

Determinants of total and specific IgE in infants with atopic dermatitis

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ETAC (Early Treatment of the Atopic Child), a multi-centre predominantly European study to investigate the potential for cetirizine to prevent the development of asthma in infants with atopic dermatitis has completed enrolment: 817 children have been randomised to 18 months' treatment with either active or placebo and a subsequent 18 months of post-treatment follow-up. Results of the therapeutic effects will not be available for some time, but the study has provided an opportunity to investigate influences on sensitization to allergens in a large cohort of 1–2 years olds with already established atopic dermatitis, resident in different countries and in different environments.

The study shows that in infants with atopic dermatitis, raised serum total IgE has significantly different determinants from that a specific allergen sensitization. In infancy, increased total IgE is more affected by factors increasing risk of intercurrent infection and non-specific airway inflammation, such as environmental tobacco smoke exposure ($p < 0.001$) and the use of gas cookers ($p = 0.02$). Specific allergen sensitization as represented by detectable IgE antibodies is influenced primarily by allergen exposure. In Sweden, low level exposure to allergens is associated with reduced specific allergen sensitization rates even though the infants already have atopic dermatitis.

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The atopic diseases, asthma, eczema and hay fever, have all increased in prevalence very considerably over the last three decades in most, if not all, developed countries around the world (1–3). The explanations for this remain unclear though much attention has focused on the environment in early life and, in particular, high allergen exposure as a major trigger to the onset of such disease. Thus far, however, attempts at prevention have produced conflicting results, some demonstrating apparently dramatic and long lasting benefits (4) while others have shown only limited effects (5) or no benefits whatsoever (6).

As there are marked variations in the prevalence, particularly of asthma, between countries in the developed world, with very high prevalence rates in the English speaking countries of the UK, Australia and New Zealand, and much lower rates in many European countries (7), there is every reason to believe that modification of environment might have an impact. However, unless detailed comparisons can be made across countries, it will not be possible to identify the key factors.

A large multi-centre, multi-national trial investigating the hypothesis that early therapeutic intervention with cetirizine in atopic eczema will prevent the development of asthma, has offered the opportunity to make some comparisons of atopic status in relation to environment in different countries. ETAC (Early Treatment of the Atopic Child) was a concept evolved by UCB Pharma in collaboration with an independent scientific advisory board which helped with the design of the protocol and subsequently with the supervision of the study. The enrolment of over 800 infants between 1 and 2 years of age, all of whom have atopic dermatitis and positive family history and are, therefore, at high risk of subsequently developing asthma, was completed in 1995.

The results of the therapeutic intervention will not be known for 18 months. However, the baseline data on demographics and atopic status have provided some unique and important observations which shed further light on the environmental factors which influence prevalence of particular allergies.

Methodology

This double-blind, randomised, parallel group, placebo-controlled study required the inclusion of at least 700 atopic infants of both genders aged 12–24 months. The inclusion criteria specified that the subjects should present atopic dermatitis for at least one month and that at least one parent and/or sibling should have a history of atopy (asthma, atopic dermatitis or allergic rhinitis); the infants should, however, be asthma-free (i.e. not have a record of an episode of wheezing or a history of cough episodes for three consecutive nights with sleep disturbances since 6 months of age). They were recruited in paediatric and dermatology outpatient clinics. The assessment of atopic dermatitis severity employed SCORAD and its application in this study is documented in another paper (8). Thus the diagnosis of atopic dermatitis was based on the characteristic skin rash, (erythema, edema/papulation, oozing/crust, excoriation, lichenification, dryness) and a first degree relative with atopic disease, but not necessarily on the basis of evidence of specific allergy or raised total IgE.

Prior to initiation of treatment with cetirizine or placebo and besides a full clinical examination, total and specific serum IgEs (house dust mite, cat, egg and cow's milk) were measured. To this effect, 5ml of blood was sampled in a SST vacuum tube by venepuncture and shipped to a central laboratory (Institut Pasteur de Lille). The total and specific IgE measurements were performed on undiluted serum using the automatic processed Pharmacia CAP®System based on FEIA (Pharmacia Upjohn Diagnostics AB). According to the manufacturer's instruction, the IgE assays were calibrated against the second international reference preparation WHO standard 70/502 for IgE in the range 0.35–100 kU/L. For the statistical analysis of the results, these variables were itemised into two categories (normal/increased). For the specific IgEs, a serum level higher than 0.35 kU_A/L and for the total IgE a serum level higher or equal to 30 kU/L were considered as increased. The former is equivalent to RAST class 1 as evidence of detectable specific IgE indicating sensitization has occurred. The latter cut-off point was based on the upper - standard deviation limit of an equivalent aged normal infant population (9).

