

Urban air pollution and respiratory allergy

G. D'Amato

ABSTRACT: *Urban air pollution and respiratory allergy. G. D'Amato.*

Evidence suggests that urbanization with its high levels of vehicle emissions, and westernized lifestyle are linked to the rising incidence of pollen-induced respiratory allergy seen in most industrialized countries. Moreover, the increase in respiratory allergy parallels an increase in outdoor and indoor air pollution. Although the role played by outdoor pollutants in allergic sensitization of airways has yet to be elucidated, it is well established that outdoor pollution exacerbates respiratory symptoms in atopic subjects.

This review focuses on the evidence implicating outdoor pollution in pollen-related respiratory diseases. Acute and chronic exposure to such components of air pol-

lution as sulphur dioxide, nitrogen dioxide, ozone and respirable particulate matter (isolated or in various combinations) enhances airway responsiveness to aeroallergens in atopic subjects. By attaching to the surface of pollen grains and of plant-derived paucimicronic particles, pollutants can modify the morphology of these antigen-carrying agents and alter their allergenic potential. In addition, by inducing airway inflammation, which increases airway epithelial permeability, pollutants overcome the mucosal barrier and so "prime" allergen-induced responses. Lastly, air pollutants such as diesel exhaust particulates can also facilitate the immunoglobulin (Ig)E response that leads to pollinosis symptoms in atopic individuals.

Monaldi Arch Chest Dis 2002; 57: 2, 136-140.

Keywords: *Air pollution and allergy, allergic asthma, hay fever and hay asthma, pollinosis, pollen allergy, air pollution/aeroallergens interaction.*

Division of Pneumology and Allergology, Department of Respiratory Diseases, Azienda Ospedaliera ad Alta Specialità di Rilievo Nazionale "A. Cardarelli", Napoli - Italy.

Correspondence: Gennaro D'Amato MD; Division of Pneumology and Allergology; Hospital A. Cardarelli; Via Rione Sirignano, 10; 80121 Napoli Italy. e-mail: gdamato@qubisoft.it

HENRY HYDE SALTER was the first to report that air pollution was implicated in respiratory allergy.

In his book "On asthma: its pathology and treatment" published in London in 1860, with great intuition he listed "Impure air, animal emanations, hay fever and foods" among the various causes of asthma [1]. He also described asthma as being "Paroxysmal dyspnea of a peculiar character, generally periodic with healthy respiration between attacks". Nearly 50 years latter, WILLIAM LLOYD postulated that hay fever was a result of urbanization and agricultural changes [2]. These early studies are supported by recent observations that allergic respiratory diseases such as hay fever and hay asthma have become more common in the last two decades in all industrialized countries [3-6]. Interestingly, communities living in urban areas tend to be more affected than those of rural areas, and within rural communities individuals exposed to traffic have a higher incidence of allergic respiratory diseases than those less exposed to traffic. For example, in Tokyo, Japan subjects living near roads with heavy traffic were more likely to develop respiratory allergy to cedar pollen than subjects living in areas with a higher concentration of cedar trees but with less traffic [5, 7]. These studies suggest that the disparity in the prevalence of allergic respiratory diseases in the two areas is attributable to exhaust pollution, which is the predominating factor in areas with high incidence of pollen-allergy.

The unification of East and West Germany in 1986 provided a unique opportunity to study whether or not lifestyle and pollution affect the incidence of allergic respiratory diseases. In 1992, VON MUTIUS and colleagues [8] reported that allergic conditions such as hay fever were more common in West Germany (Munich) than in East Germany (Leipzig), and that the prevalence of chronic bronchitis was higher in East Germany. The difference was attributed to the different types of air pollutants present in the two zones, more sulphur dioxide and reductant smog in East Germany and more nitrogen dioxide and respirable particulate matter from car exhaust emissions in West Germany. In a more recent study they reported that the frequency of hay fever in schoolchildren aged 9-11 years in Leipzig increased from 2-3% in 1991-1992 to 5.1% in 1995-96, whilst the prevalence of atopic sensitization increased from 19.3% (1991-92) to 26.7% (1995-96) [9]. In other words, the differences in the respiratory disorders have largely disappeared since the unification of East and West Germany. This is probably the result of the change in air pollution patterns and in living habits in the former East Germany [10]. Hence, differences in the prevalence of allergic respiratory symptoms between Eastern and Western Europe are decreasing, as lifestyle in Eastern Europe becomes more "westernized".

