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ABSTRACT

Presented in this preliminary report is one of seven assessments conducted by a special task force of Project Clean Air, the Human Health Effects Task Force. The reports summarize assessments of the state of knowledge on various air pollution problems, particularly in California, and make tentative recommendations as to what the University of California can do through Project Clean Air to alleviate those problems. In this report biomedical effects of air pollution are evaluated from epidemiological evidence and from experimental studies. Human hazards are emphasized to establish whether enough evidence exists to set air quality standards because of demonstrated human health effects. Section I provides a review of the findings and suggests basic and applied research that is needed. Section II enumerates: (1) the biomedical effects of fossil fuel combustion, (2) effects of individual pollutants, (3) effects of inherited metabolic patterns on air pollutant susceptibility, and (4) environmental carcenogens, mutagens, and teratogens. The last section offers tasks recommended for the Project in the nature of mission-oriented programs. Literature cited is listed. A related document from the Automobile Engine Development Task Force is ED 052 938. (BL)

PROJECT CLEAN AIR

TASK FORCE NO. 2

HUMAN HEALTH EFFECTS

TASK FORCE ASSESSMENT

Preliminary Report

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For

The Executive Director
of
Project Clean Air

U N I V E R S I T Y O F C A L I F O R N I A

June 30, 1970

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FOREWORD

This preliminary report was prepared by one of the seven special Task Forces of Project Clean Air. Prepared for the Executive Director of Project Clean Air, this and the related preliminary reports from the other six Task Forces summarize assessments of the state of knowledge on various air pollution problems, particularly in California, and make tentative recommendations as to what the University of California can do through Project Clean Air to alleviate those problems. The Task Forces and their air pollution assessment areas are as follows:

Task Force No. 1	Automobile Engine Development
Task Force No. 2	Human Health Effects
Task Force No. 3	Social Sciences
Task Force No. 4	Meteorology and Simulation Models
Task Force No. 5	Power, Industry, Agriculture, and Ecology
Task Force No. 6	Instrumentation Development
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ABSTRACT

Photochemical air pollution in California and in other regions produces demonstrable respiratory disability, reduced capacity for outside work or athletic exercise, decrease auditory and visual perception apparently contributing to auto accidents, higher frequency of chronic progressive lung disease and of lung cancer and low grade chronic progressive lead poisoning. These disabilities are greater in urban centers where the chief source of pollution is auto exhaust.

Major photochemical pollutants are carbon monoxide, unburned or incompletely burned hydrocarbons, oxides of nitrogen which react with the latter materials to form oxidants and lead. Particulates are present, are recognized as sites of atmospheric reactions, as carriers of carcinogenic hydrocarbons and as co-factors in production of lung cancer as well as of the irritant effects of polluted air. Stationary sources are important contributors to pollution at both the area-wide and local levels. Industrial and agricultural processes add not only to photochemical pollution related to automotive emissions but are also sources of odorous and toxic compounds. Materials known to produce, or suspected as causes, of cancer, chromosome damage and birth defects in animals are present in gasoline, in agricultural and industrial processes and in polluted air.

Automotive emission must be reduced in total quantity or must no longer contain oxides of nitrogen, carbon monoxide, incompletely burned hydrocarbons or lead. Other emissions containing these materials must also be abated. Additional materials which are odorous, toxic and potential causes of cancer and genetic damage should be eliminated as they are recognized.

Effects of contemporary air pollution on impairment of human behavior and performance in critical situations, such as highway driving, must be identified with the view to prevention of accidents. Studies on the effects of air pollution exposure should be extended or expanded with emphasis on recognition of the proportion of the population which has acquired or inherited increased susceptibility to air pollutants. Such persons should be observed with the view to offering preventive or therapeutic advice or care.

Mechanisms of action of photochemical pollution, of individual pollutants and of mixtures of pollutants must be studied as a guide to prevention or treatment of effects of contemporary exposure. These effects are known or suspected in causation or aggravation of lung and heart disease and lung cancer. The basic mechanisms of injury to organs, defense against injury or its consequences (as infection), of repair of injury and of adaptation to injury must be better understood in order to predict health hazards, recommend abatement of injurious materials and prevent or treat injury by efforts at the level of the community or the individual.

As innovations occur in transportation systems, fuels, power generation and in agricultural and industrial processing, new types of pollution may be expected. Research should be directed at advanced testing of potential health effects before these new systems are deployed.

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Section 1

INTRODUCTION AND SUMMARY

1.1 INTRODUCTION

Objects of this assessment document are (1) to evaluate biomedical effects of air pollution from epidemiologic evidence and from experimental studies of known single components and of crude natural or simulated pollutants. Human hazards in particular will be reviewed from the standpoint of epidemiologic and experimental studies under community and laboratory circumstances. The purpose of the emphasis on humans is to establish whether enough evidence exists to set air quality standards because of demonstrated human health effects; (2) To identify biologic responses in animals exposed to realistic pollutant concentrations in those cases in which human health effects may not have been demonstrated but are suspected; (3) To review animal models of disease production which may serve as sensitive detectors of biomedical hazard; (4) To review biologic studies which might reveal mechanisms of action of air pollutants, so as to develop protective measures which might be offered to special risk persons and the population at large. (5) To define future studies aimed at predicting hazards to health as control measures are taken, as present types of pollution increase, and as innovations occur in transportation systems, fuels, power generation, agricultural and industrial processing.

1.2 REVIEW OF FINDINGS

1.2.1 Respiratory Symptoms and Short-Term Disability

Human disability and disease is caused by community air pollution in California. Disability and potential aggravation of disease during periods of photochemical pollution has been reported in outdoor workers experiencing more severe respiratory symptoms, in track athletes demonstrating impaired performance, in asthmatic patients in Pasadena having increased attacks without correlated increase in pollen counts and in residents of Los Angeles and the San Francisco Bay Area having asthma or bronchitis and experiencing increased severity of respiratory symptoms. Low temperature and certain patterns of photochemical pollution promoted transmission of infection or development of respiratory disease under conditions of maximal saturation with auto emissions in Manhattan.

Confirming evidence in animals lies in reduced resistance to infection following inhalation of simulated crude photochemical pollution or of specific pollutants at levels present in community air. Additional experiemntal evidence in man and animals lies in the production of respiratory symptoms or reduced lung function during exposure to realistic or greater levels of specific pollutants.

1.2.2 Chronic Lung Disease and Cancer

Crippling lung disease and lung cancer are commoner in older persons living in polluted urban centers than in non-polluted urban centers or in rural zones. This indicates that slowly progressive fatal disease results from long standing exposure to pollution at levels which cause respiratory symptoms but do not cause persons to move to non-polluted areas. Smoking contributes to the frequency of these diseases but an "urban" factor can be distinguished from the effect of smoking.

Confirming evidence in animals reveals slow development of chronic lung diseases after long periods of exposure to levels of pollutants which occur in community air. Concentrated extracts of pollutants collected on air filters in urban centers, or fractions of these extracts, cause cancer in animals by testing methods used to determine the safety of materials for human consumption.

1.2.3 Relation of Air Pollution to Auto Accidents and Heart Disease

In very recent studies to be reported at this Conference, an association has been found between automobile accidents and periods of increased oxidant levels in Los Angeles. Case fatality rates in myocardial infarction is associated with high levels of carbon monoxide in Los Angeles air. Both types of pollutants influence visual and auditory perceptions and ability to perform work. The effects of both may be greater on hot days. Carbon monoxide speeds the occurrence of heart disease and atherosclerosis in animals.

1.2.4 The Presence and Hazards of Lead

All animals, including man, are exposed to lead in unnatural quantities. At all levels of human exposure, abnormalities are detectable in an important metabolic system, namely the enzymes required for formation of red blood cells and for permitting oxygen to be used by the body. The abnormalities observed in people exposed to urban air are not accompanied, as yet, by signs of illness, but the abnormalities are the same as those observed in lead poisoning. The community is experiencing chronic low grade exposure to lead which is a cumulative poison.

1.2.5 Persons with Special Susceptibility to Air Pollution

Certain groups of persons are genetically susceptible to the development of severe progressive lung disease, to asthma, to atherosclerosis and development of coronary artery disease, to the destruction of red blood cells and to failure of the protective action of white blood cells. These persons represent unknown proportions of the population of California. Such persons would be expected to experience aggravation of their genetically conditioned abnormality if they were exposed to carbon monoxide, lead or photochemical oxidants.

1.2.6 Potential Chromosome Damage and Birth Defects

Mutagenic and teratogenic effects are predicted for man on the basis that chemical known to have or suspected of having these effects in

animals are present in gasoline, in industrial and agricultural processes and in polluted air. Male infertility and increased early infant mortality have been described in mice exposed to irradiated auto exhaust suggesting damage to chromosomes.

1.2.7 Suspected Major Pollutants

Major components of photochemical pollution, primarily due to automotive emissions, are carbon monoxide, unburned or incompletely burned hydrocarbons, oxides of nitrogen which react with the latter materials to form oxidants, and lead. Particulates are present, are recognized as sites of atmospheric reactions, as carriers of carcinogenic hydrocarbons and as co-factors in production of lung cancer as well as of irritant effects of polluted air.

Stationary sources are important contributors to pollution at both area-wide and local levels. Industrial and agricultural processes add not only to photochemical pollution related to automotive emissions but are also sources of odorous and toxic compounds. Materials known to produce, or suspected as causes, of cancer, chromosome damage and birth defects in animals are present in gasoline, in agricultural and industrial processes and in polluted air.

1.3 BASIC AND APPLIED RESEARCH NEEDED

In some instances the data leading to identification of health effects in the foregoing section are new and are in the process of expansion and refinement. For example, the correlation of auto accidents with elevated oxidant levels has been recorded within the past few weeks. Such studies demonstrate the power of epidemiologic methods for recognition of community wide effects of air pollution. In other instances, observations of significance have been reported once and should be repeated and extended. For example, reduced fertility in male mice exposed to irradiated auto exhaust and production by these males of infants which die within a few days of birth has been observed twice but in only one laboratory. Continuation and expansion of current epidemiologic and laboratory research is needed as well as pursuit of new basic research directed toward better recognition, prevention or treatment of health hazards is therefore needed.

1.3.1 Effects of Pollutants on Human Performance

Impairment of human performance by contemporary air pollutants has been identified with carbon monoxide (laboratory investigation) and high ambient levels of oxidant (epidemiologic study of highway accidents). Further laboratory and epidemiologic study is needed to extend the data base, seek clearer cause and effect relationships and develop recommendations for prevention of adverse effects on performance.

1.3.2 Effects of Pollutants on the Respiratory System

Since respiratory symptoms and infections are increased during periods of increased photochemical pollution associated with "oxidant" and oxides of nitrogen, further research is needed to identify the proportion of the population experiencing respiratory effects or having

special susceptibility to adverse effects and to identify modes of action of such oxidizing atmospheres with the view to prevention or treatment of adverse effects.

1.3.3 Effects of Pollutants on Cardiovascular Disease

In Los Angeles an association of carbon monoxide pollution and case fatality rates in patients with myocardial infarction has been observed. Study of this association should be extended as a contribution to knowledge of cause or aggravation of coronary artery disease, as a means to recognize the extent of hereditary predisposition to coronary artery disease and myocardial infarction and as a guide to prevention of the adverse effects of air pollutants on the cardiovascular system.

1.3.4 Measurements of Lead and its Effects in the Population

Blood lead levels in normal subjects have been shown to be closely correlated with activity of RBC ALA dehydrase, and epidemiologic studies in normal subjects have shown that atmospheric lead exposure is closely correlated with blood lead levels. A natural step linking these two observations is a wide-scale study correlating atmospheric lead exposure with urinary ALA levels. This might determine whether atmospheric lead exposure can be found to alter pyrrole metabolism in normal subjects. Those levels of environmental lead which are associated with such biochemical effects should be defined.

Introduction of simple, rapid tests for blood and urinary lead, and for urinary ALA should make it more feasible to investigate lead poisoning in the general population, especially in ghetto children. Since lead in hair samples has been shown to be highly accurate in determining acute and/or chronic lead intoxication, such sampling should be both valuable and easily accepted by parents and child alike.

1.3.5 Potential Prevention of Oxidant Effects by Antioxidants

The biochemical mechanisms by which oxidants, including nitrogen dioxide, cause cellular disfunction have not been adequately investigated. The hypothesis has been advanced that some of the toxic effects of this class of agents are due to biological oxidation and resultant free radical formation. Of practical significance is the corrollary hypothesis thatpre-treatment with high levels of anti-oxidants such as vitamin E and C might prevent the deleterious effects of biological oxidation and free radical formation. The above hypotheses are amenable to contemporary investigation.

1.3.6 Integrated studies of toxic, carcinogenic, mutagenic and teratogenic potential of materials in the environment

Pollutants to which man is exposed must be tested for acute and chronic toxicity per se, and also for the more specific effects of carcinogenicity, teratogenicity, and mutagenicity. Historically, each of these effects has been studied and applied independently and by non-converging

disciplines; toxicity per se has largely been the province of classical pharmacologists, generally with little interest in carcinogenesis. This apparent parochialism is exemplified in the view that the chronic toxicity test is inappropriate for determining carcinogenicity. Mutagenesis has been even more isolated from other aspects of toxicology. New organizational patterns and training programs are needed to coordinate toxicological approaches, and to have toxicology reflect current needs, especially at the laboratory level.

1.3.7 Improved monitoring of environmental exposure

Research and development are required in the area of monitoring exposure to photochemical pollutants. More personalized sampling devices which can detect a variety of pollutants quickly, accurately, cheaply, and conveniently must be developed. Further definition of emission of precursor pollutants and factors resulting in specific chemical combinations are necessary. The eliminating of certain precursor pollutants may contribute significantly to the reduction of photochemical pollutants in general.

Section 2

STATE OF THE ART

2.1 INTRODUCTION

Objects of this assessment document are (1) to evaluate biomedical effects of air pollution from epidemiologic evidence and from experimental studies of known single components and of crude natural or simulated pollutants. Human hazards in particular will be reviewed from the standpoint of epidemiologic and experimental studies under community and laboratory circumstances. The purpose of the emphasis on humans is to establish whether enough evidence exists to set air quality standards because of demonstrated human health effects; (2) To identify biologic responses in animals exposed to realistic pollutant concentrations in those cases in which human health effects may not have been demonstrated but are suspected; (3) To review animal models of disease production which may serve as sensitive detectors of biomedical hazard; (4) To review biologic studies which might reveal mechanisms of action of air pollutants, so as to develop protective measures which might be offered to special risk persons and the population at large. (5) To define future studies aimed at predicting hazards to health as control measures are taken, as present types of pollution increase, and as innovations occur in transportation systems, fuels, power generation, agricultural and industrial processing.

This presentation does not cover every aspect of the known biomedical effects of air pollution because all sources of information could not be brought together in the short period available for development of this document. Because of the shortage of time, it has also not been possible to enlist the help of all interested University faculty members. The current review of the state of knowledge about the health hazards of polluted air may be incomplete in that all types of pollution are not dealt with but it will be as accurate as possible about the animal and human health effects of those pollutants with which it deals.

2.1.1 Cause-Effect Relationships

In developing statements of the relationship between air pollution levels and the effects caused by these levels, many critical decisions must be taken as to the existence or extent of cause-effect relationships. These relationships become quite indistinct in the interpretation of 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. Doubt exists on how to extrapolate to man data on controlled experiments involving exposure of experimental animals. Doubt also exists

on how to extrapolate short-term experiments using relatively pure substances to the exposure of humans and animals to the aged-irradiated mixture of precursors and reaction products that constitutes our real atmosphere.

In the process of identifying cause and effect relationships between disease and air pollution, certain questions continually recur. One is what we mean by injury or damage. As experimental techniques improve, we are increasingly able to detect subtle physiological and psychological deviations from the norm that can be attributed to pollution. The norm in this case is exposure to unpolluted air and the deviation may be reversible when exposure to the pollutant stops. Some will argue that only irreversible deviations should be considered and that any deviation, however reversible, 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 we are willing to allow such a deviation to occur. Prudence would argue for considering measurable 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 may occur. This argument is invoked in regulations on smoking (and drinking) by airplane pilots and may be equally applicable to ordinary citizens driving on the freeway at times of high air pollution. Thus temporary, presumably reversible, physical effects of air pollution cannot be dismissed for lack of lethal potential.

2.1.2 Population at Risk

Air pollution levels must be safe for not only the healthy adult but also the ill, the infant, and the aged, who are recognized as being most susceptible to the threatening effects of air pollution. Even among healthy adults, we can recognize differences in the levels of pollution that may so interfere with oxygen utilization of an athelete as to prevent him from achieving a record-breaking performance but may produce no presently measurable diminution in the performance of a sedentary clerical worker.

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 medical treatment. Answers to this question require the best possible information as to how large the percentage at risk really is and as to the nature of the disability (for example, respiratory vs. psychomotor) with respect to functions to be performed by persons exposed to polluted air.

2.2 BIOMEDICAL EFFECTS OF FOSSIL FUEL COMBUSTION

Emphasis is laid on pollution by fossil fuel combustion (automotive exhaust, etc.) with production of primary pollutants and photochemical smog. This emphasis should not be taken to exclude stationary sources emitting industrial effluents but to reflect a focus on one topic of statewide concern. Stationary source pollution will be considered in program development by the Health Effects Task Force.

2.2.1 Nature of the Pollutants

Ambient air pollution can be classified as caused by two major kinds of pollutants: primary pollutants and photochemical pollutants. Sulfur dioxide, suspended particulate matter, lead aerosols and particles, carbon monoxide, volatilized hydrocarbons and oxides of nitrogen, are examples of primary pollutants which represent the result of the combustion of fossil fuels and the release into and dilution by the ambient air. The concentrations of these pollutants are an index of how dirty the air is.

