

Trends in Asthma Prevalence, Admission Rates, and Asthma Deaths

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There is now clear evidence that asthma prevalence increased significantly, especially in developed countries, during the second part of the 20th century. What caused this increase is currently unknown. Recent reports from the United States and the United Kingdom suggest that asthma prevalence may have plateaued between 1995 and the first few years of the present century. This stabilization, and even some decrease in asthma prevalence, especially in countries with high baseline rates, was confirmed by the International Study of Asthma and Allergies in Children. The hospitalization rate for asthma (as a proportion of asthma patients) decreased significantly in the United States between 1980 and 1995, then remained stable between 2001 and 2004. However, the asthma death rate (as a proportion of subjects with asthma) did not decrease significantly during either of those periods. A better understanding of what determines the stable asthma death rate is urgently needed, especially since inhaled corticosteroids have been shown to prevent asthma deaths in persons who take them regularly. Key words: asthma; fatal asthma; asthma, epidemiology; asthma, diagnosis. [Respir Care 2008;53(5):561–565. © 2008 Daedalus Enterprises]

Introduction

There has been great recent interest in the changes that have occurred in asthma prevalence during the last quarter

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century. There is now widespread consensus that the proportion of persons with a diagnosis of asthma increased markedly after 1980 and up to 2000, and this increase has been called the "asthma epidemic."¹ Several hypotheses have been proposed to account for the increase, but there is still controversy, and the issue remains unresolved. The most likely explanation is a conjunction of different epidemiologic and contingent factors, such as diagnostic transfer, coding changes, and medical care.² I have reviewed elsewhere the hygiene hypothesis,³ which appears to have wide consensus in the scientific community as a partial explanation for the increase in asthma and allergies in

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recent decades. In summary, in its current, most widely held version, the hygiene hypothesis postulates that the social and cultural changes associated with the so-called western lifestyle have dramatically decreased the microbial burden to which the immune system is subject, especially during early life, so the normal maturation process of the immune system is altered in such a way that abnormal responses to allergens, viruses, and autoantigens are more likely to become established, especially during the growing years. A more detailed review of this hypothesis goes beyond the scope of this paper.

I will review herein the latest major reports regarding the asthma epidemic, with special emphasis on the changes in prevalence, need for hospitalization, and asthma-related deaths since the beginning of this century.

Asthma in the United States

The United States Centers for Disease Control and Prevention recently published the results of its third National Asthma Survey,⁴ which covers the period 1980 through 2004. For this survey, asthma prevalence and asthma attack data were obtained from the National Health Interview Survey, emergency department data were from the National Hospital Ambulatory Medical Care Survey, hospitalization data were from the National Hospital Discharge Survey, and death data were from the National Vital Statistics System. Further methodological details are provided in the original Centers for Disease Control and Prevention publication.⁴ One important addition to this report was calculation of rates with 2 different denominators: the United States population appropriate for the particular data source (the so-called population rate), and the corresponding number of persons with asthma (the so-called at-risk rate).

Prevalence

The estimated number of persons with self-reported asthma during the previous 12 months increased from 6.8 million in 1980 (3.1%) to 14.9 million (5.6%) in 1995. Because of changes in the questionnaires introduced in 1997, it is not possible to directly compare the asthma prevalence in 2001 through 2004 to that of 1980 through 1995. However, the prevalence of persons who said they “still had asthma” after answering positively the question “has a doctor . . . ever told you that you had asthma” remained relatively stable between 2001 and 2004, ranging between 7.3% in 2001 and 6.9% in 2003. Using this definition of current asthma, there was an average of 20 million persons with asthma in the United States in 2001 through 2003, with higher prevalence in children (8.5%) than in adults (6.7%). Prevalence was higher in males among children and in females among adults, and higher

