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CURRENT CONCEPTS

The Asthma Epidemic

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The prevalence and incidence of asthma are very high in the Western world. There is widespread concern that the prevalence of asthma is still rising in developed countries, but the economic and humanitarian effects of asthma are probably greater in the developing world, where the prevalence is also rising. Primary prevention strategies to combat the asthma epidemic are therefore urgently sought, but they must be based on a sound understanding of the various determinants of the onset of asthma. In this synopsis of the temporal trends and determinants of asthma and associated features such as atopy, we seek to provide insight into the complex nature of this illness.

Time Trends

Diagnosis of Asthma

According to the Centers for Disease Control and Prevention, the prevalence of asthma among U.S. children increased from 3.6% in 1980 to 5.8% in 2003. Asthma is the third leading cause of hospitalization among persons under 18 years of age in the United States, exceeded only by pneumonia and injuries. Increases in the prevalence of asthma of similar or even greater magnitude were reported from other countries during the second half of the 20th century (Fig. 1A). For example, in 1964, 19% of Australian children were reported by their parents to have had asthma or wheezing at some time during their first 7 years of life; in 1990, such symptoms were reported for 46% of children. For many countries, there are no data on temporal changes in the prevalence of asthma before the 1990s (Fig. 1A). After the 1990s, estimates of temporal trends in the prevalence of asthma in several European and Asian countries are conflicting. In some populations, the prevalence of diagnosed asthma is still rising, whereas in others it appears to be stable or decreasing slightly (Fig. 1A). There are no clear differences in trends in prevalence between children and adults, between severe and mild asthma, or between developed and developing countries; however, there are few studies from developing countries.

Symptoms of Asthma

Trends in the prevalence of symptoms suggestive of asthma show greater variation than trends in the prevalence of diagnosed asthma (Fig. 1B). The prevalence of asthma symptoms increased in most countries up to the 1990s, but since then there has been no clear temporal pattern. The variability among countries may in part be attributable to differences in definitions of asthma symptoms, such as wheezing, shortness of breath, and asthma attacks. Recent data from the International Study of Asthma and Allergies in Childhood (ISAAC) phase 3 showed that in the mid-1990s, the prevalence of wheezing increased in most centers where the prevalence had been low and decreased or remained unchanged in most centers where the prevalence had been high.
No single instrument can be used to identify asthma with certainty. Asthma is a clinical diagnosis made by physicians on the basis of a patient’s medical history, physical examination, assessment of the reversibility of airway obstruction, and exclusion of alternative diagnoses that mimic asthma. In epidemiologic studies, questionnaires are used to ascertain whether subjects have had symptoms of asthma or have ever received a diagnosis of asthma from a physician. The prevalence rates of both symptoms and diagnoses of asthma are heavily dependent on an awareness of asthma in the population studied. In recent decades, asthma has received widespread publicity, education of the public about asthma has increased, and new medications for asthma have been introduced. These measures may have increased public awareness of asthma and the rates of reporting of the disease. In Scotland, the proportion of children reporting asthma symptoms who received a diagnosis of asthma increased from 28% in 1964 to 64% in 1999, a result suggesting that part of the increase in the prevalence of asthma is attributable to changes in diagnostic labeling. The magnitude of the resulting bias in different populations is, however, difficult to appraise.

**AIRWAY HYPERRESPONSIVENESS**

Airway hyperresponsiveness, the exaggerated narrowing of the airways after the inhalation of various stimuli, is a key feature of asthma. The difficulties with the diagnosis of asthma discussed above have prompted researchers to include airway challenges as an objective measure of asthma in their studies. The results are inconclusive, and no clear time trends in the prevalence of airway hyperresponsiveness have been seen in children or adults (Fig. 2). The variability in the results may be due in part to the different types of challenge tests used (pharmacologic and physiological), the low sensitivity of the tests, the difficulty of standardizing the tests conducted at different times and in different locations, and the variable nature of asthma and of airway re-

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**Figure 1. Changes in the Prevalence of Diagnosed Asthma and Asthma Symptoms over Time in Children and Young Adults.**

Data in Panel A are from Australia, the United States, Switzerland, Germany, the United Kingdom, Norway, Finland, Estonia, Poland, Italy, Spain, Israel, Singapore, Hong Kong, Taiwan, and Korea. Data in Panel B are from Australia, the United States, Switzerland, Germany, the United Kingdom, Norway, Finland, Estonia, Italy, Spain, Israel, Singapore, Hong Kong, Taiwan, and Korea.
sponsiveness. Measurements of airway responsiveness appear to reflect the activity and severity of asthma at the time of measurement rather than to define the prevalence of the illness over a lifetime or over a specific period; data on long-term prevalence may be better obtained by questionnaires.