Photochemical pollutants present the complicating feature that their appearance in the atmosphere is dependent upon chemical reactions. Oxides of nitrogen and hydrocarbons emitted generally from auto exhaust combine to release a series of oxidants. These chemical reactions are dependent upon variables such as sunlight and temperature as well as dilution in the ambient air, and are therefore more difficult to use for quantifying levels of exposure than are the primary pollutants. The photochemical pollutants which are generally measured as oxidants include nitrogen dioxide, ozone and other oxidizing agents as peroxyacyl nitrates. Polycyclic aromatic hydrocarbons, alexins, aldehydes and singlet oxygen are additional conbustion or photoreaction products of importance but are less commonly measured in present monitoring systems. Between 1963 and 1965, the recorded maximum hourly average for oxidants in Log Angeles was 0.58 ppm (Clean Air Quarterly, 1966). The recorded peak level for oxides of nitrogen was 3.7 ppm, and for nitrogen dioxide was 1.3 ppm (State of California, 1966). Methane concentration measured in Los Angeles in 1961 ranged between 1.15-3.69 ppm (Altschuler, Bellar, 1963). These levels provide guide lines for judging the relevance of experimental exposures, many of which far exceed these ambient levels.

2.2.2. Effects of Ambient Photochemical Pollution on Man

2.2.2.1 Respiratory Symptoms

Table 1 summarizes cross sectional epidemiologic investigations in normal populations with varying exposures to levels of photochemical pollutants. Compared to studies of primary pollutants, the number of

Table 1

EPIDEMIOLOGIC STUDIES IN POPULATIONS WITH AND WITHOUT EXPOSURE TO PHOTOCHEMICAL POLLUTANTS

Nature of Study	No. of Subjects	Measure of Pollution	Associations found and sought	Remarks	Reference
Acute illness in Nursing Students from two areas	104 students	Daily maximum oxidant levels	Eye discomfort only symptom which correlated with levels of pollutant	Weekly diaries kept by students	Hammer, et.al.(1965)
Pulmonary function in school children from two areas	78 children	Daily mean oxidant levels	Children from less polluted area had lower peak expiratory flow rates than children from more polluted area. Upper respiratory tract infection more common in less polluted area	Differences in oxidant levels minimal	McMillan, et.al. (1969)
Questionnaire and pulmonary function test in outside workers	508 men	Los Angeles vs. San Francisco	Age group 40-49, no differences in symptoms or pulmonary function tests. Age group 50-59, significant excess (2x) of persistant cough and sputum in workers from Los Angeles. No difference in pulmonary function tests	Differences not explained by social class, occupation or smoking habits	Deane, et.al. (1965)
Athletic performance	11-30 high school boys	Hourly oxidant levels prior to track meet	Team performance inversely related to level of oxidants	10 fold range of oxidant levels from 0.03-0.3 ppm	Wayne, et.al. (1967)
Lung cancer rates	305 lung cancer deaths	Los Angeles vs. San Francisco Bay Area and San Diago Counties	Age and smoking habit adjusted mortality rates indicate slight excess risk in less photochemical polluted areas. Heaviest smoking group from more polluted area had slight excess in mortaltiy	Excess smoking may act synergistically with photochemical pollution	Buell, et.al. (1967)

investigations has been small. The results have not revealed substantial effects associated with photochemical pollutants; however, the range of observations and levels of pollutants has been quite restricted. Deane, Goldsmith and Tuma (1965) were able to demonstrate significant differences in respiratory symptoms in outside telephone workers from two areas in California with different levels of photochemical pollution.

Athlethic performance was shown to be reduced among high school athletes when oxidant levels were high prior to track meets. The range of oxidants measured varied from 0.03 to 0.3 ppm (Wayne, Wehrle and Carroll, 1967).

In 1956, as part of the California Health Survey, the California State Department of Public Health attempted to study the effects of photochemical pollution on a random sample of the residents of the state. The data on almost 7,000 residents were tabulated as Los Angeles County residents, San Francisco Bay area residents, and the rest of the state. Selected findings from that study are presented in Table 2. The frequency in each part of the state of cardiorespiratory symptoms or diseases was remarkably similar. However, when the subjects were asked:

> "Does it (this condition) bother you more on some days than others? (Question 17 b-1)
> If yes: "What is it about these times that makes you feel worse?" (Question 17 b-2)

the response in those who stated that the condition was worse at times was consistently more often attributed to air pollution by Los Angeles residents compared to San Francisco residents in all conditions except bronchitis (Hauskneckt, 1960). A selected panel of those subjects who stated that at times their condition worsened was followed over a three year period. Residents of Los Angeles with asthma or bronchitis reported that their condition worsened as a result of air pollution more often than did residents from San Francisco with the same conditions (asthma 51% vs 6%, bronchitis 22% vs 11%) (Hauskneckt, 1962).

Several physiologic studies have attempted to define the effects of ambient levels of photochemical pollutants on patients with respiratory disease (Motley, Smart and Leftwick, 1959; Rokaw and Massey, 1962; Remmers and Balchum, 1966). No significant correlations between pulmonary function tests and levels of exposure could be found. Three major methodologic problems were not resolved in these studies: (1) The effect of cigarette smoking was not controlled; (2) the patients were so severely ill that no significant response could possibly occur; or (3) the physiologic techniques were not sensitive enough to demonstrate subtle changes.

Table 2

SELECTED RESULTS FROM CALIFORNIA HEALTH SURVEY 1956 (Hauskneckt, 1960)

	Los Angeles		San Francisco Bay Area	
Number seen	2892		1847	
Number with symptoms	2223		1244	
	per cent. with:	per cent. worsened by air pollution	per cent. with:	per cent. worsened by air pollution
Coughing	28	3.9	26	1.5
Sinus trouble	20	11.3	24	3.7
Shortness of breath	17	8.1	18	0
Hay fever	10	15.0	18	5.1
Chest pain	11	8.8	10	3.2
Heart trouble	7	5.9	4	0
Bronchitis	6	25.9	6	28.9
Asthma	4	62.1	4	17.1

from: Hauskneckt, R. Air pollution effects reported by California residents. California State Dept. of Public Health, Berkeley, Calif., 1960.

Table 3 summarizes the retrospective epidemiologic data on mortality and morbidity in association with acute exposure to varying levels of ambient pollution primarily in the Los Angeles area. No correlations between acute weather patterns and mortality or change in morbidity in patients with significant respiratory disease have been found. The data, at best, are crude since the environmental measurements rely on stationary source samples generally placed at specific locations for reasons not related to these epidemiologic investigations. Factors associated with mortality and morbidity are extremely variable and in retrospective studies, often unobtainable.

While studies on patients with advanced stage chronic respiratory disease in California did not conclusively prove that photochemical air pollution is fatal to the pulmonary cripple, studies elsewhere have clearly shown that urban air pollution can cause increased morbidity and mortality in such patients. Sickness and death due to air pollution and potential pathogenetic effects in chronic respiratory disease will be discussed in Section 2.2.2.2 below.

Summary

The epidemiologic studies in normal populations exposed to significantly varying levels of photochemical pollutants, although limited in number, still provide the best clues to the effect of environmental exposure on respiratory function in ambulatory persons. The data from outside telephone workers, student athletes, and from the California Health Survey suggest that carefully planned epidemiologic investigations provide evidence on the association of respiratory conditions and levels of exposure (Deane, et al., 1965; Wayne, et al., 1967; Hauskneckt, 1960). Because cigarette smoking is an important factor in the development of respiratory disease, relatively large numbers of subjects are required to standardize for the effect of smoking so that significant effects of environmental exposure can be demonstrated (U.S. Department of Public Health, 1968).

The epidemiologic evidence that air pollution is associated with cancer and respiratory infections will be reviewed in a following section.

2.2.2.2 Pathogenesis of Chronic Obstructive Lung Disease

In addition to recognition of respiratory or other symptoms associated with episodic pollution, as outlined in the preceding section, clinical and investigative concern has focused upon two fundamental questions: (1) Does air pollution play a pathogenetic role in chronic bronchitis, emphysema and/or asthma?; and (2) Does air pollution increase morbidity and/or mortality in patients with preexisting respiratory disease?

Review of the available evidence indicates that prolonged exposure to atmospheric pollution can increase both morbidity and

Table 3

EPIDEMIOLOGIC STUDIES OF ACUTE EFFECTS OF AMBIENT LEVELS OF PHOTOCHEMICAL POLLUTANTS ON MORTALITY AND MORBIDITY IN MAN

Nature of Study	No. of Subjects	Measure of Pollution	Associations Found or Sought	Remarks	Reference
Mortality					
Daily mortality rates 1950 - 1955 Aged 65 or older Los Angeles County	8030 deaths	Daily temp. and oxidant level from single source	No independent effects of oxidant level on daily mortality Mortality affected by temp. increase No consistant pattern of oxidant effect when temp. level constant	Pollution index crude	Calif. (1957)
Mortality of nursing home residents Los Angeles July - Dec. 1955	approx. 550,000 person days at risk	Maximum daily temp. Occurance of smog alert day (Ozone ≥0.30 ppm)	Striking increase in mortality associated with significant heat wave No association with smog alert days	Pollution index crude	Calif. (1957)
Mortality from cardiac and respiratory diseases Los Angeles 1956 - 1958	Death rates between 1 - 1.3/100,000	Oxidants, temperature, carbon monoxide	No significant correlations between mortality and pollutants	Fourier curves may mask real environmental factors	Hechter and Goldsmith (1961)
Mortality in Los Angeles County nursing homes 1955	720 deaths in 132 days	Oxidant values from >0.2 ppm to 0.8 ppm	Correlation coeffient of .206 $p < .01$	Omitted days of excessive heat	Mills (1957)
Morbidity					
Hospital admissions for cardiac and respiratory diseases	368 admissions	Total oxidants from single stationary monitor	No correlations observed with levels of oxidant and respiratory disease Negative correlation with cardiovascular disease	Patients came from much wider area than that being monitored by single comp-	Brant (1965); Brant, et al., (1964)

Table 3, continued.

Nature of study	No. of subjects	Measure of pollution	Associations found or sought	Remarks	References
(Morbidity, cont.)					
Aggravation of chronic disease by acute exposure	137 patients with asthma	Total oxidant levels, particulates, CO, humidity and temp.	Daily diaries for 98 days Total of 3435 attacks in 118 patients No significant correlations between attacks and pollutant levels	Single stationary sampler for pollutants. Most attacks were mild. 8 individuals experienced the majority of attacks associated with oxidant levels.	Schoettlin and Landau (1961)
Aggravation of chronic disease by acute exposure	166 men, approx. half with chronic respiratory disease	Max. and mim. temp., humidity, mean oxidant, max. oxidant, max. SO_2, max. NO and NO_2, percent leaf damage, haze, pollen count	No significant correlation with symptoms, signs, or pulmonary function tests in multiple regression analyses	In spite of lack of statistically significant findings, trends in direction of disease group being more affected by pollutants were found. 166 selected from 400 possible participants	Schoettlin (1962)

mortality in persons with pre-existing bronchitis and emphysema (Higgins, Oldham, Cochrane and Gilson, 1956; Higgins, 1957; Ferris and Anderson, 1962; Anderson, Ferris and Zichmantel, 1965; Brit.M.J., 1961; Zeidberg, 1967). Specific pollutants, climatic conditions, socioeconomic factors, smoking, genetic factors, etc., have all been recognized components in aggravation of existing chronic lung disease but without successful "isolation" of prime factors. In the air pollution disasters of Donora and London (Schrenk, 1949; Heimann, 1961) no single smog component was identified as causal but the common denominator in each instance was a thermal inversion which resulted in prolonged exposure to the usual pollutants. In these disasters, persistence of pollution was associated with aggravated morbidity of existing respiratory diseases, and there were over 4020 excess deaths. Thus air pollution, albeit not of the photochemical type, can be lethal.

A recent study by Ishikawa provides data which suggest a pathogenetic role for air pollutants in emphysema (Ishikawa, Bowden, Fischer and Wyatt, 1969). This retrospective, pathologic study compared autopsy material from Winnipeg, Canada and St. Louis, Missouri. Winnipeg is recognized for its low level of industrial pollution while St. Louis is characteristic of cities with high levels of industrial pollutants. The two cities are quite different in climatic character. The data revealed that emphysema was seven times more common in St. Louis for ages 20-49, and twice as common over the age of 60. Smoking correlated significantly with disease, but could be identified as a separable factor.

The limitations of the studies listed above include the following: (1) In many studies measurements of specific air pollutants were not made to establish an association between these pollutants and physiologic compromise; 2) In others measurements of specific air pollutants were made but the role of personal smoking histories was ignored; 3) Differences in climatic conditions were ignored; 4) Often pollutants were measured at a central air pollution control station which was separated from population concentrations by up to twenty or more miles; 5) Attempts were not made to separate the roles of gaseous versus particulate pollutants; 6) Possible synergistic effects between gaseous and particulate pollutants were ignored; and 7) Data from one region of the country were applied to other regions. Goldsmith has identified the elements needed in effective epidemiologic studies on cause and effect of air pollution in pathogenesis of disease (Goldsmith, 1969).

Summary

Although air pollution is a national problem the nature of pollutants does have regional variation. In California, pollutants are of an oxidizing nature and not of the reducing nature (SO_2, SO_3) common to the industrial east and England, where the latter type of air pollution is regarded as contributory to promotion, aggravation and causation of excess mortality due to chronic obstructive lung disease (Brit. M.J.,1961). Since many of the studies listed above have been conducted in regions with reducing type of pollutants, further studies

are warranted with reference to the specific effects of oxidant pollutants in California. Initial studies as to the role of such pollutants in the production of asthmatic attacks (Schoettlin and Landau, 1961) and aggravation of baseline pulmonary function in patients with known pulmonary disease (Motley, Smart and Leftwich, 1959) are suggestive of aggravating effects.

2.2.2.3 Air Pollution and Infectious Respiratory Disease

Studies on various populations over different time periods and utilizing different techniques, including studies of panels, families, children, hospital patients, hospital admissions, and industrial absenteeism all tend to show some relationship between increased levels of atmospheric pollution and acute respiratory illness.

2.2.2.3.1 Population Studies

One of the largest population studies is that conducted by McCarroll, et al (Cassell, McCarroll, Ingram and Wolter, 1965; McCarroll, 1967; McCarroll, Cassell, Wolter, Mountain, Diamond and Mountain, 1967; Mountain, Cassell, Wolter, Mountain, Diamond and McCarroll, 1968; Cassell, Lebowitz, Mountain, Lee, Thompson, Wolter and McCarroll, 1969; Thompson, Lebowitz, Cassell, Wolter and McCarroll, 1970) which followed 18 individuals in Manhattan for an average period of 46 weeks, each, over a three year period. The study correlated a verbal report of daily symptoms with air pollution and meteorologic information. Using the symptomatology reported by participants, many different statistical analyses showed a small, but significant, relationship between symptoms of upper respiratory infection and increased levels of sulfur dioxide, particulate matter, and carbon monoxide. The relationship became stronger when symptoms reported three days after periods of higher pollution were examined, suggesting increased pollution might increase susceptibility to upper respiratory infection. A defect of this study, shared by most other population studies, is the lack of objective diagnostic data, and the subjective nature of the health data. Furthermore, several of the weather parameters, including temperature, humidity, solar radiation, and wind speed, were shown to bear a much stronger relationship to both incidence and prevalence of acute respiratory disease symptomatology than did increased levels of pollution. Furthermore, the relationship with both pollutants and weather vary from season to season and year to year, so that no consistent pattern could be demonstrated.

Many studies of families and special groups have been carried out with generally similar results. Lidwell, et al. (1965) accumulated a considerable series of records of the incidence of common colds over a period of six years in a group of offices and in families of the office workers. These reported infections were then correlated with weather and pollutant information in nearby monitoring stations. A strong inverse correlation was found between the incidence of "common colds" and low temperatures three days previously and, also, some

evidence of an association between "common colds" and an increase in atmospheric pollution on the same day. Their opinion was that low temperature and some air pollution may promote transmission of infection, or development of disease. Again, no objective diagnostic certification of the infections was made.

2.2.2.3.2 Studies in Children

Studies in children have certain obvious advantages in eliminating cigarette smoking and similar factors, and several of these studies have shown some relationship between air pollution and acute respiratory disease. Kononova and Aksenova (1961) reported an increased incidence of respiratory illness among children living near a synthetic alcohol plant around which increased levels of hydrocarbons, sulfur dioxide, and hydrogen sulfide were present, as compared with a control group living farther away. The incidence of respiratory infection among children living close to the plant was two-to-three times that of the control group.

Watanabe (1969) and Toyama (1964) both reported on respiratory illness in Japanese school children in Osaka and Tokyo, respectively, and concluded that air pollution might affect respiratory tracts of young children, based on a slightly greater incidence of respiratory disease in children in more polluted areas.

Douglas and Waller (1966) followed 3,900 British school children from their birth in 1946 until leaving school in 1961. The children were classified into one of four pollutant areas, based on the consumption of domestic coal in 1952. Morbidity information was obtained, both by interviews and during examinations by school doctors. Hospital admissions were also recorded, as were school absentee records. Both the frequency and severity of lower respiratory tract infections increased directly with increasing levels of air pollution. No difference was found between sexes, or social classes.

Lunn, et al. (1967), studying 800 school children in Sheffield, England, living in areas of widely differing air pollution, did show an association between air pollution and incidence of both upper and lower respiratory illness. Social class, number of children in the home, and bedroom sharing did not appear to influence disease rates.

As in all previously cited studies, sulfur dioxide and some measure of particulate matter, or smoke, were used as the indices for air pollution.

