Formula one: best is no formula

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Breast is best; formula is worst: in between, there may be a typically British compromise!
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"Begin at the beginning," the King said, very gravely, "and go on till you come to the end: then stop" (Lewis Carroll, Alice in Wonderland). Sometimes, however, ignoring this excellent advice may be beneficial to the editorialist. So, starting at the end, how do patients reach a point of premature airflow obstruction (or chronic obstructive pulmonary disease (COPD) to those who think that an arbitrary physiological ratio in spirometric measures of lung function is a disease, even though it may be within the normal range for age)? For a long time, the prevailing view was that most individuals achieve normal or near-normal maximal lung function in early adult life, following which those who go on to develop COPD suffer a rapid decline as a result of various environmental exposures (predominantly smoking) [1]. However, the crucial importance of the level of lung function attained in early adulthood has been highlighted in a recent study, which demonstrated that the level of lung function in early adult age, at its physiological plateau, is as important in the genesis of COPD as its rapid decline in later years. The manuscript describes two trajectories to a reduced forced expired volume in 1 s/forced vital capacity (FEV_1/FVC) ratio [2]. In the first, there was failure to reach the normal plateau of maximally attained spirometric function in early adulthood (at age 20–25 years), with a subsequent normal rate of decline. In the second, the group attained a normal plateau, but declined more rapidly. Individuals who did not reach the expected lung function plateau had a 26% chance of going below the "magic" FEV_1/FVC of 70%, while among those in whom a normal plateau was reached, the risk was 8%. Importantly, both trajectories contributed equally to the community burden of COPD. Of note, neither this nor any of four other major studies of decline in lung function with age [3–6] managed to find consistent associates of accelerated lung function decline (including smoking, politically unpalatable though this statement may be). Indeed, data from the CAMP [7] and Tucson cohort (which identified a group of individuals with a persistently low lung function trajectory between ages 11 and 32 years, which comprised nearly 1 in 10 participants) [8] confirmed that abnormal lung growth patterns are established early in life. Clearly, starting at the end turns the spotlight firmly on the beginning: early life, which is where efforts at prevention of COPD must be focused if they are to have any chance of success.

The evidence is mounting that genetic and early environmental effects and their interactions are pivotal in causing abnormal lung growth, but also an accelerated decline of spirometry decades later. Based mostly on cross-sectional data, several factors in childhood, including obesity [9], lower socioeconomic status [10], pre-term birth [11], exposure to residential soil silt [12], rhinovirus infection [13], cigarette smoking and short duration of breast feeding [14] have been reported to be associated with diminished adult lung function. For example, the ECFS study identified five indices of childhood deprivation as predictors of reduced FEV_1, accelerated decline in FEV_1, and increased risk of COPD. These were maternal, paternal and childhood asthma; maternal smoking; and severe childhood respiratory infections [15]. Underlying these risk factors are a mix of other environmental exposures, genetic factors and their interactions, operating

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ante- and post-natally, and probably even trans-generationally [16, 17]. There are numerous candidate genes; for example, ADAM-33 is important in antenatal airway branching morphogenesis [18], with effects being modulated by maternal atopy [19], and polymorphisms are related to preschool lung function [20] and also to an accelerated decline in lung function [21]. Genetic variants in *VEGF-A* are associated with low lung function in childhood, and this effect may persist into adulthood [7], while polymorphisms in CC-16 are not only associated with worse childhood lung function and failure to attain the normal plateau, but also accelerated decline in adult life [22].

The long-term adverse environmental effects of nicotine exposure and environmental pollution are well known, and have recently been reviewed [23, 24]. That adverse effects can operate ante- and post-natally is well known, with the COPSAC group [25] suggesting that 60% of airflow obstruction at age 7 years is post-natal and 40% antenatal, offering at least the potential to move from hand-wringing to action. Such action hitherto meant continued assaults on the tobacco and e-cigarette industries, and continued attempts to engage politicians in reducing air pollution, but not much else. To move forward, we desperately need to understand the mechanisms of the early inception of respiratory morbidity and diminished lung function. It must be emphasised that the factors responsible for disease onset are very different from those responsible for disease persistence and severity (which is indirectly confirmed by early pathological studies [26], and the abject failure of inhaled corticosteroids to modify the natural history of asthma and wheezing in childhood [27–29]).

