

The New England Journal of Medicine

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Volume 332

JANUARY 19, 1995

Number 3

ASTHMA AND WHEEZING IN THE FIRST SIX YEARS OF LIFE

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Abstract Background. Many young children wheeze during viral respiratory infections, but the pathogenesis of these episodes and their relation to the development of asthma later in life are not well understood.

Methods. In a prospective study, we investigated the factors affecting wheezing before the age of three years and their relation to wheezing at six years of age. Of 1246 newborns in the Tucson, Arizona, area enrolled between May 1980 and October 1984, follow-up data at both three and six years of age were available for 826. For these children, assessments in infancy included measurement of cord-serum IgE levels (measured in 750 children), pulmonary-function testing before any lower respiratory tract illness had occurred (125), measurement of serum IgE levels at nine months of age (672), and questionnaires completed by the children's parents when the children were one year old (800). Assessments at six years of age included measurement of serum IgE levels (in 460), pulmonary-function testing (526), and skin allergy testing (629).

Results. At the age of six years, 425 children (51.5 percent) had never wheezed, 164 (19.9 percent) had had at least one lower respiratory tract illness with wheezing during the first three years of life but had no wheezing at six years of age, 124 (15.0 percent) had no wheezing be-

fore the age of three years but had wheezing at the age of six years, and 113 (13.7 percent) had wheezing both before three years of age and at six years of age. The children who had wheezing before three years of age but not at the age of six had diminished airway function (length-adjusted maximal expiratory flow at functional residual capacity [$\dot{V}_{max}FRC$]) both before the age of one year and at the age of six years, were more likely than the other children to have mothers who smoked but not mothers with asthma, and did not have elevated serum IgE levels or skin-test reactivity. Children who started wheezing in early life and continued to wheeze at the age of six were more likely than the children who never wheezed to have mothers with a history of asthma ($P<0.001$), to have elevated serum IgE levels ($P<0.01$) and normal lung function in the first year of life, and to have elevated serum IgE levels ($P<0.001$) and diminished values for $\dot{V}_{max}FRC$ ($P<0.01$) at six years of age.

Conclusions. The majority of infants with wheezing have transient conditions associated with diminished airway function at birth and do not have increased risks of asthma or allergies later in life. In a substantial minority of infants, however, wheezing episodes are probably related to a predisposition to asthma. (N Engl J Med 1995; 332:133-8.)

ALTHOUGH asthma may originate soon after birth,¹ the natural history of the disease is poorly understood. Many infants have episodes of wheezing associated with viral respiratory illnesses.² Neither the pathogenesis of these episodes nor their relation to asthma has been completely elucidated.³ In older children and adults, the prevalence of asthma is strongly correlated with serum IgE levels and with skin-test re-

activity to allergens,^{4,5} but in one study no such relation was evident between early wheezing and serum IgE levels at birth.⁶ Infants who have respiratory illnesses with wheezing in the first year of life have lower levels of lung function before any lower respiratory illness develops than do infants who do not have illnesses with wheezing.⁷ This finding suggests that small airways predispose many infants to wheezing in association with common viral infections. However, it is possible that acute bronchial obstruction may have a variety of causes in early life, and a minority of infants with asthma may coexist with a larger group of infants with wheezing who have a more benign condition that is not mediated by IgE.

Older children with asthma have lower levels of lung function than children without asthma.⁸ It is not known whether the reductions in lung function present before asthma develops contribute to asthma and con-

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Supported by a Specialized Center of Research Grant (HL14136) from the National Institutes of Health.

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tinue to be present later in life or whether reduced lung function in children with asthma is the consequence of chronic airway inflammation.

We studied the natural history of wheezing in the first six years of life. Specifically, we assessed the factors that affect wheezing before the age of three years and their relation to wheezing at six years of age.

METHODS

The children we studied were enrolled as newborns between May 1980 and October 1984 in the Tucson Children's Respiratory Study.⁹ Their parents were patients of Group Health Medical Associates, a large health maintenance organization in Tucson, Arizona, and were contacted shortly after their children were born. Informed consent was obtained from the parents of 1246 newborns.

