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Title
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Permalink
https://escholarship.org/uc/item/8d96v5jc

Journal
Journal of Allergy and Clinical Immunology, 63(4)

ISSN
0091-6749

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Publication Date
1979-04-01

DOI
10.1016/0091-6749(79)90106-4

Peer reviewed

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Original articles

Development of allergy in children

I. Association with virus infections

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Children born into allergic families, with two allergic parents, are at high risk of developing allergy within the first 5 years of life. In order to observe possible external factors in the sensitization process, a prospective study of 13 such children was done, in which serial clinical and immunologic observations were made at 3- to 6-month intervals over a period of 1 to 4 yr. Eleven of these children are now clinically allergic; 5 have asthma. Immunologic evidence for allergic sensitization was observed in these 11 children by RAST, antigen-induced leukocyte histamine release, lymphoblastogenesis, and rise in serum IgE. Upper respiratory infections (URI) occurred in these 11 allergic children 1 to 2 months prior to the onset of allergic sensitization. In 10 of these 11 URI children, complement-fixing antibodies to viruses (parainfluenza, RSV, CMV) increased in the same blood samples in which immunologic allergic sensitization was first evidenced. This coincidence suggests that certain viruses may contribute to the allergic sensitization process.

Are children born into allergic families already "over the hill" at birth in regard to developing allergies later? Or, are there environmental events that trigger allergic sensitization and symptoms in such children?

Atopy usually appears in childhood and may last a lifetime, with symptomatic periods alternating with quiescent periods. This is the time during which effective optimal preventive or therapeutic measures can minimize any permanent damage from atopy. Therefore, if external events can trigger allergy in children, then preventing or overcoming the effects of such events might prevent allergic onset.

Special abbreviations used

CMV	cytomegalic inclusion virus
HR	histamine release
LTT	lymphoblast transformation test
PHA	phytohemagglutinin
RAST	radioallergosorbent test
RSV	respiratory syncytial virus
URI	upper respiratory infection

That allergy, e.g., asthma, is hereditary was known even by such ancients as Maimonides.[1] Later, Cooke and Vander Veer,[2] in the first extensive study of heredity in allergy, found that 48% of 504 allergic patients had an immediate family history of allergy, while only 12% of a comparable nonallergic group had such a family history. In individuals whose parents were both allergic, 68% developed allergy before the age of 10; with one allergic parent, 51% developed allergy; and 38% had no family history of allergy. This suggested a simple mendelian inheritance. However, in subsequent genetic studies the inheritance of allergy was complex and polygenic,[3] probably involving the immune response genes of the histocompatibility region.[4]

We here report our prospective study of 13 chil-

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Supported by the United States Public Health Service Allergic Diseases Center Grant AI11010 and Training Grant AI00011.
Parts of this paper were presented at the American Congress of Allergy, New York, March 30, 1977, and at the Federation of Experimental Biology and Medicine, Chicago, April 5, 1977.
Received for publication May 16, 1978.
Accepted for publication Oct. 11, 1978.

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0091-6749/79/040228+14$01.40/0 © 1979 The C. V. Mosby Co.

TABLE I. Comparison of clinical symptoms of allergy in children from "allergy-prone" and "nonatopic" families

System with symptoms	13 children from allergic families				28 random children from well-baby clinic			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Gastrointestinal (including "colic")	5	1	1	7	2	1	0	3
Skin (chronic eczema>1 mo	6	6	1	13	6	1	0	7
(non-diaper area); urticaria)	0	2	0	2	0	0	0	0
Nose (chronic>1 mo)	2	8	1	11	6	0	0	6
Chest (chronic cough or wheeze with URI)	5	6	0	11	2	0	0	2
Otitis (recurrent)	3	3	1	7	2	1	0	3
Totals: Number positive/number total possible.				51/65				21/140
% positive.				80%				15%

$p < 0.01$.

dren, who had a biparental allergic history, for the onset of symptoms and immunologic evidence of allergy. In this study we focused on the possible external events associated with the onset of allergy, such as infections, immunizations, or new foods.

MATERIALS AND METHODS

Patients

Allergy-prone group. Thirteen allergic pregnant women with allergic husbands were selected from the Allergy and Obstetrical Clinics of the University of California, San Francisco and the Kaiser-Permanente Hospital in San Francisco, between 1973 and 1976. All parents had asthma, hay fever, or eczema, either singly or in combination. At birth, the authors examined the infants and collected cord blood with viable leukocytes and plasma for immunologic studies. The 13 offspring have been studied at 3-month intervals for the first 2 years, and at 6-month intervals up to 4 years.

We acted as observers, but informed the family pediatrician of any significant findings in the laboratory tests; in some instances the pediatrician acted on that evidence, e.g., changed the formula. He also gave routine immunizations at the appropriate times. Nursing was strongly encouraged and supplemented with soy or casein hydrolysate (Nutramigen) formula feedings.

The clinical diagnosis of allergy in infants involved the criteria discussed in the following paragraphs.

ECZEMA. Mild was a pruritic maculopapular rash on the face and flexural surfaces of the limbs persisting for more than one month, i.e., observed on 2 or more visits. Moderate was such a rash observed for 6 or more months, or involving, in addition, trunk and extensor surfaces of limbs. Severe was such a rash that was scratched open and became infected and/or persisted 9 months or more.

ALLERGIC RHINITIS. Mild was recurrent sneezing and clear or white nasal discharge observed on 3 or more occasions; moderate was such a discharge plus nose rubbing on 3 successive visits for 6 months; severe was a constant profuse white discharge with intermittent purulent episodes on 3 visits.

ASTHMA. Mild was 4 weeks of persistent cough and mild wheezing with infections; moderate was cough persisting beyond 4 weeks and wheezing without infection and requiring intermittent bronchodilators; severe was constant coughing interfering with sleep or exercise or wheezing of sufficient severity to require daily bronchodilators.

OTITIS. Intermittent otitis lasting 6 months or more was mild; 9 months of otitis with persistent fluid was moderate; such otitis or persistent fluid that required placement of tympanostomy tubes was severe.

COLIC. Infantile colic meaning prolonged crying, cramps, and frequent flatus and persisting for one month or more was mild; such colic persisting 2 months and/or associated with vomiting was moderate; these symptoms associated with diarrhea and dehydration were severe.

