

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 13, 2003

VOL. 348 NO. 11

## Factors Associated with the Development of Peanut Allergy in Childhood

Gideon Lack, M.B., B.Ch., Deborah Fox, B.A., Kate Northstone, M.Sc., and Jean Golding, Ph.D.,  
for the Avon Longitudinal Study of Parents and Children Study Team

### ABSTRACT

#### BACKGROUND

The prevalence of peanut allergy appears to have increased in recent decades. Other than a family history of peanut allergy and the presence of atopy, there are no known risk factors.

#### METHODS

We used data from the Avon Longitudinal Study of Parents and Children, a geographically defined cohort study of 13,971 preschool children, to identify those with a convincing history of peanut allergy and the subgroup that reacted to a double-blind peanut challenge. We first prospectively collected data on the whole cohort and then collected detailed information retrospectively by interview from the parents of children with peanut reactions and of children from two groups of controls (a random sample from the cohort and a group of children whose mothers had a history of eczema and who had had eczema themselves in the first six months of life).

#### RESULTS

Forty-nine children had a history of peanut allergy; peanut allergy was confirmed by peanut challenge in 23 of 36 children tested. There was no evidence of prenatal sensitization from the maternal diet, and peanut-specific IgE was not detectable in the cord blood. Peanut allergy was independently associated with intake of soy milk or soy formula (odds ratio, 2.6; 95 percent confidence interval, 1.3 to 5.2), rash over joints and skin creases (odds ratio, 2.6; 95 percent confidence interval, 1.4 to 5.0), and oozing, crusted rash (odds ratio, 5.2; 95 percent confidence interval, 2.7 to 10.2). Analysis of interview data showed a significant independent relation of peanut allergy with the use of skin preparations containing peanut oil (odds ratio, 6.8; 95 percent confidence interval, 1.4 to 32.9).

#### CONCLUSIONS

Sensitization to peanut protein may occur in children through the application of peanut oil to inflamed skin. The association with soy protein could arise from cross-sensitization through common epitopes. Confirmation of these risk factors in future studies could lead to new strategies to prevent sensitization in infants who are at risk for subsequent peanut allergy.

From the Department of Paediatric Allergy and Immunology, St. Mary's Hospital at Imperial College, London (G.L., D.F.); and the Unit of Paediatric and Perinatal Epidemiology, University of Bristol, United Kingdom (K.N., J.G.). Address reprint requests to Dr. Lack at the Department of Paediatric Allergy and Immunology, Ground Floor, Salton House, St. Mary's Hospital, Praed St., London W2 1NY, United Kingdom.

N Engl J Med 2003;348:977-85.  
Copyright © 2003 Massachusetts Medical Society.

**L**IFE-THREATENING ALLERGIC REACTIONS to peanuts can occur in children and adults.<sup>1-4</sup> Although reports suggest that atopy, a family history of peanut allergy,<sup>5,6</sup> prenatal maternal consumption of peanuts,<sup>5</sup> or consumption of peanuts or peanut oil by infants<sup>7</sup> may cause sensitization to peanuts, not all these findings have been replicated.<sup>8</sup> The use of maternal breast creams containing peanut oil<sup>9</sup> and consumption of soy milk or soy formula by the infant may be linked to the development of peanut allergy, because both peanuts and soybeans belong to the legume family.<sup>6</sup> Although breast-feeding may prevent the early manifestation of eczema,<sup>10,11</sup> there is no evidence that it protects against the development of peanut allergy.

Previous studies of the causes of peanut allergy have failed to define peanut allergy on the basis of double-blind, placebo-controlled food challenge and have not used longitudinal data to identify its antecedents. The Avon Longitudinal Study of Parents and Children was designed to collect information prospectively from early pregnancy and throughout childhood and thus provided an opportunity to investigate the antecedents of peanut allergy.

## METHODS

### SUBJECTS

The study enrolled pregnant women who resided in the Avon Health Authority area in southwest England whose expected date of delivery was between April 1, 1991, and December 31, 1992; follow-up has continued since enrollment. The study was designed to determine the features of the environment that might interact with genetic factors to cause health, behavioral, or developmental problems. The data sources include regular questionnaires completed by parents, medical records, and biologic samples including cord blood.<sup>12,13</sup> The mother's history with respect to allergy was determined by a questionnaire administered before delivery. Questionnaires were administered 1, 6, 15, and 18 months after birth and approximately every 6 months thereafter to obtain information on specific types of rash observed in the child and their severity, medications given to the child, and details of the child's diet.

