

Links between pediatric and adult asthma

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Connections between events occurring in early life with adult asthma suggest that both the altered regulation of airway caliber and tone and the changes in airway structure present in many asthma cases may have their roots in developmental patterns established during infancy and childhood. The Melbourne epidemiologic study, the British 1958 birth cohort, and the Tasmanian asthma survey all provide important information on the outcomes of childhood asthma in later life. Among the findings, these studies showed that in a large proportion of asthmatic children, asthma remits in early adulthood, and the severity of asthma tracks significantly with age. Newer longitudinal studies have measured lung function shortly after birth, before any respiratory symptoms have occurred. Several lines of evidence suggest that those children who will go on to have more severe and persistent asthma symptoms already have immune responses skewed toward the T-helper type 2 (T_H2) at the time of the very first episodes of airway obstruction in infancy. In most children whose asthma is triggered mainly by respiratory infections, asthma symptoms appear to remit by the adolescent years. Congenital and acquired deficits in lung function, however, may lead to recurrence of these symptoms during adult life and after long periods of remission, especially among active smokers. (*J Allergy Clin Immunol* 2001;107:S449-55.)

Key words: Airway obstruction, asthma birth cohorts, atopy, longitudinal studies, pediatric asthma, persistent wheezers

The increase of interest in the possible connection between events occurring in early life with adult asthma and other forms of obstructive lung disease is clearly justified. Strong evidence has emerged from longitudinal studies indicating that most children with moderate or severe asthma still have symptoms during adult life.¹ Moreover, among adult patients with asthma, especially those who are nonatopic and who show marked declines in lung function with age, a history of having "respiratory troubles" before age 16 years occurs more frequently than among those having normal rates of decline.² These connections suggest the beguiling hypothesis that both the altered regulation of airway caliber and tone and the changes in airway structure present in many cases of asthma may have their roots in developmental patterns

Abbreviations used

IFN- γ : Interferon-gamma
LRI: Lower respiratory illness
RSV: Respiratory syncytial virus

established during infancy and childhood.³ A natural corollary of this hypothesis is the proposal that early management of asthma and other forms of airway obstruction may help to prevent the development of chronic airflow limitation in adults.⁴

Several obstacles make the testing of such hypotheses a demanding task. The daunting difficulties involved in the longitudinal studies required to assess the relationships between events occurring across intervals of 30, 40, or 50 years are obvious. An additional burden, however, is the complexity of the clinical expression of airway obstructive disease at both ends of the life spectrum. Under the common label of asthma (or any of its many derivatives: asthmatic bronchitis, spastic bronchitis, wheezy bronchitis, etc) falls an array of different conditions with perhaps different causes and different disease mechanisms. Given the lack of specific treatments for these different conditions, and to prevent the danger of undertreating airway obstruction with the available potent anti-inflammatories, most treatment guidelines have avoided dealing with the heterogeneous nature of the disease. This has given rise to noticeable contradictions. For example, whereas asthma is defined as a chronic inflammatory disease, no anti-inflammatory treatment is recommended in at least 50% of all persons with asthma (ie, those with "mild intermittent" asthma).⁵ Given our lack of knowledge of the specific characteristics of the inflammatory process in each asthma phenotype, these contradictions are justifiable, but simply lumping all forms of asthma in childhood and adult life under a common label may make the potential connections between specific forms at both ends of the age spectrum less evident.

The objective of this article is to succinctly characterize the different forms of asthma identified in childhood and to speculate about possible links between these and asthma-like symptoms in adult life. Asthma is very generically defined here as recurrent airway obstruction at least partially reversible either spontaneously or by adequate treatment. This analysis is based on the premise that the most important and meaningful outcome analysis of childhood asthma will be a new understanding of its potential impact on health and pulmonary function in adult life and senescence.

