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ATMOSPHERIC POLLUTION: THE HAZARD TO HUMAN HEALTH

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ATMOSPHERIC POLLUTION: THE HAZARD TO HUMAN HEALTH

I. Principal Air Pollutants

A. Particulates

1. General Consideration

A "particle" may be defined as "any dispersed matter, solid or liquid, in which the individual aggregates are larger than simple small molecules (about 0.0002 μ in diameter) but smaller than about 500 μ" (1). The term "suspended particulates" is generally applied to particles between 0.1 - 10 μ. Suspended particulates are of particular concern in consideration of health effects of air pollution for several reasons:

a. They comprise the largest mass of air pollutants

b. They reflect local emission sources (and to some extent, local soil) by chemical composition; and

c. Their size permits significant deposition in the respiratory tract.

Multiple sources contribute to the atmospheric load of particulate matter. Very small particles (<1 μ) are generally formed by condensation and thus tend to reflect principally the products of combustion and photochemical reactions. Particles between 1 - 10 μ generally derive from combustion and industrial processes. Larger particles (>10 μ), termed "dustfall" are of limited interest because their size limits their distribution in the atmosphere and in the respiratory tract.

2. Measurement

Because of the relative simplicity of measurement far more data has been accumulated on particulates than any other air contaminant. Dustfall may be estimated with several types of impacting devices but this measurement is usually obtained by collecting specimens in open bottles (dustfall jars) or on adhesive surfaces. Following a prolonged exposure (usually several weeks), the specimen is weighed and the result expressed either as mg/cm^2 or $tons/mi^2$. Obviously, this is a crude index which is fraught with potential error.

Suspended particulate matter is measured by drawing large volumes of air either through a fine mesh filter and weighing (hi-volume sampler) or through a strip of filter paper and measuring the resultant reduction in light transmission (AISI tape sampler).

Results from the former are expressed as mcg/m^3, from the latter in terms of "coefficient of haze" (coh) units - the latter units are similar to those used to describe "smoke" in some areas. The gravimetric system has been preferred in the U. S., although tape samplers are still widely used. Material collected on a filter is readily available for further characterization; relatively little use is made of this potential except to determine the amount which is benzene soluble as a measure of organic particulates.

Measurements of suspended particulates vary considerably in the U. S., reflecting local emissions, topography, and mete rology (Table 1). As indicated, Dallas levels are intermediate; background levels in this area are about 20 mcg/m^3 (2).

TABLE 1

Suspended Particulate Concentrations In The Air Of Various U.S. Cities (Geometric Mean 1961-65) (1)

	$\mu g/m^3$
Chicago - Gary	177
St. Louis	168
Denver	147
Los Angeles	146
Cleveland	134
Dallas	99
New Orleans	93
Seattle	77
Miami	58

3. Toxicology

In general, toxic effects of particulate matter depend on the material, site of deposition, and the effectiveness of respiratory tract clearance mechanisms. While the majority of particulates are apparently inert, ambient air may contain small amounts of substances with known toxicity such as lead or asbestos; these will be considered in a subsequent section. The site of deposition within the respiratory tract depends on particle size, density, and to a lesser extent, the pattern of breathing (3-5). Alveolar deposition is maximum with particles in the 1 - 2 μ range, minimum retention occurs near a size of 0.3 μ, but retention rises as particle size further decreases, as the predominant force in deposition shifts from gravitational settling to diffusion.

In man, inhalation of massive amounts of inert dust produces an increase in airway resistance (6). McDermott examined the airway responses of normal men breathing varying concentrations of coal dust with a particle size of 1 - 7 μ; no response was seen up to 9 mg/m^3 but progressive increases in airway resistance occurred at 19, 33, and 50 mg/m^3 (7). These concentrations clearly greatly exceed ambient levels of particulate matter.

There is considerable evidence that inert particles modify the response of the lung to noxious materials. "Dust loading" evokes a brisk increase in numbers and metabolic activity of alveolar macrophages (8), and an increase in the rate of pulmonary clearance of subsequent challenges (9, 10).

On the other hand, Boren has studied the dual administration of NO_2 and carbon in mice; carbon alone produced no pathologic changes, NO_2 alone produced pulmonary edema, but NO_2 absorbed to carbon produced focal destructive lesions (11). Other studies have suggested that the combination of benzo (a) pyrene and hematite particles produces pulmonary neoplasms in a high percentage of experimental animals when benzo (a) pyrene alone did not (12). The interaction of various types of particulate matter and other substances in the atmosphere is difficult to study because of the complex composition of polluted air and this important area has received little attention. Also, particulate aerosols containing certain micro-organisms or allergens may have significant toxicity for susceptible individuals.

Thus, particulate matter may play an important role in human disease by modifying respiratory tissue responses to other materials, serving as the carrier agent for certain absorbed substances, as well as through direct toxic effects. Particulates, in addition, serve as an easily measured index of atmospheric pollution.

B. Sulfur Oxides

1. General

The combustion of sulfur containing fossil fuels produces the oxides of sulfur, sulfur dioxide (SO_2) and sulfur trioxide (SO_3). SO_2, the most prevalent product, is a highly water soluble, colorless gas which is a potent irritant in the respiratory tract. SO_3 may be produced directly or formed by the oxidation of SO_2 in the atmosphere. SO_3 combines immediately with water to form sulfuric acid. The oxidation of SO_2 may occur by either catalytic or photochemical mechanisms.

2. Measurement

The standard measurement of SO_2 adopted by the National Air Pollution Control Agency is a modification of the West-Gaeke Method, a colorimetric assay. Assay equipment has been automated so that continuous measurements can be obtained. Lead peroxide "candles" are used to detect the presence of all sulfur containing compounds which are capable of forming sulfates. The candle is exposed for prolonged periods, usually 1 month, and the lead sulfate formed determined. Such measurements are useful guides to average levels of sulfation but give no information about peak values. "Suspended sulfate" may be determined by analysis of material trapped on the filter of a hi-volume sampler.