Well-baby control group. Our original intent was to follow the same protocol in a group of infants born into families with no allergic family background, but we were prevented from doing so by a lawsuit brought by a member of our Human Experimentation Committee over the issue of serial venous blood sampling in normal children. Therefore, we made clinical observations on the development of allergic symptoms in a group of 28 infants with nonallergic parents from our Well-Baby Clinic. These 28 children were followed at 3-month intervals for 1 year or more for signs of allergy. An additional 7 children were followed but were not included in the control group when it was discovered that close relatives had allergies. The 2 infants in the allergy-prone study group (S. G. and M. J.) who failed to develop significant allergic symptoms or positive immunologic tests served as internal controls, in that they had the same bilateral family history of allergy but had few colds.

Single blood samples from 10 nonallergic age-matched children undergoing cardiac catheterization served to establish baseline values for our immunologic tests. Single blood samples from 24 age-matched known allergic children (symptomatic-positive skin tests) served to test the validity of our immunologic assays. While our controls were not optimal, they were the best possible under the legal constraints imposed.

TABLE II. Comparison of immunologic responses with common allergens in 3 tests in "allergy-prone" and "control" children

Patient groups	Immunologic tests		
	RAST >1.5 e/c (3x)	WBC >10%	LTT Ag >1.7 e/c
	No. positive allergens*/total tested		
Infants of allergic families (n = 13)	38/65 = 58.5%	21/46 = 45.6%	23/42 = 57.7%
Allergic child controls	32/40 = 80% (n = 20)	46/50 = 92% (n = 24)	8/13 = 62% (n = 11)
Nonallergic control children (n = 10)	2/18 = 11%	1/20 = 5%	1/10 = 10%

*Dog or cat; grass pollen; house dust or mite; cow's milk; soy.

TABLE III. Complement-fixing virus antibodies in 11 "allergy-prone" children before and after allergic sensitization

	Parainfluenza 3	RSV	CMV	Total no. children
Rise in virus antibody titer	2* (2-fold) 3 (4-8 fold)	2 (2-fold) 1 (4-fold)	1 (4-fold)	8/11
High virus antibody titer (not rising)	2	—	1	2/11
Low virus antibody titer (no change)	4	8	9	1/11

*Number of children.

Immunologic tests

Allergens included cat pelt allergen (kindly supplied by Dr. H. Baer, Food and Drug Administration, Bethesda, Maryland), dog dander, house dust (Berkeley Biologicals, Berkeley, California), mite *(Dermatophagoides farinii)*, whole cow's milk, soybean and rye grass pollen *(Lolium multiforme)* extracts (Hollister-Stier Laboratories, Spokane, Washington).

Serum immunoglobulin (IgG, A, M) concentrations were determined by the Mancini immunodiffusion method[5] using Partigen immunoplates (Behring Diagnostics, Somerville, New Jersey). *Total serum IgE* was determined by a double-antibody method[6] (PRIST Pharmacia, Piscataway, New Jersey).

Radioallergosorbent test (RAST).[7] RAST was used for IgE antibodies to a panel of 7 allergens common for children (cat or dog dander, house dust, and mite *(D. farinii)*, rye grass pollen as representative for grass or cereal antigen, whole cow's milk, and soybean). The allergens were coupled to Whatman No. 1 filter paper discs activated with cyanogen bromide, mixed with 50 μl 1:5 diluted serum, and incubated 24 hr at room temperature, with slow rotation. After centrifugation, the discs of sorbent-allergen antibody mixed with 50 μl ^{125}I rabbit antihuman IgE (40,000 cpm) were incubated for 18 hr, recentrifuged, washed, and counted on an Auto-Gamma Spectrometer (Searle 1185). Results from children's sera were compared with cord sera from infants of nonallergic families and diluent. RAST of 2 times greater than base was considered positive, and 1.5 times base was borderline; this choice of significance has been established for our laboratory for 5 years.

Histamine release (HR) from leukocytes.[8] Leukocytes were separated by dextran from 5 to 10 ml heparinized blood, mixed with antigen in 3 or more decimal (dilutions) or with rabbit antihuman IgE serum, incubated 40 min at 37° C, and cells were removed by centrifugation. Histamine was extracted from the supernatant in *n*-butanol in NaOH, then in *n*-heptane and HCl, cooled, and made fluorescent with *o*-phthaldialdehyde. Acidified fluorescent histamine was quantitated by spectrofluorometry (Aminco SPF-125). Perchloric acid (4%) was used to completely lyse one aliquot of cells for total histamine content; antigen-induced histamine release was expressed as percent of total histamine present in cells. Antigen-induced histamine of 10% or more than control was considered positive.

Lymphoblast transformation test (LTT).[9] Lymphocytes were collected from heparinized blood by first separating erythrocytes in dextran; the supernate was then layered on Ficoll-Hypaque and centrifuged. Six 10-fold dilutions of antigen or PHA 100 μl were added to 1,000 μl lymphocytes (10^5) in tissue culture TC 199-20% autologous serum suspension. Cultures at 37° C in 5% CO_2 were carried 3 days for PHA and 7 days for antigen; then, ^{3}H-thymidine (0.5 μCi) was added to 0.1 ml culture and harvested after incubation for 4 hr. Incorporation of ^{3}H-thymidine was mea-