### IDENTIFICATION OF CHILDREN WITH PEANUT ALLERGY

We identified children up to the age of 38 months who had peanut allergy on the basis of responses to questions about food avoidance and reactions to particular foods. There was a response to at least

one question for 12,090 of the 13,971 children in the cohort (a response rate of 86.5 percent). Affected children were also identified from responses to questions on the questionnaire regarding previous hospitalizations and clinical investigations. Forty-nine mothers of children who had a reaction to peanuts according to questionnaire responses were interviewed in detail over the telephone about the reaction. The interviewer, who was blinded to the mothers' questionnaire responses, also telephoned control subjects.

Children who were found to have had a reaction to peanuts (age range, four to six years) underwent skin testing and double-blind, placebo-controlled food challenge between February 1997 and April 1998 in the day-care unit of St. Mary's Hospital in London. Skin testing was performed with peanut (concentration, 1:20 [wt/vol] in 50 percent glycerol) (Soluprick, ALK-Abelló). Saline was used as a negative control, and 1 mg of histamine per milliliter of saline was used as the positive control. The skin-test site was measured after 15 minutes, and the mean diameters of wheals and flares were calculated. A skin test was considered positive if it resulted in a palpable wheal at least 3 mm in diameter. Allergy was confirmed by a positive food challenge with peanuts, as previously described.<sup>14</sup> Peanut challenge was carried out in a ward adjacent to the pediatric intensive care unit with an intravenous catheter in place, with the use of graded doses until a reaction occurred or 8 g of dry-weight equivalent had been consumed. Children with negative responses on the blinded peanut challenge were tested for confirmation by open challenge (peanut-butter sandwich).

### LABORATORY TESTS

Cord-blood samples stored at birth were retrieved for children with peanut allergy and were analyzed after storage at  $-70^{\circ}\text{C}$  for specific IgE to peanuts with a fluorescence enzyme immunoassay (Pharmacia CAP, Pharmacia), according to the manufacturer's directions.

### SELECTION OF CONTROLS

The first control sample was an atopic group, consisting of 70 subjects randomly selected from among children who were reported to have had eczema in the first six months of life and whose mothers had a history of eczema. The second control sample was a group of 140 children without peanut allergy who were randomly selected from the cohort. Case children and controls were not matched.

**TELEPHONE INTERVIEWS WITH PARENTS**

Key questions not included in the prospective questionnaires were asked during telephone interviews with the parents of the children. These included questions about maternal consumption of peanuts during pregnancy and lactation, the presence or absence of a family history of peanut allergy, and the use of specific skin lotions and creams. The interviewer was unaware of which skin preparations contained peanut oil.

**STATISTICAL ANALYSIS**

Unadjusted comparisons were performed by the chi-square test, with Fisher's exact test and the Mantel-Haenszel test for trend used where appropriate. Statistical comparison with the whole sample and with the two control groups was performed by multivariate logistic regression, resulting in the estimation of adjusted odds ratios and 95 percent confidence intervals. All reported P values and confidence intervals are two-sided. SPSS for Windows (version 10.1) was used for all analyses.

---

**RESULTS**


---

**CLINICAL CHARACTERISTICS**

Forty-nine children (28 boys and 21 girls) were identified as having a clear history of adverse reactions to peanuts, which was highly suggestive of type I hypersensitivity. Thirty-six of these children (73 percent) underwent further testing at St. Mary's Hospital. Two children were not tested further because they had moved and could not be located, two because they had previously had an anaphylactic reaction, and nine because their parents refused consent. Twenty-nine of the 36 tested had positive reactions to peanuts on skin testing. The mean ( $\pm$ SD) age at the first reaction to peanuts was  $23.4 \pm 14.4$  months. The mean number of reactions was  $1.54 \pm 1.02$ , and the mode was 2. Allergy was confirmed by double-blind, placebo-controlled food challenge in 23 children, with the dose that provoked a reaction ranging from 50 mg to 8 g; all reactions occurred within 40 minutes after ingestion. These 23 children had at least one of the following responses: bronchospasm (6 children), stridor (1 child), altered level of consciousness (3 children), vomiting (8 children), urticaria (14 children), angioedema (7 children), rhinitis (17 children), and conjunctivitis (4 children). Three children required intramuscular epinephrine; all responded promptly to treatment. There were no reactions to the placebo. All