The tendency of SO_2 measurements to vary rather widely within a given locality has caused considerable uncertainty about the most significant expression of SO_2 concentrations. Since it is an irritant and may have short-term biologic effects, measurements have been expressed using 5 minute average concentrations. Because of the variation in such expressions, however, SO_2 concentrations are usually reported as a 24-hour mean. Representative results from several U. S. metropolitan areas are given in Table 2. Long-term sampling data based on colorimetric assays (West-Gaeke) is available from relatively few sites; most of the literature on health effects is based on lead peroxide candle measurements or "sulfation rates".

TABLE 2

Sulfur Dioxide Concentrations In The Air Of Various U. S. Cities
SO_2 (ppm) - 24-hour average

	Annual Geometric Mean	Peak
Chicago	0.121	0.79
Denver	0.015	0.06
Los Angeles	0.015	0.06
San Francisco	0.007	0.08
Dallas	0.003	--

3. Toxicology

SO_2 is detectable by most persons by taste at concentrations of 0.3 - 1.0 ppm (part per million) in air. Amdur has studied the acute effects of SO_2 extensively in experimental animals and man. These results may be summarized as follows:

a. In guinea pigs, air flow resistance increases progressively between SO_2 concentrations of 0.16 - 835 ppm

b. In humans, airway resistance increases at concentrations of SO_2 of about 5 ppm

c. In both animals and human studies, a wide individual variation in response has been noted with a tendency for individuals with higher baseline airway resistance to show increased sensitivity to SO_2.

d. Whether the subject is breathing through his nose, mouth, or tracheostomy makes a large difference in response to SO_2. Being highly water soluble, a significant fraction of inspired SO_2 is absorbed in the upper respiratory tract (14, 15).

The effects of combined particulate matter and SO_2 aerosols are again heavily based on Amdur's work (16). In the guinea pig, submicron particles (NaCl) potentiate the response to SO_2. Aerosol material capable of catalyzing the oxidation of SO_2, such as ferrous iron, manganese and vanadium, also potentiate the response. No clear pattern has emerged from the few human studies on SO_2 exposure combined with particulate aerosols. When an involved technique, such as airway resistance measurement by body plethysmography is employed, the number of subjects studied is small and differences between results of individual investigators may be explained by the number of "hyper-responders" in the study, as well as technical considerations of particle size, control, duration of exposure, mouth or nose breathing, etc. As Amdur has stated, blanket statements that "particulate matter potentiates the response to SO_2" cannot be made on the basis of available data (14).

Chronic exposure of animals to SO_2 has led to some interesting findings of unknown significance. Reid has worked extensively with animal models of chronic bronchitis produced by 5 - 6 weeks of exposure to SO_2 in the range of 300 - 400 ppm (17). The response of individual species to SO_2 depends on the location and type of mucus secreting cells in the respiratory tract. Exposure to SO_2 in the concentrations more nearly that of ambient air have shown no effect in guinea pigs after 1 year of SO_2 (0.1 and 1.0 ppm). Guinea pigs exposed to 5.0 ppm for 1 year had a significantly higher survival rate than controls (18).

Toxicologically, SO_2 is an irritant which produces bronchoconstriction in sensitive individuals at concentrations not greatly different from those which may occur in the atmosphere. In experimental animals, massive exposure is required to produce histologic alterations in the lung. The widespread concern that SO_2 is instramental in producing chronic disease is not supported by toxicologic evidence.

C. Oxidants, Hydrocarbons, and Nitrogen Oxides

1. General

These compounds will be considered together since they arise from common sources, the combustion of fossil fuels, and their concentrations in the atmosphere are interrelated. A detailed review of current knowledge about these compounds is available (19). In brief summary, incomplete combustion of fossil fuels (coal, petroleum products, natural gas) leads to the emission of unsaturated hydrocarbons, carbon monoxide, and aldehydes; the high combustion temperatures oxidize atmospheric nitrogen to nitric oxide (NO) and sulfur contaminants in the fuel to SO_2; in the atmosphere, under the influence of sunlight (hence "photochemical"), further oxidation occurs with the formation of a new series of compounds, some of which can oxidize reagents not readily oxidized by oxygen and are termed "oxidants". Ozone, NO_2, and peroxyacetyl nitrate (PAN) account for most of these photochemical oxidants.

2. Measurement

The recommended reference technique for oxidant measurement is the neutral-buffered KI method in which oxidants liberate free iodine which can be measured colorimetrically or coulometrically. Continuously recording instruments for these measurements are available. One major drawback is that reducing substances, like SO_2, interfere with the reaction and can be only partially removed. Thus, the measured concentration of oxidants may be lower than that actually present. Reference techniques for measurement of NO_2 and hydrocarbons have not been published by NAPCA.

Oxidant measurements have been made on two occasions in Dallas (Table 3). Additional information has been obtained by measuring the depth of cracks in exposed rubber strips, an effect related to ozone exposure.

TABLE 3

Oxidant Concentrations In The Air Of Various U. S. Cities
Oxidant (ppm) - hourly average