ATOPY

Atopy, which can be detected by specific serum IgE or skin-test reactivity to environmental allergens, is often associated with asthma. The prevalence of atopy has increased over time in some populations, whereas in others there has been a decrease or a plateau in prevalence since 1990 (Fig. 3). Asthma and atopy can occur either independently or jointly in patients, in populations, and over time. In the United Kingdom,2,18 and Australia,4 the prevalence of both asthma and skin-test reactivity has increased, whereas in Hong Kong,39 Germany,11,12 and Italy,51 the prevalence of atopy but not of asthma has increased. In some populations, the prevalence of asthma associated with allergies has increased more than that of nonatopic asthma,39 whereas in others the prevalence of the two types of asthma has increased to a similar degree.39,24,25

Today it is still not known what factors cause asthma in a person with atopy or what factors cause atopy in a person with asthma.60

Several factors have been proposed to account for the increasing prevalence of asthma. It is agreed that genetic changes in populations would be too slow to account for such a rapid change in prevalence. Most information on the effects of environmental exposures on the risk of asthma comes from cross-sectional studies that do not take temporal changes into account. Robust data linking changes in the environment to changes in the prevalence and incidence of asthma over time are still lacking. Changing environmental exposures may not affect disease prevalence immediately. If exposures exert their effect in utero or early in life, changes in the prevalence of asthma may take more than a generation to become apparent.

**EXPOSURE TO TOBACCO SMOKE**

Some environmental exposures have rather consistently been shown to influence the incidence of asthma. The most consistent association is that with passive or active exposure to tobacco smoke. A thorough meta-analysis has concluded that parental smoking is very likely to be causally related to acute lower respiratory tract illnesses in infancy and to childhood asthma and wheezing.61 A number of studies have also shown that active smoking is associated with the onset of asthma in adolescents and adults.62-64

**EXPOSURE TO AIR POLLUTION**

There is sufficient evidence to suggest that air pollutants, such as ozone and particulate matter, decrease lung function, trigger exacerbations of asthma, and increase rates of hospitalization for asthma.65 Whether air pollution also contributes to the initial development of asthma remains unclear. Because the rates of asthma and atopy in areas of Germany with a high level of exposure to products of coal combustion have been found to be
much lower than those in less polluted areas, the focus of research has shifted toward pollution from motor vehicles. Children living within 100 to 400 m of motorways or within 50 to 90 m of major roads are at risk for wheezing but not airway hyperresponsiveness. The proportion of children living in such high-exposure areas, however, is rather small. The overall evidence that exposure to pollution from motor vehicles is a risk factor for asthma is thus relatively weak.

**Exposure to Allergens**

Exposure to environmental allergens has been analyzed in numerous studies over the past few decades. It seems likely that the level of exposure to allergens such as house-dust mites and cat dander affects a person’s risk for the development of IgE antibodies against these allergens. There is, however, more recent evidence to suggest that exposure to house-dust mites early in life is unlikely to be an important risk factor for the onset of asthma. Several prospective birth-cohort studies have found no association between increased levels of exposure to house-dust mites early in life and various phenotypes of childhood asthma. Furthermore, intervention studies have failed to find convincing evidence of a reduction in the risk of asthma among children 1 to 8 years of age after the implementation of allergen- and food-avoidance strategies. Some studies have found that exposure to pets early in life actually decreases the risk of asthma, but consistency among studies is lacking. Indoor exposure to allergens may, however, contribute to the persistence of symptoms among children with allergic asthma.

**Obesity and Diet**

Obesity is a major cause of morbidity that has been increasing in prevalence over the past few decades. The parallel trends in the increase of asthma and obesity may indicate a potential link between the conditions. There is increasing evidence relating body-mass index to the prevalence and incidence of asthma in both children and adults, although most consistently in adolescent girls. It is unlikely that the association is attributable to reverse causation — that is, that people with asthma exercise less because exercise induces symptoms of asthma. Rather, weight gain can antagonize the development of asthma. Weight loss by patients with asthma tends to improve lung function. Potential explanations for the association of obesity and asthma are that the development of both conditions is determined in early life, that mechanical factors promote symptoms of asthma, or that gastroesophageal reflux resulting from obesity induces asthma. Physical inactivity may promote both obesity and asthma. A British study found that trends in overweight and obesity did not explain the increase in the incidence of asthma from 1982 to 1994. The association between asthma and obesity may therefore be of recent origin, suggesting that recent changes in lifestyle and diet are now associated with both asthma and overweight.

