PAPER NO. 1

CHEMICAL INTERACTIONS IN COMPLEX ATMOSPHERES AND THE EFFECT ON UPTAKE OF INDIVIDUAL COMPONENTS BY THE LUNG

Michael T. Kleinman

University of California, Irvine
Department of Community and Environmental Medicine
California, Irvine 92717

INTRODUCTION

The fraction of an inhaled toxic compound which penetrates the upper airways to the lung parenchyma will constitute the biologically effective dose; this dose can be altered by several phenomena. The principles involved have been reasonably well documented for particulate matter and for individual gases and vapors. Relatively complex gas, vapor, and particle mixtures are, however, more difficult to characterize. Among the likely processes which might alter the magnitude or site of deposition are the alteration of particle size, changes in the aerodynamic properties of the airways themselves, adsorptive phenomena that allow otherwise easily removed gases or vapors to penetrate more deeply within the respiratory tract, and the formation of new, labile (but potent) toxic agents.

Changes In Particle Size

The locus of deposition for an aerosol in the respiratory system depends upon the particles' aerodynamic size, their shape, and the aerodynamic characteristics of the airways through which they are moving. These factors have received a great deal of attention over the years, and many of the important considerations are well enough understood to have been incorporated into reasonably predictive mathematical and conceptual models. For example, several models are published which predict deposition of inhaled particles as functions of size, airway characteristics, and respiration rate and volume (Yeh et al., 1976; Yeh and Shum, 1980; Chan and Lippmann, 1980). These models generally assume that particle size does not change while in the airways. Other models predict changes in the size of hygroscopic aerosols in the atmosphere (due to accretion of water) as a function of humidity. Currently, there are efforts underway to combine these

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SESSION I

FACTORS INFLUENCING LUNG TOXICITY OF ATMOSPHERES

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T. Timothy Crocker, M.D.
University of California, Irvine
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relationships, thus determining the patterns of deposition of hygroscopic aerosols from ambient atmospheres entering the relatively saturated humidity of the respiratory system (Martonen, 1984).

Changes In Aerodynamic Characteristics Of Airways

Changes in the thickness and composition of the airway's mucus coating and alterations in airway diameters, airway branching angles, ventilation frequency, and tidal volume are all factors that might affect the patterns of particle and gas deposition along the respiratory tract. Such changes might be induced if, for example, one were to inhale a toxic material that had irritant properties. Thus, inhalation of an irritant that affects the upper airways, such as sulfur dioxide (SO_2), can provoke bronchoconstriction in sensitive individuals (Sheppard et al., 1980) and a shift to slower and deeper breathing patterns (Kane and Alarie, 1979). This breathing pattern should maximize the absorption of inhaled SO_2 on upper airway surfaces, reducing the amount that might penetrate to target sites in the deep lung (Kleinman, 1984). Figure 1 shows, for a hypothetical airway, how penetration of a water soluble gas varies as a function of airway diameter and ventilation rate. On the other hand, the inhalation of a less water soluble gas, ozone (O_3), which is a deep lung irritant, triggers a shift to a rapid, shallow breathing pattern; an opposite shift to that observed with SO_2. Reducing the depth of breathing should, presumably, lower the probability of the O_3 penetrating to the parenchyma. These shifts are apparently "protective" reflex reactions under most circumstances. If, however, O_3 and SO_2 are present simultaneously in inspired air, the "antagonistic" responses to each gas might vitiate any protective benefits of the altered breathing pattern.

Bronchoconstriction induced by inhaled irritant gases in a gas/particle mixture might also lead to increased particle deposition in sensitive airways. Phalen et al. (1985) have reported that tracheobronchial deposition of particles would be increased if the diameters of those airways were reduced in size (as if one were to compare child and adult-sized airways).

Adsorption Of Gases On Aerosols

Several studies have demonstrated increased biological responses to inhaled irritant gases when the gases were administered concurrently with aerosols; the aerosols were considered to be innocuous if administered alone.

