

with normal or near normal lung function are not just pretty pictures but are clinically important because they identify individuals at high risk of COPD progression and lung cancer. In such individuals it may be highly cost-effective to intervene with aggressive tobacco treatment programmes and with close observation and follow-up.

On 4 November 2010 the US National Cancer Institute (NCI) released the initial results from the National Lung Screening Trial (NSLT), showing a reduction of 20% in lung cancer mortality and a reduction of 7% in total mortality among ex-smokers and current smokers screened with low-dose CT compared with those screened with chest x-rays.¹⁵ Notwithstanding the costs associated with HRCT scans, these and other data on screening CT for lung cancer will probably lead to an exponential increase in the number of thoracic HRCT scans that will be performed over the next few years. This will present new opportunities for clinical care and research for the respiratory community. In addition to using these CT scans as tools for lung cancer screening, the data by Mohamed Hoesein *et al* suggest that chest physicians can also use them to identify high-risk patients who are likely to experience rapid COPD progression and to aggressively treat them for tobacco addiction (if they are current smokers) and to institute therapies for their COPD when clinically appropriate. With agreed protocols to acquire and analyse the images, the widespread use of thoracic CT scans may also provide

a tremendous opportunity for researchers to understand the natural history of COPD in individuals with 'subclinical' COPD (based on CT only) and its associated comorbidities such as lung cancer, cardiovascular disease and osteoporosis. Perhaps, by doing so, we can maximise the value of screening lung CT scans and make these pretty pictures worth a thousand words (or dollars)!

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Every breath you take

Allan R Glanville

To paraphrase the ubiquitous warning applied to the perverse products of the tobacco industry, 'breathing may be dangerous to your health', in particular if you are a lung transplant recipient. This is especially true if you live near a major road in a region with high levels of traffic-related air pollution. Alone among solid organ transplants, the lung allograft is exposed to the ambient environment with

every breath. Some environments are toxic, some more so, and the paper by Nawrot *et al* in *Thorax* (see page 748) presents a compelling argument that traffic air pollution is a strong component of the toxic environmental risk which has measurable and deleterious effects on pulmonary allograft function and recipient survival, accounting for 28% of deaths.¹ Specifically, this landmark study reports for the first time the relationship between traffic air pollution and the development of the bronchiolitis obliterans syndrome (BOS) in a large and well-characterised sample of lung transplant recipients from a region where air pollu-

tion levels are high by global standards. BOS is the major risk factor for death after lung transplantation, so it is not surprising that exposure to air traffic pollution, defined by residential proximity to a major road, was also a risk factor for death after transplantation. Importantly, other potential risk factors were rigorously examined to prevent confounding and the relationship was highly significant regardless of whether distance categories from a main road were expressed as a dichotomous or continuous variable. In addition, there was a strong relationship between distance from a main road and the finding of a bronchoalveolar lavage neutrophilia, an association that implies but does not prove an aetiological link. Importantly, it makes biological sense. The findings are illuminating and may explain in part some of the reported

Correspondence to Professor Allan R Glanville, The Lung Transplant Unit, Xavier 4, St Vincent's Hospital, Victoria Street, Darlinghurst, NSW 2010, Australia; aglanville@stvincents.com.au

differences in the incidence of neutrophilic bronchoalveolar lavage between countries and perhaps the short-term beneficial effects of macrolide therapy in selected recipients reported by the same group.² We do not know the effect of relocation from a polluted environment, how long the inflammatory response takes to resolve, if at all, or the effect of prolonged hospitalisation, presumably in a hermetically sealed, air-conditioned environment. Traffic pollution is the elephant in the room that is at once dangerous but largely ignored as an unavoidable factor of contemporary life in large city urban environments. Of course, most hospitals capable of providing a lung transplantation service also reside in centres of great population density with proximity to airports and main roads. There are occasional bucolic exceptions to this rule, but it is the residence of the recipient which is important. Whether the residence of the lung organ donor is also relevant has not been addressed, but perhaps the seed has already been sown for some recipients at the time of transplant.