Studies have examined dietary intakes of fruits, vegetables, cereals and starches, various fatty acids, vitamin A, vitamin C, vitamin E, minerals (sodium, magnesium, copper, zinc, and selenium), and antioxidants for possible associations with asthma. Diet is complex and difficult to measure, and standardized tools are still lacking. Variation
in methods of determining the frequency of intake, which individual foods are consumed, eating habits, and serum nutrient levels can introduce substantial misclassification, and the close correlations among the intakes of different nutrients make it difficult to identify independent effects. In cross-sectional surveys, a wide range of nutrients appear to have an effect on asthma outcomes. The evidence from prospective studies and randomized clinical trials, however, is far less consistent and conclusive. Maternal nutrition during pregnancy may have a role, but data on this subject remain scarce. Intervention studies promoting avoidance of cow’s milk and eggs during pregnancy have failed to protect the infants from asthma, and breast-feeding also does not protect children from asthma. Recent studies showing a positive association between breast-feeding and asthma may reflect adherence to recommendations for children at risk for asthma rather than breast-feeding’s being a causal factor for asthma.

EXPOSURE TO INFECTIONS

Over the past decade, the so-called hygiene hypothesis has received much attention. According to this hypothesis, the development of asthma is due in part to a lack of exposure to infections and microbial products early in life. There is widespread evidence that the number of older siblings affects the risk of hay fever and eczema: the risk decreases as the number of older siblings increases. Whether this effect is attributable to an increase in the number of infections transmitted by unhygienic contact with older siblings remains a matter of debate. Other, unknown factors associated with an increased number of pregnancies may also have a role in the development of atopy, supporting the importance of prenatal exposure for the inception of this condition.

The role of viral infections early in life in the development of asthma has been fiercely debated. Viruses are potent triggers of exacerbations of asthma, and the inability to restrict the symptoms of rhinovirus infections to the upper respiratory tract may be considered a hallmark of asthma at all ages. Moreover, infection with respiratory syncytial virus can result in bronchiolitis in infancy, which, if severe, further increases the risk of subsequent wheezing episodes up to school age. Host factors such as reduced lung function and immature immune responses at birth may contribute to the expression of asthma induced by viral infections. Population-based studies assessing infectious exposure either indirectly, by recording whether a child has attended day care, or directly, by performing serologic tests for viruses (hepatitis A virus and herpes simplex virus) and other microorganisms (Helicobacter pylori and Toxoplasma gondii), have found that exposure to infectious agents protects against asthma. Chronic infestation with helminths may also confer protection, but short-lived episodes of infestation may exacerbate atopic disorders. Much of the inverse association between infections and asthma may be attributable to atopy.

EXPOSURE TO MICROBIAL SUBSTANCES IN THE ENVIRONMENT

Microbial exposure may occur primarily in the gut, and antibiotic use may contribute to the inception of asthma by altering the gut microflora. Because asthma-like illnesses, particularly in young children, are still treated with antibiotics in many countries, there is an association between the use of these drugs and the risk of asthma. Only studies taking into account the indication for prescribing antibiotics and the use of antibiotics before the onset of asthma can adequately address the question of the association between antibiotic use and asthma, and studies conducted in this manner have not found such an association. Likewise, there is no evidence to suggest that vaccination appreciably affects the onset of asthma. The use of acetaminophen has also been linked to the onset of asthma, but the effects appear to be small and so far do not justify avoiding exposure to this drug.

Exposure to microbes can occur in the absence of overt infection. Viable germs and nonviable parts of microbial organisms are found in various concentrations in most indoor and outdoor environments. Exposure to environments rich in these substances, such as stables and barns of traditional dairy farms, has consistently been shown to significantly reduce the risk of asthma and atopy.

Differences in the level of microbial exposure may also in part contribute to differences in the prevalence of asthma between urban and rural areas, particularly in developing countries. Furthermore, objective measures of bacterial and fungal exposure have documented inverse asso-
associations with asthma and wheezing. Endotoxin, which is found in the cell walls of gram-negative bacteria, has two opposing effects: it protects against atopy but is a risk factor for nonatopic asthma and wheezing.