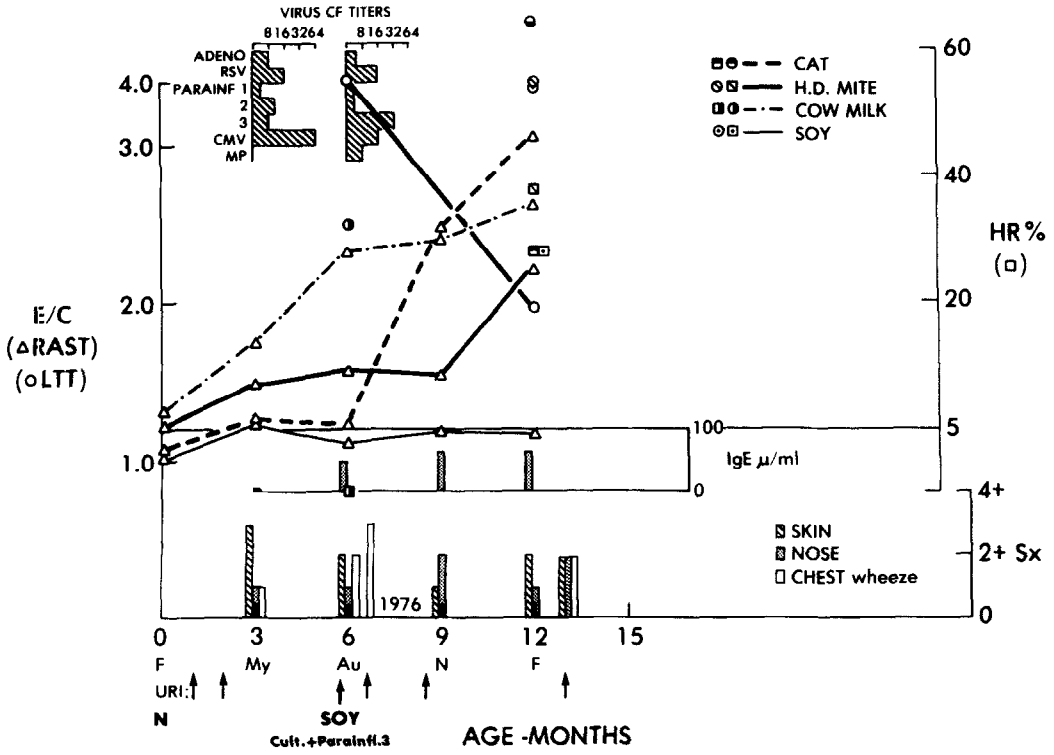

FIG. 1. Chronologic record of symptoms (Sx) and immunologic tests: RAST, HR, LTT, total IgE, and complement-fixing virus antibodies in Patient C. F. At bottom are months, February (F), May (My), August (Au), and November (N). Arrows indicate time of URI. Feedings are indicated by N (nursing), S (soy formula), and CM (cow's milk).

sured by counting samples in a liquid scintillation spectrometer (Mark III, Searle). Lymphocyte transformation indices were ratios of ^{3}H-thymidine in cultures with (E = experimental) or without (C = control) antigen or PHA. A ratio of E/C greater than 2.0 was considered positive, and 1.7 was borderline.

Virus antibodies. Complement-fixing antibodies were determined before and after respiratory infections by utilizing a panel of 7 common childhood respiratory virus antigens: influenza A, parainfluenza 1, 2, 3; adenovirus, RSV, CMV, and *Mycoplasma pneumoniae.*[10] These tests were kindly performed by Dr. A. Back, Director of Laboratories, Department of Public Health, San Francisco, California. Routine bacteriologic and viral cultures from the nasopharynx were made at times of acute respiratory infection. For virus cultures, alginate nasal swabs were dipped in 1 ml of Hanks balanced salt solution containing penicillin and gentamicin; 0.1 to 0.2 ml was immediately added to 2 tubes each of: rhesus monkey kidney, WI-38 human diploid fibroblasts and HEP-2 cells (Flow Laboratories, Rockville, Maryland). Cell monolayers were incubated at 35° to 36° C on roller drums for 2 weeks (for HEP-2 and monkey kidney) and 4 weeks (WI-38) with weekly feedings. The presence of viruses was detected by cytopathic effects and/or hemadsorption, and the identity was confirmed by reaction with the specific antiserum.

β-adrenergic status assessment. In two children at the age of 6 months we determined blood sugar, free fatty acids, and total eosinophil baselines, then gave epinephrine injection (10 μg/kg) subcutaneously, and repeated the blood sampling at 20, 40, and 60 minutes. This evaluation was again repeated in the two children at 12 or 18 months after each had developed allergic symptoms.

RESULTS

Allergy-prone group. All 13 children showed some symptoms of allergy (Table I). All had recurrent rashes; 7 had moderate to severe atopic dermatitis involving the face, ears, flexural creases, trunk, and extensor surfaces of the limbs; the remaining 6 had a mild but persistent maculopapular rash on the face and limbs. Two infants had recurrent episodes of urticaria, 1 from cat exposure and 1 from ingestion of beef.

Respiratory tract involvement occurred in 11 children, with moderate to severe chronic nasal discharge in 9 and milder intermittent discharge in 2. Six children had persistent cough and wheezing that required bronchodilators intermittently; 3 are now considered to be moderate asthmatics. Five others had mild cough or wheezing with infections only.

Recurrent otitis was observed in 7 children: 3 mild, 3 moderate, and 1 severe. Gastrointestinal symptoms occurred repeatedly in 7 children, 4 with mild to

TABLE IV. Onset of allergic sensitization in infants

Patient	Age (mo) last visit with no allergic symptoms and all negative immunologic tests	Age (mo) URIs	Age (mo) virus* complement-fixing antibodies		Age (mo) first allergic symptoms	Age (mo) first immunologic tests positive†	IgE serum (IU/ml)	
			Pre-URI	Post-URI			Pre-URI	Post-URI
C. F.	3	1, 2	3 p 8	6 p 32	3½ ecz; 6 wheeze	6 R-CM, 2.3 L-CM, 2.5 L-H, 4.0	2	51
J. H.	3	6, 11	6½ p 4 RS 16	9 p 64 RS 8	6½ nose	6½ R-CM, 2.1 R-H, 1.6 H-C, 40	1	3
D. M.	3	2½	7 p 8	10 p 16	6 nose; rash	7 R-D, 2.7	1.4	5.5
M. S.	NB	2, 3, 5	4 RS 16	9 RS 32	4 nose; 6 urtic	6 R-C, 1.8 H-C, 85 H-H, 55 L-H, 1.8	1.5	2.5
R. J.	3	3½, 5½	3 CM 8 p 64	6 CM 32 p 64	6 nose	6 R-G, 2.1 L-G, 2.0 R-S, 1.8	0	5.8
M. M.	6	7, 8, 12	9 RS 16	12 RS 64	8 nose; wheeze	9 R-H, 1.8 H-H, 60 L-H, 7.5 H-O, 90	1	1.4

*Virus: p, parainfluenza 3; RSV, respiratory syncytial virus; CM, cytomegalovirus.
†R: RAST (numbers indicate E/C); H: HR (numbers indicate % histamine); L: LTT (numbers indicate E/C—lymphoblastogenesis). C: cat; D: dog; G: grass pollen; H: house dust; CM: cow's milk; O: oat; N: nursing; S: soy; W: wheat.
‡AR: allergic rhinitis. Asth: asthma; Ecz: eczema; SOM: serous otitis media.

moderate colic and 3 with recurrent vomiting, 1 of whom had severe diarrhea and dehydration that required feeding changes and hospitalization for intravenous fluids.

Well-baby control group. Of the 28 children in this group, 7 had a chronic mild skin rash, 6 of whom had a nasal discharge which lasted over one month, and 3 had recurrent otitis.