23 children had a positive skin test for peanuts and had reacted to their first known exposure to peanuts. The remaining 13 (6 of whom had a positive skin test) had negative results on the food challenge.

**CORD-BLOOD ANALYSIS**

Samples of previously frozen cord blood from 23 of the 49 children with peanut allergy were obtained; analysis did not reveal detectable specific IgE to peanuts in any of the samples tested ( $<0.35$  kU per liter, class 0 response in all samples). Total IgE (polyclonal) was identifiable, indicating that the absence of specific IgE to peanuts was not due to degradation of IgE or to an inability of the test to detect IgE.

**ANALYSIS OF PROSPECTIVELY COLLECTED DATA**

No statistically significant associations were found between peanut allergy or a positive peanut-challenge test and any socioeconomic factor or environmental tobacco smoke (data not shown). There were significant associations between a maternal history of atopy, specific allergies, or asthma and a positive peanut food challenge (Table 1). There were no significant associations with maternal dietary factors (unfortunately, no specific question on peanut consumption during pregnancy was asked prospectively). There was an association between the duration of breast-feeding and both peanut allergy (P for trend=0.03) and a positive peanut-challenge test (P for trend=0.07).

Of the total cohort of children, 8.3 percent had consumed soy milk or soy formula in the first two years, as compared with 24.5 percent of those with peanut allergy and 34.8 percent of those with a positive peanut challenge ( $P < 0.001$  for both comparisons). Of the 10 children for whom data on the first consumption of soy milk or soy formula were available, 9 had consumed soy before reacting to peanuts.

Rash over joints and skin creases and oozing, crusted rash were significantly associated with peanut allergy and a positive result on the peanut challenge ( $P < 0.001$  for both associations). The severity of rash was scored for each of the four types of rash (Table 1) as 3 ("very bad"), 2 ("quite bad"), 1 ("mild"), or 0 ("not a problem" or no rash). There was a trend toward an association between the severity of rash in the first six months and the prevalence of peanut allergy and of a positive result on the peanut challenge ( $P < 0.001$  for both associations).

All the significant factors listed in Table 1 were

**Table 1. Questionnaire Data from the Total Sample of Children, from Children with Peanut Allergy, and from Those with a Positive Reaction to Peanut Challenge.\***

Variable	Total Sample		Peanut Allergy		Positive Peanut Challenge	
	No.	No.	Unadjusted OR (95% CI)	No.	Unadjusted OR (95% CI)	
<b>Maternal history</b>						
Asthma						
Yes	1,327	8	1.55 (0.72–3.32)	7	3.42 (1.40–8.32)	
No†	10,279	40	1.00	16	1.00	
P value			0.26		0.01‡	
Eczema						
Yes	2,671	16	1.69 (0.92–3.08)	9	2.17 (0.94–5.01)	
No†	8,983	32	1.00	14	1.00	
P value			0.08		0.08‡	
Hay fever						
Yes	3,614	19	1.46 (0.82–2.60)	11	2.04 (0.90–4.63)	
No†	8,040	29	1.00	12	1.00	
P value			0.20		0.08	
Other allergies						
Yes	4,995	27	1.67 (0.94–2.96)	16	2.97 (1.22–7.22)	
No†	6,447	21	1.00	7	1.00	
P value			0.08		0.01	
Atopy						
Yes	4,734	34	1.66 (0.89–3.10)	20	4.57 (1.36–15.41)	
No†	6,920	14	1.00	3	1.00	
P value			0.11		0.007	
<b>Maternal diet during pregnancy</b>						
Soybean meat						
Yes	877	4	1.09 (0.39–3.03)	1	0.54 (0.07–4.02)	
No†	10,475	44	1.00	22	1.00	
P value			0.79		1.00†	
Nuts (including peanuts)						
Yes	3,504	15	0.98 (0.53–1.81)	8	0.84 (0.35–1.98)	
No†	7,848	33	1.00	15	1.00	
P value			1.00		0.66	
<b>Infant's diet</b>						
Ever breast-fed						
Yes	8,410	39	3.11 (0.73–13.32)	19	2.14 (0.91–5.04)	
No†	2,769	6	1.00	2	1.00	
P value			0.08		0.11	
Duration of breast-feeding						
None†	2,769	6	1.00	2	1.00	
<3 mo	3,611	13	1.66 (0.63–4.38)	7	2.67 (0.56–12.82)	
3–5 mo	1,420	7	2.28 (0.77–6.80)	3	2.91 (0.49–17.38)	
≥6 mo	3,379	19	2.60 (1.04–6.53)	9	3.67 (0.80–16.94)	
P value			0.03		0.07	
Soy milk or soy formula in 1st 2 yr						
Yes	1,027	12	3.60 (1.87–6.92)	8	5.90 (2.50–13.96)	
No†	11,297	37	1.00	15	1.00	
P value			<0.001		≤0.001‡	