The lung allograft is already hampered by denervation, reduced mucociliary function, infection of the allograft from community-acquired respiratory viruses as well as endogenous and other pathogens, assault by gastric and biliary contents due in part to gastric stasis related to surgery, inevitable size and possible gender donor–recipient mismatch plus a host of other known and unknown risks. Is there any wonder pulmonary allograft survival is so limited? It is a wonder enduring survival is ever achieved, but it is and therein lies part of the mystery and challenge of the discipline of lung transplantation. Moreover, as we move into the fourth decade of technically successful lung transplant surgery, it behoves us to provide greater assurances to our patients that enduring survival is possible and regularly achievable. A critical mass of transplant recipients now exists, which, coupled with an ever-expanding and improving cohort of scientific researchers, lends hope to the dream of achieving better, if not complete, tolerance of the allograft, which should increase the probability of long-term survival. The current work identifies one possible modifiable risk but more importantly highlights a potential pathogenic mechanism that can be addressed. Simply put, the hypothesis that is yet to be fully tested commences when toxic respirable particles principally derived from vehicle exhaust fumes, especially diesel, initiate an irritant

response within the transplanted lungs. The irritant response involves the generation of an acute neutrophilic bronchitis/bronchiolitis depending on particle size and density of exposure. As a secondary phenomenon, upregulation of antigens on epithelial surfaces leads to expression of both HLA class 1 and 2 antigens plus or minus other cryptic antigens such as collagen-V and, indirectly, bronchial microvascular endothelial antigens.³ This prepares the way for allorecognition and a subsequent alloimmune response mediated by clonal expansion of memory B cells driving an antibody-mediated inflammatory response targeted at the airway epithelium and/or microvascular endothelium. While the short-term effects of the neutrophilic bronchitis/bronchiolitis may be ameliorated by neomacrolide therapy, the damage is done, the die is cast and the long-term outcome is death within 2 years of subsequently developing chronic allograft dysfunction, irrespective of its phenotype.⁴ Paradoxically, lymphocytic bronchiolitis, diagnosed by typical lymphocytic bronchiolar wall infiltrates, is also associated with the finding of a neutrophil predominant bronchoalveolar lavage, even in the absence of demonstrable infection.⁵ It is interesting to speculate to what degree and by what mechanism lymphocytic bronchiolitis takes part in this continuum.⁶ Evidence suggests that community-acquired viral infection in particular may trigger a decline in allograft function that is out of proportion to the severity of the initiating viral illness and given the stereotypic capacity of the lung to respond to insult and injury, it is conceivable that severe air traffic pollution may trigger a similar response. Cellular as well as antibody-mediated inflammatory responses often coexist. Unfortunately, in the crucible of clinical practice where it is so important to secure a precise diagnosis, our tools to examine the allograft tissue are blunt. Sampling error, which invalidates grading in between one-third and one-half of cases, and poor interobserver correlation of grading of transbronchial biopsies work against accuracy of tissue diagnosis.⁷ In particular, it is the so-called normal biopsies where sampling error, usually due to insufficient tissue, is most relevant. Notwithstanding these limitations, future studies are needed to fully examine the relationship between trigger factors and the stages of development of allograft dysfunction and whether any therapy can halt progression. The final pathway, however, is obliterative bronchiolitis,

which brings full-circle the observations of Ross *et al* in 1997, also from a city noted for temperature inversion and photochemical smog, that steroid therapy alone was inefficient in arresting the progress of lymphocytic bronchiolitis despite the occasional brave beat of a distant drum.^{8,9}

Despite all the difficulties inherent in assessing the influence of multiple time-dependent values that so beset the determination of risk factor assessment after (lung) transplantation, the current study provides a sufficiently robust examination of the available data to support a strong association with the development of BOS, even if we do not know precisely when the risk begins. Critically, it would appear that another mortality risk has been identified. Now we just need a solution; we cannot all live on an island by the sea!

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