AIR POLLUTION—1968

Part 2

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
AIR AND WATER POLLUTION

OF THE

COMMITTEE ON PUBLIC WORKS
UNITED STATES SENATE

NINETIETH CONGRESS

SECOND SESSION

ON

AIR QUALITY CRITERIA

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AIR POLLUTION—1968

MONDAY, JULY 29, 1968

U.S. SENATE,
SUBCOMMITTEE ON AIR AND WATER POLLUTION
OF THE COMMITTEE ON PUBLIC WORKS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:30 a.m., in room 4200, Senate Office Building, Senator Edmund S. Muskie presiding.

Present: Senators Muskie and Baker.

Staff present: Richard B. Royce, chief clerk and staff director; and Richard D. Grundy, professional staff member.

OPENING STATEMENT

Senator BAKER. Will the subcommittee come to order.

This morning we have four distinguished witnesses who will testify. We also have an internationally recognized authority in the field of environmental health who has appeared on many occasions before the Japanese Legislature, Dr. Michio Hashimoto, Chief, Environmental Pollution Control Section, Bureau of Environmental Sanitation, the Ministry of Health and Welfare of Tokyo.

We welcome you to these hearings, Doctor.

The Clean Air Act of 1963 called for the development of air quality criteria which accurately reflect current knowledge on the relationships between airborne contaminants and health and welfare. This approach was reaffirmed last year in the Air Quality Act of 1967 which directed the Department of Health, Education, and Welfare to issue "air quality criteria" and "recommend control techniques." This information is to be used by the States in the establishment of air quality standards in designated air quality control regions.

Air quality criteria are intended to delineate, on the basis of the best available scientific and medical evidence, the effects of individual contaminants, combinations of contaminants, or categories of contaminants on the constantly changing, somewhat indeterminate environment of man. Thus, economic and technological considerations are not relevant with regard to the establishment of ambient air quality criteria; they will be given full attention in the standard-setting procedures.

This series of hearings are part of the broad oversight function of the Subcommittee on Air and Water Pollution. We shall receive testimony from medical and scientific authorities concerning the basic assumptions and methodology in the development of air quality criteria.

We do not have all the answers on the relationships between air pollution and health and welfare effects, but there is sufficient evidence

to indicate a cause for concern. This evidence is reflected in previous testimony before the subcommittee and the recent staff report, entitled "Air Quality Criteria."

There are those who will challenge any criteria which lack final and absolute proof of a direct and causal relationship. But responsible public policy cannot wait upon a perfect knowledge of the cause and effect. Where the best available evidence indicates a health or welfare effect from environmental exposures, Government must move to minimize these exposures by interposing barriers between the public and the causative agents producing stress.

The witnesses during the next 3 days are experts in public health, respiratory diseases, and air pollution. The subcommittee intends to invite witnesses from Government and industry for a later series of hearings at a time to be scheduled.

The first witness is Dr. John R. Goldsmith, Chief, Environmental Hazards Evaluation Unit, California Department of Public Health, Berkeley, Calif.

Dr. Goldsmith, we welcome you to these hearings. You may proceed in any manner you wish. If you have a statement, we will be happy to receive it at this time.

STATEMENT OF DR. JOHN R. GOLDSMITH, CHIEF, ENVIRONMENTAL HAZARDS EVALUATION UNIT, CALIFORNIA DEPARTMENT OF PUBLIC HEALTH, BERKELEY, CALIF.

Dr. GOLDSMITH. Thank you, sir.

The statement which I have has been distributed and will be inserted in the record. In order to conserve time I shall only mention its highlights.

I am John R. Goldsmith. I am Chief of the Environmental Hazards Evaluation Unit of the California State Department of Public Health.

My areas of professional concern are both with the establishment of scientifically valid air quality criteria and with the conduct of epidemiological studies related to the effects of air pollution.

In this respect, we have had a number of recent publications and findings concerning such matters as the relationship between air pollution and motor vehicle accidents, the storage of toxic substances in the body and its possible relation to exposures, particularly with respect to lead, and recent studies on the possible role of carbon monoxide in influencing the case fatality rate of myocardial infarction.

I am qualified by the American Board of Internal Medicine; I have conducted research in respiratory physiology but most recently my interest has been in the field of epidemiology.

I have been on the staff of the State health department since August of 1957 except for a 2-year leave of absence during which I was an environmental epidemiologist in the Environmental Pollution Unit of the World Health Organization. I have listed in my prepared testimony a number of other qualifications.

CALIFORNIA'S AIR QUALITY STANDARDS

My involvement in air quality criteria officially began in 1959 when the California government called on the department to develop and publish standards for the quality of the air in the State. I have given the legislative citation which defines this in an appendix to my statement.

My personal responsibility was to organize the then-available data and to prepare recommendations for the State board of health concerning air quality standards.

I should like to emphasize that at the time this task was initiated, I had the feeling that we didn't know enough to do this job well. I was asked to do it anyhow and in the course of the work I have altered my views.

I think the more one is required to answer the question as to how much the evidence available can be used for policy purposes, the more one finds useful evidence. I know that some of my colleagues, for example, are concerned that we have too little knowledge about air pollution health effects to make constructive decisions, and I think that my experience in this respect should be relevant to their reservations.

MOTOR VEHICLE CONTROL

Following the adoption of these standards and the implementation of our historic program for motor vehicle exhaust control in California, I have frequently had an opportunity to discuss these standards before a variety of groups—Manufacturing Chemists' Association, Air Pollution Control Association, the Air Pollution Research Planning Seminar of the Public Health Service, several American medical association meetings and several meetings of the National Tuberculosis Association.

I have a number of publications in the Archives of Environmental Health of the American Medical Association of which I am a member of the editorial board.

MEDICAL RESEARCH CONFERENCE

Because the scientific basis for air quality standards depended so much on current knowledge of research in this field, I was involved with my colleagues in the organization of a series of air pollution medical research conferences, the first seven of which were organized under my direction and proceedings of which were published under my editorship.

The eighth and ninth have been organized and sponsored by the American Medical Association in cooperation with other agencies. The ninth just convened last week and I and my colleagues had a number of contributions to make. If the committee wishes, some of the more recent findings can be referred to at a later time.

AAAS AIR CONSERVATION COMMISSION

Recognizing the possibility that the general scientific community would find these standards difficult to understand or would have publicly notorious differences in the interpretation of evidence on air pollution health effects, an effort was undertaken with the American Association for the Advancement of Science to provide for the general scientific community information on air pollution, its health effects and relevant policy issues.

This resulted in an organization of an Air Conservation Commission of the AAAS, the report of which was published by the association as monograph No. 80 in its monograph series entitled "Air Conservation." In this instance, I was chairman of the organizing committee and a member of the commission.

WORLD HEALTH ORGANIZATION

In 1963, the World Health Organization convened an interregional symposium and adopted certain definitions set forth in appendix B of my prepared testimony.

The upper three levels used were from the California air quality standards plus a fourth level proposed by the Soviet Union indicating the lowest level producing any effect which could be determined.

Following the World Health Organization definitions and present usage by the Public Health Service, the initial California report on air quality standards may and probably should be considered also reports on air quality criteria.

CRITERIA DEVELOPMENT

Personally, I regret the confusion in these terms which has developed and I fully support the distinction which is now being made by the present legislation and by the Public Health Service. We could come back to that later, if you wish.

From 1966 to the present, I have been engaged with colleagues in preparing a series of technical reports on air quality criteria. Work is virtually complete for a document on oxidants, ozone, and peroxyacetylnitrates.

A second document is partially complete on carbon monoxide.

As a part of the joint effort by the Public Health Service and our department, we have made substantial contributions to documents on sulfur oxides and particulates. The work is partly supported by the Air Pollution Control Administration. The department is required by California statutes to recommend air quality standards based on health effects to the air resources board of that State.

We have agreed in conferences with the chairman of the board that the basis on which we will make these recommendations will be technical documentation of air quality criteria and we will then assist the board in interpreting these with respect to air quality standards as indeed the law now requires.

PHILOSOPHY OF CRITERIA AND STANDARDS

I have been asked to comment on the philosophy of the environmental quality criteria and standards. Public concern and awareness about a number of environmental problems comprise an imperative to which the governments must react. These problems include increasing levels of air pollution and water pollution, housing inadequacy, waste management problems, urban noise, radiation hazards, pesticide levels in food, difficulty in access to recreational opportunities, hazardous modes of transportation, and a host of other problems which degrade the quality of man's habitat and increase the risks which his technology poses to his health.

Governments may react arbitrarily to the wishes of the citizens of the business community on the basis of a superficial analysis. Additionally, governments may recognize that there are times when immediate decisions with inadequate information are necessary and they may support studies of various sorts.

AVAILABLE EVIDENCE

There then arises the inevitable question of how much information is needed for satisfactory policy decision. Governments may then elect to draw into these decisions the very strengths of science and technology which have permitted populations to grow, cities to develop, and technology to flourish.

A scientifically valid set of environmental quality criteria is in fact the utilization of this latter alternative and it provides both the best scientific judgment for these decisions and a robust guide for the additional research which is necessary.

There are, of course, times when immediate decisions with inadequate information are imperative and it is both economically and socially prudent to organize the fund of knowledge, even if it appears to be insufficient, in such a way that when these imperatives arise this informations is available.

Thus, even if confident predictive statements in the field of environmental quality criteria cannot easily be made, it is of great value to have compiled the necessary material that might be relevant. For example, one could list the possible reactions to environmental exposures that might be hazardous. Even though quantitative statements cannot be made, the availability of qualitative statements concerning likely effects of exposure under realistic conditions can be of great value.

CRITERIA VERSUS STANDARDS

I believe that quite simply stated environmental quality criteria can either be qualitative or quantitative statements concerning the likely effects on defined populations of defined environmental exposures.

Environmental quality standards, however, are simply defined as the politically sanctioned goals toward which an environmental management system is directed.

In some circumstances, environmental quality standards may have the effect of regulation; for example, if there is a single source of a specified pollutant in a given area. However, the major functions of environmental quality standards, in my opinion, are the promulgation of identifiable social, community and political goals. A practical plan for reaching these goals completes the needed policy and managerial apparatus.

Environmental quality criteria may be related to environmental quality standards on a 1-to-1 basis as was in fact the case for the California standards for ambient air quality in 1959, or there may be various factors of safety by which environmental quality criteria are related to environmental quality standards.

It is, of course, possible also that environmental quality standards can exist in the absence of environmental quality criteria, but in this case there is inevitable uncertainty concerning their instrument of use as a policy.

Intrinsic to the philosophy of environmental quality criteria and standards are three points:

First, that the relation of evidence to these statements will be explicit and available to all interested parties;

Second, that all relevant evidence is considered; and

Third, that the health effects be considered in a broad context and not strictly limited to the specific diseases which have so frequently preoccupied medical scientists.

By definition, environmental standards are not only the reflection of environmental and biological reactions to alterations in environmental quality but also reflect economics and technical feasibility. They may differ from one location to another as these latter factors may differ.

Conversely, the nature of environmental quality criteria, in my opinion, is such that if they are thoroughly developed and include all relevant sources of information from any scientist, any place in the world, they may be universally applicable.

EMISSION STANDARDS

Obviously, emission standards and operating practice standards are also an important part of the environmental management system. In my opinion, the development in a systematic form of environmental quality criteria, environmental quality standards, and environmental management programs for reaching these politically sanctioned goals are the essential and necessary triad for reaching the goal of environmental health planning.

I believe that we should keep that long-term goal firmly in mind because of the relevance to other environmental problems of what is now being said and done, considered, and researched in the field of air pollution and its health effects.

CLASSIFICATION OF EFFECTS

There is a spectrum of possible effects on defined populations. The spectrum is often not considered in its full extent. Paraphrasing the World Health Organization definitions, these would include, first, exposure producing detectable but not necessarily harmful effects; second, those having effects on comfort, enjoyment, or well-being but not producing bodily damage or disease; third, those exposures interfering with important functions of the body and/or with long continued exposures which contribute to development or aggravation of chronic illness; and, fourth, exposures contributing or producing acute illness or fatality.

Now, this classification does not include some effects which are of current interest and precisely how they should be characterized still requires scientific discussion. For example, what does one say about the contributory effect of community air pollution to the increased frequency of motor vehicle acidents, or what does one say about the storage in the body of potentially harmful materials which under certain circumstances may be released and cause harmful effects in the body?

It is to be hoped that these ambiguities can soon be clarified, indeed in an appropriate scientific forum they can be promptly clarified. Explicit consideration of the possible impairment of longevity and of the possible production and mutation should also be included in the classification of criteria.

CRITERIA CONSIDERATION

It is important to stress that air quality criteria should consider all possible effects even if all of the consequences of any or all of them are not entirely known. It also follows that the effects to be considered most seriously are those occurring under realistic conditions and that means the likely presence of not only a given pollutant but perhaps groups of pollutants or of climatological or other conditions of exposure which includes exposures from other sources to the same materials.

ROLE OF EPIDEMIOLOGY

There are, therefore, real problems of estimation of population effects. That is, the function of epidemiology in these fields to define these population attributes and the nature of their exposures and effects. This is the bulk of what my own investigative work is directed toward.

VARIATION IN SUSCEPTIBILITY

There are, of course, wide ranges of variation in any real population in susceptibility to a given atmospheric pollution exposure and there is the inevitable problem as to what sector of this population the whole apparatus of air pollution control should be directed toward. Should it be directed to the average person, the normal worker? Should it be directed to those that are defined as the most feeble and most sensitive

under the most extreme conditions—the premature infant, the elderly person with chronic illnesses whose health is declining?

SUSCEPTIBLE GROUP DEFINITION

These problems were rather seriously and thoroughly considered at the time the California air quality standards program was initiated and we have adopted the definition that the standards should be designed to protect the "most susceptible group in the community provided they can be defined in terms of age and medical status."

Now, such a definition excludes the single and uniquely susceptible individual and leaves it to his private physician and his private resources to provide protection. As long as it is possible to define a sensitive group in the population a priori then it is the view of the California department that it is this group to which standards and control programs should be directed.

It also follows that if this is put into practice that such a group should be defined in the documents which set forth the air quality standards, and this indeed has been the practice in California.

EXPOSURE FREQUENCY

Recently, our department has been directed by legislature to add to the intensity of air pollution related to health effect, the elements of the frequency and duration of exposure to excessive levels which have to be considered in order to define what the legislature asked us to define which was "a substantial threat to health."

We have ended a fairly extensive discussion and public hearings by adopting a definition including any occurrence of a "serious" or "emergency" level. If the so-called adverse or the lowest level of the California standard is exceeded on three or more successive days or for seven times in any 3-month period, this is defined at the present time by our department as a "substantial threat from air pollution."

(The precise definition is as follows:)

DEFINITION OF "SUBSTANTIAL THREAT FROM AIR POLLUTION"

Title 17. Public Health.
Chapter 5. Sanitation (Environmental).
Subchapter 5. Air Sanitation.
Article 1. Standards for Ambient Air Quality.
30502. Definition of "Substantial Threat from Air Pollution" for Purposes of Health and Safety Code Section 426.3.

Atmospheric contamination sufficient to pose a substantial threat to the public health including irritation to the senses or to interfere with visibility or damage vegetation exists in any area of the state where:

1. The "serious" or "emergency" level of the air quality standard adopted by the State Department of Public Health in Section 30500–30501 of this code is reached or exceeded for any contaminant; or

2. The concentration of any contaminant reaches or exceeds that specified as the "adverse" level of the air quality standard adopted by the State Department of Public Health in Section 30500–30501 of this code in either of the following ways:

(*a*) When the frequency of occurrence exceeds seven days in any three-month period.

(*b*) When the duration of an episode is three or more consecutive days.

NOTE.—In the application of these definitions to the evaluation of air quality in any area, the measurements of contaminant concentration must be obtained from sampling locations representative of the area, and by methods recognized as being suitable for air quality evaluation.

LABORATORY STUDIES

One of the dilemmas in relating experimental studies to air quality criteria is that most of the experimental evidence is based upon so-called square wave exposures. There is a period in which there is no exposure; suddenly the exposure is altered to a fixed level and then abruptly the exposure is terminated after a specified period of time. Unfortunately for the interpretation of such evidence most realistic air pollution exposures have no such time course; they fluctuate in a reasonably predictable pattern given certain probability factors.

But the systematic exposure of experimental animals or experimental human subjects to the fluctuating exposures likely to occur in community air pollution is not very common. This is only one of the additional reasons why the use of epidemiologic studies is particularly urgent.

It is convenient and common to use time weighted averages to accommodate for the fluctuation measurement and exposure data but it must be done with some caution. For example, it does not necessarily follow that exposure to 1,000 parts per million for example of carbon monoxide for 6 minutes, a tenth of an hour, is necessarily equal to the exposure for 100 hours at one part per million, and so forth.

CATEGORIES OF INFORMATION

In the technical work which we have done in order to develop reports on air quality criteria, we have divided the material relevant to this into three major areas:

(1) Environmental aspects which for convenience can include effects on visibility and materials;

(2) Toxicological aspects which includes all experimental work whether on man or animals; and

(3) Epidemiological aspects which includes "natural" experiments and unplanned exposure of humans, animals, and plants.

In general, the epidemiological studies are more costly and require more advanced planning and result in a different class of conclusions than do toxilogic or experimental studies. For example, epidemiological studies lead to statements of association and are less likely to result in statements of causation. Laboratory studies on the other hand can usually be replicated, are usually less expensive and may lead to statements of causation.

It is perfectly obvious that the experimental exposure of human subjects to all classes of air pollution has very strict ethical limitations. And it is for this reason that epidemiologic work has been most significant in the adoption of the various air quality criteria that we have been mostly concerned with.

ROLE OF TOXICOLOGY

With respect to the relative roles of research in toxicology and epidemiology, the Department of Commerce Technical Advisory Board in its program, "A Program for Progress", points out the methods of funding and research administration particularly appropriate for existing research programs have not been satisfactory.

Much has been said in the past about the inability of experimental studies to replicate the findings during air pollution disasters. When this kind of conflict occurs, it seems to me it is reasonable to assume that the experiments have been inadequately realistic and not that the epidemiological phenomenon did not occur.

ROLE OF EPIDEMIOLOGICAL STUDIES

It follows from this and the other remarks that I have made, that the relative importance of epidemiological studies is generally accepted as taking precedence over comparably good laboratory studies in the establishment of air quality criteria. However, the laboratory research has a crucial role of helping to identify those variables to which epidemiological studies must pay attention and also to identifying the mechanisms of observed effects.

Another virtue of epidemiological studies, sir, is that it is not essential to understand the mechanisms by which the associations occur as long as it is clearly demonstrated that the associations exist and that when the associations are weakened the undesirable health effects are also diminished.

It is such a set of logical premises that led to the control of smallpox, typhoid, and rabies before the mechanisms of their transmission and their pathogenesis were known.

GAPS IN KNOWLEDGE

Identification of gaps in knowledge is an inevitable result of a systematic approach to air quality criteria. It indeed is one of the secondary purposes and a very important one to highlight those particular gaps in knowledge which inhibit the statements of needed policies for air pollution control and air pollution standards.

I shall not speak further about concepts underlying air pollution standards since in the field of economic and feasibility and technical matters I do not consider myself an expert.

ROLE OF WHO

I have already referred to the role of the World Health Organization and to its assistance in defining air quality criteria. In my opinion, while the World Health Organization and other international agencies provide an excellent forum for policy decisions in the field of air and other environmental quality criteria, this does not preclude the national and State agencies from proceeding to develop, publish, comment upon, and define criterion of their own.

An ideal arrangement would be for the World Health Organization to be able to establish one or more reference centers in various countries to which governments could be referred for the most up-to-date information relating to pollution exposure and probable effects.

Such an arrangement could be developed in this country were we willing to provide resources for one or more centers in this country on the condition that other countries did likewise and that the entire effort was coordinated by the World Health Organization. Such a

system exists with respect to many of the other programs of the World Health Organization.

I can speak from personal experience as to WHO's interest and qualifications to manage a set of international reference centers. I believe in a reasonably short period of time that such international teamwork would pay handsome dividends to the people of this country with respect to the resources that it might require.

ROLE OF FEDERAL GOVERNMENT IN STANDARD DEVELOPMENT

By contrast, air quality standards could and probably should be developed on a more localized basis. The role of the Federal Government in the field of air quality criteria is clearly to provide a focus for, collecting information and for its systematic interpretation.

Whether it can best do this with its own staff, by contract, or by dealing directly with various scientific agencies is still being explored. In this respect, the work of the National Research Council and the National Academy of Sciences is particularly noteworthy, and an approach in this direction appears to be just starting.

However, there are many nongovernmental scientific bodies or there are many less comprehensive in their scope which are also very much interested.

The level of scientific and technical competence required for the acceptable interpretation of complex sets of data with respect to air quality criteria has generally been underestimated. This has led on some occasions to the simple compilation of abstracts of scientific reports being put out as equivalent somehow to air quality criteria. I reject the premise that such a compilation is adequate. In general, it requires as much sophistication to make a systematic interpretation of research as it does to conduct research.

For this reason, I strongly recommend that those involved in the judgments respecting air quality criteria be qualified scientists themselves.

Such a high level of staff competence devoted to the interpretation of research in behalf of air quality criteria is particularly important since what is desired is that there be a consensus by scientists in the interpretations. The most suitable proponent of such a consensus is generally a scientist, himself.

ROLE OF PRIVATE GROUPS

In the absence of a consensus or mechanism for establishing it, I would submit that this is the role where the private agencies and professional societies should be greatest. That is to say, documents on air quality criteria could most constructively be submitted to such private agencies and professional societies for determination as to whether their interpretations are acceptable and reasonably in accord with their judgment.

With respect to standards, it seems that the major responsibility need not rest with scientific organizations but then this depends a good deal on the particular problem.

CRITERIA VERSUS STANDARDS

I feel very strongly that a clear distinction should be made between criteria and standards as these terms are now used. There is always the temptation to use as a standard the lowest level which some criterion report says is capable of producing an effect. If this is done blindly, it will lead to much unnecessary restriction and it will lead, of course, to the equivalents between criteria and standards, and I feel that this would be undesirable from many points of view.

Another implicit assumption is that the work on air quality criteria must be thorough and deliberate. Considerable difficulty arises when very short deadlines are given and consultants or professional societies feel that their consideration of major propositions has to be hasty.

LEGISLATIVE CONSIDERATIONS

There is, of course, always the temptation for Congress and legislatures to adopt numerical standards, and under some circumstances this is a perfectly legitimate use of their goal-setting authority. However, the extent to which such decisions are capable of modification when new evidence becomes available is often inadequate.

In any event, it should be clear that the legislative process is an inappropriate one for setting criteria but it may be an appropriate one for setting standards.

Administrative practice in other environmental health problems has made it clear that it is best to leave a setting of standards based on technical considerations to the technically best qualified group. Insofar as the major considerations are those of community values, it is entirely appropriate to consider the best qualified group to be the Congress or the legislature. Where considerations involve technical aspects that go substantially beyond this, it might be better to leave the establishment of standards to a health agency or a resource agency and to restrict the role of the Congress or the legislature to the establishment of procedural guidelines.

CRITERIA FEASIBILITY

It is my personal opinion that there are sufficient data to set predictive air quality criteria for oxidants and ozone under conditions which occur in Los Angeles, to establish joint criteria for particulates and sulfur oxides under conditions of temperate climate, to establish criteria for carbon monoxide and to state at what level the community exposure to lead is likely to lead to detectable increases in storage of this substance within the body.

This is not the appropriate time for discussing all other criteria but I would like to stress that if there is insufficient data to come to a predictive, quantitatively valid statement on which a scientific consensus can be reached, then the people responsible for setting air quality criteria should be left the option of stating so. When there is no such consensus, no criteria would be set.

CONCLUSION

In conclusion, the process of applying scientific judgment to the development of air quality criteria which have predictive validity is a process which, in my opinion, can protect health and encourage technical development without undue risk on the one hand or unnecessary investment on the other. The process must draw extensively on the scientific community and can promise the scientific community in return that this process will lead to the more precise definition of more precise research goals.

It would follow that if this process is carried out in this fashion, the support of the indicated research should be most readily justified.

Thank you, Senator.

(The complete prepared statement of Dr. Goldsmith follows:)

COMPLETE PREPARED STATEMENT OF DR. JOHN R. GOLDSMITH

My name is John R. Goldsmith. My position is Chief of the Environmental Hazards Evaluation Unit, Division of Environmental Health, California State Department of Public Health. I have been associated with that Department since August of 1957 except for a two-year leave of absence. During that two-year period I was an environmental epidemiologist in the Environmental Pollution Unit of the World Health Organization with headquarters in Geneva. My service in the World Health Organization was from September 1964 to September 1966.

Since I am no longer officially connected with the World Health Organization, my remarks do not necessarily reflect the views of that organization.

My professional relationships with the questions under consideration by this Subcommittee are as follows:

(*a*) In 1959 the Governor and Legislature of California called on the California State Department of Public Health to "develop and publish standards for the quality of the air of this state." The precise Legislative citation is given in Appendix A of my testimony. My responsibility was to organize and prepare the recommendations for the State Board of Health concerning air quality standards. In this, of course, I was assisted by other associates in the Department, particularly Mr. John Maga, and by numerous consultants whose association with our program has remained cordial and highly effective.

(*b*) Following adoption of these standards and the implementation of California's historic program for motor vehicle exhaust control, I was called on on a number of occasions to interpret and discuss these standards and their philosophy. Notable among the groups addressed was the Manufacturing Chemist's Association, the Air Pollution Control Association, the Air Pollution Research Planning Seminar, of the Public Health Service. My publications have included those in the Archives of Environmental Health of the American Medical Association, and in many other periodicals and presentations.

(*c*) In particular the scientific basis for air quality standards based on health effects has been supported by reports derived from a series of air pollution medical research conferences which were organized under my direction and the proceedings of which were published under my editorship. The eighth and ninth in these series of conferences have been organized and sponsored by the American Medical Association in cooperation with other agencies.

(*d*) Recognizing the possibility that the general scientific community would fail to understand or differ strikingly in its interpretation of the evidence on air pollution health effects, an effort was undertaken with the American Association for the Advancement of Science in order to provide to the general scientific community information on policy issues that were relevant. This resulted in the organization of an Air Conservation Commission, the report of which was published by the American Association for the Advancement of Science as Monograph #80 in its monograph series entitled "Air Conservation". In this effort I was Chairman of the Organizing Committee and a member of the Commission.

(*e*) In 1963 the World Health Organization convened an interregional symposium on Air Quality Criteria and Methods of Measurement in which I was a participant. The symposium adopted certain definitions and particularly agreed on a four-level set of air quality criteria which are given in Appendix B. These definitions were incorporated in the Expert Committee Report of the World Health Organization, Technical Report Number 271.

Following the World Health Organization definitions, and present usage by the Public Health Service, the California report on Air Quality Standards may also be considered air quality criteria.

(*f*) From 1966 to the present date, I have been engaged with colleagues in preparing series of technical reports on Air Quality Criteria. Work is virtually complete for a document on oxidants, ozone, and peroxyacetylnitrates. A second document is partially complete on carbon monoxide. As a part of a joint effort by the Public Health Service and our Department, contributions have been made toward documents on sulfur oxides and particulates. Our work is partly supported, now, by the Public Health Service, National Center for Air Pollution Control, though the Department is required by California Statutes to recommend air quality standards based on health effects to the Air Resources Board of the State.

PHILOSOPHY OF ENVIRONMENTAL QUALITY CRITERIA AND STANDARDS

Public concern and awareness about a number of environmental problems comprise an imperative to which governments must react. These problems include increasing levels of air pollution and water pollution, housing inadequacy, waste management problems, urban noise, radiation hazards, pesticide levels in food, difficulty in access to recreational opportunities, hazardous modes of transportation, and a host of other problems which degrade the quality of man's habitat and increase the risks which his technology poses to his health. Governments may react impetuously and parochially, forbidding this, restricting that, or appropriating funds for studies or take other steps which do not draw adequately on the available fund of relevant information. Alternatively they may elect to draw into the necessary decisions, the very strengths of science and technology which have permitted populations to grow, cities to develop and technology to flourish. A scientifically valid set of air quality criteria permits the second alternative to be chosen.

Recognizing that there are times when immediate decisions with inadequate information are necessary, it is both economically and socially prudent to organize the fund of information as well as it can be done, in order to make the necessary decisions reasonable and widely acceptable. Thus, environmental quality criteria and standards are perceived as the result of a necessary process for the efficient and safe use of technology in the habitat of modern man. Quite simply stated Environmental Quality Criteria are qualitative or quantitative statements concerning the likely effects on defined populations of defined environmental exposures. Environmental Quality Standards are simply defined as the politically sanctioned goals toward which an environmental quality management system is directed. In some circumstances environmental quality standards may have the effect of regulation; for example, if there is a single source of a specified pollutant in a given area. However, the major function of environmental quality standards are the promulgation of identifiable goals. Environmental quality criteria may be related to environmental quality standards on a one-to-one basis as was in fact the case for the California Standards for Ambient Air Quality in 1959 or there may be various factors of safety by which environmental quality criteria are related to environmental quality standards. A final possibility is that environmental quality standards can exist in the absence of criteria but in this case there is an element of uncertainty concerning them. When and if new data are made available the criteria and standards may need to be changed.

Intrinsic to the philosophy of environmental quality criteria and standards are two points: 1) that the relation of evidence to these statements will be explicit and available to all interested parties and 2) that as new evidence is developed the criteria and standards are subject to alteration. By definition, Environmental Quality Standards are seen as not only the reflection of environmental quality and biologic reactions related to this but also of economic and technical feasibility. Thus they may differ from one location to another according to geographic and climatologic factors and also according to social and economic aspects. Conversely, the nature of environmental quality criteria is such that they may be uni-

versally applicable if they are thoroughly developed and include all relevant sources of information.

Emission standards and operating practice standards are also an important part of an environmental management system. They will not, however, be treated further here other than to point out that environmental quality standards may lead directly and obviously to emission standards and/or standards of good practice.

CONCEPTS UNDERLYING AIR QUALITY CRITERIA

For most pollutants it is obvious that there is a spectrum of possible effects on defined populations. These may be fitted by the four levels of criteria as defined by the World Health Organization which will be paraphrased as—

1. detectable but not necessarily harmful effects;
2. effects on comfort, enjoyment, or well-being but not necessarily producing bodily damage;
3. effects which interfere with important functions of the body and/or, with long continued exposure, may be a contributory factor to chronic illness;
4. effects which have an immediate and obvious relation to acute illness or fatality.

This classification does not include some effects which are of current interest, and precisely how they should be characterized is still to be established. For example, what does one say about the contributory effect of community air pollution to increased frequencies of motor vehicle accidents; or what does one say about the storage in the body of potentially harmful materials which may under certain circumstances be released. It is to be hoped that these ambiguities will soon be clarified. It may also be hoped that some explicit consideration of impairment of longevity would be included in the set of criteria.

From this discussion, however, one important biological concept follows and that is that air quality criteria should consider all possible effects whether or not the full consequences of any or all of them are known. It also follows that effects to be considered are those occurring under realistic conditions which means in the likely presence of other pollutants or of climatological or other conditions of exposure including that from other sources that are to be expected by real populations. Present concepts do not accept alone as biologically relevant a level of air quality such as "a non-polluted atmosphere" or a pollution no greater than some hypothetical or measured background level. Such concepts have been extensively used in radiation criteria and it is tempting to apply them particularly from substances such as ozone which have a measurable background. In air quality criteria work (apart from radiation) this is not yet an established concept.

It follows from what has been said before that there is marked variability among any real population in susceptibility to a given atmospheric pollution exposure. This faces the environmental management system with the problem: which group one should protect? Should it be every single individual in a large metropolitan complex of millions of people; or should it be only the normal individuals among this group; should it be only those for whom a reasonable presumption of susceptibility can be defined *a priori*? The California Air Quality Criteria and Standards have opted for the latter decision, namely that the standards should be designed to protect the "most susceptible group in the community provided they can be defined in terms of age and medical status." An extension of this definition has included susceptibility due to other common exposures such as to occupational pollution or to cigarette smoking. This definition leaves the isolated individual who is highly or unpredictably sensitive to be protected by individual measures. It also requires of those who wish to set air quality standards that they make articulate their premises about the most susceptible group which they are seeking to protect.

CONCEPTS OF RISKS

It becomes necessary in defining air quality criteria to identify the populations at different levels of risks and to determine the duration of the exposure which is likely to produce specified effects. Characteristically, laboratory data are available for so-called "square-wave" exposures in which for a given period of time the exposure is suddenly altered from zero to some finite value where it remains for minutes or hours when it immediately returns to zero. With respect to atmospheric pollution, this is quite unrealistic, in that most exposures are

fluctuating and there is, for many pollutants, a measurable background level; the increase is gradual, and for realistic periods of time there may be extensive fluctuations in the exposure level. This has led to the convenient but not always reliable concept of equivalence of time-weighted averages, and these are widely used. Thus, however, it is incorrect to consider as equally severe an exposure of 100 ppm of carbon monoxide for one hour and an exposure to 10 ppm for ten hours. In general, for the use of products of time and concentration for exposure are handy but have to be used cautiously and within defined limits.

RESPECTIVE ROLES OF EPIDEMIOLOGICAL AND LABORATORY STUDIES, GAPS IN KNOWLEDGE AND NEW STUDIES REQUIRED

In general, epidemiologic studies are costly, require substantial planning and result in statements of association but are less likely to result in statements of causation. Laboratory studies, on the other hand, can usually be replicated, are relatively less expensive and may lead to statements of causation. Naturally, the limitations of the experimental study of humans are substantial and so the most extensive substitution of epidemiologic for laboratory studies occurs in relation to human reactions.

Laboratory experiments have generally failed to make entirely clear why there was so much illness and excess mortality under conditions prevailing during the air pollution disasters in London and Donora. There are several possible explanations for this, none of them universally accepted. One is that the realistic combinations of pollutants and particularly of gaseous material and particulate matter have not been replicated in the experiments. The second possibility is that persons who are otherwise susceptible have not been studied. Where conflicts of this sort occur, it is the most reasonable premise that the experiments have been inadequately realistic and not that the epidemiologic phenomena did not occur. Accordingly, the relative importance of the best of epidemiologic studies is generally accepted as taking precedence over comparably good laboratory studies. However, the laboratory research has the crucial role of helping to identify those variables to which epidemiologic studies should pay attention and also to identify mechanisms for any observed effects.

Every systematic review of the fund of knowledge on air pollution-health interactions leads inevitably to the identification of gaps in this fund of knowledge. Identification of such gaps should be considered an important but secondary role for work on air quality criteria. It is, indeed, one of the major reasons for widely disseminating the technical reports on the subject.

CONCEPTS UNDERLYING AIR QUALITY STANDARDS

This witness does not feel competent to discuss extensively the desired attributes of air quality standards. It is felt important that wherever possible the standards be based upon criteria in a defined and explicit fashion. When this is not done the standards should be qualified as tentative or unsubstantiated or speculative or similar conditional adjectives.

ACTIVITIES OF INTERNATIONAL, FEDERAL, STATE AND PRIVATE AGENCIES

Insofar as scientific communication is truly international and agreement among scientists follows from such communication, and insofar as air quality criteria are to be based on the findings and judgments of scientists, they ought, if at all possible, to be international. The World Health Organization has a widely recognized responsibility for interpreting and facilitating agreement on air quality criteria. It is unfortunate that it has been rather modestly supported in this effort, the more so since a similar effort could obtain air quality criteria both for community and occupational exposure and the organization is well qualified to translate experience in air quality criteria into other environmental quality criteria.

While the World Health Organization and other international agencies provide an excellent forum for policy decisions in the field of air and other environmental quality criteria, this does not preclude national and state agencies from proceeding to develop, publish, seek, comment upon, and define criteria on their own. The ideal arrangement would be for the World Health Organization to be able to establish one or more reference centers to which governments could be referred for the most up-to-date information relating pollution exposure and probable effect. Such centers could serve the additional purpose of providing a

focus for the interpretation of such evidence and for the training of staff scientists from different countries in the concepts and procedures affecting air quality criteria.

By contrast, air quality standards could and probably should be developed on a more localized basis since variation in climate and technical development and in economic considerations are likely to vary from one place to another.

The role of the Federal Government in the field of air quality criteria is clearly to provide a focus for the collection of information and its systematic interpretation. Whether it can best do this with its own staff, by contract, or by dealing directly with various scientific agencies is still being explored. The level of scientific and technical competence required for the acceptable interpretation of complex sets of data with respect to air quality criteria has generally been underestimated. This has lead, on some occasions, to the feeling that the compilation of scientific reports is the equivalent to the systematic interpretation thereof. In general, it requires as much sophistication to make a systematic interpretation of research as it does to conduct research. This is the more important since what is generally sought is a consensus by scientists that the interpretation of their own research findings is reasonable. In the absence of such a consensus, the role of private agencies and of professional societies which are non-governmental appears to be larger but in our opinion the goal should be to obtain the consensus from the start. In this event efforts by private agencies and professional societies is best directed to their primary goals. However, it could well be through professional societies that the question of consensus may be tested.

The foregoing statements are only intended to apply to air quality criteria. With respect to standards, it seems reasonable that the major responsibility should rest with state agencies or even local agencies with advice and assistance by the Federal Government and when indicated by private agencies or professional societies. The role of international agencies in air quality standards would seem to be more important in developing countries than in the United States.

Within the previous discussion it is extremely important to stress that an open and skeptical attitude toward the relationship of criteria and standards is essential if these remarks are to have validity. This is important since there is always the temptation to use as a standard of the lowest level which a criterion report says is capable of producing an effect. If this is done blindly, it will lead to the equivalence between the establishment of criteria and setting of standards.

Another implicit assumption is that the work on air quality criteria must be thorough and deliberate. Considerable difficulty arises when very short deadlines are given and consultants or professional societies feel that their consideration of major propositions is hasty.

There is, of course, always the temptation for Congresses and Legislatures to adopt numerical standards and under some circumstances this is a perfectly legitimate use of their goal-setting authority. However, the extent to which such decisions are capable of modification when new evidence becomes available is very important. In any event it should be clear that the legislative process is an inappropriate one for setting criteria but it may be an appropriate one for setting standards. Administrative practice in other environmental health problems has made it clear that it is best to leave setting of standards which are based on technical considerations to the technically best qualified group. Insofar as the considerations are those of community values, it is entirely appropriate to consider the best qualified group to be the Congress or the Legislature. When considerations involve technical aspects that go substantially beyond this, however, it is better to leave the establishment of standards to a healthy agency or a resource agency and to restrict the role of the Congress or Legislature to establishing procedural guidelines.

It is a personal opinion of this witness that there is a sufficient data to set predictive air quality criteria for oxidants and ozone under conditions occurring in Los Angeles, to establish joint criteria for particulates and sulfur oxides under conditions of temperate climate, to establish criteria for carbon monoxide and to state at what level the community exposure to lead is likely to lead to detectable increases in storage of this substance in the body.

The present time is not a suitable one for discussing all other possible criteria but it is extremely important in the view of this witness that the inability to draw a reasonable predictive inference from the available data be permitted to those agencies which are required to set air quality criteria. Thus, the absence of an air quality criterion could mean either one of two things:

1. that there was no known effect of a certain class under realistic conditions; or

2. that an effect might be occurring but the quantative relationship of defined population exposures to this effect were not clear.

Conclusion

The process of applying scientific judgment to the development of air quality criteria which have predictive validity is a process which can protect health and encourage technical development without undue risk on the one hand or unnecessary investment on the other. The process must draw extensively on the scientific community and can promise in return that the process will also lead to the more precise identification of topics upon which additional research is needed. It would follow that if this process is carried out in this fashion the support of this indicated research should be readily justified.

Appendix A

Laws Relating to the Enactment of Standards for Ambient Air Quality and Motor Vehicle Exhaust

The 1959 Legislature enacted the following additions to the Health and Safety Code (see Chapters 200 and 1949, Chaptered Laws of 1959) :

426.1. The State Department of Public Health shall, before February 1, 1960, develop and publish standards for the quality of the air of this State. The standards shall be so developed as to reflect the relationship between the intensity and composition of air pollution and the health, illness, including irritation to the senses, and death of human beings, as well as damage to vegetation and interference with visibility.

The standards shall be developed after the department has held public hearings and afforded an opportunity for all interested persons to appear and file statements or be heard. The department shall publish such notice of the hearings as it determines to be reasonably necessary.

The department, after notice and hearing, may revise the standards and shall publish the revised standards, from time to time.

426.5 It shall be the duty of the State Director of Public Health to determine by February 1, 1960, the maximum allowable standards of emissions of exhaust contaminants from motor vehicles which are compatible with the preservation of the public health including the prevention of irritation to the senses.

The standards shall be developed after the department has held public hearings and afforded an opportunity for all interested persons to appear and file statements or be heard. The department shall publish such notice of the hearings as it determines to be reasonably necessary.

The department after notice and hearing may revise the standards, and shall publish the revised standards, from time to time.

Appendix B

Criteria and Guides for Air Quality

The Committee, in its deliberations on this subject, carefully reviewed the report of the WHO Inter-Regional Symposium on Criteria for Air Quality and Methods of Measurement, held in Geneva from 6 to 12 August 1963, and endorsed the general approach outlined therein and the principles and definitions quoted below:

"1. Criteria for guides to air quality are the tests which permit the determination of the nature and magnitude of the effects of air pollution on man and his environment.

"2. Guides to air quality are sets of concentrations and exposure times that are associated with specific effects of varying degrees of air pollution on man, animals, vegetation and on the environment in general.

"3. In the light of present knowledge, guides to air quality may be presented as four categories of concentrations, exposure times and corresponding effects. These four categories are defined by limiting values which may vary for a given pollutant according to the anticipated effect or the criteria used and in relation

to other co-existing pollutants and the relevant physical factors, and which take into account the varying responses of different groups of human beings. The Symposium agreed to define the four categories in terms of the following levels:

"Level I. Concentration and exposure time at or below which, according to present knowledge, neither direct nor indirect effects (including alteration of reflexes or of adaptive or protective reactions) have been observed.

"Level II. Concentrations and exposure times at and above which there is likely to be irritation of the sensory organs, harmful effects on vegetation, visibility reduction, or other adverse effects on the environment.

"Level III. Concentrations and exposure times at and above which there is likely to be impairment of vital physiological functions or changes that may lead to chronic diseases or shortening of life.

"Level IV. Concentrations and exposure times at and above which there is likely to be acute illness or death in susceptible groups of the population.

"For some known pollutants, it may not be possible to state concentrations and exposure times corresponding to all four of these levels because (a) the effects corresponding to one or more of these levels are not known to occur with the substance in question, or (b) exposures producing effects corresponding to certain levels also produce more severe effects, or (c) the present state of knowledge does not permit any valid quantitative assessment (e.g., of threshold levels for carcinogenic substances).

"The possibility that some pollutants may have mutagenic effects must be borne in mind; however, at the present time, too little is known about this subject to permit classification of such pollutants in the above categories."

The Committee stressed that pollution of the air by biologically harmful substances resulting from man's activities should be avoided to the maximum extent possible.

The Committee agreed that international guides to air quality, embodying the principles enunciated above are desirable and should be compiled in the near future. It believed that guides can be most expeditiously developed for those pollutants that have received the most study and attention and that are most widespread in their distribution, for example, the oxides of sulfur. It suggested, therefore, that WHO take appropriate action to accomplish this aim. The Committee recognized the existence between Level I and Level II of a zone of concentrations and exposure times in which some pollutants may produce demonstrable responses, the significance of which is at yet uncertain.

Emission standards are obviously related to the concentrations of pollutants that will be found in the ambient air, but since this relationship is largely dependent upon local meterological and other factors, international standardization of emissions of pollutants is virtually unattainable and the prescription of such standards must be left to the discretion of individual governments or local administrative authorities.

Specific programmes and problems on which research is needed are discussed elsewhere in this report (see sections 6 and 7). The Committee believed, however, that a programme of financial and technical assistance would be helpful in facilitating the exchange of information and the fostering of international studies relative to the development and justification of air quality guides.

Senator MUSKIE. Thank you very much, Dr. Goldsmith.

I apologize for being late. The delay was contributed to by another air pollution, too many airplanes in the airways at the same time over Washington. I guess I was flying over the city about a quarter of 10; it took me an hour to get here. So I did miss the early part of your testimony. Perhaps I can get into it, at least what you consider to be the high points, with some questions.

The first question I would like to put is this:

SUSCEPTIBLE GROUPS

Previous testimony before this committee has indicated that elderly individuals in our population are especially susceptible to exposure during high levels. Would you care to comment on the possible groups who are particularly susceptible to long-term, low-level air pollution

exposures and whether or not there are factors other than age which may make particular groups especially susceptible?

Dr. GOLDSMITH. Sir, I would list three major factors in addition to age.

CHILDREN

First, I believe that for long-term exposures recent evidence makes it quite clear that children are unusually susceptible. Now, the bulk of the evidence on this point has come from other countries. It comes from some work that was done under the auspices of our colleague from Japan who was earlier introduced, Dr. Michio Hashimoto. It has come from the United Kingdom. It has come from several countries in Europe—Italy and Czechoslovakia.

I believe there has been an inadequate amount of epidemiological work on the effects of air pollution on children in this country in view of the evidence available, and this merely illustrates my feeling that international efforts in air quality criteria are highly significant and have been somewhat neglected. We must consider that children are also a susceptible group, particularly with respect to chronic respiratory conditions.

METABOLIC ERRORS

The second group unusually susceptible are those with inborn metabolic errors. There is very little work that has been done which is adequate to clearly define this population, I must say, and perhaps I am speaking more from the point of view of the research scientist's interest in further elucidating an important question.

Individuals with different types of hemoglobin, for example, may be unusually susceptible to carbon monoxide exposure; we simply do not know. The evidence on this point is scant. Individuals with difficulty in handling that substance called porphryn; that class of individuals with inherited disorders in the metabolism of porphyrin, are said to have porphyria. There may be relatively few in the population but they may be unusually susceptible to exposure to lead. We do not know the answer to such a question.

There may be individuals, of course, with various other inherited disorders.

We have learned of a particular inherited defect that leads to emphysema quite frequently. Just last week, I received a letter from the director of Cardiovascular Research Institute in the University of California at San Francisco, Dr. Comroe, asking if we would have an opportunity to collect and follow a population of such individuals in order to see in what way their emphysema differs from the much more widespread condition. Possibly they are also more susceptible to air pollution.

CARDIO-PULMONARY PATIENTS

The third basic category of susceptibility would be those people with well-established diseases, people with chronic circulatory and pulmonary conditions, who are unusually susceptible to respiratory disease or things which concern transport of oxygen in the tissues. No doubt you will hear more testimony on this problem from other persons.

I think one should add to this that exposures do occur from multiple sources. There is much debate and discussion concerning whether peo-

ple, for example, who are exposed to the inhalation of cigarette smoke are unusually susceptible. But if they are so, it could also be because other disease processes are initiated by such exposure. In general, both because of such processes and because of their increased body burden of pollutants also present in the air they should also be considered an unusually susceptible group. The same could be true of people who are occupationally exposed. It is one of the major assignments in epidemiology to identify such populations.

AVAILABLE INFORMATION ON SUSCEPTIBILITY

Senator MUSKIE. Now, you have indicated a number of areas as uncertainties or unknowns. You have said that in your judgment all these various groups of people are susceptible to air pollutants. You have indicated that we don't know how large these groups are; we don't know who they are. We have not fully defined either the nature of their susceptibility or the size of the group, but you are convinced that they are harmed by air pollution.

Dr. GOLDSMITH. Senator, I have no doubt that the health of many, many people has been harmed by air pollution and I have perhaps unnecessarily stressed what we did not know. I think we know a great deal about the effects of air pollution on school children at least under conditions occurring in other countries, and some of those conditions are easily translatable to conditions in this country.

We also know a great deal about the effects of air pollution on persons with various difficulties. We have had studies reported at the meeting last week, the Ninth Air Pollution Medical Research Conference, on the effects of Los Angeles smog on people with emphysema. Our own group reported the first paper on possible effects of carbon monoxide on people with myocardial infarction.

We have a great deal of information as to how frequent these conditions are in the population. I think we have abundant information to make a fairly constructive start toward using the available fund of information in establishing scientifically dependable air quality criteria.

The mere fact that I identified things we do not know should not be considered as evidence, that we would have difficulty, in my opinion, in establishing such criteria and having them widely accepted as scientifically sound.

CRITERIA FEASIBILITY

Senator MUSKIE. The question will be debated, I suppose, as to how certain our informations must be before we establish criteria. I am sure you cannot answer that question with too much specificity but I wonder if you might elaborate on it.

Dr. GOLDSMITH. I would be happy to, sir.

I believe that we have abundant evidence and have had an adequate period of discussion and review so that we can make reasonably confident statements concerning the effects of sulfur oxides and particulates on the aggravation of chronic respiratory conditions and we can make these statements in quantitative terms. I believe we have a fund of evidence to indicate the effects of carbon monoxide as reflected in the carboxy-hemoglobin level of circulating blood.

I believe we have abundant evidence although I know there are still some that debate this concern, of the effect of community exposure of lead to the body as reflected in blood lead levels.

I believe that we have abundant evidence to set scientifically air valid criteria for photochemical oxidants and ozone. In short, despite the many things that we do not know I think that we know quite enough to provide a medically, epidemiologically and biologically sound basis for making air pollution control dependent upon the scientific consensus concerning this knowledge.

CRITERIA VERSUS STANDARDS

Senator MUSKIE. With respect to that last statement you have made, you are not—I know you are not, but I want to make it clear in the record—confusing the distinction between criteria and standards?

Dr. GOLDSMITH. No, sir.

Senator MUSKIE. In other words, when you say that we know enough about the health effects of air pollutants to form a medical basis for controls, you are not commenting upon the economic or technological feasibility of control?

Dr. GOLDSMITH. Indeed not, sir. I believe that my previous testimony made that very clear. I feel that the control process should be thoroughly informed of the full spectrum of possible effects of air pollution on health insofar as there is or can be obtained a scientific consensus.

My remarks had to do with the fact that I believe the scientific consensus can be obtained. I speak on the basis of having prepared and having had reviewed by a number of review groups, a technical report and air quality criteria for photochemical oxidants, ozone, and nitrate; on the basis of having participated in review groups for air quality criteria on sulfur oxides and on particulates and on the basis of documents which I have prepared and circulated and gotten comments on from the department advisers—that is, the California State Health Department advisers, and also from participants in a World Health Organization symposium with respect to the possible basis for air quality criteria for carbon monoxide and lead.

So, I am speaking with a good deal of experience of having tested these interpretations before groups of scientific peers.

Senator MUSKIE. So that it is possible that we can establish causal connection between specific pollution and harm to health and still not have the technological means for correcting the situation?

Dr. GOLDSMITH. Sir, I have already disqualified myself as an expert on technological means of control. I think we do have more resources in this field than we have used.

Senator MUSKIE. What I am really addressing myself to and will again and again in these hearings is that distinction between criteria and standards.

Dr. GOLDSMITH. Yes, sir.

Senator MUSKIE. There are those that would say we ought not to issue criteria until we have the specific technological answer to the specific problem. That is not my concept of criteria; I don't think it is the one that is embodied in the law. I think we ought to have the criteria whether or not we are able to do anything about the harm

caused by specific pollutants. We ought to know what the harm is, what the causal connection is. Perhaps a suggestion as to methods or approaches to criteria ought not to be withheld until we have a technological answer to our problem.

CALIFORNIA STANDARDS

Dr. GOLDSMITH. Indeed, sir, I would say the experience in California only underlines this. We established air quality standards—which, as I said earlier in my testimony, should be read as air quality criteria because the same process was used that we are now using for criteria—and motor vehicle emission standards before it was known that the motor vehicle industry would be able to meet the standards which we establish.

Subsequent legislation provided an incentive to the motor vehicle and other industries to meet the requirements of the State of California which, to a certain extent, they have done.

There are still standards that have been set by our department which the motor vehicle industry has not indicated that it can meet or will meet with technically, or economically feasible methods.

I simply want to reiterate, as you pointed out, that we have been in the process of setting air quality criteria when we had no assurance that the technical or economic feasibility was in sight and I believe this has been very constructive.

Senator MUSKIE. I think it has, Dr. Goldsmith.

I am going to yield at this point to Senator Baker who was here since the outset. While he is questioning you, I will hastily review the testimony.

Senator BAKER. Dr. Goldsmith, I thank you for your testimony this morning which I found very thorough and very logical. I appreciate the opportunity to enter into a limited dialogue with you now.

I would like to know this now in general terms. Are all the atmospheric contaminants for which we know there are deleterious effects, those for which we have not established criteria or standards, what do you see as the greatest threat to the problem at the moment?

Dr. GOLDSMITH. Sir, I take it your comments concerning those for which we have not established criteria and standards means that the Federal Government has not established them because I would think I would put quite high on the list carbon monoxide for which the State of California has a standard.

However, we are in the process of revising it and I believe that carbon monoxide would come quite high on my list.

PHYSIOLOGICAL EFFECTS OF CARBON MONOXIDE

Senator BAKER. If I may interrupt, what are the direct effects, physiological effects, on human beings of exposure to carbon monoxide?

Dr. GOLDSMITH. The most direct effect is to tie up some of the circulating blood so that it is incapable of transport of oxygen. The quantitative relationship is well established between exposure and the amount of carboxy-hemoglobin, which is an index of this effect.

Senator BAKER. What happens to a human being when this happens?

Dr. GOLDSMITH. His blood circulates without carrying oxygen. In other words, his circulatory efficiency is impaired. The exact extent of the impairment is subject to some discussion but the fact that there is impairment and that the amount of carboxy-hemoglobin can be clearly related to the exposure is not debatable.

Senator BAKER. Doctor, what I am trying to get at is, what are the symptoms?

Dr. GOLDSMITH. May I continue?

Senator BAKER. Yes, sir.

Dr. GOLDSMITH. Now, there are two very large questions about this.

The first question has to do with the extent to which this interferes with the functions of the central nervous system. This has been reasonably well established as occurring with exposures producing 5 percent or more carboxyhemoglobin. There is some question as to whether an exposure which produces as little as 2 percent carboxyhemoglobin may not produce measurable interference with accurate estimation of intervals of time.

I stress at this point this is not the equivalent of producing disease or necessarily of producing harm in complex performance but it suggests that such harm may be produced and it, of course, makes it more imperative to study such things as motor vehicle accident frequency and relation to atmospheric levels of carbon monoxide.

The second major question has to do with the effects of given levels of carboxyhemoglobin on the circulatory system.

Apropos Senator Muskie's question, individuals who have acute insufficiency of the circulation would be very vulnerable to exposure to carbon monoxide insofar as they are the ones most critically dependent on the blood's oxygen transport functions.

Accordingly, we are studying the survival of persons who have acute myocardial infarction. Epidemiologically, we have shown an association between the levels of carbon monoxide in the atmosphere and the probability of dying from this condition after being admitted to a hospital. This problem, like many others, is beset with two difficulties: One of them is the difficulty of dealing with complex statistical problems, and the other is the exclusion of another possible cause.

It is possible that there were certain effects of time of year that could have influenced this, though in our study we took such precautions as seemed reasonable to exclude this. We probably only succeeded in diminishing such an effect and not altogether excluding so that there are some questions as to how much carbon monoxide exposure might be necessary in order to decrease the likelihood of survival with persons of this condition.

Nevertheless, that there are levels of carboxyhemoglobin which do impair the likelihood of survival can scarcely be argued.

CARBON MONOXIDE EFFECTS ON DRIVERS

Senator BAKER. Can the ordinary driver of an automobile discern symptoms other than defects in time judgment that might warn him that he has been exposed to an excess level of carbon monoxide such as nausea, dizziness, or anything of that sort?

Dr. GOLDSMITH. Senator, the earliest symptoms reported in large scale studies are headache and generally later dizziness. These symp-

toms are so nonspecific that it makes it extremely difficult to relate the symptoms and the exposure one to the other.

I think many of us feel that there are symptoms occurring in motor vehicle drivers under conditions in which the carbon monoxide levels are high. This may occur with vehicle malfunctioning which is often overlooked.

I have said before, and I have no reluctance to say now, that even though I think carbon monoxide is a particularly pernicious pollutant with respect to its possible health effects there are very few, almost no complaints concerning this because it is not an overtly irritating substance and most people are unaware of their being exposed.

Senator BAKER. I have imposed on your technical knowledge to test the hypothesis that relates to a recent trip I made. I have an air-conditioned automobile and in driving to Washington recently I developed a severe headache, a numbness, and finally nausea. I stopped for a number of hours and found that I had a defective muffler. I am not sure there is a connnection between the two, but your testimony afforded me the opportunity to impose on you for a diagnosis in this respect.

Dr. GOLDSMITH. I don't usually practice medicine in such a form, sir, but I believe your observations are particularly relevant.

I might say, if I might impose on your patience, that the methods for estimating the amount of carboxy-hemoglobin in the circulating blood without taking a blood specimen is not as widely known as it should be. This can be done very rapidly, in a few moments, by an accurate technique using breath holding.

Under such circumstances, had you called on a physician he was most unlikely to have known about this which I would regret because the technique is very convenient and very valid.

Senator BAKER. Is there any sort of simple test or device that could be installed in automobiles to detect the presence of excess levels of carbon monoxide? I know this is done sometimes in aircraft and I wonder if it is impractical in terms of automobiles.

Dr. GOLDSMITH. I think this is a question beyond my technical competence but I see no reason a priori why this could not be done.

We use instruments which are rather a costly type, but there are such things as color indicator tubes which have been proposed for this purpose. We have tested some of these in our laboratory and they are not terribly accurate, that is to say, the true result may be 50 to 100 percent different than what appears. However, under the circumstances that you describe, it might have been quite adequate.

CRITICAL CRITERIA FOR DEVELOPMENT

Senator BAKER. Doctor, aside from carbon monoxide as a potential health hazard for which there is no Federal grant or criteria, what others would you rank of superior importance?

PARTICULAR CRITERIA

Dr. GOLDSMITH. I think most epidemiologists that I have discussed the matter with would place particulate matter very high on the list. This is an awkward one to stress because particulate matter can mean so many different things.

In this context, I think I would restrict my remarks to particulate matter derived from the combustion of fossil fuels and in the presence of sulfur oxides or other irritating matter which is so often present, for example, in association with the wood smoke or other inefficient types of combustion.

The reasons why I stress this are that the controls for particulate matter are much nearer at hand than that for other pollutants. The occurance of it is much more widespread. The ability to carry on systematic monitoring and determination of health effects has been impaired because of the relevance of particle size to effects as well as to the identification of effects of exposure.

Nevertheless, as I say, I believe most physicians will feel that particulate matter derived from combustion in the presence of other products of combustion, particularly sulfur oxide and other irritants, comprises the most serious of the long-term exposures from the point of view of health effects alone.

The evidence on the effects of particulate matter is, unfortunately, particularly influenced by different methods of measurement, and, of course, different sources, but the bulk of the evidence I think is unequivocal on this point.

To simply illustrate it, if I may take a little more time, if one raises the question about the possible effects of air pollution on lung cancer, and I have been noted for saying that I think the evidence, while important, is not very convincing on this point—nevertheless, if one controlled particulate pollution to the extent that it is technically feasible in many areas, one would greatly diminish the likelihood of any exposure likely to produce lung cancer for community air pollution. I think this would be true for exposures likely to produce bronchitis as well.

There is some reservation in my mind about pulmonary emphysema which may be influenced by oxides of nitrogen. This is a research problem that is at the moment unresolved but, nevertheless, since many people who have pulmonary emphysema have also chronic bronchitis, it would seem prudent to take the steps in an attempt to reduce the severity and extent of the former.

Senator BAKER. Doctor, this one final question.

EPIDEMIOLOGICAL STUDIES

Much of your knowledge of the subject is derived from statistical analyses rather than clinical observation?

Dr. GOLDSMITH. Yes.

Senator BAKER. Would it follow, then, that the establishment of criteria or standards for contaminants that have not yet been sufficiently identified as a causal factor of a given illness increase the body of statistical information to the point where further scientific introductions might be made that might be of diagnostic value?

Dr. GOLDSMITH. I think I understand your question. I am mulling over the terms of reference because I perhaps am unusually sensitive to the use of statistical in the sense that you have used it.

I don't believe that the studies are statistical studies. Statistics is a method; it is a logical process. It has its techniques but so does physical chemistry, so does analytical chemistry. The studies that are usually referred to as statistical studies, I think, are properly described

as epidemiologic. Statistics are used for, of course, laboratory exposure, as well.

I apologize for the circumlocution, sir.

RESEARCH NEEDS

I believe that the effort of establishing air quality criteria would much more clearly define areas where research is needed and would provide a stimulus to have additional research. I think, for example, in my prepared testimony I have indicated the importance of combining exposures to particulate matter and sulfur oxides in setting of criteria.

The setting of such criteria could greatly stimulate the precise definition of which particulate matter, what states of oxidation, what particle size, what humidity is really necessary in order to produce the effects that are now epidemiologically obvious.

Similarly, the establishment of criteria for carbon monoxide based, say on carboxy-hemoglobin levels could greatly stimulate the needed study on the consequences to the circulatory system of specified levels of carboxy-hemoglobin.

So, the answer to your questions, sir, is that they would have a very stimulating effect.

Senator BAKER. I think that is the answer I was searching for. I apologize for the imposition of terms but I used the term of the man who relied on statistics to prove that all Indians have six fingers because the one I saw did.

Dr. GOLDSMITH. Yes, sir; I understand your problem.

Senator MUSKIE. Thank you, Senator.

THRESHOLD EFFECTS

I have just one more question, Dr. Goldsmith, although we may submit others for your consideration.

The question quite frequently arises as to whether a particular concentration of a substance has to be reached before any effect is elicited. That is the threshold.

Dr. GOLDSMITH. Yes, sir.

Senator MUSKIE. In 1962, a WHO's expert committee made the following statement regarding this question and I would like your comment on it. It said:

> The concept of safe or acceptable exposure levels rested initially on the assumption of thresholds for early effects. However, with the accumulation of data and experience with various toxic substances, delayed effects attributable to exposure to toxic agents have appeared long after exposure at levels previously thought to have been safe, for instance in the case of beryllium. This necessitated downward revision of many of the recommended maxima.

If this is an accurate statement, the danger is that in setting criteria initially you may set threshold levels that would subsequently prove to be inadequate.

Would you want to comment on that?

Dr. GOLDSMITH. Yes, sir.

The use of thresholds is a common one in industrial hygiene practice and, indeed, the formulation of what is known about the effects of occupational exposure is stated as so-called threshold limit values.

I believe that there are no good reasons why the universal application of such threshold concepts should be encouraged in this field and, indeed, the use of multiple-valued criteria statements is a defense against this. We will not necessarily protect ourselves from the possibility that something which is now not innocuous will subsequently be proven harmful by using such multiple-valued statements.

But in this area, it seems to me, particularly with the great inertia that exists between making a scientific decision concerning air pollution health effects and doing something constructive to reduce the exposure so that these effects do not occur, that we should start the process constructively with the least arguable basis, and that is why I think multiple-valued criteria provide such a base. Exactly how far we must go in the control is not so easily discernible.

I think that it is prudent at this time to portray before policy-setting groups such as the Congress, legislatures, or various boards who are setting standards, the full extent of our knowledge concerning effects. Then, for example, if we include among those effects, as I think we should, the storage in the body of potentially harmful materials, we have at least alerted such bodies and the scientific community as to what the nature of the substances are which are being stored.

I believe that with this precaution the undue reliance on threshold hazards can be avoided. I think, for example, that carbon monoxide is an excellent case in point—very small exposures can appreciably increase carboxy-hemoglobin. We are going to have to make numerical statements but it seems to me the best thing to do is to put forth in as concise and understandable form the knowledge we have.

Senator MUSKIE. It strikes me if we do this on the basis of the knowledge we have, the initial criteria are likely to be conservative.

Dr. GOLDSMITH. Sir, I think that the criteria should not be subject to such adjectives. I think that the standards might be conservative based on the lowest level of criteria, but the criteria should be as nearly descriptive of what is known and what is agreed upon as possible, providing an opportunity for conservative standards.

Senator MUSKIE. The reason I put the question, I recognize the validity of your objection to it, is that I suspect that as we have in the past we are going too far in setting the criteria we set—in other words, they are too liberal. With apologies to your professional revulsion against those adjectives, I think in that context they would be more conservative than liberal if we act on the basis of what we know.

Dr. GOLDSMITH. I think that a suitable set of criteria is a way to encourage a conservative[1] approach to environmental quality management and that is something I would like to see undertaken.

Senator MUSKIE. You would have been a good lawyer with that attitude.

Dr. GOLDSMITH. Thank you, sir.

Senator MUSKIE. Thank you, Dr. Goldsmith.

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[1] By conservative Dr. Goldsmith means with a substantial margin of safety even if it means restricting certain otherwise desirable activities.

I know we will have questions to submit to you but out of deference to our other witnesses who are scheduled today I think we have to get on with them.

(The question submitted by Senator Muskie and the response of Dr. Goldsmith are as follows):

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. JOHN R. GOLDSMITH,
Chief, Environmental Hazards Evaluation Unit,
California Department of Public Health,
Berkeley, Calif.

DEAR DOCTOR GOLDSMITH: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. JOHN R. GOLDSMITH

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

3. What is the current usefulness and limitations of vital statistics on causes of death (disease mortality), in epidemiological studies and how could they be improved?

4. To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

5. To what extent are the reported effects of air pollution affected by the study methods employed?

6. A number of air pollution episodes that have been studied, however, the cause and effect mechanism is reportedly not known. What is the value of laboratory studies in providing answers on the mechanism involved?

7. In this regard, what are the advantages and limitations of clinical studies?

8. It has been mentioned that elderly individuals are especially susceptible to air pollution during hig levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low-level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

9. What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

10. There are atmospheric contaminants that have their primary effect on other than the respiratory system. What environmental contaminants deserve particular attention because of their potential effects on other than the respiratory system?

DEPARTMENT OF PUBLIC HEALTH,
Berkeley, Calif., September 19, 1968.

HON. EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution,
U.S. Senate,
Washington, D.C.

DEAR SENATOR MUSKIE: I regret the delay in replying of August 2, but I have been out of the country attending meetings and engaged in scientific conferences in Czechoslovakia, Yugoslavia, Geneva, and the United Kingdom and I have just returned. I am pleased to submit the answers to the questions you have transmitted to me. I also thank you very much for the opportunity to discuss these matters with you and your subcommittee.

I am very impressed with the logic that has been embodied in the Air Quality Act and with your leadership in drawing as heavily as possible on the scientific and technical resources that are available.

Sincerely,

JOHN R. GOLDSMITH, M.D.,
Chief, Environmental Hazards Evaluation Unit.

[Enclosure]

QUESTION 1

The Air Quality Act of 1967 provides for the deveolpment of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

Air quality criteria for atmospheric exposure to ozone and photochemical oxidants (a contaminant and a group of contaminants respectively) have been prepared and reviewed extensively by our Department and by consultants. For sulfur oxides and particulate matter I believe there is sufficient scientific and medical evidence to establish air quality criteria, some of which will be conditional; that is to say some of which will require the simultaneous presence of sulfur oxides and particulate matter largely derived from combustion. Vice versa for air quality criteria for some particulates; some will require the presence also of sulfur oxides. For each of these contaminants however there will be a few statements that are referrable to their presence alone. It is likely that with additional work a simplification of this set of criteria can be developed based on the measurement of atmospheric levels of sulfuric acid, the estimation of the health responses to these exposures.

We are currently working on the development of criteria documents for carbon monoxide and this effort will be completed within a few months. Criteria are also planned for nitrogen oxides and hydrocarbons. I am hopeful but not certain that the evidence will be adequate to obtain agreement on these criteria. Air quality criteria for atmospheric lead will be next in order. There is some data concerning one or two of the possible criteria. The most important criterion, the effect on human biochemical reactions, has scanty data only. Thus the criterion for lead exposure based on biochemical responses of human populations is not yet adequately supported by evidence. The criterion for the storage of lead in the body in my opinion is adequately supported by evidence.

I believe criteria can and possibly will be developed for a number of other substances including fluorides, ethylene, hydrogen sulfide, beryllium, asbestos and odorous materials. However at the moment the work on these is not sufficiently advanced to make firm statements as to whether the medical and scientific evidence will be sufficient to obtain agreement.

QUESTION 2

The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

Additional epidemiologic studies would be useful to confirm or refine air quality criteria as follows: for ozone and oxidants, studies on the relation of eye and respiratory irritation in locations other than in California. Parenthetically the study of whether or not there is human tolerance to ozone exposures is necessary

but this study could probably be better done with an experimental design than an epidemiologic design. Studies of the effects of the photochemical oxidants and ozone on the health of children particularly on their school and athletic performance is necessary. Combined epidemiologic and laboratory studies of changes in oxy-hemoglobin dissociation are indicated.

For sulfur oxides and particulates, work is needed on the occurrence and particle size distribution of sulfuric acid, and in association with this exposure the health effects that might be related. These studies also should be combined epidemiological and experimental studies.

Particular importance attaches to the study of the effects on children. The occurrence of lower respiratory tract conditions in children exposed to realistic levels of sulfur oxide and particulate pollution has been demonstrated in the United Kingdom but so far has not been looked at adequately in the United States. Concerning carbon monoxide further study of the possible and likely realistic effects of CO exposures on the case fatality rate in myocardial infarction is of high priority. This should be combined with studying CO exposures from cigarette smoking in relation to the same phenomenon. The second major consideration should be given to the possible carbon monoxide effect on the capacity of motor vehicle drivers to safely operate their vehicles. Of particular importance would be the measurement of carboxyhemoglobin in persons involved in motor vehicle accidents in relationship to carefully matched control population of the same age, smoking history and driving experience. A laboratory and epidemiologically-related problem is required to deal with the extent to which carbon monoxide exposures cause shifts in the carboxyhemoglobin dissociation curve. This could be studied epidemiologically or in the laboratory but preferably should be done by both types of studies.

Since the study of carbon monoxide exposures from community air pollution can only with difficulty be separated from the study of carbon monoxide exposures associated with cigarette smoking, it is strongly recommended that both these be undertaken by the same groups of people and that the epidemiological problem of whether or not there is a more than additive relationships between these two classes of exposures should also be explored.

Concerning nitrogen oxides and hydrocarbons it seems possible that one could identify a number of occupationally-exposed groups having nitrogen dioxide exposures, for long-term follow-up. So far this has not been done extensively. There is the possibility of developing laboratory procedures which would estimate the extent of the effects of nitrogen oxides on structural proteins in the lung in humans. There also exists the possibility that methemoglobin could be used as an index of exposure to nitrogen dioxide and nitric oxide.

Concerning lead, there is an urgent need to study the values of delta-aminolevulinic acid in blood and urine in groups exposed to realistic levels of atmospheric lead. Preliminary studies are now being instituted in occupationally exposed populations. So far as I know community studies of this type have not been undertaken. They can be done with available methods and would be extremely important in determining whether there are biochemical reactions to realistic lead exposures.

Additional epidemiologic studies concerning other pollutants are clearly indicated, but their discussion does not at the moment seem likely to be as relevant as the foregoing. Epidemiologic work has suffered from a lack of long term support. There are no groups who have been given the responsibility and adequate resources for carrying out these studies and the basic procedures for research grant support have generally been inadequate since the number of specialists required for this type of work, the administrative sponsorship, and the duration of planning needed are all substantially different than for experimental studies. To be specific, survey statisticians, laboratory biochemists and physiologists, internists, pediatricians, respiratory disease specialists, pathologists, mathematical statisticians and computer experts are all needed for an adequate program of epidemiologic studies. Such groups are difficult to assemble, and are usually found only in conjunction with major research centers, whereas the populations to be studied may be some distance removed. Accordingly, it is also necessary to provide access to the appropriate populations and this is generally not as readily available to research institutes as it is to official agencies. Finally epidemiologic studies often take from five to twenty years for adequate data collection and analysis. Some studies of course can be carried over shorter periods of time but it is necessary to provide a more stable and complex pattern of funding for these studies or the needed information is not likely to be obtained and analyzed.

QUESTION 3

What is the current usefulness and limitations of vital statistics on causes of death (disease mortality), in epidemiological studies and how could they be improved?

The usefulness and limitations of these reflect the relative lack of attention and support given to vital statistics work in recent years. Appended is a statement prepared at the Air Pollution Epidemiology Seminar of the New York Academy of Science concerning this general problem. Much of the work of epidemiologists now consists of analyzing and validating current vital statistics information. Much of this could and should be done centrally by computer. Nevertheless these data remain quite helpful in reviewing the possible effects of air pollution. However, to answer specific questions concerning air quality-health interactions, studies specially designed for the purpose are usually necessary and their planning and execution would be greatly facilitated by more adequately developed vital statistical operations. Among the most important current needs are data for current sickness incidence by major metropolitan area by day or week. Such information could be obtained from the records of large health insurance organizations if plans were made to do so. But generally speaking these plans have not been developed.

QUESTION 4

To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

There are three major differences between industrial hygiene exposures and community air pollution exposures. First, the former are more intense and more clearly defined. Secondly, the former are generally restricted to a maximum of the forty hour working week out of the one hundred and sixty-eight hours possible per week, whereas community air pollution exposures may be more or less continuous and fluctuating. Thirdly, the occupational exposures involve selected individuals, usually males, of twenty to sixty-five years of age and usually in good health. Community air pollution exposures characteristically have their greatest impact on the unusually sensitive groups in the population, the ill, the very young or the elderly. Nevertheless, industrial hygiene and occupational health studies can provide important leads concerning what effects one might look for. It is usual that the occupational exposures are more intense except for a few types of pollutants, for example ozone, in which occupational and community exposures are of similar intensity. In these cases a great amount of useful information can be obtained from occupational data.

QUESTION 5

To what extent are the reported effects of air pollution affected by the study methods employed?

The effects of air pollution which have been reported to date do indeed reflect both the methods employed and also the types of effects looked for. In the early stages of research on air pollution health effects, specific illness and excess mortality were the commonest effects searched for. More recently it has become clear that aggravating effects of air pollution on preexisting illness and interference with body function are more common and probably more valuable as guides for the prevention of air pollution related health impairment. Only a small proportion of the body of research on air pollution effects utilizes the measurement of biochemical or physiological reactions. So recent is the attention to this problem there is some difference of opinion as to how these data should be interpreted. Our experience in California, however, indicates that it is quite valuable if it is carefully interpreted.

QUESTION 6

A number of air pollution episodes that have been studied, however, the cause and effect mechanism is reportedly not known. What is the value of laboratory studies in providing answers on the mechanism involved?

The mechanisms underlying acute air pollution effects can be best understood by a combination of laboratory and epidemiologic studies. Since these effects were first discovered by epidemiologic methods the value of laboratory studies in confirming the mechanisms of these effects is very great. But it also follows that laboratory exposures to air pollution may indicate what types of unreported

reaction should be looked for most carefully. A close relationship therefore between laboratory and epidemiological work is indicated and unfortunately this is not always achieved.

QUESTION 7

In this regard, what are the advantages and limitations of clinical studies?

Presumably the phrase "clinical studies" refers to the observation of people under the care of a physician and also to certain classes of ethical experimentation. The advantages of clinical studies are that they often provide the first evidence of air pollution effects and hence they are of very substantial value. By ethically indicated experiments is meant particularly the experimental exposure of possibly sensitive subjects to levels of pollution which are likely to occur in the community, but under carefully controlled conditions, so that any unfavorable reaction of the experimental subject can be promptly observed and effectively countered. In this sense provocative tests such as skin tests in eczema are given as an example. This field of work has been inadequately developed for materials involved in air pollution via respiratory exposures.

The reports of physicians provide an unusually varied source of impression and fact. Part of the limitations of such individual reports is that it is often extremely difficult to reconstruct the sequence of events upon which the observations are made. Since such data often involve a single observer, there is the possibility of some subjectivity. For example one has observed that physicians who are heavy cigarette smokers are unusually likely to attribute respiratory illness in their patients to community air pollution when in fact cigarette smoking may be a major factor.

QUESTION 8

It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

A major factor which renders individuals especially susceptible to long term low level air pollution exposures would be the presence of inherited metabolic defects. This remains a major hypothesis rather than an established fact. There are, however, powerful analogies which make this hypothesis a rather plausible one.

Children are also likely to be especially susceptible to long term effects of air pollution and a number of studies have indicated that respiratory tract illness is more common among children who live in heavily polluted, in comparison to less polluted areas when other factors as income, occupation of parent, number of children per household, etc. are controlled for. Another source of exposure which may also increase susceptibility is exposure to cigarette smoking which increases the susceptibility to chronic pulmonary disease associated with air pollution.

QUESTION 9

What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

There have been all too few studies of the health effects of air pollution on children. As these studies are reported, and a number are now under way, they should have a substantial impact on air quality criteria. Speaking as a citizen I would be more concerned about effects of a given level of air pollution on health of children than I would be for a similar effect on the health of men 45 to 60. This however is a value judgment and one which should be properly made by legislative agencies and not by medical scientists alone.

QUESTION 10

There are atmospheric contaminants that have their primary effect on other than the respiratory system. What environmental contaminants deserve particular attention because of their potential effects on other than the respiratory system?

Carbon monoxide and lead are two substances which have their major effects on body systems other than the respiratory system. The major effect of carbon monoxide appears to be on the transport of oxygen by the red cell pigment of the

blood. In addition at about the same levels as are likely to cause appreciable interference with oxygen transport, carbon monoxide also appears to interfere with the function of the central nervous system. The effect of lead is on the metabolism of porphyryns, a class of substances vital to the synthesis of red cell pigments and enzymes in the body. Thus low level lead exposures under occupational conditions may lead to mild anemia or the excretion from the body of intermediate products produced in the synthesis of porphyryns. There is also some evidence that ozone exposures at realistic levels might interfere with the oxygen transport function of the blood.

PROPOSAL FOR INCREASED SUPPORT FOR HEALTH STATISTICS

Historically, vital statistics have provided the background of information on the causes of death and the distribution of diseases. These have served as indicators of epidemics and health problems and the means of defining the nature and extent of the severity of the disease or health problems, the populations affected, the geographical areas involved, the factors associated with the cause of death, and the direction of the most effective areas of investigation and control. Through the years there has been an increase in the nature and complexity of these health problems. We are creating also new problems associated with changes in environment, and the concurrent increase in population, industrialization, and urbanization.

Although financial support has been appropriated for specialized health programs in many areas of interest and concern, there has been inadequate support for the fundamental resources of vital statistics needed to deal with these problems and programs.

Contemporary problems and technology call for and permit increasingly effective use of vital statistics and health data. Effects of population mobility, occupational exposure and air pollution on health, for example, are of high priority and potentially capable of being favorably influenced. Yet studies of these effects, which could be based on recorded data, are now laborious to the point of requiring prohibitive amounts of time and effort. Because of inadequate attention to health data processing much of it is not now being used.

Health planning uses

The recorded data are not now being used as effectively as they might be in planning and evaluation of comprehensive health programs. It is difficult to process by the customary methods the large volumes of records required for reliable regional or neighborhood areas, yet these are areas towards which major health planning and program efforts are directed. Urban slums are known to contribute disproportionately to the health and social problems of our country. Health data are needed, for example, in poverty areas, but are exceedingly difficult to obtain.

Increased reliability of data can be expected if the providers of data can more clearly see the use which is made of it. For example, if physicians were able to relate what they see in practice to trends and patterns in their immediate as well as in larger areas, their interest in providing the data would be quickened. It is in general a responsibility of government to show that the data provided by citizens is being used for their benefit. Many citizens are contributors to the data pool and deserve to have effective use made of it.

Uses for epidemiology

Even when, by present methods, information on excess morbidity or mortality does become available it is often so long after the event as to be ineffective in guiding action. Yet present technology has advanced to the point where such excesses might readily be detected early enough to provide a guide for intervention.

One of the most effective methods of studying the long-term effects of environmental exposures is to classify a population by the degree of exposure and follow the cohort to determine its subsequent illness, disability and mortality. Such studies could be much more readily and cheaply carried out if regularly collected health data were more easily accessible through the use of modern automated procedures. It would also add greatly to the usefulness and flexibility of vital statistics data if a nationwide central resource were available for such purposes as death clearance.

Manpower implications

The nation has a shortage of trained health researchers. To the degree that modern technology can free available manpower from the unnecessarily laborious computations and tabulations required to utilize the information in regularly available health records, additional skilled man-hours become available.

Conclusions

It is recognized that the modernization of health and statistics resources and data are essential to the further advancement of health and the timely solution of public problems associated with our complex society. Advanced technology and equipment and adequate staff are necessary for the adequate recording, validation, analysis and current accessibility of vital statistics and health data in the U.S., and in State and local Government. It is the recommendation, therefore of the Working Group on Epidemiology of Air Pollution and Human Disease of the New York Academy of Sciences that the Surgeon-General, along with representatives of other Departments convene a committee which will recommend prompt and adequate measures to meet the present deficiencies, so that the full potential value of vital and health statistics to the health and welfare of this country can be realized.

Senator MUSKIE. Our second witness this morning is Dr. Roger S. Mitchell, director of Webb-Waring Institute for Medical Research at the University of Colorado Medical Center.

Dr. Mitchell, it is a pleasure to welcome you here this morning.

STATEMENT OF DR. ROGER S. MITCHELL, DIRECTOR, WEBB-WARING INSTITUTE FOR MEDICAL RESEARCH, UNIVERSITY OF COLORADO MEDICAL CENTER, DENVER, COLO.

Dr. MITCHELL. Thank you, Senator.

My name is Roger S. Mitchell, and I live in Denver, Colo.

Senator MUSKIE. Do you have a Rhode Island background?

Dr. MITCHELL. I was born in Pennsylvania and went to school in Boston.

My present occupation is professor of medicine and head of the division of pulmonary diseases of the department of medicine, University of Colorado School of Medicine, and director of the Webb-Waring Institute for Medical Research at the University of Colorado Medical Center in Denver.

I appear before you in vigorous support of efforts to reduce and control air pollution. My reasons for attempting to achieve this goal include economic, esthetic, and health considerations. I wish to confine my remarks to the health aspects of air pollution.

NATURE OF AIR POLLUTION EFFECTS

Air pollution, clearly, in my opinion, plays a significant contributory and probably causative role in three major diseases of the lungs: lung cancer, chronic bronchitis, and emphysema.

Unfortunately—and I emphasize the plural, the causes of these diseases are not precisely known. We do know that they are very much more common in men than in women, and in cigarette smokers than in nonsmokers. The latter fact complicates the problem from the standpoint of consideration of the role of air pollution.

In addition, these diseases appear to be more closely related to cigarette smoking than to air pollution. Of course, cigarette smoking

may be regarded as a highly concentrated form of personal air pollution.

The evidence associating air pollution with the cause or aggravation of lung cancer, chronic bronchitis, and emphysema is considerable, but indirect. For example, persons living in cities are more prone to develop these diseases than are those who live in rural environments. However, air pollution is probably not the only petrinent factor peculiar to the urban environment.

Children

Children who grow up in cities have more chest infections and poorer lung function than do comparable children from rural areas. This is of considerable interest since many observers believe that frequent respiratory infections early in life play a significant role in the later development of chronic bronchitis and emphysema.

Immigrant studies

British cities have been known for their heavy air pollution, especially in the past. British immigrants to New Zealand and to South Africa have been found to have a higher incidence of lung cancer than persons born in these countries, when cigarette smoking habits are held constant. This observation suggests the operation of some British urban factor in their early lives, most likely the heavy air pollution of British cities, in contrast to the relatively clean air in New Zealand and South Africa.

Persons suffering from acute flareups of chronic bronchitis and emphysema have shown significant objective improvement when removed from Los Angeles air to rooms provided with thoroughly filtered clean air.

Asthmas

So-called "Tokyo-Yokahama asthma" is a classic example of a wheezing bronchitis clearly related to exposure to very heavy industrial air pollution, and occurring almost exclusively in cigarette smokers. So-called "New Orleans asthma" is another example of a wheezing bronchitis due to a special type of air pollution.

