AIR POLLUTION

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The Effects of Air Pollution

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Effects of Air Pollution on Human Health

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associations shown by epidemiological studies, as well as their concordance with experimental studies in animals or man.

Natural variability in responsiveness to air pollution is observed in all populations. Generally speaking, susceptibility is great among premature infants, the newborn, the elderly, and the infirm. Those with chronic diseases of the lungs or heart are thought to be at particular risk. Because of the wide variation in sensitivity to air pollution of different groups in the population, data concerning health effects on healthy persons may not be as important as the responses of the individuals most likely to be sensitive. Preschool and school children appear to be both sensitive and specifically reactive to air pollution health effects (see Section III,C). The control of air pollution, to the extent that it is based upon health effects, should be based on the most sensitive groups of persons. This principle requires that these sensitive groups be definable in terms of age and/or medical status.

The effects of air pollution on personal or community health are (*2*): (a) acute sickness or death; (b) insidious or chronic disease, shortening of life, or impairment of growth or development; (c) alteration of important physiological functions, such as ventilation of the lung, transport of oxygen by hemoglobin, sensory acuity, time interval estimation, or other functions of the nervous system; (d) impairment of performance, such as in athletic activities, motor vehicle operation, or complex tasks such as learning; (e) untoward symptoms, such as sensory irritation, which in the absence of an obvious cause, such as air pollution, might lead a person to seek medical attention and relief; (f) storage of potentially harmful materials in the body; and (g) discomfort, odor, impairment of visibility, or other effects of air pollution sufficient to cause annoyance or to lead individuals to change residence or place of employment.

Objectionable odor, visibility interference, or vegetation damage are useful guides to the likelihood or severity of health effects. A gray pall over a city or industrial area can have a depressing effect and impair the enjoyment of life. Survey methods, carefully applied, are capable of measuring such reactions and effects. Adaptation to many pollution effects is likely, even expected and relied upon; nevertheless, adaptive capabilities, while innate in human populations, are not to be used as an excuse to permit exposures to unnecessary pollution, since adaptive reactions are associated with a cost that is hard to estimate. A public exposed to sensible pollution will not wait for the demonstration that an unpleasant atmosphere causes disease. They will insist that the air be free of substances that interfere with visibility, have a bad odor, or cause irritation. There is no doubt, however, that the urgency with which steps are taken associations shown by epidemiological studies, as well as their concordance with experimental studies in animals or man.

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In Sections III–V, the effects of specific pollutants on health are discussed. In Section VI, the relationship between pollution and disease states is discussed. To some extent, these interests and this treatment will overlap. We have, however, chosen for emphasis in Sections III–V pollutants for which studies have yielded information concerning dose–response relationships. In Section VI, we have cited those studies in which the quantitative relationships between exposure and effects are not well established, but a qualitative relationship was sought and evaluated.

First priority has properly been given to whether air pollution kills, next to whether it causes disease, and only somewhat later to whether it is a contributory factor along with other exposures to aggravating disease. Although laymen have long recognized the effects of pollution on the impairment of well-being and scientists have recognized the interference with normal functions of the body, only recently has a systematic study been undertaken of the effect of air pollution on annoyance reactions and on the more subtle biological or physiological changes of an unfavorable nature.

B. Relation of Air Pollution Effects to Other Exposures

1. Occupation

Many common air pollutants are also substances to which persons are exposed in their occupations. This is true, for example, of sulfur dioxide, carbon monoxide, and lead, as well as of smoke and many dusts. The downtown traffic policeman, the automobile mechanic, and the truck driver in a large metropolitan area may all have substantial exposures to carbon monoxide and lead in association with their occupations. Since these substances may also be found in community pollution, cessation of work does not necessarily terminate their exposure. Therefore, such individuals have an unusually high risk from exposure to community air pollution. Workers in the fields of occupational medicine and industrial hygiene have given us a wealth of information about the effects on human health of specific contaminants. This information has been organized and evaluated in the so-called threshold limit values (TLV) or maximum allowable concentrations (MAC), which really are neither thresholds, nor, for certain groups, allowable.

While industrial health experience is often relevant to community air pollution exposures, the quantitative relationships between these two types of exposure are neither constant nor dependable. The American

Conference of Governmental Industrial Hygienists (*3*), which has for years sponsored the publication of threshold limit values (Table I) (*4*), states:

> Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. Because of wide variation in individual susceptibility, however, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a preexisting condition or by development of an occupational illness. . . . These limits are intended for use in the practice of industrial hygiene and should be interpreted and applied only by a person trained in this discipline. They are not intended for use, or for modification for use, (1) as a relative index of hazard or toxicity, (2) in the evaluation or control of community air pollution nuisances, (3) in estimating the toxic potential of continuous uninterrupted exposures. . . .

2. Cigarette Smoking

The dose of pollutants from cigarette smoking is high and intermittent, relative to that from community air pollution. For example, 400 ppm (440 mg/m^3) carbon monoxide for 5 minutes with frequent repetition may be a representative cigarette smoking dose, while from 10 to 30 ppm (11–33 mg/m^3) carbon monoxide for 4–8 hours may represent a frequent community air pollution exposure. Each of these alone may produce inactivation of up to 5% of the circulating hemoglobin. Together, of course, the effect is greater, but because of the dynamics of carbon monoxide uptake and excretion, it is less than additive.

The exposure to oxides of nitrogen present in cigarette smoke may be assumed to be about 100 ppm each of nitric oxide and nitrogen dioxide (*5*). The average exposure to severe air pollution over periods of about an hour will not exceed about 1.5 ppm (2.8 mg/m^3). However, cigarette smoking produces intermittent exposures, while community air pollution is more constant. Such continuous exposure to nitrogen dioxide may produce effects different from acute exposure (*6*). Exposure to other substances from cigarettes is more variable, but at least include carcinogenic tars, aldehydes, and hydrogen cyanide, as well as lead and other metals.

As far as causing lung cancer or chronic disabling pulmonary disease in the whole population, effects of cigarette smoking are more important than effects of air pollution (*7*), but when both factors are present, they apparently have a more than additive effect. This means that cigarette smokers are at unusual risk if they live in areas with substantial air pollution and that the effects of air pollution on chronic disabling pul-

Table I Comparison of Industrial Threshold Limit Values with Selected Maximal Air Pollution Values

Substance	*Industrial threshold limit values (3, 4)* ppm	mg/m³	*Maximal community air pollution levels*		*Place and date where observed*
Gases					
Acrolein	0.1	0.25	0.011	ppm	Los Angeles, California, 1960
Benzene[a]	10	30	0.057	ppm	Los Angeles, California, 1967
Carbon monoxide	50	55	360	ppm	London, England, 1956
Formaldehyde[a]	2	3	1.87	ppm[b]	Pasadena, California, 1957
n-Heptane	400	1600	4.66	ppm[c]	Los Angeles, California, 1957
n-Hexane	100	360	0.04	ppm	Los Angeles, California, 1966
Hydrogen sulfide	10	15	0.9	ppm	Santa Clara, California, 1949–1954
Methane	—	—	3.69	ppm	Los, Angeles, California, 1963
Nitric oxide	25	30	3.7	ppm[e]	Los Angeles, California, 1966
Nitrogen dioxide[a]	5	9	1.3	ppm	Los Angeles, California, 1962
Ozone	0.1	0.2	0.90	ppm	Los Angeles, California, 1955
Sulfur dioxide	5	13	3.16	ppm	Chicago, Illinois, 1937
Particulates					
Arsenic	—	0.25	0.069	mg/m³	Zemianske Kostol', Czech-oslovakia, 1964
Asbestos[f]	(5 fibers/ml >5 μm in length)		1 fiber/ml		San Lucas, California, 1972
Beryllium[d]	—	0.002	0.0011	mg/m³	Pennsylvania, 1958
Fluoride (as F)	—	2.5	0.56	mg/m³	Ural Alum, USSR
Lead (inorganic)	—	0.15	0.042	mg/m³	Los Angeles, California, 1949–1954
Sulfuric acid	—	1	0.7	mg/m³	London, England, 1956
Vanadium (V_2O_5)	—	—	0.0007	mg/m³	Mihama, Japan, 1964
Dust	—	0.5	—		—
Fume[d]	—	0.05	—		—

[a] Ceiling value, rather than a time-weighted 8-hour average.
[b] Aldehydes as formaldehyde.
[c] Total hydrocarbons.
[d] Neighborhood, i.e., ambient levels (threshold limit values) also have been set uniquely for this substance at 0.00001 mg/m³ as a 30-day average.
[e] Combined oxides of nitrogen.
[f] Current discussion is concerned with lowering this or including submicroscopic fibers. Air pollution level based on electron microscopic counting of submicroscopic fibers.

monary diseases are more likely to occur in cigarette smokers. Such interpretations are based in part on studies carried out in the United Kingdom (*8, 9*) and on evidence from the United States (*10*). Nevertheless, nonsmokers may be the group in which air pollution effects can be most readily detected. This is because response indicators (impairment of lung function, symptoms of cough or sputum production) are less variable in nonsmokers than in smokers.

3. Domestic Pollution*

Home heating and cooking are capable of generating a group of air pollutants (carbon monoxide, sulfur oxides, oxides of nitrogen, sooty and oily aerosols) whose health effects have commonly been overlooked. During periods of low winds and still weather, the dissipation of such domestic pollution will be impaired to a similar extent as the dissipation of outdoor air pollution. In general, oxidants are about half as concentrated within buildings in polluted areas as they are outside, but carbon monoxide and nitric oxide are likely to occur at similar concentrations indoors and out, since they are influenced neither by the walls of rooms nor by air conditioners and filters (*11*). If smoking or cooking occurs indoors, exposures to carbon monoxide and nitrogen oxides may be quite high.

C. Routes of Absorption of Particulates and of Gases

Absorption may be defined as entry into the body by the passage of a substance across a membrane. The substance may be retained at the local site of absorption for long periods of time or may be transported to other parts of the body. This definition is in accord with a statement for metals by the Task Group on Metal Accumulation (*12*). Pulmonary absorption is the most important route for the entry of air pollutants into the human body. Varying amounts of substances deposited in the pulmonary tract may be transported to the gastrointestinal tract via the mucociliary escalator. This comprises the mucus lining of the conducting part of the respiratory system. The mucus is moved by tiny hairlike cilia toward the back of the throat from which it is usually swallowed.

Air pollution may contaminate grain, vegetables, soil and water and secondarily give rise to an exposure via ingestion. Absorption through the skin is not an important route for an air pollutant to enter the body. Eye irritation from pollutants implies impact on the conjunctiva, but little is known about absorption via the conjunctiva.

* See also Chapter 3, this volume.

The chemicophysical properties of an aerosol or a gas determine whether or not the substance will be inert or give rise to local injuries or systemic effects. Ninety percent or more of sulfur dioxide is normally removed in the upper airways (*13, 14*), while if the gas is adsorbed, e.g., on soot particles, the deposition may take place to a great extent in the deeper airways, depending on the size of the particles. This may well change the absorption rate and thus the toxicity of the gas as well as of the particle itself; synergistic effects have been proven in animal experiments for mixtures of sodium chloride aerosols and sulfur dioxide (*15*). However, synergism for such mixtures has not been proven in human experiments (*16*).

1. Absorption by Inhalation

a. ABSORPTION OF PARTICLES. Absorption of particulates is influenced by three different mechanisms—deposition, mucociliary clearance, and alveolar clearance. A model of the three processes (Fig. 1) (*12, 17*) shows the various routes of deposition and subsequent fate that an inhaled aerosol can undergo. D_1 and D_2, respectively, represent the aerosol in the inhaled air. D_3, D_4, and D_5 depict the deposition in the nasopharyngeal compartment (nose and throat), the tracheobronchial compartment (the windpipe and large airways) and the pulmonary compartment (the gas-exchanging portions of the lung itself), respectively. The letters a–j stand for the different translocations that deposited particles can undergo within the lung or systemically. These processes are of fundamental importance in evaluating pulmonary absorption of particles.

i. *Deposition of particles in the respiratory tract.* Three mechanisms govern the deposition of an aerosol in the airways—impaction, sedimentation, and diffusion. The relative importance of these parameters varies with differences in the anatomy of the airways and with ventilatory parameters, but is, above all, dependent upon the aerodynamic properties of the aerosols.

Impaction means that the particle, due to its inertia, is deposited on the mucous membranes, perferentially at a site where the airstream changes its direction. It depends on the particle mass (size and density) and shape, but it is also dependent on the velocity of the airstream within the respiratory tract. Impaction will be of particular importance in the nose, mouth, and upper respiratory tract for unit density (unit density means that the specific gravity is 1.0) particles larger than a few microns in diameter.

Sedimentation is dominant for large, high density particles particularly

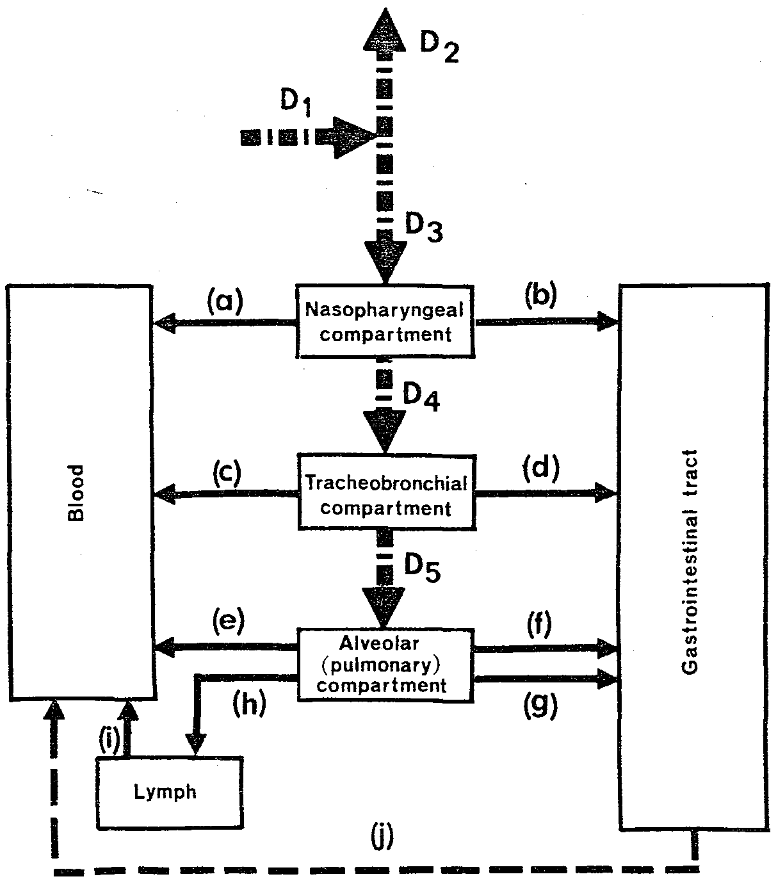

Figure 1. Respiratory tract clearance model for inhaled dust (*12, 17*): D_1 = total dust inhaled, D_2 = dust in exhaled air, D_3 = amount of dust deposited in nasopharyngeal compartment, D_4 = amount of dust deposited in tracheobronchial compartment, D_5 = amount of dust deposited in alveolar compartment. Mechanism: (a) rapid uptake of material deposited in nasopharyngeal compartment directly into the blood; (b) mucociliary clearance from nasopharyngeal compartment to gastrointestinal tract; (c) rapid uptake of material deposited in tracheobronchial compartment directly into the blood; (d) mucociliary clearance; (e) direct absorption of dust from the alveolar compartment to blood; (f) inclusion of alveolarly deposited particles by macrophages and their transport by the mucociliary escalator to the gastrointestinal tract; (g) same as f, but slower process; (h) slow removal of particles by the lymph system; (i) transport of dust cleared by h into the blood; (j) gastrointestinal absorption of particles cleared to the gastrointestinal tract by processes b, d, f, and g.

in regions where the airstream is moving slowly. This means that gravitational sedimentation is of importance mainly for large particles (above a few microns).

Diffusion, which is dependent on Brownian motion of the air molecules, is of importance only for small particles; it is negligible for unit density particles above about 0.5 μm in diameter. Diffusion is especially important for deposition in the alveoli.

Much of our knowledge of areosol deposition in the lungs is based on experimental studies by Wilson and LaMer (*18*) and Brown *et al.* (*19*) and on basic theoretical studies on deposition by Findeisen (*20*) and Landahl (*21*). Deposition in the nasopharyngeal, tracheobronchial, and pulmonary compartments of the body of the International Commission for Radiation Protection (ICRP) "standard man" are shown in Figure 2 for a tidal volume (volume per breath) of 1450 ml and 15 respirations per minute, which represents moderate activity. With larger tidal volumes at the same rate, or with slower respiration at the same volume per breath, there tends to be more deposition deeper in the lung as well as a higher fraction retained. Ambient air aerosols usually have a log normal particle size distribution (Chapter 3, Vol. I). It has been shown (*17*) that the deposition in the different compartments can be predicted using values for mass median aerodynamic diameter. The estimated deposition is not influenced substantially by differences in geometric standard deviation of particle size distribution. Junge (*22*) and Friedlander and Wang (*23*) have shown that particle agglomeration in the air is such that most

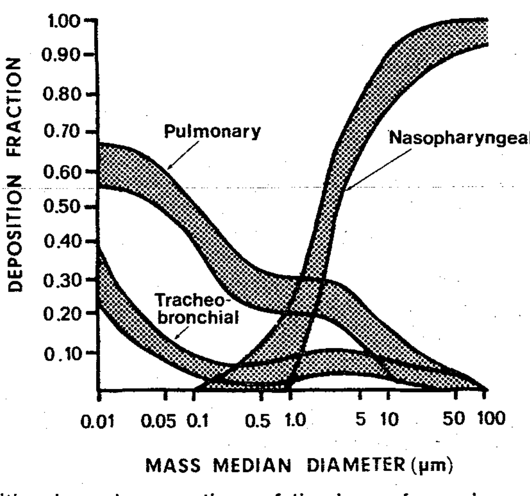

Figure 2. Deposition in various sections of the lungs for various particle populations (*17*). Each of the shaded areas (envelopes) indicates the variability of deposition for a given median (aerodynamic) diameter in each compartment when the distribution parameter σ varies from 1.2 to 4.5 and the tidal volume is 1450 ml.

natural aerosols "age" in the air to a predictable particle size distribution (Chapter 3, Vol. I). This adds to the importance of such deposition predictions. Studies with monodisperse aerosols in man have shown that in the 2–5 μm particle size range, deposition patterns fit the above model, but that there may be large individual variations (*24*). Individual differences in aerosol deposition have also been shown in animals (*25,26*).

ii. *Mucociliary clearance of insoluble particles.* Mucociliary clearance involves the transport of particles upward in the respiratory tract by means of the mucus flow and ciliary activity in the tracheobronchial and nasopharyngeal compartments. The ultimate fate of transported particles is either that they reach the gastrointestinal tract or are expectorated (*25*). Studies of inhaled insoluble particles tagged with radioactive isotopes have shown that the clearance of particles deposited in the tracheobronchial compartment usually is completed within about 8 hours (*26*). The mucus flow in the upper respiratory tract is faster than in the lower part. This and the fact that larger particles are deposited higher in the tracheobronchial tree result in faster clearance for larger particles than for smaller ones.

There are considerable differences among individuals with respect to mucociliary clearance. Some subjects have very slow clearance, while others have a mucociliary clearance that is complete within about 1 hour. Such differences to some extent seem to have a constitutional origin. Monozygotic twins have very similar clearance rates, while dizygotic twins differ almost as much as individuals within the general population (*27*). The medical significance of differences in clearance rates is not known in any detail, but it may well be that subjects with a slower clearance rate are more at risk from harmful effects of particles, as this may indicate a slow mucociliary transport and a higher deposition in the alveolar region in such persons.

Clearance of inhaled aerosols of bacteria and viruses are of particular importance. Their deposition will follow ordinary laws governing deposition. Clearance, however, will be influenced also by bactericidal properties of the tissue cells and the secretions of the lung. By studying the clearance of viable inhaled bacteria and killed bacteria tagged with radionuclides, Rylander (*28*) in animal experiments has estimated how much of the total clearance is due to mechanical clearance and how much to bactericidal action. Similar studies have been done by Laurenzi *et al.* (*29*) and Goldstein *et al.* (*30*).

iii. *Alveolar clearance.* Alveolar clearance can take place by transport of particles from the alveoli to the mucociliary escalator. The different mechanisms for this transport are not known, but uptake by alveolar scavenger cells is considered the most important mechanism (*12*). After passing the alveolar membrane, the particles may either remain within the pulmonary tissue or pass into blood and lymph for further translocation to different organs within the body. If the particle is weakly soluble or capable of surface reactions (as is true, for example, for fractured silica) these reactions tend to occur in the lung tissue. Mercer (*31*) has proposed a solubility model that indicates that the more soluble the particle, the larger the part that is translocated directly from the alveoli to the systemic circulation. Few hard data exist for most insoluble particles either in humans or animals. Concerning quantitative aspects of alveolar clearance, it is not known how much is absorbed systemically directly from the alveoli and how much is translocated to the mucociliary escalator. Asbestos particulates, with their long fibers, behave differently with respect to both deposition and clearance than spherical or near-spherical particulates. This tends to increase the likelihood of alveolar reactions and migration of ultramicroscopic fibrils of asbestos to the outer surfaces (pleura) of the lung (see Section V,A). These processes are just beginning to be studied by electron microscopy (*32*).

b. Absorption of Gases. As a general rule the solubility of a pollutant gas determines what proportion is deposited in the upper airway and what proportion reaches the terminal air sacs of the lung, the alveoli. For example, sulfur dioxide, which has high water solubility, is absorbed high in the airways and has as its primary reaction pattern irritation and increased airway resistance (*33*). Frank and Speizer (*14*) have shown that at relatively high concentrations, the largest proportion of sulfur dioxide is removed in the upper airways, i.e., the nasopharynx. However, Strandberg (*13*) has shown that at low concentrations, a high proportion is carried deep into the lung. Nitrogen dioxide and ozone are examples of relatively water-insoluble gases. They have their major biological reactions at the alveolar level. Depending on their ability to penetrate epithelial membranes, gases are absorbed to a varying degree. Since the alveolar cells are thought to be covered by a phospholipid layer, lipid solubility is probably of importance for penetration of the alveolar membrane.

2. Absorption by Ingestion

Substances entering the gastrointestinal tract may do so directly as contaminants of food and water. A substantial part, however, may be a result of the translocation from the lungs by means of the mucociliary clearance. The rate of absorption of substances from the gastrointestinal tract is highly dependent on the substance in question. For example, methylmercury is absorbed to about 95%, irrespective of whether it is administered as a salt in water solution or in protein-bound form (*34*), whereas mercuric mercury, orally administered, in tracer dose experiments is absorbed only to about 15% (see Section V,D). With respect to their rates of absorption, salts of metals are important only to the extent that ionization increases or decreases the absorption of the compound in the gastrointestinal tract. After metals have reached the small intestine, they are mainly bound to organic molecules, so that the nature of the anion is not highly important.

Great interindividual differences in absorption and variations related to sex and age may exist. Hursh and Suomela (*35*) measured lead absorption in three human volunteers using lead-212 and found that the absorption ranged from about 1 to 25%. Wetherill *et al.* (*36*), in a metabolic study using stable isotopes lead-204 and/or lead-207 to label food, studied two adult males. They found 6–9% absorption from the gut and a residence time in the metabolic pool of 35–50 days. Several factors may interact with the absorption of ingested air pollutants; e.g., reduction of dietary calcium increases the absorption of lead and cadmium (*37–39*). Six and Goyer (*40*) have further found that a lowering of dietary iron increases lead absorption. Increased lead uptake has also been found related to the protein content in food (see Section V,B).

II. Acute Air Pollution Effects and Their Detection

A. Air Pollution Episodes

1. Characteristics Common to Episodes

Several disastrous episodes have focused attention upon air pollution as a health problem. These episodes have made it obvious that the air quality of a community may deteriorate enough to damage the health of its citizens. The observed relationship of air pollution disasters to the presumptive exposures permits several general conclusions. The toll of excess mortality and morbidity in disasters has never been appreciated at the time of the episode; therefore, protective measures were usually not taken. The episodes have always occurred under extraordinary meterological conditions that reduced the effective volume of air in which the pollutants were diluted. Most have occurred under circumstances in which small water droplets were present and, therefore, it is likely that a combination of aerosols and gaseous pollutants was involved. Only since 1952 have valid contemporary measurements been made during episodes.

2. Meuse Valley, Belgium, 1930

On Monday, December 1, 1930, the narrow valley of the Meuse River was afflicted by an unusual and widespread weather condition that persisted during the remainder of the week. In this valley, 15 miles (24 km) in length and with hills about 300 feet (90 m) high on either side, a thermal inversion confined emitted pollutants to the air volume contained in the valley. In the valley were located a large number of industrial plants, including coke ovens, blast furnaces, steel mills, glass factories, zinc smelters, and sulfuric acid plants. On the third day of this unusual weather, a large number of people became ill with respiratory tract complaints and before the week was over, 60 had died. In addition, there were deaths in cattle. Older persons with previously known diseases of the heart and lungs had the greatest mortality; however, illness affected persons of all ages and was best described as an irritation of all exposed membranes of the body, especially those of the respiratory tract. Chest pain, cough, shortness of breath, and eye and nasal irritation were the most common symptoms. Treatment with antispasmodic drugs was of some help. Frequency of symptoms decreased strikingly on December 5, but fatalities occurred both on December 4 and 5. Autopsy examinations showed only congestion and irritation of the tracheal mucosa and large bronchi. However, there was some black particulate matter in the lungs, mostly within the phagocytes.

The chemical substances responsible for the illness and fatalities have been disputed. In the original report on the episode (*41*), it was estimated (since no measurements had been made during the event) that the sulfur dioxide content of the atmosphere was from 25 to 100 mg/m^3 (9.6–38.4 ppm). Assuming oxidation of the sulfur dioxide, high sulfuric acid mist concentrations might have resulted. Some have raised the question as to whether fluorides were possibly the cause of the episode (*42*). It is generally felt now that a combination of several pollutants may have been associated with this, as well as with other community disasters. Certainly strong suspicion attaches to sulfur oxides, but it is more likely that sulfur dioxide, when dissolved or combined with water droplets and in the presence of a multiplicity of other pollutants, was oxidized to sulfuric acid mist with a particle size sufficiently small to penetrate deeply into the lung. Firket (*41*) remarked prophetically that "the public services of London might be faced with the responsibility of 3200 sudden deaths if such a phenomenon occurred there."

3. Donora, Pennsylvania, 1948

The impact of the Donora disaster has been eloquently described by Breton Roueché (*43*):

> The fog closed over Donora on the morning of Tuesday, October 26. The weather was raw, cloudy and dead calm, and it stayed that way as the fog piled up all that day and the next. By Thursday, it had stiffened adhesively into a motionless clot of smoke. That afternoon it was just possible to see across the street, and except for the stacks, the mills had vanished. The air began to have a sickening smell, almost a taste. It was the bittersweet reek of sulfur dioxide. Everyone who was out that day remarked on it, but no one was much concerned. The smell of sulfur dioxide, a scratchy gas given off by burning coal and melting ore, is a normal concomitant of any durable fog in Donora. This time it merely seemed more penetrating than usual.

During this period, again, temperature inversion and foggy weather affected a wide area. Donora is located on the inside of the horseshoe-shaped valley of the Monongahela River. The city contained a large steel mill, a sulfuric acid plant, and a large zinc production plant, among other industries. The hills on either side of the valley are steep, rising to several hundred feet. At the time there were about 14,000 people living in the valley. About half of the population was made ill during the episode. Curiously, many of the persons who were not ill were unaware of the extent of ill health. Cough was the most prominent symptom, but all portions of the respiratory tract and the eyes, nose, and throat were irritated in at least some persons. Many complained of chest constriction, headache, vomiting, and nausea. The frequency and severity of illness increased with the age of the population. Most of those who became ill did so on the second day of the episode; of the 20 deaths, most occurred on the third day. Among those who died, pre-existing cardiac or respiratory system disease was common. A meticulous health survey of the population was made within a few months of the episode (*44*). The investigation was directed at the health effects that occurred among people and animals, the nature of the contaminants, and the meterological conditions. Interviews were obtained from persons who were ill and from physicians in the community. X-rays and blood tests were taken, and teeth, bone, and urine samples were studied to determine whether fluorides might have been involved. From examinations made for fluorides, it was felt that fluorine was probably not involved. Retrospective examination of mortality records indicated that a similar event might have occurred in April of 1945. Autopsy examinations of the 1948 fatalities gave nonspecific findings, but there was abundant evidence of respiratory tract irritation.

Environmental measurements had not been made during the episode, but it was inferred that sulfur dioxide had ranged between 1.4 and 5.5 mg/m^3 (0.5 and 2.0 ppm). Particulate matter was undoubtedly present. The calls for medical assistance in Donora ceased rather abruptly on Saturday evening despite the fact that the fog remained quite dense. This suggests that some change in the physical nature of the fog droplets may have occurred; for example, the particles may have increased sufficiently in size so that they were deposited in the upper airway instead of penetrating deeply into the lung. The population affected was restudied in 1952 and 1957 and was found to have a less favorable mortality and morbidity experience than persons not affected in 1948 (*45*). This could either be because those susceptible in 1948 would have had a less favorable experience in any event or because the exposure in 1948 had long-term effects.

4. Poza Rica, Mexico, 1950

Another type of community disaster resulting from the discharge of a toxic gas from a single source befell the small town of Poza Rica, Mexico (*46*). Here, a new plant for the recovery of sulfur from natural gas put a portion of its equipment into operation on the night of November 21, 1950. One of the steps in the process was the removal of hydrogen sulfide from natural gas. In order to do this, the hydrogen sulfide was concentrated in a system in which it was intended to be burned. During the early morning of November 24, the flow of gas into and through the plant was increased; the weather was foggy with weak winds and a low inversion layer. Between 4:45 a.m. and 5:10 a.m., hydrogen sulfide was released inadvertently and spread into the adjacent portion of the town. Most of the nearby residents were either in bed or had just arisen. Many were afflicted promptly with respiratory and central nervous system symptoms. Three hundred and twenty were hospitalized and 22 died. The characteristic manner in which the hydrogen sulfide affected these individuals was to produce loss of sense of smell and severe respiratory tract irritation (see also Section IV,E). Most of the deaths occurred in persons who had such central nervous system symptoms as unconsciousness and vertigo. A number of affected individuals also had pulmonary edema. Persons of all ages were affected and pre-existing disease did not seem to have much influence on which persons were afflicted.

5. London, England, 1952

From December 5 through 9, 1952, most of the British Isles was covered by a fog and temperature inversion. One of the areas most severely affected was London, which is located in the broad valley of the Thames. During this period, an unusually large number of deaths occurred and many more persons were ill. The illnesses were usually sudden in onset and tended to occur on the third or fourth day of the episode (*47*). Shortness of breath, cyanosis, some fever, and evidence of excess fluid in the lungs were observed. Most of those seriously ill were in the older age groups. Admissions to hospitals for the treatment of respiratory diseases were increased markedly, but so were admissions for heart disease. An increase in mortality among all ages was observed. However, the very old, those in the seventh and eighth decades, had the highest increment. The most frequent causes to which deaths were ascribed were chronic bronchitis, broncho-pneumonia, and heart disease. Of particular interest was the fact that mortality remained elevated for several weeks after the weather had improved. This observation has led to speculation that acutely increased pollution may start in motion a process that could continue to operate even after pollution has returned to normal. One such process could be lowered resistance to such infectious processes as influenza. The total excess was between 3500 and 4000 deaths, distributed as shown in Figure 3. Autopsy examination did not reveal any characteristic mode of death other than evidence of respiratory tract irritation. Measurements were available for the amount of suspended smoke and sulfur dioxide. The highest values reported were 4.46 mg/m^3 of smoke and 1.34 ppm (3.75 mg/m^3) of sulfur dioxide.

Search of the past records of meteorology and mortality indicated that periods of excessive mortality had occurred previously. Three hundred excess deaths occurred in the winter of 1948; detectable increases in mortality associated with fog were found in December 1873, January 1880, February 1882, December 1891, and December 1892. Subsequent episodes have occurred in 1959 and 1962 (*48, 49*). None of the other episodes, however, was quite as severe as the one in 1952. For further discussion of the 1962 episode, see Section 9, below.

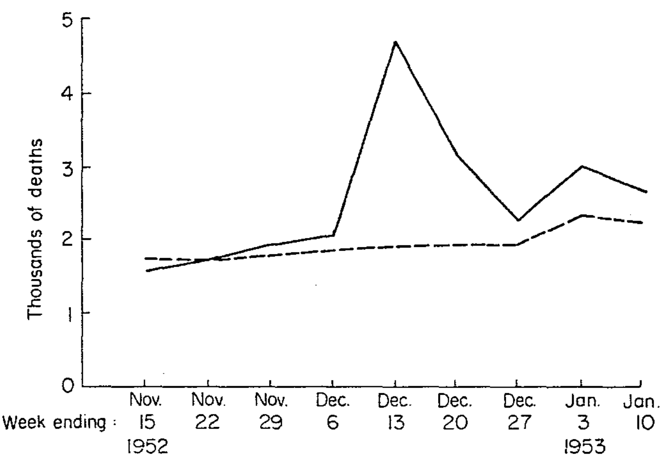

Figure 3. Deaths registered in greater London, England, associated with air pollution episode of December 5–8, 1952. Broken line indicates average deaths for 1947–1951.

6. New York, New York, 1953

From November 18 to 22, 1953, there was recorded a substantial increase in sulfur oxide and pollutant levels associated with a widespread atmospheric stagnation affecting much of the eastern United States (*50, 51*). Compared with the deaths by day for New York City during the month of November in 1950–1952 and in 1954–1956, there appeared to be an excess for 1953 during the period November 15 to 24.

7. New Orleans, Louisiana

In 1958 a series of unusual episodes of increased frequency of asthma was reported in certain districts of New Orleans. Frequency of visits to Charity Hospital increased to a maximum of 200 per day compared with the expected 25. Gentle winds, usually from the same direction, have been associated with these episodes (*52, 53*). It is thought that a single or closely grouped source of pollutants is likely to be involved because of the geographic distribution of cases.

When these episodes were first investigated, it was found that they had been occurring at least since 1955, that they tended to occur in October and November, with occasionally lesser episodes in June and July. The characteristic pattern of the outbreaks is shown in Figure 4. Use of skin tests on subjects who had acute asthmatic reactions, using as antigens

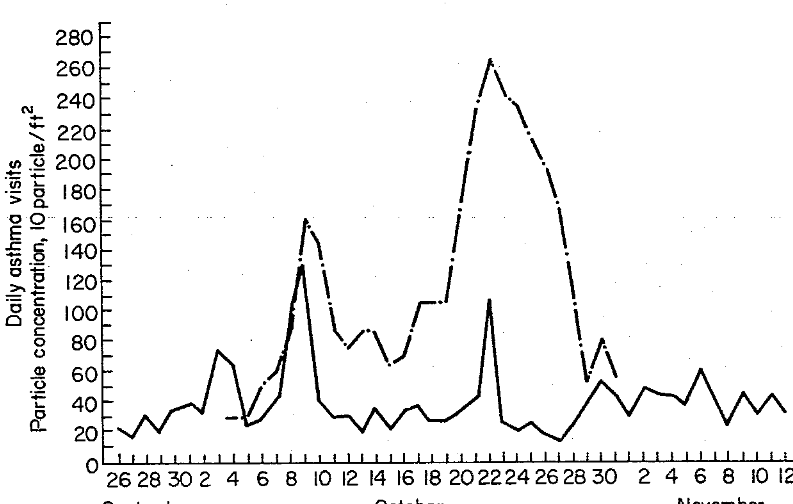

Figure 4. Asthma clinic visits (solid line) and particle concentrations (broken line) in New Orleans, Louisiana, autumn 1963.

extracts from air pollution samples, gave some valuable suggestions. It is thought possible that dust from a flour mill may have been involved (*54*). At any event, particulate matter in certain size ranges correlated well with the outbreaks (*55*). Efforts to find similar outbreaks in other cities have been unsuccessful (*56*). The study of asthma outbreaks in New York City has suggested only that they tend to occur at the time when the weather suddenly becomes cold (*57*).

