm, Sweden.) was supplemented. CM was introduced after 6 months of age and products containing eggs after 9 months of age.

The D group comprised 65 infants, and the ND group, 50 infants. The diet of the D group mothers was free from EW, CM, and fish products and was started immediately after birth and continued for 3 months. The time of 3 months was chosen to minimize dietary mistakes and to obtain maximal compliance. The selection criteria for the study groups have been reported in detail previously.⁴ We consider the D and ND groups comparable because the same antenatal and postnatal selection criteria were used and because the groups were similar with regard to heredity for atopic disease, percentage of mothers excluded for not fulfilling antenatal criteria, and infants not fulfilling postnatal criteria or not completing the study (two and four, respectively), pattern of breast-feeding, number of dietary errors, and distribution of cord-blood IgE values.

Clinical criteria

The clinical criteria of atopic manifestations and adverse reactions have been described previously.⁴ Briefly, AD was defined as chronic or chronically relapsing, noninfectious dermatitis of typical morphology and distribution based on the suggestions by Hanifin and Rajka.⁵

An episode of bronchial obstruction was accepted only if the diagnosis was made by a physician and after examination of the case record by one of the authors. Three or more episodes of bronchial obstruction were regarded as asthma. Rhinitis was considered as allergic if it appeared at least twice after exposure to a particular allergen. Urticaria was defined as allergic if it appeared at least twice within 1 hour after exposure to a particular antigen. Positive exposure to an allergen was defined as an obvious reaction within 1 hour after exposure on at least two occasions.

Examination

All infants were examined neonatally and at 3, 6, 9, 12, and 18 months of age. A history was obtained with a standardized questionnaire, and a physical examination was done, focusing particularly on symptoms of atopy/allergy. During the first 18 months of age, 22 (33.8%) of the D group infants and 21 (42%) of the ND group infants developed atopic manifestations.

Venous blood was sampled at all visits. Sera were frozen, stored at -20°C , and analyzed "blindly" when infants had completed clinical follow-up at 18 months of age.

In the D group, two additional visits were made, one for follow-up of the maternal diet and blood sampling at 6 weeks of age and another for blood sampling at 3½ months, that is, 2 weeks after cessation of the D diet.

Laboratory methods

IgE concentrations were determined by Phadebas IgE PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden), according to the manufacturer's recommendations. Cord-blood specimens and specimens with levels <5 kU/L were analyzed with a modified test with a sensitivity of 0.1 kU/L.¹

IgE antibodies were determined by a modified procedure of Phadebas RAST (Pharmacia Diagnostics AB).¹ Briefly, sera that were RAST negative, that is, <0.35 PRU/ml, which corresponds to the D reference of the Phadebas RAST reference system, were tested a second time with a modified RAST assay. In this modified procedure, the first incubation was extended overnight, and the tubes were shaken continuously. The reference serum was further diluted in a RAST-negative serum with a low IgE level and used at 0.35, 0.175, 0.1, 0.088, 0.044, and 0.022 PRU/ml. Values up to and above 0.1 PRU/ml, approximately corresponding to a count rate twice the background, were regarded as positive. The EW and CM allergens were based on frozen dried egg powder and whole milk protein, respectively.

IgG and IgA antibodies were assayed by anti-OA and anti-BLG micro-ELISA. Flat-bottom microtiter plates (Dynatech Laboratories, Inc., Alexandria, Va.) were coated overnight at 4°C with $100\text{ }\mu\text{l}$ of OA (type III) (Sigma Chemical Co., St. Louis, Mo.), diluted to $20\text{ }\mu\text{g/ml}$ in Tris HCl buffer, pH 8.2, or BLG (Sigma Chemical Co.), diluted to $100\text{ }\mu\text{g/ml}$ in the same buffer. The plates were then washed with PBS, pH 7.4, containing 0.05% Tween 20. Nonspecific binding in the final immunoassay was decreased by incubating the wells with $200\text{ }\mu\text{l}$ of PBS, supplemented with 0.5% HSA for 60 minutes at room temperature. Optimal coating concentration and assay conditions were determined by prior checkerboard titrations against positive/negative sera and conjugates. In the final assay, patient serum samples were diluted 1/10 in PBS-HSA and incubated in the wells ($100\text{ }\mu\text{l}$ per well) 60 minutes at room temperature for BLG and at 37°C for OA. Appropriate dilutions of peroxidase-conjugated antihuman IgG and antihuman IgA (Dakopatts, Glostrup, Denmark) in PBS-HSA were used to detect bound antibodies.