In recent years, it has been strongly suggested that minute quantities of asbestos inhaled into the lungs are responsible for certain forms of malignant lung tumors.

ANIMAL STUDIES

Numerous efforts have been made to create an animal model that will be comparable to the situation in man. Various animal species have been exposed to numerous individual constituents of air pollution in varying concentrations. They have also been exposed simply to polluted air, for example, automobile exhaust fumes.

While much has been learned from these studies, many difficulties have been encountered. In the first place, most laboratory animals do not live very long, not nearly as long as man is exposed to polluted air. Animal exposures, therefore, have had to be more concentrated than those which occur under natural circumstances in man, in order to produce any detectable changes.

The anatomy and function of animals' lungs differ in various ways from those of man. For these and other reasons, even after obtaining

positive findings, it may not be possible to extrapolate from experience in animals to man in this regard.

MULTIPLE FACTORS IN CAUSATION

One of the most difficult problems in studying lung cancer, chronic bronchitis, and emphysema is that they almost certainly have multiple causes; at the very least, multiple factors appear to play a role in their causation.

One factor involved in these diseases seems to be some kind of lung tissue susceptibility, very possibly genetic, to which Dr. Goldsmith referred earlier, making it possible for many nonsusceptible people to live in cities, smoke cigarettes heavily, have repeated respiratory infections and still not develop any of there three diseases. It would be most helpful if we had some practical test for identifying such people.

CAUSATIVE AGENTS

Various specific chemicals found in polluted air have been studied in both man and animals. The so-called oxidants, especially ozone, and the sulfur oxides in quite low concentrations, will temporarily paralyze the cilia lining the airways and thus interfere with mucociliary clearance of foreign material, bacteria and mucus, in both the normal, and especially in the abnormal, human respiratory tract.

The nitrogen oxides, produced by the combustion of petroleum products, are classic examples of the numerous highly irritant substances in air pollution which have so far been identified. Benzpyrene and other carcinogenic agents have also been found in urban air pollution, especially from the exhaust gases from automobiles.

Carbon monoxide

Carbon monoxide is a very common contaminant of city air. The concentrations of carbon monoxide found in human blood from residents in our highly congested cities are not high enough to be harmful to healthy, normal people, according to present knowledge. However, in persons already ill with chronic lung or heart disease, the interference with oxygen transport caused by the absorption of even small amounts of carbon monoxide may be considerable and, it is believed, can cause serious aggravation of their chronic disability.

Lead

The minute quantities of lead put into the atmosphere from leaded gasolines have so far not done any detectable harm to man. However, the amount of lead being found in human cadavers today is more than it was a few years ago. And lead is a dangerous poison.

PAN

Substances given off by combustion often react in the presence of sunlight and moisture to form so-called free radicals, one of which is peroxyacetylnitrate (PAN). PAN has been identified as the cause of the death of plants and trees along the highways of southern California.

Very small concentrations of PAN have also been found to interfere with the exercise performance of human beings under experimental conditions. What more serious effects PAN and other of these

highly reactive, transient and irritating substances may have on man can only be speculated at present.

Not all of the constituents of air pollution are biologically active. A number of substances found in polluted air, such as fly ash or carbon, are inert. When these inert materials are inhaled, however, they often slow down the normal mucociliary clearance mechanism of the airways and may contribute to the biologically adverse effects by holding adsorbed active substances in contact with lung tissues longer than otherwise would have occurred.

MORTALITY RATES

The U.S. mortality experience with lung cancer, chronic bronchitis, and emphysema in the past 50 years amounts virtually to an epidemic of these diseases. Deaths from these three diseases have been rising at an alarming rate from very low figures at the turn of the century. I would estimate that about 100,000 Americans will die prematurely of these three diseases in 1968.

My colleagues and I at the University of Colorado Medical Center have studied the causes of death in two series of autopsied subjects: One, those whose reported cause of death was chronic bronchitis and emphysema; and, second, those whose reported cause of death was not either of those diseases.

We have concluded, in a paper soon to be published, that the reported death rates from chronic bronchitis and emphysema in recent years have understated the true mortality from these diseases in our hospital population dying past the age of 40, by about 30 percent.

AIR POLLUTION EPISODES

It must not be overlooked that air pollution can kill man directly when severe enough, and/or the accompanying meteorological conditions are just right. Some eight or 10 such air pollution disasters have been recorded, as I am sure you are aware.

Dr. Goldsmith referred to the Ninth AMA Research Conference held in Denver a week ago, and I would like briefly to review seven topics presented at that meeting which struck me as important.

CONTRIBUTORY FACTORS

Additional impressive evidence was presented regarding the effects of air pollution on both children and adults. First, an additional factor has again been identified in the city environment. In my own opinion, this socioeconomic factor amounts not only to more exposure to air pollution, but also poverty, poor education, neglect of illnesses, especially respiratory illnesses, more cigarette smoking, and perhaps a constitutional inferiority as well.

Temperature

While cold weather increases the frequency of respiratory infections, it may temporarily reduce severity of urban air pollution.

Aveolar macrophaxe

The second finding was the adverse effect of various pollutants upon the scavenger—the alveolar macrophaxe—which plays an important role in the self-cleansing function of human lungs.

Urban environment

Third, the lungs from people who live in one heavily populated city—that is, St. Louis, Mo.—showed more destructive emphysema; that is, more anatomic destruction of their lungs when examined at autopsy, than did the lungs from a comparable population; namely, Winnipeg; the two populations differed relatively little in their smoking.

Age

Fourth, numerous new techniques for studying the effects of air pollution on living animals or living material were presented. The lungs of older animals appear to show the adverse effects of air pollution more than those of young animals. Very small concentrations of ozone, namely, one part per 100 million, were shown to have a deleterious effect upon an essential enzyme system; that is, upon the integrity of normal tissue.

Stomach cancer

Fifth, persons exposed to air pollution have an increased risk of stomach cancer. The nature of the pollutant or pollutants involved, however, is not known.

Heart attack

Sixth, living in a polluted environment has an adverse effect upon survival from myocardial infarction—that is, heart attack—this is thought to be related to increased exposure to carbon monoxide. This was confirmatory of previous work to which Dr. Goldsmith referred.

Asbestos

Finally, there was additional confirmatory evidence of the harmful effects of inhaling asbestos: mesothelioma, a malignant tumor of the lung or abdomen is very much more common in the exposed than in the unexposed.

From this brief and incomplete review of the evidence, it must be apparent to you that that which is available is not of the simple cause-and-effect variety. However, the medical scientific community, I believe, is in broad general agreement that the evidence comes from numerous different sources, and is not subject to any interpretation other than that air pollution is harmful to human health.

AIR POLLUTION TRENDS

Of even greater importance, we know the severity of air pollution is rapidly getting worse and that it takes many months, usually years, even after it has been decided to do something about it before any substantial improvement can be achieved.

Your attention is called in particular to the fact that in the Los Angeles area virtually all sources of air pollution other than those emanating from automobiles and trucks have been essentially controlled for the past several years; yet they still have a severe air pollution problem. This means, parenthetically, that the automobile has been the major source of Los Angeles air pollution. It also reflects the fact that the number of automobiles has also been increasing rapidly. Furthermore, it should not be overlooked that the problem persists in spite of the several positive but partial steps already taken to cut down on the air pollution emanating from internal combustion motors.

The Los Angeles experience has had one excellent dividend; that is, the automobile and petroleum industries now are apparently willing to acknowledge that their products play a major role in the air pollution problems of Los Angeles and of the entire United States at this time.

CONTROL PROBLEM

The problem of the ultimate control of automobile air pollution is so monumental, in my opinion, as to stagger the imagination. The proposals of an electric car, a steamcar, of atomic energy or a fuel cell or some other means of propulsion, appear wholly impractical at this time.

Mass rapid transit, such as is being created in the San Francisco-Oakland Bay area, is a partial answer; however, this is extremely costly, time consuming to accomplish, and must be broadly accepted by the public as a better means of transportation than their automobiles, in order for it to work.

CRITERIA DEVELOPMENT PROBLEM

I have been asked to direct my remarks toward the problems facing this Committee on Air Quality Criteria as they may affect the conditions of air quality standards.

It is quite easy for me, as you can gather by this time, to recommend that air quality criteria include health effects and should cover those forms of air pollution known to be related to health. The need for more knowledge is obvious.

ENVIRONMENTAL QUALITY CRITERIA

It is quite impractical and even unwise to consider air pollution problems without also considering the problems of water pollution and waste disposal. The three problems are unavoidably mingled. We have to dispose of wastes.

The correction of air pollution without concomitant attention to water pollution would inevitably lead to more trouble with our water. This consideration brings to mind the importance of monitoring the results of any air pollution control activity, since it is altogether possible that one air pollutant may modify the effect of another—either favorably or unfavorably—upon man.

FEDERAL GOVERNMENT ROLE

In conclusion, I urge strongly that the Federal Government take the necessary legislative steps to do all that is possible to reduce and control air pollution throughout this country. We have no time to lose. I believe it is dangerous for us to wait for more positive proof that air pollution is the cause, or a cause, of any human disease. I believe that proof of a direct cause-and-effect relationship between air pollution and lung cancer, chronic bronchitis and emphysema, is many years away. This does not in any way alter my conviction that air polution is probably one of the causes of each of these diseases, has already been seriously harmful to our health, and will be more so in the future unless mastered.

Senator MUSKIE. Doctor, your closing paragraph raises some question, it seems to me, as to the viability of the air quality criteria and standards, and approach to controlling air pollution. I don't know whether that is what you had in mind or not but I think we ought to explore it a little.

On the top of page 6 of your statement as well as in the closing paragraph you make reference to this point and I will read from the top of page 6.

> The medical scientific community is in broad general agreement that the evidence comes from numerous different sources, and is not subject to any interpretation other than that air pollution is harmful to human health.

That depends perforce on the establishment of criteria which are intended to identify the health effects of scientific pollutants.

Now if proof of a direct cause and effect relationship is many years away, what are we talking about when we talk about establishing criteria?

Are we going to be able to establish the health effects of specific groups as a basis for the control by standards?

Dr. MITCHELL. Sir, your question is extremely difficult for me to answer since I believe that we do not know the causes of the diseases with which we are concerned. The precise knowledge that tuberculosis, for example, is due to the tubercle bacillus has been gnown since the stablishment of Koch's postulates. This kind of proof with regard to air pollution related diseases is the kind of proof that we don't have. I think that all I can say is that it is my opinion for the reasons given—and others, which I didn't have time to go into—that these three diseases are related to air pollution although the absolute final proof is not yet available.

Particulate effects

Senator MUSKIE. Let's take particulates, which Dr. Goldsmith mentioned. Are we in a position to say what concentrations of particulates may have harmful health effects?

Dr. MITCHELL. I do not feel competent to answer this. I think that other people are far better able to make such a judgment than I am. I think they are harmful, I think they probably impair the lung clearance mechanisms and hold other substances in contact with the lungs and therefore are particularly harmful for these reasons.

Sulfur oxides

Senator MUSKIE. Are you able to say what concentrations of sulfur oxide are harmful to health?

Dr. MITCHELL. I can only refer to what others have said. I cannot myself render an opinion on that.

Senator MUSKIE. Should we know what concentrations are harmful before we undertake to establish criteria?

Dr. MITCHELL. It depends on how you mean "know."

Senator MUSKIE. Well, I guess that is the definition I need from you.

Dr. MITCHELL. I just am not able to be precise about this. I am convinced that sulfur oxides do specific unfavorable things. In addition they aggravate other things. As to whether they cause any of these diseases on the other hand, I cannot say. The trouble is that it is not just

a simple matter of sulfur oxides; we are dealing with a mixture of sulfur oxides with nitrogen oxides and oxidents and other pollutants, with different concentrations at different times. We are not going to be able to reproduce in animals the complex situation that occurs in man right away. Therefore, I doubt that we are going to come up with the kind of precise information which you need.

Approaches to control

Senator MUSKIE. One approach that your observation suggests is that since we are convinced, if we are and you are, that particulates and sulfur oxides and others have harmful health effects, but it is difficult for us to pinpoint the exact concentrations which are harmful, then we ought simply to require that any emissions which produce them are to be prohibited as fast as technology makes it possible. We also ought not to try this more sophisticated and precise approach of establishing air quality criteria leading to control standards.

Which of these two approaches——

Dr. MITCHELL. I am sorry, which are the two approaches?

Senator MUSKIE. The first one is to satisfy ourselves, as you have satisfied yourself, that there are harmful health effects. If we are satisfied then we just prohibit all emissions of these harmful pollutants, a blanket prohibition, as fast as we can develop the technology to do it. That is one. Now the approach that I can see as being the basis of present conversation is that we have tried to identify the specific health effects with specific rules and then aim control standards at those concentrations which we know to be harmful.

As knowledge improves, we refine the criteria or the standards, and we try to relate our control standards to the concentrations of pollutants which we satisfy ourselves, in some way or the other, are harmful.

Dr. MITCHELL. Esthetically the first would be more pleasant but highly difficult to achieve and extremely expensive. The second is far more practical.

Concentration effects

Senator MUSKIE. Do we know enough about concentrations?

Dr. MITCHELL. No, we need to know a great deal more. Dr. Goldsmith said we do know enough about some things and he is more experienced in this regard than I. I would go along with him on what he testified but I think we need to know a great deal more, and I am sure he would agree.

Senator MUSKIE. In other words, your experience is related not to concentration of pollutants but to the effect of air pollution as it exists upon the health of human beings.

Dr. MITCHELL. Exactly.

RESEARCH NEEDS

Senator MUSKIE. What kinds of studies do you feel would be required to determine whether air pollution has a direct effect on health or whether it aggravates an existing respiratory condition?

Causative agents

Dr. MITCHELL. We should determine what foreign substances are present in lungs, especially in emphysematous lungs, that may have been inhaled, that might have been responsible for the damage—we

should design an experiment where humans are exposed under controlled conditions, and other factors are held constant; this would be an epidemiologic study and would have to be done under carefully controlled conditions where no serious harm to the humans would be involved.

Animal studies

As you can see, I am concerned with our ability to extrapolate from animal studies. We can learn a lot of preliminary information from animal studies: we can separate various pollutants out in various concentrations. The fact is, however, that we are dealing with an extremely complex mixture of substances to which we are exposed. I think that studies in animals should involve realistic concentrations of for example the actual material exhausted from automobiles rather than one specific pollutant, perhaps, in various, often higher than natural, concentrations.

Lung tissue biochemistry

We need to know the fundamental biochemistry of lung tissue and how tiny concentrations of pollutants affect them. We did hear some preliminary information in Denver last week about this. If we understood the cell biochemistry better, we could understand better how it can be adversely affected.

Epidemiological studies

The most practical studies now appear to be extensions of epidemiological studies because they refer to humans. they are extremely expensive and time consuming, however.

Senator MUSKIE. We don"t have as much time as we need.

Dr. MITCHELL. That is the problem.

Senator MUSKIE. At this point are there any questions of Dr. Mitchell?

LEAD

You made a statement with reference to lead on page 4. You say:

> The minute quantities of lead put into the atmosphere from leaded gasolines have so far not done any detectable harm to man. However, the amount of lead being found in human cadavers today is more than it was a few years ago. And lead is a dangerous poison.

Now should we delay doing anything about lead until we are able to establish detectable harm which may be established only after the amount of lead in human cadavers is higher than it is today, than on a general basis?

BERYLLIUM

Dr. MITCHELL. You referred earlier to "beryllium." I understand your concern about lead because the exposure to "beryllium" occurred as long as 15 years before the onset of the dreadful condition beryllium granulomatosis and was often very slight. I don't think there is any evidence that lead should be feared in this way.

I think we can keep watching the situation with lead while our attention should be directed toward correcting more immediately serious potential problems.

Senator MUSKIE. Thank you very much, Doctor. We really appreciate your testimony this morning.

Dr. MITCHELL. Thank you.

(Questions submitted by Senator Muskie and the response by Dr. Mitchell are as follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. ROGER S. MITCHELL,
Director, Webb-Waring Institute for Medical Research,
University of Colorado Medical Center,
Denver, Colo.

DEAR MR. MITCHELL: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

QUESTIONS SUBMITTED TO DR. ROGER S. MITCHELL

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What types of studies would be useful to confirm or refine air quality criteria?

3. To what extent are the reported effects of air pollution affected by the study methods employed?

4. Recognizing that your specialty is respiratory diseases: Are there individuals, or groups of individuals, in the general population who are particularly susceptible to air pollution under conditions of either chronic or acute exposures?

5. The health effects of air pollution on children have been discussed. What kinds of effects would you expect to observe, and should they be of concern to public health officials in the development of air quality criteria?

6. In your statement mention is made that reported causes of death from bronchitis and emphysema may, in recent years, have been understated by about 30 percent. In light of that fact, do you feel that currently reported vital statistics of causes of death (mortality) are adequate for epidemiological purposes, and if not, how could they be improved?

7. In your statement you mention the British immigrant studies and the fact that the risk of developing lung cancer is affected by their former environment and the length of exposure in the environment. What do you consider the significance of these studies in terms of public health policy?

8. The work of Haenszel and his colleagues, cited in the staff report, suggests that the risk of developing lung cancer is higher in those individuals born in the country who move to the city, then in those born in the city who remain there all their lives. Recognizing that we live in a highly mobile society, would you care to comment on the significance of these findings?

9. Dr. Lawther (page 48 of the staff report) has suggested that the preliminary stages of bronchitis are presumably in response to inhaled irritants, and during this phase the effects are certainly reversible. However, later infection supervenes which is frequently followed by destruction of lung substance which leads to emphysema. Would you comment on present research capabilities to detect these changes and their implications with regard to public health policy?

THE WEBB-WARING INSTITUTE FOR MEDICAL RESEARCH,
UNIVERSITY OF COLORADO MEDICAL CENTER,
Denver, Colo., August 20, 1968.

Hon. EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution, U.S. Senate, Washington, D.C.

DEAR SENATOR MUSKIE: Your letter of August 2 unfortunately did not arrive here until after I had left Denver for ten days. I am now just returned.

I will do my best to answer your nine questions.

QUESTION 1

The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

The presently available scientific and medical evidence is sufficient in my opinion, to begin the development of air quality criteria for the following individual contaminants: carbon monoxide, inert carbonaceous fly ash or dust fall, and the sulphur oxides. The nitrogen oxides and the oxidants including PAN, are acutely irritative; however, clearcut evidence of long term damage to man is still not definite. The carcinogens are not too well identified as yet. The sulphur oxides—and probably also the nitrogen oxides and oxidants—work together with dust fall. The details of this additive or synergistic action are again not entirely clear.

QUESTION 2

The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What types of studies would be useful to confirm or refine air quality criteria?

The studies most useful to confirm or refine air quality criteria will have to be the exposure of various species of experimental animals to single and multiple contaminants in various concentrations—including realistic ones—over long periods of time, plus carefully designed and carried out epidemiologic studies of man in various environments. In short, we need much more of the sort of studies which are already under way.

QUESTION 3

To what extent are the reported effects of air pollution affected by the study methods employed?

The methods of study employed may affect results substantially. The animal species, the contaminant(s), the concentrations, the duration of exposure and other factors such as cigarette smoking must all be taken into consideration. All studies in animals must necessarily be checked as well as possible by observations and possibly experiments in man.

QUESTION 4

Recognizing that your speciality is respiratory diseases: Are there individuals, or groups of individuals, in the general population who are particularly susceptible to air pollution under conditions of either chronic or acute exposures?

Unquestionably, in my opinion, some individuals are more susceptible to the adverse effects of air pollution than others. I am not now referring to the elderly, chronic cardiac or pulmonary patient who is much more apt to die during peak air pollution episodes. This is not the question you have asked, I believe. How to identify those at greater risk of harm from air pollution is not possible at present. New techniques such as the speed and adequacy of mucociliary clearance of technesium 99 or tantalum powder blown into the bronchial tree may be able to tell us that some persons' lung self-cleansing mechanisms work better than others. This would be a good start except for three considerations: Does such impair-

ment really indicate future difficulty? Is the impairment acquired or genetic or developmental? And how would we go about testing all persons?

QUESTION 5

The health effects of air pollution on children have been discussed. What kinds of effects would you expect to observe, and should they be of concern to public health officials in the development of air quality criteria?

The evidence relating urban living with acute and chronic respiratory infection in children is convincing to me. The possibility that frequent respiratory infections in children play a role in the later development of chronic airway obstruction—i.e. chronic bronchitis and emphysema—is also quite likely.

QUESTION 6

In your statement mention is made that reported causes of death from bronchitis and emphysema may, in recent years, have been understated by about 30 percent. In light of that fact, do you feel that currently reported vital statistics of causes of death (mortality) are adequate for epidemological purposes, and if not, how could they be improved?

I believe that improved medical education, including improved criteria for accurate diagnosis of chronic bronchitis and emphysema, both during life and at death—and this is occurring at present—is the only realistic way of dealing with the under-reporting and diagnosing of these diseases. In the meantime, studies similar to ours might be made at other centers and, if our observations are confirmed, public health officials should readjust their estimates of mortality accordingly.

QUESTION 7

In your statement you mention the British immigrant studies and the fact that the risk of developing lung cancer is affected by their former environment and the length of exposure in the environment. What do you consider the significance of these studies in terms of public health policy?

The British immigrant studies of lung cancer incidence are interesting epidemiologic demonstrations serving to back up the general concept that urban living, almost certainly related to air pollution in this instance, plays some role in the pathogenesis of lung cancer.

QUESTION 8

The work of Haenzel and his colleagues, cited in the staff report, suggests that the risk of developing lung cancer is higher in those individuals born in the country who move to the city, than in those born in the city who remain there all their lives. Recognizing that we live in a highly mobile society, would you care to comment on the significance of these findings?

The work of Haenszel et al to which you refer of course needs substantiation. However, we do know that animals exposed to ozone definitely develop a tolerance to it over a period of time. This may also occur in those who live all their lives in contaminated air, and might conceivably diminish the risk of lung cancer while possibly increasing the risk of emphysema and chronic bronchitis for all we know.

QUESTION 9

Dr. Lawther (page 48 of the staff report) has suggested that the preliminary stages of bronchitis are presumably in response to inhaled irritants, and during this phase the effects are certainly reversible. However, later infection supervenes which is frequently followed by destruction of lung stubstance which leads to emphysema. Would you comment on present research capabilities to detect these changes and their implications with regard to public health policy?

Experiments exposing animals, first to air contaminants and later to various kinds of infection are presently underway, I believe. Dr. Lawther's observations in man are quite in line with the most acceptable current hypothesis for the pathogenesis of chronic bronchitis and emphysema. More and more of this sort of work is needed to be sure of our ground. In the meantime this is another bit of information indicating the need for improvement of air quality, in my opinion.

If I may add, we know how harmful inhaling tobacco smoke is. Tobacco smoke consists of many of the very substances found in urban air pollution, especially carbon monoxide, nitrogen dioxide and various carcinogens. The nicotine is extra and, on the other hand, there is little or no sulphur dioxide and no "inert" dust in cigarette smoke. Other differences include the facts that polluted city air is usually filtered through the nose rather than taken straight down through the windpipe like tobacco smoke, and city air is inhaled all the time while cigarette smoke is only inhaled intermittently. In spite of these differences, I think it is fair to draw some conclusions with regard to polluted city air parallel with those which we have drawn with regard to tobacco smoke. They are both harmful, the degree dependent upon the total amount inhaled, which is related to both concentration and time.

The Public Health Service already has accumulated massive and, I think, conclusive evidence that cigarette smoking is harmful to human health. The same conclusion—for essentially the same reasons—may be drawn with regard to urban air pollution.

The automobile is the most common source of air pollution today. It is particularly threatening because of the population explosion, urban concentrations of people and the projected increase in the number of automobiles in the future. The present methods of controlling the automobile's contribution to our air pollution problem are less than 50% effective. And getting these control measures put widely to use takes a very long time. Improving the technology of controlling the air pollution arising from automobiles is, in my opinion, the best possible way to spend the money available for air pollution control today.

Again thank you for the oppprtunity to express my views to you and to your Committee.

Very sincerely yours,

ROGER S. MITCHELL, M.D.

(The complete prepared statement of Dr. Mitchell follows:)

COMPLETE PREPARED STATEMENT OF DR. ROGER S. MITCHELL

My name is Roger Sherman Mitchell, M.D., and I live at 245 Kearney Street, Denver, Colorado. My present occupation is Professor of Medicine and Head of the Division of Pulmonary Diseases of the Department of Medicine, University of Colorado School of Medicine, and Director of The Webb-Waring Institute for Medical Research at the University of Colorado Medical Center in Denver.[1]

I appear before you in vigorous support of efforts to reduce and control air pollution. My reasons for attempting to achieve this goal include economic, esthetic and health considerations. I wish to confine my remarks to the health aspects of air pollution.

Air pollution clearly, in my opinion, plays a significant contributory and probably causative role in three major diseases of the lungs: *lung cancer, chronic bronchitis* and *emphysema.* Unfortunately, the causes of these diseases are not precisely known. We do know that they are very much more common in men than in women, and in cigarette smokers than in non-smokers. The latter fact complicates the problem from the standpoint of consideration of the role of air pollution. In addition, these diseases appear to be more closely related to cigarette smoking than to air pollution. Of course, cigarette smoking may be regarded as a highly concentrated form of personal air pollution.

The evidence associating air pollution with the cause or aggravation of lung cancer, chronic bronchitis and emphysema is considerable, but indirect. For

[1] I received an A.B. in 1930 and an M.D. in 1934 from Harvard University. After postgraduate work at Boston City, Massachusetts General and Children's Hospitals in Boston, I practiced internal medicine in Glens Falls, N.Y., for six years, then spent 2½ years as a medical officer in the Army Air Force, then 19 months as a Medical Resident in North Carolina (tuberculosis) Sanatorium, McCain, North Carolina, then was Associate Director, later Clinical Director of Trudeau-Saranac Institute, Saranac Lake, New York, for the next seven years. Also during this time, I was Assistant Clinical Professor of Medicine at the University of Vermont School of Medicine. In 1955, I assumed my present duties, which consist in research, teaching and medical care in the field of pulmonary diseases.

I am a Fellow of the American College of Physicians, a Diplomate of the American Board of Internal Medicine and of its subspecialty Board of Pulmonary Diseases. I was President of the American Thoracic Society in 1959–60 and have been a Member of the Board of Directors of the National Tuberculosis and Respiratory Disease Association since 1959. I am a member of the Technical Advisory Committee, Regional Air Pollution Control Association, Denver, Colorado.

example, persons living in cities are more prone to develop these diseases than are those who live in rural environments. However, air pollution is probably not the only pertinent factor peculiar to the urban environment.

Children who grow up in cities have more chest infections and poorer lung function than do comparable children from rural areas. This is of considerable interest since many observers believe that frequent respiratory infections early in life play a significant role in the later development of chronic bronchitis and emphysema.

British cities have been known for their heavy air pollution, especially in the past. British immigrants to New Zealand and to South Africa have been found to have a higher incidence of lung cancer than persons born in these countries, when cigarette smoking habits are held constant. This observation suggests the operation of some British urban factor in their early lives, most likely the heavy air pollution of British cities, in contrast to the relatively clean air in New Zealand and South Africa.

Persons suffering from acute flareups of chronic bronchitis and emphysema have shown significant objective improvement when removed from Los Angeles air to rooms provided with thoroughly filtered clean air.

So-called "Tokyo-Yokohama asthma" is a classic example of a wheezing bronchitis clearly related to exposure to very heavy industrial air pollution, and occurring almost exclusively in cigarette smokers. So-called "New Orleans asthma" is another example of a wheezing bronchitis due to a special type of air pollution.

In recent years it has been strongly suggested that minute quantities of asbestos inhaled into the lungs are responsible for certain forms of malignant lung tumors.

Numerous efforts have been made to create an animal model that will be comparable to the situation in man. Various animal species have been exposed to numerous individual constituents of air pollution in varying concentrations. They have also been exposed simply to polluted air, for example automobile exhaust fumes. While much has been learned from these studies, many difficulties have been encountered. In the first place, most laboratory animals do not live very long, not nearly as long as man is exposed to polluted air. Animal exposures, therefore, have had to be more concentrated than those which occur under natural circumstances in man, in order to produce any detectable changes. The anatomy and function of animals' lungs differ in various ways from those of man. For these and other reasons, even after obtaining positive findings, it may not be possible to extrapolate from experience in animals to man in this regard.

One of the most difficult problems in studying lung cancer, chronic bronchitis and emphysema is that they almost certainly have multiple causes; at the very least, multiple factors appear to play a role in their causation. One factor involved in these diseases seems to be some kind of lung tissue susceptibility, very possibly genetic, making it possible for many nonsusceptible people to live in cities, smoke cigarettes heavily, have repeated respiratory infections and still not develop any of these three diseases. It would be most helpful if we had some practical test for identifying such people.

Various specific chemicals found in polluted air have been studied in both man and animals. The so called *oxidants*, especially *ozone*, and the *sulfur oxides* in quite low concentrations, will temporarily *paralyze the cilia* lining the airways and thus interfere with mucociliary clearance of foreign material, bacteria and mucus, in both the normal, and especially in the abnormal, human respiratory tract. The *nitrogen oxides*, produced by the combustion of petroleum products, are classic examples of the numerous highly *irritant* substances in air pollution which have so far been identified. Benzpyrene and other *carcinogenic* agents have also been found in urban air pollution, especially from the exhaust gases from automobiles.

Carbon monoxide is a very common contaminant of city air. The concentrations of carbon monoxide found in human blood from residents in our highly congested cities are not high enough to be harmful to healthy, normal people. However, in persons already ill with chronic lung or heart disease, the interference with oxygen transport caused by the absorption of even small amounts of carbon monoxide may be considerable, and, it is believed, can cause serious aggravation of their chronic disability.

The minute quantities of *lead* put into the atmosphere from leaded gasoline have so far not done any detectable harm to man. However, the amount of lead

being found in human cadavers today is more than it was a few years ago. And lead is a dangerous poison.

Substances given off by combustion often react in the presence of sunlight and moisture to form so-called *free radicals*, one of which is *peroxyacetylnitrate*, (*PAN*). PAN has been identified as the cause of the death of plants and trees along the highways of southern California. Very small concentrations of PAN have also been found to interfere with the exercise performance of human beings under experimental conditions. What more serious effects PAN and other of these highly reactive, transient and irritating substances may have on man can only be speculated at present.

Not all of the constituents of air pollution are biologically active. A number of substances found in polluted air—such as *fly ash* or *carbon*—are inert. When these inert materials are inhaled, however, they often slow down the normal mucociliary clearance mechanism of the airways and many contribute to the biologically adverse effects by holding absorbed active substances in contact with lung tissues longer than otherwise would have occurred.

The U.S. mortality experience with lung cancer, chronic bronchitis and emphysema in the past 50 years amounts virtually to an *epidemic* of these diseases. Deaths from these three diseases have been rising at an alarming rate from very low figures at the turn of the century. I would estimate that about 100,000 Americans will die prematurely of these three diseases in 1968.

My colleagues and I at the University of Colorado Medical Center have studied the causes of death in two series of autopsied subjects: one, those whose *reported* cause of death was chronic bronchitis and emphysema, and second, those whose reported cause of death was not either of those diseases. We have concluded, in a paper soon to be published, that the reported death rates from chronic bronchitis and emphysema in recent years have understated the true mortality from these diseases in our hospital population dying past the age of 40, by about 30 per cent.

It must not be overlooked that air pollution can kill man directly, when severe enough and/or the accompanying meterological conditions are just right. Some eight or ten such acute air pollution disasters have been recorded as I am sure you are aware.

From this brief and incomplete review of the evidence, it must be apparent to you that that which is available is not of the cause and effect variety. However, the medical scientific community, I believe, is in broad general agreement that the evidence comes from numerous different sources, and is not subject to any interpretation other than that air pollution is harmful to human health. Of even greater importance, we know that the severity of air pollution is rapidly getting worse and that it takes many months, usually years, even after it has been decided to do something about it before any substantial improvement can be achieved.

Your attention is called to the fact that in the Los Angeles area virtually all sources of air pollution other than those emanating from automobiles and trucks have been essentially controlled for the past several years, yet they still have a severe air pollution problem. This means parenthetically that the automobile has been the major source of Los Angeles air pollution. It also reflects the fact that the number of automobiles has also been increasing rapidly. Furthermore it should not be overlooked that the problem persists in spite of the several positive but partial steps already taken to cut down on the air pollution emanating from internal combustion motors.

The Los Angeles experience has had one excellent dividend: i.e., the automobile and petroleum industries now are apparently willing to acknowledge that their products play a major role in the air pollution problems of Los Angeles and of the entire United States at this time.

The problem of the ultimate control of *automobile air pollution* is so monumental as to stagger the imagination. The proposals of an electric car, a steam car, of atomic energy or a fuel cell or some other means of propulsion appear wholly impractical at this time. Mass rapid transit, such as is being created in the San Francisco-Oakland Bay area, is a partial answer; however, this is extremely costly, time-consuming to accomplish and must be broadly accepted by the public as a better means of transportation than their automobiles, in order for it to work.

I have been asked to direct my remarks toward the problems facing this Committee on Air Quality Criteria and Standards. It is quite easy for me, as

you can gather by this time, to recommend that air quality criteria be quite strict and should cover all known sources of air pollution as thoroughly as is feasible and economically sound at this time. I am not competent to be specific to you, however, on air quality standards.

It is quite impractical and even unwise to consider air pollution problems without also considering the problems of water pollution and waste disposal. The three problems are unavoidably mingled. We have to dispose of wastes. The correction of air pollution without concomitant attention to water pollution would inevitably lead to more trouble with our water. This consideration brings to mind the importance of monitoring the results of any air pollution control activity, since it is altogether possible that one air pollutant may modify the effect of another—either favorably or unfavorably—upon man.

In conclusion, I urge strongly that the Federal Government take the necessary legislative steps to do all that is possible to reduce and control air pollution throughout this country. We have no time to lose. I believe it is dangerous for us to wait for more positive proof that air pollution is *the* cause, or *a* cause, of any human disease. I believe that *proof* of a direct cause and effect relationship between air pollution and lung cancer, chronic bronchitis and emphysema is many years away. This does not in any way alter my conviction that air pollution is probably one of the causes of each of these diseases, has already been seriously harmful to our health and will be more so in the future unless mastered.

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Senator MUSKIE. Our third witness is Dr. Stephen M. Ayres, director of the cardiopulmonary laboratory, St. Vincent's Hospital, New York.

Dr. Ayres, it is a pleasure to welcome you this morning.

STATEMENT OF DR. STEPHEN M. AYRES, DIRECTOR, CARDIOPULMONARY LABORATORY, ST. VINCENT'S HOSPITAL, NEW YORK, N.Y.

Dr. AYRES. Thank you very much, Senator.

I am Stephen M. Ayres from St. Vincent's Hospital in New York City. I am director of the cardiopulmonary laboratory. I currently am serving on the boards of directors of the New York County Tuberculosis & Respiratory Association and the New Jersey State Tuberculosis Association.

In addition I have functioned on the Medical Advisory Board of the New York City Department of Air Pollution Control.

Now I have some prepared testimony which I believe you have and in the interest of time I don't plan to read it in its entirety. I would like to speak to several questions that were presented in Mr. Grundy's staff report and also indicate my own major field of research.

STUDIES OF HUMAN REACTIONS

As a cardiopulmonary physiologist my major work has been on understanding of the reaction of the human being to take a variety of air pollutants.

Animal models

I would like to stress that while animal models are extremely useful in formulating hypotheses they fall down in a direct extrapolation to human beings. One very important example, for example, is the guinea pig. The guinea pig is extremely sensitive to low-level concentrations, but, unfortunately, it appears that at least the adult human is much less sensitive.

Perhaps the immature human, the child, the baby, may be as sensitive as the guinea pig but that is an area where very little is known.

Human studies

My field has been the investigation of certain specific pollutants (the oxides of sulfur, and carbon monoxide) and attempting to determine their reaction in the human being.

Obviously this area is fraught with difficulty in experimental design, ethical problems, and the problems of an informed consent.

If you tell an individual what he is going to breathe, and of course you have to do this in order to get an informed consent, you cannot be sure whether his reaction is in truth a chemical or psychological reaction. It is possible to skirt the issue, however, and still obtain an informal consent.

Another approach we have been exploring lately is to reverse the procedure. Instead of exposing humans to pollutants, it is important, to study them in clean atmospheres. Patients with a variety of human diseases—emphysema, asthma—may be studied breathing normal New York City air and then breathing clean air.

Plant studies

There have been some fragmentary studies in this area. The plant biologists have shown that plants raised in clean atmosphere, for example, are much stronger, much sturdier, much healthier. There have been a few studies that have shown the same with human beings. I would suggest by differentially filtering atmosphere, removing certain contaminants and not others, one could make some rather useful deductions about which pollutants were playing a major role.

SUSCEPTIBILITY MODEL

Now I would like to mention what I believe to be a workable model of the disease we call emphysema and its sister disease, bronchitis. This relates to one of Mr. Grundy's questions about whether air pollution can initiate or aggravate constructive lung disease.

Emphysema and bronchitis, in my view, result from a susceptible tracheobronchial tree and a variety of inhaled particulates, pollutants, and various infectious agents. I think it is important to stress these two, susceptibility and inhaled material. This presupposes that if you were not susceptible you could inhale a good deal and if you were very susceptible but never inhaled anything you would probably be all right. This multifactorial approach to bronchial emphysema is, I believe, a very fruitful one. Let me give an example.

In a population of cigarette smokers only 40 or 50 percent have a cigarette cough. Now these must be the more susceptible members of the population. I think this expresses the concept of susceptibility.

HUMAN RESPONSE VARIATIONS

Now what about the variations in human response to air pollutants? One of the approaches that we have used is to take a relatively large experimental population of several hundred people—normals, normal nonsmokers, emphysemas, bronchitics, asthmatics—these five groups and expose them to a standard concentration of a single pollutant, sulfur dioxide. This was a relatively high-level exposure for a short period of time. The purpose was to demonstrate the variability in response. Some people had no change at all. The majority had a modest decrease in pulmonary function and about 10 percent had a very profound one.

Some subjects actually improved demonstrating the variability in response. This is one way to pick out those members of our community that are more susceptible.

As you might expect, the most sensitive ones were asthmatics, people with chronic bronchitis and heavy cigarette smokers. They had rather marked responses to the dose.

Carbon monoxide

While we are on the subject of susceptibility, I would like to also mention our carbon monoxide studies referred to in the prepared testimony. We have administered a test dose of carbon monoxide. Of great interest, I think, is that when we raise the blood carboxyhemoglobin level to between 5 and 8 percent with acute exposure, certain individuals have no effect at all. Other individuals have a most profound effect and this group includes those with preexisting heart diseases, particularly diseases of the coronary arteries.

We find that when men with coronary artery disease are given carbon monoxide they demonstrate definite abnormalities at quite low levels. I will develop this in just a moment.

ACTION OF COFACTOR

Now the other point that I would like to make at this time is the question of cofactor, because cofactor was mentioned in Mr. Grundy's questions, and I think it is an important area.

Cigarette smoking

In diseases as complicated as coronary arteries, emphysema, there are obviously not single causes, as Dr. Mitchell pointed out. A very good example, I think, of a cofactor that we must constantly consider is that of cigarette smoking. While cigarettes are a form of air pollution, at least in the context of this committee they function as cofactors.

Asbestos

The recently presented data of Dr. Selikoff is an excellent example, I think, of how the cigarette function can enter into this. Dr. Selikoff has been investigating the role of asbestos as a very important air pollutant not only to asbestos workers but to insulation workers and perhaps to other people who are unknowingly exposed to asbestos from recently installed insulation, automobile brake linings or other unsuspected sources.

Autopsy studies, for example, show that a large number of normal individuals have asbestos fibers in their lungs.

Certain lessons may be learned from these observations. First is the latent period. Asbestos workers who had their first exposure some 20 or 30 years ago are only today developing various forms of malignancy and the most common one is the common lung cancer. So one lesson from the asbestos exposure is latency. This is important because it may suggest there are other pollutants that we are discovering today which may not produce effects for 20 or 30 years. This of course gives rise to the concept of the prudent man in general. Point 1 is latency.

Point 2 is the fact that while there is a marked increase in lung cancer in asbestos workers, this increase is only seen in those who are cigarette smokers. In other words, a cigarette smoking asbestos worker has many times the incidence of lung cancer as smokers in general.

SULFUR OXIDES

In the prepared testimony I have attempted to stress my belief that sulfur oxides have been used as markers of pollution. I think there is a good deal of misunderstanding, however, because the use of sulfur oxides for criteria does not imply that a particular level of sulfur oxide of itself is capable of causing human disease.

PARTICULATES

I have chosen to discuss in the prepared presentation particulate concentrations as a model of human effect. I think the evidence is accumulating that the particle acts as a catalytic agent, as a concentrating agent, as a carrier of absorbed gases.

The particles we believe carry gases into the lung and because of the method by which particles are cleared they persist for a very long period of time.

Lung removal rates

Now you or I would breathe in any gas—take neon, for example, which is gas. We could breathe this in and in 10 minutes it would be completely cleared from our lungs. On the other hand, if we breathe in a particle, of a particular size they may remain for 4 or 5 days, several weeks, and many of these particles may remain for life.

A good example is the asbestos particle. So the particle has a very important physiological role in that it is not readily cleared by the lung.

Now when you take the particle, surround it by water vapor, nitrogen, hydrocarbons and other gases, then you can understand how the particle acts to incite this irritating potential.

INDICES OF POLLUTION

Now, having said this, how can one arrive at reasonable criteria? I would like to submit that we know that certain environments—New York City in Thanksgiving in 1966, for example—are extremely irritating. We would like to take a little volume of that air and say this is bad air—this is not the kind of air we would like to have—we need

certain markers of that kind of air. It does seem to me that sulfur oxides and particulates serve as useful bellwethers, useful markers of the eastern type of polluted air.

Now this varies from region to region and in California there may be a need to use oxidants or some other type of marker of pollution. But I would like to stress that when one suggests a particulate level or a level of sulfur dioxide as being useful for a criteria and being associated with human diseases this does not necessarily imply that it of itself is the only culprit.

Sulfur dioxide

Let me expand on that just for a moment. In a guinea pig it has been shown that an extremely low level, one-tenth to two-tenths part per million of sulfur dioxide can actually produce a physiological effect. It is very difficult, if not impossible to produce a physiological effect in the human, at anything much less than five parts per million.

On the other hand, the major episodes have had significantly lower concentrations. This suggests that it is not gaseous sulfur dioxide itself, but this mix that I have been talking about. When we pick criteria and say that a given concentration of sulfur dioxide is a useful marker, it does not mean that that concentration of gaseous sulfur dioxide is necessarily the major irritant component.

Sulfuric acid and sulfate salts may be more harmful than sulfur dioxide itself. Particulate sulfur, aluminum sulfate, zinc aluminum sulfate may be much more harmful directly than the actual gaseous sulfur dioxide.

Particulates

Now I have listed as strictly a model in this testimony some of the particulate concentrations observed by Dr. Winkelstein in a study of his and I have only meant to introduce this as one way of handling epidemiological data in an effort to set criteria.

CHRONIC RESPIRATORY DISEASE EFFECTS

I think the part of Dr. Winkelstein's study which demonstrates an increased death rate from chronic respiratory disease with increasing levels of air pollution shows the general relationship between air pollution and disease.

It may not be possible to demonstrate an actual threshold but these may, instead, be a continuing response, a continuous function rather than an actual step function.

Now, regardless of this, we still have to select thresholds for criteria and standards but in truth the effect may not be one of threshold but continuing.

Aging process in man

This leads me to one other important point and that is that the effects of air pollution in general may well be related to the aging process in man. We know that emphysema, chronic bronchitis, these diseases are much more common in the older individuals. We also know that the estimation of emphysema is underestimated by clinical studies, by death certificate studies and yet if we perform pathologic studies of the type I mentioned earlier today the incidence is quite striking.

Now it may be that some of what we regard as normal aging phenomena may actually be the consequences of a long exposure to low levels of air pollutants. The lungs in older people change their elastic properties. Important questions are what is senile emphysema? Why does the older individual have a large chest? Why does he lose lung tissue?

We have always considered this to be a manifestation of aging but it may in fact be a result of exposure to pollution.

CARBON MONOXIDE

Finally I would like to say a word about carbon monoxide. This has been mentioned in some detail today by Dr. Goldsmith. I too share his view that it is an extremely important pollutant and one that I feel has been underestimated in terms of its overall position in this field.

I would like to indicate that it is a very simple pollutant. In contrast to the other pollutants, the effect of carbon monoxide is relatively well understood. It ties up hemoglobin, depriving the body of oxygen and is roughly similar to the effect of high altitude. It is also similar to breathing a low concentration of oxygen. There is excellent evidence that patients who have coronary heart disease and angina pectoris, for example, may become much more severely symptomatic when they inhale low concentrations of carbon monoxide. While with other pollutants we have difficulty in establishing a correlation between dose and effect, we have very good information that when the blood-carboxyhemoglobin level rises to between 5 and 10 percent there is definite response.

Central nervous system responses

Below 5 percent carboxyhemoglobin there may be central nervous system responses and above 10 percent carboxyhemoglobin there are vascular responses in the healthy population. At lower levels there are definite responses in the patients with coronary heart disease and emphysema.

Air quality criterion

For that reason I would like to ask that our air quality criteria, insofar as possible, be tied into measurements of blood-carboxyhemoglobin.

I believe we should so write our air quality criteria that the carboxyhemoglobin should not be allowed to exceed 5 percent.

AVAILABLE EVIDENCE

In summary, then, I would like to indicate that I feel sufficient evidence is available to begin the job of having realistic criteria. I subscribe to the importance of your view of the importance of criteria and standards.

I believe that criteria should be on the basis of scientific information unrelated to economic feasibility and technological feasibility.

RESEARCH NEEDS

Finally, one note about further investigation. I have mentioned the use of clean rooms to estimate the effects of pollutants. I would also like to encourage various investigators to attempt to measure pulmonary function in various parts of our country where the pollution burden differs.

For example, last week I was in Huntington, W. Va., which was the site of an abatement hearing. Huntington, W. Va., is very high in terms of suspended particulates and very low in sulfur oxides. I think if one knew what the pulmonary function was of long-term residents of this area, it might be possible to separate the effects of particulates from sulfur oxides.

Thank you very much.

Senator MUSKIE. Dr. Ayres, your prepared statement will be included in the record in full. I must say your oral testimony was excellent.

(Dr. Ayres' prepared statement follows:)

COMPLETE STATEMENT OF DR. STEPHEN M. AYRES

THE DEVELOPMENT OF AIR QUALITY CRITERIA

The breathing of polluted air has been suspected of injuring health since coal made possible the Industrial Revolution. Most of the evidence relating to the role of air pollution and health depends on epidemiologic and statistical interpretations which appear imposing to the average physician and which may be exaggerated or minimized depending upon the point of view of the investigator or reviewer. The continuing statistical debate over the relationship between tobacco smoking and health demonstrates the cloud of confusion surrounding a considerably clearer and simpler pathogenetic system. Although the question could be approached more directly by the deliberate administration of pollutant mixtures to various study populations, the obvious ethical dilemmas limit the application of this experimental method. Decisions must, in consequence, be based on carefully controlled epidemiologic studies buttressed where possible by human and animal exposure studies.

Almost all observers acknowledge that sudden increases in air pollution of the type occurring in London, New York City, and Donora, Pennsylvania produce increased death and illness rates. Many scientists agree that the incidence of chronic bronchitis and emphysema is higher in individuals exposed for long periods of time to lower levels of pollutants. Little agreement exists, however, as to which pollutants are responsible for the increased death rates and to the levels at which they become dangerous.

Sulfur dioxide has become synonymous with "air pollution" in many minds because of the exhaustive studies performed with this pollutant, but gradually accumulating evidence suggests that gaseous sulfur dioxide may not itself be responsible for the irritant potential of city air. While certain pollutants such as asbestos (lung cancer) and beryllium (lung fibrosis) produce specific effects in the human lung, it has been difficult to determine which pollutants account for the observed increase in chronic respiratory disease. Although a given polluted atmosphere may be conceded to have a deleterious effect on health, it has not been possible to reproduce the health effect by the experimental administration of single pollutants. For example, while epidemiologic evidence suggesting a deleterious effect on health is found when the concentrations of sulfur dioxide reach 0.5 to 1.0 ppm, administration of this concentration of pure sulfur dioxide to volunteers does not reproduce the same health effects. Evidence such as this has led scientists to conclude that *the irritant potential of city air is due to the interacting effects of multiple pollutants.*

Central to this concept is the position of the particle. All air contains particles and city air may contain over one and one-half million particles in each cubic foot. These particles are constantly moved through the upper and low airways during normal breathing but only a fraction are deposited in lung tissue. Lung retention of these particles depends upon size: larger particles (above five micra) are removed by the upper airway and do not penetrate to the alveoli, while extremely small particles (below one micron) are rapidly cleared. As a result of these two factors, particle retention is maximum for particles between one and three micra in diameter and as much as sixty percent of these particles may remain in the lung indefinitely. In contrast, inhaled gases are cleared from the lungs in several minutes. For example, a breath of sulfur dioxide will remain in the lung for several minutes, while a breath of carbon particles might remain in the lung for several days (some, forever).

The particle may serve as a vehicle for the retention of gas particles in the lung. Molecules of irritant gas may well remain in the lung for several days instead of being cleared in several minutes. In addition, the particle apparently acts as a concentrating surface (sponge effect) and also as a catalytic surface for multiple chemical reactions. Activated carbon is commonly used as an adsorbing agent and catalyst and may well serve this same function in the human lung. Sulfur dioxide and water vapor adsorbed to a carbon particle might well chemically interact and produce sulfuric acid in distal areas of the lung.

The concept of pollutant interaction probably explains the inability to reproduce air pollutions effects with single pollutants but complicates the problem of establishing air quality criteria. Since we know that the air in New York City during Thanksgiving 1966 was definitely irritant to the human lung, we need some technique for identifying that air mixture when it occurs again. Sulfur dioxide and particle concentrations become excellent *markers* of pollution and serve as warnings against an irritant air mix even though these substances themselves may not necessarily be dangerous. This statement deserves reiteration since the use of sulfur dioxide as an indicator of quality does not indicate that it is a harmful gas itself. *It merely serves as an indicator or marker of pollution.* Many who have criticized the use of sulfur dioxide criteria on the basis of the relative benignity of gaseous sulfur dioxide have missed the point that it is used as an indicator much as canaries were used as indicators of carbon monoxide in Welsh coal mines.

The use of indicators to protect public health is a common medical practice. Water may be polluted by many agents, but human fecal contamination was long ago recognized as a major health hazard. Since it was impossible and cumbersome to measure all ingredients of human feces to determine water pollution it was decided to measure the concentration of coliform bacteria as an index of water pollution. When the coliform index reaches a certain level the water is declared unsafe for human consumption even though that concentration of coliform bacterial itself probably is not sufficient to produce human disease. A recent outbreak of water pollution was identified by an increase in coliform counts and control measures immediately instituted. Several cases of viral hepatitis were identified several weeks after the episode of water pollution but a serious hepatitis epidemic had been avoided by the prompt application of control measures. The coliform count served as an indicator of serious water pollution—in this instance, hepatitis virus—and alerted public health officials. Our problem in air pollution control is to determine which pollutants should constitute our "coliform" or early warning system.

I feel strongly that provisional air quality criteria must be formulated. While continuous research is obviously necessary to validate and improve upon these criteria, target goals for air quality are needed at this time. What is an air quality criterion? What is the philosophy underlying its construction? How can it be selected?

Air quality criteria should be based on scientific evidence rather than feasibility or financial consideration. Pharmacologists and the Food and Drug Administration have provided a sensible model. Drugs are evaluated in terms of dosages required to produce lethal or other serious effects. If five tablets are capable of killing a patient, the average therapeutic dose should be considerably less—say, one tablet. The drug standard is based on scientific evidence and is a generally accepted standard. The physician might well increase the dose several-fold in an individual patient, accepting the inevitable risk (provided the patient is informed). I believe this parallel applies to the setting up of air quality criteria

Just as drug dosages are held well below levels known to produce harmful effects and the coliform count is held well below levels known to produce intestinal symptoms, so should air quality criteria be held well below levels known to produce or aggravate human disease.

Which pollutants should be chosen as markers or belwethers of serious air contamination? The pollutant composition of the ambient air is closely related to economic development. The term "smog," a popular conjugation of "smoke" and "fog," was used to describe the English particulate-laden environment produced by the universal burning of coal. Coal-generated particulate smog was the common type of polluted environment until the widespread use of petroleum products, together with a decrease in the use of coal, led to the hydrocarbon and oxidant photochemical smog first recognized in Los Angeles. Since the atmospheric pollutants closely parallel man's ingenuity in developing new substances, it may be safely predicted that the composition of the atmosphere will constantly change, preventing the direct application of yesterday's air-sampling and health-effects data to tomorrow's air pollution problem. The pollutants selected for markers may well apply to but one region; others need be selected for other regions. For example, particulate density and sulfur dioxide appear to be important indicators in Great Britain and the Eastern United States, while a measure of total oxidant activity is important in Los Angeles.

The density of particulates in the atmosphere appears to correlate well with human discomfort, air cleanliness, and health effects. The following discussion is intended as a model upon which to base quality standards rather than an actual criterion itself. The model seeks to demonstrate that data is available which could be used to formulate sensible standards.

High volume samplers have been used to measure the weight of solid material suspended in the atmosphere in both the United States and Great Britain. The gross weight does not indicate the range of particle size or the nature of the particles but does serve to indicate the total amount of solid pollutants in the atmosphere. Studies performed by the National Air Sampling Network have shown, for example, that New York City has an average of 179 micrograms of solid material per cubic foot of air compared to 36 in Cheyenne, Wyoming. Pittsburgh average 147, Newark 123, and Chicago 140 (1965 statistics).

A number of epidemiologic studies have used particulate density as an indicator of air pollution. Winkelstein (1) noted the following death rates for chronic respiratory disease (controlled for economic level) and related them to particulate levels. Increasing death rates were noted with increasing particulate levels.

Particulate level	*Deaths per 100,000*
Less than 80 micrograms per cubic meter	44
80 to 100 micrograms per cubic meter	62
100 to 135 micrograms per cubic meter	94
Greater than 135 micrograms	129

Wyatt and associates (2) observed the incidence of emphysema (measured at autopsy in an unselected series) to be considerably higher in St. Louis, Missouri, than in Winnipeg, Manitoba. Seventy percent of individuals above the age of fifty living in St. Louis had some evidence of emphysema. The average particulate density in St. Louis is 152 micrograms per cubic meter per 24 hours (1965 statistics).

A questionnaire study by Stalker and Robison (3) in Birmingham, Alabama, demonstrated that about one-third of the individuals became "annoyed" at air pollution when particulate concentrations reached 150 micrograms. About ten percent of those questioned were always annoyed, but a threshold for increasing numbers of annoyed individuals was observed at about 100 micrograms of solid material per cubic meter.

Holland (4) has observed significant increases in the incidence of bronchitis and emphysema in London compared to that in rural areas in England. Smoking differences did not explain the varying incidence, although bronchitis was more common in heavy smokers. The average particulate density in London during the year of Holland's study was between 200 and 222 micrograms per cubic meter. (5)

Another index of particulate material in the atmosphere is the coefficient of haze or smoke shade measurement. This measures the black particles in the air, largely carbon, and has a rough correlation with suspended particluate

material. Since carbon may well be an important catalytic particle in the production of lung irritant, and since considerable data on smoke shade is available, smoke shade measurements may also be used to develop air quality standards.

Five air pollution episodes in New York City have been carefully studied (6, 7, 8) and the following smoke shade observations made during periods of increased human discomfort:

	Smoke shade		Sulfur dioxide	
	Early	Peak	Early	Peak
November 1962	3.0	6	0.3	0.7
December 1962	3.5	6	.1	.5
February 1963	3.5	7	.15	.45
February 1964	2.0	5	.3	.7
November 1966	5.0	8	.4	1.0

Analysis of these studies permits the tentative conclusion that particulate densities above 100 micrograms per cubic meter and smoke shade indices above 3–4 COH units are associated with definite discomfort, increased disease incidence, and mortality. Air quality criteria should obviously be somewhat lower than this level. Might it not be reasonable, for example, that particulate levels not exceed 50 percent of the level known to produce illness?

This presentation is obviously an oversimplification designed to demonstrate that meaningful air quality criteria can be formulated. It should not be considered an endorsement for 50 micrograms per cubic meter per 20 hours (yearly average) since such a blanket standard neglects the major problem of time and concentration. Is, for example, 100 micrograms for 2 days the same as 50 micrograms for 4 days? This approach attempts to discover specific pollutants which could alert public health officials to high-level air pollution disasters and to use currently available data in the formulation of tentatives quality criteria.

THE PROBLEM OF CARBON MONOXIDE

Carbon monoxide will be discussed separately here because it is a unique pollutant considerably different in chemical and physiologic behavior from the previously described pollutants. In contrast to the other pollutants adequate data exist at this time to select meaningful criteria, but these criteria must be "blood" rather than "air" standards.

Carbon monoxide produced primarily by the internal combustion engine is known by every schoolboy to be a colorless, odorless, and tasteless killer. Its only action is to displace oxygen from hemoglobin, producing a new pigment called "carboxyhemoglobin." The displacement of oxygen from hemoglobin not only serves to inactivate part of the body's supply of hemoglobin but also interfers with the oxygen-binding ability of the remaining hemoglobin. It is known that death occurs when between 30 to 50 percent of the circulating hemoglobin is combined with carbon monoxide; headache and vomiting may occur at considerably lower concentrations.

While it is difficult to establish the relationship between atmospheric pollutant level and health effect for the other pollutants, the health effects of carbon monoxide are *directly related to blood carboxyhemoglobin concentrations.* A number of recently reported studies have shown that carboxyhemoglobin concentrations below five percent may interfere with mental acuity and perception, while levels between five and ten percent may have a deleterious effect on the heart. (9) It seems clear, therefore, that air quality criteria for carbon monoxide must be so designed that blood carboxhemoglobin levels do not reach above five percent.

Unfortunately, however, air measurements cannot be used with any validity to assess the impact of carbon monoxide on various individuals. Since carbon monoxide is produced by multi-point sources (the automobile) the highest concentrations are found in the street while considerably lower concentrations are found at progressive distances from the source. The air intake-system of most automobiles is unfortunately designed, so that the exhaust from one car is fed into the driver's seat of the following car with the result that the highest concentration of carbon monoxide is generally found within automobiles. Since this gas interfers with judgment and reaction-time, it may well be an explanation for the rising toll in traffic accidents.

The change in carbon monoxide concentrations at different locations makes the institution of a single air quality criterion impossible. For example, the concentration of carbon monoxide may be 250 parts per million at street level, 150 ppm on the sidewalk, 50 ppm on the third floor, and only 10 ppm on the tenth floor. Which level is the critical one? The only way to assess the true impact of carbon monoxide on a given population is to make frequent measurements of blood carboxyhemoglobin. Regardless of the ambient air concentration, the blood level gives an accurate and integrated picture of the danger to the individual subject. It is obviously unpopular to approach large groups of people with needles and syringes and make multiple blood studies. Methods for analyzing expired air (similar to the drunkometer, which reflects blood alcohol) are available and extremely accurate.

I suggest that frequent measurements of blood carboxyhemoglobin be made each day, by the indirect expired air method, on drivers in traffic, pedestrians, and other exposed individuals—such as, patrolmen and taxicab drivers. *The air quality criteria should state that the blood carboxyhemoglobin concentration must not rise above five percent.*

The utility of such a blood system seems obvious. During the air pollution episode which occurred in New York City during Tranksgiving 1966 relatively high carbon monoxide levels (up to 35 parts per million) were recorded in the laboratory of the Department of Air Pollution Control. Considerable discussion was initiated with the Department of Traffic to consider whether existing traffic patterns should be altered for the duration of the emergency. Should midtown Manhattan be closed to most automobiles? Should private cars be banned from the city for a short period? Had a regular program of sampling been available, indirect blood measurements would have aided the decision-making process, since a general increase in blood carboxyhemoglobin levels to above five percent would signify a significant health hazard. Furthermore, the distribution of high blood-caroxyhemoglobins would assist the Department of Traffic in rerouting traffic. If high levels of blood carboxyhemoglobin were found only in the Times Square Area, control measures could be limited to that area; if they were found throughout the entire city, more general measures would be necessary.

SUMMARY

Industry and government appear ready to cooperate in joint ventures designed to control air pollution. Realistic air quality criteria must be adopted as targets and should be based on the best available data. The criteria should be derived on scientific evidence, independent of technical or economic considerations, even though they cannot be realized for several years. Finally, criteria must always be considered as tentative and provisional, subject to constant revision when new data are available.

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Senator MUSKIE. I am a little embarrassed that I have to go to the floor for a vote. We have one more witness this morning, Dr. Whipple, who I understand must leave this afternoon. I will have to leave quickly for the vote, and I will try to come back quickly to take Dr. Whipple's testimony.

My regret as far as you are concerned is that there are apparently no questions, because obviously you are highly qualified in this field, and I suspect that you have a great deal of information that would be useful to us. I guess I will have to content myself with submitting questions to you and perhaps even inviting you back, if you are agreeable. It was excellent testimony and I appreciate it.

Dr. Whipple, I will be back as soon as I can after I vote.

Thank you very much, Dr. Ayres.

Dr. AYRES. Thank you.

(Questions submitted by Senator Muskie and the response by Dr. Ayres, are as follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. STEPHEN M. AYRES,
Director, Cardio-Pulmonary Laboratory, St. Vincent Hospital, New York, N.Y.

DEAR DR. AYRES: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. STEPHEN M. AYRES

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What types of studies would be useful to confirm or refine air quality criteria?

3. To what extent are the reported effects of air pollution affected by the study methods employed?

4. Recognizing that your specialty is respiratory diseases: Are there individuals, or groups of individuals, in the general population who are particularly susceptible to air pollution under conditions of either chronic or acute exposures?

5. The health effects of air pollution on children have been discussed. What kinds of effects would you expect to observe, and should they be of concern to public health officials in the development of air quality criteria?

6. On June 4, 1968, at the New York Symposium on Air Quality Criteria, Professor B. D. Dinman suggested that there are individuals in the general popula-

tion particularly susceptible to carbon monoxide. Would you care to comment on the public health significance of these individuals?

7. Dr. J. H. Schulte, Director, Division of Occupational Medicine, Ohio State University, suggested at the New York Symposium on Air Quality Criteria on June 4, 1968 that in the case of carbon monoxide, the concept that if an ill or unhealthy individual can tolerate a given concentration of a known toxin for a specified period of time (in this case carbon monoxide) without untoward reactions, then this is ipso facto evidence that a healthy individual can tolerate at least the same concentration of that toxin for the same amount of time and possibly an even greater concentration of the toxin for the same or a longer period of time without untoward effects is untrue. Would you be able to comment on Dr. Schulte's remarks in the context of critical or susceptible population groups?

8. The work of Haenszel and his colleagues cited in the staff report, suggests that the risk of developing lung cancer is higher in those individuals born in the country who move to the city, than in those born in the city who remain there all their lives. Recognizing that we live in a highly mobile society, would you care to comment on the significance of these findings?

9. Dr. Lawther (page 48 of the staff report) has suggested that the preliminary stages of bronchitis are presumably in response to inhaled irritants, and during this phase the effects are certainly reversible. However, later infection supervenes which is frequently followed by destruction of lung substance which leads to emphysema. Would you comment on present research capabilities to detect these changes and their implications with regard to public health policy?

10. In your statement you suggest that available evidence has led scientists to conclude that the irritant effect of air pollution is due to the interacting effects of multiple contaminants rather than any individual contaminants. Are there any other biological stresses, for example, cold or influenza, which may contribute or enhance the effect of air pollution?

11. You have discussed the role of particulate pollution in causing air pollution health effects. Do you mean to imply there is sufficient medical evidence to suggest that control of particulates alone would provide for the protection of public health from other contaminants also present in the atmosphere?

ST VINCENT'S HOSPITAL AND MEDICAL CENTER OF NEW YORK,
New York, N.Y., August 23, 1968.

EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution, U.S. Senate, Washington, D.C.

DEAR SENATOR MUSKIE: It was a pleasure to participate in the hearings on Air Quality Criteria and I hope my testimony was of some value to your committee. I was extremely impressed by the scope of your questioning and would like to go on record as offering my services to your committee at anytime in the future.

The following are answers to the questions contained in your letter of August 2, 1968:

QUESTION 1

The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

I believe sufficient scientific evidence exists for the development of criteria for sulfur oxides, particulates, and carbon monoxide. These three pollutants have been monitored throughout the United States and Great Britain and are the basis for most of our present knowledge relating health effects to atmospheric contamination. It is important to select the type of measurement upon which to base quality criteria, and I would suggest using both suspended particulate and smoke-shade measurements for evaluation of particulate contamination. Smoke-shade is important because it appears to relate to the quantity of carbon in the atmosphere and carbon is a well-known catalyst which may play a role in the toxicity of particles. It is obviously important to standardize the analytical method for sulfur oxides.

There is also excellent scientific evidence for ozone which is generally taken as representative of oxidant pollution. While I do not consider myself expert in the field of trace metals, I suspect there is also enough evidence to develop criteria for lead.

QUESTION 2

The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What types of studies would be useful to confirm or refine air quality criteria?

Although a great deal of scientific and medical evidence is currently available, I am critical of the fact that many relatively simple experiments have not been performed. I feel strongly that the Public Health Service should attempt to direct research even though the concept of "directed research" is anathema to many investigators. Many conferences have been called to review the existing data; I feel that a conference to outline future studies is long overdue. The following projects are extremely important and could be accomplished with relatively little effort.

(a) Application of a standard pulmonary function technique to large populations in a number of representative cities studied by the Public Health Service. While there is considerable air quality data on these cities, there are but few health effects studies. The pulmonary function studies should include both smokers and non-smokers and also school children. It would be particularly important, for example, to study pulmonary function yearly in school children and see whether pulmonary function increases (as it should with increasing stature) at the same rate in city areas as in rural areas. As a suggestion, this type of study could be tied in with a pre-abatement conference study program.

(b) Development of clean air facilities in high pollution areas and close observation of the effect of residents in these clean rooms on pulmonary function. This would not only be a service to those individuals afflicted by bronchitis or emphysema, but would also provide significant information as to the levels of pollution responsible for aggravating human disease. For example, if three or four days in a clean air environment in New York City significantly improved pulmonary function, one could conclude that the type of New York atmosphere present during the period of study was definitely deleterious.

(c) Measurements of blood carboxyhemoglobin levels in large populations in urban areas, particularly effecting the level in motorists traveling through congested areas and in other exposed individuals such as policemen, taxi drivers, and others employed out-of-doors. In the summer, for example, it would be particularly important to measure carboxyhemoglobin levels in children in city parks at street level. These tests can be done by measuring the carbon monoxide level in lung air and do not require direct blood sampling.

(d) Since carbon monoxide is a relatively simple pollutant, detailed exposure studies should be carried out to determine what levels of carboxyhemoglobin show beginning human effect both in normal and diseased individuals.

QUESTION 3

To what extent are the reported effects of air pollution affected by the study methods employed?

The report of the effects of air pollution are markedly affected by study methods. A very sensitive method may produce false positive results while an insensitive method may miss the effect. Epidemiologic studies in particular are hampered by the complicating effects of climate, infectious disease such as influenza, and by cigarette smoking. One important improvement would be to standardize the type of pulmonary function studies used. In accomplishing the pulmonary function studies mentioned in paragraph #2, it would be worthwhile for a single organization to standardize the type of pulmonary function study used much as many other medical groups have standardized various tests.

QUESTION 4

Recognizing that your specialty is respiratory diseases: Are there individuals, or groups of individuals, in the general population who are particularly susceptible to air pollution under conditions of either chronic or acute exposures?

There is a marked variation in the sensitivity to the effects of air pollution. Individuals with preexisting chronic lung disease and older individuals with heart disease and heart failure are much more sensitive to the effects of the

irritant pollutants. Of even greater importance is the increased susceptibility of cigarette smokers to the effects of air pollution and also to certain individuals who have some type of constitutional susceptibility. This latter group has not been emphasized but is typified by the young individual who considers himself "bronchial". These individuals may have a history of allergy or frequent colds and may or may not be smokers.

The major effects of carbon monoxide is to deprive the body of oxygen. Individuals who are already oxygen deficient are particularly sensitive to the effects of carbon monoxide. This group includes patients with coronary artery disease (present perhaps in one-third of the male population), people with hardening of the arteries in the extremities or any organs including the brain, older individuals who have experienced strokes, people with anemia and people residing at high altitudes.

QUESTION 5

The health effects of air pollution on children have been discussed. What kinds of effects would you expect to observe, and should they be of concern to public health officials in the development of air quality criteria?

The health effects on children are extremely important as the urban population increases and more children are concentrated in areas of increasingly higher pollution. In general, small animals demonstrate greater effects because their ventilation rate, the rate in which they take in pollutants, is proportionately higher. This is the reason why the canary was of such value in the Welsh coal mines and why Haldane in his classic experiment on carbon monoxide used a mouse to warn him of the effects of that gas. All the effects seen in adults, particularly the development of a chronic cough and bronchitis, would be expected to exist in children. Since children with prominent tonsils and adenoids frequently have a number of respiratory infections, air pollution would also be expected to aggravate this situation. Finally, one might expect that the overall growth rate would be signficantly less in these individuals. It must be pointed out that epidemiologic studies may exaggerate the effect of air pollution on children since most children living in high pollution city areas are in low income groups and they have other reasons for poor growth rates. Studies, such as those in Buffalo which attempt to separate out the poverty question, are important here.

QUESTION 6

On June 4, 1968, at the New York Symposium on Air Quality Criteria, Professor B. D. Dinman suggested that there are individuals in the general population particularly susceptible to carbon monoxide. Would you care to comment on the public health significance of these individuals?

As discussed under question #4, any individual suffering from chronic oxygen lack is particularly susceptible to carbon monoxide. Since a high proportion of our population does in fact have coronary artery disease, this suggests that at least one-third of the population is particularly susceptible to carbon monoxide.

QUESTION 7

Dr. J. H. Schulte, Director, Division of Occupational Medicine, Ohio State University, suggested at the New York Symposium on Air Quality Criteria on June 4, 1968 that in the case of carbon monoxide, the concept that if an ill or unhealthy individual can tolerate a given concentration of a known toxin for a specified period of time (in this case carbon monoxide) without untoward reactions, then this is ipso facto evidence that a healthy individual can tolerate at least the same concentration of that toxin for the same amount of time and possible an even greater concentration of the toxin for the same or a longer period of time without untoward effects is untrue. Would you be able to comment on Dr. Schulte's remarks in the context of critical or susceptible population groups?

I heard Professor Dinman's presentation at the New York Symposium on Air Quality Criteria and also Dr. Schulte's discussion. I believe Dr. Schulte was attempting to criticize that concept as an over simplification. The principle of the susceptible population groups is a valid one and, in general, healthy individuals are less affected by a given pollutant than sick individuals. However, physical activity and place of residence within a city area, may modify the response and probably forms the basis for Dr. Schulte's comments. For example, if two men

drive through traffic in an automobile and are each exposed to the same concentration of carbon monoxide, their blood carboxyhemoglobin levels are roughly the same. If one individual who has heart disease reaches his office and performs desk work for an extra few hours while the other healthy individual performs vigorous physical activity, the healthy individual might be expected to show untoward reactions from the same concentration of carboxyhemoglobin. In other words, a variable of exercise has been added. Another example, a patient with chronic bronchitis during a period of high air pollution may remain indoors and have diminished activity. A healthy individual may stay out-of-doors and may exercise a good part of the time increasing his rate of ventilation and the amount of irritant pollutants reaching his lung. In this situation, the healthy individual might have a greater health effect.

I do not think the dialogue is particularly important and in view that Dr. Schulte in general agrees with the principle of susceptible population. He as warning against the uncritical acceptance of the thesis mentioned in your question.

QUESTION 8

The work of Haenszel and his colleagues, cited in the staff report, suggests that the risk of developing lung cancer is higher in those individuals born in the country who move to the city, than in those born in the city who remain there all their lives. Recognizing that we live in a highly mobile society, would you care to comment on the significance of these findings?

While one could develop a number of theories attempting to explain the data of Haenszel, it would seem important to confirm this valuable study. Careful studies should be performed to determine if lung cancer, and indeed other types of cancer, is more common in city dwellers and whether it is related to other factors such as economic class, previous residence and cigarette smoking.

QUESTION 9

Dr. Lawther (page 48 of the staff report) has suggested that the preliminary stages of bronchitis are presumably in response to inhaled irritants, and during this phase the effects are certainly reversible. However, later infection supervenes which is frequently followed by destruction of lung substance which leads to emphysema. Would you comment on present research capabilities to detect these changes and their implications with regard to public health policy?

Dr. Lawther's comments could be the text for an entire paper on the development of bronchitis and emphysema. It seems likely that inhaled irritants injure the tracheal-bronchial tree causing an outpouring of mucous and a chronic cough. This serves to diminish the lungs' ability to protect themself from outside infection. One cannot culture infectious organisms from a normal lung but they are common in the lungs of patients with bronchitis. The inhaled irritants alter the ability of the lung to fight off infection and within several days a variety of infectious agents (both bacterial and viral) enter the lung and set up a serious infection. The infection progresses and actually destroys the lung substance, leading to emphysema. It is likely that the bacteria themselves produce various enzymes which actually destroy lung tissue.

These observations are confirmed by the experience in air pollution epidemiology. Health effects do not decrease at the same time that air pollution levels decrease following an episode. Instead, patients continue to have increasing cough and sputum production, bacterial bronchitis, and pneumonia. These usually may be found for two to three weeks following subsidence of the initial episode. The pollutant has weakened the lung and infection has supervened.

It is obviously important for patients with preexisting lung disease to take antibiotics during periods of high air pollution.

It is possible to detect these changes by a number of pulmonary function and bacteriologic studies. It is also possible to detect them after the fact with careful autopsies. Again I feel that an organized program of pulmonary function testing in our urban areas should be constructed to detect the frequency of both bronchitis and emphysema. We have concentrated much of our medical muscle on the fight of heart disease. Chronic lung disease appears to be increasing at a rapid rate and is probably preventable. I feel strongly that identification of the environmental factors producing chronic lung disease and the recognition of individuals with early chronic lung disease would be an extremely important contribution to the nation's health.

QUESTION 10

In your statement you suggest that available evidence has led scientists to conclude that the irritant effect of air pollution is due to the interacting effects of multiple contaminants rather than any individual contaminants. Are there any other biological stresses, for example, cold or influenza, which may contribute or enhance the effect of air pollution?

The famous London Smogs were probably extremely irritant because of their high concentration of multiple pollutants (sulfur dioxide and particles), the high humidity and the cold temperature. There is also evidence that the consequences of an infection with influenza virus are modified by air pollution, so that many more cases of influenza may be found in high pollution areas during influenza epidemics. Cold air or high humidity alone are probably not particularly harmful but together with polluted air and infectious particles may combine to form an extremely toxic environment.

QUESTION 11

You have discussed the role of particulate pollution in causing air pollution health effects. Do you mean to imply there is sufficient medical evidence to suggest that control of particulates alone would provide for the protection of public health from other contaminants also present in the atmosphere?

Control of particulates would go a long way towards reducing the irritant potential of urban air. It obviously would not modify the effect of certain pollutants such as carbon monoxide or lead for example. Particulates appear to have a central role in the causation of human disease and for this reason particulate control is extremely important. I would like to amend the second sentence of your question and suggest that there is sufficient medical evidence to indicate that control of particulates alone would significantly decrease the effects of certain other pollutants on man. I would go a step further, however, and recommend that gases such as the oxides of nitrogen, ozone, carbon monoxide and hydrocarbons also be controlled. Most of the trace metals exist as particulates and would be controlled by general particulate techniques.

The obvious exception is the automobile engine which produces a mixture of gases and particulates and probably needs both controlled.

Sincerely yours,

STEPHEN M. AYRES, M.D.

(Brief recess.)

Senator MUSKIE. The committee will be in order.

I apologize for the delay but there were two rollcall votes and there seemed to be no point in trying to come back between the two.

We will go on with our final witness of the day.

First, may I recognize the presence of Dr. Michio Hashimoto from Japan. We realize he has an international reputation as an authority in this field, and we are delighted that he should come to our hearing.

I would like to invite Dr. G. Hoyt Whipple to testify. I apologize, sir, for the delay in getting to you.

STATEMENT OF DR. G. HOYT WHIPPLE, PROFESSOR OF RADIOLOGICAL HEALTH, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF MICHIGAN

Dr. WHIPPLE. Senator Muskie, unlike the previous three witnesses I am a biophysicist, not a physician.

For the past 10 years or more my teaching, research, and consulting have concerned in large part the radioactive wastes produced by the nuclear industry.

The statement I am about to make gives my views of the present standards of radioactive waste disposal, the implications which these

standards have for air quality criteria in general, and some suggestions for putting these criteria on a firm scientific basis.

However, before doing this, I should like to make a few general observations about wastes, pollution, and environmental quality criteria.

WASTE DISPOSAL PRACTICES

A waste is something which, in the prevailing economic circumstances, is cheaper to throw away than to use. Thus, a waste is defined in purely economic terms. A material which is discarded as a waste at one time may at some later time no longer be thrown away for one of several possible reasons.

New technologies

First, a technical development may make the material too valuable to throw away. The advent of the internal combustion engine converted gasoline from a troublesome waste in the production of kerosene to the mainstay of the petroleum industry.

Economic considerations

Second, extraction methods may improve so that it becomes economic to reduce the quantity or toxicity of the material that is discharged. The reworking of mine tailings is such an example.

Restrictions

Finally, restrictions in the form of laws and public opinion may reduce the amounts of waste which are thrown to the winds.

Note that new uses and more efficient recovery will result in a cheaper product, but that legal restriction will increase the cost of the product. It is with the third alternative that this subcommittee is concerned.

EFFECTS OF CONTROL

The only hope that your recommendations will not raise costs lies in the possibility that the pressure of these recommendations will call forth sufficient ingenuity in new uses and efficient recovery to offset the increased costs of acceptable air quality criteria.

However, whatever this cost may be, it is the price of a habitable world in time to come; it is the difference between shortrun economics and long-term economics.

WASTE MANAGEMENT PRACTICES

As I understand it, the ultimate objective of this subcommittee is to make the best present estimate of something corresponding to the perpetual yield concept in lumbering. In principle, there is a rate at which a waste material can be discharged forever that will just not produce any unacceptable changes in the environment. This principle is by no means easy to apply. The criteria, standards, and practices in radioactive waste disposal go farther toward this objective than is the case for any other wastes. For this reason, it is appropriate to consider the standards for radioactive wastes.

The standard for radiation control in the public environment is 0.5 rem per year added to natural background radiation.

Not all of you may be familiar with the rem. It is a unit of dose for ionizing radiation. The average dose of natural radiation in the United States is about 0.1 rem per year.

This natural background dose is caused by cosmic radiation from outer space and by the natural radioactive materials in air, water, soil, food, building materials, and in our own bodies. We are all exposed to these radiations throughout our entire lives. In some places, such as Denver, Colo., the natural radiation is as much as four times the average.

Starting with the dose limit of 0.5 rem per year, one calculates the amount of each radioactive isotope which will produce the limiting dose in the body. Next, one calculates the daily intake by inhalation and by ingestion which will just maintain the body content at the level producing the limit dose.

Finally, the concentrations in air, water, and food which, under average conditions, will separately produce the maximum daily intake are calculated. These concentrations, called maximum permissible concentrations, constitute the environmental quality standards for radioactive materials, and there are several hundred of them.

FACTORS IN SETTING EMISSION STANDARDS

In going from the environmental quality standards for radioactivity to the corresponding effluent standards, one applies at least four qualifying factors:

Multiple routes of exposure

1. If an individual were to breathe air at the maximum permissible concentrations for a given radioisotope, drink water at the maximum permissible concentration for the same isotope, and eat fish that would produce the maximum daily intake, he would be taking into his body three times as much of this isotope as is compatible with the 0.5 rem yearly limit. Thus, summation by multiple routes to the body is recognized.

Multiple agents

2. If an individual were to breathe air containing carbon-14 and sodium-24, both at their respective maximum permissible concentrations, his body would shortly be exposed to twice the yearly radiation limit. Thus, summation of exposure from multiple agents is recognized.

Susceptible individuals

3. If a small child were to drink milk produced by a cow grazing in a pasture where the air is at one maximum permissible concentration for iodine-131, the dose to the child's thyroid would be several hundred times greater than that to the thyroid of an adult breathing the air in the pasture. Thus, concentration along food chains, and the possibility of individuals with higher than average susceptibility are recognized.

Unknowns

4. Finally, when all the calculations, estimates, and conservative assumptions have been made, one knows that the actual exposure of every individual in the environment will not be exactly what is predicted. Thus, a factor of one-third is applied to cover disparities between theory and fact.

Using these concepts with some judgment and a few arbitrary assumptions, one is able to calculate the maximum rate of release for some of the radioisotopes which disperse readily in the environment, such as krypton 85 and hydrogen 3. With a few more assumptions, he can estimate the maximum rate of nuclear power production, nuclear explosive detonations, and isotope use in industry, medicine, research, et cetera, compatible with the environmental quality standards.

The concepts outlined here have led to practices of air cleaning, liquid waste treatment, and ground storage of waste that other industries find almost unbelievable. Most of the time, at most nuclear powerplants, the air at the top of the stack and the waste water at the point of discharge are fit for continuous human consumption.

IMPLICATIONS FOR AIR QUALITY CRITERIA IN GENERAL

One cannot, as far as I am aware, make the calculations or estimates for nonradioactive pollutants in the manner that is done for radioactive pollutants. The concentrations of nonradio active pollutants which are acceptable on a long-term basis are not known; the rates of removal from the environment are not known; the manner in which the effects of different pollutants are summed are not known.

AVAILABLE KNOWLEDGE

It has been said that we know relatively more about the effects of radiation and radioactive materials than we do about any other toxic materials. The reason is simply that more money and effort have been devoted to studies of radiation than to any other pollutant.

IMPLICATIONS OF CURRENT PRACTICES

The fact that the nuclear industry was born and is thriving under stringent air and water quality standards has three important implications for criteria and standards for nonradioactive pollutants:

(1) A method for establishing criteria and standards has been developed.

(2) Methods for cleaning effluent gases and liquids to meet these standards have been evolved and put into practices.

(3) An industry can meet these standards and still show a profit.

There are a few suggestions I would like to offer.

The limit to the amount of waste of any kind which can be discharged to the atmosphere will be set by one of three considerations: Human inhalation; human ingestion; effects on the environment itself: soiling, visibility, corrosion, domestic and wild organisms.

RESEARCH NEEDS

It is obvious that extensive studies are needed in all three areas.

It will take an enormous amount of work to establish the long-term acceptable concentrations of nonradioactive pollutants in air and water. This work will be more difficult than that with radioactive pollutants, because most of the nonradioactive pollutants act by different mechanisms.

Inhalation studies

Long-term inhalation experiments with animals, and careful epidemiological studies of large populations will be required to determine concentrations for conventional pollutants acceptable for human inhalation. There are no easy solutions or shortcuts that I can see. Only years of painstaking and expensive research will provide these answers.

Effects on food

There is a means, I believe, for determining the concentrations of airborne pollutants which do not render human food unfit to eat and which do not produce undesirable changes in the environment. This method is not particularly quick or easy, but it does appear capable of providing reliable answers in a systematic manner.

The method is this: Two large sealed chambers will be constructed. Weather conditions typical of some portion of the country will be produced in these chambers: temperature, sunlight, humidity, precipitation, wind, et cetera. Soil, plants, insects, animals, fish and domestic animals and crops typical of the region will be established in the chambers.