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ALLERGIC ASTHMA IN CHILDHOOD AND ASTHMA IN ADULT LIFE

Only a few reports have addressed the connections between atopic asthma in early life and asthma in adult life. The most important sources of information are the Melbourne epidemiologic study of childhood asthma,⁶ the British 1958 birth cohort,⁷ and the Tasmanian asthma survey.⁸ In the Melbourne study, children who had recurrent episodes of wheezing by the ages of 7 to 10 years were enrolled together with a small control group without wheezing. These individuals were then monitored with periodic reassessments, and data were published up to age 35 years. Unfortunately, in the Melbourne study, information about the patient's age on initiation of symptoms was obtained from questionnaires. Thus data on what we now know to be a crucial period of life for asthma's development may have been biased by preferential recall. Moreover, many cases of nonatopic or transient wheezing may have been missed because follow-up was started rather late in life, at a time when many such cases may have already remitted.⁶ In the British 1958 birth cohort, more than 18,000 people born on March 3 to March 9, 1958, were enrolled,⁷ and 31% of these persons contributed information for ages 7, 11, 16, 23, and 33 years. As with the Melbourne study, information for the first 7 years of life was obtained retrospectively at age 7 years. Finally, the Tasmanian asthma survey enrolled more than 8000 children born in 1961 who were first contacted at age 7 years. Two thousand of these children were randomly chosen and re-examined when they were 29 to 32 years of age.⁸ As with both previous studies, information on wheezing before age 7 years was obtained from retrospective questionnaires. Despite their shortcomings, these 3 studies provide important information on the outcome of childhood asthma in adult life.

ASTHMA REMISSION RATES AND TRACKING OF ASTHMA SEVERITY FROM CHILDHOOD TO ADULTHOOD

Two very important findings of all 3 studies are that in a large proportion of asthmatic children, asthma remits in early adulthood, and the severity of asthma tracks significantly with age. This second point is important because it reflects a "stability" in the disease (children with moderate symptoms have moderate symptoms as adults, and children with severe symptoms have severe symptoms as adults). The researchers involved in the Melbourne study divided their population of wheezing children at enrollment into 5 groups: control (no wheezing), mild wheezy bronchitis (fewer than 5 lifetime episodes of wheezing associated with colds), wheezy bronchitis (5 or more such episodes), asthma (wheezing apart from colds), and severe asthma (selected at age 10 years based on severe impairment of lung function). Whereas both groups of children with wheezy bronchitis were unlikely to show frequent asthma episodes (wheezing during the previous 3 months, but less than once a week) or persistent asthma

(once a week or more) at age 35 years (only 23% to 25%), 50% of those with asthma and 75% of those with severe asthma had frequent or persistent wheezing at age 35 years.⁶ It is interesting that the British 1958 cohort reached similar results: 27% of all children whose parents reported they had wheezed before age 7 years reported wheezing during the previous year at age 33 years.⁷ In the Tasmanian cohort, 25.6% of the patients with "asthma or wheezy breathing" by the age of 7 years reported current asthma at the age of 29 to 32 years, whereas only 10.8% of patients without parental reports of childhood asthma had asthma as adults.⁸ As in the Melbourne study, those with more severe asthma in early life (more than 10 attacks) were almost twice as likely to have persistent wheezing as adults.

ATOPY AS A DETERMINANT OF ASTHMA PERSISTENCE

In the Melbourne study, severe asthma in early life was associated with a significantly higher prevalence of allergic rhinitis at age 35 years. In the British cohort, allergic symptoms (eg, allergic rhinitis or eczema) were significantly associated with persistence of symptoms into adult life. Finally, in the Tasmanian cohort, having a history of eczema in early life was also significantly associated with persistent wheezing at ages 29 to 32 years.

LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS IN EARLY LIFE

Both the Tasmanian and the Melbourne studies assessed lung function in early life and related it to the subsequent persistence of asthma. Among children who wheezed during the first years of life, low lung function was a significant predictor of subsequent wheezing. The Melbourne study provided an additional, very important finding by tracking each category of wheezing children up to 35 years of age.⁹ By definition, children with severe asthma at age 10 years had very low initial levels of lung function, because deficits in lung function were used to classify them as having severe asthma in the first place. When compared with their peers, these children did not show further deficits in lung function growth with age, and by age 35 years, their position relative to subjects with milder symptoms or with no asthma was substantially unchanged. A similar pattern of relatively stable lung function growth was observed for patients with mild asthma who had shown loss of lung function at enrollment, albeit much less pronounced than persons with severe asthma (Fig 1).