SYNOPSIS OF FINDINGS

The disparity and heterogeneity of findings in the asthma literature are daunting, reflecting the complex nature of the illness. A basic requirement for the demonstration of a causal relation between a given exposure and a disease is knowledge of the temporal sequence of events. Only exposures occurring before the first symptoms of an illness can influence its inception. In a large proportion of patients, asthma starts in the first years of life. New-onset asthma also occurs during puberty and later in adulthood, but many cases of asthma in adults represent the reappearance of symptoms in persons who were transiently free of problems during adolescence and young adulthood. The environmental exposure causing asthma is likely to be important during fetal life and the early years and during the period before the onset of asthma in adults and adolescents.

Any potential risk factor must eventually interact with an underlying, genetically determined pathway to result in the manifestation of disease. We do not fully understand the underlying mechanisms of asthma; they are likely to involve both inflammation and control of airway tone and reactivity. Asthma is probably not one illness, but a syndrome. The disease has different phenotypes with respect to its course and prognosis and its association with atopy. In infants with transient wheezing and in toddlers with nonatopic wheezing, self-limited airway obstruction develops after viral infection, whereas chronic, persistent asthma is more likely to develop in those with IgE-mediated wheezing. Asthma in adults includes phenotypes not seen in childhood, such as aspirin-induced and occupational asthma. However, these different phenotypes cannot readily be distinguished clinically. The disease is analogous to anemia, in which a number of different pathways related to congenital defects, dietary deficiencies, chronic infections, cancers, and autoimmune reactions all result in pallor and fatigue in affected patients.

Another aspect of the causation of asthma is the context in which exposures occur and interact with a subject's individual pathophysiological pathways. Variation in these pathways is determined by genes. Environmental exposures interact with these pathways, and these interactions can be detected through interactions between genes and the environment. However, these interactions do not occur in isolation. Pathways have more than one component, and the function of each component is determined by the gene or genes contributing to and regulating the processes. Not one but several genes involved in the construction and regulation of pathways are likely to contribute to the expression of a disease. If in fact more than one pathway leads to the development of asthma (as is the case with anemia), then not only many genes with small individual contributions, but also many environmental factors and gene–environment interactions will eventually be found to contribute to disease manifestation. Hence, different contexts in which a number of different exposures interact with various genetic backgrounds in a range of racial or ethnic groups will eventually result in changes in the incidence of asthma as a result of changes in pathways involving atopy, airway inflammation, airway hyperresponsiveness, or other still unknown factors (Fig. 4). The challenge in the years to come will be to integrate complex interactions between multiple exposures and numerous genetic variants to achieve an understanding of the causation of asthma.

CONCLUSIONS AND PRACTICAL IMPLICATIONS

There is evidence that, in some areas of the Western world, the prevalence of asthma may have plateaued. The environmental factors causally driving the temporal changes remain largely unknown. Therefore, there are few truly justified recommendations for the prevention of asthma. Avoidance of passive and active exposure to smoke is warranted for many other health reasons and also for asthma prevention, because the epidemiologic evidence strongly suggests a causal link between exposure to smoke and the onset of asthma. By contrast, many other proposed avoidance strategies, such as reducing allergen levels, implementing changes in diet, withholding vaccinations or treatment with antibiotic and antipyretic agents, administering probiotics, or even exposing...
children to pets early in life, are either ineffective or unverified as primary prevention measures. Our view, however, is that the rapid progress in the identification of protective microbial substances has great potential for the development of prevention strategies to combat the asthma epidemic.

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Figure 4. Effect of the Interaction between Various Types of Exposures and Various Genetic Backgrounds in a Range of Racial and Ethnic Groups on the Prevalence of Asthma through Pathways Involving Atopy, Airway Inflammation, Airway Hyperresponsiveness (AHR), or Other, Unknown Factors.

Data on farming environments are from Braun-Fahrlander and Lauener90; data on occupational exposures are from Mapp et al.95; data on mainland China are from Wong et al.96; data on inner-city United States are from Gruchalla et al.97; data on affluent countries are from Schaub and von Mutius,79 van Vliet et al.,67 Oosterlee et al.,68 Strachan and Cook,21 Strachan et al.,62 and Karmaus and Botezan85; data on eastern European countries are from Bjorksten et al.98; and data on developing countries are from Yazdanbakhsh and Wahyuni.88

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