

Effects of air pollution on asthma: A review

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Interest in air pollution and its effects on health and disease has been increasing steadily. A majority of physicians and scientists have been impressed that air pollution cannot help but aggravate diseases of the upper and lower respiratory tracts, although it has been questioned whether there is firm evidence that this is an established fact; some have called air pollution "a cause in search of a disease."¹ The intent of this review is to describe concisely the current state of knowledge about the effects of air pollution on asthma, with the understanding that the primary etiologic factors in the asthmatic response are generally not characterized for the study populations in the reports to be reviewed. Good reviews of other various aspects of air pollution effects on health have been published in recent years.¹⁻⁴

For the purpose of this discussion, a modified definition of air pollution has been adapted from that of the Air Conservation Commission⁵: "that state resulting from the production of man-made wastes produced so rapidly that they accumulate in concentrations which cannot be dispersed by the normal self-cleansing propensities of the atmosphere." This definition excludes naturally appearing materials such as pollens, molds, and infectious agents. *Localized* air pollutants such as cigarette smoke and occupational exposures will also be excluded, although they are important factors in selected cases.

The major components of "air pollution" will be described with the understanding that (1) they exist to varying degrees in different communities and atmospheric conditions, (2) air pollutants do not occur as individual entities but in combination, frequently with synergistic effects, and (3) there may be other pollutants or adjunctive factors equally important whose role is not yet appreciated. The U.S. Air Pollution Control Administration (a division of the Environmental Protection Agency) is currently investigating 42 types of atmospheric pollutants, only a few of which are considered here. The major known pollutants are particulate matter, oxides of sulfur, photochemical constituents, carbon monoxide, and metals.

MAJOR POLLUTANTS

Particulate matter

Forms of this are fog, mist, dust, smoke, and soot, as distinguished by size and physical state of the particles. They are produced either by industrial

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activities, such as combustion or grinding, or by condensation of the non-particulate pollutants, either man-made or naturally occurring. Particulate pollutants are important because of direct effects on health and also catalytic effects on other air pollutants,⁶ particularly the oxidation of sulfur dioxide.⁷ Amdur⁸ and Speizer,⁹ among others, emphasized the significance of small-sized particulate matter (frequently sub-micron) acting as catalytic aerosols to produce irritation in the lower respiratory tract. However, much has to be learned concerning the chemical and other characteristics that make particulate matter "irritating" to the human, whether directly or through an associative action with irritant gases. The number and size distribution of atmospheric particles is controlled by the balance between the continual generation, transport, alteration, and removal of such particles. They are subject to daily, weekly, and seasonal variations with a tendency for increased concentrations in large urban areas. Typical dust fall measurements per square mile per month are 10 to 100 tons for rural areas and 500 to 1,000 tons in heavily polluted industrial areas.² More detailed measurements of levels of particulate matter of varying sizes have now been attempted.¹⁰

Oxides of sulfur (sulfur dioxide, sulfur trioxide, sulfuric acid, and sulfate salts)

The man-made emission of sulfur, while actually only half of that from natural sources like decaying vegetable matter, represents a problem because it is concentrated mainly in urban areas secondary to production by power stations, industry, refuse burning, public and private transportation, etc. As sulfur dioxide enters the atmosphere, part of it is oxidized and converted to sulfuric acid and sulfate salts. It is mainly the product of oxidation, sulfuric acid and sulfates, which appears to exert injurious effects on the respiratory tract.⁸ Sulfur dioxide itself appears to lead only to mildly irritating effects in most individuals until a relatively high concentration is reached in the ambient air. However, the oxidation of SO_2 in combination with certain small-sized particulate materials leads to a much more prominent irritant effect in the smaller airways. Sulfate compounds may constitute 5 to 20 per cent of the total airborne particulate material in some urban centers. Urban concentrations of sulfur oxides (calculated as SO_2) generally are in the range of 0 to 1 part per million (ppm).¹¹

Photochemical constituents (oxidants)

Hydrocarbons come mostly from incompletely combusted automobile fuels and some industrial processes. *Nitrogen oxides* are generated mainly by power stations and automobile fuel combustion. When atmosphere contaminated by a mixture of these gases is irradiated by sunlight, a series of reactions occur, leading to formation of *ozone* and a variety of organic gases and particulates. These include compounds of low volatility that condense to form characteristic haze and eye-irritating compounds like acrolein and peroxyacetyl nitrate (PAN). The nature of these photochemical reactions is incompletely understood, with recent findings¹² suggesting roles for free hydrogen and electronically excited oxygen. When these substances are present in excess, a state described

as "photochemical smog" is present. Typical concentrations of hydrocarbons and nitrogen oxides in smoggy atmospheres range between 0.1 and 1.0 ppm,² although they may reach higher levels in certain localized areas.