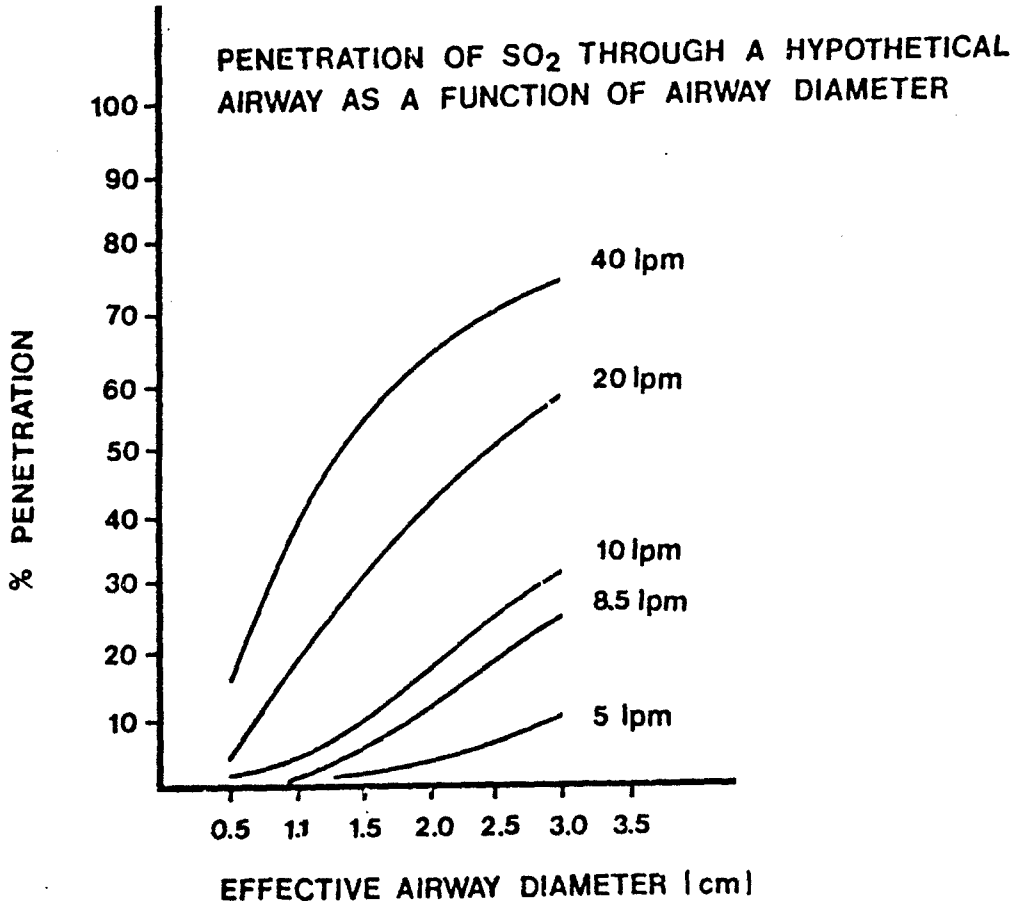

Figure 1. Changes in penetration of a gas through an airway as a function of ventilation rate and effective airway diameter.

For example, SO_2 plus sodium chloride (NaCl) aerosol was found to increase airway resistance in a sensitive animal model (McJilton et al., 1973; 1976) and in allergic, non-asthmatic human volunteers (Koenig et al., 1982) even though responses to SO_2 alone, at the same concentration, were not significantly different from controls. A likely mechanism that might account for this enhancement is that the toxic gas adsorbed onto the water soluble aerosol and might thus penetrate deeper into the lung than if the gas had been administered alone (Winchester et al., 1984). In other instances, however, such adsorption might be protective, as in the case where the adsorption of ammonia onto inhaled acidic particles results in the complete, or at least partial , neutralization of the particle's acidity (Larson et al., 1977).

Formation Of New Toxic Compounds

Aerosols, gases, and vapors may interact to yield products that may play an important role in altering the severity of health effects caused by exposure to pollutant mixtures. Epidemiological analyses of data from severe air pollution episodes have linked exposure to sulfur and nitrogen oxides (both gases and particles) to effects on health. Human clinical and animal toxicological studies of individual gaseous compounds and even some gas mixtures at "worst-case" ambient levels do not, however, convincingly support these findings. Ozone is an exception; health effects are observed after inhalation exposures to concentrations in the 0.1 to 0.3 ppm range when an additional stress such as exercise is imposed on the test subjects. One can therefore hypothesize that some of the epidemiologically observed health effects may be due, not to the gas phase materials alone, but to the products of the complex interactions of the gaseous and particulate components which were present in the atmosphere during those severe episodes.

The de novo toxic agents are likely to be highly reactive and, hence, short-lived. Because of their lability, such compounds are difficult to detect and measure in complex atmospheric mixtures; it is also difficult to isolate their effects in toxicological studies. We can examine a relatively simple example of this type of gas/particles interaction; that between SO_2, aerosols, and oxidant gases, all components of urban air pollution.