The potential role of bronchial hyperresponsiveness in early life has been explored only in a smaller study in The Netherlands.¹⁰ Approximately 100 asthmatic children originally studied at ages 6 to 14 years were subsequently assessed during their 20s. The proportion of children still wheezing in early adult life was higher (43%) than observed in the previously described 3 studies, probably because children older than 7 years of age were included in

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FIG 1. Forced expiratory volume in 1 second/forced vital capacity over period of study in participants classified according to their original groups. The figure shows the mean of all available participants, with 95% CI for 3 of the groups. The mean values at specific ages have been moved slightly to avoid overlapping points. *Closed circle/pink line* represents Controls; *triangle/yellow line*, mild wheezy bronchitis; *orange square/line*, wheezy bronchitis; *diamond/green line*, asthma; *blue square/line*, severe asthma. (From Oswald H, Phelan PD, Lanigan A, Hibbert M, Carlin JB, Bowes G, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997;23:14-20. Copyright © 1997 Wiley-Liss, Inc. Reprinted by permission of Wiley-Liss, a subsidiary of John Wiley & Sons, Inc.)

this study, and they were almost invariably allergic.¹¹ The 2 most important predictors of persistent wheezing into adult life were the level of lung function and the degree of bronchial hyperresponsiveness to histamine in early life.

RELAPSES OF PATIENTS WITH ASTHMA WHOSE ASTHMA REMITTED IN CHILDHOOD

Only the British cohort study explored the factors that determined asthma relapses. They identified a group of more than 1300 persons with a history of wheezing illnesses from birth to age 16 years who at age 23 years denied attacks of asthma or wheezy bronchitis since their 16th birthday. This group was 50% more likely to report wheezing at age 33 years than those with no history of asthma or wheezy bronchitis during childhood ($P < .001$). It is interesting that the association between early childhood asthma and relapses of asthma in adult life was independent of the 2 main determinants of the prognosis of childhood asthma, namely, allergies and smoking in adult life.⁷ The authors speculated that persistent, asymptomatic abnormalities in pulmonary function could explain their findings.

SUMMARY OF LONG-TERM LONGITUDINAL STUDIES

Childhood asthma that persists into early adulthood occurs in approximately one quarter of cases. The main independent factors associated with this prognosis are allergic symptoms, bronchial hyperresponsiveness, and

lung function at the onset of follow-up. Wheezing in mid-adult life is significantly more frequent among patients whose asthma had relapsed between ages 16 and 23 years than among those who had no reported asthma before age 16 years. Levels of lung function observed at age 7 years tracked markedly with age, suggesting that most of the deficits observed in asthma during childhood and early adulthood were either present at birth or acquired during the early years of life (Fig 1).

Therefore lung function during childhood is a crucial determinant of the long-term prognosis of childhood asthma. The most important question, however, remains unanswered: are the deficits of lung function (and the associated bronchial hyperresponsiveness) the cause or the consequence of persistent asthma? Although the Melbourne study suggested that most of the deficits in lung function observed in patients with persistent asthma are already present by age 10 years, it was not possible to determine from any of the studies whether these deficits were present at birth or had been acquired after birth, perhaps as a consequence of persistent disease activity. This question has now been addressed in newer longitudinal studies in which lung function was measured shortly after birth and before any respiratory symptoms occurred.

THE ASTHMA BIRTH COHORTS

The Tucson Children's Respiratory Study from the United States¹² and the longitudinal asthma study from Perth, Australia,¹³ enrolled children at birth, assessed

their lung function in early life, and subsequently monitored them during their early years for the development of asthma symptoms.

In both studies lower levels of lung function, as assessed by the chest compression technique during the first months of life, preceded and predicted the development of wheezing respiratory illnesses during the first 2 to 3 years of life.^{12,13} Similar results were obtained with specific airway conductance as a measure of airway function shortly after birth.¹⁴

The interpretation of these data, however, is complicated by the heterogeneous nature of wheezing illnesses during the first years of life. It is now well established that many (if not most) cases of chronic, allergy-related asthma have their first clinical manifestations during this period.¹⁵ Young children who will go on to have chronic asthma, however, coexist with and may have clinical manifestations similar to those of young children with a more transient condition primarily triggered by respiratory infections. Only in the Tucson study was an attempt made to identify those children who wheezed in early life and who would go on to have recurrent episodes of wheezing during the early school years. These children (called "persistent wheezers") started life with levels of airway function that were not significantly different from those of children who never wheezed during the first 6 years of life. By age 6 years, however, these same children had parameters of airway function significantly lower than those of children with no reports of wheezing by age 6 years.¹² Deficits in lung function observed in persistent wheezers (and most likely future persons with asthma) were, to a significant extent, acquired after birth and may have been the consequence of the asthma disease process.