"Photochemical smog" differs in several respects from the industrial smog seen during periods of thermal inversion in highly industrialized cities. In thermal inversions, a combination of meteorologic events, including the lack of sufficient dispersing wind currents, lead to the build-up of a mass of cool air at or close to ground level that cannot rise above a layer of warm air above it. In and under this heavy "blanket" of cool air are trapped pollutants discharged from industrial plants, home, automobile fuel consumption, etc., where they stay until a change in meteorologic conditions leads to dispersal of the cool air mass. Many urban areas in valleys or surrounded by mountain ranges will have a temporary period of thermal inversion in the morning until the sun is high enough to heat the low-lying cool air mass. In many, if not most, instances of air pollution occurring in large urban areas, elements of both photochemical oxidation and thermal inversion may play etiologic roles at one time or another.

Carbon monoxide

This is the most abundant gaseous pollutant and is mainly due to exhausts from internal combustion engines. In areas of highly restricted ventilation and heavy motor traffic, very high concentrations of 100 to 300 ppm have been recorded.

Metals

A variety of metallic salts or organometallic compounds are frequently components of particulate air pollution. Lead is a major metallic airborne contaminant, produced by tetraethyl lead in automobile fuels (some metallic salts may catalyze the oxidation of SO₂ as described previously).

EPIDEMIOLOGIC EVIDENCE OF ADVERSE EFFECTS OF AIR POLLUTION

Although air pollution exerts adverse effects on physical structures and plant life, the most serious potential danger is its contribution to human illness. This effect appears to be the most difficult to put on a firm quantitative basis. Complicating the evaluation are variances in the patterns of air pollution from place to place and time to time. Any study is affected by the interrelationships of air pollution with meteorologic changes, as well as the consideration of cigarette smoking and its effect on respiratory disease. Overall estimates have been made¹⁴ that a 50 per cent reduction in air pollution levels in the major urban areas of the United States would lead to approximately a 50 per cent reduction in the morbidity and mortality from chronic obstructive bronchopulmonary disease and a net saving of 2 billion dollars yearly in medical costs and lost earnings. On what evidence is this adverse effect on health (with particular reference to asthma) postulated? Several types of evidence, mostly epidemiologic, have been tendered, and these will be considered in turn.

Patterns of activity of allergic respiratory disease during periods of very high exposure to air pollutants

Although the results of such episodes appear quite dramatic and clear-cut because of the sudden change in the morbidity of patients with allergic respiratory disease, the results of such studies are often difficult to evaluate because (1) the exposure was unexpected, (2) the investigation was therefore retrospective, and (3) the defects in precise diagnosis were those inherent in any such large-scale epidemiologic study. With those inherent limitations in mind, several such "air pollution catastrophe" episodes are described in the paragraphs that follow.

In the small, highly industrialized town of Donora, Pennsylvania, a period of extended thermal inversion in 1948 was accompanied by markedly increased levels of air pollutants, particularly SO_2 . Practically all the asthmatics in the area were adversely affected compared to adverse effects in 40 per cent of the general population.¹⁵

The severe air pollution episode in London in 1952 was accompanied by significantly higher morbidity and mortality in asthmatics than in the general population.¹⁶ Another episode of air pollution in this city in 1962, following more stringent controls of fuel burning, was associated with an apparently lower morbidity in asthmatics.¹⁷

Since 1954, an increased incidence of asthmatic episodes has been reported^{18, 19} in military personnel stationed in the highly industrialized Tokyo-Yokohama area. This locale on the Kanto Plains is subject to frequent thermal inversions; in addition, there has been relatively little effort to control emissions from many factories and home furnaces. A high incidence of smoking and family histories of allergy characterize the affected individuals. Dramatic improvement frequently followed removal of the patient from the area, although residual pulmonary function abnormalities have reportedly persisted in some individuals.

