Air pollution and infection in respiratory illness

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The detrimental effects of air pollution on health have been recognized for most of the last century. Effective legislation has led to a change in the nature of the air pollutants in outdoor air in developed countries, while combustion of raw fuels in the indoor environment remains a major health hazard in developing countries. The mechanisms of how these pollutants exert their effects are likely to be different, but there is emerging evidence that the toxic effects of new photochemical pollutants such as nitrogen dioxide are likely to be related to infection. This review discusses the relationship between air pollution and infection and will explore some of the mechanisms of how both could act synergistically to cause respiratory illnesses especially in exacerbating symptoms in individuals with pre-existing respiratory conditions such as asthma and chronic obstructive pulmonary disease.

A lesson from history

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It is recognized that severe air pollution episodes have occurred in the UK since the early 17th century, but with rapid industrialization, such episodes became more severe and more frequent towards the 19th century. Legislation at this time led only to a reduction in smoke from industry, and difficulties in implementation gave little improvement in air quality until the early 20th century. Severe smog episodes through industrial and domestic combustion of solid fuels (coal) occurred during calm, winter weather. Between 1948 and 1962, eight air pollution episodes occurred in London, but the now well described 'Great Smog' episode in December 1952 was the most significant. Smoke concentration rose >50 times above the average limit, and at the National Gallery visibility was poor enough for individuals not to see their own feet. An estimated excess death toll of 4000 occurred during this period, a three-fold increase

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over the expected mortality rates for the time of year. Most deaths were among infants and elderly people. Similar episodes of severe air pollution in the United States after the Second World War and in Belgium in 1930 had aroused public concerns about the health effects of air pollutants.

Increased public and parliamentary concern led to effective legislation. In the UK, subsequent Clean Air Acts of 1956 and 1968 and similarly the Clean Air Act of 1970 in the USA had considerably reduced air pollution from stationary sources from homes, commerce and industry. Both the emission of smoke then sulphur dioxide (SO_2) fell dramatically. However, it is now accepted that any air quality benefits have been at least partially offset by increasing emissions of other visible and photochemical pollutants from mobile 'sources' such as car exhaust fumes. There is increasing awareness that new stationary sources in homes are also sources of the newer photochemical pollutants such as the oxides of nitrogen from unflued gas cookers and heaters[1].

The historical perspective of traditional air pollutants continues to interest contemporary air quality researchers. During the 1952 smog episode, there was a sharp rise in hospital admissions and visits to primary care physicians, but recent re-analysis[2] of the mortality data indicates the number of deaths was underestimated and was nearer 12,000. While the majority of deaths occurred in individuals with chronic respiratory disease, the steep rise in mortality was sustained for several months and did not drop immediately after the resolution of the smog episode (as might be expected if it were simply a triggering phenomenon). This raises issues of the mechanisms of how these pollutants may have caused the deaths perhaps through acidification with sulphuric acid that overwhelmed the buffering capacity of the lungs, interaction with other pollutants, toxic effects at subsequently lower and hitherto 'normal' levels of pollutants or perhaps more importantly, interaction with other co-factors such as infections. It has been assumed that many of the exacerbations of pre-existing respiratory illnesses that occurred during the smog episodes were the result of acute respiratory infections (ARIs). Recent evidence from developing countries confirms the direct exposure–response relationship between indoor air pollution by combustion of biomass fuels generating high levels of particulates and sulphur dioxide with increased acute respiratory infections in adults and children[3]. These observations have renewed interest in how air pollutants may exert their toxic effects through interaction with infection. This brief historical review of air pollution events confirms that air pollution by whatever mechanism can kill and equally importantly, that with sufficient public interest and the political will, effective legislation can reduce the mortality effects of such pollutants.