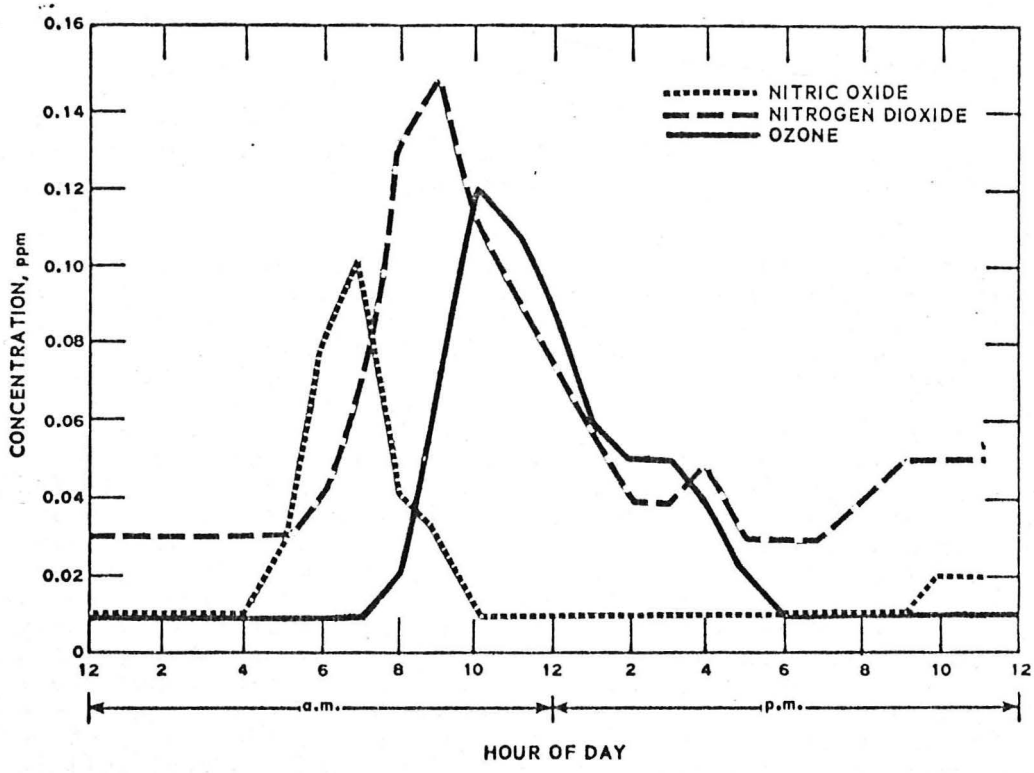
	Annual Average	Max. Hourly Average
Pasadena	0.042	0.46
Denver	0.036	0.25
Philadelphia	0.026	0.25
Chicago	0.028	0.19
Dallas	0.030*	0.19

*Based on a 30-day sample in May, 1969. Exceeds by a factor of 10 the only other measurements in Dallas obtained during 6 months of sampling, January - June, 1969.

NO_2 has been measured by the National Air Surveillance Network (NASN) Station in Dallas; samples range between 0.018 - 0.164 ppm. NO_2 alert stages begin in Los Angeles at concentrations of 3.0 ppm.

The diurnal variation in concentrations of these substances is presented graphically in Figure 1. While this particular graph was obtained from Los Angeles data, the pattern is basically the same in all cities.

FIGURE 1



Diurnal variation of NO, NO_2, and O_3 concentrations in Los Angeles, July 19, 1965 (19).

3. Toxicology

Hydrocarbons exert virtually no demonstrable acute toxic effects at levels which are likely to occur in the atmosphere. Some aliphatic and alicyclic hydrocarbons produce minor symptoms at levels approximately of 5000 ppm. Aromatic hydrocarbons such as benzene, have well known toxicity but only at concentrations exceeding 25 - 100 ppm. The significance of the class of compounds in the atmosphere arises from their interactions with other compounds and their role as potential carcinogens.

There have been several studies of experimental exposure to oxidants in human volunteers. These include: ozone 0.6 - 0.8 ppm for 2 hours (measured D_{LCO}) (20), ozone 0.1 - 1.0 for 1 hour (airway resistance) (21), ozone 0.5 ppm for 3 hours/day for 12 weeks ($FEV_{1.0}$) (22). Each of these functional parameters was significantly altered by the stated exposure.

An alternative exposure was studied by housing patients with COPD in an environmental chamber in Los Angeles and exposing them to ambient or filtered air for a week at a time (23). Pulmonary function studies repeated daily showed a significant relation between increasing oxidant concentration and increasing airway resistance.

Accidental exposure of man to high concentrations of ozone or NO_2 results in acute pulmonary edema. High concentrations of NO_2 may occur in silos ("silo-fillers disease"), from welding, or in fires consuming certain materials (the Cleveland Clinic fire in 1929 burned 50,000 nitrocellulose x-ray films and produced estimated concentrations of NO of 51,500 ppm, CO 39,825 ppm, and HCN 5,435 ppm) (24). Although probably not directly extrapolatable to man, the concentrations required to produce pulmonary edema in animals are ozone, 3.2 - 6.0 ppm (25, 26) and NO_2, over 25 ppm (27). These concentrations represent a relatively narrow tolerance over levels which may occur in the atmosphere. Irreversible structural changes, including "emphysema" and fibrosis, occurred in several animal species chronically exposed to ozone, 1 ppm (28). Of greater interest is the demonstration that a synthetic smog exposure, with concentrations of several oxidants and NO_2 paralleling those found during alerts in Los Angeles, or NO_2 exposure alone, 5 - 16 ppm, produce pulmonary damage within 1 - 3 hours (29, 30). Using mice, rabbits, and dogs, these investigators described similar lesions characterized by endothelial cell swelling which obliterated alveolar capillaries, associated with the local accumulation of PMN's. This sequence of events may prove to be highly significant in the pathogenesis of emphysema.

Chronic exposure to low levels (1 - 18 ppm) of NO_2 produces hyperplasia of the epithelium of terminal bronchioles and lung hyperinflation (31). Whether or not this represents emphysema is unclear

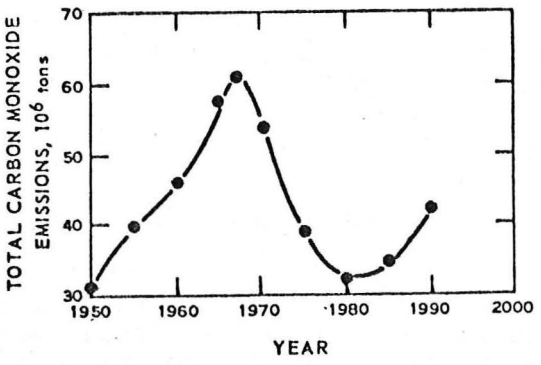
as the hyperinflation and dilatation of air spaces has been reported to be reversible (27). This conflict typifies the controversy over the adequacy of experimental emphysema models which arises principally when one tries to relate the results of different investigators using different techniques. Also, the problem of infection is difficult to control during prolonged exposures to toxic gases. Ozone, NO_2 and SO_2 have been demonstrated to inhibit the bacterial clearance mechanisms of the lung (32, 32a). Since the lungs of apparently normal laboratory animals frequently show evidence of chronic mycoplasmal or viral disease, it seems likely that infection may account for some of the variation in response noted. Exposure of germ-free mice to NO_2, 40 ppm for 6 - 8 weeks, resulted in the terminal airways' hyperplasia only; evidence of parenchymal tissue destruction was not seen (33).

