

The relevance of maternal immune responses to inhalant allergens to maternal symptoms, passive transfer to the infant, and development of antibodies in the first 2 years of life

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Background: Asthma and other atopic diseases are strongly hereditary. Although the mother might play a special role, the mechanisms for such an effect are not clear.

Objective: We sought to investigate the influence of maternal immune responses to cat and mite allergens on (1) maternal symptoms, (2) the development of immune responses in the infant, and (3) the development of allergic disease during the first 3 years of life.

Methods: In sera from 465 mothers and 424 infants (cord blood), as well as in sera from 230 of the children at age 2 to 3 years, total IgE and IgE antibodies were measured by using CAP testing; IgG and IgG4 antibodies for the cat allergen Fel d 1 were measured by means of radioimmunoprecipitation.

Results: In both mothers and children, approximately 15% of sera contained IgG antibodies to Fel d 1 without IgE antibodies to cat. The strongest predictor of the maternal IgG antibody response was exposure to greater than 8 µg of Fel d 1/g of dust. Thus approximately 70% of children living in a house with a cat had received IgG antibodies from their mothers. In many cases the infant received IgG and IgG4 antibodies to Fel d 1 from a nonallergic mother. Maternal IgE antibodies were consistently associated with asthma; by contrast, the IgG antibody was not independently related to asthma but was related to rhinitis in the mothers (odds ratio, 2.6; 95% CI, 1.1-6.2) and to eczema in children. At age 3 years, 13 of 230 sera contained IgE antibodies to mite, but only 5 had IgE antibodies to cat.

Conclusions: A significant proportion (approximately 15%) of mothers and children exposed to high concentrations of cat (but not mite) allergens have serum IgG antibodies without IgE antibodies. This IgG antibody is freely transferred to the infant and might influence IgG antibody production in the

child. The results indicate the importance of understanding the mechanisms of tolerance to cats and raise questions about the independent role of the mother in the inheritance of allergy. (*J Allergy Clin Immunol* 2003;111:123-30.)

Key words: Asthma, cord blood, IgG antibody, IgG4 antibody, eczema, cat, dust mite, maternal inheritance

Over the last 30 years, asthma has increased both in prevalence and severity.¹⁻³ In children and young adults this disease is consistently associated with immediate hypersensitivity to common inhalant allergens.⁴⁻⁶ In addition, there is evidence that many of the children who have asthma had some lung symptoms during the first 2 years of life.^{7,8} Thus it is not surprising that research has focused on identifying events occurring either during or before infancy that could predispose children to becoming allergic. Inevitably, the parents play a large role because they provide both the genes and the environment with which the infant has to cope. The mother plays a special role because the uterine environment influences the development of the fetus; thus it is undoubted that maternal smoking during pregnancy is associated with decreased lung size in infants.^{9,10} Furthermore, infectious agents, food antigens, and specific antibodies can cross the placenta during pregnancy.¹¹⁻¹³ On the other hand, it is not clear whether inhalant allergens are present in sufficient quantities to influence the fetal immune system or whether passively transferred maternal IgG antibodies to mite or other allergens can influence the response of the fetus or infant. Evidence about immune responses in early childhood can be obtained from skin tests, serologic studies, or in vitro studies on T cells.^{6,14-16} Prospective and cross-sectional studies have shown that IgG and IgE antibodies to dust mite allergens develop in parallel and are related to exposure.^{4,14} Furthermore, for all allergens, most nonallergic individuals who have low exposure have no detectable antibodies.

For allergens other than dust mite, the serologic and T-cell data are much less extensive; however, several recent studies have suggested that the presence of a cat in the house is associated with a decreased risk of asthma and

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TABLE I. Prevalence of IgE and IgG antibodies in maternal sera

Allergen (sera tested)	Specific IgE†	IgG antibodies by RIP*		Relationship of IgE to illness†	
		IgG+ve/IgE+ve§	IgG+ve/IgE-ve§	Allergic rhinitis, OR (95% CI)	Asthma, OR (95% CI)
Cat (n = 465)	146	93 (122)	70 (42)	2.1 (1.2-3.6)	3.8 (2.1-6.7)
Dust mite (n = 464)	169	104 (120)	41 (20)	1.0 (0.6-1.6)	2.2 (1.2-3.8)
Cockroach (n = 463)	52	—	—	0.9 (0.4-1.7)	3.0 (1.5-6.2)
Ryegrass (n = 454)	117	—	—	2.2 (1.3-3.8)	1.1 (0.6-1.8)
Ragweed (n = 454)	116	—	—	1.7 (1.0-2.9)	0.8 (0.5-1.4)
Any IgE antibody (n = 460)	278	—	—	7.5 (4.6-12.2)	2.7 (1.7-4.4)

*IgG antibody was measured by means of radioimmunoprecipitation (RIP) with Der f 1 for dust mite and Fel d 1 for cat.