When things have settled down to their natural state and the two chambers have been shown to be similar to one another and to the region being simulated, the pollutant to be studied will be introduced into one chamber at such a rate that the air in this chamber is maintained at a constant concentration of the pollutant for weeks or months.

When the crops are harvested, the eggs are gathered, and the cows are milked, it will be possible by direct measurement to determine the relations between the air concentrations and the concentrations in human food, and to deduce from these relations what air concentration is compatible with human health by way of food.

The air concentration compatible with an acceptable environment can be found by increasing the concentration in the experimental chamber in successive steps until a concentration is reached which produces some undesirable change. Throughout these experiments the second chamber serves as a control to which changes observed in the experimental chamber can be compared.

The method outlined here is expensive and time-consuming; it will take millions of dollars and years of careful work, but it is the best way I can suggest to establish sound environmental quality criteria.

It has been a privilege to be asked to make a statement before this subcommittee, and I thank you for the opportunity of doing so.

Senator MUSKIE. Thank you, Dr. Whipple.

CRITERIA FEASIBILITY

Do you mean to suggest that we wait years before we begin the establishment of criteria?

Dr. WHIPPLE. I am not suggesting, sir, that you wait. I share your impatience; I think we should start and make approximations as best we can as soon as we can. The methods that I have suggested and discussed briefly are for refinements.

Senator MUSKIE. This I assume was your intent. From our experience in the field of radioactivity, what lessons can we learn about the transition period and how to handle it?

NATURE OF THRESHOLD EFFECTS

Dr. WHIPPLE. I was rather hoping you might ask me a question about threshold, and if I may I would give my answer.

Senator MUSKIE. You may regard that as implicit in my question.

Dr. WHIPPLE. Well, I am glad you asked that question. It seems to me that there are three things to be said about thresholds. The first is that as I read the literature, most thresholds are, from a scientific point of view, artifacts of the limits of measuring techniques or of the experimental design.

The second thing to be said about thresholds is that morally they are a very great convenience. If one believes, in fact, that there is a threshold dose below which there is no effect at all, then the setting of criteria can be done readily and one can sleep nights; therefore from a moral point of view in making such judgments, thresholds are highly desirable.

In radiation we have not been allowed the luxury of assuming a threshold, or one can phrase it in another way and say we have had so much money to do the experiments with that the thresholds, by-and-large, disappear.

DOSE-RESPONSE RELATIONSHIPS

However, in establishing provisional quality criteria, it seems to me that to do away with the threshold concept, makes the way easier.

What one does is to take the lowest dose that produces any effect, make the not unreasonable assumption that zero dose produces zero effect and draw a straight line—dotted if you wish, but a straight line.

ACCEPTABLE INJURY

Then you are faced with the moral judgment of how much injury is acceptable. Once you have fought your way through that moral judgment, then you have the beginning of a quality criteria beyond which you can refine as points accumulate down the way.

It seems to me that this is the way to go about it. You cannot make decisions on information you do not have, so you put down the information you do have, you draw a line which is an assumption and then you struggle with your conscience.

Senator MUSKIE. You may also have to struggle with a court.

You are talking about the setting of standards, leading to the imposition of controls on effluent emissions. I think the language of the

act is economical and technical feasibility of the controls. But, conceivably, the question of whether or not the controls, however economic and feasible, are geared to real injury or potential for real injury may become part of the test.

Now I raised this question of, I think, Dr. Mitchell, and perhaps of other witnesses as to how specific must we be to be satisfied. How specifically must we be satisfied as to the relationship between particular concentrations and specific injury before we move?

Dr. Ayres' testimony especially was a little disturbing on this because he indicated that it was a mixture. He dwelled on that a little more heavily than the other witnesses, that it is the mixture that probably is more responsible than specific pollutants. At least that was my impression.

RADIATION STANDARD EXPERIENCE

Dr. WHIPPLE. This is why I think the experience of the nuclear industry is useful to you in this regard; we started out this way.

We had no choice. Yet by anything we know today the impact of the nuclear industry operating under the standards that have been set is very small indeed and it seems to me this offers you, in your position of trying to bring order in other pollutants, a valuable model.

Senator MUSKIE. When you said that the standard for radiation control in the public environment is 0.5 rem per year, was it always that or at what point in time did it become that? What was it before that?

Dr. WHIPPLE. As far as I am aware, that is the only limit we have ever had in the public domain. Perhaps you were thinking of occupational limits, radiation limits for people engaged in radiation work.

Senator MUSKIE. I am thinking of something more general than that. You recall the controversy in the 1956 presidential campaign on this question and Governor Stevenson's alarm about potential hazards from radioactivity. Yet, I have heard it since then in a general way that the estimates then used to divide between harmful and nonharmful radioactivity were too conservative. You said that word once before this morning so I would like to have your reaction in those terms.

In other words, as we began our efforts to control radioactive pollution, did we start out with too conservative estimates of the levels of harm?

Dr. WHIPPLE. There are at least two ways to try to answer that question and I will try them both if I may. From the practical point of view one can say that since we have an economic nuclear power industry, the standards are not too conservative.

NUCLEAR INDUSTRY

On the other hand, if one compares the standards in the nuclear industry with the standards, where they exist at all, for other pollutants, most of us feel that the standards for radioactive pollutants are considerably lower—one could therefore conclude perhaps too conservative.

My own view is that the fault is on the other side; I don't think the other limits as they exist are conservative enough.

So on balance I am saying that I do not personally feel that the limits that we are operating under for radioactive pollutants are too conservative.

Senator MUSKIE. Were they in the beginning? Has there been an evolution? That is what I am concerned about. In the evolutionary process have we found it possible to be more strict? Have we found it necessary to be more strict in our imposition of controls than when we began approximate control right after World War II?

Dr. WHIPPLE. For all practical purposes there were no standards or criteria for environmental radioactivity more recently than the last 10 or 15 years.

Senator MUSKIE. But that takes us back to 1953, 1954.

Dr. WHIPPLE. Along about then is when this figure was advanced and it finally began to appear in print and then in regulations.

Senator MUSKIE. The 0.5 rem?

Dr. WHIPPLE. The 0.5 rem, and the figures based on them.

Senator MUSKIE. So some consideration was given to this before controls were actually imposed?

Occupational exposures

Dr. WHIPPLE. Yes; but of course during the war years the only people on whom controls could be imposed were the Manhattan District, the Atomic Energy Commission, and they were imposing their own controls.

Senator MUSKIE. So, the 0.5 rem came out of that experience?

Dr. WHIPPLE. Partly from that experience and partly from the deliberations of the several scientific bodies that make recommendations, the National Committee on Radiological Protection and the corresponding international group.

Senator MUSKIE. Do you think that that figure has been well tested now and sufficiently well tested so that it is an acceptable threshhold in the long run?

Dr. WHIPPLE. May I object to your use of the word "threshold" in that connection.

Senator MUSKIE. Yes; because I am being educated on that one this morning.

Dr. WHIPPLE. Because as I mentioned earlier we live without benefit of believing in threshold variation.

From all that I know, I consider this an acceptable number.

Evaluation of standards

Senator MUSKIE. What are the means by which we test the acceptability of that figure from time to time? Is there a continuous testing of it? Is there a continuous monitoring of it? Is there a continuous evaluation of it?

Dr. WHIPPLE. There is a continuous evaluation of radioactivity in the environment at various places. If by monitoring you mean epidemiological studies, there is no hope of ever being able to measure the effects it is estimated that 0.5 rem per year will produce even on a population the size of that of the United States. Epidemiological studies have been initiated recently on radiation workers, a much smaller group, but a group exposed to much larger amounts of radiation. Even there the hopes of obtaining statistically valid conclusions, even with populations of hundreds of thousands, is rather small.

Senator MUSKIE. Would that justify the conclusion that the 0.5 rem figure is a rather arbitrary one?

Dr. WHIPPLE. That it is arbitrary; yes. I have said before and repeat again, that in my opinion it is a reasonable arbitrary figure.

Senator MUSKIE. Well, in my business you cannot be reasonable and arbitrary at one and the same time.

LESSONS OF PAST

I probe this because it seems to me that there are lessons to be drawn from the radiological field, the pollution field, and that this may be one of them. In other words, to have to have a combination of reasonably arbitrary criteria when we deal with specific pollutants in that field without the urgency that makes them acceptable.

You could be arbitrary and reasonable perhaps if there is a reasonable sense of urgency, but you accept the arbitrariness of the judgment. In the pollution field I don't think there is anything like that feeling of urgency as yet, so there is going to be more reasonableness and less arbitrariness.

Dr. WHIPPLE. I think the only thing I can apply to that is that my position here is as a technical expert and you are speaking of political problems.

MUTAGENIC CHEMICALS

Senator MUSKIE. It has been suggested here today and in the committee staff report on page 55 that:

> Some chemicals may induce genetic damage similar to those introduced by radiation. Two kinds of mutation rates can be used by these chemical agencies. Second, a chemical compound presumed to be innocuous is in fact highly mutagenic, and large numbers of individuals are exposed before the end result is realized.

What would you consider to be a good public health policy?

Dr. WHIPPLE. It seems to me that where the possibility that a compound is mutagenic has been demonstrated, we must proceed as we have with radiation and attempt to establish dose-effect relations as has been done with fruit flies and with mice.

In fact, it is these studies with radiation which determine the public limit that you have before you. I can see no alternative to such studies on chemical pollutants. The thing that is appalling about this is that there is such a vast variety of them and that they can change from one to another, become more effective or less effective as they are passed through the environment.

One thinks of the millions of dollars that have been spent in the study of radiation, which is relatively simple. I can only say I recognize the magnitude of what I am suggesting and the only defense that one can offer is there seems to be no other way.

USE OF CRITERIA

Senator MUSKIE. In other words, what you seem to be saying is that the use of criteria leading to standards is perhaps the only viable method of developing effective controls.

Dr. WHIPPLE. It seems to me this is so.

Senator MUSKIE. Yet we are going to have to do so on the basis of perhaps less precise and exact knowledge as to the specific relationship between particular pollutants and harmful effects than we might like, and that the price of that approach may be greater cost, greater burden for industry in order to avoid the risks that were not controlled strictly enough.

RISKS VS. COST

Dr. WHIPPLE. It seems to me, personally, better to spend the money and avoid a risk that may not be there, than to save money and delay and find that it was.

Senator MUSKIE. The whole question is, How far do you recall in establishing the margin for error, assuming that the margin for error ought to lean in the direction of human health, rather than away from it?

I gather that I have got to go to the floor again.

Mr. Grundy gives me this question which he thinks might be useful for you to answer.

Animal studies have been used, extensively, in studies of the health effects of radiation—strontium 90 studies—used dogs—what are the lessons that have been learned on the usefulness of animal studies to evaluate the effects of environmental conditions? Do you have some comment on that this morning?

Dr. WHIPPLE. Not a very helpful one, perhaps. Animal studies have served to guide all manner of toxicological work, radiation, radioactive, as well as otherwise. One must always be exceedingly cautious of extrapolating the results of animal experiments. It seems to me that such experiments play the same part in medical studies that work with models do for an engineer. An engineer makes a small model of an airplane and puts it in the wind tunnel, or a small model of a ship and puts it in a flume, and is able to learn a good deal from this—not everything; mistakes are made. But certainly one can learn a good deal, saving considerable time and money while doing it. It seems to me that animal studies are quite analagous to models in their strength, and in their limitation.

I fear this is not a very helpful remark.

Senator MUSKIE. Although we are dealing with something that would invite scientific insights and knowledge and experience, we are dealing with a very imprecise problem and a very precise way of dealing with it.

I guess what we are trying to probe here is the possibility of narrowing the gap between precise knowledge and reasonable controls.

Dr. Whipple, we thank you very much.

(Questions submitted by Senator Muskie and the response by Professor Whipple follow:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Prof. G. HOYT WHIPPLE,
School of Public Health,
University of Michigan,
Ann Arbor, Mich.

DEAR PROFESSOR WHIPPLE: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on, Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO PROFESSOR G. HOYT WHIPPLE

1. The question quite frequently arises as to whether a particular concentration of a substance has to be reached before any effect is elicited (threshold level). In 1962 a WHO's expert committee made the following statement regarding this question:

"The concept of safe or acceptable exposure levels rested initially on the assumption of thresholds for early effects. However, with the accumulation of data and experience with various toxic substances, delayed effects attributable to exposure to toxic agents have appeared long after exposure at levels previously thought to have been safe, for instance in the case of beryllium. This necessitated downward revision of many of the recommended maxima."

Would you care to comment on this statement's application to our discussions on the development of air quality criteria?

2. Recognition is given in radiological health practices to individuals in the general population with higher than average susceptibility. Does this concept have application to other environmental contaminants, and how would you propose that these individuals be identified?

3. Testimony before the Subcommittee has emphasized the associations between air pollution and respiratory diseases; however, there has been some discussion of contaminants which are stored in the body and effect the total body system. Would you comment further on an air quality criteria versus environmental quality criteria approach to these contaminants, and applicable experience in the radiological health field?

4. It has been suggested in recent studies that chemicals may induce genetic damage in man similar to those induced by radiation. Two kinds of effects are suggested. First, a small increase in mutation rates is produced by these chemical agents.

Second, a chemical compound presumed to be innocuous is in fact highly mutagenic and large numbers of individuals are exposed before the danger is realized.

Should these studies be confirmed and indicate the widespread use of chemical mutagens, what would you consider to be an effective public health policy?

5. Reportedly animals have been used extensively in studies on the health effects of radiation. For example, the strontium–90 studies using beagle dogs. What are the lessons that have been learned on the usefulness of animal studies to evaluate the effects of environmental contaminants?

THE UNIVERSITY OF MICHIGAN,
SCHOOL OF PUBLIC HEALTH,
Ann Arbor, Mich., August 13, 1968.

Senator EDMUND S. MUSKIE,
Committee on Public Works,
U.S. Senate,
Washington, D.C.

DEAR SENATOR MUSKIE: My comments on the questions which accompanied your letter of August 2 are enclosed. Since I do not have a copy of the transcript with me, it may be that these comments duplicate portions of my oral response. If so, my apologies to Dick Grundy, who will have to fit them together.

Thank you for your kind remarks and for the opportunity to testify.

Sincerely yours,

G. HOYT WHIPPLE.

[Enclosure]

QUESTION 1

The question quite frequently arises as to whether a particular concentration of a substance has to be reached before any effect is elicited (threshold level). In 1962 a WHO's expert committee made the following statement regarding this question:

"The concept of safe or acceptable exposure levels rested initially on the assumption of thresholds for early effects. However, with the accumulation of data and experience with various toxic substances, delayed effects attributable to exposure to toxic agents have appeared long after exposure at levels previously thought to have been safe, for instance in the case of beryllium. This necessitated downward revision of many of the recommended maxima."

Would you care to comment on this statement's application to our discussions on the development of air quality criteria?

The statement of the WHO expert committee concerning threshold levels seems to me sound, and I would generalize this statement by saying that in many, perhaps most, and possibly in all cases, the apparent threshold doses are artifacts of the experiments. There is no reason to believe that improved methods of measurements and improved experimental procedures will not bring about further downward revision of the recommended maximum exposure levels.

The application of the WHO statement, and of the implications I have drawn from it, to your development of air quality criteria is difficult and also important.

If there are not, or may not be thresholds for air pollutants, then one is forced to abandon the idea of absolute safety, and must adopt in its stead an acceptable risk or injury. The formulation of a suitable basis for an acceptable risk is a matter to which the NCRP and ICRP have devoted years of deliberation, the end to these deliberations is not in sight. The decision is not a technical one, but a moral one: to whom are these levels acceptable, and for whom?

However, as I tried to make clear in my testimony, the lack of a threshold, or the lack of faith in a threshold, has certain practical advantages in developing air quality criteria.

First, you are freed from having to wait further years and decades while toxicologists try to find thresholds with more and more sensitive methods.

Second, you can draw the most reasonable line for the dose-effect relation from available data and extrapolate it to zero effect at zero dose.

Third, you can avail yourself of the NCRP–ICRP deliberations to select a provisionally acceptable risk, and then, with the dose-effect relation produced above, establish a provisional air quality criterion.

Criteria can be established in this way without waiting for further experimental or epidemiological data. The criteria so established will be the best possible with existing data. They will probably not be as good as those we now have for radioactive pollutants because the data on which they can be based are not as good as the radiological data.

QUESTION 2

Recognition is given in radiological health practices to individuals in the general population with higher than average susceptibility. Does this concept have application to other environmental contaminants, and how would you propose that these individuals be identified?

The concept of individuals in the general population who have higher than average susceptibility to non-radioactive environmental pollutants applies to a greater degree than it does to radioactive pollutants. With radiation, there is nothing corresponding to an allergic reaction, so the range of susceptibilities to radioactive materials will in general be much smaller than the ranges for materials which do bring on an allergic reaction in particularly sensitive people.

It is beyond my competence to suggest how such sensitive individuals could be identified. Suggestions should be sought from allergists and toxicologists.

QUESTION 3

Testimony before the Subcommittee has emphasized the associations between air pollution and respiratory diseases; however, there has been some discussion of contaminants which are stored in the body and affect the total body system. Would you comment further on an air quality criteria versus environmental qual-

ity criteria approach to these contaminants, and applicable experience in the radiological health field?

My comment on an air quality criteria approach *vs.* an environmental quality approach is simply that consideration of air alone is likely to lead one to overlook routes to man more important than direct inhalation. The case of radioactive iodine in inhaled air *vs.* that in the air-pasture-cow-milk pathway is an example.

The limits for concentrations of radioactive materials in air, water and food are set out of consideration for storage in the body and rate of elimination from the body. To what extent these concepts are applicable to non-radioactive materials, I cannot say with authority, but it seems to me that they could be applied with profit in a number of cases.

QUESTION 4

It has been suggested in recent studies that chemicals may induce genetic damage in man similar to those induced by radiation. Two kinds of effects are suggested. First, a small increase in mutation rates is produced by these chemical agents.

Second, a chemical compound presumed to be innocuous is in fact highly mutagenic and large numbers of individuals are exposed before the danger is realized.

Should these studies be confirmed and indicate the widespread use of chemical mutagens, what would you consider to be an effective public health policy?

If mutagenic chemicals pollute the atmosphere, I see no reason why they should not be subject to air quality criteria as stringent to those applied to radioactive materials released to the atmosphere. The criteria for radioactive materials in the atmosphere have been set in large part out of consideration for mutagenic effects in the population. Similar treatment of mutagenic chemicals would be an effective public health policy, perhaps *the* effective policy.

QUESTION 5

Reportedly animals have been used extensively in studies on the health effects of radiation. For example, the strontium-90 studies using beagle dogs. What are the lessons that have been learned on the usefulness of animal studies to evaluate the effects of environmental contaminants?

The environmental and occupational quality criteria for radiation have been established out of respect for three effects of chronic radiation exposure: genetic mutations, life-span shortening, and induction of leukemia. Of these, only one, leukemia, has been observed in humans; the other two have been observed only in animals. The animal data have been cautiously extrapolated to give estimates of dose-effect relations in humans. These estimates constitute a useful and important foundation for our evaluation of chronic exposure to radioactive materials in the environment.

The lesson is that animal studies, even of long-continued chronic exposures, have important value in evaluating environmental contaminants.

Senator MUSKIE. May I express my appreciation again for all four witnesses who have appeared this morning. They have added to the education of this Senator, and I hope through us to all Senators, policymakers of this group.

We will recess until tomorrow morning at 9:30 to continue our education.

Mr. MOODY. Mr. Chairman, may I address the Chair?

Senator MUSKIE. Yes, Joe.

Mr. MOODY. Is the "Grundy report"[1] part of the record?

Senator MUSKIE. No; it is not as yet.

Mr. MOODY. I think it should be, because we have to work from it and there are questions that have been referred to here time and again as Grundy questions and they are part of the report.

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[1] Actual title is "Air Quality Criteria," prepared for the use of the Subcommittee on Air and Water Pollution, Committee on Public Works, U.S. Senate.

Senator MUSKIE. Well, we will examine that. We are sometimes limited in our expenditure of funds for printing if we are dealing with a subject that has already been printed by the committee. So whether or not we can get it—it would be duplicate printing in this case. In any case, it is part of the committee files and available for reference.

Mr. MOODY. Your statement is on the record now.

Senator MUSKIE. Yes. It is in the record in the sense that it is part of the files.

We are in recess until 9:30 tomorrow morning.

(Whereupon, at 1:37 p.m., the committee was recessed, to reconvene at 9:30 a.m., Tuesday, July 30, 1968.)

AIR POLLUTION—1968

TUESDAY, JULY 30, 1968

U.S. SENATE,
SUBCOMMITTEE ON AIR AND WATER POLLUTION
OF THE COMMITTEE ON PUBLIC WORKS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:35 a.m., in room 4200, Senate Office Building, Senator Edmund S. Muskie presiding.

Present: Senator Muskie.

Also present: Leon G. Billings and Richard D. Grundy, professional staff members.

OPENING STATEMENT

Senator MUSKIE. The subcommittee will be in order.

I thought it might be useful to begin this morning by summarizing some of the points which I think we made in yesterday's hearing.

Today the Subcommittee on Air and Water Pollution continues hearings on air quality criteria. Yesterday, the witnesses agreed that there is ample evidence to justify air pollution control. At the same time, they agreed that responsible public policy cannot wait upon a perfect knowledge of the cause-effect relationship between air pollution and health.

Several air contaminants were mentioned as warranting the development of air quality criteria, based on current medical and scientific evidence, while many other contaminants were mentioned as suspect.

The testimony that has been received and the witnesses today will provide the subcommittee with useful information on the basic assumption and methodology in the development of air quality criteria.

As mentioned yesterday in Senator Baker's opening statement, and I quote to repeat it and add emphasis:

> There are those who will challenge any criteria which lack final and absolute proof of a direct causal relationship. But responsible public policy cannot wait upon a perfect knowledge of the cause and effect. Where the best available evidence indicates a health or welfare effect from environmental exposures government must move to minimize these exposures by interposing barriers between the public and the causative agents producing stress.

Again we have a distinguished group of witnesses this morning.

Our first witness will be Dr. Samuel S. Epstein, Children's Cancer Research Foundation, Boston, Mass.

Dr. Epstein, it is a pleasure to welcome you this morning. We appreciate your interest and your taking the time to come here to be of assistance to us.

STATEMENT OF DR. SAMUEL S. EPSTEIN, CHILDREN'S CANCER RESEARCH FOUNDATION, BOSTON, MASS.

Dr. EPSTEIN. Mr. Chairman, the subject of my presentation this morning is "Cancer and Mutation-Producing Chemicals in Polluted Urban Air."

My professional background and experience, as stated in the attached appendix, broadly relates to the study of hazards due to chemical contaminants in the human environment.

CHEMICAL CARCINOGENS AND MITAGENS

These contaminants are often ubiquitous and include defined chemicals such as pesticides, food additives, or those used in industry, and partially defined chemicals such as complex mixtures found in water and air pollutants.

Therapeutic drugs represents an additional, but relatively more restricted and special type of defined chemical contaminant.

HAZARDS

The potential hazards posed by these classes of chemical contaminants include toxicity or poisoning, teratogenicity or production of developmental abnormalities in the growing embryo, carcinogenicity or the production of cancer, and mutagenicity or the production of genetic damage.

The scope and magnitude of these enivronmental hazards is illustrated by recent estimates that the majority of all human cancers may be chemical in origin; such cancers hence may be ultimately preventable. With relation to genetic damage, a recent authoritative report (Crow, 1968) is equally explicit, although more alarming, in statements such as:

> A number of chemicals—some with widespread use—are known to induce genetic damage in various systems.
>
> Identity of the genetic material in all organisms implies that a chemical that is mutagenic to one species is likely to be in others and must be viewed with suspicion.
>
> Some compounds are "highly mutagenic in experimental organisms in concentrations that are not toxic and that have no direct effect on fertility." Mutations thus can be propagated to future generations. "Perhaps most insidious are compounds that induce point mutations without chromosome breakage," and thus cannot be detected microscopically.
>
> Compared with radiation hazards, chemical mutagens may be the submerged part of the iceberg.

In this presentation on "Cancer and Mutation-Producing Chemicals in Polluted Urban Air," I will restrict myself to two major potential hazards, carcinogenicity and mutagenicity, posed by chemicals contained in urban community air pollutants. Specifically, I will briefly summarize the status of current information with relation to each hazard, review some personal experimental data, and finally attempt to interpret the significance of these data with respect to man.

The next few pages of my testimony deal with the background of established information relating air pollution to lung cancer. I will omit this from my verbal presentation.

I now turn to page 10.

Senator MUSKIE. The material will be included in the record.

REVIEW OF INFORMATION RELATING AIR POLLUTION TO LUNG CANCER

Lung cancer

Dr. EPSTEIN. The dramatic increase in mortality from lung cancer over the last few decades is now approaching epidemic proportions. The epidemiologist Clemmesen recently stated (1961), "It seems impossible to escape the conclusion that we are now facing one of the major catastrophes in medical history." Figure 1 emphasizes the exponential nature of this increased mortality which, although general, is particularly steep for Great Britain (Doll, 1955).

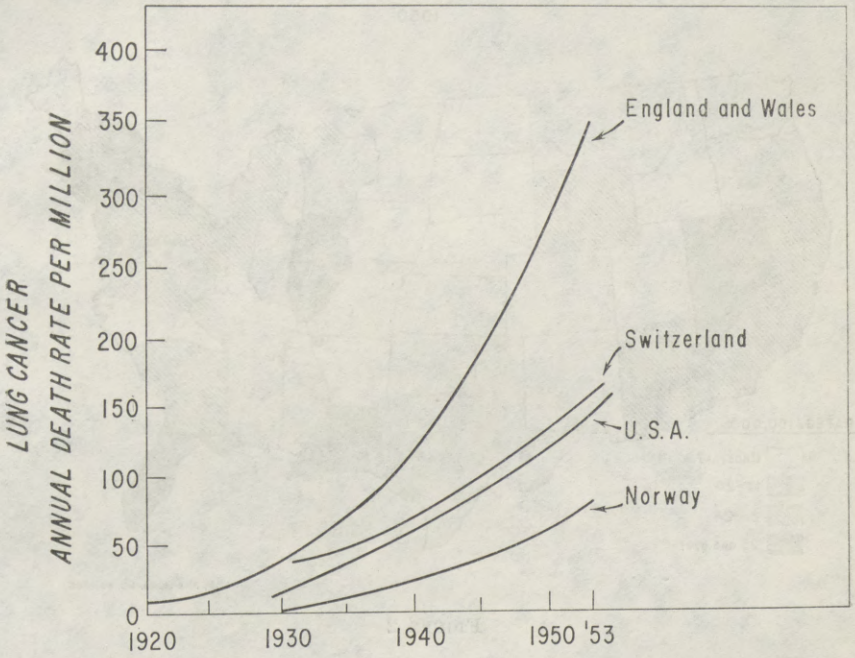

FIGURE 1

While there is little doubt that cigarette smoking is a major cause of lung cancer, as well as of other chronic respiratory diseases, there is also good evidence incriminating the role of air pollution. This statement is based on three types of information:

1. *Epidemiological.*—There are marked regional differences in mortality patterns in the United States of America (fig. 2); increased mortality is clearly related to increased urbanization and to increased levels of organic pollutants in the air (fig. 3). The higher lung cancer rates in urban areas cannot be fully explained by factors such as smok-

ing or occupation. In a survey some 10 years ago, lung cancer rates in the United States of America, standardized for smoking besides age, were found to be 39/100,000 in rural areas and 52/100,000 in cities with populations in excess of 50,000 (Hammond and Horn, 1958); similar surveys in England also confirmed the importance of this urban factor (Stocks, 1960), and stressed its interaction with smoking (fig. 4). This urban excess, of 25 percent in U.S. mortality, is generally regarded as being due to air pollution. Confirmatory evidence also is afforded by several studies on immigrants who tend to retain the incidence pattern of lung cancer of their country of origin, even though they assume the smoking and other habits of their country of adoption.

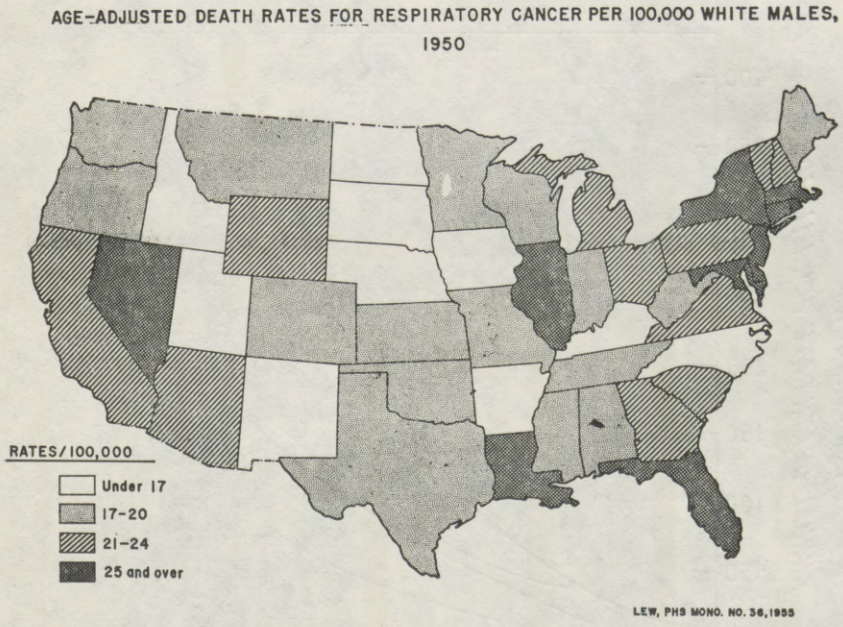

FIGURE 2

2. *Chemical.*—Incomplete combustion of organic matter produces soots containing a variety of compounds, many of which have been chemically defined and some of which are carcinogenic (Table 1). An important group of these compounds are polynuclear hydrocarbons, of which benzo[a]pyrene has been the most extensively studied. Many additional classes of poorly defined chemical carcinogens have been recently recognized in atmospheric pollutants, including alkylated polycyclics and azaheterocyclics (Sawicki, 1967). However, the predictive value of chemical techniques is seriously restricted, as certain pollutant fractions, such as the oxy-neutral and aliphatic, contain unidentified carcinogens. Additionally, the carcinogenicity of defined or undefined chemicals, can be profoundly influenced by the presence of other chemicals which by themselves are noncarcinogenic.

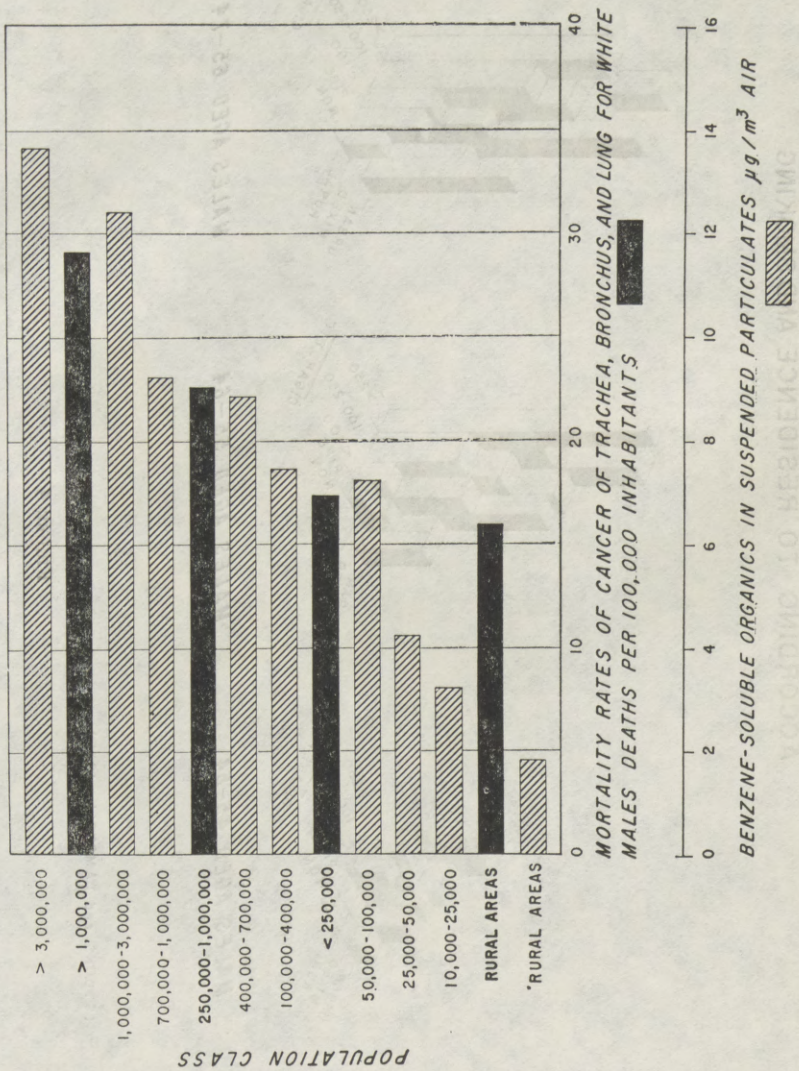

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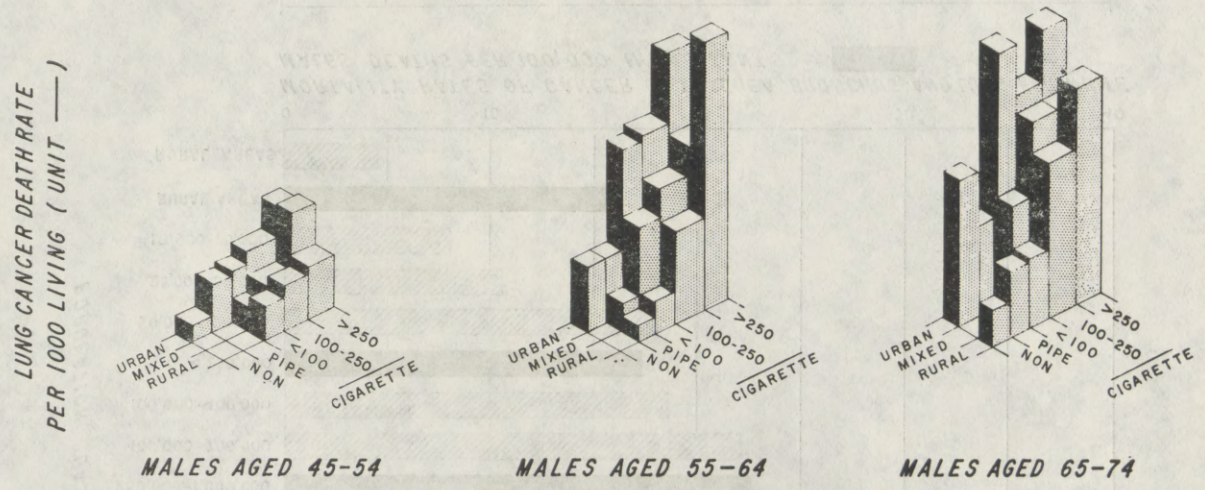
FIGURE 3

LUNG CANCER MORTALITY RATE IN MALES ACCORDING TO RESIDENCE AND SMOKING



(STOCKS and CAMPBELL - 1955)

FIGURE 4

TABLE 1.—CHEMICAL CARCINOGENS IN THE AIR

1. Polynuclear aromatic hydrocarbons
   - Benz (*a*) anthracene and R-benz (*a*) anthracenes
   - R-chrysenes
   - Benzo (*b*) fluoranthene and benzo (*j*) fluoranthene
   - Benzo (*a*) pyrene
2. Polynuclear aza heterocyclics
   - R-benz (*a*) acridines and R^1,R^2-benz (*a*) acridines
   - R-benz (*c*) acridines and R^1,R^2-benz (*c*) acridines
   - Dibenz (*a*,*h*) acridine
   - Dibenz (*a*,*j*) acridine and R-dibenz (*a*,*j*) acridines
3. Polynuclear and imino heterocyclics
   - 11 H-benzo (*a*) carbazole
   - 3 H-benzo (*b*) carbazole
   - 7 H-benzo (*c*) carbazole
4. Polynuclear carbonyls
   - 7 H-benz (*de*) anthracene-7-one
5. Alkylating agents
   - Aliphatic and olefinic epoxides
   - Peroxy compounds, lactones
6. Miscellaneous
   - Metals—As, Se, Co, Ni, Cr, Be
   - Radioactivity
7. Promoting agents
   - Phenols
   - Long chain aliphatic hydrocarbons

(Based on Sawicki.)

It is of interest to compare the very approximate relative amounts of the carcinogen benzo[a]pyrene theoretically inhaled under different conditions. The one pack-a-day smoker, inhales 0.3 μg daily (Surgeon General's Advisory Committee on Smoking and Health, 1964), which is similar to the amount inhaled by a nonsmoker in heavily polluted urban air and about three times that inhaled in "average" urban air (Sawicki, 1960). However, the worker engaged in roof tarring inhales an amount of benzo[a]pyrene in an 8-hour day, equivalent to that contained in about 200 packs of cigarettes (Schueneman, 1963).

3. *Biological.*—Standard biological techniques for demonstrating the carcinogenicity of extracts of particulate atmospheric pollutants depend on repeated skin painting or subcutaneous injection of pollutants in adult rodents. These techniques, however, require comparatively large amounts of pollutants and generally result in low yields of local tumors after long latency periods (table 2).

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

Reference	Particulates	Extract	Administration	Latent period (months)	Percent tumor yield		Comments
					Local	Distant	
Leiter et al. (1942)	Filtration and precipitation	Benzene-ether	Subcutaneous × 1 (~50 mg)	12	6		5 urban sites sampled.
Leiter & Shear (1942)	Large capacity collectors	Benzene	do	16	8		Similar tumor yields from 5 urban sites sampled.
Gurinov et al. (1945)	Filtration and sedimentation	Dichloroethane	Painting 3 × weekly (10 percent benzene solution).	6	38	Multiple adenomas.	3 urban sites sampled.
Kotin et al. (1954)	Large volume collectors	Benzene	Painting 3 × weekly (acetone solution)	15	42		Particulates from Los Angeles.
Clemo et al. (1955)	Ventilation filters	Benzene and 2 fractions.	Painting 3 × weekly (1 percent benzene solution).	7	45	Multiple adenomas 16.	Particulates from Liverpool.
Kotin et al. (1956)	Oxidation products of aliphatics	Benzene	Painting 3 × weekly (acetone solution)	14	20		Aromatic-free aerosol collected in shepherd traps.
Clemo et al. (1960)	Filtration of city smoke	do	Painting 6 × only (1 percent benzene solution).	18	20		Particulates from Newcastle.
Hueper et al. (1962)	Composite NASN samples	Benzene and 3 fractions.	Subcutaneous × 24 (organic ~130 mg), (aromatic ~13–33 mg), (oxygenated ~12 mg), (aliphatic ~24 mg). Painting 2 × weekly (aliphatic and oxygenated).	9–26	2–10		Different tumor yields from 8 urban sites. In general, low tumor yields obtained.

Effects of organic extracts

In a recent PHS study (Hueper et al., 1962), the effects of organic extracts and three derived fractions from eight cities were tested by standard techniques employing local administration to the skin of mice and rats. The resulting tumor yields were low, ranging from 2–10 percent, with latent periods extending up to 2 years. Only local tumors were produced, and extracts from all the cities, with exception of Los Angeles, were carcinogenic.

It would, of course, appear more logical to use the lung rather than skin for carcinogenicity testing of atmospheric pollutants. However, nobody has yet consistently produced bronchogenic carcinoma in animals by inhalation of community air pollutants, and in fact, relatively few attempts to do so have been made. Campbell (1939) increased the incidence of pulmonary adenomas in mice by exposing them to road dust in inhalation chambers. Kotin and Falk (1956) likewise increased the incidence of pulmonary adenomas in mice by exposing them to ozonized gasoline, which is considered to bear chemical similarities to Los Angeles photochemical smog. Kotin and Wiseley (1963), exposed mice to influenza virus and subsequently to ozonized gasoline, thereby producing squamous lesions resembling bronchogenic carcinoma. Saffiotti (1965) produced squamous lung cancers by tracheal intubation of hamsters with suspensions of benzo[a]pyrene absorbed on an inert carrier. More recently, Laskin (1967) has been successful in inducing squamous lung cancer in rodents by prolonged inhalation of benzo[a] pyrene and SO_2.

Recent Techniques for Measuring the Carcinogenicity of Air Pollution Extracts

In our laboratories at the Children's Cancer Research Foundation in Boston, and supported by contracts from the National Center for Air Pollution Control, USPHS, we have developed two highly sensitive biological techniques for measuring the carcinogenicity of organic extracts of atmospheric pollutants.

1. *Indirect screening test for carcinogenicity based on measurement of photosensitizing compounds in pollutant extracts.*—Polynuclear compounds are among the most important chemical pollutants in the air. For this class of compounds, a strong relationship has been previously demonstrated between their carcinogenicity and ability to lethally sensitize single cells to the otherwise harmless effects of long-wave ultraviolet light (Epstein et al., 1964). Photosensitizing ability thus affords an indirect index of the carcinogenicity of pollutants and can be measured simply and rapidly by relatively nonspecialized personnel. This procedure, known as the photodynamic test, can be completed in 3 hours and only needs 1 milligram of pollutant materials (Epstein et al., 1963).

Pollutant extracts

Extracts of atmospheric pollutants, and their various fractions from over 100 urban and nonurban U.S. sources, have been studied with this test and the results have been related to chemical and other data (Epstein, 1966). Photodynamic potencies, expressed on a mass

basis, indicate the degree of biological activity in extracts and fractions, and thus characterize source emissions without reference to the factor of atmospheric dilution (fig. 5). For this reason, activities in some nonurban samples are similar to those of urban samples. Potencies, expressed on an air volume basis, however, provide an indication of the degree of atmospheric dilution of total emissions; using this more meaningful measure of atmospheric pollution, the nonurban samples are found to be relatively inactive (fig. 5). As can be seen, this test yields data which discriminates widely between pollutants from different sources, and even more widely between various fractions of pollutant extracts derived from any one source. Characteristically, densely populated cities with predominant usage of solid fuel have high potencies in their organic extracts and fractions. Further, it can be seen that on a mass basis, the basic fraction is, generally, the most active of all. Even when potency is expressed on an air volume basis, the basic fraction still ranks disproportionately high.

For illustrative purposes, it may be mentioned that of the cities studied, Boston ranked in the top 20 percent for atmospheric concentrations of photosensitizing polynuclear compounds and in the top 30 percent for concentrations of the carcinogen benzo[a]pyrene (table 3). The use of this test, additionally, is enabling the identification of hitherto unrecognized polynuclear carcinogens in certain fractions of organic extracts of particulate atmospheric pollutants (Epstein, 1968).

TABLE 3

Atmospheric pollutants	Number cities tested	Median concentrations	Boston, 1963	
			Concentration	Ranking, top (percent)
Particulate ($\mu g/m^3$)	106	127	114	70
Sulfates ($\mu g/m^3$)	66	12	13	50
Organics ($\mu g/m^3$)	106	9	10	40
Benzo[a]pyrene ($\mu g/1{,}000m^3$)	47	4	10	30
Photosensitizing compounds ($\mu gBaP/1{,}000m^3$)	103	1	7	20

Note: Ranking of Boston with relation to other cities in regard to concentrations of certain pollutants and carcinogens in air.

Animal studies

2. *Direct carcinogenicity tests based on administration of pollutant extracts to newborn mice.*—The use of newborn animals (neonates) for the carcinogenicity testing of pure chemicals has been well documented over the last 10 years. Neonates have been shown by others to be highly sensitive to defined carcinogens, administration of which in very low concentrations generally results in high tumor yields with relatively short latency periods. However, there are no published data on the use of neonates for the demonstration of carcinogens in undefined crude mixtures, such as organic extracts of particulate atmospheric pollutants.

The present studies have established the very high sensitivity of neonatal mice to carcinogens extracted from air (Epstein et al., 1966). Neonates were injected with suspensions of organic extracts of atmospheric particulates derived from various urban sources in the United States of America, including Chicago, Cincinnati, Los Angeles, Phila-

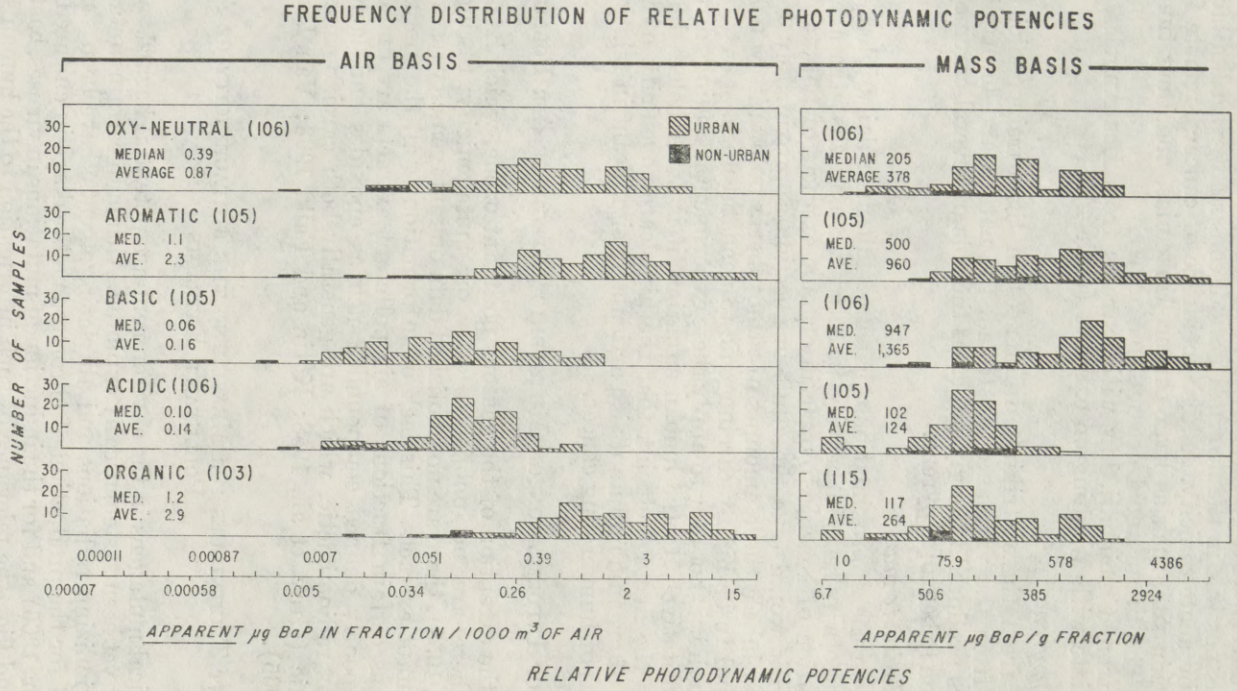

FREQUENCY DISTRIBUTION OF RELATIVE PHOTODYNAMIC POTENCIES
AIR BASIS
MASS BASIS
NUMBER OF SAMPLES
OXY-NEUTRAL (106)
MEDIAN 0.39
AVERAGE 0.87
URBAN
NON-URBAN
AROMATIC (105)
MED. 1.1
AVE. 2.3
BASIC (105)
MED. 0.06
AVE. 0.16
ACIDIC (106)
MED. 0.10
AVE. 0.14
ORGANIC (103)
MED. 1.2
AVE. 2.9
(106)
MEDIAN 205
AVERAGE 378
(105)
MED. 500
AVE. 960
(106)
MED. 947
AVE. 1,365
(105)
MED. 102
AVE. 124
(115)
MED. 117
AVE. 264
0.00011
0.00087
0.007
0.051
0.39
3
0.00007
0.00058
0.005
0.034
0.26
2
15
10
75.9
578
4386
6.7
50.6
385
2924
APPARENT μg BaP IN FRACTION / 1000 m³ OF AIR
APPARENT μg BaP/g FRACTION
RELATIVE PHOTODYNAMIC POTENCIES

FIGURE 5

delphia, Washington, D.C., and New York City. Doses, ranging from 5–55 milligrams, were fractionally administered during the first 3 weeks of life, commencing within a few hours of birth. Dosage schedules were developed to permit injection of maximal amounts of extracts as early as possible in the neonatal period, consistent with limitations imposed by acute toxicity. A high incidence of cancers, remote from the injection site, such as liver cancer, leukemias, and lung tumors, resulted. The tumor incidence was particularly high with pollutant extracts from Cincinnati, low with extracts from Los Angeles, and intermediate with Washington extracts (table 4).

Benzo(a)pyrene

Apart from these striking differences in the carcinogenicity of extracts from the various cities tested, the nature and multiplicity of tumors produced strongly indicates the role of several carcinogens in addition to benzo[a]pyrene.

Extrapolation to man

Based on the approximations that an adult man daily inhales 0.3 μg of benzo[a]pyrene in heavily polluted air, and that the average concentration of benzo[a]pyrene in organic extracts of pollutants in 500 μg/g, it would take the adult in question approximately 1 to 3 months to inhale those amounts of atmospheric pollutants which we have found to be highly carcinogenic to neonatal mice.

Although it is not easy to apply these experimental findings directly and quantitatively to the human situation, it is nevertheless difficult to escape the firm conclusion that the high carcinogenicity of trace amounts of organic pollutants is particularly significant in relation to the causes of human lung cancer.

Review of Information on Mutagenic Effects of Air Pollution

With the exception of the gaseous pollutant ozone, which has been 1958), there are no published data on mutagenicity testing of (Fetner, 1958), there are no published data on mutagenicity testing of air pollutant extracts. This lack of information is all the more surprising, as certain fractions of air pollutant extracts are known to contain poorly defined compounds, such as epoxides and lactones, known as radiomimetic, which are generally both carcinogenic and mutagenic (Gray, et al., 1958; Kotin and Falk, 1963; Van Duuren et al., 1965).

Recent Techniques for Measuring the Mutagenicity of Air Pollutant Extracts

Chemical mutagens in the environment are potential hazards which have not yet been systematically explored. Although certain mutagens, notably ionizing radiations and alkylating agents, have been studied in detail for the production of chromosome breakage in cultured cells (Legator, 1966) and for the induction of mutations in viruses, bacteria, fungi, and flies, the relevance of such information to the human situation is not always apparent. The use of more appropriate and direct systems based on mammals, such as the specific locus test (Russell et al., 1960), and the dominant lethal test (Bateman 1962) have received relatively little practical recognition because of their alleged expense

TUMOR INCIDENCE FOLLOWING INJECTION OF ORGANIC ATMOSPHERIC POLLUTANTS TO NEONATAL MICE

Treatment Group	GROUPS					% TUMOR INCIDENCE **			
	No. Neonates Injected	% Mortality Prior to Weaning	Sex	Nos. at Weaning	Nos. at Risk*	Pulmonary Adenomas Solitary	Pulmonary Adenomas Multiple	Hepatomas	Lymphomas
Controls (0 mg)	190	16	M	82	73	12	0	4	0
			F	77	75	5	0	0	1
Chicago (25 mg)	127	39	M	41	21	29	52	14	5
			F	37	36	19	22	0	0
Cincinnati (25 mg)	133	53	M	32	17	24	59	29	6
			F	31	28	11	71	4	11
Los Angeles (25 mg)	137	61	M	32	18	22	17	6	6
			F	22	20	5	15	0	0
New Orleans (15-25 mg)	110	29	M	39	31	23	29	32	0
			F	39	35	17	14	0	6
Philadelphia (15-25 mg)	105	35	M	27	17	6	29	24	0
			F	41	38	16	24	0	13
Washington, D.C. (25 mg)	137	53	M	38	23	22	48	17	0
			F	27	25	28	40	0	4

*Excluding deaths < 50 weeks from unrelated causes, notably obstructive renal failure in males, also losses due to cannibalism or autolysis.

**Tests terminated at ca. 50 weeks.

TABLE 4

and complexity. We have shown that this viewpoint is not justified particularly in relation to the dominant lethal test, which we have simplified, modified, and applied for the testing of air pollutants besides drugs, food additives, and pesticides.

Dominant lethal tests

The dominant lethal test is a measure of major chromosomal damage. It is of particular interest as approximately 80 percent of gene mutations in man have been shown to be attributable to dominant autosomal non-sex-linked traits (report U.N. Committee on Effects Atomic Radiation, 1966). This test is based on breeding of untreated female rodents with males previously injected with test agents; mutagenic effects are evidenced by early death of the developing embryo (fig. 6). Associations between mutagenic and antifertility effects can also be studied with this system.

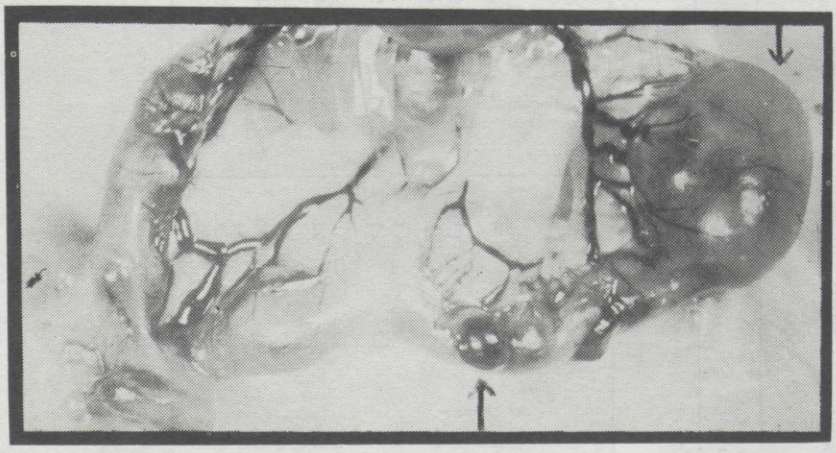


FIGURE 6

Benzo(a)pyrene

The carcinogenic air pollutant benzo[a]pyrene has been shown to be mutagenic in mice following a single dose of 750 or 1000 mg/kg, corresponding to individual animal doses of 22.5 or 30 mg, respectively. As can be seen in Table 5, the mutagenic index for normal control mice is 0.4 and for benzo[a]pyrene, this index is approximately 20 times greater. Additionally, benzo[a]pyrene clearly produces antifertility effects in male mice, as judged by the relatively low incidence of pregnancies. For contrast's sake, the effects of a benzo[a]pyrene-free acid fraction of extracts of New York pollutants, and of Thiotepa, an alkylating agent used as a chemosterilant insecticide and in the treatment of cancer, are included in Table 5; the air pollutant fraction produces effects in the control range, but the alkylating agent is highly mutagenic.

TABLE 5

Substance tested	Dose (mg/Kg)	Number mice mated		Females pregnant		Implants (including foetal deaths)		Measures of mutagenicity				
								Foetal deaths		Females with one or more early deaths		Early foetal deaths as percent of implants "mutagenic index"
		M	F	Number (P)	Percent	Total (I)	Mean number per pregnant female (I/P)	Total early deaths (ED)	Mean number per pregnant female (ED/P)	Number	Percent	ED/×100
Control		10	30	24	80	281	11.7	1	0.04	1	4	0.4
Benzo[a]pyrene	1,000	5	15	5	33	42	8.4	5	1.00	3	60	11.9
	750	6	18	7	39	53	7.6	5	.71	2	29	9.4
Thio-tepa	50	8	24	9	38	64	7.1	32	3.56	8	89	50.0
	25	8	24	16	67	141	8.8	39	2.44	11	69	27.7
Acid air fraction	666	9	27	18	67	207	11.5	1	.06	1	6	.5
	333	7	21	14	67	162	11.6	1	.07	1	7	.9

Research needs

These studies on the mutagenic effects of air pollutants have just begun. They should be extended to a wide range of various fractions and defined components of atmospheric pollutants following single and chronic exposures by injection and inhalation. It is at this stage difficult to clearly assess the human implications of these findings. However, these data are sufficiently clear to indicate a high degree of urgency in the further clarification of this vital area.

I would like to introduce an aside for just a moment and talk about probable differences between risks of environmentally-induced cancer and mutation. You and I have perhaps 30 more years to go before we die of cancer, stroke, or, if we are lucky, just of old age. When we consider mutations we are considering a risk to future and unborn generations. This risk, I think, is one of the greatest which threatens mankind, and I believe the risks from mutagenicity may well transcend those of cancer.

Thank you.

Senator MUSKIE. Thank you very much, Dr. Epstein, for this very disturbing paper.

CARCINOGENIC EFFECTS

On the first page of your paper, the introduction, you make this statement:

"The scope and magnitude of these environmental hazards"—to which you have just referred—"is illustrated by recent estimates that the majority of all human cancers are chemical in origin; such cancers hence are ultimately preventable."

Now, is it an inescapable conclusion on that fact that air pollutants raise a high risk of cancer?

Dr. EPSTEIN. I find difficulty in answering yes or no to this.

One can say that, apart from epidemiological and chemical leads, experimental data clearly indicates that there are chemicals in air pollutants which are highly carcinogenic to animals. Extrapolating from such information to human lung cancer is different.

I believe that there is an interrelationship between air pollution and smoking and that air pollution is an important factor in the pathogenesis of human lung cancer.

Risks

Senator MUSKIE. Yesterday's testimony was that because of these risks in air pollutants, the risk is greater for smokers than nonsmokers.

Dr. EPSTEIN. I agree with that, sir.

Air pollutants

Senator MUSKIE. Is the risk sufficiently great as to justify and indeed to support and even to make urgent the control of emissions upon that basis alone?

Dr. EPSTEIN. I would submit, sir, that the evidence does clearly indicate that there is a high cancer-producing element in air pollutants.

Senator MUSKIE. You have impressed me with the urgency of the second page in which you referred to mutagenic effects of air pollutants. As is the case with so much knowledge or lack of knowledge in this field, we find ourselves at the threshold of the necessary studies with tremendous concern. We realize that what we would learn may be learned at a time when some of the results may be irreversible. Is that a danger in this field?

Dr. EPSTEIN. This most certainly is the great danger implied in genetic hazards, as by the time we appreciate these it may be too late.

Existing evidence

Senator MUSKIE. If time and the expansion of our knowledge demonstrates that there are such things as serious as you implied, maybe then we will have been proven seriously wrong if we at this point delay drastic measures. Is that accurate?

Dr. EPSTEIN. Yes; however, I wouuld personally like to see a crash program on mutagenicity testing on air pollutants on a wide scale before answering that firmly.

The only evidence on the mutagenic effects of air pollutants that exists at present is that which I have given you this morning. This information is grossly inadequate; it is just scratching the surface.

Adequacy of test procedures

Senator MUSKIE. Are the experimental test techniques adequate at this point to a crash program?

Dr. EPSTEIN. I think so.

Senator MUSKIE. What do we need, additionally, for a crash program, simply money?

Dr. EPSTEIN. Money; yes, sir.

Senator MUSKIE. Do you have any estimate as to the extent of the program that ought to be undertaken?

Dr. EPSTEIN. Yes; I think that defined chemicals known to be present in air pollutants should be tested in mice and possibly one other species following acute and chronic exposures by inhalation and injection.

Additionally, undefined crude fractions and subfractions and sub-sub-fractions of various extracts of particulate and nonparticulate air pollutants should be tested.

Ozone studies

We are now in the middle of experiments on the possible mutagenic effects of ozone, but we don't know what these are going to show. I must, however, emphasize that mutagenicity is a problem which transcends air pollution alone; it is a problem relating to the whole human environment, and includes pesticides, food additives, drugs and so forth. We are surrounded by a complexity of chemicals which pose a variety of dangers to man. Some of these dangers have been

defined and some have not. It is to me incomprehensible that, some 10 to 20 years after radiation hazards have been assessed in some measure, we have no firm knowledge as to mutagenic hazards of chemicals in the human environment. Air pollution is just one part of this picture.

Research needs

Senator MUSKIE. If money were no limitation, how much time would be minimal in a crash program?

Dr. EPSTEIN. One could get a pretty good preliminary impression in 1 year. I would say that within 5 years one could probably lay the subject wide open.

Senator MUSKIE. How much money is required to do this for air pollutants alone?

Dr. EPSTEIN. For mutagenicity testing in mammals of air pollutants alone, I would assess approximately one-half to 1 million a year. Ancillary screening tests might increase these costs by a further million.

Senator MUSKIE. To some of us around here that is peanuts.

Thank you very much for your excellent testimony.

Dr. EPSTEIN. Thank you, sir.

Senator MUSKIE. Dr. Epstein, I ought to make this part of the record.

Current investigations

As I understand this kind of research at the present time is being done only in two places.

Dr. EPSTEIN. Am I correct, sir, in stating your question as, is this research on air pollutants being done in more than one place?

Senator MUSKIE. To what extent is it being done now?

Dr. EPSTEIN. It is being done nowhere. We have ceased for lack of funds.

Senator MUSKIE. It is not being done in Bar Harbor?

Dr. EPSTEIN. No. In Oak Ridge, four chemicals unrelated to air pollutants in the last 2 years have been tested for dominant lethal effects in mammals, but, apart from the studies I reported on this morning, there is no work being done on air pollution with specific reference to mutagenicity testing in animals anywhere in the world, to my knowledge.

(Questions subsequently submitted by Senator Muskie and response by Dr. Epstein follow:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. SAMUEL S. EPSTEIN,
Children's Cancer Research Foundation,
Boston, Mass.

DEAR DR. EPSTEIN: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. SAMUEL S. EPSTEIN

1. There are a number of chemicals which are suspected of causing genetic damage. From your experience, do you feel this possibility has received adequate attention in laboratory or other research?
2. Should these effects actually occur as a result of environmental exposure, do the study techniques exist to detect them in the general population?
3. What is the value of laboratory studies in providing understanding of these causes and relationships?
4. Considering the nature of the effects discussed, what would be a suitable public health policy regarding these types of materials?

CHILDREN'S CANCER RESEARCH FOUNDATION, INC.
Boston, Mass., September 12, 1968.

Senator EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution,
U.S. Senate, Committee on Public Works,
Washington, D.C.

DEAR SENATOR MUSKIE: Thank you for your letter of August 2, 1968. It was a privilege to have testified before you.

I am enclosing my replies to the four questions you have raised. Please accept my apologies for the delay as I have only just returned from vacation.

Sincerely yours,

SAMUEL S. EPSTEIN, M.D.
Chief, Laboratories of Environmental Toxicology and Carcinogenesis.

[Enclosure]

RESPONSE OF DR. S. S. EPSTEIN TO QUESTIONS RAISED BY SENATOR MUSKIE IN HIS LETTER OF AUGUST 2, 1968

QUESTION 1

There are a number of chemicals which are suspected of causing genetic damage. From your experience, do you feel this possibility has received adequate attention in laboratory or other research?

The main categories of chemicals in which mutagenicity may be anticipated include alkylating agents, nucleotide analogs, and compounds that interfere with nucleic acid synthesis.

Possibly as few as three laboratories in this country (Dr. M. Legator's at the Food and Drug Administration, Dr. R. F. Kimball's at Oak Ridge, and Dr. S. S. Epstein's at the Children's Cancer Research Foundation, Boston), are specifically evaluating the potential health hazards of chemical mutagens. Only one of these laboratories (at the Children's Cancer Research Foundation, Boston) has developed definitive and practical systems suitable for large scale mutagenicity testing in mammals and has already adapted this to testing of air pollutants and a wide range of other materials. However, in the past few years the scientific community has become increasingly but belatedly aware of this problem, and several sessions have been held or are now scheduled for reviewing this field and planning future action.

At the present time, however, well planned systematic investigations on existing or newly introduced chemical agents in our environment that could produce adverse genetic effects are almost nonexistent. Inadequate attention to this area,

with a consequent lack of appropriately directed research, represents a major deficiency in public health policy with regard to environmental hazards.

There is an imperative need for an immediate crash research program on chemical mutagens in the totality of the human environment, to include air and water pollutants, pesticides, food additives, and drugs. This program should be action-oriented toward developing rapid information which would provide a rational basis for legislation analogous to that existing for radiation hazards.

QUESTION 2

Should these effects actually occur as a result of environmental exposure, do the study techniques exist to detect them in the population?

At the present state of the art, a number of procedures, the majority of recent origin, are available for characterizing potentially mutagenic agents.

Available systems currently employed to evaluate potential mutagens are best considered in the two categories of screening and definitive tests. Screening tests can provide useful and rapid preliminary information of an indirect nature. Definitive tests using reproductive studies, are generally more time consuming but, especially those based on mammalian systems, provide information of more direct relevance to man.

Screening tests

a. Physico-chemical studies with isolated DNA.—The reaction of potential chemical mutagens, such as alkylating agents, with DNA can be followed in cell-free systems by various techniques such as equilibrium dialysis, spectroscopy, and thermal hyperchromicity. These studies are usually carried out following biological identification of mutagenic activity and to determine if the mutagenic chemical acts directly on nonreplicating DNA.

b. Transforming studies with isolated DNA.—Transformation is a process of intracellular transfer of genetic information, in which a fraction of donor cell DNA penetrates into a related bacteria and replaces, through a process of recombination, a specific nucleotide sequence of the recipient genome. The exposure of isolated transforming DNA to various chemicals allows measurement of both inactivating and mutagenic effects of a given chemical, i.e. linked transformation in *B. subtilis.*

c. Classical microbiological tests. —In bacteria, yeast, and molds both forward and reverse mutation frequency can be simply measured after exposure to mutagenic agents. In certain systems, such as the adenine-3 locus of Neurospora and the histidine operon of Salmonella, fundamental information as to the specific type of DNA alteration can also be determined.

d. Host-mediated assay.—This recently introduced method incorporates a microbial indicator in an animal system to quantitate and characterize mutagenic agents. Such a screening system appears capable of detecting microbial mutagenic activity in compounds which remain active or become physiologically active after administration, as well as excluding compounds that are no longer mutagenic in an in vivo system.

e. Cytogenetic studies.—Effectiveness of suspected mutagens, in producing chromosome breaks and their sequelae in somatic or germinal mammalian cells, can be tested cytogenetically, in vivo or in vitro, on serial biopsies, necropsy specimens, or on cultured cells.

Cell cultures can be readily obtained from the peripheral blood or marrow of animals or man exposed to a suspected mutagen. In addition, confirmative in vitro tests are possible following addition of the mutagen to mammalian cells in culture. While no phenotypic markers are readily available to determine mutagenic activity in cell cultures, however, DNA synthesis, mitotic index, and cytogenetic studies can be undertaken to characterize genetically active compounds. The versatility of this method and the rapidly advancing techniques for automated cytogenetic analysis make chromosomal analysis one of the most promising systems for mutagenic screening of chemicals.

Definitive reproductive tests

a. Drosophila.—The response of the banana fly to X-irradiation and various other mutagens has been extensively studied with reference to fundamental genetics. This represents a useful technique for the scoring of visible and lethal mutations. Both cytogenetic and reproductive effects can be detected.

b. Specific locus test.—This depends on the expression of recessive homozygous mutations in mice. The test is complicated, time consuming, and expensive.

Although it is quite impractical for routine use, it may have restricted and special applications in an overall program on mutagenicity testing.

c. Dominant lethal test.—This test provides a measure of major chromosomal damage. It is of particular interest as approximately 80 percent of gene mutations in man have been shown to be due to dominant autosomal, nonsex linked traits. This test is based on breeding of untreated female rodents with males previously injected with test agents; mutagenic effects are evidenced by early death of the developing embryo.

This test has been simplified and modified and it now affords the only practical method for routine testing of dominant mutagenic effects on mammalian systems.

d. Human population studies.—Carefully controlled statistical studies on sex ratios in large populations may possibly be helpful in detecting drug or other chemically-induced mutations.

In summary it may be said that no one procedure is adequate for screening and testing all known mutagenic agents, but a combination of the procedures outlined above will probably detect most known classes of mutagens.

QUESTION 3

What is the value of laboratory studies in providing understanding of these causes and relationships?

Laboratory procedures are the only available means for providing an understanding of the basic mechanisms and the relation between various chemicals and their genetic effects.

While cytogenetic studies on human material may yield useful indirect evidence, particularly for drugs, no direct evidence in man is possible in terms of a specific mutagen. The long delay for genetic damage to occur, as much as several generations after the introduction of the mutagen, would probably obscure any cause and effect relationship. A conceivable exception could be created by the introduction into our population of a chemical agent that would increase the mutation rate drastically, resulting in a detectable genetic emergency. Under present conditions, this is a very real possibility.

QUESTION 4

Considering the nature of the effects discussed, what would be a suitable public health policy regarding these type of materials?

For many years radiation and radioactive substances have been known to damage genetic material, and the need for appropriate detection and control measures has been widely accepted. The need to limit radiation exposure to the lowest possible level is a well-established eugenic principle. For over two decades, various chemicals have been known to induce the same type of genetic damage as radiation. Present information suggests that the chemicals to which we are exposed in our environment are genetically more dangerous than radiation.

It is important to realize that we are exposed to many chemicals that our ancestors were not, and that therefore we have not adapted to these through natural selection. The exposure of our population to chemical pollutants in the environment has increased explosively. This is primarily a result of developments in the synthetic organic chemical industry and its offshoot, the pharmaceutical industry. To date, few of these substances have been evaluated for their mutagenic activity. Among these substances are food additives, drugs such as narcotics and antibiotics, pesticides, air and water pollutants. With our extremely high background of genetic defects, one might well wonder why these various substances have not been evaluated for long-range genetic damage.

Programs should immediately be initiated both to detect chemicals presently in our environment that may be mutagenic, and also to routinely screen new compounds before their introduction into commerce and general use. Such chemicals that are or will be widely used by a large segment of our population of child bearing age should receive particular priority.

The importance of mutagenic research in evaluating and limiting our exposure to genetically destructive compounds, and concerning ourselves with practical genetic hygiene cannot be overstated. Our concern must be not only for the contemporary generation but for generations yet to come.

SAMUEL S. EPSTEIN, M.D.

Senator MUSKIE. Thank you very much.
(The complete prepared statement of Dr. Epstein follows:)

COMPLETE STATEMENT OF DR. SAMUEL S. EPSTEIN

CANCER AND MUTATION-PRODUCING CHEMICALS IN POLLUTED URBAN AIR

A. Introduction

Gentlemen, my professional background and experience, as stated in the attached appendix, broadly relates to the study of hazards due to chemical contaminants in the human environment. These contaminants are often ubiquitous and include defined chemicals such as pesticides, food additives, or those used in industry, and partially defined chemicals such as complex mixtures found in water and air pollutants. Therapeutic drugs represent an additional, but *relatively* more restricted and special type of defined chemical contaminant. The potential hazards posed by these classes of chemical contaminants include *toxicity* or poisoning, *teratogenicity* or production of developmental abnormalities in the growing embryo, *carcinogenicity* or the production of cancer, and *mutagenicity* or the production of genetic damage.

The scope and magnitude of these environmental hazards is illustrated by recent estimates that the majority of all human cancers are chemical in origin; such cancers hence are ultimately *preventable*. With relation to genetic damage, a recent authoritative report (Crow, 1968) is equally explicit although more alarming, in statements such as:

1. "A number of chemicals—some with widespread use—are known to induce genetic damage" in various systems.
2. "Identity of the genetic material in all organisms implies that a chemical that is mutagenic to one species is likely to be in others and must be viewed with suspicion."
3. Some compounds are "highly mutagenic in experimental organisms in concentrations that are not toxic and that have no direct effect on fertility." Mutations thus can be propogated to *future* generations.
4. "Perhaps most insidious are compounds that induce point mutations without chromosome breakage," and thus cannot be detected microscopically.
5. "Compared with radiation hazards, chemical mutagens may be the submerged part of the iceberg."

In this presentation on "Cancer and Mutation-Producing Chemicals in Polluted Urban Air," I will restrict myself to two major potential hazards, carcinogenicity and mutagenicity, posed by chemicals contained in urban community air pollutants. Specifically, I will briefly summarize the status of current information with relation to each hazard, review some personal experimental data, and finally attempt to interpret the significance of these data with respect to man.

B. Review of information relating air pollution to lung cancer

The dramatic increase in mortality from lung cancer over the last few decades is now approaching epidemic proportions. The epidemiologist Clemmesen recently stated (1961), "It seems impossible to escape the conclusion that we are now facing one of the major catastrophes in medical history". Figure I emphasizes the exponential nature of this increased mortality which, although general, is particularly steep for Great Britain (Doll, 1955). (Figure 1 appears at p. 609.)

While there is little doubt that cigarette smoking is a major cause of lung cancer, as well as other chronic respiratory disease, there is also good evidence incriminating the role of air pollution. This statement is based on three types of information:

1. Epidemiological.—There are marked regional differences in mortality patterns in the USA (Fig. 2); increased mortality is clearly related to increased urbanizations and to increased levels of organic pollutants in the air (Fig. 3). The higher lung cancer rates in urban areas cannot be fully explained by factors such as smoking or occupation. In a survey some ten years ago, lung cancer rates in the USA, standardized for smoking besides age, were found to be 39/100,000 in rural areas and 52/100,000 in cities with populations in excess of 50,000 (Hammond and Horn, 1958); similar surveys in England also confirmed the importance of this urban factor (Stocks, 1960), and stressed its interaction with smoking (Fig. 4). This *urban excess*, of 25% in US mortality, is generally regarded as being due to air pollution. Confirmatory evidence also is afforded

by several studies on immigrants who tend to retain the incidence pattern of lung cancer of their country of origin, even though they assume the smoking and other habits of their country of adoption. (Figures 2, 3, and 4 appear at pp. 610–612.)

2. Chemical.—Incomplete combustion of organic matter produces soots containing a variety of compounds, many of which have been chemically defined and some of which are carcinogenic (Table 1). An important group of these compounds are the polynuclear hydrocarbons, of which benzo[a]pyrene has been the most extensively studied. Many additional classes of poorly defined chemical carcinogens have been recently recognized in atmospheric pollutants, including the alkylated polycyclics and azaheterocyclics (Sawicki, 1967). However, the predictive value of chemical techniques is seriously restricted, as certain pollutant fractions, such as the oxy-neutral and aliphatic, contain unidentified carcinogens. Additionally, the carcinogenicity of defined or undefined chemicals, can be profoundly influenced by the presence of other chemicals which by themselves are non-carcinogenic. (Table 1 appears at p. 613.)

It is of interest to compare the very approximate relative amounts of the carcinogen benzo[a]pyrene theoretically inhaled under different conditions. The one pack-a-day smoker, inhales 0.3 μg daily (Surgeon General's Advisory Committee on Smoking and Health, 1964), which is similar to the amount inhaled by a non-smoker in heavily polluted urban air and about three times that inhaled in "average" urban air (Sawicki, 1960). However, the worker engaged in roof tarring inhales an amount of benzo[a]pyrene in an eight-hour day, equivalent to that contained in about two hundred packs of cigarettes (Schueneman, 1963).

3. Biological.—Standard biological techniques for demonstrating the carcinogenecity of extracts of particulate atmospheric pollutants depend on repeated skin painting or subcutaneous injection of pollutants in adult rodents. These techniques, however, require comparatively large amounts of pollutants and generally result in low yields of local tumors after long latency periods (Table 2). (Table 2 appears at p. 614.)

In a recent PHS study (Heuper et al., 1962), the effects of organic extracts and three respective fractions from eight cities were tested by standard techniques employing local administration to the skin of mice and rats. The resulting tumor yields were low, ranging from 2–10%, with latent periods extending up to two years. Only local tumors were produced, and extracts from all the cities, with exception of Los Angeles, were carcinogenic.

It would, of course, appear more logical to use the lung rather than skin for carcinogenicity testing of atmospheric pollutants. However, nobody has yet consistently produced bronchogenic carcinoma in animals by inhalation of community air pollutants, and in fact, relatively few attempts to do so have been made. Campbell (1939) increased the incidence of pulmonary adenomas in mice by exposing them to road dust in inhalation chambers. Kotin and Falk (1956) likewise increased the incidence of pulmonary adenomas in mice by exposing them to ozonized gasoline, which is considered to bear chemical similarities to Los Angeles photochemical smog. Kotin and Wiseley (1963), exposed mice to influenza virus and subsequently to ozonized gasoline, thereby producing squamous lesions resembling bronchogenic carcinoma. Saffiotti (1965) produced squamous lung cancers by tracheal intubation of hamsters with suspensions of benzo[a]pyrene adsorbed on an inert carrier. More recently, Laskin (1967) has been successful in inducing squamous lung cancer in rodents by prolonged inhalation of benzo[a]pyrene and SO_2.

C. Recent techniques for measuring the carcinogenicity of air pollutant extracts

In our laboratories at the Children's Cancer Research Foundation in Boston, and supported by contracts from the National Center for Air Pollution Control, USPHS, we have developed two highly sensitive biological techniques for measuring the carcinogenicity of organic extracts of atmospheric pollutants.

1. Indirect screening test for carcinogenicity based on measurement of photosensitizing compounds in pollutant extracts.—Polynuclear compounds are among the most important chemical pollutants in the air. In this class of compounds, a strong relationship has been previously demonstrated between their carcinogenicity and ability to lethally sensitize single cells to the otherwise harmless effects of long wave ultraviolet light (Epstein *et al.*, 1964). Photosensitizing ability thus affords an indirect index of the carcinogenicity of pollutants and can be measured simply and rapidly by relatively non-specialized personnel.

This procedure, known as the photodynamic test, can be completed in three hours and only needs 1 mg of pollutant materials (Epstein *et al.*, 1963).

Extracts of atmospheric pollutants, and their various fractions from over one hundred urban and non-urban USA sources, have been studied with this test and the results have been related to chemical and other data (Epstein, 1966). Photodynamic potencies, expressed on a mass basis, indicate the degree of biological activity in extracts and fractions, and thus characterize source emissions without reference to the factor of atmospheric dilution (Fig. 5). For this reason, activities in some non-urban samples are similar to those of urban samples. Potencies, expressed on an air volume basis, however, provide an indication of the degree of atmospheric dilution of total emissions; using this more meaningful measure of atmospheric pollutions, the non-urban samples are found to be relatively inactive (Fig. 5). As can be seen, this test yields data which discriminates widely between pollutants from different sources, and even more widely between various fractions of pollutant extracts derived from any one source. Characteristically, densely populated cities with predominant usage of solid fuel have high potencies in their organic extracts and fractions. Further, it can be seen that on a mass basis, the basic fraction is, generally, the most active of all. Even when potency is expressed on an air volume basis, the basic fraction still ranks disproportionately high. (Figure 5 appears at p. 617.)

For illustrative purposes, it may be mentioned that of the cities studied, Boston ranked in the top 20% for atmospheric concentrations of photosensitizing polynuclear compounds and in the top 30% for concentrations of the carcinogen benzo[a]pyrene (Table 3). The use of this test, additionally, is enabling the identification of hitherto unrecognized polynuclear carcinogens in certain fractions of organic extracts of particulate atmospheric pollutants (Epstein, 1968). (Table 3 appears at p. 616.)

2. Direct carcinogenicity tests based on administration of pollutant extracts to newborn mice.—The use of newborn animals (neonates) for the carcinogenicity testing of pure chemicals has been well documented over the last 10 years. Neonates have been shown by others to be highly sensitive to defined carcinogens, administration of which in very low concentrations generally results in high tumor yields with relatively short latency periods. However, there are no published data on the use of neonates for the demonstrating of carcinogens in undefined crude mixtures, such as organic extracts of particulate atmospheric pollutants.

The present studies have established the very high sensitivity of neonatal mice to carcinogens extracted from air (Epstein *et al.*, 1966). Neonates were injected with suspensions of organic extracts of atmospheric particulates derived from various urban sources in the USA, including Chicago, Cincinnati, Los Angeles, Philadelphia, Washington, D.C., and New York City. Doses, ranging from 5–55 mg, were fractionally administered during the first three weeks of life, commencing within a few hours of birth. Dosage schedules were developed to permit injection of maximal amounts of extracts as early as possible in the neonatal period, consistent with limitations imposed by acute toxicity. A high incidence of cancers, remote from the injection site, such as liver cancer, leukemias, and lung tumors, resulted. The tumor incidence was particularly high with pollutant extracts from Cincinnati, low with extracts from Los Angeles, and intermediate with Washington extracts (Table 4). Apart from these striking differences in the carcinogenicity of extracts from the various cities tested, the nature and multiplicity of tumors produced strongly indicates the role of several carcinogens in addition to benzo[a]pyrene. (Table 4 appears at p. 619.)

Based on the approximations that an adult man daily inhales 0.3 μg of benzo[a]pyrene in heavily polluted air, and that the average concentration of benzo[a]pyrene in organic extracts of pollutants in 500 μg/g, it would take the adult in question approximately one to three months to inhale those amounts of atmospheric pollutants which we have found to be highly carcinogenic to neonatal mice.

Although it is not easy to apply these experimental findings directly and quantatively to the human situation, it is nevertheless difficult to escape the firm conclusion that the high carcinogenicity of trace amounts of organic pollutants is particularly significant in relation to the causes of human lung cancer.

D. Review of information on mutagenic effects of air pollutants

With the exception of the gaseous pollutant ozone, which has been shown to produce chromosome damage in *Vicia faba* cells (Fetner, 1958), there are no published data on mutagenicity testing of air pollutant extracts. This lack of in-

formation is all the more surprising, as certain fractions of air pollutant extracts are known to contain poorly defined compounds, such as epoxides and lactones, known as radiomimetic, which are generally both carcinogenic and mutagenic (Gray, *et al.*, 1958; Kotin and Falk, 1963; Van Duuran *et al.*, 1965).

E. Recent techniques for measuring the mutagenicity of air pollutant extracts

Chemical mutagens in the environment are potential hazards which have not yet been systematically explored. Although certain mutagens, notably ionizing radiations and alkylating agents, have been studied in detail for the production of chromosome breakage in cultured cells (Legator, 1966) and for the induction of mutations in viruses, bacteria, fungi, and flies, the relevance of such information to the human situation is not always apparent. The use of more appropriate and direct systems based on mammals, such as the *specific locus* test (Russell *et. al.*, 1960), and the *dominant lethal* test (Bateman, 1962) have received relatively little practical recognition because of their alleged expense and complexity. We have shown that this viewpoint is not justified, particularly in relation to the dominant lethal test, which we have simplified, modified and applied for the testing of air pollutants besides drugs, food additives and pesticides.

The dominant lethal test is a measure of major chromosomal damage. It is of particular interest as approximately 80% of gene mutations in man have been shown to be attributable to dominant autosomal, non-sex linked, traits (Report, U.N. Committee on Effects Atomic Radiation, 1966). This test is based on breeding of untreated female rodents with males previously injected with test agents; mutagenic effects are evidenced by early death of the developing embryo (Fig. 6). Associations between mutagenic and anti-fertility effects can also be studied with this system. (Figure 6 appears at p. 620.)

The carcinogenic air pollutant benzo[a]pyrene has been shown to be mutagenic in mice following a single dose of 750 or 1000 mg/kg, corresponding to individual animal doses of 30 or 22.5 mg, respectively. As can be seen in Table 5, the mutagenic index for normal control mice is 0.4 and for benzo[a]pyrene, this index is approximately 20 times greater. Additionally, benzo[a]pyrene clearly produces anti-fertility effects in male mice, as judged by the relatively low incidence of pregnancies. For contrast sake, the effects of a benzo[a]pyrene-free acid fraction of extracts of New York pollutants and of Thio-tepa, an alkylating agent used as a chemosterilant pesticide and in the treatment of cancer, are included in Table 5; the air pollutant fraction produces effects in the control range, but the pesticide is highly mutagenic. (Table 5 appears at p. 621.)

These studies on the mutagenic effects of air pollutants have just begun. They should be extended to a wide range of various fractions and defined components of atmospheric pollutants following single and chronic exposures by injection and inhalation. It is at this stage difficult to clearly assess the human implications of these findings. However, these data are sufficiently clear to indicate a high degree of urgency in the further clarification of this vital area.