Summary

The majority of epidemiologic studies of many disparate populations have shown some evidence of a relationship between both the incidence and prevalence of acute respiratory infections and elevated air pollution.

The relationship, however, is of low degree and could account for only a very small percentage of all acute respiratory infections.

However, since acute respiratory disease is by far the commonest illness experienced by most persons and accounts for the vast majority of absenteeism from industry, school, and normal activities, even the small percentage of infections that may be related to air pollution amount to a very large number, and represent a tangible and significant dollar loss to the community.

All studies considering meteorologic factors agree that weather plays a far more important role in both incidence and prevalence of acute respiratory disease than does air pollution.

No single pollutant, by itself, can be demonstrated to play a major role in upper respiratory disease. It is probable that the pollutants monitored in the various studies merely represent the total pollution of an area, and an elevation in one is likely paralleled by an increase in most others.

In all the epidemiologic studies cited above, there are defects in the control populations, of one type or another, which may not make them truly comparable to the population under scrutiny.

2.2.2.4 Air Pollutant Exposure and Respiratory Cancer

There are now identified a dozen or so inhalants that on chronic exposure are related to increased risk of lung cancer. Other sites of the respiratory tract, such as the nasal cavity, nasal sinuses, and larynx, are also involved in carcinogenesis with some of the materials. Most of such inhalants are complex mixtures rather than pure chemicals, as in usual occupational and more general environmental situations.

Hueper (1961) listed the following environmental carcinogens involving the respiratory system of man (Table 4).

TABLE 4

Carcinogen	Recognized	Suspected
Arsenic	Lung	Larynx
Asbestos	Lung	
Chromium	Lung, Nasal Cavity	
Nickel	Nasal Cavity, Sinuses, Lung	
Aromotic 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
Ionizing radiations	Lung	
Epoxides		Lung
Chlorinated hydrocarbons		Lung
Beryllium		Lung
Iron		Lung
Macromolecular polymers		Lung

It can thus be accepted that a wide variety of chemical inhalants under occupational conditions produce cancer of the respiratory tract in man (Breslow, Hoaglin, Rasmussen and Abrams, 1954; Hueper, 1961; Shimkin, 1959). It is therefore reasonable to suspect that populations exposed to similar agents as part of their general environment also share to some degree the increased risk to respiratory cancer. The supposition of respiratory cancer hazard to the general population from environmental inhalants is supported by data on lung cancer among urban and among rural inhabitants (Buell, Dunn and Breslow, 1967; Haenszel, Marcus and Zimmerer, 1956). Wherever general epidemiologic studies have been carried out, there is a relationship between urban residence and an increased risk to lung cancer. This urban-rural difference is more evident among men than among women. The risk is related to the size of the city; inhabitants of cities with populations of over a million are at higher risk than those in cities of under 100,000.

Sophisticated analyses of the urban-rural difference show that the urban excess of lung cancer persists when occupation, smoking of cigarettes, and other factors are considered separately and corrected for (Haenszel and Shimkin, 1956). There is thus an "urban factor" that contributes to this excess risk. Environmental carcinogens that are inhaled from polluted urban atmosphere appears to be the explanation. An important consideration is the increase in risk to respiratory cancer when several carcinogenic factors are involved. In the case of cigarette smoking and urban residence, the effect of both appears to be additive. That is, the total risk is a simple sum of the two. In contrast, the effect of asbestos inhalation and tobacco smoking is synergistic, being greatly in excess of the risk attributable to the sum of the two factors (Selikoff, Hammond and Churg, 1968). Among asbestos workers who do not smoke, bronchogenic cancer is rare, but among asbestos workers who smoke the risk to bronchogenic cancer is eight-fold that of equivalent smokers.

Recently, attention has been focused upon the possibility that chemical carcinogens may interact with viruses. Thus, the risk to 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 epidemiologic data on human populations are supported by laboratory studies on animals.

It should be pointed out that the respiratory neoplasms in animals arise under conditions in excess of pollution levels to which man is exposed. The generalization of hazard to man, however, remains firm if it is accepted as a principle that such hazards should be defined and controlled at the stage when they are demonstrable in rats or mice, and not await the tragic surety of cancer and death in man.

Summary

Air pollution represents an important health hazard to man and other animal species. The hazards include the development of

cancers of the respiratory tract, especially the lung. This conclusion is well supported by epidemiologic studies on human populations, and by laboratory studies on animals.

The degree of carcinogenic hazard from air pollution is related to the presence of cancer-producing and cancer-accelerating materials in the atmosphere, as well as their concentration and physical state. The basis of air pollution control policies must be two-fold: the reduction of the total contaminants, and the selective elimination of particularly hazardous chemicals as they are defined.

2.2.3 Effects of Ambient or Simulated Photochemical Pollution in Animals

Gardner, Loosli, Hanes, Blackmore and Teebken (1970) recently reported the results of prolonged exposure of mice to atmospheric levels of oxidants in Los Angeles. Animals exposed to ambient air had significantly more episodes of infections than did those animals receiving filtered air. The two groups, however, were not totally comparable, as pointed out by the authors, since those receiving ambient air had wider ranges of temperature exposure than did those receiving filtered air. Gardner's preliminary observation of mice exposed to ambient air in Los Angeles found accelerated tumor formation (Gardner, 1966). However, his later report did not confirm these findings (Gardner, et al, 1970). In fact, if anything, there appeared to be a deficiency of pulmonary tumors in those animals breathing ambient air compared to those breathing filtered air. Studies of other species including rats (Gardner, Loosli, Hanes, Blackmore and Teebken, 1969), dogs (Catcott, McCammon and Kotin, 1958), and man (Buell, et al. 1967) have not shown an excess rate of development of lung tumors from exposure to ambient air in Los Angeles.

Physiologic studies of animals exposed to low levels of photochemical pollutants have revealed consistent findings suggesting the development of increased airway resistance in a dose response fashion (Table 5). Not included in Table 5 are the demonstrations of reduced activity among mice exposed to ambient or filtered air at U.C. Riverside for 13 months (Emik and Plata, 1969) nor the increased neonatal mortality of mice born in irradiated automotive exhaust atmospheres containing commonly measured levels of photochemical pollutants and the lethal mutations and infertility induced by pre-exposure of the sires of such litters to this "realistic" atmosphere. The latter studies were conducted at Cincinnati by Lewis, Hueter and Busch (1967). The same system used by Lewis, et al. was employed by Coffin and Blommer,(1967) in demonstrating that irradiated automobile exhaust increased the lethality of bacterial infection after 4 hours of exposure to pollutant containing 25 ppm CO and 0.15 ppm oxidant.

Summary

Animal studies at ambient or well-simulated levels of photochemical pollution demonstrate that respiratory functional impairments comparable to those suspected or recognized in ambulatory human subjects can be produced. Lethal mutations and sterility in male mice and high mortality of infant mice suggests areas for more active study in human populations.

Table 5

PHYSIOLOGIC STUDIES IN ANIMALS OF EXPOSURE TO LOW LEVELS OF PHOTOCHEMICAL POLLUTANTS

Pollutant	Length of Exposure	Observed Effect(s)	Species	Remarks	References
Oxidant 0.33 - 0.82 ppm	4 hours	Increased expiratory flow resistance 20 - 120% Increased inspiratory flow resistance 40% Decreased respiratory frequency 15 - 35%	Guinea pigs	Flow resistance returned to normal within 90 minutes after exposure stopped	Murphy, et. al. (1963)
Ambient air vs. filtered air	2 years	No difference in air way resistance between exposed and unexposed animals	Guinea pigs	Forced oscillation technique	Swann, et. al. (1965)
Ambient air oxidant >.5 ppm	continuous	Significant increases in airway resistance	Guinea pigs	Forced oscillation technique Cannot exclude other ambient air pollutants	Swann and Balchum (1966)
Ozone 2 ppm	3 hours	Decrease in minute ventilation Maximum decrease in O_2 uptake recorded 8 hours after exposure	Rats	Return to normal after 20 hours	Scheel, et. al. (1959)
Ozone 0.3 - 1.35 ppm	4 hours	Tidal volume decreased 20% Respiratory rate increased 30% (both peaking before exposure ended) Increased flow resistance at higher concentrations	Guinea pigs	Dose response curve noted; returned to normal within 2 hours after exposure stopped	Murphy, et.al. (1964)
Irr. auto exhaust or NO_2 0.5-1.0 ppm + 0.2 ppm NO or NO 1.5-2.0 ppm + 0.2 ppm NO_2	16 hours per day, 18 months	No change in diffusing capacity No change in compliance No change in airway resistance	Dogs	Measurements made under pentathol anaesthesia outside exposure chamber	Vaughan, et. al. (1969)

2.3 EFFECTS OF INDIVIDUAL POLLUTANTS

Study of the effects of naturally-occurring environmental pollution is essential for evaluation of real health hazards. In order to set goals for abatement of pollution, the most obvious toxic pollutants have been studied individually. These studies aid not only in reduction of exposure to the specific pollutants but also in overall abatement since each pollutant is usually one of many.

2.3.1 Carbon Monoxide (CO)

The present maximum allowable atmospheric concentration, or threshold-limit value, for occupational exposure in industry is 50 parts per million, for 8 hours. The limit was reduced from 100 parts per million in 1964 because of new evidence of possible adverse effects, mostly on the central nervous system, from exposures in the range of 50 to 100 parts per million (Documentation of Threshold Limit Values, 1966).

2.3.1.1 Carbon Monoxide in Man (Goldsmith and Landaw, 1968)

The major effect of CO depends upon its ability to impair oxygen transport by blood, through two distinct mechanisms. First, since the affinity of human hemoglobin is 210 times greater for CO than it is for oxygen, a small quantity of CO can reversibly inactivate a substantial percentage of the oxygen-carrying capacity of the blood. Second, COHb interferes with the release of the oxygen carried by the hemoglobin molecule (Ayres, Giannelli, Armstrong, 1965; Bartlett, 1968; Roughton and Darling, 1944; Lilienthal, Riley, Proemmell and Franke, 1946).

A shift in oxyhemoglobin dissociation means that the avidity of hemoglobin for oxygen is increased. At high partial pressures of oxygen, such as occur in the pulmonary capillaries, the oxygen content is nearly maximal and is unlikely to be increased very much by this shift. However, at the tissue level, where the oxygen content of the capillary blood has been reduced to approximately 40 percent of saturation, the shift can substantially decrease the oxygen tension supplying the tissues. This shift is known to increase the hazard of CO toxicityat high concentrations of COHb (around 40 percent) as compared to an equivalent reduction of blood oxygen by hypoxia or altitude. More accurate measurements are needed on the effect of COHb in the 0- to 20-percent range on oxygen transport to the different tissues.

In general, the signs and symptoms of acute CO toxicity depend on the proportion of hemoglobin which is combined with CO. This is a function of the concentration of the CO in the inhaled air and the volume of air breathed per minute. Carbon monoxide is excreted almost entirely from the capillaries of the lung, in the expired air, after dissociation of the COHb complex. The half-time of excretion for low concentrations is from 2 to 4 hours.

Since the effect of CO 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 CO will be correspondingly more severe. The recommended CO threshold-limit value for work at 5000 to 8000 feet (1500 to 2400 meters) is only 25 parts per million (Documentation of Threshold Limit Values, 1966).

The population group most susceptible to the adverse effects of atmospheric CO, according to the California State Department of Public Health, includes persons with severe anemia or impairment of circulation to vital organs of the body. It has been predicted that, in such individuals, community exposures which produce a 5-percent concentration of COHb, added to the burden attributable to occupational and smoking exposures, could increase mortality and morbidity rates. This COHb level can be produced by average exposures to a CO concentration of 30 parts per million for 8 hours, which is a sufficient time for equilibrium to be reached. This exposure (a concentration of 30 parts per million in 8 hours) was adopted by the Department as an air quality standard at the second or "serious" level (the level likely to lead to insidious or chronic disease or to significant alteration of important physiologic function in a sensitive group). Confirmation of the prediction concerning morbidity and mortality will require study on a scale wider than has so far been attempted.

Since the State of California first set air quality standards for CO, in 1959, there have been three developments which suggest the need for reevaluation. They are (i) an increase in knowledge concerning endogenous CO production and CO metabolism, (ii) clearer definition of the effects of CO on selected functions of the nervous sytem, and (iii) improvement of methods for epidemiologic study of possible CO effects.

Endogenous Carbon Monoxide Production: Recent Findings

Roughton and Root (1945) demonstrated conclusively that there was a small, but measurable, amount of CO in normal human blood. Later, Sjöstrand (1949) confirmed these findings and showed that, in non-smokers, the CO concentration was higher in expired air than in inspired air, thus demonstrating that CO is actually produced within the body. He estimated CO production to be approximately 0.5 to 1.0 milliliter per hour in the normal adult female, values which are in close agreement with those now accepted.

Patients undergoing anesthesia produce CO concentrations within rebreathing anesthesia circuits which often exceed 50 to 100 parts per million (Middelton, Poznak, Artusio and Smith, 1965) --higher than the threshold-limit value for industrial workers. To prevent impairment of oxygenation, Middleton, et al. suggested that closed rebreathing systems be opened and flushed periodically during the operative procedure in order to remove this excess CO. Increased COHb concentrations, due to both normal and abnormal hemolysis, were also seen in newborn infants (Bjure and Fallstrom, 1963; Oski and Altman, 1962). The endogenous production of CO in these newborns led to increased COHb concentrations (as high as 12 percent), implying markedly impaired oxygen transport function.

It is conceivable that the animal-plant cycles proposed for use on long space flights to produce oxygen and remove waste products will themselves be a source of CO, as a result of the decomposition of chlorophyll, the green respiratory pigment of plants, which contains a cyclic tetrapyrrole structure similar to heme. Mature leaves have been shown to produce large quantities of CO, presumably from degradation of this pigment (Wilks, 1959).

The fate of atmospheric CO is not entirely known, but it has been suggested that a true CO cycle exists in nature, since CO can be produced by plants and by many lower animal species (Loewus and Delwiche, 1963; Simpson, Talbot and Westlake, 1960; Westlake, Roxburgh and Talbot, 1961; Wittenberg, 1960), can be utilized for metabolic purposes in certain bacteria and plants (Yagi, 1958; Krall and Tolbert, 1957), and may be oxidized to CO_2 at show rates in animals and man (Clark, 1950; Luomanmaki, 1966).

Effects of Low Concentrations on the Central Nervous System

In work done during World War II on the effects of CO on visual threshold, MacFarland, Roughton and their colleagues (1944) detected an effect at a COHb concentration of about 5 percent. Schulte studied the effect on firemen of exposure to low concentrations of CO (Schulte, 1963). He evaluated pulse rate, respiratory rate, changes in blood pressure, and neurologic reflexes and conducted a battery of psychomotor tests. On some of these tests, significant changes in response were found after exposure to CO. For some of the tests, variations in performance were found at COHb levels well below 5 percent,possibly even at levels as low as 2 percent.

Beard and Wertheim (1967) have reported distinct effects upon the ability to perceive differences in the duration of auditory stimuli among healthy subjects exposed for 90 minutes to CO in concentrations as low as 50 parts per million. 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 CO concentrations as low as 50 parts per million for 45 minutes. Such an exposure could have produced COHb concentrations of less than 2 percent.

We can only speculate upon the importance to driving performance of the capacity to estimate a 1-second interval to within an eighth of a second. It would seem sufficiently important to warrant testing to find whether similar levels of CO, commonly occurring in heavy traffic, are capable of influencing vehicular operations. Such effects should be detectable by epidemiologic methods.

Epidemiologic Study of the Effects of Carbon Monoxide on Human Health

Data most relevant to the question of acute reactions in the general population would be data which show whether there are CO-associated increases in such relatively frequent events as motor vehicle accidents or

in fatality rates for persons with myocardial infarction.

The complex temporal patters of traffic accidents and CO exposure pose a formidable difficulty for conventional correlation analysis, since CO concentrations will be positively correlated with traffic density and probably with accidents. Ury (1968) has developed a helpful nonparametric approach which should avoid this difficulty. From data for Los Angeles, pollutant levels and accident frequencies for each hour of each day of the week are tabulated. The data for adjacent weeks are then compared. If--to take an example--the CO level for 7 to 8 a.m. on Monday of week 13 of the year is lower than that for 7 to 8 a.m. on Monday of week 12 and the accident frequency for the same period is also less for week 13 than for week 12, a plus is scored. Had both the pollutant level and the accident frequency been higher for week 13 than for week 12, a plus would also have been scored; that is, a plus indicates concordant changes. If, however, a difference in CO level has a sign opposite to the sign for a difference in accident frequency, a minus is scored. If either the pollutant levels or the accident frequencies have identical values in adjacent weeks, a zero is scored. The pluses, minuses, and zeros are then cumulated for all pairs of weeks and tested by sign test statistics against random probability estimates. Pooling of the results not only permits a statistical inference for the set of data but makes it possible to isolate the contribution of different days, hours, seasons, and so on. Computer programs are now being developed for the many comparisons needed. The comparisons will be applied to 4 years of pollutant and accident data for Los Angeles.

Another approach to the accident problem is obviously that of measuring the COHb concentrations in persons involved in accidents. Chovin (1967) made a study which showed that drivers thought to be responsible for accidents had substantially higher COHb concentrations than workers being examined for possible occupational exposure to CO, and that both groups had higher COHb concentrations than private individuals possibly exposed to CO from household devices.