Combustion of biomass fuels and infections

Acute respiratory infections are the leading cause of the global burden of disease accounting for more than 6% of worldwide disease and mortality in developing countries[4,5]. Acute lower respiratory infections were attributed to have caused up to 4 million deaths worldwide from 1997 to 1999[4]. In developing countries, smoking amongst women is rare and outdoor pollution is restricted to larger cities yet both women and children suffer a huge burden of respiratory illness, largely through ARIs, which are responsible for nearly a third of all deaths in children under 5 years old[6]. Poor sanitation, low birth weight and poverty contribute to the causes of infections but the combustion of biomass fuels remains a rapidly growing problem. The main source of indoor air pollution globally is the combustion of biomass fuels (wood, dung, charcoal) as this is the main source of domestic energy. They produce small amounts of energy but large amounts of indoor pollutants, often emitting 50 times more pollutant concentrations than energy equivalent natural gas[7]. The often poor ventilation and dispersion characteristics of dwellings in developing countries allow pollutant concentrations to rise further and indoor concentrations of particulates between 500 and 100,000 $\mu g/m^3$ are not uncommon[3,8], and levels of indoor particulates 20 times greater than those due to cigarette smoking have been described[8]. Combustion of biomass fuels emits a variety of pollutants including particulates (PM_{10}), nitrogen dioxide (NO_2), carbon monoxide (CO), sulphur dioxide (SO_2) and hydrocarbons. Several studies from different parts of the world provide an indication of indoor pollutant concentrations, and whereas there are no internationally recognized standards for indoor air quality, the WHO estimates the number of people exposed to unacceptable levels indoors to exceed the number exposed to unacceptable levels of outdoor pollutants in all of the world's cities collectively.

The evidence for a relationship between indoor pollution and respiratory infections in developing countries is clear and has been recognized for at least two decades. The elderly, cooking mothers and the very young who spend most time indoors are likely to be at highest risk. Infant girls in Gambia whose mothers carried them on their back while cooking had more respiratory infections than girls not carried on their backs[9], children in Zimbabwe with recurrent pneumonia were more likely to come from homes where wood was used for fuel[10], and infants and children in Nepal who reported more time spent next to stoves suffered more life threatening episodes of acute respiratory infection[11]. The effects of these indoor pollutants on chronic respiratory illness in cooking women has also been reported with rates of chronic bronchitis of 18% in women who have never smoked[12] and rates of COPD of >30% in women over 50 years of age in Kashmir[13].

The effect of biomass fuel combustion has also been studied in developed countries. Children from Arizona, USA from homes using woodstoves for heating and cooking were four times more likely to suffer physician confirmed ARIs[14]. The Harvard Six Cities Study reported the use of wood stoves to be associated with a 30% increase in respiratory symptoms ranging from chronic cough to asthma in children aged 7–10 years[15]. The importance of indoor pollution in children has recently been reviewed[7].

Contemporary indoor and outdoor pollutants and infections

The combustion of fuels indoors in homes from developed countries produces a variety of pollutants. The main (and most consistently reported) pollutant among them is nitrogen dioxide which is produced in both indoor and outdoor air from sources such as unvented gas stoves and motor cars, respectively. There is an increasing body of evidence to suggest that exposure to this pollutant is linked to respiratory disease in children and adults in the developed world, although until recently, less has been known about the potential mechanisms involved. Many of the epidemiological studies of outdoor NO_2 exposure have found associations between exposure to the pollutant and health effects, often at levels well below current WHO guidelines. These health effects have included accident and emergency room visits[16,17], hospital admissions[18,19], mortality[20,21], increased symptoms[22,23] and reduced lung function[24,25]. The APHEA project (Air Pollution on Health: European Approach) incorporated data from 15 European cities, with a total population in excess of 25 million people. An increase of 50 $\mu g/m^3$ NO_2 (1 h maximum) was associated with a 2.6% increase in asthma admissions and a 1.3% increase in daily all-cause mortality[26]. There are many methodological issues that complicate interpretation of outdoor exposure studies such as exposure misclassification, confounding, co-linearity and insensitive measures of health effects. Nonetheless, this study strongly suggested a role for NO_2, or other pollutants for which NO_2 is a marker, in precipitating acute exacerbations of respiratory disease, although it has been difficult to separate the individual effects of the pollutant from the complex mixture of pollutants found in outdoor air.