Several lines of evidence suggest that those children who will go on to have more severe and persistent asthma symptoms already have immune responses skewed toward the T_H2 at the time of the very first episodes of airway obstruction in infancy.¹⁶⁻¹⁸ It has been hypothesized that these T_H2 type responses may be associated with a cytokine and growth factor milieu in the airways that alters the process of physiologic lung remodeling normally occurring during the preschool years, a period of very fast lung growth. It is reasonable to conclude from available data that these alterations in lung and airway development may be associated with significant deficits of lung function measured in children with persistent asthma. These acquired deficits in lung and airway function and the increases in bronchial responsiveness associated with them may be an important connection between asthma in childhood and asthma in adult life.¹⁹

INFECTION-ASSOCIATED ASTHMA IN CHILDHOOD AND ASTHMA IN ADULT LIFE

It has been known for decades that many young children show signs of apparent lower airway obstruction (wheezing often associated with cough, stridor, and shortness of breath) almost exclusively during respiratory infections.²⁰ It is now well established that

most of these children begin having symptoms during the first 2 or 3 years of life, usually in association with infections with the respiratory syncytial virus (RSV) but also with other viruses such as parainfluenza and adenovirus.²¹ Many of these infants and young children have quite severe symptoms, and a small proportion of them are hospitalized with the diagnosis of either bronchiolitis, pneumonia, or laryngo-tracheo-bronchitis, conditions that have been grouped under the term lower respiratory illnesses (LRIs). Recent longitudinal analyses suggest that, rather than being different diseases, these different expressions of lower airway involvement during RSV infection are part of a continuum of disease severity with similar disease mechanisms.²²

Outcome of RSV-LRIs

The natural history and risk factors for this specific form of childhood asthma have been a matter of intense debate. The long-term outcome of children who had LRIs caused by RSV and other agents during the first 3 years of life has been extensively studied as part of the Tucson Children's Respiratory Study.²³ More than 1000 unselected children were enrolled at birth, and most acute LRIs were assessed during the first 3 years of life.²⁴ Most episodes of LRI occurred primarily in an outpatient setting. These same children then underwent follow-up to the age of 13 years, and the association was studied between early LRI and subsequent asthma-like symptoms, allergic sensitization, total serum IgE levels, and lung function.²³ This study showed that, independent of most known potential risk factors for asthma and wheezing, children with confirmed RSV-LRI were at marked increased risk of having episodes of airway obstruction at the age of 6 years. It is interesting that the risk of subsequent wheezing decreased markedly with age and became statistically insignificant by the age of 13 years. There was no consistent association between LRIs resulting from other causes and the subsequent development of wheezing episodes.

Children who had RSV-LRIs (or LRIs caused by other viruses) were not more likely to become sensitized to local aeroallergens by the age of 11 years, and their geometric mean total serum IgE levels were not higher than those of children who had no LRIs. The only factor that appeared to be clearly associated with having had RSV-LRIs was a diminished level of lung function present up to 11 years after the initial episode, and these lower levels of lung function were present both in children who were still wheezing during the school years and in those who were not.

The results, similar to others,^{25,26} suggest that RSV-LRIs are either a marker or the trigger for a peculiar response to viral infection that persists during childhood but that tends to recede with age. This pattern of asthma expression during childhood corresponds to what is often observed in clinical practice. Most toddlers with asthma usually have symptoms during the winter months (viral season), and only a fraction of these children with asth-

ma show positive skin test responses to aeroallergens.¹² Children hospitalized with RSV infections, however, have also shown association with subsequent asthma and with allergic sensitization.²⁷ It is plausible to surmise, however, that children predisposed to the development of asthma may be more prone to severe lower airway involvement during RSV bronchiolitis and may thus be more likely to be hospitalized than are children without such predisposition.

If the IgE-mediated mechanisms of disease observed in atopic asthma are not directly involved in infection-associated asthma, what determines which children respond to common viral infections with recurrent airway obstruction? One potential clue comes from the finding that children with RSV-LRIs have significantly lower levels of lung function many years after their initial acute episode. These lower levels of lung function may be either acquired after birth (ie, the consequence of early life insults) or congenital. Our own studies suggest that these deficits may be due to increases in airway tone, because they are to a great extent reversed by a single dose of an inhaled bronchodilator.²³ It is plausible to surmise that children born with airways that are structurally or functionally more narrow than those of their peers may be more prone to show signs of bronchial obstruction during viral infections than children with larger airways. Infants who will go on to have LRIs during the first years of life have diminished lung function shortly after birth, before any LRI has occurred. Data from animal models further suggest that infection itself may play a role in acquired deficits of lung function and will be discussed in the following text.