A comparison of symptoms of allergy in the two groups (Table I) shows 51 chronic symptoms in 5 organ systems in the 13 allergy-prone children, for a maximum possible score of 65 (5 symptoms × 13 children) for an 80% (51/65) incidence, whereas 21 symptoms in a possible score of 140 (5 × 28 children) or 15% were observed in the control group. This is significant at a p value of <0.01 (chi-square with Yates correction for small numbers).

Immunologic responses

The 3 tests for immunologic response to specific allergens were positive for about half of those in the allergy-prone group (Table II). The percent of positive tests in children of allergic families compared with the nonallergic controls are statistically significant ($p < 0.01$) for all 3 tests using the t test for paired samples.

In two children at the age of 6 months, subcutaneous epinephrine injection (10 μg/kg) caused a normal rise in blood glucose and free fatty acids and a drop in total eosinophils measured at 20-min intervals for 1 hr. When the tests were repeated on these two children at 12 and 18 months, respectively, after they had each developed allergic symptoms, subcutaneous epinephrine (10 μg/kg) caused a similar normal rise in blood glucose and free fatty acids and a fall in total

Feeding history	Current age (yr) (6/78)	Current allergic status (6/78)‡
N 5½ mo; S	2½	Asth mod Ecz mod
N 5½ mo' CM	4	AR mild Ecz mod
N 1 mo; CM S 12 mo	4 5	Asth mod AR & ecz mild AR & urtic, cat
N 26 mo + S suppl	3½	AR mod
N 7 mo + nutr; S 12 mo	4½	Asth mod AR mod

eosinophils. There was no evidence of an increase in β-adrenergic blockade following allergic sensitization.

We could make no association of allergic sensitization with the type of infant feeding, i.e., breast feeding, cow's milk, or soy formula; however, the number of children[13] is too few for an association to be made on a statistical basis.

Of note is that the onset of allergic symptoms and positive immunologic response to one or more allergens coincided with a URI in the previous month. Plasma samples, taken before and after the respiratory infection in 11 children from allergic families, were tested for complement fixing antibodies to a panel of common respiratory viruses and mycoplasma (the same plasma samples in which a change in allergic immunologic reactivity was observed).

From Table III, it is evident that 4 children had a rise in parainfluenza 2 and 3 antibodies (3 had ≥ 4-fold rises, 2 had a 2-fold rise); 2 had already high antibody levels to these viruses. With RSV, 3 had rising titers; 1 had a rising titer to cytomegalic virus, and another had a stable high titer. Only one child had low titers to all the panel viruses. That these are not unusual viruses in this age group is evidenced by the presence of complement-fixing antibodies in our 10 control nonallergic cardiac catheterization children. Three had antibodies to parainfluenza 3, and 2 had RSV titers of 1:8 or more. What was striking was the onset of allergic sensitization coincident with a rise in antibody titer to these respiratory viruses.

Nasopharyngeal cultures were taken in 15 of the 23 URIs reported in the 13 infants. Two cultures were positive for pathogenic bacteria (*Staphylococcus aureus*, coagulase-positive in Patient C. F., and pneumococcus in Patient J. H.). The rest of the cultures were reported as containing normal bacterial flora.

Table IV is a tabulation of the pre- and postinfection clinical and immunologic test results and ages in months when changes were observed in the individual children. Feeding history and current allergic status assessment are tabulated. In the first 11 children that developed allergic symptoms and positive immunologic tests for a particular allergen, a URI preceded the allergic sensitization by 2 to 6 weeks. These infections were associated with a rising virus antibody titer in 8/11 children; another 2 already had high titers. In 7 children, two different immunologic tests for a particular allergen were positive in the first postinfection plasma sample (column 7). In 10 children, tests for two allergens were positive. Of these tests, one-third (13/35) were borderline-positive: RAST and LTT E/C, 1.7-1.9, and HR < 15% on this first examination; on subsequent samplings, 9 became more positive (E/C > 2), 3 remained the same, and 2 became negative. Postinfection IgE levels increased 3-fold or more in 7/11 children when compared with the preinfection sample taken 3 months before. However, in only 2 infants did IgE levels rise to above 10 U/ml in the postinfection sample.

Seven children were breast-fed for 5½ months or longer; 2 of these were breast-fed for more than two years. Of these 7 nursing infants, only 2 required supplemental soy or casein hydrolysate formulas. Three were on soy formula and 3 were maintained on cow's milk formula. In all children, solid foods were introduced conservatively at 4 to 6 months of age. The current allergic assessment of these 13 children indicates that 5 have asthmatic episodes, 9 have perennial allergic rhinitis, 4 continue to have eczema, 2 have recurrent otitis, and 1 has intestinal symptoms from wheat and milk; only 3 are considered not allergic.

The association between virus infections and onset

TABLE IV. Cont'd

Patient	Age (mo) last visit with no allergic symptoms and all negative immunologic tests	Age (mo) URIs	Age (mo) virus* complement-fixing antibodies		Age (mo) first allergic symptoms	Age (mo) first immunologic tests positive†	IgE serum (IU/ml)	
			Pre-URI	Post-URI			Pre-URI	Post-URI
J. M.	5	8	5 p 16	9 p 32	9 nose; ecz	9 R-H, 1.8 H-G, 23 L-G, 4.8 L-CM, 2.6	1	4
G. B.	3	2½, 7	6 CM 64	9 CM 64	6 ecz; nose; GI-W	6 R-W, 1.9 R-D, 1.9	1	1.6
S. J.	NB	2, 3	—	—	3 ecz and nose; 5½ wheeze	3 R-D, 3.4 H-D, 13 R-G, 1.8 R-CM, 1.7	2.6	11
J. D.	NB	3, 6	4 p 64	7 p 64	4 nose; ecz	4 R-D, 2.2 R-G, 1.8 H-G, 17 7 R-H, 2.2 L-H, 3.0	0	1
J. Z.	3	2, 2½	7 p 8	12 p 64	3 ecz	7 R-D, 2.0 R-W, 1.8	2	7.5
S. G.	36	6, 11	6 p 8	9 p 8	None	None	0	1.2
M. J.	18	4,6	Virus cult neg 4 mo		None	None	0	1.8

of allergic sensitization may be more evident when one examines the clinical and immunologic course for individual patients.