A positive serum sample was used as an internal standard, and the final optical density, read in a Dynatech Minireader

TABLE I. Total IgE (kilounits per liter) in high-risk infants of mothers with and without diet restrictions

Age (mo)	Group	N	IgE in infants						Reference	
			Non atopic		N	Atopic				
			M	90%		M	90%	M	90%	
0	D	42	0.15	1.2	20	<0.1	1.45	<0.1	0.60	
	ND	29	<0.1	1.1	21	0.2	0.4			
3	D	42	1.1	6.8	22	0.95	13.8	2.1	5.0	
	ND	28	1.3	6.0	19	3.2	34.0			
6	D	43	5.1	30.0	22	7.6	27.0	3.0	13.5	
	ND	25	6.8	32.0	18	7.3	110.0			
9	D	43	11.0	36.0	21	11.0	34.0	3.0	13.5	
	ND	28	5.8	54.0	18	36.5	215.0			
12	D	43	11.5	33.0	22	13.7	52.5	3.0	13.5	
	ND	26	5.7	80.0	19	24.0	420.0			
18	D	42	12.3	47.0	21	16.0	60.0	3.0	13.5	
	ND	26	5.4	77.5	17	23.0	500.0			

n, Number of available sera; M, median.

The median and 90th percentile are presented for infants developing atopic/allergy symptoms (atopic) and infants without symptoms (nonatopic).

Reference values were obtained from 55 infants without atopic/allergy symptoms who were unselected for family history.²

II (Dynatech Laboratories, Inc.), was expressed in arbitrary units. The intra-assay variation in both assays was <10% for IgA antibodies and <15% for IgG antibodies. The interassay variation was <13% for IgA antibodies and 15% for IgG antibodies.

Statistical methods

Total IgE and IgE antibody concentrations against EW and CM in the various groups of infants were presented as percentiles, since neither the values themselves nor the logarithms fitted into a normal distribution. Consequently, a nonparametric test, that is, Mann-Whitney, was used for the estimation of differences between groups of data. Wilcoxon's signed-rank test was used for the comparison of two groups in paired samples. Possible differences in groups of subjects were analyzed by Fisher's two-tailed test.

Ethics

All parents whose babies participated gave their informed consent. The study was approved by the Human Research Ethics Committee of the Medical Faculty, University of Linköping.

RESULTS

Total IgE

Cord-blood IgE of the D group infants did not differ significantly from that of the ND group infants. Neither did the cord-blood IgE of the D or ND group infants differ significantly from that of our normal reference values.² Furthermore, the cord-blood IgE values of the D or ND group infants who developed atopic symptoms during the 18-month study period

did not differ significantly from values of the non-atopic D or ND group infants or from values of our normal reference values (Table I).

At 3, 6, 12, and 18 months of age, the median values of the D group infants did not differ significantly from corresponding values of the ND group infants. Likewise, there was no difference between the IgE values of the D group infants and the ND group infants without AD or between the IgE values of the D and ND group infants with AD.

IgE antibodies to EW and CM

IgE antibodies to EW and CM were detected in 62 infants (54%) during the study period. The development of IgE antibodies is illustrated in Fig. 1. At 3 months of age, nine infants had antibodies to EW or CM. Analyses of their cord-blood sera demonstrated no detectable IgE antibodies. Specimens from infants at 6 weeks of age were available for the D group infants, but only in one specimen were IgE antibodies found (0.25 PRU/ml to EW) and only from this age.