The role of breast feeding in terms of respiratory benefits to the baby and its effect on allergy has been controversial, whatever the undoubted merits of the practice in other health domains. In this issue of the *European Respiratory Journal*, the CHILD study investigators report the beneficial effects of breast feeding on wheezing illness in infancy among the children of asthmatic mothers [30]. The strengths of the study include the large numbers of babies studied, and the prospective recording of symptoms and feeding practices. The conclusions are greatly strengthened by the demonstration of a dose–response effect; the longer the infants were breast fed, the lower was the prevalence of wheezing, and those exclusively breast fed also wheezed less. Importantly, it was the introduction of formula milk, rather than complementary food that abrogated the protective effects of breast feeding. The potential effects on allergy are also important, and in this regard the data are reassuring. The early introduction of complementary foods to prevent allergy did not interfere with the protective effects of breast milk on wheezing illness. Mothers are uniquely privileged to be in receipt of all sorts of usually mutually contradictory and hopelessly impractical advice from all and sundry, and whether adding in complementary foods is a good thing or not was not addressed by this study. Dare it be suggested that, in the absence of hard evidence, mothers should be left to their own devices when it comes to the introduction of allergenic foods?

There are, of course, difficulties in the interpretation of these data. The maternal asthma diagnosis may be questionable, because diagnosing asthma and wheezing disorders is difficult and many adults and children are misdiagnosed [31, 32]. Secondly, the word "wheeze" is used notoriously imprecisely by parents [33–36], and studies relying purely on questionnaires may be misleading. It is a pity that the authors did not have access to video-questionnaires to bolster the diagnosis of wheeze [34, 35]. It is also by no means clear what the first-year respiratory illnesses betoken. Their implications and epidemiology are highly variable [37], and it is likely that the underlying pathology is very different from childhood and adult asthma [26]. The trend for a stronger protective effect of breast feeding among boys is interesting but merely a trend, and should not be over-interpreted. More prolonged follow-up of this cohort is needed to understand these challenging data.

The next crucial question is about the mechanisms of the observed protective effect of breast feeding, and how the introduction of formula milk may abrogate this protection. It is of considerable interest that the observed effects did not appear to be due to the reduction in the prevalence of respiratory infections, but only the babies' response to them. The authors confirmed the expected adverse effects on respiratory outcomes of several risk factors described previously, including maternal smoking and asthma, and late pre-term delivery [38–40]. However, they did not look for any effects of low birthweight and rapid weight gain [41], which may be one obvious way in which formula feeding may be contributing to respiratory symptoms.

There may be other potential mechanisms, which open potentially fruitful lines of enquiry. Studies in Amish and Hutterite communities provide fascinating evidence on how early environmental exposures can lead to key differences in the innate but not adaptive immune systems, and dramatically reduce the prevalence of asthma [42]. The present study has shown that exclusive breast feeding is not necessary for protection, but only the absence of formula feeding. So, is there some factor in formula milk that induces a switch of the innate immune system to a more pro-allergic condition? Or is it the loss of protective microbial exposure among formula-fed infants which can profoundly modify babies' immune responses at different levels? After all, it is the consumption of fresh raw cow's milk (yes, even in the first year of life) that is associated with strong protection against asthma and allergies among children growing up on farms [43]. Does this give us

further clues to the pathways involved and more hope of modulating them, than just sending pregnant women off in droves to deliver their babies in stables (although the historical precedent for this is celebrated annually by many)? Is the situation now ripe for intervention studies in humans, and innovative studies in a neonatal animal model (although perhaps formula feeding mouse pups could be a challenge to even the most determined investigator) [44]?

The public health implications are stark. The extent of use of formula feeds described in this study is nothing short of a disgrace. Although it is clear that there are some women who cannot breast feed for the best of medical reasons, for example HIV infection, and therefore perforce have to use formula feeds, there is no reason at all why more than half these mothers did not breast feed for more than a year. Those nurses, midwives, health visitors and primary care paediatricians who are responsible for the care of babies need to take a long hard look at themselves and ask why their promotion of breast feeding is such a failure. Women with asthma need to understand the benefits to their child of avoiding formula milk. Would it be too radical to suggest formula milk should be made prescription only for children of asthmatic mothers? Perhaps, but something needs to be done; and that effectively and soon.

In summary, we are currently heading for a respiratory Armageddon of COPD deaths. The urgency of tackling this tsunami of death is only matched by the utter feebleness and complacency of our public health responses. If the tide is to be turned, it must be turned early in life, even antenatally. We need a "Right from the Start" programme for lungs (http://right-from-the-start.org/), with buy-in from all those responsible for the care of pregnant women and babies and children, as well as policy-makers. Smoking, e-cigarettes and environmental pollution must be tackled much more effectively, and the potential effects of formula feeds also highlighted. The CHILD investigators have done us a service by pointing out that breast feeding has its part to play in reducing infant morbidity, and the many long-term cohort studies all have the same message: if you are wrong from the start, you remain wrong forever. Of course, formula milk is not as sinister as nicotine, but nor is it as pure and innocent as the driven snow, and maybe it should carry a health warning for specific subgroups. Overall, the message is stark and clear – get it right in little lungs or it will go wrong and stay wrong in big ones.

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