A 15-month old oriental boy (C. F.) with a 3-year-old brother with severe asthma and eczema was breast-fed for 5½ months and then placed on soy formula for 6 months and whole cow's milk at 12 months (Fig. 1). His brother transmitted two respiratory infections to him at 1 and 2 months of age, but cultures from the nasopharynx were negative for bacterial pathogens. At 3 months, he presented with moderately severe eczema and mild nasal congestion. CMV titer was 64 and parainfluenza 3 titer was 8. Total IgE was less than 5 U/ml. Cow's milk RAST while breast feeding was borderline (E/C = 1.7). Cat and mite RAST were negative. At 6 months, he had another URI, although rhinitis had been constant for the preceding 3 months, but eczema was somewhat improved. There was a 4-fold rise in parainfluenza 3 antibody titer to 1:32. Total IgE rose 10-fold to 51 U/ml. Results of RAST and LTT to cow's milk were positive (E/C = 2.3 and 2.5, respectively) and they were positive to mite (E/C = 1.5 borderline and 4.1, respectively). At 7 months, he developed another URI; parainfluenza 3 was recovered from a nasopharyngeal swab; moderate wheezing was relieved with theophylline. At 9 months, in addition, RAST to cat was positive (E/C = 2.6). Although there was no cat in his home, 5 days per week the children were at a baby sitter's home where there was a cat. By 12 months, he had continuous rhinitis with nasal eosinophilia, moderate eczema, wheezing with respiratory infections, and was considered to be asthmatic. RAST was positive for cat, cow's milk, and mite

Feeding history	Current age (yr) (6/78)	Current allergic status (6/78)‡
N 12 mo; CM	2½	Asth mild AR SOM
N 24 mo	4½	Diarrhea & vomiting c wheat & milk AR & ecz mild
CM	2½	Asth mild AR mod
CM 1 mo, colic; S	2½	Normal
N 6 mo; S	3¼	AR mod SOM mod
S	3	Normal
N 1 mo; CM	1½	Normal

(E/C = 3.0, 2.7, 2.1, respectively). In this child, onset of allergic sensitization to 3 or 4 allergens coincided with respiratory infections associated with positive nasopharyngeal cultures and rising antibody titer for parainfluenza 3.

The Caucasian boy (J. H.), now 4 years of age, was breast-fed for 5 months and weaned to cow's milk (Fig. 2). He did well his first 5 months and developed a URI when throat pneumococcus was cultured. At 6 months, his nose continued to run, but virus titers were all negative, except 16 for RSV. His RAST was positive to cow's milk (2.1) and borderline to mite (1.6). At 9 months, no new colds had occurred, but his parainfluenza 3 titer had risen from undetectable to 1:64, probably as a result of his cold at 5 months. However, by 9 months RAST titers had all fallen and he had a mild rash and nasal congestion. Between 9 and 15 months, he developed 3 more URIs (not associated with specific viral agents), more flexural rash, profuse watery nasal discharge, and rhonchi. Cat histamine release (55%) and RAST (1.8) were positive at 12 and 15 months, but fell by 18 months. Although there was no cat in his home, he stayed with his grandmother several days each week; she has a house cat. At 23 months, he developed severe diarrhea, high fever and dehydration, negative pathogenic bacterial stool culture, and was hospitalized 2 days. One month later, his skin and chronic nasal congestion were worse; RAST to mite, cat, and cow's milk were all more positive, as was mite LTT. His total IgE was steady at 5 IU, but after the diarrhea it rose to 18, suggesting that gastrointestinal infection might have boosted his allergic sensitization.

The 18-month-old girl (S. G.), although from a bilaterally allergic family, might be considered a control because she has had only 2 mild colds and minimal evidence of allergic sensitization, i.e., mild rash and nasal congestion, only borderline RAST to grass (1.5) and mite (1.6), and negative HR and LTT (Fig. 3). Another 18-month-old boy (M. J.) has had a similar benign course, with no immunologic evidence of allergic sensitization.

Most dramatic was a 3-year-old girl (M. S.) from a household with 3 cats, one of which slept in her room when she was 3 months of age (Fig. 4). The mother refused to acknowledge animal allergy. She had 2 URIs by 3 months and at that time had an RSV antibody titer of 1:16. At 3 months, cat RAST (1.8) and HR (10%) were borderline-positive; she had mild nasal congestion and coughing. At 5 months, she developed otitis media and markedly increased persistent nasal congestion. At 7 months, she developed generalized urticaria and eyes swollen shut whenever she was near the cat. Her cat HR was markedly positive (80%) and cat RAST (1.6) and lymphocyte transformation (1.5) were borderline. Mite by these 3 tests were also positive (HR = 55%, RAST = 1.8, LTT = 1.8). The RSV titer rose to 1:32. She had recurrent serous otitis media for the first 15 months and at 3 years still has persistent chronic rhinitis and hives when near cats. At 12 months, she was switched from human to cow's milk, with repeated infections. Cow's milk RAST (2.1) became positive within 2 months. RASTs to cat (1.6) and mite (1.4) were borderline. At 2 years, cat and mite HR remain positive (38% and 25%, respectively) while mite RAST (1.8) is borderline. It appears that early close exposure to cat triggered the allergy by 3 months of age and may have coincidentally followed two respiratory infections before that time. No immunizations had been given.

