Specific and Nonspecific Obstructive Lung Disease in Childhood: Causes of Changes in the Prevalence of Asthma

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Reversible airway obstruction in childhood includes two major groups of patients: those with recurrent wheezing following bronchiolitis in early childhood, and those with allergic asthma, which represents an increasingly large proportion of cases through the school years. Over the last 40 years of the 20th century, allergic asthma has increased in many countries and in relation to several different allergens. Although this increase has differed in magnitude in different countries and also in the social groups most affected, it has had several features in common. The increase generally started between 1960 and 1970, has been progressive since then, and has continued into the 1990s without a defined peak. Among children 5–18 years of age, the increase has predominantly been among allergic individuals. Theories about the causes of the increase in asthma have focused on two scenarios: *a*) that changes in houses combined with increased time spent indoors have increased exposure to relevant allergens, or *b*) that changes in diet, antibiotic use, immunizations, and the pattern of infections in childhood have led to a change in immune responsiveness such that a larger section of the population makes T_H2, rather than T_H1 responses including IgE antibodies to inhalant allergens. There are, however, problems with each of these theories and, in particular, none of the proposed changes can explain the progressive nature of the increase over 40 years. The fact that the change in asthma has much in common with epidemic increase in diseases such as Type II diabetes or obesity suggests that similar factors could be involved. Several lines of evidence are reviewed that suggest that the decline in physical activity of children, particularly those living in poverty in the United States, could have contributed to the rise in asthma. The hypothesis would be that the progressive loss of a lung-specific protective effect against wheezing has allowed allergic children to develop symptomatic asthma. What is clear is that current theories do not provide either an adequate explanation of the increase or a practical approach to reversing the current trend. *Key words*: allergens, asthma, cat, childhood, cockroach, exercise, increase, mite, physical activity, RSV. — *Environ Health Perspect* 108(suppl 4):725–731 (2000).
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Although there are many causes of airway obstruction in childhood, the vast majority of cases are related to bronchopulmonary dysplasia, cystic fibrosis, or reversible airway obstruction. Reversible airway obstruction presenting as bronchiolitis, postviral wheezing, or as asthma has increased over the last few decades (*1–3*). Evidence for the increase has been obtained from population studies, school absenteeism, and the number of children receiving treatment. In addition, in some sections of the population, both hospitalization and mortality from asthma have also increased (*4*). As with any other disease, understanding the etiology is an important part of developing rational treatment. Indeed, the scale of the increase in asthma is so great that without understanding the causes of the increase it is unlikely that we will provide effective treatment. At present, the real causes of the increase are not clear, and it is important to recognize that increases in the known causes of the disease may not explain the phenomenon. Thus it is not clear that sensitization to dust mite or cockroach allergens or the prevalence of rhinovirus infections or respiratory syncitial virus infections have increased on a scale sufficient to explain the rise in asthma. The situation is further complicated by the fact that there appear to be two separate but overlapping syndromes of reversible airway obstruction in childhood, and that these two syndromes are inevitably confused. The first syndrome usually starts with an episode of bronchiolitis in the first year of life, followed by multiple episodes of viral induced wheezing. The second form, characterized by eosinophil-rich inflammation of the airways, occurs predominantly in allergic children and generally becomes apparent after 2 years of age. By 10 years of age, allergic asthma is the dominant form of the disease (*5–9*). This distinction is important because immune responses are highly relevant to allergic asthma but are not clearly related to bronchiolitis. Thus, studies of factors that might influence the early life immune response of the infant can only be evaluated relative to allergic asthma, which may not be possible until the children are over 5 years of age. Equally, evidence that a large proportion of children have an episode of respiratory distress in the first 2 years of life may not be relevant to understanding the increase in asthma, which has been most clearly documented among school children and young adults (*10*). In the present article we consider case–control, population-based, and prospective studies as well as studies on the immune response that are relevant to understanding the two forms of the disease in childhood.