The number of infants with IgE antibodies to food did not differ significantly between the D and ND groups at any age (at 3 months of age, $p = 0.057$). However, the number of positive tests, that is, against either EW or CM, was significantly higher ($p = 0.008$) in the ND group (10 positive tests) than in the D group (two positive tests) at 3 months of age. After this age, no significant differences were found.

Most of the 26 infants with IgE antibodies up to

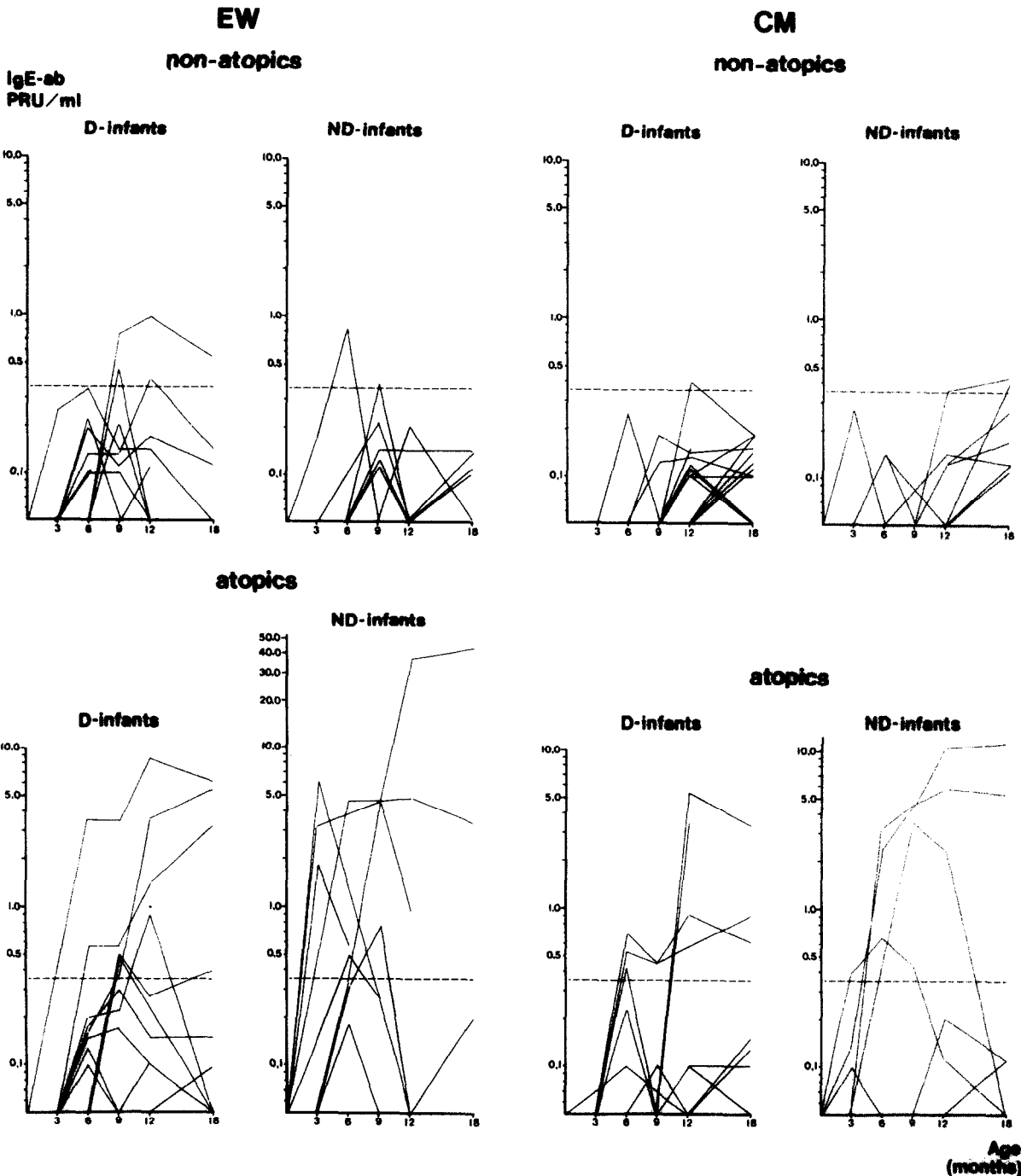


FIG. 1. Development of IgE antibodies (*IgE-ab*), expressed in PRU per milliliter, to EW in high-risk infants of mothers with diet restrictions (*D*) and without (*ND*). The dotted horizontal line indicates 0.35 PRU/ml, which is the lower limit of Phadebas RAST class 1.

and above 0.35 PRU/ml, that is, RAST class 1, are illustrated in Fig. 1 to have developed atopic symptoms of allergy during the follow-up period.

IgE antibodies to EW appeared before known introduction of EW into the diet in all infants developing such antibodies and to CM before know introduction of CM into the diet in most of the infants developing such antibodies during the study period.

IgG antibodies to OA and BLG

The number of specimens with detectable IgG antibodies to OA was 103 at birth, and 96, 94, 99, 105, and 111 at 3, 6, 9, 12, and 18 months of age, respectively. The numbers were similar in the D and ND group infants. The concentrations of IgG antibodies to OA are illustrated in Fig. 2. There were no significant differences between the D and ND groups