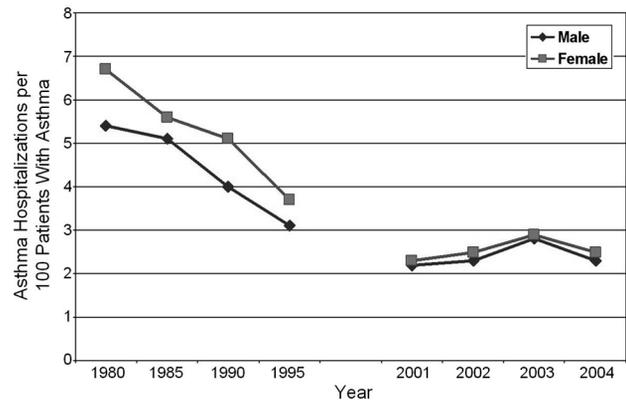


Fig. 1. Rate of hospital discharge with asthma as the first listed diagnosis per 100 persons with asthma, by sex. For 1980 through 1995 the 12-month prevalence of asthma was used as the denominator. For 2001 through 2004 the current prevalence was used as the denominator (see text). Therefore, the rates can only be compared within the 2 periods, and not between them. (Data from Reference 4.)

in black than in white children (12.5% vs 7.7%), but more similar among adults of both ancestries (7.6% vs 6.7%, respectively). Hispanics of Mexican ancestry had the lowest asthma prevalence (5.4%), whereas those of Puerto Rican ancestry had the highest (14.5%). In summary, the data suggest a steady, linear increase in asthma prevalence in all age and ethnic groups between 1980 and 1995, then an apparent stabilization of the rate during the first 4 years of this century.

Rates of Asthma Attacks, Emergency Room Visits, and Hospitalizations

Among persons with asthma, 55.6% reported one or more “attacks” during the previous year in 2001, and this proportion reached 63.1% among children. There was no significant change in these rates between 2001 and 2004, when 54.0% of persons with asthma reported an attack. Unfortunately, no data on asthma attacks were available before 2001. For emergency department visits, the population rate increased between 1992 and 1995 (from 57.3 to 71.0 per 10,000 persons), but showed no discernible trend thereafter, ranging from 59.8 in 2001 to 68.0 in 2002.

The asthma hospitalization rate, calculated as a proportion of persons with asthma in the previous 12 months, decreased markedly between 1980 (6.0%) and 1995 (3.4%) (Fig. 1). Subsequently the hospitalization rate as a proportion of persons with current asthma (not comparable to the rate above) remained relatively stable between 2001 and 2004 (see Fig. 1). When expressed as a population-based rate, asthma hospitalizations remained stable between 1980 and 2004.

In summary, the data suggest that, as a proportion of the whole population, asthma severe enough to require hospitalization has remained relatively stable in the United States in the last 25 years. Since the prevalence of asthma increased markedly up to 1995 and apparently stabilized during this century, there are 2 possible explanations for these findings: (1) only the prevalence of mild asthma that did not require hospitalization increased between 1980 and 1995 and then stabilized, whereas the prevalence of severe asthma remained unchanged, or (2) all forms of asthma increased equally between 1980 and 1995 but changes in asthma therapy (eg, the introduction of inhaled corticosteroids) during those years decreased the likelihood of hospitalization among subjects with underlying severe asthma. Which of these hypotheses better explains the United States trends described above is currently unknown, but data from the United Kingdom and Canada, which I will discuss below, provide new insights.

Asthma Deaths

Contrary to asthma hospitalizations, from 1980 to 1995 the population-based rate of asthma deaths increased from 14.3 to 20.6 per million, but little change occurred between 1990 (20.9 per million) and 1995. In 1999 the tenth revision of the International Classification of Diseases was implemented, so the rates for the 2000–2004 period are not comparable to those from the preceding period. Nevertheless, the population-based rate of asthma deaths decreased steadily between 2000 and 2004 (from 16.1 to 12.8 per million), and 50% of these deaths occurred in persons ≥ 65 years old, and almost two thirds in women. However, when deaths were expressed as a proportion of persons with asthma in the corresponding category (the at-risk rate), a very different picture emerged; expressed in relation to 12-month prevalence of asthma, the death rate was very stable between 1980 and 1995 (ranging between 4.7 in 1990 to 3.8 per 10,000 persons in 1995), with no discernible pattern (Fig. 2). Equally, and expressed in relation to current asthma, the rate remained stable between 2001 and 2003 (see Fig. 2).