Bronchiolitis and Respiratory Syncitial Virus in the First Two Years of Life

A large proportion of infants who present to hospital with bronchiolitis, wheezing, or breathlessness have recently been infected with respiratory syncitial virus (RSV). The evidence for this can be obtained from cultures, antigen detection, or serologic responses compared with random controls (*11–13*). Similar results have been obtained in population-based studies (*14*). In many of these reports the association between RSV infection and bronchiolitis is so strong that it has been assumed that the relationship between the two is causal. However, when children are evaluated at 2 years of age, most show serologic evidence of an immune response to RSV regardless of whether they have had a symptomatic event (*15,16*). There are three central questions about the response to RSV:

- What factors in the young child influence the severity of the response to RSV?
- Are the initial responses to RSV infection or subsequent episodes of wheezing influenced by the immune response to RSV?
- Does the immune response to RSV influence the subsequent response to inhalant allergens?

Taussig and his colleagues in Tucson, Arizona, established that small lung size at birth increased the risk of bronchiolitis (*14*). In addition, it is well established that maternal smoking during pregnancy decreases lung size at birth and increases the risk of symptomatic viral infections in early life (*17*). The relevance of the immune response to RSV has

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been debated for many years. Welliver and his colleagues reported the presence of nasal IgE antibodies specific for RSV (*11*). Their studies suggested that those children who developed a response were more likely to develop persistent asthma. However, the low titers of IgE ab to the virus lead to questions about their significance, and other authors have not been successful in detecting IgE ab to RSV (*18*). The issue is important because early episodes of bronchiolitis/wheezing are very common—occurring in up to 40% of all children—and inevitably some of these children will go on to develop allergic asthma. The problem is to find markers in early childhood that identify those children whose symptoms will persist. Several factors have been identified that are associated with increased risk:

- eczema requiring treatment under 2 years of age (*19,20*);
- eosinophilic response to viral infections from very early in life (*14,17*);
- elevated serum IgE relevant by 4 years of age and perhaps by 9 months but not in cord blood (*5,14,21,22*);
- IgE antibodies to egg proteins in the first 2 years of life (*23*); and
- exposure to high concentrations of dust-mite allergen (*5,7,24*).

However, none of these are specifically related to RSV.

Following an episode of bronchiolitis in early childhood, many children continue to have episodes of wheezing that either are or appear to be triggered by viral infections. Many or most of these children are nonallergic. Thus, any analysis of symptomatic episodes in children between the age of 2 and 10 years of age will include both syndromes. Using skin tests as a method of separating allergic from nonallergic children (at 6–8 years of age), the risk factors for wheezing in the two groups of children are strikingly different (*25*) (Table 1). In this cohort of children in Sweden, several factors (e.g., breast feeding for less than 3 months or reported signs of damp in the house) that were assumed to relate to allergic immune responses were found to be significant only among nonallergic children (*25*). In our prospective study in Poole, Dorset, United Kingdom, 1978–1990, those children who wheezed before 5 years of age but did not have asthma at age 10 were no more allergic at age 10 than those who had never wheezed (*5*). This implied that there was a significant group of early wheezing children whose wheezing was unrelated to allergy and who recovered. Recent results from the prospective study in Tucson, Arizona, have taken this one step further and shown that the risk for wheezing episodes related to early childhood RSV bronchiolitis declines steadily with age and is no longer significant by age 13 years (*26*).

