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# Howling for the moon

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Rennard and Vestbo have sounded a ringing call to arms (*see page 643*).<sup>1</sup> Instead of trying to make minor improvements in the rate of decline of spirometry in patients with chronic obstructive pulmonary disease (COPD), they call for an all out effort to find a cure. Their arguments have attractions, but we believe that the evidence shows it would be easier to hatch out chickens from a plate of scrambled eggs than to cure COPD in adults.

COPD is defined for epidemiological and most clinical purposes by spirometry. When the underlying pathological changes cause spirometric measures to cross over a given threshold COPD is diagnosed. However, the crossing of this threshold depends on two factors, first the peak lung function attained as a young adult and secondly the deterioration with ageing accelerated by smoking and probably other environmental exposures.

First, some notes of caution. Spirometers are dangerous instruments in many contexts, not least public health. Extensive distal airway obstruction will not be detected by spirometry, and 'a normal' first second forced expired volume (FEV<sub>1</sub>) is very far from being reassuring that all is well. By the time the potential patient with COPD has lost FEV<sub>1</sub>, extensive and irreparable lung destruction will be present. Although well performed spirometry has a high reproducibility, extensive distal airway obstruction can occur before it is detected. Furthermore, the normal range of spirometry is very

wide and so an individual who starts off with very good lung function can still be in the normal range, but for them it is a major loss of lung function.

Peak lung function is reached at 16–18 years in females and 20–25 years in males.<sup>2–3</sup> The height of that plateau depends on two factors: the starting point for airway function immediately after birth, and the rate of growth between birth and the time of the physiological plateau. The starting point will be determined by antenatal factors, of which maternal smoking, maternal atopy and maternal nutrition are the most important;<sup>4</sup> however, other factors such as antenatal exposure to air pollution,<sup>5</sup> maternal diabetes, chorioamnionitis and maternal antibiotic use may also be significant.<sup>4</sup> There are likely to be significant gene by environmental interactions, for example null mutations in maternal and fetal GST (glutathione S-transferase) exacerbate the effect of tobacco smoke exposure on the fetus.<sup>6</sup> After birth, a number of cohort studies have delineated what happens to lung function. In the largest and most convincing, there is partial catch up in lung function until age six years in the group with impaired lung function at birth, transient wheezers, but they never attain normal lung function, even twenty years later. It is important to note that no intervention has ever been shown to achieve catch up in growth of airway function at any time period in any context. Factors which likely impact on outcomes include maternal smoking; maternal, paternal and childhood asthma; and childhood respiratory infections. Indeed, combinations of these childhood factors lead to lower lung function in adult life, with no catch-up; a faster rate of decline in lung function; and a greater risk of COPD. Thus, the signal from childhood disadvantage is at least as strong as that from heavy smoking. Exposure to air traffic pollution has been shown to reduce the rate of normal lung growth.

Furthermore, in the CAMP study, 25% of subjects with mild childhood asthma had reduced growth in airway function irrespective of allocated treatment. Premature delivery and low birth weight are other important factors which impact on long-term lung health. Finally, in all the childhood cohort studies, lung function at best tracks; there is no evidence of any catch-up growth after the preschool years.

It is clearly difficult to determine whether a particular factor operates to the detriment of the individual antenatally or postnatally, or both, but the key message is that a combination of factors may lead to young adults entering the decline phase in lung function at a substantial disadvantage. The best known cause of an accelerated decline in lung function is smoking, but other factors are likely to be important, including air pollution, exposure to biomass fuels in low and middle income countries, and tuberculosis. The evidence about childhood factors causing an accelerated decline in lung function is equivocal. Some studies have shown that a low lung function as a young adult is associated with decline in lung function, but others have not. Aberdonian children with 'wheezy bronchitis' (or episodic viral wheeze, as it would now be termed), who by extrapolation from other studies probably had airway obstruction in the early years, had an accelerated rate of decline in spirometry in middle age.<sup>7</sup> Again, although this accelerated decline can be halted by, for example, stopping smoking, no treatment has ever been able to ameliorate the normal physiological rate of decline in spirometry, thus undoing the damage of the past.