Cohen, Deane, and Goldsmith (1968) have analyzed data for 3080 persons with myocardial infarction admitted to 36 Los Angeles hospitals, in relation to average levels of CO for the Los Angeles area. Case fatality rates were found to be associated with the CO level on the day of admission; there was a low but statistically significant correlation coefficient for all days and for weekdays. Since CO levels increase in winter, because of low average inversion height, and since there is a tendency for death rates also to increase in winter, it is possible that a correlation could be spurious, being due to the effect of time of year on both case fatality rates and CO levels. A possible effect of autocorrelation was avoided by analyzing days of the week separately. All the significant associations involved patients in hospitals thought to be located in areas of relatively high pollution. A temporospatial strategy was applied to test the hypothesis that the differences between case fatality rates in high-pollution and low-pollution areas was greatest in weeks when CO levels were high. It was felt that this procedure should reduce the effect of time of year on the correlation. Of the 13 weeks with the highest mean CO concentrations, a significant number (Forbes, Sargent and Roughton, 1945) showed higher case fatality rates in high-pollution-area hospitals than in low-pollution-area hospitals.

This result was obtained by the relatively insensitive sign test and was confirmed by the Wilcoxon matched-pairs signed-ranks test. Cohen et al. (1968) conclusde that an association may exist between atmospheric CO pollution and case fatality rates from myocardial infarction. Obviously, in future tests of this association it would be desirable to obtain smoking histories and data on COHb concentrations at the time of admission of the patients to the hospital.

Further study of these problems will require the collection of a large number of data, since there is a complex temporal fluctuation, both of the exposure and of the underlying process.

Summary

Exposures to CO are widespread. For the U.S. urban population, cigarette smoking is probably the most important source, followed in importance by motor vehicle exhaust, occupational sources, and home heating and cooking devices. The median COHb concentration for one-pack-a-day cigarette smokers who inhale is 5.9 percent--a concentration sufficient to imply a serious threat to health in persons with underlying vascular insufficiency. This level of exposure may account for some of the excess mortality from cardiovascular disease observed among cigarette smokers. Community air pollution may produce COHb concentrations in nonsmokers similar to those observed in smokers, and the effects of these concentrations will be greater at high altitude.

Endogenous production of CO from heme catabolism has been abundantly documented. Such production provides a tool for the study of hemolytic disorders, is a hazard to infants in respirators and to men in submersibles and space capsules, and may add to the risk of closed-circuit anesthesia.

Low and commonly occurring CO exposures may impair accurate estimation of time intervals as well as the performance of more complex psychomotor tasks. A possible role of CO in motor vehicle accidents is suggested by data which show higher levels of COHb in drivers involved in accidents than in policemen and in other occupationally exposed populations. In Los Angeles an association of CO pollution and case fatality rates in patients with myocardial infarction has been observed.

2.3.1.2 Effects in Animals

Cardiac Effects

Animal exposure studies, with continuous or intermitten long-term exposure to a CO concentration of 50 parts per million, have given conflicting results suggesting that, in at least some species, changes in myocardial function can occur. For example, Stupfel et al. (1968) find a transiently diminished QRS-complex amplitude in the electrocardiogram of the unanesthetized rat exposed continuously to a CO concentration of 50 parts per million. Musselman, et al. (1959), using the same exposures, observed no electrocardiographic or other changes in dogs, rats, or rabbits. But Lindenberg et al. (1962) obtained significant results on exposing 15 dogs to a CO concentration of 50 parts per million for 6 weeks; seven of the dogs were exposed for 6 hours a day for 5 days a week, the others continuously. All showed electrocardiographic changes and, at

autopsy, dilatation of the right side of the heart, with scarring of the heart muscle in some cases and fatty degeneration in others. Astrup et al. (1966) have shown that exposure to CO concentrations of 200 to 350 parts per million increased atheromatous processes in cholesterol-fed rabbits.

These experimental data suggest that exposure to low concentrations of CO may have a role in the development of human heart disease. This becomes an important question for epidemiologic study.

CO and Gaseous Synergists

This area is reviewed by Stokinger and Coffin (1968).

2.3.2 Lead

Like gaseous pollutants, lead is airborn and subject to inhalation. Unlike gaseous pollutants, lead accumulates in top soils and surface waters where it is incorporated into aquatic and terrestrial organisms (Warren and Delawault, 1962; Chow, 1970; Motto, Daines, Chilko and Motto, 1970; Page and Ganje, 1970).

The distribution of industrial lead chemicals in our environment is extensive. Until recently, the emphasis of lead pollution research has been on urban air quality (Mueller, Helvig, Alcocer, Gong and Jones, 1964; U.S. Public Health Service, 1965; American Industrial Hygiene Association 1969; Goldsmith, 1969; Landau, Smith and Lynn, 1969; Altshuller, 1969). However, the polluted lead aerosols suspended in the atmosphere will eventually enter the hydrosphere as runoff or precipitation. The industrial production of lead is so large compared to its natural concentration in air and water that men may be seriously disturbing the biogeochemical cycles of lead.

2.3.2.1 Mode and extent of lead pollution

Lead pollution originates overwhelmingly from the burning of lead alkyl additives in automotive fuels (Chow and Earl, 1970). In the United States in 1967 alone, more than two hundred and fifty million kilograms of lead were combusted as antiknock additives (U.S. Bureau of Mines, 1968). About ten percent of this amount, i.e., 25 million kilograms of lead, were emitted into the ambient atmosphere within the State of California; and the majority of these lead pollutants were discharged in the densely populated San Francisco Bay area and Southern California region.

Lead is naturally dispersed in the crust of the earth at concentrations of about 15 parts per million. This lead concentration is much lower than that in air-borne particulate matter in most metropolitan areas which has a lead content of several percent (Chow and Earl, 1970). Therefore, the air-borne soil dust is not a significant source of lead in urban atmospheres. On the contrary, the upper soil layers of the earth are being contaminated by gasoline exhaust lead.

Other sources of lead pollution are of local importance. The only primary lead smelter in California, located in Selby, refines 60,000 tons of lead per year, and in the process, introduces about 12,000 kilograms of lead into the environment per year.

About 150,000 kilograms of lead are sprayed annually as lead arsenate pesticide for control of the codling moth in northern California (State of California, 1967). This chemical can be a source of contaminating local watersheds.

Lead aerosol emission also occurs when lead-bearing materials are burned. This includes municipal incineration, burning dumps and junk cars, and burning waste materials associated with building demolition. For the most part data pertaining to these sources are lacking.

In most of the major cities of California, there are a number of secondary smelteries, battery, paint and cable manufacturers, printing firms, canneries and other industries using lead. For Los Angeles County, total lead emission to the atmosphere from all industrial sources is estimated to be less than 100,000 kilograms per year.

Lead in each ore deposit has its characteristic isotopic composition fixed during mineral genesis (Brown, 1962), and this unique characteristic can be an useful tool in identifying the source of industrial lead pollutants (Chow and Johnstone, 1965). Comparison of the isotopic composition of lead in the sourthern California aerosols with that of the average local gasoline lead shows that these two kinds of lead are isotopically identical. Lead aerosols in other cities are also isotopically identical with their respective gasoline leads. This indicates that the excess lead in the environments can be only attributed to automotive exhausts.

Lead aerosols are eventually removed from the atmosphere through precipitation either in rainfall or as dustfall.

Fine lead aerosols have been shown to travel long distances and are washed out of the atmosphere in rain and snow. One way of finding out whether lead pollution is increasing with time is to analyze the precipitated lead in chronological layers of old preserved snow strata (Murozumi, Chow and Patterson, 1969).

Analyses of lead in annual ice layers from the interior of northern Greenland shows that lead concentration increases from less than 0.005 microgram of lead per kilogram of ice at 800 B.C. to more than 0.2 microgram per kilogram today. The ice layer at 1750 A.D. corresponds to the beginning of the European Industrial Revolution and it can be seen that the lead concentration there at this date is already more than 25 times higher than natural levels. The sharpest rise occurs after 1940. The increase of lead with time in north polar snows is ascribed mainly to lead smelteries before 1940 and to burned lead alkyls after 1940. Today, lead concentrations in Greenland snows are well over 400 times above natural level.

2.3.2.2 Ecologic Effects of Lead Pollution

Lead is not considered essential to the nutrition of animals or human beings. Foreign to the human body, lead is a cumulative poison. It tends to be deposited in bone structure and inhibits enzymatic activity. Lead poisoning usually results from the cumulative toxic effects of lead after continuous consumption over a long period of time, rather than from occasional doses. Immunity ot lead cannot be acquired.

Lead may enter the body through food, air, water and other beverages. Consequently, the total intake of lead must be considered in setting standards for air and water. The intake that can be regarded as safe cannot be assigned definitely because the sensitivity of individuals to lead differs considerably. The exact level at which the intake of lead by human body will exceed the amount excreted has not been established.

Farm animals are poisoned by lead from various sources more frequently than by any other metallic poison. It is not unusual for cattle to be poisoned by lead in the water; the lead need not necessarily be in solution, but may be in suspension.

For aquatic communities; the general conclusion from various investigations is that lead pollution has the effect of reducing the number of species and the number of individuals (Klein, 1962; Pringle, Hissong, Katz and Mulawka, 1968; Waldichuk, 1969; Sprague, 1969). There is a marked gradation in the tolerance of different organisms. Fish are the most sensitive, being eliminated in water containing about 300 micrograms per liter, at which concentration the invertebrate fauna is little affected. With increase in concentration, the fresh water limpet is eliminated, then other Mollusca and malacostracan Crustacea, followed by Oligochaeta, Leeches and Trichoptera leaving a fauna restricted to certain insects, entomostracan Crustacea and some Planarian. In highly polluted waters containing 3,000 to 6,000 micrograms of lead per liter, the population is further restricted to the larvae of the midge and the may-fly nymph.

2.3.2.3 Effects of Lead in Man

Goldsmith and Hexter (1967) have shown a close correlation between blood lead levels and estimated exposure to lead in inspired air. These results were strengthened by finding higher blood levels in normal subjects living within 250 feet of freeways than in subjects living near the coast and more than 1 mile from a freeway (Thomas, 1967).

Hernberg and Kikkanen (1970) have shown a strong negative correlation between blood lead levels and RBC delta aminolevulinic acid (ALA) dehydrase activity in normal medical students never occupationally exposed to lead. A virtually identical regression was found to fit blood lead and RBC ALA dehydrase in 142 workers representing various degrees of occupational exposure to lead. It thus appears that "normal" levels of blood lead are associated with alterations in activity of this RBC enzyme, and there was no lead level on the regression lines below which it could be stated that no inhibition occurred. It appears that normalcy for lead exposure is relative, and that enzyme inhibition can be shown for the ranges of blood lead previously considered to be "safe". Whether these findings are related to significant disease or disability in the general population or in selected persons in special high risk categories is not clear at this time.

Following acute exposure to lead, urinary ALA excretion may remain abnormal for many years (Saita and Moreo, 1964). These levels of ALA correlate closely with blood lead levels in occupationally exposed subjects (Goldsmith, 1969). Thus, testing for increased urinary ALA would seem to be a sensitive indicator of present or past exposure to toxic amounts of lead.

Metabolic Effects of Lead

The major known biochemical alterations in lead poisoning are concerned with deranged heme metabolism. At the present time, there appear to be at least 3 steps in porphyrin synthesis which appear affected:

a. ALA Dehydrase
b. Coproporphyrin Oxidase and/or Decarboxylase, and
c. Heme Synthetase

All 3 of these enzyme systems are known to have essential -SH groups (Goldberg, 1968), and it has been shown that the inhibition of ALA dehydrase by lead in kidney and bone marrow can be completely reversed by the addition of glutathione an agent known to protect -SH groups (Lichtman and Feldman, 1963).

Berk et al. (1970) have reported that there may be increased turnover of heme-containing compounds in the liver and/or bone marrow in lead poisoning. Acute gouty arthritis (saturnine gout) occurs occasionally in patients with renal insufficiency and prolonged lead intake (Ball and Sorensen, 1969). Other furnctional tubular defects such as glycosuria and aminoaciduria have been reported in association with chronic lead exposure (Studnitz and Haeger-Aronsen, 1962).

Hematologic Effects of Lead

Lead inhibits several steps in the formation of hemoglobin heme, so that a relative bone marrow depression may result. Peripheral RBC in lead intoxication in animals and man have shortened survival (Berk, Tschudy, Shepley, Waggoner and Berlin, 1970; Griggs and Harris, 1958) characterized by increased random hemolysis. The lead appears to be bound to the RBC membrane (Novak and Majsky, 1960), possibly to lipoprotein components. Once bound to the RBC, lead may interfere with a number of RBC functions, by deactivation of -SH groups (Rabino, Coscia Perrelli and Parigi, 1964), and irreversible interference with the potassium pump (Vincent and Blackburn, 1958).

In workers occupationally exposed to lead, accelerated senescence of RBC was seen; the shortening in survival being well correlated with blood lead levels (Hernberg, Nurminen and Hasan, 1958).

2.3.2.4 Animal Studies of Kinetics and Body Distribution of Lead

Retention of environmental lead within the body depends not only on the route of entry, but also on the physical nature of the lead. When lead (as ^{212}Pb) was inhaled as a vapor, 99% was fixed initially in the body, with 33% subsequently excreted in feces (Booker, Chamberlain, Newton and Scott, 1969), suggesting that the lead was removed from the upper respiratory passages by ciliary action, swallowed, and then excreted. In contrast, when lead was inhaled as an aerosol (particle size estimated as 0.05-0.5 micron) 34 to 60% was retained, of which about 75% was cleared into the blood. When the lead was injected intravenously, only small amounts were excreted in urine or feces, with slow clearance from the blood. In similar studies involving inhalation of ^{212}Pb aerosols (estimated particle size 0.2 micron) 14 to 45% was deposited in the lung, with about half eventually appearing in RBC, and very little appearing in urine or feces (Hursh, Schraub, Sattler and Hoffman, 1969).

When ^{210}Pb was injected intravenously into dogs, less than 10% was excreted in urine and feces, with the remainder having a mean time within the body of years to decades (Fisher, 1969). When ^{210}Pb was injected via the same route into rats, cumulative excretion over the next 2 weeks was 16% in the urine and 36% in feces, with 40-50% remaining in the skeleton (Castellino and Aloj, 1964), from which the loss was so slow that as estimate of its turnover time was not possible.

2.3.3 Oxidants (O_3, PAN)

Photochemical air pollution is a complex mixture of substances among which one group may be collectively measured as "oxidant". This measurement, ozone (O_3), nitrogen dioxide (NO_2) and peroxyacyl nitrates (PAN). Most of the relevant studies concerning health effects of oxidants have focussed on a single ingredient under carefully controlled laboratory conditions. The effects noted, in the case of human experimentation, are the result of acute exposures only. Information resulting from long term exposures is chiefly from animal studies.

2.3.3.1 Effects of Ozone in Man

Sensory Effects

In areas where oxidant type air pollution is at its worst, e.g. in Los Angeles, over 90% of the measured oxidant is present as ozone. The odor threshold for ozone is 0.02 ppm which was detected in less than 5 minutes by nine out of ten subjects (Henschler, et al., 1960). At 0.2 to 0.5 ppm for 3 hours there is a decrease in visual accuity in the dark adaptation and middle vision ranges (Lagerwerff, 1963). Based on subjective complaints from both experimental and occupational exposures to ozone, the threshold for nasal and throat irritation appears to be about 0.3 ppm. Ozone is not an eye irritant at these concentrations.

Effects on the Lung

Both short- and long-term experimental exposures of humans to ozone produce reversible changes in pulmonary function. The most sensitive test found so far appears to be the diffusing capacity for carbon monoxide (DL_{CO}). Young, et al. (1964) report that all eleven of their subjects experienced a transient lowering of the DL_{CO} (mean decrease 25%) after exposure to 0.6 to 0.8 ppm for 2 hours. The subjects had almost returned to normal 1 hour after the end of the exposure. Young, et al. (1964) concluded that the reduction in the diffusing capacity could be attributed to the development of a slight transitory inflammatory edema in the walls of the alveoli.

A feature of the study by Young et al. (1964) is the extreme variability in sensitivity among the subjects. The individual responses had a mean drop of 25% but varied from 12.1 to 44% below the pre-exposure values.

This marked variability in sensitivity between subjects has also been observed by Goldsmith and Nadel (1969) who reported that all four of their subjects suffered an increase in airway resistance following exposure to 1 ppm ozone for 1 hour which was significant. Some of their subjects responded to concentrations as low as 0.1, 0.4 and 0.6 ppm although the response was not linear. Other studies have shown that concentrations greater than 1 ppm cannot be tolerated by some people for more than a few minutes (Hallett, 1965). Similar, if not greater, variability in sensitivity can be expected in response to environmental exposures.

A single study employing repeated exposure to ozone over a long period of time suggests the possibility of a sustained effect. Bennett (1962) observed a significant decrease in the average $FEV_{1.0}$ (1 second forced expiratory volume) in six subjects exposed to 0.5 ppm ozone for 3 hours a day, six days a week for 12 weeks. The effect was detectable after 10 weeks of exposure. The subjects did not return to pre-exposure levels until 6 weeks after the final exposure. There were no symptoms (Kleinfeld, et al., 1957; Challen, et al., 1958; Young, et al., 1963) but the subjects could detect the ozone by smell. The observed lag period before the onset of the changes in pulmonary function and the subsequent lag period during recovery also, are suggestive of damage at the structural level.

The use of FEV, or of airway resistance as conventionally measured, to evaluate the effects of deep lung irritants may be criticized on the basis of studies by Macklem and Mead (1967). These investigators have shown that the central airways contribute 90% to the total airway resistance whereas the peripheral airways only contribute 10%. Thus were ozone to exert its effect mainly on the peripheral airways, the total airway resistance of FEV as conventionally measured would be a very insensitive indicator of an effect. The present data with respect to ozone and airway resistance may thus grossly underestimate the effect actually taking place. Narrowing of the peripheral airways has serious implications. It is likely to be associated with a stiffening of the

lung with unequal distribution of inspired air and consequently with impairment of gas exchange. Thus judging from a single study, other physiologic criteria have to be developed to study the long-term effects of ozone in humans.