Allergic Asthma among School-Age Children

A few allergic children with asthma present to hospital as young as 2 years of age or even 1 year; however, they represent a minority of the children with reversible airway obstruction at this age (*5,12,13,27*). By the time children have reached middle school (10–13 years of age), asthma is very strongly associated with positive skin tests to common inhalant allergens. At this age the odds ratios for wheezing among sensitized compared to nonsensitized individuals are often 6 or higher (*5–9,28–30*) (Table 2). The evidence that allergens can contribute to asthma relates to both seasonal and perennial allergens. However, in most population-based studies using multivariate analysis, the strongest independent risk factor for symptomatic bronchial hyperreactivity (BHR) (i.e., asthma) is sensitization to one or more of the allergens found indoors. The important sources of allergens inside houses include dust mites, animal dander, and the German cockroach. The evidence that these allergens cause asthma comes from the combination of many different types of studies (*31,32*). Given the strength of the association, the fact that provocation with allergen can induce typical eosinophil-rich inflammation, and evidence that avoidance of allergens can lead to decreased BHR, it seems reasonable to assume that the relationship is causal. However, even if dust mites and other allergens are important causes of both sensitization and asthma among sensitized individuals, this leaves many unanswered questions:

- When does the relevant exposure occur and how does the quantity of exposure influence the prevalence of sensitization?
- Why do some/many allergic individuals have no lung symptoms even when they live in an environment with high concentrations of allergen?
- What are the causes of the increase in asthma among allergic children?

Relevance of Exposure Early in Life

The fetus is capable of making an immune response to foreign antigens from the second trimester onward. Thus in theory, relevant exposure could occur *in utero*, in the first year of life, or at any time afterward. There are several lines of evidence interpreted as suggesting that relevant exposure occurs in the first year of life or before that:

- First, in a prospective study the concentration of mite allergen in the child's bed at 1 year of age was more relevant to asthma at age 11 than the concentration of mite allergen in the house at age 11 (*5*).
- Second, Peat et al. (*7*) in Australia observed that early sensitization to dust mite allergens was more significant in relation to asthma than sensitization after 3 years of age.
- Third, considerable evidence from animal studies indicates that there is a restricted time in early childhood when animals are prone to make T_H2 responses. If this also applies in man, early exposure could be more relevant than later exposure (*33*).
- Finally, several groups report that cord blood lymphocytes proliferates when incubated with dust mite antigens *in vitro* (*34–36*).

The evidence about cord blood T cells is from several laboratories and includes responses to pollen as well as to dust-mite

Table 1. Odds ratios for asthma in Norbotten, Sweden: logistic regression analysis on 2,149 children 7–8 years of age.[a]

	Allergic asthma	Nonallergic[b] asthma	Ever asthma
Male sex	1.3	1.6*	1.5**
Family history	3.0***	3.6***	3.4***
House dampness	1.4	1.8*	1.5
Mother smoker	1.2	1.6*	1.3
Pets at home[c]	0.6*	0.8	0.7*
Breast feeding			
< 3 months	1.1	1.9**	1.8***

[a]Data from Ronmark et al. (*25*). [b]Skin test negative. [c]The presence of pets at home is associated with a reduced risk of asthma. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 2. Sensitization as a risk factor for asthma.

Country	Study design	Relevant perennial allergen	Odds ratios for asthma: Indoor allergen	Odds ratios for asthma: Pollen	Author
United Kingdom	Prospective[a]	Mite (cat)	19.7**	NS	Sporik et al. (*5*)
New Zealand	Prospective[a]	Mite (Asp.)	6.6**	NS	Sears et al. (*6*)
Sweden	Population	Cat, dog	3.9**	Birch*	Ronmark et al. (*29*)
Australia	School[a]	Mite	≥ 10.**	NS	Peat et al. (*7*)
United States					
Virginia	School[a]	Mite (cat, CR)	6.6**	NS	Squillace et al. (*9*)
Atlanta, GA	Acute (ER)	Mite (CR)	8.2**	NS	Call et al. (*30*)
Arizona	Prospective	Alternaria	**	NS	Halonen et al. (*8*)
New Mexico	School[a]	Cat, dog	6.2*	NS	Sporik et al. (*28*)

Abbreviations: Asp, aspergillus; CR, cockroach; ER, emergency room; NS, nonsignificant. [a]Studies in which asthma was diagnosed by objective tests of bronchial hyperreactivity using histamine provocation. *$p < 0.01$; ** $p < 0.001$.