D. Carbon Monoxide

1. General

Worldwide emissions of CO amount to approximately 200 million tons annually (34). Despite this atmospheric loading, background levels of CO do not appear to be rising and are on the order of 0.03 - 1.0 ppm. Motor vehicles account for nearly 60% of CO emissions nationwide and approach 100% in some areas. With the abatement legislation currently in force, emissions of CO from motor vehicles will decrease between 1970 and 1980, despite an increasing number of cars (Figure 2).

FIGURE 2



Forecast of total carbon monoxide emissions from motor vehicles (34)

2. Measurement

CO may be measured with a variety of techniques; the best currently available device is the nondispersive infrared analyzer which can operate continuously and measure concentrations between 1 and 25 ppm. Gas chromatographic techniques are being developed for semicontinuous operation which will extend the range of observation.

CO concentrations fluctuate widely within a locality, parallel traffic activity in the immediate vicinity of the sampler, and rise notably in stagnant air conditions. Because blood COHb levels equilibrate in 8 hours in people breathing low concentrations of CO, ambient measurement of CO is usually expressed in 8-hour averaging times. Representative results are presented in Table 4.

TABLE 4

Carbon Monoxide Concentrations In The Air Of Various U. S. Cities
CO (ppm) - 8-hour average

	Annual Geometric Mean	Maximum
Chicago	13.4	44
Denver	6.9	37
Los Angeles	9.9	32
St. Louis	5.6	21
Dallas	6.0*	21

*Based on a 30-day sample in May, 1969.

3. Toxicology

More than any other atmospheric pollutant CO presents the dichotomy between well established toxicity data relating to acute exposures and the search for deleterious effects associated with chronic exposure to low concentrations. Several reviews of the latter have been published recently (34 - 36) and only brief comment will be made here.

While microscopic damage has been observed in the myocardium of dogs exposed to 100 ppm CO for 6 - 11 weeks (37), more recent studies have had a functional orientation. A variety of psychomotor tests have been used to study the CNS effects of CO exposure. Modification of learned behavior in animal species from rats to monkeys has been studied. In man, a number of tests of visual thresholds, time perception, flicker-fusion, driving ability, and EEG changes have been reported (34, 35). In summary of these experiments it can be stated only that impairment of certain isolated

visual functions may occur at COHb concentrations of 2.5 - 5.0% -- further substantiation of these data and studies of their significance are required.

Ayres, et al, have studied myocardial blood flow and metabolism during cardiac catheterization in a small group of patients in whom COHb concentrations of 5 - 10% were produced (38). Coronary blood flow increased in patients with noncoronary heart disease but not in patients with coronary artery disease. Myocardial oxygen extraction (ml/100 ml blood flow) decreased in all patients and was associated with lactate production in the patients with coronary artery disease. This study indicates that relatively modest levels of COHb may cause a hypoxic stress of the myocardium in patients with compromised coronary circulation.

Lastly, Astrup, et al, have presented evidence that CO exposure in cholesterol-fed rabbits accelerates the appearance of atheromatous disease (39). Similar but less marked changes were seen with hypoxia.

It should be noted that cigarette smoke has a CO concentration of about 20,000 ppm (2%). The average concentration inhaled is about 4 - 500 ppm. Thus, COHb levels are clearly higher in smokers than nonsmokers, 5.9% versus <1.0%. Continuous exposure of nonsmokers to CO, 30 ppm, results in COHb concentrations of about 4% in 4 hours, 5% in 8 hours (34). Under usual ambient air conditions, smokers will excrete CO as the pCO of alveolar capillary blood exceeds that of ambient air. The net effect of this is that, for a given environmental exposure, the %COHb of smokers will decrease while that of nonsmokers will increase. Elevation in ambient CO concentration will slow the role of excretion of CO by smokers as there is less gradient for diffusion, thus exposing them to a higher mean COHb concentration.

In summary of the information presented, it is clear that the toxicologic approach has not provided much evidence that various air pollutants tested are causally related to disease states in man. Some of the shortcomings of a toxicologic approach have been mentioned. In particular it should be emphasized that demonstration of an "effect" does not constitute evidence of disease, nor the potential for producing disease. The bronchoconstriction that follows the experimental administration of various pollutants may be interpreted as a normal defense mechanism in response to a noxious stimulus. The intriguing area of adaptation to various agents has not been mentioned -- it is conceivable that the mechanism which causes a diminished response to ozone on repeated exposure, for example, is responsible for long-term alterations, not the ozone per se.

II. Epidemiologic Considerations

Epidemiologic studies encounter the problems of selecting representative populations, recognizing the effect or disease under study and, in particular, encounter the pitfall of assigning causality to associated phenomena. In the following discussion the term "associated with" is not meant to imply a cause and effect relationship -- while this formulation may be distressing to physicians trained in the concept of Koch's postulates, it appears to be a necessary restraint in the evaluation of these data.