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APPENDIX

I. Personal curriculum.
II. Personal publications relevant to hazards of air pollutants.
1. "Photodynamic Bioassay of Polycyclic Air Pollutants", Arch. Environ. Health, 7, 531–537, 1963.
2. "On the Association between Photodynamic and Carcinogenic Activities in Polycyclic Compounds", Canc. Res., *24*, 855–862, 1964.
3. "Photodynamic Bioassay of Polycyclic Atmospheric Pollutants", J. Air Poll. Control Assoc., *15*, 174–176, 1965.
4. "Two Sensitive Tests for Carcinogens in the Air", J. Air Poll. Control Assoc., *16*, 545–546, 1966.
5. "Carcinogenicity of Organic Particulate Pollutants in Urban Air After Administration of Trace Quantities to Neonatal Mice", Nature, *212*, 1306–1307, 1966.
6. "Photodynamic Assay of Neutral Subfractions of Organic Extracts of Particulate Atmospheric Pollutants", Environ. Sci. & Tech., *2*, 132–138, 1968.
7. "Use of Mammals in a Practical Screening Test for Chemical Mutagens in the Human Environment", Nature, *In Press*, 1968.

III. The Crow report on "Chemical Mutagens as a Possible Health Hazard", Scientist and Citizen, *In Press*, 1968.

Appendix I.

Samuel S. Epstein

PERSONAL

Born: April 13, 1926, Middlesborough, Yorkshire, England. British citizen—married—three children.

Private address: 33 Powell Street, Brookline, Mass. 02146 U.S.A.

Professional address: Children's Cancer Research Found., 35 Binney Street, Boston, Mass. 02115, U.S.A.

QUALIFICATIONS

1947: B.Sc. (Physiology) London University, England.

1950: M.B.B.S. (Bachelor of Medicine, Bachelor of Surgery) (Double Honors) London University.

1952: D.T.M.H. (Diploma of Tropical Medicine and Hygiene, Bacteriology and Parasitology) London University.

1954: D. Path. (Diploma of Pathology) London University.

1958: M.D. (Doctorate of Medicine, Thesis in Pathology and Bacteriology) London University.

1963: Diplomate, in Public Health and Medical Laboratory Microbiology, of the American Board of Microbiology.

POSITIONS HELD

1950: Demonstrator, Morbid Anatomy, Guy's Hospital, London.
1951: House Physician, St. John's Hospital, London.
1952: Postgraduate Student in Tropical Medicine, Pathology Bacteriology and Parasitology, Royal Army Medical College, London.
1952–1955: Specialist in Pathology, Royal Army Medical Corps.
1955–1958: Lecturer in Pathology and Bacteriology, Institute of Larynogology and Otology, University of London.
1958–1960: British Empire Cancer Campaign Research Fellow, in conjunction with the Chester Beatty Cancer Research Institute and Tumor Pathologist at the Hospital for Sick Children, Great Ormond Street, London.
1960: Consultant in Pathology, the Memorial Hospital, Peterborough England.
1961–: Research Associate in Pathology and Microbiology, The Children's Hospital Medical Center and The Children's Cancer Research Foundation, Boston, Massachusetts.
1961–: Chief, Laboratories of Carcinogenesies and Toxicology, Applied Microbiology and Histology, The Children's Cancer Research Foundation, Boston.
1962–To date: Senior Research Associate in Pathology. The Children's Cancer Research Foundation, Boston, and Research Associate in Pathology, Harvard Medical School, Boston.

AWARDS

Military Awards in Royal Army Medical Corps, 1953; (*a*) Montefiore Gold Medal in Tropical Medicine, (*b*) Montefiore Prize in Tropical Hygiene, and (*c*) Ranald Martin Prize in Military Surgery.

SOCIETY MEMBERSHIPS

British Medical Association, Association of Clinical Pathologists, Society for Pathology and Bacteriology, Society for General Microbiology, Society of Protozoologists, Air Pollution Control Association, American Association of Pathologists and Bacteriologists, American Society for Experimental Pathology, American Association for Cancer Research, American Board of Microbiology, and American Society of Toxicologists.

COMMITTEES

(*a*) Chairman, Committee on Biological Effects of Air Pollution, The Air Pollution Control Association; (*b*) Member, Technical Council of the Air Pollution Control Association; and (*c*) Member, Committee on the Relation of Protozoology to Public Health, The Society of Protozoologists.

PUBLICATIONS

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Photodynamic Bioassay of Polycyclic Air Pollutants

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Introduction

Assay on rodent skin is the most practicable and least indirect method available for assessing the carcinogenic hazard of polluted air, yet the lengthy procedure and other factors involved limit its general application.[1,2] The development of spectrophotometric methods for quantitating benzo[*a*]pyrene (BaP),[3,4] the most potent known atmospheric carcinogen, suggested the use of BaP concentration as an index of presumptive carcinogenic hazard.[5] Interest attaches to this index, in view of the claim that the ratio of concentrations of BaP to all other common polycyclic hydrocarbons in most urban atmospheres is, in general, approximately constant.[4,5] However, the lack of correlation between BaP concentrations and carcinogenicity of fractions derived from air particulates [2] seriously restricts the utility of such chemical methods.

This report presents a pilot study in which a small number of fractions derived from particulate air samples were assayed for photodynamic activity. The photodynamic response of *Paramecium caudatum* to various polycyclic aromatic hydrocarbons, including BaP, and a rapid bioassay with satisfactory reproducibility and sensitivity, based on this response, have been described recently.[6-8]

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Materials and Methods

Materials.—Samples for photodynamic bioassay were obtained from the Division of Air Pollution,

US Public Health Service. Fifteen crude benzene extracts and chromatogrammed fractions of organic atmospheric particulates were collected from various American cities by methods reported elsewhere.[5,9]

Some of the collateral atmospheric data necessary for complete evaluation of the results were, unfortunately, not available. Requisite data, for example, should have included grams of particulate matter per 1,000 cubic meters of air, with a subdivision into benzene-soluble and insoluble portions. Available data, however, showed that in seven air samples the benzene-soluble material constituted an average of 10% by weight of all particulate material. Separation of the benzene-soluble material gave the following results: aliphatics, average 20% (range 13%-32%); aromatics, average 18% (range 11%-22%); oxygenated, average 24% (range 21%-28%).

Photodynamic Assay Procedure.—The bioassay procedure, which depends on the ability of various polycyclic hydrocarbons to sensitize *P caudatum* to the otherwise nontoxic effect of long-wave ultraviolet light, has been described.[6-8] The time required for immobilization of 90% of the motile ciliates (LT_{90}) was selected as the end-point of this photosensitizing effect. The existence of a linear inverse relationship between the log LT_{90} and the log BaP concentration over a wide response range was demonstrated.[8]

BaP was used as an arbitrary reference standard in the assays reported here. Fresh aqueous suspensions of BaP and individual air samples were prepared from benzene solutions of known concentrations, generally by techniques previously described for BaP.[8] Results of preliminary assays at tenfold dilutions from 10^{-1} to 10^{-5} of aqueous suspensions of the air samples defined a region in which a definitive asay could be performed. For definitive assays, the activities of five concentrations of BaP, ranging from 0.32μg to 0.02μg per milliliter and five concentrations of air samples were compared. In general, two to five air samples were assayed simultaneously in duplicate against four replicates of each concentration of the BaP standard. Individual samples were assayed on at least four separate occasions.

Photodynamic asays were done on nine polycyclic hydrocarbons commonly present in the atmosphere, and also on artificially enriched air samples, to determine the percentage BaP recovery.

Statistical Procedures.—Statistical characteristics of the photodynamic assay have been described, and difficulties arising in the application of parallel line assay procedures to situations with dissimilar test and standard agents have been anticipated.[8] Such difficulties were manifest in the assay of air samples and polycyclic hydrocarbons, where slopes of the response curves generally were nonparallel to and shallower than those for BaP.

Results obtained were ana'yzed by fitting separate response lines, not necessarily parallel, to the data for the test and standard. Each line was characterized, as suggested in the earlier report, by its assay slope value, $-b$, and by its C_{10} value, ie, that concentration yielding an LT_{90} of ten minutes.[8] Relative potencies of two similar preparations can properly be based on the ratio of their C_{10} values (or rather, on the reciprocal of the ratio), but, in the present instance where dissimilarities exist, the term *apparent relative potency* has been applied.

Chemical Assay Procedures.—Crude benzene air extracts and derived fractions were analyzed for ten major polycyclic hydrocarbon constituents by using previously described chromatographic and spectrophotofluorimetric techniques.[4,5] The procedure includes the elution of 15 to 150 mg of the material from an alumina column with pentane-ether solutions of the following volumes (milliliters) and percentages of ether: 100, 0; 100, 3; 100, 6; 250, 9; 100, 12; and 50, 100.

Results

Photodynamic Assay of Air Samples.—Table 1 shows individual and median apparent relative potencies, in terms of micrograms of benzo[*a*]pyrene per gram of material for each air sample, together with the corresponding assay slopes. Assay slopes for air samples are generally low and are of the order of one third to one half that for the BaP standard. A typical example of air fraction assay data is illustrated in Fig 1.

Photodynamic activity was found in all six crude benzene extracts (samples 1-6, Table 1), and was high for the one aromatic fraction (sample 12, Table 1). The five aliphatic fractions tested (samples 7-11, Table 1) all lacked activity. The three oxygenated fractions tested showed photodynamic activity, such activity being especially high for Nashville (sample 13, Table 1).

Chemical Assay of Air Samples.—Concentrations of ten major polycyclic hydrocarbons in the samples assayed, expressed as micrograms per gram of benzene-soluble fraction, are shown in Table 2, together with the median apparent relative potency of each sample as determined by bioassay.

Photodynamic Assay of Major Polycyclic Hydrocarbon Atmospheric Constituents.—Median apparent potencies and assay slopes of ten polycyclic hydrocarbons relative to BaP are listed in Table 3. It may be noted that activity and high assay slopes were

TABLE 1.—*Photodynamic Assay Results for 15 Air Samples: Apparent Relative Potencies and Slope Ratios on Each Occasion of Testing and Medians of Such Determinations Are Shown*

Air Sample No.	Source and Date	Solvent Fractions	Apparent Relative Potencies μg Benzo[a]pyrene/Gm		Assay Slopes: Test Slope/BaP Slope (Decrease in Log LT_{90}/Unit Increase in Log Dose)	
			Median Value	Individual Values *	Median Test / Median BaP	Individual Slope Ratios *
1	Birmingham; Aug, 1958	Crude benzene extract	320	250; 270; 320; 380; 380	0.54/1.03	0.47/0.89; 0.54/0.78; 0.45/1.05; 0.56/1.03; 0.54/1.14
2	Composite USA, 200 cities; 1957-1959	Crude benzene extract	670	380; 530; 670; 700; 900	0.39/1.03	0.31/0.78; 0.32/1.14; 0.39/0.89; 0.42/1.05; 0.52/1.03
3	San Francisco; Aug, 1958	Crude benzene extract	71	23; 50; 53; 71; 104; 107; 111	0.34/0.89	0.26/0.78; 0.27/1.03 0.29/1.14; 0.35/0.89; 0.43/1.05; 0.34/0.64; 0.44/0.85
4	Cincinnati; July-Aug, 1958	Crude benzene extract	70	57; 60; 80; 408	0.34/0.92	0.24/0.84; 0.34/1.04; 0.34/1.00; 0.40/0.65
5	Philadelphia; June, 1958	Crude benzene extract	164	50; 104; 220; 230	0.27/0.92	0.27/1.00; 0.26/1.04; 0.26/0.84; 0.33/0.65
6	Atlanta; July, 1958	Crude benzene extract	360	87; 260; 460; 490	0.48/0.86	0.33/0.84; 0.45/1.20; 0.52/0.66; 0.72/0.88
7	San Francisco, 1959	Aliphatic	—	No activity detected	—	—
8	Nashville; Dec, 1958	Aliphatic	—	No activity detected	—	—
9	San Francisco; Jan, 1959	Aliphatic	—	No activity detected	—	—
10	Nashville; Dec, 1958	Aliphatic	—	No activity detected	—	—
11	Los Angeles; Jan-March, 1959	Aliphatic	—	No activity detected	—	—
12	Detroit; Sept, 1958	Aromatic	6,500	3,300; 5,400; 6,300; 6,800; 8,800; 14,800	0.61/0.98	0.60/0.88; 0.78/1.00; 0.62/0.97; 0.69/1.23; 0.57/0.99; 0.51/0.76
13	Nashville; Dec, 1958	Oxygenated	5,400	1,050; 3,700; 5,400; 5,400; 7,800	0.44/1.00	0.40/1.00; 0.32/1.04; 0.50/0.65; 0.44/0.64; 0.45/1.00
14	Los Angeles; Jan-Feb, 1959	Oxygenated	154	15; 97; 115; 193; 210; 260	0.35/0.92	0.26/1.00; 0.32/1.04; 0.30/1.00; 0.43/0.64; 0.38/0.84; 0.38/0.65
15	San Francisco; Jan, 1959	Oxygenated	260	80; 170; 210; 300; 350; 410	0.35/0.92	0.30/1.00; 0.34/1.04; 0.35/0.84; 0.45/0.64; 0.34/1.00; 0.40/0.65

* Individual values of apparent relative potency are arranged in ascending order. Individual slope ratios are arranged to agree with the order of the corresponding relative potency.

found for four polycyclics, activity being high for benzo[*e*]pyrene and benz[*a*]anthracene.

BaP Recovery Assays.—Table 4 shows the estimated total concentrations of BaP in three enriched samples (samples 2, 5, and 13) as determined by this assay. These values are compared with the sum of both components, the known BaP enrichment plus the apparent relative potency of the air sample. It may be noted that, in all instances, the estimated recovery exceeds 100%.

Comment

The photodynamic bioassay described here is simple, rapid, and economical. Replicates of numerous air samples can be conveniently assayed, daily. Attempts at further improvement and simplification of this assay are in progress.

Since the standard and test materials compared are dissimilar, the results are, perforce, expressed as apparent relative potencies, a term appropriate to nondilution assays. This measure provides a useful, though not ideal, index of activity. The problem of nondilution assays has been reviewed recently.[10] It was there pointed out that the assumptions leading to the classical analytic dilution assay are rarely met in biological practice, and, in fact, when such conditions do obtain, chemi-

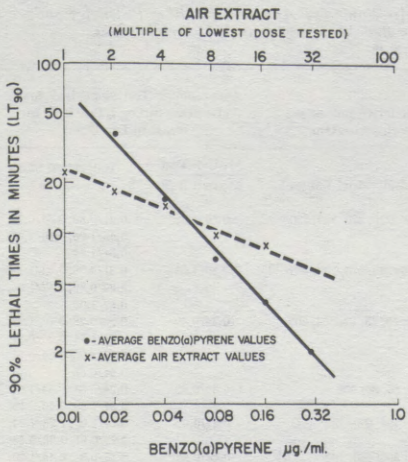

Fig 1.—Photodynamic bioassay of an air sample (sample 1) illustrating a characteristic shallow dose-response line.

cal analysis may well be preferable to bioassay.

Benzo[*a*]pyrene was selected as the reference standard because it is both the most photodynamically active [11] and potent known atmospheric carcinogen. It must be emphasized that the photodynamic assay is not specific for BaP or, indeed, for polycyclic hydrocarbon carcinogens; photodynamic activity to a lesser and varying degree is elicited by other polycyclic hydrocarbons.[11] The present results (Table 3) show high activity for two polycyclic hydrocarbons other than BaP: benzo[*e*]pyrene and benz[*a*]anthracene. Of these two, only benzo[*e*]pyrene is commonly found at atmospheric concentrations [5] high enough to influence materially the results of bioassay.

The data of Table 2 reveal a general pattern of correlation for the six crude benzene extracts (samples 1-6) between apparent relative potencies determined by photodynamic bioassay, and BaP concentrations determined by chemical analysis. All aliphatic fractions were devoid of photodynamic activity, and chemical analysis confirmed the absence of polycyclic hydrocarbons (samples 7-11, Table 2). The single aromatic fraction tested had high photodynamic activity (sample 12, Table 2). Although chemical data for this particular sample were unavailable, BaP concentrations of aromatic fractions, in general, are approximately five times higher than for parent crude benzene extracts.[2] Significant photodynamic activity in two oxygenated fractions (samples 14-15, Table 2) and high activity in the remaining oxygenated fraction (sample 13, Table 2) were observed. The oxygenated fraction,

TABLE 2.—*Comparison of Photodynamic and Chemical Assay Results for 15 Air Samples*

Air Sample No.	Photodynamic Assay Median Activity, µg BaP/Gm	Chemical Assay Results, µg/Gm, Benzo [*a*] pyrene	Benzo [*e*] pyrene	Pyrene	Perylene	Benzo [*g,h,i*] perylene	Benz [*a*] anthracene
Crude benzene extracts							
1	320	370	410	370	38	590	—
2	670	510	560	550	51	750	350
3	71	120	270	—	13	940	—
4	70	280	160	33	—	300	—
5	164	170	220	120	12	560	94
6	360	140	330	26	20	670	—
Aliphatic fractions							
7	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—
9	—	—	—	—	—	—	—
10	—	—	—	—	—	—	—
11	—	—	—	—	—	—	—
Aromatic fraction							
12	6500	(Insufficient for analysis)					
Oxygenated fractions							
13	5400	—	—	—	—	—	—
14	154	—	—	—	—	—	—
15	260	—	—	—	—	—	—

largely chemically undefined, contains oxygenated or other polar derivatives of 3 to 7 ring polycyclic aromatic hydrocarbons, and also larger polycyclics. Chemical analyses of the three oxygenated fractions tested confirmed the absence of BaP and other polycyclic hydrocarbons of known structure commonly found in atmospheric particulates.

Carcinogenic bioassays of atmospheric particulates in rodents have demonstrated greater potency in crude benzene extracts, aromatic and oxygenated fractions, and lesser potency in aliphatic fractions.[2] The absence of correlation between carcinogenic potency and BaP concentration in these fractions has been emphasized.[2] Illustrating this lack of correlation is the higher carcinogenicity of oxygenated, rather than aromatic, fractions, in spite of the absence of BaP from the former.[2] * Factors contributing to this lack of correlation probably include the presence of promoting agents, nonspecific irritants, and chemically unidentified carcinogens, the latter especially in oxygenated fractions, and anticarcinogens,[1,2] again especially in oxygenated fractions (Fig 2). Interestingly, in the latter connection, the photodynamic recovery experiments gave no indication of such biological antagonism between constituents of atmospheric particulates and BaP (Table 4).

The possibility exists that photodynamic toxicity and carcinogenicity of oxygenated fractions are both attributable to the same or related agent or agents, which may represent as yet unidentified oxygenated products of polycyclic aromatic hydrocarbons. This hypothesis is being tested in an attempt to identify and characterize the carcinogenic agents in oxygenated fractions.[13]

The limited number of air samples so far tested precludes general conclusions as to the comparative photodynamic activity of atmospheric pollutants from various cities. The highest activities observed were with fractions from Detroit and Nashville (samples 12 and 13, Tables 1 and 2). These two cities, in the winter of 1959, ranked first and third highest, respectively, among 12 selected large American cities on the basis of BaP and other polycyclic hydrocarbon contents of suspended atmospheric particulates.[5]

The sensitivity of the photodynamic bioassay to certain polycyclic carcinogenic constituents for air pollutants *inter alia* suggests that this assay may provide an empirical index of potential carcinogenic hazard attributable to polycyclics, without the obligate

* The data reported by Hueper et al,[2] Table 20, showed an over-all incidence of 4.3% cancers when crude benzene extracts were injected subcutaneously into mice. When the three eluted fractions were tested separately, dosage being adjusted so as to represent the same initial amounts of crude extract, the tumor incidences were: aromatic fraction, 2.1%; oxygenated fraction, 3.1%; aliphatic fraction, 1.1%.

With Related Atmospheric Data

Chrysene	Coronene	Anthanthrene	Fluoranthene
—	200	19	300
500	200	14	470
—	620	8	—
—	110	—	—
250	130	—	—
—	300	—	—
—	—	—	—
—	—	—	—
—	—	—	—
—	—	—	—
—	—	—	—
—	—	—	—
—	—	—	—
—	—	—	—

TABLE 3.—*Photodynamic Activity of 10 Polycyclic Hydrocarbons Commonly Found in Atmospheric Particulates*

Polycyclic Hydrocarbons	Apparent Relative Potency, μg BaP/Gm	Assay Slope Ratio: Test Slope/BaP Slope
Benzo [a] pyrene	1,000,000 (by definition)	—
Benzo [e] pyrene	420,000	0.88/0.89
Pyrene	53,000	0.77/0.89
Perylene	<800	No activity noted
Benzo [g,h,i] perylene	<16,000	0.30/0.89
Benz [a] anthracene	680,000	1.10/0.89
Chrysene	<800	0.07/0.89
Coronene	<800	0.32/0.89
Anthanthrene	<800	0.11/0.89
Fluoranthene	57,000	0.79/0.89

TABLE 4.—*Recovery of Benzo[a]pyrene From Enriched Air Samples by Photodynamic Assay*

Air Sample	% Enrichment With BaP	Apparent Relative Potency of Enriched Sample, μg BaP/Gm Air Sample	Benzo [a] pyrene Content of Enriched Sample by Components, μg BaP/Gm Air Sample			Estimated Recovery, %
			Added BaP	From Air Sample by Separate Bioassay	Total	
2	4.13	63,000	41,300	700	42,000	150
5	0.78	9,400	7,800	200	8,000	118
13	21.7	356,000	217,000	5,000	222,000	160

Explanation, using sample 2 data: The bioassay of sample 2 plus added BaP yielded an estimated content or 63,000μg BaP/gm of sample 2 in the mixture. The separate bioassay of sample 2 (see Table 1) indicated a potency of about 700μg BaP/gm. Since the added BaP amounted to 4.13% by weight of the air sample used, it should have contributed 41,300μg BaP/gm of the air sample to the mixture. The estimated content of 63,000μg BaP/gm air sample for the mixture compares then with a total of about 42,000μg BaP/gm based on the separate components.

need for identification of these carcinogens. Further evaluation of this concept requires correlated photodynamic and carcinogenic bioassays on large numbers of crude benzene extracts and oxygenated fractions and chemically defined aromatic fractions.

A possible limitation, at this stage, to such correlated bioassays is the variation in the results of the present investigation. For example, Table 1 shows rather wide ranges of relative activities for the fractions assayed on different occasions. In addition, Table 4 shows, in two instances, BaP recovery percentages of 150, or more. In the absence of variation, such recoveries might have suggested enhanced activities. Excess variation has been previously noted between individual assays of BaP, despite the high uniformity of results at a single occasion of assay.[8] This variation was largely attributed to a particle size effect. The use of BaP solutions, rather than suspensions, not only simplifies assay procedures, but also reduces variation between successive assays.[14]

The between-assay variation noted in no way invalidates the principal conclusions of this investigation. Differences between the various fractions would still be as found, and, in addition, the use of replicate assays has minimized the effect of such variation. It is a merit of the photodynamic bioassay that its simplicity and short duration have made possible the detection of its deficiencies, thus facilitating requisite improvement. Corresponding deficiencies in an assay of prolonged duration might, of necessity, pass undetected.

Summary

Fifteen fractions of organic atmospheric particulates from several American cities were bioassayed for photodynamic activity, and results obtained were expressed as ap-

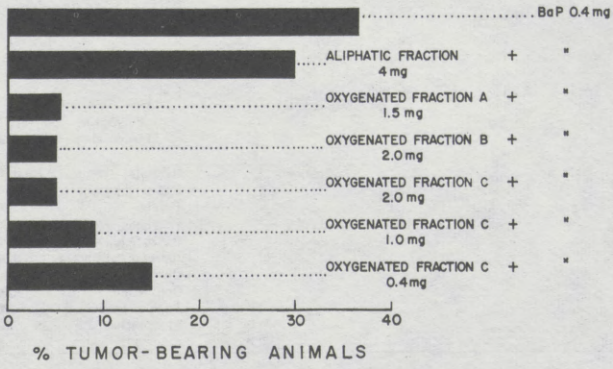

Fig 2. — Anticarcinogenesis by fractions of atmospheric pollutants. C_{57} BL mice were injected subcutaneously with benzo[a]pyrene (BaP) in ethyl laurate or with BaP mixed with pollutant fractions. Animals were observed for 17 months. This figure is based on material reported by Falk and Kotin.[12]

parent potencies relative to an arbitrary benzo[*a*]pyrene standard.

All six crude benzene extracts assayed showed photodynamic activity, with a correlation evident between apparent relative potencies as determined by bioassay, and benzo[*a*]pyrene concentrations as determined by chemical analysis. Five aliphatic fractions were photodynamically inactive. The single aromatic fraction tested had high activity. Three oxygenated fractions showed photodynamic activity, despite the absence from them of benzo[*a*]pyrene and other polycyclic hydrocarbons of known structure commonly found in atmospheric particulates. Such oxygenated fractions are reportedly carcinogenic.

In recovery experiments, the constituents of neither crude benzene extracts nor oxygenated fractions interfered with the activity of added benzo[*a*]pyrene. Photodynamic bioassay of nine other polycyclic hydrocarbons commonly found in atmospheric particulates showed that their activities and/or atmospheric concentrations, generally, were so limited as not to contribute materially to the potencies of the air samples.

This pilot study suggests that photodynamic bioassay may provide a rapid, simple, and economical biological index of potential carcinogenic hazard attributable to polycyclic hydrocarbons. The utility of the assay for this purpose should be further evaluated.

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APPENDIX II—2

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On the Association between Photodynamic and Carcinogenic Activities in Polycyclic Compounds*

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SUMMARY

The photodynamic activities of 157 polycyclic compounds of wide structural range were determined, with the use of *Paramecium caudatum*. High photodynamic activity was largely confined to polycyclic compounds, either homocyclic or heterocyclic, with four or five fused rings. Significant absorption of light was shown to be prerequisite but not sufficient for high photodynamic activity. A significant statistical association between photodynamic activity and carcinogenicity was demonstrated. It was shown that compounds with high photodynamic activity had 4 times greater odds of being carcinogenic than compounds with low activity. However, the photodynamic assay cannot identify a particular polycyclic compound as being carcinogenic or noncarcinogenic.

In the phenomenon known as photodynamic action, a combination of light energy and chemical sensitizer produces effects induced by neither component alone (1, 4, 9, 10, 17). The photodynamic activity of polycyclic compounds in general, and of some polycyclic carcinogens in particular, against a variety of *in vitro* and *in vivo* systems is well established (6, 7, 10, 14, 16). On the basis of studies on restricted numbers of selected compounds, claims have been made that high correlation exists between photodynamic activity and carcinogenicity (2, 6, 14, 16, 18). It is the object of this paper to report on the photodynamic activity of a large number of polycyclic compounds, with the use of *Paramecium caudatum*, some characteristics of such activity, its relationship with carcinogenicity, and its evaluation as a short-term test for carcinogenicity.

MATERIALS AND METHODS

Polycyclic compounds.—One hundred and fifty-seven polycyclic compounds of wide structural range were obtained from a variety of sources (Table 1). The majority of these compounds were synthesized by private investigators and were received in a state of high purity. The remainder were of commercial origin and were tested as received. These compounds are grouped according to their grade of carcinogenicity: +++ carcinogens, ++ carcinogens, + carcinogens, and noncarcinogens. These gradings are a composite of surveys of the literature and the experience of the authors. The final and fifth group consists of compounds of untested carcinogenicity. Within each of these groups both homocyclic and heterocyclic compounds are arranged on the basis of their number of rings from tricyclic to octacyclic. Molecular weights are also shown.

Preparation of compounds for test.—Stock solutions in acetone, in general at 100 μg/ml, were stored in the dark at 4° C. Aqueous suspensions were freshly prepared prior to test by evacuating acetone under reduced pressure from mixtures of water and compounds in solution. By serial dilution, suspensions of 10, 1, 0.1, and 0.01 μg/ml were prepared for photodynamic assay.

Photodynamic assay.—Cloned cultures of *Paramecium caudatum* were maintained axenically in the dark at 28° C. in a semisynthetic medium (10). Suspensions of approximately 30 cells, of 8–12 days' culture age, in medium diluted with distilled water, were mixed on glass depression slide wells, 18 mm. in diameter and 0.75 mm. in depth, with aliquots of aqueous compound suspensions and of water. After a minimum of 2½ hours' incubation in dark moist chambers at 28° C. the slides were irradiated with long-wave ultraviolet light and observed directly with a binocular stereoscopic microscope at 10 × under conditions of fixed geometry. The source of irradiation was a 100-watt high-pressure mercury vapor lamp, producing a 6.5° beam of 8,750 μwatts/sq cm at 18 inches, filtered to transmit light from 310 to 400 mμ, and with a peak at 366 mμ (Chart 1). Fluctuations in lamp intensity were

* Data on which this paper is based in part were presented at the VIIIth International Cancer Congress, July 22–28, 1962, at Moscow, U.S.S.R., and at the 47th Annual Meeting of the Federation of American Societies for Experimental Biology, April 16–20, 1963, Atlantic City, New Jersey.

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TABLE 1

RESULTS OF PHOTODYNAMIC ASSAY

The 157 compounds tested are classified by grade of carcinogenic activity, and data on total relative absorption of light from the experimental irradiation system are also given

COMPOUND AND SOURCE*	No. RINGS†	MOLECULAR WEIGHT	TOTAL RELATIVE ABSORPTION	MEDIAN 90% LETHAL TIME (LT_{90}) IN MIN. AT 4 CONCS. (μG/ML)				RECIPROCAL OF CONCS. PRODUCING LT_{90} OF 30 MIN. ($1/C_{30}$)
				10	1	0.1	0.01	
+++ Carcinogens:								
1. 7-Methylbenz[*a*]anthracene[1]	4	242.3	405	3	6	27	>60	12.50
2. 12-Methylbenz[*a*]anthracene[1]	4	242.3	465	0.5	5	24	>60	14.29
3. 7,12-Dimethylbenz[*a*]anthracene	4	256.4	354	0.8	3.8	54	>60	5.88
4. 6-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	389	1	3	21	>60	16.67
5. 5,6-Dimethylbenz[*c*]acridine[2]	4^N	257.3	451	6	9	42	>60	6.25
6. 7,9-Dimethylbenz[*c*]acridine[2]	4^N	257.3	429	1	2.5	13	58	50.00
7. 7,10-Dimethylbenz[*c*]acridine	4^N	257.3	399	5	8.5	47	>60	5.56
8. Benzo[*a*]pyrene	5	252.3	844	0.5	1	3.5	18	>100.00
9. 6-Methylbenzo[*a*]pyrene	5	266.4	768	8	12	32	55	8.33
10. 3-Methylcholanthrene	5	268.4	255	4	8	42	>60	6.25
11. Dibenz[*a*,*h*]anthracene[4]	5	278.3	435	42	>60	>60	>60	<0.10
12. 4,9-Dimethyl-2,3,5,6-dibenzothiophanthrene[5]	5^S	312.4	628	8	20	>60	>60	1.79
13. 4,9-Dimethyl-2,3,7,8-dibenzothiophanthrene[5]	5^S	312.4	325	9	17	>60	>60	2.08
14. 6,12-Dimethylbenzo[1,2-*b*:4,5-*b*′]bis[1]benzothiophene[5]	5^{SS}	318.5	373	26	>60	>60	>60	0.13
15. 6,12-Dimethylbenzo[1,2-*b*:5,4-*b*′]bis[1]benzothiophene[5]	5^{SS}	318.5	336	26	>60	>60	>60	0.13
16. 5,6-Benzopyrido[2′,3′:1,2]carbazole[3]	5^{NN}	268.3	519	31	57	>60	>60	<0.10
17. 5,6-Benzopyrido[3′,2′:1,2]carbazole[3]	5^{NN}	268.3	366	42	>60	>60	>60	<0.10
18. 3,4,8,9-Dibenzpyrene[6]	6	302.4	170	>60	>60	>60	>60	<0.10
19. 3,4,9,10-Dibenzpyrene	6	302.4	769	24	48	>60	>60	0.20
++ Carcinogens:								
20. Benzo[*c*]phenanthrene[1]	4	228.3	53	11	>60	>60	>60	0.29
21. 5-Methylbenzo[*c*]phenanthrene[1]	4	242.3	166	15	>60	>60	>60	0.23
22. 6-Methylbenzo[*c*]phenanthrene[1]	4	242.3	136	15	>60	>60	>60	0.23
23. 5-Methylbenz[*a*]anthracene[1]	4	242.3	307	5.8	6.5	13	63	52.6
24. 8-Methylbenz[*a*]anthracene[1]	4	242.3	554	1	1.8	5.5	28	>100.00
25. 3-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	450	1.3	3	13	69	31.25
26. 9-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	364	2	3	31	>60	9.80
27. 10-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	315	0.8	2	15	70	27.78
28. 6,11-Dimethylbenzo[*b*]naphtho[2,3-*d*]thiophene[5]	4^S	262.4	700	2	3.8	16	61	27.78
29. Benzo[*c*]fluoranthene	5	252.3	453	6.5	8.3	50	>60	5.26
30. Dibenz[*a*,*h*]acridine[2]	5^N	279.4	708	24	54	>60	>60	0.18
31. 1,2,3,4-Dibenzpyrene	6	302.4	209	48	>60	>60	>60	<0.10
32. 1,2,4,5-Dibenzpyrene	6	302.4	586	41	>60	>60	>60	<0.10
33. 1,2,4,5,8,9-Tribenzpyrene	7	352.4	889	64	>60	>60	>60	<0.10
34. Naphtho[2′,1′-*a*]perylene[7]	7	352.4	830	32	>60	>60	>60	<0.10
+ Carcinogens:								
35. 2-Aminoanthracene	3	193.2	339	>60	>60	>60	>60	<0.10
36. 2-Methylbenzo[*c*]phenanthrene[1]	4	242.3	71	8	55	>60	>60	0.48
37. 3-Methylbenzo[*c*]phenanthrene[1]	4	242.3	100	11	41	>60	>60	0.56
38. Chrysene	4	228.3	115	37	>60	>60	>60	<0.10
39. Benzanthrone[8]	4	230.3	437	3.5	11	48	>60	4.76
40. Benz[*a*]anthracene	4	228.3	462	1.8	2.5	13	58	35.71
41. 6-Methylbenz[*a*]anthracene[1]	4	242.3	362	1	2	13	>60	25.64
42. 7-Aminobenz[*a*]anthracene[8]	4	243.3	169	9.5	23	56	>60	2.00
43. 9-Methylbenz[*a*]anthracene[1]	4	242.3	389	0.8	2	5	37	76.92
44. 10-Methylbenz[*a*]anthracene[1]	4	242.3	409	7	9	15	64	31.25
45. 12-[2′-pyridyl]benz[*a*]anthracene[7]	4	305.4	316	2.3	14	58	>60	3.33
46. Benzo[*a*]carbazole	4^N	217.3	102	28	51	>60	>60	0.13
47. 7-Chloro-5,6-dimethylbenz[*c*]acridine[2]	4^N	291.8	306	3.5	7.5	19	>60	18.52
48. 9-Chloro-5,6-dimethylbenz[*c*]acridine[2]	4^N	291.8	475	20	33	56	>60	0.56
49. 10-Chloro-5,6-dimethylbenz[*c*]acridine[2]	4^N	291.8	339	13	18	58	>60	2.70
50. 11-Chloro-5,6-dimethylbenz[*c*]acridine[2]	4^N	291.8	313	15	38	>60	>60	0.56
51. Dibenz[*a*,*j*]anthracene	5	378.3	328	41	>60	>60	>60	<0.10

TABLE 1—CONTINUED

COMPOUND AND SOURCE*	No. RINGS†	MOLECULAR WEIGHT	TOTAL RELATIVE ABSORPTION	MEDIAN 90% LETHAL TIME (LT_{90}) IN MIN. AT 4 CONCS. (μG/ML)				RECIPROCAL OF CONCS. PRODUCING LT_{90} OF 30 MIN. (1/Cm)
				10	1	0.1	0.01	
Noncarcinogens:								
52. Phenanthrene	3	178.2	14	>60	>60	>60	>60	<0.10
53. 3-Methylphenanthrene	3	192.3	24	58	>60	>60	>60	<0.10
54. 9,10-Quinonephenanthrene[9]	3	208.2	176	Toxic		>60	>60	<0.10
55. 9,10-Dihydrophenanthrene	3	180.2	46	54	>60	>60	>60	<0.10
56. Anthracene	3	178.2	455	11	>60	>60	>60	0.29
57. 1-Amino-6-chloro-9,10-quinoneanthracene	3	257.7	118	>60	>60	>60	>60	<0.10
58. 2-Sulfonylchloride-9,10-quinoneanthracene[10]	3	306.7	84	>60	>60	>60	>60	<0.10
59. 9,10-Dihydroanthracene	3	180.2	0	57	>60	>60	>60	<0.10
60. Fluorene	3	166.2	2	>60	>60	>60	>60	<0.10
61. Carbazole	3^N	167.2	42	>60	>60	>60	>60	<0.10
62. Acridine	3^N	179.2	438	15	>60	>60	>60	0.23
63. Pyrene	4	202.2	367	15	>60	>60	>60	0.23
64. 1-Methylpyrene	4	216.3	1036	7.5	42	>60	>60	0.63
65. 3-Methylpyrene	4	216.3	1032	7	35	>60	>60	0.77
66. 4-Methylpyrene	4	216.3	1056	10	>60	>60	>60	0.30
67. 6-Aminochrysene[8]	4	243.3	407	4.5	6.5	33	>60	9.09
68. Fluoranthene	4	202.2	415	14	>60	>60	>60	0.24
69. Benzo[*a*]fluorene	4	216.3	84	>60	>60	>60	>60	<0.10
70. Benzo[*b*]fluorene	4	216.3	121	>60	>60	>60	>60	<0.10
71. Benzo[*c*]fluorene	4	216.3	208	>60	>60	>60	>60	<0.10
72. Triphenylene	4	228.3	12	>60	>60	>60	>60	<0.10
73. Naphthacene	4	228.3	126	11	24	>60	>60	1.41
74. 1-Methylbenz[*a*]anthracene[1]	4	242.3	554	2.8	4.3	14	>60	23.81
75. 2-Methylbenz[*a*]anthracene[1]	4	242.3	259	7	8	22	>60	15.87
76. 3-Methylbenz[*a*]anthracene[1]	4	242.3	519	1	1	3.5	33	90.91
77. 4-Methylbenz[*a*]anthracene[1]	4	242.3	423	4.5	3.8	6.5	24	>100.00
78. 7-[1′-Naphthyl]benz[*a*]anthracene[7]	4	354.4	303	38	>60	>60	>60	<0.10
79. 7-[2′,4′-Dimethylphenyl]benz[*a*]anthracene[7]	4	332.4	378	30	60	>60	>60	0.10
80. 7-[4′-Dimethylaminophenyl]benz[*a*]anthracene[7]	4	347.4	498	35	62	>60	>60	<0.10
81. 7-[4′-Carbomethoxy]benz[*a*]anthracene[7]	4	362.4	621	20	60	>60	>60	0.24
82. 7-[4′-Hydroxyphenyl]benz[*a*]anthracene[7]	4	320.4	571	Toxic	30	>60	>60	>1.00
83. 8-[1′-Naphthyl]benz[*a*]anthracene[7]	4	354.4	341	59	>60	>60	>60	<0.10
84. 12-[3′-Pyridyl]benz[*a*]anthracene[7]	4	305.4	392	3.8	14	>60	>60	2.38
85. 12-[4′-Pyridyl]benz[*a*]anthracene[7]	4	305.4	415	>60	>60	>60	>60	<0.10
86. 12-[2′,3′-Dimethylphenyl]benz[*a*]anthracene[7]	4	332.4	515	24	64	>60	>60	0.18
87. 12-[3′-Methylphenyl]benz[*a*]anthracene[7]	4	318.4	734	20	36	>60	>60	0.50
88. 12-[4′-Methylphenyl]benz[*a*]anthracene[7]	4	318.4	352	21	53	>60	>60	0.24
89. 7,12-Dionebenz[*a*]anthracene[11]	4	258.3	229	6.5	7.8	13	>60	25.00
90. 4-Chloro-7-bromobenz[*a*]anthracene[12]	4	341.6	465	4.5	6	28	53	15.38
91. 5-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	404	1	2	12	74	32.26
92. Benzo[*b*]diphenyleneoxide	4^O	218.3	208	>60	>60	>60	>60	<0.10
93. 5H-Benzo[*b*]carbazole[8]	4^N	217.3	261	60	>60	>60	>60	<0.10
94. 12-Methylbenz[*a*]acridine[3]	4^N	243.3	351	1	5.5	33	>60	8.33
95. 6,6-Dimethyl-6,11-dihydrobenz[*b*]acridine[2]	4^N	258.3	20	34	>60	>60	>60	<0.10
96. 6,6-Dimethyl-11-keto-6,11-dihydrobenz[*b*]-acridine[2]	4^N	273.3	197	19	42	>60	>60	0.38
97. 6,6-Dimethyl-12-carboxy-6,11-dihydrobenz[*b*]-acridine[2]	4^N	303.4	41	>60	>60	>60	>60	<0.10
98. 6,6,11-Trimethyl-11-hydroxy-6,11-dihydrobenz-[*b*]acridine[2]	4^N	289.4	34	>60	>60	>60	>60	<0.10
99. Benz[*c*]acridine[2]	4^N	229.3	522	1.3	4.5	24	>60	14.71
100. 7-Acetoxy-5,6-dimethylbenz[*c*]acridine[2]	4^N	315.4	348	66	>60	>60	>60	<0.10
101. 5,6-Dimethylbenz[*c*]acridone[2]	4^N	272	229	56	>60	>60	>60	<0.10
102. Benzo[*e*]pyrene	5	252.3	256	14	24	49	>60	2.08
103. Dibenz[*a,c*]anthracene[4]	5	278.3	133	57	>60	>60	>60	<0.10
104. Benzo[*k*]fluoranthene	5	262.3	675	20	38	>60	>60	0.45
105. Benzo[*ghi*]fluoranthene	5	226.3	464	5	18	>60	>60	2.00
106. Benzo[*a*]chrysene	5	278.3	175	>60	>60	>60	>60	<0.10
107. Benzo[*b*]chrysene	5	278.3	670	42	63	>60	>60	<0.10
108. Perylene	5	252.3	235	58	>60	>60	>60	<0.10
109. Dibenz[*a,j*]acridine	5^N	279.4	448	29	>60	>60	>60	0.11

TABLE 1—CONTINUED

Compound and source*	No. rings†	Molecular weight	Total relative absorption	Median 90% lethal time (LT_{90}) in min. at 4 concs. (μg/ml)				Reciprocal of concs. producing LT_{90} of 30 min. ($1/C_{30}$)
				10	1	0.1	0.01	
110. Quinolino[3,4-*b*]1H-benz[*g*]indole[3]	5^{NN}	268.3	251	0.5	2.8	12	69	33.33
111. 1,2,6,7-Dibenzpyrene[6]	6	302.4	124	>60	>60	>60	>60	<0.10
112. Benzo[*ghi*]perylene	6	276.3	637	4.8	9	15	34	55.56
113. Anthanthrene	6	276.3	348	29	53	>60	>60	0.11
114. Anthanthrone[8]	6	306.3	253	22	>60	>60	>60	0.16
115. Coronene	7	300.4	383	19	51	>60	>60	0.29
116. 7,16-Quinonedibenzo[*a,o*]perylene[8]	7	382.4	108	24	>60	>60	>60	0.14
117. 1,2,8,9-Dibenzpentacene	7	378.5	321	17	>60	>60	>60	0.22
118. Pyranthrene	8	376.5	367	24	>60	>60	>60	0.15
Untested carcinogenicity:								
119. 7-Ethyl-2-aminofluorene[8]	3	209.0	193	>60	>60	>60	>60	<0.10
120. 1,10-Phenanthroline	3^{NN}	180.2	13	>60	>60	>60	>60	<0.10
121. 1-Methylbenzo[*c*]phenanthrene[1]	4	242.3	94	11	>60	>60	>60	0.29
122. 1-Aminopyrene[8]	4	217.2	873	1.8	8	23	>60	15.38
123. 4-Aminofluoranthene[8]	4	217.2	374	5	10	39	>60	6.25
124. Naphthacenequinone[6]	4	256.3	166	32	44	56	>60	<0.10
125. 1,2-Quinoneaceanthrene[8]	4	232.2	244	>60	>60	>60	>60	<0.10
126. 4-Heptadecanoylbenz[*a*]anthracene[12]	4	480.4	462	>60	>60	>60	>60	<0.10
127. 5-Cyanobenz[*a*]anthracene[12]	4	253.3	639	4.3	11	56	>60	4.17
128. 7-Octadecanoylbenz[*a*]anthracene[12]	4	494.7	172	25	43	>60	>60	0.23
129. 9-Octadecanoylbenz[*a*]anthracene[12]	4	494.7	203	>60	>60	>60	>60	<0.10
130. 9-Octadecanoylbenz[*a*]anthraceneoxime[12]	4	509.7	204	>60	>60	>60	>60	<0.10
131. 10-Octadecanoylbenz[*a*]anthracene[12]	4	494.7	279	>60	>60	>60	>60	<0.10
132. 6,8-Dimethylbenz[*a*]anthracene[1]	4	256.4	372	1.5	3.5	24.5	>60	14.29
133. 1-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	382	0.75	2	22	>60	16.67
134. 2-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	385	0.75	3	11	65	33.33
135. 4-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	305	4	4	13	72	33.33
136. 11-Fluoro-7-methylbenz[*a*]anthracene[1]	4	260.3	377	0.5	0.75	13	67	33.33
137. Thionaphtheno[2,3-*b*]thionaphthene[5]	4^{SS}	240.4	18	37	>60	>60	>60	<0.10
138. Thionaphtheno[3,2-*b*]thionaphthene[5]	4^{SS}	240.4	151	52	>60	>60	>60	<0.10
139. 1,4-Dimethylbenz[*c*]acridine[2]	4^{N}	257.3	676	27	54	>60	>60	0.14
140. 7-Phenoxy-5,6-dimethylbenz[*c*]acridine[2]	4^{N}	340.4	277	12.5	41	>60	>60	0.56
141. 7-Morpholino-5,6-dimethylbenz[*c*]acridine[2]	4^{N}	342.4	563	4.5	16	78	>60	2.50
142. 11H-Indeno[1,2-*b*]quinoxaline[2]	4^{NN}	218.3	619	1.5	5	24	>60	14.29
143. 11-Hydroxy-11-methyl-11H-indeno[1,2-*b*]-quinoxaline[2]	4^{NN}	248.3	1099	5.5	20	62	>60	2.27
144. 11-One-11H-indeno[1,2-*b*]quinoxaline[2]	4^{NN}	232.2	478	9.5	16	>60	>60	2.22
145. 5-Oxide-11-one-11H-indeno[1,2-*b*]quinoxaline[2]	4^{NN}	248.2	324	12	16	>60	>60	2.22
146. 5,10-Di-N-oxide-11-hydroxy-11-methyl-11H-indeno[1,2-*b*]quinoxaline[2]	4^{NN}	280.3	415	40	>60	>60	>60	<0.10
147. 5-11-Dihydroquinoxalino[2,3-*b*]quinoxaline[8]	4^{NNN}	234.1	79	>60	>60	>60	>60	<0.10
148. 6-Aminobenzo[*a*]pyrene[8]	5	267.3	312	10	19	>60	>60	1.85
149. Benz[*e*]acephenanthrylene-9,12-quinone[8]	5	282.3	268	19	59	>60	>60	0.24
150. 2,3,5,6-Dibenzothiophanthrene[5]	5^{S}	284.4	241	2.5	5.3	26	>60	12.50
151. 2,3,7,8-Dibenzothiophanthrene[5]	5^{S}	284.4	14	23	>60	>60	>60	0.15
152. Dibenz[*a,c*]acridine[2]	5^{N}	279.4	576	24	56	>60	>60	0.19
153. 1,2,3,4-Tetrahydrodibenz[*a,c*]acridine[2]	5^{N}	283.4	590	16	26	>60	>60	1.33
154. 7,14-Dihydrodibenz[*a,j*]acridine[13]	5^{N}	281.4	898	27	>60	>60	>60	0.12
155. 11,12-Dimethyldibenzo[*a,c*]phenazine	5^{NN}	308.2	436	34	>60	>60	>60	<0.10
156. 11,16-Quinonenaphtho[2,3-*g*]chrysene[8]	6	358.4	405	>60	>60	>60	>60	<0.10
157. 7,12-Quinonenaphtho[2,1,8-*qra*]naphthacene[8]	6	332.2	857	58	>60	>60	>60	<0.10

* Source: [1]Dr. M. S. Newman, The Ohio State University, Columbus, 10, Ohio; [2]Dr. N. H. Cromwell, The University of Nebraska, Lincoln, 8, Nebraska; [3]Dr. N. P. Buu-Hoï, Institut du Radium, Paris (Ve) France; [4]Dr. C. Heidelberger, McArdle Memorial Laboratory, The University of Wisconsin, Madison, 6, Wisconsin; [5]Dr. B. D. Tilak, University of Bombay, Bombay, 19, India; [6]Dr. G. S. Fell, Royal Beatson Memorial Hospital, Glasgow, Scotland; [7]Dr. F. A. Vingiello, Virginia Polytechnic Institute, Blacksburg, Virginia; [8]Dr. E. Sawicki, Robert A. Taft Sanitary Engineering Center, Cincinnati, 26, Ohio; [9]Dr. C. J. Kensler, Arthur D. Little, Inc., 30 Memorial Drive, Cambridge, Massachusetts; [10]Dr. T. S. Oakwood, Pennsylvania State University, University Park, Pennsylvania; [11]Dr. E. Moriconi, Fordham University, New York, 58, N. Y.; [12]Dr. M. C. Kloetzel, University of Southern California, Los Angeles, 7, California; [13]Dr. B. L. Van Duren, Institute of Industrial Medicine, New York University Medical Center, New York, N. Y.: to all of whom grateful acknowledgements are made.

† Superscript indicates the nature of heterocyclic compounds—e.g., 4^{SS} is tetracyclic with two ring sulfur atoms. Homocyclic compounds are not annotated.

minimized with a voltage stabilizer and monitored by a selenium photocell and microammeter.

For each compound the duration of irradiation in minutes required to produce lethality, as indicated by immobilization, of 90 per cent of the motile ciliates (LT_{90}), was determined at each of the four test concentrations, with a general arbitrary observation limit of 60 minutes. Most compounds were tested five times, and with fresh stock solutions on at least two occasions. Up to ten compounds were tested at each assay. The sensitivity of each assay was controlled by reference to benzo[*a*]pyrene, an arbitrarily selected and highly active photodynamic standard (12).

Spectral measurements.—Aliquots of stock solutions were dried and stored under nitrogen. Each compound was dissolved at 10 or 1 μg/ml in benzene. Absorption spectra were determined with a Beckman DK-2A ratio recording spectrophotometer from 280 to 440 mμ, and fluorescence spectra with a modified DU spectrophotometer with excitation at 365 mμ and also with the Aminco-Keirs spectrophosphorimeter.

The term *total relative absorption* is used to designate the approximate amount of light which each compound can absorb from the experimental irradiation system. For this purpose, the absorption spectrum was divided into three segments: 320–340, 340–380, and 380–400 mμ. The average light energy outputs in these three segments, derived from the manufacturer's specifications (Chart 1), were approximately in the ratio of 4:12:3. For each compound these three numbers were applied as factors to the planimetrically determined areas of each segment of the absorption spectrum. Thus, the total relative absorption for a compound was taken as 4 (area in 320- to 340-mμ segment) + 12 (area in 340- to 380-mμ segment) + 3 (area in 380- to 400-mμ segment). The proportional relation between absorption area and concentration is indicated in Chart 2, where it can be seen that a tenfold increase in benzo[*a*]pyrene concentration resulted in a tenfold area increase. Total relative absorption values were thus properly also expressed on a molar basis.

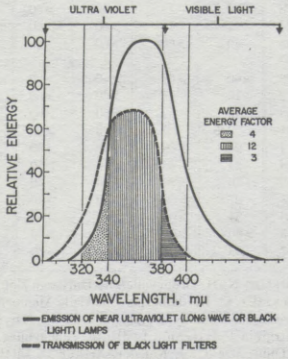

CHART 1.—Emission characteristics of the experimental irradiation system. (Manufacturers specifications. Black Light Eastern, Westbury, Long Island, N.Y.)

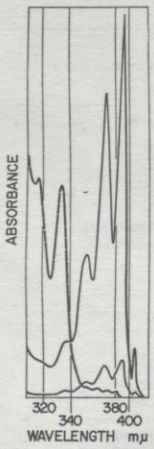

CHART 2.—Method for measurement of *total relative absorption*.

MEASUREMENT OF TOTAL RELATIVE ABSORPTION

		PLANIMETRIC AREA (SQ. CM.) OF ABSORPTION SEGMENTS (Mμ)			TOTAL RELATIVE ABSORPTION
	μg/ml	320–340	340–380	380–400	
Benzo[*a*]chrysene	10	29.2(×4)	4.8(×12)	0.1(×3)	174.7
Benzo[*a*]prene	10	10.0(×4)	60.2(×12)	27.1(×3)	843.7
Benzo[*a*]pyrene	1	1.0(×4)	6.2(×12)	2.7(×3)	86.5

* Factor for average light energy output in parentheses.

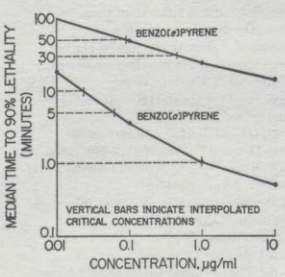

CHART 3.—Illustration of photodynamic assay results and method of interpolation for concentrations yielding specified times to 90 per cent lethality (LT_{90}). For purposes of extrapolation, an arbitrary value of 100 minutes was assigned when the LT_{90} exceeded the observational limit of 60 minutes (e.g., benzo[*e*]pyrene at 0.01 μg/ml).

RESULTS

Experimental data for each compound are the median times producing 90 per cent lethality (LT_{90}) at the four test concentrations, and values for total relative absorp-

tion (Table 1). Because the nonparallelism in dose-response relationships precluded over-all quantitative comparisons, photodynamic activities were also expressed in concentrations yielding LT_{90} values at selected time intervals. These concentrations were derived by interpolation and occasionally extrapolation, and their reciprocals were considered as measures of photodynamic potency (Chart 3). Table 1 lists reciprocals of concentrations, $\mu g/ml$, yielding LT_{90} values at 30 minutes ($1/C_{30}$).

With the exception of benzo[*ghi*]perylene, high photodynamic activity (e.g., $1/C_{30} \geqq 2.0$) was restricted to molecules of four or five fused rings (Table 1). Also, high total relative absorption appeared essential, but not sufficient, for high photodynamic activity. Compounds with high absorption might have high or low activity, but, where absorption was low, photodynamic activity was, perforce, low. Photodynamic activity was not determined by the precise location of absorption peaks (Chart 4), although this neglects the possibility of intracellular spectral shifts (1, 3). To compensate for absorption differences, $1/C_{30}$ values were divided by total relative absorptions to yield absorption-adjusted activities. Although these adjusted activities are not given, they were used to make analyses of associations between photodynamic and carcinogenic activities. High photodynamic activity was observed with nonfluorescent compounds (e.g., Nos. 89, 144, Table 1).

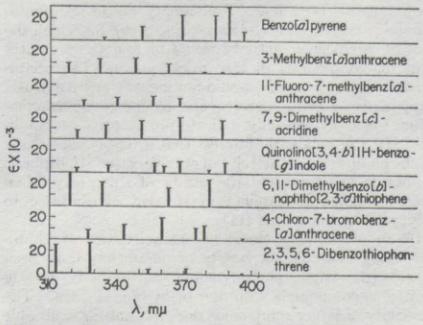

CHART 4.—Absorption spectra of eight polycyclic compounds with high photodynamic activity.

Excluding compounds of untested carcinogenicity, photodynamic and carcinogenic activities were collated in a variety of ways. Each panel of Chart 5 represents a different grade of carcinogenicity and shows photodynamic activity, plotted against total relative absorption. Although there was wide variation, carcinogens, generally, had greater photodynamic activity. Most noncarcinogens fell in the minimal photodynamic category, with a scaling down of the frequency at higher levels of activity (Chart 6). Among the carcinogens (though the proportion of photodynamically inactive compounds is also large, generally comprised of polycyclics with more than five fused rings) the relative frequency was markedly increased at high levels of activity. Additional analyses were made with data derived from Table 1, with LT_{90}

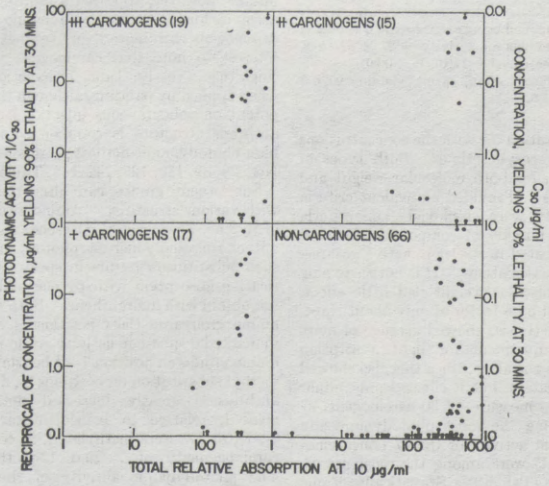

CHART 5.—Photodynamic activity of carcinogens by grade of carcinogenicity and noncarcinogens. Photodynamic activity for each compound is plotted against its absorption to permit adjusting for such absorption in making comparisons. Arrows are used to indicate instances where activity was not within the limits tested.

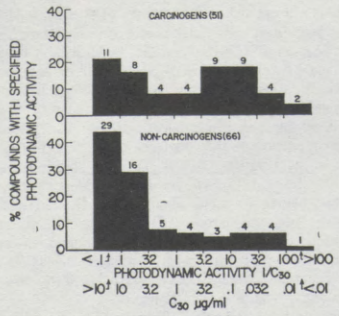

CHART 6.—Percentage distribution of carcinogenic and noncarcinogenic compounds by degree of photodynamic activity. Figures above the rectangles represent the number of compounds falling within the specified range of activity.

TABLE 2

ASSOCIATION OF CARCINOGENIC AND PHOTODYNAMIC ACTIVITIES

	PHOTODYNAMIC ACTIVITY (1/C30)		
	Strong*	Weak	Totals
Carcinogens	27	23	50
Noncarcinogens	15	52	67
Totals:	42	75	117

"Relative odds" of a compound being carcinogenic if it falls in the category of strong photodynamic activity = $27 \times 52/15 \times 23 = 4.07$. Continuity corrected, $\chi^2 = 11.10$, $P < 0.001$.

* $1/C_{30}$ (reciprocal of concentration, µg/ml, yielding 90 per cent lethality at 30 min.) ≥ 2.0.

times at varying concentrations or with the concentrations yielding LT_{90} values at varying times. Both types of results, corrected or not, for both molecular weight and absorption, were analyzed. Provided equivalent criteria of photodynamic activity were employed—i.e., criteria under which a constant number of compounds, for convenience 50, were demarcated in the more active group—all analyses gave similar associations. It is not surprising that adjustments for molecular weight had little effect, since these weights varied by a factor of only about three, whereas photodynamic activities showed a range of more than 1000-fold. The adjustment for light absorption could have changed the association, since this also showed a 1000-fold range of variation, but it effected only minor changes. With the $1/C_{30}$ measure, of 50 carcinogens, 27 (54 per cent) were among the most photodynamically active, 23 among the least active; for the 67 noncarcinogens, fifteen (22 per cent) were among the most active, 52 among the less active (Table 2). Statistically, if one assumes the compounds to be representative random samples of carcinogens and noncarcinogens, this difference is highly significant: $\chi^2 = 11.10$, $P < 0.001$. If a compound is in the higher photodynamic activity group, the estimated relative odds (5) that it is a carcinogen are increased approximately fourfold (Table 2).

DISCUSSION

The present findings suggest a clear but limited relationship between photodynamic and carcinogenic activities of polycyclic compounds, with recognition of discrepancies in grading of the latter (13). Such a relationship may have applications in carcinogen screening, because of the ease and low cost of the photodynamic assay. From a practical standpoint, polycyclic compounds without significant light absorption might logically be excluded from photodynamic screening. Preliminary use of the photodynamic assay would select a *passing group* for which the odds of carcinogenic activity would be four times greater than for compounds in the *failing group*. The photodynamic assay, however, would not identify any particular compounds as being clearly carcinogenic or noncarcinogenic; the assay can only indicate presumptive probabilities. It is of incidental interest that a recent pilot study on the photodynamic activity of crude organic atmospheric pollutants has suggested the utility of this assay as an index of potential carcinogenic hazard attributable to polycyclic hydrocarbons (11).

In an attempt to elucidate characteristics of photosensitizing molecules, a variety of parameters have been considered. High photodynamic activity is largely limited to compounds with four or five fused rings. The inactivity of larger compounds does not appear explicable by insolubility alone, since solubilization yielded no significant increase in their photodynamic activity: cellular uptake, however, appeared a limiting factor and possibly accounts for the weak photodynamic activity of polycyclic carcinogens with more than five rings.[1] It is of incidental interest to note that carcinogens with more than five rings (e.g., No. 19, Table 1) have generally low potency when applied by painting, although they may be extremely potent on subcutaneous injection.[2] Although the phenanthrene structure is common to many compounds of high photodynamic activity, compounds lacking this (e.g., Nos. 28, 39, 110, 123, 142–145, Table 1) are highly active.

Substituent groups can alter the activity associated with various structures. Amino groups on the 1-position of pyrene, 6-position of chrysene, and 4-position of fluoranthene markedly increase photodynamic potency. While such substitution results in spectral shifts and increased relative absorption with pyrene and chrysene, this does not obtain with fluoranthene. Both methyl and especially amino groups on the 6-position of benzo[*a*]pyrene result in marked decrease in activity, as do methyl and especially amino groups on position 7- of benz[*a*]anthracene. Monomethyl substitution on positions 3-, 4-, 8-, or 9- of benz[*a*]anthracene greatly increased activity. Activity decreased, relative to benz[*a*]anthracene when positions 2-, 7-, or 12- were methylated, in contrast to heightened carcinogenicity of 7- and 12-methylbenz[*a*]anthracene. The photodynamic activity of the potent carcinogen, 7,12-dimethylbenz[*a*]anthracene is decreased still further;

[1] S. S. Epstein, I. Bulon, W. Park, and M. Small unpublished data.

[2] N. P. Buu-Hoï, personal communication.

this decrease is not seen with the corresponding 7,12-dione. Large substituents on benz[*a*]anthracene decrease activity. Illustrating this is a comparison of 9-octadecanoylbenz[*a*]anthracene and the 12-pyridylbenz[*a*]-anthracenes, with their corresponding methyl substituents. The gradation in activity from the 2′-, to 3′-, to 4′-pyridyl isomers may reflect differences in bonding capacity of the lone pair of electrons on the nitrogen atom.[3]

Compared with benz[*c*]acridine, there is marked increase in activity with the 7,9-dimethyl and successive decrease with the 5,6-dimethyl, 7,10-dimethyl, and 1,4-dimethyl substituents. The 5,6-dimethyl structure shows activity increased with chlorine in position 7-, decreased with chlorine in position 10-, and decreased further with 9- or 11-chloro substituents. In contrast to the high activity of 7-chloro-5,6-dimethylbenz[*c*]acridine is the successive decrease in activity when the 7-substituent is morpholino, phenoxy, and acetoxy. Among the indenoquinoxalines, the activity of 11-H-indeno[1,2-*b*]quinoxaline is decreased by various substituents (e.g., Nos. 143–146, Table I).

Physicochemical properties considered do not reveal specific characteristics sufficient for high photodynamic activity. The spectroscopic data reported indicate that significant absorption is prerequisite but not sufficient for photodynamic activity. The precise locations of absorption peaks do not appear important. Contrary to accepted views (1, 4), there is no obligate relationship between fluorescence and photodynamic activity. High electron density at K regions is considered important in determining carcinogenicity (15). However, high photodynamic activity was found in linear compounds. A positive association has been found between photodynamic activity and charge transfer complex formation, but (contrary to the established literature) not between the latter and carcinogenicity (8). In view of recent evidence of photo-induced free radical formation from charge transfer complexes (19), this positive association is of further interest in relation to possible mechanisms of photodynamic injury.

That the association observed in this investigation between carcinogenic and photodynamic activities is only statistical does not preclude the possibility of an underlying relationship more fundamental in character. It is unlikely, however, that any of the parameters considered here underlies, by itself, the observed association.

[3] F. A. Vingiello, personal communication.

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APPENDIX II-3

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Photodynamic Bioassay of Polycyclic Atmospheric Pollutants*

A photodynamic bioassay which can be conducted on one mgm amounts of organic atmospheric particulates is described. The results of a pilot study on pollutants from several American cities indicate that the assay may provide a rapid, simple and economical biological index of potential carcinogenic hazard attributable to polycyclic compounds. The utility of the assay for this purpose is under further evaluation.

The mortality from lung cancer in many parts of the world has reached alarming proportions. The existence of close associations between lung cancer, urbanization, and atmospheric pollution is now generally accepted. Although the mode of interaction of the latter factors and smoking is debated, the importance of multiple etiologic factors has become apparent (Figs. 1, 2).[8–12] These considerations emphasize the paramount need for methods which will yield simple and rapid estimates of the potential carcinogenic hazard of polluted atmospheres. Such information could possibly then serve as a basis for action designed to reverse lung cancer mortality trends.

The carcinogenicity of atmospheric particulates is, at present, generally determined by the mouse-skin test. This is the most practicable and least indirect method generally available. However, its routine application is limited by a variety of factors. These include the lengthy duration of the test which thus provides *post hoc* data, the large quantities of materials required, and the sensitivity of this test system to undefined anti-carcinogens in extracts of organic pollutants (Fig. 3). Carcinogenic bioassays in mice of pollutant fractions, separated by standard procedures (Fig. 4), have demonstrated greater potency in crude benzene extracts, aromatic and oxygenated fractions, and lesser potency in aliphatic fractions.[8] The lack of correlation in these fractions between carcinogenic potency and concentrations of benzo-[*a*]-pyrene (BaP), the most potent known atmospheric carcinogen, was also emphasized. Illustrating this was the higher carcinogenicity of the BaP-free oxygenated fractions (Fig. 4), rather than the aromatic, clearly indicating the presence of potent but as yet undefined polycyclic carcinogens in the former. This lack of correlation also restricts the utility of spectrophotometric methods for quantitating known polycyclic hydrocarbons, particularly BaP, in polluted atmospheres as an index of presumptive carcinogenic hazard.

In view of these considerations, it was decided to explore the utility of an alternative assay based on the phenomenon known as photodynamic action. In this phenomenon, a combination of light energy and chemical sensitizer produces effects induced by neither component alone. Photodynamic activity is demonstrated by the immobilization and death of *Paramecium caudatum*, a motile ciliate, when exposed to otherwise harmless long-wave ultraviolet light following incubation with photosensitizing polycyclic compounds in pure state or in crude organic mixtures.[1–6] The time required for immobilization of 90 per cent of the motile ciliates was selected as the end-point, and reflects concentrations of the photosensitizing agents.

In a recent study of 157 polycyclic

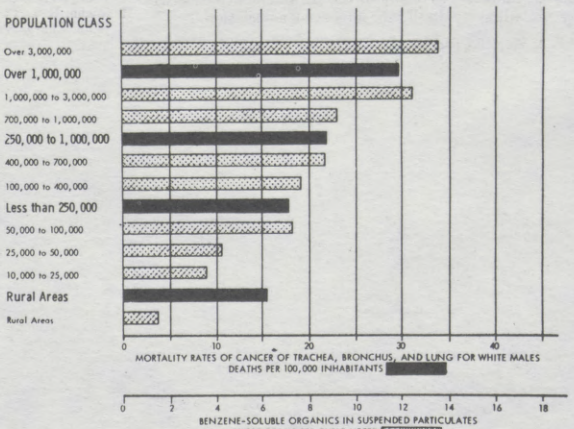

Fig. 1. Relationship between atmospheric pollution, urbanization, and lung cancer rates. (Reproduced by kind permission of U. S. Senate Committee on Public Works[10].)

* This investigation was supported in part by Research Grants No. CY-3335 and No. C-6516 (to The Children's Cancer Research Foundation) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

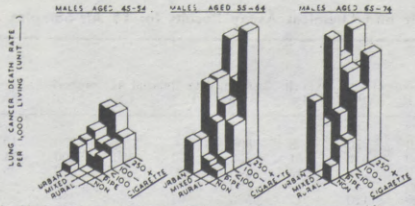

Fig. 2. Relationship between smoking, urbanization, and lung cancer rates. (Reproduced by permission of Sir Percy Stocks and the Editor of the British Medical Journal[11].)

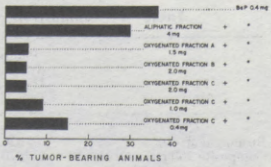

Fig. 3. Anti-carcinogenesis by fractions of atmospheric pollutants $C_{57}BL$ mice were injected subcutaneously with benzo(a)pyrene (BaP) in ethyl laurate or with BaP mixed with pollutant fractions. Animals were observed for 17 months. Based on data reported by Dr. H. Falk and Dr. P. Kotin.[7]

compounds of wide structural range a significant statistical association has been demonstrated between photodynamic and carcinogenic activities.[5–6] It was shown that compounds with high photodynamic activity had four times greater odds of being carcinogenic than compounds with lesser activity. On a more restricted basis, a still higher degree of association obtains between the photodynamic and carcinogenic activities of the major polycyclic hydrocarbons found in polluted atmospheres.[4]

This test procedure was applied in a pilot study to a total of 15 samples of crude benzene extracts and eluted fractions of atmospheric particulates collected from various American cities by the Division of Air Pollution, U. S. Public Health Service.[4] BaP was used as an arbitrary reference standard, since a linear inverse relationship has been demonstrated between concentrations in the sub-microgram range and responses, as measured by immobilization times.[3] Furthermore, BaP is not only the most photodynamically active polycyclic compound tested, but is also the most potent known carcinogen in the atmosphere.

Aqueous suspensions were prepared from benzene solutions of both the air fraction and BaP standard. These were mixed with suspensions of cloned axenic cultures of *P. caudatum* on multiple depression slides and incubated in dark moist chambers for a minimum of two and one-half hours. The slides were subsequently exposed, under conditions of fixed geometry, to long-wave ultraviolet irradiation with a peak of 3660 Å, and the time required to produce 90 percent immobilization of the cells determined by direct observation with a binocular stereoscopic microscope. Numerous replicates of many fractions can be conveniently assayed in a few hours with high precision and satisfactory reproducibility. The results of preliminary assays at 10-fold dilutions of aqueous suspensions of the air samples from 100 to 0.001 μg/ml defined a region in which a definitive assay could be performed. For definitive assays, the activity of five concentrations of BaP at doubling dilutions ranged from 0.32 to 0.02 μg/ml and five concentrations of air samples were compared. In general, two to five samples were assayed simultaneously in duplicate against 4 replicates of each concentration of the standard. Individual samples were assayed on at least four separate occasions.

Response lines fitted to the data for tests and standards were found to be non-parallel, reflecting dissimilarities in the materials tested. Data were compared on the basis of concentrations yielding a 90 percent lethal time at 10 minutes, and results were expressed as apparent potencies relative to the BaP standard. The use of apparent rather than true potencies is appropriate to non-dilution assays, and provides a reproducible index of activity. Assay slopes for air samples are generally low and of the order of one-third to one-half that for the BaP standard. A typical example of air fraction assay data is illustrated in Fig. 5.

The results of photodynamic bioassay and spectrophotometric analysis for 10 major polycyclic constituents, including BaP, were compared (Table I). The data for the six crude benzene extracts tested, showed a general pattern of correlation between apparent relative potencies as determined by photodynamic bioassay and BaP concentrations as determined by chemical analysis. All aliphatic fractions were devoid of both photodynamic activity and BaP. The single aromatic fraction tested had high photodynamic activity. While chemical data for this sample were unavailable, BaP concentrations of aromatic fractions are, in general, five times higher than for the parent crude extracts. Oxygenated fractions demonstrated activity, despite the absence from them of benzo [a] pyrene and other known polycyclics of less than seven rings.

The possibility exists that photodynamic toxicity and carcinogenicity of oxygenated fractions are both attrib-

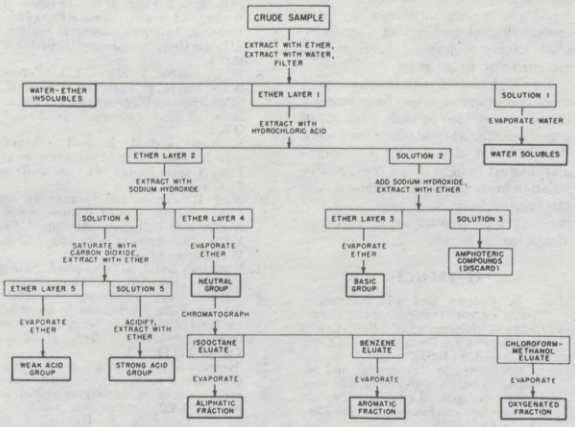

Fig. 4. Procedures for separation and fractionation of crude benzene extracts of particulate atmospheric pollutants. (Reproduced by permission of Dr. E. C. Tabor and the Editor of the A.M.A. Archives of Environmental Health[12].) Aliphatic fractions are polycyclic-free and aromatic fractions contain approximately five times the concentration of Benzo(a)pyrene present in the parent crude benzene extracts. Oxygenated preparations are benzo(a)pyrene-free and largely chemically undefined, containing polar derivatives of polycyclic hydrocarbons with three to seven fused benzene rings and also polycyclics with more than seven rings.

Table I—Comparison of Photodynamic and Chemical Assay Results for 15 Air Samples

Air Sample	Photodynamic Assay, μg BaP/Gm	Chemical Assay Results, μg/Gm. with Related Atmospheric Data: BaP	BeP	Py	Per	B Per	BaA	Ch	Co	An	Fl
CRUDE											
Birmingham; 1958	320	370	410	370	38	590	—	—	200	19	300
Composite 200 cities; 1957–59	670	510	560	550	51	750	350	500	200	14	470
San Francisco; 1958	71	120	270	—	13	940	—	—	620	8	—
Cincinnati; 1958	70	280	160	33	—	300	—	—	110	—	—
Philadelphia; 1958	164	170	220	120	12	560	94	250	130	—	—
Atlanta; 1958	360	140	330	26	20	670	—	—	300	—	—
ALIPHATIC											
San Francisco; 1959	—	—	—	—	—	—	—	—	—	—	—
Nashville; 1958	—	—	—	—	—	—	—	—	—	—	—
San Francisco; 1959	—	—	—	—	—	—	—	—	—	—	—
Nashville; 1958	—	—	—	—	—	—	—	—	—	—	—
Los Angeles; 1959	—	—	—	—	—	—	—	—	—	—	—
AROMATIC											
Detroit; 1958	6500	(Insufficient for analysis)									
OXYGENATED											
Nashville; 1958	5400	—	—	—	—	—	—	—	—	—	—
Los Angeles; 1959	154	—	—	—	—	—	—	—	—	—	—
San Francisco; 1959	260	—	—	—	—	—	—	—	—	—	—

BaP = Benzo(*a*)pyrene Py = Pyrene B Per = Benzo(*ghi*)perylene Ch = Chrysene An = Anthanthrene.
BeP = Benzo(*e*)pyrene Per = Perylene BaA = Benz(*a*)anthracene Co = Coronene Fl = Fluoranthene.

utable to the same or related agents, which may represent as yet unidentified oxygenated products of polycyclic aromatic hydrocarbons. This hypothesis is at present under test and procedures for concentrating high photodynamic activity in oxygenated subfractions have been established.[14]

It is of interest to note that in recovery experiments, it was found that neither the constituents of crude benzene extracts nor of oxygenated fractions interfered with the photodynamic activity of artificially added BaP. Furthermore, photodynamic bioassay of other polycyclic hydrocarbons commonly found in atmospheric particulates showed that their activities, in relation to atmospheric concentrations, generally, were so limited as not to contribute materially to the photodynamic potencies of the air samples.[4]

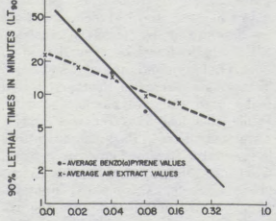

Fig. 5. Photodynamic bioassay of an air sample illustrating a characteristic shallow dose-response line. (Reproduced by permission of the Editor of the A.M.A. Archives of Environmental Health).[4]

The economy, rapidity and simplicity of the photodynamic bioassay, which can be conducted on less than one mgm. amounts of organic extracts, are attractive features. The limited data presented here suggest that the bioassay may provide a biological index of potential carcinogenic hazard attributable to polycyclic compounds. However, evaluation of this concept demands correlated photodynamic carcinogenic and chemical studies on numerous samples and fractions of organic atmospheric pollutants collected from sources exemplifying a wide epidemiological spectrum of respiratory tract cancer incidence. Such studies are currently in progress.

Very high photodynamic activity and steep dose-response slopes have recently been demonstrated in basic fractions of organic particulate pollutants from more than 50 U.S.A. cities. This is of particular interest in light of the presumptive isolation of di-alkylated azaheterocyclic carcinogens from basic fractions,[15] and the very high photodynamic activities of such carcinogens.[5]

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APPENDIX II-4

Two Sensitive Tests for Carcinogens in the Air

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Two Sensitive Tests for Carcinogens in the Air

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Presently, the carcinogenicity of polluted air is determined by repeated skin painting or subcutaneous injection of crude organic extracts of atmospheric particulates in adult mice. In general such techniques are not ideal, inasmuch as large amounts of extracts are required to produce significant yields of local tumors, and these may take one to two years to develop. A photodynamic bioassay for polycyclic atmospheric pollutants, based on the previous demonstration of a positive and significant association between high photodynamic activity and carcinogenicity in a large series of polycyclics, has been developed in an attempt to provide a simple and rapid, but presumptive, indirect index of carcinogenicity attributable to polycyclic compounds. Photodynamic activity, measured with Paramecium caudatum, *was found to vary widely between organic extracts, and even more widely between 6 eluted fractions thereof, from over 100 different sources in the U.S.A. Additionally, the carcinogenicity of organic extracts of atmospheric pollutants has been directly measured with newborn mice, based on the well-known enhanced response of neonates to a variety of defined chemicdl carcinogens. Mice were injected subcutaneously with extracts at doses of 55 mg or less, fractionally administered in the first 21 days of life. A high incidence of pulmonary adenomas, and hepatomas, and a lower incidence of lymphomas developed over a period from 12 to 50 weeks. Current correlative evaluation with chemical and other data indicates the practical utility of both assays for carcinogenic air pollutants.*

Existing methods for demonstrating the carcinogenicity of atmospheric pollutants fall into two broad categories—the chemical and the biological. Chemical methods depend on the identification and measurement of known carcinogens, such as Benzo (a) pyrene, (BaP), in organic extracts of particulate atmospheric pollutants. These, however, are of restricted value as various organic fractions, such as the oxy-neutral, contain undefined or unknown carcinogens. Furthermore, this approach ignores the possibility of biological interactions between various components in the pollutants. Existing biological methods generally depend on repeated skin painting or subcutaneous injection of pollutants in adult rodents[1]. These techniques, however, require comparatively large amounts of pollutants and in general result in low tumor yields after long latent periods.

For these reasons, an attempt has been made to develop alternative approaches, and this report describes briefly two new bioassays, the photodynamic and mouse neonate, which have been developed recently as *indirect* and *direct* measures, respectively, of the carcinogenicity of organic atmospheric pollutants.

Photodynamic Bioassay

The photodynamic assay measures concentrations of photosensitizing polycyclic compounds in organic extracts of atmospheric particulates, and reflects the ability of these compounds to sensitize cells to the otherwise nontoxic effects of long-wave ultraviolet light[2–4]. The relevance of this assay to carcinogenicity depends on the previous demonstration, in a large series of polycyclic compounds, of a strong positive association between photodynamic toxicity, using the motile ciliate *Paramecium caudatum*, and carcinogenicity attributable to polycyclic compounds.[5,6]

A simple photodynamic assay has been developed for the purpose of rapid and large-scale screening by relatively nonspecialized personnel of extracts of particulate atmospheric pollutants. The assay has been applied to organic atmospheric pollutants, and six fractions thereof, from more than 100 different sources in the U.S.A. exemplifying a wide spectrum of urban and rural pollutant characteristics. Pollutants were assayed over a range from 100 to 1 μg/ml, using BaP over a range from 100 to 0.001 μg/ml, as a standard.

This assay provides a rapid and sensitive biological measure of photosensitizing polycyclics in organic extracts of suspended particulates. It yields results which discriminate widely between pollutants from different sources and even more widely between various fractions of pollutant extracts derived from any one source[7–9]. Relative photodynamic potency, expressed as *apparent* μgBaP/g fraction or as *apparent* μgBap/1000m³ of air, bears no relationship to atmospheric concentrations of particulates, organics, or derived fractions. For the aromatic fraction, which contains nearly all the BaP present in its parent organic extract, photodynamic potencies are strongly and positively correlated with BaP concentrations.

In an attempt to further analyze the significance of this photodynamic data, its correlation with a variety of other parameters relating to each emission source, such as patterns of fuel consumption, population density, and mortality and morbidity from respiratory disease, are now being studied.

Mouse Neonate Assay

The use of neonatal animals for the carcinogenicity testing of pure chemicals is well documented[10, 11]. Neonates have been shown to be highly sensitive to defined carcinogens, administration of which in very low concentrations, in general results in high tumor yields with relatively short latent periods. However, there is no published data on the use of neonates for the testing of carcinogens in undefined crude mixtures, such as organic extracts of particulate atmospheric pollutants.

The present studies, although primarily methodological, have established the high sensitivity of neonatal mice to carcinogens extracted from air. Neonates were injected with tricaprylin suspensions, at 100 mg/ml concentration, of benzene-soluble extracts of organic atmospheric particulates derived from various sources in the U.S.A., including Chicago, Cincinnati, Los Angeles, Philadelphia, Washington, D. C., and New York. Doses ranging

from 5 to 55 mg. were fractionally administered during the first 21 days of life, commencing within a few hours of birth. Dosage schedules were developed to permit injection of maximal amounts of extracts as early as possible in the neonatal period, consistent with limitations imposed by acute or subacute toxicity. Additionally, some limited time-dose-response effects were studied. A high incidence of pulmonary adenomas, both solitary and multiple, and hepatomas, a lower incidence of malignant lymphomas, and a very low incidence of local fibrosarcomas at injection sites, has been demonstrated in the majority of test groups.[12] The incidence of these different tumors shows marked variation from city to city.

The pattern of tumors produced by organic extracts of atmospheric pollutants suggests that their effects are due to more than a single carcinogen.

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CARCINOGENICITY OF ORGANIC PARTICULATE POLLUTANTS IN URBAN AIR AFTER ADMINISTRATION OF TRACE QUANTITIES TO NEONATAL MICE

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THE methods which exist for demonstrating the carcinogenicity of atmospheric pollutants are either chemical or biological. The chemical methods depend on the identification and measurement of known carcinogens, such as benzo(*a*)pyrene, in organic extracts of atmospheric particulate pollutants. Such methods, however, are of limited value because various organic fractions, such as the oxy-neutral and basic, contain undefined or unknown carcinogens[1–3]. Furthermore, this approach ignores the probability of *in vivo* interactions between various components of pollutants. Existing biological methods usually make use of repeated skin painting or subcutaneous injection of pollutant extracts in adult rodents. These techniques, however, require comparatively large amounts of materials and usually give relatively low yields of tumours after long latent periods[2].