8. Minneapolis, Minnesota, 1956

The Minneapolis campuses of the University of Minnesota are surrounded by storage and processing plants of the grain industry. Outbreaks of asthma have occurred there from time to time, and it has been thought that perhaps this is due to some pollutants from the neighboring plants. Two hundred and eighty eight records of asthmatic attacks were reviewed to see if there was any systematic pattern. This small number made it difficult to detect a pattern. Skin tests with grain dust were helpful (*54*) and showed cross reactions with the particulates from New Orleans. Further, subjects affected in New Orleans reacted to extracts from Minneapolis grain dust.

9. Worldwide Episode, November–December, 1962

A remarkable air pollution episode with serious health effects swept from west to east across certain portions of the earth between November 27 and December 10, 1962. It illustrates, among other things, that health effects are likely to be found where trained personnel collect the right kind of information and undertake a careful analysis of it.

In the eastern United States, November 27–December 5, pollution levels were noted to be high in Washington, D.C.; Philadelphia, Pennsylvania; New York, New York; and Cincinnati, Ohio (*58*). In two different studies that were made in New York City, an increase in respiratory symptoms was detected. Among a group of elderly persons, an increase in upper respiratory complaints was noted (*59*). In a continuing study of respiratory and other conditions in a study area in Manhattan, New York City, an increase in persistent cough was observed (*60*).

In London, December 5–7, the sulfur dioxide levels exceeded those of the episode in 1952, but the particulate pollution level was somewhat lower. Over this period of time and subsequently 700 excess deaths were reported in London, and there was also an increase in morbidity (*49*).

In Rotterdam, The Netherlands, December 2–7, the sulfur oxide level increased to nearly five times the normal level, and there was a small increase in mortality and hospital admissions, especially in people over 50 years of age with cardiorespiratory conditions. There was also a report of an increase in sickness absenteeism (*61, 62*).

In Hamburg, Federal Republic of Germany, December 3–7, sulfur dioxide levels rose to more than five times the usual level, and dust pollution was more than double. Small increases, though not statistically significant, were thought to have occurred in mortality due to heart disease, though there was no change in respiratory disease frequency (*63*).

Increased pollution levels were also recorded in Paris, France; the Ruhr and Frankfurt, Federal Republic of Germany; and Prague, Czechoslovakia, but concomitant health studies have not been reported.

In Osaka, Japan, December 7–10, pollution levels were high. Mortality studies were under way in Osaka and demonstrated 60 excess deaths (*64*).

This episode did not occur in all parts of the world. The data available for Sydney, Australia, and the west coast of the United States indicate that there were no increases in pollution levels. Such an episode may be related to large-scale anomalous meterological conditions thought by Namias (*65*) to be related to an episode of warming of waters of the North Pacific, which occurred earlier that year.

10. Combined Oxidant and Sulfate Episode, Tokyo, Japan, 1970

Since March of 1967, elevated measurements of oxidants had been reported by the monitoring station of the Tokyo Metropolitan Public Health Research Laboratory. The level had exceeded 0.15 ppm during the daytime in summer on 12 days in 1967, 14 days in 1968, and 9 days in 1969 (*66*). On July 18, 1970, a thick fog was present in the early morning. As the sun rose, the fog dispersed, but visibility was less than 2 km (1.2 miles) even in the center of the city. Between 11:00 a.m. and 1:00 p.m., complaints of eye irritation mounted, and in one school 45 youngsters complained of smarting eyes, sore throat, and difficulty with breathing. Several had to be taken to hospitals where they were treated for "smog poisoning." The pollutant concentrations being measured by the Metropolitan Public Health Research Laboratory rose quite abruptly between 8:00 a.m. and noon, reaching a peak of photochemical oxidant of 0.34 ppm and an hourly average of 0.295 ppm. Characteristic vegetation damage was also observed, and at 5:30 p.m. that day, the Metropolitan Government issued a statement that the symptoms and impairment of visibility were caused by photochemical pollution. During several subsequent days, additional persons were affected. The number of persons reporting smart-

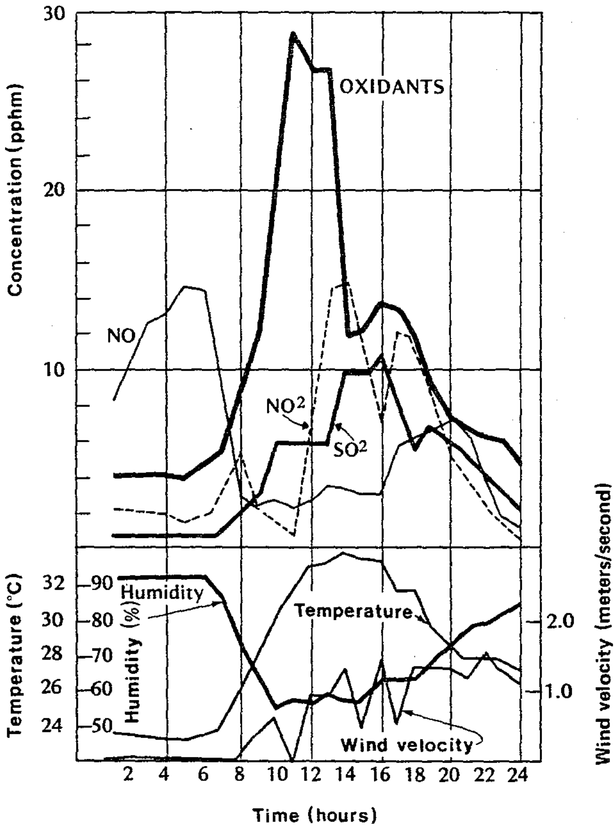

Figure 5. Hourly variation of pollutants and meteorological variables during July 18, 1970, in Tokyo, Japan. The complementary change in nitric oxide and oxidant level is characteristic of photochemical oxidant pollution. The presence of substantial amounts of sulfur dioxide makes it likely that sulfur trioxide, sulfuric acid, and/or acid sulfate aerosols were formed.

ing eyes and sore throat exceeded 6000. Sulfur dioxide reached a maximum of 0.39 ppm. It is inferred from this that the photochemical oxidant reacted with sulfur dioxide to produce a sulfuric acid mist. Figure 5 shows the time course of the pollution during this episode.

11. Methodological Problems of Detecting Acute Air Pollution Health Effects

Methods for detecting acute pollution effects have been developed and presented by Martin and Bradley (*48*), Martin (*67*), Greenburg *et al.* (*59*), McCarroll and Bradley (*68*), Cassell *et al.* (*69*), McCarroll *et al.*

(*70*), Hechter and Goldsmith (*71*), Ipsen *et al.* (*72*), Hexter and Goldsmith (*73*), Schimmel and Greenburg (*74*), and Buechley *et al.* (*75*). All make use of daily mortality or morbidity data. Martin has presented correlations of pollution levels and deviations from moving averages of daily mortality. On the basis of these and similar data, Lawther (*76*) has concluded that when both sulfur dioxide level exceeds 0.71 mg/m^3 and suspended smoke exceeds 0.75 mg/m^3, under conditions prevailing in London, increased mortality can be predicted to occur. Greenburg *et al.* (*50*) have compared the weeks before and after an episode with the same dates and years before and after. They have shown that periods with unusually high pollution are associated with small increases in mortality. Hechter and Goldsmith (*71*) have shown the applicability of auto- and cross-correlation to the time series problems of acute air pollution reactions. More extensive use of these methods has been made by McCarroll *et al.* analyzing data for New York, New York (*70*).

Ipsen *et al.* (*72*) have studied regression coefficients of environmental variables on sickness absence data from the Philadelphia, Pennsylvania, area and used canonical functions for combining sickness absence data for a series of days. This analysis, based on a relatively small population, did not support the hypothesis of an effect of air pollution on respiratory disease morbidity independent of climatic effects. The World Health Organization Symposium on Air Pollution Epidemiology (*77*) has pointed out the need for having a very large population (at least 500,000 and preferably several million) in order to detect acute effects on mortality.

Tucker (*78*), examining data on morbidity and mortality in Los Angeles, California, nursing homes, assumed that the number of deaths occurring in any day is distributed as a Poisson distribution (an often asymmetrical distribution applying to rare events occurring in a large population, with the mean and the variance or squared standard deviation of identical magnitude).

If unusual weather conditions caused an increase in mortality, the expected Poisson distribution would not be the same for the affected population as it would in other periods, and a test for this lack of homogeneity of the distribution was applied to the daily nursing home mortality data. No effect of air pollution was found. The sensitivity of this method partly depends on the choice of days for study as well as on other factors.

Other factors that complicate the interpretation of morbidity data are seasonal fluctuations, day-of-week biases in hospital admissions, concurrent infectious diseases occurring within the community, and a general scarcity of morbidity data. Another problem is the determination of how well recent reports of pollutant concentrations reflect ambient exposures of human populations. Evaluation of Continuous Air Monitoring Program (CAMP) data (Chapters 2 and 3, Volume I) will help in determining the relationship among such measurements as peak or mean values of pollutants for varying periods of time. Such systematic evaluations in conjunction with morbidity data will point the way toward more medically meaningful reporting of the ambient concentrations of pollutants.

Lebowitz *et al.* (*79*) have presented over fifteen reports on the association of various morbidity reactions to environmental and air pollution factors based on a 3-year diary study of daily symptoms, pollution, and weather in midtown Manhattan (New York, New York) for 1962 to 1965. In general, the reports indicate that symptom frequencies increase with a set of changes in pollution concentrations and meteorological circumstances that makes it difficult to identify any disease state or specific symptom with a specific pollutant. However, their data show convincing evidence that there are joint variations in the prevalence of a variety of respiratory symptoms and the associated increases in pollutants. In general, a 36-hour lag time has been observed between the peak of pollution and the peak of symptoms.

A series of studies have been reported of the possible relationships of daily mortality to air pollution, including one by Hexter and Goldsmith (*73*), Los Angeles, California, 1963–1965, and one by Schimmel and Greenburg (*74*), New York, New York, 1963–1968. A number of technical problems have been identified by the investigators, but when those problems are suitably treated, the capacity to find an association between pollution concentrations and mortality in very large urban areas appears to be established. However, the urban area must, in general, have a population base of several million, and a number of adjustments in the computations are necessary. For example, the roles of temperature, time of year, trend in the base population, wind, relative humidity, and sky cover should be accommodated for or represented in some way or other. The dominant form of pollution in New York City, that due to sulfur oxides and particulate matter, has been shown by Schimmel and Greenburg to have a significant association with fluctuations in daily mortality. Schimmel and Greenburg have used ten different mortality classes, and all except infant diseases were significantly correlated with the pollution variables, whether they were used in a crude, temperature-corrected, or a "fully adjusted" form taking into account variations due to time of year.

Buechley *et al.* studied daily mortality during the years 1962–1966 in the New York–New Jersey–Connecticut air quality control region. The population of the area in 1960 was nearly fourteen million persons. The mean number of deaths per day was 413.04. For each day, a ratio of observed daily deaths to this number was computed. Other variables included (a) influenza prevalence, (b) data from a single monitoring station for sulfur dioxide and (c) for particulate matter by COH (coefficient of haze) units, (d) the day's temperature difference, (e) the week's temperature difference, (f) the three-day extreme temperature (exponential) index, (g) holidays, (h) day of week, and (i) time of year reflected by a smoothed temperature cycle. After computing the regression weights for the full set of nine variables, the authors removed the contribution of sulfur dioxide variation, resulting in what they designated as a partial predicted mortality. Subtracting these from the observed mortality by classes of day within sulfur dioxide levels, a relationship was observed in which, with increasing sulfur dioxide there were first negative then positive deviations of residual mortality. For example, during the 260 days (out of 1826 total) on which sulfur dioxide exceeded 500 $\mu g/m^3$, the mortality deviations were from 1.75% to slightly more than 2% higher than the mean. This was equivalent to from about 7 to about 8 deaths per day in the population of fourteen million.

In reviewing data for subsequent years during which sulfur dioxide concentrations were much lower, a similar relationship is found (*78a*). The most likely explanation is that sulfur dioxide is behaving as an index of other pollutants, and not as a specifically causal agent.

The studies of Hexter and Goldsmith (*73*) dealing with Los Angeles, California, were adjusted for time of year by using Fourier terms and the trend in the size of the base population. After these adjustments, it was found that temperatures with lags of several days and polynomial forms with interactions accounted for a very large part of a remaining variance. The logarithm of carbon monoxide accounted for a small fraction of the variance.

Oechsli and Buechley (*80*) have reported on excess mortality associated with three Los Angeles, California, September heat spells in 1939, 1955, and 1963. The one in 1955 was also associated with excessive levels of photochemical smog. They show by fitting exponential equations to maximal temperature that age specific mortality excess in 1955 can be explained by temperature alone. The excess mortality was more clearly seen in deaths due to vascular diseases of the central nervous system than in other causes.

B. Determining Cause–Effect Relationships

In the years between 1965 and 1972, a major effort was undertaken to review data on effects of specific pollutants. The results are compiled in various reports on air quality criteria (*81–88, 88a*) for sulfur oxides, particulate matter, oxidants, carbon monoxide, hydrocarbons, and oxides of nitrogen. In developing statements of the relationship between air pollution levels and the effects caused by these levels, many critical decisions have to be taken as to the existence or extent of cause–effect relationships. These relationships may be quite indistinct when interpreting mortality and morbidity data on people and animals exposed for their lifetime to a multiplicity of stresses, only one of which is air pollution. For many of these stresses, including air pollution, there are inadequate measurements. Extrapolation to man of results from experiments involving exposures of experimental animals is a procedure that raises doubts. Doubt also exists on how to extrapolate short-term square-wave experiments (experiments where pollutant exposures are abruptly increased or decreased), using relatively pure substances, to the exposure of humans and animals to the fluctuating aged and irradiated mixture of precursors and reaction products that constitutes our real atmosphere.

In the process of identifying cause-and-effect relationships between health impairment and air pollution, certain questions continually recur. One is, what is meant by health impairment, injury, or damage? As experimental techniques improve, we are increasingly able to detect subtle physiological and psychological deviations from the norm, some of which can be attributed to pollution. The norm in this case is the health status of an individual or a population in the absence of exposure to polluted air. The deviation observed may be reversible when exposure to the pollutant stops. Some will argue that only irreversible deviations should be considered and that any reversible deviation should be considered benign until proved deleterious. However, the fact that a deviation is reversible upon cessation of exposure to the pollutant is not, of itself, assurance that allowing many such deviations to occur is without lasting harm. Prudence would argue for considering measurable, repeated deviations from the norm as deleterious until proved benign. If a temporary reduction in sensory perception or reaction time occurs, for example, during operation of a motor vehicle or other machines with moving parts, fatal accidents could occur. Thus, temporary, presumably reversible, effects of air pollution should not be dismissed as of no consequence to health, even though, with present data, we can demonstrate neither disease aggravation nor fatal potential.

The question is sometimes raised as to what percentage of the population (i.e., 99.9%, 99.99%, etc.) we should seek to protect by ambient air quality control; and what percentage (i.e., 0.1%, 0.01%) we should take care of by other means, such as their relocation to areas or structures having a cleaner air supply or by supportive medical treatment. Epidemiology is the special discipline with competence to obtain and interpret information relevant to this question. The question must ultimately be referred for answer to value-oriented, that is political, authorities, and the role of medical and other scientists is to inform, but not to decide. The answer to the question is a political one, because it should be based on alternative uses of resources and the values attached to health, to technology, to convenience, etc.

While it is well known that pollution exposures are to a heterogenous, poorly characterized mixture of materials, it remains a critical assumption that specific, measurable, physical or chemical agents are responsible for most of the detectable effects on health. If this assumption be valid, it becomes possible to apply toxicology to air pollution control in a manner that prevents or abates effects on health. If the assumed specificity were not valid, while we could attach blame to sources such as automobiles, a factory, or to coal burning, we would not know other than by trial and error, in what way, and in what magnitude, we should make modifications in the automobile, factory, or combustion chamber to abate or prevent specified health effects.

The application of this assumption, which occurs throughout Sections III–V, should not obscure the artificial nature of specificity. Pollutants do not usually act alone, nor are all of the effects of a given pollutant specific to that pollutant. For example, geographic factors, such as latitude and time of day or year affect the energy spectrum of photochemically active sunlight at the earth's surface. Time of year and climatological and meteorological variables affect human reactions and defences against a given pollution exposure.

C. Relationship of Epidemiological and Toxicological Evidence

Epidemiological and toxicological research are complementary approaches in studying and interpreting the effects of pollution exposures on health. While the most important evidence on health effects concerns the effect on natural populations of humans under realistic conditions, for reasons given above, we have difficulty in making precise, quantitative, universal statements based on such epidemiological evidence. However, the precise, quantitative, specific data from toxicological experiments may not reflect the complexity of real life. In general, interpretations of causation from epidemiological studies should not be based on a single study, but on the convergence of evidence derived from several independent epidemiological studies and related experiments. The conclusion that cigarette smoking was a major cause of cancer of the lung was based on such convergence (*7*).

Experimental data generally do not include long-term exposures of human subjects and therefore cannot allow us to estimate accurately the magnitude of long-term pollution effects. Epidemiological studies generally are affected by a large number of coexisting and fluctuating variables and often do not yield the specificity that control strategies seek. Epidemiological studies tend to produce nonspecific but realistic data. Inferences relating control to prevention of effects must utilize both types of data.

III. Combined Effects of Sulfur Oxides and Black Suspended Matter*

Sulfur oxides and suspended particulates are considered together because most of the epidemiological studies reported represent a combined exposure; furthermore, in ambient air they are found to fluctuate together. Thus, epidemiological data will not necessarily reveal whether or not an observed effect associated with emissions from a combustion source can be referred to one pollutant alone.

For particulate matter, most of the epidemiological studies reported, including those referred to here, have been concerned with particles produced by burning fossil fuels. Particulate matter may arise from several other sources, industrial as well as natural. Its effects may differ widely, depending not only on its chemical composition, but also on particle size and on its physical form. Epidemiological studies concerned with particles produced by burning fossil fuels should be extrapolated with caution to situations where sulfur oxides occur in combination with other forms of particulate matter.

A. Acute Effects

With very high concentrations, such as occurred during the well-known episodes in London, Donora, and New York (Section II,A), immediate effects were detectable in terms of increased mortality and morbidity. Effects were primarily seen in those already ill, old, or enfeebled. Excess mortality and increased hospital admissions have been identified when levels of suspended smoke particles and sulfur dioxide for 24 hours each has exceeded 500 $\mu g/m^3$ (*88*).

* The term "black suspended matter" is used because most of the epidemiological studies that have given results relevant to a discussion of dose–response relationships have used the British Standard Procedure, which measures black suspended material. The term "total suspended matter" describes what is measured when high-volume samplers are used; this is the commonest measure used in the United States.

Lawther *et al.* (*89*) report on the exacerbations of bronchitis in relation to air pollution. During several periods between 1954 and 1968, diaries were sent to patients with chronic bronchitis in London and Manchester. The patients had to report daily over several months, whether or not their symptoms were worse than usual. Daily measurements of sulfur dioxide [hydrogen peroxide method—titrimetric DSIR (Department of Scientific and Industrial Research, England)] and smoke (smoke stain index) were made. Data were given as 24-hour average values. It could be shown that an association occurred between high concentrations of sulfur dioxide and particulate matter on the one hand and an exacerbation of symptoms on the other hand (Fig. 6). There was no clearcut association between visibility, temperature, or humidity and these exacerbations. The lowest values where effects were clearly seen were 250–500 $\mu g/m^3$ of sulfur dioxide together with about 250 $\mu g/m^3$ of smoke.

During the later years of the studies, high peaks of sulfur dioxide and particulates were not found. On the other hand, even during the winter period of 1967–1968, when the daily data were treated statistically, a significant correlation (5% level) was found with both smoke and sulfur dioxide, with mean smoke concentrations of only 68 $\mu g/m^3$ (standard deviation = 48), and 204 $\mu g/m^3$ (standard deviation = 100) of sulfur dioxide.

The method used by Lawther *et al.* has not been validated, in the sense that objective evidence of aggravation has supported the subjects' own

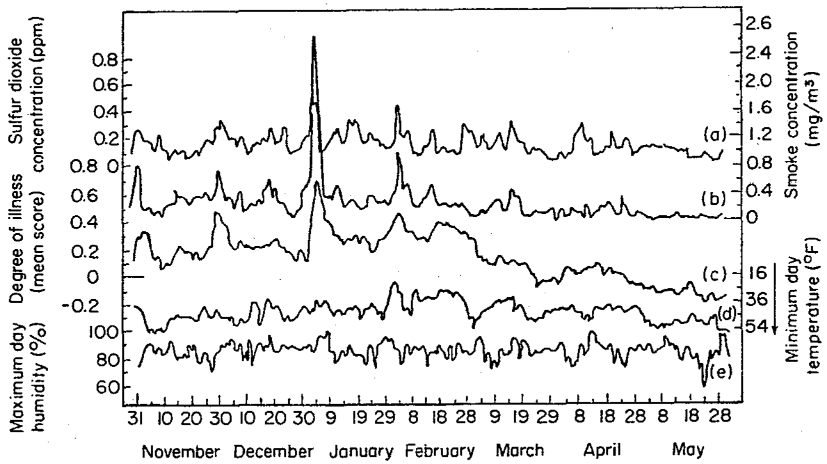

Figure 6. Degree of illness (c) of a group of 180 patients in greater London (1955–1956) with chronic bronchitis plotted with smoke (b) and sulfur dioxide (a) concentrations, temperature (d), and humidity (e) (89).

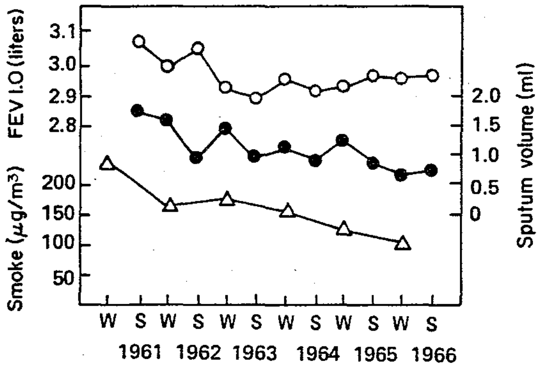

Figure 7. Mean values of $FEV_{1.0}$ and sputum volume in working men aged 30–59 in London with winter smoke concentrations (△) (*91*) (1951–1956). ○ = mean $FEV_{1.0}$ of all men who attended at least one of the last four surveys; ● = mean sputum volume of all men who attended at least one of the last four surveys; × = Mean concentration of black smoke during winter at seven sampling sites in London; W = winter; S = Summer.

report of symptoms. In summary, though, it is generally accepted that the association shown between high levels of smoke and sulfur dioxide on the one hand and exacerbation of chronic bronchitis in bronchitis patients on the other hand is real (*90*). When two winters (1959–1960 and 1964–1965) were compared in terms of the associations of exacerbation with sulfur dioxide, the general impression was of a slightly reduced and less consistent effect during the later period. The mean smoke concentrations had then decreased from a mean of 342 μg/m³ in 1959–1960 to 129 in 1964–1965, while the sulfur dioxide concentrations had decreased only from 296 to 264 μg/m³.

Fletcher (*91*) reported some data on a group of men aged 30–60 working in London from 1961 to 1966 that support the hypothesis of the beneficial effects of reducing particulates. Mean sputum volume decreased steadily even in men who had not changed their smoking habits. Over this period, the mean smoke concentration in seven sampling stations in London had dropped from approximately 420 μg/m³ in 1959 to approximately 100 μg/m³ in 1965. There was no corresponding drop of the concentration of sulfur dioxide (300 in 1959 and 260 μg/m³ in 1965) (Fig. 7).

B. Chronic Effects on Adults

Holland *et al.* (*92–94*) studied post office and telephone workers in England and the United States. The prevalence of respiratory symptoms was studied using the British Medical Research Council's short questionnaire for respiratory symptoms. For measuring lung functions, the $FEV_{1.0}$* was used. Aerometric data were scant. Table II shows, however, that both mean and highest 24-hour values are higher in London, England, than in the rural towns, which, in turn, had higher values than United States cities for suspended particulates as well as for sulfur dioxide. Brasser *et al.* (*95*) have furnished some further sulfur dioxide values; London (St. Pancras) summer average 100 $\mu g/m^3$, winter average 500 $\mu g/m^3$; Gloucester, Petersborough and Norwich, England, 75 $\mu g/m^3$ and 200 $\mu g/m^3$, respectively, for summer and winter averages, representative of rural areas in the United Kingdom.

These studies show a close relationship between smoking habits and respiratory dysfunction and a gradient with regard to place of residence. Respiratory disorders were most prevalent in London, less in rural England and still less in the United States (Fig. 8). When smoking habits were taken into consideration, an urban effect was seen in smokers, but not in nonsmokers and exsmokers. The deterioration of lung function, however, was evident also in nonsmokers and exsmokers (Fig. 9). Considering the difference in effects between English rural towns and the United States cities, one may interpret the data as if the lowest values at which effects have been observed are about 75 $\mu g/m^3$ for sulfur dioxide together with about 200 $\mu g/m^3$ for suspended particulate matter (see also Section VI,A).

Reid *et al.* (*9*) report on an Anglo-American comparison of the prevalence of bronchitis. The British study was carried out on a random sample of men and women aged 40–64 drawn from the practice lists of 92 physicians working in urban and country areas of Britain. The United States data are a probability sample of residents in Berlin, New Hampshire, for whom it was possible to get a similar sex and age distribution. The British Medical Research Council's questionnaire was used for diagnosing chronic bronchitis and the Wright peak flow meter for measuring lung function. The results show that there is a difference in prevalence of bronchitic symptoms, tending to show that after standardization for age and lifetime cigarette consumption, the United States data for men would be about equal to the British rural data for men. Considerably higher prevalence was found in United Kingdom towns and cities. It is not known whether differences in socioeconomic status could have been factors of importance. Also, the standardization for lifetime cigarette smoking is

* $FEV_{1.0}$ stands for forced expiratory volume in 1 second, which is defined as the amount of air one can expel in 1 second with maximal effort after maximal inspiration.

Table II Comparison of Respiratory Findings among Outside Workmen Age 40–59 in the United Kingdom and the United States and Representative Pollutant Levels for Each Area (*93*)

	United Kingdom				*United States*			
	London		*Rural areas*		*Baltimore, Maryland; Washington, D.C.; and Westchester County, New York*		*San Francisco and Los Angeles, California*	
	Age 40–49	*Age 50–59*	*Age 40–49*	*Age 50–59*	*Age 40–49*	*Age 50–59*	*Age 40–49*	*Age 50–59*
Number of men examined	113	137	267	159	396	229	361	119
Persistent cough and phlegm (%)	25.7	38.7	24.0	18.9	22.2	25.8	21.6	24.4
Persistent cough and phlegm and chest illness episode (%)	10.6	10.9	7.5	5.0	6.8	7.0	4.0	7.6
$FEV_{1.0}$ (liters) mean values[a]								
Nonsmokers	2.8	2.6	3.0	2.8	3.5	3.1	3.7	3.3
Cigarette smokers								
1–14/day	2.6	2.3	2.8	2.6	3.4	3.0		
15–24/day	2.6	2.2	2.8	2.5	3.2	2.8	3.4	2.8
25 or more/day	2.5	2.1	2.7	2.5	3.2	2.9		
Sputum volume, 2 ml or more (%)	28.9	42.9	22.1	23.5	7.1	10.0	8.6	14.3
Suspended particulates ($\mu g/m^3$) 24 hour								
Mean	220		200		120		120	
Maximum	4000		3000		500		340	
Sulfur dioxide (ppm) 24 hour								
Mean	0.1		0.02		0.04[b]		0.01[c]	
Maximum	1.3		0.26		0.25		0.06	

[a] $FEV_{1.0}$ = forced expiratory volume in 1 second.
[b] Washington, D.C., 1962–1963.
[c] San Francisco, California, 1962–1963.

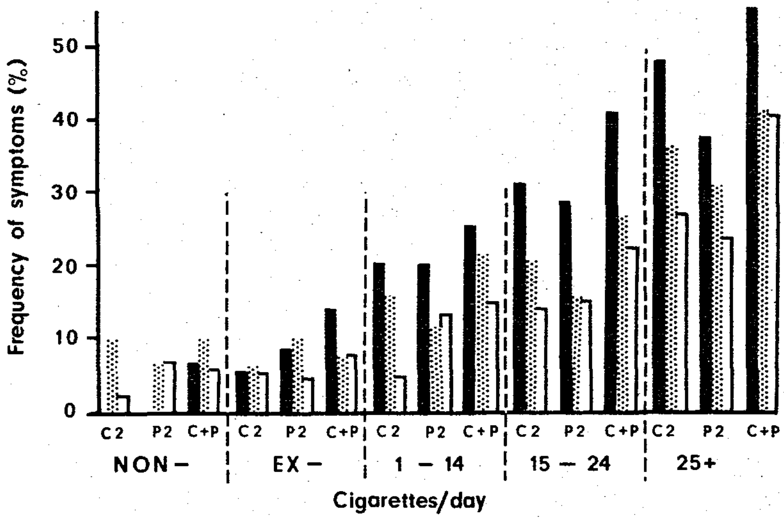

Figure 8. Frequency of cough grade 2 (C2), phlegm grade 2 (P2), and persistent cough and phlegm (C + P) in men from London (solid bars), three rural (shaded bars) towns, and the United States (white bars) by smoking habits (1961–1962) (*93*). Grade 2 means that the symptom continues during day or night for as much as 3 months each year.

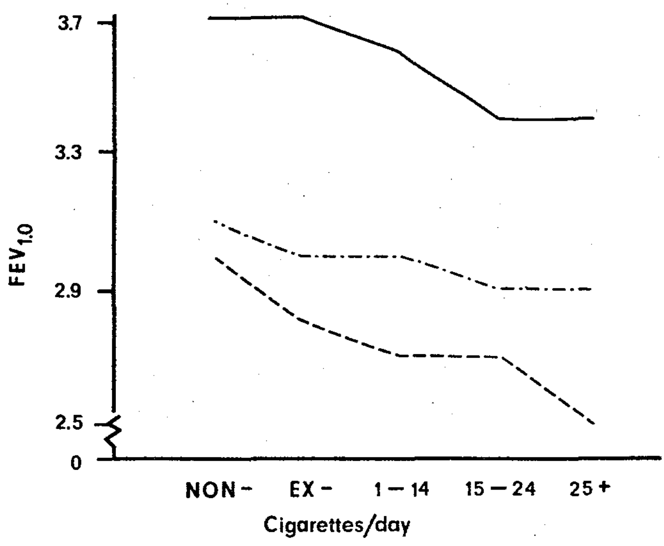

Figure 9. The $FEV_{1.0}$ (liters) standardized to age 40 in men from London (– – –), rural towns (–•–•–), and the United States (——) by smoking habits (*93*). 1961–1962.

questionable, in view of the fact that the bronchitic symptoms seem to be closely related to fairly recent exposure.

In the first Berlin, New Hampshire, study (in 1961), nonsmokers in the more polluted area of the town had a higher prevalence of chronic respiratory disease than did nonsmokers in less polluted areas (Table III) (*96*). Indeed, the prevalences among male nonsmokers in the polluted area resemble those for pack-a-day smokers. As Ferris (*97*) points out the two- to threefold difference in pollution may have had effects that are understated by Table III. He believes that internal migration may have occurred among families that initially lived in the more polluted area, who, after experiencing pollution effects, moved to other areas. The pollutant exposure in Berlin is largely that due to a kraft paper mill and may not be representative of the more common types of pollution effects from sulfur oxide and black suspended matter.

Ferris and Anderson (*98*) in 1963 studied a random sample from Chilliwack, British Columbia, Canada, and compared results with the more polluted city, Berlin, New Hampshire. Respiratory symptoms, when standardized for age and cigarette smoking, tended to be higher in Berlin than in Chilliwack. Tests of pulmonary function ($FEV_{1.0}$, peak expiratory

Table III Prevalence of Nonspecific Respiratory Disease in Nonsmokers by Relative Pollution at the Place of Current Residence, Berlin, New Hampshire, 1961 (*96*)

	Least polluted		*Intermediate*		*Most polluted*	
Subjects	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Males						
Population	36	100.0	65	100.0	23	100.0
Chronic nonspecific respiratory disease	6	16.7	10	15.4	9	39.1[a]
Chronic bronchitis	3	8.3	9	13.9	7	30.4
Irreversible obstructive disease	4	11.1	2	3.1	5	21.7[a]
Females						
Population	106	100.0	178	100.0	86	100.0
Chronic nonspecific respiratory disease	21	19.8	27	15.2	18	20.9
Chronic bronchitis	11	10.4	16	9.0	8	9.3
Irreversible obstructive disease	14	13.2	11	6.2	12	13.9

[a] Differences significant comparing most polluted and both other locations for males. All other differences are not significant.

flow rate) after standardization for age, height, sex, and smoking category also showed some differences. There are several difficulties in interpreting these data. It seems reasonable that slight changes in respiratory symptoms and pulmonary function were related to pollution levels, sulfur oxides, and particulates. Particulate matter was estimated by high volume (Hi-Vol) samplers (see footnote on p. 483). The studies were repeated in 1966–1967 in Berlin, New Hampshire, and in this period, there was a lower prevalence of respiratory symptoms than in 1961 (*99*). Sulfation levels had also dropped, but total suspended particulate matter had not changed significantly.

In a number of papers (*100–102*), data from extensive studies in the Ruhr industrialized area of Germany covering about 8000 people are reported. Due to several biasing factors, e.g., high nonresponse rate and different sampling procedures used for different areas with large differences in occupation, the risk that selective factors have been operating seems to be high. There is some experimental evidence that ozone may have a comparable role to black suspended matter in promoting health impairment due to SO_2 (see Section IV,B,1).

C. Chronic Effects on Children

Douglas and Waller (*103*) report on the prevalence of upper and lower respiratory symptoms in children during an 11-year period beginning in 1952. The children were followed medically by health visitors and by medical examination at school. Levels of air pollution were estimated by the amount of coal consumed in a given area. In 1962, a validation of the estimation procedure was made using available aerometric data from a number of the study areas. Douglas and Waller noticed an increased occurrence of lower respiratory tract infections in areas with increased air pollution. The data can be interpreted as if effects were seen already at concentrations of about 140 $\mu g/m^3$ (± 9) of smoke and about 130 $\mu g/m^3$ (± 9) of sulfur dioxide, in both cases expressed as mean annual concentration. Aerometric data were based on the hydrogen peroxide method (sulfur dioxide) and smoke stain index (particulates).

Lunn *et al.* (*104*) report on the prevalence of respiratory symptoms in children 5 years of age and living in four different areas of Sheffield. England, with different air pollution exposure. Air pollution was measured (hydrogen peroxide method and smoke stain index) for the 3 years of the study. They found increased chronic upper respiratory infection in relation to the level of air pollution. Certain differences in social structure between the study areas were evident. However, for several symptoms, the gradient between the areas would hold true even when the groups were divided into social class, number of children in house, and so on. Data, divided into social class, for persistent or frequent cough for the different areas are given in Table IV. Comparing aerometric data with the medical findings yields the conclusion that symptoms may occur at concentrations (for both smoke and sulfur dioxide) of about 200 $\mu g/m^3$, but are not expected to occur when these concentrations are about 100 $\mu g/m^3$. A follow-up study by Lunn *et al.* (*105*) showed that with the reduction of smoke levels in Sheffield, England, the respiratory condition differences between the groups of children had decreased.