allergens (*37*). Furthermore, Holt and his colleagues in Perth, Australia, claim that the response can be seen with peptides and is major histocompatibility complex restricted (*35,38*). It has also been reported that the cord blood responses to pollen reflect exposure of the mother to the relevant pollen during the period when she was pregnant (*37*). This result potentially provides strong evidence that an inhaled allergen could cross the placenta. However, there are many problems with the interpretation of the results with cord blood lymphocytes:

- The responses in the cord blood have not been shown to predict subsequent clinical or immunologic outcome (*34–38*).
- More recent results found no effect of maternal exposure to pollen during pregnancy on cord blood response to relevant pollen antigens (*39*). Furthermore, several groups have now reported that cord blood responses to dust mite are not related to maternal exposure (*36*).
- In almost all studies the responses are based on a limited number of replicates, usually 3, and the stimulation indices are modest. Furthermore, the numbers of control cultures are inadequate to define random variation under the conditions used. T cells respond to many different stimuli *in vitro*, and it is not possible to establish statistically that the modest responses seen in a minority of infants reflect a significant response or priming *in utero* (*34,35*). Some of the studies on cord blood T cells have used a serum-free medium, which in other laboratories appears to inhibit all responses except those to dust mite (*40,41*). It is important to remember that none of these responses have been confirmed by repeated testing since responses are negative at 6 months (*34*).

Some authors claim that cord blood responses to dust mite can predict clinical outcome at 2 years of age (*38*). This is very confusing, since only a minority of the children who are going to become allergic can be identified at age 2 (*5,6*). Because of the quantities of mite antigen inhaled by the mother (i.e., 5–20 ng/day), it is difficult to believe that sufficient antigen crosses the placenta. In addition, the transfer of allergen (if it occurs) would be strongly influenced by maternal IgG antibody. However, IgG ab specific for mite allergen is strongly correlated with IgE antibodies. At present, the possible relevance of maternal IgG antibody has not been adequately studied.

Conclusions regarding early exposure. There are valid reasons for considering that early exposure and early sensitization to dust mite allergens are a significant factor in the development of asthma. However, it is not clear whether early means the first 6 months or the first 3 years of life. What is certain is that definitive evidence of sensitization (i.e., skin test or serum antibodies) is rare under 2 years of age (*5,42*). Thus, in most cases, neither skin tests, IgE ab, or IgG antibodies to inhalant allergens develop until the third year of life or later. At present the available evidence is not sufficient to interpret the reported results on proliferation of cord blood lymphocytes. The responses observed could reflect nonspecific activation of T cells by peptides of related structure or simply random activation of T cells *in vitro*. Since the results do not predict subsequent outcome, there seems to be no basis for concluding that significant sensitization or priming to inhalant allergens occurs *in utero*.

Dose Response for Dust Mite and Other Allergens

One of the pieces of evidence supporting the relevance of dust mites to asthma is the dose–response relationship between exposure and the prevalence of sensitization (*32,43*). Limited available evidence suggests that a dose–response relationship also exists between exposure to cockroach allergen and sensitization (*44–47*). The studies establishing the dose response have predominantly been on children 7–13 years of age. Thus, it is logical to assume that exposure before age 5 is relevant to sensitization and that decreasing exposure prior to this age could reduce sensitization. However, most of the data cannot answer whether exposure at some particular time prior to 5 years of age is critical.