2.3.3.2 Effects of Ozone in Animals

Stokinger, et al. (1957) have reported that chronic bronchitis, bronchiolitis, emphysematous and fibrotic changes occur in the lung tissues of mice, rats, hamsters and guinea pigs exposed daily to about 1 ppm ozone. In addition to these irreversible pathologic changes there is considerable evidence supporting the theory that ozone can accelerate the natural aging process.

The aging theory has not been developed to a point where concepts of the more far reaching subtle effects of oxidants are possible (Stokinger, 1969). The current concepts that have evolved from investigations on the biochemical factors in the aging process are summarized by Tappel (1967). Oxygen becomes toxic when conditions permit its peroxidation of polyunsaturated fats. Lipoperoxidation sets off a sequence of damaging reactions to cells ending in accumulation of age pigments in vital body organs, e.g. heart.

The far higher energy content of the free radicals of photochemical oxidants, confers on these oxidants greater potential to initiate auto-oxidation of polyunsaturated fats and initiate a sequence of damaging reactions in body tissue. Buell, et al. (1965) showed production of carbonyl compounds (cross-linking agents) in the lungs of rabbits exposed to 1 and 5 ppm ozone for 1 hour. Goldstein, et al. (1969) recently observed that lipid peroxidation occurs in-vivo in mice following exposure to 0.4 to 0.7 ppm ozone for 4 hours. Thus increasing amounts of evidence from a variety of directionsmake plausible a role for photochemical oxidant air pollutants in accelerating the aging process.

Much has been made of the development of "tolerance" as being a significant protective mechanism against ozone. Tolerance has been defined as the increased capacity of the host to resist the effects of subsequent exposures to lethal doses of the same agent or different agents (cross-tolerance). Stokinger and Coffin (1968) note that irreversible changes which impair lung function develop in animals tolerant to the acute inflammatory effects of ozone and furthermore they suggest that the development of tolerance may initiate some chronically toxic processes. Thus the available data suggest that the protection afforded by tolerance is against the edamagenic effects of ozone only. Other endpoints are required to demonstrate tolerance before it can be said to have a significant protective effect. More profitable avenues for protection lie in the use of antioxidants (Tappel, 1967).

Miller and Ehrlich (1958), observed that animals challenged with infectious aerosols of Klebsiella pneumoniae suffered a higher incidence of infection, as measured by mortality rates, when previously exposed to ozone compared to a group of animals not exposed to ozone. The effect

has been noted in mice and hamsters with single exposures of 1.3 to 4.4 ppm ozone for three hours (Purvis, et al., 1961) or with multiple exposures of 0.84 ppm for 4 hours a day, five days a week for two weeks. The increased susceptibility to infection, lasting for up to 27 days, was noted when exposure to ozone occurred either before or after challenge with the infectious aerosol. Coffin, et al.,(1967) have shown the effect can occur with concentrations as low as 0.08 ppm for 3 hours.

Coffin, et al. (1968) have recently shown that rabbits exposed to 0.3 ppm ozone for 3 hours produce an influx of heterophilic leucocytes and a diminution of pulmonary alveolar macrophages obtained by pulmonary-lavage. This dose also impaired the in-vivo phagocytic properties of the macrophages.

2.3.3.3 Peroxyorganic Nitrates

Data from a single study carried out on humans have suggested that exposure to peroxyacetyl nitrate (PAN) results in increased oxygen uptake during exercise. Smith (1965) exposed several male college students via a mouthpiece to 0.3 ppm PAN for 5 minutes while at rest. Immediately following the exposure the subjects exercised on a bicycle ergometer. There was a statistically significant ($p < 0.05$) increase in oxygen uptake during exercise without any change at rest. The changes could possibly be a reflection of an increase in the work of breathing or due to an increase in airway resistance. The published report of this work does not adequately describe the experimental design or the statistical analysis and thus these results require confirmation before any conclusive statement can be made.

Experimental Studies on Eye Irritation

Laboratory studies have shown that the effective eye irritants are the products of photochemical reactions. Although oxidant concentrations have been shown to correlate with the severity of eye irritation, the precise identification of all of the irritants has not been achieved. Ozone the principal contributor to the measured oxidant is not, by itself, an eye irritant. The chemical identities of the effective irritants in simple synthetic photochemical systems have been identified as follows: formaldehyde peroxybenzoyl nitrate (PBzN), PAN and acrolein although the latter contribute to only a minor extent (Schuck, et al., 1966; Heuss and Glasson, 1968). Formaldehyde, PAN and acrolein have been identified in ambient air but they do not exist in sufficient concentration to account for the degree of the eye irritation experienced (Renzetti and Bryan, 1961).

PBzN has recently been identified as a product of the photo-oxidation of aromatic olefins and nitric oxide (NO) (Heuss and Glasson, 1968). It has subsequently shown to be a lachrymator 200 times more potent than formaldehyde. The existence of PBzN in the atmosphere has yet to be demonstrated. This is likely to be a difficult task since it is very unstable after sampling. It is unlikely that only one compound is responsible for all of the eye

irritation experienced in Los Angeles. ormaldehyde probably makes a significant contribution but other substances such as the peroxyorganic nitrates, some of which have yet to be identified, also play a part. Although there has been considerable effort made to identify the substance(s) responsible for the eye irritant properties of photochemical smog, no effort has been made to determine the nature of the interaction between the irritant and the eye. The cause of eye irritation remains to be studied from this point of view.

2.3.4 Oxides of Nitrogen (NO, NO_2)

Of the seven oxides of nitrogen known to exist, only two are present in ambient air which are of toxicological importance. They are NO and NO_2. At present there are no data from either animal or human studies which are suggestive that NO is a health hazard at concentrations encountered in ambient air. It has a toxic potential because it is readily oxidized to NO_2. It is transformed in the lung tissue to nitrosoamines some of which may be carcinogenic, and it may be transferred across the lung-blood barrier to form methemoglobin. While some studies have been done to demonstrate the reliability of these possibilities, much remains to be done in order to obtain definitive information on the significance of these reactions. This section deals with NO_2 as the representative of this group of compounds.

Evidence demonstrating that exposure to nitrogen dioxide is deleterious to respiratory function comes from two sources. Acute exposure of humans to high levels of nitrogen dioxide invariably results in respiratory disease. Animals exposed to elevated levels of atmospheric nitrogen dioxide develop pathologic changes resembling emphysema and an enhanced susceptibility to bacterial infection.

2.3.4.1 Effects of NO_2 in Man

The average level of nitrogen dioxide in the atmosphere of smog-ridden areas of California is 0.25 ppm (Cooper and Tabershaw, 1967). Air pollution surveys indicate a maximal concentration of 3.5 ppm of nitrogen dioxide (Ehrlich, 1966). Acute exposures to higher levels of nitrogen dioxide are an uncommon occupational hazard of workers manufacturing nitric acid (Patty, 1962), farmers exposed to silage (silo-fillers' disease) (Lowry and Schuman, 1956; Grayson, 1956), and electric arc workers (Norwood, et al., 1966). A range of adverse effects correlating with the degree of exposure have been described. Eye and nasal irritation occurs after exposure to 15 ppm of nitrogen dioxide (Lowry and Schuman, 1956). Pulmonary discomfort is noted at levels of 25 ppm and bronchiolitis with focal pneumonitis occurs after exposures of 25 to 75 ppm of nitrogen dioxide. The duration of all of these exposures has been less than one hour (Lowry and Schuman, 1956). Comparably short periods of exposure to 150-200 ppm causes fatal pulmonary fibrosis. Higher exposures are associated with acute pulmonary edema and/or death (Lowry and Schuman, 1956). These studies demonstrate conclusively that elevated concentrations of nitrogen dioxide are extremely toxic to human respiratory tissues; lower levels are also deleterious, leading to chronic pulmonary disease among persons occupationally exposed to levels well above those in photochemical smog.

Volunteer studies further support the hypothesis that acute exposure to non-physiologic, but low concentrations of nitrogen dioxide, will impair pulmonary function. Abe observed an increased expiratory and inspiratory flow resistance in healthy adults exposed for 10 minutes to 4 to 5 ppm of nitrogen dioxide (1967). Higher levels of exposure (50 ppm) for 1 minute have been shown to cause significant nasal irritation and pulmonary discomfort (Meyers and Hine, 1961).

2.3.4.2 Effects of NO_2 in Animals

Pathologic Abnormalities Following Exposure to Nitrogen Dioxide

The majority of studies concerned with the pathology of prolonged exposure to nitrogen dioxide have utilized rodents (Steadman, et al., 1966; Freeman, et al., 1968, 1966; Haydon, et al., 1965). Rats exposed to 10, 12.5, or 25 ppm of nitrogen dioxide for three or more months develop enlarged thoracic cavities, dorsal kyphosis and an inflated appearance. Microscopically, there is distention of alveolar ducts, dilation of alveoli and hyperplasia of bronchiolar epithelium. Alveolar septa are occasionally missing, but destruction of parenchyma is unusual (Freeman, et al., 1968, 1966). These pathologic features are similar but not identical with those of human emphysema. A critical difference is the lack of alveolar necrosis. Destructive bullous lesions are the sine qua non of emphysema (American Thoracic Society, 1962); bullae are absent in rodent models. Also, it should be noted that rats exposed to lower concentrations of nitrogen dioxide (0.8 to 2.0 ppm) for their entire lifetime do not develop the above lesions. The lungs from these animals are grossly normal; microscopic examination shows only minor degrees of ciliary loss, epithelial hypertrophy and "cytoplasmic blebbing" (Freeman, et al., 1966; Haydon, et al., 1965). These animals live out a normal life span and die of diseases unrelated to nitrogen dioxide (Freeman, et al., 1968).

Mice are more susceptible to the toxic effects of nitrogen dioxide than rats. Continuous exposure to 0.5 ppm of nitrogen dioxide for three months causes loss of cilia, alveolar cell disruption and obstruction to respiratory bronchioles (Blair, et al., 1969). Exposures of longer duration cause more severe changes and pneumonitis (Blair, et al., 1969). These pathologic abnormalities are unlike the changes of emphysema in man.

Haydon et al. (1967) exposed rabbits to atmospheres containing 8 to 12 ppm of nitrogen dioxide for 3 to 4 months and reported destructive changes in alveolar walls and abnormal enlargement of the distal air spaces. These findings closely approximate the emphysematous lesions observed in humans. Unfortunately, there are no reports about data obtained from rabbits exposed to lower, commonly encountered concentrations of nitrogen dioxide.

The abnormalities that occur in guinea pigs exposed for 3 weeks to 22 ppm of NO_2 are not consistent with emphysema in man (Balchum, et al. 1965). The dog appears to be particularly resistant to the toxic effects

of NO_2. Wagner et al. (1965) exposed dogs to 5.0 ppm of NO_2 for 15 to 18 months and did not find differences between the lungs of treated and control animals. These distinctive results have been confirmed by other investigators (Steadman, et al., 1966; Vaughan, et al., 1969). Investigations with monkeys are currently in progress but have not yet been reported (Albert, et al., 1967).

2.3.4.3 Effect of NO_2 on Pulmonary Antibacterial Defense Mechanisms

Man's lungs are normally sterile (Laurenzi, et al., 1961; Kalinske, et al., 1967; Pecora, 1963; Green and Kass, 1964). Numerous studies have shown that despite continuous exposure to environmental bacteria, the region from the primary bronchus downward is free of bacteria. Experimental evidence which will be discussed later indicates that the defense mechanisms responsible for the sterile state are phagocytosis by the pulmonary macrophage system (Green and Kass, 1964) and physical removal of invading bacteria via the mucociliary stream (Bang, 1961; Kilburn, 1967). Data concerning the relative significance of each of these mechanisms in man is meager. Radioisotope techniques have been developed which allow study of the mucociliary stream (Albert, et al., 1967; Albert and Arnett, 1955; Morrow and Gazioglu, 1966; Luchsinger, et al., 1968). These studies show transport rates between 10 and 20 mm/min and clearance of more than 90% of material deposited on the mucosa in less than one hour. Studies performed in patients with chronic lung disease have demonstrated impaired mucociliary clearance, presumably due to alterations in ciliary activity.

In contrast to the limited amount of data from humans, there is a large body of experimental evidence in animals pertaining to host resistance to pulmonary infection. Experiments using murine models have demonstrated that in both mice and rats intrapulmonary phagocytosis is the primary defense against inhaled bacteria (Green and Kass, 1964; Goldstein, et al., 1970).

The intrapulmonary bactericidal system is altered by abnormalities of the host that are associated clinically with increased susceptibility to pulmonary infection. The experimental induction of hypoxia (Green and Kass, 1964), starvation (Green and Kass, 1964), acute renal failure (Goldstein and Green, 1966; 1967), metabolic acidosis (Goldstein, et al., 1970), viral infection (Klein, et al., 1969), and ethanolic intoxication (Green and Kass, 1964) cause inhibition in bactericidal function. The pulmonary defense mechanism is hampered by physiologic derangements, but is relatively resistant to anatomic injuries such as are produced by silica (Goldstein and Green, et al., 1969).

Physical removal of inhaled bacteria and small particle pollutants is accomplished by the mucociliary stream, cough reflex and to a much lesser extent, the lymphatic system. While the mucociliary stream may play a role in pulmonary bacterial defense, its importance appears to be considerably less than that of the intrapulmonary bactericidal activity of the lung (Green, 1968). Mucociliary function is affected adversely by certain environmental abnormalities [drying (Dalhamn, 1956), cooling (Dalhamn, 1956; Krajina, 1964), cigarette smoke (Dalhamn, 1964; Ballenger, 1960), inanition (Taramin, et al., 1965)] and these deleterious changes may enhance susceptibility to infection; as yet, definitive

studies have not been performed.

Effect of Nitrogen Dioxide

Ehrlich and co-workers in a series of experiments have shown that acute and chronic exposure to relatively low levels of nitrogen dioxide depresses pulmonary resistance to infection (Ehrlich, 1966; Ehrlich and Henry, 1968, Henry, et al., 1970;Blair, et al., 1969; Henry et al., 1969).

Mice were exposed for two hours to concentrations of nitrogen dioxide (1.5 to 25 ppm) prior to infection. Significant increases in mortality occurred in the groups exposed to levels above 3.5 ppm. Deaths did not occur in uninfected mice exposed to identical concentrations of nitrogen dioxide (Ehrlich, 1966).

These investigators have also shown that continuous exposures to levels of nitrogen dioxide only slightly above ambient (0.5 ppm or more for three months) depressed murine resistance to pulmonary infection (Ehrlich and Henry, 1968).

Effect of Nitrogen Dioxide on Alveolar Macrophage Function

From the previously cited in vivo studies exposure to nitrogen dioxide appears to inhibit alveolar macrophage function (Ehrlich, 1966; Ehrlich and Henry, 1968; Henry, et al., 1970; Blair, et al., 1969; Henry, et al., 1969).

In vitro methods for measuring the effect of in vivo exposures to gaseous pollutants upon macrophage function have also been developed (Coffin, et al., 1968). These techniques have been applied to investigations of ozone toxicity and have allowed demonstration of inhibition of phagocytosis at pollutant levels as low as 0.3 ppm. These techniques can readily be modified to study the effect of nitrogen dioxide.

Nitrogen Dioxide as a Biological Oxidant

The similarity of the effects of nitrogen dioxide to those of ozone suggests the hypothesis that some of the toxic effects of nitrogen dioxide are due to biological oxidation and resultant free radical formation (Stokinger and Coffin, 1968). Analytical methods have been developed for quantitating free radical concentrations (Chio, et al., 1969) and experiments of this nature offer the potential of new insights into the pathogenesis of nitrogen dioxide-induced injury. Pre-treatment with high levels of anti-oxidants such as vitamin E and C might prevent nitrogen dioxide induced bactericidal impairment.

2.4 EFFECTS OF INHERITED METABOLIC PATTERNS ON AIR POLLUTANT SUSCEPTIBILITY

Potential effects of inherited metabolic patterns on air pollutant susceptibility are discussed under the following 6 situations:

Familial pulmonary emphysema and serum antitrypsin deficiency.

Susceptibility to lead poisoning and R.B.C. G-6-PDase deficiency.

Male susceptibility to chronic granulomatous disease and leucocytic G-6-PDase deficiency.
Atherosclerosis, from CO in persons with altered coronary artery patterns.

2.4.1 Familial Pulmonary Emphysema and Serum Antitrypsin Deficiency

Recently (1965) an association between familial pulmonary emphysema (FPE) and a deficiency in the serum of α_1-antitrypsin (SAT) was discovered in Sweden (Laurell, 1963; Eriksson, 1965); 25 of 38 patients with serious deficiencies in SAT (12% of normal) had chronic obstructive pulmonary disease. The first such association found outside of Sweden was described from the Chest Service Bellevue Hospital, N.Y.C. in 1966 (Briscoe, et al., 1966). Other cases soon were reported from the Harvard Medical School, Boston, Massachusetts; 2 families with 12 individuals, showing chronic pulmonary disease, had reduced SAT levels (Talamo, et al., 1966)

The Swedish study (Eriksson, 1965) indicated a gene frequency for recessive hemizygotes of 4.7% calculated according to the Hardy-Weinberg law on a determined frequency of 0.057% for homozygotes from a population of 6,995. Estimation of the gene frequency of hemizygotes in various locations in the U.S.A. from far smaller populations indicated for 193 whites in Georgia an SAT deficiency of 2.1%, calculated from a provisional estimate of homozygotes of 0.01% (Kueppers, et al., 1969). About the same heterozygote frequency (2.6% was found for the San Francisco Bay area (Kueppers, et al., 1969). Considerably higher frequency was found among the Swedish population in Minnesota (Kueppers, 1968).