Holland *et al.* (*106*) and Colley and Reid (*107*) each have carried out studies on about 10,000 children in different parts of England. The object was to measure respiratory disease and associate the disease with different environmental factors including air pollution and social class. Holland *et al.* were studying primarily peak expiratory flow rate, and Colley and Reid were studying upper and lower respiratory tract symptoms and also peak expiratory flow rate. Levels of smoke were measured in Holland's study during 5 months in the winter of 1966–1967. The mean for that period in the most polluted area, Rochester, England, was 70 and for the least, 35 $\mu g/m^3$. The averages for the worst month were respectively 96 and 70 $\mu g/m^3$, and the highest daily concentration was 282 $\mu g/m^3$. In

Table IV Relationship of Persistent or Frequent Cough in British Children of Sheffield by Area, Pollution Levels, and Social Class (*104*)

	Greenhill	*Longley*	*Park*	*Attercliff*	*All areas*
Mean daily pollution levels ($\mu g/m^3$)					
Smoke	97	230	262	301	
Sulfur dioxide	123	181	219	275	
Number of days with readings over 500 $\mu g/m^3$					
Smoke	4	30	40	45	
Sulfur dioxide	1	11	16	32	
Percent of children with cough (numbers in parenthesis)					
Total	22.6 (350)	36.4 (162)	37.1 (105)	50.7 (71)	31.0 (688)
Social Class					
I and II (highest)	0.0 (23)	60.0 (5)	50.0 (2)	50.0 (2)	15.6 (32)
III	24.2 (260)	33.9 (109)	30.9 (55)	45.7 (46)	29.4 (470)
IV and V (lowest)	23.9 (67)	39.6 (48)	43.8 (48)	60.9 (23)	37.5 (186)

pollution levels occur here with daily averages of sulfur dioxide and particulate matter exceeding 240 $\mu g/m^3$ on more than 7 days a month during the winter. Screening spirometric tests showed no extraordinary findings. Nineteen children with the lowest values of forced expiratory volume were studied further, using more sensitive methods. In 6 of the 19, significant reduction in maximal flow rates at low lung volumes were found. This indicates unfavorable changes in small-caliber airways.

Kerrebijn *et al.* (*108a*) studied two groups of communities in an area with intense use of greenhouses for floriculture and horticulture. Most were heated by oil which produce high levels of SO_2 and smoke pollution; in the low-pollution area, gas was used. Fifth and fourth grade children were studied. Depending on criteria used, chronic respiratory disease prevalence in the more polluted area ranged between 5.3 to 12.7%, while in the clean area the range was 3.3 to 9.8%. The differences between the areas were statistically significant. Ventilatory function tests showed no differences.

IV. Effects of Gaseous Pollutants

A. Sulfur Dioxide

1. Absorption of Sulfur Dioxide and Experimental Exposures in Man

Sulfur dioxide, being a very soluble gas, is nearly completely absorbed during quiet breathing in the nose and upper airway. It was at first assumed that, under these conditions and with the low to moderate levels of exposure that occur in community air pollution (up to 2 ppm), no effects on the function of the lung could occur. This assumption must be qualified or discarded on the bases of the experimental work in cats by Widdicombe (*109*) and Nadel *et al.* (*110*) showing that many of the airway caliber changes produced by pollutants are mediated by reflexes. They have shown, for example, that sulfur dioxide or other stimuli given to the upper airway, which is anatomically isolated from the lower respiratory tract, will nevertheless produce increased airway resistance in the lung via the vagal nerve and that this can be abolished by cutting or otherwise interrupting the transmission of impulses in that nerve.

In addition, variability of response of different persons to sulfur dioxide exposure under experimental conditions has been documented (*82*, *110–112*) (Table V) by a number of investigators. This is manifested by unusually severe impairment of lung function with exposures to between 2

Table V Effects of Breathing Sulfur Dioxide on the Airway Resistance in Normal Subjects (*112*)

		Mean airway resistance ($cm\ H_2O/liter/second$)				
Subject	*Sex*	*Control*	*After sulfur dioxide*	*After subsequent bronchodilator*	*Sulfur dioxide concentration (ppm)*	*Exposure time (minutes)*
B.B.	F	1.37	2.33	1.32	2	3
J.B.	F	1.13	1.67		2	6
J.B.	F	1.54	1.87	1.14	5	4
P.S.	F	1.80	1.82	1.61	5	4
D.H.	M	0.69	0.76		2	3
R.M.	M	1.15	8.54	1.22[a]	5	10
J.N.	M	1.10	2.74	0.98	5	10

[a] After previous bronchodilator, value was 0.92.

and 5 ppm or, in some cases, the development of a moderately severe attack of asthma in an otherwise healthy subject with no recent history of asthma. Whether these reactions are due to variability in sensitivity or to an exaggerated response to a dose to which any subject might react is not clear. Among the healthy subjects studied, about one in ten may manifest such an exaggerated reaction. We do not know how these data apply to persons with a history of chronic diseases. Nor do we know whether the same or similar phenomena apply to other gaseous pollutants. It is a reasonable hypothesis that soluble, odorous pollutants generally behave as does sulfur dioxide, producing some of their effects by reflex action initiated in the nose and with a proportion of the population manifesting exaggerated reactions. Similarly, mouth breathing whether due to exertion or disease is likely to lead to greater effects for such pollutants.

The effects at low concentrations include the distasteful odor, detectable at about 0.5 ppm (*113*). At slightly higher concentrations, the irritating effects lead to increased airway resistance. Chronic cough and mucus secretion may result from repeated exposures, although most of the exposures to which these effects appear to be related are probably not due to sulfur dioxide alone.

2. Epidemiological Evidence

Smelters are large sources of sulfur dioxide, and in studies done in the vicinity of Port Kembla, Australia, Bell and Sullivan (*114*) documented the excess occurrence of chronic respiratory symptoms in those populations with the greatest exposure. This study appears to represent predominant effects of sulfur dioxide. Other epidemiological studies that appear to reflect effects of sulfur dioxide are most likely due to its interactive effects with other pollutants, whether measured or not.

B. Ozone and Other Oxidants

The reaction of nitric oxide with hydrocarbon vapors in the presence of sunlight leads to production of ozone and nitrogen dioxide in the atmosphere, along with many other compounds. When such photochemical pollution is of more than mild intensity, ozone is the dominant species, but other active agents, such as nitrogen dioxide, peroxyacyl nitrate, and peroxybenzoyl nitrate account for some effects. Collectively, they have been estimated by their oxidizing properties and are designated "oxidants." Experimentally, the reproduction of this mixture and its transient products is difficult. Hence, most experimental data are reported as an effect of ozone (or peroxyacyl nitrate, peroxybenzoyl nitrate, etc.), while most of the epidemiological data are related to measurements of oxidant.

The experience of human populations with oxidant air pollution is likely to be variable, because among other reasons, the photochemical mixture is composed of different constituents at different times and at different locations. The human "symptoms" of photochemical smog, respiratory and eye irritation, were first observed in the Los Angeles, California, basin. The "diagnosis" can be confirmed because of the presence of the three other manifestations—production of ozone, interference with visibility, and characteristic forms of vegetation damage. Experience with occupational exposure to ozone and with human experimental exposures to ozone are helpful in separating the effects due to ozone and those due to other portions of the photochemical mixture. For example, eye irritation at oxidant concentrations observed in the Los Angeles, California, area cannot be reproduced experimentally by ozone; therefore, ozone itself is thought not to be the eye irritating ingredient in photochemical pollution. The exact substances that cause eye irritation are still not defined. They are now thought to include formaldehyde, acrolein, peroxybenzoyl nitrate, and peroxyacyl nitrate. The respiratory effects of photochemical pollution, some of which can be produced by the amount of ozone present, are thought to be aggravated by these other substances.

In a series of studies, Huess and Glasson (*115*) and Glasson and Tuesday (*116*) have sought to obtain and define a relationship between eye irritation potency of various photochemically reacted materials and their chemical reactivity. The eye irritation potency is estimated from the

Table VI Average Results of Irradiation of 2 PPM of Various Hydrocarbons and 1 PPM of Nitric Oxide (*115, 116*)

Class and compound	Nitrogen dioxide production (ppb/minute)	Percent hydrocarbon reacted[a]	Product yields (ppm)			Eye irritation average threshold time (seconds)	Eye irritation index (0 to 3 scale)
			Ozone maximum	Form-aldehyde	PAN[b]		
Alkanes							
n-Butane	4.6	5	0.16	0.15	0	240	0.0
n-Hexane	6.5	18	0.17	0.19	0	240	0.0
Isooctane	4.7	10	0.19	0.25	0	219	0.2
Benzene	1.6	13	0.05	0.08	0.01	216	0.2
Alkylbenzenes							
Toluene	5.7	39	0.30	0.14	0.10	114	2.0
Ethylbenzene	7.2	29	0.21	0.11	0	138	1.6
n-Propylbenzene	5.7	30	0.21	0.10	0.01	111	2.5
Isopropylbenzene	6.6	33	0.19	0.28	0.01	202	0.6
n-Butylbenzene	6.0	33	0.24	0.11	0	86	2.3
Isobutylbenzene	5.0	28	0.17	0.10	0	104	2.5
sec-Butylbenzene	7.6	21	0.26	0.16	0	197	0.6
tert-Butylbenzene	3.8	28	0.13	0.15	0.01	219	0.3
Multialkyl benzenes							
o-Xylene	13.6	52	0.32	0.45	0.40	186	0.9
m-Xylene	15.5	54	0.39	0.39	0.50	171	1.3
p-Xylene	7.7	42	0.26	0.22	0.40	180	1.1
1,3,5-Trimethylbenzene	26.0	66	0.46	0.70	0.67	166	1.0

Olefins							
Ethylene	5.8	45	0.28	0.83	0.01	216	0.3
Propylene	12.1	73	0.54	1.17	0.35	148	1.2
1-Butene	13.1	85	0.47	0.90	0.05[c]	210	0.7
1-Hexene	9.6	80	0.41	0.78	0.02	157	1.2
Internal olefins							
trans-2-Butene	38.0	85	0.44	0.75	0.63	186	0.5
cis-2-Butene	28.0	90	0.44	0.69	0.36	201	0.6
2-Methyl-2-butene	50.0	95	0.49	0.68	0.85	195	0.5
Tetramethylethylene	170.0	95	0.60	0.63	0.65	207	0.7
Polyolefins							
1,3-Butadiene	25.0	92	0.48	0.80[d]	0.02	73	3.0
Estimated reproducibility[e] (%)	14	10	19	10	10[f]	8	22

[a] Corrected for dilution.
[b] PAN is peroxy-acetyl nitrate.
[c] PPN (peroxy-propionyl nitrate) also formed.
[d] 0.73 ppm of acrolein also formed.
[e] Calculated from the average of the average deviations from the mean for all hydrocarbons listed.
[f] Only one determination for each hydrocarbon. Reproducibility estimated from calibration.

time interval from exposure of experimental human subjects to their awareness of eye irritation. The chemical reactivity is estimated by either rate of hydrocarbon disappearance or rate of conversion of nitric oxide to nitrogen dioxide (Table VI). Within the several classes, there seems to be a relationship of chemical reactivity to eye irritation potency.

1. Effects of Ozone, Based on Toxicological Evidence

At a concentration of 0.02 ppm (40 $\mu g/m^3$), ozone can be detected by odor (*117*). When first detected, the odor is not an objectionable one. This has made it possible for ozone to be used for such purposes indoors as deodorization, which unfortunately often exposed residents to concentrations of ozone we now know to be excessive. This use was based on an apparent decrease in sensitivity to other odorants when a subject was exposed to low levels of ozone. It is not clear whether the ozone reacts primarily with the odorant or with the odor-detecting membranes in the nose.

At concentrations of about 0.3 ppm (590 $\mu g/m^3$) with exposures of a few minutes, the irritating effects of ozone are detected (*118*). These are readily detected at half a part per million by most individuals and may be detected at lower concentrations by some (*119–121*). The irritation includes a sense of dryness of the throat. Such irritation may occasionally be observed in places where ultraviolet lamps are used, and these can, of course, produce ozone. Under normal conditions of breathing through the nose, the irritation occurs high in the respiratory tract and does not affect the gas-exchanging part of the lung to the same extent. If the ventilation rate is sufficiently high, and mouth breathing occurs, the mechanisms of scrubbing the incoming air to remove the relatively insoluble gas are inefficient and the ozone may reach the deeper parts of the lung.* A more severe effect of ozone exposure is alteration in the airway resistance. This was shown by studies of Goldsmith and Nadel (*121*) to be detectable at concentrations between 0.1 and 1.0 ppm, but there was not a consistent dose–response relationship in the four individuals who were studied (Fig. 11). Subsequently, Mohler *et al.* (*122*) exposed three nonsmoking subjects to 0.6 to 0.8 ppm ozone for 60 minutes with spirometry and plethysmography at 30 minute intervals. No physiologically significant change in any subject occurred. The subjects had headache, nausea, and anorexia. With exercise, the subjects had coughing and chest pain. The experiments of Goldsmith and Nadel were carried out in an exposure chamber; four subjects were exposed for an

* For discussion of respiratory transport and absorption of ozone, see Chapter 7 of NAS–NRC report (*121a*), particularly Tables 7-1 and 7-4, which compare ozone and other gaseous pollutants. Figure 7-5 provides a comparison of dosage of sulfur dioxide and ozone per breath by level in the respiratory tract.

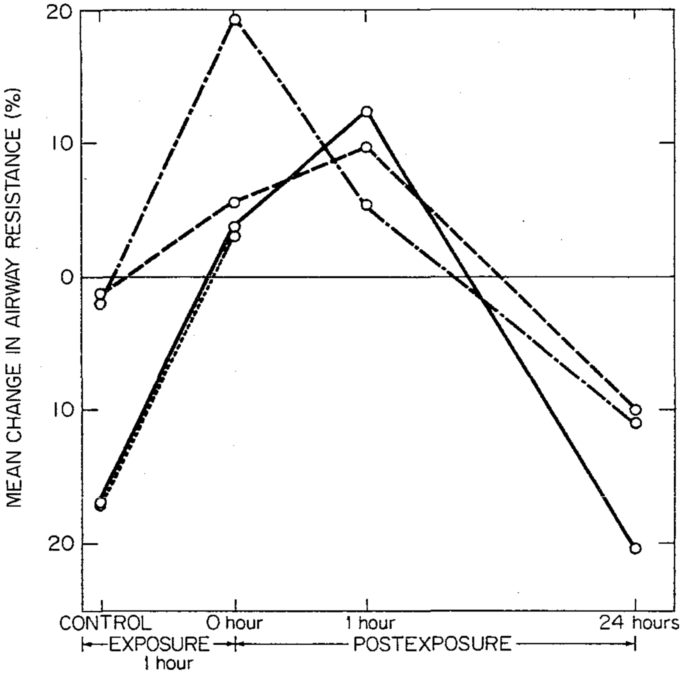

Figure 11. Effect of ozone on airway resistance, in four, presumably normal, male subjects (*121*). With 0.1 (····) and 0.4 (——) ppm, only one subject had significant increases, but with 1.0 ppm (–·–·–) all four did have significant increases; (–––) indicates 0.6 ppm.

hour simultaneously and then they were required to walk several hundred feet to a body plethysmographic laboratory on another floor. These circumstances of the experiment could have permitted a transient effect to be missed; perhaps there was a reaction to removal to ozone-free air. Nevertheless, the differences in methods should have led the results of Goldsmith and Nadel's study to be less positive. More definitive studies of lung function following 0.75 ppm ozone inhalation for 2 hours in subjects who were exercised have been published by Bates *et al.* (*123*). Most of the 10 subjects had chest soreness and a sensation of shortness of breath. Maximal transpulmonary pressure dropped, as did maximal flow at half of the vital capacity. Exercise accentuated the effects. Pulmonary resistance, most of which is in the larger airways, increased. Results varied among the subjects, however. Ozone at 0.37 ppm for 2 hours produced little change in lung function, but when combined with 0.37 ppm sulfur dioxide, marked and persisting changes were found by Bates and Hazucha (*124*).

Representative of the four lung function tests reported (*124*) are results for the $FEV_{1.0}$ resulting from 2-hour exposures with intermittent exercise in healthy adults. At 0.37 ppm of SO_2 there was on average no change in $FEV_{1.0}$ (although changes did occur with more sensitive tests). Exposure to 0.37 ppm ozone produced 8% decrement. Exposure to 0.75 ppm ozone produced an average decrement of 22%, 0.75 SO_2 an average decrement of 10%, and the combination of 0.37 ppm ozone and 0.37 ppm SO_2 a decrement of 19%. It thus appears that above a minimal ozone exposure level, the joint presence of the two pollutants affects lung function as though all the dose was of ozone. This impression is of special concern in areas with both photochemical pollution and sulfur oxide pollution, since it suggests that oxidant can have a comparable effect to black suspended matter in promoting the harmful effects of sulfur dioxide.

The most characteristic toxic effect of relatively high-level ozone exposure is pulmonary edema (*125*), by which is implied a leakage of fluid into the gas-exchanging parts of the lung. This is that part of the lung in which gas diffuses through what is normally a short distance between the terminal alveoli and the capillary. After exposure to sufficient ozone, the amount of water present in the tissues is increased, presumably through some change in cell permeability, and the path for gas diffusion is increased. Estimation of this effect has been done by Young *et al.* (*126*), who have calculated the amount of fluid that might be required to produce the interference with diffusion of gases which they have observed. This effect occurs at concentrations only slightly in excess of what is likely to be produced by community air pollution in Los Angeles, California. Pulmonary edema, if severe, can be crippling and fatal.

The ability of animals exposed to a few tenths of a part per million to tolerate subsequent exposures within a few hours of 6–10 ppm, which would otherwise be fatal (*127*), had not been shown for man.* With continued (i.e., several hours a day, several days a week for as long as a year) exposure to ozone at moderately elevated levels, 1960 $\mu g/m^3$ (1 ppm) in experimental animals, some species, but not all, react by developing fibrotic lung changes (*128*). The question of whether man has this type of reaction to similar exposures is unresolved. While ozone exposures have been reported to cause the appearance of tumors in tumor-prone animals at an earlier period in their life cycle and with a higher frequency than they would otherwise occur, a role of ozone in tumor production of man has not been shown.

A great deal of discussion promoted by these observations concerns the possibility that ozone is a radiomimetic agent. By this is meant that

* Several lines of evidence suggest that the same process occurs in man. The evidence is reviewed in the report by the National Academy of Science, National Research Council (*121a*).

it produces effects that mimic the effects of exposure to X-ray and other forms of radiation. To some extent, this is a valid and provocative possibility, but in other respects the exposures to ozone are not radiomimetic. For example, no increased level of leukemia occurs from ozone exposure as has been observed from exposure to radiation; no effects on the production of white blood cells occur, nor are there effects on other rapidly dividing tissues with ozone exposure, but these have been reported with radiation. By contrast, pulmonary edema is not a common low-level radiation reaction, nor is respiratory irritation. Some of these differences depend on how the agent is distributed and interacts with the cells that are first affected. Ozone's relative insolubility leads to a rather restricted site of impact, namely, the surface layers of the respiratory system, in contrast to radiation, at least of some sorts, which is penetrating. In some ways, ozone exposures can mimic effects of radiation, but the overlap is not sufficient so that they can be treated as equivalent (*83, 129*). Ozone has been shown (*129a*) to produce chromosomal abnormalities in human lymphocytes in subjects exposed to 0.5 ppm. The implications of this are yet to be determined.

2. Epidemiological Studies of Photochemical Oxidants and Ozone

a. DAILY MORTALITY IN RELATION TO PHOTOCHEMICAL OXIDANT VARIABILITY. The occurrence of episodes of photochemical smog in the fall of 1954 in Los Angeles, California, following, as it did, the widespread discussion of a London, England, smog disaster, led to understandable anxiety as to whether there might be a fatal effect of photochemical smog. The association of photochemical oxidant with high temperatures has made it difficult to study this possibility. In the fall of 1955, for example, a very substantial heat wave occurred that did lead to excess mortality (*80, 130, 131*). Despite early reports that excess mortality was due to photochemical oxidants, more careful analysis of the data suggests that the elevation of mortality coincides with, or very slightly follows, the occurrence of excessive temperatures. In particular, the occurrence of high ozone concentrations, that is ozone alerts with pollution levels in excess of 0.5 ppm, for several days following the peak of the heat wave could not be shown to lead to an increase in mortality. It could be argued that the most susceptible groups in the population had been reduced in number by the excessive temperatures, and second, if there had been a small increase in mortality due to ozone it could not have been detected. Neither of these arguments can be refuted; however, neither can one demonstrate that there is convincing positive evidence that excess mortality during this episode was associated with elevated levels of photochemical oxidants. Accordingly, the analysis of heat waves has been an important feature of the effort to identify excess mortality associated with photochemical oxidants. The effort of Hexter and Goldsmith (*132*), for example, failed to identify a contribution of photochemical oxidants to variation in daily mortality in 1962–1965 in Los Angeles, California, although a detectable effect of carbon monoxide was shown. Other methods that have been attempted to look for this include the so-called "two community" method of Landau *et al.* (*133*), which consists of attempting to divide the area of Los Angeles County, California, into regions that had expected similar autumn temperatures but differing oxidant levels; these two regions were then examined to see whether there was any difference in daily mortality attributable to differences in oxidant concentration. None was found. This is an example of the so-called temporaspatial strategy that has also been applied by Toyama, (*134*), and by Cohen *et al.* (*135*). While photochemical oxidant could have had a role in mortality, no role has so far been proven.

b. EPIDEMIOLOGICAL STUDIES RELATING PHOTOCHEMICAL POLLUTION AND DISEASE CAUSATION. Pulmonary emphysema is the major illness for which an epidemiological association of oxidant pollution has been sought. This is based on laboratory experiments with oxides of nitrogen that show this substance to be capable of producing a condition in animals that simulates emphysema in man (*136*). So far, no adequate test of this hypothesis has been undertaken. Monitoring of the number of emphysema deaths by year in Los Angeles County and other parts of California has been undertaken, and no excess has been observed in Los Angeles. Data collected by Buell *et al.* (*137*), however, suggests that there could

Table VII Total Chronic Respiratory Disease Mortality in an American Legion Study Population—California, 1958–1962[a] (*137*)

	Los Angeles County		*San Francisco Bay Area and San Diego County*		*All other counties*	
Residency (years)	*Mortality rate[b]*	*Total deaths*	*Mortality rate[b]*	*Total deaths*	*Mortality rate[b]*	*Total deaths*
10+	38.4	31	28.3	15	45.6	40
<10	41.2	14	45.6	8	41.3	17
Unknown	139.1	12	59.8	3	39.7	4
	46.7	57	34.0	26	44.4	61

[a] Age and smoking adjusted by the direct method to the total study population.
[b] Per 100,000 man-years.

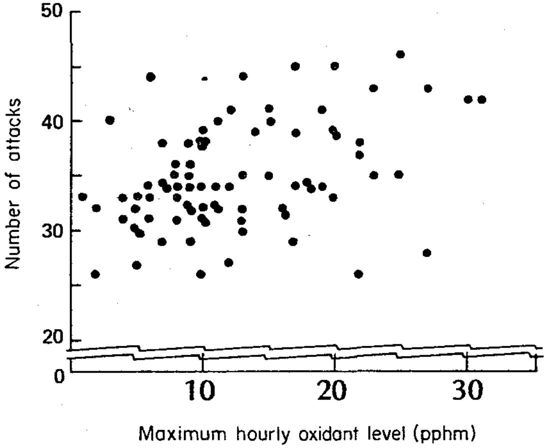

Figure 12. Association of the number of attacks of asthma of a panel in Pasadena, California, with the maximum hourly oxidant concentration (potassium iodide method) for the preceding day (*138*) (1956).

be a contribution of living in Los Angeles to excess mortality from chronic respiratory disease (Table VII). When respiratory disease mortality among this population of military veterans and their spouses living in Los Angeles and in the San Francisco Bay Area are compared with that of residents of other parts of California, the data, while suggestive, are not conclusive.

c. Epidemiological Studies of Disease Aggravation. Schoettlin and Landau (*138*) examined the occurrence of asthmatic attacks in a population in Pasadena, California, during the fall of 1956. Individuals in the study reported each week the occurrence of asthma attacks and the factors they felt might be related to them. A calculation of the association between smog levels estimated by oxidant and asthma attacks showed a statistically significant association and suggested that approximately 8 individuals out of 137 might have been responding to variation in severity of photochemical smog. There was a statistically significant excess of asthma attacks on days where the peak oxidant, measured by the potassium iodide method, was greater than 0.25 ppm (500 $\mu g/m^3$). This corresponds during the days actually measured to an hourly average of 0.20 ppm (400 $\mu g/m^3$) (Fig. 12).*

* In 1974 a discrepancy in oxidant calibration procedures was detected. According to the California Air Resources Board all oxidant monitoring data prior to June 1, 1975 (excluding Los Angeles County data) should be adjusted downward by about 20%. (See *140a* for more complete discussion.)

Remmers and Balchum (*139*) and, later with the same data, Ury and Hexter (*140*) examined impairment of respiratory function in a population of patients with established chronic respiratory disease at Los Angeles, California, County Hospital. The patients stayed in air conditioned rooms, and during alternate weeks in one with an activated charcoal filter that kept photochemical oxidants to a very low level. The most sensitive physiological index of impairment appeared to be airway resistance, which is normally elevated in chronic respiratory conditions. Among the smokers and the nonsmokers taken separately, there is a statistically significant association between the photochemical oxidant and airway resistance (Fig. 13). This is interpreted as being disease aggravation, since airway resistance is a valid indicator of the severity of disease in this syndrome. Los Angeles residents with chronic respiratory disease report aggravation during periods of photochemical pollution. Hammer *et al.* (*141*) studied acute illness in nursing students in two California areas, Santa Barbara and Los Angeles County, and compared the daily maximum oxidant level with the recorded acute symptoms and illnesses. Eye discomfort was the only symptom that occurred in close association with levels of pollution Table VIII, (Fig. 14).

Studies were undertaken in Los Angeles, California, from September through December 1954 to see whether hospital admissions themselves are related to photochemical pollution. While the data show some seasonal trend, particularly for certain diseases of the lung, no association between oxidant air pollution and hospital admission rates due to diseases of the the cardiovascular respiratory system could be found (*142*). A study of the relationship between cardiovascular admissions and pollution was

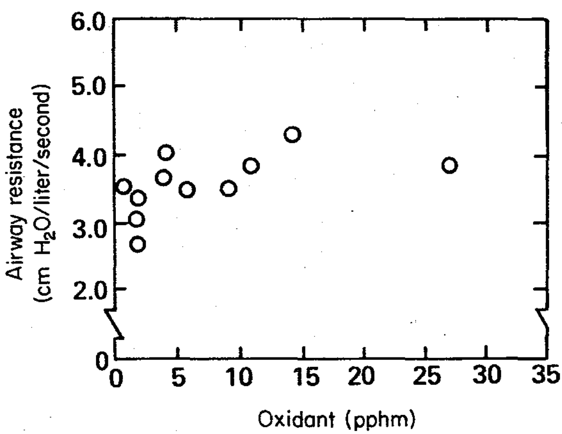

Figure 13. Airway resistance regression on afternoon (2 p.m.) oxidant levels for a typical patient with chronic pulmonary disease, a nonsmoker. The subject shows increases in resistance with oxidant. Correlation coefficient; $\gamma = 0.64$.

Table VIII Relationship of Average Daily Percentage of Symptoms to Photochemical Oxidant Levels (668 days, November 1961–May 1964) (*149*)

Daily maximum hourly oxidant level (ppm)	*Number of days*	*Average daily percentage of symptoms reported*[a]			
		Headache	*Eye discomfort*	*Cough*	*Chest discomfort*
≤0.08	413	10.6	5.2	9.5	1.8
0.09	35	10.6	5.6	10.2	1.9
0.10–0.14	176	11.0	5.9	9.4	1.8
0.15–0.19	144	11.4	6.9	9.7	1.7
0.20–0.24	63	11.6	9.2	9.1	1.6
0.25–0.29	25	11.5	11.2	9.6	2.0
0.30–0.39	9	13.4	17.8	11.7	2.3
0.40–0.50	3	15.0	31.8	16.9	5.8
Overall average		10.9	6.3	9.5	1.8

[a] All days on which the symptom was reported along with "feverish," "chilly," or "temperature" are excluded.

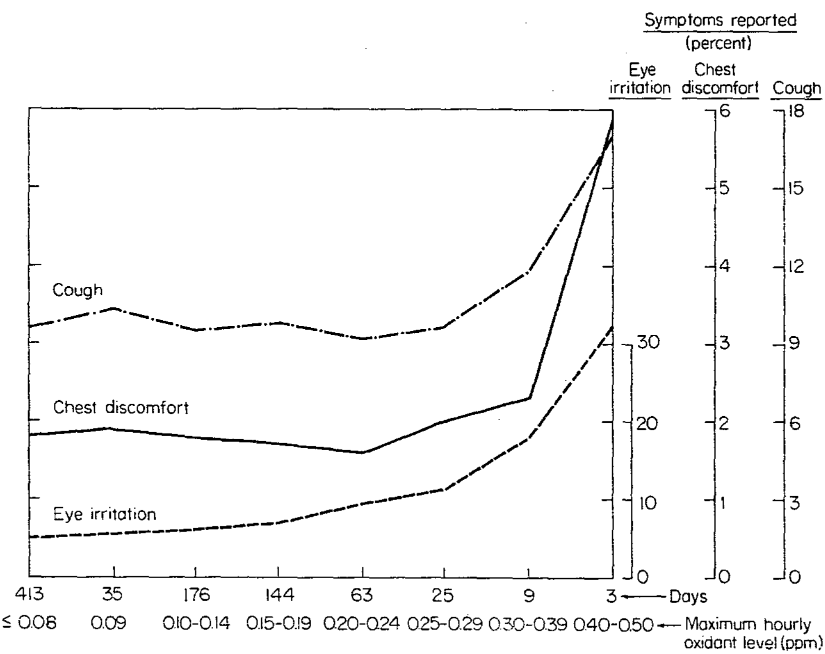

Figure 14. Proportion of a student nurse panel reporting eye irritation and respiratory symptoms at various levels of oxidant (reported as ozone) in Los Angeles, California, 1961–1964. (*149*). (For data see Table VIII.)

made in collaboration with the Los Angeles, California, County Medical Society in thirty-five hospitals for the year 1958. No significant findings relevant to oxidant were obtained. However, for associations of this population with carbon monoxide, see Section IV,C.

Schoettlin (*143*) studied a population of 166 men in a veteran's domiciliary unit in West Los Angeles, California, half of whom appeared to have signs or symptoms of chronic respiratory disease. The other half had similar ages and smoking histories but no evidence of chronic respiratory disease. These men were studied throughout the fall of the year. Maximal oxidant and oxidant precursor consistently accounted for more of the variations in signs and symptoms in the diseased group than in the nondiseased group. For example, maximal oxidant precursor accounted for 30% of the variations of symptoms in subjects with chronic respiratory conditions, compared to an insignificant 4% in the control population.

Rokaw and Massey (*144*) carried out a study of persons in a Los Angeles, California, chronic disease hospital to see whether there was any systematic variation in pulmonary function in association with fluctuations in photochemical oxidant. No positive findings were reported. Among outside plant telephone workers, Deane *et al.* (*145*) determined the prevalence of respiratory symptoms and lung function using the British Medical Research Council questionnaire. The same methods, equipment, and interviewers were used in both Los Angeles and San Francisco California, and the east coast United States cities, as well as in several cities in the United Kingdom. In the Los Angeles area, among the age group 50–59, a significant excess of persons with cough was observed, compared with San Francisco and other United States cities (Fig. 15 and

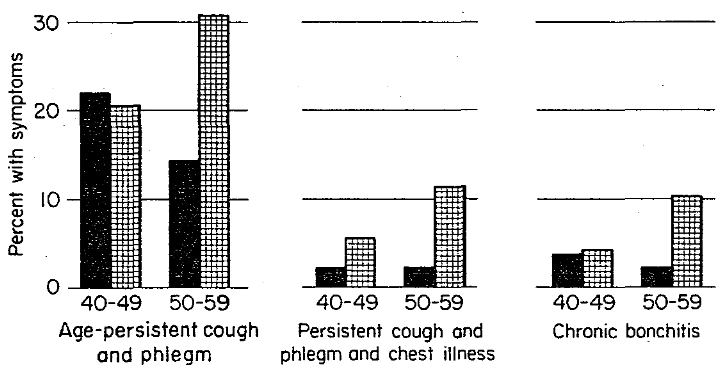

Figure 15. Comparison of respiratory symptom prevalence by age and location in a study of outside telephone workers in San Francisco (solid), Los Angeles (hatched), California in 1963. The proportions of smokers in the groups were similar (*145*).

Table II). These differences could not be explained by social class, occupation, or smoking habits. There were no differences detected in pulmonary function, comparing Los Angeles and other United States populations.

Kagawa and Toyama (*145a*) have reported effects of photochemical pollution on lung function among Japanese school children. Twenty normal 11-year-old Tokyo school children were studied weekly from June to December 1972. Ozone was significantly associated with increased airway resistance. Two of the subjects appeared to be unusually reactive to environmental factors. Temperature strongly affected lung function tests.

d. ACUTE RESPIRATORY DISEASE AND POLLUTION IN CALIFORNIA. Durham (*146*) has reported a comparative study of illness reported to student health services at seven California universities during the 1970–1971 academic year. Using temporospatial strategy, factor analysis, and time series analysis, he found associations of pollutant elevations with increased pharyngitis, bronchitis, colds, and sore throats. From the analysis, the effects of oxidants cannot be isolated from the contributions of sulfur oxides and nitrogen oxides. Comparing selected high and low pollution days, a 16.7% difference in these complaints can be shown for the Los Angeles schools situated in places with lowest and highest contaminant concentrations.

e. EYE AND RESPIRATORY IRRITATION FROM PHOTOCHEMICAL OXIDANTS. Eye irritation remains the most common relationship between photochemical oxidants and health status. The data first obtained during the Air Pollution Foundation Study by Renzetti and Gobran (*147*) and from panel studies indicate that above about 0.14 ppm, there is an increasingly impressive association between eye irritation and photochemical oxidant. A similar association was observed by Richardson and Middleton (*148*) and Hammer *et al.* (*149*) (Table VIII, Fig. 14) and has been reported by a number of other authors in the California area. Similar associations are not yet clearly established for other locations. The data from Tokyo, Japan, certainly indicate that eye and respiratory irritation occurs with photochemical oxidants. Based on data obtained in the California Health Survey (*150*), while eye irritation may be the most frequent cause of difficulty, there also was a high proportion of respondents (about 5% in some areas) who had a feeling of difficulty in breathing during smog episodes. Table VIII and Figure 14 show characteristic results obtained by Hammer *et al.* in a study of student nurses at Los Angeles County Hospital in California.

f. ATHLETIC PERFORMANCE. Wayne *et al.* (*151*) studied high school track athletes to determine whether there are factors in the environment that

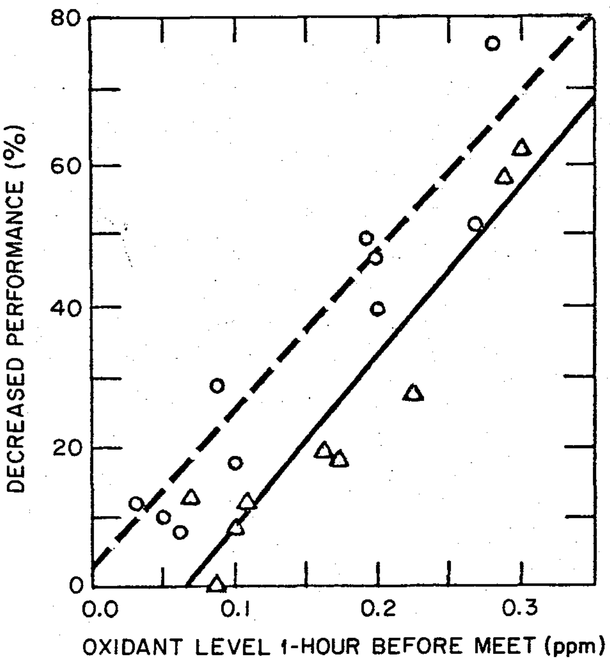

Figure 16. Relationship between oxidant level in the hour before an athletic event and percent of team members with decreased performance (*151*). Solid line is for 1959–1961, broken line for 1962–1964; r = 0.945.

affect their track performance. The data on performance were obtained in advance of any effort to see whether there was an association with photochemical pollution. It was assumed that these athletes would improve their performance steadily. The analysis shows that the proportion who failed to improve showed an association with photochemical oxidants (Fig. 16). The range of points runs from an oxidant level of about 0.5 to 0.3 ppm. However, only when points above 0.2 ppm oxidant are added to values at lower concentrations can a regression be said to be present.*

g. Oxidants and Motor Vehicle Accidents. Ury *et al.* (*152*) studied the association of motor vehicle accident frequency by hour and day in Los Angeles, California, with both oxidant levels and carbon monoxide during summer and winter periods from 1963 to 1966. They identified a

* Twenty-eight subjects were exercised during ozone exposures of 0.37, 0.5, and 0.75 ppm for 2 hours. Altered respiratory patterns were observed, with increase in rate and decrease in depth of breathing, presumably due to irritation, which was highly correlated to ozone dose (*151a*).

number of confounding variables, of which the number of vehicles at risk was the most obvious. By assuming that for a given hour of day and day of the week the number of vehicles at risk was only subject to random variation, they applied a simple nonparametric statistical test for adjacent week pairs. They found that more often than not ($p < 0.0001$) increasing oxidant levels are accompanied by increasing frequency of motor vehicle accidents, but such a significant effect was not found for carbon monoxide.

