

Structurally Unsound? Why Airways Become Asthmatic

Acute wheeze in infancy and the preschool years negatively impacts an individual's quality of life, but even more importantly, it is a sign of life-long abnormalities in lung health. We know that lung function shortly after birth is negatively impacted by intrauterine exposures such as nicotine and environmental pollution, which adversely affect lung structure, birth weight, and immunological function in early life. Similarly, exposures such as nicotine and indoor and outdoor pollution, and major respiratory infections negatively impact lung growth in childhood (1). Furthermore, early multiple aeroallergen sensitization and acute attacks of wheeze are markers for an abnormally reduced lung growth trajectory and later atopic asthma (2), and a series of overlapping birth cohort studies (reviewed in Reference 1) showed that reduced lung function before school age results in failure to attain normal airway growth and tracks into late middle age. It is increasingly recognized that the roots of chronic obstructive pulmonary disease lie antenatally and in the preschool years, and if we are to make any impact on the burden of this killing disease, we must focus on very early lung health. By the time adulthood is reached, the problem is largely unfixable.

The recent *Lancet* Commission called for our research focus to move beyond palliating the symptoms of asthma to preventing its development in the first place (3). We do know that there is scope for intervention, as two important studies showed that highly significant reductions in childhood wheezing illnesses could be achieved (4, 5). The Amish and Hutterite communities both fled religious persecution in Europe and came to the United States. Despite having virtually identical genetic backgrounds, the Amish people have a much lower prevalence of atopy and asthma than the Hutterites. The Amish use traditional farming methods, whereas the Hutterites have embraced modern methods. Dust in the Amish environment has very different bacterial components and more LPS compared with that in the Hutterite environment. It was shown that Hutterites have more peripheral blood eosinophilia, whereas the Amish are neutrophilic and have a suppressive monocyte phenotype and higher median levels of innate, but not adaptive, cytokines, and these findings could be recapitulated in a murine model (4). A large randomized controlled trial in the COPSAC (Copenhagen Prospective Studies on Asthma in Childhood) cohort in Denmark that compared fish oil with olive oil (as a placebo) supplementation in pregnancy resulted in improved respiratory outcomes at age 5 years in the offspring (5). However, we lack detailed knowledge of the pathways that lead apparently healthy babies to established school-age asthma, and thus we cannot design appropriate interventions. We also lack positive predictive indices that would enable us to target therapies. There is a pressing need for a major research drive in preschool children to try to remedy this.

In this issue of the *Journal*, Bonato and colleagues (pp. 458–466) report on the follow-up of a large cohort of preschool children

who were investigated in early life with the use of fiberoptic bronchoscopy (6). They aimed to determine which features on initial endobronchial biopsy were predictive of asthma. In a multivariate analysis, they found that only reticular basement membrane thickening, and not eosinophilic inflammation, was associated with a diagnosis of asthma a median of 5 years later. Also associated with subsequent asthma were low birth weight and the symptom pattern of multiple trigger wheeze. The major strengths of the study are the prolonged follow-up and the very careful attempts to characterize airway disease in childhood. Clearly, and unavoidably, the patients studied were a highly selected group, and extrapolation of the findings to more mildly affected children should be done with caution.

How does this large study advance the field? One difficulty is the definition of “asthma.” If a preschool child has eosinophilic airway inflammation and structural changes, then that child has an airway treatable trait (eosinophilic inflammation) and should respond to inhaled corticosteroids (3). Most would apply the diagnostic label of eosinophilic asthma at that time, so is it reasonable to say that these features were more prominent in those who developed asthma? It is also clear from the authors' Figures 2–4 that although there is statistical significance in their measurements in subjects who did or did not have an asthma diagnosis at follow-up, the overlap between the groups is such that even if it were feasible to use bronchoscopy widely to determine prognosis in preschool wheeze, these measurements would not help the management of the individual patient. What is of marked interest is that in the multivariate analysis, eosinophilic inflammation no longer predicted asthma. However, reticular basement membrane thickness, an early marker of airway wall remodeling, remained an independent predictor, together with low birth weight and multiple trigger wheeze.

Very few invasive studies have been conducted in this age group. Saglani and colleagues also found that children with severe multiple trigger wheeze had airway wall eosinophilia and structural changes at a median age of 29 months (7), but in a different cohort, even those with atopy and reversible airflow obstruction at a median age of 12 months had an essentially normal airway wall (8). Follow-up of the former group suggested that increased airway smooth muscle, another structural airway wall change (which could not be measured by Bonato and colleagues), but not airway eosinophilia or reticular basement membrane thickness, was associated with a school-age diagnosis of asthma (9), whereas in the 1-year-old cohort, no pathological feature predicted outcome at age 8 years (10). The findings of these studies suggest that, far from inflammation being the root cause of structural airway wall changes, it may be that the primary event is remodeling and inflammation is secondary—a very novel paradigm indeed. This would account for the signal failure of

the early use of inhaled corticosteroids to modify the disease process (11–13), and the predictive power of very early airway hyperresponsiveness, presumably the result of altered airway geometry, long before any evidence of infection or inflammation, for long-term asthma outcomes (1, 14).

So where do these results emphasizing airway wall changes in early life lead to next? Both Bonato and colleagues and Saglani and colleagues highlight the need to focus our attention on the very earliest years of life if we are to prevent the development of asthma. Neither group was able to determine bronchoscopic markers predictive of a later asthma diagnosis at an individual level, nor, indeed, if we are to make progress in the community, is bronchoscopy the answer. We need to determine the pathways to asthma and find accurate, noninvasive biomarkers of risk and response to interventions. The increasing use of breath-based techniques and the use of upper-airway cell sampling as a surrogate for the lower airway offer promise (15). But above all, the lessons of the Amish/Hutterite and fish-oil studies show us that asthma is not set in stone in genes and epigenetics, and that the environment makes an important contribution that can be modulated. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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