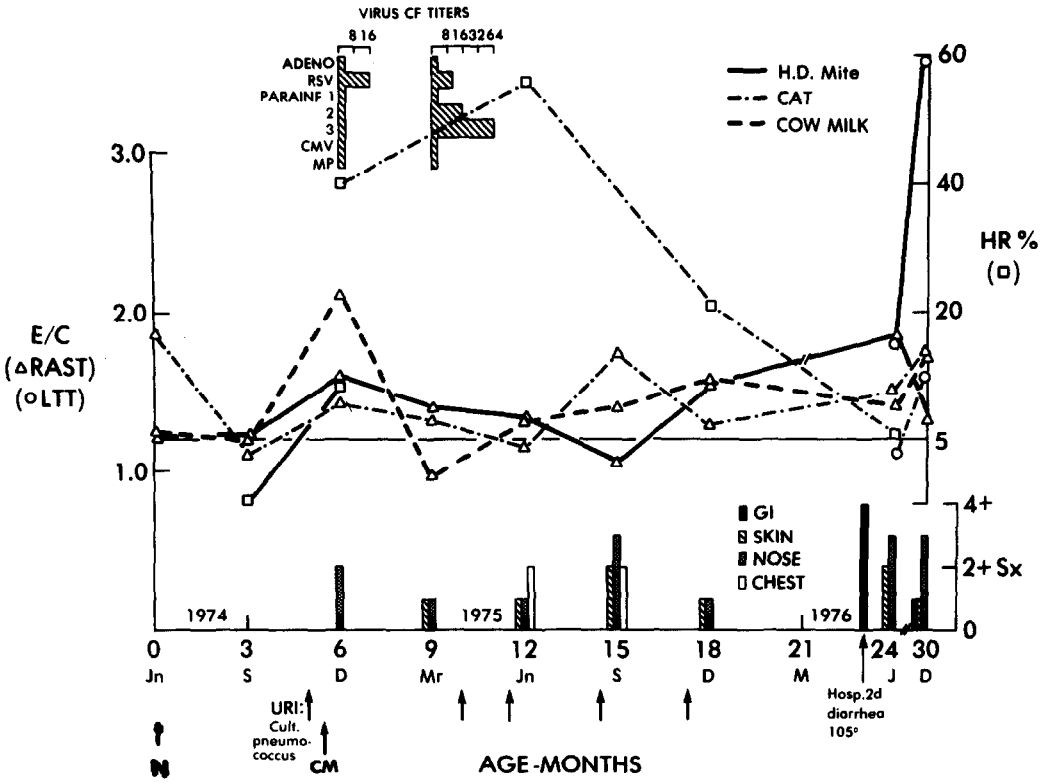

FIG. 2. Chronologic record of symptoms (Sx) and immunologic tests in Patient J. H.

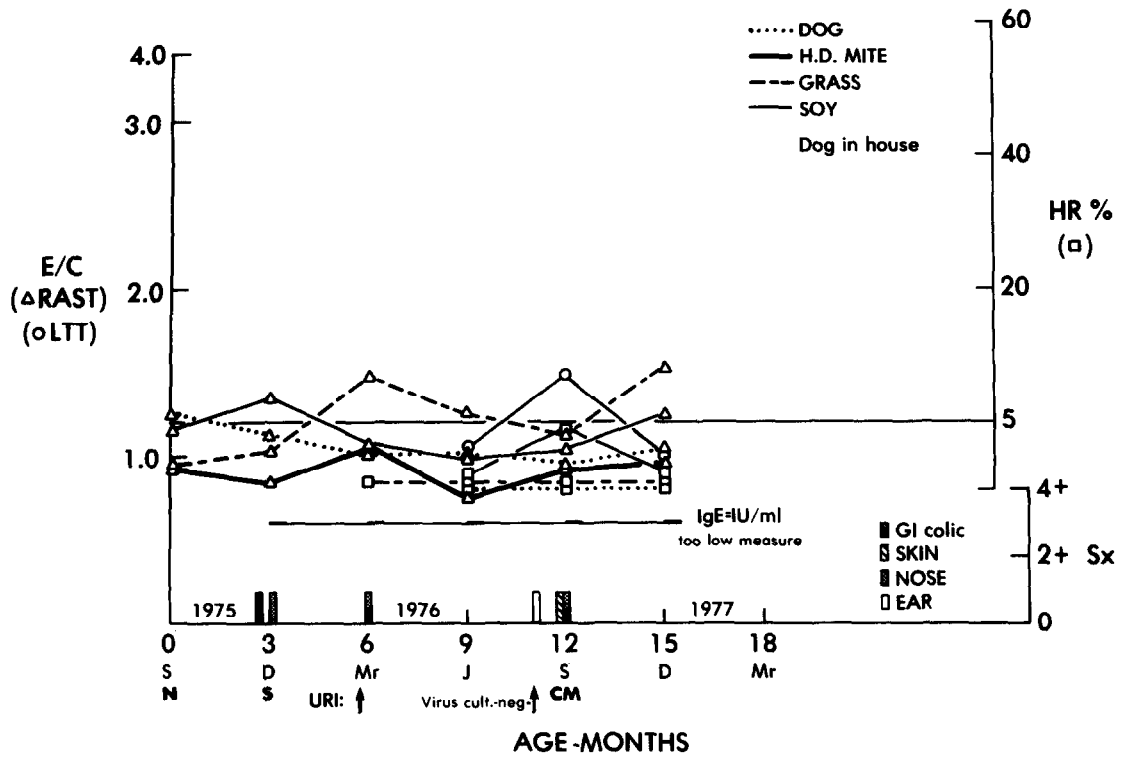

FIG. 3. Chronologic record of symptoms (Sx) and immunologic tests in Patient S. G., who is considered an internal control.

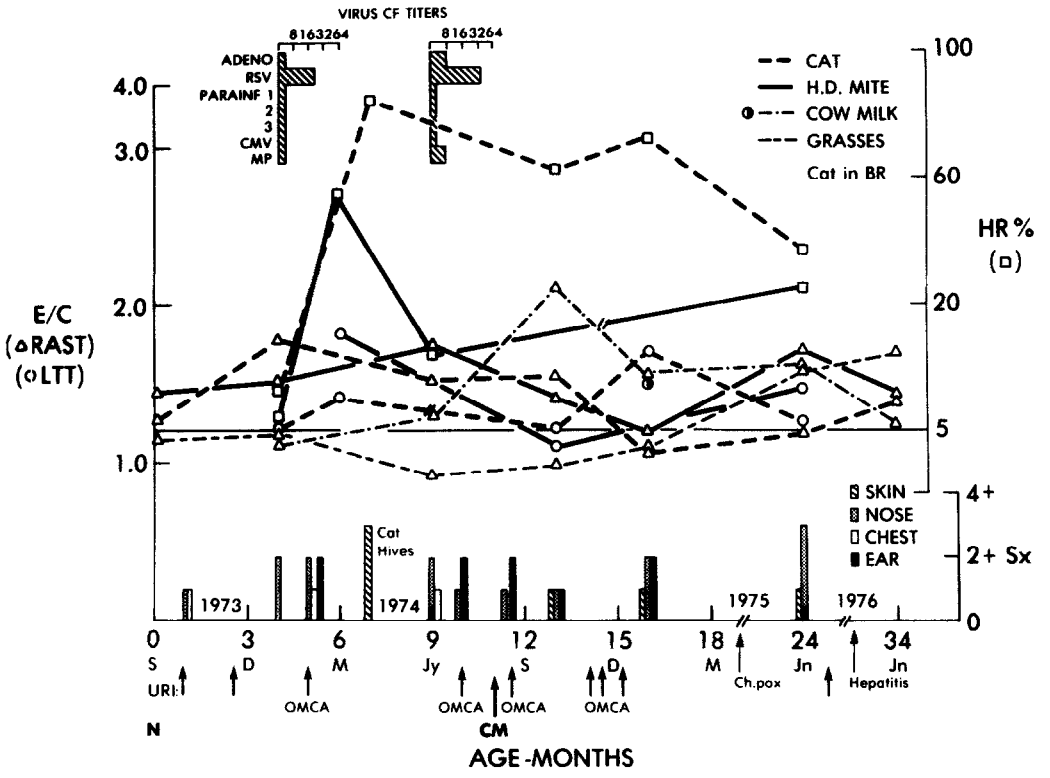

FIG. 4. Chronologic record of symptoms (Sx) and immunologic tests in Patient M. S.