For cat allergen, available data are confusing. It has been known for some time that children living in a community where cats or dogs are common are at risk of sensitization. Furthermore, in these communities it has been clear that sensitization to cat dander is a major risk factor for asthma (*25,28,48,49*). Thus, in multivariate analysis of risk factors for asthma in the Norbotten region of Sweden or in Los Alamos, New Mexico, sensitization to cat (or dog) allergens is the strongest independent risk factor (*28,29*). It has also been clear that in communities where very few of the homes have domestic animals, sensitization is unusual and not significantly associated with asthma (*30,48*). In studies such as the Multicenter Atopy Study in Europe, there is a clear-cut dose–response relationship between cat allergen and sensitization to cat (*49*). However, this has not been obvious in other studies. Indeed, there have been several reports that the presence of a cat in the house can decrease the risk of sensitization (*25,50*). In a recent report on a population of middle school children, we found that the presence of > 20 µg Fel d 1/g of dust in the child's house was associated with a decreased risk of sensitization, compared to that in children exposed to between 2 and 20 µg Fel d 1/g of dust (*45*) (Table 3). It is easy to assume that the exposure measurements are not sufficiently accurate or that families that are allergic chose not to have cats. However, the decreased prevalence of sensitization was clear among children who were atopic as determined by a positive skin test to some other allergen. Furthermore, the prevalence of IgG ab to Fel d 1 correlated closely with exposure and the IgG ab response included IgG4 in both allergic and nonallergic children (*51*). These results imply that exposure to high concentrations of cat allergen can induce an immune response not associated with symptoms and should be considered to be a form of tolerance.

Being skin-test positive to any of the major indoor allergens carries a risk of asthma. Although this risk appears to be associated with exposure, it does not show a consistent dose response (Table 3) (*52*). Indeed, being allergic to one of the major indoor allergens appears to confer a risk of asthma over a wide range of exposure (*31,45,48*). In all studies there are some allergic individuals who are living in houses and who have significant exposure but do not report symptoms or have BHR. It is important to note that many allergic and exposed children do not wheeze, which makes it clear that there must be significant risk factors for asthma that are different for allergy. In addition, the fact that there have always been a large number of allergic children who do not wheeze means that the prevalence of asthma can increase among allergic children without an increase in allergy.

Table 3. Allergen exposure, sensitization, and asthma among middle school children: a population-based (n = 1,621), case–control study.[a]

		Atopic children	Asthma among the children		
	µg/g	specifically sensitized	Sensitized	Not	Odds ratio
Mite[b]	< 0.2–0.6	22/56	7/22	8/70	3.6 (0.98-13)
(Group I)	0.62–10.0	26/54	8/26	8/76	4.0 (1.14–14.2)
	10.2–155	40/54*	19/40	8/69	6.9 (2.4–20)
Cat[b]	< 0.5–1.9	15/56	8/15	17/92	5.0 (1.4–18)
(Fel d I)	2.0–23.0	23/54	8/23	10/74	3.4 (1.01–11.5)
	23.4–920	11/54**	6/11	11/88	8.4 (1.8–39)

[a]Data from Sporik et al. (*28*), Squillace et al. (*9*), and Sporik et al. (*45*). [b]Highest concentration in the house in µg/g Group I dust mite or Fel d 1. Chi-square test for trend on 6 exposure categories. *p < 0.001; **not statistically significant, p = 0.3.

The Evidence for Causality

In general, it is difficult to prove that the relationship between a given exposure and a chronic lung disease is causal (*53*). However, the problems in defining causality are not the same for the several different factors that have been associated with obstructive lung disease in childhood. The relationship between RSV infection and bronchiolitis in early childhood is almost certainly causal. In most studies the prevalence of RSV antigen in the cases is much higher than in the controls (in one study RSV was present in 70% of the cases and in < 5% of the controls) (*13*). Furthermore, the reaction in the lungs is consistent with the known characteristics of this virus. The important question is why do some infants get more severe disease. It appears that children with small or damaged lungs are at risk. Bronchopulmonary dysplasia (BPD) and maternal smoking during pregnancy are the most important risk factors that have been defined. The view that RSV can cause prolonged effects in the lung is enhanced by recent evidence that immunizing infants with BPD using Respigam can improve their clinical outcome over 4 years (*54*).