For these reasons, an attempt was made to devise alternative approaches to this problem[4]. A photodynamic bioassay was developed as an indirect index of the carcinogenicity of polycyclic compounds, in order to permit rapid and large scale screening of organic atmospheric pollutants[5–7]. The assay has been applied to benzene-soluble organic extracts of particulate atmospheric pollutants, and also to six fractions thereof, obtained from more than a hundred different sources in the United States, comprising a wide range of urban and rural pollutants[8,9]. The photodynamic assay

provides a measure of the concentrations of photosensitizing polycyclic compounds and reflects their ability to sensitize cells to the otherwise non-toxic effects of long-wave ultra-violet light[10–12]. The relevance of this assay to carcinogenicity was established by the previous demonstration, in a large series of polycyclic compounds, of a positive association between photodynamic toxicity and carcinogenicity, attributable to polycyclic compounds, in the ciliate *Paramecium caudatum*[13,14]. The present article describes the development of another bioassay that uses neonatal mice in a highly sensitive and direct estimation of carcinogenicity as a result of all components in organic extracts of particulate pollutants. Although many data are available concerning the enhanced sensitivity of newly born animals to defined carcinogens (for example, refs. 15 and 16), their use for carcinogenicity testing of undefined crude organic mixtures has not hitherto been recorded.

Atmospheric particulates were collected during 1963 with National Air Sampling Network high-volume samplers at Continuous Air Monitoring Program sites in Chicago, Cincinnati, Los Angeles, Philadelphia, New Orleans and Washington, D.C.; they were combined by sites and extracted with benzene[17]. Tricaprylin suspensions in concentrations of 100 mg/ml. were prepared from the organic extracts derived from these annual composites. Swiss mice (*ICR/Ha*) were injected subcutaneously in the nape of the neck with 0·05 ml. of pollutant suspensions on the first day of their life and with 0·1 ml. on both the seventh and fourteenth days, yielding a total dose of 25 mg; 1 ml. tuberculin syringes and 27 gauge needles were used. The final injection was omitted for some groups, because of a shortage of materials, so that they only received 15 mg (Table 1). These dosage schedules were developed to permit administration, as early as possible in the neonatal period, of the greatest amounts of extracts consistent with limitations imposed by the high mortality of acute toxicity. The mice were usually weaned and sexed between the ages of 30–40 days. Groups of five or fewer mice, separated according to their sex, were housed in hanging metal cages and given Purina chow and water *ad libitum*. The animals were inspected daily and weighed at weekly intervals for the first month of their life, and at approximately monthly intervals thereafter. The mice were allowed to survive until the experiments were brought to an end after 50–52 weeks, with the exception of moribund animals, which were killed earlier. All the animals were autopsied except in a few instances of severe autolysis or cannibalism; samples were taken for histological examination from any lesion or tumour and usually also from liver, spleen, heart, lungs, kidneys, adrenals, thymus, lymph glands, and sternal marrow. They were fixed in Tellyesniczky fluid,

Table 1. TOXICITY AND OBSTRUCTIVE UROPATHY INDUCED IN SWISS MICE AFTER NEONATAL SUBCUTANEOUS INJECTIONS OF SUSPENSIONS OF BENZENE-SOLUBLE ORGANIC EXTRACTS OF PARTICULATE ATMOSPHERIC POLLUTANTS

Treatment group*	Initial No. of mice in each treatment group (corresponding No. of litters in parentheses)	Mortality before weaning (per cent)	Sex and No. at weaning	Weight mice (g)				Obstructive uropathy	
				At weaning		At 50 weeks			
				Average	80 per cent† central range	Average	80 per cent central range	No.	Incidence as a percentage of male mice alive at weaning and later autopsied
Controls	190 (19)	16	M 82	28·3	23–32	53·7	46–63	19	24
			F 77	23·2	21–26	48·2	38–64	—	—
Chicago (25 mg)	127 (13)	39	M 41	24·7	19–29	49·5	42–59	29	76
			F 37	21·5	17–26	53·8	37–73	—	—
Cincinnati (25 mg)	133 (14)	53	M 32	22·9	19–28	55·2	53–56	21	70
			F 31	23·4	19–26	59·0	41–84	—	—
Los Angeles (25 mg)	137 (14)	61	M 32	28·5	24–33	57·7	46–75	18	60
			F 22	25·3	21–28	51·6	41–69	—	—
New Orleans (15–25 mg)	110 (11)	29	M 39	28·1	24–32	54·5	48–63	12	33
			F 39	23·9	21–27	50·3	39–71	—	—
Philadelphia (15–25 mg)	105 (11)	35	M 27	30·1	24–35	60·6	48–73	15	63
			F 41	23·8	21–28	55·3	39–72	—	—
Washington, D.C. (25 mg)	137 (15)	53	M 38	26·8	23–31	55·6	45–70	21	60
			F 27	23·4	20–28	58·0	43–75	—	—

* The following treatment groups are combined here (the corresponding initial number of mice in each group is given in parentheses): controls, uninjected controls (90) + tricaprylin controls (100); New Orleans, 15 mg dosage (100) + 25 mg dosage (10); Philadelphia, 15 mg dosage (49) + 25 mg dosage (56).

† This is the range in weights of mice after excluding the 10 per cent lowest and 10 per cent highest. The number of excluded observations is taken to the nearest whole integer.

and 5μ sections were stained with haematoxylin and eosin.

Toxicity was clearly indicated by death before weaning of between 29 per cent and 61 per cent of the mice given the pollutant extracts, as compared with the death of 16 per cent of the control animals. There was, however, no parallel evidence of loss in weight either at the time of weaning or at the termination of the experiments (Table 1). Death before weaning occurred largely in the first week of life, so that differences in mortality between the different groups appeared at the same time. The number of survivors of each sex at weaning did not differ too markedly, and therefore it would appear that pre-weaning mortality rates for the sexes were comparable. Substantial sex differences in mortality did, however, develop after weaning in some groups; this was largely as a result of the death or destruction of male mice developing obstructive uropathy, a syndrome characterized by perineal ulceration, urinary obstruction, hydronephrosis, and uraemia[18,19]. Its incidence was markedly greater in all treatment groups (33–76 per cent) than with controls (24 per cent) (Table 1). This is particularly interesting because of the similar incidence of uropathy in controls and in mice treated, when newly born, with a variety of other substances, including carcinogenic combinations of piperonyl butoxide and fluorocarbon propellants[20].

The total number of different individual tumours, all of which were histologically confirmed or identified, and their incidence at corresponding intervals when death from tumours or killing occurred, is listed in Table 2 for the various treatment groups. In several instances, which are identified in Table 2, multiple tumours were noted. The majority of these associations involved hepatomata and pulmonary adenomata. Of the three control mice with hepatomata, one also had a pulmonary adenoma. In the combined groups receiving pollutant treatment, of twenty-seven male mice with hepatomata, seven also had solitary pulmonary adenomata, and fifteen also had multiple pulmonary adenomata. The overall incidence of tumours in groups treated with pollutants was markedly greater than in the controls. There were also differences in the incidence of tumours for pollutants from city to city; these reflect in part the varying number of animals at risk. In these experiments, the high incidence of remote tumours, together with the exceptionally low incidence of fibrosarcomata at the injection site (Table 2), was in contrast to the relatively low yield of local tumours and the rarity or absence of distant tumours after repeated skin painting or subcutaneous inoculation of adult mice with extracts of air pollutants[2].

A high incidence of hepatomata occurred in all pollutant groups, with the exception of that receiving treatment with pollutants from Los Angeles; it was highest with the

Table 2. TUMOURS INDUCED IN SWISS MICE BY NEONATAL INJECTIONS OF ORGANIC EXTRACTS OF PARTICULATE ATMOSPHERIC POLLUTANTS

Treatment group	Sex	No. of mice, later autopsied, alive at the beginning of each period (Nos. at risk) Weeks 11–20	21–30	31–40	41–50	51+	Hepatomata* No.	No. tumours in each period as percentage of No. of mice at risk Weeks 11–20	21–30	31–40	41–50	51+	Malignant lymphomata* No.	No. tumours in each period as percentage of No. of mice at risk Weeks 11–20	21–30	31–40	41–50	51+	Solitary pulmonary adenomata No.	No. tumours in each period as percentage of No. of mice at risk Weeks 11–20	21–30	31–40	41–50	51+	Multiple pulmonary adenomata No.	No. tumours in each period as percentage of No. of mice at risk Weeks 11–20	21–30	31–40	41–50	51+	Misc.† tumours No.
Controls	M	78	78	78	71	67	3[a]	0	0	0	0	4	0	0	0	0	0	0	9	0	0	0	1	12	0	0	0	0	0	0	1
	F	75	74	74	72	68	0	0	0	0	0	0	1	0	0	0	0	1	4	0	0	1	0	4	0	0	0	0	0	0	0
Chicago	M	39	37	33	22	11	3[b]	0	0	0	0	27	1	0	0	3	0	0	6	0	5	0	5	27	11	0	0	3	18	55	0
(25 mg)	F	36	35	34	33	33	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	21	8	0	0	0	0	24	0
Cincinnati	M	30	27	21	12	6	5[c]	0	0	0	0	83	1	0	0	0	0	17	4	0	4	0	17	17	10	0	4	19	8	67	0
(25 mg)	F	28	27	27	24	22	1[d]	0	0	0	0	5	3[e]	4	0	0	0	9	3	0	0	4	0	9	20	0	0	7	8	73	0
Los Angeles	M	30	30	23	22	13	1[f]	0	0	0	0	8	1	0	0	0	0	8	4	0	0	4	9	8	3	0	3	0	0	15	2[j,k]
(25 mg)	F	20	20	18	18	15	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	7	3	0	0	0	6	13	0
New Orleans	M	36	36	36	32	29	10[g]	0	0	0	0	34	0	0	0	0	0	0	7	0	0	3	0	21	9	0	0	3	0	28	0
(15–25 mg)	F	35	34	34	33	30	0	0	0	0	0	0	2	3	0	3	0	0	6	0	0	0	3	17	5	0	0	0	0	17	2[l,m]
Philadelphia	M	24	24	22	18	13	4[e]	0	0	0	0	31	0	0	0	0	0	0	1	0	0	0	6	0	5	0	0	5	6	23	1[f]
(15–25 mg)	F	38	38	36	32	27	0	0	0	0	0	0	5[h]	0	0	6	9	0	6	0	0	0	6	15	9	0	0	0	3	30	2[m,n]
Washington	M	35	35	28	19	13	4[i]	0	0	0	0	31	0	0	0	0	0	0	5	0	6	0	5	15	11	0	3	0	16	54	1[l]
(25 mg)	F	25	24	22	21	16	0	0	0	0	0	0	1	4	0	0	0	0	7	0	4	0	5	31	10	0	0	0	14	44	0

* The following instances of coexistent multiple tumours occurred, each tumour being individually listed: *a*, 1 hepatoma with a solitary pulmonary adenoma; *b*, 1 with a solitary pulmonary adenoma, 2 with multiple pulmonary adenomata; *c*, 1 with a solitary pulmonary adenoma, 3 with multiple pulmonary adenomata, and 1 with multiple pulmonary adenomata and a malignant lymphoma; *d*, with multiple pulmonary adenomata; *e*, 2 with multiple pulmonary adenomata; *f*, with a solitary pulmonary adenoma; *g*, 3 with solitary pulmonary adenomata, 4 with multiple pulmonary adenomata; *h*, 1 with a solitary pulmonary adenoma, 1 with multiple pulmonary adenomata; *i*, 1 with a solitary pulmonary adenoma, 2 with multiple pulmonary adenomata, and 1 with pulmonary adenomata and a pulmonary adenocarcinoma.

† *j*, Fibrosarcoma and a solitary pulmonary adenoma; *k*, papilloma gall bladder and multiple pulmonary adenomata; *l*, pulmonary adenocarcinoma and multiple pulmonary adenomata; *m*, mammary adenocarcinoma; *n*, thyroid adenoma.

extracts from Cincinnati (Table 2). Hepatomata were all found in mice killed at the end of experiments and almost exclusively in males. As already noted, hepatomata were frequently coexistent with multiple pulmonary adenomata, and less frequently with solitary pulmonary adenomata. An increased incidence of malignant lymphomata was also noted, especially with the extracts from Philadelphia and Cincinnati. Malignant lymphomata that developed before the age of 40 weeks were usually poorly differentiated and apparently thymic in origin, as compared with others which were lymphocytic or histocytic and non-thymic. A high incidence of multiple pulmonary adenomata occurred in all pollutant groups, particularly with extracts from Cincinnati, in contrast to their low incidence with extracts from Los Angeles and their complete absence in controls. This also contrasted with the occurrence of solitary pulmonary adenomata, the incidence of which in some treatment groups was similar to that for controls.

The relatively low tumour yields in the groups receiving extracts from Los Angeles, paralleled in other work by the non-carcinogenicity of atmospheric organic extracts from this city after administration to adult rodents[2], were associated with low photodynamic potencies[9] and low concentrations of benzo(*a*)pyrene in the corresponding organic extracts (Tables 2 and 3). Conversely, the high tumour yields with extracts from Cincinnati were associated with high photodynamic potencies and benzo(*a*)pyrene concentrations (Tables 2 and 3). These data are too limited, however, for a formal analysis of associations, especially as there is little justification for assuming that the main carcinogens or classes of carcinogens in organic pollutants are restricted to the polycyclic compounds listed in Table 3. It is likely that, apart from gaseous and inorganic components of atmospheric pollutants, which have not been considered here, there are also other classes of organic carcinogens, such as polynuclear azaheterocyclics, polynuclear ring carbonyls, aliphatic epoxides and alkylating agents[1,3,21], the importance of which cannot as yet be assessed. It is possible that some of the latter compounds have contributed to the tumour yields reported here, such as the hepatomata, although high concentrations of benz(*a*)anthracene administered to newly born mice have also been shown to produce these tumours[22].

It would take about 3–4 months for an adult human being in one of the cities considered to inhale the amounts of atmospheric pollutants which we have found to be highly carcinogenic to newly born mice. It is, however, difficult to make valid quantitative extrapolations to the human situation. For example, if the surface area rule for extrapolating between species[23] applies here, an increase in the level of exposure by a factor of about 200

Table 3. Photodynamic Potency and Polycyclic Concentrations of Organic Atmospheric Particulates

City	Mean concentration* (μg/m^3 air)	Photodynamic potency apparent μg BaP/g organics	Atmospheric organics: Concentrations of polycyclic hydrocarbons (μg/g organics) BaP†	BeP	Py	Per	BghiP	Anth	Cor	BaA	Chr	Fl
Chicago	9·4	85	630	570	380	69	1,100	40	280	280	450	250
Cincinnati	8·8	100	670	430	310	75	1,070	35	180	130	290	230
Los Angeles	12·7	< 10	110	180	65	15	690	10	330	43	150	43
New Orleans	8·8	58	320	470	200	27	790	16	210	140	300	120
Philadelphia	9·1	70	470	370	250	55	900	32	320	230	350	180
Washington	9·0	62	530	510	200	57	1,020	53	260	210	490	200

* Data from *Air Pollution Measurements of the National Air Sampling Network, Analyses of Suspended Particulates* 1963. U.S. Department of Health, Education, and Welfare, Public Health Service, Division of Air Pollution, Cincinnati, Ohio, 1965.

† BaP, benzo(*a*)pyrene; BeP, benzo(*e*)pyrene; Py, pyrene; Per, perylene; BghiP, benzo(*ghi*)perylene; Anth, anthanthrene; Cor, coronene; BaA, benz(*a*)anthracene; Chr, chrysene; Fl, fluoranthene.

might be necessary to produce cancer when particulates are inhaled by an adult man. Nevertheless, it is difficult to escape the conclusion that the high carcinogenicity of trace amounts of organic urban atmospheric pollutants is highly significant.

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Photodynamic Assay of Neutral Subfractions of Organic Extracts of Particulate Atmospheric Pollutants

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■ A composite neutral fraction of organic extracts of particulate atmospheric pollutants was separated chromatographically into 217 subfractions; nine polynuclear aromatic hydrocarbons and five polynuclear ring carbonyl compounds were identified in these subfractions. The distribution of photosensitizing polynuclear compounds in these subfractions was determined using a photodynamic bioassay with *Paramecium caudatum;* photodynamic potency affords an indirect index of carcinogenicity owing to polynuclear compounds.

Atmospheric pollutants contain diverse chemical carcinogens (Table I, based on Sawicki, 1967). The carcinogenicity of organic extracts of particulate atmospheric pollutants has been investigated by skin painting or subcutaneous injection in rodents (Table II). Benzene-soluble extracts of particulate atmospheric pollutants are more carcinogenic than their derived aromatic or oxygenated fractions; these latter fractions have similar carcinogenicity (Hueper, Kotin, *et al.*, 1962). These findings incriminate carcinogens other than just benzo[*a*]pyrene (BaP), as BaP in the original benzene-soluble extract is concentrated in aromatic and absent from oxygenated fractions. That other carcinogens are involved is further confirmed by a high incidence of induced hepatomas, not ordinarily produced by BaP, as well as lymphomas and pulmonary adenomas, after parenteral administration of organic pollutant extracts to neonatal mice (Epstein, Joshi, *et al.*, 1966).

Therefore, identification of carcinogens in oxygenated fractions was attempted by correlated chemical and biological studies. As large neutral samples are required to provide enough oxygenated subfractions for carcinogenicity testing, pilot studies on fractionation procedures were made using a photodynamic bioassay—a presumptive test for carcinogenicity due to polynuclear compounds (Epstein, Bulon, *et al.*, 1964; Epstein, Small, *et al.*, 1964)—to see how biological activity was distributed in subfractions; the photodynamic activity of organic atmospheric pollutants and their major fractions has been reported (Epstein, 1965; Epstein, Small, *et al.*, 1963, 1965). The procedures used to fractionate a composite neutral fraction and the photodynamic activity of individual neutral subfractions and polynuclear compounds in these subfractions are presented here.

Table I. Chemical Carcinogens[a] in the Air

1. Polynuclear aromatic hydrocarbons
   - Benz[*a*]anthracene and R-benz[*a*]anthracenes
   - R-Chrysenes
   - Benzo[*b*]fluoranthene and benzo[*j*]fluoranthene
   - Benzo[*a*]pyrene
2. Polynuclear azaheterocyclics
   - R-Benz[*a*]acridines and R′,R″-benz[*a*]acridines
   - R-Benz[*c*]acridines and R′,R″-benz[*c*]acridines
   - Dibenz[*a,h*]acridine
   - Dibenz[*a,j*]acridine and R-dibenz[*a,j*]acridines
3. Polynuclear imino heterocyclics
   - 11*H*-benzo[*a*]carbazole
   - 3*H*-benzo[*b*]carbazole
   - 7*H*-benzo[*c*]carbazole
4. Polynuclear carbonyls
   - 7*H*-benz[*de*]anthracen-7-one
5. Alkylating agents
   - Aliphatic and olefinic epoxides
   - Peroxy compounds, lactones
6. Miscellaneous
   - Metals—As, Se, Co, Ni, Cr, Be
   - Radioactive compounds
7. Promoting agents
   - Phenols
   - Long-chain aliphatic hydrocarbons

[a] Alkyl or dialkyl substituents indicated by R or R′R″, respectively.

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[2] National Center for Air Pollution Control, Cincinnati, Ohio

Table II. Tumor Induction in Mice Following Cutaneous Administration of Organic Extracts of Particulate Atmospheric Pollutants

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

Materials and Methods

Composite Neutral Fraction. Aliphatic, aromatic, and oxygenated fractions of a benzene-soluble extract of atmospheric particulates, collected from a single urban location by the National Air Sampling Network (NASN No. 30), were recombined to give a composite benzene-soluble neutral fraction weighing ca. 500 mg.

Column Chromatographic Separation. A column, 20 mm. o.d., containing 50 grams of silica gel, 0.05- to 0.2-mm. mesh diameter (Brinkman Instruments, New York) with a fritted filter, 75- to 100-mμ pore size, was used. The entire sample was dissolved in ca. 5 ml. of methylene chloride, added to ca. 2 grams of silica gel, and the solvent was evaporated. The residue was added to a silica gel column and eluted successively with pentane, pentane-ether mixtures, and chloroform-methanol (Table III, Sawicki, Stanley, *et al.*, 1965b). Initially, 217 subfractions were collected and dried in vacuo at room temperature; these subfractions were collected successively and numbered in sequence. Only 209 subfractions were, however, finally available, as subfractions 2 to 10 were combined after determination of absorption spectra, because of their small individual weights. The absorption spectrum of each subfraction was determined from 250 to 450 mμ in pentane on a Cary spectrophotometer (Model 15). Nine polynuclear aromatic hydrocarbons—pyrene, fluoranthene, benzo[*a*]-anthracene (BaA), BaP, benzo[*e*]pyrene, perylene, benzo-[*ghi*]perylene, anthanthrene, and coronene—were qualitatively identified in aromatic subfractions.

Thin-Layer Chromatographic Separation. Aromatic subfractions, 2 to 20 with coronene as the cutoff point, were separated on aluminum oxide plates, 20 × 20 cm. × 250 microns, developed to 15 cm. in ca. 1 hour with pentane-ether (19 to 1, v./v.). Remaining subfractions, 20 to 217, were separated on cellulose plates, 20 × 20 cm. × 500 microns (Brinkman Instruments, Inc., New York), developed to 15 cm. for ca. 2.5 hours in a thin-layer chromatographic chamber containing 200 ml. of *N,N*-dimethylformamide–water (35 to 65, v./v.); chambers were equilibrated overnight before use. The developed chromatograms were examined in a Chromato-Vue cabinet (Ultra Violet Products, Inc., San Gabriel, Calif.) under 2600- and 3600-A. light sources. R_f values and fluorescence, before and after treatment with trifluoroacetic acid, were compared with standards on the same plate (Sawicki, Stanley, *et al.*, 1965a, b). Five polynuclear ring carbonyl compounds—xanthen-9-one and 7*H*-benz[*de*]anthracen-7-one (BO), phenalen-1-one and 7*H*-dibenzo-[*c,h*]xanthen-7-one and 9-acridan-one—were separated and identified qualitatively in aromatic and oxygenated subfractions.

Table III. Chromatographic Separation of a Composite Neutral Fraction on Silica Gel

Neutral Fraction	Solvent	Solvent Volume, Ml.	Subfraction Tube No.
Aliphatic	Pentane	100	1
Aromatic	Pentane 3%, ether	200	2–24
Aromatic and oxygenated	Pentane 9%, ether	600	25–70
Oxygenated	Pentane 12%, ether	200	71–82
	Pentane 15%, ether	200	83–93
	Pentane 20%, ether	200	94–108
	Pentane 28%, ether	200	109–126
	Pentane 36%, ether	200	127–143
	Pentane 44%, ether	200	144–151
	Pentane 52%, ether	200	152–164
	Pentane 60%, ether	200	165–182
	Chloroform 50%, methanol	400	183–217

Photodynamic Bioassay. Stock acetone solution of each of the 209 subfractions, at concentrations of 1000 μg. per ml., were stored in the dark at −20° C., and assayed within 7 days. Fresh aqueous suspensions, at concentrations of 100, 10, and 1 μg. per ml., were prepared by serial dilution from stock solutions. On each occasion of assay, three concentrations of seven subfractions were mixed in separate wells of multiple depression disposable plastic trays with aliquots of water and suspensions of log-phase *Paramecium caudatum*, adjusted to contain ca. 30 cells per well. Cells were cultured in semidefined medium of low protein concentration (Epstein, Burroughs, *et al.*, 1963). As a standard (Epstein, Koplan, *et al.*, 1963), five serial 10-fold dilutions of BaP from 10 to 0.001 μg. per ml. were simultaneously assayed, making a total of 26 wells under test in each tray. Additionally, 15 standard polynuclear compounds identified in aromatic and oxyneutral subfractions were assayed over the same range as the BaP standard. Duplicate trays were incubated in dark moist chambers at 28° C. for 2 hours and then simultaneously irradiated from a high-pressure mercury vapor tube emitting long-wave ultraviolet of 750 to 950 ergs per sq. cm. at 20 cm. and with a narrow peak at 360 mμ. Irregularities in energy yield along the mercury tube were compensated by different positioning of the test materials in the paired trays. All assays were replicated.

The times required for immobilization of 90% of the motile cells (LT_{90}), as end points of the photosensitizing effect (Epstein and Burroughs, 1962; Epstein, Koplan, *et al.*, 1963), were determined with a binocular stereoscopic microscope at (12X) through which all wells were individually scanned with an observational limit of 90 minutes. High photodynamic activity is manifested by low LT_{90} values and low activity by high LT_{90} values.

In view of the satisfactory uniformity of data from individual BaP assays, a composite BaP standard, based on 123 determinations, was used for statistical convenience. The potency of each subfraction and polynuclear compound was determined by referring its LT_{90} values to the steepest portion of the composite log-log BaP standard curve, from 0.001 to 0.01 μg. per ml. with LT_{90} values of 51 and 17 minutes, respectively (Figure 1). If any LT_{90} value of a subfraction fell within these limits, the BaP concentration yielding an equivalent LT_{90} was determined from the standard curve. Apparent potency of the subfraction or polynuclear compound was derived from the ratio of BaP to subfraction concentrations yielding the observed LT_{90} value and was expressed as microgram equivalents of BaP per gram of subfraction; thus by definition the BaP standard has a potency of 1,000,000 μg. per gram. Principles involved in the use of BaP as a standard, in nondilution assays as with air pollutant extracts, have been discussed (Epstein, Koplan, *et al.*, 1963; Epstein, Small, *et al.*, 1963). Where more than one level of the subfraction yielded an LT_{90} value between the critical limits of the standard curve, the apparent potency relative to BaP was based on the LT_{90} values at the lower concentration. Where no LT_{90} values fell within the critical limits, potency determinations were made by interpolation or extrapolation of the concentration of subfraction or compound required to yield an LT_{90} of 34 minutes, corresponding to the approximate midpoint of the critical portion of the standard curve.

Results and Discussion

Mean photodynamic activities and apparent relative potencies of 209 neutral subfractions and 15 polynuclear compounds in these subfractions, are listed in Tables IV and V; mean values are based on four determinations, with the exception of BaP, which was also the composite standard, whose mean is based on 123 determinations. Photodynamic activities of the subfractions, which were collected and numbered in sequence, and BaP standard at 1 μg. per ml. concentrations are presented in Figure 2 in terms of LT_{90} values; the range of distribution of polynuclear compounds and the solvent mixtures used to elute individual subfractions are also identified for correlative purposes.

High photodynamic activity, $LT_{90} < 45$ minutes at 1 μg. per ml., and high photodynamic potency, > 1000 μg. of BaP per gram of subfraction, is substantially restricted to three subfraction ranges, 12 to 23 (excluding tube 13), 33 to 41, and 56 to 68 (Table IV and Figure 2); additional isolated instances of high activity were found in tubes 118 and 137. Of the polynuclear compounds identified in aromatic and oxygenated subfractions, only three—BaP, BaA, and BO—

(text continues on page 138)

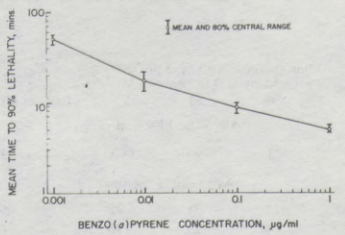
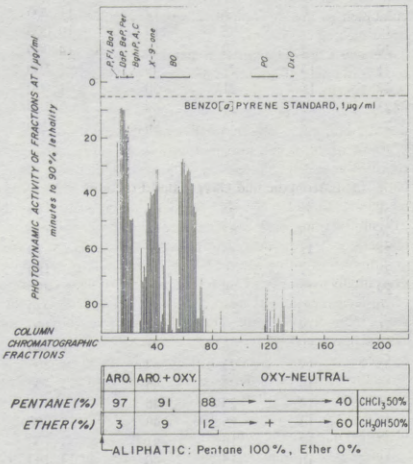


Figure 1. Composite photodynamic response curve for the benzo[a]pyrene standard



P-Pyrene; Fl-Fluoranthene; BaA-Benz[a]anthracene; BaP-Benzo[a]pyrene; BeP-Benzo[e]pyrene; Per.-Perylene; BghiP-Benzo[ghi]perylene; A-Anthanthrene; C-Coronene; X-9-one-Xanthen-9-one; BO-7H-benz[de]anthracen-7-one; PO-Phenalen-1-one; DxO-7H-dibenzo[c,h]Xanthen-7-one

Figure 2. Photodynamic bioassay of a composite neutral fraction of a benzene extract of atmospheric particulates

Table IV. Photodynamic Activity and

Tube No.	Photodynamic Activity, Min. to 90% Lethality at 3 Concns. μg/Ml. 100	10	1	Photodynamic Potency, μg. Equiv. BaP per Gram
	Aliphatic Fraction			
1	33	>90	>90	24
	Aromatic Fraction			
2-10	13	31	>90	290
11	4	23	>90	560
12	2	6	22	6,200
13	30	49	>90	110
14	3	5	9	100,000
15	3	5	9	100,000
16	3	6	10	72,000
17	5	7	10	85,000
18	6	8	17	11,000
19	7	8	17	10,000
20	7	9	16	14,000
21	13	21	49	1,100
22	15	21	50	1,000
23	22	31	49	1,100
24	28	34	90	240
	Aromatic and Oxygenated Fractions			
25	29	>76	>90	33
26	28	47	>90	120
27	31	>76	>90	29
28	22	39	86	180
29	21	26	60	430
30	20	35	72	230
31	18	30	67	300
32	18	28	71	370
33	17	23	47	1,200
34	18	23	44	1,400
35	14	25	46	1,300
36	13	15	40	1,800
37	12	16	41	1,700
38	10	15	40	1,700
39	10	14	38	1,900
40	8	12	31	2,800
41	8	11	31	2,900
42	7	24	60	520
43	8	26	>86	440
44	8	22	>84	580
45	8	22	66	580
46	7	22	58	580
47	8	25	>90	460
48	8	23	>87	540
49	7	25	75	440
50	7	24	70	480
51	6	24	>89	490
52	7	25	>90	470
53	8	27	>90	380
54	7	25	85	440
55	7	25	>89	440
56	4	9	37	2,000
57	5	9	40	1,700
58	4	7	29	3,400
59	4	8	37	2,000
60	4	8	29	3,400
61	4	9	33	2,500
62	5	8	32	2,700
63	6	12	31	2,900
64	5	11	32	2,700
65	6	12	36	2,100
66	6	13	36	2,200
67	6	12	45	1,300
68	6	12	47	1,200
69	7	21	>85	680
70	10	28	85	370
	Oxygenated Fraction			
71	10	28	74	370
72	10	28	>70	370
73	11	29	>83	330
74	10	32	>90	260
75	11	30	>85	300
76	11	35	>90	230
77	9	30	>90	320
78	9	43	>90	140
79	10	32	>90	270
80	8	27	>89	380
81	8	29	>90	350
82	9	32	>90	280
83	10	35	>90	230
84	11	29	>90	340
85	9	23	>90	540
86	9	22	>83	590
87	9	24	>90	510
88	10	34	>90	250
89	10	26	>90	440
90	14	42	>90	160
91	24	>88	>90	52
92	22	>88	>90	58
93	>84	>90	>90	<10
94	26	>86	>90	44
95	19	72	>90	81
96	3	70	>90	33
97	24	>84	>90	50
98	15	50	>90	100
99	16	64	>90	51
100	16	52	>90	42
101	15	50	>90	100
102	11	55	>90	36
103	15	54	>90	42
104	35	>90	>90	23
105	18	86	>90	98
106	13	64	>90	46
107	14	76	>90	53
108	9	42	>90	150

Potency of 217 Neutral Subfractions

Tube No.	Photodynamic Activity, Min. to 90% Lethality at 3 Concns. μg./Ml. 100	10	1	Photodynamic Potency, μg. Equiv. BaP per Gram
109	12	54	>90	36
110	13	56	>90	40
111	12	35	>90	230
112	8	32	>90	280
113	8	28	>90	370
114	9	36	>90	210
115	7	31	>90	290
116	7	30	>90	320
117	10	37	87	200
118	5	15	55	1,700
119	8	27	75	390
120	8	28	>90	360
121	9	30	83	310
122	9	30	>90	320
123	9	32	>90	270
124	9	26	79	410
125	10	28	>90	350
126	11	29	87	350
127	11	30	85	320
128	11	35	>90	230
129	12	30	87	300
130	12	29	75	330
131	12	29	81	320
132	13	34	>90	240
133	17	40	>90	170
134	20	41	>90	160
135	22	51	>90	100
136	20	49	>90	110
137	6	13	53	3,100
138	19	43	>90	150
139	22	58	>90	59
140	26	53	>90	41
141	19	43	>90	140
142	17	40	>90	170
143	18	45	>90	130
144	17	38	>90	190
145	17	42	>90	150
146	20	47	>90	120
147	32	61	>90	28
148	16	43	>90	150
149	21	47	>90	120
150	22	47	>90	120
151	22	48	>90	120
152	23	49	>90	110
153	32	63	>90	27
154	15	38	>90	190
155	22	58	>90	63
156	16	51	>90	100
157	16	54	>90	44
158	14	47	>90	120
159	16	52	>90	42
160	25	61	>90	47
161	32	52	>90	27
162	34	71	>90	24
163	32	69	>90	27
164	31	72	>90	29
165	31	63	>90	29
166	32	61	>90	28
167	20	53	>90	77
168	27	78	>90	40
169	22	76	>90	58
170	22	72	>90	62
171	24	76	>90	50
172	25	>90	>90	47
173	32	85	>90	28
174	35	>90	>90	23
175	24	65	>90	50
176	15	59	>90	47
177	22	60	>90	58
178	14	56	>90	42
179	21	64	>90	69
180	17	58	>90	49
181	17	58	>90	49
182	24	75	>90	51
183	26	64	>90	42
184	30	84	>90	30
185	15	51	>90	40
186	26	68	>90	44
187	52	>90	>90	<10
188	22	59	>90	58
189	23	53	>90	54
190	44	>90	>90	14
191	25	75	>90	44
192	23	73	>90	54
193	22	66	>90	59
194	26	77	>90	42
195	23	52	>90	55
196	29	>90	>90	34
197	9	73	>90	40
198	43	>90	>90	14
199	>90	>90	>90	<10
200	>90	>90	>90	<10
211	>90	>90	>90	<10
202	>90	>90	>90	<10
203	62	>90	>90	<10
204	56	>90	>90	<10
205	>90	>90	>90	<10
206	50	>90	>90	<10
207	67	>90	>90	<10
208	55	>90	>90	<10
209	66	>90	>90	<10
210	43	>90	>90	15
211	39	>90	>90	18
212	44	>90	>90	14
213	30	>90	>90	32
214	30	>90	>90	31
215	44	>90	>90	14
216	44	>90	>90	14
217	49	>90	>90	11

Table V. Photodynamic Activity and Potency of Polynuclear Aromatic Hydrocarbons and Ring Carbonyl Compounds

Polynuclear Compound	Localization of Compound Subfraction Tube Nos.	Photodynamic Activity, Mean Times (Min.) to 90% Lethality at Specified Concns. μg./Ml. 10	1	0.1	0.01	0.001	Photodynamic Potency, μg. Equiv. BaP/Gram of Compound
Hydrocarbons							
Benz[*a*]anthracene	11–13	5	6	8	13	23	5,100,000
Pyrene	11–13	5	7	11	32	70	250,000
Fluoranthene	11–13	3	6	15	39	>77	170,000
Benzo[*a*]pyrene	14–18	4	6	10	17	49	1,000,000
Benzo[*e*]pyrene	14–18	13	18	31	58	>84	8,800
Perylene	14–18	>90	>90	>90	>90	>90	<10
Benzo[*ghi*]perylene	19–23	61	70	>86	>90	>90	<10
Anthanthrene	19–23	77	>89	>90	>90	>90	<10
Coronene	24	>90	>90	>90	>90	>90	<10
Ring carbonyls							
9-Acridanone	32–40	>90	>90	>90	>90	>90	<10
Xanthen-9-one	34–38	58	>90	>90	>90	>90	21
7*H*-Benz[*de*]anthracen-7-one	44–64 (max. 51–56)	7	8	10	14	20	7,400,000
Phenalen-1-one	108–128 (max. 115–119)	20	58	>90	>90	>90	710
7*H*-Dibenzo[*c,h*]xanthen-7-one	136–137	>90	>90	>90	>90	>90	<10

had potency ≧ 1000 μg. of BaP per gram (Table V); as indicated above, the BaP standard in these assays has by definition a potency of 1,000,000 μg. per gram. The presence of BaP and BaA in subfractions 12 to 23 and BO in subfractions 56 to 68 is associated with and probably accounts for the high potency of these subfractions. It was, however, not possible to account for high activity in subfractions 33 to 41, as xanthen-9-one, the only polynuclear compound as yet identified in this range, has very low photodynamic potency.

BO is a recently recognized atmospheric pollutant with an average concentration, ca. 500 μg. per gram of organics, similar to that of BaP (Sawicki, Stanley, *et al.*, 1965a). The photodynamic activity of BO and of oxygenated subfractions containing it, indicates that BO or associated compounds may be involved in the carcinogenicity of oxygenated fractions. The carcinogenicity of polynuclear ring carbonyl compounds, in general and of BO, in particular, has not been adequately explored, although BO has been inconclusively tested and reported as equivocally carcinogenic (Hartwell, 1951). More recent tests, using neonatal mice, have shown that BO is a very weak carcinogen (Epstein and Fujii, 1967).

The chromatographic techniques, used here for fractionating the neutral extract, satisfactorily distributed photosensitizing polynuclear compounds among a wide range of subfractions. These techniques thus offer a convenient and practical model which can be scaled up to provide subfractions of oxygenated neutrals adequate for carcinogenicity testing and make identification of major individual carcinogens possible.

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APPENDIX II–7

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USE OF MAMMALS IN A PRACTICAL SCREENING TEST FOR CHEMICAL MUTAGENS IN THE HUMAN ENVIRONMENT

Chemical mutagens in the environment are a hazard not yet systematically explored. Although certain mutagens, notably ionizing radiations and alkylating agents, have been studied in detail in bacteria [1, 2] and *Drosophila*,[3, 4] relevance to man is not always apparent. M. Legator (personal communication) has considered the influence of host-mediated drug effects by studying mutagenicity in bacteria in a mammalian environment. Lüning,[5] in discussing mutagenicity testing, stated: "The use of mammals in such tests would be both expensive and time-consuming, and might slow down even more the development of new drugs." Bateman,[6] however, considered use of mammals in mutagenicity testing to be practical and more meaningful than studies with other systems in the context of human hazards. We present preliminary data on the feasibility of mutagenicity testing in mice based on screening a wide variety of environmental pollutants, including carcinogens, air and water pollutants, pharmaceuticals, food additives and pesticides.

In the dominant lethal test, treated males are sequentially mated with groups of females. The females are subsequently dissected at mid-term of pregnancy to evaluate the incidence of dominant lethal mutations. Such effects conveniently reflect mutagenic activity and represent foetuses killed *in utero* by mutations directly induced in male germ cells. The possibility of systemic drug effects in females is thus excluded.

In general, $L.D._{.5}$ doses were selected for testing. Where strong anti-fertility effects were evidenced at these doses, testing was repeated at lower levels. Test materials were prepared freshly and generally injected intraperitoneally in tricaprylin solution or suspension in 0.1 ml volume. Male Swiss mice (CD–1), 8–10 weeks old, were dosed in minimal groups of 5. Groups of 10 male mice, injected with tricaprylin, served as controls for concurrent testing of 7–9 samples. Within 2 h of injection, each male was caged with 3 virgin females, 8–10 weeks old, for 7 days. After 7 days, the females were replaced with fresh virgin animals. This breeding schedule was maintained for 8 consecutive weeks, the duration of the spermatogenic cycle in the mouse. All females were autopsied 13 days from mid-week of their mating; pregnancy thus ranged from 9–15 days. In general, fertilizations were maximal during the middle portion of each mating week. At autopsy, animals were scored for total implantations, early deaths, appearing as small black deciduomata, and late deaths. Corpora lutea were counted under a low-power dissecting microscope.

A mutagenic index (M. I.), reflecting the incidence of dominant lethal mutations in an experimental group of animals, is conventionally calculated as follows:

$$\text{M. I.} = \frac{\text{deciduomata} + \text{late deaths}}{\text{total implantations}} \times 100$$

This index, however, is limited in that it is, perforce, increased by reduction in total implantations alone; additionally, it reflects neither anti-fertility effects nor the distribution of deciduomata in affected animals.

Results are summarized in Table 1, where all effects are listed for the third mating week, with the exception of aflatoxin (week 4) and methyl methane sulfonate (week 2). The average composite control value of M.I., based on 150 females, for the third week was 1.0 per cent, with a range from 0 to 3 per cent. Control M. I. values of 3–10 per cent have been reported for other strains of mice.[7, 8] The incidence of late deaths was extremely low; one late death appeared

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in each of 5 out of a total of 45 compounds tested, for the third mating week. In control females for third week, 3 late deaths were seen. Mutagenic activity was, in general, maximal in weeks 2 and 3.

Among the carcinogens tested, of particular and potential practical interest, aflatoxin and benzo[*a*]pyrene were mutagenic. The aflatoxin sample, a mixture of aflatoxins B_1 and G_1, displayed a singular response in that activity commencing in week 3 persisted through week 5. Work on this substance, in collaboration with Prof. G. T. Wogan, is continuing. M. I. values of other carcinogens tested were at control levels throughout the 8-week breeding cycle. The ethyleneimine alkylating agents, TEPA METEPA, THIO-TEPA, and triethylene melamine were all strongly mutagenic in weeks 2 and 3. The effects of methyl methane sulfonate, mutagenic as previously reported (see note 7, above), were maximal in week 2, and declined to control levels by week 3. Organic extracts of atmospheric particulate pollutants and of finished drinking water displayed control M. I. levels. The latter samples consisted of a reconstituted mixture of ethanol and chloroform adsorbate extracts in an aqueous solvent. Butylated hydroxytoluene and the 3 xanthines tested, including caffeine, showed control M. I. values. Caffeine breaks chromosomes in human cell cultures,[9] is mutagenic in bacteria,[10] and also in mice, for whom the induction of dominant lethal mutants has been claimed by W. Ostertag (personal communication), on the basis of indirect evidence of preimplantation loss following chronic administration in drinking water. Inconsistent results, however, have been reported in *Drosophila*.[11,12] The pesticides tested yielded M. I. values in the control range. Captan was administered both intraperitoneally and, at higher doses, orally.

Sensitivity of mice to this representative sampling of mutagenic agents is generally restricted to post-meiotic stages of spermatogenesis, consistent with an action on non-replicating DNA. The present testing schedule might therefore be simplified with little sacrifice of screening efficacy. Primary screening might be based on administration of a single LD_5 dose to 5 male mice who would then be mated only during the second and third week following injection. The number of animals required would thus be greatly reduced. Controls apart, only 30 females and 5 males would be needed for each drug. Positive findings revealed by this screen could be further explored. Testing could then cover the whole of the spermatogenic cycle, more animals, alternative routes of short and long-term drug administration and a wider dose range.

The diversity of potential chemical mutagens to which man is exposed urges the development of practical screening procedures. The dominant lethal test would appear suitable, especially as 80% of gene mutations in man are attributable to dominant autosomal traits.[13] The test, however, provides no information on point or recessive mutations nor on non-mutagenic sperm damage, which may, nevertheless, modify nucleic acid bases. Modification of the test procedures to evaluate the role of chronic low level exposure to environmental mutagens, either singly or in combination, is currently in progress. Possibly, differences between the reproductive cycles in mouse and man may, additionally, perturb direct extrapolation of risk. Primates aside, however, lower mammals provide the simplest means of relating mutagenic effects to human genetic hazard.

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Note added in proof: The mutagenicity of aflatoxin has been confirmed a pure sample of B_1

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TABLE 1.—MUTAGENIC EFFECTS IN MICE OF ENVIRONMENTAL POLLUTANTS: CARCINOGENS, AIR AND WATER POLLUTANTS, PHARMACEUTICALS, FOOD ADDITIVES, AND PESTICIDES

Compound	Dose mg./kg.	Number females bred	Number pregnant (percent)	Total number implants	Average number implants per mouse	Total number deciduomata	Mutagenic index
A. Controls		150	116 (77)	1,434	12.4	12	1
B. Carcinogens:							
Aflatoxin	[1] 68.0	9	7 (78)	73	10.4	8	11
Benzanthrone	1,000.0	12	10 (83)	125	12.5	0	1
Benzo[a]pyrene	750.0	18	7 (39)	53	7.6	5	[2] 11
Butter yellow	216.0	21	14 (67)	170	12.1	2	1
Cumene hydroperoxide	34.0	15	13 (87)	167	12.8	5	3
1,2,3,4-Diepoxybutane	17.0	21	17 (81)	206	12.1	4	[2] 2
Dimethylhydrazine	25.0	21	14 (67)	165	11.8	2	1
Dimethylnitrosoamine	8.0	15	11 (73)	132	12.0	3	2
Hydrazine	[3] 42.0	12	12 (100)	135	11.3	1	1
3-Methylcholanthrene	100.0	15	12 (80)	113	9.4	2	2
4-Nitroquinoline-1-ozide	5.0	21	17 (81)	204	12.0	3	2
Urethan	1,000.0	15	13 (87)	156	12.0	2	[2] 2
C. Organic extracts of atmospheric particulate pollutants:							
Boston 1966	333.0	21	16 (76)	200	12.5	4	2
Acid fraction, New York, 1967	333.0	21	13 (62)	159	12.2	0	0
Basic fraction, New York, 1967	666.0	18	14 (78)	163	11.6	2	1
Insoluble fraction, New York, 1967	333.0	21	18 (86)	222	12.3	5	2
D. Foods and food additives:							
Butylated hydroxytoluene	1,000 0.	9	4 (44)	46	11.5	0	0
Caffeine	168.0	21	12 (57)	124	10.3	0	0
Theobromine	380.0	18	12 (67)	132	11.0	2	2
E. Organic extracts of finished drinking water:							
Maine 1961	333.0	21	9 (43)	95	10.6	1	1
Yonkers 1961	699.0	21	11 (52)	139	12.6	1	1
F. Pesticides:							
Captan	9.0	21	20 (95)	210	10.5	2	1
Captan	[4] 500.0	18	15 (83)	171	11.4	1	1
DDT	105.0	18	13 (72)	135	10.4	4	3
Maleic hydrazide	500.0	15	11 (73)	121	11.0	1	1
G. Pharmaceuticals:							
Aminopterin	10.0	12	9 (75)	88	9.8	0	0
Azaribine	[4] 1000.0	21	14 (67)	151	10.8	1	1
5-bromodeoxyuridine	500.0	27	21 (78)	248	11.8	1	0
Chloramphenicol	333.0	21	14 (67)	128	9.1	2	2
Chlorpromazine	[3] 8.3	27	20 (74)	237	11.9	1	0
Griseofulvin	750.0	18	14 (78)	175	12.5	3	2
Hydroxyurea	[3] 500.0	21	14 (67)	160	11.4	0	0
5-Iododeoxyuridine	250.0	21	16 (76)	192	12.0	2	1
Metepa	40.0	21	16 (76)	145	9.1	39	27
Methyl methane sulfonate	50.0	24	19 (79)	164	8.6	47	29
Tepa	7.0	18	13 (72)	115	8.8	44	38
Thio-tepa	[3] 5.0	18	15 (83)	114	7.6	21	18
Triethylene melamine	.2	21	15 (71)	137	9.1	36	26
H. Miscellaneous:							
Acriflavine	10.6	21	14 (67)	172	12.3	0	0
Acrolein	1.5	15	12 (80)	152	12.7	7	5
Dimethyl sulfate	23.0	18	14 (78)	150	10.7	1	1
Formaldehyde	20.0	24	19 (79)	233	12.3	4	2
Methylhydroxylamine	[3] 140.0	21	12 (57)	133	11.1	0	0
Pinacyanole	1.9	12	8 (67)	99	12.4	1	1

[1] Dimethyl sulfoxide suspension.
[2] Late death occurred in each of these instances.
[3] Aqueous solution.
[4] Oral administration.

APPENDIX III

CHEMICAL MUTAGENS AS A POSSIBLE HEALTH HAZARD

(By James F. Crow, Genetics Laboratory, University of Wisconsin)

The discovery that some chemicals are highly mutagenic without being overtly toxic has led to considerable interest and concern, within government agencies and elsewhere. On September 14, 1966, the Genetics Study Section, Division of Research Grants, National Institutes of Health, sponsored a small conference on

this subject at the Jackson Laboratory in Bar Harbor, Maine.[1] Since the information developed is of interest to a wider audience, a review of the problem and the conclusions reached by this group are presented here.

I. GENERAL CONSIDERATIONS

That radiation causes genetic damage has been known for many years and the need for appropriate protection is widely recognized. The principle that exposure to radiation should be kept at the lowest practicable level and that there should be no additional exposure unless the harmful effects are outweighed by anticipated benefits is well established in public policy. The concern is not only for the health and welfare of contemporary populations, but also for future generations.

There is reason to fear that some chemicals may constitute as important a risk as radiation, possibly a more serious one. Although knowledge of chemical mutagenesis in man is much less certain than that of radiation, a number of chemicals—some with widespread use—are known to induce genetic damage in some organisms. To consider only radiation hazards may be to ignore the submerged part of the iceberg.

Recent investigations have revealed chemical compounds that are highly mutagenic in experimental organisms in concentrations that are not toxic and that have no overt effect on fertility; examples are ethyl methane sulfonate and methyl-nitro-nitrosoguanidine. Perhaps most insidious are compounds that in some concentrations induce point mutations without chromosome breakage.

We identify two kinds of problems:

1. The first is the production of a small increase in mutation rate by chemical agents. Such a slight increase could be the effect of chemical exposures that, either because the effect on mutation rate is small or the number of persons exposed is not large, produce only a slight increase in the average mutation rate. Special attention should be given to the danger of very low concentrations of highly mutagenic compounds that might be introduced into foodstuffs or otherwise be brought into contact with large populations. Even though the compounds may not be demonstrably mutagenic to man at the concentrations used, the total number of deleterious mutations induced in the whole population over a prolonged period of time could nevertheless be substantial. Such increase in mutation rate probably could not be detected in a short period of time by any direct observations on human beings. Protection from such effects must depend on prior identification of mutagenicity.

2. The second problem is one that we hope is unlikely, but which is certainly not impossible. This is that some compound presumed to be innocuous is in fact highly mutagenic and that large numbers are exposed before the danger is realized. Such a situation we shall call a "genetic emergency." This could be detected by human observations only if the effect were very large—such as a 10-fold increase in the mutation rate. If the mutational effect were accompanied by chromosome breakage, this might be detected by chromosome studies in human leukocytes. If not, it might conceivably be detected by an increased incidence of certain genetic diseases. The hope would be to detect the effect early enough that the cause might be identified before the damage became more extensive.

The general consequences of an increased mutation rate have often been discussed in connection with radiation hazards and will not be repeated here.

II. SOME KINDS OF CHEMICAL MUTAGENS

The most sensitive tests of mutagenicity employ microorganisms; hence it is no surprise that there are a number of chemicals that are clearly mutagenic in these organisms but whose effect on higher organisms, and man in particular, is unknown. Nevertheless, identity of the genetic material in all organisms implies that a chemical that is mutagenic to one species is likely to be in others and must be viewed with suspicion.

Demonstration that a chemical is mutagenic or not in experimental organisms does not prove that it is the same for man. Some chemicals may not be distributed to the appropriate organs or tissues in man, or they may be detoxified by human enzymes. On the other hand, some compounds not mutagenic themselves may pos-

[1] The members of the Genetics Study Section when the report was prepared were: Alexander G. Bearn, Allan M. Campbell, Barton Childs, C. Clark Cockerham, J. F. Crow, A. H. Doermann, A. Dale Kaiser, Alfred G. Knudson, Jr., Edward B. Lewis, David L. Nanney, Elizabeth S. Russell, Margery W. Shaw, Adrian M. Srb, H. Eldon Sutton, and William J. Welshons.

sibly be converted into mutagens in the human body. Nevertheless, almost all of the mutagens now known for higher organisms (and many carcinogens) are mutagenic for microorganisms. Furthermore, those mutagens that have been widely tested are usually mutagenic for a variety of organisms. Demonstration of mutagenicity in several experimental organisms plus knowledge of the distribution and metabolism of the compound in man or other mammals would be useful in identifying compounds that are potentially mutagenic in man. In general, the greater the variety of organisms and systems tested and the closer these are to man, the more reliable is the prediction of the effect on man.

Many mutagenic compounds are chemically related to the nucleic acid bases. Others, such as nitrous acid and some alkylating agents, are known to react with nucleic acid components. Still others are strongly reactive compounds whose specific action on the genetic material is not known.

At present, some reasonably accurate predictions or guesses about mutagenicity can be made from chemical structure. Also, many carcinogenic compounds are mutagenic, and vice versa. However, a direct test for mutation production in living organisms is more definitive.

An example of a compound that should have further study is caffeine, particularly because it is consumed so widely and in large amounts. Caffeine is known to enhance the mutation rate in several microorganisms, and to break chromosomes in plants and in human cell cultures. On the other hand the existing evidence from Drosophila and mouse studies is not clear.

The kinds of compounds that should be examined for mutagenicity, either because of a high probability of being mutagenic or because of widescale use, include (a) industrial chemicals; (b) agricultural chemicals, particularly herbicides, food additives, insecticides, and chemosterliants; (c) pharmaceutical chemicals including antibiotics, vaccines, contraceptives, and cosmetics; (d) processed foods; and (e) air pollutants.

As knowledge grows it becomes increasingly important that it become easily available. We believe that there should be some centralized repository of information on mutagenic chemicals. This should include such things as the chemical nature, quantiative information on mutagenicity and the particular test systems on which this information is based, and other biological effects (such as carcinogenesis). With such information intelligent judgments can be made as to whether the potential benefits of the chemical outweigh its probable risks. It should be realized that we almost never have direct human information (except possibly on chromosome breakage) and hardly ever good information from any mammal, but shall have to rely primarily on the more sensitive test system of insects, plants and microorganisms.

Recommendation 1.—That an up-to-date register of mutagenic chemicals be kept and the information made generally available.

III. MEANS OF ASSAYING CHEMICALS FOR MUTAGENICITY

The unfortunate fact is that usually the more sensitive the assay system is, the further removed it is from man. Ideally, we would measure the effect on man or other primates; next best might be a mammal, such as the mouse; next might be a multicellular animal, such as Drosophila; and so on.

Some examples of assay systems that might be employed in routine screening of chemical compounds are:

1. *DNA transformation.*—One system that is well developed involves the tryptophane synthetase system in *B. subtilis.*

2. *Virus systems.*—Bacteriophage provides a variety of well characterized mutations whose reversions can be selectively scored with very high efficiency. The system provides methods for measuring the effects of mutagenic agents both on replicating and on nonreplicating DNA and permits good discrimination between mutagens causing base substitutions, deletions or additions, or grosser alterations.

3. *Bacterial systems.*—Several gene loci in *E. coli* and *Salmonella* can be used for a rapid screening. Both forward and reverse mutations can be studied simply and efficiently. In addition, one can analyze for the mutagenic specificity and for the type of alteration (e.g. base change or frame-shift).

4. *Yeast.*—This has the advantage over bacteria of permitting both haploid and diploid tests, and of being a eukaryote. The purine biosynthesis system permits a rapid visual screening.

5. *Neurospora.*—The Adenine-3 locus is adapted to rapid tests for both forward and reverse mutations.

6. *Higher plants.*—Several systems permit rapid scoring for chromosome breaks.

7. *Drosophila.*—Relatively inexpensive scoring of visible and lethal mutations and genetic tests for chromosome changes are possible.

8. *Mouse.*—Although less sensitive and more expensive; tests for dominant lethals, specific locus recessives, and teratogenic effects are available.

9. *Human tissue cultures.*—Tests for chromosome breaks are available, and tests for point mutations are being worked out.

It should be emphasized that these are intended only as possible examples and not as specific suggestions. They are not necessarily the best test systems available.

The efficient, sensitive, and inexpensive tests on micro-organisms could be carried out on the same scale as toxicity tests are now done. We believe that simple tests for mutagenicity and for chromosome breakage, loss, and nondisjunction should be a part of the routine testing of new chemicals to which humans are exposed. The more expensive tests on organisms closer to man could be employed for those substances to which man is exposed on the largest scale.

Recommendation 2.—That tests for mutagenicity be a routine part, such as toxicity tests now are, of the testing of chemicals that are used as food or drugs, or to which large numbers of persons may be exposed for other reasons.

Recommendation 3.—That research to develop more sensitive and cheaper assays of mutagenicity and chromosome breakage, or assays based on organisms more closely related to man, be encouraged and supported.

IV. MONITORING THE HUMAN POPULATION

As has been emphasized already, mutagenicity of a chemical in one organism is no guarantee that it will be mutagenic in another. This is particularly true if the comparison is from bacteria to man. For this reason it is possible, even with the most rigorous screening procedures, that there will be widespread unwitting exposure of human populations to potent mutagens.

At present there is no feasible way of detecting promptly a small or moderate increase in the human mutation rate. But it might be possible to discover a change so great as to constitute a genetic emergency.

There are several possibilities of which two seem most feasible. The first is chromosome monitoring. This could be done by regular sampling of human blood cells and searching for gross chromosomal changes. Cord blood from newborn infants is easily available and sampling this might have the advantage of studying the part of the population that is perhaps most susceptible to chemical influences, i.e., the unborn.

At the present time wide scale studies of this type are very expensive and there is a shortage of properly trained personnel. However, there is a reasonable hope that computerized methods capable of detecting gross changes will become feasible.

Detection of an increase in mutation rate unaccompanied by somatic chromosome breakage would be still more difficult, and only an enormous increase could be detected. However, it is just such an enormous increase that is most important to detect.

One possible means would be a monitoring of frequencies of certain genetic diseases. To be maximally effective as an indicator of changed mutation rate the disease should be:

(1) dominant, so as to appear in the first generation following exposure;

(2) present at birth or early childhood, so as to reflect promptly an increased rate;

(3) conspicuous, so as not to be overlooked;

(4) of a characteristic phenotype, not mimicked by other traits not of mutational origin;

(5) of a nature leading to death or sterility with a high probability so that a high fraction of the cases are new mutants.

Achondroplasia might possibly be a suitable example. Some X-chromosome recessives might be used. These would be less satisfactory, in that only ⅓ or less of the cases are new mutations; but they would provide an opportunity to study recessive conditions.

A dramatic change in sex-ratio might also be indicative, but is neither so sensitive nor so unambiguous in interpretation, as an increase in known dominant conditions.

Such a system of up-to-date genetic monitoring of births would be both difficult and expensive. Its expense might be mitigated by being combined with a search for increased anomalies such as might arise from teratogens.

Recommendation 4.—That the feasibility of genetic monitoring of the human population for chromosome breakage and increased genetic disease be explored.

Our next witness this morning is Dr. E. Cuyler Hammond, vice president, department of epidemiology and statistics, American Cancer Society of New York.

Dr. Hammond I appreciate your being with us.

STATEMENT OF DR. E. CUYLER HAMMOND, VICE PRESIDENT, DEPARTMENT OF EPIDEMIOLOGY AND STATISTICS, AMERICAN CANCER SOCIETY, NEW YORK, N.Y.

Dr. HAMMOND. Mr. Chairman, if you will permit me, before beginning I would like to congratulate the staff of your committee on this perfectly excellent review. I have studied it carefully and I can honestly say that it is by far the best review of this complicated subject that I have seen so far. I think that I would like to congratulate them.

Senator MUSKIE. I appreciate that very much, Dr. Hammond. I think I ought to add my own appreciation for the staff's efforts. They have done work of this quality in other areas. They have been complimented but I guess this is the first time I have done it for the record.

Thank you.

Dr. HAMMOND. It has long been known that certain air contaminants are harmful to human beings. The degree of harm depends upon the type of contaminant, its concentration in the air, and the duration of exposure.

There is reason to suspect that air contaminants of almost all types can, in high amounts, be injurious to health; however, we have little or no knowledge of the possible effects of a vast number of different types of contaminants to which millions of people are exposed. It may be that in some instances serious harm is done not by a single contaminant but by a combination of contaminants acting in concert.

MODES OF EXPOSURES

A very large proportion of our citizens are exposed to complex combinations of various air contaminants—in two or more different ways. For the purposes of this discussion, it is convenient to divide these into four categories:

(1) General pollution spread over a wide area with everyone living in that area being exposed. In metropolitan areas, the bulk of the contamination comes from the burning of organic material. In rural areas, aeroallergens may be of prime importance.

(2) Neighborhood air pollution to which people living in a restricted area are exposed. An example of this would be asbestos fibers, exhausted from a plant, contaminating the air within a radius of perhaps half a mile. I think that this type of neighborhood air pollution deserves very special consideration at the present time.

(3) Occupational exposure to various dusts, fumes, and gases. This may be more common than is generally supposed. In a recent study of 456,000 men living in 1,121 counties in 25 States, we found that 29.0 percent of those living in cities or metropolitan areas and 53.8 percent of farmers reported that they had occupational exposure of this type.

(4) Cigarette smoking.

CONSIDERATIONS IN STUDY DESIGN

I understand that this hearing is primarily concerned with the problem of general air pollution and neighborhood air pollution. However, from the standpoint of scientific investigation of effects upon health, it is necessary to take at least two, if not three, of the four modes of exposure into consideration in order to obtain sound information about any one of them. There are two reasons for this:

(1) An individual may be exposed to the same air contaminant in several different ways. For example, a cigarette-smoking automobile mechanic who lives in a large city inhales carbon monoxide while breathing general city air; inhales carbon monoxide in higher concentration while at work; inhales an additional amount while smoking cigarettes.

Carbon monoxide, I should say, is the greatest air contaminant (if judged by weight) and I think more work should be done on this particular problem.

(2) There is the possibility that serious effects are produced by a combination of contaminants from different sources. I will give you an example of this in a moment.

STUDY OF EMPHYSEMA IN METROPOLITAN AREAS

To illustrate the problem and also to provide some pertinent information, I would like to describe the preliminary results of a current study.

My primary purpose in making the study was to obtain information on the prevalence of pulmonary emphysema in metropolitan areas in contrast with the prevalence of pulmonary emphysema in rural areas (other factors being taken into consideration).

My second purpose was to obtain information on the possible effects of common occupational exposures to dust, fumes, and gases upon the occurrence of emphysema. Cigarette smoking was taken into consideration as a control variable.

Study group

The subjects of the investigation were 126,986 men between the ages of 45 and 74 who had been enrolled in a prospective epidemiological study by volunteer workers of the American Cancer Society in late 1959 and early 1960, and the subjects then traced for a period of 6 years. Of these men 82,100 lived in metropolitan counties containing a city of over 500,000 population. There were 21 such cities in the United States in 1960 and 17 of them were included in the study. The remaining 44,886 men lived in rural counties (as defined by the Census Bureau), these counties being in 24 different States.

TABLE 1.—NUMBER OF SUBJECTS AND NUMBER WITH PULMONARY EMPHYSEMA OR COMPLAINTS SUGGESTIVE OF EMPHYSEMA BY AGE, BY PLACE OF RESIDENCE, BY OCCUPATIONAL EXPOSURE TO DUST, FUMES, GASES, AND BY SMOKING HABITS

['Metropolitan county" here means county in a metropolitan area containing a city of over 500,000 population; "rural county" means a county so defined by the Bureau of the Census; but miners living in such counties are excluded]

Age and residence	Occupational exposure to dust, fumes, gases	Never smoked regularly		Current cigarette smokers							
				1 to 9 a day		10 to 19 a day		20 to 39 a day		40-plus a day	
		Total	With finding [1]	Total	With finding [1]	Total	With finding [1]	Total	With finding [1]	Total	With finding [1]
(a) Men aged 45 to 54:											
Metropolitan	No exposure	11,085	34	1,557	14	3,648	43	14,135	411	3,710	234
Rural	do	4,841	19	648	9	1,413	20	4,789	181	967	84
Metropolitan	Exposure	4,124	24	561	12	1,508	37	6,134	325	1,393	123
Rural	do	3,793	42	474	6	1,077	34	3,793	244	658	78
(b) Men aged 55 to 64:											
Metropolitan	No exposure	7,524	41	1,069	23	2,273	62	6,701	315	1,408	139
Rural	do	4,782	35	586	13	1,058	37	2,607	145	380	34
Metropolitan	Exposure	2,374	25	314	15	812	34	2,428	207	468	64
Rural	do	2,735	50	345	22	583	33	1,523	148	239	38
(c) Men aged 65 to 74:											
Metropolitan	No exposure	3,855	32	511	12	836	46	1,476	110	202	15
Rural	do	4,032	39	352	15	451	29	741	79	72	12
Metropolitan	Exposure	1,025	24	143	15	244	18	503	56	79	13
Rural	do	1,357	32	104	6	163	17	302	41	21	3

[1] "With finding" means emphysema or complaints suggestive of emphysema.

Table I, which you will find in the back of the report, sir, shows the subjects classified by residence; by occupational exposure to dust, fumes, or gases; and by smoking habits. For simplicity, we confined the investigation to men who had either never smoked regularly or who were currently smoking cigarettes regularly at the time of enrollment.

Upon enrollment, each subject answered a lengthy questionnaire containing questions on past and present diseases, present physical complaints, occupation, occupational exposure, and smoking habits. They were traced for 6 years and causes of death were ascertained from death certificates.

Extent of problem

Until recently, emphysema has not been an important cause of death in the United States; but it is a major cause of disability and the incidence of the disease is rapidly increasing. The Public Health Service estimates that emphysema is probably the second cause of disability in the United States today.

The chief symptom is shortness of breath—usually accompanied by chronic coughing and a tendency to fatigue easily; it is often accompanied by pain or discomfort in the chest. It is likely that a man has emphysema if he has a combination of these symptoms in the absence of asthma, tuberculosis, heart disease, or high blood pressure, which could produce some of them.

Since emphysema is a chronic disease, any subject who died of it within 5 years after the start of the study almost certainly was suffering from it at the time he enrolled.

Table I shows the number of subjects in each of various categories—residence, occupational exposure, and smoking habits—who either died of emphysema or had complaints suggestive of emphysema. (I should say that severe shortness of breath and a tendency to fatigue easily can be disabling whether or not they are due to emphysema.) Therefore, findings in relation to these complaints are important regardless of whether or not they are technically called emphysema.

Table 2 shows percentages based upon the figures on table I. I merely divided them into two tables for ease of reading.

TABLE 2.—PERCENT OF SUBJECTS WITH PULMONARY EMPHYSEMA OR WITH COMPLAINTS SUGGESTIVE OF EMPHYSEMA BY AGE, BY PLACE OF RESIDENCE, BY OCCUPATIONAL EXPOSURE TO DUSTS, FUMES OR GASES AND BY SMOKING HABITS

Residence	Occupation exposed to dust, fumes, gases	Never smoked regularly	Current cigarette smokers			
			1 to 9 a day	10 to 19 a day	20 to 39 a day	40-plus a day
(a) Men aged 45 to 54:						
Metropolitan	No exposure	0.3	0.9	1.2	2.9	6.3
Rural	do	.4	1.4	1.4	3.8	8.7
Metropolitan	Exposure	.6	2.1	2.5	5.3	8.8
Rural	do	1.1	1.3	3.2	6.4	11.9
(b) Men aged 55 to 64:						
Metropolitan	do	.5	2.2	2.7	4.7	9.9
Rural	do	.7	2.2	3.5	5.6	8.9
Metropolitan	Exposure	1.1	4.8	4.2	8.5	13.7
Rural	do	1.8	6.4	5.7	9.7	15.9
(c) Men aged 65 to 74:						
Metropolitan	No exposure	.8	2.3	5.5	7.5	7.4
Rural	do	1.0	4.3	6.4	10.7	16.7
Metropolitan	Exposure	2.3	10.5	7.4	11.1	16.5
Rural	do	2.4	5.8	10.4	13.6	14.3

Note: "Metropolitan" as here used means residence in a county containing a city of over 500,000 population. There were 21 such cities in America in 1960 and 17 of them were included in this study. "Rural" means residence in a county classified as rural by the Bureau of the Census. Miners living in such counties were excluded from this analysis.

Occupational effects

Table 3 was condensed from the data shown on the two early tables. It is designed for ease of comparison between men with occupational exposure to dust, fumes, or gases and men without such exposure, within classes, by cigarette smoking and age. The figures indicate the percent of men who died of emphysema or had complaints suggestive of the disease.

TABLE 3.—PERCENT OF SUBJECTS WITH PULMONARY EMPHYSEMA OR COMPLAINTS SUGGESTIVE OF EMPHYSEMA BY PLACE OF RESIDENCE, BY OCCUPATIONAL EXPOSURE TO DUSTS, FUMES, OR GASES, AND BY SMOKING HABITS. DATA ARRANGED SO AS TO SHOW DIFFERENCE BETWEEN MEN WITH OCCUPATIONAL EXPOSURE AND MEN WITHOUT OCCUPATIONAL EXPOSURE

Men aged 45 to 64

Residence	Occupations exposed to dust, fumes, gases	Never smoked regularly	Current cigarette smokers		
			10 to 19 a day	20 to 39 a day	40-plus a day
Rural	Exposed	1.45	4.45	8.05	13.90
	Not exposed	.55	2.45	4.70	8.80
	Difference	.90	2.00	3.35	5.10
Metropolitan	Exposed	.85	3.35	6.90	11.25
	Not exposed	.40	1.95	3.80	8.10
	Difference	.45	1.40	3.10	3.15

Note: Based upon percentages shown on table 2 for men aged 45 to 54 and men aged 55 to 64. Each percentage shown here is the average of the percentages for the 2 age groups.

This table shows that among both rural and metropolitan residents and for each smoking category, indications of emphysema occurred more frequently among men with occupational exposures than among men without occupational exposures to dust, fumes, or gases. The differences associated with occupational exposure were somewhat more pronounced among men living in rural areas than among men living in metropolitan areas.

Combined effects

Of particular interest is what appears to be a combined effect of occupational exposure and cigarette smoking, taken together. For example, consider rural residents. Only 0.55 percent of those who neither smoked nor were occupationally exposed to dust, fumes, and vapors had indications of emphysema. On the other hand, 1.45 percent of nonsmokers with occupational exposure had such indications. This is a difference of 0.90 percent. In contrast, 8.80 percent of very heavy cigarette smokers without occupational exposure and 13.90 percent of very heavy cigarette smokers with occupational exposure had indications of emphysema. This is a difference of 5.10 percent.

These findings suggest that occupational exposure to dust, fumes, or gases has a far greater effect (in respect to emphysema) upon cigarette smokers than upon nonsmokers. To put it another way, the combination of the two factors appears to have a far greater effect than might be expected from the effect of each of the two alone.

Urban-rural differences

Table 4 contains the same figures as table 3 but arranged in such a way as to facilitate comparison between rural and metropolitan resi-

dents. The results surprised me when I saw them. Among both men with and men without occupational exposure and for each smoking category indications of emphysema were more common among rural residents than among metropolitan residents.

TABLE 4.—PERCENT OF SUBJECTS WITH PULMONARY EMPHYSEMA OR COMPLAINTS SUGGESTIVE OF EMPHYSEMA BY PLACE OF RESIDENCE, BY OCCUPATIONAL EXPOSURE TO DUST, FUMES, OR GASES, AND BY SMOKING HABITS. DATA ARRANGED SO AS TO SHOW DIFFERENCE BETWEEN MEN LIVING IN RURAL AREAS AND MEN LIVING IN METROPOLITAN AREAS

Men Aged 45 to 64

Occupations exposed to dust, fumes, gases	Residence	Never smoked regularly	Current cigarette smokers		
			10 to 19 a day	20 to 39 a day	40-plus a day
Exposed	Rural	1.45	4.45	8.05	13.90
Do	Metropolitan	.85	3.35	6.90	11.25
Do	Difference	.60	1.10	1.15	2.65
Not exposed	Rural	.55	2.45	4.70	8.80
Do	Metropolitan	.40	1.95	3.80	8.10
Do	Difference	.15	.50	.90	.70

This difference is greater among men with occupational exposures than among men without occupational exposures and is much greater among cigarette smokers than among nonsmokers. The mechanisms underlying the effects of multiple factors are unknown except in a very few instances, but a growing body of evidence suggests that multiple factors may be involved in the etiology of some chronic diseases.

Specificity

Now, I should like to point out certain problems relating to the specificity of the information I have just given and the danger in drawing general conclusions concerning the effects of rural versus urban air pollution from findings such as these.

While different brands of cigarettes vary somewhat, the smoke from all brands contains nicotine, carbon monoxide, and certain hydrocarbons. Furthermore, we have information on the degree to which each subject was exposed to cigarette smoke. Thus, with respect to cigarette smoking, the exposure information in this respect is both specific and quantitative.

In respect to occupational exposures, our information is not quantitative. As shown on these tables, it is not specific since a great many different types of occupational exposure to dust, fumes, and gases are grouped together—garage mechanics with chemical workers.

However, we at least know which men did and which men did not have such exposures. Furthermore, we have data with which we can make an analysis by type of occupational exposure; and hopefully this will help to clarify the matter. It will take a year or two to complete that. In all probability, some types of occupational exposure are seriously harmful in respect to emphysema while others may be relatively innocuous in this respect.

The situation is entirely different in respect to rural versus metropolitan residence which provides no specific information on the exposures of individuals. True, general air pollution in some rural areas may (at some time of the year) contain far more aeroallergens than general air pollution in metropolitan areas; and perhaps this in-

creases the occurrence of emphysema or complaints suggestive of emphysema in rural areas. However, this is only one of a host of differences between rural and urban living; and some other factor associated with rural residence (perhaps simply exposure to elements) may account for the findings. A farmer has to take care of his chickens whether or not it is raining.

Variations in air quality

More important, general air pollution varies greatly from place to place and from time to time, in respect to both composition and concentration. Thus, it is meaningless to speak of general air pollution as though it were a single descrete entity. The problem is further complicated by the fact that many metropolitan dwellers are additionally exposed to specific neighborhood air pollution of various types.

When I first conceived of the study described above, I was hopeful that air pollution control authorities throughout the country could provide me with some reasonable estimates of the types and amounts of air pollution present in the many neighborhoods in which I planned to collect information on the health of residents. This turned out to be a false hope.

Causative agents

It is now urgent that pertinent environmental data on air pollution (both general and neighborhood) be collected and correlated with data on the health of individuals. Primary consideration should be given specific types of air contaminants which are likely to have an effect upon health in contrast to reporting on such things as soiling index and similar phenomena. Team work between epidemiologists and air pollution control authorities is essential for success in this undertaking. Some such work has been done, but pitifully little in relation to the importance of the problem.

While I thoroughly agree that it is wise at this time to reduce air pollution of all types insofar as it is feasible and economically possible to do so, much of the effort and huge sums of money may be wasted unless we obtain more information on just what air contaminants are most important in relation to health and the concentrations at which they become dangerous.

LUNG CANCER CAUSATION

Before closing, I must say a word about the problem as it relates to cancer. There is abundant evidence that cigarette smoking and occupational exposure to a few specific types of air contaminants enormously increase the risk of lung cancer.

Asbestos

There is evidence that at least one type of neighborhood air pollution, asbestos dust, which has been studied, can, under some circumstances, increase the risk of mesothelioma (a type of cancer) and it may increase the risk of lung cancer. In my opinion, this problem requires further investigation. Attention should be given to the possible danger of various other types of neighborhood air pollution.

Special attention should be given to pollutants known to cause an increase in cancer among industrial workers who are exposed to them.

At the present time, there is no firm evidence that general air pollution increases the risk of cancer. However, as I have said before, general air pollution varies greatly in type and concentration from one area to another. Present evidence does not rule out the possibility that in some areas there are special types of general air pollution which involve at least a slight risk of cancer. If so, the risk might be negligible except among people with multiple exposures.

Thank you, sir.

Senator MUSKIE. Thank you very much, Dr. Hammond.

I gather that you and Dr. Epstein have different levels of concern about the risk of cancer from general air pollution. You are in a better position to evaluate his testimony than I am, really, so I would like to ask whether or not that is true.

Dr. HAMMOND. Having heard his testimony, I think it is probable that we are in considerable disagreement; but perhaps that is not so. He spoke mostly about animal experimental work.

ANIMAL STUDIES

Now, the American Cancer Society supports a great deal of research work on animals and I am all for it; it is particularly useful in ascertaining mechanisms. However, what we find out about cancer in the experimental animal does not necessarily apply to human beings. Some things that do not cause cancer in experimental animals can cause it in human beings and vice versa. For example, we know that exposure to arsenic can cause cancer of the skin in human beings. Yet, at least up to my last hearing, nobody has even been able to produce cancer by applying arsenic to the skin of experimental animals. In order to find out what causes cancer in man, we have to study man.

Animal experimentation gives very valuable information. I thoroughly agree with Dr. Epstein's program to locate suspects; but having found the suspects in animals, then we have to see whether human beings are affected in the same way as animals.

In my opinion, the greatest opportunity we have to study this is to find groups of people who are occupationally exposed to various agents in relatively high concentrations and then determine whether these people have a high incidence of cancer. This is the closest we can come to experimenting on human beings.

Let me give an example of what I have in mind.

ASBESTOS STUDY

Extremely heavy occupational exposure to asbestos dust causes a serious and often fatal lung disease known as asbestosis. With lighter occupational exposure, relatively few workers die of asbestosis; but after 20 years or so, they have a very high death rate from lung cancer and some die of mesothelioma.

There is evidence that somewhere between 20 and 50 percent of people living in certain American cities have some asbestos fibers in their lungs. The question is whether the small amount of asbestos does them any harm.

To investigate the matter, Dr. Irving Selikoff and I plan to study a group of people who were exposed to neighborhood air pollution from asbestos dust. These people lived for some years in the vicinity of an asbestos plant—now closed—which exhausted asbestos dust into the outside air. They presumably had far less exposure than workers in the plant but more exposure than most people who never lived near such a plant. Our plan is to trace all of them and determine whether or not they had an unusually high death rate from lung cancer, other lung diseases, or mesothelioma.

CHEMICAL CARCINOGENS

Senator MUSKIE. What, if any, chemicals which are found in general air pollution have a potential for creating cancer?

Dr. HAMMOND. The general air pollutant that has been most frequently discussed in relation to cancer is 3,4-benzopyrene. It is present in cigarette smoke and it is present in general air pollution. German investigators have found trace amounts of it in many plants; and they have expressed the opinion that plants need it for cell division.

This agent causes cancer in experimental animals. Therefore, some people suspect that it may be capable of causing cancer in man.

Study of occupational groups

Dr. Selikoff and I are looking into the matter with the cooperation of the roofing trade. In putting flat roofs on buildings, the workers put down paper or felt and then they pour molten material over it, sometimes using asphalt and sometimes using pitch. Pitch is derived from coal tar and fumes rising from the hot material contain an enormous concentration of 3,4-benzopyrene as compared with city air or cigarette smoke.

So, we are studying these workers to see whether they in fact have an increased death rate from lung cancer or cancer of any other type. This will be a human test to see whether the animal experiments do or do not apply to man.

Senator MUSKIE. When will you begin to get results from tests of that kind?

Dr. HAMMOND. Well, on this particular one, we are very nearly finished, sir. I hate to put in the public record what the results are because we have not quite finished.

Dr. Patrick Lawther, who is the head of the Air Pollution Research Unit of the British Medical Research Council, has cooperated. His laboratory has probably done more work on these chemicals than any other laboratory. We had roofing workers all over the country wear masks while at work to collect the material which they would otherwise have inhaled. We then sent the filters to London for chemical analysis. We are tracing all members of the roofers union to determine their death rate from lung cancer, emphysema, and other causes.

Factors influencing effects

Senator MUSKIE. Are there any other chemicals in general air pollution which have the potentials of cancer?

Dr. HAMMOND. It is a little hard to answer it for this reason, sir: I am coming more and more to the conclusion that most human cancers are not produced by extremely high exposure to a single chemical

agent. Except in a few industrial situations people just don't get that sort of exposure. For example, I cannot think of any extremely heavy such exposure that a lawyer would get; but many lawyers develop cancer. We do know and have known a long time from animal experimentation that there are certain agents called cocarcinogens which don't produce cancer in themselves but which enormously increase the cancer-producing potential of small amounts of some other agent.

My suspicion, though I have not proved it yet, is that this is a major cause of human cancer. There is no use in screening such agents to see whether they produce cancer because they don't by themselves. They produce cancer only in the presence of certain other agents.

Asbestos

With asbestos, we have the very interesting finding that the lung cancer incidence was far higher in a group of asbestos workers as in the general public. But in this study, lung cancer has only occurred among the asbestos workers who were smokers. Smoking asbestos workers had eight times as much lung cancer as cigarette smokers not exposed to asbestos. We are studying this further in a larger group of people to see whether this finding holds up.

The present impression is that asbestos works as a cocarcinogenic agent, enormously increasing the cancer-producing potential of cigarette smoking. This is why I am worried about combinations of agents rather than simply looking for one agent that is harmful in itself.

EPIDEMIOLOGICAL STUDIES

Senator MUSKIE. Since there is no effective way to test humans exposed only to general air pollution, how do we get at that point?

Dr. HAMMOND. Well, sir, I think your staff found out in reviewing the literature that this is an extraordinarily difficult problem. We can get some hints from experiments. My own feeling is that the best way to proceed is to make more intensive studies than we have in the past of occupational groups and then move from there to neighborhood groups with lighter exposure to the same air contaminants.

Senator MUSKIE. I would like to ask two questions related to the current law, of the techniques of the current law to deal with the problem.

CRITERIA FEASIBILITY

First of all, the development of specific criteria. Is this a valid approach to the problem of establishing a medical basis or a medical judgment at least for control policies and mechanisms?

Dr. HAMMOND. I am not an expert in the field of controls of this sort. I can oly give you my opinion, sir, and I have thought about it a good deal before coming down here.

There are two aspects of it. I would say that we in actual fact have no basis for specifying a particular amount of a particular substance in the atmosphere saying above this amount the substance is harmful and below this amount the substance is not harmful. There is simply no evidence and I don't think we will ever get evidence precise enough for that.

On the other hand, I think the evidence we have, particularly about episodes of severe smog (which are described in the report of your

staff and which I didn't put in my testimony) indicates that a very strenuous effort should be made to reduce air pollution from all sources insofar as we can.

It is very much like what you said in your opening remark. We cannot pinpoint the exact concentration at which certain agents become harmful. At the same time, there is so much general evidence that it would be foolish to risk the health of our whole population. It may turn out we are wrong in worrying about present levels of air pollution. But I would rather be wrong in controlling air pollution unnecessarily than be wrong in not controlling it and later finding that it causes enormous damage in the future.

Air pollution indices

Now, there is one thing that dose worry me somewhat and I would like to put it on the record. I hate to say this but many of our air pollution control people seem to measure what is easy to measure rather than what is of any particular importance in relation to health. Soiling index, I suppose, is important to the person hanging out her wash; but that is not the thing that we are most concerned about.

Dust counts are often made. At a meeting one person presented a report on how he was classifying dust particles in the air. Some of us started laughing. What he was counting and analyzing was what we considered to be large rocks. They were so big they could not be inhaled. They might dirty the hands; but this is trivial as compared with the damage which can be done by particles small enough to be inhaled.

Sulfur has been greatly studied, not that there is much evidence that it is harmful in low concentrations. Yes, it is harmful in high concentration, but it has received great attention mainly because it is easy to measure.

We have paid too much attention to indices of air pollution as distinguished from studying specific compounds, interactions between them and what they do to human beings.

Sulfur oxides

Senator MUSKIE. Since you touched on sulfur, what are the risks that can flow from the presence of sulfur in the air?

Dr. HAMMOND. I would say that information on this is very shaky. Studies have been made in Washington, Baltimore, and I think Westchester County, as compared with London and certain English cities and an English town. There was more sulfur in the air in British places, including the British town, than there was in Washington and Baltimore. There was more chronic bronchitis in the British situation than there was here.

There are unexplained reasons for the very high rate of bronchitis in the British Isles. Possibly it is because of their climate, possibly because of the way they heat—or, I should say—don't heat their houses; we don't really know.