Of two separate studies of 73 patients with chronic obstructive pulmonary disease, including pulmonary emphysema, one revealed 23.7% of the males hemizygous for the deficiency gene and 31.8% of the females, average 25.5% (Kueppers, et al., 1969). The other study of 66 patients hospitalized for pulmonary emphysema, 25.8% were found to be SAT deficient, and 23 such patients under 50 years of age, 48% (Lieberman, 1969). These observations suggest that antitrypsin deficient individuals would be more susceptible to respiratory irritants. Indeed, Stokinger and Mountain (1967) and later Lieberman (1969) have urged the use of the SAT deficiency test in the job preplacement examination to avoid improper placing of such individuals in situations involving irritating fumes. Dr. Lieberman is urging the use of this test on a national basis (Med. World News, 1970).

2.4.2 Glucose-6-Phosphate Dehydrogenase Deficiency in Erythrocytes

Susceptibility to Lead Poisoning and DDT.

Rubino, et al., (1963) were among the first to point out that glucose-6-phosphate dehydrogenase activity in the erythrocyte is depressed in acute, subacute and chronic lead poisoning. It follows that individuals with an inherited G-6-PDase deficiency would be more susceptible

to the effects of lead on the red blood cell than those with normal G-6-PDase activity. Similarly, Wasserman (1968) has pointed out that DDT depresses the activity of G-6-PDase and warns that other organochlorine pesticides may act similarly making groups with this deficiency more susceptible to hemolytic effects.

2.4.2.3 Glucose-6-Phosphate Dehydrogenase Deficiency in Leukocytes

Chronic Granulomatous Disease

In 1965 Washburn, et al. proposed a genetic explanation for the preponderance of males found among patients with severe bacterial infections such as sepsis andmeningitis. It has now become clear that both immunoglobulin systhesis and thymic function are affected by the genetic loci on the X chromosome. Washburn, et al., consider the female's greater resistance to infection results from her heterozygosity for genes on the X chromosome controlling immunoglobulin synthesis, providing her with a greater heterogeneity of response. Many of the immune deficiency disorders have an X-linked mode of transmission including congenital agammaglobulinemia, thymic alymphoplasia, disgammaglobulinemia type I and others. Chronic granulamatous disease is now considered another X-linked type of deficient resistance to infection (Bridges, et al., 1959).

A specific biochemical basis for Washburn's hypothesis has been described by Schlegel and Bellanti (1969). Their findings were consistent with either a variant G-6-PDase protein or an enhanced degradiative system affecting G-6-PDase activity. The preponderance of data favored the former. G-6-PDase has a genetic locus on the X chromosome. They found that patients with chronic granulomatous disease had reduced G-6-PDase activity in leucocytes (and erythrocytes). Considerable other evidence pointed to the role of G-6-PDase in phagocytosis. Newborn infants, whom they showed to have reduced leucocytic G-6-PDase activity are especially susceptible to bacterial infections, regardless of sex, although males appear to be at special disadvantage. The functional metabolic defect results in a diminished activity of the pentose-phosphate pathway, causing failure to develop the respiratory burst normally associated with an essential for phagocytosis. Bellanti, et al., using a marker of leucocyte pentose phosphate system activity, have shown a diminution of this activity in chronic granulomatous disease and in young infants.

In light of the repeated demonstrations by Purvis, et al., 1963, 1961) and more recently by Coffin and Blommer (1967) on the capacity of air pollutants to alter the pathogenic role of streptococal in the lungs (of mice), it would seem that further attention to the role of the defective leucocyte in reference to the response of such individuals to urban air pollutants should be given.

The ethnic groups with the highest incidence of red blood cell G-6-PDase deficiency and hence presenting the greatest susceptibility to air-pollutants to be sought in the U.S.A. are the following, as culled from world-wide investigations:

	Percentage Incidence	
	M	F
American Negro (African)	12.0	8.7
Filipinos	12.7	---
Turkish	9.1	4.5
Yamenites	8.1	6.0
Kardish Jews	60.0	---
Sardinians	13.0	---
Punjabis	13.5	---
Chinese	5.0	---
East Indians	11.0	---

As can be seen, the greatest concentration of this deficiency originates in areas around the Mediterranean, with few exceptions.

As far as is known, there is no necessary correlation between the groups with the highest incidence of erythrocytic G-6-PDase deficiency and leucocytic; e.g., the American Negro with the red cell deficiency is normal in the leucocytic form.

2.4.2.4 Altered Coronary Artery Patterns, Carbon Monoxide and Atherosclerosis

Heredity has become of late recognized as one of the multiple factors predisposing to coronary atherogenesis. Genetically determined coronary artery patterns have been suggested since 1940 (Schlesinger, 1940; White, 1960) as playing a significant role in vulnerability to coronary atherogenesis and myocardial infarction. Schlesinger identified 3 major branching patterns in man and considered hearts with a left coronary artery pattern to be most vulnerable to fatal coronary artery occlusion, and those with balanced patterns, least. Subsequent pathologic classification has extended and tended to confirm the original hypothesis of Schlesinger. Recently, Bloor and Leon (1968) have reported further evidence of distinct differences in coronary artery patterns in 2 strains of albino rats, thus confirming in animals what had been found in man and providing a laboratory model for further investigations of the effect of environment on the genesis of coronary artery patterns.

Kjeldsen, et al., (1968) believe they may have identified another factor, carbon monoxide, that contributes to the development of atherosclerosis; animals with continuous levels of HbCO of 10 - 15% developed atherosclerotic changed similar to those seen in man. Higher levels of HbCO were found in atherosclerotic individuals than in non-atherosclerotic individuals. The reverse was also true; rabbits had lower cholesterol values when maintained on hyperbaric O_2. Certain distinct differences were found also between the effects produced by the hypoxia caused by CO and those from O_2 lack.

It would seem altogether probable that individuals with hereditarily altered coronary artery patterns would fare less well upon exposure to CO than those not so disposed in regard to the tendency toward coronary artery disease.

2.5 ENVIRONMENTAL CARCINOGENS, MUTAGENS AND TERATOGENS

In an extensive review included as an appendix to this report, Samuel S. Epstein presents experimental animal evidence for carcinogens and informed predictions as to potential mutagens and teratogens in the environemtn, including polluted air. In addition, he described sensitive methods for measuring not only toxicity of environmental pollutants but also carcinogenicity, mutogenicity and teratogenicity of suspect compounds or environments in an integrated testing system. The review by Epstein will serve as a useful reference source in future planning.

The present brief excerpt demonstrates carcinogenicity of samples of polluted air in rodents. This section recalls the dictum offered by Shimkin (Section 2.2.2.4) and the Delaney Bill that demonstrate unacceptable risk to man.

2.5.1 "Carcinogenicity of Atmospheric Pollutants to Rodent Skin

The carcinogenicity of atmospheric pollutants in mice has been demonstrated with organic extracts collected from various sources by various techniques (Table 6). Administration of pollutant extracts to mouse skin, whether by painting or subcutaneous injection has generally yielded local tumors, papillomas, carcinomas or sarcomas, sometimes accompanied by multiple pulmonary adenomas. A notable exception was the high incidence of distant tumors, hepatomas, and lymphomas, in addition to multiple pulmonary adenomas, together with a virtual absence of local tumors, following subcutaneous injection of relatively small concentrations of organic pollutant extracts in infant mice (Epstein, et al., 1966). Marked variation in the carcinogenicity of organic extracts from various urban sites, incidentally with low activity in Los Angeles, has been noted (Hueper, et al., 1962; Epstein, et al., 1966). In addition to benzo(a)pyrene (BaP), the role of other carcinogens in crude organic extracts is now generally accepted. Evidence for this includes, tumor production by BaP-free pollutants, such as aliphatic aerosols of a synthetic smog (Kotin, et al., 1956), and by aliphatic and oxygenated fractions of organic extracts of particulate atmospheric pollutants (Hueper, et al., 1962), lack of parallelism between carcinogenicity of organic extracts and their BaP concentrations (Hueper, et al., 1962; Epstein, et al., 1966), and finally by the pattern and multiplicity of tumors developing following injection of pollutant extracts in infant mice (Epstein, et al., 1966)."

Selected pure chemical carcinogens, such as BaP, known to be present in polluted air have been shown to be carcinogenic for lungs of rodents by intratracheal instillation. To this finding has been added evidence of synergism between SO_2 and BaP during exposure by inhalation rather than by intratracheal instillation (Laskin, et al., 1970).

Squamous carcinoma production by intratracheal instillation of BaP adsorbed on hematite (Saffiotti, et al., 1967) has confirmed the essential requirement of particles as well as carcinogen for production of experimental lung cancer. This concept probably applies to man, though the particle may be asbestos or an aerosol (tobacco smoke) rather than hematite. Vitamin A inhibited the carcinogenic effect of BaP plus hematite

TABLE 6. TUMOR INDUCTION IN MICE FOLLOWING CUTANEOUS ADMINISTRATION OF ORGANIC EXTRACTS OF PARTICULATE ATMOSPHERIC POLLUTANTS[2]

Reference*	Particulates	Extract	Administration	Latent Period, Months	% Tumor Yield		Comments
					Local	Distant	
Leiter, *et al.* (1942)	Filtration and precipitation	Benzene-ether	Subcutaneousxl (∿ 50 mg.)	12	6	0	5 urban sites sampled
Leiter, *et al.* (1942)	Large capacity collectors	Benzene	Subcutaneousxl (∿ 50 mg.)	16	8	0	Similar tumor yields from 5 urban sites sampled
Gurinov, *et al.* (1954)	Filtration and sedimentation	Dichlor-oethane	Painting 3xwkly (10% benzene sol.)	6	38	8 (Pulm. adenomas)	3 urban sites sampled
Kotin, *et al.* (1954)	Large volume collectors	Benzene	Painting 3xwkly (acetone sol.	15	42	0	Particulates from Los Angeles
Clemo, *et al.* (1955)	Ventilation filters	Benzene and 2 fractions	Painting 3xwkly (1% benzene sol.)	?	45	16 (Pulm. adenomas)	Particulates from Liverpool
Kotin, *et al.* (1956)	Oxidation products of aliphatics	Benzene	Painting 3xwkly (acetone sol.)	14	20	0	Aromatic-free aerosol collected in shepherd traps
Clemo, *et al.* (1960)	Filtration of city smoke	Benzene	Painting 6xonly (1% benzene sol.)	18	20	0	Particulates from Newcastle
Hueper, *et al.* (1962)	Composite NASN samples	Benzene and 3 fractions	Subcutaneousx24: (organic ∿ 130 mg.) (aromatic ∿ 13-33 mg) (oxygenated ∿ 12 mg.) (aliphatic ∿ 24 mg.) Painting 2xwkly: (aliphatic and oxygenated)	9-26	2-10	0	Different tumor yields from 8 urban sites. In general, low tumor yields obtained
Epstein, *et al.* (1966)	Composite NASN camp samples	Benzene	Subcutaneousx3 to neonates (15-25 mg.)	3-12	1	8-33 (Hepatomas) 1-17 (Lymphomas) 13-75 (Pulm. adenomas)	Different tumor yields from 6 urban sites. Results suggest role of several carcinogens

*References are included in Appendix L

and reduced squamous metaplasia in the hamster tracheo-bronchial tree (Saffiotti, et al., 1967). A potential protective mechanism against lung cancer warrants further study.

2.5.2 Chemical Mutagens

The most direct link between photochemical pollution and lethal mutations was reported by Lewis, et al., (1967) in male mice exposed to irradiated auto exhaust during the full length of the spermatogenic cycle. The pregnancies resulting from the mating of these male mice were smaller in number than controls (indicating reduced fertility) and early infant deaths suggested lethal mutations in the products of conception.

Section 5

TASKS RECOMMENDED FOR PROJECT CLEAN AIR

In this preliminary list, studies of Human Health Effects have been divided into seven mission-oriented "Programs". Some Programs are interdisciplinary in that collaboration between 2 or more Task Forces is specifically required or recommended.

5.1 Health Effects of Present and Future Modes of Transportation

A procedure should be developed for evaluating the health effects of anticipated innovations in transportation systems. New systems include not only modified automative engines and fuels but also future types of surface and air transport. The evaluation procedure should include review of relevant epidemiologic and toxicologic literature, physico-chemical characterization of pollutants, experimental biomedical studies, and epidemiologic surveillance of populations. The literature review, characterization and experimental studies should take place as an integral part of the design and development, prior to deployment, of new or modified transportation systems. Evaluation should not be delayed until new processes and devices have been commercially introduced. Complete characterization of, for example, automotive emissions will identify and quantify biologically active pollutants. On the basis of these findings, certain health hazards can be predicted. Standard biological testing systems should be developed for use in experimental studies of those components for which prediction may be limited. The Automobile Engine Development and Instrumentaion Task Forces are already aware that pollution patterns will change as transportation systems evolve. These Task Forces should be assisted by the Health Effects Task Force in carrying out biologic and health effects evaluations as part of, for example, the development of engines and fuels.

5.2 Health Effects of Present and Future Stationary Source Pollution

The health effects of stationary source pollution should be better defined by procedures similar to those in Program 1. Changes in pollutants may result from existing or future control of stationary source pollution. Altered pollutants should be characterized and health benefits should be assessed or hazards predicted. It is particularly important that the health effects of new types of pollution should be evaluated during the development of new processes. Because stationary sources often affect local populations, epidemiologic studies, combined with good instrumentation for monitoring pollutants, should be undertaken now and continued during a period when control measures can be anticipated. This might require collaboration among the Health Effects, Instrumentation, Power, Industry and Agriculture and Social Sciences Task Forces. Among the sources to be considered are:

a. Pulp and paper plants
b. Oil refineries and petrochemical plants
c. Smelters and foundries
d. Electrical power plants (including substitution of atomic for oil fuel)
e. Kilns and cement plants
f. Agricultural operations

5.3 Population Health Surveillance

Permanent air pollution response surveillance systems covering both the general population and sensitive groups should be developed and put into operation. Such systems would serve to identify health effects not otherwise detectable or measurable and to determine the proportion of the population having special susceptibility to environmental pollution. The systems would also provide a continuing flow of information on the population effects of current and evolving community air pollution.

5.4 Detection and Prediction of Pollutants Causing Cancer, Chromasome Damage and Birth Defects

The capacity to evaluate carcinogenic, mutagenic and teratogenic effects of pollutants should be improved and coordinated. A broadly applicable set of methods is needed for the following classes of pollutants:

a. Organic compounds (hydrocarbons, pesticides, cigarette smoke, etc.)
b. Metals
c. Gases
d. Airborne high energy particles, such as singlet oxygen and radioactive compounds.

Similar efforts are needed for occupational intoxication and water and soil pollution. While these environmental health hazards are not encompassed in Project Clean Air, awareness of these sources of potential injury is essential in assessing the effects of air pollution.

5.5 Short-term and Long-term Health Effects of Exposure to Air Pollutants

Repeated, apparently reversible, physiological and biochemical effects of pollutants can reasonably be expected to have long term pathogenic effects in children and adults. There should be a systematic study applicable to humans of the relationship between short and long term effects and disease processes. Typical studies would:

a. Attempt to relate changes in airway resistance to the pathogenesis of chronic respiratory disease.
b. Investigate the relationship of acute carbon monoxide poisoning and consequent impaired oxygen transport to the development of atherosclerosis.
c. Study the possible effects of repeated low level lead exposure on hemoglobin synthesis, and on other porphyrin-dependent functions.

5.6 Prediction of Medical Risks, Prevention and Treatment of Illness Due to Air Pollution

Clinical responses to air pollutant exposure as well as prevention and/or therapy for its effects should be better defined. Clinicians need specific information about the dangers of particular pollutant levels, which patients are unusually susceptible, and what facilities for air filtration are available and how they should be used.

5.7 Effects of Air Pollution on Behavior, Performance and Accidents

Effects of air pollution on human behavior and performance need to be better defined. Among the groups whose performance might be studied are auto and truck drivers, factory workers, students taking exams, and student athletes. Generalized survey methods for exposure to eye irritants and odors are needed and should be systematically applied to communities with such problems. Such work will involve sociologists, demographers, and survey statisticians and may be a basis for involving the Social Science Task Force (#3).

SECTION 6

LITERATURE CITED

Abe, M.
1967. Effects of mixed NO_2-SO_2 gas on human pulmonary functions. Bull. Tokyo. Med. Dental Univ. 14:415-433.

Albert, R.E. and Arnett, L.C.
1955. Clearance of radioactive dust from the lung. Arch. Ind. Hlth. 12: 99-106.

Albert, R.E., Lippmann, M., Spiegelman, J., Liuzzi, A., and Nelson, N.
1967. The deposition and clearance of radioactive particles in the human lung. Arch. Environ. Hlth. 14:10-15.

Altshuller, A.P.
1969. Anal. Chem. 41(5), 1R.

Altschuler, A.P. and Bellar, T.A.
1963. Gas chromatographic analysis of hydrocarbons in the Los Angeles atmosphere. J. Air Poll. Control. Assoc. 13:81-87.

American Industrial Hygiene Association
1969. "Community Air Quality Guide, Lead". Detroit, Michigan.

American Thoracic Society: Definitions and Classifications of chronic bronchitis, asthma and pulmonary emphysema.
1962. Amer. Rev. Resp. Dis. 85:762-764.

Anderson, D.O., Ferris, B.G., Jr., and Zichmantel, R.
1965. Chilawich Respiratory Survey, 1963. III. Prevalence of Respiratory Disease in Rural Canadian Town. Canad. M.A.J., 92:1007-1016.