**Table 1. (Continued.)**

Variable	Total Sample		Peanut Allergy		Positive Peanut Challenge	
	No.	No.	Unadjusted OR (95% CI)	No.	Unadjusted OR (95% CI)	
<b>Rashes in 1st 6 mo</b>						
Rashes over joints and in skin creases						
Yes	2,580	27	4.66 (2.61–8.31)	16	11.01 (4.03–30.07)	
No†	8,824	20	1.00	5	1.00	
P value			<0.001		<0.001‡	
Oozing, crusted rash						
Yes	2,003	27	7.07 (3.89–12.86)	19	44.66 (10.40–191.88)	
No†	9,330	18	1.00	2	1.00	
P value			<0.001		<0.001	
Diaper rash						
Yes	6,354	27	1.08 (0.61–1.93)	14	1.60 (0.65–3.97)	
No†	5,087	20	1.00	7	1.00	
P value			0.79		0.30	
Cradle cap						
Yes	8,500	41	2.38 (1.01–5.61)	20	6.94 (0.93–51.66)	
No†	2,952	6	1.00	1	1.00	
P value			0.041		0.024‡	
Severity-of-rash score						
0–3†	5,301	7	1.00	1	1.00	
4–6	4,102	15	2.77 (1.13–6.81)	3	3.88 (0.40–37.29)	
≥7	2,087	25	9.17 (3.96–21.22)	17	43.52 (5.79–327.13)	
P value			<0.001		<0.001‡	

\* Total samples differ among variables because not all mothers answered all questions. P values were calculated by the chi-square test, unless otherwise noted. OR denotes odds ratio, and CI confidence interval.

† This group served as the reference category.

‡ P values were calculated by Fisher's exact test.

entered into a regression analysis. Early soy consumption, rash over the joints and skin creases (eczema), and oozing, crusted rash remained independent risk factors for peanut allergy and for a positive peanut-challenge test after adjustment for other factors (Table 2). It is likely that children with allergy to cow's milk or with eczema are at increased risk for food allergies, and soy consumption in infancy is increased in response to these atopic disorders. Indeed, a history of allergy to cow's milk (reported prospectively at six months) was significantly associated with peanut allergy ( $P=0.03$ ). However, of the 289 children in the entire cohort reported to be allergic to cow's milk (2.7 percent), only 4 (0.1 percent) were allergic to peanuts. Milk allergy was not independently associated with peanut allergy ( $P=0.5$ ), since the relation was completely explained by exposure to soy. Similarly, allergy to eggs did not confound the association between peanut allergy and soy consumption. Furthermore,

the association with soy consumption was not altered when rash was included in the regression analysis.