C. Carbon Monoxide (Goldsmith)

Carbon monoxide and lead are examples of pollutants whose effects depend on how much is in the body, and this, in turn, depends on a balance between uptake and excretion. Both are also pollutants for which substantial exposures to the public occur from sources other than air pollution.

1. Uptake, Excretion, and Body Burden

Carbon monoxide is not irritating. Experimental carbon monoxide studies usually expose man or animals to square-wave doses, that is, with an abrupt increase above or decrease to background, which permits a smooth prediction of resulting carboxyhemoglobin. However, most real carbon monoxide exposures fluctuate quite widely (Fig. 17). Its effects are related to both the amount in any given breath and to the amount held in the body most of which is combined with hemoglobin.

Carbon monoxide is produced under natural conditions in the human body. Sjöstrand showed that the body breaks down hemoglobin (a process that permits the recycling of the iron it contains) with the release of four molecules of carbon monoxide for each molecule of hemoglobin broken down (*153, 153a*). When red blood cell destruction is greater, as for instance, with a transfusion reaction, the amount of carbon monoxide produced is increased (*154, 155*). As a matter of fact, the rate of breakdown of red blood cells and other related molecules (*156, 157*) can be estimated by the production and excretion of carbon monoxide. Hemoglobin binds carbon monoxide and carries it through the body. The amount of carbon monoxide carried by the hemoglobin is used as an estimate for how much carbon monoxide is in the body. Nearly all the carbon monoxide in the hemoglobin is excreted unchanged, via the lungs, with the expired air. It is relatively easy to determine the amount of carbon monoxide in the body by measuring the carbon monoxide concentration of the expired air after breath holding (*156, 158–160*).

Since the body's hemoglobin provides the critical mechanism for carrying oxygen from the lungs to tissues and carbon dioxide from tissues to

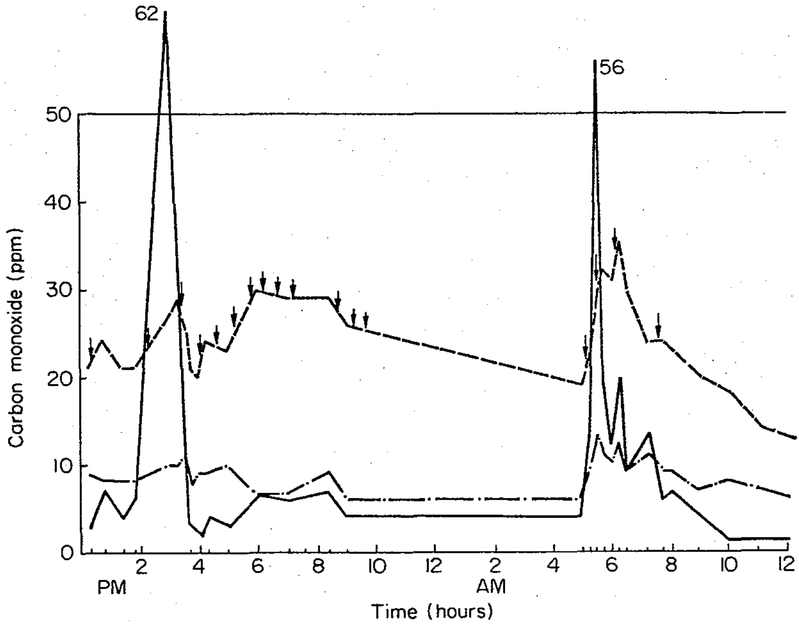

Figure 17. Carbon monoxide levels of the ambient air (—) and expired air after 20-second breath-holding of a smoker (---) and a nonsmoker (-•-), Los Angeles and Pasadena, California. Arrow represents the time of cigarette smoking. The exposure between 2 and 4 p.m. is in a parking garage, and between 5 and 8 a.m. during morning traffic congestion on streets and freeways. The subjects spent the night at a Pasadena motel.

lung, the resulting interference with the functioning of hemoglobin is important. Carbon monoxide is bound to hemoglobin 245 times more firmly than is oxygen. This means that if a gas mixture of oxygen and carbon monoxide is bubbled through blood in such proportions that half the hemoglobin will be combined with oxygen and half with carbon monoxide, the gas mixture must contain 245 molecules of oxygen for every molecule of carbon monoxide. If we know the ratio of oxygen to carbon monoxide in the air in the lung, we can find the ratio of the carbon monoxide to the oxygen combined with the hemoglobin molecules, assuming sufficient time for equilibrium to occur. This relationship was first expressed by the British physiologist J. B. S. Haldane and is known by his name (*161–163*) The Haldane equation for carbon monoxide at equilibrium is:

$$\frac{\%\text{COHb}}{\%\text{O}_2\text{Hb}} = M\frac{p\text{CO}}{p\text{O}_2} \qquad (1)$$

where M is usually cited as 245, %COHb and %O_2Hb represent the amount of hemoglobin combined with carbon monoxide and oxygen, respectively, and pCO and pO_2 represent the proportions of gas molecules in air, which are, respectively, carbon monoxide and oxygen. This equation not only permits us to estimate the equilibrium percent of carboxyhemoglobin, but also (a) the effect of high altitude (low pO_2) on carbon monoxide uptake—it will increase it; (b) how to help the body get rid of excess carboxyhemoglobin—increase the oxygen content in the inspired air; and (c) the effects of carbon monoxide—it blocks hemoglobin's oxygen transport function. Since in the arterial blood leaving the lung the gas binding sites on hemoglobin are normally almost full of oxygen or carbon monoxide, the sum of %O_2Hb and %COHb is expected to be 100. Thus, if %COHb in the arterial blood is increased, %O_2Hb must decrease. That is the first effect of breathing carbon monoxide.

The Haldane equation describes only what happens when the situation is in equilibrium. Since all the body's blood is not in the lung at the same time, and since carbon monoxide transport across the lung and red cell membranes takes time, and since the amount of carbon monoxide leaving the gas phase is not replaced until the next breath, it takes time for the body's hemoglobin to reach the equilibrium shown by Equation (1). In fact, it takes about 4 hours for a resting adult male to reach half saturation value; it takes about 3 hours for females, because of their smaller body size and lesser blood volume. In a person who is exercising, circulation and breathing occur faster, and the time taken to reach equilibrium is shorter. Similarly, an infant or child because of smaller body size takes less time to reach equilibrium. Since there is both uptake and excretion at the same site—in the capillary vessels in the wall of the alveoli (the ultimate air sacs of the lung)—the transfer rate of carbon monoxide is a net result of the amount in the gas in the alveoli and the amount in the blood. During uptake, since the greater the amount in the blood, the less leaves the alveoli each time the blood passes through the lung, the uptake is exponential. The same is true for excretion (Fig. 18) (*164*).

2. Quantitative Relationships

For continuous exposures to concentrations of less than 100 ppm, the California State Department of Public Health (*165*) has derived, from published data, the equilibrium condition equation

$$[\mathrm{CO}] \times 0.16 = \%\mathrm{COHb} \qquad (2)$$

where [CO] is the concentration of carbon monoxide in parts per million by volume, and %COHb is the percentage of carboxyhemoglobin *at*

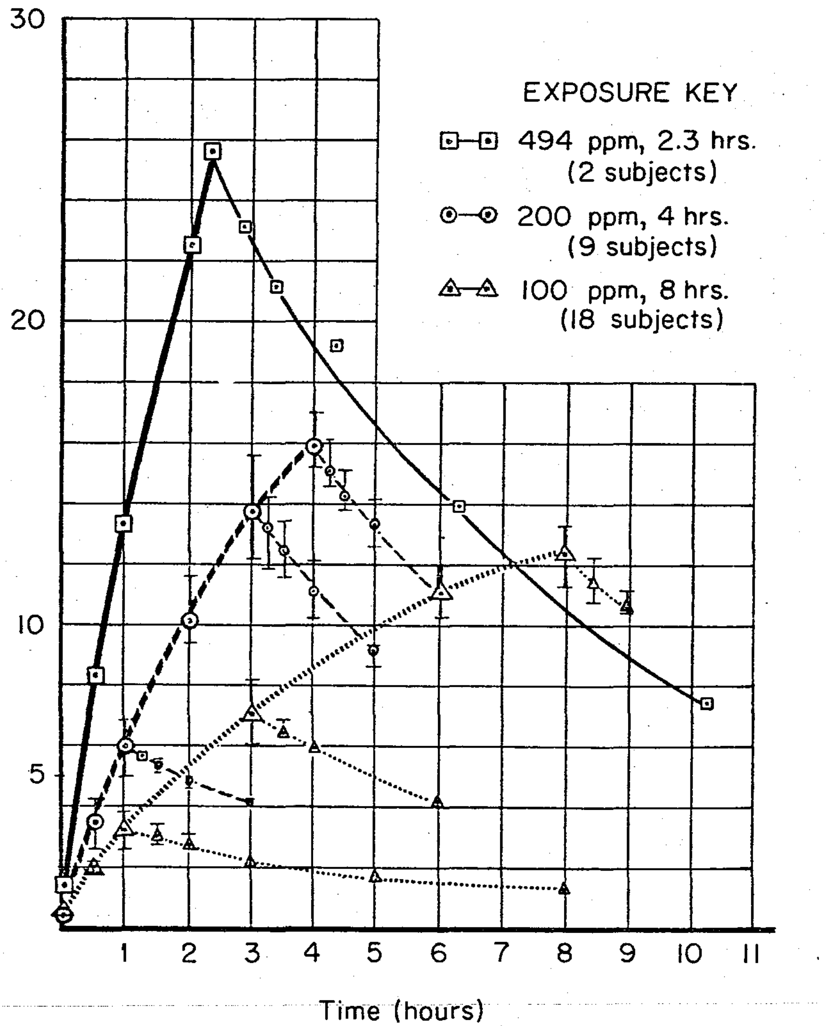

Figure 18. Carbon monoxide absorption and excretion in healthy, sedentary, non-smoking, Caucasian males (*164*).

equilibrium at sea level for healthy subjects. This equilibrium relationship is, as noted, not reached for several hours. Forbes *et al.* (*166*) studied the rate of uptake of carbon monoxide for exposures of from 100 to 2000 ppm.

A more complex relationship has been expressed by Coburn *et al.* (*166a*) called the CFK equation. Peterson and Stewart (*166b*) have shown its validity, and applications to community pollution are appropriate.

Since the effect of carbon monoxide is an impairment of transport of oxygen to the tissues, at high altitudes and in other situations where oxygen tensions are low, the effects of a given concentration of carbon monoxide will be correspondingly more severe. California and Nevada have adopted an 8-hour air quality standard of 6 ppm carbon monoxide for high altitude areas, i.e., about two-thirds the sea level standard. In California it applies to the Lake Tahoe Air Basin; in Nevada to all areas above 5,000-feet elevation.

3. Uptake of Carbon Monoxide from Community Air

The relationship between the exposure to carbon monoxide pollution and the resulting carboxyhemoglobin are not immediately obvious from the measured data because of the time delay between exposure and the build-up of carboxyhemoglobin levels in the blood and its effect on the tissue. Chovin studied (*167*) the levels of carbon monoxide before and after work in a group of traffic policemen in Paris, France. During their work, the policemen were not permitted to smoke cigarettes. The data can be divided, therefore, into two population groups—cigarette smokers and nonsmokers. The averaged occupational exposure was between 10 and 12 ppm. The nonsmokers, as a population, showed an increase during the 5 hours between coming on duty and leaving their place of work, but some of the smokers showed a decrease; that is they had a net excretion of carbon monoxide. The extent to which a smoker and a nonsmoker absorb carbon monoxide has been demonstrated by two medical students who took a car from a Los Angeles, California, garage, drove on the freeway, spent the night in a motel in Pasadena, California, during which both decreased their carboxyhemoglobin, and then after the cigarette smoker had had his morning smoke, returned to the freeways. Both subjects showed detectable effects of freeway exposure and of exposure in the parking garage, but the influence of cigarette smoking was greater than that of exposure in the garage or on the freeway (Fig. 17).

Stewart *et al.* (*167a*) obtained blood samples from persons who appeared at various blood banks in a number of urban areas in the United States. Table IX shows a sample of such data for smokers and nonsmokers in Los Angeles, California; Chicago, Illinois; Denver, Colorado; and New York, New York. The locations chosen for presentation in Table IX are large cities, their airports, and a less urban town in the vicinity. The nonsmokers showed lower COHb in the suburbs, and at some airports; urban donors had higher COHb than in the suburban areas. Smokers showed similar patterns. The fact that urban populations have carboxyhemoglobin levels so much above the expected background level of about 0.5 to 0.9% COHb suggests that there is a systematic contribution from pollution. In addition, the difference between the three subpopulations for with a relatively high carboxyhemoglobin, excreted some carbon monoxide through their lungs and ended up after work with a lower carboxyhemoglobin level; the other which arrived on duty with a low carboxyhemoglobin and had some uptake during the day. There is a range of carboxyhemoglobin at which no apparent uptake or excretion occurred (from about 4 to 7% COHb).

The magnitude of exposure to carbon monoxide from smoking has been estimated in a population of longshoremen (*169*) examined prior to their work shift and during a time when there was little community air pollution. The results, therefore, reflect primarily the effects of smoking. Exposure estimates were based on measurements of carbon monoxide in expired air after the individual had held his breath for 20 seconds. The results are shown in Table X. The median value for moderate cigarette smokers who inhale is 5.9% COHb. The relatively low levels in pipe smokers and cigar smokers (see below for exception) are due to the fact that less smoke is usually inhaled when tobacco is used in these forms. Inhaling clearly increases the uptake of carbon monoxide. Landaw (*170*) has accurately measured uptake and excretion of carbon monoxide during and after smoking. He calculated that 8.6 ml of carbon monoxide was taken up with each cigarette based on blood measurements (7.10 ml based on expired air measurements). Some cigar smokers who were formerly cigarette smokers (*171*) continue to inhale with resulting high uptake of carbon monoxide. Apparently, this is more likely with so-called little

Table X Proportion of Smokers and Median Expired Carbon Monoxide among 3311 Longshoremen (*169*)

	Smoking pattern (%)	*Median CO in expired air (ppm)*		*Median COHb estimated from regression (%)*	
Never smoked	23.1	3.2		1.2	
Ex-smoker	12.1	3.9		1.4	
Pipe and/or cigar smoker only	13.4	5.4		1.7	
		Inhaler	*Non-inhaler*	*In-haler*	*Non-inhaler*
Cigarette smokers					
Light smoker (half pack or less)	13.0	17.1	9.0	3.8	2.3
Moderate smoker (more than half pack, less than 2 packs)	31.3	27.5	14.4	5.9	3.6
Heavy smoker (2 packs or more)	7.0	32.4	25.2	6.8	5.6

cigars. Russell *et al.* (*172*) studied uptake of carbon monoxide by nonsmokers and smokers in poorly ventilated rooms. With a duration of exposure of 78 minutes to an average carbon monoxide concentration of 38 ppm, there was an average increase in carboxyhemoglobin of nonsmokers of from 1.6 to 2.6%. The cigarette smokers increased from 5.9 to 9.6% COHb. Rylander (*172a*) has reviewed a series of studies on the effect of environmental tobacco smoke on nonsmokers. Carbon monoxide is often used as the indicator substance in such studies (*172b*).

Breysse and Bovee (*173*) used expired air samples to estimate occupational exposures of stevedores and gasoline-powered forklift truck drivers and winch operators. Forty (5.7%) out of 700 determinations of carboxyhemoglobin were in excess of 10%. Carboxyhemoglobin levels in excess of 5% were found in 30% of smokers but in only 2% of nonsmokers.

The present maximum allowable atmospheric concentration, or threshold limit value (TLV), for occupational exposure in industry in the United States is 50 ppm for 8 hours. The limit was reduced from 100 ppm in 1964 because of new evidence of possible adverse effects, mostly on the central nervous system, from exposures in the 50–100 ppm range. The United States National Institute of Occupational Safety and Health criteria report proposes a 35 ppm threshold limit value and notes the importance of exposure hazard in men with heart disease.

Open fires and charcoal braziers produce a substantial amount of carbon monoxide (*174*, *175*). Carbon monoxide is a particular risk for residents in houses heated by improperly vented kerosene or gas stoves. A survey by the United States Department of Health, Education, and Welfare (*176*) concludes that "there is a definite health hazard from carbon monoxide poisoning in dwelling units and in vehicles during cold weather." In selected communities, 3–30% of housing units were found to have evidence of a carbon monoxide problem. This form of indoor air pollution has been neglected. Cigarette smoking may also produce a form of indoor air pollution with carbon monoxide.

5. Effects of Carbon Monoxide on Cardiovascular Disease

When air quality standards were first set by the state of California in 1959, the effects of carbon monoxide on the limitation of oxygen transport function were predictable from physiological experiments (*177*). It was thought that among persons who were at unusual risk were those with cardiovascular disease, particularly those who had had acute episodes and required a maximal capacity to transport oxygen to tissues for their health or survival. Among groups thought to be vulnerable were persons with recent myocardial infarctions. This hypothesis was further elaborated by Permutt and Fahri (*178*), who emphasized that the heart muscle (myocardium) might be particularly vulnerable because it had a high oxygen extraction ratio, that is, because it ordinarily removed a high proportion of the oxygen brought to it by the blood. Most of the organs of the body that need to increase their oxygen supply can do so by increasing the amount they remove from the blood brought to them by the arteries. This is not the case for the heart muscle, because under normal circumstances, a high proportion of the oxygen brought to it is removed. The only way the oxygen supply can be increased is by the increased flow of blood. In persons with coronary heart disease, because of the rigid blood vessels supplying the heart muscle, it is hard for the circulation to deliver more oxygen when needed.

Long-term exposure experimental studies in animals were undertaken by Lewey and Drabkin (*179*), Stupfel and Bouley (*180*), and Preziosi *et al.* (*181*). These investigators did not always produce results that were entirely consistent, but their data suggest that for exposures over long periods to 50 or 100 ppm, there were some circumstances under which one observed transient changes in the electrocardiogram and loss of tissue in the heart muscle. Some experiments also demonstrated loss of central nervous system tissue.

In another series of experiments, Astrup and colleagues (*182–184*) showed that rabbits that were exposed to elevated levels of carbon monoxide (producing about 11% COHb) over a sufficient period of time and were fed diets high in cholesterol manifested increased fatlike deposition in the walls of the great blood vessels. This fatty material resembled the early process of what is called arteriosclerosis or hardening of the arteries. The same result could be reproduced if the animals were exposed to simulated high altitude, that is they breathed air containing a decreased amount of oxygen.

In a series of experiments, Ayres (*185, 186*) and his colleagues have shown that the experimental administration of carbon monoxide sufficient to increase the carboxyhemoglobin to around 9% in human subjects diminishes the amount of oxygen removed from the blood by the heart. The effect in general is greater than the relative binding of carbon monoxide represented by the percent of carboxyhemoglobin. In addition, they were able to show that the subjects who had already had disease of the arteries affecting the heart muscle were unable to increase the rate of blood flow to the heart muscle sufficiently to keep the metabolism in good working order. The effect they observed was a shift to a type of energy production that builds up a deficit requiring increased amounts of oxygen at a later period. This deficit is called "oxygen debt." In the second set of studies with humans (*186*), effects were seen to be more moderate when a given level of carboxyhemoglobin (9–10%) was approached slowly with exposure to 0.1% carbon monoxide than when it was approached rapidly by a high dose (5% carbon monoxide for 60–90 seconds). This discrepancy suggests that some of the effects on the heart muscle may be produced by carbon monoxide combining with substances other than hemoglobin, substances that are within the muscle tissue itself. Patients with coronary vascular disease showed significant metabolic changes in the heart muscle with elevation of carboxyhemoglobin above 6%. According to Ayres, dogs were less sensitive than man, and significant changes were not observed in dogs until the carboxyhemoglobin saturation exceeded 25%. Chevalier *et al.* (*187*) exposed nonsmokers to high concentrations of carbon monoxide (5750 mg/m^3) for a few minutes in order to produce a carboxyhemoglobin level similar to that in smokers. This resulted in carboxyhemoglobin levels of 3.95%. Increase in the amount of oxygen consumed after exercise (oxygen debt) was observed after exposure.

Epidemiological Studies of Carbon Monoxide Effects on the Cardiovascular System. A large body of data has already been assembled concerning the relation of cigarette smoking to diseases of the heart. In general, this shows that there is a substantially higher rate of heart disease in moderate to heavy cigarette smokers than is true for lighter cigarette smokers, and, in turn, these people have a higher mortality than those who are nonsmokers. The gradients are especially steep in younger smokers (Table XI). In addition, smoking tends to aggravate manifestations of a disease called angina pectoris. This is a disease in which mild exercise, because of insufficient oxygen supplied to the heart muscle, produces symptoms of pressure or pain in the chest. The person then either must stop walking or stair-climbing or take medication to cause the blood vessels to dilate. In persons who are exposed to cigarette smoking, it has been shown systematically by Aronow *et al.* (*188*) that there is a decrease in the amount of exercise that can be tolerated before the chest pain of angina occurs. At first Aronow's studies implicated nicotine in this reaction, but even in subjects who are smoking cigarettes that do not contain nicotine this effect will occur (*189*) when the carbon monoxide becomes sufficiently elevated.

To test the effects of urban carbon monoxide pollution, Aronow and his colleagues (*190*) drove subjects with angina pectoris around streets and freeways in Los Angeles, California, for 90 minutes. The samples of air taken contained approximately 50 ppm carbon monoxide. After this exposure, there was an increase in the carboxyhemoglobin of the subject. Two hours later, carboxyhemoglobin had come part way back to normal.

Table XI Relationship of Median Percent Carboxyhemoglobin[a] (COHb) in Smokers (California Health Department) and Coronary Heart Disease Mortality Ratio (CHDR) by Age (Hammond) Relative to Nonsmokers (*169*)

		Smoking class for current cigarette smokers					
		Fewer than 10 cigarettes/day		*Cigarettes/day*			
	Nonsmokers			*10–19*	*10–39*	*20+*	*40+*
Age	*COHb*	*CHDR*	*COHb*	*CHDR*	*COHb*	*CHDR*	*COHb*
<45	*0.89*	—[b]	*3.8*	—[b]	*6.0*	—[b]	*6.7*
45–54	*0.89*	2.4	*2.6*	3.1	*5.3*	3.2	*6.7*
55–64	*0.89*	1.5	*3.5*	1.9	*5.0*	2.0	*5.3*
65–74	*0.89*	1.3	*2.6*	1.6	*3.3*	1.6	—[c]
75–84	*0.89*	1.2	—[c]	1.4	*2.9*	1.1	—[c]

[a] COHb percent estimated from expired air carbon monoxide (CO) using the regression COHb = 0.21 + 0.19 (CO).
[b] No subjects available in this age group in Hammond's study.
[c] COHb data cited only if 10 or more subjects were tested.

There was a statistically significant association between the increase in carboxyhemoglobin and the decrease in the exercise capacity, both immediately after exposure and 2 hours later (Fig. 19). Aronow *et al.* have further demonstrated (*191*), in a double blind study, that exposure to 50 ppm of carbon monoxide for 2 hours will reproduce, in general, the effects observed in the angina patients exposed on freeways and streets. They have also shown (*192*) that the same exposure will decrease exercise performance in persons with sclerotic changes in the arteries of the legs, presumably due to impairment of the delivery of oxygen to leg muscles.

A study of the survival of persons having myocardial infarctions admitted to thirty-five hospitals in Los Angeles, California, has been reported by Cohen *et al.*, (*135*). The study used a set of data obtained for another purpose, and therefore was dependent on the available air pollution monitoring data for the year in which the hospital admission data were obtained, the year 1958. The authors divided the hospitals according to whether they were in an area thought to have high air pollution or low air pollution, based on Los Angeles, California, Air Pollution Control District data. A comparison was then made between the case fatality rate in high and low pollution areas. The case fatality rate is the proportion of persons admitted to the hospital with acute myocardial infarction who died before being discharged. The case fatality rate was higher in the higher pollution area, and this elevation occurred only during the fourth

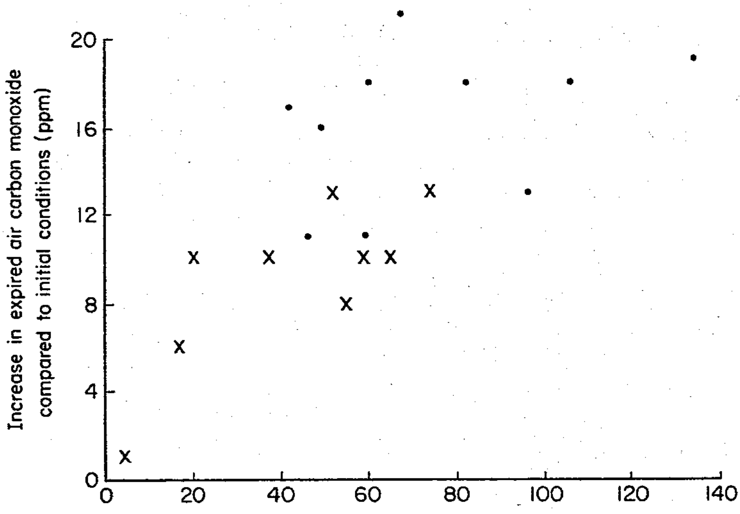

Figure 19. Relation of increases in carbon monoxide in expired air to impairment of exercise tolerance in men with angina pectoris after 90-minute freeway exposure (•) and 2 hours after such exposure (×) (*190*).

quartile of weeks of the year in which pollution by carbon monoxide was high (Table XII). In a later study, Hexter and Goldsmith (*73*) compared the environmental factors that contributed to variation in the daily mortality in Los Angeles County, California, for the years 1962–

Table XII Proportion of Weeks That Case Fatality Rates for Hospitalized Myocardial Infarction Cases Are Greater in More and Less Polluted Areas by Quartile of Weekly Average Carbon Monoxide[a], Los Angeles, California, 1955 (*135*)

	Quartile 1	*Quartile 2*	*Quartile 3*	*Quartile 4*
Average weekly carbon monoxide (ppm)	5.36–5.87	5.96–6.95	6.97–8.43	8.49–14.53
Number of weeks with higher case fatality rate in:				
More polluted area	8	6	9	12
Less polluted area	5	7	4	1
Significance	Not significant	Not significant	Not significant	$p < 0.01$

[a] Weekly average carbon monoxide at downtown station tested by sign test.

1965. After adjusting for trend and using trigonometric terms to represent the contribution of time of year, a major contribution to reducing the variance was made by temperature and various polynomial and lagged terms concerning temperature. In addition, the logarithm of the basin average of carbon monoxide concentration made a statistically significant contribution to explaining the variability in mortality. The authors concluded that this was suggestive but not conclusive evidence of a role of carbon monoxide in daily mortality. Most of the variation in daily mortality associated with carbon monoxide occurred in deaths attributed to arteriosclerotic heart disease. Thus, this study tends to support the possible role of carbon monoxide in heart disease mortality suggested by the observations of Cohen *et al.* (*135*).

Anderson *et al.* (*193*) have studied effects of 4-hour exposures to 50 and 100 ppm of carbon monoxide on 10 men with angina pectoris. At 50 ppm (58 mg/m^3) there was an average increase of 1.5% carboxyhemoglobin (1.4 to 2.9%). At 100 ppm (115 mg/m^3) there was an average increase of 2.9% (1.6 to 4.5%). Mean duration of exercise before pain was significantly shortened with both levels of exposure, and the duration of pain was significantly prolonged after 100 ppm. Gordon and Roger (*194*) studying fire fighters exposed to carbon monoxide while fighting fires in the Denver, Colorado, area observed that carbon monoxide exposure produced changes in the electrocardiogram of persons without known heart disease.

The possibility that carbon monoxide exposures repeated frequently may contribute to the occurrence, severity, or progress of the arteriosclerotic process is suggested by the work of Astrup (*195*), Kjeldsen (*196*), and Wald *et al.* (*197*). Kjeldsen observed a number of factory workers and found that compared with people of the same age and smoking history, patients with heart or peripheral vascular disease had substantially higher carboxyhemoglobin levels. Wald *et al.* (*197*), using Kjeldsen's data, found that among moderate cigarette smokers (smoking 10–20 cigarettes per day) aged 30–69, the proportion who had atherosclerotic disease increased with the amount of carboxyhemoglobin. For example, of 122 persons in this category with a carboxyhemoglobin of between zero and 3.9%, two, or 1.6% of the total had atherosclerotic disease, whereas of the 20 persons with 8% carboxyhemoglobin or more, four, or 20%, had atherosclerotic disease. In the intermediate group, between 4 and 7.9% carboxyhemoglobin, 5 of 126 persons had atherosclerotic disease, i.e., 4%. Wald *et al.* are cautious, however, in their interpretation and it is made clear in the discussion that carbon monoxide may not be causally associated with the effects; several other factors might have operated.

Interpretation. From these reports, we may hypothesize that there are four possible ways by which carbon monoxide can affect the heart: (a) decreasing the probability of survival of persons who have a myocardial infarction and possibly other cardiovascular diseases; (b) producing aggravation of existing circulatory conditions, particularly angina pectoris and peripheral arteriosclerosis, as shown by Aronow *et al.* (*188–192*) and Anderson *et al.* (*193*) [Angina affects about 2% (3,800,000) of the United States population (*199*)]; (c) causing unfavorable changes in a healthy person (*194*); (d) as a factor in the onset and progression of cardiovascular disease, a possibility for which evidence is still only suggestive. These data are therefore suggestive of an association of carbon monoxide exposure with cardiovascular disease. Materials other than carbon monoxide, inhaled with cigarette smoke, could also be partially responsible for the findings associated with smoking. The role of genetic factors in cardiovascular reactions of smokers has been shown to be of importance by twin studies by Friberg *et al.* (*200*) and Cederlöf *et al.* (*201*). Carbon monoxide is at most only one factor in the pathogenesis of cardiovascular disease, but the importance of this agent is increasingly recognized (*202, 203*).

6. Effects of Low Concentrations on the Central Nervous System

In work done during World War II on the effects of carbon monoxide on visual threshold, McFarland (*198*) detected an effect at a carboxyhemoglobin concentration of about 5%. Schulte (*204*) studied the effects on fireman of exposure to low concentrations of carbon monoxide. He evaluated pulse rate, respiratory rate, changes in blood pressure, and neurological reflexes and conducted a battery of psychomotor tests. In some of these tests, significant changes in response were found after exposure to carbon monoxide. For some of the tests, variations in performance were found at carboxyhemoglobin levels well below 5%, possibly even at levels as low as 2%. Schulte predicted that similar studies in a larger group of subjects might show significant variations in performance at even lower carboxyhemoglobin levels. However, at the lowest carboxyhemoglobin levels, there was a somewhat erratic change in response as concentrations were increased, a fact that casts some doubt on the validity of this prediction. In any event, the tests used are rather complex and are not readily related to other types of behavior.

Beard and Wertheim (*205*) have reported distinct effects upon the ability to perceive differences in the duration of auditory stimuli among healthy subjects exposed for 90 minutes to carbon monoxide at concentrations as low as 50 ppm (Fig. 20). In supplementary tests to determine whether the effect was due to impairment of hearing or to impairment of temporal discrimination, the subjects were asked to estimate time intervals of 10 and 30 seconds; these tests showed that discrimination was impaired, not hearing. The results for the test subjects were significantly different from those for controls following exposure of the test subjects to carbon monoxide concentrations as low as 50 ppm for 75 minutes. Such an exposure could have produced an increase of carboxyhemoglobin concentrations of less than 2%.

There have been some experimental efforts to repeat the findings of Beard and Wertheim. Stewart *et al.* (*205a*) and Mikulka (*206*) have not been able to confirm Beard and Wertheim's findings despite considerably higher carbon monoxide exposure. It is not known to what extent differences in study design and technique may be responsible. The possibility of faulty technique in the work of Beard and Wertheim has been raised. The internal consistency of the studies from this laboratory is impressive; however, for the time being this effect is considered controversial.

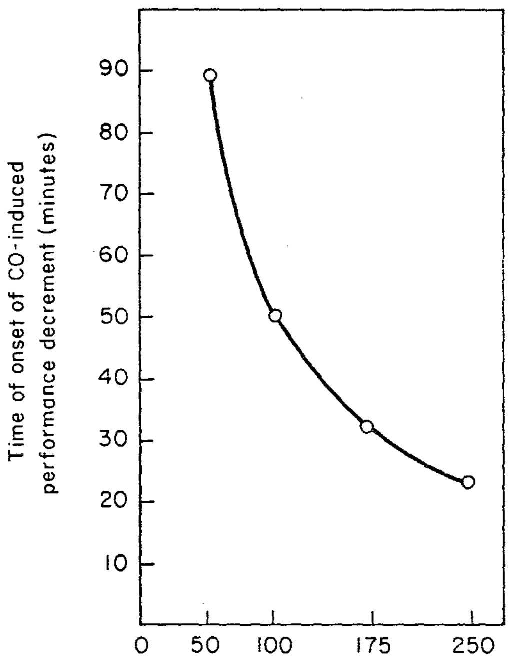

Figure 20. Dose–response relationship for impairment of estimation of time interval for individual subjects exposed to carbon monoxide in acoustical booths. The time of onset of significant decrement of performance below control conditions is shown. (*205*)

7. Carbon Monoxide Exposures and Motor Vehicle Accidents

We do not know whether possible effects of low concentrations of carbon monoxide on the nervous system could be of importance in connection with motor vehicle accidents.

Such effects, if present, should be detectable by epidemiological methods, and perhaps special attention should be paid to experiences of drivers in vehicles with which they were not familiar.