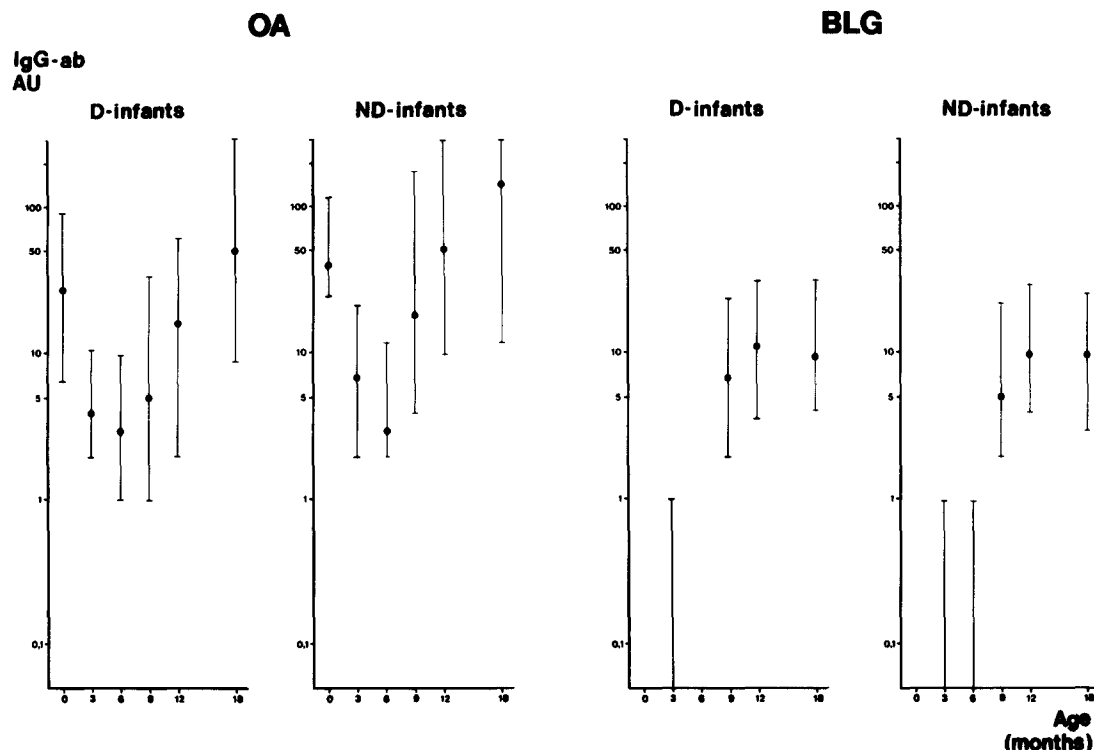


FIG. 2. The development of IgG antibodies (*IgG-ab*) to OA and BLG, both expressed in arbitrary units (AU) in high-risk infants of mothers with diet restrictions (D) and without (ND). The median (●) and the upper (┐) and lower (┌) quartiles are illustrated. The medians of IgG-ab to BLG at 3 and 6 months of age were below the detectable limit, as was the upper quartile of the D group infants at 6 months.

nor between the atopic and nonatopic infants within the D or ND groups.

Decreasing levels of IgG antibody to OA from birth to 6 months of age ($p < 0.001$) and then increasing levels ($p < 0.001$) are illustrated in Fig. 2. In the D group infants, serum samples were also obtained at 6 weeks of age. The concentrations at this age were lower than concentrations at birth ($p < 0.001$) but higher ($p < 0.001$) than concentrations at 3 months. There was no significant change ($p = 0.215$) in the concentrations of IgG antibody to OA between 3 and 6 months of age.

In the 10 D group infants developing high levels of IgE antibody to EW (≥ 0.35 PRU/ml), the concentrations of IgG antibody to OA were significantly higher than the concentrations in the remaining 55 infants at 6 months ($p = 0.011$), at 9 months ($p < 0.001$), and at 12 months ($p = 0.0025$) (Fig. 3).

In the 12 ND group infants with high levels of IgE antibody to EW, a tendency to higher concentrations of IgG antibody was noted (Fig. 3).

IgG antibodies to BLG were demonstrated at 3 months of age in only 37 and at 6 months in only 29 infants, whereas the number of positive specimens

rose to 95 at 9 months. At 12 and 18 months of age, all but three infants had developed such antibodies. The occurrence of the IgG antibodies to BLG was similar in the D and ND groups.

The concentrations of IgG antibody to BLG were similar in the D and ND groups (Fig. 2). There were no significant differences between atopic and nonatopic infants within the D or ND groups nor between infants with AD and infants without.