†Doctor-diagnosed allergic rhinitis or asthma; ORs are adjusted for age, race, area poverty, income, education, and any other allergy.

‡IgE antibodies of 0.35 IU/mL or greater.

§The first number refers to the presence of IgG to Fel d 1 in the presence (IgE+) or absence (IgE-) of IgE to cat. The numbers in parentheses refer to the presence of IgG to Fel d 1 (cat) or Der f 1 (mite) with or without any specific IgE antibodies.

||Total positive result to cockroach, mite, cat, dog, ryegrass, ragweed, *Alternaria* species, or *Aspergillus* species or IgE levels of 200 IU/mL or greater.

Abbreviation used

OR: Odds ratio

decreased risk of sensitization to cat allergen.¹⁷⁻¹⁹ More recently, we have reported that a significant proportion of children exposed to high concentrations of cat allergen have had IgG antibody responses to the cat allergen Fel d 1 without becoming allergic.²⁰ In a longitudinal birth cohort of 499 families, we hypothesized that cat allergen levels in the home would influence IgG antibody levels in the pregnant mother and that the IgG to cat would be passed on to the child, which might influence the development of immune responses or symptoms in the child. Thus we investigated (1) cat allergen levels in the home as a predictor of antibodies to cat (IgG and IgE) in the pregnant mother, cord blood, and serum at 2 to 3 years of age; (2) maternal IgG levels to cat as a predictor of cord IgG and IgG to cat at age 2 to 3 years; and (3) IgG levels to cat as an independent predictor of maternal and child symptoms of allergy or asthma.

METHODS

Subjects

This is a follow-up analysis in the Epidemiology of Home Allergens and Asthma Study, an ongoing longitudinal birth and family cohort study in Boston, Massachusetts. As such, the criteria for inclusion have been described previously.²¹ Women living in Boston who delivered a full-term healthy child between September 1994 and June 1996 were screened. If either parent had a doctor's diagnosis of asthma or allergic rhinitis, the family was eligible for inclusion. A total of 499 mothers entered the study, and sera were obtained from 465. Umbilical cord samples were obtained from 424 infants, and sera were obtained from 230 children at age 2 to 3 years.

Dust collection

Within 2 to 3 months after the infant's birth, 4 dust samples were collected from the home with a Mighty-Mite vacuum cleaner (Model 3621; The Eureka Co, Bloomington, Ind). They were sieved through a 425- μ m mesh and weighed. Allergen levels in the dust samples were determined by means of ELISA and reported as micrograms per gram of dust.^{22,23}

IgE measurements

Maternal serum samples were assayed for total IgE, as well as for specific IgE antibodies to dust mite, cat, cockroach, dog, ryegrass, ragweed, *Alternaria* species, and *Aspergillus fumigatus* by using the CAP FEIA system (Pharmacia, Uppsala, Sweden). In the children total serum IgE and specific IgE levels to dust mite and cat were determined by using the same system. Sensitivity was determined by using a cut-off point of 2.0 IU/mL for total IgE and 0.35 IU/mL for specific IgE.^{24,25} Cord blood samples were assayed for total IgE by using a modification of the protocol to provide a cut-off point of 0.2 IU/mL.

IgG and IgG4 measurements

IgG titers were determined in the sera of the mothers and children by means of radioimmunoprecipitation. Allergen labeled with iodine 125 was incubated with each serum sample for 2 hours at room temperature.^{26,27} After addition of precipitating polyclonal goat anti-human IgG antibody (Strategic Biosolutions, Ramona, Calif), the samples were incubated overnight at 4°C. The precipitates were washed 3 times and counted. IgG4 antibody levels were determined by using the same process with the addition of an intermediate 2-hour incubation at room temperature with monoclonal mouse anti-human IgG4 antibody (Clone HP6023; Accurate Chemical and Scientific Corp, Westbury, NY).^{20,28} The precipitating polyclonal goat anti-mouse IgG antiserum was adsorbed twice over cyanogen bromide-activated sepharose (Amersham Pharmacia Biotech AB, Uppsala, Sweden) coupled with human IgG (Sigma, St Louis, Mo) to remove cross-reactive constituents.