The possibility of an effect is suggested by the findings of Chovin (*167*) and Clayton *et al.* (*210*), although the work of neither of these investigators is conclusive. Chovin, for example, has shown in a 5-year population study by the Prefecture of Police in Paris, France, that drivers involved in and thought to be responsible for motor vehicle accidents had, on the whole, significantly higher carboxyhemoglobin levels in their blood than did two other populations studied in his laboratory. Without estimating the effect of alcohol ingestion, which is more common in smokers, we cannot attribute this effect to carbon monoxide alone. Wright *et al.* (*207*) concluded that an increase of 3.4% COHb is sufficient to prejudice safe driving, but McFarland (*208*) reports from a different set of experiments that 6% COHb did not appear to seriously affect the ability to drive motor vehicles.

Ury (*152, 211*) has presented a resourceful, nonparametric, statistical method for determining the possible association of motor vehicles accidents and urban air pollution, using data from the Los Angeles, California, area as a basis. The method depends on the comparison of the frequencies of accidents for a given hour of the day, and day of the week, across adjacent weeks, with comparable data for pollution concentrations. He has shown highly statistically significant evidence of an association of photochemical oxidants and accident frequencies. In the early papers in this series, the effects of carbon monoxide were not statistically significant. More recent analysis, using lagged terms, has given suggestive evidence that carbon monoxide may contribute to traffic accident frequencies.

Negative findings were reported by Waller and Thomas (*212*), who collected blood samples from individuals involved in accidents and from a control population in Vermont. Here, the role of carbon monoxide could not be detected against the background of the very substantial contributions of alcohol.

D. Nitrogen Dioxide and Other Nitrogen Oxides

Of the seven oxides of nitrogen known to exist in the ambient air, only two are thought to affect human health. These are nitric oxide (NO) and nitrogen dioxide (NO_2). At the present time there are no data either from animal or human studies showing that nitric oxide at the levels encountered in the ambient air is a health hazard. Nitric oxide is readily oxidized to nitrogen dioixde. This oxidation may occur in the atmosphere or in the membranes and tissues lining the airways.

1. Hemoglobin Reactions

Both nitric oxide and nitrogen dioxide, if transferred across the lung–blood barrier, can produce inactive forms of hemoglobin, the most important of which is called methemoglobin. Studies undertaken in Los Angeles, California, indicate that methemoglobin levels in school children and in commuting adults have ranged up to 5.2% and among groups of commuters average between 2.0 and 2.5% (*213*). This is higher than the 1% that had previously been thought normal. The methemoglobin levels appear to vary with time and place in a way that could be evidence of an effect of air pollution, but the role of cigarette smoking among adults is not detectable in these elevations. Since cigarette smoke contains high levels of oxides of nitrogen, this is negative evidence concerning inhaled oxides of nitrogen being responsible for this variation.

In vitro, nitric oxide is so closely bound to hemoglobin that it will readily replace carbon monoxide; however, the lack of observation of a human nitric oxide–hemoglobin complex *in vivo* implies that the combination occurs only under conditions in which oxygen is nearly absent. While some questions remain about hemoglobin reactions with oxides of nitrogen, there is no positive evidence that nitric oxide exposure is a health hazard associated with community air pollution.

2. Nitrogen Dioxide Reactions with Lung Tissue

Nitrogen dioxide is found as a pollutant in association with certain types of rocket fuel* and is known to cause occupational disease. Nitrogen dioxide effects tend to occur many hours after exposures have ceased. Persons occupationally exposed are often unaware of the severity of their exposure. The resulting pulmonary edema may progress for a number of hours after the exposure has ceased. It is very difficult both to estimate the magnitude of occupational exposure and to isolate the effect of nitrogen dioxide. The major basis for concern about oxides of nitro-

* Hatton, *et al.* (*213a*) report the biochemical evidence of breakdown of collagen, presumably from lung, in three U.S. astronauts resulting from an accidental exposure to NO_2 at an estimated concentration of 250 ppm for four minutes and forty seconds. Chest roentgenograms showed a chemical pneumonitis which cleared in five days.

gen as a low-level–long-term exposure hazard, therefore derives from animal studies (see Chapter 5, this volume).

3. Occupational Effects of Nitrogen Dioxide

Among occupations with nitrogen dioxide hazards are the manufacture of nitric acid (*214*), exposures of farmers to silage that has had high nitrate fertilization (*215–217*), electric arc welding (*218, 219*), and mining utilizing nitrogen compounds as explosives (*220*). In the manufacture of nitric acid, exposures estimated at 30–35 parts per million of nitrogen dioxide did not appear to show effects of injury (*221*); however, Russian studies (*222*) report chronic lung disease from lower levels of exposure, 3–5 years at concentrations below 3 ppm of nitrogen dioxide. Norwood *et al.* (*218*) and McCord *et al.* (*219*) reported that methemoglobin is elevated in workers using electric arc welding with coated rods. The maximum observed value was 3% methemoglobin. On the basis of the reports cited above in Section IV,D,1, there is doubt how much elevation this really represents. They estimated that the "nitric gas" was 13 ppm, expressed as nitrogen dioxide.

It is estimated that eye and nasal irritation will be observed after exposure to about 15 ppm of nitrogen dioxide and pulmonary discomfort after brief exposures to 25 ppm (*223*). It is likely that pathological changes can be detected on the basis of exposures of 25–75 ppm for short time periods (*216*). It is also thought that exposure to 150–200 ppm of nitrogen dioxide will lead to gradual production of fatal pulmonary fibrosis. Meyers and Hine (*223*) exposed individual volunteers experimentally to up to 50 ppm for 1 minute and produced significant respiratory tract irritation.

4. Human Experimental Studies at Low Levels (5 ppm and less)

Abe (*224*) studied sulfur nitrogen dioxide separately and together and had shown the lowest level of effect on normal subjects (see *397*a) Of the 5 subjects used, all were free from a history of respiratory disease and were from 21 to 40 years old; four of them were nonsmokers. Exposure was to 5 ppm of nitrogen dioxide for 10 minutes. Exposures led to increased inspiratory and expiratory resistance at 10 minutes after stopping the exposure; a further increase in resistance was observed 20 minutes after stopping, and a marked increase 30 minutes after cessation of exposure. Expiratory resistance increased on the average by 77% and inspiratory resistance by 92%. Effective lung compliance decreased 30 minutes after exposure to 40% of the control value. In these experiments, the effects of sulfur dioxide appeared to occur independently.

Shalamberidze (*225*) reports reactions to sulfur and nitrogen oxides on reflexes. According to Henschler, nitrogen dioxide is detectable by odor at 0.12 ppm (*226*). Rokaw *et al.* have experimentally exposed people to nitrogen dioxide (*227*). As can be seen in Figure 21 when the exposure of one subject was at 0.9 ppm for an hour, there was no change in airway resistance with exercise, but when the subject was exposed to 2.0 ppm with exercise, there was a substantial increase in specific airway resistance which exceeded that of the control. There appears to be individual variability in response to nitrogen oxide exposures that makes it quite difficult

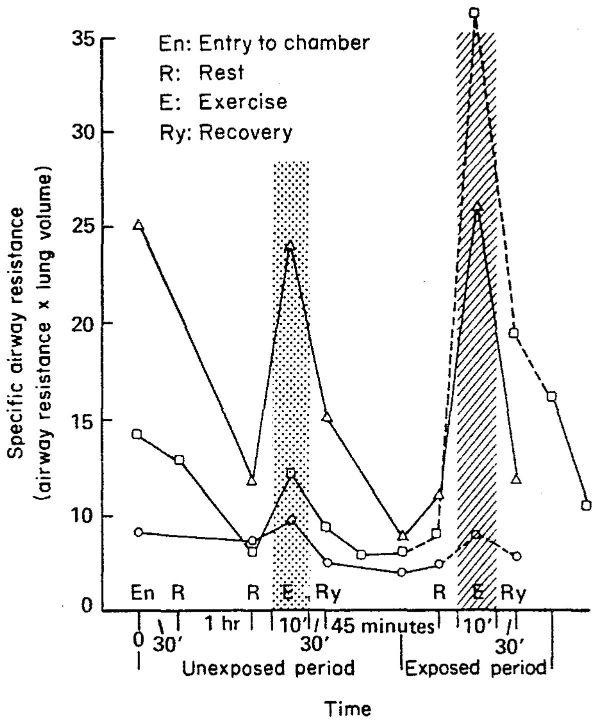

Figure 21. Airway resistance in response to nitrogen dioxide exposure and exercise in one subject on three occasions (*227*). Note that with exercise but no nitrogen dioxide, there is an increase in specific airway resistance (left-hand shaded area), and that recovery was incomplete after 30 minutes. There is substantial day-to-day variation in both resting and exercise measurements, but lesser within-day variation. With exposures to 0.9 and 2.0 ppm, no effect is noted at rest, but with exercise, a substantial increase in resistance occurs. Broken line indicates nitrogen dioxide exposure; △ = control day, ○ = 0.9 ppm exposure day, □ = 2.0 ppm exposure day.

to predict its specific effects. The delay in the occurrence of serious effects should be interpreted as a need for caution.

5. Effects of Nitrogen Dioxide on Pulmonary Antibacterial Defenses

A series of studies has examined the extent to which nitrogen oxides and, for that matter, other materials interfere with mechanisms of defense against infection. One basic method, that of determining survival in the lung of bacteria at different times after inhalation, was first demonstrated using bacterial aerosols by Laurenzi (*29*). Many other things can interfere with the pulmonary defense mechanisms, and if pulmonary edema occurs with impairment of oxygen uptake, this, of course, can produce some of these effects. There is no affirmative evidence concerning such a process in man, however. Further details of animal studies will be found in Chapter 5, this volume.

6. Epidemiological Studies of Nitrogen Dioxide as a Community Pollutant

The observations by Remmers and Balchum (*139*) of airway resistance alterations in persons with chronic respiratory disease in Los Angeles, California, has been reanalyzed to see whether the effects on airway resistance that were associated with oxidant exposure could have been a result of nitrogen dioxide. These analyses indicate that there was no significantly positive effect of nitrogen dioxide for either smoking or nonsmoking subjects. In nitrogen oxide and sulfur oxide polluted areas of Czechoslovakia, Petr and Schmidt (*228*) found in children elevated levels of methemoglobin (above an average of 2.5% methemoglobin in one community). In addition, these workers observed an apparent effect on lymphocytes and monocytes in peripheral blood, but it was not thought possible to separate the effects of nitrogen dioxide and sulfur dioxide on blood cells (see Section VI,F).

In a series of studies in the Chattanooga, Tennessee, area, Shy *et al.* (*229*) and Pearlman *et al.* (*230*) observed adverse effects on both adult and childhood respiratory illnesses and pulmonary function as well as acute lower respiratory illness in children living near TNT plants emitting nitrogen dioxide. The authors report what they believe to be an effect of oxides of nitrogen on respiratory disease prevalence both in children and in adults. The second grade children in all four areas were enrolled in the study and the forced expiratory volume in three-quarters of a second was measured weekly during the months of November 1968 to March 1969 and adjusted for height. This test value reported was significantly higher in control than in "high nitrogen dioxide" areas. There was no significant difference between the tests on children from the "particulate" area and the control areas. The incidence of acute respiratory illness was obtained for all household members, a total of 4445 individuals in 960 families. There was a similar respiratory illness pattern by time of year in all four areas, but "nitrogen dioxide" areas had more respiratory illness than the control area. In the "high nitrogen dioxide" area, 0.1 ppm of nitrogen dioxide was exceeded 40, 18, and 9% of the days in each of three stations of the area, but in one of the control areas, this level was exceeded on 17% of the days at one station. Heuss *et al.* (*231*) have pointed out that one of the schools, school 3, is included in the "high nitrogen dioxide" area but that the nitrogen dioxide exposure was apparently the same as that in control area 1. They have also noted that the differences in the pulmonary function tests are very small. One of the areas had a high particulate level, and this area had a slightly lower socioeconomic level than the other areas, although the authors felt this was not a significant difference. There have also been criticisms of the method used to measure nitrogen dioxide.

A World Health Organization Task Group on Environmental Health Criteria for Oxides of Nitrogen (*232*) concluded that a nitrogen dioxide concentration of 940 $\mu g/m^3$ (0.5 ppm) was established to be the lowest level at which adverse effects, due to short-term exposure, can be expected to occur. A maximum one-hour exposure of 190–320 $\mu g/m^3$ (0.10–0.17 ppm), no more frequently than once a month, was felt to be consistent with protection of the public health.

E. Hydrogen Sulfide and Mercaptans

Hydrogen sulfide is a colorless gas having a characteristic disagreeable odor often described as that of rotten eggs. The presence of low concentrations is evidenced by its odor, the discoloration of some paints, and the tarnishing of brass and silver. Exposures for short periods can result in fatigue of the sense of smell. This is particularly serious in industrial exposures, because the sense of smell is lost after 2–15 minutes of exposure to 100 ppm or more (*233*). Irritation of the mucosa is thought to be based on the formation of sodium sulfide (*234*). It is thought that the gas is absorbed as the sulfide ion.

One air pollution episode during which hydrogen sulfide caused deaths has already been discussed in Section II,A,4. A common human effect of hydrogen sulfide is sensory irritation.* Reports in the Russian literature indicate that the odor of hydrogen sulfide can be

* In Rotorua, New Zealand, a town situated in a geothermally active area, hydrogen sulfide emissions have collected in depressed areas, such as, cellars, and have caused fatalities.

detected at 0.072 ppm (*235*). The Soviet Union atmospheric standard for a maximum single value is 0.036 ppm, this being the odor threshold value (0.072 ppm) divided by two. Katz and Talbert (*236*) indicate that for a panel of observers, the odor threshold level is 0.13 ppm. The California State Department of Health conducted experiments on odor threshold concentrations for hydrogen sulfide with a panel of 16 persons. Each person was tested for the approximate concentration at which he detected odor in an air stream containing continuously increasing hydrogen sulfide. He was exposed to three inhalations per test of each of several air streams containing increasing concentrations of hydrogen sulfide in 0.01 ppm increments. The lowest concentration detected was recorded as the threshold odor concentration. The subject was exposed to the next higher concentration of hydrogen sulfide and invariably detected it also. The range of detection was 0.012–0.069 ppm, and the geometric mean and standard deviation was 0.029 ± 0.005 ppm.

Methyl mercaptan (CH_3SH) and ethyl mercaptan (C_2H_5SH) are among the most potent odorants. For practical purposes, they have no other effect on human health at the concentrations at which they are odor nuisances (see Section VI,E,3). The mercaptans are emitted in mixtures of pollutants from some pulp mills (*237*, *238*), petroleum refineries, and chemical manufacturing plants. Mercaptans are often added to natural or manufactured gas supplies so that leakage of gas will be noticed.

F. Hydrocarbon Vapors

Some of the hydrocarbon vapors in the atmosphere have health implications. Among the aldehydes of importance are formaldehyde and acrolein, both potent irritants. Based on data from Los Angeles, California, formaldehyde is present in the atmosphere in a concentration of up to 0.1 ppm. Total aldehyde concentrations occur at concentrations up to 1.3 ppm. Among the aromatic hydrocarbons, benzene is present in concentrations up to 0.06 ppm; toluene and xylene to approximately 0.1 ppm. Formaldehyde is the pollutant present in concentrations nearest the level producing health effects under occupational conditions (Table I, Section I,B,1). Its effects are primarily irritating. It is thought to be a major contributor to the eye and respiratory irritation of photochemical smog. Formaldehyde is the leading candidate among pollutants that may have a health effect in photochemical air pollution and that are not being systematically monitored or studied.

Benzene was a popularly used solvent, but its industrial use is now restricted because sufficient exposure to it interferes with the formation of red blood cells in the bone marrow. Leukemia occurs in some individuals with long-term occupational exposures. The range in which any hazardous effects have been observed in occupationally exposed workmen has its lower bound between 5 and 25 ppm, which is two orders of magnitude greater than reported air pollution concentrations. However, the alterations in chromosomes from lymphocytes in persons who had recovered from occupational exposure to benzene, reported by Forni *et al.* (*239*), require that we treat any exposure as a serious matter.

V. Particulate Pollutants and Their Effects

A. Asbestos

The occupational hazards of asbestos were first recognized in 1924 (*240, 241*). For the mineralogy of asbestos, see Hendry (*242*) and Gaze (*243*). Observed reactions were primarily the deposition of asbestos in the lung with production of fibrotic reactions and stiffening of the lung, resulting in shortness of breath. The awareness that asbestos exposure is likely to cause increased cancer frequency dates from 1949 (*244–246*). A series of studies by Selikoff and Hammond (*247*) and Selikoff *et al.* (*248–250*) has presented the health experience of asbestos insulation workers who were followed prospectively. Among these workers, the frequency of cancer of the lung is exceptionally high, especially in cigarette smokers. The frequency of respiratory diseases, including cancer of the lung, is such as to cause the number of observed deaths of those who have worked with asbestos for 20 years or more to be nearly double the number of expected deaths. In addition, there is a rare type of tumor of the lining of the chest or abdominal cavity called malignant mesothelioma that is now recognized as being due, in most cases, to exposure to asbestos (*251–253*).

The risk of cancer in asbestos-exposed workers is apparently dose related. The occurrence of lung cancer is far more common among cigarette smokers exposed to asbestos than in cigarette smokers with no asbestos exposure. There is no detectable excess of lung cancer among asbestos-exposed nonsmokers. By contrast, the dose–response relationship for mesothelioma is poorly defined. It is felt that exposure to chrysotile (one of the mineral forms of asbestos) is less likely to lead to this type of tumor than is exposure to crocidolite. Cigarette smoking does not appear to be important in the development of mesothelioma.

Mesothelioma has occurred in persons who were not occupationally exposed but whose residence was near shipyards or other industries where asbestos is used abundantly; there is also an excess of asbestos-related disease among household members of workers heavily exposed to asbestos (*253a–253f*). Pulmonary reactions to inhaled asbestos have been widely observed in urban populations of South Africa, Great Britain, and the United States (*254*). For example, the frequency of observation of so-called asbestos bodies appears to have increased between 1936 and 1966 in London, England (*255*). A hundred consecutive autopsy examinations in 1936, 1946, 1956, and 1966 at hospitals in London have shown that the prevalence of observed asbestos bodies was 0, 3, 14, and 20%, respectively. The increase could not be explained by change in the age at death nor by other phenomena. However, in New York, New York, no increase in asbestos bodies was observed at autopsies performed in 1934 and 1967, respectively (*256*).

There is uncertainty as to whether light microscopy adequately detects the asbestos present in air samples. Electron microscopy reveals a larger number of particles than does light microscopy. Despite their length, the particles are so narrow that they have relatively small mass. A threshold limit value of 5 fibers/ml is equivalent to 12,500 ng/m^3 of 5 μm long fibers. The precision of the counting procedures for electron microscopy is relatively poor, so that even in a well-equipped and experienced laboratory, 10 ng/m^3 may mean anything between 3 and 30 ng/m^3.

Asbestos mines, mills, shipyards, fabricating plants, and spraying of steel framed skyscrapers with an asbestos-rich fire retardant mixture

Table XIII Occurrence of Mesothelioma in Occupational and Nonoccupational Asbestos Exposures in Selected Populations[a]

Total number of cases	*Clear occupational exposure*	*Home contact with occupationally exposed*	*Neighborhood nonoccupational exposure*	*No known exposure*	*Study location*	*Reference*
87	12	—	75	—	South Africa	(*253a*)
76	31	9	11	25	England	(*253b*)
21	17	—	—	4	Netherlands	(*253c*)
42	10	3	8	21	Pennsylvania	(*253d*)
17	15	—	2	—	New Jersey	(*252*)
80	50	—	6	24	Scotland	(*253e*)
165	41	14	1	109	Canada	(*253f*)
488	176	26	103	183		

[a] Populations are selected in various ways, and classification is inferred in some cases.

are likely to spread asbestos fibrils for a considerable distance. Brake lining commonly is made with asbestos, and wear of such brake lining adds to street dust. Most of the abraded material is assumed to be structurally altered so that it is no longer a health problem (*257*). That this may not be entirely true is shown by the threefold excess of asbestos fibrils found in air samples in New York City near the Hudson River Tunnel toll station compared to a control area (*258*).

Although direct, quantified, evidence of community asbestos exposure and specific asbestos-related disease is not available, the occurrence of mesothelioma in persons living in the vicinity of mines, mills, and shipyards suffices to indicate the need for careful handling of this hazardous substance. A comparable study of cancer of the lung among those with nonoccupational exposure would be difficult, owing to the concomitant role of cigarette smoking in this disease. Nevertheless, the occupational data indicate that the combined effect of asbestos exposure and smoking is more than additive.

From the evidence, it is accepted that serious reactions to asbestos may take up to 30 years between the first exposure and the appearance of a tumor. For this reason, it has been decided in the United States that there are "known serious effects of the uncontrolled inhalation of asbestos materials in industry and uncertainty as to the shape and character of a dose response curve in man. . . ." Accordingly, it is generally agreed that "it would be highly imprudent to permit additional contamination of the public environment with asbestos" and "the major sources of man-made asbestos emissions into the atmosphere should be defined and controlled" (*257*).

B. Lead

The major source of exposure to lead is from food and water, with estimated intake of 0.12–0.35 mg/day (*259*). From 5 to 10% of ingested lead in adults may be metabolically absorbed, whereas from 20 to 50% of the lead inhaled from community air pollution may be metabolically absorbed into the body (*36*). The percentage absorbed tends to be higher with smaller particle sizes. Acute forms of toxicity are manifested when blood levels in adult males are greater than 75 μg/100 gm. Kehoe provided guidelines (*260, 261*) that indicated that "absorption from all routes of 120 micrograms of lead a day might be harmful, while a total of 60 micrograms is presumably safe."

Three types of toxicity are documented—gastrointestinal cramps (lead colic), central and peripheral nervous system effects (lead encephalitis, wrist drop), and anemia. Kidney disease, excess frequency of hypertension, and vascular disease have been reported but are not universally accepted as long-term effects.

In children ingesting sufficient lead paint, anemia and effects on the brain are universally recognized. Mental retardation (*262, 263*) and hyperactivity (*264*) have been reported to be associated with high blood lead levels or history of lead intoxication, but proof of lead as the causative agent for these long-term effects is disputed, since mental retardation and hyperactivity may be a cause rather than the effect of ingestion of lead and other nonfood materials.

The so-called Three City Study (*265*) documented a substantial and persistent excess of lead in blood samples from urban dwellers as compared to rural populations. With increasing respiratory exposure, there tended to be increasing blood levels. In a 1966 study (*266, 267*) in Los Angeles, California, samples of blood were taken from two groups of 50 persons each, the homes of the first group being adjacent to a heavily traveled freeway; the homes of the second were near the sea coast, in an area with substantially less atmospheric lead. There was a consistently significant excess of blood lead among the population living near the freeway, compared to coastal residents, independent of age, sex, or ethnic status. However, the freeway values did not deviate markedly from the values found for other populations in the community as a whole (Los Angeles, California).

1. Relation of Body Burden to Ambient Air Level

Goldsmith and Hexter (*268*) found a logarithmic regression of mean blood lead of males on estimated atmospheric exposure for community and occupational groups exposed to vehicular pollution; this regression agrees closely with experimental data reported by Kehoe (*269*). The estimated nonoccupational mean exposures range from 0.12 $\mu g/m^3$ to 2.4 $\mu g/m^3$. Of seven urban population groups, only the long term exposures of those from Pasadena, California, and Philadelphia, Pennsylvania, exceeded an average of 2 $\mu g/m^3$. The groups occupationally exposed to motor vehicle exhaust had 24-hour average exposures estimated at 2.1–6.5 $\mu g/m^3$. According to the authors, these data imply that long-term increases in atmospheric lead will result in predictably higher blood lead levels in the exposed populations. A later (*259*) report by the United States National Academy of Sciences concluded that ". . . it is not possible, on the basis of epidemiological evidence, to attribute any increase in blood lead concentration to exposure to ambient air below a mean lead concentration of about 2 or 3 $\mu g/m^3$."

The so-called seven-city study (*270–272*) showed annual geometric mean values ranging from 0.14 $\mu g/m^3$ (Los Alamos, New Mexico) to 4.55

$\mu g/m^3$ (Los Angeles, California). One station in Cincinnati, Ohio, two in Houston, Texas, and two in Washington, D.C., had values averaging more than 2 $\mu g/m^3$. The data showed there were higher lead concentrations in most of the identical locations in 1968–1969 than in 1961–1962. For Los Angeles, which had the most consistent increase, the eight stations showed an increase of from 32 to 63%.

In the seven-city study, blood and some 24-hour fecal samples were obtained from women. Female smokers had higher blood lead values than nonsmokers. Urban women had higher blood lead levels than rural women and were exposed to higher levels of atmospheric lead. No significant area differences were found in fecal lead levels. Presumably, this reflects lack of differences in dietary lead ingestion to account for area differences. There was a tendency in locations with higher atmospheric lead for female residents to have higher levels of blood lead, with several communities being deviant. This result confirms for women, over a narrower range of exposure, what Goldsmith and Hexter showed for men (*268*). Tepper and Levin (*271*) concluded that "there was no clear association between air and blood lead levels. . . ," meaning that there was not a statistically significant tendency. However, Hasselblad and Nelson (*272*), carrying out an analysis for the United States Environmental Protection Agency, conclude. "The contributions of air lead gradient and urban–suburban contrast on blood levels are shown to be significant with each explaining approximately 18 percent of the total area variation in blood lead concentrations". Kehoe's experimental data have been amplified by the experimental exposure data of Knelson (*273*) at levels of 3.2 and 10.9 $\mu g/m^3$ for 18 weeks. Such levels are shown to regularly increase body lead burdens.

Regardless of epidemiological data, a theoretical approach shows that a considerable part of the body burden comes from inhaled lead. If we conservatively assume that 10% of ingested lead (about 150 μg/day) is absorbed and that 20% of inhaled lead is absorbed ($2\ \mu g/m^3 \times 20\ m^3$/day), this gives a contribution from ingested lead of 15 μg/day and from inhaled lead of 8 μg/day. Thus, inhaled lead would contribute about one-third of the total exposure. With lower exposure via inhalation, it would contribute less and vice versa.

2. Biochemical Effects

Hernberg *et al.* (*274*) have shown in various population groups that aminolevulinic acid dehydratase values are closely (inversely) correlated with blood lead, and Selander and Cramer (*275*) have shown that increased excretion of aminolevulinic acid in urine is evidence of increased lead exposure. The NAS–NRC report (*259*) suggests that several levels be defined (for adults). This implies that at blood lead levels below 40 μg/100 gm of blood, no demonstrable effects other than decreased aminolevulinic acid dehydratase are expected. No one has shown that this decreased aminolevulinic acid dehydratase has medical significance. From 40 to 60 μg/100 gm, a subclinical metabolic effect may be manifested by a slight increase in urinary aminolevulinic acid. Above these levels, shortened red blood cell life span can be observed. The CEC–EPA Symposium (*270*) did not produce any contrary evidence.

Children are more vulnerable to lead exposures than are adults. Their ingestion is distributed to a smaller tissue mass; their gastrointestinal absorption is estimated by Karhausen (*276*) to be 25%, as compared to 8% for adults. This estimate is consistent with the results reported by Alexander *et al.* (*277*). Some children are also exposed to ingestion of dirt and paint chips by their lesser discrimination as to what is edible; their more rapid growth rate and metabolism makes them more vulnerable. These considerations assume greater weight in light of the reported association of elevated levels of lead excretion in children with the behavior disorder called hyperactivity syndrome. These children may have blood lead levels below 40 μg/100 gm (*264*). The biological limits proposed by Zielhuis (*278*) to protect children and adults are shown in Table XIV.

Urban children have higher blood lead levels than rural ones. In one study of 230 rural children, 19 had elevated levels of blood lead, and 18 of the 19 lived in homes with at least one accessible paint surface containing more than 1% lead. A similar source of leaded paint could be identified in only 60% of the 68 out of 272 urban poverty-area children who had "elevated" levels. About one-fourth of the urban children had blood lead values above 40 μg/100 gm, compared to less than one-tenth of the rural children (*279*).*

Ninety percent of 1- to 5-year-old children living in a rural area near a lead smelter in El Paso, Texas, had blood lead values greater than 40 μg/100 gm. No paint exposure occurred in this area, and levels of lead in dirt (0.4–0.5%) are not markedly different from similar levels in city streets and parks. These elevations reflect either primary respiratory exposure or secondary exposure to re-entrained dust. Similar findings were reported by Loveless *et al.* (*280*). In two California communities with

* Efforts to detect and prevent excess lead exposure in children, based on screening for free erythrocyte porphyrins and blood lead, have been mounted in the U.S. Values in urban areas in excess of 35 μg/100 gm are so frequent that lead-based paint exposures are unlikely to account for them. Direct air pollution exposures, and orally ingested lead in dust as a secondary pollutant, are likely to be assigned a major role.

Table XIV Acceptable Limits[a] of Lead and Its Biochemical Indices Proposed as Guidelines for Public Health Hazard Appraisal (*278*)

	Individual upper limit	*Group average*	*Unit*
For adults			
Blood Lead (PbB)	≤40	≤25	μg Pb/100 ml
Urine ALA[b]	≤ 6	≤ 3	mg/liter urine
Blood ALA dehydratase	≥20	≥30	Percentage decrease from 100% at PbB = 10 μg Pb/100 ml
For children			
Blood Lead (PbB)	≤35	≤20	μg Pb/100 ml
Urine ALA	≤ 5	≤ 3	mg/liter urine
Blood ALA dehydratase	≥30	≥40	Percentage decrease from 100% at PbB = 10 μg Pb/100 ml

[a] These limits should not be regarded as fine lines discriminating innocuous from harmful environments; however, if these limits are exceeded, the possibility of undue acute effects and/or chronic sequelae increases. The data for population groups should be interpreted by experts who can judge the representativeness of the population sample. Single values moderately exceeding upper limits in individuals should cause awareness and caution; the measurement should be repeated.

[b] ALA–amino levulinic acid.

similar (high) socioeconomic status, children living in the community with higher lead values in air had higher blood levels (*281*) (Table XV).*

Thus, for acute lead poisoning in children, much of the increase in body burden of lead and most of the damaging effects to the nervous system are due to lead paint; air pollution, directly or through increased lead levels of dirt in streets, parks, and other areas where children play, can make a measurable contribution to elevated lead burdens in children.

Table XV Lead Concentration in Air and in Blood of Primary School Children in Two Comparable California Communities—1972 (*281*)

Community	*Lead concentrations in air* (μg/m³)[a]	*Lead in blood of children* (μg/100 gm)[b] *Male*	*Female*
Burbank	3.27 ± 1.59 (10)	23.3 ± 4.70 (17)	20.4 ± 2.91 (19)
Manhattan Beach	1.87 ± 1.37 (10)	16.8 ± 4.01 (21)	17.1 ± 4.37 (19)

[a] Mean ± standard deviation; number in parentheses indicates number of samples.

[b] Mean ± standard deviation; number in parentheses indicates number of children. Differences between blood levels of both sexes are statistically significant at the 1% level.

* Roels *et al.* (*281a*) studied the biochemical impact of lead exposures on both children and adults near a smelter in Belgium. Their data supports the sensitivity of the test for free erythrocyte porphyrins (FEP) as an index of lead exposure. Based on this test they recommend a maximum lead in blood of children of 25 μg/100 gm.

Table XVI Weighted Average Weekly Exposure to Lead for Occupational and Nonoccupational Groups in Zagreb, Yugoslavia (*282*)

A. Lead-exposed occupational groups

Population group	*Concentration (μg Pb/m³) × time (hours/week)* — *Occupational*	*Nonoccupational* — *Outdoor*	*Nonoccupational* — *Indoor*	*Total concentration × time*	*Weighted average weekly exposure (μg/m³)*
Lead smelter workers	650[a] × 42	40 × 35	24 × 91	30,884	184
Inhabitants of lead smelter areas	—	40 × 35	24 × 133	4,592	27
Lead article manufacturers	139[a] × 42	0.3 × 14	0.1 × 112	5,851	35
Customs officers	6.2 × 42	0.3 × 14	0.1 × 112	275.8	1.64
Traffic policemen	8.2 × 35	0.3 × 14	0.5 × 124	437.2	2.60
Streetcar drivers	3.9 × 42	0.3 × 14	0.5 × 112	308.0	1.83

B. Average citizen not occupationally exposed (on basis of location)

Location	*Average Concentration (μg Pb/m³)*	*Time (hours/week)*	*Concentration × time*	
Working place	1.2	42	50.4	
Outdoor activities	6.3	14	88.2	
Recreation	0.2	6	1.2	
At home				
Rest of day	0.7	22	15.4	
Night	0.3	48	14.4	
Weekends	0.5	36	18.0	
Nonoccupational exposure:				1.1

[a] Respirable fraction.

Fugas *et al.* (*282*) show a weighted average weekly exposure of 1.1 $\mu g/m^3$ lead for citizens of Zagreb, Yugoslavia (Table XVI). This represents a useful model for evaluating community lead exposures.

C. *Cadmium* (Friberg)

1. Sources

The cadmium emitted from industrial and domestic sources either will be inhaled by humans or animals or will be deposited in soil, vegetation, or water. Irrigation with cadmium-contaminated water and the use of cadmium-containing fertilizers and sludge from sewage treatment plants can build up cadmium levels in soil so that uptake of cadmium in the growing plant will be increased. Wheat and rice have been shown to absorb significant amounts of cadmium (*283, 284*). Cadmium in paints and plastics may sooner or later end up in incinerators whose effluent may become airborne. Cadmium has been measured at up to 1% in children's plastic toys, but the risk for children who might chew on the toys is small, since the cadmium seems to be firmly bound to the plastic.

The normal concentration of cadmium in air is about 0.001 μg/m³ and will not contribute significantly to the daily intake of cadmium. Cadmium concentrations in air around cadmium-emitting factories, however, may be several hundred times greater (*285*). This can increase the concentration of cadmium in moss, as has been shown near a factory producing copper–cadmium alloys in Sweden (*286*), and Kobayashi (*286a*) has shown the same process affecting mulberry leaves in the vicinity of a Japanese cadmium smelter.

Smoking was first mentioned as a source of cadmium exposure in 1969 (*287*). A mean content of 1.5 μg per cigarette was found in a comparison among eight types of West German cigarettes. Of this amount, 0.1–0.2 μg of cadmium could be inhaled by smoking one cigarette. In a pack-a-day smoker, this would add up to 2–4 μg of cadmium per day.

2. Uptake and Metabolism

A toxicological and epidemiological appraisal of cadmium in the environment has been published by Friberg *et al.* (*285*), and those who wish a comprehensive treatment of the subject are referred to that monograph. Absorption via inhalation will vary with different chemical forms of cadmium and different particle sizes. Some data from animal experiments tend to show that the respiratory uptake may vary between 10 and 40% (*288, 289*). The gastrointestinal absorption ratio is much lower (*290, 291*). Animal experiments show an absorption of about 1–3%. Rahola *et al.* (*292*) have studied the uptake of radioactive cadmium in humans after a single exposure. They found uptakes varying from 4.7 to 7.9%.

Once absorbed, cadmium will be found in blood, organs, and excreta. With chronic exposure, the cadmium in blood will be found primarily in the red cells (*293*). A major part of the cadmium will be transported to the liver and kidneys, where it accumulates. These two organs at chronic low-level exposure contain as much as 75% of the retained cadmium. High concentrations of cadmium are found also in the pancreas and the salivary glands. Only low concentrations of cadmium have been found in the bones and in the central nervous system (*285*).

Cadmium in the body is mainly bound to a low molecular weight (6000–7000) protein, metallothionein. This protein is involved both in the transportation and selective storage of cadmium. It can bind up to 11% metal as cadmium or zinc due to the fact that it has a large number of sulfhydryl groups. This protein is found in large amounts in liver from cadmium-exposed animals, but similar proteins also have been found in the gastrointestinal tract, and it is possible that the transport from the gastrointestinal tract takes place with cadmium bound to proteins similar to metallothionein. As metallothionein has a low molecular weight, it can pass the glomerular (filtering) membrane of the kidney and then be almost completely reabsorbed in the proximal tubules as long as kidney function is normal. This probably explains the rather selective accumulation of cadmium in the kidneys.