A questionnaire survey was made on the environment in which the children were living, in order to investigate potential effects of outdoor (residency, pollution), and indoor (gas cooking, carpeting in the child's bedroom, passive smoking, pets, cats, nursery attendance) environmental factors on allergological parameters. Other non-environmental factors (gender, atopic diseases in close relatives and duration of exclusive breast-feeding) were recorded with

the same objective in mind. For the statistical analysis, the duration of exclusive breast-feeding was itemised in two categories (<3 months/> or = 3 months).

The statistical analysis was performed using the SAS (6.10) statistical package. The relationship between environmental factors, non-environmental factors and allergological variables was investigated using both univariate (Chi-square test) and multivariate (stepwise logistic regression) techniques. Logistic regression was used to predict increased sensitization for an allergen on the basis of potentially prognostic factors. With the stepwise approach only the variables significantly contributing to the prediction of the outcome variable were selected. All statistical tests were performed two-sided and because of the large number of analyses, we only comment on those at or below the 2% level of significance.

The study complies strictly with EU GCP requirements. The written consent of at least one of the parents or the legal representative was obtained for each child before inclusion. Written approval was received from all the centres local ethics committees/institutional review boards.

Results

Between February 1994 and December 1995, 817 infants were recruited and included from 56 centres located in 12 European countries and Canada. The mean age of the infants was 16.9 (s.d.=4.2) months (range 9.6–27.6), the mean body weight 10.9 (s.d.=1.6) kg (range 7.6–17.5) and the mean height 80.5 (s.d.=5.2) cm (range 63–98). Table 1 shows the predominance of boys (62%) over girls. Overall, 56%

Table 1.

Demography and patient characteristics (N = 817)			
Continuous Variables	Mean	Median	Standard Deviation
Age (year)	1.41	1.38	0.35
Height (cm)	80.5	80.0	5.2
Weight (kg)	10.9	10.8	1.6
Discrete Variables	Number (percentage)		
Boys	506 (62%)		
Breastfeeding ≥3 months	340 (41%)		
Urban residence	456 (56%)		
Industrial pollution	363 (44%)		
Gas cookers	483 (59%)		
Bedroom fitted carpet	398 (49%)		
Exposed to tobacco smoke	329 (40%)		
Pets	292 (36%)		
Cats	140 (17%)		
Nursery	226 (28%)		

Table 2.

Increased total IgE and sensitization for specific IgEs	
	Number (percentage)
Increased total IgE	348/735 (47.3%)
Sensitization for:	
Cow's milk - F13	235/727 (32.3%)
Egg - F1	268/590 (45.4%)
House dust mite - D1	118/712 (16.6%)
Cat - D2	132/645 (20.5%)
Sensitization for at least one of the specific IgEs	386/641 (60.2%)
Sensitization for at least one of the specific IgEs or total IgE	457/665 (68.7%)

Allergens kindly provided by Pharmacia UpJohn

of patients recruited lived in an urban environment, 44% in the vicinity of industrial pollution, 49% slept in carpet fitted bedrooms, 59% lived in houses equipped with gas cookers, 36% had pets (17% cats), 28% attended a nursery, 42% were exclusively breast-fed for 3 months or more and 40% were exposed to tobacco smoke. The severity of atopic dermatitis was in the mild to moderate range, with a mean SCORAD of 25 (s.d. 14).

The dependence of each of the allergological variables (total serum IgE, four specific serum IgE's) from the patient characteristics and the environmental and non-environmental factors was investigated by means of stepwise logistic regression. In this population of atopic children there was, for each allergological variable, a significant relationship with one or more of the environmental/non-environmental factors.

The percentage of children with increased levels of total IgE is shown in Table 2. The factors found associated with an increased probability of a raised total serum IgE in atopic children (Table 3) were the use of gas cookers (OR = 1.4, $p = 0.020$), passive smoking (OR = 1.8, $p < 0.001$) and the absence of a cat (OR = 0.5, $p = 0.001$).