In some cases of allergic asthma the circumstantial evidence strongly suggests that a given exposure (e.g., cat in domestic houses other than that of the patient or rat urinary allergen in an animal house) exacerbates asthma. Indeed, some patients have no symptoms unless they are exposed to a defined allergen. On the other hand most cases of asthma are chronic, and the relevant exposure is on a daily basis in their own house. Under these circumstances the patient is generally not aware of the relationship of exposure to the disease. It then becomes a problem to decide whether the exposure is a cause of the disease. However, there are several levels at which the question can be asked:

- Does exposure cause sensitization? Here the evidence is very strong and the dose–response data for dust mite are well established (*31,43,49,52,55*).
- Is allergen exposure responsible for the changes in the bronchi that underlie chronic asthma? As many authors have pointed out, this question cannot be answered definitively (*56,57*), at least in part because we cannot study the bronchi of children prospectively.
- Does allergen exposure contribute to the symptoms and severity of the disease among allergic individuals? This question is clearly answerable and is important because it directly relates to management (*31,58,59*).

Using the criteria for causality proposed by Hill in 1965 (*53*), we can assess the evidence, attempting to distinguish evidence related to sensitization, development of asthma, and the contribution to current symptoms (Table 4). The important feature is that evidence comes from many different studies. Thus, there is a very strong association between sensitization and asthma, and for dust mite there is excellent evidence of a dose–response relationship between exposure and sensitization. It is also clear that bronchial challenge of allergic patients can induce most of the changes typical of asthma. Finally, those controlled trials of avoidance that have decreased exposure have also been successful clinically (*59*). Overall, one has to conclude that for dust mite, a strong body of evidence supports the view that dust-mite exposure is a cause of asthma. For many other allergens the evidence is less complete. However, on a world basis, dust-mite sensitization is associated with the largest number of cases. Among the inner city populations of the United States, cockroach allergens appear to be most important. Here too there is increasing evidence supporting a causal relationship (*30,44,48,60*).

Table 4. Criteria for causality proposed by Hill[a] and the evidence for dust-mite exposure and asthma.

The strength and association between sensitization and asthma: population, case–control, and prospective studies.
Consistent observations in different populations: United Kingdom, Europe, United States, Australia, etc.
Response is specific, i.e., asthma [no other lung disease].
There is a dose–response relationship.[b]
Experimental evidence: avoidance studies, challenge studies.
The mechanism is biologically plausible.

[a]Data from Hill (*53*). [b]Data from Sporik et al. (*32*).

Causes of the Increase in Asthma

Given that perennial exposure to common indoor allergens appears to be a major cause of asthma among allergic children, it was logical to assume that the increase in asthma in the community had been caused by either an increase in allergen exposure or a change in immune responsiveness. The two main hypotheses over the last 20 years have focused on these explanations for the increase in asthma. However, the scale of the increase in asthma among school children is now far too large to be explained by a change in immune response from T_H1 to T_H2 or by changes in housing. Any hypothesis should take into account the increase observed in a wide range of countries, i.e., England, New Zealand, Finland, Sweden, Japan, Australia, and the United States. Furthermore, the increase has had a similar time course and progressive nature in each of these countries. Both the timing and magnitude of changes in housing, air pollution, tobacco use, and diet in these countries have been very different (*61,62*). Although many areas of the temperate world have changed to tighter, hotter, or over-furnished housing, there are areas such as the Southern States of the United States, Hong Kong, or Sao Paulo, Brazil, where ventilation rates remain high. There are well-defined mechanisms by which air pollution could contribute to asthma; however, chronic wheezing has increased in New Zealand and in other areas where air pollution is not a major factor as much as it is in Philadelphia, Pennsylvania, and in other cities with severe air pollution (*63*).

Given the confusing nature of the arguments, it is clear that we need to consider the possible role of all the changes that have occurred in Western society. Indeed, the question is whether asthma should be considered along with such diseases as hypertension, Type II diabetes, coronary artery disease, and obesity as a primary disease of Western society. Obviously, many changes have occurred over the last 40 years. These include the widespread use of broad-spectrum antibiotics, changes in diet, increase in motorized transport, and the progressive decline of physical activity. In the last few years, the rise in obesity in the United States has become obvious. In addition, recent reports have established a correlation between obesity and asthma (*64–66*). Clearly, the increase in obesity must represent some combination of increased dietary intake and decrease in exercise. However, the Centers for Disease Control and Prevention in Atlanta, Georgia, has recently accepted that the decline in physical exercise is a primary factor in the increase in obesity in the United States. Our experience in Atlanta is that many school children participate in very little physical exercise. In particular, they go to school on school buses, refuse to take part in physical exercise classes at school, have no recess, and after school has ended for the day and they return home, 80% of the children with asthma have access to a television/video monitor in their own room (*67*).