The cord-blood samples of the 20 infants with the highest concentration of IgG antibodies to BLG at 3 months of age were analyzed for IgG antibodies to BLG. The concentrations decreased significantly ($p < 0.001$) from birth to the age of 3 months. There was no significant change in the concentrations between 3 and 6 months of age but a significant rise from 6 months ($p < 0.001$). The concentrations of IgG antibodies to BLG thus had a two-phase pattern similar to the pattern for IgG antibodies to OA (Fig. 2).

IgA antibodies to OA and BLG

IgA antibodies to OA in the D group infants were detected in 17, 24, 30, 37, and 35 infants at 3, 6, 9, 12, and 18 months of age, respectively. The corre-

sponding values for the ND group infants were 14, 13, 21, 23, and 21 infants.

IgA antibodies to BLG in the D group infants were found in 3, 4, 20, 31, and 31 infants at 3, 6, 9, 12, and 18 months of age, respectively. The corresponding values for the ND group infants were 1, 2, 10, 21, and 14 infants. The concentrations of IgA antibodies to both OA and BLG were just above the detection levels, and there was no difference between the D and the ND groups and no correlation in the individual babies with either IgE or IgG antibody levels.

DISCUSSION

The only statistically significant serologic difference between the D and the ND group infants was a lower rate of specimens with IgE antibodies to EW and/or CM in the D group infants at 3 months of age ($p = 0.008$). This indicates a lower sensitization rate because of the maternal antigen avoidance during the first 3 months of lactation, which agrees with the lower rate of AD found in the D group infants.⁴ However, the numbers of AD were similar only from 9 months of age, whereas rates and concentrations of IgE antibodies were almost identical from 6 months of age.