Immunoglobulins G and M in our study group have followed a normal distribution for age. Serum IgA was also within the normal range for age, but consistently in the low range (Fig. 5).

DISCUSSION

Infants with a biparental history of allergy were chosen for this prospective study because of the prevalence and early onset of allergy in such children. The heritability of allergy is more complex than the original suggestion of a simple mendelian-recessive gene, based upon the observations of Cooke and Vander Veer.[2] Van Arsdel and Motulsky[3] suggested an incomplete recessive gene or a polygenic inheritance pattern.

The discovery of immune response genes in animals[11] and their association with histocompatibility antigens[12] led others to look for such associations in man. Levine, Stember, and Fotino[4] described a hay fever haplotype in seven families allergic to ragweed. One haplotype occurred in all ragweed-allergic family members, but not all members with that haplotype were allergic. However, no member of the family allergic to ragweed failed to have that haplotype. In different families, different haplotypes were associated with ragweed allergy. This was confirmed by Yoo, Flink, and Thompson.[13] No single haplotype was associated with ragweed allergy. Certain B cell (HLA-D) haplotypes were associated with extrinsic asthma within families.[14] Other genetic controls in allergy affect the serum levels of IgE.[15, 16] Therefore, it may be possible by histocompatibility typing of newborn infants from allergic families to determine which infants are at risk of allergic sensitization. We are conducting such a study in the families of these allergic children in our group.

Our study confirms the heritability of allergy in that all but 2 of our 13 children of two allergic parents developed significant allergic symptoms and immunologic evidence of allergic sensitization within the first year of life. However, the intensity of this allergic sensitization appears to be transitory, both clinically and immunologically, and seems to be associated with virus infections.

The association of attacks of asthma with proved upper respiratory virus infections in children is now quite well established.[17–20] Boesen[17] pointed out that asthmatic children usually have their first attacks in conjunction with a respiratory infection, the initial diagnosis usually being "asthmatic bronchitis." In our study, we are suggesting a possible association between the allergic sensitization process and viral infections.

Culture-proved respiratory virus infections, pre-

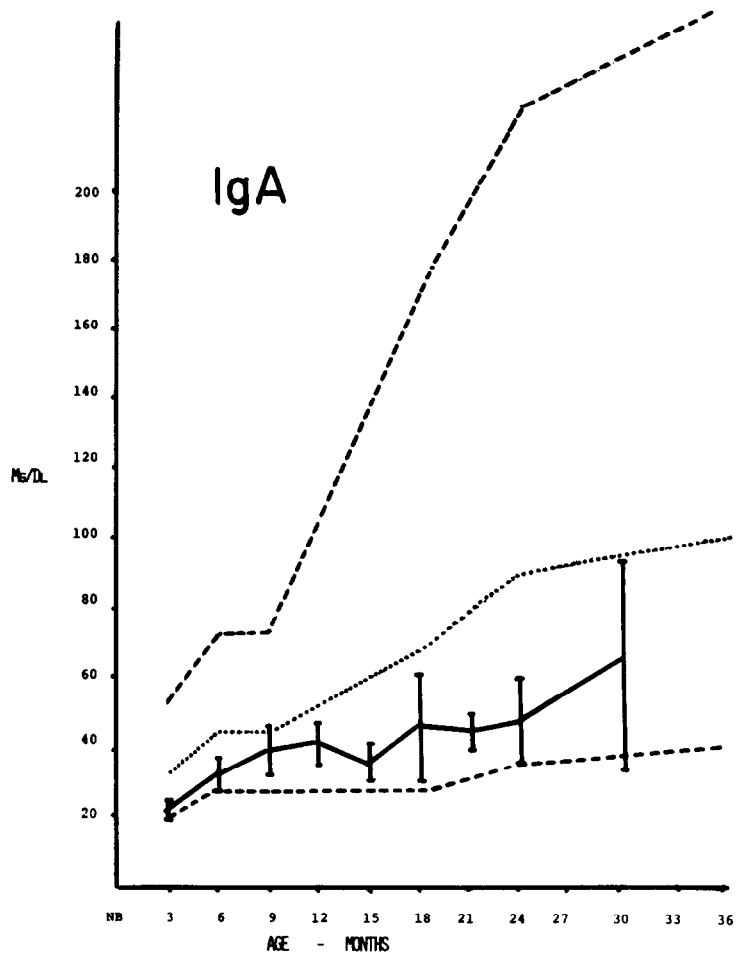

FIG. 5. Serum IgA concentrations for the "allergy-prone" children (I——I) compared to a normal age-matched population (· · · · = mean and 2 SD range).

dominantly parainfluenza 1 and 3 and RSV, occurred in 27% of the expiratory wheezing episodes in a retrospective study of 357 young (most under 2 years old) children.[18] Wheezing was associated with allergy and positive skin tests in 39% of those under 18 months, and in 73% of those over 18 months. Berkovich, Millian, and Snyder[19] found influenza A_2 and parainfluenza most frequently associated with the onset of wheezing in 40 asthmatic children; several also had adenovirus and mycoplasma. McIntosh and coworkers,[20] who investigated prospectively 32 hospitalized asthmatic children under 5 years of age with bacterial and viral cultures at the onset of each acute respiratory illness which subsequently led to wheezing, found 42% (58/129) of wheezing episodes associated with identifiable viral infections; almost half were due to RSV; next in frequency were parainfluenza and coronavirus. Infections with influenza A_2 (Hong Kong) and pathogenic bacteria had no statistical association with wheezing. Therefore, in young asthmatic children, wheezing was associated predominantly with RSV, parainfluenza, and occasionally other viruses.