Definitions and statistical analysis

Definitions for maternal self-reported diagnosis of allergic rhinitis, asthma, and markers of race and socioeconomic status have been described previously.²¹ Among the mothers, *any IgE antibody* was defined as a positive IgE result to one or more of the 8 specific allergens (cat, dust mite, cockroach, dog, ryegrass, ragweed, *Alternaria* species, or *Aspergillus* species) or a total IgE level of greater than 200 IU/mL. Four mothers who had total IgE levels of greater than 200 IU/mL but negative IgE antibody results (n = 1) or missing results for IgE antibodies (n = 3) were included in the any IgE antibody group. We investigated the relationship between childhood disease (eczema, rhinitis, or recurrent wheeze) and 2 alternative definitions of child IgE antibodies (Table IV): having any IgE antibody (positive IgE results to cat, dust mite, cockroach, or egg white) or having IgE antibodies to inhalant allergens (positive IgE results to cat, dust mite, or cockroach). Child eczema and allergic rhinitis were defined as ever having a doctor's diagnosis of these ill-

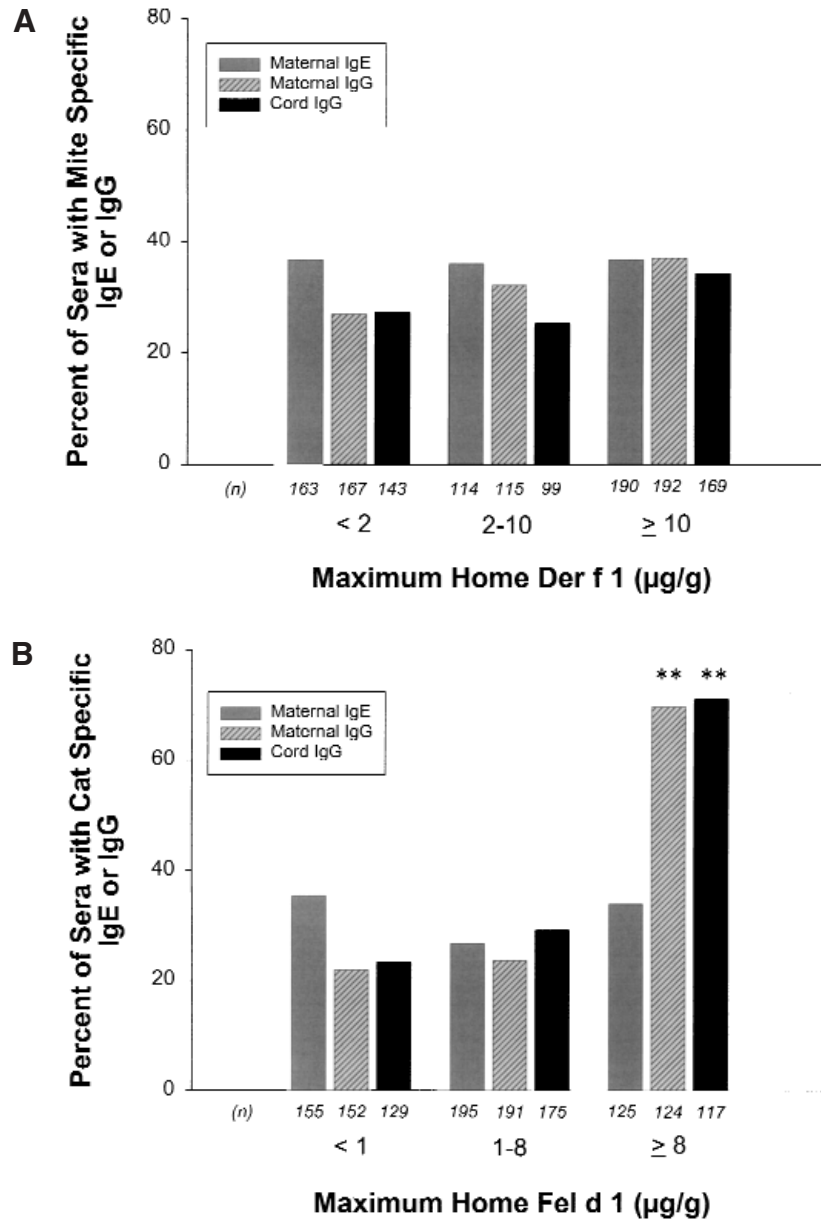


FIG 1. IgE and IgG antibodies in maternal sera and IgG antibodies in cord sera relative to exposure to allergens at home. Numbers below each column indicate numbers of sera tested. Dust samples were collected at age 3 months and assayed for Der f 1 and Fel d 1. **A**, Percentage of maternal sera with IgE antibodies to mite, maternal sera with IgG antibodies to Der f 1, and cord blood with IgG antibodies to Der f 1. Values are not related to exposure ($P > .1$). **B**, Percentage of maternal sera with IgE antibodies to cat, maternal sera with IgG antibodies to Fel d 1, and cord blood with IgG antibodies to Fel d 1. Prevalence of IgG antibodies to Fel d 1 was significantly higher in those subjects with greater than 8 µg of Fel d 1 at home ($P < .001$ for maternal sera and cord blood).