Table 3 reveals details of the stepwise logistic regression analysis. Increased sensitization for cat was strongly related to the possession of a cat (OR = 2.6, $p < 0.001$) and the presence of a bedroom fitted carpet (OR = 1.5, $p = 0.036$). Sensitization for house dust mite was higher for boys than for girls (OR = 1.757, $p = 0.011$) and also higher for children from a rural compared with an urban environment (OR = 1.7, $p = 0.011$). The presence or absence of bedroom fitted carpet did not emerge as a factor influencing

Table 3.

Relationship between increased total and specific IgEs and prognostic variables - stepwise logistic regression					
Variables considered in the analysis: sex (M/F), residence (urban/rural), industrial pollution, gas cooker used, bedroom fitted carpet, smoking, pets, cats, nursery, AD mother, AD father, PA mother, PA father (Y/N), duration of breastfeeding (< 3 month, ≥ 3 month)					
Dependent variable: Total IgE (normal/increased)					
Variables entered into the model:					
		Crude OR	Odds Ratio	p-value	95% CI on OR
Gas cooker	Increased odds for total IgE: when gas cookers are used	1.5	1.4	0.020	(1.1 ; 1.9)
Smoking	when exposed to smokers	1.8	1.8	<0.001	(1.3 ; 2.4)
Decreased odds for total IgE:					
Cat	in the presence of a cat	0.5	0.5	0.001	(0.3 ; 0.7)
Dependent variable: IgE Cat (normal/increased)					
Variables entered into the model:					
		Crude OR	Odds Ratio	p-value	95% CI on OR
Cat	Increased odds for IgE cat: in the presence of a cat	2.7	2.6	<0.001	(1.6 ; 4.0)
Floor	in the presence of a bedroom fitted carpet	1.6	1.5	0.036	(1.0 ; 2.3)
Dependent variable: IgE cow's milk (normal/increased)					
Variables entered into the model:					
		Crude OR	Odds Ratio	p-value	95% CI on OR
Gas cooker	Increased odds for IgE cow's milk: for presence of gas cooker	1.5	1.7	0.003	(1.2 ; 2.3)
Smoking	for presence of smokers	1.6	1.6	0.008	(1.2 ; 2.2)
Sex	for boys	1.5	1.5	0.013	(1.1 ; 2.2)
Breastfeeding	with longer duration of breastfeeding	1.4	1.5	0.024	(1.1 ; 2.1)
Decreased odds for IgE cow's milk:					
Pets	presence of pets	0.6	0.6	0.002	(0.4 ; 0.8)
Nursery	presence of nursery	0.5	0.5	0.001	(0.4 ; 0.8)
PA father	for presence PA father	0.6	0.6	0.013	(0.4 ; 0.9)
Dependent variable: IgE Egg (normal/increased)					
Variables entered into the model:					
		Crude OR	Odds Ratio	p-value	95% CI on OR
Bedroom carpet	Increased odds for IgE egg: in presence of bedroom fitted carpet	1.4	1.6	0.006	1.1 ; 2.2
Smoke	in the presence of smokers	1.3	1.4	0.042	(1.0 ; 2.0)
Decreased odds for IgE egg:					
Pets	in the presence of pets	0.6	0.5	<0.001	(0.4 ; 0.7)
Dependent variable: IgE House Dust Mite (normal/increased)					
Variables entered into the model:					
		Crude OR	Odds Ratio	p-value	95% CI on OR
Living conditions	Increased odds for IgE HDM: for rural environment	1.7	1.7	0.011	(1.1 ; 2.5)
Sex	for boys	1.7	1.8	0.011	(1.1 ; 2.7)
Dependent variable: IgE Grass Pollen (normal/increased)					
Variables entered into the model:					
		Crude OR	Odds Ratio	p-value	95% CI on OR
Sex	Increased odds for IgE pollen: or boys	3.0	3.0	0.001	
Decreased odds for IgE pollen:					
Cat	in the presence of a cat	0.2	0.2	0.008	(0.1 ; 0.7)
Nursery	in the presence of a nursery	0.4	0.5	0.028	(0.2 ; 0)

Table 4.