At the time of enrollment, the parents completed a questionnaire about their history of respiratory illness, smoking habits, and education. They were instructed to take their children to the pediatrician whenever the children had any of a defined set of signs and symptoms of lower respiratory tract illness (deep or "wet" chest cough, wheezing, hoarseness, stridor, or shortness of breath). The pediatricians obtained a detailed history at the time of such illnesses and recorded all relevant signs and symptoms (including wheezing on auscultation). Figure 1 shows the number of children for whom complete follow-up information on lower respiratory tract illnesses and complete data from questionnaires and tests were available.

Parents completed a questionnaire during their child's second year of life (mean [±SD] age, 1.6±0.4 years). Among other questions, parents were asked whether the child's "chest had ever sounded wheezy or whistling apart from colds" and how frequently the child wheezed. Parents were also asked whether their child ever had a runny nose apart from colds and whether a doctor had ever given the child a diagnosis of eczema. When the children reached a mean age of 6.3±0.9 years, parents again answered a questionnaire about the child's respiratory illnesses (referred to as the 6-year survey). In that questionnaire, current wheezing was defined as at least one episode of wheezing during the previous year.

During the first year of life, 176 infants underwent pulmonary-function testing. A detailed description of the selection criteria and the medical and social characteristics of these infants, as compared with those who were not tested, was reported earlier⁷; the frequency of a family history of asthma or allergies did not differ significantly between the infants who underwent pulmonary-function testing and those who were not tested. Of the 176 infants initially tested, 125 were tested before any lower respiratory tract illness occurred; complete follow-up data to the age of six years were available for these infants. Their mean age at the time of testing was 2.4±2.0 months.

Partial expiratory flow-volume curves were obtained by the chest-compression technique.¹⁰ Briefly, informed consent was obtained from the parents, and the children were usually sedated with chloral hydrate (50 to 60 mg per kilogram of body weight). A plastic bag connected to a pressure reservoir was tightly wrapped around the child's chest and abdomen. A mask connected to a pneumotachygraph was sealed around the child's mouth and nose, and tidal flow-volume loops were displayed on a monitor. At end-tidal inspiration, the bag was rapidly inflated to a known pressure, compressing the child's chest and forcing air out of the lungs. The flow at the end-tidal expiration point was recorded from the forced flow-volume loops. This maneuver was repeated with increments in pressure of 5 to 10 cm of

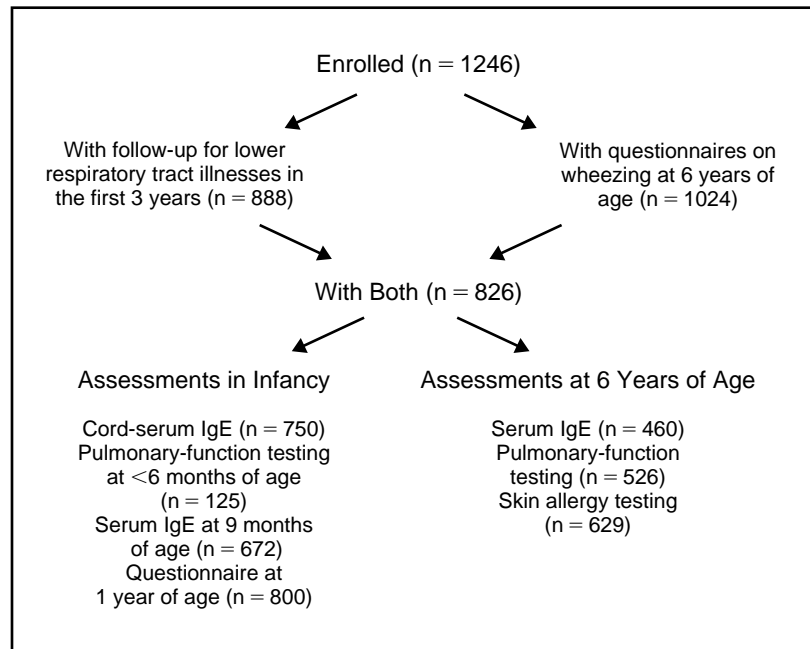


Figure 1. Number of Subjects Enrolled, Number with Complete Follow-up for Lower Respiratory Tract Illnesses in the First Three Years of Life, and Number for Whom Complete Data Were Available from Questionnaires and Tests.