If we accept the observation that decline in physical exercise and the associated rise in obesity are major features of specifically that population that has the most severe asthma, in what ways could they be connected? It is important to recognize that obesity can easily be measured with a scale, whereas measuring physical activity is not simple. Assessments of physical activity that are focused on organized sports can be misleading. The real decline in physical activity comes from decreased unorganized play; being driven most places in an automobile; the use of remote control devices; and spending prolonged sedentary periods using computers, playing video and electronic games, or watching television. It is important to recognize that although obesity

has been found to increase the risk for asthma among children, the prevalence of wheezing is high even among children in the lowest quartile for weight (*64,65*). If the observed correlation between obesity and asthma is real, there are several possible explanations:

- Obesity and the associated hormonal changes could influence inflammatory mechanisms in the lung and thus increase inflammatory disease of the lungs. That hormonal changes influence the development of wheezing in girls is certain, since the largest increase in wheezing among girls occurs at the time of puberty (*68*).
- Obesity can act mechanically to prevent full expansion of the lungs and full extension of bronchial smooth muscle (*69,70*). This effect could in theory result in an increase in bronchial muscle tone. The problem with this view is the lack of evidence for a chronic effect of full expansion of the lungs, and it would not explain apparent increases in inflammation associated with asthma.
- If, as we suspect, the real correlation is with physical activity rather than with obesity, it is possible that prolonged physical activity including expansion of the lungs could have an anti-inflammatory effect. Although many patients describe effects of this kind, they have not been well documented. The possible mechanisms include accelerated healing of inflammation or direct effects on inflammatory cytokines.

It has been known since the 1960s that full expansion of the lungs decreases lung resistance. In addition, Skloot et al. (*71*) and Parham et al. (*72*) demonstrated that when normal individuals do not take a deep breath for 40 min, they develop BHR . Recently, Fredburg and his colleagues (*69*) provided a direct explanation for the effects of full expansion of the lungs. On the basis of *in vitro* studies on bronchial smooth muscle, they concluded that extension of smooth muscle was a more potent bronchodilator than isoprenaline. They also speculated that a decreased rate of sighing could lead to BHR (*69*). At present, the remarkable gap is in evidence about the effects of exercise on established asthma. Although many patients and physicians are convinced that regular exercise is important for patients with asthma, there are very few controlled trials that address the issue. A major problem is that exercise can induce attacks of asthma, and it is still not clear how much exercise-induced bronchospasm involves mediator release. If mediators are released, then exercise-induced bronchospasm would be seen as proinflammatory. Thus, according to this hypothesis, the correct treatment for asthma would be exercise under conditions that do not induce bronchospasm.

The epidemic of asthma among families living in poverty in the United States presents a major hurdle for all theories about the reasons for the increase in asthma. Many of the associations and extrapolations made in European studies simply do not apply here. In particular, the observation that increased family size decreases the risk of asthma has not been found in this population (*60*). Similarly, the overcrowded roach- and rat-infested tenements of the South Bronx in New York and Chicago, Illinois, cannot be described as conditions of excessive cleanliness. Furthermore, the suggestion that infections early in childhood may be protective or harmful does not apply, since there have been no consistent changes in infections on a scale sufficient to explain the increases in asthma. There are inner-city areas where incinerators, excess traffic, or industrial sites represent an important cause of outdoor pollution. However, a detailed analysis of asthma deaths in Philadelphia showed an inverse relationship to outdoor air pollution (*63*). Dietary changes are widespread in Western societies but may be more marked among lower socioeconomic groups in the United States. Several features of dietary change could be relevant: increased sodium relative to potassium, increased fat intake, or decreased omega-3 fatty acids. In addition, many infants receive solid food, particularly eggs, from a very early age, which may influence subsequent sensitization to inhalant allergens. Any discussion of diet should recognize that for diseases such as arteriosclerosis, hypertension, and diabetes, it is the relationship between diet and activity that determines the outcome. It would not be surprising if the same were true for asthma.