nesses up to and including age 3 years. Recurrent wheeze was defined as having a report of wheeze at age 3 years and in the first 2 years of life.

All univariate and multivariate logistic regression analyses used SAS statistical software (SAS Institute, Inc, Cary, NC). Odds ratios (ORs) and adjustment of potential confounders were made by means of multiple logistic regression. Given the nonlinear distribution of the antibody levels, the correlations between IgE or IgG levels in 2 groups were calculated by using Spearman rank correlation.

RESULTS

Immune response of mothers to cat and mite allergens

In keeping with the criteria for enrollment, a large proportion of the mothers had IgE antibodies to common inhalant allergens. Sensitization to each of the indoor allergens (dust mite, cat, and cockroach) was strongly

TABLE II. Maternal doctor-diagnosed allergic rhinitis and asthma according to IgG to cat and any IgE antibody*

Maternal predictors	N	Maternal allergic rhinitis (n = 210)			Maternal asthma (n = 154)		
		Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Cat IgG positive/any IgE antibody positive†	122	8.6 (3.9-18.8)	8.2 (3.7-18.3)	13.5 (7.0-26.3)	1.8 (0.83-4.1)	1.9 (0.85-4.4)	4.9 (2.6-9.1)
Cat IgG positive/IgE antibody negative	42	2.6 (1.1-6.2)	2.4 (0.97-6.0)	2.5 (1.0-6.2)	1.6 (0.63-3.8)	1.7 (0.65-4.5)	1.7 (0.67-4.6)
Cat IgG negative/any IgE antibody positive	154	6.4 (3.4-12.0)	6.5 (3.4-12.2)	7.8 (4.2-14.3)	1.3 (0.69-2.6)	1.3 (0.69-2.6)	2.1 (1.2-3.8)
Cat IgG negative/IgE antibody negative	140	1.0	1.0	1.0	1.0	1.0	1.0
Cat IgE‡	147	1.8 (1.0-3.3)	1.8 (1.0-3.3)	—	3.2 (1.7-6.0)	3.2 (1.7-5.9)	—
Fel d 1 ≥8 µg/g	131	—	1.2 (0.66-2.1)	1.1 (0.62-2.0)	—	0.86 (0.48-1.5)	0.80 (0.45-1.4)

*OR with multivariate analysis adjusted for age, race, area poverty, income, and education.

†Any IgE antibody positive, Positive IgE result to cockroach, dust mite, cat, dog, rye grass, ragweed, *Alternaria* species, or *Aspergillus* species or IgE levels of 200 IU/mL or greater.

‡Cat IgE antibodies of 0.35 IU/mL or greater.