#### ANALYSIS OF DETAILED INTERVIEW DATA

Of the 23 children with a positive peanut-challenge test, 4 (17) percent had a family history of peanut allergy (one mother, two fathers, and one sibling), as compared with none in both control groups ( $P<0.001$ ). Maternal peanut consumption during pregnancy varied from none to more than 28 times per week in mothers of children allergic to peanuts. Sixty-five percent of the mothers of infants with a positive peanut-challenge test did not recall consuming peanuts during pregnancy, a percentage similar to those for the atopic and normal control groups (61 percent and 71 percent, respectively;  $P>0.1$ ). However, 17 percent of the mothers of infants with a positive peanut-challenge test consumed peanuts at least seven times per week during lac-

**Table 2. Results of Stepwise Logistic Regression for Children with Peanut Allergy and Those with a Positive Reaction to Peanut Challenge.\***

Variable	Peanut Allergy	Positive Peanut Challenge
	Adjusted OR (95% CI)	
Consumption of soy milk or soy formula		
Yes	2.61 (1.31–5.20)	3.15 (1.27–7.80)
No	1.00	1.00
P value	0.006	0.01
Rash over joints and in skin creases		
Yes	2.60 (1.35–4.99)	3.88 (1.36–11.04)
No	1.00	1.00
P value	0.004	0.04
Oozing, crusted rash		
Yes	5.22 (2.68–10.19)	24.62 (5.47–110.87)
No	1.00	1.00
P value	<0.001	<0.001

\* The variables were adjusted for one another; maternal atopy and duration of breast-feeding were not statistically significant after adjustment. OR denotes odds ratio, and CI confidence interval. Children without the factor in question served as the reference category.

tation, as compared with 5 percent of the mothers in the atopic and normal control groups combined ( $P=0.03$ ). This association was no longer significant after adjustment.

The retrospective data were analyzed for maternal use of breast creams containing peanut oil (with concentrations ranging from 0.3 percent to 100 percent). The mothers of 35 percent of children with a positive peanut-challenge test had used such creams; this percentage was not significantly different from those for mothers in the atopic control group (47 percent) or the normal control group (24 percent).

In contrast, analysis of data on creams applied to the infant's skin revealed that 84 percent of the children who were allergic to peanuts and 91 percent of those with a positive peanut-challenge test had been exposed to creams containing peanut oil during the first six months of life — a significantly higher percentage than that of atopic (53 percent) and normal (59 percent) controls ( $P<0.001$ ) (Fig. 1A). Use of these creams occurred largely during the period when children were suffering from rashes and preceded the onset of symptoms of peanut allergy. In contrast, there was no significant difference among the three groups in the rate of use of infant creams not containing peanut oil (Fig. 1B).

Because one of the control groups was selected

on the basis of the presence of eczema, logistic-regression analysis of the case-control data did not consider the independent effects of rash. However, the data on topical exposure to peanut oil were analyzed to ensure that these effects were not secondary to those of rash and consumption of soy milk or soy formula, which had already been shown to be important (Table 3). The association remained significant when the results were adjusted for rashes and consumption of soy milk or soy formula.

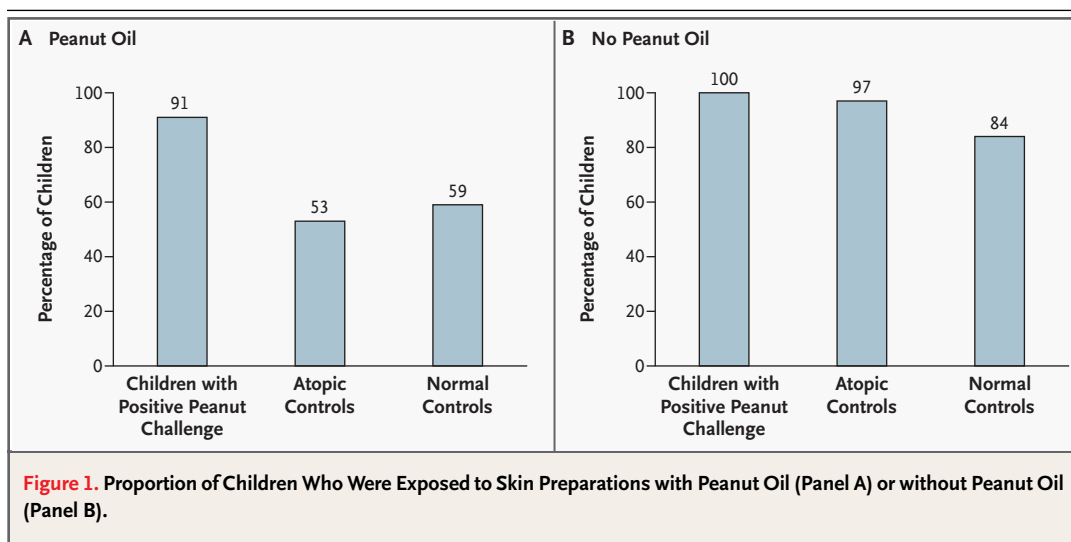
Further analysis was performed on the number of different peanut-oil-containing preparations used by the children in the three groups. On average, children who were allergic to peanuts were exposed to 1.91 peanut-oil products, as compared with 0.93 and 0.81 for the atopic and normal controls, respectively ( $F=11.62$ ,  $P<0.001$ ). Confining the comparisons only to the children who were exposed to these products within each group produced values of 2.10, 1.75, and 1.37, respectively ( $F=4.30$ ,  $P=0.015$ ).