Smoking during pregnancy

The factors that determine levels of lung function shortly after birth are beginning to be understood. Genetic factors are almost certainly involved, because infants whose parents report a history of asthma¹⁴ or respiratory troubles during childhood²⁸ have lower levels of lung function and are more likely to wheeze in early life than those whose parents do not report such a history. The most widely studied and best-established determinant of lung function in early life is maternal smoking during pregnancy.³¹ Exposure to tobacco smoke products in utero alters lung function in infants^{29,30} and older children. The effect is most marked among girls,^{29,32} who show maximal flows (as a function of lung size) in early life larger than those of boys and are therefore less likely to wheeze during viral respiratory infections. The effects of maternal prenatal smoking on the likelihood of a child's wheezing are mainly concentrated during the child's first years of life.³² The increased risk of early wheezing associated with in utero exposure to tobacco products may be attributable to consequent alterations in lung and airway growth.

Immune factors

Although the connection between altered lung growth and the risk of recurrent wheezing episodes in early life

seems well established, it is unlikely that this connection alone explains all forms of infection-associated childhood wheezing. It is legitimate to surmise that the immune response to the virus itself may also play a significant role. Unfortunately, most efforts in this area have been concentrated almost exclusively in attempting to elucidate the role of RSV and other viruses in triggering or initiating T_H2-mediated responses. Much less attention has been paid to other potential immune mechanisms that may predispose to recurrent wheezing associated with viral infections.

Very recently, the potential role of monocyte³³ and epithelial cell³⁴ responses to RSV infection has been assessed. RSV readily infects both these cell types, known to be actively involved in immune responses to viruses. In a study of the cytokine responses by whole blood cells to stimulation with lipopolysaccharide and interferon-gamma (IFN- γ) in infants with or without recurrent wheezing after an initial episode of RSV bronchiolitis, the assumption was made that IL-10 and IL-12 production after lipopolysaccharide/IFN- γ stimulation came mainly from monocytes.³⁵ Among children who had recurrent wheezing episodes within 1 year of the original RSV-LRI, IL-10 production by blood cells during the convalescent phase after LRI was significantly higher than IL-10 production in children who did not have such episodes. Moreover, IL-10 responses correlated significantly with the number of wheezing episodes occurring during follow-up. There was no association between recurrent wheezing and either IL-4 responses or IFN- γ responses by blood cells to stimulation with phytohemagglutinin or α CD28.³⁵ The lack of a T_H2-like cytokine pattern of response (presumably by T_H cells) in children with recurrent wheezing prompted the authors to conclude that the immune mechanisms involved in asthma may not be responsible for recurrent wheezing after RSV bronchiolitis. This conclusion is in substantial agreement with the epidemiologic evidence cited previously.

The potential mechanisms by which increased production of IL-10 monocytes leads to recurrent wheezing after RSV remain to be elucidated. IL-10 is known to suppress T-helper type 1 (T_H1) type responses by antagonizing IL-12 in vitro.³⁶ The lack of any changes in IL-12 responses or in IFN- γ /IL-4³⁵ responses does not support this as an explanation for the association. IL-10 is also a potent inhibitor of antigen presentation by macrophages, mainly because IL-10 inhibits the expression of major histocompatibility complex molecules in the cell surface.³⁷ It is thus conceivable that IL-10 may suppress lower airway antiviral immune responses, thus enhancing RSV's ability to invade local tissues and cause airway obstruction.

Does RSV infection cause deficits in lung function?

The nature of the immune responses to RSV may predispose the patient to subsequent recurrent wheezing. If this mechanism is independent of an enhanced T_H2 response, a potential mechanism exists by which RSV itself can predispose to deficits in lung function later in life.