A total of 826 children had follow-up data at three and six years of age and were included in the study.

water. The maximal pressure applied to the thorax was the pressure at which no further increase in flow was obtained; this value — the maximal expiratory flow at functional residual capacity (\dot{V}_{\max} FRC, expressed in milliliters per second) — was recorded and used in the analysis. \dot{V}_{\max} FRC is believed to reflect the size of the intrapulmonary airways.¹¹

At the time of the six-year survey, partial expiratory flow-volume curves were obtained with maneuvers to measure voluntary maximal expiratory flow.¹² Tidal flow-volume loops were recorded on a computer screen as described above. As the child approached end-tidal inspiration, he or she was encouraged to expel air forcefully, and a partial flow-volume curve was obtained. \dot{V}_{\max} FRC was calculated from at least three acceptable expirations; the highest value obtained was used in our analyses.

Total serum IgE levels were measured with the paper radioimmunosorbent test (Pharmacia Diagnostics, Piscataway, N.J.) in samples obtained from cord blood, from blood obtained at a median age of 9.3 months (referred to as the 9-month sample), and from blood obtained at the time of the 6-year survey.

Skin allergy tests were performed concomitantly with lung-function testing at the time of the six-year survey with extracts of seven common aeroallergens in the Tucson area (Hollister-Stier Laboratories, Everett, Wash.). A child was considered to have atopy if he or she had at least one positive skin-test reaction (>2 mm of induration) to an aeroallergen. The aeroallergens tested were house-dust mix, alternaria, Bermuda grass, careless weed, mesquite, mulberry, and olive.

Statistical Analysis

Total serum IgE levels were expressed in international units per milliliter (1 IU per milliliter corresponded to 2.4 μ g per liter). Log IgE values were adjusted for age according to standard regression techniques and expressed in terms of the median age (9.3 months) of the sample.

Values for \dot{V}_{\max} FRC were logarithmically transformed for both age groups and adjusted for length or height. Results were standardized to the children's average length (57.4 cm) before the age of one year or height (110.3 cm) at the age of six.

Analysis of variance, Duncan's multiple-comparison test, chi-square tests, and logistic regression were used to compare means and proportions.¹³ The 95 percent confidence intervals for odds ratios were calculated with standard algorithms.¹⁴ Statistical significance was defined by a two-sided alpha level of 0.05.

This research was approved by the Human Subjects Committee at the University of Arizona. The parents signed separate consent forms for the infants' initial enrollment and for the other studies described in this report.

RESULTS

When the 826 children included in this study were compared with the 420 who were excluded because of incomplete data, the frequency of a family history of asthma and the distribution of ethnic backgrounds were similar. However, the children with complete data tended to belong to families with a higher socioeconomic status and a lower prevalence of maternal smoking (data not shown).

Children were assigned to four categories according to their history of wheezing: those who had no recorded lower respiratory tract illness with wheezing during the first three years of life and had no wheezing at six years of age (children who had never had wheezing); those with at least one lower respiratory tract illness with wheezing during the first three years of life but no wheezing at six years of age (those with transient early wheezing); those who had no lower respiratory tract illness with wheezing during the first three years of life but who had wheezing at six years of age (those with wheezing of late onset); and those who had at least one lower respiratory tract illness with wheezing in the first three years of life and had wheezing at six years of age (those with persistent wheezing). A total of 425 children (51.5 percent) were classified as never having wheezed, 164 (19.9 percent) as having had transient early wheezing, 124 (15.0 percent) as having wheezing of late onset, and 113 (13.7 percent) as having persistent wheezing.