Astrup, P., Hellung-Carsen, P., Kjeldsen, K., Mellengaard, K.
1966. Scand. J. Clin. Lab. Invest. 18:450.

Ayres, S.M., Giannelli, S., Jr., Armstrong, R.G.
1965. Science 149:193.

Balchum, O.J., Buckley, R.D., Sherwin, R. and Gardner, M.
1965. Nitrogen dioxide inhalation and lung antibodies. Arch. Environ. Hlth. 10:274-277.

Ball, G.V. and L.B. Sorensen.
1969. Pathogenesis of hyperuricemia in saturnine gout. New Eng. J. Med. 280:1199.

Ballenger, J.J.
1960. Experimental effect of cigarette smoke on human respiratory cilia. New Eng. J. Med. 263:832-835.

Bang, F.B.
1961. Mucociliary function as protective mechanism in upper respiratory tract. Bact. Rev. 25:228-236.

Bartlett, D.
1968. Arch. Environ. Health 16:719.

Beard, R. and G. Wertheim
1967. Amer. J. Public Health 57:2012

Bennett, G.
1962. Ozone contamination of high altitude aircraft cabins. Aerospace Med. 33:969-973.

Berk, P.D., D.P. Tschudy, L.A. Shepley, J.G. Waggoner, and N.I. Berlin.
1970. Hematologic and biochemical studies in a case of lead poisoning. Am. J. Med. 48:137.

Bjure, J. and S. Fallstrom.
1963. Acta Paediat. 52:361.

Blair, W.H., Henry, M.C. and Ehrlich, R.
1969. Chronic toxicity of nitrogen dioxide. II. Effects on histopathology of lung tissue. Arch. Environ. Hlth. 18:186-192.

Bloor, C.M., Leon, A.S.
1968. The genetic determination of coronary artery patterns: a possible factor in atherogenesis. Amer. N.Y. Acad. Sci. 149, Art. 2, 860.

Booker, D.V., A.C. Chamberlain, D. Newton and A.N.B. Scott.
1969. Uptake of radioactive lead following inhalation and injection. Br. J. Radiol. 42:457.

Brant, J.W.A.
1965. Human cardiovascular disease and atmospheric air pollution in Los Angeles, California. Intern. J. of Air Water Pollution, 9:219-231.

Brant, J.W.A. and Hill, S.R.G.
1964. Human respiratory diseases at atmospheric air pollution in Los Angeles, California. Intern. J. of Air Water Pollution, 8:259-277.

Breslow, L. Hoaglin, L., Rasmussen, G. and Abrams, H.K.
1954. Occupations and cigarette smoking as factors in lung cancer. Am. J. Publ. Health 44:171-181.

Bridges, R.A., Berendes, H., Good, R.A.
1959. A fatal granulomatous disease of childhood; the clinical, pathological and laboratory features of a new syndrome. Am. J. Dis. Child. 97:387.

Briscoe, W.A., Kueppers, F., Davis, A.L., Bearn, A.G.
1966. A case of inherited deficiency of serum alpha antitrypsin associated with pulmonary emphysema. Am. Rev. Resp. Dis., 94:529.

Brown, J.S.
1962. Econ. Geol. 57:673.

Buell, P., Dunn, J.E. and Breslow, L.
1967. Cancer of the Lung and Los Angeles-type air pollution. Cancer 20:2139-2147.

Buell, G.C., Tokiwa, Y. and Mueller, P.K.
1965. Potential crosslinking agents in lung tissue. Formation and isolation after in vivo exposure to ozone. Arch. Environ. Hlth. 10:213-219.

Cassell, E., Lebowitz, M., Mountain, I., Lee, H., Thompson, D., Wolter, D. and McCarroll, J.
1969. Air pollution, weather, and illness in a New York population. Arch. Environ. Health, 18:523-530 (April).

Cassell, E., McCarroll, J., Ingram, Wm., and Wolter, D.
1965. Health and the urban environment - air pollution and famiiy illness: III. Two acute air pollution episodes in New York City: Health effects. Arch. Environ. Health 10:367-369.

Castellino, N. and S. Aloj.
1964. Kinetics of the distribution and excretion of lead in the rat. Brit. J. Industr. Med. 21:308.

Calcott, E.F., McCammon, J., and Kotin, P.
1958. Pulmonary pathology in dogs due to air pollution. J. Amer. Med. Assoc., 133:331-335.

Challen, P.J.R., Hickish, D.E. and Bedford.
1958. An investigation of some health hazards in an inert-gas-tungsten arc welding shop. Brit. J. Indust. Med. 15:276-282.

Chio, K.S., Reiss, U., Fletcher, B. and Tappel, A.L.
1969. Peroxidation of subcellular organelles: Formation of Lipofusein like fluorescent pigments. Science 166:1535-1536.

Chovin, P.
1967. Environ. Res. 1:198.

Chow, T.J.
1970. Nature 225 (5229), 295.

Chow, T.J. and Earl, J.L.
1970. Science (In Press)

Chow, T.J. and Johnstone, M.S.
1965. Science 147 (3657), 502.

Chronic Bronchitis in Great Britain: National survey carried out by respiratory diseases study group of College of General Practitioners.
1961. Brit. M.J., 2:973-979.

Clark, R.
1950. Amer. J. Physio. 162, 560.

Clean Air for California
1957. California State Dept. of Public Health. Berkeley. Initial Report, March 1955, Second Report, March 1956, Third Report, 1957.

Clean Air Quarterly.
1966. California State Dept. of Public Health, 10: No. 4.

Coffin, D.L., Blommer, E.J.
1967. Acute toxicity of irradiated auto exhaust and its indication of enhancement of mortality from streptococcal pneumonia. Arch. Envir. Hlth. 15: 36.

Coffin, D.L., Blommer, E.J., Gardner, D.E. and Holzman, R.S.
1967. Effect of air pollution on alteration of susceptibility to pulmonary infection. Presented at the 3rd. Annual Conference on Atmospheric Contamination in confined spaces. Dayton, Ohio, May 9-11.

Coffin, D.L., Gardner, D.E. Holzman, R.S. and Wolock, F.J.
1968. Influence of ozone on pulmonary cells. Arch. Environ. Hlth. 16:633-636.

Cohen, S., M. Deane, J. Goldsmith.
1968. Paper presented at the 9th Air Pollution Medical Research Conference, Denver, July.

Cooper, W.C. and Tabershaw, I.R.
1967. The oxides of nitrogen in air pollution. Report to the California Department of Public Health. July, pp. 1-107.

Dalhamn, T.
1956. Mucous flow and ciliary activity in the trachea of healthy rats exposed to respiratory irritant gases (SO_2, H_3N, CHO) - a functional and morphologic (light microscopic and electron microscopic) study with special reference to technique. Acta Physiol. Scand. 36 Suppl. 123:1-161.

Dalhamn, T.
1964. Studies on tracheal ciliary activity: Special reference to the effect of cigarette smoke in living animals. Am. Rev. Resp. Dis. 89:870-877.

Deane, M., Goldsmith, J.R., and Tuma, D.
1965. Respiratory conditions in outside workers: Report on outside plant telephone workers in San Francisco and Los Angeles. Arch. Environ. Health 10:323-331.

Documentation of Threshold Limit Values
1966. American Conference of Governmental Industrial Hygienists, rev. ed., pp. 33-36.

Douglas, J.W.B. and Waller, R.E.
1966. Air pollution and respiratory infection in children. Brit. J. Prev. Soc. Med., 20:1-8.

Ehrlich, R.
1966. Effect of nitrogen dioxide on resistance to respiratory infection. Bact. Rev. 30:604-614.

Ehrlich, R. and Henry, M.D.
1968. Chronic toxicity of nitrogen dioxide. I. Effect on resistance to bacterial pneumonia. Arch. Environ. Hlth. 17:860-865.

Emik, L.O. and Plata, R.L.
1969. Depression of Running Activity in Mice by Exposure to Polluted Air. Arch. Environ. Health 18:575-579.

Epstein, S.S., Joshi, S., Andrea, J., Mantel, N., Sawicki, E., Stanley, T. and Tabor, E.C.
1966. Nature 212, 1305.

Eriksson, S.
1965. Studies in α_1-antitrypsin deficiency. Acta Med. Scand. Suppl. 177.

Ferris, B.G., Jr., and Anderson, D.O.
1962. Prevalence of chronic respiratory disease in New Hampshire town. Am. Rev. Respiratory Dis. 86:165-177.

Firket, J.
1936. Fog along the Meuse Valley. Trans. Faraday Soc. 32:1192-1197.

Fisher, H.L.
1969. A model for estimating the inhalation exposure to radon-222 and daughter products from the accumulated lead-210 body burden. Health Phys. 16:597.

Forbes, W., F. Sargent, F. Roughton.
1945. Amer. J. Physiol. 143:594.

Freeman, G., Furiosi, N.J. and Haydon, G.B.
1966. Effects of continuous exposure of 0.8 ppm NO_2 on respiration of rats. ARch. Environ. Hlth. 13:454.

Freeman, G., Stephens, R.J., Crane, S.C. and Furiosi, N.J.
1968. Lesion of the lung in rats continuously exposed to two parts per million of nitrogen dioxide. Arch. Environ. Hlth. 17:181-192.

Gardner, M.B.
1966. Biological effects of urban air pollution: III. Lung tumors in mice. Arch. Environ. Health, 12:305-313.

Gardner, M.B., Loosli, C.G., Hanes, B., Blackmore, W., and Teebken, D.
1969. Histopathologic findings in rats exposed to ambient and filtered air. Arch. Environ. Health, 19:637-647.

Gardner, M.B., Loosli, C.G., Hanes, B., Blackmore, W., and Teebken, D.
1970. Pulmonary changes in 7000 mice following prolonged exposure to ambient and filtered Los Angeles Air. Arch. Environ. Health 20: 310-317.

Goldberg, A.
1968. Lead poisoning as a disorder of heme synthesis. Seminars in Hemat. 5: 424.

Goldsmith, J.R.
1969. Air pollution epidemiology: A wicked problem, an informational maze, and a professional responsibility. Arch. Environ. Health 18:516-522.

Goldsmith, J.R.
1969. Epidemiological bases for possible air quality criteria for lead. J. Air Pollution Control Assoc. 19: 714.

Goldsmith, J.R.
Air quality criteria for oxides of nitrogen epidemiological appraisal. Unpublished manuscript.

Goldsmith, J.R. and A.C. Hexter.
1967. Respiratory exposure to lead: epidemiological and experimental dose-response relationships. Science 158:132.

Goldsmith, J.R. and Landaw
1968. Carbon Monoxide and Human Health. Science 162:1352.

Goldsmith, J.R. and Nadel, J.A.
1969. Experimental exposure of human subjects to ozone. J. Air Pollut. Control Assoc. 19: 329-330.

Goldstein, E. and Green, G.M.
1966. The effect of acute renal failure on the bacterial clearance mechanisms of the lung. J. Lab. Clin. Med. 68:531-542.

Goldstein, E. and Green, G.M.
1967. Alteration of the pathogenicity of Pasteurella pneumotropica for the murine lung caused by changes in pulmonary antibacterial activity. J. Bact. 93:1651-1656.

Goldstein, E. and Green, G.M.
1969. The effect of silicosis on the antibacterial defense mechanisms of the murine lung. J. Inf. Dis. 120:210-216.

Goldstein, E., Green, G.M. and Seamans, C.S.
1970. The effect of acidosis on pulmonary bactericidal function. J. Lab. Clin. Med. 75:912-923.

Goldstein, B.D., Lodi, C., Collinson, C. and Balchum, O.J.
1969. Ozone and lipid peroxidation. Arch. Environ. Hlth. 18:631-635,

Grayson, R.R.
1956. Silage gas poisoning: nitrogen dioxide pneumonia, a new disease in agricultural workers. Ann. Int. Med. 45:393-408.

Green, G.M.
1968. Pulmonary clearance of infectious agents. Ann. Rev. Med. 19: 315-336.

Green, G.M. and Kass, E.H.
1964. Factors influencing the clearance of bacteria by the lung. J. Clin. Invest. 43: 769-776.

Green, G.M. and Kass, E.H.
1964. The role of the alveolar macrophage in the clearance of bacteria from the lung. J. Exp. Med. 119:167-176.

Griggs, R.C. and J.W. Harris.
1958. Erythrocyte survival and heme synthesis in lead poisoning. Clin. Res. 6:188.

Haenszel, W., Marcus, S.C. and Zimmerer, E.G.,
1956. Cancer morbidity in urban and rural Iowa. Publ. Health Monograph 37, U.C. Govt. Printing Office.

Haenszel, W. and Shimkin, M.B.
1956. Smoking patterns and epidemiology of lung cancer in the United States: are they compatible? J. Nat. Cancer Inst., 16:1417-41.

Hallett, W.Y.
1965. Effect of ozone and cigarette smoke on lung function. Arch. Environ. Hlth. 10:295-302.

Hammer, D.I., Portnoy, B., Massey, F.M., Wayne, W.S., Oelsner, T. and Wehrle, P.F.
1965. Los Angeles pollution and respiratory symptoms: Relationship during a selected 28 day period. Arch. Environ. Health. 10: 475-480.

Hauskneckt, R.
1960. Air pollution effects reported by California residents. California State Dept. of Public Health, Berkeley, Calif.

Hauskneckt, R.
1962. Experiences of a respiratory disease panel selected from a representative sample of the adult population. Amer. Rev. Respirat. Dis. 86: 858-866.

Haydon, G.B., Davidson, J.T., Lillington, G.A. and Wasserman, K.
1967. Nitrogen dioxide-induced emphysema in rabbits. Am. Rev. Resp. Dis. 95: 797-805.

Haydon, G.B., Freeman, G. and Furiosi, N.J.
1965. Covert pathogenesis of NO_2 induced emphysema in the rat. Arch. Environ. Hlth. 11:776-783.

Heckter, H.H. and Goldsmith, J.R.
1961. Air pollution and daily mortality. Amer. J. Med. Sci. 241: 581-588.

Heimann, H.
1961. Effects of air pollution on human health. In: Air Pollution, Columbia University Press, New York, page 159.

Henschler, D., et al.
1960. The odor threshold of some important irritant gases (sulfur dioxide, ozone, nitrogen dioxide) and the manifestations of the effect of small concentrations on man. Arch. Gewerbepathol. Gewerbehyg. 17:547-570.

Henry, M.C., Ehrlich, R., Blair, W.H.
1969. Effect of nitrogen dioxide on resistance of squirrel monkeys to Klebsiella pneumoniae infection. Arch. Environ. Hlth. 18:580-587.

Henry, M.C., Findlay, J., Spangler, J. and Ehrlich, R.
1970. Chronic toxicity of NO_2 in squirrel monkeys. III. Effect on resistance to bacterial and viral infection. Arch. Environ. Hlth. 20:566-570.

Hernberg, S. and J. Nikkanen.
1970. Enzyme inhibition by lead under normal urban conditions. Lancet Jan. 10, pp. 63-64.

Hernberg, S., M. Nurminen and J. Hasan.
1967. Nonrandom shortening of red cell survival times in men exposed to lead. Environmental Res. 1:247.

Heuss, J.M. and Glasson, A. Hydrocarbon reactivity and eye irritation.
1968. Env. Sci. and Tech. 2:1109-1116.

Higgins, I.T.T.
1957. Respiratory symptoms, bronchitis and ventilatory capacity in random sample of agricultural population. Brit. M.J., 2:1198-1203.

Higgins, I.T.T., Oldham, P.D., Cochrane, A.L., and Gilson, J.C.
1956. REspiratory symptoms and pulmonary disability in industrial town: survey of random sample of population. Brit. M.J. 2:904-910.

Hueper, W.C.
1961. Carcinogens in the human environment. Arch. Path. 71:237-267, 355-380.

Hueper, W.C., Kotin, P., Tabor, E.C., Payne, W.W., Falk, H. and Sawicki, E.
1962. Arch. Pathol. 74:89.

Hursh. J.B., A. Schraub, E.L. Sattler, and H.P. Hoffman.
1969. Fate of ^{212}Pb inhaled by human subjects. Health Phys. 16:257.

Ishikawa, S., D.H. Bowden, V. Fischer, and J.P. Wyatt.
1969. The emphysema profile in two midwestern cities in North America. Arch. Environ. Health, 18:660-666.

Kjeldsen, K., et al.
1968. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. J. Atheroscl. Res. 8:835.

Kalinske, R.W., Parker, R.H., Brandt, D. and Hoeprich, P.D.
1967. Diagnostic usefulness and safety of transtracheal aspiration. New Eng. J. Med. 276: 604-608.

Kilburn, K.H.
1967. Cilia and mucus transport as the determinants of the response of lung to air pollutants. Arch. Environ. Hlth. 14:77-91.

Klein, J.O., Green, G.M., Tilles, J.G., Kass, E.H. and Finland, M.
1967. Effect of intranasal reovirus infection on antibacterial activity of mouse lung. J. Inf. Dis. 119:43-50.

Klein, L.
1962. River Pollution. Butterworths, London.

Kleinfeld, M., Giel, C. and Tabershaw, I.R.
1957. Health hazards associated with inert-gas-shielded metal are welding. Arch. Environ. Hlth. 15:27-31.

Kononova, V.A. and Aksenova, V.B.
1961. Atmospheric air pollution with discharges from a synthetic alcohol plant and its effect on morbidity, sanitary and living conditions of the population. Gig. i Sant., 26:3-7 (September).

Kotin, P., Falk, H. and Thomas, M.
1956. Cancer 9:905.

Krajina, G.Z.
1964. Damage of the respiratory mucus membrane of rats exposed to cold. Acta Otolaryng. 57:342-351.