TABLE III. Predictors of child IgG antibodies to cat (Fel d 1) at 2 to 3 years of age

	N	Child IgG to cat (n = 41)				
		Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)	Model 4, OR (95% CI)	Model 5, OR (95% CI)
Maternal cat IgG/maternal IgE antibody*						
IgG positive/IgE antibody positive	60	7.8 (2.5-24.5)	—	4.4 (1.3-15.3)	—	—
IgG positive/IgE antibody negative	19	13.1 (3.4-50.6)	—	4.8 (1.1-21.0)	—	—
IgG negative/IgE antibody positive	70	1.1 (0.3-4.4)	—	2.9 (0.6-14.0)	—	—
IgG negative/IgE antibody negative	62	1.0	—	1.0	—	—
Cord cat IgG/maternal IgE antibody						
IgG positive/IgE antibody positive	56	—	—	—	5.0 (1.6-16.1)	2.9 (0.8-10.4)
IgG positive/IgE antibody negative	21	—	—	—	8.6 (2.3-32.9)	3.6 (0.8-16.0)
IgG negative/IgE antibody positive	50	—	—	—	0.5 (0.1-2.7)	1.5 (0.2-12.1)
IgG negative/IgE antibody negative	50	—	—	—	1.0	1.0
Cat allergen at 2 to 3 mo						
Fel d 1 ≥8 µg/g	71	—	29.9 (6.8-131.6)	46.3 (5.4-395.5)	—	34.2 (4.0-290.2)
Fel d 1 <8 µg/g	84	—	3.3 (0.7-16.5)	6.0 (0.7-50.2)	—	3.6 (0.4-33.4)
Fel d 1 <1 µg/g	75	—	1.0	1.0	—	1.0

*Maternal IgE antibody, Positive IgE result (≥0.35 IU/mL) to cockroach, dust mite, cat, dog, ryegrass, ragweed, *Alternaria* species, or *Aspergillus* species or IgE level of 200 IU/mL or greater.

associated with asthma (Table I).²¹ Serum IgG antibodies were measured by using major allergens from dust mite and cat (ie, Der f 1 and Fel d 1). The prevalence of IgG antibodies to Fel d 1 was higher than for Der f 1; specifically, there were twice as many sera with IgG antibodies but without IgE antibodies (Table I). The prevalence of IgE antibodies to mite or cat was not associated with current allergen exposure (Fig 1). Equally, the prevalence of IgG antibodies to Der f 1 was not associated with mite allergen levels in the home (Fig 1, A). By contrast, there was a highly significant increase in the prevalence of IgG antibodies to Fel d 1 in the group with the highest exposure to this cat allergen (Fig 1, B). Thus the highest exposure group included 48 mothers (ie, 12% of the total) who had IgG antibodies to Fel d 1 but not IgE antibodies to cat. Using an isotype specific assay for IgG4 antibodies to Fel d 1, we compared this isotype with total IgG antibodies. The prevalence and quantity of Fel d 1-specific IgG4

antibodies was very similar in sera with or without IgE antibodies to cat. Thus the correlation between IgG and IgG4 was at an *r* value of 0.64 in sera with IgE antibodies to cat and 0.67 in sera without IgE antibodies.

Relevance of maternal IgG antibodies to Fel d 1 to maternal symptoms

Maternal IgE antibodies to different allergens were strongly associated with doctor-diagnosed asthma and allergic rhinitis. Because IgG antibodies to these allergens were present in a large proportion of the sera with IgE antibodies, it is not surprising that IgG antibodies were associated with symptoms. The question was therefore whether IgG antibodies without IgE antibodies contribute to symptoms. In a preliminary analysis we found that IgG antibodies to Fel d 1 without IgE antibodies to cat (n = 70) showed no association with maternal asthma (OR, 1.01; 95% CI, 0.49-2.07) but was significantly

TABLE IV. Univariate predictors of child eczema, rhinitis, and recurrent wheeze by 3 years of age

	N	Child eczema (n = 214), OR (95% CI)	N	Child rhinitis (n = 35), OR (95% CI)	N	Child recurrent wheeze (n = 67), OR (95% CI)
Maternal cat IgG/maternal IgE antibody*						
IgG positive/IgE antibody positive	119	1.7 (1.0-2.8)	119	1.9 (0.7-5.3)	118	1.2 (0.6-2.5)
IgG positive/IgE antibody negative	44	1.8 (0.9-3.6)	44	1.5 (0.4-6.2)	44	1.4 (0.5-3.7)
IgG negative/IgE antibody positive	144	1.8 (1.1-3.0)	139	2.1 (0.8-5.7)	138	1.6 (0.8-3.2)
IgG negative/IgE antibody negative	128	1.0	127	1.0	127	1.0
Child cat IgG 2-3 y/child IgE antibody†						
IgG positive/IgE antibody positive	9	11.8 (1.4-96.7)		—‡	7§	4.1 (0.9-19.4)
IgG positive/IgE antibody negative	32	3.3 (1.4-7.3)		—	34	0.9 (0.3-2.7)
IgG negative/IgE antibody positive	20	1.2 (0.5-3.1)		—	10	1.4 (0.3-6.8)
IgG negative/IgE antibody negative	166	1.0		—	175	1.0
Cat allergen exposure						
Fel d 1 ≥8 µg/g	130	1.1 (0.7-1.7)	130	0.8 (0.4-2.0)	130	1.1 (0.6-2.2)
Fel d 1 >1 and <8 µg/g	197	0.9 (0.6-1.3)	196	0.7 (0.3-1.5)	194	0.8 (0.4-1.5)
Fel d 1 <1 µg/g	148	1.0	143	1.0	143	1.0