A. General Mortality

A crude assessment of a potential health hazard is the total mortality rate and that adjusted for age, sex, and race. Using population data published for 114 Standard Metropolitan Statistical Areas and air quality measurements in these areas published by the National Air Pollution Control Administration, Lave and Seskin utilized the statistical technique of multiple regression analysis to show that both total and infant mortality rates are significantly related to both minimum values of suspended particulates and minimum sulfates (40). They calculated that a 10% reduction in particulates would decrease the total death rate by 0.5% and the infant death rate by 0.7%. Other factors of significance in determining the death rates were: the proportion of the population over 65, the proportion of nonwhites, the proportion of poor families, and the population density. One may question this conclusion on several grounds, besides an inherent distrust of statistics; the relation of the residence of the population to the air quality measurements reported is unknown, the reliability of the measurements is unknown, but most significantly the authors have assigned causality to air pollution and death by implying that a reduction in one, through abatement, would decrease the other. However, this is an important study in several regards. Air pollution and death rates show seasonal periodicity, both increasing during cold weather (41). By using death rates and pollution levels averaged over 3 years, Lave and Seskin avoid this problem. Also, by the large number of areas represented the effect of climate alone tends to disappear. Their analysis indicates that minimum levels of pollution are a more significant factor than peak or average values - this represents a notable departure from traditional views and would have major importance if substantiated.

Studies of death rates within a given community tend to support some of these conclusions. In Buffalo, New York, the major air pollution sources are located along the lake and prevailing winds produce 2 wide bands of heavy pollution traversing large sectors of the community (42). The city was divided into 4 regions with different levels of pollution and further divided in socioeconomic classes by census tract. Socioeconomic level had a strong correlation with pollution levels, i.e., poor people

lived in highly polluted areas but not in low, while the opposite pertained to higher socioeconomic classes. When standardized for economic status (middle income familes lived in all areas) a positive correlation between particulate pollution and death rate of white men and women 50 - 69 and over 70 years of age was found. Women were said to be of particular interest since they avoid, for the most part, the confounding variable of occupational exposure. A strong correlation was noted between levels of pollution and deaths from chronic respiratory disease. Respiratory deaths increased 300% from the area with the lowest average particulate level (<80 $\mu g/m^3$) to the highest (>135 $\mu g/m^3$). Unfortunately, information about smoking habits was not available.

The Nashville study has revealed a significant correlation of total respiratory disease deaths with sulfation and dustfall, and of postneonatal mortality with sulfation (43, 44). This study involved over 100 sampling sites and has provided by far the best aerometric information about variations in levels of air pollution occurring in a given city. It also serves to illustrate one of the problems with disease - specific mortality rates in that no correlation was found for emphysema/bronchitis deaths and levels of pollution. Mitchell, et al, have estimated that the frequency of underreporting of emphysema as a cause of death is approximately 50% (45). Emphysema, not including that associated with scars, was found in about 50% of autopsies when careful examination of inflated lungs was carried out and was severe in 6.5% of males (46). Emphysema/bronchitis appeared only 101 times in 32,000 deaths covering a 12-year period in Nashville.

Another factor which may be difficult to detect is the tendency of chronically ill persons to move out of heavily polluted areas, thus reducing the correlation with pollution levels (47). Of interest is that both the Nashville and Buffalo studies noted a significant correlation of gastric cancer and particulate levels which was not dependent on socioeconomic class.

The best study of lung pathology in relation to air pollution of which I am aware compared the incidence and extent of emphysema in 300 autopsies in St. Louis and Winnipeg using standardized examination of inflated lungs (48). Occupational and smoking histories were obtained in each case. Although the populations seem similar (age, length of residence, % women, % smokers), emphysema appeared earlier and progressed more rapidly in St. Louis. In the 20 - 49 year old group, emphysema was 7 times more common in St. Louis. Severe emphysema was found only in smokers, but rarely in Winnipeg, despite smoking. Air pollution levels are low in Winnipeg due to very favorable meteorologic conditions and little industrialization. This study needs to be confirmed in other localities, using similarly detailed tissue examination and historical information, to remove inherent racial, climatologic, and other factors which may explain the results.

B. Acute Mortality

A more sensitive index of the health effects of air pollution appears to be short-term (daily - weeks) mortality, especially that for respiratory and cardiovascular disease. Boyd analyzed the effects of temperature, humidity, SO_2 and smoke on winter mortality in London and the rural area of East Anglia between 1947-54 (49). In both areas, there was a high correlation of deaths from bronchitis (and pneumonia and heart disease) with low temperatures and high humidity occurring 1 - 2 weeks previously. Standardization of data for smoke and SO_2 lowered the correlation slightly which was interpreted to show that while levels of pollution did influence bronchitis death rates, climatology factors were more important.

Excess mortality was related to SO_2 and smoke concentrations of 0.4 ppm and 2000 mcg/m^3 respectively during the winters of 1954-57 in London (50). Analysis of daily mortality figures for 1958-60 in London led Martin to conclude that it would be "difficult to fix any threshold value below which levels of air pollution might be regarded as safe" (51). Peaks of mortality have been associated with increased levels of air pollution in New York City on several occasions (52 - 54). The measured levels of smoke in these episodes have been in excess of 5 - 6 coh units and of SO_2 in excess of 0.6 ppm. These episodes serve as examples of phenomena which have been noticed in other European countries, as well as Great Britain, Japan, and the U. S. They are reminiscent of the well-known episodes which occurred in the Meuse Valley, Belgium in 1930, Donora, Pennsylvania, 1948, and London, 1952, in that all occurred in cold weather, under prolonged thermal inversions and in areas with relatively high levels of air pollution under normal circumstances (55).

In seasonal occurrence and mortality effects many of these episodes parallel influenza activity. Indeed, epidemic influenza appeared in London during the December, 1952, air pollution disaster, and again in subsequent pollution peaks during December, 1957, and the winter of 1958-59 (56). A marked increase in mortality was noted in New York City during January - February, 1963, when high levels of air pollution (SO_2, 0.46 ppm; hourly average for 2 weeks; smoke, coh $\geq$4 units for same 2 week period), cold weather, and A_2 influenza coincided (57). When compared to control years with either similar air pollution, climatic or influenza conditions, the 1963 experience indicated an additive effect of the three on cardiovascular and respiratory mortality. Other causes of death were not affected.