Of 277 children who had wheezing before the age of three, 164 (59.2 percent) had not wheezed during the previous year when they were evaluated at six years of age. Maternal asthma, maternal smoking, rhinitis apart from colds, eczema during the first year of life, male sex, and Hispanic ethnic background were all independently associated with persistent wheezing. Of the variables we considered, only maternal smoking was significantly associated with transient early wheezing (Table 1). Children with wheezing of late onset were significantly more likely than those who had never wheezed to have mothers with asthma, to be male, and to have had rhinitis in the first year of life. Those with persistent wheezing were significantly more likely than those without wheezing to have mothers with asthma ($P < 0.001$). The results in each cate-

Table 1. Adjusted Odds Ratios for Transient Early Wheezing, Late-Onset Wheezing, and Persistent Wheezing, According to Risk Factors Present at One Year of Age, and Prevalence of Risk Factors.*

RISK FACTOR	NO WHEEZING (N = 403)	TRANSIENT EARLY WHEEZING (N = 147)	LATE-ONSET WHEEZING (N = 112)	PERSISTENT WHEEZING (N = 100)
Eczema				
Odds ratio (95% CI)	1.0	1.3 (0.7–2.5)	0.7 (0.3–1.6)	2.4 (1.3–4.6)
Prevalence (%)	7.7	10.2	6.3	18.0
Rhinitis apart from colds				
Odds ratio (95% CI)	1.0	1.1 (0.7–1.7)	1.7 (1.1–2.7)	2.0 (1.2–3.2)
Prevalence (%)	24.8	27.2	35.7	42.0
Maternal asthma				
Odds ratio (95% CI)	1.0	1.6 (0.8–3.2)	2.8 (1.4–5.5)	4.1 (2.1–7.9)
Prevalence (%)	6.7	10.2	16.1	22.0
Hispanic ethnic background				
Odds ratio (95% CI)	1.0	1.5 (0.9–2.7)	1.7 (0.9–3.1)	3.0 (1.6–5.5)
Prevalence (%)	10.7	13.6	14.3	22.0
Male sex				
Odds ratio (95% CI)	1.0	1.0 (0.7–1.5)	2.1 (1.3–3.4)	1.9 (1.2–3.0)
Prevalence (%)	42.7	44.2	61.6	61.0
Maternal smoking				
Odds ratio (95% CI)	1.0	2.2 (1.3–3.7)	1.6 (0.9–2.9)	2.3 (1.2–4.4)
Prevalence (%)	11.4	21.2	17.0	21.0

*Three different logistic regressions were performed comparing each of the three groups with wheezing with the children who never had wheezing. Subjects without a given risk factor were assigned a value of 0 and those with the risk factor a value of 1. Sixty-four patients had missing data for explanatory variables and were excluded from this analysis (22 who never had wheezing, 17 with transient early wheezing, 12 with late-onset wheezing, and 13 with persistent wheezing). The odds ratios have been adjusted in the logistic-regression model for all the other risk factors listed. CI denotes confidence interval.

gory of wheezing were not changed by adjustment for the parents' level of education.

When compared with the children with transient early wheezing, those with persistent wheezing were more than twice as likely to have wheezed often or very often (odds ratio, 2.3; 95 percent confidence interval, 1.4 to 3.8; $P = 0.001$) and were more likely to have had wheezing without colds during infancy (odds ratio, 1.8; 95 percent confidence interval, 1.0 to 3.4; $P = 0.05$). At six years of age, 22.5 percent of children with late-onset wheezing had been given a diagnosis of asthma, as compared with 46.0 percent of children with persistent wheezing ($P < 0.001$); 25.0 percent of children with late-onset wheezing had been given a diagnosis of bronchitis without asthma, as had 22.1 percent of those with persistent wheezing ($P = 0.7$).