Finally, the latest long-term follow-up of the Melbourne asthma cohort has just been reported in abstract form.<sup>8</sup> First, nearly half the subjects with severe childhood asthma recruited at age 10 years had COPD at age 50; and severe asthma in childhood gave a stronger signal than later smoking. Secondly, when the whole cohort was rephenotyped at age 50, those with COPD had (unsurprisingly) lower lung function, which tracked right back to the school age years. Other data which

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unequivocally established that COPD has its roots in early life came from David Barker's group,<sup>9</sup> illustrating the timeless principle that if you cannot measure something accurately, measure it over and over again. They used death certificate data from a huge number of communities to show that the infant mortality rate from bronchitis and pneumonia was closely correlated with standardised mortality rates for COPD 50 years later. In other words, if for public health reasons we want to identify a high risk group for COPD, the primary school is the place to do it.

So in summary, why do people get COPD? A major reason is because significant damage has occurred in a substantial proportion of individuals in early life. Onto this substrate, smoking and the use of biomass fuels puts them over the edge to develop COPD.

So what does this mean for a cure for COPD? In adult life, palliation is all that is going to be possible, at least until we can use stem cells or other techniques to reconstruct obliterated airways. We will need to know how to recapitulate the normal first trimester airway developmental process in adult life, a tall order indeed. We agree that pharmacology may ameliorate the inflammatory processes, but all that will do is slightly reduce the speed at which the train is careering over the cliff—it cannot restore health. The remorseless logic is that prevention or cure can only be found in early life, or even preconception.

There is much talk of identifying a 'high risk' group of adults, and intervening to try to prevent COPD. However, a much more radical approach is surely needed; by the time the child has entered primary school, it is probably already too late,<sup>10–13</sup> never mind adult life. So should we begin in the antenatal booking clinic? Given the increasing evidence of trans-generational, epigenetic influences on asthma prevalence,<sup>14</sup> even this may be too late. However, as a start, the answers to three simple questions to the mother defines a high risk fetus<sup>15</sup>:

1. Do you have asthma
2. Do you smoke?
3. Does the father have asthma (if it is known who he is!)?

What interventions can be put in place? Smoking cessation is always indicated, but there may be added urgency in mothers who know their unborn baby already has major risk factors; avoidance of pollution, which even antenatally may be harmful; and close monitoring of fetal growth. Postnatally, the sort of multifaceted

intervention which shows benefit in adults should be instituted,<sup>16</sup> with a big emphasis on the avoidance of passive smoke exposure, and environmental pollution. Socio-economic status is another association of poor lung function; dare we suggest to governments that encourage education for all by increasing the costs that poverty and diseases such as COPD go hand in hand? The twin challenge is to maximise normal lung growth potential, and prevent the accelerated rate of decline thereafter, and smoke and pollution exposure are both important in this regard.

So rather than trying to find ever more expensive medications, or reaching for surreal means of growing a new lung, we need really effective public health measures, and here is the problem. The detrimental effect of tobacco has been known for >50 years, but it has taken governments all over the world many years before active legislation on the sale and advertising of tobacco has been instituted. It has taken even longer for measures such as smoke-free restaurants, bars and workplaces. There is still much to be done in terms of effective anti-smoking legislation. However, damage to the lungs goes beyond this, and particulate pollution and airborne pollution related to the internal combustion engine is important. However, governments have shown little appetite for seriously dealing with this.

Rather than diverting money to stem cell research, which is unlikely to be of widespread use for such a common disease as COPD, we should campaign for the following:

- Even more effective tobacco legislation, including prevention of passive smoking exposure for children in cars and at home. Legislation works<sup>17</sup>—or, if it does not, let us prorogue parliament at once!
- Recognition that airborne pollution is a human rights issue—if you live in a Western city you cannot avoid air pollution.
- The roots of much disease are in poverty—and yet it is not only low and middle income countries that are affected. All major Western countries still have substantial poverty affecting children.
- Finally, invest in research to understand early lung development, and devise interventions to operate before the lungs are shot to pieces.

Or instead, shall we 'nudge'<sup>18</sup> while Rome goes up in smoke (literally), and

continue to spend money on treatments which can only palliate the effects of the underlying problem rather than lead to a cure?

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