VON MUTIUS and colleagues also studied the association between skin test positivity and techniques of cooking and heating in the homes of

more than 5000 West German schoolchildren and found that the frequency of atopy and hay fever was significantly higher in the population living in homes with central heating, oil furnaces and gas ovens than in children living in homes where coal or wood were used for cooking and heating [11]. This finding is consistent with studies showing that also domestic gas and oil-derived air pollutants are involved in allergic respiratory diseases and they show that nitrogen dioxide is an indoor as well as outdoor pollutant [11, 12].

Pollen allergy is one of the models most frequently used to study the interrelationship between air pollution and allergic respiratory allergy. However, despite compelling evidence of a link between the increased prevalence of pollinosis and the increase in air pollution, the mechanisms underlying this link are still widely debated and the possible interaction between air pollution and aeroallergens is still speculative. To cloud the issue further, the results of some studies are difficult to interpret, because of the confounding effects of cigarette smoke, exposure to allergens in atopic subjects, meteo-climatic conditions and socio-economic factors. In addition, it is important to recall that an individual's response to pollution exposure depends on the source and components of air pollution, and climatic agents. Indeed, some air pollution-related incidents do not depend only on the increased amount of air pollution but rather on climatic factors that favour the accumulation of air pollutants at ground level. Other variables are related to the mode of inhalation (mouth or nose breathing), deposition in the airways, health status (presence or not of airway hyperresponsiveness), and exposure to more than one agent.

Another aspect to consider is that measurements made in the lab do not consistently reflect what happens "in the wild". In fact natural exposure can be vastly different to simulated exposure. In the lab we still do not have the technology to reproduce accurately in all its nuances, on-the-street exposure. In other words, although it is plausible that ambient air pollution might play a role in the onset and in the increasing prevalence of asthma and other allergic respiratory diseases, including pollen allergy, it is difficult to demonstrate that this happens at a public health level [13].

Below I shall examine the data linking air pollution with the increased incidence of pollen-induced respiratory diseases.

Interaction between air pollution, climatic factors and allergenic plants

The effect of air pollution on allergenic plants

Environmental ozone reduces pollen viability [14], and the effects of ozone seem to be enhanced by the presence of ultraviolet radiations [15]. In addition, by affecting plant growth, air pollutants can affect both the amount of pollen produced and the amount of allergenic proteins contained in pollen.

A recent study showed that pollen grains of plants stressed by air pollution express enhanced levels of allergenic protein [16] and leaves of birch trees exposed to high levels of pollution have much greater levels of *Betula verrucosa* (Bet v 1) antigen than do leaves of birch trees growing in non-polluted areas [17].

The effect of climate on allergenic plants

The climatic variations consequent to the greenhouse effect, i.e. global warming caused by the emission into the atmosphere of carbon dioxide and ozone that has occurred over the last 25 years, affect the presence and growth of plants that produce allergenic pollen. Moreover, particular meteorologic conditions (i.e. sunny days) favour not only the transformation of nitrogen dioxide into ozone but also the flowering of plants such as *Parietaria* that cause a high frequency of allergic respiratory symptoms [18].

Interaction in the atmosphere between components of air pollution and pollen grains

It has been suggested that air pollutants may promote sensitization and subsequent development of allergic respiratory disease by modulating the allergenicity of airborne allergens.

Several groups have examined how air pollutants can interact with pollen grains to modulate (increasing or reducing) their allergenic potency. Thomas et al. studied the effect of exposure for 4 hours to 50-200 ppb nitrogen dioxide on viability, germination and protein release of freshly collected birch, rye, alder and hazel pollen grains, and showed that exposure to 100 ppb nitrogen dioxide adversely affected the ability of all species of pollen to germinate, with consequences on protein content [19].

BEHRENDT *et al.* reported that pollen grains collected from roadsides with heavy traffic and from other areas with high levels of air pollution were covered with large numbers of airborne microparticulates (about 5 µm or less in size) [20]. They suggest that interaction between pollen allergens and these components results in altered antigenicity of pollen allergens. Incidentally, the quantity of inorganic components of air pollution attached to the surface of pollen grains could serve as a marker of air pollution [21].