Krall, A. and N. Tolbert.
1957. Plant Physiol. 32:321.

Kueppers, F., Fallat, R., Larson, R.K.
1969. Obstructive lung disease and α_1-antitrypsin deficiency gene heterozygosity, Science 165:899.

Kueppers, F.
Communication to the author.

Kueppers, F., Briscoe, W.A., Bearn, A.G.
1969. Hereditary deficiency of serum α_1-antitrypsin. Science 146: 1678.

Lagerwerff, J.M.
1963. Prolonged O_3 inhalation and its effects on visual parameters. Aerospace Med. 34:479.

Landau, E., Smith R. and Lynn, D.A.
1969. J. Air Pollution Control Assoc. 19(9), 684.

Laskin, S., Kuschner, M. and Drew, R.T.
1970. In Inhalation Carcinogenesis, AEC Symposium, Series 18, pp. 321.

Laurell, C.B. and Eriksson, S.
1963. Electrophoretic α_1 globulin pattern of serum in α_1-antitrypsin deficiency. Scand. J. Clin. & Lab. Invest. 15:132.

Laurenzi, G.A., Potter, R.T. and Kass, E.H.
1961. Bacteriologic flora of the lower respiratory tract. New Eng. J. Med. 265:1273-1278.

Leon, A.S., Bloor, C.M.
1968. Quantitative analysis of coronary artery inheritance. J. Hered. 59:48.

Lewis, T.R., Hueter, F.G. and Busch, K.A.
1967. Irradiated automobile exhaust. Its effects on the reproduction of mice. Arch. Environ. Health 15:26-35.

Lichtman, H.C. and F. Feldman.
1963. In vitro pyrrole and porphyrin synthesis in lead poisoning and iron deficiency. J. Clin. Invest. 42:830.

Lidwell, O.M., et al.
1965. The epidemiology of the common cold. IV. The effect of weather. J. Hyg., Camb. 63:427.

Lieberman, J.
1969. Hetero- and homo-zygous alpha$_1$-antitrypsin deficiency in pulmonary emphysema. N.E.J. Med. 281, 279.

Lilienthal, J.L., R.L. Riley, D.D. Proemmell, R.E. Franke.
1946. Amer. J. Physiol. 145, 351.

Lindenberg, R., D. Levy, T. Preziosi, M. Christensen.
1962. Paper presented at a meeting of the American Industrial Hygiene Association, Washington, D.C.

Loewus, M. and C. Delwiche
1963. Plant Physiol. 38:371.

Lowry, T. and Schuman, L.M.
1956. Silo-Filler's Disease syndrome caused by nitrogen dioxide. J.A.M.A. 162:153-160.

Lunn, J.E., et al.
1967. Patterns of respiratory illness in Sheffield infant school-children. Brit. J. Prev. Soc. Med. 21:7-16.

Luomanmaki, K.
1966. Ann. Med. Exp. Biol. Fenniae (Helsinki) Suppl. 44, 2.

MacFarland, R., F. Roughton, M. Halperin, J. Niven.
1944. J. Aviation Med. 15:381.

Macklem, P.T. and Mead, J.
1967. REsistance of central and peripheral airways measured by a retrograde catheter. J. Appl. Physiol. 22:395-401.

Martin, A.E.
1964. Mortality and morbidity statistics and air pollution. Proc. Roy. Soc. Med. 7:969-975.

Med. World News.
1970. Who are the 5% whose genes invite emphysema? June 19.

McCarroll, J., Cassell, E., Wolter, D., Mountain, J., Diamond, J. and Mountain, I.
1967. Health and the urban environment. V. Ari pollution and illness in a normal urban population. Arch. Environ. Health 14:178-184 (January).

McCarroll, J.
1967. Measurements of morbidity and mortality related to air pollution. J. Air Pollut. Contr. Ass. 17:203-209 (April).

McMillan, R.S., Wiseman, D.H., Hanes, B., and Wehrle, P.F.
1969. Effects of oxidant air pollution on peak expiratory flow rates in Los Angeles school children. Arch. Environ. Health, 18:941-949.

Meyers, F.H. and Hine, C.H.
1961 Some experiences with nitrogen dioxide in animals and man. 5th Air Pollution Med. Research Conference, Los Angeles.

Middelton, V., A. Poznak, J. Artusio, S. Smith.
1965. Anesthesiology, 26:715.

Miller, S. and Ehrlich, R.
1958. Susceptibility to respiratory infections of animals exposed to ozone. Susceptibility to Klebsiella pneumoniae. J. Infect. Dis. 103:145-149.

Mills, C.A.
1957. Respiratory and cardiac deaths in Los Angeles smogs. Amer. J. Med. Sci., 233:379-386.

Morrow, P.E. and Gazioglu, K.
1966. The clearance of dust from the lower respiratory tract of man: An experimental study. In Davies, C.N. (ed) Cambridge, England.

Motley, H.L., Smart, R.H. and Leftwick, C.I.
1959. Effect of polluted Los Angeles air on lung volume measurements. J. Amer. Med. Assoc., 171:1469-1477.

Motto, H.L., Daines, R.H., Chilko, D.M., and Motto, C.K.
1970. Environ. Sci. Technol. 4(3), 231.

Mountain, I., Cassell, E., Wolter, D., Mountain, J., Diamond, J., and McCarroll, J.
1968. Health and the urban environment. VII. Air pollution and disease symptoms in a "normal" population. Arch. Environ. Health 17: 343-352. (September).

Mueller, P.K., Helvig, H.L., Alcocer, A.E., Gong, W.K. and Jones, E.
1964. A.S.T.M. Special Tech. Publication No. 352.

Murphy, S.D., Leng, J.K., Ulrich, C.E., and Davis, H.V.
1963. Effects on animals of exposure to auto exhaust. Arch. Environ. Health, 7:60-70.

Murphy, Ulrich, C.E., and Frankowitz, S.H.
1964. Altered function in animals inhaling low concentrations of ozone and nitrogen dioxide. J. Amer. Ind. Hyg. Assoc. 25:246-253.

Murozumi, M., Chow, T.J. and Patterson, C.C.
1969. Geochim. Cosmochim. Acta 33:1247.

Musselman, N., W.A. Groff, P.P. Yevich, F.T. Wilinski, M.H. Weeks, F.W. Oberst,
1959. Aerospace Med. 30:524.

Norwood, W.D., Wisehart, D.E., Earl, L.A., Adley, F.E. and Anderson, D.E.
1966. Nitrogen dioxide poisoning due to metal culting with oxyacetylene torch. J. Occup. Med. 8:301-306.

Novak, J. and A. Majsky.
1960. The binding of lead on erythrocytes. Cas. Lek Ces. 97:71, 1958. Abstracted in Blood 15:567, 1960.

Oski, F. and A. Altman,
1962. J. Pediat. 61:709, 1962.

Page, A.L. and Ganje, T.J.
1970. Environ. Sci. Technol. 4(2), 140.

Patty, F.A., editor.
1962. Industrial Hygiene and Toxicology. Vol. 2, pp. 920-923. Wiley Interscience, New York.

Pringle, B.H., Hissong, D.E., Katz, E.L., and Mulawka, S.T.
1968. J. Sanit. Eng. Div. Am. Soc. Civil Eng. 94:(SA-3), 455.

Pecora, D.V.
1963. A comparison of transtracheal aspiration with other methods of determining the bacterial flora of the lower respiratory tract.. New Eng. J. Med. 269:664-666.

Purvis, M.R. and Ehrlich, R.
1963. Effect of atmospheric pollutants on respiratory infection. J. Inf. Dis. 113:72.

Purvis, M.R., Miller, S., and Ehrlich, R.
1961. Effect of atmospheric pollutants on susceptibility to respiratory infection. I. Effect of ozone. J. Infect. Dis. 109:238-242.

Rabino, G.F., G.C. Coscia, G. Perrelli, and A. Parigi.
1964. Behavior of glutathione, glutathione stability test, and glucose-6-phosphate dehydrogenase activity in lead poisoning. Minerva Med. 54: 930, 1953. Abstracted in Blood. 23:707, 1964.

Remmers, J.E. and Balchum, O.J.
1966. Effects of Los Angeles urban pollution upon respiratory function of emphysematous patients. A.M.A. Air Pollution Med. Res. Conf., Los Angeles.

Renzetti, N.A. and Bryan, R.J.
1961. Atmospheric sampling for aldehydes and eye irritation in Los Angeles smog. J. Air Poll. Cont. Assoc. 11:121-124.

Rokaw, S.N., and Massey, F.
1962. Air pollution and chronic respiratory disease. Amer. Rev. Respirat. Dis., 86: 703-704.

Roughton, F. and R. Darling.
1944. Amer. J. Physiol. 141:17.

Roughton, F. and W. Root.
1945. J. Biol. Chem. 160:123.

Rubino, G.F., Coscia, G.C., Perelli, G., Parigi, A.
1963. Comportamento del glutatione, del test di stabilita glucosio-6-fosfato-daidrogensasica nel saturnismo. Minerva Med., 54, 930.

Saffiotti, U., Montesano, P., Sellakumar, A.R. and Borg, S.A.
1967. Cancer 20: 857.

Saita, G. and L. Moreo.
1964. Determination of blood and urinary delta-amino-levulinic acid in the diagnosis of past lead poisoning. Med. Lavoro. 55: 357.

Scheel, L.D., Dobrogorski, O.J., Mountain, J.T.,Svirbely, J.C. and Stokinger, H.E.
1959. Physiologic, biochemical, immunologic, and pathologic changes following ozone exposure. J. Appl. Physiol. 14:67-80.

Schlegel, R.J., Bellanti, J.A.
1969. Increased susceptibility of males to infection. Lancet, Oct. 18, p. 825.

Schlesinger, M.J.
1940. Relation of anatomic pattern to pathologic conditions of the coronary arteries. Arch. Path. 30:403.

Schoettlin, C.E. and Landau, E.
1961. Air pollution and asthmatic attacks in the Los Angeles area. Public Health Reports 76:545-548.

Schoettlin, C.E.
1962. The health effect of air pollution on elderly males. Amer. Rev. Resp. Dis., 86:878-897.

Schrenk, H.H.
1949. Air Pollution in Donora, Pa., Epidemiology of the unusual smog episode of October 1948: preliminary report by H.H. Schrenk and others. Federal Security Agency. Public Health Service, Bureau of State Services, Division of Industrial Hygiene. Public Health Service Bulletin #306. United States Government Printing Office, Washington, D.C.

Schuck, E.A., Stephens, E.R. and Middleton, J.T.
1966. Eye irritation response at low concentration of irritants. Arch. Env. Hlth. 13:570-575.

Schulte, J.
1963. Arch. Environ. Health 7:524.

Selikoff, I.J., Hammond, E.C. and Churg, J.
1968. Asbestos exposure, smoking, and neoplasia, J. Am. Med. Assn. 204:106-12.

Shimkin, M.B.
1959. On the etiology of bronchogenic carcinoma. In Spain DM (ed.). Tumors of the Chest, Greene and Stratton, Inc., New York, pp. 1-16.

Simpson, F., G. Talbot, D. Westlake
1960. Biochem. Biophys. Res. Commun. 2:15.

Sims, V.M. and Pattle, R.E.
1957. Effect of possible smog irritants on human subjects. J. Amer. Med. Assoc. 165: 1908-1913.

Sjöstrand, T.
1949. Scand. J. Clin. Lab. Invest. 1:201.

Smith, L.E.
1965. Peroxyacetyl nitrate inhalation. Arch. Environ. Hlth. 10:161-164.

Speizer, F.E.
1969. An epidemiological appraisal of the effects of ambient air on health: Particulates and oxides of sulfur. J. Air Poll. Control Assoc. 19: 647-655.

Sprague, J.B.
1969. Water Research 3(11), 793.

State of California. Department of Public Health. The oxides of nitrogen
1966. in air pollution, Berkeley.

State of California, Department of Public Health, Air Resources Board,
1967. Lead in the Environment and its Effects on Humans.

Steadman, B.L., Jones, R.A., Rector, D.E. and Siegel, J.
1966. Effects on experimental animals of long-term continuous inhalation of nitrogen dioxide. Toxicol. and Appl. Pharm. 9:160-170.

Stokinger, H.E.
1969. Cummings Memorial Lecture. The spectre of today's environmental pollution - USA brand: new perspectives from an old scout. Am. Ind. Hyg. Assoc. J. 30:195-217.

Stokinger, H.E., Mountain, J.T.
1967. Progress in detecting the worker hypersusceptible to industrial chemicals. J. Occup. Med. 9:537.

Stokinger, H.E., Wagner, W.D., and Dobrogorski, O.J.
1957. Ozone toxicity studies 111. Chronic injury to lungs of animals following exposure at a low level. Arch. Ind. Hlth. 16:514-522.

Stokinger, H.E. and Coffin, D.L.
1968. Biologic effects of air pollutants. In Stern, A.C. Air Pollution and Its Effects. Chapter 13, pp. 445-546. Academic Press.

Stupfel, M., G. Bouley, S. Dekov, M. Bourgeous, A. Rousell.
1968. Bull, Inst. Nat. Sante Rech. Med. 23:309.

Swann, H.E., Brunol, D., Wayne, L.G. and Balchum, O.J.
1965. Biological effects of urban air pollution: II. Chronic exposure of guinea pigs. Arch. Environ. Health 11: 765-769.

Swann, H.E. and Balchum, O.J.
1966. Biological effects of air pollution: IV. Effects of acute smog episodes on respiration of guinea pigs. Arch. Environ. Health, 12: 698-704.

Talamo, R.C., Blennerhassett, J.B., Austen, K.B.
1966. Familial emphysema and alpha$_1$-antitrypsin deficiency. N.E.J. Med. 275:1301.

Tappel, A.L.
1967. Can nutrient antioxidants slow aging process? Current Concepts of Nutrition. March 20.

Taramin, A., Wannamaker, B. and Srubny, L.M.
1965. The effect of inanition on the submendibular salivary glands and exocrine pancreas of the rat. Ann. N.Y. Acad. Sci. 121: 609-624.

Thomas, H.V., et al.
1967. Blood lead of persons living near freeways. Arch. Environ. Health 15:695.

Thompson, D. Lebowitz, M., Cassell, E., Wolter, D. and McCarroll, J.
1970. Health and the urban environment. VIII. Air Pollution, weather, and the common cold. Amer. J. Public Health 60: 731-739. (April).

Toyama, T.
1964. Air pollution and its health effect in Japan. Arch. Environ. Health 8:161-181 (January).

Ury, H.
1968. Arch. Environ. Health 17:334.

U.S. Bureau of Mines, Minerals Year Book.
1967. U.S. Government Printing Office, Washington, D.C.

U.S. Dept. of Health, Education and Welfare.
1968. The Health Consequences of Smoking. 1968 supplement to 1967 Public Health Service Review. Public Health Service Publ. No. 1696, Washington, D.C.

U.S. Public Health Service.
1965. Survey of Lead in the Atmosphere of Three Urban Communities. Publication No. 999-AP-12.

Vaughan, T.R., Jennelle, L.F., and Lewis, T.R.
1969. Long-term exposure to low levels of air pollutants; effects on pulmonary function in the beagle. Arch. Environ. Health 19:45-50.

Vaughan, T.R., Jr., Jennelle, L.F. and Trent, T.R.
1969. Long term exposure to low levels of air pollutants. Effects on pulmonary function in the beagle. Arch. Environ. Hlth. 19:45-50.

Vincent, P.D., and C.R.B. Blackburn.
1958. Effects of heavy metal ions on the human erythrocyte. II. Effects of lead and mercury. Aust. J. Exp. Biol. Med. Sci. 36:589.

vStudnitz, W. and B. Haeger-Aronsen
1962. Urinary excretion of amino acids in lead-poisoned rabbits. Acta Pharmacol. Toxicol. 19: 36.

Wagner, W.D.
1965. Experimental study of threshold limit of NO_2. Arch. Environ. Health 10:455-465.

Waldichuk, M.
1969. J. Water Pollution Control Federation 41(9).

Warren, H.V. and Delavault, R.E.
1962. J. Sci. Food Agr. 13:96.

Washburn, T.C., Medearis, D.N., Jr., Childs, B.
1965. Pediatrics, Springfield, pp. 35, 57, 798.

Wasserman, M.
1968. In discussion of Hemoglobinopathies, Israel J. Of Med. Sci. 4:485.

Watanabe, H.
1969. Effect of air pollution on the school children. (Presented at U.S.-Japan Joint Cooperative Science Group on Air Pollution Health Seminar, Boston, February.

Wayne, W.S., Wehrle, P.F. and Carroll, R.E.
1967. Oxident air pollution and athletic performance. J. Amer. Med. Assoc., 199:901-904.

Westlake, D., J. Roxburgh, G. Talbot.
1961. Nature 189:510.

White, P.D.
1960. The importance of heredity in coronary heart disease. Circulation 22:296.

Wilks, S.S.
1959. Science 129:964.

Wittenberg, J.
1960. J. Exp. Biol. 37:698.

Yagi, T.
1958. Biochem. Biophys. Acta 30:194.

Young, W.A., Shaw, D.B. and Bates. D.V.
1964. Effect of low concentrations of ozone on pulmonary function in man. J. Appl. Physiol. 19:765-768.

Young, W.A., Shaw, D.B., and Bates, D.V.
1963. Pulmonary function in welders exposed to ozone. Arch. Environ. Hlth. 7:337-340, 1963.

Zeidberg, L.D., Harton, R.J.M., and Landau, E.
1967. The Nashville air pollution study: V Mortality from disease of the respiratory system in relation to air pollution. Arch. Environ. Health 15:214-224.