Glasser, Greenburg and Field,²⁰ and Chiaramonte and associates²¹ reported increased asthmatic episodes both in older adults and in children during a 1966 period of high air pollution in New York City, with peak frequency of asthmatic flare-ups treated in emergency rooms on the third day of the air pollution episode.

Chronic observation studies

Zeidberg, Prindle, and Landau²² followed the clinical course of 84 asthmatic patients in Nashville over a period of one year and found a threefold increase in acute episodes on days characterized by high, as compared with low, sulfate content in the air. Schoettlin and Landau²³ found that 137 asthmatic patients in Pasadena, California, manifested significantly more symptomatic flare-ups during a 3 month observation period when oxidant levels were greater than 0.14 ppm. This study suggested that one asthmatic in 20 was markedly affected by smog. Winkelstein and co-workers²⁴ collected data in the Buffalo area and found that the mortality rate for asthma, bronchitis, and emphysema in white males 50 to 69 years old increased by more than 100 per cent in high pollution, as compared to low pollution, areas.

Carnow and associates²⁵ reported an ongoing study of the effects of air pollution on chronic obstructive pulmonary disease in Chicago. Advantages of this study, compared to most other epidemiologic projects, included multiple-point monitoring of air pollution levels and the use of personal semiquantitative symptom diaries by the subjects. This would hopefully result in a more sensitive measure of any changes in symptomatology related to local air pollution levels. This study reported increased morbidity of advanced obstructive bronchopulmonary disease at the time of high sulfur dioxide air levels.

A limitation of many of these epidemiologic studies is the lack of distinction within the patient group of those with asthma as compared with other obstructive bronchopulmonary disease. This lack of distinction in classification is especially significant, because in some studies the socioeconomic characteristics of the study groups are not defined. It has been found²⁶ that cigarette smoking is more prevalent in the lower socioeconomic group, which appears to constitute an increasing percentage of the residents in older "center city" areas near potential sources of industrial air pollution.

In this regard, data concerning the symptom patterns of allergic-asthmatic children without the effects of cigarette smoking are relevant. Girsh and associates²⁷ found a threefold increase in acute bronchial asthma requiring emergency room treatment during periods of "noteworthy air pollution" (greater than the top tenth percentile of the range of pollutants over a 2 year period). Chiaramonte and associates²¹ studied the pattern of emergency room visits for acute asthmatic attacks during the November, 1966, air pollution episode in New York City. They found a significant rise of obstructive bronchopulmonary symptoms related to the several days of high sulfur dioxide levels, as compared with the weeks preceding and following the pollution episode. This increase in asthmatic episodes was more evident for the 2 consecutive days starting 72 hours following peak SO₂ levels. The affected children had a high incidence of extrinsic allergic manifestations as defined by anamnestic and skin testing criteria. Sultz and his colleagues²⁸ found a significant increase in the hospitalizations for flare-ups of asthma and eczema in Buffalo, New York, in local areas of "high," compared to "low," air pollution. These differences in hospitalization rates occurred in children of all socioeconomic levels.

However, Lewis, Gilkerson, and McCalden²⁹ found no association between the daily frequency of visits to Charity Hospital for the treatment of asthmatic episodes and the levels of air pollution in New Orleans. In the study in Los Angeles by Schoettlin and Landau,²³ the association noted between increased atmospheric sulfates and increased asthmatic morbidity was much less impressive for children than for adults.

In these large-scale epidemiologic surveys, the evaluation of findings is further complicated by the effects of meteorologic components, either as a direct factor or through an indirect influence on the level of air pollutants. For example, Girsh and his colleagues²⁷ found a fourfold increase in asthma in children during days of high barometric pressure, but no particular association of asthma morbidity with cold weather. Salvaggio and associates³⁰ noted an increased incidence of asthma associated with low temperatures (frequently with

sudden drops in temperature) and low humidity. Greenburg and co-workers³¹ reported an increase in emergency clinic visits for asthma in New York City at the beginning of the cold weather period during the autumn when heating systems are turned on. These observations are compatible with the experience of many clinicians in areas where ragweed pollinates; an increase in asthma morbidity is seen *following* the major period of ragweed pollination (called "post-ragweed" asthmas by some clinicians).