RECENT EXPERIMENTAL STUDIES

Kleinman et al. (1984a; 1985) have demonstrated that ammonium sulfate droplet aerosols, "laced" with iron and manganese ions as catalysts, will adsorb $^{35}SO_2$ (5.0 ppm) at a rate equivalent to 0.03% per hour, in a laboratory simulation of the aging of pollutant mixtures. The experiments were carried out in a unique plug-flow reactor system which is shown, schematically, in Figure 2. The aerosol concentration was 1 mg/m^3; the particles had a mass median aerodynamic diameter of 0.5 μm. When oxidant gases, either O_3 (0.6 ppm) or nitrogen dioxide (NO_2, 5.0 ppm), were added to the SO_2/aerosol mixture, the rate of adsorption increased; 25-fold for NO_2 and 50-fold for O_3 (Figure 3). The eventual fate of the adsorbed SO_2 is conversion from the sulfur (IV) to sulfur (VI) state; the end-product is most likely sulfuric acid; however, several other toxic intermediate compounds may be present as well.

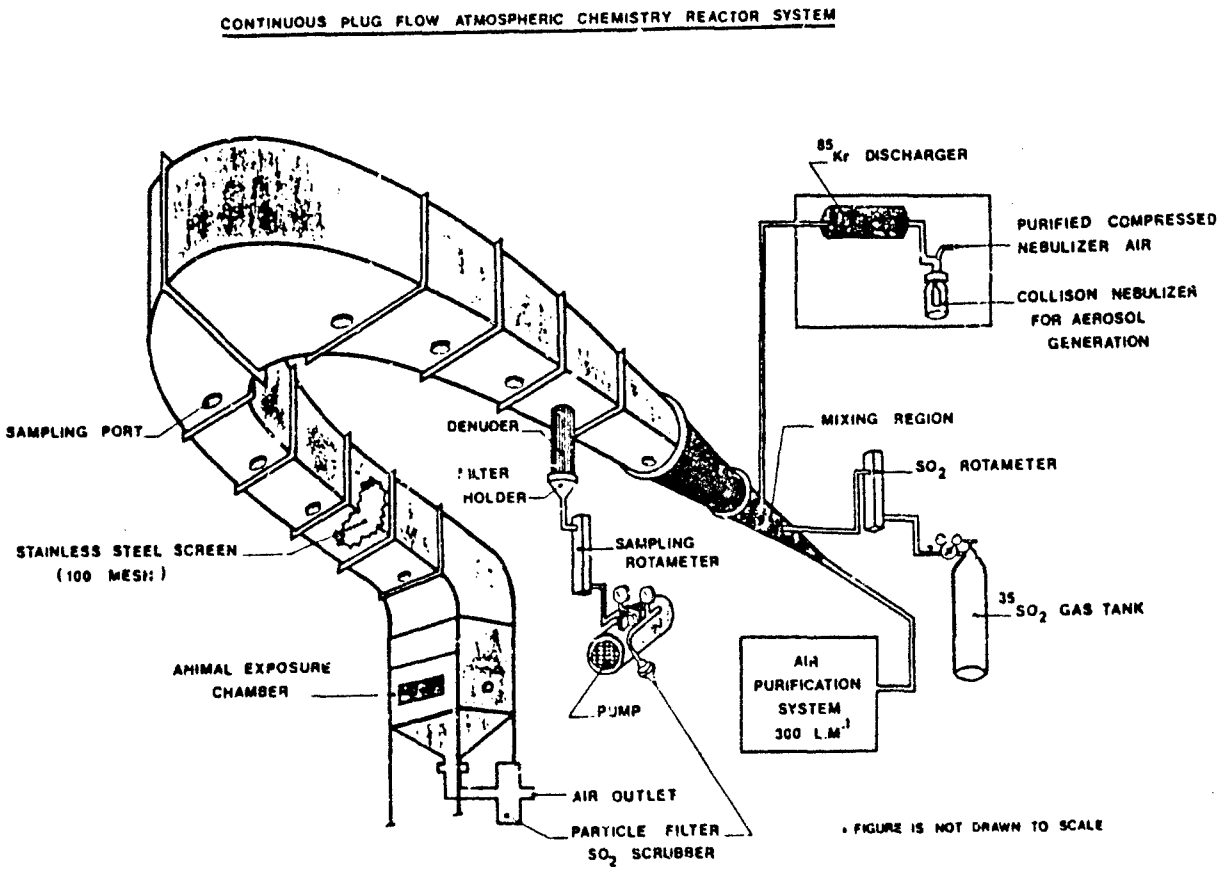

Figure 2. Schematic representation of the Air Pollution Health Effects Laboratory Aging Line system for atmospheric chemistry and inhalation toxicology studies.