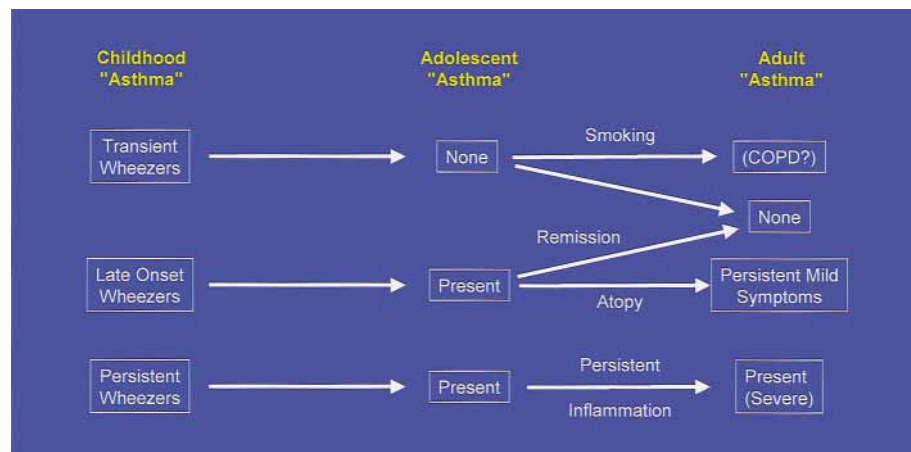


FIG 2. Hypothesis of progression of asthma from childhood to adulthood. This figure presents a summary of a working hypothesis of the progression of pediatric phenotypes of asthma into adult phenotypes, based largely on the Tucson Children's Respiratory Study and the Melbourne study. *COPD*, Chronic obstructive pulmonary disease.

It is possible that high IL-10 responders may be more prone to RSV-mediated changes in airway structure or function. Recent data from animal models provide support for this contention.³⁸ Cotton rats infected in early life with human RSV had significant increases in the airway's neurally mediated cholinergic contractile responses and reduced nonadrenergic noncholinergic inhibitory responses.³⁸ Both these alterations would be expected to increase airway smooth muscle tone and decrease resting airway caliber. It is interesting that the alterations in nonadrenergic noncholinergic inhibitory responses persisted up to 20 weeks after the original insult. The mechanisms by which RSV can induce these long-term changes in the regulation of airway tone are not understood. A recent study³⁹ showed that IL-10-deficient mice do not have the increased bronchial hyperresponsiveness associated with allergic sensitization in mice despite the fact that IL-10-deficient mice had all other immune markers (including local eosinophilic and IgE responses) characteristic of this animal model. IL-10 may alter the regulation of airway tone by acting directly on the smooth muscle or by an indirect mechanism not dependent on the local allergic response. Because RSV is known to trigger brisk IL-10 responses by both epithelial cells⁴⁰ and macrophages,⁴¹ it is tempting to speculate that individuals with enhanced IL-10 responses to RSV may have long-term alterations in the regulation of airway tone that predispose them to recurrent airway obstruction. This hypothesis will require further experimental verification.

ASSOCIATION BETWEEN NONATOPIC ASTHMA OF CHILDHOOD AND ASTHMA IN ADULTHOOD

Children who have recurrent episodes of airway obstruction during the early years of life, mainly during respiratory infections, and who do not become sensitized to local aeroallergens, are highly likely to show remis-

sions in their airway symptoms by their early adolescent years.²³ Until recently, it was not known whether these children could be more likely to relapse than those patients who never wheezed during childhood. The data from the British 1958 cohort cited earlier⁷ provide the first evidence that the association between early life symptoms and wheezing at age 33 years was independent of both these risk factors, although both allergic symptoms and active smoking were strongly associated with symptom relapses.⁷ These results raise the possibility that children who wheeze in early life, mainly in association with acute respiratory infections, may be at increased risk of having asthma relapses as adults after long periods of complete symptom remission, and this may be especially true for those who start smoking. In support of this hypothesis, a separate study² showed that asthma-like symptoms and further deficits in lung function were more likely among adult smokers with a history of "childhood respiratory troubles" than among those without. The relative role of congenital abnormalities in lung function versus deficits in lung function that are the consequence of viral insults occurring in early life remains to be elucidated.

CONCLUSIONS

Recent findings by both long-term longitudinal epidemiologic and experimental studies provide new clues to the understanding of the links between asthma in childhood and in adulthood. Fig 2 presents a summary of a working hypothesis of the progression of pediatric phenotypes of asthma into adult phenotypes, based largely on the Tucson Children's Respiratory Study¹² and the Melbourne study.⁹ Transient wheezers do not wheeze as adolescents or have asthma as adults. However, they may be at increased risk for the development of chronic obstructive pulmonary disease if they become smokers. Late-onset wheezers manifest asthma as adolescents but

may go into remission and subsequently manifest no asthma. However, if they become atopic, they are at increased risk of having mild persistent asthma as adults. Persistent wheezers in childhood maintain their reduced airway function during adolescence, and if inflammation persists, they have severe asthma in adulthood.

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