Children with transient early wheezing had significantly lower length-adjusted values for \dot{V}_{\max} FRC in infancy than all the other groups (Table 2). The children with persistent wheezing or wheezing of late onset had \dot{V}_{\max} FRC values that were not significantly different from those of the children who had never had wheezing. At the age of six, the children with transient early wheezing still had significantly lower height-adjusted \dot{V}_{\max} FRC values than those who had never wheezed, and the children with persistent wheezing had the lowest levels of lung function of all the groups. As compared with the children who had never wheezed, those with persistent wheezing were significantly more likely to have diminished values for \dot{V}_{\max} FRC ($P < 0.01$). Children with late-onset wheezing had \dot{V}_{\max} FRC levels that were not significantly different from those of the children who had never wheezed.

Cord-serum IgE levels were unrelated to a later history of wheezing (Fig. 2). Only children with persistent

Table 2. Maximal Expiratory Flow at Functional Residual Capacity (\dot{V}_{\max} FRC) during the First Year of Life and at Six Years of Age, According to History of Wheezing.*

AGE	NO WHEEZING		TRANSIENT EARLY WHEEZING		LATE-ONSET WHEEZING		PERSISTENT WHEEZING		F	P VALUE
	NO.	\dot{V}_{\max} FRC ml/sec	NO.	\dot{V}_{\max} FRC ml/sec	NO.	\dot{V}_{\max} FRC ml/sec	NO.	\dot{V}_{\max} FRC ml/sec		
<1 year	67	123.3 (110.0–138.0)	21	70.6 (52.2–93.8)†	21	107.1 (87.5–129.6)	16	104.6 (73.6–144.5)	5.95	<0.001
6 years	260	1262.1 (1217.4–1308.1)	104	1097.7 (1034.9–1163.5)‡	81	1174.9 (1111.1–1241.1)	81	1069.7 (906.9–1146.5)‡	9.60	<0.001

*A total of 125 children underwent pulmonary-function testing during the first year of life, and 526 were tested at six years of age. Values for \dot{V}_{\max} FRC are geometric means (95 percent confidence intervals). The F-test and associated P values indicate significant differences in lung function between the four groups.

†P<0.01 for the comparison with the children who never wheezed and P<0.05 for the comparisons with the children with late-onset wheezing and persistent wheezing, by Duncan's multiple-comparison test.

‡P<0.01 for the comparison with the children who never wheezed, by Duncan's multiple-comparison test.

wheezing had significantly higher IgE levels at nine months of age than those who had never wheezed (P<0.01). The geometric mean IgE levels were 3.4 IU per milliliter (95 percent confidence interval, 3.0 to 3.9) for children who had never wheezed, 3.7 (95 percent confidence interval, 3.1 to 4.4) for those with transient early wheezing, 3.8 (95 percent confidence interval, 2.9 to 5.0) for those with wheezing of late onset, and 5.2

(95 percent confidence interval, 3.8 to 7.2) for those with persistent wheezing. The risk of belonging to any of the three groups with wheezing was evaluated according to the level of IgE at nine months of age (Fig. 2). A direct relation between IgE levels and wheezing was seen only for children with persistent wheezing (P=0.02).