While it is virtually impossible to remove the effects of weather, viral infections, and other unknown factors in the analysis of episodic mortality, the number of separate phenomena

occurring in a variety of localities, under varying conditions, but all associated with increased levels of air pollution supports the hypothesis that air pollution per se exerts a deleterious effect on human health. Chronically ill individuals, particularly those with chronic respiratory and cardiovascular diseases, are more susceptible.

C. Morbidity

1. Prevalence of chronic pulmonary disease

A number of studies have surveyed segments of the population for the prevalence of chronic pulmonary disease using questionnaires, x-rays and pulmonary function tests. The populations studied have varied from entire small towns to various employee groups such as New York mailmen to schoolchildren. Children offer certain advantages as a population group: they don't smoke, they have no occupational exposure, and they tend to live, attend school, and play within a small geographical region, thus standardizing their exposure to pollutants. Several large studies, showing that over-all 14% of schoolchildren in Great Britain have bronchitis, have indicated that: there is a marked inverse correlation between prevalence of chronic cough and social class; there is a strong correlation between bronchitis and upper respiratory tract disease, including otitis; the prevalence of bronchitis in children parallels that in adults geographically; children living in areas of high air pollution have more bronchitis (58 - 61). Studies in Japan, Canada, and the U. S., have also demonstrated that schoolchildren living in areas of heavy air pollution have more respiratory symptoms and a lower $FEV_{1.0}$ or peak expiratory flow (62 - 64).

Similar studies in adult populations have shown very clear trends but have not particularly clarified the role of air pollution. By far the most impressive trend is that virtually every epidemiologic study has demonstrated a difference in pulmonary function between smokers and nonsmokers which becomes greater with increasing age and/or increasing smoking history. The percentage of white males in the U. S. who have never smoked is less than 25%, for women 50 - 75%. The effect of this variable is so strong, both in producing respiratory symptoms and in reducing pulmonary function, that additional analysis of the data seems questionable. Factors besides the difficulty of obtaining accurate smoking histories and pulmonary function data complicate this type of analysis. The symptom of "cough" was found to have a reproducibility of 17% in 2 surveys of the same population of healthy women 6 months apart (65). The factor of "internal migration", or the tendency of symptomatic individuals to move out of heavily polluted areas has been mentioned. This was found to

be particularly true of persons who were still smoking - apparently they blamed their symptoms on the polluted air. In some of these studies (62, 65 - 71), it was concluded that air pollution contributed significantly to the occurrence of COPD in adults; in others, this effect, if present, was obscured by other factors (72 - 76).

2. Respiratory symptoms

Another epidemiologic approach utilized to study the effect of air pollution has been the relation of respiratory tract symptoms to pollution measurements in normal subjects or those with COPD. Symptoms are recalled by a questionnaire or recorded in a diary kept by the subject. Many of the studies cited previously have included questionnaires, including the studies in schoolchildren. An association between acute respiratory illness and air pollution (smoke and SO_2) was shown in Italian schoolchildren (77). An interesting study of New York City families found a rather surprising relationship between "summer colds" in children under 8 years of age and local levels of suspended particulates and CO (78). The relationship was not as clear during the winter months when, as all studies have shown, there is a marked increase in acute respiratory disease. Analysis of a large mass of data from these 469 families (a total of 61,000 subject weeks) showed that symptom complexes tended to occur under different but definable circumstances. Thus, "sore throat" occurred either on cold, wet, windy days with low levels of pollution, or on sunny, still days when oxidant levels were high (79). These authors stress that symptoms rarely correlate with single air pollutants.

Absenteeism from school or work because of acute respiratory disease is characterized by the same seasonal periodicity; however, such studies encounter the additional factors that absenteeism is higher on Mondays and Fridays. The relationship that emerge from these studies are that: the incidence of acute respiratory disease correlates well with the weather; air pollution varies with weather and also day of the week, tending to rise between Monday and Friday. Some studies have handled the cycles of weather and day-of-week effect statistically and have shown a deleterious effect of air pollution, others have not (80 - 82). Dohan found that the occurrence of acute respiratory disease lasting over 7 days was significantly related to particulate sulfates (83).

Groups of patients with COPD have been closely followed, principally by diary and frequent visits, both in the U. S. (84, 85) and in Great Britain (86, 87). The English studies and one from Chicago (84) showed increasing symptoms correlated with increasing SO_2 or SO_2 and smoke. The other study (85), also from Chicago,

showed a similar strong correlation between the patient's symptoms and levels of several pollutants. However, the authors concluded that simultaneous changes in weather were more significantly associated with changes in symptoms.

A panel of 137 patients with asthma were followed to determine whether Los Angeles smog, as reflected in oxidant measurements, was related to their symptoms (88). Of 3,435 attacks reported, less than 5% were spontaneously associated with smog by the patients - one-third of these by a single patient. Most of the weak correlation with high levels of oxidants were explained by 8 patients whose symptoms were related to oxidant concentrations.

3. Other indicators of acute morbidity

Rates of hospital admissions for certain diseases and length of hospital stay, might be a more sensitive indicator of health effects than mortality rates. A single group of data, based on hospital admissions covered by Blue Cross in Los Angeles in 1961, has been analyzed three times by increasingly complex statistical techniques (89 - 91). An increasing correlation was found between various pollutants (particulates and gases) and the length of time patients with "relevant diseases" remained in the hospital as analysis improved. The statistical problems encountered in these data deserve comment because they amplify those encountered in previous sections: air pollutants are lower on Monday than any other weekday and show seasonal, as well as day-of-week cycles; hospital admissions are lowest on Friday and Saturday but peak on Monday, and also show seasonal cycles; patients admitted on weekends (presumably relative emergencies) remain in the hospital longer despite lower levels of pollution. This type of recurring periodicity is best handled by long-term observations so that, for instance, one can compare hospital admissions, or any dependent variable in question, on a series of Sundays in October. This kind of data is not yet available. The authors (91) also emphasized that the incorporation of multiple pollutants improved the correlation over that obtained with single agents.