The only piece of evidence on this that I have seen that seems to hold water is a study made by an English doctor among people in London who were suffering from chronic lung disease. Every day he got a postcard from them saying whether they felt a little bit better or a little bit worse. Then he compared their reports with the sulfur

content of the air. Many of these people seemed to feel worse when the sulfur was high than when the sulfur was low.

Senator MUSKIE. Let me ask you a more general question perhaps related to that one.

Air pollution episodes

There have been no episodes of this kind in California or in Los Angeles but there have been in New York and London.

Dr. HAMMOND. In New York, I am not so certain of the evidence, sir. In London, there is no doubt at all concerning what happened during and after the great smog episodes. The mechanisms are unclear. There are some very interesting findings. Overall, the increase in death rates covered the whole range of chronic diseases, most particularly heart diseases and lung diseases.

There may have been an epidemic of influenza hitting at the same time. If there was, it is very possible in my mind the air pollution created a situation in which influenza spread more rapidly. It is a very complicated situation.

I would say one would be very foolish, however, to disregard the evidence. I would say it is almost certain that by one mechanism or another these occasional episodes of very high air pollution have brought disaster.

Senator MUSKIE. Well, your view appears to be that it is difficult and it probably will continue to be difficult to relate health effects to concentrations of specific pollutants.

Dr. HAMMOND. Yes, sir.

Senator MUSKIE. That it is difficult and probably will continue to be difficult to relate it to combinations of chemicals in the air but that nevertheless we should move forward to reduce emissions and exposures to these chemicals.

The difficulty then still faces us as to how much specific knowledge ought we to have before we move and how much control ought we to impose upon the volumes of emissions that we get from the specific kinds of industries with respect to specific kinds of pollutants.

APPROACHES TO CONTROL

Without assuming anything about the fairness of asking you such a question, could you suggest other approaches to control that would be more realistic, more valid, and perhaps more sound in the light of the difficulties that we face in getting the specific information on the relationships?

Dr. HAMMOND. I think you implied a division between two parts of this question.

For example, consider the situation in Birmingham with air pollution from steel mills. I think with a real effort within 2 or 3 years we could get very sound information as to the hazards, if any, of this particular type of air pollution. Records are available if they would be made available to the investigator—it is very hard to get them.

Union groups are now beginning to cooperate in making their records available to research workers. Where we have gotten such records, we have gotten answers rather quickly.

I think it is fair to assume that if workers are exposed to several hundred times the concentration of something that other people are and do not get ill, do not have ill effects, you can be fairly sure that minor concentrations of the same substances in general air pollution are not harmful. If they do get ill, then you have to take steps to protect the workers. This is usually not too difficult. If people living in the vicinity also show ill effects, then steps can be taken to prevent the harmful substances from getting into the air of the community.

When it comes to such things as the burning of coal or the burning of trash in incinerators, I think I will have to say this, which I am afraid is not very satisfactory to you. I think that just from the standpoint of nuisance—the dirtying of buildings, window sills, and clothes and the interference with visibility—there is good reason to reduce general air pollution from these sources as much as you can.

For that purpose, soiling index and visibility index are valid criteria. If you reduce air pollution for this purpose, you will certainly be taking a step in the right direction. In the meantime we can make more specific studies and hopefully come out with an identification of which air pollutants are most important from the standpoint of health.

I do worry, however, when the solution of the air pollution problem from coal in New York is talked about as using coal without sulfur in it. Sulfur in the air is an index of the degree of air pollution from coal which contains sulfur. For all we know, substituting a different sort of coal might be much worse. We simply don't know. Reduction in the index would not necessarily be accompanied by a reduction in air pollution from agents which may be far worse than sulfur.

Senator MUSKIE. One further question suggested by the interesting evidence you had on the rural-urban difference here.

URBAN-RURAL DIFFERENCES

Is it possible that the urban dweller or the statistics on the urban dweller indicate his capacity for adapting to these pollutions?

Dr. HAMMOND. Frankly, these results were surprising to me. I thought that they were going to go in the other direction; but this is evidence and evidence is better than preconceived opinions.

I think probably there is a real rural factor. I am not sure, but I think it is very likely that aeroallergens play a part—ragweed and the like. With additional work, perhaps we can identify the culprit.

There is a limit to how much I can do on this personally since my major field is cancer research; but somebody should push it.

There are other differences between rural and urban living which could easily have an effect upon lung disease. For example, the farmer has to go out and take care of the cattle and the pigs regardless of the weather, regardless of whether he has a cold, and in many rural counties there are no doctors readily available to treat him if he develops a lung ailment.

Senator MUSKIE. Thank you very much, sir, for your excellent testimony and the colloquy that has been useful to me.

Dr. HAMMOND. Thank you.

(Questions submitted by Senator Muskie and the response by Dr. Hammond follow:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. E. CUYLER HAMMOND,
Director, Department of Epidemiology and Statistics, American Cancer Society, New York, N.Y.

DEAR DR. HAMMOND: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional question shave arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. E. CUYLER HAMMOND

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, of combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

3. What is the current usefulness and limitations of vital statistics on causes of death (disease mortality), in epidemiological studies and how could they be improved?

4. To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposure under environmental conditions?

5. To what extent are the reported effects of air pollution affected by the study methods employed?

6. It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low-level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

7. What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

8. There are atmospheric contaminants that have their primary effect on other than the respiratory system. What environmental contaminants deserve particular attention because of their potential effects on other than the respiratory system?

9. You have done considerable work on asbestos, which has a 20- to 60-year incubation period between exposure and the development of tumors. What are the public health implications of these findings?

AMERICAN CANCER SOCIETY, INC.,
New York, N.Y., August 14, 1968.

Hon. EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution,
U.S. Senate, Washington, D.C.

MY DEAR SENATOR MUSKIE: This is in reply to your letter dated August 2, 1968. You asked me nine questions concerning the problem of air pollution. I will answer each of them to the best of my ability.

QUESTION 1

For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

In a number of different industrial situations, workers are (or were in past years) exposed to certain specific types of dust, fumes or gases in such concentrations and for such periods of time as to produce serious and sometimes fatal disease. In some instances, dust, fumes or gases are exhausted from such plants and contaminate the air in the surrounding area.

For the protection of the workers, standards have been set limiting the in-plant concentration of air contaminants of the types mentioned above. These standards could be used as a basis for establishing air quality criteria applicable to air outside of such plants. In my opinion, these criteria should be much stricter than the standards set up for the protection of the workers. I say this for the reason that the general public includes people who are chonically ill and probably contains individuals who are unusually sensitive to the harmful effects of some of the agents in question.

Aside from the above, general air pollution (which varies in composition as well as in degree from place to place) contains a great multitude of different contaminants from various sources. Little is known about the possible harmful effects of many of these contaminants. Others are known to be harmful in relatively high concentration, but there is no precise knowledge as to the concentration below which they are innocuous. At this time, I lack the knowledge required to make a list of the specific contaminants for which air quality criteria should be established for the purpose of protecting the health of the public.

QUESTION 2

What type of epidemiological studies would be useful to confirm or refine air quality criteria?

In my opinion, epidemiological studies of workers occupationally exposed to specific types of air contaminants would be most useful in this respect. When indicated, these should be followed by studies of people exposed to specific types of what I have referred to as "neighborhood air pollution."

If I were in charge of a large scale program of research on this problem, I think I would proceed about as follows:

(*a*) Make a list of air contaminants now known to cause disease under conditions of occupational exposure. Conduct research on workers with various degrees of exposure to these contaminants. Determine whether air in the vicinity of indicated plants or mines is contaminated with agents to which the workers are exposed. When such proves to be the case, make an epidemiological study of persons living in the neighborhood. (The epidemiological studies would include chemical and physical studies of the contaminants under suspicion).

(*b*) Make studies to determine the concentration of each of the various contaminants in the air of various places in the United States where air pollution may be a problem. (This would include neighborhoods in the vicinity of various plants as well as metropolitan areas not in close proximity to such plants). For each contaminant found in appreciable concentration, try to find an industrial situation in which workers are occupationally exposed to that contaminant. Make epidemiological studies of such worker.

QUESTION 3

What is the current usefulness and limitations of vital statistics on causes of death (disease mortality), in epidemiological studies and how could they be improved?

Many important epidemiological studies are based upon death rates from specific diseases in relation to various characteristics and exposures of specified groups of people. Official vital statistics information on causes of death is obtained from death certificates. Ordinarily, most health departments only code a single disease or accident as the "underlying cause of death" and report death rates accordingly. It would be most helpful if the National Center for Health

Statistics would: a) code every disease mentioned on a death certificate; b) put this information together with identifying information (name, address and social security number) on computer tape and c) provide copies of the computer tapes to qualified investigators for analysis in relation to special research studies. There would be no need to routinely publish all of the material in complete detail (which would entail great expense). The important thing is to make copies of the computer tapes available to all qualified research workers at minimal cost to them. (The price should be no more than the actual cost of the reels of tape plus the small cost of reproduction.)

Aside from the above, the value of death certificate information is dependent upon the accuracy of the diagnoses recorded. Quality of diagnoses, at least in respect to cancer, has improved considerably during the last several decades. The quality of diagnoses in respect to some important diseases other than cancer leaves much to be desired. The situation can be improved only by the cooperative efforts of physicians, hospitals and local health departments.

QUESTION 4

To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

I believe that this question is covered by my answer to question #2 above.

QUESTION 5

To what extent are the reported effects of air pollution affected by the study methods employed?

I think that I would answer this question in about the same way in respect to almost any field of investigation. Some methods of investigation are more reliable than others and some investigators are more thorough and skillful than others. Poor methods (or good methods badly used) can and sometimes do lead to erroneous results or conclusions.

For reasons which are adequately discussed in the excellent report of your staff, it is extremely difficult to ascertain the possible effects of long term exposure to general air pollution of the types and degrees now prevailing in many urban areas in the United States. In my opinion, it is likely to take many years of laborious work on the part of skillful investigators to obtain accurate answers on the matter.

Under the circumstances, it is to be expected that the results of some studies will appear to contradict the results of other studies. In some such instances, the conflicting results may be due to the use of different methods of study or to lack of skill on the part of one or both of the investigators.

QUESTION 6

It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes").

Individuals with severe chronic lung diseases appear to be most affected during periods of very high levels of air pollution. In several extreme episodes, there has been a marked increase in death rates from a wide range of severe chronic diseases (i.e. not just lung diseases).

Generally, old people have been most severely affected in such episodes. This is probably only because chronic diseases are far more prevalent among old people than among young people. Chronological age as such (in the absence of chronic disease) is probably unimportant in this respect.

"What factors do we feel render individuals especially susceptible to long-term low-level air pollution exposures?"

In my opinion, it has not yet been clearly demonstrated that long-term low-level general air pollution exposure has an adverse effect upon health. Lacking such evidence and lacking a precise definition of the term "low-level", it is extremely difficult to answer your question. I can only speculate on several possibilities as described below.

(*a*) I suspect (but do not know) that unrecognized epidemics of virus infections are responsible for or contribute to the severity of some human

ailments. For example, they may perhaps precipitate the death of some people suffering from cardio-vascular or severe chronic pulmonary diseases. It is possible that some air pollutants (even at very low levels) contribute to the spread of certain virus infections either by providing favorable conditions for the survival of the virus or by increasing susceptability of the host.

(*b*) Even at extremely low levels, some aeroallergens may produce serious effects upon highly susceptible individuals.

(*c*) Exposure to the same agent from two or more different sources may result in a dangerous level of total exposure. One of these sources may be occupational exposure while at work—the other exposure to general air pollution during non-working parts of the day.

(*d*) Exposure to two different agents can (in some instances) produce far more serious effects than exposure to either one of them alone. It may be that in some instances one of the two agents is present in general air pollution while some individuals are exposed to the other agent from some source other than general air pollution.

QUESTION 7

What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

I have had no experience with studies of the possible health effects of air pollution upon children. They might perhaps develop a means of investigating the possibility of certain acute effects.

QUESTION 8

There are atmospheric contaminants that have their primary effect on other than the respiratory system. What environmental contaminants deserve particular attention because of their potential effects on other than the respiratory system?

In my opinion, research on the possible effects of carbon-monoxide (at levels present in the air of many American cities) deserves special attention in relation to diseases other than diseases of the respiratory system.

QUESTION 9

You have done considerable work on asbestos, which has a 20- to 60-year incubation period between exposure and the development of tumors. What are the public health implications of these findings?

Occupational health is generally considered to be in the field of public health. Direct occupational exposure to asbestos has very serious consequences upon the health of the workers involved. Both the asbestos workers union and the asbestos industry are giving us their full cooperation and support in an attempt to solve this important problem.

Many workers (particularly in the building trades) may have what is known as "indirect occupational exposure" to asbestos dust. For example, on a building site where asbestos is being used, workers other than asbestos workers may be exposed to absestos dust. Such workers probably have far less exposure (over a period of many years) than do men regularly employed as asbestos workers. We are seeking to determine whether such indirect occupational exposure has a serious effect upon the health of many workers. If such turns out to be the case, we, with the cooperation of the union and the industry, will try to find means of preventing such exposures. An alternative solution would be to treat asbestos materials in some way such as to make them harmless. We are investigating the possibility of doing so.

In my verbal testimony before your committee, I discussed the problem of "neighborhood air pollution" and "general air pollution" exposure to small amounts of asbestos dust. Dr. Irving Selikoff and I are engaged in research on this matter. At the present time we can only say that many urban dwellers (other than asbestos workers and members of the building trades) have some

particles in their lungs which appear to be coated asbestos fibers (i.e. "asbestos bodies") The amount of such material found in the lungs of these people is very small as compared with the amount found in the lungs of members of the asbestos workers union. At the present time we do not know whether this small amount of material does any appreciable harm.

Sincerely,

E. CUYLER HAMMOND, Sc.D.
Vice President,
Epidemiology and Statistics.

Senator MUSKIE. Our next witness is Dr. Seymour Calvert, director of the Air Pollution Research Center of the University of California, Riverside, Calif.

Dr. Calvert, we appreciate your being here this morning.

STATEMENT OF DR. SEYMOUR CALVERT, DIRECTOR, AIR POLLUTION RESEARCH CENTER, UNIVERSITY OF CALIFORNIA, RIVERSIDE, CALIF.

Dr. CALVERT. Good morning, Senator Muskie.

I appreciate having the opportunity afforded by your invitation to testify at these hearings.

To introduce myself, in a little more detail, I have a Ph. D. in chemical engineering; am dean of engineering at the University of California, Riverside campus; and director of the University of California Statewide Air Pollution Research Center.

I am a member of the National Air Pollution Control Administration's Air Quality Criteria Advisory Committee and on that committee I am chairman of the Subcommittee on Particulate Matter Criteria.

AIR QUALITY CRITERIA DEVELOPMENT

The subject of my statement is the nature of air quality criteria and our route to developing them. Because I am a member of the Air Quality Criteria Advisory Committee, it would be improper for me to comment on any specific or quantitative relationships prior to full deliberation and publication by that committee. I should also add for clarity that I feel no present compulsion to make such comment.

Philosophy

The need for action is clear and the signs of some general unease concerning our ability to establish meaningful criteria at present do compel me to speak on the philosophy and basic concepts of criteria. While these have been discussed by numerous people in the past, a large part of the uneasiness seems to stem from confusion about what air quality criteria are and how they fit into the total process of getting the air purity we need.

As an introduction, I will quote some pertinent sections from my paper on "Federal Role in Emission Criteria and Standards," which was presented at the National Conference on Air Pollution, December 13, 1966:

Before proceeding with this discussion, let me ensure that we are all thinking about the same question by defining "Emission Criteria and Standards". Criteria are any factors which should be taken into account when judging the suitability of an emission. Standards are those factors (criteria) which have been set in the form of definite rules or measures by the proper authority. Generally, stand-

ards are in terms of measurable properties of the pollutant emission such as its quantity per unit time, concentration, color, opacity, height emission, and suitable means of measurement.

Standards are the language of action. They give the emission operator a useful unequivocal target which is directly related to the source operation. Control officials, too, can function strictly within their enforcement powers without need for quasi-legislative or quasi-judicial deliberations over what constitutes pollution or whether extenuating circumstances should be considered. Standards mean that the arguments have been heard, the decisions made, the votes cast and that society now requires conformity or will permit exceptions only after due legal course.

Criteria are the voices of conflicting demands. They tell us that:

(1) the omission should be judged in terms of its effects and that we should control only to the point of no effect, or

(2) there should be no pollution regardless of effects, or

(3) there must be technical feasibility to limit the emission by control equipment or alternative processes or devices, or

(4) there must be economic feasibility taking into account the desire to conserve investment capital and to maintain a favorable competitive price position so that we should control only to the limit of economic comfort, or

(5) that local factors of terrain, industrial density and meteorology are more or less favorable than in other locations.

When standards are established, it is implicit that decisions have been made regarding all pertinent criteria and that compromises must be involved. Who might set emission standards and what has been done so far? Trade associations and professional organizations have gratuitously proposed standards and model ordinances. Consultant and research organizations can be retained, and have been by governmental bodies. And, of course, the government agencies through their staffs and advisory bodies have the final responsibility.

At present very few emission standards are in effect as legislation. Particulate matter is limited by opacity (Ringleman scale), by concentration based on variants of the ASME Model Ordinance or the Allegheny County Code, or by a process weight variant of the Los Angeles County Code. Standards for specific particulate composition and industries, aside from the California automotive and hydrocarbon limitations, include little beyond a 1,000 ppm standard for sulfur dioxide.

We obviously need standards for many more specific emissions. How are we going to get them? They could be set by some of the non-governmental bodies mentioned before or by the Federal Government and then adopted by a state or local government. But the originators must do a complete job of investigation, and come to an optimum conclusion, and report the entire process. Only then can the adopting body decide that it would have come to the same conclusion; otherwise, there would be an abdication of legislative responsibility.

Except for cases in which there exists a reliable air quality criterion, and it is agreed that control will be based on effects only, there is no logical basis for standards upon which we will all agree. What it comes to is that we can obtain all the control we want for a price and there is difference of opinion as to how much pollution we should have, how much to spend to eliminate it and whose money is to be spent.

The legislature with the burden of decision needs authoritative advice on ambient air quality requirements, technical feasibility of control, alternative methods or substitutes, economics, measurement methods, atmospheric dispersion and other matters of fact. It must contribute the philosophical and political dictates as to whether clean air is every man's right or a luxury to be purchased or given, whether to wait until the effects are absolutely known before taking action in order to fail safe for investment capital or to act now and fail safe for health, whether the desire for aesthetic values and the conservation of an extravagantly beautiful environment are suitable bases for control. This dramatic phraseology is intentional. Standards are not set on the basis of fact alone.

Even after legislation has been passed, the debate is not over. There are several points in the enforcement process where the argument is re-opened and the facts are needed again. Whenever the administrator makes quasi-legislative or quasi-judicial decisions, or there are requests for variances, or there exist appeals to review boards or court cases; there is a re-evaluation of standards.

There has been the hope that we could separate air quality considerations from the various problems relating to emission control; that we could decide how pure the air should be without complicating the picture with cost and technology.

As it turns out, there is such a large region of uncertainty about air pollution effects on health and so many cases where the loss is economic or esthetic, or otherwise not of human health, that we cannot judge the suitability of air quality in terms of effects alone.

ISSUES TO BE CONSIDERED

Thus, while the paper quoted above dealt with emissions rather than air quality, the issues raised are pertinent here. To expand further on the nature of air quality criteria, let us list some of the issues which have to be faced by the people who will set standards and some positions they might take as to the acceptability of air quality.

A. What is air pollution? (1) Pollution exists only when there is an undesirable effect, so it should be reduced to a point where there is no effect. (2) Pollution results from any introduction of a potentially harmful substance into the atmosphere, regardless of whether any effects will result in the specific case, so no such act should be tolerated.

B. What proof of effect is required? (1) Proof that some effect results from a specific exposure to a pollutant must be unequivocal and scientifically unassailable if it is to be used as a basis for air pollution control. (2) A reasonable presumption of cause-effect relationship may be used as a basis for air pollution control, (*a*) where health effects are concerned, (*b*) where any types of effects are concerned. (3) Proof that an effect could not be caused by a given exposure must be unequivocal and scientifically unassailable or the relationship will be used as a basis for control, (*a*) for health effects only, (*b*) for any type of effect.

C. How many people must be affected? (1) The rights of the individual take precedence and pollution exists if only one person is affected. This will be consistent with protecting the most susceptible members of the population. (2) A significant number of people must be affected in order to establish that a state of pollution exists.

D. What proof of cause is required? In order to determine control requirements and costs, ambient air quality must be related to emission rate. (1) The pollution level consequent to a specific source must be measured in order to relate air quality to the source rate as a basis for control. (2) The relationship between air quality and source size may be predicted by reasonable methods in order to establish control requirements.

E. What control costs can be tolerated? (1) Any cost up to that of complete prohibition is worth paying, (*a*) where human health is definitely imperiled, (*b*) where human health might possibly be affected, (*c*) in any case where discernible air pollution effects would result. (2) Reasonable cost is an acceptable limit so long as human health is protected. (3) No net cost burden should be placed on a polluter so long as human health is protected.

F. Should suitable technology exist if control is required? The answer to this is really in the economic realm, the equivalent question being: Can we afford the cost of an alternative to this operation?

It is obvious that one's position on matters such as those listed above is dependent on political, social, and economic philosophy plus specific circumstances. Reaching accord on such things is traditionally done through our democratic governmental processes. There is, however, the substantive or factual information which will indicate the relationships among air quality, interacting circumstances, and effects.

CRITERIA AS A PRELUDE TO STANDARDS

The real point of introducing the concept of criteria as a prelude to standards is that we want to isolate those things we can readily agree upon from those which are highly debatable and make rapid progress where we can. We can't seem to hang on to that happy simplification despite repeated efforts to explain it.

People are frequently unable to restrict their concern to defining the cause-effect relationships and are simultaneously trying to judge: "Would this be a suitable basis for air pollution control?" Consequently, they are very critical and unwilling to move rapidly.

I think that much of the difficulty is due to the fact that "criterion" is the wrong word to describe what we want. Webster's New World Dictionary of the American Language (1966) defines criterion as "a means of judgment, a standard."

CASUAL RELATIONSHIPS

As previously discussed, it takes more than casual relationships to determine whether a given level of air quality is suitable. Furthermore, we will always encounter confusion between criteria and standards no matter how long it is protested that they are not synonymous—despite Webster.

"Corollary" is the word we want. Webster says of it: "(1) a proposition that follows from another that has been proved; (2) an inference of deduction; (3) anything that follows as a normal result: as, improved public health is a corollary of slum clearance."

We are seeking now to set forth the inferences of various states of air quality. The next stage, to be done by other people, is to add in the decision of whom and what to protect, from what consequence, based on how much certainty, and at what cost. The present efforts would have a clearer purpose if they were titled "Air Quality Corollaries." There is also the relief from Latin singular and plural forms.

Having dealt with overall perspective and the clearer designation of factual relationships, I will turn to the details of what we need in an air quality corollary. As we consider the significant pollutants one at a time, we want to know what responses will result from exposure to a range of pollutant concentrations. We have learned that there are many interacting factors so that only the very extreme cases such as lethal dose levels approach simplicity. In the general case we must

look for complexity in each of the four main components of an air quality corollary; the environmental properties, the exposure, the receptor, and the response.

INTERACTION BETWEEN CONTAMINANTS

How much do we have to know about the composition and flow of the air environment in order to be certain of its influence? Concentration and chemical composition are obviously important. The size, shape, and density of particles will determine how far they will travel from the source and where and how they will be deposited on a receptor.

The adsorption or absorption of gases on particles may cause or catalyze chemical reactions and may determine the site of deposit or attack on the receptor.

Combinations of gases and/or particles may have effects which are additive or subtractive or greatly different than those of the constituents taken singly. Especially in low wind conditions there may be greatly different concentrations in the main windstream and in sheltered areas so that the concentration and composition under a canopy of trees or in a house will depend on the rate of transfer of pollutant into the sheltered domain of the receptor.

Exposure to a given mixture of air and pollutant(s) is rarely constant because the ambient concentration(s) will depend on the rate of emission—which can vary—and upon the wind speed, direction, turbulence, temperature structure, and interactions with terrain and buildings. The time and intensity of exposure with relation to the age or state of development of the receptor can also be very significant; the young may be more or less susceptible than the mature or the very old.

OTHER STRESSES

Other stresses may interact with pollution exposure. Disease may make a subject more sensitive to pollutant injury or, conversely, pollution effects can predispose a subject to disease.

Further complicating the picture are the possible stresses of temperature, light, humidity, pressure, exercise, noise, and anything contributing to psychological tension.

RESPONSE VARIATIONS

The receptor can be greatly variable, especially if we are talking about biological entities such as people, plants, and animals. Physical characteristics such as age, size, and conformation can partly characterize the subject, but there will remain striking differences in individual susceptibility which are unexplained by the things we measure and observe.

Additionally, there is the influence of health state apart from the existence of a known or active disease syndrome.

Given the above information about a subject, we still may not know how a specified exposure will affect him—or it. Breathing habit or pattern can influence the region of deposition of pollutants within the respiratory tract and also the rate of transfer from the air to the receptor. Variations in clearance mechanism(s) can also affect the amount of pollutant accumulated in the individual. This clearance might be the expulsion of particles by ciliary action or the excretion of dissolved substances such as lead in body fluids or the neutralization of dissolved substances by chemical or biological action within the body.

PREDICTION OF EFFECTS

Now, if there is a known combination of the environmental properties, the exposure, and the receptor, what will happen? Health effects can range from death and lesser acute responses to chronic disease and to reversible subliminal effects on central nervous system functions or irritation or offense by odor or tactile annoyance due to grit.

Materials can be soiled, corroded, discolored or deteriorated in other ways. The atmospheric properties can be altered so that visibility is decreased, weather patterns or microclimate influenced, radiation reaching the ground diminished, and general—air, earth, and water—temperature changed.

CAUSAL RELATIONSHIPS

What has just been described is a system of causal relationships which are real, or the true intrinsic properties. What we know about a given situation is generally less than the truth; it is what we perceive. Our perception of reality is biased by what observations we choose to or know enough to make, the methods used, and the ways in which we can or choose to define a particular state of affairs.

For example, we must examine any study of the effects of pollution by asking a number of questions: 1. What happened? 2. How do you know—what means did you use to determine—the following: (*a*) Environmental properties? (*b*) Exposure details? (*c*) Receptor characteristics? (*d*) Response(s)?

STUDY DESIGN

The value and utility of a study will depend on how good a job the investigator did in performing and in describing these aspects of the research. In some cases we will be able to infer some information from other knowledge; for example, we may have knowledge of weather conditions during the same or similar period so that we can estimate what the exposure variables were even though they were not measured or reported in the study at hand.

TABLE 1.—FACTORS INVOLVED IN AIR QUALITY COROLLARIES

	Reality	Perception	
	Intrinsic properties	Measurable (objectively)	Observable (subjectively)
Environmental properties	1. Concentration. 2. Size distribution. 3. Chemical composition. 4. Mineralogical (morphological). 5. Adsorbed or absorbed gas (es). 6. Coexisting gas (es). 7. Physical state (solid, liquid, gas). 8. Multiple particle populations. 9. Rate of transfer to receptor domain.	1. Filter by hi vol. 2. Filter by paper tape. 3. Dust fall (rate of deposition). 4. Condensation nuclei counter. 5. Impinger (liquid filled). 6. Cascade impactor. 7. Electrostatic precipitator. 8. Light scattering meter. 9. Chemical analysis. 10. Gas analysis (nonadsorbed). 11. Adsorbed gas analysis.	1. Light scattering or attenuation (Ringleman or visibility observation). 2. Colored suspension. 3. Nucleation of precipitation. 4. Stabilization of fog, etc. 5. Odor. 6. Taste.
Exposure	1. Variations in concentration and duration with time. 2. Other stress(es) (temperature, pressure, humidity, noise, exercise, etc.).	(1).	(1).
Receptor	1. Physical characteristics. 2. Individual susceptibility. 3. Rate and site of transfer to receptor. 4. Health state	(1).	(1).
Response	1. Human health (direct effects and predisposition to disease) and comfort. 2. Animal health. 3. Plant health. 4. Soiling. 5. Effects on atmospheric properties. 6. Alteration of radiation and temperature. 7. Corrosion of materials. 8. Deterioration of materials. 9. Objectional deposit on surface.	(1).	(1).

[1] So many perceptive methods might have been used that they cannot all be listed here.

CRITERIA CONSIDERATIONS

Table I, factors involved in air quality corollaries, is a checklist of the factors which must be taken into consideration as part of the cause-effect relationships—corollaries—of air pollution. In order to make a prediction of effect(s) we have to specify: If you have a polluted atmosphere with (1) these properties. (2) as measured in this way, (3) varying this way, (4) with or without these stresses—before, during or after exposure, (5) and you are concerned about this kind of receptor, (6) you will observe the following effects as defined according to these methods and rules for classification.

STANDARD SETTING

Air quality corollaries which will be useful to the people who set standards have to provide unequivocal statements of what we know about the consequences which will ensue from a specified circumstance. These people will generally be incapable of or unwilling to draw inferences from scattered individual items of technical information.

On the other hand, they are the ones who have to decide who and what to protect, from what consequence(s), and at what cost(s).

TECHNICAL JUDGMENT

Technical judgments have to be made by the Air Quality Criteria Advisory Committee consultants and the Air Pollution Administration staff as to what we know and how sure we are of various items. Under the heading of what is known they must provide the following:

(1) A critical bibliography of all studies containing useful information, with definition of content in terms such as table I.

(2) Integrated corollary relationships over the range of pollutant levels, exposure, et cetera. It will also be necessary to describe and justify the rules for interpolation and extrapolation of data to other special cases.

(3) Example relationships for the major types of air basins in the United States, for typical receptor classes (such as respiratory disease sufferers), and for probable situations of interaction with other pollutants.

AVAILABLE INFORMATION

A big problem in this kind of endeavor is that there is never enough information about all possible variations and effects. Consequently, we have various levels of conviction about things and we can make quantitative estimates of these levels in terms of probabilities. Word descriptions of the probability levels pertinent are:

(1) Certain—can think of no reason it shouldn't happen.

(2) Probable—some factors not tied down but judged unimportant.

(3) Conceivable—might happen—50–50 chance.

(4) Improbable—converse of probable.

(5) Certainly won't—converse of certain.

ENGINEERING APPROACH

Conclusion: The main points I want to make today can be summed up under the conviction that we have to take an engineering approach to the ultimate problem of building our way to air quality standards. I know that some other professions utilize the same basic approach and I ask your indulgence of my describing it in terms of my personal frame of reference.

The points are:

(1) Define objectives clearly, in perhaps tedious detail.

(2) Establish a method of approach and a division of responsibilities.

(3) Do the best job possible with the available information and resources. There are never "enough" of either for a perfect job.

(4) Determine what has to be done in order to do the job better next time.

(5) Estimate the probable consequences of different alternatives and of being in error.

(6) Decide on what will work satisfactorily at suitable cost.

(7) Do it.

RESPECTIVE ROLES

Who is to do what in this scheme? The Federal Government has taken the responsibility for points 1 through 5 and the States have the primary responsibility for points 6 and 7. It is further incumbent upon the Federal Government to provide basic information and assistance to the States in support of their role. That is, the Federal Government must illuminate all of the pertinent issues and all of the pertinent facts for the State governments.

We should strive to do the best job we can, as soon as we can, and to develop the means for making improvements the next time around. In terms of air quality criteria, we should separate out the task of preparing air quality corollaries and get on with it. We should not slow or halt this effort on corollaries because of extraneous considerations such as "were the climatological conditions the same there as here," or "do we diagnose bronchitis the same way as they do," or "what is the population at risk." Extrapolation to a specific setting and decisions as to whom to protect from what can and should be made at another time.

RESEARCH

Unquestionably we need more research and the Federal research grant program is greatly inadequate to the need. Yet, there are some things we know now and we should use them. To paraphrase from another area of great current political concern, we are ready for clean air.

Thank you.

Senator MUSKIE. Thank you very much, Dr. Calvert.

PARTICULATE CRITERIA DEVELOPMENT

How long a process is this business of setting up air quality criteria or air quality corollaries? How long a process is it or how long should it be?

Dr. CALVERT. The people who have been retained by the Public Health Service and now the National Center for Air Pollution Control to write chapters, for instance, on the particulate matter criteria, have been working on this for about a year. There have also been a number of people who have been retained on a consultant basis to review this material and comment on it.

There have been, I think, three stages of revision thus far. There have been something like 70 people, I am told, who have been involved in that.

I believe that several more months will be required in obtaining the agreement upon and preparing the document on particulate criteria up to the point that we are presently aiming at; that is, this document will not cover all particulate matter but will relate to those things which can be defined in terms of the previously referred to methods of dust fall, measurement of suspended particulate, measurement of soiling.

There, additionally, will be a few specific chemical species included in this, and carcinogenic materials will also be included; but there will be a number of particulates which won't be covered in this first document and they will have to be picked up at times in the future.

I would expect that the full coverage of particulate matter would require a time period of an additional 1 to 2 years. It is something like painting the Golden Gate Bridge; it never will be done; you start again at the beginning as soon as you finish the first time through.

Senator MUSKIE. With respect to those which will not be included in the initial study, is the delay due to the fact we need to know more about their effects or would the delay be due to some other causes?

Dr. CALVERT. I think that the philosophy in choosing the first batch was we have measurements or characterization of the air environment in terms of dust fall, suspended particulates, soiling, let us utilize that.

As I think of it, it is a matter of asking what do we know and what can we predict if we know dust fall, suspended particulate, and soiling, so that the choice is made on the basis of here is where we have the most information.

Now, as has previously been stated by other witnesses here, we have not been measuring all of the right things. You have to know more about particulates than simply how many of my programs per cubic meter will be accepted. You have to know particle size, chemical composition, size, shape, and so on—really the items listed in this table I which is intended to be a checklist of all things would could possibly be important here.

These are the items you really have to know in order to be able to characterize an air pollutant or a polluted environment. Generally, we don't know all of these things.

AVAILABLE EVIDENCE

Senator MUSKIE. Do you think that with respect to all predicaments we will have this information so that criteria, or, as you prefer, corollaries, can be developed within a year or two?

Dr. CALVERT. We will not have all of this information. Our information is fragmentary. I say that we need all of this information. We have to do a better job of measuring it in the future.

So far as retrospective consideration of available technical information is concerned, we have to make our best estimates as to what these variables might have been.

Senator MUSKIE. In addition to being chairman of the Subcommittee on Particulate Matter, you are a member of the full advisory committee?

Dr. CALVERT. Yes, sir.

Senator MUSKIE. What other pollutants will you be developing criteria for in the reasonably near future?

Dr. CALVERT. There are two criteria of papers being worked on. One is on the particulates within the limited scope I have described, and the other is the oxides of sulfur criteria which is being restudied.

WHITE PAPER

There is a third subcommittee or task group of the full advisory committee, and this subcommittee is working on the preparation of a so-called white paper on criteria or a definition of criteria—their meaning, scope, methodology, and method to be used and so forth. I believe that Dr. Fred Sargent will be talking about that later.

RESEARCH NEEDS

Senator MUSKIE. I gather that as your advisory committee considers the criteria, prudent basic research has also been initiated. Is that an accurate guess?

Dr. CALVERT. Well, the work of the advisory committee is distinct from that task of initiating basic research. We don't direct that research be done.

Senator MUSKIE. I understand you don't direct it but do you know whether or not those who do authorize the basic research are related to your work in developing criteria, in establishing priorities for the necessary research?

Dr. CALVERT. We do not have sufficient funds available for the support of research on questions which relate to air quality criteria, if this is what you mean.

Senator MUSKIE. Are you saying that with respect to the particulates that you are now working on the research effort is inadequate to do the job of setting criteria?

Dr. CALVERT. Yes.

Senator MUSKIE. In other words, for particulates, the sulfur oxides, you ought to have more research underway than you now have underway?

When I say "you," I mean the Department.

Dr. CALVERT. Yes.

Senator MUSKIE. In order to do an adequate job of setting criteria?

Dr. CALVERT. I don't think I want to answer that one as yes. What I have been trying to say in my statement is that we do have some information available now and we should set that down.

We ought to indicate what we know, what we don't know. We ought to indicate the certainties and the uncertainties. We should simply get the record straight on this.

Now, when I say that we don't have sufficient funding and that we don't have sufficient ongoing research, I am talking about filling in the blanks for the next time around and the next time. This will be a never-ending study. We are simply never going to have enough information.

This is common of all kinds of endeavors, including engineering, where you never have enough information to answer all of your questions and there is an absolute certainty but you do have to get on with the job. This is the point I want to make.

I certainly would not want to abandon that in order to emphasize that we should have an intensified research effort.

Senator MUSKIE. I understand. I am not trying to ask an embarrassing question; I am simply trying to get the philosophy of the approach of the committee.

In other words, what you are now saying, if I understand you correctly, is that you should have enough information on hand as to the effects of particulates of sulfur oxides so that you are in a position to set the initial criteria within a reasonable period of time without being dependent on additional results of additional basic research.

Dr. CALVERT. Well, yes; within my meaning of criteria.

Senator MUSKIE. I understand. In other words, you are going to have some of the guidelines which you would prefer to describe as corollaries.

Dr. CALVERT. Yes, sir.

Senator MUSKIE. I think there is some merit to your analysis of that point but perhaps the word "criteria" would come to mean what "corollaries" mean to you.

In any case, you have what is necessary to take the first step with respect to these two pollutants without being dependent upon more adequate funding for additional basic research, recognizing that the initial product would be far from what we ultimately will need?

Dr. CALVERT. Yes. To simply make it quite clear, I believe that our task is to set down all of the available information and to set down a description of the technological, the scientific consensus regarding that and its validity.

Now, once we do this, it is going to be up to other people to decide what action they can take on the basis of that information. I am not saying now that the information will or will not be sufficient for someone to set standards. What I am saying is that we can certainly say what we know now.

What I am reaching for is clear separation of that task. Let us get on with that without clouding the minds, I suppose consciences of people involved with future implications of these facts. How are these facts going to be used? Let's make that step 1 or 2.

Senator MUSKIE. In other words, we are sufficiently certain now of the undesirable effects of air pollutants?

Dr. CALVERT. Some of them.

Senator MUSKIE. Well, about those which you are working on specifically, at least, that we ought to get on with controlling them even though we do not know all of the implications, all of the effects.

Dr. CALVERT. Yes.

REQUIREMENTS FOR ACTION

Senator MUSKIE. Let me put it this way. I think that most people now regard the air as a natural resource, that most of us regard air pollution as offensive. We know at least three things about it: One, that there may be certain identifiable public health effects. There may be; there are with respect to some.

Second, that there are obvious welfare effects such as soiling, damage to buildings, crop losses.

And, third, that air pollution is something in the nature of a nuisance—not using that word in its technical, legal sense—in a society which becomes increasingly conscious of its aesthetic environment.

Is it fair to say that control is justified on that third point alone if only because air is a public property and not a private property?

The question then arises if this is a fair analysis—I guess "fairness" is not a good word.

CONSEQUENCES OF BEING WRONG

Are we wasting time and money in measuring and evaluating effects and should we not go ahead and spend the money on the control system to eliminate the pollutants?

Dr. CALVERT. That might be. I think it is worth taking a look at. This is why I stress and have said at other times, and I believe I do in the paper on emission standards and criteria, that we should look into the consequences of being wrong. That is, what if we do fail safe for health, what will it cost us? If we cannot afford it, then I would say versus a person's convictions by all means let's take out a health insurance policy. So this should be evaluated.

Now, I know that there will be some instances in which absolute control would be extremely expensive or, let's say, the control to the point of zero emissions doubtless would be intolerable.

The real question is, how far down do we have to push it? I think that as the first approach you can do everything that you know is absolutely necessary and everything that you can afford and it is up to someone to define what "afford" means.

Next time around, how do we trim this up? Do we have to push it still further? Do we need better control in some areas? This is where we need to research.

Senator MUSKIE. I think the question inevitably arises as one considers the testimony we have had over the past 2 years as to the difficulty in developing the precise information on effects, precise information on causal relationships. I don't know.

I think the testimony has been excellent. I think that in your statement you undertook to develop an analytical process approaching the problem which is very necessary.

Thank you very much.

Dr. CALVERT. Thank you, Senator.

(Questions submitted by Senator Muskie and the response by Dr. Calvert follow:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. SEYMOUR CALVERT,
Director, Air Pollution Research Center,
University of California, Riverside, Calif.

DEAR DR. CALVERT: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand

on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. SEYMOUR CALVERT

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?
2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?
3. To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?
4. To what extent are the reported effects of air pollution affected by the study methods employed?
5. As a member of the National Air Quality Criteria Advisory Committee, would you care to comment on how the committee operates?
6. There has been discussion of special risk or susceptible population groups. What in your opinion is their relevance to public health policy?

UNIVERSITY OF CALIFORNIA, RIVERSIDE,
Riverside, Calif., August 23, 1968.

HON. EDMUND S. MUSKIE,
U.S. Senate, Chairman, Subcommittee on Air and Water Pollution, Committee on Public Works, Washington, D.C.

MY DEAR SENATOR MUSKIE: In response to your request for my replies to your questions as transmitted on August 2, I have prepared the enclosed document. I have inadvertently misplaced the transcript of my testimony which your staff requested me to proofread. If it is not to late, I would be pleased to review another copy if it could be sent to me.

Your interest in my comments regarding air quality criteria is welcomed.

Sincerely,

SEYMOUR CALVERT,
Director.

[Enclosure]

QUESTION 1

The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

If by air quality criteria we intend a meaning which is more precisely described as air quality corollaries, then we have sufficient evidence to develop them for all atmospheric contaminants. We can describe the known relationships between environmental properties, exposure, receptor, and response even though our knowledge is incomplete. It would, to my way of thinking, be perfectly permissible to state that we know nothing about a given set of circumstances if the consensus of competent opinion supports that conclusion.

Whether some incomplete state of knowledge comprising a given air quality corollary is a sufficient basis for action by some state government in enacting a system of air quality standards and control procedures is another question. I would expect that under the provisions of the Air Quality Act of 1967 it would be possible for the state government to reach that kind of conclusion concerning

a contaminant and for the Secretary of Health, Education, and Welfare to concur. In other words, I do not see why the publication of a criterion or corollary would inevitably lead to the establishment of an air quality standard within 15 months or whatever time period might legally ensue.

QUESTION 2

The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

Although I have discussed this question with members of the Air Pollution Research Center Staff who are in the bio-medical professions, I am not personally qualified to comment on the strictly medical aspects of epidemiological studies and will not do so here. Viewing epidemiological studies from the outside, or from the viewpoint of one who might use the results of such studies, I can make some comment.

In general the studies should be structured and carried out so that they will provide as much as possible of the kind of information listed in Table I of my testimony before the subcommittee on July 30, 1968. It is especially important to involve engineering and scientific personnel in the responsibility for defining the environmental properties and the exposure. Medical people would have the primary competence in definition of receptor and response.

QUESTION 3

To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

Industrial and occupational exposures can certainly yield worthwhile information concerning the response of very healthy people to high levels of contamination with periodic (i.e. working day) exposure. This knowledge would give us an upper limit to the tolerable pollution levels so that we would be able to conclude that we definitely would not want to exceed those levels in the ambient atmosphere. The difficulty comes in extrapolating from industrial exposure conditions to community conditions with all of the differences of environment and receptor.

Because of the peculiar willingness of men to work under what are at least apparently adverse conditions, industrial and occupational exposures afford us a valuable opportunity to study human responses to contaminated atmospheres with a variety of interacting stresses. We should make the most of this opportunity.

QUESTION 4

To what extent are the reported effects of air pollution affected by the study methods employed?

The answer to this question is implicit in the material included in my Table I and the discussion pertaining to that. Any concept of reality must be filtered through our perceptive and then our communicative processes and must therefore in general be subject to bias. We do not make observations and measurements of things which we do not expect to be important. Consequently, there is an inevitable reiterative upgrading of our experimental efforts as we gain an understanding of the system we are studying. This is simply a matter of scientific intellectual fact and is one more reason why we can never expect to write the final, all-inclusive document on air quality corollaries.

QUESTION 5

As a member of the National Air Quality Criteria Advisory Committee, would you care to comment on how the committee operates?

The comments concerning the National Air Quality Criteria Advisory Committee will be restricted to the question of how it has operated and what is anticipated. Dr. Frederick Sargent, who is chairman of our subcommittee which is drafting a white paper on criteria, would be the most logical source of information concerning overall policies of the advisory committee.

The advisory committee has met three times as a whole and subcommittees have met on occasion. The subcommittees and their chairmen were elected by

the membership of the Air Quality Criteria Advisory Committee for the following tasks:

1. Preparation of a White Paper on air quality criteria;
2. Preparation of a report on criteria for particulate matter; and
3. Preparation of a reissuance of the sulfur oxide document.

The White Paper on air quality criteria should be nearing the final draft stage having been reviewed twice by the full committee. I have received no word concerning further progress on this document since the May 21, 1968 meeting. A group of consultants have prepared a complete draft of the particulate matter report for review by the subcommittee and discussion before a meeting of the air committee. These latter steps have not yet taken place. The schedule of activities then calls for a redrafting of the document which will be followed by a review by the entire committee, more changes, a final review by the entire committee, and then approval or disapproval by the committee. There has been no communication regarding committee activities on this document since our May 21st meeting.

The sulfur oxides document is scheduled to go through a similar sequence of drafts and revisions following its drafting by a panel of consultants. The committee has been informed of progress on this document since our May 21st meeting. We anticipate that once the backlog of previously started criteria documents are under control, the committee will exercise more initiative with regard to subject matter and scheduling. At present the operational mode is essentially entirely responsive to the initiative of the National Air Pollution Control Administration.

QUESTION 6

There has been discussion of special risk or susceptible population groups. What in your opinion is their relevance to public health policy?

Public Health policy must protect the most sensitive elements of the population as a matter of humanitarian concern, as a consequence of our dedication to the democratic principle that the rights of the individual are immutable, and as a precaution or safety factor to cover the possibility that we may be presently unaware of our sensitivity to certain pollutants.

Senator MUSKIE. I do have to go to the floor very briefly so I will recess for what I hope will not be more than 10 or 15 minutes.

(A brief recess was taken.)

Senator MUSKIE. Our next witness this morning is Dr. Eric J. Cassell, associate professor, Mount Sinai School of Medicine, New York City.

STATEMENT OF DR. ERIC J. CASSELL, ASSOCIATE PROFESSOR, MOUNT SINAI SCHOOL OF MEDICINE, NEW YORK, N.Y.

Dr. CASSELL. The philosophy of the health professions in the 20th century, and increasingly the philosophy of our whole society is that a clean environment contributes to health and well-being.

From this philosophy and from the scientific evidence that has fathered it, it is not necessary any longer to prove harm to health from air pollution in order to insist upon its control. But control is a joint effort of the public, industry, the academic and other research institutions, and Government.

When air pollution control is not a joint effort, but rather a battle between opposing forces, the ultimate aims are delayed and the final solutions frequently poor and costly.

LIMITATION OF APPROACH

The air quality criteria required by the Air Quality Act of 1967 have caused major problems and considerable conflict. The disagreement does not derive from the general objective of choosing air quality

criteria, because it is generally agreed that criteria which represent statements of the quantitative relationship between specific levels of specific pollutants and specific and reproducible effects are necessary for the development of precise air pollution standards.

The problem comes simply from the fact that, in terms of health effects at least, it is not possible to produce a quantitative statement of cause and effect for any major pollutant at realistic levels. Therefore, it seems to me, the problem is how to handle a situation of this type where numbers seem to be necessary, and where real, honest, and meaningful conflict exists over the choice of the numbers.

The air quality standards that have been proposed or enacted into legislation in varying parts of the United States clearly represent the desire of the people to have air that is as clean as can be obtained in our industrialized society.

The paramount question is whether these standards, written into law, will be effective in cleaning the air. And, even more, the question might be, will they possibly delay effective air pollution control?

It is my opinion that the setting of fixed standards for individual pollutants, one at a time, through the range of known pollutants may signify the desire of a community for clean air but does not rest upon sound evidence nor promote effective air pollution control.

Further, it is my opinion that the requirement of the act for air quality criteria and subsequent standards tends to inhibit the development of alternative control philosophies, concepts, and technologies.

NATURE OF PROBLEM

The great importance of our concern over this matter comes not only from the importance of air pollution as a public health problem but from the fact that air pollution is a prototype problem. It is a prototype problem because, like our other modern public health problems such as noise, crowding, poverty, nutrition, et cetera, air pollution is intimately linked with the texture, problems, and activities of modern urban life and multifactorial in nature.

There is nothing new in the concept of many factors playing a part in the origin of diseases. What is different is that in the public health problems of which air pollution is the prototype no one factor is so dominant that by its removal or control alone, the problem to which it contributes will be solved.

Where one factor is so dominant, for example the automobile in auto accidents, its role in society is so pervasive that its removal is not possible. In a sense, these dominant factors are the urban industrialized society and they cannot be completely removed except at the cost of the society as it is.

Therefore, how we go about controlling air pollution, what we learn and how our philosophy changes is of great importance to our understanding of the other problems.

RESEARCH OBJECTIVES

We use the research on the health effects of air pollution to do two things: First, to make us aware of the dangers of fouling our environment, and, second, to provide a basis for effective control legislation. The precision of the information required for these two aims is quite different and it is important not to confuse the two when legislation is drawn.

CONTROL OBJECTIVES

It is sometimes difficult to realize how much progress has been made toward the goal of air pollution control in the past decade. An aroused public, an increasingly responsible industry, and responsive government have marked this progress. These changes have been brought about largely through an awareness of the dangers to health of uncontrolled pollution.

If these dangers have been overstated on occasion, no harm was done, since the purpose of the statement of dangers was to produce a supportive and aware public. If undue emphasis has been given to some pollutants over others in the statements of danger, or the mechanisms of action that were portrayed were inaccurate, again, no harm was done in making the public aware of the need for action.

However, if legislation is based on overstated, oversimplified, or inappropriate statements of the evidence, then the legislation stands a very good chance of being equally oversimplified and inappropriate. Note clearly that the problem is not should there be air pollution control—but, rather, what is the most effective way of achieving control?

CAUSATIVE AGENTS

The evidence on the health effects of air pollution strongly supports the view that the health effects are not due to a single pollutant acting alone, but, rather, from the complex interactions of air pollutants and weather in the atmosphere. I would like to discuss at some length the nature of the research problem of determining the effects of air pollution on man, because I think they are very important in seeing where our problem lies.

This is a problem in toxicology, determining for humans, the relationship between the dose of the noxious agent in the atmosphere and the adverse response in man.

CONTRIBUTING FACTORS

Several important factors complicate the research. The examples that follow are based primarily on sulfur dioxide but I think the generalizations are true of the other pollutants, as well.

First of all, the dose, sulfur dioxide, except under the most bizarre and rare circumstances, is present in the urban atmosphere in very low concentrations and over a very narrow range. The peaks themselves are usually not above one part per million. One part per million is about the bottom of the range frequently used in the laboratory. The highest level to which populations are exposed therefore are so low that they are seldom used in laboratory experiments.

Second, sulfur dioxide or any other pollutant does not exist alone in the atmosphere. When it is present, numerous other substances which may or may not have an effect on man are also present. Concentrations of the other substances will be increased at the same time that the sulfur compounds are increased. It is difficult, therefore, for the scientist to know whether an effect he has observed was caused by the sulfur compounds or by the other materials present.

The third and related complication of such studies is that all the various substances do not coexist without interaction.

We are now well aware that the atmosphere is a dynamically active chemical retort in which substances change themselves and react with

other materials to produce new and sometimes unknown substances, with this atmospheric chemical factory variously affected by wind, sun, and humidity.

Fourth, how do we really know what is in the atmosphere? We know about sulfur dioxide, for example, because we have instruments to measure it, and have had for some time. But all we know is that there are substances in the atmosphere of whose nature and presence we know nothing, and that the number of such substances probably is increasing as our technology expands. For example, what happens to a plastic bag when incinerated; and what is the effect in the atmosphere of the catalytic metals used as gasoline additives? And, as I noted this morning, what makes up that nice orange blanket that extends all the way down from New York to Washington?

The fifth complication is the meaning of what pollution measuring instruments say. When a study reports that the population was exposed to, for example, 0.25 parts per million of sulfur dioxide, what does that really mean? Generally, the instrument did not even really measure sulfur dioxide. If it was of the conductivity type commonly in use, the instrument only reflects sulfur dioxide when that gas exists alone—but, as we noted, that ideal is rarely met in the atmosphere.

The measurement is interfered with in numerous ways that cast serious doubt on any interpretation of experimental results that are presented as though the exposure were really to sulfur dioxide. In our studies, at one point, we had two instruments side by side, one measuring so-called true sulfur dioxide—by the West-Gaeke—and the other employing the conductivity method; not infrequently their readings bore no relationship to each other.

In our publications, we carefully used the words "whatever is represented by the measurement of sulfur dioxide," but when we are quoted, that important note of caution is left out or forgotten.

Similarly, in some studies the average sulfur dioxide of one area is compared to that of another and then the research findings are said to be related to sulfur dioxide. But sulfur dioxide levels are an index of many things: the weather, fuel patterns, degree of industrialization, socioeconomic level of the population, crowding; and probably a host of other factors, all of which have a bearing on disease.

But legislation which proposes a numerical standard for sulfur dioxide does not deal with "whatever is represented by the measurement of sulfur dioxide"; it deals with the gas sulfur dioxide.

Finally, the effect of sulfur dioxide on man is further complicated by the effect of the atmosphere, itself. Temperature and humidity have an unquestioned and well-known effect on health, quite apart from the effect they may have on the pollutants in the atmosphere.

EPIDEMIOLOGICAL STUDIES

The most sharply defined mortality peaks in New York City between 1962 and 1965 which was our study period occurred during heat waves on two successive summers; and in that 3-year period there were more than a dozen air pollution episodes.

These research difficulties are not blocks to the revelation of the truth; they are a part of the truth themselves and they cannot be disregarded in the search for rational air pollution control.

The problems that beset the epidemiologist in trying to determine the degree of exposure of his study population to the pollutant in question are not greater than the problem of trying to determine the responses of the individuals in the population.

There appear to be no responses in man or animals that are solely caused by or unique to the common air pollutants. The effects are primarily the result of irritation of the mucous membrane and as such are shared by a host of other disease determinants: cigarette smoking, infection, allergy, stress, emotional factors, and the list is much longer than that.

The problem is further complicated by the fact that there has been no way thus far to get experimental populations who are alike in all respects except their exposure to air pollutants.

The markers we have used to determine an effect of air pollution on health have varied from the certitude of death to the faintest physiologic change. Interference from other hazards to health is inevitable and the interpretation of results is consequently difficult.

To disentangle the multiplicity of factors at play, we use mathematical tools provided by our statistical colleagues. These tools, so helpful where a single factor or a few factors are at play, are in their infancy in the interpretation of complicated multifactorial problems. Thus they too add weakness where we would like strength.

These are, in brief, a review of the difficulties that stand in the way of research meant to support the objectives of air quality criteria and the standards based on them; that is, to establish a quantitative relationship between a concentration of a specific pollutant and a specific and reproducible effect in man.

Recognizing these complexities will not weaken air pollution control if it forces us to find contingency solutions that take them into account rather than returning repeatedly to approaches more appropriate to public health problems of the past such as typhoid and tuberculosis where cause and effect seem clear. If simplistic research approaches have failed so probably will simplistic legislation approaches.

AVAILABLE EVIDENCE ON SULFUR DIOXIDE

Despite all the difficulties and weaknesses in the research, sufficient evidence has accumulated over the past years to allow certain very meaningful conclusions.

Air pollution episodes

The air pollution disasters, laboratory studies, studies on chronic pulmonary disease and the epidemiology of air pollution in normal populations have been the four main sources of evidence on the effect of air pollution on health. Although the air pollution disasters have been few in number and perhaps overpublicized, they provide inescapable evidence that uncontrolled air pollution may be extremely harmful or fatal.

While initially the air pollution disasters seemed to indict sulfur dioxide as the cause of their health effects, more recent and careful review of the data has seemed to indicate that a complex of factors, including sulfur dioxide, particulate matter, and certain weather phenomenon must be present for the fatal potential to be realized.

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Laboratory studies

Higher concentrations of sulfur dioxide occurring in the absence of the other factors has apparently not been associated with mortality. Virtually every common pollutant has been studied in the laboratory to determine its effect on animals and man. Almost all of these studies have shown that the pollutants had adverse effects on health. However, in such studies before an effect could be demonstrated a concentration of the pollutant well in excess of the concentrations found in our dirtiest urban atmospheres has been required.

These experiments have shown, for example, that sulfur dioxide, the gas, existing alone is really quite innocuous in the usual atmospheric concentrations. The paradox of an apparent effect in the urban atmosphere and yet little effect in the laboratory has troubled us all. However, in reviewing the evidence relating sulfur dioxide to health, one is forced to conclude that for an effect of atmospheric sulfur dioxide on health to be demonstrated epidemiologically, particulate matter must also be present in an atmosphere, and I think weather is important.

Causative mechanism

This conclusion finds support in the work of Dr. Mary Amdur and her group, who, over the years, have provided increasing evidence of the mechanism by which sulfur dioxide, sulfuric acid, and certain particles act together to produce adverse physiologic responses in animals. In some of her more recent studies, the levels of sulfur dioxide required to produce an effect when the proper catalyzing particle was present have approached those found in our urban atmosphere.

MORBIDITY STUDY

Findings from our own Cornell Family Illness Study illustrate the interactions at play.

Early analyses of the data repeatedly showed relationships between respiratory symptoms in a normal New York City population and certain air pollutants, but the same symptom was associated with more than one pollutant or meteorologic variable. Recently the more sophisticated analysis has shown how a symptom or symptom complex may be associated with one group of pollutants during one kind of weather and the same symptoms associated with very different pollutants during different weather conditions.

What emerges is a complex ball of a man with a limited potential. You can only have a sore throat in cold weather in the winter. He gets a sore throat or a cold and pollutants may or may not be present. At another time of the year, the same man complains of a sore throat but only complains in sunny weather of some inversion of a lot of the oxidant-type pollutants but the man is still complaining of a sore throat.

So that, if one looked just for the symptom against air pollutants, it would be lost because in the summer it is with one set of pollutants and in the winter it is another set of pollutants and another set of weather phenomenon. In other words, it is the whole mix that is necessary to produce the symptoms and it is the mix that it is so hard for us to get at.

I might also say that to portray this we have tried to do it with graphs and had to give up the graphs and make cartoons of people walking through the snow with air pollutants because it was the only way that we could get a man in his environment—he was not just a throat-in-the-air environment.

CONCLUSIONS

From all the lines of evidence, we must come to the same general conclusion:

Air pollution, as a generality, has an unquestionably adverse effect on health varying from the association with symptoms at normal urban concentrations to the association with death during disasters. But the mechanism is complex, and the effect of the whole appears to be greater than the sum of the parts.

The ability to provide positive evidence of the effect of air pollution in the natural setting disappears when the individual pollutants are looked to as the unique or direct cause of illness or mortality. In the face of the foregoing, one can understand the difficulties that arise in attempting to set air quality standards.

Let us not forget that the biological sciences have provided a firm basis for the belief that air pollution is harmful to health and that, therefore, there is a rational health basis for the control of air pollution.

They have also begun to make clear the multifactorial nature of the relationships and thus cast considerable doubt on individual ambient air standards as a basis for control in the present state of knowledge. The health effects evidence clearly supports air pollution control; it clearly points up areas for further research; but it does not support individual quantitative air quality standards at the present time—no matter how desirable that goal might be.

The research has done something else, as well. It has provided the basis for a change in public attitude that would not be hard to document. A public apathetic at first and difficult to arouse has now remained interested and active at hearing after hearing in city after city. It has become less necessary to produce marked evidence of the harm caused by individual pollutants while gradually there has been an acceptance of the fact that pollution is bad in and of itself.

Policy requirements

I think that the evident and growing desire of society for an improvement in the total environment provides a mandate for newer control philosophies and methods. However, the proliferation of air quality standards continues and any person or group that suggests higher numbers would be accused of suggesting dirtier air, and there can be no seemingly persuasive argument for filthier air.

But the argument is persuasive that individual standards will not achieve clean air but may well delay effective air pollution control. Standards frequently create a climate of misunderstanding between industry and government; often require local variances that are self-defeating; may lull public opinion into quiet, believing that something has been achieved at the very time when continued effort toward cleaner air is required. They are, as has been pointed out, at odds with the scientific realities of the problem. The setting of standards by the

States required by the Air Quality Act of 1967 and the funding system dependent on standard setting may well tend to discourage the development of other control philosophies or even produce deceit in compliance.

Meanwhile, other knowledge has grown, allowing considerable sophistication in fuel, combustion process, and emission control as the basis for air pollution abatement if only control philosophy can change sufficiently to allow them free play. But there must be an alternative to control based primarily on ambient air standards and I think that the rise in these abatement technologies plus the other social and scientific change has provided that alternative.

Feasible control

I have suggested in the past that air pollution control be based on the concept of the control of pollutant emissions to the greatest degree feasible employing maximum technological capability. Do not be deceived by the apparent simplicity of this concept. The key words are feasible, and the use of maximum technology.

The degree that is presently feasible; what could be done with present knowledge and technique, is quite good, and if this degree were met in all industries, in all processes, the air would be very much cleaner without necessarily threatening the economic structure of an industry.

In addition, determining feasibility and technological capability for any process, although I agree it is difficult, is vastly easier than determining the level in the atmosphere at which an individual pollutant may be safe or unsafe.

Furthermore, the statements feasible and maximum technological capability have built into them continued progress, whereas fixed standards are notably difficult to change. In addition, these concepts provide a focus for research and process development, improved fuel and control devices. Industry, the academic community, and government can join together in their pursuit—as a matter of fact, they bring into play industrial competition. They are forced apart by the present pursuit of numerical standards.

Emission control

If you think about it, it is actually the method we use. When an ambient air standard is set, it must be translated into an emissions standard to be useful. Where the emission standard is feasible it is forced into effect. When it is not feasible because of the lack of technological capability or real economic pressure, then, generally speaking, a variance is granted or the industry given further time to meet the standard, or we go all the way back and reset the standard.

The problem is that each pollutant must be dealt with separately awaiting its ambient air standard. It is inconceivable that we will ever develop standards at a rate equivalent to our development of pollutants.

I also believe that in the problem we are absolutely in the most primitive stage and we are just beginning to understand how to go about it because we have just begun to accept that we cannot go about it as individual determinants of disease.

Process control

In essence, this is process control rather than pollutant control. Process control recognizes the fact that any avoidable soiling of the environment is undesirable. What is avoidable or not avoidable is determined by feasibility and technological capability.

I note that in the staff document that I received this is really quite similar to the British approach as detailed, I think, on page 48 of the staff document.

The advance in philosophy represented by process control is made possible by advances in two areas. The decreasing necessity to show harm from each individual pollutant provided by the advances in biological research and the increasing social demand. It would not be an original trend in our time for the social mandate to provide an impetus to push public health practice out ahead of public health science.

SANITARY MOVEMENT

The sanitary movement of the 19th and early 20th centuries was responsible for the greatest public health advances of all time—all the sanitary codes, all the U.S. Department of Health, all the changes in British sanitation came from that group, and that group had no science on which to base its control. Science came many, many years later.

The justification for a change in underlying control philosophy is evident from the nature of the biological problem and research evidence; from the realities of pollutant production and the spawning of new pollutants; and from the increasing mandate from society for a cleaner and healthier environment as the right of man in an affluent state.

Thank you.

Senator MUSKIE. Thank you very much, Doctor, for your very useful paper.

Now as I understand your recommendation for air control criteria philosophy, it is that we should control any emission whether or not it is demonstratively harmful.

Dr. CASSELL. Yes, if we can; if it is possible.

SULFUR OXIDES CONTROL

Senator MUSKIE. With respect to sulfur oxide, for example, what would be the implications of this control philosophy recognizing that sulfur oxides are emitted by many different kinds of industries?

Dr. CASSELL. Well, I actually think that within limitations and within limitations of my knowledge, we are not talking about that many processes in sulfur oxide production. There are a few in which it is a byproduct of chemical production and it is in the acid or phosphate industry, a great many where it is the byproduct of power production.

What I am saying, really, is that that process that produces the sulfur oxide really produces particulate matter which we accept but it also produces oxides of nitrogen which we really don't have very

much knowledge about yet but is really next on the scene. It would not have been first on the scene if we had better instruments a number of years ago. The attempt has to be to look at the process and see what is the best way of reducing all its emissions. If sulfur oxides can be produced by staff process, for example, then our push has to be our attempt to get that going, not arbitrarily say it is sulfur oxides we want to eliminate. We want to take it out of the fuel. It is particulate matter we are going to prohibit so we take it out of the stack. In the meantime, the others continue because we have not paid attention to them. It is a process rather then looking at a pollutant.

Senator MUSKIE. Let's take the question of sulfur oxides now. They are produced by large industrial plants. They are also produced by homes using sulfur content fuels.

Home heating

Now what would be the implication of your control philosophy for home heating?

Dr. CASSELL. Well, I think that the implication of that is that low sulfur fuels should be what are used for home heating. In essence, that is what is happening anyway. Also the implication is that the evidence provides some, or in and of itself may not be so important that we have to go pursue it down to its last milligram per cubic meter—that it would be more important to control the particulate matter that comes from the home or associated process like consideration.

Feasibility

Senator MUSKIE. I understood you control philosophy that anything that was emitted into the atmosphere should be to the degree that is feasible.

Dr. CASSELL. To the degree that it is feasible.

Senator MUSKIE. Now the quantity of low sulfur fuel is not limitless, it is quite limited, as a matter of fact. I know of only one oil company, for example, that has access to significant amounts of low sulfur oil. By law I mean one to two parts per million.

Now if there is a limit to the amount of fuel, low sulfur content that is available, how does that fit into your concept? An individual home is not a great contributor.

Dr. CASSELL. That is right.

Senator MUSKIE. In New England hundreds of thousands of homes together may very well discharge into the atmosphere quantities of sulfur oxides that are significant. I have no idea of the relative quantites from industrial sources, power sources, and home and institutional sources. I suspect that in the mass they are all significant.

The implications of what you are saying seems to me to be this: that if you have individual sources which have sufficient volume in and of themselves that you control, that if you have individual sources whose individual volume is insignificant, you don't control it, or is that the case?

Dr. CASSELL. I think the implication is that it is not per se sulfur dioxide chased down to the very end, it is the question of it allows you to establish priorities. For example, in the example you gave——

Senator MUSKIE. You seem to dismiss the individual home in that way.

Dr. CASSELL. I am dismissing the individual home for the moment.

Senator MUSKIE. In other words, the individual home in the mass is an insignificant source of pollutant?

Dr. CASSELL. I think in terms of feasibility that I am dismissing for the moment the individual home as a major high priority point of attack for sulfur dioxide control, and not because I don't think of the individual homes en masse if all of them burned high sulfur fuels in the same amount, but en masse we don't all burn high sulfur fuels and we don't seem to be a major contributor.

Senator MUSKIE. We use residual fuel oil of which by and large a great deal is for institutional burning and in the mass if you add them all you may have as much. I am putting this as a hypothesis. I don't know.

Dr. CASSELL. I don't really know either.

Senator MUSKIE. Let's put it this way: if you have enough evidence at this time to give it proof in the atmosphere, in the sum total of all these homes and institutions which burn sulfur content fuels as you do from industrial sources which individually are larger, are you saying that you control the one and not the other wholly upon the basis of the fact that one is easier to control than the other?

Dr. CASSELL. Well, I want to answer yes, really, but I don't want it to come out quite that simple. Yes, I do believe that once you control what one can control I think that the individual home could better be compared with the automobile, if you would. This is a multimillion source air pollution problem that is a major air pollution problem. You control it not by going after individual automobiles, really, although that is what the end effect is, as going after the process of the internal combustion engine, which is where it is produced.

Senator MUSKIE. Eighty million individual combustion plants.

Dr. CASSELL. Yes.

Senator MUSKIE. Now the individual homes involve x million combustion plants.

Dr. CASSELL. Exactly. We go to the automobile by going back to where it is manufactured and make the attack and change in manufacture. In other words, we don't take the 80 million automobiles and go back after each one but we say it is the responsibility of the industry that produces the pollutant producing process to change it. I think the same thing would be true of homes.

Senator MUSKIE. So you would control the homes?

Dr. CASSELL. Yes; if I could get at their source without having to track each one down. I don't want to get overly involved in this particular example.

Senator MUSKIE. One way of getting at it is getting at the combustion mechanism.

Dr. CASSELL. Yes.

Senator MUSKIE. How about the fuel?

Dr. CASSELL. Again I think that it is a matter of priorities.

Senator MUSKIE. Isn't there another way of getting at it?

Dr. CASSELL. There is, but we have a limited amount of low sulfur fuel. I think if I were looking at it, and we both assume for the moment—because my knowledge is not adequate—I assume that the major power producers would go to them as a solution rather than I would individual homes.

STIMULATION OF NEW TECHNOLOGY

Senator MUSKIE. How do you create the compulsion of the stimulus for expanding the horizons or pushing back the horizons of technological possibility? If you run out of low sulfur fuel, another approach is to clean up high sulfur content. You say that you use this only as it becomes technologically feasible.

How do you apply the pressure to that for the expansion of technology if you have no standard of air quality by which to measure what you insist shall be the result of it?

Dr. CASSELL. I like that question better.

Senator MUSKIE. I don't necessarily ask questions because you like them.

Dr. CASSELL. I understand. I think that I don't apply the pressure you do. You do by not locking us at the moment into a controlled philosophy but, rather, providing impetus in the research. We reward people who come up with process control, we give them research funds to develop it and if they develop it they have an economically salable item. We reward that. We reward the industry that controls by whatever mechanism, tax or whatever mechanism that is to make it economically sound for them to increase their process control. We reward research ideas that seem to go in that direction; that is, we grant funds when it seems to point toward control rather than for example, medical research. Their views there is an effect on people with bronchitis which we have heard a couple of times.

Senator MUSKIE. Let's take sulfur fuels again. You say you reward them. In what way? Providing grants of research money to private industry? To the oil refineries for the specific requirement that they clean up their fuels? To what extent should they be forced to clean up their fuels before they are rewarded?

Dr. CASSELL. I think what we are doing in that sense, what we are saying is we would like you to clean up your process. One of the ways of cleaning up the process is by cleaning up the fuel. We are encouraging research into desulfurization of fuel at the same time that we encourage research into desulfurization of flue gases. Which one becomes economically more feasible is going to come up out of that research. I don't want to oversimplify the problem. I am aware of how long it takes to do a piece of research and how unsatisfying the result may be, but what we do is apply a research pressure in the areas in which we are interested. We apply an economic pressure; that is, we reward people whose stack gases are less. How they achieve the lower stack emission, I think, is not our problem, that is theirs.

Senator MUSKIE. It is not our problem under the present law how they do it.

Dr. CASSELL. We could encourage them to do it a number of different ways.

PRIORITIES

Senator MUSKIE. It seems to me that what you are saying is in order to provide the incentives and the rewards, we must be able to identify the areas of research in order to do that, so we must establish priorities as among the pollutants.

Dr. CASSELL. I think we are establishing priorities among the processes. I mean the men who——

Senator MUSKIE. Well, the processes produce the pollutants.

Dr. CASSELL. Yes.

Senator MUSKIE. But we must decide in what areas we will authorize the research and what areas we will reward the research. And it seems to me that you have got to establish some kinds of benchmarks of accomplishment in order to establish your scale of rewards or prizes or whatever it is that you are going to provide. Simply providing research money to fund the establishment of a laboratory to keep people busy I don't think is a sufficient incentive to produce the results.

Dr. CASSELL. No; but you see in a sense we do it a different way also. When we begin to encourage this kind of research we also encourage the development of air pollution control devices. We make it possible for them to be a salable item beyond an individual pollutant.

For example, at the present time if somebody really came up with an economically sound, a quick and direct way of getting sulfur out of flue gases. It would be a very salable item.

TECHNICAL FEASIBILITY

Senator MUSKIE. Let me give you a comparison. When we were talking about controlling emissions from automobiles, California had funded research on the so-called tailpipe device—that is, the add-on, substitute for a muffler—individual small companies undertook to apply themselves to the idea of adding a device in the form of a muffler to a tailpipe. So California provided money for its own research where others got money for research dependent upon their ingenuity.

The automobile companies apply no money to that kind of research and the oil companies apply no kind of money to that kind of research. When we undertook to explore the possibility of legislation in this field in 1964 and 1965, the company said the add-on device was useless, they would not consider it, they were not interested in it, they were not about to buy it, that it was not necessary to have standards or legislation, that they were in the process of developing their own devices that would ultimately emerge and be useful.

It was not until we finally passed the law in 1965 that the automobile companies did produce their own method of controlling. What was the law? What did the law say?

The law said the Secretary has the authority to set standards if he wishes.

Dr. CASSELL. I have no objection to him issuing standards whatsoever.

Senator MUSKIE. This is the setting of a benchmark.

Dr. CASSELL. I have no objection to that. I think what the Secretary did in essence is say we believe this is feasible. We believe this is technologically possible, it could be achieved.

Senator MUSKIE. Let us take up the first point and then the second.

The point we are making first is that we had to set a goal required for performance before we began to get results. Now, it is relatively easy to do this with a single technological development and internal combustion engine, but when you are talking about atmospheric pollution it is the product of at least multiple sources. Are you going to set by law specific emission standards for every one of them?

Dr. CASWELL. Well, yes, because in the long run the setting of the standard for the automobile did not come because somebody set a carbon monoxide standard. We all would have a rough time chasing that up the tailpipe.

Senator MUSKIE. The Secretary set standards on carbon monoxide emissions and on hydrocarbons.

Dr. CASSELL. From the tailpipe?

Senator MUSKIE. Yes.

Dr. CASSELL. What I am saying is we would have a hard time to set an ambient air standard. I have no objection to emission standards. The testimony is directed solely at ambient air standards for individual pollutants in an attempt to control.

I do believe that it all relates to emission standards and that emission standards are in fact the result of several things. One is our knowledge of what we can do and the second is legislative pressure to do it and I have no objection to that whatsoever. I don't want us doing it by sulfur dioxide alone.

Senator MUSKIE. Well, that buzzer reminded me that in 10 minutes I have to be away from here and we have another witness. I would like to pursue this further. I just would like to make this one comment.

Obviously I have not had an opportunity to evaluate the full implication of what you have suggested but what troubles me, frankly, is the suggestion that technical and economic feasibility alone should be the key to the achievement of air pollution that protects public health and welfare. It seems to me that the problem is such that you must give consideration and apparently less measurable consideration.

It seems to me that we may have to force uneconomic policies or close down industries in particular locations that don't have a technological answer to the problem. I don't know of any illustration of that ultimate kind of decision but it seems to me that to tie ourselves purely and simply to the idea of moving only as fast as somebody judges economically and technologically feasible is not going to get us the results we need in terms of the public welfare and public health.

Dr. CASSELL. Could I summarize for just a moment. I think that the present feeling is that the sulfur dioxide—we have some evidence that is bad and therefore we can go to the man that makes it.

Senator MUSKIE. Incidentally, on that point I don't think, to use your phrase, that the law requires that criteria be established as only the basis of deciding what may be safe or unsafe.

Dr. CASSELL. Or esthetic or unesthetic.

Senator MUSKIE. Desirable or undesirable in the public interest. There is nothing that says a criteria can't be developed for the roots of pollutants either although we talk about related specifics.

Dr. CASSELL. You know, I really picked this solution to the problem because I don't believe you have to show something bad for health. It soils the environment. We have a right to have a clean environment to the extent we can achieve it.

Senator MUSKIE. Criteria related not only to health. It is the health and welfare effects.

Dr. CASSELL. I understand.

Senator MUSKIE. That is what the law speaks of and that includes soiling, it includes esthetic consideration to the extent that those who develop them can be significant or important in the public interest.

This is a most provocative statement, I take no objection to it. I think it is what we want. When we get an opportunity to understand its full implications, I think we want to get into it a little more. I think you have raised some important and relevant questions about the criteria code. I simply have not had a chance to study your alternative to the extent that I would like.

I do appreciate your coming very much.

Dr. CASSELL. Thank you.

(Questions submitted to Dr. Cassell by Senator Muskie are as follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. ERIC J. CASSELL,
Associate Professor, Mount Sinai School of Medicine,
New York, N.Y.

DEAR DR. CASSELL: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. ERIC J. CASSELL

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What types of studies would be useful to confirm or refine air quality criteria?

3. It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low-level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

4. What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

5. There are atmospheric contaminants that have their primary effect on other than the respiratory system. What environmental contaminants deserve particular attention because of their potential effects on other than the respiratory system?

(The response by Dr. Cassell was not available for this printing and will appear in volume III which will be published at a later date.)

Senator MUSKIE. Dr. Louis C. McCabe, chairman of the board of Hazleton Laboratories, Inc., Reston, Va., is our next witness.

Doctor, we are delighted to have you with us this morning.

I understand Harold MacFarland will read Dr. McCabe's statement. Dr. MacFarland is head of the Inhalation Division at Hazleton

Labs and is largely responsible for the design of the two experiments described in Dr. McCabe's paper, as I understand it.

STATEMENT OF DR. LOUIS C. McCABE, CHAIRMAN OF THE BOARD, AND HAROLD MacFARLAND, DIRECTOR, INHALATION DIVISION, HAZLETON LABORATORIES, INC.

Dr. MacFarland. Senator Muskie, I am Dr. MacFarland, and I will read Dr. McCabe's statement. The statement is divided into a number of sections. The first is Philosophy of Criteria and Standards.

NEED FOR REGULATIONS

A need exists for air quality regulations that can be reached now. We cannot wait to determine the absolute levels of safety. We must work with the knowledge that we now have and establish regulations which are meaningful. In exercising the judgment necessary to select meaningful values, there should be no compromise with any level which will affect the health of human beings. The level of air quality which we must have to protect human life and health has not been clearly established except for a few exotic or very toxic materials. We will probably be doing research on this problem for the rest of man's existence. But, rather than wait for the ultimate knowledge, we must do what we can with the information available.

TECHNICAL FEASIBILITY

I believe that air quality levels should be established which are attainable. I believe also that what can be done to improve air quality should be done. By this, I mean that the existing regulations should be enforced where it can be demonstrated that they are necessary and where there is a reasonable assurance that the regulations are attacking the right contaminants.

GOALS

The air quality levels that we establish as goals should be based on a number of criteria, of which health is only the first. Other factors include economics, availability of equipment for evaluation and control, and the needs and desires of each community. The goals should be redefined as more exact information becomes available. The goals should not be unreachable, nor should they be predicated on highly controversial and novel research. They should be pragmatic but subject to reevaluation.

TERMINOLOGY

A considerable amount of confusion exists between various terms—criteria, standards, regulations—with all these terms frequently being used interchangeably. The use of criteria by State and local governments will vary with individual judgment, but there has been a tendency to use some of the terms out of context. It may be more sensible to promulgate regulations only or to clearly define the meaning of the terms as used by the Public Health Service. The term criteria

as originally used by the Public Health Service was meant to be advisory and that in developing criteria there would be a statement of the reasons for the levels recommended. The term criteria has come to mean essentially the same as regulations. Such may not be the case at all. Use of the term criteria, for regulatory purposes, involves judgment factors which usually only the authors and the reviewers of the original documents thoroughly understand.

I believe that it is best to establish regulations that are practical within the limits of the technology and which fill the needs of each community. I believe that regulations should be revised as the knowledge of the atmospheric contaminants improves. To confuse them with other terms, however, does a disservice to the whole concept of air pollution control. The next section is concerned with the underlying concepts of air pollution.

AIR CONTAMINANTS

Smoke has been recognized as an air contaminant for several hundred years. The great technological developments, new products, and equipment which have come in this century, together with the great increase in populations, have brought many complex air pollution problems which only recently have been recognized.

Some 40 years ago the adverse effects of sulfur dioxide on crops in the Salt Lake Valley caused a study of the effects of this gas on crops. Many other investigators have since observed the effects of other atmospheric pollutants on plant life; notably fluorine, ozone, oxidized hydrocarbons, and so forth. A few years ago California set up several criteria of atmospheric pollution based on their effects on plants. Plants are used to monitor the presence of air contaminants. Some plants show injury at levels considerably below the sensory levels of human response. Aside from their use in prevention of injury to crops, they are good indicators of the possible effects of air contaminants on man. Plants may point out the need for research into the possible effects of some rather obscure air contaminants on people.

SULFUR OXIDES

Sulfur dioxide and sulfuric acid aerosols are both irritating to the respiratory mucosae but are not generally regarded as being of great intrinsic toxicity. Because of their high aqueous solubility, these two airborne contaminants are primarily upper respiratory tract irritants. However, it has been shown that the depth of penetration of these materials may be markedly increased in the presence of particulates. Thus, a system containing both sulfur dioxide and fly ash might well prove to be irritating to the lower respiratory tract, including the alveoli.

Toxicity studies

Several studies have been reported on the toxicity of sulfur dioxide and sulfuric acid mist and their effects on certain of the parameters of pulmonary function. In general, both sulfur dioxide and sulfuric acid mist in sufficient concentrations cause an increase in pulmonary flow resistance and a decrease in lung compliance.

Human studies

A number of studies have been performed using the human as subject. Some controversy developed when Amdur reported that the inhalation of sulfur dioxide in the range of 1 to 8 parts per million by normal human subjects caused an increase in pulse rate and the development of shallower and more rapid respiration. These observations were challenged by Lawther—report attached—who, in a series of carefully controlled experiments, employing 18 normal subjects exposed to 5 to 10 parts per million of sulfur dioxide, was unable to find consistent changes in tidal volume, respiratory rate, or pulse rate.

It is apparent from the brief review presented above that some deficiencies exist in both the experimental and clinical studies that have been reported on the effects of sulfur dioxide, sulfuric acid mist, fly ash, and their various combinations.

Inadequacies of available information

Because of the inadequacies in the presently available data, the problem of establishing air quality standards of scientific validity has resulted in the promulgation of different standards for sulfur dioxide, no agreement on a final standard for sulfuric acid mist, no recommendations relating to fly ash specifically, and no recommendations for combinations of these pollutants.

The particular defects that may be noted in published studies include a failure to work at realistic concentrations of the pollutants the use of small rodents without concomitant employment of larger species, particularly subhuman primates, and a haphazard approach to the question of examination of mixtures instead of an orderly and systematic exploration of the important possible combinations.

LABORATORY STUDY

A proposal which was submitted from Hazleton Laboratories, Inc., was designed to overcome these objections.

The concentrations suggested in that proposal cover the ranges of interest. Guinea pigs and monkeys used in the experimental studies will provide the requisite guidelines for a subsequent clinical program. By limiting the number of pollutants to be examined to three, and also by limiting the number of concentrations, or particule sizes to be tested, it will be possible to investigate an adequate variety of the important combinations.

Criteria of reponse have been selected which are highly sensitive. At termination of the proposed series of investigations, it will be possible by statistical evaluation of the results to make well-supported recommendations for air standards and to design safe and meaningful studies with the human subject.

This proposed research is now being sponsored by the Edison Electric Institute, the National Coal Association, the Tennessee Valley Authority, and the Los Angeles division of water and power.

Sulfur oxides

The first of these studies is designed to provide objective information on which air quality standards for certain pollutants may be rationally based. The pollutants under examination are sulfur dioxide, sulfuric acid mist, and fly ash. Mixtures of these substances are now being exam-

ined in a program which will run for nearly 6 years. The investigation has been in operation for 2 years at this time. It is unique in the following ways:

1. Low concentrations of the pollutants, at levels actually measured in polluted air, are being examined; unrealistically high concentrations which are never observed in practice are not being examined.
2. Exposures are for essentially 24 hours a day, 7 days a week, for periods of a year or a year-and-a-half in each test.
3. Although some work is performed on small rodents, the bulk of the studies is centered on the responses of subhuman primates.
4. In addition to the performance of the more conventional types of hematological and biochemical procedures, an unusually complete battery of highly sensitive pulmonary function tests constitutes the main technique for assessing the responses of the animals.
5. Advanced statistical treatment of the results, aided by computer techniques, is used to derive the maximum amount of information from the investigation.

