Growing, Growing, Gone: The Double Whammy of Early Deprivation and Impaired Evolution of Lung Function

The achievements of the Wright brothers in constructing a Heath-Robinson aircraft that flew a few hundred yards have been subsumed by intercontinental jet and even supersonic travel. Similarly, the Childhood Asthma Management Program (CAMP) initially recruited children with relatively mild asthma and proven airway hyperresponsiveness to a treatment trial comparing either regular budesonide or nedocromil with as-needed short-acting bronchodilators (1). The subjects' asthma was then so mild that it was rightly deemed ethical not to treat the majority with inhaled corticosteroids (ICS). As with the Wright brothers, the initial trial question has become of minor historical interest only, but the continued follow-up and detailed study of the CAMP children, now young adults, has led to a stream of important insights into the nature and evolution of childhood asthma and lung growth.

In this issue of the *Journal*, Izadi and colleagues (pp. 776–787) have studied the CAMP trial participants in adolescence and young adulthood to determine the factors that predict evolution from relatively mild to severe asthma (2). The huge strengths of the study include the longitudinal, prospective design and an amazing 65% retention rate of their subjects. They report that 12% and 19% of patients in late adolescence and early adulthood, respectively, had severe asthma, but only 6% were consistently severe. The most important factors predicting evolution to severe asthma were reduced FEV_1/FVC ratio, adverse lung growth trajectory (reduced growth and early decline), and maternal smoking in pregnancy, as well as being of the weaker sex (male). Of note, maternal smoking in pregnancy is not merely associated with reduced lung function soon after birth (3); it also increases the child's subsequent vulnerability to environmental challenges, such as smoking (4) and occupational irritants (5), and is associated with more rapid lung function decline (6). The CAMP data presented in this issue of the *Journal* have not only prognostic importance but also mechanistic implications that I propose should lead to a change in public health policy.

Any study of severe asthma immediately poses the question of how rigorously it has been possible to determine who has true severe, therapy-resistant asthma and who has difficult asthma, just needing to get the basics right (7). Obviously, clinical manifestation of asthma depends not just on the severity of the underlying airway disease but also on fluctuating social and environmental factors, as well as comorbidities (8). Thus, the changes in severity status in the CAMP follow-up may reflect, for example, changes in adherence to ICS rather than a change in fundamental asthma pathobiology. This, however, could not be determined, because the study did not have the scope to do the sort of detailed, multidisciplinary evaluation that such children merit (9). Nevertheless, mild childhood asthma becomes truly severe in probably 5–10% of patients, according to other data cited by the authors, and this is useful prognostic information for parents. It also underscores that mild to moderate childhood asthma is not a trivial condition but may have long-term severe consequences and needs to be taken seriously. Furthermore, measuring lung growth will help to identify risk of progression to severe asthma, and this domain of risk needs to be an important part of asthma guidelines, as has been argued elsewhere (10).

Hence, the present study (2) turns the spotlight firmly onto lung growth as the root of deteriorating asthma and, yet again, the importance of early life deprivation. Although type 2 inflammation is very important in the pathophysiology of childhood asthma, and antiinflammatory treatment with ICS has revolutionized asthma outcomes, there was no association between biomarkers and associations of type 2 inflammation (peripheral blood eosinophil count, total IgE, sensitization, and exposure to aeroallergens) and outcome (their Figure 3). Interestingly, it is possible that the *absence* of childhood hay fever predicted later severe asthma. Being randomized to antiinflammatory treatment in the original CAMP study did not impact risk. Therefore, although ICS treatment is clearly the cornerstone therapy for reducing asthma attacks and controlling symptoms, it seems highly unlikely that treating inflammation is going to impact lung growth, and new approaches are needed. Although of course biologicals such as omalizumab and mepolizumab were suggested by Izadi and colleagues (2) as therapies that might modulate remodeling, the studies of inflammation and remodeling in early life do not suggest that inflammation is the root cause of change in airway caliber but rather that inflammation and remodeling are parallel processes (11). Furthermore, the logistics of getting agreement from families and funders for the preventive treatment of a child with perhaps only mild asthma with long-term injections of an expensive biologic are not trivial. Finally, the importance of these CAMP data is enhanced because the double whammy of both impaired lung growth (12) and childhood severe asthma (13) are associated with long-term risk of chronic obstructive pulmonary disease, meaning that addressing lung growth and remodeling is of urgent and fundamental importance.

It is one thing to identify a problem and quite another to be able to address it. The difficulties are twofold; the first is that we know too little about the biology of normal and abnormal airway growth and how to modulate it, and the second is that by the time most children in the community as opposed to the research laboratory (14) can perform reliable spirometry, it is almost certainly too late to intervene to improve lung growth (15). There is a tantalizing hint that there

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may be a pathway(s) from Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort data (16), which showed that those with late puberty had catch-up growth, but currently, all we can do is to try to prevent further deterioration in lung function by minimizing exposure to, for example, pollution, tobacco smoke, vaping, and addressing obesity. However, perhaps there is an alternative public health strategy to at least be considered. There is a strong relationship between parental and offspring spirometry (17); around 30% of the variance in offspring spirometry relates to the parental measurements. So should we be measuring spirometry in school children to delineate a population whose own children will be at risk of asthma and long-term worse respiratory and all-cause morbidity and mortality? That way preconception and antenatal preventive measures could be applied in the time window wherein prevention may be most effective. This would need buy-in from the public, but given that by the time the child first walks through the school gates it is currently too late to improve lung function and long-term outcomes, new radical approaches are needed if the multimorbidity burden of COPD is to be ameliorated. We should not of course give up on trying to protect the current generation, but later interventions are just not good enough, and we need a change in focus. And although it may be a politically unpopular statement, until childhood health inequalities and social deprivation are firmly tackled, the flood tide of adult respiratory disease will not be turned back. ■

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