With the recognition that indoor combustion sources contributed significantly to NO_2 levels inside homes and to personal NO_2 exposure, a number of studies have focused on indoor exposures. In most of the investigations, exposure to indoor pollution or NO_2 has been classified on the basis of the presence of a gas stove or other major source of fuel combustion in the home, and there have been fewer studies where actual levels of NO_2 or other pollutants indoors have been recorded, and even

fewer where personal exposure has been estimated or directly measured, consequently some of the evidence has been inconsistent. Methodological limitations of the studies can readily explain the lack of definitive data, in particular in terms of misclassification of exposure and health outcomes and the incorrect (and therefore inaccurate) grouping of subjects with regard to exposure and disease. Although some studies have measured indoor NO_2 levels at fixed points, our own observations confirm that neither fixed site monitoring nor use of categorical variables such as gas or electric cooking accurately predict personal NO_2 exposure[27]. We have also confirmed that personal NO_2 exposure (at least in children) is not consistently related to either outdoor or indoor NO_2 exposure[28]. In considering the effects of indoor NO_2 exposure, information from a wide range of cross-sectional and longitudinal studies was brought together in a meta-analysis that estimated that the odds ratio of respiratory illness in children exposed to a long-term increase of 30 $\mu g/m^3$ in NO_2 exposure (comparable to the presence of a gas cooker) was 1.20[29], and up to 1.29 in children aged 5–6 years and 1.60 in infants[30].

The link with infection

There has been a series of studies alluding to the link between infection and air pollution particularly by nitrogen dioxide. Two studies investigated the incidence of croup (laryngo-tracheo-bronchitis usually due to influenza or parainfluenza viruses) and air pollution. The effects of NO_2, TSP (total suspended particulates) and SO_2 exposure were investigated in more than 6000 paediatrician-reported cases of croup and more than 4500 cases of 'obstructive bronchitis' in five German cities over 3 years[31]. Increases in TSP and NO_2 levels of 10 and 70 $\mu g/m^3$ were associated with a 27% and 28% increase in cases of croup, respectively. In illustration of the point made earlier, the close relationship between TSP and NO_2 levels did not allow their causal effects to be separated. In three other German towns[32], levels of SO_2, NO_2, CO, O_3 and dust were analysed with 875 cases of croup over a 24-month period. There was a significant association between croup frequency and the daily means of NO_2 for the peak period between September and March (the peak virus season), and with daily NO_2, and CO for the whole year. Another three cities in Finland from 'high' and 'low' pollution levels were studied over a 12-month period including 679 cases and 759 controls[33]. The annual mean concentration of NO_2 in the more polluted city was 15 $\mu g/m^3$ higher. The odds ratios for one or more upper respiratory infections in children in the polluted city *versus* those in the less polluted cities were 2.0 in the younger age group and 1.6 in the older age group. The authors did not separate the

effects of the individual pollutants in the analyses. In another case-control study of outdoor NO_2 in Stockholm, 197 children admitted to hospital because of wheezing bronchitis (reasonably assumed to be of infective aetiology) were compared with 350 controls. Time-weighted personal NO_2 exposures were estimated based on outdoor levels. The risk of wheezing bronchitis was significantly related to outdoor NO_2 exposure in girls ($P = 0.02$) but not in boys, and presence of a gas stove in the home appeared to be a risk factor only for girls.

More recently, several studies have suggested that air pollution may modify symptoms in individuals who may already be infected. Short-term effects of SO_2 and particulate matter (but with low acidity) were studied in 89 children with asthma for 7 months. Exposure to elevated levels of air pollution was associated with decreased peak expiratory flow rates, increased respiratory symptoms, increased school absence and fever, and increased medication use. Furthermore, there was evidence that exposure to air pollution might have enhanced the respiratory symptoms while children were experiencing respiratory infections[34]. In another study, the impact of air pollution on 321 non-smoking adults was investigated recording the daily incidence of respiratory symptoms over a 6-month period. The incidence of lower respiratory tract symptoms was related to the 1-h daily maximum ozone levels (OR = 1.22). The use of a gas stove in the home was also associated with lower respiratory tract symptoms (OR = 1.23), and the effects of ozone were significantly greater in individuals with a pre-existing respiratory infection[35]. Another study investigated the relationship between use of anti-inflammatory asthma medication and susceptibility to the effects of air pollution in 22 asthmatic children from non-smoking households. The associations between air pollution (mainly particulates) and symptoms were notably stronger in 12 asthmatic children who were not taking anti-inflammatory medications *versus* 10 subjects who were[36]. Another study examined specifically short-term indoor NO_2 exposures at school and in the home in 388 children aged 6–11 years. Exposure to NO_2 at hourly peak levels of the order of $<160\ \mu g/m^3$ compared with background levels of $40\ \mu g/m^3$ was associated with a significant increase in sore throat, colds and absences from school, although infection was not confirmed[37]. Also, significant dose–response relationships were demonstrated for these four measures with increasing levels of NO_2 exposure.