Children with transient early wheezing and those

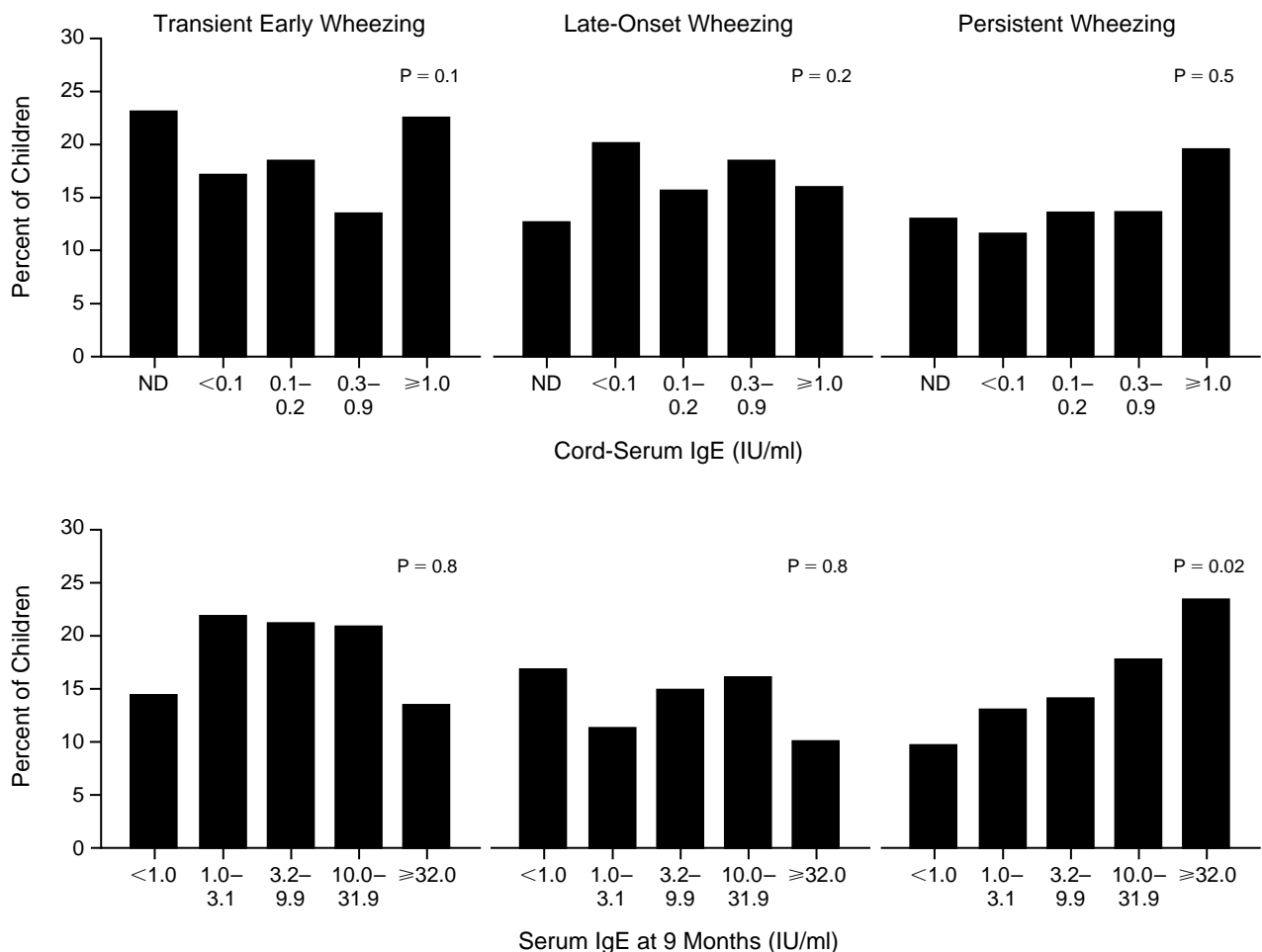


Figure 2. Proportion of Subjects Who Had Transient Early Wheezing, Wheezing of Late Onset, and Persistent Wheezing, According to Cord-Serum IgE Levels and Serum IgE Levels at Nine Months of Age.

The categories of wheezing are defined in the text. The numbers of children with the various IgE levels were as follows: for cord serum, not detectable (ND), 290; <0.1 IU per milliliter, 296; 0.1 to 0.2 IU per milliliter, 117; 0.3 to 0.9 IU per milliliter, 20; and ≥1.0 IU per milliliter, 10; for serum at nine months, <1.0 IU per milliliter, 83; 1.0 to 3.1 IU per milliliter, 230; 3.2 to 9.9 IU per milliliter, 209; 10.0 to 31.9 IU per milliliter, 123; and ≥32.0 IU per milliliter, 27. P values for trend within the groups were determined by the chi-square test.