In summary, when expressed as the at-risk rate (ie, as either the proportion of subjects with 12-month asthma or of subjects with current asthma), the asthma death rate appears to follow a very different pattern from that of the hospitalization rate. Whereas the death rate remained relatively stable during the 2 periods (1980–1995 and 2001–2004), the hospitalization rate decreased markedly during the first period and remained stable during the second. Explanations for these patterns remain speculative. Hypothetically, both mild asthma and lethal asthma could have increased between 1980 and 1995, whereas non-lethal but severe asthma could have remained stable, which would explain the different trends in asthma deaths and hospital-

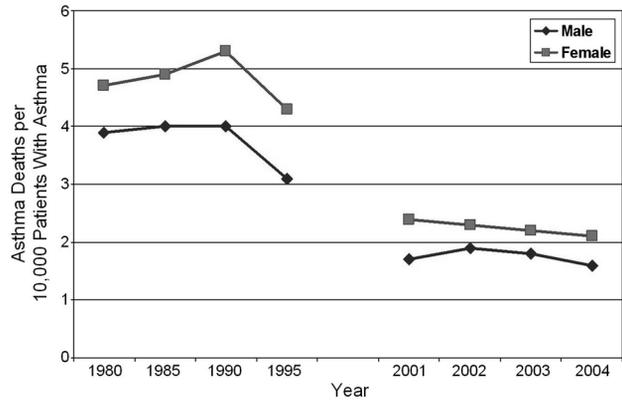


Fig. 2. Rate of death with asthma as the underlying cause per 10,000 persons with asthma, by sex. For 1980 through 1995 the 12-month prevalence of asthma was used as the denominator. For 2001 through 2004 the current prevalence was used as the denominator (see text). Therefore, the rates can only be compared within the 2 periods, and not between them. (Data from Reference 4.)

izations, but this appears unlikely. More plausibly, the 1980–1995 lethal asthma rate may not have been affected by changes in asthma therapy, but the latter could explain the marked decrease in the hospitalization rate during that period.

Asthma in the United Kingdom

Anderson and co-workers² recently comprehensively reviewed national surveys and reported trends in asthma prevalence, hospital admissions, and mortality in the United Kingdom between 1955 and 2004. Although only population rates were presented, comparison of these rates with those in the United States provides interesting insights. The United Kingdom trends in the prevalence of childhood asthma were similar to those reported in the United States: marked increases up to the mid-1990s, then an apparent stabilization. Hospital admissions show a complex pattern that differed between children and adults: the hospitalization rate increased for all age groups up to the early 1970s, then stabilized until the mid-1970s in adults, but continued to increase in children up to the mid-1980s. Starting in the mid-1970s the admission rate increased again in adults and reached a peak in the mid-1980s. Subsequently, the rate decreased markedly among children (especially those < 5 y old), but remained stable among adults. Interestingly, the population rate for asthma admissions among persons ≥ 15 years old (10 per 10,000) are very similar in England and Wales today to those in 1984. The age-specific mortality rate increased during the late 1970s in adults: a trend that continued until the late 1980s, when a plateau of 14 deaths per 10,000 among persons ≥ 65 years old and 5.5 deaths per 10,000 among persons

45–64 years old was reached. The rates have gradually declined since then. No explanation has been provided for the increase in asthma deaths during the 1980s in the United Kingdom.

In summary, whereas the admission rate among adults remained stable in the United Kingdom since the mid-1980s, the mortality rate steadily decreased. Thus, much like the data from the United States, these findings suggest that the epidemiology (and perhaps the biology) of non-lethal severe asthma that requires hospitalization may differ from that of lethal asthma.

Worldwide Trends in Childhood Asthma

Although data on long-term trends in asthma prevalence are mainly available from developed countries such as the United States and the United Kingdom, longitudinal comparisons of asthma rates in almost 200,000 children, ages 6–7 years, in 37 countries, and over 300,000 13–14-year-olds in 56 countries, were recently reported as part of the International Study of Asthma and Allergies in Childhood.⁵ The surveys were conducted a mean of 7 years apart. The first survey took place between 1992 and 1998, and the second survey between 1999 and 2004. Apart from the worldwide scope of the study, an important merit of the International Study of Asthma and Allergies in Children is the availability of a succinct, standardized questionnaire, which was used (with appropriate and often validated translations) in all countries and in both surveys. An important source of bias in these types of comparative studies is regression toward the mean: countries in which prevalence was the highest in the first survey will tend to show a spurious decrease in prevalence during the second survey, even if there was no change in the underlying prevalence, and the opposite will tend to happen in countries with the lowest initial prevalence. To circumvent this source of bias, the authors used Bland-Altman plots, in which the mean change in prevalence between surveys is plotted against the mean prevalence in the 2 surveys.⁶