The body of evidence thus strongly suggests a link between air pollution and severity of illness associated with respiratory infection, and that individuals with pre-existing lung disease may be at greater risk. The majority of the studies of air pollution and infection have been conducted in children, although until recently studies had not clarified the exact nature of the respiratory illness and infection. There now is good evidence of such a link in children with pre-existing asthma. However,

the link with chronic obstructive pulmonary disease in adults has been less clear. Time-series analyses from Australia, Europe and North America suggest an association between air pollution and admissions to hospital for adults with COPD. An increase in daily maximum 1-h concentration of NO_2 and particulates was associated with a 4.60% and 3.01% increase, respectively in admissions for COPD in Sydney[38]. Another study of hospital admissions in Birmingham, UK, reported associations between PM_{10} and all respiratory admissions, pneumonia and deaths from COPD without a threshold effect[39]. A recent time series study from Rome investigated the relationship between air pollution levels and admissions for respiratory diseases over 3 years. A same day increase in outdoor NO_2 was associated with a 2.5% increase in all respiratory admissions per interquartile range (IQR) change. The effect of NO_2 was stronger on acute respiratory infections (4.0% increase) and on asthma among children (10.7% increase). A similar increase in carbon monoxide was also associated with a 2.8% increase in admissions for all respiratory admissions, a 5.5% increase for asthma and a 4.3% increase for COPD[40]. Further data from the APHEA project in six European cities of differing climates, has also shown[41] that a variety of pollutants including SO_2, black smoke, NO_2, total suspended particulates and ozone were associated with daily admissions for COPD with low relative risks ranging from 1.02 to 1.04. Another study from Minneapolis-St. Paul reported that an increase of 100 $\mu g/m^3$ in daily PM_{10} was a risk factor for admissions for pneumonia (RR = 1.17) and admissions for COPD (RR = 1.57). Similarly, an increase of 100 $\mu g/m^3$ in daily ozone concentration was associated with admissions for pneumonia (RR = 1.15)[42].

This array of studies of indoor or outdoor pollutants and acute respiratory infections (or respiratory symptoms in general) in children and adults suggests a relationship but none have confirmed infection microbiologically but instead relied on clinical criteria based on symptoms or use of health services. Consequently little is known of the spectrum of infectious agents or whether these pollutants increase susceptibility to infection or whether they exacerbate pre-existing morbidity following infection.

We have confirmed that respiratory tract viral infections are the major precipitants of acute exacerbations of asthma in children[43] and that episodes of viral infection are strongly associated in time with increases in hospital admissions for asthma[44]. In the former study human rhinoviruses alone accounted for 50% of exacerbations. If adequate virus detection methods are used, rhinoviruses and respiratory syncytial virus are detected in the vast majority of children (>80%) and infants (up to 100%) admitted to hospital with acute upper and lower respiratory illnesses. These data demonstrate that acute episodes of upper and lower respiratory illnesses in predisposed children both in the community and in those admitted to hospital are related to virus infections. Most of the epidemiological indoor pollution studies have alluded to the presence of respiratory infection as

the health effect following NO_2 exposure, although very few studies (including those from the developing world) had until recently attempted to confirm the presence of infection microbiologically.

Our own recent observations provide the first direct evidence of a link between upper respiratory virus infections, personal NO_2 exposure and the severity of asthma exacerbations in children. This study is unique so far, in that it confirmed the presence of infection microbiologically. A cohort of 114 asthmatic children aged 8–11 years prospectively recorded daily upper and lower respiratory-tract symptoms, peak expiratory flow (PEF), and measured personal NO_2 exposures every week for up to 13 months. Nasal aspirates were taken during reported episodes of upper respiratory-tract illness and tested for infection by common respiratory viruses and atypical bacteria with RT-PCR assays. Severity of associated asthma exacerbations was analysed in relation to high *versus* low NO_2 exposures in the week before the viral infection. There were significant increases in the severity of asthma symptoms with 60% increased severity for all virus and >200% for respiratory syncytial virus infections for high compared with low NO_2 exposure in the week before the start of the virus-induced exacerbation. The highest category of NO_2 exposure was also associated with more severe falls in peak expiratory flow with virus infection by up to 75%. These effects were observed at levels within current air quality standards[45].