*Maternal IgE antibody. Positive IgE result to cockroach, dust mite, cat, dog, ryegrass, ragweed, *Alternaria* species, or *Aspergillus* species or IgE level of 200 IU/mL or greater.

†Child IgE antibody. Positive IgE result to cockroach, dust mite, cat, or egg white in analysis of risk for eczema.

‡Insufficient numbers with rhinitis to estimate OR.

§Child IgE antibody. Positive IgE result to cockroach, dust mite, or cat in analysis of risk for recurrent wheeze.

||Homes were visited to collect allergen when the child was 2 to 3 months of age.

associated with allergic rhinitis (OR, 2.2; 95% CI, 1.16-4.2). However, because IgE antibodies to other allergens can contribute to both asthma and rhinitis, we elected to analyze the influence of IgG antibodies in mothers without any IgE antibodies (n = 42, Table II). The results confirm that IgG antibodies were not associated with asthma but were associated with maternal rhinitis, even when exposure to cat allergen was included in the model (OR, 2.41; 95% CI, 0.97-6.01).

Transfer of IgG antibodies to the infants and total IgE levels in cord blood

IgE and IgE antibodies. Cord blood was assayed for IgE by using an enhanced assay for low levels, allowing measurements of as little as 0.2 IU/mL. In keeping with previous results, the cord blood results were, on average, less than 1% of maternal IgE levels. The 35 sera with IgE levels of greater than 3 IU/mL were also assayed for IgE antibodies to 5 allergens, but all the results were negative.

IgG and IgG4 antibodies. Measurement of IgG antibodies to Fel d 1 and Der f 1 in the cord sera showed a close quantitative correlation with the maternal results ($r = 0.97$ and 0.96 , respectively). Given the results in the mothers, it is clear that a large number of infants received IgG antibodies to Fel d 1 from a mother who did not have IgE antibodies to cat. The cord sera with IgG antibodies to Fel d 1 were tested for IgG4 antibodies to Fel d 1, and the results also showed a close correlation with the maternal results ($r = 0.87$, $P < .001$).

Serum IgE, IgE antibodies, and IgG antibodies at age 2 to 3 years

Sera were obtained from 230 of the children in the cohort during their second and third years. As in previous cohort studies, the prevalence of IgE antibodies at this

age was relatively low. Overall, 29 had IgE antibodies to one or more of the 4 allergens tested; however, only 13 of the children had IgE antibodies to mite antigens, and only 5 had IgE antibodies to cat. By contrast, 41 of the sera had IgG antibodies to Fel d 1, whereas only 11 had IgG antibodies to Der f 1. Of these children, 36 had IgG antibodies to Fel d 1 without IgE antibodies to cat, whereas only 6 had IgG antibodies to Der f 1 without IgE antibodies to mite. In univariate analysis both maternal IgG to Fel d 1 and exposure to Fel d 1 were associated with IgG antibodies at age 2 to 3 years. Child IgG to cat was not predicted by maternal IgE antibodies, maternal total IgE levels, or cord blood IgE (data not shown). In multivariate analysis exposure to Fel d 1 at 8 µg/g of dust or greater was the strongest risk factor for IgG antibodies to Fel d 1; however, maternal IgG remained a significant predictor of IgG at age 2 to 3 years (OR, 4.4; 95% CI, 1.3-15; Table III). Cord blood IgG antibodies to Fel d 1 showed similar associations with IgG antibodies at age 2 to 3 years, but the effect was weaker when adjusted for exposure (Table III).