Synthetic effects

The second significant program in progress at Hazleton Laboratories is being supported by the American Petroleum Institute. The investigation is primarily concerned with adducing evidence on the question of synergistic effects among mixtures of pollutants.

Initially, the substances under examination include sulfur dioxide, carbon monoxide, nitrogen dioxide, a lead-containing particulate, and a particulate sulfate. Approximately one-third of all the theoretically possible mixtures of these materials have been carefully selected for study in this 3½ year program. Techniques, similar to those mentioned above in connection with the first program, which emphasize the use of sensitive pulmonary function tests in the primate are also being employed in this synergism study. Again, long-term continuous exposures to low and realistic levels of the compounds constitutes one of the valuable features of the investigations.

Lawther has pointed out that—

> During temperature inversions, when the normal turbulence of the air ceases and pollution accumulates in stagnant pools, concentrations may reach 20 or 30 times the mean annual concentrations. During episodes of high pollution, the excess deaths are among the old and frail, the newborn, and those suffering from diseases of the respiratory and cardiovascular systems.
>
> Chronic bronchitis is much more prevalent in large towns than in rural areas; the relationship between prevalence and size of community is close. There is, therefore, likely to be an urban factor involved in the genesis of the disease. Many people believe this factor to be air pollution. Of course, the temptation to assume this to be the cause is great and indeed much careful epidemiological work lends support to this belief. But, again, the problem is not simple. Chronic bronchitis is an ill-defined disease which may begin in childhood and end in old age with gross emphysema—a condition in which the lungs become distended and inefficient, causing severe shortness of breath and strain on the heart and circulation.

FEASIBILITY OF AIR QUALITY STANDARDS

We come now to the question of concepts underlining air quality standards.

In my opinion we have moved too fast in the control of sulfur oxides. Meeting the criteria which have been set of 1 percent sulfur in coal and residual fuel oils and 0.1 part per million as the maximal allowable

in the ambient air would eliminate much of the coal now mined from the market and would add a considerable additional cost for fuel oils. It is now 21 years since Los Angeles began its work on air pollution. There has been excellent research devoted to the problem there but the one major source of pollution—automobile exhaust—has not been removed although many steps have been taken toward its control.

The medical editor of a column which recently appeared in the July 22, 1968, issue of the Washington Post discussed the additional problem of pollution in confined places. This is reproduced in the attached copy. With regard to fuel, there has been a thought that the electric power industry might escape a sulfur problem by the use of atomic energy. However, in an article in Science, July 12, 1968, there is outlined some of the difficulties that have developed with new power stations which make it questionable whether we are ready to replace all fossil fuels with atomic energy.

In the case of the sulfur oxides, perhaps an additional 4 or 5 years may be required to develop a method or methods for prevention of excessive amounts of these gases to reach the ambient air. Satisfactory removal of sulfur from stack gases will probably succeed in four or five methods now under development. Recently, Chemical Week carried an article pointing up the availability of a method for removal of sulfur which optimistically forecasts a lower power cost in the use of the method developed by a large private firm. This will require considerable pilot plant operation to verify cost and recovery levels.

RESEARCH NEEDS

The following is a list of research needed:

1. Automobile exhaust:
   - (*a*) Additives to fuel and their effect on vegetation and man.
   - (*b*) Production of satisfactory exhaust or substitution of power elements.
2. Sulfur oxides and other air contaminants.
   - (*a*) Developments in recovery of sulfur dioxide.
   - (*b*) Clinical and experimental studies on exposure of man and animals to air contaminants.
     - (1) Supplemental current research by private and public research laboratories.
     - (2) Further studies on man and animals.
     - (3) Tolerance levels of animals and man.
     - (4) Concentrations of sulfur oxides encountered on inspiration and expiration by cigar, pipe, and cigarette smokers.
   - (*c*) Ambient air investigations related to sulfur oxides and other air contaminants.
     - (1) Tolerance levels of plants; effects on life and condition of decorative trees and resistant strains of trees and other vegetation in metropolitan areas. Development of plants for cities.

(2) Tolerance levels of animals and man.
(3) Survey of levels of pollution (SO_2, H_2SO_4, CO, hydrocarbons, carcinogens, et al) in living space (for example, conference rooms, airplanes, etc.).

(*d*) Instrument development required.
(1) More specific and reliable instruments. (Today we do not have satisfactory continuous monitoring equipment for particulates and for sulfur dioxide from power stations or other industrial sources.)
(2) Measurements responsive to effects of pollutants.

(*e*) Abatement equipment:
(1) To handle odors, fumes, and gases.

3. Basic research on air contaminants:
(*a*) Gross and long-time effects on our environment.
(*b*) Degradation and cycle of pollutants in relation to time.
(*c*) Weather modification and other effects of pollutants on environment.
(*d*) Interrelationship of air and water pollution.

(The attachment to Dr. McCabe's statement follows:)

[From Science, July 12, 1968]

NUCLEAR POWER—ROSY OPTIMISM AND HARSH REALITY

A dramatic confrontation between rosy optimism and harsh reality is now gripping the attention of the electrical power industry. During 1966 and 1967, in a bandwagon atmosphere, large numbers of nuclear power plants were authorized. As of 1 April 1968, about 35 percent of scheduled additions to electrical capacity were nuclear. Recent events, however, have caused some observers to fear that optimism was overdone. The utilities have gambled heavily on unproven equipment, some of which will be brought on line far behind schedule. Power shortages could result.

A conspicuous example is the installation at Oyster Creek, New Jersey, which is now about a year and a half behind schedule. During field hydrostatic testing of the reactor pressure vessel on 29 September 1967, a leak was detected. A dye-penetrant test revealed that the leak was the result of flaws in a field weld made to join a control rod housing to a stub tube in the pressure vessel. Detailed examination revealed localized intergranular cracking in 123 of 137 stainless steel stub tubes, and welding defects in each of the 137 field welds joining the stub tubes and the control rod housings.

Many of the defects found were minor, and it seems unlikely that complete failure of a weld would have occurred had the weaknesses not been discovered. Even had such failure occurred, there would not have been a violent nuclear accident. However, if a leak or a weld failure had occurred after the reactor had operated for some time, the difficulty of repairing the defect would have been great, owing to intense radioactivity.

Before the Oyster Creek facility can be operated, it must be licensed. Three different groups will pass on the matter. First, there is the Division of Reactor Licensing of the Atomic Energy Commission, then the statutorily constituted Advisory Committee on Reactor Safeguards, and finally the Atomic Energy Commission itself. These bodies cannot be expected to act hastily. Defects in one aspect of the plant raise specters of other, yet undetected, flaws, and it is not certain that procedures used for repair of the defects will be acceptable. When the Oyster Creek generating plant will become operational is anybody's guess, but it could be in the distant future.

These delays will be costly in money and prestige. The Oyster Creek plant represented a courageous gamble by the General Electric Company, which, in 1963, undertook to guarantee delivery of a completed plant involving new design features at a stunningly low price. Announcement of the contract for the plant was widely regarded as signifying that nuclear power had come of age.

Following this event, other large nuclear installations were authorized at an increasing rate. Then came a great outcry against air pollution associated with coal-fired plants. The move toward nuclear power became a stampede. Delays at the bellwether Oyster Creek plant will have a sobering effect. An additional deterrent is the fact that costs of nuclear installations have increased by 40 percent during the last 2 years. Nuclear plants also have been tagged as important potential contributors to thermal pollution, since they are relatively less efficient thermally than coal-fired plants.

All of these difficulties will be surmounted, and nuclear power one day will furnish a substantial fraction of this country's electrical energy. How distant that day will be will depend mainly on how long it takes industry and labor to achieve new and higher standards of design excellence and quality control.

—PHILIP H. ABELSON.

[From the Washington Post, July 22, 1968]

HOW TO KEEP WELL

(By Dr. Theodore R. Van Dellen)

CIGARETTE POLLUTION

Pollution is making many of our industrial cities floating garbage dumps, even though measures are being taken to minimize the problem. But few authorities mention one of the most damaging air pollutants—the cigarette. Smokers face the greatest risk, but those of us who meet in smoke-filled rooms also are exposed, often against our will.

Dr. Philip H. Abelson, editor of Science, recently wrote an informative editorial along these lines. Most of us associate carbon monoxide gas with the automobile and heating units. Humans are very susceptible to the gas because it replaces oxygen in the blood. According to Dr. Abelson, inhaling a concentration of 120 parts of carbon monoxide to a million parts of air for an hour inactivates 5 per cent of the body's hemoglobin (iron). Dizziness, headache and lassitude ensue.

Concentrations of 100 parts per million (p.p.m.) frequently are found in garages, tunnels and behind automobiles. A smoker inhales 42,000 p.p.m. and survives because he breathes between puffs. I wonder how much air is found in smoke-filled rooms?

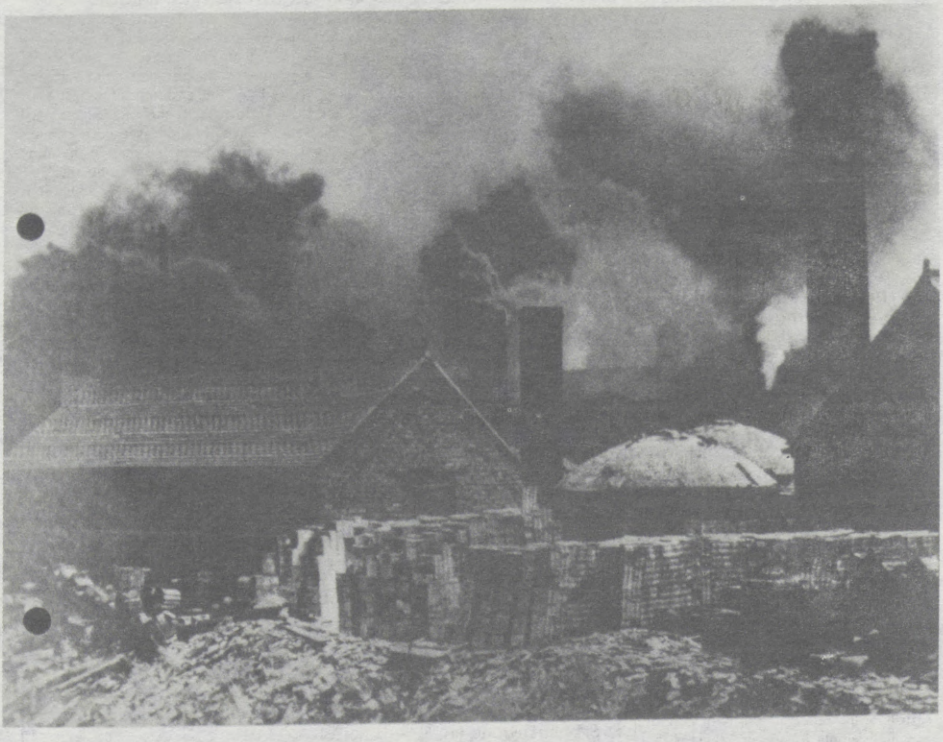
Nitrogen dioxide (NO_2) also is found in automobile exhausts. Concentrations of 3 p.p.m. have been noted in Los Angeles (5 p.p.m. is considered dangerous). Cigarette smoke contains 250 p.p.m. NO_2. Hydrogen cyanide does not have a counterpart in ordinary air pollution. There are 1600 p.p.m. in cigarette smoke and long-term exposure to levels above 10 p.p.m. is dangerous.

Dr. Abelson also mentions the synergistic effect of cigarette smoke and other chemicals. This may explain why there is more lung cancer among smokers living in the city than those residing in the country. Of 283 asbestos workers who smoked, 24 of 78 deaths were due to lung cancer. Of 87 in this group, who abstained, none succumbed to lung cancer over the same period.

Air pollution

Confusion about the nature and effects of urban air pollution often results from underestimating the complexity of the problem. What part does air pollution really play in the genesis of diseases such as bronchitis and lung cancer?

P. J. Lawther



Pollution of the air occurs wherever fuel is burned. When combustion is complete and its products are discharged high into the atmosphere and well-dispersed by winds there is no hazard to health. But all too often sulphur-containing coal and oil is burned, or even distilled, in inadequate supplies of air and the resulting effluents discharged near the ground where they may accumulate in concentrations sufficiently high to kill old and infirm people. Industry is not always the worst offender; the domestic open grate, a grossly inefficient means of providing warmth, is one of the most serious sources of pollution at ground level.

Confusion concerning the nature and effects of urban air pollution is common and often results from a tendency to underestimate the complexity of the problem and from unwarrantable extrapolation of results of observations and experiments in simple models. The chemical and physical constitution of pollutants is complex, and man himself, a resilient creature, adds further to the confusion by the way he adapts rapidly but often inconsistently to noxious features of his environment. Thus the design of experiments with pollutants and the interpretation of their results becomes correspondingly difficult.

Deposited matter (grit and dust), smoke, and sulphur dioxide are the pollutants most commonly measured in Great Britain. Deposited matter is of little medical interest since particles which rapidly fall out of the air are too big to penetrate far into the respiratory tract. Smoke consists of carbon, tar, salts, acids, minerals and many complex organic compounds present as particles or droplets of less than 10 μ diameter. Those less than 7 μ diameter may enter, and be retained in, the depths of the lung. Sulphur dioxide is measured because it is obviously corrosive and irritant. Frequent and wide-spread measurements of concentrations of smoke and sulphur dioxide provide useful indices of pollution produced by burning fuel. However, the temptation to attribute the observed effects of pollution on man simply to one or other of these two substances must be resisted; for research purposes many other contaminants are measured and studied.

From city to laboratory

Concentrations of pollution may vary greatly in time and place. Towns are dirtier than rural areas but the difference is not simply related to size—some small towns can be much dirtier than the centre of London. During temperature inversions, when the normal turbulence of the air ceases and pollution accumulates in stagnant pools, concentrations may reach twenty or thirty times the mean annual concentrations (*see Table below*). These sharp increases in pollution which occur during calm winter weather are accompanied by increased deaths, and many people suffer from respiratory distress. The precise reasons for the increase in deaths and distress are as yet unknown. During episodes of high pollution the excess deaths are among the old and frail, the newborn, and those suffering from diseases of the respiratory and cardiovascular systems. The same classes of patient also suffer from respiratory distress. The irritation produced in the lungs by air pollution of the concentration encountered in these "smogs" can cause coughing, and there are many people in a city of 8,000,000 inhabitants for whom prolonged coughing could prove to be a final intolerable stress.

Commonly one finds evidence of increased pulmonary airway resistance during smogs: patients wheeze and find difficulty in getting air in and out of their lungs. This increase in airway resistance may be produced by the narrowing of the bronchial tubes when their muscular coat contracts in response to irritation or by excessive secretion of mucus in the airways of the lung. Experiments in the laboratory are designed to try to identify the substance, or combination of substances, causing these changes. The inhalation of high concentrations of sulphur dioxide and sulphuric acid can raise the airways resistance in man and in experimental animals, but experimental exposures to SO_2 or sulphuric acid in the kind of concentrations which may be found in towns, have never resulted in significant or consistently reproducible increases in airway resistance in human subjects. The effort, therefore, has been directed to experiments with combinations of pollutants. Several workers have shown that the effects on animals of exposure to sulphur dioxide can be enhanced by the addition of aerosols of salts. Unfortunately this simple 'combined action' effect has not yet been demonstrated in experiments on man using realistic concentrations of pollutants.

Obviously there are many combinations of pollutants which may be tried and the experiments to test them are complex and time consuming. However, the evidence obtained so far directs suspicion more to particulate matter than to the simple gaseous irritants. A current long term experiment on myself is of interest here. There is a reasonably close relationship between my airway resistance, measured daily immediately on entering the laboratory each morning after a walk of 2 miles, and pollution measured in terms of smoke or SO_2. Yet I am able to inhale

Maximum and typical winter concentrations of some pollutants measured in Central London, 1954-64

	Maximum concentration	Typical winter concentration
Smoke (mg/m^3)	10	0.2
Carbon monoxide (p.p.m.)	360*	10*
Sulphur dioxide (p.p.m.)	2.0	0.2
Sulphuric acid (mg/m^3)	0.7	0.01
Nitric oxide (p.p.m.)	1.1	0.05
Nitrogen dioxide (p.p.m.)	0.2	0.03
3:4-benzpyrene ($\mu g/100m^3$)	222	5

* As measured close to traffic in busy streets: concentration is much lower in general atmosphere.

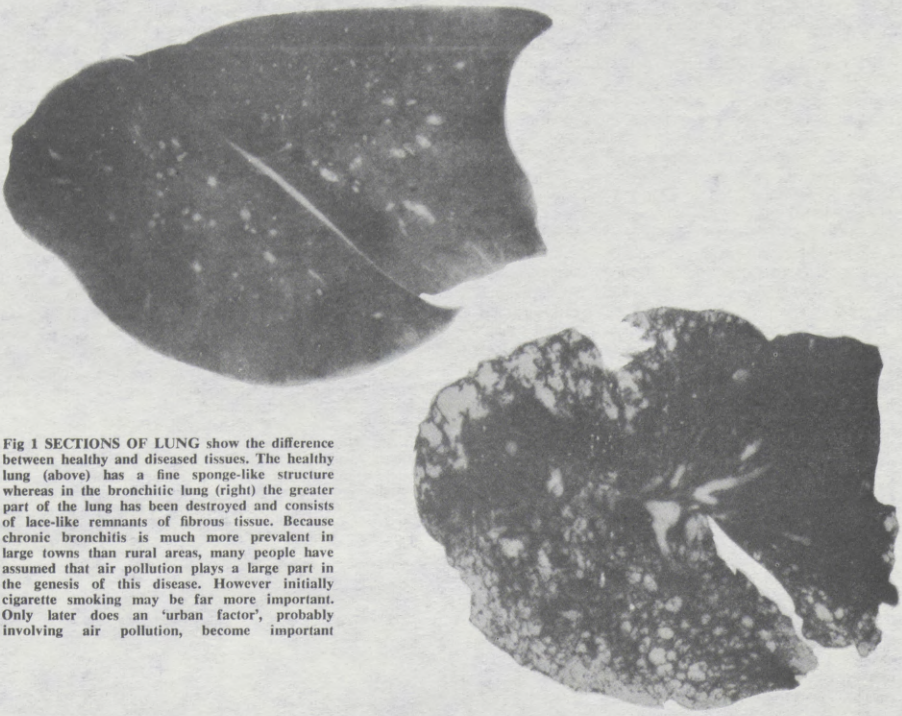


Fig 1 SECTIONS OF LUNG show the difference between healthy and diseased tissues. The healthy lung (above) has a fine sponge-like structure whereas in the bronchitic lung (right) the greater part of the lung has been destroyed and consists of lace-like remnants of fibrous tissue. Because chronic bronchitis is much more prevalent in large towns than rural areas, many people have assumed that air pollution plays a large part in the genesis of this disease. However initially cigarette smoking may be far more important. Only later does an 'urban factor', probably involving air pollution, become important

30 parts per million SO_2 (15 times the maximum concentration measured in town air) without developing any increase in resistance. Other experiments using simpler techniques in which members of the Unit and bronchitic patients have taken part show a disappointing lack of correlation with variations in pollution; infection and stress seem to be more powerful factors. But these negative results probably reflect merely the insensitivity of the methods used and indicate the need to study large groups of patients.

In contrast, striking relationships between illness and variations in pollution have been demonstrated in two other types of experiment. In one simple investigation, bronchitic patients were given diaries in which they were asked to record each day whether they felt better, same, or worse than on the day before. The response of groups of patients of between 200 and 1000 strong leaves no doubt that pollution (measured in terms of SO_2 or smoke) has a much greater effect than any other meteorological factor. Likewise, a current study of applications to the Emergency Bed Service for admission to hospital because of increases in the severity of respiratory disease shows a remarkably close association with pollution. Obviously other factors, such as the lower temperatures often associated with pollution in Britain may also play a part but by making a long series of observations in these two types of experiment the separate effects of these inter-related factors may be discerned.

Development of disease — pollution . . .

Chronic bronchitis is much more prevalent in large towns than in rural areas; the relationship between prevalence and size of community is close. There is, therefore, likely to be an "urban factor" involved in the genesis of the disease. Many people believe this factor to be air pollution. Of course, the temptation to assume this to be the cause is great and indeed much careful epidemiological work lends support to this belief. But, again, the problem is not simple. Chronic bronchitis is an ill-defined disease which may begin in childhood and end in old age with gross emphysema—a condition in which the lungs become distended and inefficient, causing severe shortness of breath and strain on the heart and circulation (*see Fig. 1*). This disease has been the subject of intense study in recent years and great advances in knowledge are being made. It seems likely that in the early stage of the disease, simple bronchitis, the glands and goblet cells in the lining of the bronchial tubes secrete excess mucus. This abnormality is manifest clinically as chronic cough needed to clear away the mucoid sputum. The over secretion of mucus, with its attendant en-

largement and proliferation of mucus secreting tissue, may well be the result of irritation; the "smoker's cough"—initially simple bronchitis—is a perfect example of a response to irritation which regresses if the irritant is withdrawn. In fact, studies of a large population of people by means of the M.R.C. Questionnaire on Respiratory Symptoms have shown that the prevalence of simple bronchitis is more closely related to smoking habits than to air pollution.

The next stage in the development of complicated bronchitis is more serious in that the changes are irreversible. Infection supervenes. Colds "go to the chest" and the patient gets attacks of acute bronchitis in which he coughs up purulent infected sputum. Commonly this infection becomes more frequent and more difficult to treat, essential tissue in the lung is damaged, gas transfer is impeded and eventually the structural changes lead to serious disruption of the respiratory and cardio-vascular systems. At this stage in the disease an "urban factor" appears to be more important than is cigarette smoking. Air pollution is rightly suspect and one would wish to find in it some factor which favoured the development and persistence of bacterial and viral infection. Again, the old simple hypothesis that "it must be smoke or SO_2" is wholly inadequate. The mechanisms producing these changes are surely subtle and of course the variety of responses shown by different individuals to noxious stimuli tends to confuse the issue further—some heavy smokers have no cough; some patients develop severe emphysema without ever having simple bronchitis. Nevertheless, the prudent man will not insult his lung with such a powerful irritant as cigarette smoke.

There are many other factors involved in the genesis of chronic bronchitis; its prevalence is closely related to social class, occupation and childhood infections. And it would be strange indeed if there were but one causal factor.

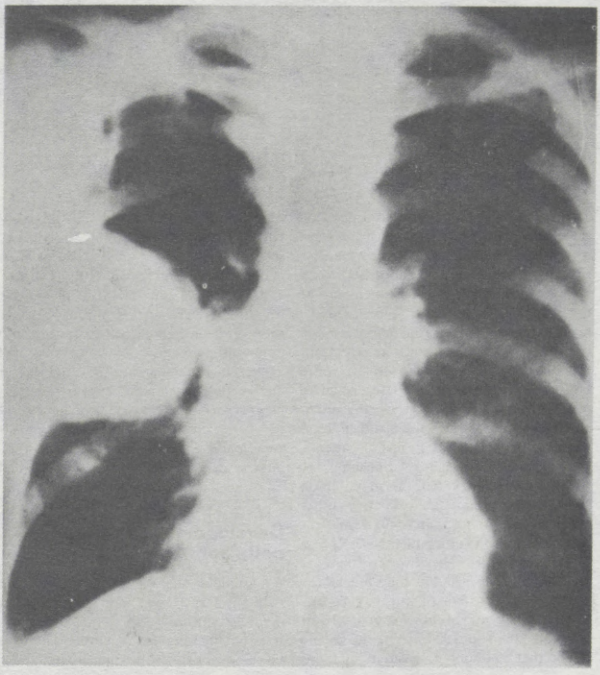
. . . or smoking

Like bronchitis, the prevalence of lung cancer (*see Fig. 2*) is closely related to the size of the community which in turn bears a rough relationship to the amount of air pollution. And, smoke contains compounds which are carcinogenic to the skin of experimental animals. Cancer of the scrotum was a common disease among chimney sweeps in the eighteenth century; skin cancer was not uncommon among gas workers. The team led by the late Sir Ernest Kennaway isolated from gas works pitch, and identified, a powerful carcinogen 3:4-benzpyrene. This compound, and many other polycyclic aromatic hydrocarbons, may be found in the soot or tar produced by the inefficient combustion of any compound containing carbon. It is certainly present in coal smoke.

Superficial scrutiny reveals few objections to the hypothesis that town smoke causes lung cancer but in reality the objections are many and overwhelming. While the number of deaths from lung cancer has been increasing—from about 200 deaths in 1906 to about 27,000 last year—pollution by smoke, with its carcinogens, has been steadily declining. Today smoke is becoming rather rare in the middle of big cities. Finland, a country with very little air pollution but bad smoking habits, suffers from a high mortality from lung cancer. The cause of the scourge is known: the incidence of lung cancer (in particular squamous-cell and oat-cell carcinomata) is closely related to the number of cigarettes smoked. The correlation with pipe smoking is much less strong, and almost vanishes in the case of cigar smokers. Studies carried out in many parts of the world have confirmed the results of the classic work of Dr R. Doll and Sir Austin Bradford Hill and the evidence on which the cigarette is indicted is lucidly set out in the Royal College of Physicians' Report on "Smoking and Health"—one of the most important publications concerning the health of the public ever issued. The larger report issued by the U.S. Surgeon General confirmed its findings and opinions.

Yet again there is an urban factor

Fig 2 RADIOGRAPH SHOWING LUNG CANCER. The tumour appears as a large white 'shadow' in the right lung. Like bronchitis, the prevalence of lung cancer is closely related to the size of the community which in turn bears a rough relationship to the amount of air pollution. Superficial scrutiny reveals few objections to the hypothesis that town smoke causes lung cancer but detailed investigations which include countries with very little air pollution such as Finland show that cigarette smoking plays a far greater rôle in the genesis of this terrible disease which causes more deaths each year



which must be considered. This factor is, we believe, far less powerful than many workers think and we are reluctant to jump to the conclusion that it is air pollution. While the urban factor is closely linked with air pollution in Britain, in the Scandinavian and Baltic countries, with their clean air, the same phenomenon is still discernable. Whatever part air pollution might play in the production of lung cancer (which is four times more common than fatal traffic accidents) one must remember that it is very rare in non-smokers and, remarkably, the risk of contracting the disease decreases sharply when the habit is abandoned.

Completing the picture

Substances other than smoke and sulphur dioxide pollute the air in cities and towns. In Los Angeles the exhausts from motor vehicles cause great trouble. There, the hydrocarbons emitted unburned or merely altered by 2·5 million cars, react with oxides of nitrogen and ozone in the strong ultra-violet light and stable air to form a haze which is extremely irritant to the eyes. Occasionally traces of this "L.A. smog" occur in Britain but there is insufficient sunlight for it to form in amounts sufficient to cause annoyance. However, carbon monoxide emitted by petrol engines is beginning to claim serious attention.

This odourless, colourless gas can act as an asphyxiant by combining avidly with the haemoglobin of the blood thereby blocking the transport of oxygen to the tissues. Recent research has shown that quite small concentrations in the blood, too small to cause symptoms, can impair perception and performance of some experimental tasks. There is often enough carbon monoxide in congested traffic to produce blood levels which can impair performance in the laboratory and the relevance of this research to safety in driving is being studied as a matter of urgency. Many devices, including "after-burners", for removing the carbon monoxide and hydrocarbons from exhaust gases, have been tried in California. The hydrocarbons are of far less importance in this country but much work is being done on methods for the reduction of carbon monoxide in petrol engine exhausts.

The diesel engine produces virtually no carbon monoxide; when badly maintained or overloaded it can produce clouds of disgusting black smoke which causes justifiable annoyance but there is no evidence that it causes disease. Indeed the use of more diesel engined public service vehicles in congested cities would lead to a reduction in carbon monoxide concentrations in busy streets.

The Clean Air Act of 1956 came forth after the Beaver Committee had reported on Air Pollution after we had been shaken by the London "smog" of December 1952. It is a good instrument in that it deals with the prevention of smoke (which can be prevented) and doesn't pretend to be able to cope with some other pollutants such as sulphur dioxide. The last ten years have seen a remarkable decline in smoke in many of our towns and this decrease is most welcome. The abatement of sulphur dioxide is recognized to be a more difficult problem. It is to be hoped that the indications derived from current research are confirmed and that the smoke which is declining might prove to be the most harmful pollutant of the air we must breathe.

FURTHER READING—*see opposite*

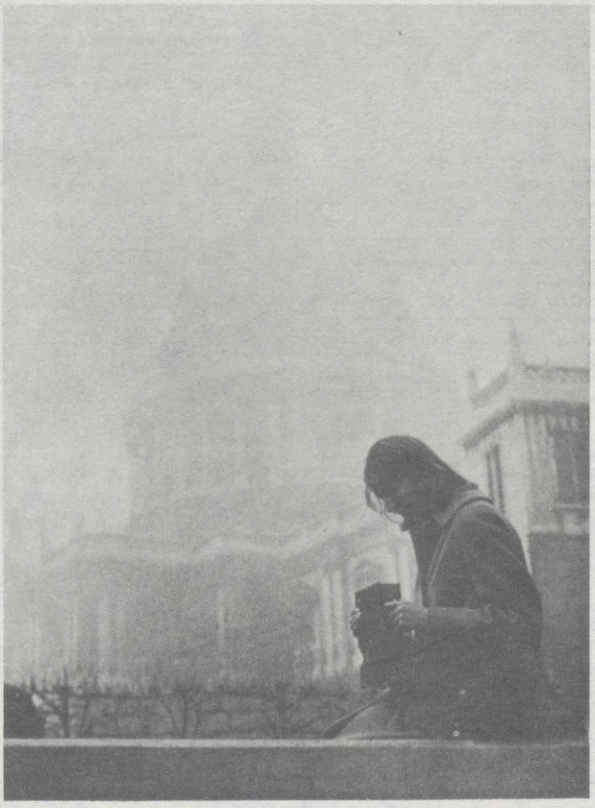


Fig. 3 MEASURING POLLUTION by sulphur dioxide near the precincts of St. Pauls Cathedral in London. The portable instrument being used was developed by the author's Unit at St. Bartholomew's Hospital. Although pollution from smoke is dwindling in most of the large cities in the United Kingdom, the abatement of sulphur dioxide is recognized as a much more difficult and so far unsolved problem

Author

DR PATRICK J. LAWTHER (*Air pollution*) is Director of the Medical Research Council's Air Pollution Research Unit and Honorary Consultant Physician in Environmental Medicine at St. Bartholomew's Hospital. He is at present working on the effects of air pollution and industrial environmental factors on man. Before reading medicine Dr Lawther worked in the chemical industry.

Further Reading

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Senator MUSKIE. Thank you very much, Dr. McFarland and Dr. McCabe.

I do have a few questions. I wonder if I might not submit those to you for replay. My schedule called for me to be somewhere else 15 minutes ago.

(Questions submitted by Senator Muskie and the response by Dr. McCabe follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. LOUIS C. MCCABE,
Chairman of the Board,
Hazleton Laboratories, Inc.
Reston, Va.

DEAR DR. MCCABE: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. LOUIS C. MCCABE

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

3. To what extent can industrial hygiene and occupational health provide answers to the effects of long-term exposures under environmental conditions?

4. To what extent are the reported effects of air pollution affected by the study methods employed?

5. In light of your association with the animal studies at the Hazleton Laboratories, what are the special contributions that animal studies have to make and their limitations?

6. Mention has been made of materials which may require special concern (e.g. carcinogens, mutagens, and asbestos). What would be a suitable public health policy for dealing with these materials?

AUGUST 23, 1968.

Hon. EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution,
U.S. Senate, Washington, D.C.

DEAR SENATOR MUSKIE: In reference to your letter of August 2nd in which you asked for assistance in developing answers for the proposed questions that were enclosed, I offer the following comments:

QUESTION 1

The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

From my knowledge of the general field, my answer is none.

QUESTION 2

The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be used to confirm or refine air quality criteria?

I do not feel qualified to answer this question. It would take a professional epidemiologist, which I am not. On the basis of general scientific principles, however, in order to make a contribution toward criteria setting, an epidemiological study would have to be able to provide an exact qualitative and quantitative description of the polluted atmosphere, the pattern and duration of the exposure of the subjects, and to delineate the specific responses in the subjects that could be properly associated with the causative circumstances.

QUESTION 3

To what extent can industrial hygiene and occupational health provide answers to the effects of long-term exposures under environmental conditions?

The type of special atmospheres studied in industrial hygiene and occupational health are readily definable in terms of their constituents. On the other hand, the ambient pollution associated with large centers, containing housing, a multiplicity of industries and contributions from transportation, is less well defined and generally contains a much longer list of pollutants. Therefore, the experience from industrial hygiene and occupational health cannot be applied in the urban situation without recognizing that the interactions among these various pollutants cannot be learned from just the industrial hygiene experience.

QUESTION 4

To what extent are the reported effects or air pollution affected by the study methods employed?

The defect in relating effects to levels of air pollution is largely a lack of definition which, in general, results in a weakening of the establishment of a cause and effect relationship. The more sophisticated, detailed and advanced the study methods are, the more reliable and definitive are the relationships between cause and effect that may be established.

QUESTION 5

Re studies at Hazleton Laboratories, what are the special contributions that animal studies have to make and their limitations?

The special contributions that are made by animal studies are that they are carried out under laboratory conditions with a very high degree of control of experimental variables. Under these circumstances, cause and effect relationships are most fully defined and established. The major defect in experimental studies is the fact that they are carried out on animal species and thus an extrapolation of the animal results to the human is always required at the end of the experiment.

QUESTION 6

Mention has been made of materials which may require special concern (e.g. carcinogens, mutagens, and asbestos). What would be a suitable public health policy for dealing with these materials?

The public health policy which is suitable for dealing with any form of pollutant can be extended to other materials, such as carcinogens, mutagens, and asbestos.

Sincerely yours,

LOUIS C. MCCABE, Ph. D.

Senator MUSKIE. May I say again how much I appreciate the testimony presented by all of the witnesses this morning. I think it has been uniformly excellent, as we have come to expect.

We will resume tomorrow morning at 9:30.

(Whereupon, at 12:43 p.m., the committee was recessed, to reconvene at 9:30 a.m., Wednesday, July 31, 1968.)

AIR POLLUTION—1968

WEDNESDAY, JULY 31, 1968

U.S. SENATE,
SUBCOMMITTEE ON AIR AND WATER POLLUTION
OF THE COMMITTEE ON PUBLIC WORKS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:35 a.m., in room 4200, Senate Office Building, Senator Edmund S. Muskie (chairman of the subcommittee) presiding.

Present: Senators Muskie and Randolph.

Also present: Richard B. Royce, chief clerk and staff director; Leon G. Billings and Richard D. Grundy, professional staff members.

Senator MUSKIE. We will be in order.

This is the third and final day of hearings in this series, and it is a pleasure to welcome four more distinguished witnesses.

The first, Dr. James H. Sterner, acting dean of the School of Public Health of the University of Texas.

Dr. Sterner, we welcome you this morning.

STATEMENT OF DR. JAMES H. STERNER, ACTING DEAN, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF TEXAS, HOUSTON, TEX.

Dr. STERNER. Thank you, Mr. Chairman.

Mr. Chairman and members of the committee, I am James H. Sterner, M.D., professor and chairman of the department of environmental health and currently acting dean of the University of Texas School of Public Health at Houston.

I should emphasize at this point that I am appearing as an individual, and that the views and ideas expressed here may or may not reflect those of the University of Texas or other organizations with which I may be identified.

It has been my privilege to have participated in a number of activities directed to the solution of environmental health problems.

I served as a member of an Office of Science and Technology committee which met with the Surgeon General of the Public Health Service in 1961 to stimulate a greater effort in mobilizing an attack on the rapidly increasing environmental health issues. The "Gross Report" on environmental health problems and an expanded Public Health Service program followed this effort.

Later I was a member of the Environmental Health Advisory Committee to the Public Health Service and, after a reorganization of that Service, became a member of the National Advisory Disease Prevention and Environmental Control Council, and continue as a consultant in environmental health matters.

Perhaps this confusing sequence, in the span of a decade, symbolizes the rapidly changing nature and the public response to the environmental health problems confronting the country.

As additional explanation for my appearance here, I serve as chairman of the American Medical Association Council on Environmental and Public Health. This body has assumed a leadership role in representing, and in stimulating and organizing, the medical profession in the attack on environmental health problems.

The series of five annual congresses on environmental health have helped to define the problems and to educate and encourage the medical profession to participate in the interdisciplinary approach required for an effective assault.

In cooperation with the National Air Pollution Control Administration and medical organizations especially concerned with pulmonary disease, the council has just held this past week the second Air Pollution Medical Research Conference, an effort which is now widely recognized as the authoritative platform for the presentation of data on health effects.

Too, I am chairman of the National Air Conservation Commission, a body established by the National Tuberculosis and Respiratory Disease Association to promote citizen interest and involvement in the attack on air pollution. The Commission, comprised of nationally prominent individuals who are identified for their interest and competence in dealing with air pollution problems, is working through the some 1,500 constituent and affiliate associations in every State, to develop an informed and involved citizen action group to function at the local level in attacking air pollution.

The National Tuberculosis and Respiratory Disease Association, with a long history of community leadership in health, has adopted the fight on air pollution as a major program emphasis.

Before coming to the University of Texas School of Public Health, I served as medical director of the Eastman Kodak Co., in Rochester, N.Y., and represented that organization as chairman of the Manufacturing Chemists Association Environmental Health Advisory Committee.

EMERGING PROBLEMS

It was my privilege and pleasure, during that tenure, to observe the profound change in attitude and response on the part of the chemical industry to the rapidly changing environmental health picture. The chemical industry, with a yearly production of 100 billion pounds of synthetic chemicals and allied products has had an exceptionally fine record of protecting the health of its employees from the chemical and physical hazards incident to employment. Many of the individuals involved in this protective mechanism, industrial hygiene, are now the leaders in the attack on air pollution.

The rapidity and magnitude of the emerging problems of environmental health, air pollution, water pollution, ionizing radiation, pesticides, noise, chemicals on the farm and in the home, compounded by the population explosion, urbanization, and the growth of industrial production, finally has exceeded the assimilative capacity of our environment for an indiscriminate disposal of waste products.

We can no longer enjoy the luxury of just throwing away our wastes from our smokestacks, from our automobile exhaust pipes, from our sewers, from our garbage cans. An increasing part of the effort and cost of producing the goods and services which man wants and needs must now be devoted to the control and elimination of these waste products, largely byproduct and unwanted, if we are to maintain a reasonably safe and healthful place to live.

In less than a decade, our society has recognized that we can never return to the relatively pristine state of a much earlier age, when there were only a few people scattered over wide space. Where there are people there will be wastes—in the air, in the water, on the land. The ever more rapidly growing population requires additional energy sources, and waste products, whether from fossil fuels or nuclear reactors, generate increasing confinement and disposal problems.

AIR RESOURCE MANAGEMENT

The problems in the management of our air resource have become so great and so complicated that there is now wide agreement that some kind of quantitative guides are necessary to permit a reasonable control effort. The development of an earlier acceptance of this concept for the control of the inplant occupational exposures, by the establishment of maximum allowable concentration values or threshold limits took 20 to 30 years or more from the time they were first seriously proposed.

In contrast, the need for air quality criteria, as recognized by the public, by legislative bodies, and by industry, excepting in a few areas such as Los Angeles where the environmental contamination presented a more severe problem, has become evident only in the past few years.

CHANGING EMPHASIS

As an index of the rapidity with which the emphasis has changed, we might look at the escalation of Federal support for air pollution activities.

In 1960 the Public Health Service received but $4 million—while for the current year I believe it is likely that the figure will be about $86 million. In retrospect, it is obvious that a more perceptive examination of the increasing contamination of our atmosphere might have permitted a more orderly and balanced program, with greater emphasis on prevention and less need for dealing with the problem as a series of crises and the necessity of measures to "restore" the quality of our environment.

CRITERIA DEVELOPMENT

We are going through an evolution of social and political mechanisms in our attempts to develop a set of air quality criteria. The Public Health Service in response to a mandate of Congress issued the first of a set of such criteria—on sulfur dioxide.

This initial effort, the product of competent and dedicated individuals, was generated largely within the circles of service personnel, though tested during the process by consultation with recognized ex-

perts outside of governmental agencies. The immediate and violent protest to the publication, ranging from scientific dispute to economic and political derogation is now common knowledge.

ADVISORY COMMITTEE

In the next round of legislative action, it was stipulated that advisory committees with representation from the scientific and professional community be appointed to the groups charged with the development of a new set of criteria for the important recognized air pollutants. This is an improvement in encouraging acceptance of the criteria, but must be subject to criticism of possible bias in the selection process.

Some time ago in considering how one could develop the greatest degree of objectivity in the establishment of such criteria—and of major importance in our democratic society, the greatest likelihood of broad acceptance of the validity and reliability of the criteria generated, the model for the development of criteria governing exposure to ionizing radiation suggested itself.

It was my privilege to serve for some years as a member of the National Council on Radiation Protection and Measurements. This body, now chartered by Congress as an independent corporate entity, has had the respect and regard of the scientific community, and a remarkable degree of acceptance for the criteria which it has generated, not only for populations exposed to radiation occupationally, but for the general population.

When the Federal Radiation Council was established to guide governmental organizations in matters of radiation exposure, the Presidential order carried the proviso that it consult with the National Council on Radiation Protection and Measurements.

NATIONAL COUNCIL ON HAZARDOUS PHYSICAL AND CHEMICAL AGENTS

On several occasions within the past year—to the American College of Preventive Medicine and to mid-year meeting of the Manufacturing Chemists Association—I have suggested the establishment of a "National Council on Hazardous Physical and Chemical Agents," to operate in a comparable manner to that of the National Council on Radiation Protection and Measurements.

Membership

Members of the Council would be nominated by professional and scientific societies with a recognized valid interest and competence in the measurement and the biological effects of the whole spectrum of physical and chemical agents of environmental health significance. A limited number of at-large members would be selected by the Council to further provide a balanced and broadly based representation. Members of the Council would not report back to their associations for confirmation of action.

Sponsoring organizations would be those scientific and professional societies with recognized interest and competence in the interaction of biological systems, with emphasis on man, with the increasingly wide variety of hazardous physical and chemical agents of importance for health and well-being.

No Council member would be selected because he represented industry, or labor, or Government, or the university, but there would certainly be individuals from all these sources, identified and chosen by their professional and scientific peers.

The Council would speak for itself, with its official pronouncements reflecting the best composite judgment of the scientific and professional community. The criteria established could be accepted or rejected by official agencies in the development of standards, an admittedly governmental responsibility.

However, the conclusions developed by the Council with objectivity and reflecting the composite opinion of presumably the most knowledgeable and most able scientists and professional people, could provide the kind of solid base from which our society can and must make the value judgments we shall need in ever greater variety, numbers, and importance.

In the manner of the National Council on Radiation Protection and Measurements, the National Council on Hazardous Physical and Chemical Agents would develop standing and ad hoc committees to deal with the specific matters meriting its attention, establishing criteria applicable to the general population, or to special populations such as occupational, geriatric, pediatric, or other. The recommendations from these special committees would then be submitted to the whole Council for final action.

Financing

Financing should be broadly based with support from foundations, professional and scientific societies, industry, and, as indicated, by grants from governmental agencies. Such an organization could develop the objectivity and scientific judgment which would give its work the prestige, the sanction, and the wide acceptance that will be needed increasingly to guide the ever more important decisions in environmental health.

For the present, I would suggest that the National Council on Radiation Protection and Measurements continue its independent and successful course, but later it could well be combined with the proposed Council to form a single substantial organization dealing with the full spectrum of hazardous physical and chemical environmental factors.

The proposed mechanism would complement a National Council of Ecological Advisers, if and when such a higher level body were established, or would provide an essential component to any mechanism or mechanisms which our society will develop to deal with environmental health problems.

The input from a National Council on Hazardous Physical and Chemical Agents would provide the important information as to biological effect, certainly an essential element in any cost-benefit equation needed to determine in an orderly manner the ultimate acceptability of a product or energy form.

Other functions such as economic, social, political, must, of course, enter into any final value judgment, but the better the data with respect to the biological effect, the more valid and reliable the final determination by any mechanism which society evolves to find solutions to these problems.

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AVAILABLE KNOWLEDGE

One must seriously question whether at this time we are sufficiently knowledgeable or sufficiently wise to justify the establishment of a mechanism which could exert such far-reaching effect. It may well be that a further period of experimentation, of trial and error, will result in a more orderly and more effective evolutionary approach to the solution of our rapidly expanding environmental health problems.

I sense, however, an ever-growing number of serious and able observers of our rapidly changing environmental scene who are convinced that only positive and firm action, taken now, can avert serious consequences for our present and future generations.

Earlier I noted the rapidity with which the problem is emerging and changing. To this factor we must add the complexity, with the increasing necessity of considering the interrelationships and interactions between what superficially may appear to be unrelated hazards.

AIR POLLUTION

In the matter of air pollution, the hope of separating the effects of the many pollutant factors and of establishing relatively simple indices of hazard is fading. When we found that some of the postulated effects of sulfur dioxide in gaseous state could not be corroborated by later studies, new explanations were sought, involving the interaction with particulates and other contaminants.

The permutations and combinations of the six or seven commonly identified air pollutants, with the possibilities of additive, subtractive, synergistic, anergistic effects, will require many years of experimental effort for a reasonable elucidation.

Sooner or later we must integrate the effects of other potential hazards with those of air pollution. As an example, there has been recent emphasis on the similarity of certain chemical agents in mimicking the genetic effects of radiation.

The finding of reasonable and valid answers to these problems which are becoming more evident and more significant each day will require of society the best, most objective, and most responsive mechanism. We cannot wait for the preponderance of experimental data which we would like for a convincing scientific conclusion. Our decisions must be based on an unequal series of value judgments. I believe that these judgments will best serve society if developed by the most knowledgeable, competent, and concerned individuals. I believe that a mechanism of the kind proposed might serve this purpose.

Thank you.

Senator MUSKIE. Dr. Sterner, I would like to refer to several points you made in your statement to shape an issue, if I may.

CRITERIA FEASIBILITY

First of all, you noted the widespread controversy which was generated by the issuance of the criteria related to sulfur oxide. I think it is a fair summation of that controversy to state that those opposed to the idea felt there was not sufficient medical basis, among other things, for the criteria that were suggested.

Then on the second page of your statement you say that some kind of quantitative guides are necessary to permit a reasonable, controlled effort. That statement would appear to be an affirmation of the need for criteria.

Then on page 8 you say:

> In the matter of air pollution, the hope of separating the effects of the many pollutant factors and of establishing relatively simply indices of hazard is fading.

So, at one point you affirmed the need for criteria and at that point of the statement I have just read you indicate the difficulty and maybe the impossibility of establishing such criteria.

I think that is enough to get us started.

Dr. STERNER. No, sir; I meant only that the problem was not quite as simple as we hoped it would be initially.

I am convinced that we need criteria, that we must have them for an adequate control method. On the other hand, the setting of one simple index is not as easy as we initially thought.

Senator MUSKIE. It seems to me the dilemma we find ourselves in—is painted more clearly with each day of testimony that we get—is this: For instance, there seems to be general agreement that relating the effects of pollutants to particular pollutants or combinations of pollutants is not an exact or precise art or science or however else you may wish to describe it.

That being true, once criteria are established for any group or combination you are going to get the same kind of controversy that we had with oxides of sulfur. There is going to be that group which says, well, you have not established the relationship clearly enough yet to justify the burdens, the costs that you are imposing on industry.

On the other side, you are going to get the argument that, since this is not a precise art, the best we can do is rough approximations and you have got the best approximations that we can get and in any case we can't wait for better ones.

This is the kind of argument you are going to get and it is going to be a running argument, and you are never going to be able to resolve it because it is not a precise art.

The question inevitably arises for those of us who have to make policy: Then are criteria viable and effective means of establishing control?

Dr. STERNER. I am in complete agreement with the problem as you have phrased it and for this reason particularly. I would like to have this judgment made by the broadest group and most competent group from the scientific community. I think this would encourage one important element, namely, acceptance of this data, to a greater degree than if it were set by a smaller, more isolated or more selected group of individuals.

I think if we could get this nebulous quantity, the "scientific community" or the "professional community," to agree that this mechanism has been established by the best possible means, the broadest possible, the most composite judgment going into the determination, we would be further along the way of getting acceptance.

Senator MUSKIE. How much time are we going to devote to that kind of deliberation? I assume the council which you recommend is

a nongovernmental one operating under its own momentum in accordance with its own sense of urgency in accordance with such resources of time and money that it may be able to develop.

Time table

Should the timetable of governmental criteria establishment be geared to a timetable of such a nongovernmental agency?

Dr. STERNER. I think this is a very good question. If such an organization could not function within the time limits, then obviously it is not serving the purpose.

Senator MUSKIE. In other words, what we should do is proceed with the tasks laid out by the Air Quality Act, and if in the meantime this effort which you have described is able to get moving, then it could be a useful advisory group.

Dr. STERNER. I think this is entirely reasonable.

Senator MUSKIE. I think we still have the time problem.

Dr. STERNER. Yes.

Senator MUSKIE. It is always dangerous to try to summarize the testimony of witnesses, but I think I have got to for the purpose of putting questions, and I apologize for any distortion in testimony that I may be guilty of in the process.

At least one witness yesterday said that it is so clear that damage flows from a whole list of pollutants that we ought not to take the time to establish causal relationships between pollutants and effects, that we ought to just begin rolling back emissions.

Do you have that kind of a feeling of urgency about this problem, Dr. Sterner?

Dr. STERNER. I do. I think we certainly must proceed with rolling them back but there is still going to be that "$64,000 question." There is still going to be the question: At what level should we level off?

This will become an increasingly difficult problem for a whole variety of agents that invade our environment.

CONCEPT OF CRITERIA

Senator MUSKIE. Let me ask you this, Dr. Sterner. One of the criticisms of the oxides of sulfur criteria was that they imposed unreasonable burdens upon industry.

My concept of criteria is that they do not do any such thing, that all criteria do is establish the nature of the effects. What we do about them then depends upon the availability of the necessary resources, money, and the availability of necessary technology, but that the effects, themselves, ought to be independent of what we do about the effects, that we ought to know what the effects are and then move toward them as fast as the economic and technological factors permit us to move.

I appreciate the fact that the establishment of the effects and the knowledge that they exist in and of themselves impose pressures on industry but they do not in and of themselves impose mandates upon industry. I think we ought to understand the difference, nevertheless.

So, I ask you the question: Did you concur with this definition of what criteria mean?

Dr. STERNER. Yes; I think essentially this is the purpose of criteria.

HAZARDOUS MATERIALS

Senator MUSKIE. Now, on page 7 there is the implication that we ought to control pollutants only to the extent that they are hazardous.

Did you mean that and, if you did, would you define what you mean by hazardous?

Dr. STERNER. I would prefer to interject here the broad interpretation of health to include well-being, too.

Senator MUSKIE. Then one other clarification.

On the same page you suggest that in establishing our standards or our guidelines or our performance indices that we ought to use a cost-benefit equation. The typical situation requires an analysis based on dollars, but the kinds of hazards that flow from pollutants cannot be measured by dollars.

COST-BENEFIT EVALUATION

So, I wondered what you had in mind as the cost-benefit equation that we could apply to this particular form.

Dr. STERNER. I would put on the benefit side not only dollars but the quality of living, too, as difficult as this is measured in specific terms.

Senator MUSKIE. It would be a subject of judgment rather than an object?

Dr. STERNER. There is not any question of this. Somewhere along the line this becomes a value judgment and not a scientific conclusion.

Senator MUSKIE. One other question related to those I have already put.

CRITERIA DEVELOPMENT

It was argued by one witness yesterday that this business of taking pollutants one by one and establishing their health and welfare effects with sufficient specificity to satisfy not only those who want controls but those who resist controls is a time-consuming process and that the time factor is aggravated by the fact that we are continuously multiplying the sources of pollutants, adding new ones, increasing old ones and so forth. I guess we just get involved in an impossible ball of wax when we try to establish criteria pollutant by pollutant.

In any case, when we get through, we will find, as we have found already, that it is not the single pollutant that causes the problem but combinations of pollutants.

With that kind of criticism of the criteria, what is your reaction?

Dr. STERNER. It is for exactly this reason that I think we ought to have the most responsive, the most intelligent, the most knowledgeable body making the judgments. In many areas, there are only fragmentary data but this group of individuals who have the competence in making these kinds of judgments I think could arrive at a more reasonable judgment than individuals who are remote from an understanding of the problem.

Senator MUSKIE. Well, as a Senator, I appreciate more than anyone else the more people you get involved, the more time you take. So that observation does not deal with the problem.

EXPERIENCE WITH RADIATION STANDARDS

Dr. STERNER. Again, I think the National Council on Radiation Protection and Measurements, while moving slowly in many areas, has come up with a degree of acceptance of its results that have far-reaching implications. Our whole structure for the control of our ionizing radiation is really based on the pronouncements and judgments derived by such a group.

Senator MUSKIE. There are two important differences between the radiation problem and the problem with which we are concerned.

In the first place, industries related to the atom and its development which were new and came into being after we knew of the hazard and their growth, therefore, could be tailored to the policy guidelines that we developed as we went along. To impose burdens on industries related to these pollutants that have been in existence all these years is a different kind of a problem.

Secondly, with the radiation hazard again you have a single source of pollution. In the case of these other pollutants, you have multiple ones interacting with each other as well as creating their own individual hazards so that the time problem involved and the urgencies involved I think could be quite different in the two cases.

JUDGMENT

Dr. STERNER. It seems to me, though, that you are posing here the question of making definitive judgments without information as opposed to perhaps a little more delay in making judgments with the best possible input of information.

In other words, if urgency is the important element in the matter, then we are going to make some very bad guestimates, some very bad judgments at this time if we move ahead too rapidly.

Senator MUSKIE. Well, let me make two points before commenting on that observation.

First of all, we are concerned not only with clinical injury, the risks of which I think can be identified with minimal loss of time, or at least can be established more easily within a reasonable time frame, and long-term risks which obviously can be evaluated only by long-term study.

There is no way that I know of telescoping the long-term effects in a laboratory upon a human being of exposure to these pollutants in a way that it would give you short-term judgments. There may be, but no one yet has identified them.

As a matter of fact, one of the witnesses dwelled upon the idea of transferring the results of experiments on animals with short lives to human beings with relatively longer lives. So how do you establish the long-term effects? How do you guess as to the long-term effects of pollutants over a lifetime upon a human being?

I put this because it seems to me that it highlights the proposal that was made yesterday that I think is deserving of consideration. Since you can't do this, since you can't afford the time to do this sort of thing, we ought to be satisfied with the knowledge that we now have that it is not good to discharge most pollutants into the air, so we ought to concentrate on stopping the emissions rather than on establishing a specific causal relationship between an unfavorable result and a specific combination of pollutants.

Now, that is more of a speech than a question but perhaps in that way I pose something you can comment on more readily.

THRESHOLD LIMITS

Dr. STERNER.I would agree that this would be an ideal relationship but again you are casting this in terms of our economic and of our technological ability to do this. This is the whole principle of threshold limits set for industry in that it is impossible to completely confine anything even with the higher, more radioactive materials. There are threshold levels that are set which we judge are safe to live with because it is impossible to work with a substance and completely confine it for all time.

WASTE REUSE

This will be the situation with the whole variety of substances which are valuable and useful to man and which we want, and it will be impossible to say that we can use this substance and completely confine it.

Senator MUSKIE. Now, while we wait, while we take the time to do this, we continue to build in vested interests in the right to pollute. Industry keeps on building new plants, human beings find new ways or new products which appeal to their appetities. As you say, wherever there are people there are wastes.

ECONOMIC FEASIBILITY

Suppose, for example, that we had waited until communities had a certain number of people before we required that they put in bathrooms. Now, at that point would you impose the requirement that toilet facilities, being as they are, would have been a tremendous economic problem?

There is nothing in the Government regulations, I guess, to stimulate the development of modern toilet facilities, but in any case people put them in as a natural development of their desire to improve their way of living. Actually, of course, in many parts of the country we would have a lesser pollution problem if more people didn't have the bathroom but relied on the old one- or two-holer. We decided it was a good thing to have the bathroom but the inevitable result of that was that we concentrated those wastes and created a problem for the community. We were much less ready to build the community bathroom than we were the bathrooms for the private homes, because we delayed building the community bathrooms.

We now have this tremendous economic problem which we have not yet found a way of dealing with effectively.

That may be a rather earthy analogy but I think it is a very apt one. Why should we not adopt a policy of requiring that every new plant make use of all existing technology to limit the wastes which it will discharge into the environment without waiting for the establishment of the scientific basis for criteria?

Dr. STERNER. I think within the technology and the economic ability to do so this is a good direction to move. I think we must at the same time say that, if absolutely no pollution is to result, then we cannot build this plant at all because it may not be possible to assure zero pollution.

Now, then, you recognize a whole spectrum of possibilities, from no pollution to absolutely no control of pollution and somewhere in between you have to come back to some kind of criteria.

Senator MUSKIE. This is what we talked about with the automobile. We said that, because it is difficult to deal with the pollution from all cars, then the more quickly we impose controls upon new cars the better our prospects for controlling the old cars, because the old cars go off the market and this is how you begin to move into more effective controls.

Now, if we did the same thing with industrial plants, perhaps that would be a viable policy.

OCCUPATIONAL EXPERIENCE

In the field of occupational hazards facing air pollution, we do have some criteria now.

Dr. STERNER. Oh, yes.

Senator MUSKIE. How useful would it be to transfer that experience to the problem that we have?

Dr. STERNER. Oh, we are dealing with an entirely different situation.

Senator MUSKIE. Would you describe the differences?

Dr. STERNER. Well, the difference is that, one, you have a more selected population through the employment procedure of putting presumably healthier individuals on the job than you have in the general population.

Two, you have a limited time factor involved for the individual exposed during his working hours. I think these are the two major factors, but I think there is general agreement that you cannot translate the 8-hour exposure, 5-day-a-week criteria to general population exposure.

Senator MUSKIE. Is it your fear that the thresholds established by using that experience would be too high or too low?

Dr. STERNER. Oh, they would be way too high.

Senator MUSKIE. I understand that the British used those values and applied it back to 30 to establish an immediate criterion until they could develop a better one.

Do you think that would make any sense?

Dr. STERNER. Some factor has to be established. I don't think that the factor of 30 is a magic number. It might be 30 for one material; it might be 100 for another material or 1,000 for another material.

Senator MUSKIE. Is that worth exploring, even though there were variations in different groups?

Dr. STERNER. Yes. I think for the general population we frequently use a factor of 100 as a working basis, recognizing that in many instances you could not accept this margin and use the material at all.

Senator MUSKIE. Dr. Sterner, I thoroughly enjoyed the chance to chat with you about this problem.

I don't think we have any other questions at this point.

CONTAMINANTS REQUIRING CRITERIA

I ought to ask you this question: What, in your judgment, are the pollutants to which we should address ourselves first in the light of their potential hazards, and using hazards in the broad sense that you define it?

Dr. STERNER. For air quality criteria?

Senator MUSKIE. Yes.

Dr. STERNER. I think the focus pretty well includes carbon dioxide, sulfur dioxide, particulates, nitrogen oxides, lead. This is the usual spectrum.

Senator MUSKIE. I quote from Dr. Goldsmith's statement Monday in which he said this:

> It is my personal opinion that there are sufficient data to set predictive air quality criteria for oxidants and ozone under the conditions which occur in Los Angeles to establish joint criteria for particulate and sulfur oxides under the particular climate, to establish criteria for carbon monoxide and to state at what level the community exposure to lead is likely to lead to detectable increases in storage of this substance within the body.

In other words, he says that we now have sufficient data to establish criteria for goals.

Would you have any comment on that?

Dr. STERNER. Yes; I would agree. Again the argument would come over the degree of reliability and validity of any figure that was chosen by any group, but I think we can move.

Senator MUSKIE. Fairly rapidly?

Dr. STERNER. I certainly do, sir.

Senator MUSKIE. Suppose we had the kind of council that you recommended. How rapidly do you think it could be done?

Dr. STERNER. Could these be established?

Senator MUSKIE. How rapidly do you think we could establish criteria for the hazardous pollutants?

Dr. STERNER. I think we are doing it now. I think the various committees are about to report, or already have reports, and I think that these will be the best value that we can work with at this time. Then I hope we keep reviewing them as we get better information.

Senator MUSKIE. Thank you very much.

Senator Randolph.

Did you have a question, Senator?

Senator RANDOLPH. Thank you, Senator. I have several.

NATIONAL COUNCIL

Dr. Sterner, first of all, I want to express my appreciation, as a member of the Subcommittee on Air and Water Pollution, for your continuing study and your ability to discuss the proposed council with such groups as those with whom you communicate.

Since we have the National Council on Radiation Protection and Measurements, you would indicate the desirability of a National Council on Hazardous Physical and Chemical Agents.

FUNDING FOR COUNCIL

Would you tell me what the funding is for the Council on Radiation Protection and Measurements?

Dr. STERNER. It has always been a difficult problem for them. Part of the contribution comes from the various societies that are involved, and this is an unequal input depending upon the size of the organization.

I think the Radiological Society contributes a relatively larger amount than does the American Industrial Hygiene Association, for example.

In addition, they have received funding from several Federal agencies; the Atomic Energy Commission has given them funds from time to time and the Radiological Health Section of the Public Health Service. They have had some help from foundations, particularly on a periodic basis when there was a change in the organizational structure.

They have had a difficult time getting enough money to operate. Many of the individuals have had their expenses paid to meetings by their own companies or by professional societies or their own university and I would visualize that the proposed council such as I have suggested would really involve a very considerable expenditure, and I am speaking of the order of a million dollars or more a year to operate.

I think it would be a tremendous commitment on the part of organizations that assigned representatives to serve as a member of the council. They would have to devote a great deal of time. There would be ad hoc committees. Somehow, expenses would have to be met and a substantial commitment to permit the organization to function.

Senator RANDOLPH. Dr. Sterner, I felt it important to discuss the council, now in being, to have your evaluation of what it is doing and how it is financed, at least in part. As you now advocate the Council on Hazardous Physical and Chemical Agencies, you say you envisage some such council as the one on radiation protection and measurements. Do you mean that this would be a private organization with the addition of Federal funds?

Dr. STERNER. Yes, sir.

Organization

Senator RANDOLPH. Now, who would organize the council?

Dr. STERNER. Well, this was my suggestion. I proposed particularly to the American College of Preventive Medicine that they serve as a convenor for the various groups that might have an interest, the various professional and scientific societies. This has been authorized by the college and, unfortunately, I was asked to chair a convening committee. When the idea was proposed, I wanted to test it among various other individuals, as to whether it had merit. I think it is quite likely that this fall we will get representatives from other professional and scientific societies together and see whether there is enough interest, activity, and support to make this worth while.

Senator RANDOLPH. Dr. Sterner, I do not want to be misunderstood. My questions are not critical; they are in an attempt to probe because I am trying to find if you are thinking in terms of a council, although private in nature, that would lean heavily on Federal funding.

Dr. STERNER. I would prefer that this be a reasonable balance of funding from the various sources—from foundations, from industry, and from Government.

I would hope that the group could be sufficiently independent that, if any one source said, "We don't like what is coming out of this so we will pick up our marbles and run away," that this would not wreck the effort of such accomplishment.

Senator RANDOLPH. Well, there are people, of course, that pick up their marbles and run away even in political campaigns because it does not go just the way they think it is going as of a certain time. So this is a problem of reality, isn't it?

Dr. STERNER. Yes.

Senator RANDOLPH. Even in a scientific community.

Dr. STERNER. I would not want this to wreck the opportunity for such a council.

Membership

Senator RANDOLPH. Dr. Sterner, on page 6, first paragraph, fourth line, you say:

> No Council member would be selected because he represented industry, or labor, or Government, or the university, but there would certainly be individuals from all these sources, identified and chosen by their professional and scientific peers.

You speak about support from industry. In what way would industry be a part of the selection of persons that would form the working body of the council?

Dr. STERNER. It would not. This should come entirely from the professional and scientific community. If in a particular organization the best representative to the council in the judgment of that professional society or scientific society came out of industry, he would be selected; if he came out of Government, he would be selected; but it would be a judgment by their professional peers.

Senator RANDOLPH. Doctor, I think I now understand your proposal. I have studied your proposal prior to this morning and I have even made references to it in at least one speech that I have given on this subject.

I believe that you are telling us that it will be the decision of industry or labor or Government to come in and to support, but to come in and support after the organization has been brought into being with persons named who are not selected per se from the units from which you will desire financial support. I think we have to make this very clear. I think it has to be understood that there is no overlapping here. It will be the decision—let's just use the example of industry to evaluate what the council proposes to do and see whether in that funding it desires to be a participant. Is that correct?

Dr. STERNER. That is right.

Senator RANDOLPH. Doctor, the Council on Radiation Protection and Measurements, how long has it been in existence, approximately?

Dr. STERNER. Thirty years, twenty-five years.

Senator RANDOLPH. It came into being for what basic reason?

Dr. STERNER. Primarily for the control of industrial occupational exposure to radiation.

Senator RANDOLPH. You say that with this 30-year history it has had a continuing problem, as I understand it, of adequate funding. Is this true?

Dr. STERNER. This is true.

Senator RANDOLPH. Is this because of opposition? Is it because of a failure to realize if the realization would be true of the work that is being done that is subjective, that is constructive, that is helpful?

Dr. STERNER. Well, I suspect there are a variety of factors. Probably because the group initially contributed much of their effort on a personal basis to the action of the committee. Furthermore, the problems were not nearly as large in the early days of the committee. They were concerned primarily with occupational exposure and it

was not until we got some fallout from nuclear detonations that the public was more broadly concerned.

Maybe the council needs the help of an outside advisory group to tell them how to raise money because this has been the incidental part of its operation. At one time, you know, it was closely allied to the Bureau of Standards and many of its publications were issued with some support from the Bureau of Standards. The council recognized that it would have a greater degree of objectivity and acceptance if it divorced itself from any identification of this sort.

It then applied for and received the charter from Congress as an independent entity.

Senator RANDOLPH. Doctor, are you saying to us that the council that you are just now discussing in your opinion has been very worth while?

Dr. STERNER. I am certain of it.

Senator RANDOLPH. You are saying then that meeting the problems that come with the latter-day development which has to do with the hazardous physical and chemical agents as did Radiation Protection and Measurements with an earlier problem that you can anticipate that there would be a contribution constructive in nature perhaps to equal or surpass that of the early council? Is that what you are saying?

Dr. STERNER. Yes, sir. I am convinced that many of these decisions will have to be made on increasingly less solid scientific data. Thus, if this kind of judgment has to be developed for the benefit of the society I think the broader the base the more objectivity would come from involving the scientific community which is responsible for making or contributing to many of the problems in the first place.

Senator RANDOLPH. Dr. Sterner, I have said that our decisions must be based on an unequal series of value judgments.

Dr. STERNER. That is right.

Senator RANDOLPH. Nothing is on the same level. One day to another, these changes are being wrought.

Dr. STERNER. That is right.

Senator RANDOLPH. Some with rapidity, some with dramatic impact. Is that correct?

Dr. STERNER. Yes.

Senator RANDOLPH. If we are to serve society, and that is what you are asking through this council's creation and operation, then, knowledgeable, competent, and concerned individuals would, of course, be involved.

Dr. STERNER. That is right.

Senator RANDOLPH. You believe that mechanism. You have used the word not "will" but you said "might" serve this purpose. You still feel then there is some question; is that right?

Dr. STERNER. Well, I think there is always the difficulty. This would depend upon the attitudes of the people brought together; the willingness of the various organizations, the conviction of the various organizations that this kind of mechanism would be effective and that they would be willing to lend their efforts to it.

Senator RANDOLPH. Mr. Chairman, I am appreciative of the opportunity to counsel with Dr. Sterner in this manner.

I feel very strongly that where we can bring into being a council such as you indicate, can be brought into being in this area that it is functional, that it is helpful. This exchange of thought, this questing for the answers, this deep probing that naturally must come without the pressures, we will say, that might exist in another body.

Mr. Chairman, I would like to join Dr. Sterner in the general purposes for which he is an ardent advocate this morning.

Senator MUSKIE. Thank you, Senator Randolph.

I have just one question which occurs to me as a result of the colloquy with Senator Randolph.

To what extent have the recommendations of the Radiation Council been accepted and to what extent have their criteria been revised over the years to reflect new information?

Dr. STERNER. Of the National Council on Radiation Protection?

Senator MUSKIE. Yes.

Dr. STERNER. There have been numerous revisions of the documents, the criteria which they have developed. Depending upon the need in a particular area, the council has tried to keep itself current with any important changes that would justifiy modification of an earlier document.

Senator MUSKIE. Thank you very much, Doctor.

(Questions submitted to Dr. Sterner by Senator Muskie are as follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. JAMES H. STERNER,
Acting Dean, School of Public Health,
University of Texas,
Austin, Tex.

DEAR DR. STERNER: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. JAMES H. STERNER

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

3. To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

4. To what extent are the reported effects of air pollution affected by the study methods employed?

5. It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low-level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

6. What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

7. There are atmospheric contaminants that have their primary effect on other than the respiratory system. What environmental contaminants deserve particular attention because of their potential effects on other than the respiratory system?

8. The question quite frequently arises as to whether a particular concentration of a substance has to be reached before any effect is elicited (threshold level). In 1962 a WHO's expert committee made the following statement regarding this question:

"The concept of safe or acceptable exposure levels rested initially on the assumption of thresholds for early effects. However, with the accumulation of data and experience with various toxic substances, delayed effects attributable to exposure to toxic agents have appeared long after exposure at levels previously thought to have been safe, for instance in the case of beryllium. This necessitated downward revision of many of the recommended maxima."

Would you care to comment on this statement's application to our discussions on the development of air quality criteria?

9. What do you envision as the differences between your proposed National Council on Hazardous Physical and Chemical Agents and the present National Air Quality Advisory Committee?

10. What do you consider the role the National Tuberculosis Association has to make to the development of environmental quality criteria?

(The response by Dr. Sterner was not available for this printing and will appear in Volume III which will be published at a later date.)

Senator MUSKIE. Our next witness, Dr. James L. Whittenberger, James Stevens Simmons professor of public health, Harvard University, in Boston.

Dr. Whittenberger, we appreciate your attendance here this morning.

STATEMENT OF DR. JAMES L. WHITTENBERGER, JAMES STEVENS SIMMONS PROFESSOR OF PUBLIC HEALTH, HARVARD UNIVERSITY, BOSTON, MASS.

Dr. WHITTENBERGER. Mr. Chairman, members of the subcommittee, my name is James L. Whittenberger.

I am a physician and director of the Kresge Center for Environmental Health at the Harvard School of Public Health. In this capacity, I participate in the research of my colleagues with respect to the biological effects of air pollution and with respect to the sources, measurement, and control of air pollution.

In addition, I have been active over a number of years with a number of Federal agencies which are concerned with the quality of the environment and specifically with air pollution.

Mr. Chairman, with your permission, although my testimony is not very long, I would like to feel that I could paraphrase and modify some of it as I go along rather than read directly.

Senator MUSKIE. Handle it any way you would like, Doctor.

Would you like the statement as written to appear in the record notwithstanding the changes you are making?

Dr. WHITTENBERGER. Yes, please. With two typographical corrections.

Senator MUSKIE. All right.

Dr. WHITTENBERGER. I support strongly the efforts of this subcommittee to foster the development of air quality criteria and standards. There are serious deficiencies of information on the biological effects of air pollution and on many aspects of control; there are competing demands for the scientific manpower needed to remedy these gaps, but it would be shortsighted not to make every effort to improve the scientific base on which standards should be developed.

HEALTH

To a considerable extent, the health effects of air pollution are determined by how one defines health. If one adopts the World Health Organization definition, to include the complete social and physical well-being of a people, then almost every city has a health problem from air pollution, measured in terms of odors and dirt, property damage, interference with visibility, et cetera.

These are real arguments for air pollution control, but not as strong as the argument that community pollution causes excess illness and deaths. Air pollution unquestionably has caused excess illness and death, in well-established episodes and in others that went unrecognized. It is suspect as a contributory cause in chronic diseases of the lungs.

EMISSION CONTROL

I would like to interject my view here that I think air pollution control can and should be based on the various effects of air pollution which I mentioned at the beginning of this paragraph, namely, odors, filth, property damage, et cetera, and that we should not have to wait for firmer evidence with respect to serious health effects.

My main objection is to a number of statements that have been made about exaggerated health effects for the sake of supporting control and such individuals do not use the already existing bases for control.

HEALTH EFFECTS

For the purposes of this testimony, my definition of health effects will include only the causation or aggravation of disease or disability, and the shortening of life. The demonstration of health effects is extremely difficult in the presence of ordinary levels of air pollution.

Many of the usual sources of toxicologic information are of little or questionable value; laboratory animals, tissue cultures, et cetera, have generally shown no effects from ordinary levels of pollution. This is not true of flowers, trees, or other plants known to be very sensitive to specific air pollutants, such as ozone or SO_2. The behavioral tests developed mainly in Europe are very sensitive, but are also nonspecific.

We avoid not only the inadequacies of animal toxicologic research but the great problem of transferring such information to human beings if we support and develop appropriate epidemiological studies.

OCCUPATIONAL EXPERIENCE

One of the standard sources of information about human effects of specific atmospheric pollutants is the exposure of workers in industry and disease state which may be associated with these exposures. This is the best source of information we have on some compound, such as lead; but, in many instances, the information is of very limited value.

Selection favors the worker most tolerant of the chemical to which he is exposed, and in any event the information pertains to a healthy worker exposed only a quarter of the time, in contrast to the continuous nature of community exposure of the whole population.

It is regrettable that we don't obtain more information from industrial exposure. There are a number of reasons for this. The large industries which, unfortunately, employ only a small fraction of the total workers in this country generally have relatively good control of toxic agents in the environment. They are usually well prepared by the capabilities in the medical departments to carry out such studies but they are exposing a relatively select population to relatively low levels of pollutant compared to the kinds of exposure that occur more abundantly in the small industries in this country which don't have good control, which don't have good medical services, often don't have any medical services.

EPIDEMIOLOGICAL STUDIES

The shortcomings of the information from the laboratory and from industry make all the more important the seeking of information in community studies. These, in general, are of three types: the search for associations between disease incidence and different levels of community pollution; the assessment of impairment in persons with chronic illness, in relation to day-to-day changes of the environment; and changes in morbidity or mortality rates with changes of atmospheric conditions.

Studies of the first type are essentially studies of chronic diseases of complex and uncertain etiology, with an attempt to rebate the disease to a low-level, long-term environmental exposure.

A case in point is chronic nontuberculous lung disease, sometimes referred to as chronic bronchitis and ending up as the pathological condition of emphysema. This disease is a very common cause of death and disability in the United Kingdom and has been increasing in this country in the past 10 to 20 years. However, it is still far commoner in the United Kingdom, being variously estimated as five to 50 times the U.S.A. rate. This presumably is associated with considerably higher levels of pollution in general in the United Kingdom.

Attempts to relate this condition to community pollution are confounded by at least two important factors relating to pollution; itself. One is that most adult Americans habitually expose their lungs to much higher concentrations of smoke (from tobacco) than they ever encounter in the community atmospheres; the other factor is occupational exposure to dusts, fumes, and gases.

There is increasing evidence that these three basic types of environmental exposure may have summation effects on individuals who are exposed to more than one of the three.

It is easy to identify a quantitative relationship between cigarette-smoking habits and respiratory disease as measured by symptoms and impairment of pulmonary function tests. The cigarette-smoking effect almost overwhelms other suspected factors in North American studies done to date.

Studies in which air pollution changes have been significantly related to symptoms of persons chronically ill have been successful in Great Britain. Similar conclusions have been made from a study in Los Angeles in which patients with advanced respiratory disease were made worse by pollution episodes and they improved more rapidly in the hospital when filtered air was breathed.

The most direct evidence of health effects is the experience of several cities during periods of pollution buildup due to atmospheric stagnation. These are too well known to be listed here. In all of these episodes, the preponderant excess of deaths was in persons already suffering from serious degrees of cardiac or respiratory disease. In none of the episodes do we have an accurate picture of what was going on in the atmosphere; smoke and SO_2 are usually high and for this reason SO_2 is often the focus of concern.

LABORATORY STUDIES

Unfortunately, epidemiologic studies thus far have provided little basis for development of air quality criteria, for a large number of reasons, some of which can be corrected in future studies.

Another approach to studying human effects is to observe carefully the responses of people to controlled pollutant exposures. This potentially valuable approach has had only very limited application. Dose-response relationships have been constructed for carbon monoxide, sulfur dioxide, and a few other air pollutants.

These studies are most important in defining specific physiologic effects and mechanisms of action, but they have severe defects in applicability to development of air quality criteria: the subjects are usually highly selected to exclude disease states, hypersensitivity, et cetera; the numbers are very small, and no attempt is made to select a sample which is representative of a community population, that is, people with varying degrees of different kinds of illnesses, presence of asthma and emphysema and so on.

Another defect is that the exposures are generally extremely short, a matter of minutes. Only the simplest of pollutant mixtures are used. With sufficient effort and skill, most of these defects could be remedied.

RESEARCH NEEDS

To determine air quality criteria for human beings, it is clear that we need better information on what happens to people exposed to community pollutants. This means more emphasis on epidemiologic studies preferably combined with laboratory type evaluations.

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We need far better information on what people actually breathe and for how long in their homes, in public places, at work, and so on. This includes more indoor air measurements, monitoring of inspired air by a device that might have to be worn on the person, better quantification of cigarette smoking, occupational exposures, and so on.

Experimental designs will have to include more accurate reflections of the range of diseases and susceptibilities which exist in human populations. The hypersentive volunteer subject should be studied more intensively and not excluded from the study.

Controlled exposures of human volunteers should be greatly increased in number and in a variety of combinations of relevant variables.

All of this, of course, would be done with full respect for the health and safety, and the rights of privacy of the individual, according to the safeguards which have been elaborated through the leadership of the Public Health Service and which are now widely applied in this country and increasingly in other countries.

I realize that standard setting and pollution control cannot and should not wait until all the scientific information is in. I also believe that the kinds of studies I have described will have many other benefits apart from their relationship to air pollution—a better understanding of disease and of the environment, and therefore a better basis for prevention of diseases.

Thank you.

(The complete prepared statement by Dr. Whittenberger follows:)

COMPLETE STATEMENT OF DR. JAMES L. WHITTENBERGER

My name is James L. Whittenberger; I am a physician and director of the Kresge Center for Environmental Health at the Harvard School of Public Health. In this capacity, I participate in the research of my colleagues with respect to the biological effects of air pollution and with respect to the sources, measurement, and control of air pollution. I am happy to have this opportunity to present my views to this Subcommittee and would welcome any questions you may have.

I support strongly the efforts of this Subcommittee to foster the development of air quality criteria and standards. There are serious deficiencies of information on the biological effects of air pollution and on many aspects of control; there are competing demands for the scientific manpower needed to remedy these gaps, but it would be short-sighted not to make every effort to improve the scientific base on which standards should be developed. I wish to make some general remarks about the health effects of air pollution, then speak directly to the biological section of the outline provided by the Subcommittee. I shall concern myself almost exclusively with human health effects, which must be a major aspect though not an exclusive concern of air quality criteria.

To a considerable extent, the health effects of air pollution are determined by how one defines health. If one adopts the World Health Organization definition, to include the complete social and physical well-being of a people, then almost every city has a health problem from air pollution, measured in terms of odors and dirt, property damage, interference with visibility, etc. These are real arguments for air pollution control, but are not as strong as the argument that community pollution causes excess illness and deaths. Air pollution unquestionably has caused excess illness and deaths, in well-established episodes and in others that went unrecognized. It is suspect as a contributory cause in chronic diseases of the lungs.

For the purposes of this testimony, my definition of health effects will include only the causation or aggravation of disease or disability, and the shortening of life. The demonstration of health effects is extremely difficult in the presence of ordinary levels of air pollution. Many of the usual sources of toxicologic

information are of little or questionable value; laboratory animals, tissue cultures, etc. have generally shown no effects from ordinary levels of pollution. (This is not true of flowers, trees, or other plants known to be very sensitive to specific air pollutants, such as ozone or SO_2.) The behavioral tests developed mainly in Europe are very sensitive, but are also non-specific.

EPIDEMIOLOGIC STUDIES

One of the standard sources of information about human effects of specific atmospheric pollutants is the exposure of workers in industry and associated disease states. This is the best source of information we have on some compounds, such as lead; but, in many instances, the information is of very limited value. Selection favors the worker most tolerant of the chemical to which he is exposed, and in any event the information pertains to a healthy worker exposed only a quarter of the time, in contrast to the continuous nature of community exposure of the whole population.

The shortcomings of the information from the laboratory and from industry make all the more important the seeking of information in community studies. These, in general, are of three types: the search for associations between disease incidence and different levels of community pollution; the assessment of impairment in persons with chronic illness, in relation to day-to-day changes of the environment; and changes in morbidity or mortality rates with changes of atmospheric conditions.

Studies of the first type are essentially studies of chronic diseases of complex and uncertain etiology, with an attempt to relate the disease to a low level long-term environmental exposure. A case in point is chronic non-tuberculous lung disease, sometimes referred to as chronic bronchitis and ending up as the pathological condition of emphysema. This disease is a very common cause of death and disability in the United Kingdom and has been increasing in this country in the past 10 to 20 years. However, it is still far commoner in the United Kingdom, being variously estimated as 5 to 50 times the U.S.A. rate. It is largely a disease of men, aged 40 or older.

Attempts to relate this condition to community pollution are compounded by at least two important factors relating to pollution itself; one is that most adult Americans habitually expose their lungs to much higher concentrations of smoke (from tobacco) than they ever encounter in the community atmospheres; the other factor is occupational exposure to dusts, fumes, and gases. Prior to 1962, epidemiologic studies failed to give adequate attention to tobacco smoking history. It is easy to identify a quantitative relationship between cigarette-smoking habits and respiratory disease as measured by symptoms and impairment of pulmonary function tests. The cigarette-smoking effect almost overwhelms other suspected factors in North American studies.

Somewhat similar findings hold for lung cancer. Urban rates of lung cancer are generally higher than rural rates and, since cancer-producing chemicals have been identified in city atmospheres, particuularly in coal-burning areas, it is tempting to relate the lung cancer difference to air pollution. However, cancer is related to history of migration, to standards of medical care and diagnosis, and other known and unknown factors. Most research workers conclude that cigarette-smoking is by far the most important factor in increasing the incidence of lung cancer; that part of the "urban effect" is due to higher smoking rates in cities, and that after correcting for this, there remains a difference that may be attributable to air pollution.

Studies in which air pollution changes have been significantly related to symptoms of persons chronically ill have been successful in Great Britain. Similar conclusions have been made from a study in Los Angeles in which patients with advanced respiratory disease were made worse by pollution episodes and they improved more rapidly in the hospital when filtered air was breathed.

The most direct evidence of health effects is the experience of several cities during periods of pollution build-up due to atmospheric stagnation. These are too well known to be disted here. In all of these episodes, the preponderant excess of deaths was in persons already suffering from serious degrees of cardiac or respiratory disease. In none of the episodes do we have an accurate picture of what was going on in the atmosphere; smoke and SO_2 are usually high and for this reason SO_2 is often the focus of concern.

LABORATORY STUDIES OF HUMAN EFFECTS

Unfortunately, epidemiologic studies thus far have provided little basis for development of air quality criteria, for a large number of reasons, some of which can be corrected in future studies. Another approach to studying human effects is to observe carefully the responses of people to controlled pollutant exposures. This potentially valuable approach has had only very limited application. Dose-response relationships have been constructed for carbon monoxide, sulfur dioxide, and a few other air pollutants.