Controlled exposure and infection studies

There is a wealth of literature on the effects of controlled photochemical pollutant exposure (O_3, NO_2, SO_2) alone and lung function effects in healthy individuals and those with pre-existing lung disease. Inhaled O_3 provokes a dose-dependent fall in lung function and an increase in bronchial hyper-responsiveness to histamine. These responses vary considerably between individuals and surprisingly, little difference has been observed between subjects with asthma and healthy individuals after O_3 exposure. Inhalation of high concentrations of SO_2 provokes acute airway bronchoconstriction in normal subjects whereas lower concentrations provoke the same response in asthmatic subjects. The response is usually rapid, and maximal effects are seen within 5 min and usually resolution is within 15–30 min. Given that SO_2 was one of the main pollutants implicated in the London smog episodes, these short lived broncho-provocant effects are unlikely to explain why the deaths associated with the worst smogs were maintained for several months after resolution of the pollution episodes. Inhalation of NO_2 at higher concentrations induced no change in resting lung function in either normal or asthmatic subjects

exposed to concentrations of 1880 μg/m^3 or less[46]. Bronchial hyperresponsiveness has been shown to increase only modestly in normal subjects exposed to >1880 μg/m^3 NO_2, and in about a third of studies in asthmatic subjects. In short, controlled exposure studies show largely modest effects on lung function and the pattern of response does not explain the epidemiological evidence, or the mechanisms of how these pollutants may interact with infectious agents.

There have been only a limited number of studies on the effects of controlled pollutant exposure and infection in humans largely through methodological difficulties and ethical constraints. There are a few studies that have suggested an interaction with infection. Three studies have investigated alveolar macrophage function after exposure to oxidant pollutant exposure *in vivo* and infection *in vitro*. In one study, nine volunteers were exposed to >1000 μg/m^3 NO_2 continuously or interspersed with three 15 min peak levels of >3500 μg/m^3 NO_2 in a sequential double blind randomized fashion (each subject served as their own control)[47]. Alveolar macrophages obtained by broncho-alveolar lavage after exposure were incubated with influenza virus. Two patterns of response were found after continuous exposure; alveolar macrophages from four of the nine subjects showed depressed inactivation of the virus [cells from these four subjects demonstrated an increase in interleukin-1 (IL-1) production after NO_2 *versus* air], whereas five showed no difference compared with control values. There were no differences from the intermittent peak exposure group. This indicates that differences in susceptibility to infection after oxidant pollutant exposure could occur in a larger population. Another study investigated the effects of high NO_2 exposure (9400, 18,800 or 28,200 μg/m^3) *in vitro* on alveolar macrophages obtained from 15 subjects[48]. After stimulation with influenza virus, both air and NO_2 exposed cells released increased amounts of IL-1 (indicating macrophage activation), but there was no significant difference between groups. The results indicated that human alveolar macrophages are resistant to injury by NO_2 *in vitro* and that toxicity effects of NO_2 may require local factors in the lung. In another 10 subjects exposed to >3500 μg/m^3 NO_2, alveolar macrophages obtained by lavage showed a 42% reduction in ability to phagocytose *Candida albicans* and a 72% decrease in superoxide production, superoxide production being important in phagocytosis[49].

A study using 152 young volunteers reported exposure to 1880 or 3760 μg/m^3 NO_2, for 2 h a day for 3 days and intra-nasal challenge with influenza A virus immediately after exposure[50]. Despite only one of the volunteers developing any symptoms, 91% were infected in the NO_2 exposed subjects as determined by virus recovery and/or antibody titres compared with 71% of air-exposed controls. This difference was not, however, statistically significant. As infected subjects did not become ill, the study could address the effect of NO_2 exposure on infection but not on the

severity of illness. These findings indicate, but do not prove, that oxidant pollutants may play a role in increasing susceptibility to respiratory virus infection.