Relationship between country and demographic and environmental factors

		B L	CD	CZ	D CH A	F	GB	I	NL	S	SP	Chi-square test (p-value)
	N=	45	10	24	79	151	105	113	177	89	24	
Boys	N	26	5	14	54	101	66	70	103	50	17	0.620
	%	58%	50%	58%	68%	67%	63%	62%	58%	56%	71%	
Breastfeeding ≥ 3 m	N	16	4	19	36	24	43	66	64	61	7	0.001
	%	36%	40%	79%	48%	16%	41%	58%	36%	69%	29%	
Urban residence	N	21	8	19	52	73	35	62	102	63	21	0.001
	%	48%	80%	79%	66%	48%	33%	55%	58%	71%	88%	
Industrial pollution	N	24	1	17	43	65	29	39	105	19	21	0.001
	%	53%	10%	71%	54%	43%	28%	35%	59%	21%	88%	
Gas cookers	N	15	1	16	16	128	57	90	141	0	19	0.001
	%	33%	10%	67%	20%	85%	54%	80%	80%	0%	79%	
Bedroom fitted carpet	N	15	9	20	64	68	100	16	97	5	4	0.001
	%	33%	90%	83%	81%	45%	95%	14%	55%	6%	17%	
Tobacco smoke	N	22	3	11	27	72	28	51	77	27	11	0.015
	%	49%	30%	46%	35%	48%	27%	45%	44%	31%	46%	
Pets	N	19	4	3	33	70	53	13	74	15	8	0.001
	%	42%	40%	13%	42%	46%	50%	12%	42%	17%	33%	
Cats	N	12	3	3	14	22	33	6	38	8	1	0.001
	%	27%	30%	13%	18%	15%	31%	5%	21%	9%	4%	
Nursery	N	18	4	0	12	57	29	22	44	33	7	0.001
	%	40%	40%	0%	15%	38%	28%	20%	25%	37%	29%	

Country: BL: Belgium+Luxembourg; CD: Canada; CZ: Czech Republic; D/CH/A: Germany+Switzerland+Austria; F: France; GB: Great Britain; I: Italy; NL: The Netherlands; S: Sweden; SP: Spain.

sensitivity to house dust mite. The sensitization for eggs was associated with the absence of pets (OR = 0.5, $p < 0.001$), with the presence of bedroom fitted carpet (OR = 1.6, $p = 0.006$), but only marginally with exposure to tobacco smoke (OR = 1.4, $p = 0.04$). The probability for raised serum IgE for cow's milk was influenced by several factors. Male gender, passive smoking, presence of gas cookers, and breastfeeding during 3 months or more increased sensitization to this allergen (OR = 1.5, ($p = 0.013$), 1.6, ($p = 0.008$), 1.7, ($p = 0.003$), 1.5, ($p = 0.024$), respectively). Furthermore, the presence of pets, the attendance at a nursery, and having a father with proven asthma decreased the odds for an increase of IgE cow's milk (OR = 0.6, ($p = 0.002$), 0.5, ($p = 0.001$), 0.6, ($p = 0.013$), respectively).

Some interesting differences between countries should be emphasized (Table 4). The frequency of boys recruited in each of the countries is comparable but for all other variables there is a highly significant difference between the countries (Chi-square test: $p < 0.02$). While in Spain, Canada and Czech children were mainly recruited in cities, in the UK they predominantly issued from rural areas; vicinity with industrial pollution was frequent in Spain and Czech, but low in Canada, Sweden and the UK. Amongst the cohort, exclusive breastfeeding for at least 3 months occurred most frequently in Czechia (79%) and Sweden (69%) and least frequently in France (16%). Attendance at a nursery is most frequent in Belgium/Luxembourg and absent

in Czechia. Great Britain was the country with the highest percentage of pets in the house (50%), while Italy (12%), Czechia (13%) and Sweden (17%) had the lowest rates. Exposure to tobacco smoke was between 27% (UK) and 49% (Belgium/Luxembourg). The frequency of children sleeping in a carpet fitted bedroom ranged between 95% (UK) and 6% (Sweden).

In order to investigate whether the differences between countries in environmental and non-environmental factors resulted in differences in sensitization rates, the frequency of increased total serum IgE and increased specific serum IgEs was broken down by country (Table 5). For each of the variables a highly significant difference was found between countries (chi-square test: $p < 0.005$).

The countries with the smallest prevalence of raised total serum IgE were Belgium/Luxembourg (23%) and Sweden (27%). For Sweden this was associated with low frequency of use of gas cookers, a low exposure to environmental smoking, and a low frequency of cats in the house.

Sensitization for cat was most frequent in Canada (43%), where there was also a high frequency of cats in the house, and was the least frequent in Italy (12%), Sweden (7%) and Spain (5%), countries with low frequencies of cats in the house.