An analysis of the association of ambient CO and deaths from acute myocardial infarction within a large metropolitan area showed that the hospital mortality rate increased as CO increased in areas with high baseline CO levels but not in those with low (92). This study design removes the seasonal factor and no obvious differences in the two groups of patients were noted.

Somewhat more innovative parameters of morbidity were reported by Wayne (93) and Ury (94). Wayne found that the performance of a high school track team was inversely related to oxidant levels just before the meet with a lower threshold of effect

noted at 0.067 - 0.163 ppm. Ury found a correlation between oxidant levels and motor vehicle accidents when daytime, non-alcohol related accidents were analyzed. A previous study failed to find any difference between blood COHb levels in individuals involved in auto accidents and controls (95). And, finally, the prevalence of chronic pulmonary disease, as detected radiographically, was significantly higher among old "city" dogs in Philadelphia than in "country" dogs living outside the city (96).

4. Cancer of the lung

At first glance, the evidence that air pollution is a significant factor in the etiology of lung cancer seems impressive:

a. Virtually all studies have shown a considerable urban to rural gradient which persists despite standardization for smoking and age, and is present in nonsmokers (97 - 100). The magnitude of the increased rate in urban male smokers in the U. S. is about 43%, for nonsmokers about 20% (98).

b. Suspected carcinogens such as 3,4 benzpyrene are present in urban air in low concentrations (104).

However, measured levels of air pollution have frequently not correlated with lung cancer rates. Studies in both England (102, 103) and the U. S. (42) have failed to find differences that were not explained by smoking, population density, or socioeconomic class. It is clear that smoking is by far the major factor in the etiology of lung cancer causing an approximate nine-fold increase in all smokers as a group (100). The "urban effect" may be related to air pollutants not being measured or other factors. It should be noted that some studies have found a positive correlation of lung cancer rates and measured levels of pollution (104, 105).

III. Trace Substances

A. Lead

A controversy is currently brewing over the use of leaded gasoline. Kehoe states that the daily intake of dietary lead in the U. S. averages between 0.11 - 0.35 mg. Fecal excretions nearly balances this and an additional average 0.03 mg of lead is excreted per liter of urine. Total urine plus fecal losses slightly exceed dietary intake - the difference presumably represents lead absorbed from the respiratory tract (106). Urban ambient air lead measurements are on the order of 1 - 3 mcg/m^3, increasing significantly near heavy traffic (107). Kehoe, on the basis of unchanging levels of blood lead observed by him for 30 years, has concluded that there is insufficient evidence to conclude that the body burden of lead is increasing (106). On the

other hand, blood lead levels were significantly higher in persons living near a Los Angeles freeway than controls (108), blood lead levels seem to increase linearly with ambient air exposure, as examined in various occupational and residential areas (107), and one study has reported that tissues obtained from U. S. autopsies showed increasing amounts of lead to age 50 while those from several less developed foreign countries did not (109).

The evidence for absorption of inhaled lead is convincing: that for an increasing total body lead content is less so, mainly due to the wide variations noted. No toxicity has been recognized in the absence of a definable exposure to excessive lead.

B. Asbestos

That pulmonary deposition of asbestos is associated with pulmonary fibrosis, an increased occurrence of bronchogenic carcinoma in smokers, and mesothelioma is well accepted (110). The recent reports of ferruginous bodies in a high percentage of lungs at autopsy (20 - 98%) (111 - 114) has awakened interest in asbestos. It should be emphasized that ferruginous bodies are not specific for asbestos (115) and that the autopsy prevalence studies have not characterized the central fibers. Also, it appears that the frequency of ferruginous bodies is directly proportional to the effort expended searching for them. There is a marked difference in the number of ferruginous bodies noted incidently at autopsy and those found in persons occupationally exposed to asbestos. Finally, there is no evidence in the studies reported thus far that incidental ferruginous bodies are associated with any lung disease.

IV. Summary

Attempting to evaluate the effects of air pollution on human health is complicated by the number of factors involved and their interrelationships. Without the availability of computers for data analysis, our present state of knowledge would be limited to the few episodes of massive air pollution associated with obviously increased mortality. When applying epidemiologic techniques to an analysis of mortality or morbidity, a major problem exists in the lack of knowledge about individual exposure. It may be that the relationships reviewed above would be stronger if based on individually determined exposures. Toxicologic investigation of individual air contaminants have not furthered our understanding of mechanisms of action for the most part. This event is predictable from the epidemiologic studies, most of which show poor or no correlation of an observed effect with measurements of a single pollutant, but increasingly strong correlation when multiple pollutants are considered. Since different classes of pollutants vary independently this seems justified.

The levels at which health effects may appear is more difficult yet to establish. It is clear that individual susceptibility varies widely but whether a "safe" concentration of various pollutants exists, or whether the effect cannot be measured in the small number of susceptible individuals affected, is less clear. This becomes a major concern when attempts are made to establish ambient air standards and emission standards, particularly for substances like CO and lead.

It seems justified to me to include air pollution as one of several factors which are important in the etiology of certain diseases. This approach, however, begs the issue raised in the title of this presentation. To avoid that shortcoming insofar as possible, I think the following 3 conclusions are warranted at this time:

1. There can be little doubt that increased levels of air pollution are associated with excess mortality. This effect is seen clearly only in areas where particulate matter and SO_2 are major components of pollution. There is not an adequate toxicologic explanation for this event but its repeated occurrence in many areas of the world over a number of years has been documented.

2. It seems likely that urban air pollution is an important factor in the causation of chronic obstructive pulmonary disease. This contention is supported by 3 lines of evidence:

a. Constituents of smog-type pollution produced ultrastructural abnormalities in the lungs of experimental animals at concentrations found in the atmosphere,

b. Detailed postmortem study of the lungs of individuals with similar smoking histories revealed a striking increase in emphysema among younger persons in a city with high levels of pollution compared to a city with little air pollution, and

c. A consistent worldwide pattern of increased prevalence of cough, respiratory infections, and decreased expiratory flow was found in children living in heavily polluted areas.