Mechanisms of interaction between infection and air pollution

The lung defence mechanisms against inhaled particles and gaseous pollutants include innate mechanisms such as aerodynamic filtration, mucociliary clearance, particle transport and detoxification by alveolar macrophages, as well as local and systemic innate and acquired antiviral immunity. In particular, alveolar macrophages provide an innate defence mechanism against bacteria and viruses. There is increasing experimental evidence that pollution exposure adversely affects lung defence mechanisms. Virus particles are ingested by phagocytosis and, in common with epithelial and other virus-infected cells, macrophages produce interferons which potently inhibit viral replication. Macrophages will also contribute to the neutralization of viral infections by removing the debris of the destroyed, virus-containing, cells and by presenting viral antigens to T-lymphocytes. In addition to the resulting humoral immune response, cell-mediated responses such as the development of cytotoxic T-lymphocytes (capable of destroying cells infected with virus) play an important role in the control of many viral infections of the respiratory tract. Many of these functions can be modulated by exposure to NO_2 and other pollutants in experimental models.

Animal infectivity models

It has now been almost 40 years since the 'infectivity model' was developed. This linked the effects of pollutants on pulmonary antibacterial activity following pollutant exposure with disease and mortality as end-points in animals. The majority of studies have been carried out using rodents, particularly mice, on the basis that the lung defence mechanisms of rodents and humans are sufficiently similar to permit their use as a surrogate. Some investigated various alveolar macrophage functions *ex vivo* but the great majority have used acute exposures to determine the concentrations of NO_2 at which antibacterial defences are overwhelmed. Different exposure regimes whereby animals have been challenged with the infectious organisms either before or after exposure to varying concentrations of NO_2, have also been used. For example, exposure to NO_2 occurred before infectious challenge in mice, whereas others were exposed to NO_2 at 1, 6 and 24 h *after* an infectious challenge. In all

instances, mice exposed to NO_2 either before or after the bacterial challenge showed increased mortality[51]. In another study, mice were challenged with *Staphylococcus aureus* and then exposed to NO_2 for 4 h: pulmonary bactericidal capacity was progressively impaired in groups exposed to 7100 μg/m^3 NO_2 or higher[52]. Short-term exposures to NO_2 and murine cytomegalovirus (MCMV) infection were investigated by Rose *et al*[53] studying a number of parameters including macrophage viability, *in vivo* and *in vitro* phagocytosis by macrophages and systemic cell-mediated and humoral responses. The minimum inoculum of viral particles capable of reliably producing infection was much lower in mice exposed to NO_2 compared with air-exposed animals. Another study addressed the risk of re-infection after NO_2 exposure. Animals were exposed to high doses of NO_2 or clean air during primary infection with MCMV. This produced infection in all animals. Thirty days later, animals were re-inoculated with the virus. The number of re-infected animals in the group which had been exposed to NO_2 was 11/20 compared with 1/22 amongst air-exposed animals, suggesting that NO_2 exposure damages the development of virus-specific immunity following a primary infection[54]. The finding is supported by the observation that splenic lymphocytes obtained from NO_2-exposed animals 30 days after primary infection failed (in contrast to lymphocytes from air-exposed animals) to proliferate in response to MCMV antigen.

Impaired bronchial immunity

Collective findings from both animal and human models provide some evidence of alterations in local bronchial immunity; acute exposure to oxidant pollutants results in ciliostasis in both the upper[55] and lower airways[56] which may prevent the nasal and bronchial mucosa filtering inhaled particles such as aero-allergens, bacteria or viruses delivered to the airway. In the studies by Devalia and colleagues (carried out in the absence of anti-oxidant protection), exposure of cultured human bronchial epithelial cells to NO_2 concentrations of >1000 μg/m^3 reduced ciliary beat frequency and caused ciliary dyskinesis. The reduction in muco-ciliary activity following NO_2 exposure up to 4700 μg/m^3 has been confirmed in a study of 24 healthy subjects *in vivo*[57]. Studies investigating single exposures to NO_2 have found increases in mast cells, lymphocytes and natural killer (NK) cells in BAL fluid[58]. Studies of repeated exposure to 7520 μg/m^3 NO_2 (on six occasions, alternate days) have shown evidence of impaired local bronchial immunity by a reduction in total macrophages, B cells, NK lymphocytes, peripheral blood lymphocytes and a reduction in the T-helper-inducer/T-cytotoxic-suppressor ratio in alveolar lavage[59].