Table 3. Total Serum IgE Levels and Prevalence of Positive Skin Tests for Reactivity to Aeroallergens in Children Six Years Old, According to History of Wheezing.*

CATEGORY	SERUM IgE†		POSITIVE SKIN TEST	
	NO. TESTED	MEAN (95% CI) IU/ml	NO. TESTED	PREVALENCE %
No wheezing	222	28.1 (22.4–35.3)	317	33.8
Transient early wheezing	95	31.0 (22.3–43.1)	125	38.4
Late-onset wheezing	68	42.1 (26.6–66.0)	97	55.7‡
Persistent wheezing	75	65.6 (45.3–94.4)§	90	51.1¶
		F = 4.94 P = 0.002		χ ² = 19.5 P < 0.001

*Of the 826 children, 629 underwent skin testing for reactivity to aeroallergens and 460 had measurements of serum IgE at six years of age. The F-test and the chi-square test (and the corresponding P values) indicate significant differences in serum IgE levels and the prevalence of positive skin tests, respectively, in association with the differences in patterns of wheezing.

†To convert values for IgE to micrograms per liter, multiply by 2.4. CI denotes confidence interval.

‡P < 0.001 for the comparison with the children who never wheezed.

§P < 0.01 for the comparisons with the children who never wheezed and those with transient early wheezing, by Duncan's multiple-comparison test.

¶P = 0.003 for the comparison with the children who never wheezed.

who had never wheezed had similar serum IgE levels and a similar prevalence of atopy at the age of six years (Table 3). Those with persistent wheezing had significantly higher levels of IgE than those who had never wheezed ($P < 0.01$). Children with late-onset wheezing did not have significantly elevated serum IgE levels as compared with those who had never wheezed. Atopy was significantly more prevalent in both groups of children with wheezing at the age of six than in the group that had never wheezed. After adjustment for skin-test reactivity with multiple regression analysis, the children with persistent wheezing had significantly higher levels of IgE at the age of six years than the children with late-onset wheezing ($P = 0.03$).

DISCUSSION

We found that wheezing in the first three years of life had a rather benign prognosis. Although one third of all children three years of age or younger had lower respiratory tract illnesses with wheezing, almost 60 percent of these children had stopped wheezing by the age of six years. Children with transient early wheezing were distinguished from the other groups who had wheezing by their lower levels of lung function, as indicated by their values for \dot{V}_{\max} FRC. As described earlier,¹⁵ this diminished lung function was evident shortly after birth and before any lower respiratory tract illness had occurred. One possibility is that this finding reflected congenitally smaller airways and predisposed these infants to wheezing in early life. We found that children with transient early wheezing still had reduced values for \dot{V}_{\max} FRC at six years of age, as compared with their peers, although the children were no longer symptomatic. As their airways grow in absolute size with age, these children may become less apt to have wheezing during viral infections.

Smoking by a child's mother was also a risk factor for transient early wheezing. The infants of mothers who smoked during pregnancy had significantly low-

er values for \dot{V}_{\max} FRC¹⁶ than the infants of mothers who did not smoke. The association between maternal smoking and transient early wheezing may be mediated, at least in part, by smaller airways in the children of women who smoke.

Children with persistent wheezing had initial values for \dot{V}_{\max} FRC that were similar to those of the children who never wheezed but were almost 50 percent higher than those of children with transient early wheezing. Factors other than small airways may cause early wheezing in infants in whom episodes of wheezing persist up to the age of six years. Children with persistent wheezing had more frequent symptoms during the first year of life than those with transient early wheezing. Most of the risk factors for persistent wheezing (eczema, rhinitis apart from colds, and maternal asthma, among others) were not associated with increased risk among the children with transient early wheezing. Maternal smoking was the only risk factor common to both groups, suggesting that exposure to tobacco smoke may have effects other than those on airway growth in utero.¹⁷