3. The evidence that air pollution is a significant factor in the causation of lung cancer is the most tenuous of all. While a consistent increase in lung cancer is found among urban dwellers, it does not correlate well with levels of currently measured pollutants. At the present, the nature of the "urban factor" remains obscure.

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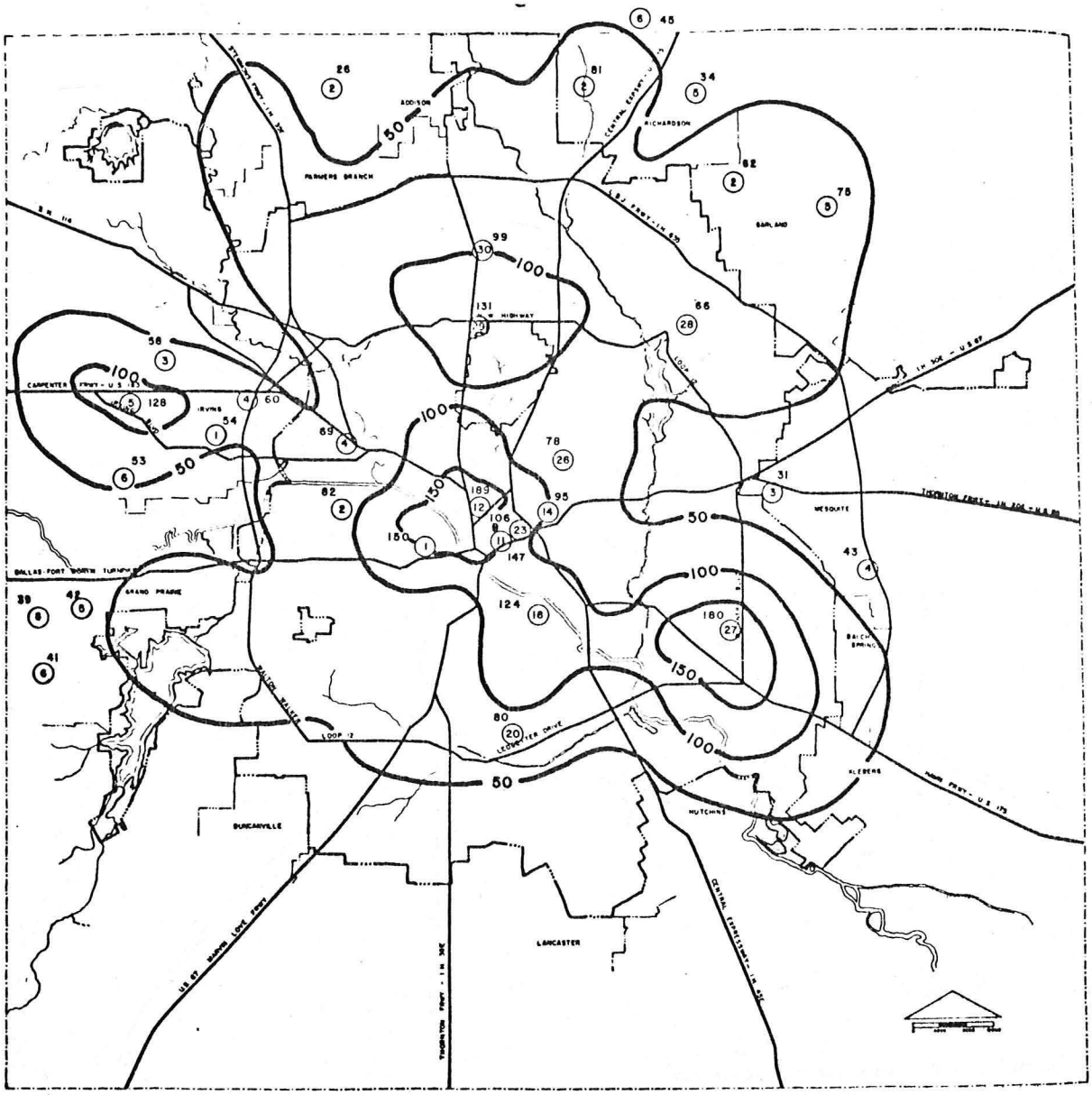
APPENDIX I

AMBIENT AIR QUALITY STANDARDS FOR THE DALLAS-FORT WORTH AIR QUALITY CONTROL REGION

	Standard	Current Measurement
Suspended Particulate Matter (Ann. Geom. Mean)	55 $\mu g/m^3$	85 $\mu g/m^3$
Sulfur Dioxide (Ann. Mean)	13 $\mu g/m^3$ (0.005 ppm)	8.6 $\mu g/m^3$ (0.003 ppm)
Carbon Monoxide (8-hr. Average)	10 mg/m^3 (8.7 ppm)	7 mg/m^3 (6.0 ppm)
Nonmethane Hydrocarbons (3-hr. Average)	130 $\mu g/m^3$ (0.2 ppm)	--
Photochemical Oxidants		
1-hr. Average	100 $\mu g/m^3$ (0.05 ppm)	60 $\mu g/m^3$ (0.03 ppm)
4-hr. Average	80 $\mu g/m^3$ (0.04 ppm)	--
Max. Concentration	200 $\mu g/m^3$ (0.10 ppm)	370 $\mu g/m^3$ (0.19 ppm)

APPENDIX II

CONTOUR MAP OF PARTICULATE AIR POLLUTION IN DALLAS
JANUARY, FEBRUARY, MARCH, 1968 (2)



DALLAS COUNTY

PARTICULATES AS MICROGRAMS PER CUBIC METER
JANUARY, FEBRUARY, MARCH, 1968

APPENDIX III

CONTOUR MAP OF PARTICULATE AIR POLLUTION IN DALLAS, DECEMBER 19, 1967

Reflecting The Influence of Reduced Wind Velocity And Morning And Afternoon Therman Inversions (2).