Despite shorter and less severe grass pollen seasons, confirmed by lower pollen counts, the prevalence of seasonal rhinitis and asthma has increased in some European cities in recent years. A case in point is London and its immediate surroundings which have seen a reduction in the length and severity of pollen seasons over the last 30 years coupled with more cases of pollen-related respiratory symptoms [22]. A possible explanation for this apparent contradiction is that air pollutants have interacted with pollen grains to make them more allergenic, besides inducing or increasing airway inflammation and reactivity in predisposed subjects.

Interaction in the atmosphere between air pollution and plant-allergen-carrying paucimicronic particles

Aerodynamic calculations suggest that airborne particles greater than 10 µm in diameter, a category that includes all allergenic pollen grains, are too large to penetrate the medium-sized and small airways. However, symptoms such as cough and asthma, which derive from the tracheo-bronchial regions, are not infrequently observed in pollen-allergic patients. Moreover, these symptoms can occur out of the pollen season, as determined by the pollen count at microscopy. The dilemma was to some extent solved by the demonstration in atmosphere of allergen-carrying paucimicronic particles (diameter between 2 and 5 µm) derived from plants [23, 24]. By virtue of their small size, paucimicronic particles are able to reach the peripheral airways with inhaled air, so inducing asthma in sensitized subjects [23–26].

The exact origin of allergenic paucimicronic particles has yet to be established. They are unlikely to be fragments of pollen, because the pollen-grain wall usually resists rupture. They could derive from plant debris other than pollen, e.g. fragments of vegetal parts of plants that can carry allergens characteristic of pollen. For instance, allergens have been detected in the leaves and stems of allergenic plants such as *Parietaria judaica* and *Dactylis glomerata* [27].

Another possibility is that pollen grain allergens could be transferred, by physical contact or by elution, to other small particles present in the atmosphere, for instance diesel exhaust particles, which can penetrate deep into the airways.

Knox and colleagues opened up yet another possibility, when they found that, under wet conditions or during thunderstorms, pollen grains (particularly from grass species) may release, after rupture by osmotic shock, part of their content, including respirable allergen-carrying starch granules (0.5–2.5 µm) into the atmosphere [28]. In this context Wallis and coworkers investigated the clinical and immunological characteristics of 640 patients attending the accident and emergency departments of several hospitals in London for treatment of acute asthma attacks or other airway disorders after a thunderstorm that occurred in June 1994 [29]. They reported that 283 of the 640 (44%) patients examined, who were not known to be asthmatics, experienced an asthma attack, and, even more interesting, 12 of the 15 patients in whom serum specific IgE was measured had a RAST score as high as 4 or more against grass pollen. The authors suggested that this asthma outbreak was probably caused by abnormal dispersal and/or disruption of pollen grains with release of their allergenic content (probably carried by starch granules) that enabled it to be inhaled more deeply into the airways than would happen under normal conditions. An offshoot of these studies is that the traditional “pollen count” may be misleading as an index of outdoor allergen exposure in particular situations. In fact with the pollen count technique,

pollen grains, collected in volumetric “pollen traps”, are examined under the microscope and their concentration per cubic meter of air is defined, whereas immunochemical methods are required to identify the allergens carried by such airborne microparticulates as starch granules [30].

Components of air pollution which can facilitate the inflammatory response of airways to pollen allergens

Some components of air pollution, in particular ozone, particulate matter and sulphur dioxide cause inflammation of the airways in susceptible subjects. This leads to increased permeability, easier penetration of pollen allergens in the mucous membranes and easier access to and interaction with cells of the immune system [13, 31]. There is also evidence that predisposed subjects have increased airway reactivity after exposure to components of air pollution with a consequent increased bronchial responsiveness to inhaled pollen allergens.