## DISCUSSION

The apparent recent increase in the prevalence of peanut allergy has been difficult to explain, although it parallels an overall increase in allergic diseases of childhood.<sup>5</sup> We found that, in a cohort of preschool children, peanut allergy proved by double-blind, placebo-controlled food challenge had important associations, which persisted after adjustment for other factors, with a family history of peanut allergy, consumption of soy by the infant, early onset of eczema, other rashes with oozing and crusting, and exposure to topical preparations containing peanut oil. The absence of an association with maternal consumption of peanuts during pregnancy, combined with our inability to detect specific IgE to peanuts in cord blood, argues against the occurrence of sensitization in utero.

Our data are not consistent with the hypothesis that sensitization occurs by means of transmission of peanut allergens in breast milk. The percentage of mothers who breast-fed and the duration of breast-feeding were not significantly associated with allergy to peanuts after regression analysis, and the mothers of the children with peanut allergy did not eat significantly more peanuts during breast-feeding than the mothers of the children in the control groups.

Consumption of soy by the infants was independently associated with peanut allergy and could



not be explained as a dietary response to other atopic conditions. It nevertheless remains possible that the association with soy consumption may have been confounded by other, unknown factors. Although immunologic coreactivity occurs among peanuts, soybeans, and other legumes,<sup>15</sup> there is a low prevalence of clinical reactivity to soy in infants with peanut allergy.<sup>16,17</sup> No subject in this study was reported to have had reactions to both peanuts and soy. Soy-protein fractions have been shown to be homologous to major peanut proteins,<sup>18,19</sup> and exposure to a common soy T-cell epitope could cause cross-sensitization to peanuts, without necessarily resulting in clinical soy allergy. High levels of consumption of peanuts by infants did not appear to precede peanut allergy. Indeed, animal models demonstrate the important role of the gastrointestinal tract in establishing tolerance to food antigens. Our data indicate that low-dose oral exposure to peanuts in breast creams that contain peanut oil is not a risk factor for sensitization.

We hypothesize that exposure to low doses of peanut antigens through inflamed skin causes allergic sensitization. The creams used were largely emollients for the treatment of diaper rashes, eczema, dry skin, and inflammatory cutaneous conditions in infancy. The observed association between use of peanut oil and peanut allergy could be explained if children who became allergic to peanuts had more severe rashes and were therefore more often exposed to these creams. However, this is unlikely, since the reported severity of eczema was equivalent in the atopic control and peanut-allergy groups,

but substantially fewer preparations containing peanut oil were used in the former group. Furthermore, the rate of use of creams not containing peanut oil was equivalent in the peanut-allergy group and the atopic control group, and the mean number of peanut-oil-containing products per exposed child was significantly greater in the peanut-allergy group than in the control groups. Reporting bias on the part of the mothers of children with peanut allergy was unlikely, since neither the mother nor the interviewer was aware of which products contained peanut oil.