Maternal antibodies, infant antibodies, and exposure: Risk factors for symptoms at age 2 to 3 years

Maternal IgE antibodies with or without IgG antibodies to Fel d 1 were significantly associated with eczema (but not rhinitis or wheeze) in the child by age 3 years (n = 435, Table IV). The presence of IgE antibodies with IgG antibodies to Fel d 1 in the child was also strongly associated with childhood eczema and marginally with recurrent wheeze. All of the children with IgE antibodies to mite, cat, or cockroach were reported to have had eczema. More surprisingly, among children with no measurable

IgE antibodies to cat, dust mite, cockroach, or egg white, IgG antibodies to Fel d 1 at age 2 to 3 years was significantly associated with eczema (OR, 3.3; 95% CI, 1.4-7.3; Table IV). This effect is unlikely to be explained by exposure to cat allergen because Fel d 1 exposure at 8 µg/g or greater was not related to eczema. The results show no association between IgG antibodies to Fel d 1 and recurrent wheeze (Table IV) or doctor-diagnosed asthma (data not shown). Children with IgG antibodies to cat but without IgE antibodies to specific allergens (cat, mite, cockroach, or egg white) had a median total IgE level (10.8 IU/mL) similar to that of children without detectable IgG antibodies to cat or IgE antibodies to specific allergens (15.5 IU/mL) but contrasting with that of children who had specific IgE antibodies without cat IgG antibodies (50.9 IU/mL) or those with both specific IgE and IgG antibodies to Fel d 1 (76.2 IU/mL).

DISCUSSION

Both in mothers and in 2- to 3-year-old children, a significant proportion of the subjects had IgG antibodies to the cat allergen Fel d 1 without IgE antibodies. In both groups the strongest risk factor for this response was exposure to cat allergen, as judged by the concentration of Fel d 1 in floor dust samples. Furthermore, in both the mothers and the children, this IgG response without IgE antibodies was not significantly associated with asthma or wheeze but was associated with rhinitis in the mothers and with eczema in the children. Although the details of this immune response are not yet clear, several features appear certain. First, the IgG antibody includes IgG4, which is normally considered to be part of a T_H2 response.²⁹⁻³² Second, although not tested here, there is extensive experience that cat allergens do not induce delayed hypersensitivity, which is an important feature of T_H1 responses. The results suggest the nonallergic individuals are of at least 2 different types: those with negative and those with positive serum antibody results. Our working hypothesis is that the subjects with positive serum antibody results have made a modified T_H2 response, whereas the subjects with negative serum antibody results might be nonresponders or have some other form of tolerance. The present results add further strength to the argument that IgE antibodies are critical for the risk of allergic asthma because the modified T_H2 response, including IgG and IgG4 antibodies, but without IgE antibodies, was not associated with asthma, either in the mothers or in the children.

It is assumed that the primary exposure to cat allergen occurs through inhaling airborne particles. Although the concentration of Fel d 1 in dust correlates well with the immune response, this concentration is only indirectly related to the quantity inhaled.^{23,33} Measurements of airborne allergen suggest that the quantity of cat allergen inhaled might be far greater than that for dust mite. We have estimated that the quantity of cat allergen inhaled is approximately 100 ng/d and that this is 10 to 100 times greater than that for dust mite (Custis et al, unpublished

results). Previous and current estimates of the quantity of pollen or mite allergen inhaled have been much lower (eg, 1 ng/d). When the conditions for inducing an IgE antibody response in mice were first investigated, it was clear that both dose and adjuvant were important. Most strains produce IgE best when immunized with low-dose antigen without Freund adjuvant. By contrast, with higher doses, the same strains produce IgG antibodies.³⁴ The details of the different IgG isotypes in mice are not helpful because there is no mouse equivalent of IgG4. However, the fact that high exposure to Fel d 1, a freely soluble protein, can give rise to IgG antibody responses without IgE antibodies is in keeping with the murine experience.

A major part of the rationale for the present study was to investigate the role of the mother in the development of allergic disease in children. It is well known that IgE is not transferred to the fetus, whereas IgG antibodies generally are. Measurement of IgG4 antibodies to Fel d 1 demonstrated 2 things: first, that in mothers without IgE antibodies, the IgG antibodies included IgG4, and second, that IgG4 antibodies cross the placenta very efficiently. This is in keeping with the known ability of the neonatal Fcγ receptor (FcγRn) to bind both IgG4 and IgG1 and protect them from proteolytic digestion in endosomes.^{35,36}

