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Day Care, Siblings, and Asthma - Please, Sneeze on My Child [Editorials]

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Parents generally agree that children who attend day care or who have older siblings

have more frequent infections. They may be surprised to learn, however, that this tendency may protect their younger children from asthma. In this issue of the Journal, Ball et al. [1] describe the relation between these surrogate markers of infection and the risk of asthma. Protection against the development of asthma or frequent wheezing in children 6 to 13 years old was linked to either day-care attendance during infancy or the presence of older siblings in the home. As two-year-olds, the children with either type of exposure were noted to have a higher frequency of wheezing than children with neither type of exposure. This increased frequency of wheezing was found to be correlated with a subsequent reduction in the relative risk of asthma.

The importance of these results is evident when they are placed in the context of the increasing prevalence of childhood asthma during the past two decades. A unified explanation for this increase has remained elusive. Equally perplexing is the wide range in the reported frequency of symptoms of asthma in children around the world, from 2 percent in China to 30 percent in areas of Britain and Australia. [2] Although there is a clear inherited predisposition to asthma, the rapid increase in its prevalence and the 15-fold disparity in reported symptoms among countries probably do not have a genetic basis. Studies in twins have indicated that many cases of asthma cannot be fully explained by genetic susceptibility and probably reflect the influence of environmental factors. [3]

Gene-environment interactions are thought to be important, if not essential, in shaping the phenotypic expression of asthma. Multiple risk factors have been linked to the occurrence of the disease; they include smoking by the parents, indoor exposure to allergens, absence of breast-feeding, and a diet containing low levels of n-3 fatty acids. [4] In prospective studies, early exposure to mite allergens has been found to correlate with the subsequent development of asthma. Yet neither genetic factors

alone nor exposure to allergens alone can explain the epidemic of asthma convincingly. This has led to speculation that alterations in lifestyle, such as the rise of indoor entertainment and the commensurate reduction in exercise and increase in obesity, may be associated with the higher frequency of asthma in more developed countries.

[\[5\]](#)

In many countries, the prevalence of asthma has increased in parallel with improvements in hygiene and health standards and with reductions in family size. As Ball et al. found, a larger number of older siblings has previously been reported to protect children against atopy. [\[4\]](#) A reduction in family size, however, by itself appears insufficient to explain the increase in the frequency of asthma. [\[6\]](#) A rural lifestyle, residence on a farm with animals near the house, or the presence of a dog in the house also protects against asthma. [\[2,4\]](#) A recent analysis of the influence of siblings and day-care attendance in children in eastern Germany mirrored the results reported by Ball et al., who studied children in Arizona; among German children 5 to 14 years old, the frequency of asthma was lower among those who had begun attending day care early in life than among those who had been enrolled in day care later. [\[7\]](#)

The relation between asthma and exposures in early life probably reflects the effect of these exposures on the developing immune system. In neonates, helper T cells respond to signals from the microenvironment that affect their conversion to either a Th1 or Th2 phenotype, each of which produces a distinctive group of cytokines. A predominantly Th2 phenotype has been consistently associated with the eosinophilic airway inflammation that is characteristic of allergic asthma. In response to an allergen, sensitized Th2 cells produce proinflammatory cytokines such as interleukin-4, interleukin-5, and interleukin-13, which stimulate IgE production and cause tissue eosinophilia and airway hyperreactivity.

The origins of asthma and other allergic diseases may lie in the uterine environment, in which the presence of Th2-type cytokines is required for successful gestation. At birth, allergen-specific mononuclear cells with a cytokine profile characteristic of Th2 cells are present in cord blood. Most children lose their fetally primed Th2 responses to inhaled allergens, and those responses are replaced by emerging Th1 responses. In children who have parents with atopy and in whom allergic symptoms develop, however, this transition is delayed, and Th2 responses persist. [8]

A common factor underlying the increased prevalence of asthma and atopic disease may be a reduction in early exposure to microbes, with a lasting influence on immune development. [9] An important signal for normal postnatal maturation of Th1-associated functions is exposure to microbes. Deprivation of these signals, particularly in infants of parents with atopy, may allow the neonatal Th2 responses to become established, a change that increases the risk of eventual asthma and atopic disease. Consistent with this hypothesis is the finding that mice raised in germ-free environments maintain a proinflammatory, Th2-type cytokine response to mucosally delivered antigens, in contrast to mice raised in a standard environment, in which Th1 responses and tolerance of these antigens develop. This process can be restored in germ-free mice if bacteria are introduced during the neonatal period, but not thereafter. [10]

Circumstantial evidence of a reciprocal relation among microbial infections, atopy, and asthma may be extrapolated from Australian Aboriginal populations, in which the incidence of asthma among children is very low but in which children have purulent respiratory infections almost constantly. In Japanese children, a reduced prevalence of asthma has been linked with positive responses to injections of bacille Calmette-

Guerin, lower serum IgE concentrations, and Th1-type cytokine responses. Atopy has been found to be negatively correlated with measles in populations in Guinea-Bissau and with hepatitis A infection in Italian military recruits. [4] It is uncertain whether viral respiratory infections - in particular, severe respiratory syncytial virus bronchiolitis - are associated with an increased risk of sensitization to allergens and an increased risk of asthma. The majority of evidence, including that presented by Ball et al., [1] indicates that the pattern of early increased wheezing with viral respiratory illness is not sustained at later times.

Questions remain concerning the interplay among host characteristics, the timing and nature of microbial and viral exposures, and a myriad of other environmental factors with regard to the development of asthma. Cohort analyses, such as that in the study by Ball et al., complement advances in basic science by providing insight into naturally occurring events that can change the epidemiologic features of a disease. For those of us who share the furtive guilt of having left marginally ill toddlers at day care, these findings also offer a sense of relief. We were perhaps only doing our part to restore the Th1-Th2 balance and to stem the rising tide of asthma and allergic disease.

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