Ozone is the component of air pollution that has been studied most. This agent is generated at ground level by photochemical reactions involving nitrogen dioxide, hydrocarbons and ultraviolet radiations. Some studies reported that ozone inhalation induces epithelial damage and consequent inflammatory responses in the upper and lower airways, as witnessed by an increase in neutrophils, eosinophils, mononuclear cells, fibronectin, granulocyte/monocyte colony-stimulating factor (GM-CSF), interleukin (IL)-6, IL-8 and PGE2 in nasal and bronchoalveolar lavage fluids [13, 31]. Molfino and colleagues observed that the mean provocation dose of allergen (ragweed) required to decrease the forced expiratory volume in 1 second (FEV₁) by 15% was significantly reduced to approximately half when the subjects were pre-exposed to ozone, compared with preexposure to air [32]. In contrast, BALL *et al.* showed that pre-exposure to ozone did not significantly decrease the concentration of allergen required to induce a 15% reduction in FEV₁ compared with preexposure to air [33]. The latter attributed the discrepancy between their findings and those of MOLFINO and colleagues to methodological differences in the sample selection, and to the consequences of repeated exposure to the allergen used for the test, before exposure to ozone and/or allergen. More recently, JORRES *et al.* showed that previous exposure to a higher concentration of ozone for a longer period of time increased airway responsiveness to inhaled allergen in exercising atopic asthmatics [34].

The city of Naples, Italy, provides a tool with which to study the interrelationship between ozone and pollen-derived allergens: heavy urban traffic with high production of photochemical smog, year-long sunny days for most of the year. Naples numbers about 2 million inhabitants including the extended conurbation. It is located in a coastal area surrounded by hills and mountains in a basin of approximately 400 km². During the summer season

the prevailing meteorologic conditions, characterized by long sunny days, which lead to the build-up of ozone, and an absence of wind and rain often favour critical air pollution episodes. The climate also favours the pollination of *Parietaria* (Pellitory of the wall), which grows in abundance throughout the city; and indeed, about 30% of Neapolitans are allergic to this plant and more than 50% of these *Parietaria* pollen- allergic subjects experience bronchial asthma and its equivalent, with a high level of bronchial hyperresponsiveness [18, 35]. We have observed that cases of pollen-induced respiratory disorders tend to increase when there is a parallel increase in the atmosphere of ozone and of *Parietaria* pollen grains. This parallel increase usually starts in January or February and reaches its peak in June or July, after which the production and release of *Parietaria* pollen usually decreases, while ozone remains high also in Autumn.

There is also a diurnal correlation of both peaks, since *Parietaria* pollen and ozone reach their highest levels in the morning: *Parietaria* peaks earlier than ozone because of the time required for the photochemical reaction to develop. However, we observed that, during sunny days in spring when outdoor levels of *Parietaria* pollen increase, the indoor levels of this pollen can be reduced by about one-third of the outdoor concentration by closing windows, while with windows open the outdoor and indoor concentrations are the same [36].

Regarding the respirable particulate matter of air pollution, an analysis of the relationship between suspended particulates less than 10 µm in diameter and asthma revealed that particulate air pollution is associated with enhanced mortality from respiratory and cardiovascular diseases, exacerbations of asthma and hospital admissions [37, 38].

In the context of airborne particulate emissions, interest has focused on diesel exhaust particulate (DEP), which has been demonstrated in experimental studies to cause respiratory symptoms [39, 40] and to modify the immune response in predisposed animals and humans.

In other words, some components of air pollution, in particular DEP, seem to have an adjuvant immunologic effect on IgE synthesis in atopic subjects, thereby influencing the sensitization to airborne allergens, in particular those from pollen [41]. Recently, DIAZ-SANCHEZ studied the effect of DEP on antigen in ragweed-sensitive subjects submitted to nasal provocation tests with DEP, the major ragweed allergen Amb a1, and to a combination of DEP and Amb a1 [39]. Nasal washes, carried out 18 hours, and 4 and 8 days after challenge, were examined for total and ragweed-specific IgE. The challenge with ragweed allergen led to an enhancement in both total and ragweed-specific IgE in nasal lavage fluid. Challenge with DEP enhanced the total, but not the ragweed-specific IgE. Challenge with both DEP and ragweed allergen increased the levels of ragweed-specific IgE 16-fold versus levels observed

after ragweed challenge alone. Therefore, it appears that, besides interacting with aeroallergens carried by pollen grains or by paucimicronic particles and increasing their allergenicity [42], DEP can also potentiate IgE synthesis. This is an area of research that warrants greater attention in view of the fact that the proportion of new cars with diesel engines is increasing in all industrialized countries.

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