Conclusion

Over the last 40 years, asthma has risen progressively to become the most important chronic disease of childhood. In the United States, but not in most other parts of the world, this increase has been most severe among the poorest sections of the population; the scale of the change in this population has eclipsed several previous hypotheses about its causes. In particular, it is no longer probable that changes in housing are the primary cause of the increase because it has been observed in areas where little or no change in housing has occurred. In addition, the increase has been related to several different allergens, e.g., cockroach, animal dander, and Alternaria, as well as dust mites. It is unlikely that parallel increases in exposure to each of these allergens have occurred over 40 years in many different countries.

The second group of theories holds that a decline in early life infections, ubiquitous use of antibiotics, and/or too much cleanliness could have allowed a progressive shift in immune responses from T_H1 to T_H2. It is proposed that this shift has allowed a progressive increase in all forms of allergic disease. The primary problem with these theories is the lack of objective evidence for an increase in T_H2 responses. In Europe a parallel increase in rhinitis has been documented (*73*). However, in general the evidence for an increase in rhinitis is only based on questionnaire data. In the United States the questionnaire data that are available do not show any increase in hay fever between 1960 and 1997 (*74*) (Table 5). Furthermore, in the United States, Australia, and Hong Kong, the increase in asthma appears to be primarily an increase in wheezing among allergic individuals. Finally, our recent evidence that children can become tolerant to cat allergens and that this response includes IgG4 antibodies strongly suggests that the default pathway is a modified T_H2 response, not a T_H1 response. This finding makes it difficult to propose that progressive changes in immune responses as a cause of the increase in those communities where cat and/or dog allergens are the primary or dominant allergen. It is against this background that we feel that it is essential to consider all the changes that have occurred over the last 40 years. The aspects of lifestyle that have changed and could be relevant to the rise in asthma include antibiotic use, diet, immunization, and changes in housing. However, one change is particularly obvious in the United States—the decline in physical activity with the associated rise in obesity.

Table 5. The prevalence of allergic rhinitis in the United States: When did the increase occur?

Date	Authors	Site	Prevalence of allergic disease	Rhinitis
1924	Spain and Cooke	New York	3.3%	
1930–1934	Jimenez	Michigan	12.0%	
1937	Rowe	California	10–13%	
1932–1950	Ratner and Silberman	New York	10–13%	
1954	Tips	Indiana	18.7%	
1959	Van Arsdale	Washington	16.7%	
1960	Mathews	Michigan	19.2%	(16.6%)
1962	Nagy and Settipane	Rhode Island	25%	(21.1%)
1997	Nathan et al.	United States	–	18.4%

Modified from Nelson (*75*), who concluded "There is no clear evidence of an increase in the last 30–40 years in the prevalence of allergic rhinitis in the US."

Given the strong evidence for an association between asthma and obesity, the possible relevance of physical activity should be considered. Increases in sedentary activity have been ubiquitous throughout Western society and now consume a larger proportion of our children's lives. The proposition presented is that decline in physical activity represents the progressive loss of a lung-specific protective effect against wheezing. However, this effect is primarily among allergic children; thus the hypothesis would be that prolonged physical activity (e.g., outside play) used to provide a protective effect that decreased the tendency of allergic children to wheeze. What is certain is that given the scale of the changes in asthma prevalence and severity, unless we correctly identify the reasons for these changes, it is unlikely that we will either successfully manage the disease or reverse the epidemic.

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