Wide variation was observed in the changes in prevalence of asthma symptoms in both age ranges (6–7 y old and 13–14 y old). However, there was a clear trend for asthma prevalence to increase in the younger age group, and this was true for all levels of mean prevalence. Similar trends were reported for allergic rhino-conjunctivitis and eczema in this age group, which supports the validity of the result for asthma symptoms. Among 13–14-year-olds an equal number of centers in different countries showed increases and decreases in the prevalence of asthma symptoms, though more countries with low mean prevalence had increases, and more countries with high mean prevalence had decreases. Conversely, allergic rhino-conjunctivitis showed a clear trend to increase during the 7-year interval in the 13–14-year-old group, and there were sim-

ilar patterns in countries with high mean prevalence and those with low mean prevalence.

Summary

In summary, the results for 13–14-year-old children in the International Study of Asthma and Allergies in Children go in the same direction as those reported for older children and adults in the United States: the prevalence of asthma symptoms appears to have plateaued some time between the mid-1990s and the beginning of this century.⁴ There is some indication that prevalence could even be decreasing slightly in the countries that had the highest prevalence and still increasing in those that had the lowest prevalence to start with. Whether this is a real phenomenon or a result of either residual regression toward the mean or random data drift is not currently clear.

Some Preliminary Conclusions and Speculations

Before definitive conclusions can be reached, some of the limitations of currently available data should be considered. Most of the surveys from which the above estimates were obtained were questionnaire-based and had no objective assessment of asthma status. Unfortunately, asthma is a heterogeneous condition at all ages.⁷ Among preschoolers, for example, 3 different asthma-like phenotypes, with different risk factors and prognoses, have been identified: transient early wheezers, persistent wheezers, and late-onset wheezers.^{8,9} Although clinical indices¹⁰ have been proposed to distinguish transient early wheezers (ie, children who wheeze before age 3 but whose wheezing episodes have subsided by age 6) from persistent wheezers (ie, children who wheeze before age 3 and still have wheezing episodes at age 6), there are no validated biomarkers that allow classifying subjects into different phenotype subgroups. This same conclusion is valid for the different asthma subphenotypes known to exist in adult life.¹¹ Therefore, it is not possible to know if the disease that appears to have recently plateaued in the United States, the United Kingdom, and other countries with a high prevalence rate, is the same condition that is still increasing in other countries with a lower prevalence.

Moreover, questionnaire assessment of prevalence is highly dependent on the judgment of the person responding to the questionnaire, and local understanding of asthma symptoms may be different in different countries and may change in a given country. Thus, the impact of drift and shift in the way asthma-like symptoms are labeled or perceived on the apparent changes in prevalence is unknown.¹² However, recent studies that used tests that indicate a propensity to develop asthma symptoms have confirmed and validated some of the trends observed in questionnaire responses. Addo-Yobo et al,¹³ for example, assessed chil-

dren 9–16 years old in Ghana, using the same methodology, 10 years apart. They found that between 1993 and 2003 the prevalence of exercise-induced bronchospasm significantly increased, from 3.1% to 5.2%, and the prevalence of sensitization to aeroallergens also doubled. This appears to correspond well with the increases in asthma prevalence observed among 13–14-year-olds in African countries in the International Study of Asthma and Allergies in Children,⁵ although, unfortunately, Ghana was not included among those countries.

Taken together, the data presented support the contention that the asthma symptom rate may have plateaued among older children and adults with asthma between 1995 and 2000,¹⁴ whereas in younger children it may still be on the rise. The “asthma epidemic,” spanning the decades 1960 through 1990, during which asthma prevalence markedly increased in the United States, the United Kingdom, and other developed countries, may thus have given way to a period of a persistently high but stable asthma rate. This pattern suggests that the factors that caused the asthma epidemic are still active but that most of the susceptible population has already been affected by these factors, thus saturating the potential population at risk. The epidemic is probably still actively causing new cases of asthma in countries with low prevalence, although it is unclear if the factors that are causing the epidemic in those countries are the same as those that caused the epidemic in countries in which the asthma rate has now stabilized.