Sensitization for house dust mite was absent in Sweden (0%) and was most frequent in France (25%) and UK (29%). The latter two countries had a high recruitment rate of children from a rural enviro-

Table 5.

	Relationship between country and biological markers										Chi-square test (p-value)
	B L	CD	CZ	D CH A	F	GB	I	NL	S	SP	
N=	45	10	24	79	151	105	113	177	89	24	
Increased total IgE >0.3.10 ³ UI/l	9 23%	4 57%	13 59%	36 50%	68 48%	37 41%	64 66%	84 52%	21 27%	12 55%	0.001
Increased IgE cow's milk >0.35 PRU/ml	6 15%	3 43%	11 50%	22 31%	37 27%	30 35%	52 53%	55 34%	10 13%	9 41%	0.001
IgE Egg >0.35 PRU/ml	6 20%	4 57%	11 69%	34 56%	46 44%	37 49%	43 49%	66 46%	12 24%	9 53%	0.004
IgE House dust mite >0.35 PRU/ml	3 8%	1 14%	4 19%	13 18%	33 25%	25 29%	12 13%	23 14%	0 0%	4 18%	0.001
IgE cat >0.35 PRU/ml	5 14%	3 43%	5 28%	15 23%	25 22%	20 24%	11 12%	43 28%	4 7%	1 5%	0.003
IgE Grass pollen >0.35 PRU/ml	0 0%	0 0%	6 32%	6 9%	19 15%	5 6%	15 16%	14 9%	3 4%	1 5%	0.002

onment, a factor that resulted in increased odds for sensitization to this allergen.

The countries with the smallest occurrence of raised sensitization for eggs were Belgium/Luxembourg (20%) and Sweden (24%). The countries with the smallest occurrence of sensitization for cow's milk are again Belgium/Luxembourg (15%) and Sweden (13%). The highest occurrence was found in Czechia (50%) and Italy (53%).

Discussion

Early Treatment of the Atopic Child (ETAC) is a unique collaboration of paediatricians, dermatologists and the pharmaceutical industry to investigate the evolution of the atopic march from atopic dermatitis through to asthma. The opportunity to investigate the demographic influences on specific allergy is the first result of this collaboration. It has highlighted several very important issues.

The atopic phenotype is characterised in successive studies by the presence of a raised serum total IgE and the appearance of specific allergies as identified either by prick skin tests or specific IgE antibody assays in the presence, or sometimes even absence, of atopic diseases (10). This characterisation has, for instance, been extensively used in gene linkage analyses which have led to highly conflict-

ing results, particularly in relation to a putative atopy/asthma gene on the long arm of chromosome 11 (11). We believe, on the basis of our own results, that the confusion may have arisen because an isolated raised serum total IgE may not be under the same influences as that of specific allergen sensitization. Another reason could be that as this study shows, over half of those with manifest "atopic" disease were not "atopic" in terms of total or specific IgE.

The key factors significantly increasing the probability of a raised total IgE amongst already atopic children were: being in a home with a gas cooker and exposure to environmental smoke. There was an unexpected negative association with the possession of a cat. This may be because of negative selection. There was a correlation between increased severity of atopic dermatitis and higher total IgE which is to be reported in another paper. More severe eczema might in turn have discouraged families from acquiring a cat. This is consistent with the additional association between milk, egg and grass pollen sensitization and an absence of pets in the home. There was no difference between urban and rural dwelling and no effect of a bedroom fitted carpet, and of being adjacent to industrial pollution. The effect of environmental tobacco smoke on total IgE level is, of course, well known and is apparent even in non-at-

opic adults (12). To our knowledge there is only one study showing an effect of air pollution on total IgE in non-allergic children (13).

Conversely, effects on specific IgE sensitization were predominantly related to allergen exposure. Thus, the strongest effect was possession of a cat on being sensitised to cat allergen. While bedroom fitted carpets unexpectedly were not particularly associated with house dust mite sensitization, they did influence sensitization to cat perhaps because of a greater reservoir concentration of the allergen. It is likely that the influences on house dust mite sensitization will take rather longer to become apparent. The frequency of sensitization between 1 and 2 years of age is relatively low and is likely to increase in subsequent years. The effect of environmental tobacco smoke was only apparent in relation to sensitization to cow's milk and to egg, while there was no effect at this age of industrial pollution and, if anything, a greater effect of rural dwelling.