Normally, only small amounts of cadmium are excreted with the urine. When tubular dysfunction of the kidneys appears in experimental animals due to the accumulation of cadmium in the kidneys, the urinary excretion of cadmium increases drastically (*294, 295*). Normal human cadmium excretion in urine is usually less than 2 μg/day. Excretion via feces is probably of the same order of magnitude (*296–300*). The biological half-time for cadmium in the kidney is very long, probably of the order of decades. This means that for a continuous exposure, it will take a very long time to reach a steady state. Whole-body accumulation does not follow a one-compartment exponential model. There is reason to believe that, for example, the biological half-time of cadmium in the liver is shorter than in the kidneys (*12, 285*). The newborn are practically free of cadmium. Henke *et al.* (*301*) found a range of 4–20 ng/gm wet weight in kidneys and less than 2 ng/gm in the liver from the newborn, making a total body burden of less than 1 μg. This indicates that the placental barrier is effective at chronic low level exposure.

Normal human exposure results in an accumulation in the kidney such that at the age of 50 it will give rise to a kidney cortex concentration of about 25–50 μg/gm wet weight of cadmium in the United States males. As about one-third of the total body burden is in the kidney, this means a total body burden of about 15–30 mg. Corresponding values in Sweden seem to be about 20–30 μg/gm of kidney cortex; and in areas not particularly contaminated with cadmium in Japan, mean values of up to 100 μg/gm kidney cortex have been shown. After age 50, cadmium concentration in the kidneys decreases. The reason for this is not yet known (*285, 302, 303*).

From both animal and human occupational data, it appears that long-term exposure may be associated with very low cadmium values in urine as well as with high values. Similar evidence comes from a normal population in Japan (*304*). Available data seem to indicate that the urinary concentration reflects kidney levels rather than liver levels. Piscator (*305*) could not find a correlation between exposure time and urinary cadmium values in workers without proteinuria. Piscator (*298*) and Miettinen (*299*) report efforts to relate blood cadmium to exposure time and to accumulation in the kidney. Blood values may reflect the most recent exposure, but they decrease more rapidly than the body burden of cadmium.

3. Effects

Inhalation of high concentrations of cadmium dust or fumes in industry may lead to kidney damage and lung damage (*289*). The most commonly found lung damage is of an emphysematous nature. The kidney dysfunction in chronic cadmium poisoning starts as a tubular dysfunction with proteinuria of a tubular type (*305*). This proteinuria is the result of defective reabsorption of low molecular weight proteins in the glomerular filtrate, and albumin will constitute, therefore, only a minor part of the total urinary proteins. Common clinical methods for detecting proteinuria, such as dipstick, boiling test, or nitric acid test, will not give positive reactions for this type of proteinuria in its early stages. Trichloracetic acid or sulfosalicylic acid should be used when screening for tubular proteinuria. To confirm the diagnosis of tubular proteinuria, electrophoretic separation of urine protein should be performed.

Since tubular proteinuria is an early sign of intoxication, screening for this dysfunction may prevent more severe damage. On the other hand, when tubular proteinuria has appeared, it is usually permanent. In a limited number of workers with proteinuria, no progress was seen when the workers were transferred to "cadmium-free" jobs. Apart from proteinuria, there may be an increased excretion of amino acids, glucose, phosphorus, and calcium. The disturbance in calcium and phosphorus metabolism may lead to osteomalacia (thinning of the bones), in turn leading to a serious disease syndrome characterized by severe pains due to multiple fractures. Such effects have been seen in industry (*306–308*) and, due to an excessive exposure from the general environment, in nonindustrially exposed persons living near the Jintzu River, Toyama, Japan. The disease in Japan has been given the name itai-itai disease (ouch-ouch disease). The occurrence of itai-itai cases in the Toyama area is only one aspect of cadmium poisoning in Japan. A large number of cases with tubular proteinuria, but without bone changes, have been found. There may well be other contributory factors in Japan for the severe manifestations of cadmium poisoning. In the Toyama area, the calcium intake is low, the fat intake is low, and the number of hours of sunlight are few. In all probability there is thus a low intake of vitamin D. The relation between cadmium and the itai-itai disease has been discussed extensively in the monograph by Friberg *et al.* (*285*).

Both animal and human data favor a critical concentration for proteinuria of about 200 μg cadmium per gram kidney cortex (*285*). The concentration of cadmium in the renal cortex in normal persons, exposed workers, and itai-itai patients is seen in Figure 22. The figure clearly shows the increase with age in normal persons. The cadmium levels in exposed workers are either higher or of the same magnitude or even lower than those in normal persons. It has been possible to show that when tubular dysfunction appears, the cadmium excretion increases, which explains the fact that the more severe the intoxication, the lower the kidney levels. This is not true for the liver, where all values in cadmium intoxicated workers and persons with itai-itai disease are considerably higher than normal (Fig. 23).

Cooper *et al.* (*309*), in multiphasic examinations of former lead smelter workers who also have had a substantial cadmium exposure, find evidence of tubular dysfunction that may also have been contributed to

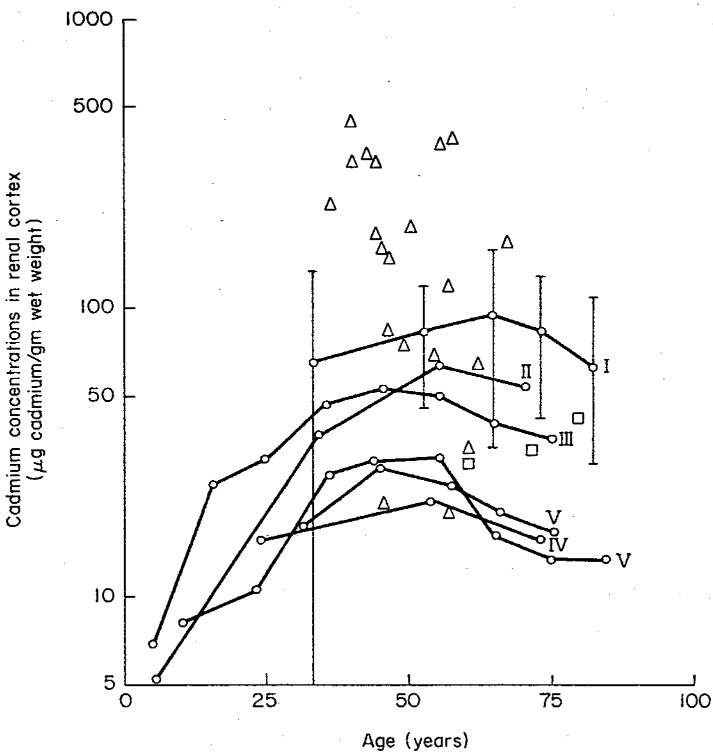

Figure 22. Cadmium concentrations in renal cortex from normal human beings in different age groups and different countries: I. Kanazawa, Japan; II. Kobe, Japan; III. United States; IV. United Kingdom; V. Sweden (two areas). Circles are mean values, vertical bars indicate range; △ = exposed workers (single values); □ = itai-itai patients (single values) (*285*).

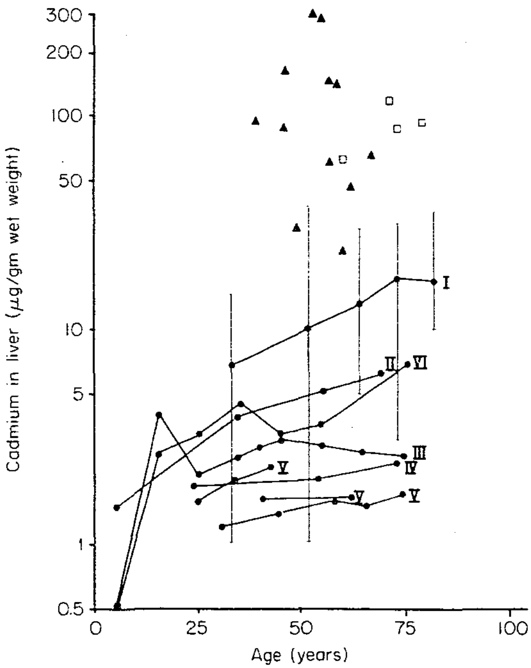

Figure 23. Cadmium concentrations in liver from normal human beings in different age groups and different countries: I. Kanazawa, Japan; II. Kobe, Japan; *III*. United States; IV. United Kingdom; V. Sweden (three areas); VI. Tokyo, Japan. Circles are mean values, vertical bars indicate range; ▲ = exposed workers (single values); □ = itai-itai patients (single values) (*285*).

by lead or other metals. Cadmium may also give rise to dysfunction of the liver and to anemia. In animal experiments, injection of single doses of cadmium can give rise to a complete necrosis of the testicles, but since such exposure does not occur in human beings, this type of damage probably does not occur in man. Industrial exposure to cadmium has been associated with an increase of lung and prostate cancer. The causal association with lung cancer is very weak and with prostate cancer is not conclusive. Animal data have shown that cadmium may give rise to a significant number of tumors at the site of injection.

Of paramount importance for the future is whether or not there is a risk that the cadmium concentrations in the kidney will increase from community exposure. If such is the case, steps must be taken very soon due to the very long biological half-time of cadmium. In order to make a prognosis, much more information is needed. There is a need to determine whether or not cadmium exposure will increase. More information on the biological half-time of cadmium is needed. The total cadmium exposure required for reaching a kidney cortex concentration of 200 μg/gm (the "critical concentration"), using different alternatives for biological half-time in the kidney cortex and for exposure times, is given in Table XVII, which is taken from Nordberg (*310*) and compiled from data by Friberg *et al.* (*285*).

D. *Mercury* (Friberg)

Mercury occurs in the environment in several physical and chemical forms. The most obvious distinction is between the inorganic forms and

Table XVII Cadmium Exposure Required for Reaching a Kidney Cortex Concentration of 200 μg Cd/gm Using Different Alternatives for Biological Half-Time in Kidney Cortex and Exposure Time (*285, 310*)

Basis of calculation[a]		*Exposure time (years)*	*Estimated biological half-time in kidney cortex (years)*	
			38	*18*
			Daily retention (μg)	
Constant daily retention during whole exposure time		10	36	39
		25	16	20
		50	10	13
			Industrial air concentration (μg/m³)	
25% pulmonary absorption, 10 m³ inhaled per work day, 225 work days/year		10	23	25
		25	11	13
			Daily cadmium intake (μg)	
Food exposure for 50-year-old person (2500 cal/day; 4.5% retention; changing caloric intake by age accounted for)		50	250	360
			Corresponding average concentration in foodstuffs (μg/gm)	
Total amount (w.w.) of food/day	300 gm	50	0.8	1.2
	600 gm		0.4	0.6
	1000 gm		0.25	0.35

[a] Assumption: One-third of whole body retention reached kidney and kidney cortex concentration 50% higher than average kidney concentration.

the organomercurials. The term "inorganic" here refers to elemental mercury vapor, mercurous and mercuric salts, and complexes in which mercuric ions can form reversible bonds to tissue ligands, e.g., thiol groups on proteins. "Organic mercury compounds" are those in which mercury is linked directly to a carbon atom by a covalent bond. The organic mercury compounds are further subdivided into the alkyl, aryl, and alkoxyalkyl groups. There is a great variation in toxicity, especially among organic forms. Two of the alkyls, methyl- and ethylmercury, for example, have been shown to be extremely toxic. Phenylmercury, an aryl form, is less toxic and could be compared to some of the inorganic forms in this respect. Phenylmercury, like inorganic forms, is converted to mercuric ion in the animal or human body, whereas the alkyls are not. A toxicological and epidemiological appraisal of mercury in the environment has been published by Friberg and Vostal (*317*). Those who wish a comprehensive treatise on the subject are referred to that monograph.

1. Sources

The largest source of atmospheric contamination is probably the burning of coals and fossil fuels (*311*). This is estimated to result in a world-wide total of 3000 tons of emitted mercury per year. Smelting and refining processes in connection with mercury mining can add to the environmental load, as can geothermal sources. The alkyl compounds have been used mainly in agriculture for seed dressing.

2. Uptake and Metabolism

A. METALLIC MERCURY. Metallic mercury enters the body primarily via inhalation. When elemental mercury is spilled in the work place or the home, vapor inhalation can occur. Elemental mercury is not absorbed to any significant degree by the gastrointestinal tract. Elemental mercury can easily diffuse from blood into tissues. Experiments in animals have shown high uptake of mercury by the brain after exposures to mercury vapor. Following absorption in the blood, metallic mercury is oxidized to mercurous ion, which is unstable and is converted into mercuric ion. Ionized mercury joins complexes with sulfhydryl groups and other ligands in the body tissues. Because this process takes some time, mercury is initially transported from the lungs to the tissues mostly as physically dissolved mercury vapor. After oxidation, the blood cells and plasma contain almost equal amounts of mercury. The placental transfer of elemental mercury has not been studied in detail. Since elemental mercury penetrates membranes easily, the placental barrier should not hinder it. Once ionized, it will act as other forms of inorganic mercury, which in animal studies have been shown to be stopped by the placental membrane.

There is uneven distribution of absorbed metallic mercury in the body. A considerable amount penetrates the blood–brain barrier. The brain is the critical organ after exposure to metallic mercury. The potential for a mercury accumulation in the brain after mercury exposure is apparent from autopsy data by Takahata *et al.* (*312*) and Watanabe (*313*), who studied brain specimens from two mercury mine workers who died of pulmonary tuberculosis. Though they died 6 and 10 years after the end of exposures, which had lasted a little over 5 years, the occipital cortex, parietal cortex, and substantia nigra still contained high concentrations (15 ppm or above in all cases) of mercury. Even within the brain the distribution is very uneven.

In a Swedish study (*314*), daily excretion in urine and feces as well as yearly retention were calculated for 30 workers exposed to mercury vapor in the chloralkali industry. Absorption was measured by 4-day running average sampling in the breathing zones of the workers. The calculated mean mercury exposure was 0.1–0.2 mg/m^3 in 10 workers' breathing zones. Their mean daily mercury outputs were 0.19 mg in urine and 0.14 mg in feces. Their yearly retention was calculated to be a mean of 51 mg.

b. Inorganic Mercury Compounds. Aerosols of inorganic mercury compounds are absorbed via the respiratory tract to a considerably lesser degree than is mercury vapor (*315*). On the other hand, there are reports of poisoning after exposure to inorganic mercury aerosols (*316*). The distribution of mercury following inorganic mercury compound exposure is also very uneven, but it differs from the distribution after exposure to metallic mercury in that the values in the brain are about ten times lower. The kidney, which generally contains the highest concentration of mercury, is the critical organ for exposures to inorganic mercury compounds. After exposure to inorganic mercury compounds, the risk of penetration of the placental barrier is considerably less than after exposure to metallic mercury.

c. Methylmercury. There are no quantitative data concerning the respiratory uptake of methylmercury compounds. Since several methylmercury salts vaporize relatively easily at room temperature, the risk may be considerable. Animal experiments as well as human data from industry (*317*) have shown without doubt that inhalation of methylmercury compounds can give rise to severe intoxication. Outside industry, gastrointestinal absorption is probably the most relevant route of methylmercury compound absorption. All recent poisonings have involved ingestion of contaminated food, mostly fish or grain. More than 90% of ingested methylmercury salts or proteinates can be absorbed, as seen in whole-body studies on human volunteers (*318, 319*). The biological half-time of methylmercury compounds seems to follow a single exponential model and averages about 70 days (*318, 319*).

3. Effects

a. METALLIC MERCURY. The most common effects after chronic exposure to metallic mercury are tremor and erethismus mercurialis (behavioral disturbances). Oral manifestations may include gingivitis and stomatitis (soreness and inflammation of mouth and gums). Occasionally, proteinuria including a nephrotic syndrome (*320, 321*) may occur. In the Soviet Union, much attention has been paid to the occurrence of micromercurialism (*322*). This is an asthenic–vegetative syndrome consisting of nonspecific signs such as abnormal tiredness, irritability, impaired memory, and loss of self-confidence. Included in the syndrome of micromercurialism are functional changes in organs of the cardiovascular, urogenital, and endocrine systems. Trachtenberg (*322*) believes that the symptomatology as a whole originates from damage to the cortical centers of the central nervous system.

For mercury in air and its effects, there are to date no large-scale environmental and epidemiological studies. In workmen occupationally exposed to mercury, some mercury may be found in exhaled breath samples, and skin and clothing may absorb mercury and disseminate it after the workman comes home to his family. Thus, an exposed workman may become a source of pollution in his own home. Industrial dose–response information is scanty. The most comprehensive study is by Smith *et al.* (*323*). They examined 567 male workers exposed to mercury vapor in chlorine production and 382 male controls. Signs and symptoms from the nervous system revealed a clear dose–response relationship. At even the lowest exposure (less than 0.01–0.05 mg/m^3), some symptoms were increased (Fig. 24).

In Russian studies (*322*), thyroid effects (increased uptake of iodine-131) have been stated to have occurred after some months of exposure to very low concentrations of mercury (0.01–0.02 mg Hg/m^3). Changes in conditioned reflexes have been reported at even lower concentrations in some Soviet studies. The Russian studies are discussed in detail by Trachtenberg (*322*) and by Friberg and Nordberg (*324*). As is noted in the latter, the medical significance of the reported changes is difficult to evaluate.

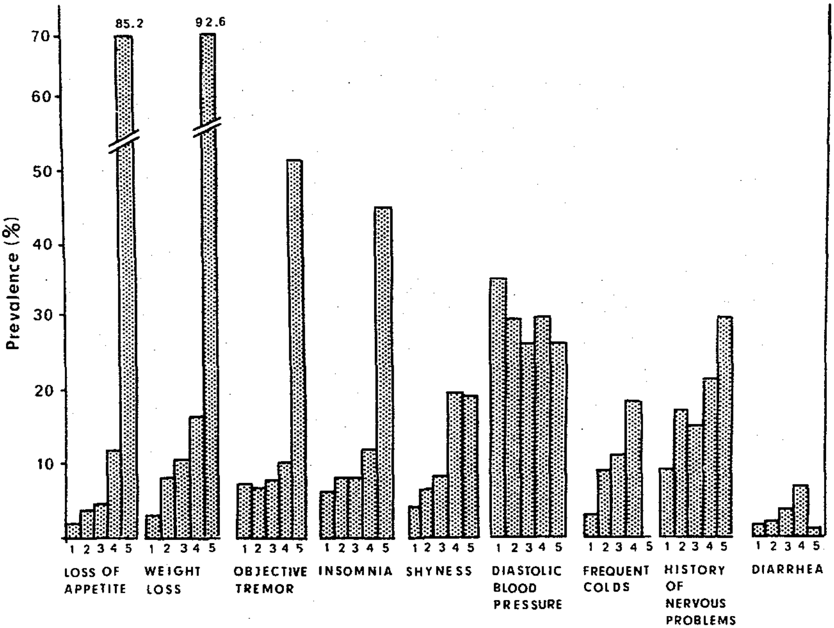

Figure 24. Percentage prevalence of certain signs and symptoms among workers exposed to mercury in relation to degree of exposure (*323*). Data on diastolic blood pressure probably mean percent below a certain level. This level is not given in the article. The numbers below each column refer to average exposures shown in milligrams per cubic meter: (1) control, (2) $<$0.01–0.05, (3) 0.06–0.10, (4) 0.11–0.14, (5) 0.24–0.27.

b. METHYLMERCURY. Methylmercury poisoning can occur prenatally, because methylmercury passes the placental barrier. Several cases from Minamata, Japan, are known. Symptoms are indistinguishable from those seen in cerebral palsy. In postnatal poisoning, cerebral and cerebellar symptoms dominate. Symptoms may include ataxia, constriction of visual fields, and sensory disturbances. Hearing may be severely impaired. The prognosis is often poor. Skerfving *et al.* (*326*) have reported an increased chromosome breakage in human lymphocyte cultures from persons without any symptoms, but with increased mercury blood levels due to excessively high consumption of fish with low-level mercury contamination. Perhaps the most well-known cases are the ones from Minamata and Niigata in Japan (*324a*), but the most extensive epidemic of methylmercury poisoning was in Iraq in 1971–1972, where 6,000 patients were admitted to hospitals and 500 deaths in hospitals were reported (*310, 324b*). A recent evaluation by a WHO task group on the environmental health criteria for mercury has shown that the first signs of methylmercury intoxication appear at concentrations of mercury (measured as total mercury) of 200–500 ng/ml in blood or 50–125 μg/gm in hair. These values correspond to a long-term daily intake of 3–7 μg/kg body weight of mercury as methylmercury (*325*).

4. Mercury in Urine and Blood as Indicators

There are no good biological indicators for evaluating long-term risks of intoxication after inhalation of mercury vapor. Neither mercury in blood nor in urine is satisfactory. On a group basis, there is an association between exposure and blood levels as well as urinary levels. Probably, the concentrations in blood and urine do not reflect the concentrations in critical organs but, instead, recent exposure. On an individual basis, the scatter is very large. For evaluating recent exposures, blood and urinary mercury probably are of importance. An exposure to about 0.1 mg Hg/m^3 of air corresponds to an average of 0.2 mg Hg/liter of urine (*323*) (Fig. 25). For methylmercury, blood levels seem to reflect the concentration in the critical organ and thus are good indicators. There is also a good correlation between exposure and blood concentration. To reach a critical concentration in the brain and the blood, the corresponding daily intake of mercury as methylmercury will be about 300 μg for a 70 kg man, corresponding to about 4 μg/kg body weight.

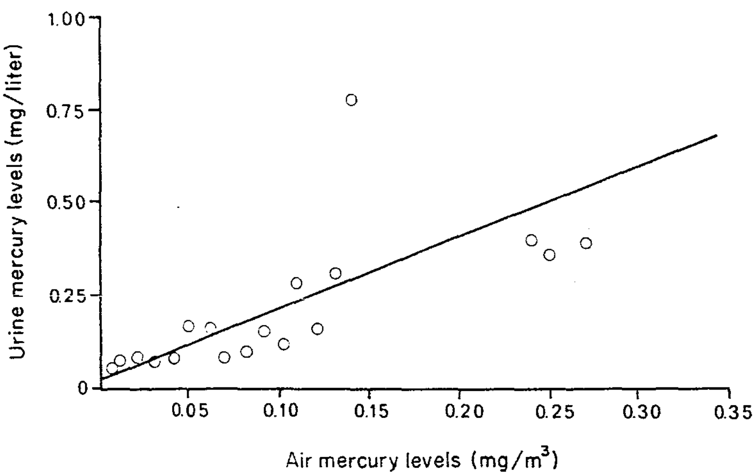

Figure 25. Concentrations of mercury in urine (uncorrected for specific gravity) in relation to time-weighted average exposure levels (323).

5. Normal Values of Mercury in Blood, Urine, and Hair as a Basis for Estimation of Exposure

It has been proposed in a World Health Organization report that 30 ng/ml of blood should be regarded as the highest acceptable "normal concentration" of mercury (*327*). This was based on a survey of 812 whole blood samples from fifteen countries. Not all the populations sampled were similar, nor were all individuals free from some excess ingestion of some pollutants. In no instance did the survey take fish consumption into account. All samples were analyzed in the same laboratory by atomic absorption. Of the subjects giving blood who were considered to have no occupational or unusual exposure, i.e., "normal," 85% had values below 10 ng/ml. In the same study, the general level of mercury in urine was 0.5 μg/liter based on the same method—atomic absorption spectrometry—1107 samples. Twenty micrograms per liter was regarded as the upper limit of normal levels. For blood and urine, no differences correlating with age, sex, or urban residence could be found.

No such international study on hair levels exists, but there are large samplings from several individual countries. In 776 samples in Canada, the range was 0–19 μg/gm scalp hair (*328*) by neutron activation analysis. The mean was ~1.8 μg/gm. In a Japanese study (*329*) on 73 samples, using the dithizone method, the mean was 6 μg/gm while the range, 0.98–23 μg/gm, was similar to that of the Canadian study.

E. Beryllium

Occupational beryllium exposures produce a chronic granulomatous disease, primarily affecting the lung. An acute pneumonic disease is also known. Cases of chronic berylliosis have been reported with some frequency in the vicinity of plants using or manufacturing beryllium. Hardy, who first clearly established the long-term toxic nature of the material, maintained a beryllium registry. In one study, of 60 persons with nonoccupational berylliosis, 18 were exposed to polluted air in the vicinity of beryllium plants (*330*). Other nonoccupational exposures were to beryllium phosphors, at one time commonly used in fluorescent lamps; they are no longer used. Other studies (*331*) show a higher proportion of cases from neighborhood exposures. Extensive use of beryllium in nuclear reactors led to much experience by the United States Atomic Energy Commission, which established a limit for beryllium exposure in the ambient air of 0.01 $\mu g/m^3$ averaged over a 30-day period. As a result of this experience and the lack of any reported cases of disease when concentrations were held below this level, the United States National Academy of Science concluded that this has been proven to be a safe level (*332*). Beryllium has been classified by the United States Environmental Protection Agency as a "hazardous air pollutant" (*333, 334*). A possible source of community beryllium exposure has been associated with gasoline or gas lamp mantles, which are made of fabric containing beryllium oxides (*335*). Beryllium exposure by inhalation will induce lung cancer in rats and monkeys (*336*) but has not been thought to be a human carcinogen (*332, 337–339*). However, Mancuso has put forward some evidence to the contrary based on occupational exposure data (*340*).

F. Arsenic

Arsenic may occur in the pentavalent or the trivalent form, the former having low toxicity and the latter relatively high toxicity. Emissions to air will largely be in the trivalent form (As_2O_3). Elevated arsenic levels in particulate matter have been found in the vicinity of coal-burning power plants in Czechoslovakia, where average concentrations of 19 $\mu g/m^3$ were found (*341*), in India, near metal mines (*342*) or smelters, in the United States (*343–345*), and in Chile (*346*).

In Czechoslovakia, (*341*) destruction of bee colonies was the first evidence of emissions after a power plant burning high-arsenic coal went into operation. Later water pollution by arsenic, elevated levels of arsenic in the hair of nearby residents, and decrease in blood counts of exposed children were shown to occur. In the studies by Birmingham *et al.* in Nevada (*344*), pustular skin eruptions in children were found. Milham and Strong (*345*) found that urinary arsenic was elevated in persons living in the vicinity of a smelter near Tacoma, Washington. In Chile, significant absorption of potentially toxic material was noted. In addition, skin sensitization to sodium arsenate was shown by patch tests among those not occupationally exposed. Long term exposure to a high concentration of arsenic trioxide via inhalation or ingestion is known to cause cancer of the skin. There is also some evidence for arsenic causing cancer of the lung (*347*).

Arsenic is found in cigarettes, the amounts having been considerably higher some decades ago when arsenates were used as insecticides in tobacco fields (*348*). Tobacco grown in fields where arsenates had been used years previously still contained substantial amounts of lead and arsenic, and cigarette smokers who use cigarettes made from such tobacco manifest elevated levels of such metals.

Increased body burden of arsenic is the best early guide to the need for control. Of the various indices, measurement of the arsenic content of hair is fairly well standardized (*349*). Hammer *et al.* (*350*) showed that the geometric mean for arsenic content of hair from fourth grade school boys varied from 0.3 ppm in an unpolluted community, to a high of 9.1 in a community with a lead–zinc smelter. Elevated lung cancer rates have been reported to occur among both men and women living in U.S. counties with non-ferrous metal smelters, but it is not yet proven that exposure to arsenic was the cause (*350a*).

G. Fluoride

Fluoride concentrations in community air occasionally have reached levels where absorption by children leads to dental mottling (*351, 352*), but the major biological effects of fluoride emissions are on vegetation (see Chapter 4, this volume) and on livestock that consume fodder high in fluoride (see Chapter 5, this volume).

H. Chromium

Trivalent chromium has low toxicity and is the form in which chromium most often occurs naturally. Hexavalent chromium has high toxicity, and its presence is usually associated with industrial activities. Both forms can occur in air (*353*). Occupational exposure to hexavalent chromium compounds, which are both irritant and corrosive, has caused symptoms in both the respiratory tract and the skin. Nasal perforation has been a common finding in workers exposed to chromates. It is also well established that lung cancer may result from occupational exposure to chromates (*354*).

In one study of effects on the general population of emissions from a chromate-producing plant in Japan, "light" cases of pharyngitis were found at a concentration of chromic acid of $<1.5\ \mu g/m^3$ (*355*). Exposure to trivalent chromium compounds has not been found to cause any significant effects. Whereas in most human body organs chromium levels do not change or even decrease during a lifetime, there is an accumulation with age in the lungs, indicating that chromium has a long biological half-time in that organ. In the Soviet Union, the threshold concentration for chromium to cause nasal irritation and reflex activity has been found to be $2.5\ \mu g/m^3$.

I. Manganese

Manganese is considered as an essential element for man and other animals, which means that some manganese is critical to normal biochemistry and physiology. Both manganese deficiency disease and manganese toxicity are known, although the deficiency state has not been identified for man but has for several animal species.

It has been suggested (*356*) that similarities between a relatively common chronic nervous system disorder, Parkinson's disease, and chronic manganese poisoning are close enough to point to a possible role of manganese ingestion or metabolism in some cases of the disease. A form of lobar pneumonia was reported among inhabitants of a Norwegian town contaminated by emissions from a metallurgical plant producing ferromanganese. Although industrial exposures to manganese have been reported in the United States with neurological effects, no community exposures have been reported to have such effects in the United States. Persons industrially exposed manifest psychological disturbances and disorders of coordination, vaguely similar to patients with Parkinson's disease.

Manganese has been shown to be a useful additive to fuel oil for reducing particulate emissions. It also has some desirable antiknock properties as a gasoline additive as MMT (methylcyclopentadenyl manganese tricarbonyl). Although no community air pollution problems from manganese are now known, if its use as a fuel additive should increase, to as much as 0.5–2.0 gm of manganese per gallon of gasoline, the amounts in the air will surely increase. The possibility of such a problem should be evaluated before such additives are widely used.

VI. Air Pollution as a Causal Factor in Chronic Disease

A. Definition of Terms

For this discussion, "causation" is defined as a high probability that a specified air pollution exposure of a specified population will augment the incidence or prevalence of a specified condition. To meet this definition, two measurements are required—the exposure and the augmentation of the condition. Variation in population susceptibility must be assumed. Judgment of causation of long-term human reactions is made on data of association and not data of experimentation. Hence, absolute proof of causation of chronic human disease is not ethically possible. Judgment as to the magnitude of the probability and the extent to which extraneous variables have been controlled will always be an important element in interpretation of possible causation.

It will be convenient to express the probability of air pollution being a causal factor in terms of "likely," "possible," and "suggested." A "likely" causal factor would be one for which there is no substantial doubt as to causation. A "possible" causal factor would be one for which there is doubt on one or more points that additional information could clarify. A "suggested" causal factor would be one for which evidence is not yet adequate for a firm judgment.

Among the factors that make for a high probability of disease causation are:

a. The number of different populations for which a similar association is observed, including different types of people, locations, times of year, and climates.

b. A progressive augmentation in reaction with a progressive increase in exposure to air pollution.

c. A decreased frequency of the condition associated with decrease in exposure.

d. A mechanism that can be hypothesized for an observed association, and which correctly predicts other associated changes.

The lack of these supporting factors, when they have been looked for, correspondingly weighs against causation. We are not, in any event, dealing with simple causal systems, whereby some exposure is necessary and sufficient for the production of disease. Instead we are likely to be dealing with a causal network of many stages and factors. Some of these stages have been suggested in the case of environmental agents and cancer by Armitage and Doll (*357*) and by Neyman and Scott (*358*). Proposals for path analytical treatment of these problems have been put forward by Goldsmith and Berglund (*359*).

B. Bronchitis and Emphysema

The respiratory system has two classes of possible reactions to air pollution readily recognized by physicians: (a) acute reactions such as the irritative bronchitis that was found among the victims of the Donora, Pennsylvania, and London, England, episodes; the impairment of ventilatory function observed among bronchitic persons in Los Angeles, California, or episodic asthma such as found in New Orleans, Louisiana, and Minneapolis, Minnesota, and (b) chronic diseases such as chronic bronchitis and pulmonary emphysema.

Standardized questions and thoroughly tested instructions have come into use to determine by a uniform method whether a subject has a persistent cough and/or sputum, whether there is shortness of breath on hurrying on the level or walking up a slight hill, and whether there are acute respiratory conditions superimposed on this. In the United States, simple chronic bronchitis is defined as chronic or recurrent increase in the volume of sputum (mucoid bronchial secretion) sufficient to cause expectoration, while in the United Kingdom, it has become customary to consider that persistent cough and sputum with at least one episode of increased symptoms lasting 2 weeks or more within a period of 2 years is equivalent to a diagnosis of chronic bronchitis. Along with these symptoms, it is customary to estimate pulmonary function. It is conventional in the United States to consider that persisting cough and sputum with shortness of breath are evidence of the possible presence of emphysema or advanced bronchitis.

Emphysema is a condition with unevenly distended air sacs of the lung, usually with loss of lung tissue. Emphysema and chronic bronchitis are commonly associated. Pulmonary function tests are used for diagnostic purposes in both conditions. For emphysema, microscopic or macroscopic study of the lung is the basic criterion, while symptoms of cough and sputum production are the basic criteria for chronic bronchitis.

1. Epidemiological Patterns

The changes in respiratory function most sensitive to acute inhalation exposure are those in airway resistance and in the closing volume (*360–362*). Somewhat less sensitive are changes in the forced expiratory volume in 1 second (or $\frac{3}{4}$ second) and in the maximal rate of expiratory air flow (*363, 364*). Measurement of changes in diffusion capacity and carbon monoxide uptake are relatively elaborate and not proportionately more sensitive as indicators of chronic bronchitis and emphysema. Vital capacity is the least sensitive of the commonly used tests for detection of bronchitis and emphysema. Changes on X-ray are of some interest, but, by most techniques, are nonspecific.

Unfortunately, most epidemiological studies have not been accompanied by adequate estimates of the air pollution to which the populations were exposed. Rather, they have used location, usually of place of residence, an an index of severity of pollutant exposure. Often the only available measurements are of the town or district, and the sampling site may not have been representative even of the community air quality. Place of residence as a criterion for air pollution exposure should not be accepted uncritically, for it is clear that place of residence is also associated with (a) cultural and ethnic traits, (b) living standards, (c) climate, (d) occupation, and (e) exposure to infectious agents. The validity of using place of residence also is qualified by the duration of time during which a person lives in a given area. Such a problem becomes exceedingly troublesome when one wishes to study air pollution effects in a location such as California, to which a substantial proportion of the population moved after having lived a large part of their lives elsewhere. Mobility within the state is also high.

2. Representative Studies

The College of General Practitioners in Great Britain carried out a survey of symptoms and lung function among patients on the registry of their members (*365*). In addition to the diagnosis of chronic bronchitis given by the practitioners, the questionnaire also permitted the definition of chronic bronchitis based on morning sputum in the winter, attacks of cough and sputum lasting at least 3 weeks over the past 2 years, and breathlessness on walking at ordinary pace on the level (Table XVIII). It is clear from these data for both sexes that from three to four times as much chronic bronchitis is present in metropolitan as opposed to rural areas. Compared to social class or residential classification, smoking accounts for a factor of two to three times increase in the frequency of bronchitis. Buck and Brown (*366*) show that for bronchitis mortality in the United Kingdom there are significant correlations with smoke and sulfur dioxide (Table XIX). See Section VI,D for discussion of the data of this study relevant to lung cancer.