In schoolchildren with intrinsic asthma, Minor and co-workers[21] found that two thirds (42/61) of the episodes of asthma occurred during symptomatic respiratory infections, mostly of viral origin. Severe asthma occurred in 14/15 of those with rhinovirus infections and in all of 6 influenza A_2 (Hong Kong) infections. This group also observed[22] that asthmatic children in a family experienced a significantly greater frequency of viral respiratory infections than their nonasthmatic siblings (5.1 vs 3.8/yr/subject; $p < 0.01$); common viruses were rhinoviruses and myxoviruses. This group had also found[23] that a larger adult population with intrinsic asthma had wheezing in 55% of infections, with positive virus cultures in about half (19/43) of the asthmatic episodes; rhinovirus and influenza A were most frequently recovered. It appears, therefore, that wheez-

ing is commonly associated with proved virus infections, but that the predominant associated virus types may differ with age of the patients.

In our study, we were struck by the frequent onset of allergic sensitization as evidenced by a change from one or more negative immunologic test results to positive and onset of allergic symptoms within weeks of a URI. We found a coincidental temporal association within 6 weeks between onset of allergic sensitization and URI (Table IV).

We employed only in vitro tests for allergic sensitization and were precluded from performing repeated skin tests because of the theoretical possibility that such repetitious antigen exposure in vivo might cause an allergy. Although this has never been shown to occur, our Human Experimentation Committee asked us to omit serial skin testing. Our choice of allergens for our in vitro tests included allergens most commonly encountered by infants and young children. Early-onset allergy to house dust occurred in 7/11, to animal danders in 8/11, and to grass pollen in 2. Among the 8 children who developed dander sensitivity, 4 had the animals in the home for years before the infant arrived. The parents did not choose to remove the pet on the chance that the child might become allergic to it. The pets were removed once the child became sensitized. The other 4 dander-sensitive children, despite having no pets at home, were exposed repeatedly at the baby sitters' homes. Grass pollen sensitization occurred in 2 children. Clinical food sensitivity to cereals (oat and wheat) occurred in 4 children. Cow's milk sensitivity occurred in 4 children; 3 were nursed—2 for 5½ months and 1 for 12 months; all of the mothers drank over one quart of cow's milk per day to maintain their own milk supply. This confirms the observation of Kaplan and Solli[24] that completely breast-fed infants often had higher cow's milk RAST than some infants fed cow's milk directly; presumably partially digested cow's milk proteins cross to the infant in the mother's milk.

Positive immunologic tests and allergic symptoms followed within 6 weeks of a URI in 9/11 infants. In the other 2 who became sensitized, there were 3- and 4-month intervals between the URI and allergy onset, respectively; a history of an intercurrent "cold" might have been missed. The history was taken without knowledge of the immunologic test results.

The type of virus infections, parainfluenza in 7 children, RSV in 3, and CMV in 2, identified with rising or high titers of complement-fixing antibodies are the same as those predominantly associated with virus-induced asthmatic attacks in children.[18, 20] These are, however, not unusual infections in young children. It may be that in children with an atopic constitution, such virus infections might trigger allergic sensitization.

If our continuing studies can show that virus infections are conclusively associated with the onset of allergic sensitization, several possible mechanisms of virus action could be postulated. In the many acute virus infections that cause a depression in T lymphocytes that lasts several weeks,[25] conceivably IgE-T suppressor cells could be depressed preferentially, thus allowing helper T cells to stimulate B lymphocytes to make IgE antibodies.

Membrane-binding organisms can accentuate β-adrenergic blockade; *Bordetella pertussis*,[26] influenza, parainfluenza, RSV, and mycoplasma all are membrane-binding organisms.[27] Ouellette and Reed[28] found an increased response, lasting 3 days, to inhaled methacholine in asthmatics after influenza A virus vaccination. Live measles virus vaccine in asthmatics also increases bronchoconstriction after inhalation of methacholine, an effect that lasts 4 weeks.[29] Szentivanyi[26] suggested that β-adrenergic blockade might preferentially stimulate IgE antibody formation.

Virus infections cause cytopathology of respiratory mucosal cells. This could facilitate mucosal penetration of allergens to the IgE-forming lymphocytes that line the respiratory mucosa, which is rich in such cells.[30] Furthermore, when Laitinen and co-workers[31] infected normal human volunteers with an attenuated live influenza A and B virus vaccine, bronchial responsiveness increased 70% to histamine aerosols as measured by airway resistance (Raw) after the virus infection. This group observed a similar increase in bronchial sensitivity to histamine in normal individuals with colds.[32] They suggested that the infection denuded the epithelial surface and exposed irritant receptors that responded easily to low concentrations of inhaled histamine ("sensitization" of sensory receptors in the airways). Histamine-induced edema might make the respiratory mucosa more permeable and facilitate entry of allergens to antibody-forming cells.

Finally, certain viruses enhance IgE-mediated HR from leukocytes of ragweed-allergic patients.[33] When cells of such patients were incubated with herpes simplex, influenza A, or adenoviruses, and subsequently exposed to ragweed or anti-IgE serum, almost twice as much histamine was released as in non–virus-treated cells. This enhanced HR from such cells was associated with interferon production. It was suggested[33] that this enhanced HR might be a co-

factor for potentiating asthmatic attacks during virus infections.

If virus infections do, indeed, have a role in initiating allergic sensitization, then the possibility exists that live attenuated virus vaccines used in routine immunizations of infants might contribute to this sensitization process. The infants in our study all received live poliomyelitis vaccine and killed pertussis vaccine (DPT) between the ages of 3 and 7 months, and live measles, mumps, and rubella vaccines at 12 to 15 months; therefore, we cannot exclude a possible role for these vaccines in the sensitization process. However, because our two internal control children did not develop allergy and also received the same immunizations, we felt that immunizations might be of subordinate interest.

Thus, there are at least four possible mechanisms whereby respiratory virus infections might induce allergic sensitization in a genetically susceptible child. These hypotheses are being tested in continuing studies in our laboratory.

Although we cannot provide a final answer to our original question, we prefer the optimistic view that certain possibly preventable environmental events may trigger allergic sensitization in a genetically susceptible child.

CONCLUSION

1. Infants from families with two allergic parents usually but not always develop allergic signs and symptoms in the first year of life.

2. In such infants onset of allergic symptoms usually coincides with a demonstrable change in the results of immunologic in vitro testing for allergy with one or more allergens.

3. Onset of clinical and immunologic evidence of allergy usually coincides with, or follows within weeks, a URI, commonly with parainfluenza or respiratory syncytial virus.

We wish to thank Mrs. Faith Ashton for her excellent technical assistance, Mrs. Anne Schmid for her editorial help, and Mrs. Wendy Carmody for preparation of the manuscript.

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