There was a significant, direct relation between the risk of persistent wheezing and the serum IgE level at nine months of age. This relation was very similar to that reported between serum IgE levels and asthma in older children and adults,^{4,5} and it contrasts with the lack of association between transient early wheezing or late-onset wheezing and serum IgE levels at nine months. No relation was found between the risk of persistent wheezing at six years of age and cord-serum IgE levels, suggesting that some form of IgE-mediated sensitization may occur during the first year of life in children with persistent wheezing. Such sensitization may contribute to early wheezing, in much the same way as it is thought to predispose older children to asthma.

We could not determine the nature of this allergic sensitization on the basis of our data. It is clear, however, that by the age of six years, children with persistent wheezing were as frequently sensitized to common aeroallergens as those with wheezing of late onset. One hypothesis is that children with persistent wheezing may have been sensitized to these antigens during the first year of life, whereas children with late-onset wheezing were not. An alternative hypothesis is that children with persistent wheezing are predisposed to produce large quantities of IgE in response to a variety of antigens and that this enhanced IgE reactivity may be expressed in response to different allergens at different ages. Further studies of allergic sensitization in early life are indicated.¹⁸

Most of the children with lower respiratory tract illnesses in our study were infected with respiratory syncytial virus or parainfluenza viruses.² Welliver et al. found a higher prevalence of specific IgE against respiratory syncytial virus¹⁹ and parainfluenza virus²⁰ in the nasal secretions of infants with wheezing who had these infections than in the secretions of infants with these infections who did not have wheezing. In infants with confirmed respiratory syncytial virus infections in the first six months of life, the frequency of persistent

wheezing up to seven or eight years of age was directly related to the level of respiratory syncytial virus-specific IgE in their nasopharyngeal secretions during the initial episode.²¹ The children who had persistent wheezing in our study may have been more prone than the others to produce virus-specific IgE in early life. This factor could explain their higher levels of IgE at a mean age of nine months.

Children with persistent wheezing had significantly reduced lung function, as indicated by \dot{V}_{\max} FRC values, at the age of six years. This deterioration in airway function is consistent with the substantial deficits in lung function reported in older children with asthma.⁸ Our data suggest that among children with persistent wheezing these deficits are not caused by poorer initial lung function but, rather, may reflect the effects of the chronic disease process on the bronchi. We do not know whether the deficits reflect irreversible damage to the airways or a reversible increase in airway muscle tone. Recent reports suggest, however, that in people with asthma, lung volume and maximal flow grow at similar, normal rates from 9 to 17 years of age and that any irreversible damage may have already occurred by 9 years of age.²²

Our data did not permit us to elucidate the mechanisms of the deficits in lung function in children with persistent wheezing. We doubt, however, that they result from direct, nonspecific injuries produced by viral infections in early life. If this were the case, similar deficits should have been seen among the children with transient early wheezing. It is possible that in children with persistent wheezing, much as in older patients with asthma, chronically elevated serum IgE levels may be associated with chronic airway inflammation,²³ persistent bronchial hyperresponsiveness,⁵ and abnormalities in the development of airway function.²⁴ Such associations could also help to explain why children with late-onset wheezing, whose serum IgE levels were not elevated at nine months of age and were only mildly elevated at six years, had lung function at the age of six that was within the normal range.

In summary, our findings suggest that most infants who wheeze have transient conditions associated with diminished airway function and have no increased risk of asthma or allergies later in life. In a minority of infants, early wheezing episodes are probably related to a predisposition to asthma. Such children already have elevated serum IgE levels during the first months of life and have substantial deficits in lung function by the age of six years.

We are indebted to Benjamin Burrows, M.D., for his advice; to Marilyn Smith, R.N., and Lydia De La Ossa, R.N., the study nurses; to Shelley Radford and Bruce Saul for technical assistance; and to Maureen Cameron for assistance in the preparation of the manuscript.

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