Recent studies have shown that refined peanut oil contains protein that, when extracted, produces IgE in patients with peanut allergy that is recognized in radioimmunoassay, elicits positive responses in leukocyte histamine-release assays in such patients, and produces positive results in skin-prick testing in such patients.<sup>20,21</sup> The presence of low levels of protein in peanut oil could cause sensitization. In vitro IgE synthesis and production of proinflammatory cytokines are favored by extremely low concentrations of allergen.<sup>22</sup> Furthermore, short peptides, such as amino acids 323 to 339 of ovalbumin, were as effective as whole ovalbumin in the induction of IgE responses in a murine model of allergic sensitization.<sup>23</sup> It is also possible that peanut oil may act as an immunologic adjuvant favoring allergic sensitization to protein. Indeed, adjuvants used in animal models contain oils that aggregate antigens, and the type of immune response is determined by the choice of adjuvants.

IgE responses to ovalbumin are easily elicited in

**Table 3. Results of Peanut-Oil–Preparation Usage in a Logistic-Regression Analysis.\***

Use of Peanut-Oil Preparations	Peanut Allergy		Positive Peanut Challenge	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
Yes	7.49 (1.71–32.8)	6.81 (1.41–32.9)	9.00 (1.15–70.4)	8.34 (1.05–66.1)
No	1.00	1.00	1.00	1.00
P value	0.008	0.02	0.04	0.045

\* OR denotes odds ratio, and CI confidence interval. Children who did not use the creams served as the reference group.

† Odds ratios have been adjusted for consumption of soy milk or soy formula; rash over joints and in skin creases; and oozing, crusted rash.

BALB/c mice by cutaneous exposure to low doses of ovalbumin.<sup>24</sup> A case report highlighted the fact that T cells responsive to peanut antigen were derived from the skin of an atopic infant before the development of peanut allergy.<sup>25</sup> Another case report describes the development of peanut allergy in a patient after receipt of a liver transplant from an allergic donor.<sup>26</sup> Chimerism was observed in the skin (but not the blood) of the recipient, suggesting that cutaneous homing of lymphocytes had occurred.

The common use of prescribed and over-the-counter preparations containing peanut oil, nut oils and proteins, and soy oil potentially represents an important cause of sensitization. Continual exposure through the skin may perpetuate<sup>27</sup> allergy and inhibit the development of immune tolerance, perhaps explaining why children are less likely to lose their allergy to peanuts than their allergies to other foods. However, topical exposure to peanut allergens need not necessarily occur through oil. Peanut butter, which is commonly consumed by adults and older children, could potentially cause sensitization by indirect exposure through the skin before peanuts are introduced into the infant's diet.

Previous studies have demonstrated the importance of foods in the exacerbation of eczema,<sup>1</sup> and one study has suggested that peanut protein may

have a role in the development of eczema.<sup>28</sup> Our data suggest a reverse causal relation: allergic sensitization to peanuts is favored by the inflammatory milieu of the skin.

In a large, population-based cohort study, we carefully defined peanut allergy and examined its possible antecedents. We conclude that a family history of peanut allergy, the occurrence of oozing, crusted skin rashes, topical use of peanut-oil–based preparations, and exposure to soy protein may be causal factors in the development of peanut allergy. Our preliminary data raise the question of whether sensitization to food allergens occurs by the cutaneous route rather than by the oral route. Confirmation of these associations in future studies would allow us to determine whether new interventions could decrease the rate of peanut allergy in the population.

Supported by the Medical Research Council, the Wellcome Trust, the Department of Health in the United Kingdom, and the Department of the Environment in the United Kingdom. Funding for this project within the Avon Longitudinal Study of Parents and Children was provided by the United Kingdom Ministry of Agriculture, Fisheries and Foods and the Food Standards Agency. The Avon Longitudinal Study of Parents and Children is part of the European Longitudinal Study of Pregnancy and Childhood initiated by the World Health Organization.

Dr. Lack reports having received research support from ALK-Abelló.

We are indebted to all the mothers who took part and to the midwives for their cooperation and help in recruitment.