This finding indicates that the appearance of IgE antibodies can precede the appearance of clinical symptoms of atopy, which is similar to our previous findings regarding food proteins in infants with no particular family history of allergy and with inhaled antigens in school children.^{1-2, 6}

The D and ND groups were recruited from two different hospitals because a true randomization would have involved the risk of ND group mothers adapting to the diet of the D group mothers. We know that many families with the experience of severe atopic disease in their family members enthusiastically try various prophylactic regimens for their potentially allergic infants. We selected therefore two matched towns of equal size located 60 miles apart in geographically and socioeconomically similar areas. A thorough examination of the comparability of the two matched groups disclosed no differences.⁴ Furthermore, the laboratory results were obtained and evaluated after the final clinical characterization.

EW appeared to cause a stronger IgE antibody response than CM. High levels of IgE antibodies to EW and/or CM, that is, levels ≥ 0.35 PRU/ml, were mainly observed in infants with present or future atopy, similar to our previous findings.^{1, 2}

In spite of the hypoallergenic diet in both groups of infants, the IgE antibodies to EW and CM appeared during early infancy and mostly before the allergens were introduced into the diet. Accordingly, sensi-

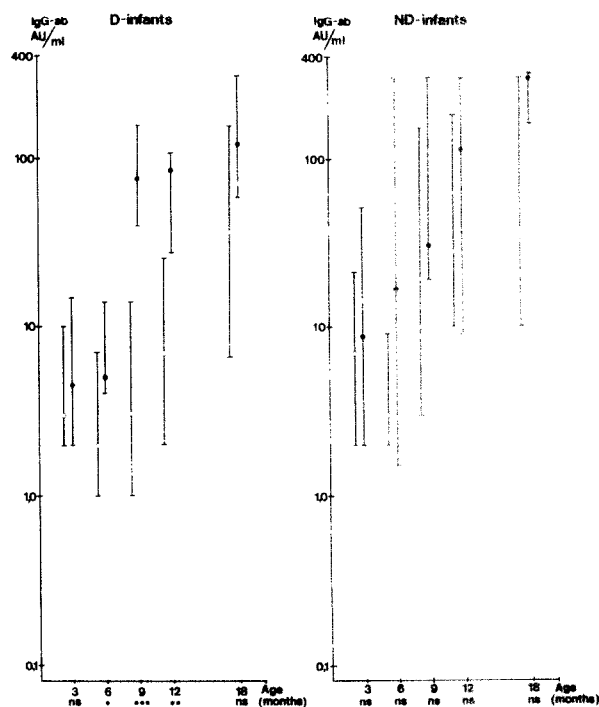


FIG. 3. IgG antibody (*IgG-ab*) concentrations in arbitrary units (AU) of antibodies to OA in D and ND group infants who developed IgE antibodies ≥ 0.35 PRU/ml to EW (●) and infants who did not (○). The median (● resp. ○) and the upper (▮) and lower (▮) quartiles are illustrated; ns, not significant; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

zation to food proteins was common in fully breast-fed infants, similar to our findings in unselected infants.¹ The most likely source of the sensitization was small doses of antigen in the breast milk. This does not exclude the possibility that less atopic symptoms may occur during ongoing lactation than during formula feeding because of antigen doses large enough to sensitize but too small to provoke symptoms. Antigens in the breast milk could explain the sensitization in all the ND group infants and all but two infants in the D group. These two infants were weaned before 3 months of age, and the mothers stated that they had adhered strictly to the diet and that no infant had been fed any CM before 6 months of age or any EW before 9 months of age. Both infants had IgE antibodies to EW and one infant to CM. Possible explanations of the sensitization include contact with small doses of antigen during the preparation of food, for example, by inhalation, an unobserved supply of EW by mouth, or a transplacental transfer of anti-idiotypic antibodies.⁷