Of particular importance are the discrepancies in the trends between the asthma hospitalization rate and the asthma death rate, both in the United States and the United Kingdom. Analyses performed on smaller databases (for example, in Singapore¹⁵) showed significant cross-correlation between decreases in these 2 rates during periods in which both declined. There is now convincing evidence from Canada and other countries that inhaled corticosteroids markedly decrease both the hospitalization rate and the death rate for asthma.¹⁶ Therefore, one could have expected similar changes in these rates in the United States and United Kingdom, but that was not the case. It is particularly urgent to better understand what caused the persistent asthma death rate (as a proportion of subjects with asthma) in the United States between 1980 and 1995 and between 2001 and 2004. In the latter period, 2 out of every

10,000 persons with asthma died of the disease each year, which is over 3,800 persons in 2004 alone.

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Discussion

Donohue: I was intrigued by the relationship of early-onset and persistent wheezing and lower lung function in adults followed for 26 years by Malcolm Sears’s group.¹ Did they control for maternal smoking in utero, in-

fections in the first year of life, and similar issues?

- Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349(15):1414–1422.

Martinez: The first thing is that these persistent wheezers *had* infections in early life; that’s what defined them. They started before the age of 3, and at that age it’s basically infection that’s the cause of their illness. With respect to the second part of your question, the answer is that it is im-

PLICIT in the definition that they had infection in early life.

Donohue: So you don't get air pollution or any of the other causes of asthma in older patients?

Martinez: I think they were all followed and had the same pollution background, in the same city. Once you control for that, we're interested in how is it that this thing develops. Of course they were exposed to different amounts of tobacco smoke, but that was controlled for, so it's not that this was modified by exposure to tobacco smoke. Exposure to tobacco smoke increases the likelihood of early asthma and it's also associated with lower lung function, but it was controlled in our studies. So we were trying to isolate the natural history.

If you started early with viral infections and then continue wheezing, then your lung function is going to be lower. That's why we had the what-turned-out-to-be revolutionary idea that we could change the natural course by treating very early, because perhaps we could avoid that initial inflammatory insult to the lung associated most likely with viral infections, but we couldn't.

Colice: Your theory was based on clinical manifestations, but with regard to lung development in children, as I understand it, during the first 2 years of life is when the alveoli multiply and septate, so airways really start to develop during age 6 through the early teen years. Is that correct?

Martinez: You can think about airways in 2 different terms. The whole set of airways subdivisions is already present very early in fetal life. The airways grow between the ages of 0 and 6 approximately proportionate to the growth of the lungs, which makes sense because you're trying to maintain a time constant: if your lungs are growing in a certain way, you want your airways to grow as fast, because

you'll have airways obstruction if they don't grow as fast. There is proportional growth of the airways and lungs at least up to the age of 6, and very fast growth of both. What is going on in these wheezing children, I think, is that their airways are lagging with respect to the growth of their lungs.

Colice: So when would be the worst time for a child to have an inflammatory airways disease?

Martinez: From 0 to 6, no doubt about it, and maybe during puberty, because during puberty they have huge increasing growth. In fact, there has been some discussion that there may be so-called dysanaptic growth during that period, that perhaps the airways don't grow as fast as the lungs. It's an old discussion, started by Jere Mead and his co-workers at the Harvard School of Public Health more than 30 years ago.¹ But without any doubt that period from 0 to 6 years is the most vulnerable. I would even say 0 to 3 years.

It is very interesting that some of the growth factors that are very important in the regulation of airway growth, such as VEGF [vascular endothelial growth factor] are produced acutely during airway inflammation. So it may be that the factors produced during inflammation interfere with the normal process. We only have about 25,000 genes, and these genes are used for different things. VEGF is a good example because it's a mediator of inflammation, but it also controls vascular growth, so it is very important for lung growth. It is this overlap between growth and inflammation that may be causing some of the changes in lung function that we're seeing in children who have chronic asthma in this age group.