In Japan, Toyama (*367*) reported a significant correlation between bronchitis mortality and dustfall in twenty-one districts of Tokyo, but no correlation was found between dustfall and mortality from cardiovascular disease, pneumonia, or lung cancer. Age-standardized respiratory morbidity rates, based on interviews, were highest in the most polluted areas and showed a gradient with presumptive pollution exposures that ranged from 4.0 to 29.0 per 1000. Such gradients were not observed for other diseases. Similar patterns were observed in frequency of

Table XVIII Age-Adjusted Male Bronchitis Prevalence Rates Based on Diagnosis by General Practitioners by Smoking Habits and Area of Present Residence (*365*)

	Total		*Rural district*		*Urban district and municipal borough*		*County and metropolitan borough*	
Subjects	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Nonsmoker	54	6	16	7	23	10	13	0
Exsmoker	141	13	27	11	64	7	30	27
Present smoker	592	18	115	13	268	18	209	24

Table XIX Correlations of Standard Mortality Ratios (SMR) for Lung Cancer and for Bronchitis with Pollution and Other Variables by Class of Area for Locations in the United Kingdom (*366*)

	London borough	*County borough*	*Metro-politan borough*	*Urban district*	*Rural district*
Number of locations	19	49	70	61	15
SMR Lung cancer	148	114	108	91	88
SMR Bronchitis	151	129	113	106	77
Persons/acre (1961)	48.9	15.6	13.3	6.4	0.8
Social index[a] (1951)	171	158	130	119	112
Average pollutant levels ($\mu g/m^3$) (March 1962)					
Smoke	168	281	203	185	85
SO_2	274	259	221	173	94
Significant correlations with male lung cancer[b]					
Persons/acre (1961)	—	0.67	0.65	0.52	—
Social index (1951)	0.69	0.49	—	—	—
Smoke (March 1962)	—	—	—	—	—
SO_2 (March 1962)	—	—	—	—	—
Significant correlations with male bronchitis[b]					
Persons/acre (1961)	—	0.46	—	—	—
Social index (1951)	0.85	0.51	0.56	—	—
Smoke (March 1962)	—	0.57	0.49	—	—
SO_2 (March 1962)	—	0.73	0.49	—	—

[a] Social index is the proportion of unskilled workers/1000 males of 15 years and over (1951 census).

[b] Significant values are said to be present when the probability of the true value being zero is less than one in a hundred. If no significant correlation is observed, no number is given.

respiratory diagnosis in National Health Insurance morbidity reports. Bronchitis is believed to be a large fraction of these cases. A high correlation of dustfall with morbidity from bronchitis and pneumonia in Ube, Japan, is reported by Nose (*368*).

In the winter of 1946, United States servicemen and their dependents stationed in the Tokyo–Yokohama area of Japan reported a high frequency of respiratory tract irritation with some asthmatic symptoms (*369*). The preceding year, some of the affected individuals reported a mild bronchitis. An allergic history was obtained infrequently, but almost all those affected were cigarette smokers. Subsequent studies (*370–375*) have confirmed the association of this condition with low winds and high pollutant levels, mostly by visual inspection (there are, regrettably, few measurements given in these reports). The condition is thought clinically and pathologically to resemble chronic bronchitis, notwithstanding the early asthmatic symptoms shown by some subjects. While acute symptoms were promptly relieved by leaving the area, some of those affected had persisting pulmonary function abnormalities consistent with emphysema. Evidence of allergic reactions in affected servicemen has been put forward by Meyer (*375*). The condition was originally thought not to occur among Japanese. However, Oshima *et al.* (*376*) reported an increase in chronic cough, sputum production, and diminished lung function among industrial employees in the Tokyo–Yokohama area compared with men having similar occupations in the less polluted area of Niigata. Symptoms were more common among cigarette smokers and those with allergic histories. They feel this pattern differed from the one affecting the servicemen.

Takahashi (*377*) has found in a population living in the city of Osaka three times as high a level of persistent cough and phlegm as among those living on a less polluted adjacent island. However, the frequencies of simple chronic bronchitis (persistent cough and phlegm) appear lower than in the United Kingdom or in the United States, but differences in methods could account for this.

Yoshida *et al.* (*378, 379*) have reported a high frequency of respiratory morbidity (including bronchitis) in Yokkaichi, Japan, seemingly related to air pollution from a power generation and petrochemical complex. Initial symptoms include asthmatic wheezing, but some of those affected had continuing symptoms and probably had the chronic bronchitis syndrome. Increased morbidity from respiratory conditions was reported by survey methods from the more polluted portions of the affected areas.

In a study of telephone workers in both the Eastern United States (*380*) and Japan the role of cigarette smoking was found in both to have similar effects, but no clearcut effects of place of residence were found.

Emphysema mortality in the United States is reported more frequently in urban than rural areas (*381*). It is also a condition that appeared to be increasing rapidly in frequency as a cause of death, but it is possible that greater diagnostic ability and interest may be responsible for some of the increase. Since 1967, the rate of increase has slowed in California. Hausknecht (*382*), in a study of a probability sample of California population, found a somewhat higher proportion with respiratory symptoms in Los Angeles than in other parts of the state. In a study using the Medical Research Council questionnaire and with methods as comparable as possible to those of Holland *et al.* (*383*), Deane *et al.* (*145*) found, among outside workmen, a greater frequency of symptoms of cough and sputum in Los

Angeles, California, than in San Francisco, California, especially among the older men. However, no differences in respiratory function were noted. The differences in symptom frequency between the two cities cannot be attributed to smoking.

Carnow *et al.* (*384*), using a number of monitoring sites in Chicago, Illinois, have followed a group of persons with chronic bronchitis, estimating for each person a weighted average of exposure at the residence and place of work. They report associations of sulfur dioxide with increased respiratory morbidity. No doubt other pollutants, including particulates, were also present. Spicer *et al.* (*385*) and Spicer (*386*) in Baltimore, Maryland, using the sensitive body plethysmographic method, observed that lung function changes among a group of chronic bronchitis patients tended to fluctuate together and to correlate with meteorological changes and with sulfur dioxide measured 38 hours previously. These studies also suggest that symptoms determined in a standardized manner may be about as sensitive an indicator of air pollution effects as are lung function tests. The data of McCarroll *et al.* (*387*) tend to support this. They have shown in longitudinal studies of a normal population in New York, New York, that cough has a lagged correlation with sulfur dioxide and particulate pollution, which is greater with a 24-hour and a 48-hour lag than it is with measurements on the same day. Winkelstein *et al.* (*388*) in Erie County, New York, have shown a correlation for total and chronic respiratory disease mortality with air pollution when economic status is controlled. No air pollution correlations were found to be significant for lung cancer.

Ishikawa *et al.* (*389*) have compared the prevalence and extent of emphysema in autopsied persons from St. Louis, Missouri, a city with a high level of air pollution, and Winnipeg, Manitoba, Canada, with much less pollution. Emphysema is more advanced and more frequent in St. Louis among both sexes and irrespective of smoking history. There is in each community more emphysematous change in smokers.

3. Interpretation

Data referrable to combined effects of sulfur oxides and particulate matter are discussed in Section III. Sufficient exposure to air pollution of various types is a likely causal factor in chronic bronchitis and a suspected one in emphysema; the likelihood clearly must be different in different locations. In no locality has its importance been better studied than in the United Kingdom, where the combined sulfur oxide and smoke pollution is thought to have synergistic (i.e., more than additive) effects with cigarette smoking. Thus, according to Reid (*390*), "It is, however, fair to say that . . . the accumulating epidemiological evidence satisfies at least some of the criteria of proof of causal relationship between air pollution and chronic bronchitis. We may thus reasonably conclude that although air pollution is certainly not the only cause, nor perhaps even the major initiating cause, it is almost certainly a promoting or aggravating factor of serious chronic lung disease." While this applies to the exposures in the United Kingdom it need not apply elsewhere, where pollutant dosage has been different.

On the question of air pollution causing respiratory disease in the Los Angeles, California, area, air pollution is a suspected causal factor of increased cough and sputum in older workmen and a likely cause of impairment of pulmonary function for persons with chronic respiratory conditions. There is suggestive evidence that populations of cigarette smokers are particularly susceptible to air pollution aggravation of their bronchitis, but that in nonsmokers the probability of the more serious consequences of bronchitis being caused by air pollution is low. There is as yet too little evidence for any firm conclusion concerning a causal relationship of community air pollution and emphysema. However, air pollution should be considered a suggested causal factor in emphysema.

C. Asthma

Acute outbreaks of asthma have been suspected as having a causal relationship to air pollution (Section II,A,7 and 8). It is commonly thought that inhaled pollens and certain dusts can produce classic asthma. Certain chemicals such as toluene 2,4-diisocyanate (TDI) are potent sensitizing agents on inhalation and can lead to asthmatic attacks in selected individuals (*391*). Accelerated impairment of lung function occurs with repeated exposure (*392*). Schoettlin and Landau showed that photochemical oxidants affected some adult asthmatics in Pasadena, California (*138*). Zeidberg *et al.* (*393*) studied populations in Nashville, Tennessee, drawn from the University Hospital Clinic. When the city was divided into areas classified according to high, medium, and low ranges of sulfation, there was a higher frequency of asthma attacks in adults, though not in children, in the more polluted areas. However, the population characteristics differed greatly by location in that 16 out of the 18 asthmatic adults living in the highly polluted area were nonwhite, whereas the total study population had about equal numbers of white and nonwhite persons.

Asthma emergency visits in Haifa, Israel, during 1969 and 1970 were analyzed by Peranio *et al.* (*394*), who found epidemic periods similar to those in New Orleans, Louisiana (see Section II,A,7), which tend to occur during times of low winds when pollutants tend to build up. No specific pollutant has been identified.

Possible sensitivity to sulfur dioxide is suggested by the report of Sim and Pattle (*395*): several human subjects of experimental exposure had a protracted period of cough, wheezing, and expectoration following exposure. Subsequent exposure to ambient pollution reactivated the symptoms. Workers in at least three other laboratories have reported development of acute asthmatic episodes when some subjects were exposed to sulfur dioxide at levels that produce only mild reactions in most subjects. In CHESS studies by EPA, sulfate aerosols are associated with increased likelihood of asthma attacks when the environmental temperature is low (*396*) or when oxidant pollution is also elevated.*

Interpretation

Pollens are almost certainly a causal factor in some cases of asthma. Other materials may, as community air pollutants, be causal factors in certain locations (New Orleans, Louisiana; Minneapolis, Minnesota). Generalized community air pollution is a suggested causal factor, but only for a small proportion of all adult asthma patients. Photochemical pollution is a likely causal factor in aggravation of asthma, in a portion of adult asthmatic patients. Sulfate aerosols are a suggested causal factor. Hyperreactivity of the airway caused by pollutants is likely to be an important mechanism in air-pollution aggravated asthma.

D. Air Pollution Exposures and Respiratory Cancer **(Goldsmith)**

1. Background of Smoking and Occupational Exposures

There are two types of evidence for judging the importance of population exposure to possible respiratory carcinogens—experimental animal data and human population data. Occupational experience is the most convincing evidence that inhalation can cause cancer (Table XX). In addition, there is an excess of lung cancer in some cities, which has been attributed to air pollution. Studies of migrants to and from polluted areas have helped in the analysis of the urban factor. Occupational exposures contribute to the urban excess and, along with the greater prevalence of long-term cigarette smoking in urban areas, may be sufficient to explain it.

Available evidence, however, is not convincing that exposures to common pollutants cause lung cancer. Part of the uncertainty

* Nadel (*397*) has analyzed the reflex nature of asthma and shown that ozone can greatly augment the reactivity of the airway as tested by histamine inhalation. Similar results for NO_2 have been found by Orehek *et al.* (*397a*) from exposures to 0.11 ppm NO_2 (210 $\mu g/m^3$) for an hour, in 13 of 20 subjects, using the bronchoconstrictor, carbachol, instead of histamine.

Table XX Inhalants Having Recognized or Suspected Carcinogenic Site(s) under Occupational Conditions

Material	*Recognized site(s) of carcinogenic effects*	*Suspected site(s) of carcinogenic effects*
Arsenic	Lung	Larynx
Asbestos	Lung	Digestive system
Chromium	Lung, nasal cavity	—
Nickel	Nasal cavity, sinuses, lung	—
Aromatic amines	Bladder	Lung
Isopropyl oil	Sinuses, larynx, lung	—
Mustard gas	Lung, larynx	—
Coal tar pitch	Larynx, lung	—
Creosote	Skin	Lung
Soots	Lung	—
Mineral oils	Skin	Lung
Petroleum, asphalt	Skin	Lung
Paraffin wax	Skin	Lung
Radon and ionizing radiations	Lung, bone, other sites	—
Bis-chloromethyl ether	Lung	—
Epoxides	—	Lung
Other chlorinated hydrocarbons	—	Lung
Beryllium	—	Lung
Iron (hematite)	—	Lung
Macromolecular polymers	—	Lung
Vinyl chloride	Liver	Kidney

can be attributed to the dominant role of cigarette smoking as a cause of lung cancer. Smoking is so important, that the lesser role of other inhalants is hard to detect. A second major cause of uncertainty is the long time spans involved. Based on what we know of smoking and occupational exposures, it usually requires several decades of human exposure before alterations in the occurrence of respiratory cancer are detectable. Residential mobility makes it difficult to find and study an adequately large population with several decades of residence and exposure in one location. All this is additional to the problems of estimating the exposure levels of populations.

It is difficult to apply occupational data to community exposure, since among other reasons, most urban exposures are usually to a mixture of agents. For several of the occupational carcinogenic agents (radon exposures in underground miners and asbestos exposures in insulation workers), the interaction with smoking exposure appears to be multiplicative rather than additive (*398, 399*). Since under occupational conditions such a wide variety of chemical inhalants can produce cancer of the respiratory tract in man (*400–407*), it is reasonable to suspect that populations exposed to similar agents as part of their general environment also share some increased risk of respiratory cancer (*408*).

2. Experimental Carcinogenicity of Atmospheric Pollutants

The carcinogenicity of atmospheric pollutants to mice has been demonstrated with organic extracts collected from various sources. Usually these have been applied to the mouse skin or injected. Administration of pollutant extracts to mouse skin, whether by painting or subcutaneous injection, has generally yielded local tumors (papillomas or carcinomas, sometimes accompanied by multiple pulmonary adenomas). A notable exception was when small concentrations of organic extracts of pollutants were injected subcutaneously in infant mice, which later showed a high incidence of distant tumors (hepatomas and lymphomas) in addition to multiple lung tumors, together with a virtual absence of local tumors (*409*). Marked variation has been noted in the carcinogenicity of organic extracts of pollutants from various urban sites, coincidentally with low activity of material from Los Angeles, California (*409, 410*).* In addition to the well known and much studied effects of benzo[*a*]pyrene, the role of other carcinogens in crude organic extracts is now generally accepted. Evidence for this includes tumor production by benzo[*a*]pyrene-free pollutants, such as aliphatic aerosols of synthetic smog (*411*) and by aliphatic and oxygenated fractions of organic extracts of particulate atmospheric pollutants. Lack of parallelism is noted between carcinogenicity of organic extracts of particulate pollution samples and their benzo[*a*]pyrene concentrations (*409, 410*). However, not all of the tumors reported are invasive. Noninvasive ones do not, in the opinion of some workers, deserve to be considered as cancers.

When bound to soot (*412*) or to hematite (*413*), pure chemical carcinogens, such as benzo[*a*]pyrene, known to be present in polluted air, have been shown to be carcinogenic for lungs of rodents by intratracheal instillation. There is evidence of more than additive effects between sulfur dioxide and benzo[*a*]pyrene following exposure by inhalation rather than by intratracheal instillation (*414*). Squamous carcinoma production by intratracheal instillation of benzo[*a*]pyrene absorbed on hematite (*413*) has suggested the importance of inert particles as carriers of carcinogens in the production of lung cancer in animals. The role of inert particles may be the same in man, though the particle may be a

* An authoritative review of migration and other epidemiological evidence from several countries on the possible association of air pollution and cancer has been published by the International Agency for Research on Cancer (*455a*).

liquid aerosol (tobacco smoke) rather than a solid one (hematite). Vitamin A appears to inhibit the carcinogenic effect of benzo[*a*]pyrene plus hematite and reduces the alteration of cell types in the hamster respiratory system. This potential protective mechanism against lung cancer deserves further study (*415*).

3. The Urban Industrialization Factor in Lung Cancer Epidemiology

Most of the relevant epidemiological studies show an association between urban residence and increased risk of lung cancer. This urban–rural difference is more evident among men than women (*137, 416–420*). These results lend support to the argument that air pollutants, found more often in an urban environment, are carcinogens affecting the general population. In Norway (*421*), the death rates for cancer of the respiratory system are more than three times greater for urban males than for rural males, with a smaller excess for females (Table XXI). In New York State (Table XXI), excluding New York City, the age-adjusted lung cancer rate is twice as high in urban portions of metropolitan standard statistical areas as in rural parts of nonmetropolitan areas. In Iowa, the urban–rural gradient is nearly threefold (Table XXI). However, in some rural parts of Finland, the age-adjusted lung cancer rate for males is higher than even in the most polluted cities (145.4/100,000) (*422*). (see also p. 569).

Mortality among different groups is often compared by means of the standardized mortality ratio. Usually, the standardization adjusts the observed data so that different age distributions of populations will not

Table XXI Rural–Urban Lung Cancer Death Rates[a] for Males and Females in Norway, New York State (excluding New York City), and Iowa

	Norway (421)		*New York State (1949–1951) (420) (age-adjusted)*		
Subjects	*1959*	*1969–71 (Age-adjusted)*	*Parts of metropolitan SMSA[b]*	*Parts of non-metropolitan areas[b]*	*Iowa (418)*
Urban					
Male	40.7	50.7	29.2	20.8	29.0
Female	6.5	8.7	3.2	3.2	7.8
Rural					
Male	12.4	20.4	23.9	15.2	10.2
Female	4.3	5.1	3.5	2.4	5.3

[a] Rates are in units of deaths per 100,000 per year.
[b] SMSA stands for standard metropolitan statistical area. Each SMSA includes at least one city with a population of 50,000 or more.

Table XXII Lung Cancer Standard Mortality Ratios in a United States Sample Adjusted for Age and Smoking History *(435, 436)*

Population	*Male*	*Female*
Counties in SMSA[a]		
500,000 and over	123	132
50,000–500,000	111	92
10,000–50,000	164	137
2500–10,000	107	104
Counties not in SMSA[a]		
10,000–50,000	89	96
2500–10,000	84	96
Rural nonfarm	80	84
Farm	65	69

[a] Standard metropolitan statistical areas, which include at least one city with a population of 50,000 or more.

distort the comparison. Adjustment may also be made to allow for the influence of smoking history, occupation, race, education, etc. and usually leads to reports given in terms of what is called a standardized mortality ratio. A standardized mortality ratio of 100 means that the population (e.g., living in a certain district or city) is affected by mortality rates at the same intensity as the population used as a basis for standardization. A ratio of 164 means there is 64% excess mortality and a ratio of 65 implies a 35% deficiency in relation to the base population. Data for Great Britain in terms of age-standardized mortality ratios shows less than a twofold difference between rural districts and London (*366*) (Table XIX). Higgins (*423*) studying trends for male lung cancer mortality between 1956 and 1970 demonstrates that in London, rates at ages less than 65 have begun to decrease. The lung cancer rates for ages 45 to 64 remain higher in London than in other parts of Great Britain and the United States. The age-adjusted mortality from lung cancer in Great Britain is about twice as high as in the United States and this is true both for men and women. Table XXII, in which data are adjusted for smoking history in the United States, data show that cities with populations from 10,000 to 50,000 have the highest lung cancer mortality ratios. There is thus evidence for an urban factor that contributes to the excess risk of lung cancer. Environmental carcinogens that are inhaled from polluted urban atmospheres have been proposed as a possible explanation.

The effects of cigarette smoking and urban residence appear to be at least additive. In contrast, the combined effect of occupational asbestos inhalation and tobacco smoking is greatly in excess of the risk attributable to the sum of the two factors (*249, 399*). Similar relationships are found for the combined effect of uranium mining and cigarette smoking (*424*). Among asbestos workers who do not smoke, bronchogenic cancer is said to be rare, but among asbestos workers who smoke, the risk of bronchogenic cancer is about eight times that of smokers with no asbestos exposure (*249*). Attention has been focused by experimental work (*425*) upon the possibility that chemical carcinogens may interact with viruses. Thus, the risk of lung cancer might be increased in individuals who are exposed to polluted air containing carcinogens while being ill with influenza and other respiratory virus infections. The possibility has been raised that this is primarily due to the infectious process breaking down the defense mechanisms, permitting the carcinogens to react with the germinal cells of the respiratory tract.

There are a number of variables other than air pollution that condition the health effects of urbanization. These include (a) demographic factors, (b) meterological and climatic factors, (c) occupational exposures (including unemployment), (d) household crowding and household dilapidation, (e) land congestion, (f) use of household fuel for cooking and heating, (g) income and education variables, (h) spread and occurrence of infectious disease, (i) nutrition, and (j) smoking. Demographic factors include ethnic origin, age, family structure, and migration history. Household crowding and dilapidation are often interrelated with low income, educational status, recent urban migration, and the spread of infectious disease. Land congestion is likely to be related to fuel emissions both from transport and domestic heating and cooking. Use of household fuels for cooking and heating may be a major cause of air pollution and may further be a basis for high-level exposures in the household. Income, education, and ethnic practices affect nutrition.

Analyses for this complex of interacting variables have been published for mortality in forty-six of the United States standard metropolitan statistical areas by Schwing and McDonald (*426*), and by Lave and Seskin (*427, 428*). This has been done on a smaller scale for Los Angeles, California, by Chapman and Coulson (*429*), and by Menck *et al.* (*430*). Using over one hundred communities within Los Angeles county as a base, Goldsmith (*431*) does not find any association of air pollution complaints in 1956 with lung cancer mortality in 1970, but an association is found for population density. The Los Angeles data (by census tracts for 1966) analyzed by Chapman and Coulson show no significant correlations for lung cancer mortality with the ethnic and income variables, percent black, percent Spanish surnamed, or average family income.

Lave and Seskin have not used age-adjusted data; thus, the most obvious demographic factor has not been controlled for. Similar studies for classes of urbanized areas in Great Britain have been reported by Buck and Brown (*366*) (Table XIX). Buck and Brown find that "lung cancer mortality in administrative districts of England and Wales is not, in general, significantly associated with corresponding levels of smoke or sulfur dioxide in the residential areas of these districts. There is a positive association between lung cancer mortality and population density within the different classes of areas which is significant and accounts for differences between classes of areas in the average mortality rates."

Lave and Seskin (*427, 428*) find that for malignant disease of the respiratory system (I.C.D. 162, 163)* for 117 standard metropolitan statistical areas for 1960, the following variables have statistically significant coefficients ($p \leq 0.05$; $t \geq 1.7$): percent of the population over 65 years; percent of the population nonwhite; persons per square mile; percent of the population male; percent of workers employed in transportation, communication, and other public utilities; percent of families with incomes less than $3,000 (negative coefficient). Among variables that did not have significant correlations were biweekly measured levels of mean, minimum, and maximum of suspended particulates and sulfates and proportions employed in other occupational groups. When Lave and Seskin excluded occupational factors, pollutant variables showed significant coefficients. In a study of nonsmokers in England, however, Doll (*432*) found no effect of population density on lung cancer mortality. Possibly, therefore, population-dense areas merely have a higher proportion of heavy smokers.

The National Academy of Sciences—National Research Council's report (*433*) on particulate polycyclic organic matter notes that median winter-spring quarter of 1959 concentrations of benzo[*a*]pyrene in urban sites were 6.6 $\mu g/1000\ m^3$ (6.6 ng/m^3) and for nonurban sites 0.4 $\mu g/1000\ m^3$. Disregarding smoking, the report "roughly associates" the apparent doubling of lung cancer in urban as compared to rural areas to the 6.2 ng/m^3 excess of benzo[*a*]pyrene.

Carnow and Meier (*434*) have published a regression analysis for lung cancer (I.C.D. 160–164) for the forty-eight contiguous states using age-adjusted data for both sexes and for white and nonwhite populations; the "independent variables" used are tobacco sales (in dollars per person of age 16 or more) and benzo[*a*]pyrene in air (micrograms/1000 m^3). The benzo[*a*]pyrene measure, however, is apparently derived by multiplying the proportion of the state's urban population, by the average urban

*I.C.D. refers to the International Statistical Classification of Diseases, Injury, and Causes of Death. The classes include 160—cancer of the nose, middle ear, and nasal accessory sinuses; 161—cancer of the larynx; 162—cancer of the trachea, bronchus, and lung, specified as primary; 163—cancer of the lung, unspecified as primary or secondary; and 164—cancer of the mediastinum. (Seventh revision of I.C.D.)

benzo[*a*]pyrene level (presumably 6.6 ng/m³) and the rural proportion by a much lower benzo[*a*]pyrene level (presumably 0.4 ng/m³); thus, the independent variable represented as benzo[*a*]pyrene appears to be an indirect measure of urbanization and may not reflect differences in air pollution exposures by state. Their tabulation yields the following apparent anomalies. Illinois and Indiana have lower values for benzo[*a*]pyrene (2.38 and 2.37) than does Idaho (2.87). Oregon and Washington have higher values (2.03 and 1.72) than Massachusetts, Rhode Island, and Michigan (1.26, 1.49, and 1.04). In addition, the difference between states in dollars spent for tobacco inadequately reflects the differential effects of smoking on lung cancer rates. This analysis appears to have been relied upon by the authors of the NAS–NRC report (*433*). In the United States in 1958, the urban to rural standardized lung cancer mortality ratio for males (adjusted for age and smoking history) showed a 43% excess in urban as compared to rural areas, and for females a 22% excess (*435, 436*). The male urban-to-rural ratio for lung cancer mortality appears to be declining.

Among nonsmokers, urban residents have about 20% higher lung cancer rates than do rural residents for both sexes. The male and female rates are similar, and for rural residents the female rates are slightly higher than the rates for males. In the United States, 51% higher rates were observed in foreign born males than in native born, for females the rates are 52% higher. For those who migrate from farms to metropolitan areas, the ratio is higher than for those who lived all their lives in metropolitan counties, 71% excess for males, 110% excess for females.

Hitosugi (*437*) studied lung cancer death rates in an area near Osaka, Japan, based on a family interview for families of 259 persons dying of cancer and a random sample of 4500 adults. Generally, high lung cancer mortality was found for exsmokers, suggesting that onset of illness may have led some smokers to become exsmokers. Among nonsmokers, no pollution gradient was shown (although the number of deaths is small). Urban factors and smoking appear, however, to have interacted in this Japanese population as they seem to have done in United States and British and other industrialized population groups.

Following a recommendation by a World Health Organization study group on epidemiology of cancer of the lung (*438*), a comparison of lung cancer, atmospheric pollution, smoking, and other variables was carried out between Dublin, Ireland, and Belfast, Northern Ireland, and between Oslo, Norway, and Helsinki, Finland (*439*), and other European cities. This study appeared to show an association between solid fuel combustion and lung cancer death rates after differences in smoking habits were taken into account. Additional studies in Northern Ireland (*440*) led to an estimation (*441*) that if the death rate from lung cancer for a symptomless rural nonsmoker is taken as the irreducible minimum, the risk of death from the disease would be about doubled for a man living in an urban area, but increased twentyfold if he smoked more than 20 cigarettes a day. According to the Royal College of Physicians (*8*), such retrospective inquiries, "although they appear to point to an urban factor in the causation of lung cancer, they do not amount to an indictment of air pollution." The Royal College report concludes, "Pollution of British towns cannot therefore be the whole explanation of the adverse experience of this country with respect to lung cancer."

Pedersen *et al.* (*422*) carried out a personal interview study of the role of cigarette smoking pollution and other variables among a group of populations in rural and urban Norway and Finland. The study includes a rural Finnish region which has lung cancer mortality in excess even of that in London, and exceeding the levels in urban Norway and Finland. They were able to show that the type and magnitude of cigarette smoking and the age at starting to smoke were the most likely explanations for the wide variations observed. Neither Winkelstein *et al.* (*442*) nor Hagstrom *et al.* (*443*) found an association of pollution indices with lung cancer in community studies in Buffalo, New York, and Nashville, Tennessee, respectively. Neither of these studies estimated or adjusted for the effects of smoking. Menck *et al.* (*430*) report that in the south central portion of Los Angeles County, California, the age-adjusted lung cancer mortality for Caucasian males for 1968–1969 is greater than for other parts of the county. This area includes most of the industralized and low-income portions of the county. The differences persist when comparisons were made of occupational groups in the lower socioeconomic categories. Similar clustering for lung cancer is not found among women, though it should be if community air pollution were a potent factor. Since heavy cigarette smoking is more common among the lower economic classes, the authors looked to see if other smoking-associated cancers were high in this area, but they were not. This area includes the highest levels of benzo[*a*]pyrene in air and soil found among four sampling sites in the county. The authors, not finding any occupational exposures to account for these findings, feel that the "most likely explanation is a synergistic action between smoking and neighborhood air pollution." The area is not one that has had high photochemical pollution relative to other parts of the county. The authors suggest that the neighborhood pollution may be related to petroleum and chemical industries in the area. However, it is likely that occupational exposures are more intense although less persistent than neighborhood exposures.

Hammond (*444*), in a prospective study of lung cancer epidemiology, reports on the role of smoking, place of residence, and presence or absence of occupational exposure. The population was enrolled by volunteer workers of the American Cancer Society beginning in October 1959 and followed for 6 years. Data were obtained in 1121 counties in 25 states and included 16 of the 20 largest cities; 2063 of the subjects died of lung cancer. Compared to nonsmokers, the mortality ratio for smokers increased from 4.62 for men who smoked 1 to 9 cigarettes a day up to 18.77 for men who smoked 40 or more cigarettes a day. The analysis of urban residence and occupation was limited to men who, at the time of enrollment, said they had lived in their present neighborhood for at least 10 years. Adjustment for age and smoking habits was based on 5-year age groups and six classes of smoking—those who never smoked regularly and five categories of smokers by type and amount smoked. Within groups by place of residence, the experience was further subdivided according to whether the respondents said they "were or ever had been occupationally exposed to dust, fumes, vapors, gases, or x-rays." These statements cover a wide range of exposures and a variety of durations and intensities. Results are shown in Table XXIII.

Disregarding place of residence, the age–smoking adjusted mortality ratio for men with "occupational exposure" was 1.09 compared to 0.96 for men without occupational exposure. In large metropolitan areas, the occupational excess was greater than in smaller and nonmetropolitan areas. For men not occupationally exposed, the high mortality ratio (1.06) was for men living in cities in large metropolitan areas, and those living in towns and rural parts of smaller metropolitan areas (1.05). If air pollution is assumed to increase with size of city, then these data, according to Hammond, "give little or no support to the hypothesis that urban air pollution has an important effect upon lung cancer death rates." Data for Los Angeles, Riverside, and Orange Counties, California, with their high-level exposures to oxidant and carbon monoxide, show high lung cancer rates for men occupationally exposed. For those with no occupational exposure, the mortality ratio (0.96) for men in Los Angeles is equal to that for the whole unexposed population.

These data suggest that once the contribution of smoking is removed a large fraction of the urban excess in lung cancer is related to occupational exposure; among the men not occupationally exposed, there is nearly as much excess in towns (2500–50,000) as in great cities. This finding resembles those of Haenszel, who found when smoking was controlled for, that the highest lung cancer rates were among residents of such towns.

In the United States, coke oven workers in the steel industry, also pre-

Table XXIII Observed and Expected Number of Lung Cancer Deaths by Place of Residence and by Occupational Exposure to Dust, Fumes, Gases, or X-Rays[a] (*444*)

Place of residence[b]	Occupationally exposed: Observed number	Occupationally exposed: Expected number	Occupationally exposed: Ratio	Not occupationally exposed: Observed number	Not occupationally exposed: Expected number	Not occupationally exposed: Ratio
Total, all subjects	576	530.5	1.09	934	979.7	0.96
Metropolitan area (pop. 1,000,000+)	165	134.1	1.23	281	285.7	0.98
City	92	69.1	1.33	168	158.3	1.06
Rural or town	73	65.0	1.12	113	127.4	0.89
Metropolitan area (pop. <1,000,000)	166	145.4	1.14	271	280.5	0.97
City	92	83.3	1.10	170	184.0	0.92
Rural or town	74	62.1	1.19	101	96.5	1.05
Nonmetropolitan area	245	251.0	0.98	382	413.5	0.92
Town	102	104.9	0.97	200	199.1	1.00
Rural	143	146.1	0.98	182	214.4	0.85
Los Angeles, Riverside, and Orange Counties, California	30	21.9	1.37	38	39.6	0.96
Farmers	63	77.6	0.81	71	92.9	0.76
8 Cities—high particulates (130–180 μg/m³)	45	32.9	1.37	66	73.9	0.89
11 Cities—moderate particulates (100–129 μg/m³)	21	18.8	1.12	39	49.5	0.79
14 Cities:—low particulates (35–99 μg/m³)	48	37.4	1.28	110	100.1	1.10
9 Cities—high benzene-soluble particulates (8.5–15.0 μg/m³)	28	21.0	1.33	52	51.5	1.01
10 Cities—moderate benzene-soluble particulates (6.5–7.9 μg/m³)	44	32.7	1.35	65	75.1	0.87
12 Cities—low benzene-soluble particulates (3.4–6.3 μg/m³)	33	29.2	1.13	76	81.8	0.93

[a] Adjusted for age and smoking habits; confined to men who had lived in same neighborhood for last 10+ years.

[b] A "metropolitan area" is defined as a county or group of contiguous counties with at least one city or pair of cities with 50,000 or more inhabitants, according to the 1960 census. A "town" means a place with 2500–49,999 people, and "rural" refers to people living in a place of less than 2500 people or in the country.

sumably exposed to high levels of benzo[a]pyrene, have in certain groups a threefold excess of lung cancer (*45, 406*). With such massive exposures (hundreds to thousands of times the levels to which other persons are exposed), the excess mortality seems small if benzo[a]pyrene is a potent respiratory carcinogen in man. In Kenya, where indoor smoke contains about ten times the benzo[a]pyrene encountered in heavily polluted air, there is a reported excess of nasopharyngeal cancer, but not of lung cancer (*445*).

One of the best criteria of malignant changes in the lung has been the appearance of the cells lining the respiratory tract. Changes studied in autopsied persons have correlated so well with epidemiological studies of lung cancer prevalence in smokers of varying types, and with results of sequential observation of animals exposed to carcinogens, that these observations may be interpreted as evidence of a mechanism that leads to human lung cancer. A well-controlled examination for these cells has been carried out by Auerbach and his colleagues (*446–448*). From a group of 1007 men and 515 women from whom multiple histological slides had been prepared, pairs were matched by age, cause of death, occupation, residence and smoking habits, and comparisons of the frequency of histological changes in matched pairs were carried out. Table XXIV gives the comparison of matched women smokers and nonsmokers of both rural and urban residence. Compared with the striking differences between women smokers and nonsmokers, the differences between urban and rural nonsmoking women are small. Women were chosen for this comparison because of the difficulty of matching, by occupation, an adequate number of nonsmoking men.

The United States National Academy of Sciences report's conclusion concerning the role of benzo[a]pyrene relies heavily on two regression analyses. One was that of Carnow and Meier discussed above. The other regression analyzes male lung cancer deaths in nineteen countries, along with average cigarette consumption per person per year. The countries are not listed, but it is based on the original analyses by Stocks of these nineteen countries (*439*).