Cord-blood IgE was a poor predictor of atopy in this study, as in our previous study of infants unselected for family history of atopy.² It is remarkable that only seven of 103 infants with double heredity

for atopy/allergy had cord-blood IgE values above the 90th percentile (0.60 kU/L) of our normal reference values and that only three of these seven infants developed atopic symptoms during the study period.² This is in agreement with several recent prospective studies in high-risk infants.⁸⁻¹⁰ In other prospective studies, however, a higher predictive capacity was reported.¹¹⁻¹⁶

The influence of the genetic predisposition to develop IgE is obvious in our series. At 9 months of age, our high-risk infants living in a hypoallergenic environment (no smoking and no furred animals) and fed a hypoallergenic diet had significantly higher IgE concentrations than our previously studied infants with no particular family history and not protected by preventive measures.^{1, 2, 4} This observation supports previous observations in animals and humans that IgE responses are strongly associated with genetic propensity and stimulation with small doses of antigen.¹⁷⁻¹⁹

The decreasing IgG concentrations to OA and BLG from birth to approximately 6 months of age indicate a passive transfer of the antibodies through the placenta to the fetus in accordance with previous studies.²⁰⁻²²

It has been suggested that estimations of IgG antibodies in infants can be used as a tool to check compliance with a prescribed diet.^{10, 23} But since the IgG antibodies to food proteins during the first months of life are mainly of maternal origin, their value during that time appears limited in this respect. The increase in IgG antibody concentrations after that age is similar to recent findings in prophylactically treated high-risk infants by Zeiger et al.¹⁰

The rise in IgG antibodies to OA preceded the introduction of EW into the babies' diet. This indicates that even small doses of EW antigen, for example, in breast milk, can cause a substantial IgG antibody response similar to the IgE antibody response.

In a previous study, it has been suggested that high IgG/IgE food antibody ratio or high IgG antibody levels to food during infancy may be a good prognostic sign, indicating a possible blocking capacity of IgG antibodies and that IgG antibody concentrations in the mothers' sera may afford protection against atopy in their offsprings.^{21, 24} This hypothesis is contradicted by the present findings of high levels of IgG antibodies to OA in infants developing high levels of IgE antibodies and atopic disease. However, the present study covers only the first 18 months of life, and a possible correlation between IgG levels and atopy at older ages remains to be evaluated at a planned follow-up. The question as to whether IgG antibodies may contribute to an aggravation of atopic symptoms, which has also

been suggested, was not evaluated by the authors.²⁵ The relation between high levels of IgE and IgG antibodies to egg antigens obtained in the present study is in accordance with studies by, for example, Dan-naeus et al.,²⁶ 1977, and Rowntree et al.,²⁷ 1985. Such a relation between IgE and IgG antibodies has recently also been reported for inhalants.²⁸ These findings imply a propensity of the atopic subject to hyperproduction of both isotypes.

The benefit in the D group infants was a lower rate of sensitization during the first 3 months of life, as reported here, and a lower rate of AD during the first 6 months of life, as reported previously.⁴ We believe that this advantage is too small to warrant general advice to families with atopy to observe antigen avoidance during lactation. Individual recommendations to this effect can be considered, however, in families with pronounced heredity and with previous familial experience of severe atopy.

CONCLUSIONS

Maternal diet restrictions for 3 months resulted in a lower rate of sensitization in the babies during the 3 months and a lower rate of AD for 6 months.

IgE antibodies to EW and CM appeared independently of the duration of complete breast-feeding and mostly before the introduction of the antigens into the diet of the infant. High levels of IgE antibodies were mainly observed in infants with present or future atopy/allergy, which documents a high diagnostic and predictive value.

IgG antibodies to OA and BLG, demonstrated during the first 6 months of life, mainly represented maternal antibodies transferred through the placenta. After that time, the IgG antibody levels increased rapidly, particularly in infants with a high response of IgE antibodies to EW. This was found even for infants exposed only to small amounts of EW.

We thank Kerstin Hagersten and Lisbet Hjalte for the IgE analysis, and Christina Reuter for the IgG and IgA analysis.

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