The interplay of meteorologic factors with the increased exposure to indoor inhalents and outdoor molds still in the air is not yet well defined. Salvaggio and his colleagues³⁰ pointed out the interrelationship between climatic factors and seasonally occurring airborne allergens in New Orleans epidemic asthma—a disorder formerly considered³² a result of chemical air pollution. Also to be considered is the effect of "priming" the susceptible atopic population by ragweed, as postulated by Connell³³. It has been suggested³⁴ that asthmatic attacks may be related to extremes of temperature and humidity. However, in a controlled study, in an environmental control unit, Fontana, Fost, and Rappaport³⁵ found that experimentally produced rapid changes in humidity lead to no significant changes in pulmonary function of 19 asthmatic children.

EXPERIMENTAL EXPOSURES TO AIR POLLUTANTS AND RELATED FACTORS

In epidemiologic studies, it has been necessary to postulate "guilt by association." Lave and Seskin¹⁴ reviewed the valid reservations that must be recognized in evaluating such associations, with special consideration to socioeconomic factors, smoking history, and unrecognized elements. Any meaningful data generated by experimentally controlled exposures of allergic persons to individual air pollutants or combinations of pollutants in levels similar to those encountered in natural exposure would, therefore, be of great potential value. Bates¹ recently postulated 3 possible loci of action of pollutants within the respiratory tract; (1) the upper airways and major bronchi, (2) the smaller airways, and (3) the alveoli with particular reference to inflammatory cellular content. Optimally, human exposure studies could assay effects of any suspect pollutant at each of these loci. Unfortunately, there is not much data from well-controlled studies in this area. Amdur⁸ reviewed the limiting factors in human subject experiments.

Experimental studies³⁶⁻³⁸ have shown a significant increase in airway resistance in humans, as well as in experimental animals, following SO₂ inhalation. Broncho constriction could occur at levels well below 12 to 15 ppm, the usual concentration of sulfur dioxide leading to irritation of the nasal mucosa. It is not yet completely ascertained whether the bronchoconstriction results from a vagal-mediated reflex or whether local intrapulmonary actions of this agent exert a significant effect independent of neurogenic reflex activity. In addition, SO₂ in concentrations of 10 to 15 ppm lead to suppression of mucosal ciliary activity. It should be emphasized that these concentrations are about 10 to 20 times that found during high levels of air pollution in urban areas.

Speizer and his colleagues^{39, 40} carried out long-term studies on a group of subjects, including asthmatics, in an urban environment. They correlated

data from frequent measurements of pulmonary function with several meteorologic parameters, including temperature, wind speed, barometric pressure, and sulfur dioxide levels. Decreases from the predicted vital capacity were correlated with increased levels of SO_2 starting at 0.5 ppm. This level is in the range where increased morbidity from asthma has been noted in some of the epidemiologic studies described previously.

Amdur³ and Clayton⁴¹ discussed some of the studies, attempting to see whether experimental exposure to particulate aerosols will potentiate the irritative effects of inhaled SO_2 in human subjects as it does in animals. Variable results have been obtained, possibly related to technologic problems.

Several clinical syndromes have been produced⁴² by experimental exposure to varying concentrations of nitrogen dioxide. The most common appears to be pulmonary edema, in localized or generalized form, sometimes associated with pulmonary fibrosis in cases of chronic low-grade exposure. The smaller airways appear to be particularly affected by nitrogen dioxide. Abbe⁴³ found a delayed onset of marked increase in airway resistance in all of 5 normal subjects exposed to 5 ppm of nitrogen dioxide for 10 minutes.

The structures in the lungs that are most sensitive to inhalations of ozone are the alveolar capillaries. Exposure of human volunteers to inhalations of 0.6 to 0.8 ppm of ozone leads to a reduction in carbon monoxide diffusing capacity but no effects on pulmonary compliance. Young, Shaw, and Bates⁴⁴ have studied effects of 0.70 ppm of ozone in the absence of all other pollutants on normal subjects. The most striking findings were inhibition of deep breathing, presumably by stimulation of receptors in the upper airways. Airway resistance was also significantly increased. Inhalation of higher concentrations caused bronchoconstriction.