Alveolar macrophage function

Evidence from animal and human studies suggests that alterations in alveolar macrophage function are important in the increased risks of infection. Activated macrophages provide protection against bacterial and viral infections by a variety of mechanisms including oxygen dependent pathways involving superoxide radical-anion mechanisms (*e.g.* myeloperoxidase) and cytokine production [particularly IL-1, -6 and -8, interferons α and β and tumour necrosis factor α (TNF-α)] which are important in mounting an immune response to infection. Exposure of human alveolar macrophages (AMs) to concentrations of NO_2 ranging from 188 to 940 μg/m^3 for short durations resulted in a significant reduction of lipo-polysaccharide (LPS)-stimulated IL-1β, IL-6, IL-8 and TNF-α (but not TGF-β)[60]. Cytotoxicity of AMs remained unaffected. The results indicate that at concentrations relevant to human exposure, there is a functional impairment of AM without significant alterations in cytotoxicity. More recent work investigated exposure to particulate pollution of three size ranges from PM_{10} to $PM_{0.1}$ and the effect on antigen presenting cells by evaluating the expression of surface receptors involved in T-cell interaction on both human AMs and blood-derived monocytes (Mo). Mo up-regulated the expression of all four receptors in response to each of the particle fractions, whereas expression was unaffected in AM. However, when Mo and AM were separately exposed to the three PM size fractions and assessed for T-helper lymphocyte chemoattraction (by production of IL-16), AM alone (and not Mo) produced IL-16, and this chemoattractant was released only in response to $PM_{2.5–10}$. This suggests that a wide size range of pollution particles contains materials that may promote antigen presentation by Mo, whereas the capability to specifically recruit T-helper lymphocytes is contained in AM stimulated with the 'coarse' PM fraction[61]. When the experiments were extended to different particle sizes and compositions, the response of AM was highly variable, leading the authors to conclude that composition rather than size was responsible for the oxidant response and that oxidant activation by various sources of particulate matter is cell specific[62]. The ability of different pollutants and particle fractions to cause variable defects in bronchial immunity may also determine the risk of symptoms following pollutant exposure and infection.

Epithelial interaction

Viral infections can cause severe pathological abnormalities in both the upper and lower respiratory tract, although the extent of epithelial damage varies between viruses. Whereas Influenza A infection causes intense inflammation of the bronchi, trachea and larynx with desquamation of

ciliated epithelial cells, rhinoviruses cause little or only patchy epithelial damage. Experimental studies of oxidant pollutant exposure show that the lower airway epithelium (particularly the transitional zone between bronchial epithelium and proximal alveolar regions) is particularly susceptible. In contrast, nasal, laryngeal and tracheal regions are not readily damaged by oxidant pollutants possibly because they have a thicker, extra-cellular anti-oxidant hypophase[63]. It is possible that the penetration of allergen into the epithelium would be facilitated both by epithelial shedding, and by reduced ciliary clearance, resulting in easier access of allergen to antigen presenting cells and therefore increased inflammation. The epithelium is also an important source of regulatory proteins or mediators with protective roles, such as nitric oxide or bronchodilator prostaglandins E_2 and I_2, which may play a role in maintaining bronchial patency.

The epithelium may also interact directly with virus infections and air pollutants. Spannhake reported experiments infecting primary human (nasal) epithelial cells and cells of the bronchial epithelial BEAS-2B line with human rhinovirus type 16 (RV16) and exposed them to 3880 $\mu g/m^3$ NO_2 or 400 $\mu g/m^3$ O_3 for 3 h. Infection with rhinovirus, NO_2 and O_3 independently increased release of IL-8 through oxidant-dependent mechanisms. The combined effect of RV16 and oxidant ranged from 42% to 250% greater than additive for NO_2 and from 41% to 67% for O_3. Both individual and combined effects were inhibited by anti-oxidant treatment. Perhaps the most interesting observation is that the surface expression of intercellular adhesion molecule 1 (ICAM-1) underwent additive enhancement in response to *combined* stimulation. These data indicate that oxidant pollutants can amplify the generation of pro-inflammatory cytokines by RV16-infected cells and suggest that virus-induced inflammation in upper and lower airways may be exacerbated by NO_2 and O_3. Given that ICAM-1 is also the receptor for the major group of rhinoviruses, a potential mechanism of how oxidant pollutants could increase susceptibility to rhinovirus infection is also suggested[64]. Another study reported by Becker investigated respiratory syncytial (RS) viral replication and virus-induced IL-6 and IL-8 production in BEAS-2B cells following exposure to approximately 1000, 2000 and 2500 mg/m^3 NO_2. The internalization, release of infectious virus, and virus-induced cytokine production were all significantly reduced at the highest category of NO_2 exposure. This led the authors to conclude that increases in viral clinical symptoms associated with NO_2 may not be caused by increased susceptibility of the epithelial cells to infection but may result from effects of NO_2 on other aspects of antiviral host defences[65].