Rural dwelling was significantly associated with house dust mite sensitization. In this respect, it is interesting to note that the recent "International Study of Asthma and Allergies in Childhood" survey in the United Kingdom has demonstrated a higher prevalence of asthma amongst rural compared with urban dwellers (14). One might question whether, amongst these infants with atopic dermatitis, there will be a higher probability of asthma developing in those with house dust mite sensitivity who, in turn, are more likely to live in a rural environment. Whether or not this is related to a higher concentration of allergen exposure remains to be established. It is perhaps more credible that aspects of urban dwelling, possibly related to pollutants, decreases the risk of sensitization while still having an effect on total IgE. This issue has particularly been apparent in the East Germany/West Germany comparisons (15). Children in East German polluted cities have a higher prevalence of respiratory infections as exemplified by bronchitis, but a significantly lower prevalence of positive prick skin tests, and asthma and hay fever. Interestingly in the East Germany/West Germany comparisons, there was no difference in eczema prevalence (16). These data would be consistent with the idea that infection might suppress allergic responses in the respiratory tract, perhaps mediated by Th1 cells generating IFN γ which suppresses Th2 (atopy associated) activity (17, 18), while not having any effect on total IgE or eczema.

Finally, cow's milk sensitivity was associated with non-nursery attendance, but was more prevalent in those homes with gas cooking. This is similar to the effects on total IgE. As having positive sensitization to cow's milk was associated with more severe atopic eczema, it is possible that children with more severe disease are less likely to be sent to

nursery because of parental concern. There was a significant gender effect with more males than females being sensitized to cow's milk, house dust mite and grass pollen. The association which we found between prolonged breast feeding and cow's milk sensitization has been observed in some (19) but not all studies (4). The differences may be due to variations in maternal exposure to cow's milk during pregnancy and lactation (17).

For the most common inhalant allergy in infants, namely to cats, allergen exposure is the key factor for specific sensitization, while for generating a raised total IgE, there were non-specific influences such as exposure to environmental tobacco smoke and gas cooker emissions. This casts some doubt on the use of total IgE as an exclusive marker of atopic constitution in infants. It is remarkable that such differences should be highlighted even within an atopic population where one might have expected a greater uniformity of effect. It remains to be seen how these factors affect the subsequent development of asthma, which will clearly be possible to establish in this longitudinal study.

To further elaborate on the environmental and biological influences on atopic sensitization, a sub-analysis was done comparing the different countries on the basis of their environmental factors, the characteristics of the patients and the percentage of increased total and specific IgEs. In Sweden, considerable efforts have been made in recent years to promote a favourable environment for infants at high risk of developing atopy. Thus, a 1-year public campaign has promoted exclusive breast-feeding, the avoidance of pet keeping, the use of hard flooring rather than carpeting and avoidance of environmental tobacco smoke (21). If this campaign is to prove of any value, then one should expect to see lower rates of sensitization to specific allergens as a consequence. This indeed appears to be the case with no house dust mite sensitization in the study population. Sweden has very low house dust mite levels, particularly in the North (22). However, as some of the centres recruiting patients were in the South of Sweden where house mites can be detected in homes, the absence of carpeting may well be important. There were also, however, significantly lower sensitization rates to eggs and milk, presumably as a consequence of more effective and prolonged breast-feeding and, in addition, significantly lower rates of cat sensitization, again because of reduced exposure. The United Kingdom is the leader in cat keeping and also amongst the leaders in cat sensitization. There are clear messages here in relation to allergen avoidance.

This study cannot, of course, yet establish whether modifying the environment has any effect on manifestations of atopic disease. Clearly all these

children were atopic with eczema. The determinants of total and specific IgE in a sub-population of children with an atopic disease may be different from those in a general population. However, it will be possible to establish whether our observations translate into any effect on the subsequent development of asthma. There are a number of studies which would suggest that this will be the case, as sensitivity to house dust mites and pre-existing atopic eczema increase the risk of development of asthma (23, 24).

We believe that this cross-sectional analysis of atopic sensitization amongst infants with atopic der-

matitis provides some important new information on the different influences on raised total IgE compared with specific allergen sensitization. It indicates that the atopic phenotype is complex and also that the only way one can establish a complete phenotype and, indeed, whether environment changes the natural history of disease, is by conducting very large longitudinal studies in accurately characterised populations. ETAC will be able to generate much data in relation to the development of asthma and related allergic disease amongst these high risk infants.

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