#### REFERENCES

1. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-75.
2. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;99:744-51.
3. Assem ES, Gelder CM, Spiro SG, Baderman H, Armstrong RE. Anaphylaxis induced by peanuts. *BMJ* 1990;300:1377-8.
4. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
5. Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996;313:518-21. [Erratum, *BMJ* 1996;313:1046.]
6. Zimmerman B, Forsyth S, Gold M. Highly atopic children: formation of IgE antibody to food protein, especially peanut. *J Allergy Clin Immunol* 1989;83:764-70.
7. Moneret-Vautrin DA, Hatahet R, Kanny G. Risks of milk formulae containing peanut oil contaminated with peanut allergens in infants with atopic dermatitis. *Pediatr Allergy Immunol* 1994;5:184-8.
8. Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. *BMJ* 1996;313:514-7.
9. Lever LR. Peanut and nut allergy: creams

- and ointments containing peanut oil may lead to sensitisation. *BMJ* 1996;313:299-300.
10. Chandra RK, Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. *Ann Allergy* 1991;67:129-32.
  11. Oldaeus G, Anjou K, Bjorksten B, Moran JR, Kjellman N-IM. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. *Arch Dis Child* 1997;77:4-10.
  12. Golding J, Pembrey M, Jones R, ALSPAC Study Team. ALSPAC — the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatr Perinat Epidemiol* 2001;15:74-87.
  13. ALSPAC. Bristol, United Kingdom: University of Bristol, 2003. (Accessed January 21, 2003, at <http://www.ich.bristol.ac.uk/alspac.html>.)
  14. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J Allergy Clin Immunol* 1978;62:327-34.
  15. Barnett D, Bonham B, Howden ME. Allergic cross-reactions among legume foods — an in vitro study. *J Allergy Clin Immunol* 1987;79:433-8.
  16. Bernhisel-Broadbent J, Sampson HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J Allergy Clin Immunol* 1989;83:435-40.
  17. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900-4.
  18. Sampson HA, Buckley N, Huang SK, Burks AW, Bannon GA. Characterization of major peanut allergens. *J Allergy Clin Immunol* 1998;101:S240. abstract.
  19. Sicherer SH, Sampson HA, Burks AW. Peanut and soy allergy: a clinical and therapeutic dilemma. *Allergy* 2000;55:515-21.
  20. Olszewski A, Pons L, Moutete F, et al. Isolation and characterization of proteic allergens in refined peanut oil. *Clin Exp Allergy* 1998;28:850-9.
  21. Moneret-Vautrin DA, Rance F, Kanny G, et al. Food allergy to peanuts in France — evaluation of 142 observations. *Clin Exp Allergy* 1998;28:1113-9.
  22. DeKruyff RH, Fang Y, Umetsu DT. IL-4 synthesis by in vivo primed keyhole limpet hemocyanin-specific CD4+ T cells. I. Influence of antigen concentration and antigen-presenting cell type. *J Immunol* 1992;149:3468-76.
  23. Renz H, Bradley K, Larsen GL, McCall C, Gelfand EW. Comparison of the allergenicity of ovalbumin and ovalbumin peptide 323-339: differential expansion of V beta-expressing T cell populations. *J Immunol* 1993;51:7206-13.
  24. Saloga J, Renz H, Larsen G, Gelfand EW. Increased airways responsiveness in mice depends on local challenge with antigen. *Am J Respir Crit Care Med* 1994;149:65-70.
  25. van Reijssen FC, Felius A, Wauters EA, Bruijnzeel-Koomen CA, Koppelman SJ. T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 1998;101:207-9.
  26. Legendre C, Caillat-Zucman S, Samuel D, et al. Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med* 1997;337:822-4.
  27. Carswell F, Thompson S. Does natural sensitisation in eczema occur through the skin? *Lancet* 1986;2:13-5.
  28. Burks AW, Williams LW, Mallory SB, Shirrell MA, Williams C. Peanut protein as a major cause of adverse food reactions in patients with atopic dermatitis. *Allergy Proc* 1989;10:265-9.

Copyright © 2003 Massachusetts Medical Society.

#### ELECTRONIC ACCESS TO THE JOURNAL'S CUMULATIVE INDEX

At the Journal's site on the World Wide Web (<http://www.nejm.org>) you can search an index of all articles published since January 1975 (abstracts 1975–1992, full-text 1993–present). You can search by author, key word, title, type of article, and date. The results will include the citations for the articles plus links to the abstracts of articles published since 1993. For nonsubscribers, time-limited access to single articles and 24-hour site access can also be ordered for a fee through the Internet (<http://www.nejm.org>).