While it is reasonable to assume that variations may be small in current cigarette consumption of comparable urbanized populations, in recently industrialized and urbanized countries there is likely to be less long-term cigarette smoking in relation to current smoking. Hence, average current cigarette consumption in a country may not have the same relevance in newly urbanized as in older urban areas. Solid fuel consumption may reflect the degree of industrialization, and to some extent, urbanization. The regression analysis, according to the National Academy of Sciences report, leads to "approximately a doubling in the lung cancer rate corre-

Table XXIV Changes in Bronchial Epithelium in Matched Pairs of Female Cigarette Smokers and Nonsmokers and in Matched Pairs of Female Nonsmokers, Urban and Rural (*446, 448*)

			Female nonsmokers	
Parameter	*Smokers*	*Nonsmokers*	*Urban*	*Rural*
Number of subjects	72	72	26	26
Number of sections with epithelium	3326	3670	1310	1284
Sections with one or more epithelial lesions (%)	91.1	24.3	26.3	18.8
Sections with three or more cell rows with cilia present (%)	85.5	11.1	14.0	9.5
Sections with cilia absent (%)	17.5	14.4	14.0	10.4
Sections with atypical cells (%)	79.7	0.7	0.3	0.8
Sections with atypical cells present with cilia absent (%)	14.6	0.1	—[a]	0.1
Sections with entirely atypical cells with cilia absent[b] (%)	2.9	0	0	0
Sections with hyperplasia and goblet cells in glands (%)	67.9	13.7	14.4	10.4
Sections with ulceration (%)	9.7	19.5	16.3	15.4

[a] Less than 0.05.
[b] Carcinoma.

sponding to an increase in smoking of a pack (20 cigarettes) per day"; this compares with a five- to twelvefold excess of lung cancer in current cigarette smokers compared to nonsmokers in seven prospective studies (*441, 449*). The regression computation does not, therefore, adequately reflect the relative contribution of long-term smoking to lung cancer, but rather the relative national differences in current cigarette smoking, which are likely to be small for the countries studied.

After listing a number of factors which fail to support the hypothesis of a causal association of benzo[*a*]pyrene and lung cancer, the National Academy of Sciences report (*433*) concludes that increased urban pollution with this material has the effect of increasing lung cancer death rates. The report asserts that reducing urban levels of benzo[*a*] pyrene, e.g., from 6 ng/m^3 o 2 ng/m^3 will reduce lung cancer death rates by 20%. This is followed by, "These data, however, are not to be interpreted as indicating that benzo[*a*]pyrene is the causative agent for lung tumors." In fact, such a decrease in benzo[*a*]pyrene has occurred (from 6.6 ng/m^3 in 1959 to 2.5 ng/m^3 in 1967 for United States urban sites in the January–March quarter). If this decrease is to lead to reduction of lung cancer death rates, it will probably do so after a latent period. Based on the decrease in lung cancer in British physicians (*450*) whose smoking has decreased, a latent period of 2–5 years will be needed. We should also see the greatest decrease in the communities that previously had the highest pollution levels. Thus, the hypothesis put forward by the National Academy of Sciences report can be tested.

4. Studies of Migrants

Changed rates of lung cancer in migrants have been used to estimate a possible effect of air pollution on lung cancer rates. Migrants from the United Kingdom to New Zealand (*451*) and to South Africa (*452*) have higher lung cancer rates than the native born, and this is especially true for those who migrated after 30 years of age. Similar data for United Kingdom emigrants to the United States and to the Channel Islands have also been reported (*453*, *454*). In dealing with the extensive migration data, the National Academy of Sciences report starts from the assumption, "if such migrants can be considered as random or representative samples of the populations of the home countries, then differences in death from those in the home countries can be ascribed to changes in environmental conditions." There is a good reason to question whether immigrants from an area are a random or representative group with respect to environmental conditions in the home countries; neither are they likely to have representative exposures in the place to which they migrate. Should they migrate to communities with less favorable housing or working conditions than the native born, immigrants may have multiple unfavorable environmental exposures in their new environments. For migrants to urban areas, this seems likely.

Mancuso and Coulter (*417*), studying immigrants from Italy and Great Britain to Ohio, show that while native-born Americans have lung cancer mortalities (for 25- to 64-year-old males) intermediate between mortality rates in Italy and the United Kingdom, immigrants from these countries into Ohio tend to approach the mortality rates of native born. For the British born, this means lower rates, for the Italian born, higher rates. Mancuso and Sterling (*454a*) have shown that black males who migrate into Ohio have much higher rates than comparable groups born in the state or lifetime residents in the states from which migrants come. The National Academy of Sciences report (*433*) says, "Lung cancer death rates of migrants are intermediate between those of native U.S. residents and persons in the home countries." However, we note that in the Reid *et al.* study (*455*) (Table XXV), Norwegian woman migrants to the United States have higher mortality than native-born United States women. This may reflect the likelihood that Norwegian immigrant women

Table XXV Age-Adjusted Death Rates for Lung Cancer[a] for Persons Born in Great Britain, Norway, and the United States, along with Rates for Migrants (*455*)

Residency	*Males*	*Females*
Great Britain residents	151.2	19.3
Great Britain-born United States residents	93.7	11.5
Native United States residents	72.2	9.8
Norway-born United States residents	47.5	10.7
Norway residents	30.5	5.6

[a] I.C.D. 162–163.

were likely to have an unusually unfavorable environmental exposure. It is difficult to believe that an excess, if real, could be associated with exceptional smoking or community air pollution exposures.

This exception to the notion that migrants have intermediate lung cancer experience between that of their origin and destination, taken with Haenszel's finding that rural migrants to urban areas have higher lung cancer rates than lifetime urban residents, indicates that migration may have more complex effects than is indicated by the National Academy of Science report.

Eastcott's studies (*451*) of migrants from the United Kingdom to New Zealand show that those who migrated before age 30 had 35% higher risk of lung cancer than native New Zealanders compared to 75% higher risk if migration had occurred after age 30.

Such an effect (not adjusted for smoking) could as well support the hypothesis of a contribution by a less favorable occupational, residential, and socioeconomic status of those migrating in later years of life as opposed to younger migrants, as it could a presumptive longer exposure to carcinogenic agents in the United Kingdom. In any event, a potent carcinogenic effect of environment in early life is not supported by these data. Possibly, therefore, the greater susceptibility of infant mice (*409*) is not applicable to man (see *409a*).

5. Principal Arguments for Air Pollution as a Causal Factor in Excess Urban Lung Cancer

a. There are potent carcinogenic agents in polluted atmospheres.

b. The urban excess of lung cancer can be associated with urban pollution.

c. Workmen occupationally exposed to benzo[*a*]pyrene, to asbestos, arsenic, and to other materials present as pollutants show excess lung cancer.

However, to behave as if urban and migration factors in lung cancer mortality are due solely to air pollution could lead to neglecting the possibility that domestic agents and occupational exposures play an important role. This would not be advisable, since these might readily be controlled, once attention is focused on them and their role is better defined. These conclusions apply to general urban air pollution and not necessarily to point source exposures in the vicinity of industrial plants.

E. Air Pollution and Cardiovascular Disease

There are three possible mechanisms by which air pollution may affect the cardiovascular system on a long term basis. The first and most important, associated with the role of carbon monoxide, was discussed earlier in this chapter, as was the effect of cadmium on cardiovascular disease, in particular on cardiovascular renal disease. The third effect depends on the interaction of the respiratory effects of pollution and the cardiovascular system. If there is respiratory irritation with coughing, the resulting internal pulmonary pressure increases. Chronic respiratory disease, particularly where extensive fibrosis or loss of lung tissue occurs, tends to be associated with cor pulmonale, or heart disease secondary to lung disease. Cor pulmonale occurs with substantial frequency in Great Britain and has been reported by Sinnett and Whyte as a most common problem in the Highland populations of New Guinea (*456*). These individuals showed a decrease in lung function and frequent attacks of pneumonia. Of five persons in the survey with heart failure, in four illness was due to underlying lung disease. The authors say "the people spend up to 12 hours per day inside smoke filled houses, and 70% of the adult males and 20% of the females smoke home-grown tobacco."

Among populations with an increased frequency of chronic respiratory conditions it is likely that secondary heart disease will be found. In the populations affected by the acute air pollution episodes, a number of deaths occurred among people with pre-existing heart disease. Whether this is due to any direct effect is hard to determine.

F. Air Pollution and Nervous System Reactions

1. Physiological Principles

The direct effects of air pollution on central nervous system functions have been studied extensively by Russian physicians utilizing Pavlovian experimental procedures, pioneered by Ryazanov (*457*) and reviewed by Izmerov (*458*). Many of these studies use the "method of optical chronaxy determination," in which a weak electrical current is applied to the eyeball, leading to a sensation of a flash of light. For a given subject, there is a minimum intensity of electrical stimulation below which this sensation does not occur, no matter how long the stimulus continues. At intensity twice that of the minimum that just produces stimulation, the length of time to produce sensation is measured. This length of time is called the "optical chronaxy." After exposure to a pollutant, there is a change in the amount of time needed to produce the sensation, i.e., a change in chronaxy, which is taken as a measure of the effect of the pollutant on the central nervous system.

Other studies have used the minimal detectable light intensity and odor threshold techniques with exposure to butyl acetate (Fig. 26).

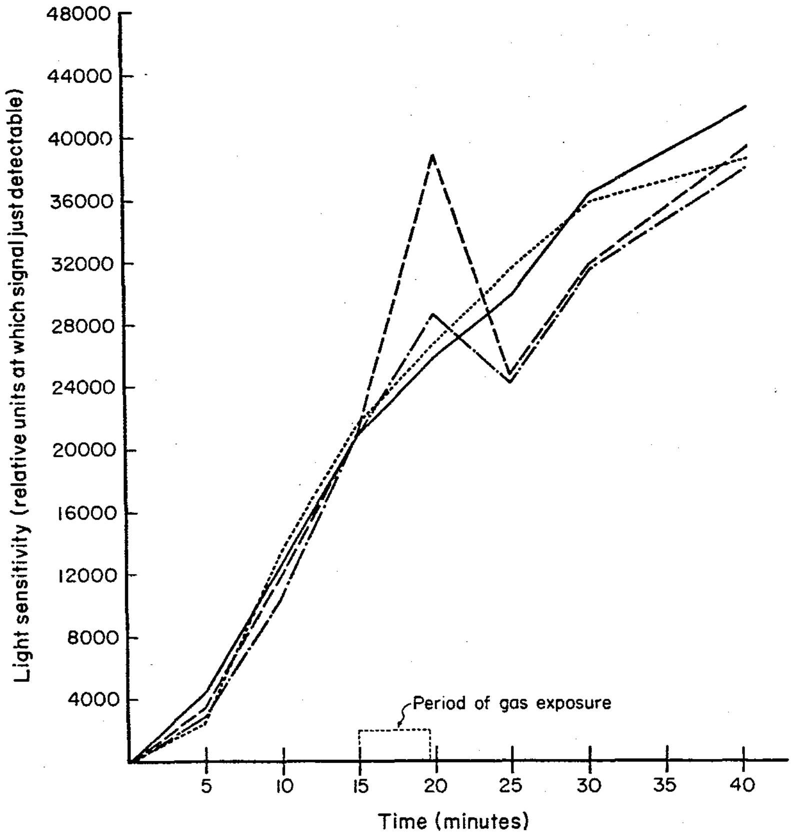

Figure 26. Changes in light sensitivity of the eye on inhalation of various concentrations of butyl acetate (*457*): (——) pure air; (– – –) 0.73 mg/m³; (–·–·–) 0.32 mg/m³; (····) 0.18 mg/m³. Note that the earliest effect is an increase in sensitivity (improvement in function) followed by impairment.

Ryazanov reported an increase followed by a decrease in minimum detectable light intensity. In this case, an exposure not detectable by odor produced first an increase in the ability to detect weak light stimuli; at a greater dose, a decrease in detection ability occurred. This biphasic effect can also occur with increasing duration of exposure. Other methods have used the alteration of electroencephalogram or brain waves. Such methods have been studied in the United States by Xinteras (*459*).

In addition to these reflexes, Nadel and Widdicombe (*109, 110, 112*), as mentioned earlier, have emphasized the importance of autonomic reflexes in many of the reactions of the respiratory system to irritants and particulate matter. Since the nervous system connections to the locations in the brain where odor is perceived are very rich, this leads to the assumption that odor must also cause reflex effects. The role of lead pollution in producing impairment of peripheral nerve conduction has been reported by Landrigan *et al.* (*460*). At this time, it is reasonable to state that central nervous system and autonomic nervous system reflexes are produced by air pollutants, but their significance has not been clearly defined. This area will benefit from further exploration.

2. Performance and Pollutant Exposures

The laboratory experiments of Beard and Wertheim (*205*) and Beard and Grandstaff (*209*) have raised the question as to whether carbon monoxide at commonly occuring exposure levels interferes with accurate time interval estimation. It has not been shown that such exposures interfere with performance of complex and unfamiliar tasks. Studies on the effect of carbon monoxide exposure on motor vehicle accidents has not produced decisive results; Wright (*207*) and McFarland (*208*), for example, present conflicting results.

Some studies have been done on school performance in relation to ozone exposure, but these, too, have failed to yield decisive results. In general, it is accepted that too much sensory irritation or too much discomfort will have an unfavorable effect on the learning process, but so far this has not been thoroughly studied. There is suggestive evidence of an effect of carbon monoxide on the performance of swimmers who are racing (*460*), and of oxidant on high school track meet performance (*151*), but beyond this, there are very few studies on these problems (*461*). It is reasonable to believe that if there were decisive evidence of community air pollution effects on performance in driving of motor vehicles or in learning in school, such data would be of great consequence for air pollution control.

3. Sensory Effects of Pollutants

a. EVALUATION OF ODORS. i. *Introduction* (see also Section IV,A and E). Exposure to odorous air pollutants constitutes an important problem in environmental health, particularly considering the number of people who may be exposed. A single point source such as a pulp mill may well give rise to serious odor problems miles away. In connection with a study around a Swedish pulp mill, it was found that 30–40% of the people interviewed reported "annoyance," even up to more than 10 miles (16 km) from the pulp mill (*462*).

If regulatory agencies are to take action in connection with odor exposure, information on relationships between the dose to which people are exposed and the annoyance reactions displayed must often be the point of departure. It is thus necessary to have methods that adequately describe the dosage as well as the response and to know the conditions under which the particular dose–response relationship is valid. Questions relating to odors in the ambient air have been discussed in detail at international symposia at Stockholm, Sweden, where methods for evaluating and measuring odorous air pollutants at the source and in the ambient air were discussed (*463*), and at Cambridge, Massachusetts, where evaluation of community air odor exposure was dealt with (*464*).

ii. *Definitions.* At the Stockholm meeting the following definitions were among those decided upon:

odor—a product of the activation of the sense of smell; an olfactory experience

odorant—any chemical compound that can stimulate the olfactory sense

iii. *Dose.* Since odor comes from a large number of substances with different chemical structures, it would be desirable if the estimation of odor could be based on certain physicochemical characteristics common to all odorous substances, for example, in analogy with measurement of sound level associations. Theoretically, it should be possible to translate chemical and physical data into psychophysical descriptions of odor intensity and quality, provided the odor intensity and quality of the individual substances as well as different mixtures of these substances are known. It is not possible to do this at present, although laboratory studies on the principles involved continue (*465–467a*). A deterrent to the use of physicochemical methods for this purpose is the very low concentrations of odorants. It is meaningless to estimate the average concentration of an odorous substance over a fairly long time period, since the nose responds not to an average odor, but to peaks that exceed the odor detection limit. Therefore, for instruments to be useful, they must have very short time period peaks, i.e., seconds. For most odorous substances, such instruments are not available. On the other hand, progress has been made on the analysis of certain sulfurous compounds (*468*) at very low concentrations.

The difficulties that may be encountered when comparing analytical data with sensory evaluation of odor can be illustrated by an example from the study at Morrum and Mönsteras pulp mills in Sweden (*469*) (Fig. 27). Odor threshold measurements (actually dilutions necessary to reach odor threshold) were carried out in parallel with chemical analysis for hydrogen sulfide, methylmercaptan, dimethyl monosulfide and dimethyl disulfide. The study aimed at seeing whether it was possible to find a single substance or a combination of substances that could be used as an index of odor. There was a correlation between the concentration of hydrogen sulfide and odor threshold. At both mills, a high concentration of hydrogen sulfide gave rise to a high odor threshold. But it is

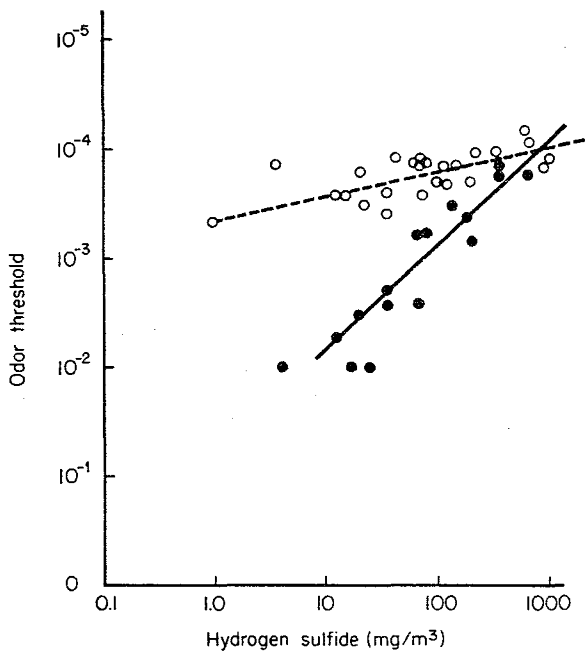

Figure 27. Correlation between hydrogen sulfide and odor threshold (*469*) near two pulp mills: ○ = Morrum ($r = 0.74$); ● = Mönsteras ($r = 0.96$). Odor threshold of 10^{-3} means that the exposure level was such that if the air sample were diluted one thousand times it would approximate the odor threshold.

obvious from the figure that the two mills differed with regard to low concentrations of hydrogen sulfide. In one, the odor threshold decreased sharply with a lowered hydrogen sulfide concentration, while in the other one, the odor threshold decreased rather insignificantly despite a decrease in hydrogen sulfide concentration from 1000 mg/m^3 to about 1 mg/m^3. Obviously, some substance other than hydrogen sulfide was responsible for the high odor thresholds at low concentrations of hydrogen sulfide.

iv. *Sensory methods.* Sensory methods, whether used for ambient air or stack gases, must include standardized experimental procedures guaranteeing an acceptable reproducibility and valid results. When measuring odors in the ambient air, an additional requirement is often a mobile odor laboratory. A large number of exposure and dosing devices, called olfactometers, using the principle of dilution of odorous gases with pure air or nonodorous gases have been adapted for both laboratory and field studies. One such is the odor chamber, in which the subject is entirely exposed to the odor to be studied. Many of the conventional olfactometers and odor chambers are not satisfactory for field work. Olfactometers should permit known and stable exposure concentration, rapid changes in concentration, and fairly natural respiratory conditions. Most investigators have chosen the odor hood as an alternative to the chamber. With the hood, only the nose, face, or head are exposed (*470–472*). By using odor hoods in air conditioned buses or trucks, it has been possible to construct high-quality mobile odor laboratories (*237; 471–476*).

A most important odor dimension is its acceptability. It is possible to study acceptability on the laboratory scale by applying direct scaling methods (*477*). Lindvall and Svensson (*478*) carried out studies in which the unpleasantness of hydrogen sulfide was compared with that of five different combustion gases. Acceptability has also been dealt with in United States field studies using a mobile laboratory for exposing test subjects to diesel exhaust gases (*479–481*).

There is no simple relationship between perception of threshold and suprathreshold intensity. Direct psychophysical scaling methods have been proposed (*482*). By these, sensation has been shown to grow as a function of stimulus intensity raised to a power. The evidence obtained in scaling intensity of many physical agents, including odors, supports the descriptive value of the power function

$$R = K(S - S_0)^n \tag{3}$$

when R is perceived intensity, S is physical intensity, S_0 is an estimate of threshold, K is a constant that depends on the units of measurement employed, and n is an exponent that depends on the sense modality. When studying intensity of odors, modern psychological scaling methods should be used (*472, 476, 483*).

Detection levels are of great importance; people may experience an odor as unpleasant at a low level of detection if it is frequent and prolonged. Particularly if the source of the odor is a point source, any change in odor intensity will influence the frequency at which the odor is perceived, i.e., the frequency with which the detection limit (absolute threshold) is exceeded in a particular area. Signal detection methodology (*484*) has been treated extensively by Lindvall (*472*), in the report from the Third Karolinska Institute Symposium on Environmental Health (*463*), and by Berglund *et al.* (*484a*). In contrast to classic threshold techniques, signal detection methodology allows for the estimation of not only the number of false positives but also the false negatives. Different modifications of the basic signal detection methodology have been used (*475, 484, 485, 486*).

b. Laboratory and Field Studies. The most extensive testing of single odorants has been done by Katz and Talbert (*487*) and more recently by Leonardos *et al.* (*113*). Psychophysical functions of perceived intensity for twenty-eight odorants have been presented by Berglund *et al.* (*488*). The exponent in the function is less than 1.0 (0.06–0.34), indicating that perceived magnitude of odor tends to be a negatively accelerated function of stimulus intensity. A model for summation of perceived intensities in odor mixtures has been suggested (*467*).

A mobile laboratory is usually required for field studies. Gas can be passed directly from the ambient air or other sources (e.g., stack gases) to the mobile laboratory. Another way is to collect samples in plastic bags, e.g., laminated Mylar (Dupont) or Hostaphen (Hoechst) (registered trademarks). Bag samples from some pulp mill effluents show only minor losses in odor intensity after a period of about 2 hours (*472*).

Sensory analysis can be used to study the relative importance of odor-generating processes. Taking such data into consideration together with the total volume of gases gives the factory and regulatory agencies valuable information as to where countermeasures should be focused (*469, 488*).

Sensory analysis can be used to study effects of countermeasures. In Table XXVI, the effects of black liquor oxidation and a chlorine scrubber on gases from a Swedish pulp mill are shown. It can be seen that black liquor oxidation brings about a reduction of odor strength (absolute odor threshold) by about ten times and chlorination a further decrease of two hundred times (since the data are based on logarithms, these are the antilogs of 1.1 and 2.3).

Table XXVI Effect of Control Measures in a Sulfate Cellulose Plant *(472)*

Source	*Odor threshold*[a]
Gas entering the oxidation tower	8.9
Gas emerging from the oxidation tower	7.8
Gas emerging from the chlorine scrubber	5.5

[a] The absolute odor thresholds are based upon group data and expressed as log dilution factors.

Several studies have been carried out in the United States on diesel exhaust gases. Emphasis has been upon the evaluation of odor intensity and quality when diluted to the suprathreshold levels typically encountered in urban areas *(474, 489–491)*. In 1969 and 1970, over 5100 individuals in five cities (three or four sites per city) were exposed to diesel exhaust gases in a mobile laboratory and answered a questionnaire indicating to what extent the odor was pleasant, neutral, unpleasant, very unpleasant, or unbearable *(481)*. Comparison was made with the United States Public Health Service odor quality–intensity kit. Studies have shown that the odor thresholds for limited samples of Swedish gasoline-powered cars did not differ considerably from those for diesels. Odor thresholds for the exhaust gases varied between dilutions of 10^3 and 10^4. Unfortunately, no studies on odor quality were performed. To provide an environment that will be free from odor from exhaust gases would be difficult to achieve in areas with heavy traffic *(474a)*. In one Swedish study *(475)*, odor levels in the ambient air were measured by signal detection methodology in a main street during rush hours. The index of detectability was found to vary in an expected fashion compatible with the traffic load.

c. Response to Odor Exposure. Possible responses involve disease and annoyance reactions. In addition, there is some evidence from laboratory studies in humans, as well as in animals, that exposure to odors may elicit transitory nervous system effects *(492, 493)*. No evidence has yet shown that odors per se are related to disease states *(464)*. However, some suggestive data keep this question open *(494–500)*. What should be focused on particularly here is to what extent possible adverse effects are due to odors per se, to some specific odorous substance, or to some substances combined with the odorous substance.

i. *Annoyance reactions from odor* (see also Section VI E,4). The presence of an odorous substance in the air may or may not be associated with awareness or reactions. If the person is aware of the odor, he may or may not have a negative reaction. Negative reactions are generally considered annoyance reactions. In addition, it is possible that there are other reactions, such as irritation or reflex responses. Of great practical importance has been the determination of annoyance reactions by standardized questionnaires and survey procedures; these have been found to be the most valid and dependable ways of estimating the health importance of odor exposure.

Several interview surveys covering people exposed to odor from pulp mills, manure, oil refineries, and motor vehicle exhausts (*462, 474, 476, 481*) have shown that odor can give rise to pronounced annoyance reactions. For city dwellers who complain strongly about the air pollution situation, the exposure to odors is one major cause of such complaints, but exposure to other agents is certainly also important.

Some quantitative data can be given on prevalence of annoyance from odor. Studies near Swedish pulp mills have shown annoyance reactions in 12% to 62% of the population, depending on distance from the mill (*462, 469*). Similar frequencies have been observed in Eureka, California, and Clarkston, Washington (*498; 501*). Studies around a Swedish oil refinery show that up to about 40% of the population in the vicinity may report annoyance reactions.

During 1969, the Japanese government received 40,000 petitions concerning a variety of environmental problems. Of these, 8000 were on odor. For comparison, 18,000 petition complaints were received for the same time interval about noise and vibration (*502*). Spontaneous complaints are not always accurate indices of exposure. This is further discussed below.

ii. *Dose–response relationships.* A complete dose–response curve has not been shown for any odor exposure. A few points on the curve for certain odors can be derived from the previously noted interview surveys in Sweden, where about 12–62% of the population around a pulp mill [depending upon the distance from the plant, within a radius of about 10–15 miles (16–24 km)] reported annoyance reactions. The odor in the main stack was believed to correspond to a dilution factor of about 10^5 times above threshold. In a study of pulp mill odor problems in Eureka, California, it was possible to find a dose–response relationship for different areas in that annoyance reactions were more pronounced in areas with presumptively higher exposure (*498*). To some extent, the United States studies previously noted on diesel exhaust gases (*474, 481*) resulted in a type of dose–response curve that can be used for estimating what effects various levels of odor control would have on relative annoyance. The only caveat is that the ratings "pleasant" to "unbearable" were made in laboratory experiments, rather than in a real-life situation with continuous exposure.

No doubt the attitude of the public toward the need for protection against adverse effects from the environment will change considerably within the coming years. It may well be that what is acceptable today will be considered unacceptable within the not too distant future. Present dose–response relations will then no longer be valid. This is one reason that efforts should be focused on the dose and on simple psychophysical relations. The ability of the human nose to detect and to make perceptual evaluations in controlled laboratory experiments should not change. If information on the dose is available, it will always be possible to establish standards for odors based on known intensities and qualities.

4. Nonspecific Annoyance Reactions

Increased attention is paid nowadays not only to proven or suspected health hazards, but also to reactions only potentially related to disease states of uncertain health significance. Such effects include annoyance reactions resulting from sensory perception of pollutants (*503*). An international symposium in Stockholm (*503*) adopted the following definition of annoyance: "A feeling of displeasure associated with any agent or condition believed to affect adversely an individual or group." References in relation to annoyance from noise can be found in several reports (*503–509*). Annoyance from air pollution can arise after exposure to odors, particulates, and irritants, or because of impairment of visibility. Often it is not possible to distinguish which air pollutants have contributed most to the annoyance reactions found.

Odors are known to give rise to annoyance reactions, well known in the case of odors from pulp mills, fertilizer factories, oil refineries, and motor vehicles, as noted in the previous section. Irritants may cause severe annoyance. Sulfur dioxide constitutes an important source of irritation to the respiratory tract. In a Los Angeles, California, study, 75% of the population was bothered by air pollution, mainly because of eye and nasal irritation (*83*).

Although aerometric techniques and monitoring are constantly being improved and expanded, it is not necessarily true that a given objectively measured air pollution level will bring about a particular human annoyance reaction. This response depends upon sensory and sociopsychological variables. Some of these depend on age, sex, social class, length of residence, group ties, education, occupation, and economic relation to the possible source of annoyance. Likewise, these variables will also determine whether a feeling of annoyance will advance to an action. Annoyance reactions are a relatively new field of study. As brought out at the Stockholm symposium (*503*), the methods of measurement, especially for the response, are neither fully developed nor validated.

To date, socioepidemiological surveys have provided most quantitative data. This is because the only means by which we can get information on subjective symptoms and experience of annoyance is through information supplied by the individual himself. The methods used involve standardized questioning techniques that elicit responses expressed in terms relevant to groups. The criteria are the same for sampling the population to be examined as in other epidemiological studies. Since the objective of many surveys is to test differences among subgroups, defined by age, sex, and exposure, statistical design often involves stratification procedures. In investigating objective data, e.g., concentrations of substances in blood or urine, the method of measurement is almost invariably described. This is also necessary for measurements of subjective symptoms in epidemiological studies. Among possible sources of error in such studies, biases due to interviewer effect, respondent effect, and instrument effect are the most important.

The "interviewer effect" means that the interviewer does not register the response correctly. The reason may be anticipatory due to preconception of the subject's answer. If the answer is not entirely clear, the interviewer may probe or interpret it in accordance with his own preconception. The training of interviewers is important, and two handbooks on this subject are recommended—Cannel and Kahn (*510*) and "Manual for Interviewers" (*511*). A way of reducing or controlling the interviewer effect is to use several interviewers and to assign the subjects at random among them. This method was used in an epidemiological interview study of about 700 people living around a shale oil factory in Sweden. The prevalence of asthma and/or bronchitis as found by fourteen interviewers varied between 10% and 43% (*512, 513*). Such a result could be very misleading if the interviewers had been allotted to certain areas or certain strata of the population.

The respondent effect is due to differences in the respondents' frames of reference or to the conscious or unconscious desire of the respondent to bring about changes in the exposure. In the same survey around a shale oil plant at one time during the studies, part of the population interviewed were informed of the purpose of the investigation, while the rest were not (*514, 514a*). Table XXVII shows how the prevalence of certain symptoms seemed to differ between the two groups as a result. One way to avoid the respondent effect is to use an introduction as neutral and correct as possible. The subsequent questions should be as explicit as possible. Psycho-

Table XXVII Prevalence of Individuals in a Survey near a Swedish Shale Oil Plant with Certain Symptoms among Subjects "Not Informed" and "Informed" about the Purposes of the Survey *(513, 514)*

	Prevalence (%)	
Symptoms	*Not informed*	*Informed*
Smell noticed	52	69
Distressed by smell	13	20
Asthma and/or bronchitis	11	20

logical scaling methods have also been suggested for studies of the response criteria variations in different populations (*515*).

The instrument effect is related to the type of questionnaire used and to the wording of the actual questions. Of paramount importance is the use of proper question design (*516*). The questionnaire has to be simple to yield a satisfactory response rate, yet studies have shown that under certain circumstances, mail questionnaires may be a good alternative to personal interviews (*517, 518*).

The use of spontaneous complaints has been relied upon by governmental agencies in several countries. Most data show that the use of spontaneous complaints is a poor method, because so many factors influence whether or not a person will complain. The occurrence of a high frequency of spontaneous complaints may, of course, show that a problem exists, but it is not possible to draw from them any firm conclusions about the magnitude of the problem. It has been shown, for example, in American, British, and Swedish surveys that less than 10% of the population report any form of complaint by writing letters, telephoning, or making personal visits to officials (*505, 506, 519*). On the other hand, studies around a Swedish pulp mill have shown that of those who signed a petition against the pulp mill, only about 50% were annoyed by its odor.

G. Hematological Reactions

The effect of carbon monoxide in interfering with the oxygen transport function of the blood has been shown in cigarette smokers to affect the number of red blood cells produced. This is shown by a small increase in the average hematocrit (i.e., the fraction of red blood cells in the whole blood) and in the mass of circulating total red cell volume. However, there are no data indicating that such an effect occurs as a result of community air pollution. Similarly, there is no evidence of hematological effects from community exposure to levels of lead resulting from motor vehicle exhaust.

However, Kapalin (*520*) has summarized findings on blood changes in groups of children living in clean areas as opposed to those in areas polluted by smoke and sulfur dioxide (Fig. 28). Children from the polluted town of Litvinov in Czechoslovakia have statistically significant higher red cell counts and lower average cell volume than children from the clean town of Liebechov. There are no differences between the hematocrit and the total amount of hemoglobin levels among these communities. When the data are plotted on cumulative probability grids and studies are repeated over several years, these findings are striking in their persistence. When youngsters are taken to summer holiday camps, the blood picture generally returns to the clean air condition. Kapalin has also shown that there is a decrease in the rate of skeletal growth of children in the more polluted towns. It is difficult to estimate the amount and type of pollution that quantitatively produces such effects. This has led to some difficulty in interpreting these resuls, but there is no doubt as to their nature.

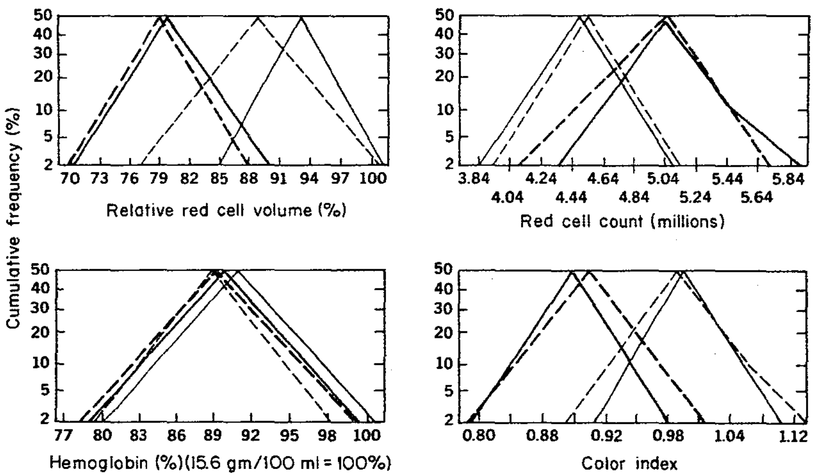

Figure 28. Distribution of values of red blood cell measurements for Czechoslovakian school children for 2 years—1962 (broken lines) and 1963 (solid lines)—in two towns—Litvinov (heavy lines), a town with pollution by smoke, and Libechov (light lines), a comparable town with clean air. While no differences occur with hemoglobin measurements, in the polluted town the cell volumes are smaller and the cell counts higher.

H. Chemical Mutation

A suggestive link between photochemical pollution and possible lethal mutations was reported by Lewis *et al.* (*521*) in male mice exposed to irradiated auto exhaust during the full length of the spermatogenic cycle. Mertz *et al.* (*129a*) have shown that ozone exposure of humans led to detectable increased frequency of mutations in lymphocytes. Increased neonatal mortality was noted in mice born in irradiated automotive exhaust atmospheres containing commonly measured levels of photochemical pollutants. Male mice exposed during the spermatogenic cycle to irradiated exhaust containing ambient concentrations of pollutants sired fewer and smaller litters per mating (reduced fertility), and had more neonatal deaths than among litters living in clean air, suggesting lethal mutations (*521*). The same system used by Lewis *et al.* was employed by Coffin and Blommer (*522*) in demonstrating that irradiated automobile exhaust increased the lethality of bacterial infection after 4 hours of exposure to a pollutant mixture containing 25 ppm carbon monoxide and 0.15 ppm oxidant.

Potential Chromosome Damage and Birth Defects

Chromosome damage and human birth defects could be suspected on the basis that chemicals known to be suspected of having these effects in animals are present in the environment. Male infertility and increased early infant mortality have been described in mice exposed to irradiated auto exhaust, suggesting damage to chromosomes by simulated photochemical pollution. Possible lethal mutations and partial sterility in male mice and high mortality of infant mice suggest areas for more active study in human populations. Human males exposed to mutagenic pollutants might be expected to father children with an increase of genetically conditioned abnormalities. Such phenomena have not been documented but should be looked for in populations exposed to both occupational and community pollution.

Bacterial mutation tests have been greatly improved recently (*523*) and can be used for rapid screening of compounds and mixtures. Such screening is also thought to be relevant to carcinogenic hazards.

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