An intriguing area requiring further study involves the possibility that certain pollutants might stimulate the production and/or liberation of some vasoactive humoral substances that play roles in allergic reactions. For example, nitrogen dioxide inhalation induces histamine release in the rat⁴⁵ Workers exposed to certain industrial inhalant pollutants showed increased sputum histamine.⁴⁷

EFFECTS OF GEOGRAPHIC CHANGES ON ALLERGIC PATIENTS

The possible beneficial effects of a geographic move for patients with allergic respiratory disease, particularly asthma, have been considered for many years. Variations in the degree of improvement, or lack of it, have been reported by many clinicians, with the admission by most investigators that multiple factors, such as allergens, climatic elements, and emotional components, in addition to air pollutants, may be playing a role. A number of studies, as reviewed by Ferris and Whittenberger,⁴⁸ have suggested an increased incidence of asthma in geographic areas of high, as compared with low, general air pollution. Some studies have the inherent defect of not taking into account other elements of life style that may differ between large urban centers and small rural communities.

More impressive would be a pattern of rapid decreases in the intensity of

asthmatic symptoms in the same subjects following moves from areas of high to those of low air pollution. This phenomenon has been reported in at least two studies.^{14, 19} There is also some information concerning movement of asthmatic patients within a geographic area. Motley, Smart, and Leftwich⁴⁹ found that lung volumes became more abnormal in patients with chronic obstructive bronchopulmonary disease (particularly emphysema) during periods of heavy smog in Los Angeles. Significant improvement in these function studies occurred following hospitalization for 40 hours in a room with filtered air. Results from studies carried out in environmental control units, such as that described by Fontana and Rappaport,⁵⁰ will be of considerable value in helping to assess the effects of sudden changes in the levels of air pollutants.

Preliminary results of a study on the migration of faculty members of the University of Alberta are available.⁵¹ Of those members of the faculty and their families who had asthma, approximately 50 per cent improved with their first move, but the improvement had no relationship to a particular geographic locale. With further moves, there was no change in the percentage of improvement. A greater number reported that they were better in urban, rather than in rural, areas and were also better indoors than outdoors.

CONCLUDING COMMENTS

This limited survey of studies investigating the possible effects of air pollution on allergic respiratory disease shows why many observers are reluctant to attribute a definite adverse role to air pollution. Most of the data¹ is epidemiologic without strong convincing evidence for pathogenetic mechanisms. It would be the easier path to assume a nihilistic attitude and demand scientifically convincing proof (preferably with controlled inhalation exposures) before one accepts that air pollution aggravates asthma. Yet, for logistic, ethical, and possibly other reasons, data meeting these scientific criteria are not yet at hand. It is sometimes difficult to determine which of the patients frequently classified together in these epidemiologic studies as "chronic obstructive bronchopulmonary disease" are asthmatic, as compared with those having chronic bronchitis. Bates¹ has pointed out that certain epidemiologic findings cannot be ignored and are probably significant to those caring for patients with asthma:

1. Episodes of acutely increased levels of sulfur dioxide and particulate material of sufficient magnitude are associated with increased morbidity and mortality from chronic obstructive bronchopulmonary disease. This is more apparent in older patients.

2. Chronic exposures to relatively high concentrations of sulfur dioxide are associated with increased morbidity from chronic obstructive bronchopulmonary disease in adults and increased respiratory infection in infants. High levels of nitrogen oxides have also been associated with increased pulmonary infection in young children.

3. There appears to be an additive element in the combination of cigarette smoking and high levels of environmental air pollution leading to adverse effects.

Data from the much less common inhalational exposure studies do not conform precisely with the epidemiologic findings, possibly because of methodology employed, acute versus chronic exposures, and differences between experimentally constructed and naturally occurring air pollutant patterns. Obviously, more studies involving controlled experimental responses are needed wherever ethically feasible.

In the interim, it seems reasonable for physicians caring for asthmatic patients to be continually aware of the possibility that air pollution may be an aggravating factor, with appropriate periodic questioning of the patient concerning sudden alteration in symptom patterns related to peaks of air pollution and changes in geographic locale.

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