Given the circumstances in which toxic end-products might form, the question remains, are gas/aerosol mixtures more toxic when compared to the effects of the gases alone? We have addressed this question in a study in which rats were exposed to mixtures of acid and non-acid aerosols (1 mg/m^3), O_3 (0.6 ppm), and SO_2 (5.0 ppm), to purified air, as a negative sham control, and to O_3 (0.6 ppm) as a positive control. Both the mixture and O_3 alone caused significant changes in the histopathology of alveolar epithelium and in the ability of the lung to clear foreign particles deposited in the airways. The mixture was slightly more effective than O_3 alone in altering clearance (Mannix et al., 1984), and there was a trend towards enhancement of O_3-induced histopathological lesions in exposed rats. As shown in Figure 3, the acidity of the aerosol correlated with the degree of enhancement (Kleinman et al., 1984b).

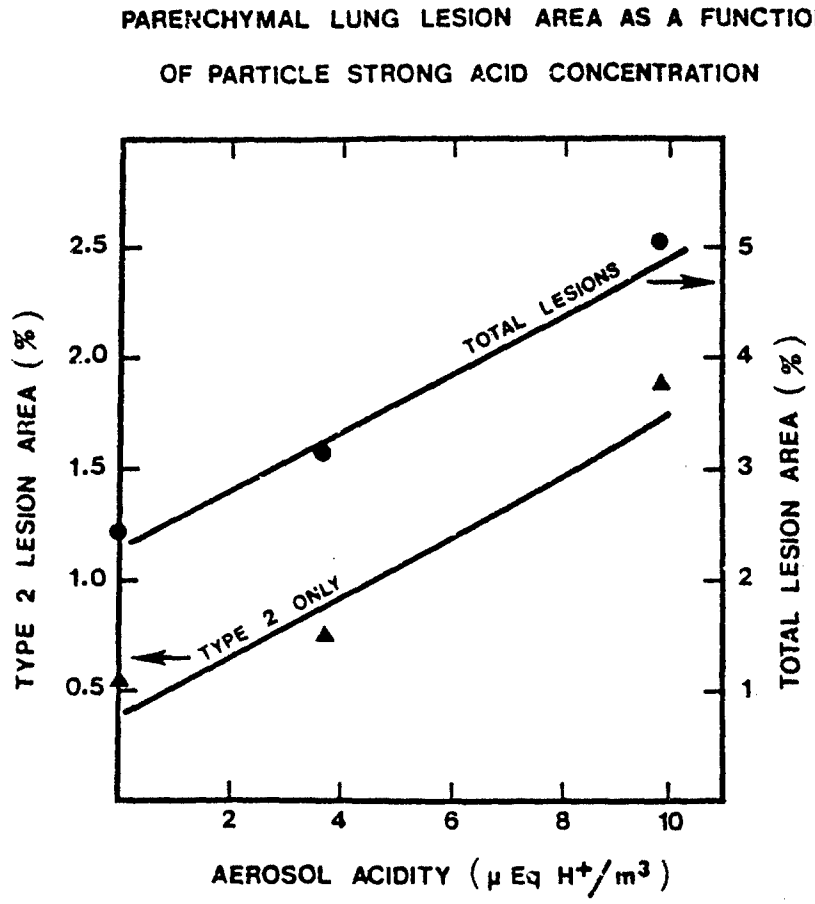

Figure 3. Enhancement of ozone-induced lung parenchymal lesions during concomitant exposure to aerosols of varying acidity. Type 2 lesions represent thickening of alveolar walls due to cellular infiltration. Type 1 lesions (not shown) represent the presence of free cells in alveolar air spaces. The totals shown are the sums of Type 1 and Type 2 lesions.

CONCLUSIONS

Chemical and physical interactions between components in complex mixtures as represented by the polluted urban atmospheres can modify the toxicity of the mixture. This poses very real problems for those responsible for establishing relevant air quality guidelines which will protect exposed populations. The data base from which one can expect to extrapolate useful health effects information is very limited with respect to the health

effects of mixtures. The problem is also of great importance to the field of Industrial Hygiene. Other factors, which were not explicitly addressed in this paper, but which should also receive consideration, might be the interactions of physical stresses such as exercise and heat exposure with effects of inhaled toxic substances. Mautz (1984) has reported that exercise greatly increases the potency of O_3 in forming lesions in the lung parenchyma. Sheppard et al. (1981) have reported that exercise can enhance SO_2-induced bronchoconstriction in individuals with asthma. Little information on heat (or cold) is available in this context; however, inhalation of cold air can cause bronchoconstriction in people with asthma. Concurrent inhalation of SO_2, at concentrations as low as 0.1 ppm can cause modest potentiation of the bronchoconstriction attributable to breathing dry, cold air (Sheppard et al., 1984). As previously noted, reduction in airway diameter may increase the amount and alter the distribution of toxic substances deposited on airways. This may in some measure explain Sheppard's results. It is hoped that greater attention will be given to these factors in future assessments of the toxic effects of inhaled pollutants and other hazardous materials.

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