The mechanisms underlying the relationship between infection and the development of lower airway symptoms after air pollution exposure are

Table 1 Putative interaction between air pollution and infection in individuals with pre-existing lung disease

Effect	Air pollution	Infection
Bronchoconstriction	++	+++
Bronchial hyperresponsiveness	+	+++
Inflammatory mediator release	++	+++
Ciliary dyskinesis	++	+++
Inflammatory cell activation	++	+++
Epithelial damage	++	++/±
T-lymphocyte function	++	+++
Alveolar macrophage function	+++	++
Interaction with allergens	++	+++
↑ Epithelial derived cytokines	++	+++
↓ Macrophage derived cytokines	++	+

Strength of effect based on an arbitrary scale: +, mild; ++, moderate; +++, severe.

not fully understood. Oxidant pollutant exposures have the potential to exacerbate the inflammatory effects of virus infections in the lower airway, especially in individuals with pre-existing lung disease. Table 1 summarizes some of the mechanisms that may be involved in the synergistic interaction.

Will improving air quality improve health?

The data discussed above strongly suggests that the vast majority of serious morbidity and mortality related to air pollution occurs *via* interactions with respiratory infection. However, a discussion of the role of air pollutants and infection is not complete without considering whether improving air quality can reduce the burden of respiratory disease. The success of the Clean Air Legislation Acts described earlier in eradicating the severe smog episodes in London, Europe and the USA provides clear proof that improved air quality can reduce adverse health effects. The clearest demonstration of this has also been observed in the Utah Valley following closure of a steel mill for 14 months in 1987 as a result of a labour strike. Outdoor particulate concentrations and respiratory hospital admissions both fell dramatically during the period of mill closure, but returned to the pre-closure levels as the mill re-opened[66]. More recently the introduction of use of low sulphur fuels in Hong Kong was associated with between 2.01% and 3.9% of reductions in cardiovascular, respiratory and all-cause deaths[67]. This provided direct evidence that control of sulphur-rich pollution has immediate and long-term health benefits and has immediate implications for how air quality may be controlled in developing countries. Similar recent descriptions of the reduction in particulate pollution in Dublin for up to 5 years after the ban of coal sales

showed a reduction of up to 15.5% for respiratory deaths and 10.3% for cardiovascular deaths, equating to 116 fewer respiratory and 243 fewer cardiovascular deaths in Dublin after the ban[68]. Whereas it is accepted that reducing air pollution is associated with beneficial effects for the traditional pollutants from stationary sources, there is now also evidence that control of traffic related pollution may have equally beneficial effects. Asthma admissions were reduced in Atlanta in parallel with traffic measures taken to reduce traffic density during the 2000 Olympic Games[69].

The future

These analyses of air pollution provide real evidence that air pollution is significantly associated with mortality and morbidity, provide evidence for possible mechanisms and interaction with infection and confirm that reducing pollutants could improve public health. Further work is still needed on the effect of indoor pollutants, especially in developing countries where the public health impact is likely to be dramatic. While there is emerging evidence confirming that air pollutants are intimately related to infections, the challenges for epidemiologists and clinical scientists remain to go beyond the short-term triggering phenomena and consider how the increase in susceptibility to air pollutants reflects fundamental interactions with co-factors such as allergens, domestic biomass fuel combustion, diet and virus infections. The challenges remain to unravel the mechanisms that drive such effects of air pollution.

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