1. Mead J. Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *Am Rev Respir Dis* 1980;121(2):339-342.

MacIntyre: It used to be said of childhood asthma that many would "outgrow it." Your data suggest that people don't outgrow asthma at all, but carry it for the rest of their lives.

Martinez: It all depends on what you call asthma. If you call transient wheezing asthma (which I don't like to call asthma), those children outgrow their symptoms. But if you have chronic asthma that starts in early life and then continues to be expressed, it is extremely persistent. There are some children, particularly males, who appear to outgrow their illness during puberty but then it comes back at about age 22.¹ It's like they had an asthma "vacation," but asthma is very persistent. If you've got it, you've got it.

1. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370(9589):758-764.

Sorkness: What have we learned from the PEAK [Prevention of Early Asthma in Kids] trial¹ that might give us some insight into treatment, especially about the phenotypic characteristics of the children who did well?

1. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in pre-school children at risk for asthma. *N Engl J Med* 2006;354:1985-1987.

Martinez: In the PEAK study what was interesting was that early in life the children who were most responsive to therapy were the ones with eosinophilia. We didn't collect sputum, but in our studies of acute asthma it was fascinating that there's a correlation between what we see in the sputum and in the peripheral blood. The peripheral blood may help determine if they're going to respond. The eosinophilic form of asthma is more responsive in that age group than is the non-eosinophilic form.

Our hypothesis about this, based on what we're finding in the PEAK study, is that perhaps the kids who have the more neutrophilic form, or non-eosinophilic—these days we're calling it neutrophilic—it's very interesting that neutrophils are biologically unresponsive to inhaled corticosteroids. Therefore it may be that we need to think about something that will work against neutrophils. Peter Barnes suggested theophylline for that purpose.¹ I've also heard him say very convincingly that zileuton is an anti-neutrophilic, so perhaps we should give zileuton for asthma in older patients. That issue is open for discussion.

Most interestingly, when we stopped the therapy, the kids who had peripheral eosinophilia had dramatically increased symptoms as soon as we stopped inhaled steroids. I would suggest that one of the lessons is that this very simple measurement of eosinophils in circulation gives us a very interesting predictor of the response to inhaled corticosteroids, at least in this age group.

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Myers: In your cohort study that Wayne Morgan published¹ you showed various phenotypes across time. And in the never-wheezed and

the transient wheezers, by the time they were about 16 years old about 5% of those groups were still having more than 4 symptoms a year. How do you define that and do those patients respond to β agonists during those symptoms?

1. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253-1258.

Martinez: I can't tell you if they do, because we are only following them, not treating them. One thing I can tell you is that those children respond to a bronchodilator when we bring them in and test their lung function. It's almost as if they have a mild form of "twitchiness" that makes them wheeze not that often; it's not very severe; it's this kind of very mild wheezing that you see in the winter, but I fear it's being called asthma and may be treated with inhaled steroids but perhaps it doesn't deserve it. It's a very mild kind of disease. We retrospectively looked at the severity, and it's the persistent wheezers who have the highest severity and the lowest lung function. That's obvious when you think about it, but it was good to confirm it once again. It's the combination of low lung function, bronchial hyperresponsiveness, and persistence of symptoms that causes the worst prognosis.

MacIntyre: You showed us the idea of trying to block allergens early in life, but what about the hygiene hypothesis that, if you are overly protective of children early in life, they don't get exposed to a certain minimum number of antigens, and their immune systems don't quite grow up and then they're more prone to asthma infections. Is the overly-protective parent doing more harm than good?

Martinez: I am going to respond indirectly to that. The hygiene hypothesis—that if you're exposed to bacteria and microbes in early life, you might get killed but you're not going to get allergies. I presume you may as well have allergies and not get killed. In any event, that's the hygiene hypothesis. There's also the hypothesis that increasing exposure to allergens in susceptible individuals will decrease the allergies because they'll become tolerant. The Immune Tolerance Network is funding a study by Patrick Holt in which they're giving large doses of house dust mites to children in early life. It's a fascinating study. The idea is that this will deviate their immune response against a TH2 [T helper cell 2] response. It will be interesting to see the results. Sometimes you don't get anything you expect; biology is very unpredictable.

MacIntyre: "What doesn't kill you makes you stronger."