In the present study IgG antibodies transferred to the infant correlated significantly with IgG antibody production at age 2 to 3 years. In multivariate analyses the maternal effect decreased when exposure to Fel d 1 was included in the analysis; however, it still predicted a 4-fold odds (95% CI, 1.3-15.3) of the presence of IgG in the child (Table III). We assume that maternal IgG antibody would bind antigen that entered the blood stream. In theory this could act to either facilitate or block antigen transfer across the placenta. The association between cat allergen measured in infancy and IgG at age 3 years is most likely to be due to the effect of chronic childhood exposure because few households changed their cat-owning status in the first 3 years of the child's life. The additional effect of maternal IgG to cat on child IgG might represent an inherited tendency to produce IgG to cat or might relate to an unmeasured immunologic effect of the mother's IgG on the child's production of IgG to cat. The present results give no support to the idea that maternal IgG antibodies would block transfer of antigen to the fetus. The evidence for mite suggests that most infants have not made any detectable antibody response by age 2 years, regardless of whether they had IgG antibodies to mite in the cord serum. Taken together, the current results would best be interpreted as showing that the infant responds slowly to environmental exposure and that maternal IgG antibody has a minor influence on this response. In keeping with our findings, the effect of maternal history on the development of allergy appears to be similar to that of paternal history after age 5 years.^{6,37,38}

In mothers and young children it is clear that there is a difference between the response to cat allergens and dust mite allergens. The radioimmunoprecipitation assays used in these studies have very little nonspecific

binding, and most sera have negative results. Studies with ELISA identify larger numbers of sera with positive results; however, it is difficult to interpret the results of assays for IgG antibodies to allergens where the antigen is in a solid phase.³⁹ In our experience the IgG antibodies to the dust mite allergen Der p 1 follows IgE antibodies to this allergen.¹⁴ Possible reasons for the different response to cat allergen (ie, IgG antibody production in up to 15% of the population starting early in life) include the lack of enzymatic activity of Fel d 1 compared with Der p 1, the heavy glycosylation of Fel d 1, and the difference in particle size.^{23,40} However, the most striking difference is that exposure to cat allergen is higher than for mite. Recent evidence from studies on circulating lymphocytes suggests that IL-10 production is a major feature of the CD4⁺ T-cell response to Fel d 1 in allergic and nonallergic individuals. We believe that cat dander, dog dander, bee venom, and rat urinary allergens can all produce this form of response.^{20,31,32,41,42} By contrast, tolerant or modified responses do not appear to be common among populations with high exposure to mite or cockroach allergens.^{43,44}

Although age 2 to 3 years is too early for the diagnosis of allergic asthma with certainty, these data provide some insight into the clinical significance of the mother-child IgG relationship. Our results strongly support the evidence that high exposure to cat allergens can induce an immune response distinct from the allergic response. The prevalence of this response is such that 70% of infants living in a house with a cat receive IgG antibodies to Fel d 1 from their mother, and in half these cases, the mother was not allergic to cats. In relation to symptoms, the data consistently show no association between IgG antibodies and asthma or wheeze. However, 3 separate observations suggest that the immunoglobulin response, including IgG antibodies, IgG4 antibodies, or both, might have a role beyond being a form of tolerance.

1. In the mothers IgG antibodies to Fel d 1 were independently associated with rhinitis. This could reflect either an irritant effect of cat dander or a role for a cat-specific immune response (without IgE) in the nose.
2. The production of IgG antibodies to Fel d 1 at age 2 to 3 years was influenced by passively transferred IgG antibodies from the mother. Although it is possible that this reflects a genetic effect of the mother, it could reflect a positive effect of the antibody.
3. In the young children IgG antibodies to Fel d 1 were independently associated with eczema. It remains possible that this reflects short-lived IgE antibody responses preceding IgG antibody responses. However, T cells or IgG antibodies could equally play a role in the skin inflammation.

Although our results do not resolve the ways in which the mother can contribute to the development of allergy in the child, they define some of the influences. Analysis of the role of the mother should include measurements of passively transferred antibody and exposure to allergens. It is also clear that high exposure to cat allergen, including the

presence of a cat in the home, can have different effects than the highest exposures to mite recorded here. Finally, our results establish that a large proportion (15%) of children from allergic families (ie, 36/230) have IgG antibodies to Fel d 1 without IgE antibodies within the first 3 years of life. Further understanding of this form of tolerance is clearly an important objective in understanding the factors influencing the development of allergic disease.

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