These studies are most important in defining specific physiologic effects, mechanics of action, etc., but they have severe defects in applicability to development of air quality criteria: the subjects are usually highly selected to exclude disease states, hypersensitivity, etc.; the numbers are very small and non-representative of a community population; the exposures are generally very short; and only the simplest of pollutant mixtures are used. With sufficient effort and skill, most of these defects could be remedied.

NEW STUDIES REQUIRED

To determine air quality criteria for human beings, it is clear we need better information on what happens to people exposed to community pollutants. This means more emphasis on epidemiologic studies, preferably combined with laboratory-type evaluations. We need far better information than we've had in the past on what people actually breathe and for how long—in their homes, in public places, at work, etc. This includes more indoor air measurements, monitoring of inspired air by a device that might have to be worn on the person, better quantification of cigarette smoking, occupational exposures, etc. Experimental designs will have to include more accurate reflections of the range of diseases and susceptibilities which exist in human populations. The hypersensitive volunteer subject should be studied more intensively, not excluded from the study. Controlled exposures of human volunteers should be greatly increased in number and in variety of combination of relevant variables.

These are some of the problems as I see them, and the approaches we must follow to provide a better scientific base for air quality criteria. I realize that standard setting and pollution control cannot and should not wait until all the scientific information is in. I also believe the studies suggested will have many other benefits apart from a relation to air pollution—a better understanding of disease and of the environment, and therefore a firmer basis for prevention of disease.

CRITERIA DEVELOPMENT

Senator MUSKIE. Thank you very much, Doctor.

Now, with respect to this statement, I realize standard setting and pollution control cannot and should not wait until the scientific information is in.

Under the present law, control depends upon the issuance of criteria.

Would it not violate your professional values to set criteria that were based on inadequate studies?

Dr. WHITTENBERGER. No.

As Dr. Sterner pointed out, the establishment of criteria has to be done and has been done on the basis of the best information currently available. This is standard procedure in the setting of standards for industry, for example. I think we have to apply the same principles here.

Senator MUSKIE. Let me ask you this. Obviously taking health in the broad sense to which you referred in the earlier part of your statement, it would be relatively simple, I take it, to set criteria related to soiling, to esthetic effects, property damage, and so on. But, assuming that the criteria also could take into account health effects, how do we take them into account if the available data and studies are inadequate? How do we go about setting threshold limits relating to health effects if the data is inadequate?

Scientific judgment

Dr. WHITTENBERGER. Well, in the same way that it is done for industry. There is a lot of scientific guesswork involved.

One takes all of the information available, animal exposures, observation of people exposed at work to known concentrations or relatively known concentrations, applies a factor of safety, and has a workable figure which is changed when new information becomes available.

For example, we have recently been involved in questioning the standard for asbestos fiber exposure by studying ship insulation workers in a plant in Maine. We have found that the concentration of atmospheric asbestos fibers previously thought safe is, in fact, not safe. A significant number of workers exposed for 10 to 20 years do have evidence of asbestosis defined by history, physical examination, and radiological examination of the chest.

This means that the standard, the threshold limit value ought to be reduced to probably not more than half what it has been.

Safety factors

Senator MUSKIE. With inadequate information, how far do you go in establishing safety factors?

Dr. WHITTENBERGER. A great deal depends how one defines the population at risk. As Dr. Sterner mentioned, the factor that he would apply is perhaps 100 to 1. He mentioned the figure of 30 for England. There are many kinds of occupational exposure in which we might say the factor should be 10 to 1. These are all matters of judgment relating to the population at risk and the conditions of exposure.

COUNCIL

Senator MUSKIE. Since this is a question of judgment, how do you react to the suggestion made by Dr. Sterner of a council established as he has suggested?

Dr. WHITTENBERGER. My reaction is favorable to the concept although I don't have very much direct knowledge of the model which he has used, the National Council on Radiation Protection. It is my secondhand impression that the Council for Radiation Protection has provided an extremely valuable service over the years, and it is for this reason that I share Dr. Sterner's feeling that a council relating to general chemical and physical hazards in environment would be definitely worth while.

CHRONIC EXPOSURE EVALUATION

Senator MUSKIE. Is there any way of shortcutting an evaluation of long-term, low-level exposures? What are the techniques that can be used to make such evaluation?

Dr. WHITTENBERGER. One method of shortcutting is one that I referred to a moment ago in the asbestos-exposed workers in the shipbuilding plant in Maine.

There was a fairly stable population there, a sufficient number of men who worked in that industry for 20 years or more, and a good history of their exposure. On this we were lucky because the same plant happened to have been observed during World War II by members of our own staff, so we could use the same instrumentation and therefore really know what the exposure was over a long period of time.

In a matter of several months in a study of these individuals, it was quite apparent that a low-level, long-term exposure had produced an undesirable change in health. In other words, you don't have to set up a population and observe it for 20 years in the future to get an answer.

Senator MUSKIE. Well, you didn't in that case because by chance you were able to find the population that had had that exposure in the past.

Suppose you don't have that fortunate situation? There is really no way; is there?

Dr. WHITTENBERGER. That was a fortunate example, but you can look for that kind of example in other situations, too. You try to get a good history over a long period of time of what people's exposure was.

I grant there were the usual changes of environmental exposure. This is extremely difficult. I think it ought to be looked for.

VALUE OF EPISODE EXPOSURES

Senator MUSKIE. Can we get any insights from the episode that would be helpful in setting criteria related to long-term exposure? Are these episodes simply to be considered rare and unusual exceptions, or can they be regarded as information warnings of effects of noncontrol?

Dr. WHITTENBERGER. We have an example of a study of workers exposed to another chemical which may be helpful in this regard. Toluene diisocyanate is a chemical in the plastics industry which is extremely toxic and a person exposed to one-tenth of a part per million will show changes in his pulmonary function, after a few hours of exposure. If he is studied after 6 months of exposure he is likely to have more loss of function than can be explained on the basis of aging.

It is only a hypothesis at this time but we think this may indicate that response to an acute exposure may indicate predisposition to a chronic effect.

EFFECTS ON VEGETATION

Senator MUSKIE. I think you indicated that the effects on plants are not particularly relevant to the human being. Is the study of effects on plants of no value, at least in setting preliminary thresholds?

Dr. WHITTENBERGER. The difference in kind of exposure is so different I would be very reluctant to try to extrapolate from effects on plants to effects on people.

Senator MUSKIE. Your reference to the canary in the coal mine does not apply here?

Dr. WHITTENBERGER. No; that is not a good analogy.

Senator MUSKIE. I assumed it was not.

Dr. WHITTENBERGER. The canary is a hypersensttive animal, with a very high metabolic rate, and a very high respiratory rate, which makes it almost ideal as a warning for human beings.

SCIENTIFIC JUDGMENT

Senator MUSKIE. What it amounts to, then, is that as we struggle with the problem of setting criteria for long-term, low-level exposure, we must resort either to the fortunate chance that we hope we can have more of them than less, that we have an opportunity to evaluate populations that have already been exposed long term to the pollution with which we are concerned or, two, we have to make the best guesses we can based upon inadequate information.

Dr. WHITTENBERGER. I think that is what we are doing.

Senator MUSKIE. Finding the best guessers that we can lay our hands on. That is about what it amounts to.

PUBLIC OPINION

Dr. WHITTENBERGER. I think so. I think we could obtain more information in communities about what people really think about air pollution. I mean, aesthetically——

Senator MUSKIE. In other words, if they were willing to control the pollution whether or not there were unfavorable health effects simply because they didn't like dirty air, then you have a basis for control that would have incidental health benefits.

Dr. WHITTENBERGER. I am not aware of any serious use of community surveys of how much people object to dirty air and all of the effects of dirty air.

Senator MUSKIE. Of course, you can get people to object to dirty air as long as they don't have to worry about the cost of removing it. Policies must, I suppose, take that into account. The act says we must take them into account.

I suspect there is a greater urgency in the public life to dirty air, which I share, which I think, as you do, but, nevertheless, in establishing policy we are forced to take into account, and I guess we should, the economic costs.

Yesterday one witness suggested that we ought to forget the criteria business and just roll back emissions as fast as economics and technology makes possible, but then when is it reasonably possible to take advantage of technology and economics?

There is also the question that from time to time we might want to roll back a machine without the economic and technological means that are feasible from those points of view.

LABORATORY STUDIES

I think you mentioned in your statement laboratory studies and physiologic effects. What indication do those studies provide about possible long-term effects resulting in impairment of health?

Dr. WHITTENBERGER. You are referring to the laboratory studies of human beings?

Senator MUSKIE. Yes.

Dr. WHITTENBERGER. Well, unfortunately, very few people have worked in this area and very little, if anything, has been done on the long-term effects with the exception of rather limited studies in human beings exposed to lead in Dr. Kehoe's laboratory.

It is a difficult kind of study to carry out, of course, and I am not aware of anyone really having done it in order to give any meaning to the point in question, again excepting occupational exposures.

EVIDENCE OF HEALTH EFFECTS

Senator MUSKIE. We got into this business with the Surgeon General in our hearings for the 1967 act and he was quite emphatic, of course. It was his insistence that there were undesirable health effects from air pollution, and he based his judgment on what he described as four types of evidence.

The first is the direct association that we have to air pollution and excess mortality, what might be termed air pollution episodes. We have already touched on that.

The second—and I would like you to comment on this—is the epidemiological evidence that shows direct correspondence between the incidence of disease in the levels of air pollution experienced by large population groups over substantial periods of time.

To what extent is such evidence available?

Dr. WHITTENBERGER. I am not aware of good studies on association between incidence of disease and community air pollution. There are a number of studies on prevalence of disease. One can't infer the differences in prevalence necessarily means difference in incidence which is much more important in terms of epidemiology.

Senator MUSKIE. Is that a fruitful area for research?

Dr. WHITTENBERGER. Yes, sir.

Senator MUSKIE. Thank you very much, Doctor.

Dr. WHITTENBERGER. Thank you.

(Questions submitted to Dr. Whittenberger by Senator Muskie are as follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. JAMES L. WHITTENBERGER,
James Stevens Simmons Professor of Public Health,
Harvard University,
Cambridge, Mass.

DEAR DR. WHITTENBERGER: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. JAMES L. WHITTENBERGER

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

3. What is the current usefulness and limitations of vital statistics on causes of death (disease mortality), in epidemiological studies and how could they be improved?

4. To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

5. A number of air pollution episodes that have been studied, however, the cause and effect mechanism is reportedly not known. What is the value of laboratory studies in providing answers on the mechanism involved?

6. It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low-level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

7. What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

8. There are atmospheric contaminants that have their primary effect on other than the respiratory system. What environmental contaminants deserve particular attention because of their potential effects on other than the respiratory system?

9. The question quite frequently arises as to whether a particular concentration of a substance has to be reached before any effect is elicited (threshold level). In 1962 a WHO's expert committee made the following statement regarding this question:

"The concept of safe or acceptable exposure levels rested initially on the assumption of thresholds for early effects. However, with the accumulation of data and experience with various toxic substances, delayed effects attributable to exposure to toxic agents have appeared long after exposure at levels previously thought to have been safe, for instance in the case of beryllium. This necessitated downward revision of many of the recommended maxima."

Would you care to comment on this statement's application to our discussions on the development of air quality criteria?

(The response by Dr. Whittenberger was not available for this printing and will appear in Volume III which will be published at a later date.)

Senator MUSKIE. Our next witness is Dr. David V. Bates, chairman, Department of Physiology, McGill University, Montreal, Canada.

Dr. Bates, it is a pleasure to welcome you. We appreciate very much your interest in testifying.

STATEMENT OF DR. DAVID V. BATES, CHAIRMAN, DEPARTMENT OF PHYSIOLOGY, McGILL UNIVERSITY, MONTREAL, CANADA

Dr. BATES. Mr. Chairman, I have not, in my document that you have before you, indicated my background interest in air pollution. Perhaps I should do that briefly.

I began research on lung disease in 1948 in London, England, and was looking after and doing laboratory work on patients with chronic lung disease at the time of the London smog episode in December 1952.

I came to Canada as an associate professor of medicine in 1956. In about 1960, I became interested in the problem of the effect of ozone on the human lung and began studies on normal subjects, trying to define the levels of ozone which would be hazardous.

This really continued work that I had been interested in for some years, my field of interest being lung function and disease. I am a fellow at the Royal Colleges of Physicians of London and of Canada, and I have worked particularly on methods developed in the last 20 years to measure more precisely the function of the lung.

This has been a key development in trying to establish the effects of substances such as sulfur dioxide, ozone, and other things on normal people.

OZONE

My interest is still in the field of ozone and is concerned with the laboratory environment in which ozone can be breathed in periods up to 8 hours without restriction of the airway—that is, without apparatus around the nose and mouth.

I felt that I would like to draw your attention, Mr. Chairman, to three problems concerned with oxidant air pollution.

Senator MUSKIE. May I interrupt to also point out what I think is the case?

You are a member of a DHEW ad hoc committee of expert scientists on air quality?

Dr. BATES. Yes.

Senator MUSKIE. And concerned with the air quality criteria in the 1967 act?

Dr. BATES. Yes. I should have mentioned that.

I should have also perhaps said I am a member of the American Society of Clinical Investigation and the American Physiological Society, but I didn't summarize these for you.

Also, I am chairman of an interdisciplinary committee at my own university, bringing together engineers, lawyers, epidemiologists, physicians, and everyone who is concerned with different aspects of this extremely complicated issue.

Los Angeles experience

I wanted to draw your attention first to the fact that the data we have from the Los Angeles area shows that the concentration of ozone reaches a peak usually between the hours of 11 in the morning and 1 o'clock in the afternoon. This is because the ozone is being formed by rearrangement of products of automobile exhaust as a consequence of its being exposed to sunlight and relatively poor air movement.

The data that I have suggests that concentrations of 0.58 parts per million of ozone have been recorded in some areas of the Los Angeles Basin over a period of an hour, and occasionally a peak concentration of up to one part per million has been measured.

Laboratory experience

What I wanted to do was to comment on work which I did and published in 1964 in which normal subjects including myself have breathed ozone without any other gas for a period of 2 hours in a laboratory environment. I have, in my document before you, published one figure from that paper which indicated that in 16 experiments on 11 normal people one indicator of the function of the lung changed as a result of this period of ozone exposure.

This indicator is the diffusing capacity of the lung, which is the best way we have of measuring the ability of the lung to transfer oxygen. When this index falls, as it did as a result of the ozone exposure, it might be due to the fact that ozone is causing some thickening of the lining membrane of the lung, or the gas may be causing a redistribution in some way of blood flow through the lung, or ventilation to it; but the fall of the index clearly indicates that one or other or both of these phenomena are occurring.

Variations in response

There was considerable individual variation in response, one of the normal subjects showing a big change, six showing a statistically highly significant reduction, and the remainder showing some reduction, but not of the same degree.

I mention this because previous speakers, indeed everyone in this field, have emphasized to you that there is always individual variation in response of this kind. The same is true of sulfur dioxide and it is also true of this gas.

Since this work in 1964, there have been two other studies of ozone in the human lung. I think the total literature is only four or five papers, and these have shown that slightly higher concentrations of ozone, about one part per million breathed for a shorter period, a half hour to an hour dose, causes a measureable increase in the resistance of the airway. This is the diameter of the bronchial tree in the lung. One part per million breathed for an hour has been shown by Dr. Goldsmith, whom you mentioned a moment ago, and Dr. Nadel to have an effect on airway resistance in normal people.

The lethal concentration of this gas is somewhere between three and nine parts per million and for understandable reasons there has been a disinclination to expose normal subjects to concentrations much above one or two parts per million.

Exposure time effects

Senator MUSKIE. Would lengthening of the time of exposure have the same effect as increasing the concentration?

Dr. BATES. It is to be presumed that there is some kind of time concentration relationship, but there is not yet enough data to run the time/base concentration curve as precisely as you can in animal studies, for example. There just is not enough data in human studies, but presumably you might breathe two parts per million for 10 minutes without effect and four parts per million for 4 minutes and on down the line but this has not been precisely determined.

Occupational standards

I mention later (in par. 9) that 0.2 parts per million seems to be without ill effect in normal people over a working day period. In fact, it is historically interesting particularly as a result of questions you have been putting this morning, Mr. Chairman, to note that the American Hygiene Organization established a concentartion of ozone for a working day, I think, 20 or 30 years ago, of 0.1 part per million, and they did that, as a matter of fact, without there being any control laboratory data of human exposure.

This was the first thing I noticed which set me off on the task of trying to define this more accurately but, in fact, the American Hygiene Association had laid down a criterion well in advance of any laboratory data.

I think that was a conservative guess because men in certain trades, particularly argon shielded welding, are probably quite commonly working in a concentration of 0.2 parts per million and, by and large, there have not seemed to be major health effects. So, somewhere about that level can probably be tolerated.

Animal studies

The point about animal experimentation, which is always a difficult one to handle, is made particularly difficult with ozone because ozone is a gas that is rapidly destroyed by a surface. Indeed, if you breathe ozone in during an experiment you never breathe any out. It is completely denatured in one breath in and one breath out.

If you pass ozone through a tube with a little bit of wire gauze in it, it is rapidly denatured. This means that there may be wide variation of ozone which gets down to the lung of different animals.

It has been suggested by a number of people that perhaps the relative resistance of the dog to ozone may be due to the fact that he has a long nose and the ozone is denatured in passage through his nose; which, of course, might not apply to the human.

I mention this because it is a unique property of ozone that it is so rapidly changed. It makes it very hard, of course, to experiment with it, and exceedingly difficult to extrapolate with confidence from the mouse to the guinea pig to the dog to the human.

This is one factor in trying to relate animal exposures to human exposures which is, I think, more difficult, for example, in the case of ozone than in the case of radiation.

Chronic effects

There is some evidence which Dr. Stokinger has produced which I think has been summarized for you, that ozone has some long-term effects in low concentration in animals, particularly mice, and one can only note these really in passing.

It has been suggested, and there is data to suggest, that long-term exposure to ozone increases the sensitivity of these small animals to respiratory infection and it has been suggested that this environment causes accelerated aging. There is this kind of evidence and it is obviously very difficult to devise an experiment which would indicate whether ozone exposures of the kind experienced by the population in Los Angeles is responsible for any such comparable phenomenon.

Critical levels

In the light of the evidence, I have said in paragraph 8 that no one should regard a peak concentration of ozone of 0.58 parts per million in a city environment for 1 hour with equanimity. It may be that overt morbidity has not occurred as a consequence of these concentrations because, for some reason, the laboratory data are not applicable to the environment situation; or because individuals develop a tolerance to ozone similar to that which it is said can be developed by animals; or because detection methods have not been sufficiently sensitive to note such morbidity, even though it may have occurred. Any or all of these observations may be correct explanations of the apparent discrepancy between laboratory data and reported morbidity.

I would like to look at these in a little more detail.

Limitations of laboratory studies

First, the laboratory data not being applicable to the open environment. The laboratory data so far has been collected, as Professor Whittenberger said, on highly selected individuals, mostly physicians in fact doing the work and they are not representative of the population at large. Furthermore, the breathing apparatus used in these experiments may influence the results.

It might be that the nose is a very important protection and if you breathe the gas through a mouthpiece, perhaps you are denying yourself protection normally available.

Also, of course, laboratory data may not be applicable because the normal human population is much more fragile than the average laboratory situation so that you have a factor working the other way.

Tolerances

The second point about tolerance is a very intriguing one because it has been shown, I think, to everybody's satisfaction that animals can develop tolerance to otherwise lethal concentrations of ozone. We know nothing about the mechanism whereby this occurs, and there are no studies indicating whether the human can do the same thing. This is one of the parts of the program I am currently engaged in, to see if you breathe ozone at concentration at the safe point of 0.2 parts per million for 2 hours a day from Monday to Thursday, whether you are then more resistant to a higher concentration on Friday than if you had been out of ozone. This is under study. We know nothing about this.

Morbidity

And, thirdly, have the detection methods really been sufficiently sensitive to note morbidity? Although I am not an epidemiologist, the kind of morbidity one might expect might be transient breathlessness of some, even a transient hospital administration, or in others the subject of getting breathless and moving out of the street into an air-conditioned environment. I am not sure that the detection methods have really yet been sufficiently sensitive to make us quite confident that these concentrations of oxidant in Los Angeles are not in fact producing morbidity.

The data I have seen suggests that there is no gross excess mortality in certain episodes, but whether morbidity and long-term effects were being produced, I feel we just don't yet know.

Suggested criterion

I have tried in paragraph 9, therefore, to see how far this data would help you if you had to set some kind of criterion. I have said that perhaps 0.2 parts per million is without ill effect to normal people; 0.6 parts per million should not be permitted for periods of longer than a few minutes. One part per million, however, would represent a direct hazard to normal subjects under most conditions.

In paragraph 10, I wished, as a physician who has done a lot of work with patients with heart and lung disease to point out that I am unwilling to provide you with the evidence as to whether 0.6 parts per million is more dangerous for a person with these diseases than it is for me, that you cannot at least await that kind of data because you are not entitled to ask that patients with moderately advanced lung disease or heart disease are exposed to this kind of concentration of this kind of gas and in the laboratory environment.

I have put in that paragraph because I have noted in some of the testimony that it is assumed that it is proper to go out and get that kind of data, and I think we have to resign ourselves to working with data for normal subjects rather than exposing people with disease to this kind of concentration of this kind of gas.

(The summary of Dr. Bates' statement is as follows:)

McGILL UNIVERSITY
MONTREAL

SUMMARY OF STATEMENT BEFORE SUBCOMMITTEE OF U. S. SENATE ON AIR AND WATER POLLUTION

by

Professor D. V. Bates, Chairman, Department of Physiology, McGill University, Montreal

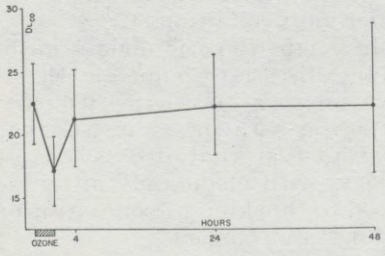
General Nature of Topic: Oxidant Air Pollution

1. Oxidant air pollution has several unique features. The oxidants are not directly produced by any pollution source, but in large part result from a rearrangement of the products of automobile exhaust as a consequence of strong sunlight and relatively still air.

2. The oxidant concentration measured as ozone is maximal in the Los Angeles area between the hours of 11 a.m. and 1 p.m. Peak concentrations of 0.58 parts per million of ozone have been recorded for an hour in this region, and transient peaks of up to 1.0 parts per million have apparently been measured. The ozone is formed particularly from oxides of nitrogen, and there is a delay of two hours approximately between the maximal oxide of nitrogen concentration and the maximal ozone concentration.

3. Assuming that any decision of maximum tolerable levels of ozone must be based on measurements of its animal and human toxicity, I wish to summarize this laboratory evidence as a guide to the Committee in attempting to reach such a decision.

4. Human experiments breathing ozone have clearly shown that this is a remarkably poisonous gas. My own experiments on normal subjects showed that 0.6 parts per million of ozone breathed for a two-hour period had an easily measurable effect on the diffusing capacity of the lung. This is illustrated in the attached figure, taken from a paper published in 1964 in the Journal of Applied Physiology (Vol. 19, pp 765-768). The mean values of the diffusing capacity of the lung are shown before and after two hours of breathing 0.6 parts per million of ozone. Sixteen experiments were conducted on eleven normal subjects. The diffusing capacity of the lung (D_{LCO}) is a sensitive indicator of the efficiency of the lung in transferring oxygen. Impairment of it, as demonstrated in these experiments, may be due either to a change in the ultra-thin lining membrane of the lung through which oxygen must pass, or may be caused by a maldistribution of ventilation and blood flow in the lung. Presumably ozone in these concentrations causes one or other or both of these phenomena.



5. There was considerable individual variation in response, one of the normal subjects showing a big change, six showing a statistically highly significant reduction, and the remainder showing some reduction, but not of the same degree.

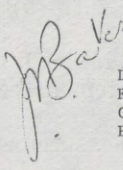
6. Experiments subsequent to this by other investigators have shown that in addition to the change of diffusing capacity of the normal human lung produced by concentrations between 0.6 to 0.8 parts per million for two hours, slightly higher concentrations breathed for a shorter period produce changes in airway resistance and presumably are evoking an acute reaction in the bronchial tree. These changes are measurable and significant at concentrations of one part per million breathed for an hour. It seems likely that concentrations of three parts per million or above might produce pulmonary edema, and there has been a natural disinclination to expose normal subjects to such dosages under laboratory conditions.

7. Animal experiments have shown a considerable species variation in sensitivity to ozone and it is not clear why this variation should exist. One possible explanation is the length of the airway leading to the lung which may be responsible for the relative insensitivity of the dog to this gas. Ozone is rapidly reduced to oxygen by any surface, and hence a long tubular arrangement leading down into the lung would result in a lower concentration reaching the depths of the lung than would be the case if the airway was short. Other animal experiments have indicated that exposure to ozone may increase the sensitivity of small animals to respiratory infection, and it has been suggested that an ozone environment causes accelerated aging.

8. In the light of this evidence, no-one should regard a peak concentration of ozone of 0.58 parts per million in a city environment for one hour with equanimity. It may be that overt morbidity has not occurred as a consequence of these concentrations because, for some reason, the laboratory data are not applicable to the open environment situation; or because individuals develop a tolerance to ozone similar to that which it is said can be developed by animals; or because detection methods have not been sufficiently sensitive to note such morbidity even though it may have occurred. Any or all of these observations may be correct explanations of the apparent discrepancy between laboratory data and reported morbidity.

9. In assessing the extensive literature on ozone, together with the relatively few papers on human ozone exposure, it would seem proper to summarize this by saying that 0.2 parts per million seems to be without ill effect in normal people over a working day period; 0.6 parts per million should not be permitted for periods of longer than a few minutes; 1 part per million or over would represent a direct hazard to normal subjects under most conditions.

10. It is to be presumed that particularly sensitive individuals or those with some types of lung and heart disease may be more affected by ozone than are normal subjects. Such information cannot be obtained in the laboratory since patients suffering from these conditions should not be experimentally exposed to gases as toxic as is ozone.



D. V. Bates, M.D. (Cantab.),
FRCP (C), FRCP (London),
Chairman, Department of Physiology,
Professor of Experimental Medicine.

13 June 1968

Senator MUSKIE. Thank you very much, Doctor.

I think this is very valuable testimony, gives us some indication of the kind of problem that is involved in evaluating health effects.

Now, first of all, we are dealing with a gas that is released in Los Angeles between the hours of 11 a.m. and 1 p.m. in concentrations which we ought to avoid.

Dr. BATES. That is right; yes.

Senator MUSKIE. You have said that 0.6 part per million should not be permitted for periods longer than a few minutes for normal people and the concentrations in Los Angeles reached peaks of 0.58 part per million, which is virtually 0.6—or at least a lawyer and Senator can think of them about the same—for periods of an hour.

SOURCE OF OZONE

Now, ozone is a product of what in the Los Angeles area?

Dr. BATES. It is a product of the materials produced by automobile exhaust which, in a way I think not yet quite understood, are rearranged in the atmosphere so that ozone is produced; probably these reactions involve oxides of nitrogen. I think that has been established, and this rearrangement takes some time to produce, so that in Los Angeles the traffic rush hour occurs between 7 and 9, approximately; the oxides of nitrogen reach a peak concentration somewhere about 10 o'clock, about an hour later, and decline. As they decline, the ozone is formed from these in the atmosphere and reaches a peak between 11 a.m. and 1 p.m. Then in the evening rush hour, because the sunlight is much diminished, the whole process does not occur. So, the evening rush hour produces the oxides of nitrogen but does not produce the ozone between 6 and 7 p.m., because the sun has disappeared.

Senator MUSKIE. Sunlight is essential?

Dr. BATES. An essential part of this process.

Senator MUSKIE. Now, do these elements assemble in every major city of comparable size and comparable automobile population?

Dr. BATES. I have not seen data for many cities on ozone. I have from Denver. I have seen some data from St. Louis, Mo., also, where high concentrations have been noted. The difficulty has been a technical one in part that there is interference with this measurement of ozone by SO_2.

In a city like New York, which has SO_2 as well as ozone, it is quite difficult to make the ozone measurement because the other is present as well.

I have not seen detailed ozone measurements for the Eastern States. It may exist but I have not seen it.

Senator MUSKIE. In any case, in any city of large population, if there is a combination of sufficient sunshine and the automobile, we are going to get ozone and the possible ill effects that you have described?

Dr. BATES. Yes.

Senator MUSKIE. In other words, this is not just simply a Los Angeles phenomenon and we don't have to worry about it elsewhere?

Dr. BATES. No.

VARIATIONS IN RESPONSE

Senator MUSKIE. If the records indicated normal people, what basis of present knowledge do you think ought to be applied? How do we get limits accepted? What do we do, buildt in a fail-safe factor of some kind? What should it be?

Dr. BATES. I think first I underline the point again made by Professor Whittenberger which is that very few normal people have been studied. The scope of these studies is small.

Obviously, if we did not only have data on 11 people, which I have been mentioning here, but on 250, we would be much better off to define these limits; the main difficulty is that the samples have been so small.

The more people you do statistically the more sensitive an individual you uncover. So, somewhere along the line there is a cutoff point. I would say that if you had no response in perhaps 100 people over a 2-hour period you could take it that there was unlikely to be a response. You might have to do another thousand people to find a individual who was sensitive.

AVAILABLE EVIDENCE

Senator MUSKIE. You are on the advisory committee that has responsibilities for air quality criteria. Do we have enough information now to set criteria for ozone?

Dr. BATES. In a preliminary way, yes, provided we have a mechanism for revision and review, which Dr. Sterner has stressed must exist.

In other words, new information, new experiments, will be continuously coming forward and it is essential that the revision can be continuous, as he mentioned. I think you have the basis for establishing a criterion. You have a better basis than the American Hygiene Society had way back when it established an arbitrary criterion in the absence of any human data.

CRITERIA DEVELOPMENT

Senator MUSKIE. Since you are on the advisory committee, I had hoped that we might be able to get into discussion of the work of that committee and the process by which it is approaching this responsibility of setting criteria.

I understand there will be a vote on the floor in about 5 minutes, and we have one more witness we ought to get to. So, I guess we will have to defer that until another time.

I wonder if you could sum up in just a minute or two of comment upon the work of the committee in relation to its responsibility in setting criteria?

Dr. BATES. I think the first stage was to be sure that all the relevant literature had been properly surveyed, not merely listed; that the relevant papers had been critically read—that is, read critically with

regard to methodology, possible sources of error, errors of interpretation, and these, of course, are often present, and then to try and place the animal data, the human data together and come up with some sort of minimal standard such as I have indicated here.

The present stage of the work, the first draft manuscript, does exist on the toxicological appraisal of oxidants which deals not only with ozone but the irritant oxidants, particularly peracetyl nitrates—PAN—which are also produced in the Los Angeles area.

I think the next step will be to make sure that the committee can form a unanimous view as to the summary of what this mass of data says. I have expressed a personal view to you here in stating that 0.2 part per million is probably broadly tolerable, 0.6 not tolerable for more than a minute or two. That is my reading of the existing data. That is the kind of comment which I would expect the committee will be able to make.

Whether the numbers will be exactly as I have said, I don't know, of course, but it should be possible to make that kind of statement at this point of time on the existing evidence.

Mr. Chairman, one member of our committee remarked we are not concerned with making Los Angeles safe for mice. There is, of course, overwhelming animal data but there is so little human data, and this is the problem. I think that with concentration on what is known on the human effects and provided the mechanisms for review and revision, then I think a preliminary statement should be able to be made on the concentrations that are safe and not safe.

The long-term effects, if for instance ozone 0.1 part per million causes, over 20 years, premature aging, nobody has that kind of data and I don't think we should wait 20 years to get it.

Senator MUSKIE. So that you are proceeding to establish your preliminary judgments on the basis of the knowledge that is already available in the literature?

Dr. BATES. That is right, sir; yes.

Senator MUSKIE. So you are making judgments as to the adequacy of that data for preliminary criteria?

Dr. BATES. That is right; yes.

Senator MUSKIE. And wherever your judgment is positive in that connection you set criteria even though ideally additional research and studies might be desirable?

Dr. BATES. I think there is enough data to do that in a preliminary way provided that it does not have the stamp of infallibility.

I think the willingness to make a preliminary statement on the clear understanding that as new data comes in and so on revision is possible, this is the right way to approach this extremely complex task. Nobody yet has studied the interaction of ozone with other pollutants. I cannot tell you whether ozone is more dangerous in the presence of particles. I don't know. I can only tell you what exists and if somebody does some work with small particles on ozone and the toxicity is much potentiated, then that will be the time when this will have to be revived accordingly.

I think the key here is a preliminary statement on the best evidence. This is what Dr. Sterner's committee must produce with a mechanism for continuous review.

Senator MUSKIE. Are your responsibilities on the committee limited to the ozone and the other substances with which you have worked?

Dr. BATES. They have been so far; yes, sir.

Senator MUSKIE. Will you be asked to form judgments with respect to other substances, as well?

Dr. BATES. I have not been.

Senator MUSKIE. I think I should make it clear for the record that the act, in section 107(b), on the point of revision says this:

> The Secretary shall from time to time revise and reissue material issued pursuant to Subsection (b) and (c) and proceed with procedures established in such subsection.

Dr. BATES. Yes.

Senator MUSKIE. Thank you very much, Doctor, for your very helpful testimony.

(Questions submitted by Senator Muskie and response by Dr. Bates follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. DAVID V. BATES,
Chairman, Department of Physiology,
McGill University,
Montreal, Canada.

DEAR DR. BATES: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. DAVID V. BATES

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

3. What is the current usefulness and limitations of vital statistics on causes of death (disease mortality), in epidemiological studies and how could they be improved?

4. To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

5. To what extent are the reported effects of air pollution affected by the study methods employed?

6. A number of air pollution episodes that have been studied, however, the cause and effect mechanism is reportedly not known. What is the value of laboratory studies in providing answers on the mechanism involved?

7. In this regard, what are the advantages and limitations of clinical studies?

8. It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low-level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

9. What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

10. Dr. Lawther has suggested that the preliminary stages of bronchitis are presumably in response to inhaled irritants, and during this phase the effects are certainly reversible. However, later infection supervenes which is frequently followed by destruction of lung substance which leads to emphysema. Would you comment on present research capabilities to detect these changes and their implications with regard to public health policy?

11. As a member of a DHEW ad hoc committee of expert scientists on air quality, would you care to comment on how the committee operates?

McGill University,
Department of Physiology,
Montreal, August 21, 1968.

Senator Edmund Muskie,
Chairman, Subcommittee on Air and Water Pollution,
U.S. Senate, Washington, D.C.

Dear Senator Muskie: I was much appreciative of the privilege of testifying before your Committee a fortnight ago and I will endeavour to answer the additional questions you have put to me. I have, however, only just returned from holiday, and in order to get my comments to you by August the 23rd as you requested in your letter, I have to warn you that I have had little time to prepare these answers and their detailed documentation would take longer than is available to me.

I have answered the questions in the order in which you sent them to me, and I sincerely hope that these additional comments may be valuable to you.

Yours sincerely,

David V. Bates, M.D.,
Chairman, Department of Physiology.

Question 1

The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

I think it is important here to differentiate levels of contaminants in regard to their known effects. It seems to me that for almost all atmospheric contaminants acting singly one can now state levels which, if existing for an eight hour period, would not cause major morbidity or excess mortality in the average city population. It would be important to stress that combinations of contaminants may be more dangerous than single substances, but precise knowledge on this matter is not yet available. It should further be possible in the case of special industrial poisons to state a permissible effluent concentration of such materials as fluorides for example, which would not in the long term give rise to dangerous exposure levels for the surrounding population. Thus I feel that for all the common atmospheric contaminants levels for an eight hour period can be established which are unlikely to lead to any major episode.

In the case of long term effects, such levels of atmospheric contaminants as would be tolerable in a city environment to avoid long term effects are inevitably at this stage a matter of intelligent guess work. However, such guesses can be made with reasonable accuracy and provided the data were to be presented in the form that these levels of contaminants existing as an average monthly concentration would be unlikely to cause long term effects, then I think the data now exists which would permit these levels to be stated. New information might lead to revision of these quantities every year, but I think it is too cautious an attitude to suggest that a start cannot be made now with such a tabulation.

QUESTION 2

The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What type of epidemiological studies would be useful to confirm or refine air quality criteria?

The epidemiological studies that are needed particularly include detailed knowledge of hospital admissions for respiratory disease, and a much more comprehensive system of comparing morbidity statistics than is presently available. In my view the day-to-day tabulation and collection of morbidity and mortality data would be best done on a centralized basis and would require the collaboration of many hospitals in any given area. With new methods of information tabulation and collection, I hold the view that given a sufficient potential such an organization could be readily achieved, and would be very valuable as it would indicate changes in trends of disease morbidity which might in the long term be correlated with changes in levels of atmospheric contaminants. Short term studies of specific populations seem to me much less useful for this kind of work, and I think the study already mentioned to your Committee of the respiratory disease morbidity in children in different parts of Britain, which established that this morbidity for lower respiratory tract infections were related to the ambient level of air pollution, provides a guide for the kind of studies which could be planned.

QUESTION 3

What is the current usefulness and limitations of vital statistics on causes of death (disease mortality), in epidemiological studies and how could they be improved?

I have heard experts in the field of vital statistics emphasizing the limitations of present methods of death certification, and it seems clear that these are of limited value as they are at present collected. There is for example no organized way of comparing the occurrence of pulmonary emphysema (which is an easily recognized pathological change) in the autopsy populations of different American cities, and a study research committee should be established to report on the feasibility of such comparisons on a nation wide basis. Tabulation of hospital admission and diagnosis data in city centers to give an indication of morbidity would undoubtedly be very valuable and probably more meaningful than mortality statistics based on present methods of death certification.

QUESTION 4

To what extent can industrial hygiene and occupational health provide answers to the effects of long term exposures under environmental conditions?

As other speakers to the Committee have emphasized, some useful information can be gained by statistics of industrial hygiene and occupational health exposures which are relevant to effects of long term air pollution. However, these cannot be the sole guide to air quality criteria since the exposed populations are very different in the two cases, and the substances to which exposure occurs are often not the same in occupational health hazards and air pollution. With specific substances such benzpyrene and lead, there is no doubt that occupational exposure data may be very valuable in giving an indication of long term effects of such substances.

QUESTION 5

To what extent are the reported effects of air pollution affected by the study methods employed?

This is a very difficult question to answer since in some instances the studies of the effects of air pollution have been too crude to give valuable data. I think it is important to stress to the Committee that the scientific approach to the problem of the effect of air pollution on health is only slowly being understood, and there will be considerable variation in the experimental design adopted in different countries with an eventual agreement on the kind of experimental protocol likely to give a definitive positive or negative answer to a specific question. The experimentation in general has however only slowly been developing. Inevitably, at this stage, some poor experiments are being conducted and some excellent ones have also been completed, and in this way the history of experimental

design and study is no different in relation to the problem of air pollution than in any other biological context. Our experience with it however is limited essentially to the past 20 years, which is a short span of time!

QUESTION 6

A number of air pollution episodes that have been studied, however, the cause and effect mechanism is reportedly not known. What is the value of laboratory studies in providing answers on the mechanism involved?

Laboratory studies, particularly those involving human subjects, are very valuable in giving answers on the mechanism of action of pollutants in the short term. Here again the experimental techniques have been steadily improved over the past 20 years, and the opportunity now exists to define quite precisely on which part of the respiratory tract any pollutant has a particular effect. However, the concentrations are likely to be high in such studies, and the longer term experiments are hardly practicable in a laboratory environment. One of the handicaps here has been the fact that there are in the country a few respiratory research laboratories capable of conducting the sort of study which is clearly needed, and the number of scientists and physicians trained in this discipline is small.

QUESTION 7

In this regard, what are the advantages and limitations of clinical studies?

Clinical studies, by which I mean studies on patients with a respiratory disease, have some advantages since they give an insight into the difference between normal people and people who already have some kind of respiratory disease in their response to pollutants. Such studies are obviously limited by proper humanitarian considerations, and for this reason high concentrations of pollutants can rarely be used to give an acute response. Clinical studies however involving patients with chronic bronchitis, asthma, and even pulmonary emphysema under the right laboratory conditions can be managed but obviously extreme caution has to be exercised. Clinical studies involving populations who have lived in certain centers exposed to known pollutants and who are either not cigarette smokers or whose smoking history is accurately known (I am thinking of workers in specific industries or factories here) provide opportunities for studying pulmonary function or the incidence of respiratory disease under good conditions. These clinical studies would be very valuable but take a lot of organization to achieve. One of the problems in our present scientific environment is that the scientific community as a whole gives very little credit indeed for this kind of scientific work. I might point out that Prof. Haldane in England who pioneered studies of the effect of carbon monoxide on human performance and who also made fundamental contributions to our understanding of hemoglobin and oxygen carriage, was never given the Nobel Prize for his work since it did not seem part of the normal scientific credo to recognize the achievements of a man who spent as much time in coal mines or in submarines, as he did at his laboratory bench. This is still largely true, and the major prizes in science are, I think, nowhere awarded to anyone working in an environmental field. This has the unhappy consequence that young men of ability are not attracted to such work, even though the questions which require answering are every bit as pressing for the community as a whole as are those which do attract the acclaim of the scientific community. I do not wish to seem to be pursuing some personal grudge here, as I think it is quite understandable how this state of affairs has come about. The relative lack of first class clinical studies of the kind we need and the relative scarcity of clinical investigators trained to perform them well is largely to be explained by the contemporary emphasis of the scientific community on what is "science" and what is not.

QUESTION 8

It has been mentioned that elderly individuals are especially susceptible to air pollution during high levels of air pollution (e.g. "episodes"). What factors do you feel render individuals especially susceptible to long-term low-level air pollution exposures? Are there other factors than age which may contribute to susceptibility?

The factors that render individuals especially susceptible to long term low level air pollution are probably the following:

(*a*) Chronic bronchitis most often caused and aggravated by cigarette smoking.

(*b*) Pulmonary congestion which may be caused either by left ventricular failure or by mitral stenosis.

(*c*) Any pre-existing respiratory disease such as pneumoconiosis, tuberculosis, bronchiectasis, or sarcoidosis.

(*d*) Thoracic deformity limiting ventilatory capacity in any way.

(*e*) Occupations which expose the individual to ambient levels of air pollution more than other individuals by virtue of the task. Thus a labourer out of doors doing heavy physical work in a polluted environment would almost certainly be more likely to be affected by such concentrations of pollutants as exist than someone who spent most of his time sitting indoors.

There are factors other than age which may contribute to susceptibility and perhaps the most likely is a reactive bronchial tree such as is found in patients with a history of allergy or even with established asthma. Such individuals may have a high morbidity as a result of exposure to air pollutants though I do not know that excessive mortality is particularly likely. However, deaths from status asthmaticus (the most severe form of asthma) do have seasonal variations being more common in Britain for example in the winter months.

QUESTION 9

What do you consider the value of studies of the health effects of air pollution on children in the development of air quality criteria?

I have already mentioned the particular study on the health effects of air pollution on children which another speaker has outlined to your committee. I consider these studies very valuable, and there is no doubt that they should be actively pursued in different centers with different types of air pollution existing. However, they are tedious and difficult to do, and one cannot expect quick results from them if they are to be properly conducted. There can be no doubt of the value of studying children in connection with air pollution and this I consider has already been established.

QUESTION 10

Dr. Lawther has suggested that the preliminary stages of bronchitis are presumably in response to inhaled irritants, and during this phase the effects are certainly reversible. However, later infection supervenes which is frequently followed by destruction of lung substance which leads to emphysema. Would you comment on present research capabilities to detect these changes and their implications with regard to public health policy?

I agree with Dr. Lawther's viewpoint, and I have attempted to set out contemporary thinking of a natural history of chronic bronchitis and emphysema on page 8 of the enclosed reprint from The New England Journal of Medicine. I would like to refer you to this since it tries to put in perspective the relative role of air pollution and cigarette smoking in these diseases. I consider that present research capabilities are quite sensitive enough to detect very early changes, and that all the data that has been accumulated in respect of pulmonary function effects in the earlier stages of bronchitis and the epidemiology of respiratory disease in cigarette smokers and city populations is very relevant to public health policy.

QUESTION 11

As a member of a DHEW ad hoc committee of expert scientists on air quality, would you care to comment on how the committee operates?

I would like to make one or two comments on the operation of the ad hoc committee on air quality on which I am serving. So far the Committee has had one full meeting held nine months ago in California, and a good deal of subsequent correspondence centering around the preparation of a manuscript which would form the basis for decisions on air quality criteria. The rate of progress has inevitably been leisurely since it is extremely difficult for a committee to prepare a document under such conditions. If there is urgency

and if there is willingness to finance the operation, much more rapid progress would be achieved if arrangements were made to bring together about fifteen people for an intensive period of a month and sit them down undisturbed by other considerations with adequate secretarial help and ask them to prepare a complete document in that time. In my view, this would be the way to proceed if there was some urgency in getting the document completed by a given time. With physicians and scientists widely scattered, it is not possible to hammer out important differences of emphasis and of opinion by mail, and it is not efficient to have a document circulated which is edited and return by individual people. I would suggest that if the work of the Committee has any measure of urgency, and if the matter is deemed sufficiently important to command the financial support which it would need, then the committee charged with the responsibility of producing a document for example on oxidant air pollution should meet in one place for a period of four weeks consecutively, and work at the document until a finished version was prepared. This would be undoubtedly the most efficient way of producing the best document in the circumstances. I feel that the problems of producing a final report have been somewhat underestimated by the administrators responsible for its execution. It is a much more difficult thing to produce than a scientific paper with limited data and bibliography, it must command the full support of all members of the Committee if everyone is to feel involved in it and happy about it, and this process involves much informal discussion before a consensus can be reached. This discussion cannot occur by mail without there being many frustrations. I would like to suggest that the advisory committees concerned with different pollutants be convened each for a period of four weeks at some center with adequate literature references available and that a period of intensive work over a month would produce a first class document. Only in this way I think can reliable criteria be established as a start. This committee should then reconvene with additional members every year for a week to consider new data that has come forward. Given some such potential as this, I think that air quality criteria could be established, but I do not see that there is as yet willingness to put this kind of potential behind this particular endeavour.

DAVID V. BATES, M.D.,
Chairman, Deparment of Physiology.

(Subsequent to the hearings the following paper was submitted by Dr. Bates and was ordered to be included at this point:)

CHRONIC BRONCHITIS AND EMPHYSEMA

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IN a keynote address to the National Tuberculosis Association in 1964[1] the Health Commissioner for the New York City Metropolitan Area emphasized the concern he felt over the rising incidence of emphysema and chronic bronchitis as major public-health problems. He stated that the emphysema death rate in New York City had increased 10 times over the past 12 years, and that of chronic bronchitis four times. The increasing use of questionnaires and simple tests of pulmonary function in different parts of the world has led to a realization that chronic respiratory symptoms are surprisingly common in many parts of the world, and papers have appeared stressing their importance not only in industrial populations[2] but, more surprisingly, in farmers in southern Egypt[3] and some rural populations in Finland[4] and Norway.[5]

It might seem to be logical in a review of recent work on these two diseases to start by quoting some contemporary definitions of them[6,7] and to proceed logically from this step to their known pathology and clinical manifestations. Such an approach, however, serves to obscure the real difficulties that exist in correlating respiratory symptoms in a living population, whose lungs are not available for autopsy, with clinical phenomena manifested by patients whose lungs are available for pathological study. Attempts to understand the factors that usually combine to determine the natural history of the condition in any given patient have led to somewhat contradictory conclusions. Accordingly, I propose to begin with a discussion of the reliability of contemporary methods of study, to review recent information on the effects of cigarette smoking more or less independently of any associated chronic respiratory symptoms and then, after describing different aspects of chronic bronchitis and pulmonary emphysema, conclude by discussing the differentiation between these two conditions. In general, I have assumed that the reader is more or less familiar with the outlines of these diseases up to the date I last had occasion to review them, and I have therefore only included material published since 1964. Since such problems as air pollution, epidemiology of chronic respiratory disease and pulmonary-function measurement, to mention only three out of many, could well have formed the only topic in such a review, I have inevitably had to be highly selective in the literature cited and in the more general topics that I have discussed.

RELIABILITY OF QUESTIONNAIRE DATA, TESTS OF FUNCTION AND AUTOPSY DIAGNOSIS

Sharp and his colleagues[2] administered the same questionnaire in 1960 and again a year later to 1887 men of an American male urban industrial population. The percentages of respondents who answered affirmatively to questions concerning persistent cough, expectoration, wheezing and chest illness were essentially the same on the two occasions. Although, as these authors emphasize, different social or national groups may interpret such questions differently, it seems that the questionnaire is a sufficiently reliable tool for one to say, without much danger of contradiction, that respiratory symptoms are commoner in British populations than in corresponding populations in the United States, and that in general symptoms amongst country dwellers are less than in those who live in towns.

If conclusions are to be drawn from a single assessment of pulmonary function in a population group, it is of critical importance to have some indication of the reliability and constancy of different kinds of pulmonary function tests.[7a] On the basis of studies of FEV_1 (one-second forced expiration) and vital capacity in 81 hospital patients, Freedman and Prowse[8] concluded that three forced expirations and two relaxed expirations were adequate for these two determinations and that little would be gained by increasing this number. In patients with chronic bronchitis the standard deviations on repetition of such ventilatory tests, and even of subdivisions of lung volume and carbon monoxide uptake, are relatively small in relation to the abnormalities that may be detected even in mild disease.[9] The standard deviation of measurements of FEV_1 is smaller in nonsmokers than in smokers,[10] and the same limitation applies to the maximal mid-expiratory flow rate (MMFR). The latter measurement appears to discriminate slightly better than the FEV_1 as between smokers and nonsmokers, the FEV difference between these two groups being 0.38 liter as opposed to an MMFR difference of 0.5 liter per second.[10]

The measurement of airway resistance using a body plethysmograph in both normal subjects and patients with bronchitis shows satisfactory repeatability,[11] and this method is sensitive enough to indicate differences produced by cigarette smoking and depth of cigarette-smoke inhalation. If this technic is used, the specific conductance, which is the conductance corrected for total gas volume, shows better discrimination between smokers and nonsmokers than the airway conductance (which is the reciprocal of airway resistance). Macklem and Mead[12] have recently pointed out that the FEV_1 and similar measurements are relatively insensitive indicators of considerable changes in airway resistance in the smaller peripheral airways. As a result of experiments on the dog lung, they conclude, "In the extreme situation . . . , where one half of the peripheral airways closed in a randomly distributed manner throughout the lung, the peripheral resistance would be doubled, but this would only cause a

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10% increase in total lung resistance if the peripheral airway resistance were only 10% of total airway resistance." This important contribution calls attention to the fact that FEV_1 data cannot be interpreted as if it were equally affected by changes in airway resistance of comparable magnitude in any part of the airway.

Thurlbeck and Angus[13] found that the Reid index* has a bell-shaped distribution curve. Morphologically, there must therefore be a gradual and imperceptible change from "normal function" to "chronic bronchitis." Definition of chronic bronchitis by certain combinations of positive replies to questionnaire symptoms, or to some arbitrary division between a normal and abnormal FEV_1, is therefore on much less certain ground than it would be if the Reid index had a bimodal distribution corresponding to two such populations. The Reid index can be replicated with a high degree of correlation, and a comparison of the index taken from any one of six sites in the bronchial tree with the mean value for all six bronchial samples showed that only one or two such samples need be taken for a valid figure to be obtained.[14] The quantitation of pulmonary emphysema also presents major problems, and several methods have been proposed to achieve it.[15-17] It is quite clear that failure to study the lung inflated at autopsy leads to major underdiagnosis of the presence of emphysema,[18] but no generally applicable method of quantitation has yet been devised. It may be fair to comment however that as a result of the intensity of recent pathological studies of the lung in emphysema, there are now larger areas of agreement between different pathologists on the basic differentiation of types of emphysema than was the case five years ago.[19,20]

Effects of Smoking

It has been known for some years that cigarette smoke acutely inhaled causes an increase in airway resistance.[21] In a study of 82 adults ranging in age from 16 to 82, Pelzer and Thomson[11] excluded all those who had a persistent morning cough or who had had an acute episode of bronchitis in the last five years. Using a body plethysmograph technic, they were able to show significant differences in conductance between smokers and nonsmokers. Specific conductance, which they calculated from the conductance and the total thoracic gas volume, was also different in the two groups. This was of interest since half of the smokers in their series smoked fewer than 10 cigarettes a day. The mean coefficient of variation of both of these measurements approximated 10 per cent. Acute changes in the ratio between airway conductance and total gas volume have been measured by Sterling at rest and again two or three minutes after 15 inhalations over five minutes from a filter-tipped cigarette.[22] The studies were then repeated 25 minutes after a subcutaneous injection of 1.2 mg of atropine sulfate. It was shown that the bronchoconstriction consequent upon inhaling cigarette smoke in smokers and nonsmokers was blocked by atropine, indicating that the vagus nerve is almost certainly involved in the reflex bronchoconstriction as originally suggested by Widdicombe. The FEV_1 appears to be less sensitive in discriminating between smokers and nonsmokers than the maximal midexpiratory flow rate,[10] and patients with chronic bronchitis show a greater increase in airway resistance than normal subjects after smoking a cigarette.[23]

Using a single breath of oxygen and subsequent comparison of the computed "inert gas distribution lung volume" and the total lung capacity measured in a body plethysmograph, Ross and his colleagues[24] found differences between smokers and nonsmokers, indicating some impairment of gas distribution related to long term cigarette smoking. In view of the fact that inhaled cigarette smoke almost certainly penetrates deeply into the lung, it is of interest that Rankin and his co-workers[25] found differences in single-breath diffusing capacity between smokers and nonsmokers in every decade of age from 20 to 60, though interestingly enough the difference between the smokers and nonsmokers was as great at 30 as at 55 years of age. The authors postulated that smoking might have an effect on diffusing capacity independently of its effect in producing chronic bronchitis. The possibility that uneven distribution of alveolar volume in relation to diffusing capacity might produce the changes observed suggests that it is premature to correlate these findings with morphologic changes ascribed to cigarette smoking.

Two studies have emphasized the relation between cigarette smoking and the frequency of respiratory-tract infections in young people. Haynes et al.[26] studied 199 adolescents, all male, 14 to 19 years of age, of whom 48 per cent were smokers and 52 per cent nonsmokers. All types of respiratory illness were more frequent among the regular smokers, and the incidence of severe lower-respiratory-tract infections occurred six and a half times more often among regular smokers than among nonsmokers and occasional smokers. A similar study by Parnell and his associates,[27] comparing respiratory infections in 47 nursing students who were regular smokers and a group of 47 nurses who had never smoked, showed that all respiratory symptoms were greater in the smokers, and the total number of days off duty per student per year was also greater for smokers. Computing the absentee time attributable to smoking in the 47 smokers, the authors concluded that smoking was responsible for 122 extra illnesses totaling 108 days in duration during the year of the study. These two papers stress the fact that "morbidity" as a result of cigarette smoking begins very early in life.

Chronic Bronchitis

Although there are still some small differences in the definition of chronic bronchitis preferred in the

*The Reid index is the width of the mucous glands in major bronchi as a fraction of the width between the inner surface of the cartilage and the lumen of the bronchus.

United Kingdom[6] from that in the United States,[7] it has become clearer that in all societies the presence of a chronic productive cough unassociated with other kinds of bronchial disease is the essential clinical criterion of chronic bronchitis. The sputum may be mucoid or infected and may vary greatly in amount, and regardless of these characteristics, the tests of ventilatory function may show a greater or lesser degree of airway obstruction. Nevertheless in all these situations the presence of "chronic bronchitis" can usually be inferred from history alone. Reports on the prevalence of chronic respiratory symptoms have come from many different populations in a dozen different countries, and a reiteration of this evidence would serve little useful purpose. However, although the disease is prevalent in most countries, recent work has clarified whether there are major differences in the frequency of chronic bronchitis and chronic respiratory symptoms between the population in the United Kingdom and the American population. An original comparison of the prevalence of bronchitis in the two countries could have been criticized because only the population of one small American town was compared to a United Kingdom sample drawn from many areas.[28] Nevertheless, the authors' conclusion that simple bronchitis differs little in prevalence between the two continents, but that complex bronchitis with repeated chest illnesses and breathlessness is more common among older men in the United Kingdom, has been confirmed by other studies. Fletcher et al.[29] have compared patients attending a bronchitis clinic in London and a similar population attending a clinic in Chicago. They found recurrent disabling chest infections to be more frequent in the London group. Comparing survey data that they obtained in an American male urban industrial population with other data in the literature, Sharp and his colleagues[2] concluded that infected bronchitis with exacerbations of chest illness was commoner both in urban England and in Jersey City than in the population that they studied from Chicago, Illinois. In a more recent description of the London-Chicago comparison, Jones, Burrows and Fletcher[30] bring forward important evidence that the number of chest infections was only slightly higher in the London group, a similar proportion of the episodes in the two cities being associated with a report of yellow sputum and an increase in breathlessness and malaise, but fever was more common in the London patients; the London patients were confined to bed more frequently during these episodes and for longer periods than their Chicago counterparts. Thus, the frequency of exacerbations of bronchitic symptoms was actually not as different in the two clinics as the answers to the questionnaires had suggested. The authors leave the reader to draw his own conclusions from this information, but bring forward no additional information that throws light on these differences.

In a most important contribution to an understanding of the epidemiology and etiologic factors involved in chronic bronchitis, Holland and Reid[31] compared the frequency of chronic respiratory symptoms and pulmonary-function tests in male van drivers in central London on the one hand, and those driving vans in areas in and around three county towns in southern England – Gloucester, Peterborough and Norwich. The authors observed significant differences between these two populations after allowing for differences in personal smoking habits, and they found not only more symptoms and greater phlegm production in the London group but also more impairment of ventilatory-function tests. They concluded, "of the factors reviewed in this study, differences in local levels of air pollution appear to be the likeliest cause of the difference in respiratory morbidity between men working in central London and those in the three rural areas." Thus, whereas chronic bronchitis may be thought of as generally very widespread and in its total frequency as closely related to personal smoking habits, other factors, particularly climatic and environmental, undoubtedly play a part in determining the seriousness of the condition in the community as a whole.

Two other recent contributions to the epidemiology of chronic bronchitis deserve special mention, for they are each in a different way of particular interest. The first, from Japan,[32] compared Japanese living in a region of lower air pollution to the population in the highly polluted Tokyo–Yokohama district. Pulmonary-function tests were performed on a total of 2765 subjects, who were also interviewed. The authors were able to show that respiratory symptoms were more frequent and airway obstructive changes more severe in the population living in the Yokohama area, although they stress the point that no symptoms were found among the Japanese that corresponded to the characteristic picture of the "Yokohama-asthma" syndrome as described in the literature. A specific understanding of this syndrome in relation to chronic bronchitis, chronic bronchiolitis and infected asthma, has not yet appeared, and it is not possible to be sure whether this syndrome was compounded of a more severe form of the kind of chronic bronchitis commonly encountered in industrial regions, or whether it had specific features not encountered elsewhere. The second contribution of particular interest was the study by Douglas and Waller,[33] who followed 5000 children from birth to the age of 16 years, examining the frequency of infections of the upper and lower respiratory tracts. The authors could not show any correlation between upper-respiratory-tract infections and the degree of air pollution in the areas in which these children had lived, but a remarkable correlation appeared between infections of the lower respiratory tract in infancy and the severity of the air pollution in the environment. Confirmatory data linking air pollution to respiratory disease in children have been published from Sheffield.[34] It would, of course, be premature to equate such data with clear evidence that the air pollution itself had been responsible for the different prevalence, and for the moment it may be safer to talk about an

'urban factor" in chronic bronchitis than to label it as proved to be due to air pollution.

New Orleans asthma seems to be mainly due to acquired bronchial reactivity to grain dust blown periodically across the city from a storage elevator on the Mississippi.[35] It does not seem to have been important in relation to chronic respiratory disease, though the long-term effects of such material to which patients have become sensitized are not clearly defined.

The interrelation between chronic bronchitis and a definable allergic process continues to be a matter of dispute. There is no doubt that the bronchial tree is hyper-reactive in chronic bronchitis as well as in patients who have a strong history of allergy or who have previously had asthmatic attacks. Several series of studies of chronic bronchitis show a high frequency of a family history of allergy in the patients being evaluated.[36] Kreukniet and Young[37] studied 41 patients with typical allergic bronchial asthma, 25 with chronic bronchitis and 27 considered to have established pulmonary emphysema. These three groups were found not to differ in the frequency of criteria of allergy, and the authors concluded from this that the three diseases must be closely related. They also found evidence of cor pulmonale only in patients with established pulmonary emphysema, and electrocardiographic evidence of right ventricular hypertrophy was also preponderantly seen in this group. On the other hand, Charpin et al.,[38] in a study of 167 adult patients, found that if those known to be asthmatic were excluded, the allergic phenomena had a minor role in chronic bronchitis. The exact interrelation between these conditions therefore is still uncertain, but it seems clear that if the immune reaction in pulmonary disease is rigorously defined, as suggested in an excellent review of this problem by Rose and Phills,[39] there are not strong grounds for considering an immune response a primary mechanism in chronic bronchitis.

In chronic bronchitis the mucus secreted appears to be normal in its biochemical structure.[40] The essential components appear to be glycoproteins that include a transferrin of bronchial origin and $beta_2$ globulin, serum albumin and different seromucoids and plasma glycoproteins, mucoids of bronchial origin and mucopolysaccharide acids. In a detailed study of these constituents, Gernez-Rieux and his associates[41] examined sputum in 13 cases of chronic bronchitis with infection and 14 without, eight cases of allergic asthma, four cases of bronchial carcinoma and two cases of alveolar carcinoma. Only the expectoration in alveolar carcinoma was found to present biochemical characteristics sufficiently distinguishable from the sputum in the other conditions for one to be able to state that it was clearly different. Masson and his colleagues[42] found that albumin and gamma-A-immunoglobulin were the main plasma proteins identified in all samples of sputum from 10 patients with noninfected chronic bronchitis. Gamma-G-immunoglobulin was present only in negligible amounts. The albumin turnover and loss of protein into the sputum of patients with chronic bronchitis has been quantitated by workers in Italy,[43] who were able to demonstrate that in bronchitic patients the total albumin pool and even the circulating albumin were not infrequently reduced. Furthermore, the turnover of albumin was much higher in the bronchitic patients than in the controls, owing to persistent loss of albumin through the bronchial tree. The consequences of this protein drain in chronic respiratory disease may not have been accorded the importance that they deserve. The electrolyte concentrations found in bronchial secretions of patients with chronic bronchitis seem to be generally normal,[44] with possibly an increase of sodium. It has been suggested[45] that the ratio of sodium and potassium in the sputum may change in relation to infection, though these differences are small. Studies on the physical properties of sputum are notoriously difficult to control, but the same author[45] has reported that viscosity of infected sputum in bronchitis is generally lower than that of more mucoid forms.

There continues to be much uncertainty of the exact importance of infection, both viral and bacterial, in chronic bronchitis. In contrast to the previous studies, and in contradiction of general teaching, Storey et al.[46] have documented the frequent recovery of *Diplococcus pneumoniae* and *Haemophilus influenzae* from the sputum of 13 patients with chronic obstructive airway disease followed for 40 consecutive days. The presence of these organisms in the sputum could not be closely correlated with acute exacerbations of infection. This observation raises the question whether the worsening of the patient with chronic bronchitis is in fact closely related to the invasion of his bronchial tree by these or any other organisms: possibly, the mechanism of worsening of function is not related to fresh bacterial invasion at all. Such a conclusion receives some support from the work of Ross and his colleagues,[47] who studied a wide range of micro-organisms in chronic bronchitis during the period 1961 to 1965. Virus studies were limited to a small group of 15 such patients intensively observed over a period of two and a half years. Paired serum specimens collected during 125 acute exacerbations were examined for antibody responses to influenza A, B and C, adenovirus group, influenza Type 1, respiratory syncytial virus, psittacosis group, Q fever, *D. pneumoniae*, and *H. influenzae*. Serum samples were also collected for measurement of titers against *H. influenzae*. The authors came to the following conclusions:

> These studies suggest that a wide range of viral agents can produce acute exacerbations of chronic bronchitis. No serological evidence was found for the association of H. influenzae with either the initiation of chronic bronchitis or acute exacerbations. It seems possible that the damaged bronchial mucosa of bronchitics encourages proliferation of H. influenzae, resulting in high antibody titres to this organism.

A new twist to the dangers of tobacco smoking was given by the studies of LeClair,[48] who was able to recover the tobacco mosiac virus from 15 of 35

sputum specimens and one of four thoracentesis fluids in heavy cigarette smokers. An attempt to evaluate the comparative importance of cigarette smoking and infection in bronchial mucus-gland hypertrophy by bronchoscopy and bronchial biopsy technics and bacteriologic studies of bronchial lavage material was reported from Egypt.[49] The frequency of mucus-gland hypertrophy was found to be similar in patients with and without overt infection, as judged by the growth of pathogens from bronchial lavage fluid, and more closely related to cigarette-smoking habits than to any other single factor. The same problem was discussed by Mitchell and his colleagues,[50] who, in a study of 175 autopsy cases, concluded that mucus-gland hypertrophy was absent in 30 of 64 cases of clinical chronic bronchitis. Ashcroft[51] found considerable variation from day to day in the amount of sputum produced by patients with chronic bronchitis, suggesting that measurement of a 24-hour sputum volume would be necessary if any reasonable evaluation of its average volume was to be obtained. Variations in sputum volume were noted by the Medical Research Council Committee endeavoring to classify chronic bronchitis[6]; it seems doubtful, however, whether the division of simple bronchitis into five groups on the basis of sputum volume, as they suggest, is really possible, for this is probably too inconstant a figure. The difference between estimated sputum volume and the amount that can actually be collected from patients with chronic bronchitis in a 24-hour period seems mainly to depend on a few patients who grossly overestimate their own sputum volume. In a group of 35 patients, for example, this exaggeration in 14 of the men with chronic bronchitis led to a difference between the volume collected and the mean estimate of 24-hour volume of 1.1 fluid ounces; the actual volume collected averaged 1.8 fluid ounces, and the estimate from interview on the day before collection gave an average estimate of 2.9 fluid ounces.[52]

Pulmonary Emphysema

The morphologic appearances of emphysema have now been well defined, and provided the pathologist is aware of the importance of inflating the lungs before they are fixed, it is unlikely that there will be much confusion about the diagnosis. Silverton[53] has reviewed methods of fixing the lung in inflation, and Thurlbeck[18] has documented the underdiagnosis of emphysema that will result if the lung is examined only in the collapsed state. The frequency of morphologic emphysema in random inflated lungs is high, approaching 50 per cent in men 60 years of age.[20] Although some differences of interpretation can be detected in matters of detail in different authors, the major contributors to this field now seem to agree on more points than they did a few years ago. Some pathologists, like Lynne Reid,[19] prefer to define emphysema in relation to an increase in size of air spaces, whereas others prefer to emphasize destruction, and the review of emphysema pathology by Gough[54] employs both these alternatives. Standardized technics have not been in use sufficiently long in pathology to provide enough comparative data of the frequency of emphysema to compare its prevalence in different societies or in different countries. Such a study is long overdue, since if emphysema is to be defined in morphologic terms, the definitive evidence of its relative prevalence in different communities must necessarily be morphologic.

Horsfield and his colleagues[55] have made casts of the lungs in patients with emphysema and illustrated very well the three-dimensional destruction that occurs in different kinds of emphysema. This work has been used as a basis for reconsideration of gaseous diffusion in the airways of the human lung by the same group of workers.[56] It seems very likely that the diffusion process at the periphery of the lung may be much slowed by the anatomic changes of even mild centrilobular emphysema. This work has placed on a sounder footing earlier but speculative ideas[57] that the critical situation of the lesion in centrilobular emphysema might have something to do with the disturbance of gas exchange commonly seen in that condition.

What might be described as the first advance toward the understanding of the etiology of emphysema for many years has occurred as a result of the observation of Eriksson[58] that some families with an unusually high frequency of panlobular emphysema unassociated with chronic bronchitis are suffering from a deficiency of α_1-antitrypsin in the serum. Several additional cases have now been described,[59,60] and a considerable amount of theoretical work has been done to ascertain why the absence of this enzyme should lead to destruction within the lung.[61,62] It seems likely that only a very small fraction of the total number of people suffering from emphysema fall into this category; nevertheless, this fact should not distract attention from the extremely important clue that Eriksson's observation has furnished concerning one of the biochemical factors that must be present if the normal lung is to be preserved from damage by external agents or possibly even from premature aging. It seems very probable that emphysema after granulomas is occasionally caused by some similar interference with normal biochemical mechanisms.[63]

Since, on occasion, severe airway disease not associated with pulmonary emphysema of either the centrilobular or the panlobular type may cause airway obstruction and even chronic hypercapnia, it is of some interest to review recent work in an attempt to see whether the extent of morphologic destruction is related to particular radiologic changes. Nicklaus and his colleagues have restudied the accuracy of simple roentgenologic diagnosis (not bronchograms) of chronic pulmonary emphysema[64] and have shown, by checking against autopsy macrosections, that the general standard of diagnostic accuracy with the use of radiography was high. This confirmed the observation of Reid and Millard[65] that in the more advanced stages of emphysema, the radiographic appearances were almost always char-

acteristic and indeed diagnostic. A study by Sutinen et al.[66] revealed the surprising finding that of 33 patients with emphysema at autopsy, 19 were apparently without significant respiratory symptomatology. The standard of radiologic diagnosis of these cases was reasonably high, and the authors concluded that the diagnostic precision was greater than had been supposed on the basis of previous work. It is evident that the radiologic diagnosis is facilitated when there are significant regions of the lung to which the vascular supply is reduced, but considerable changes in blood distribution in the lung in emphysema on a gross regional basis are not invariably present.[67,68] It may be deduced, therefore, that the greatest difficulty in the radiologic diagnosis of emphysema probably arises when there is centrilobular emphysema of mild to moderate extent distributed fairly uniformly through the lung, and less difficulty is experienced in diagnosis of cases of panlobular emphysema much more severe in some regions than in others.

Nakhjavan, Palmer and McGregor[69] have documented the occurrence of significant obstruction to the inferior vena cava in some patients with advanced emphysema, leading to hepatomegaly and leg edema without hypercapnia and pulmonary hypertension.

"Chronic Obstructive Nonspecific Lung Disease" or Chronic Bronchitis and Emphysema

It was pointed out earlier that chronic bronchitis can be defined and even classified on a basis of symptomology.[6] It is agreed by everyone that pulmonary emphysema has to be defined in morphologic terms. The changes so elegantly illustrated by Reid[19] can be readily seen by anyone. Furthermore, the common clinical presentation of one or the other or both of these conditions is similar in the United States of America and in Britain, an observation well summed up by the title of the paper by Fletcher et al.: "American Emphysema and British Bronchitis."[29] These observations, however, conceal differences of opinion about the comparative roles of chronic bronchitis and emphysema in the production of respiratory symptoms and in relation to prognosis. This complex argument is the source of considerable confusion in the minds of those who have heard different experts speak on these two diseases; and many authors are frankly ambiguous in their use of the words. For example, a recent paper entitled "Effect of Venesection on Arterial Gas Values and Ventilatory Function in Patients with Chronic Bronchitis,"[70] states in the Methods section, "emphysema was tentatively diagnosed in all subjects on the basis of the clinical, radiological, and pulmonary function studies."

To sketch the basis of this problem in an attempt to arrive at some sort of conclusion for the general reader, it may be useful to start with a statement of some issues on which there is unanimity. It is agreed that chronic bronchitis in both clinical and morphologic terms is commonly associated with pulmonary emphysema. It is agreed that airway obstruction, which may have its genesis partly in the bronchitic process and partly because of the destructive changes of emphysema, is the prime incapacitating feature of both these diseases. It is agreed that derangement of ventilation-perfusion distribution may occur in patients who have little or no morphologic emphysema, and that the gas tension derangement to which this maldistribution gives rise is most usually the precursor of right ventricular failure, which is the most serious complication of both conditions. It is generally agreed that lumping all these patients into a general classification such as "chronic obstructive lung disease" may be useful from some points of view but does not serve to illuminate the relation between the two entities.

In 1965 Briscoe and Nash[71,72] suggested that the cases might be divided according to 10 clinical criteria into Type A or Type B. These criteria were primarily clinical, the Type A criteria being related to emphysema and the Type B to chronic bronchitis as the original lesion. The total lung capacity and residual volume were larger in Type A than Type B; there was little to choose between the ventilatory capability of the two groups, and chronic hypercapnia was present in all the patients in Type B but absent in four of the seven patients in Type A. Subsequent atuopsy studies on four of the patients tended to confirm the validity of the differentiation. In 1966 Burrows and his colleagues[73] correlated the emphysematous and bronchial types of chronic airway obstruction with autopsy findings. Using criteria similar to those of Briscoe and Nash, with the supplementary observation that the diffusing capacity was usually low in Type A and normal in Type B, they added an intermediate type of patient with irreversible airway obstruction who did not fulfill their criteria for either Type A or Type B. They concluded that their criteria corresponded with the degree of emphysema as judged at autopsy and that the Type B patients more commonly showed congestive heart failure and chronic hypercapnia than the Type A group. Jones[74] found a greater fall of arterial oxygen tension on exercise in the Type A than in the Type B patients. Studying the diffusing capacity of patients in the two groups, Bedell and Ostiguy[75] confirmed the greater reduction of CO exchange in Type A than in Type B. In the same year Mitchell and his colleagues[50] reported on correlation between morphologic features and clinical features in 175 autopsied cases. They stressed the difficulty of making such a comparison, and the correspondence between morphologic chronic bronchitic changes and clinical chronic bronchitis was not particularly good. However, they concluded, "The only characteristic and nearly unique clinical manifestation of patients with mucus gland hyperplasia (always in association with at least mild destructive emphysema) was the combination of hypoxia, pulmonary hypertension, right heart failure,

and secondary polycythemia which was observed in 46%." These considerations have led Filley[76] to conclude that "Hypoxemia in life is much more often associated with mucus gland hyperplasia than with destruction of the lung by emphysema." Fletcher,[77] in a recent symposium on chronic bronchitis comparing the characteristics of emphysema and chronic bronchitis, goes so far as to state that right ventricular hypertrophy is "absent" with emphysema and "present" with bronchitis, and that the arterial P_{CO_2} is normal in emphysema but raised in bronchitis.

Thurlbeck and his colleagues[78] correlated pulmonary function during life with morphologic appearance in 33 patients. The total lung capacity was relatively insensitive as an indicator of the extent and severity of morphologic emphysema, which could be more sensitively measured by the departure of the residual volume from predicted numbers. CO transfer showed a satisfactory correlation with the extent of anatomic emphysema. These authors also noted that a lesser morphologic grade of emphysema may be present with greater evidence of right ventricular hypertrophy. Jenkins et al.[79] demonstrated a good correlation between the single-breath diffusing capacity and the extent of morphologic emphysema, but were unable to confirm Fletcher's conclusion that the total lung capacity might be discriminatory and closely related to morphologic emphysema.

The attempt to correlate arterial-blood gases with morphologic changes is made much more difficult by the very real possibility that hypoventilation may coexist with chronic bronchitis, and by virtue of the resulting chronic hypercapnia and hypoxemia may play a much more important part in determining cor pulmonale than the morphologic chronic bronchitis itself. McNicol and Pride[80] have carefully documented this situation in four patients, all of whom had chronic bronchitis, but in all of whom the clinical presentation with disordered blood gases was attributable in major part to unexplained hypoventilation. The only patient we have encountered in whom we were able to show at autopsy that the only lesion was chronic bronchitis, but in whom the clinical picture was dominated by hypoventilation,[57] was moderately obese, whereas McNicol's patients were not notably obese. McNicol and Pride report detailed case histories and results of lung-function tests "to show how this condition may be distinguished from chronic bronchitis and emphysema with which it can easily be confused." This important contribution is not the only reason for some hesitancy in accepting the straightforward hypothesis equating chronic bronchitis with all the responsibility for ventilatory defect and ventilation-perfusion imbalance however. In the papers cited above, there are several unusual observations. Thus, in Burrows's report[73] only two of the 11 patients with Type A disease according to the new criteria are noted to have had congested heart failure. Yet in the follow-up data from the same study presented by Jones et al.,[30] one finds that in the Chicago and London study as a whole, edema subsequently developed in 18 patients in whom it had been absent before the first interview, and 12 of these were in Type A, three in Type B, and three in Type X. Logically, this suggests that patients with pure emphysema (in whom disturbance of blood gases and cor pulmonale is believed by these authors to be usually absent) subsequently acquire chronic bronchitis with the development of cor pulmonale. No comment is made on this surprising finding, nor whether its observation would lead to reconsideration of the original grouping of the patients. A further difficulty in the analysis of the cases studied by Burrows et al.[73] is that in four of the original 11 cases in Type B "severe bronchiectasis was found." If these cases are removed from the series, and since the complication of hypoventilation as documented by McNicol and Pride[80] is not specifically excluded, the evidence linking "chronic bronchitis" with a definitive pattern of function derangement may be much less secure than it appears. Oswald,[81] in a follow-up study of patients with both chronic bronchitis and emphysema, found that the death rate over a five-year period was twice as high in those with radiologic evidence of emphysema as in those with normal x-ray films. The expectation of life was also substantially lower the more breathless the patient. This suggests that it is not solely chronic bronchitis that is important in determining the prognosis.

Finally, the method of grading the extent of pathological emphysema in the cases reported by Burrows et al. was that described by Heard and Izukawa,[82] and these two pathologists were responsible for the assessment of these particular cases. Yet their report on the frequency of "pulmonary emphysema in 50 consecutive male necropsies in London" contains the sentence, "Each of the four patients dying from chronic bronchitis and cor pulmonale had over 10 units of emphysema" (out of a possible maximum of 18 units). This observation hardly accords with a point of view that equates chronic bronchitis alone with cor pulmonale.

It therefore seems premature to emphasize either chronic bronchitis or emphysema as individually responsible for greater or lesser degrees of ventilation/perfusion ($\dot{V}/\dot{Q}$) abnormality or dyspnea. It is probably true that patients at either end of the spectrum can be distinguished from each other with a fair degree of certainty — the nonbronchitic, purely panlobular emphysema of the familial type should be distinguishable from the man with a severe bronchitic history, a normal total lung capacity, a normal pulmonary vasculature on x-ray examination and a normal CO diffusing capacity. When the two conditions coexist, however (as is by far the most common event), it is erroneous to attempt to apportion the effects of the two lesions as if one were existing without the other.

Natural History of Chronic Bronchitis and Emphysema

The considerable number of papers published since 1964 and some recent data that have not yet been published in detail justify an attempt to synthesize the total body of information relevant to natural history to provide a body of ideas or a working hypothesis. In this section, therefore, different channels of information have been brought together in an attempt to provide a coherent and consecutive description of the very complex changes that occur in the lung from the first day a person smokes a cigarette or goes to live in an atmosphere of heavy urban pollution to the (by no means inevitable) death from respiratory failure or cor pulmonale forty years later. Many of the data are preliminary, and I am doing no more than suggesting one way of arranging the pieces of this incredibly complex jigsaw puzzle.

To begin with, the primary effect of cigarette smoking first occurs at the level of the small bronchioles. There is impairment in normal defense mechanisms against infection, leading to slower convalescence from ordinary lower-respiratory-tract infections than in nonsmoking subjects.[26,27] These early effects will be aggravated if the person lives in an area of high industrial air pollution, a factor that, alone, may be responsible for an increased prevalence of respiratory infection in childhood.[33,34]

Secondly, after some years of cigarette smoking, the time being affected by whether or not the subject lives in a clean atmosphere or in a city,[31,83] the effect of these agents on the lung will have become measurable. At the earliest stage little sputum may be produced,[2] the FEV may be normal or nearly so,[25,36,52] the gas distribution will be impaired,[24,36,52] and the residual volume will be somewhat increased.[52] The FEV and total airway resistance are relatively insensitive to considerable changes in small airways, which normally contribute such a small part of total airway resistance.[12] Changes in peripheral airways are indicated, however, by the fact that the dynamic compliance of the lung has become frequency dependent, although the recoil is normal.[84,85] Studies with radioactive xenon (^{133}Xe) demonstrate impairment of gas exchange over individual counterfields not reflected by gross regional changes in distribution of ventilation and perfusion,[67,68] but reflected in expired gas analysis at the mouth.[84] The P_{CO_2} will be normal at this time though the P_{O_2} may be slightly lowered and may be frequency sensitive, though this has not, as far as I am aware, been critically measured. The changes at this stage may presumably be completely reversible.

Continued exposure to cigarettes and other pollutants leads to the next stage, in which considerable hypertrophy of mucus glands occurs, the Reid index rises, and the sputum production becomes heavier and a more evident part of the syndrome. The FEV falls as these changes occur in the larger airways. During all this time, presumably, bronchioles are continuing to disappear, and depending on how many have gone, variable areas of the lung will be dependent on collateral drift ventilation for their gas exchange. The ventilation/perfusion ratio may therefore be unfavorable in some regions of the lung, and the impairment become acutely very severe if bronchiolitis or bronchopneumonia occurs in such a lung as a consequence of acute infection or imitation. At this stage the lung is abnormally susceptible to any physical agent, and the bronchial tree as a whole has become hyper-reactive. Its cleansing mechanisms, particularly those in the small bronchioles, must be impaired, and its resistance to any infection may be lower than in a normal lung. If this situation is complicated by a respiratory center relatively insensitive to CO_2 and hypoxia, the addition of significant hypoventilation will lead to severe blood gas derangement and even cor pulmonale at this stage of the disease,[80] though only a small proportion of cases of chronic bronchitis (as defined in epidemiologic terms) will go on to such a severe stage. Although the FEV may have fallen and the residual volume will be increased, at this stage lung recoil is preserved and the diffusing capacity and CO exchange are still normal.[52,84]

The next stage is one of breakdown of lung tissue (occurring earlier in cigarette smokers and city dwellers) most often initially at the end of the respiratory bronchiole, presumably in alveoli that have been exposed to inspired material in heavier concentration. This centrilobular emphysema is always accompanied by changes in bronchioles, of which some may have disappeared and others show chronic inflammatory change to a greater or lesser degree. Some larger regions of the lung will now be ventilated by collateral drift ventilation, and the disordered architecture of the lung leads to failure of gas equilibration within the centrilobular spaces, severely aggravating the $\dot{V}/\dot{Q}$ maldistribution phenomenon that existed in the earlier stage.[55,57,68,84-86] The aggravation of the pre-existing maldistribution of $\dot{V}/\dot{Q}$ may be enough to send the patient into chronic hypercapnia and hypoxia at this stage.

Alternatively, the failure of cell nutrition may not be localized to the center of the lobule but may occur more generally throughout the lung. When this occurs (and it is known that it can occur as a result of a deficiency of the enzyme α_1-antitrypsin),[58] the result is panlobular emphysema causing loss of lung elastic recoil, with secondary consequences on air flow resistance. This change can occur in parallel with the changes sketched as a consequence of centrilobular emphysema.

Superimposed on these changes is the effect of normal aging on the lung whereby elastic recoil diminishes progessively, resulting in closure of small airways at a progressively higher lung volume[87] and causing further maldistribution of ventilation particularly when the tidal volume is small. This total effect will impair still further the drainage and clearance mechanisms in parts of the lung to which the bronchioles are abnormal.

Finally, in all types of emphysema the actual number of terminal bronchioles will be found to be much reduced,[88] so that the severe limitation of ventilation is not now reversible. Atrophic changes in the walls of major bronchi may contribute to this final stage of the condition by causing their collapse during expiration.[89]

Effects of Treatment in Chronic Bronchitis and Emphysema

It is obvious from the cardinal role of cigarette smoking in the genesis of these two diseases that the most important and urgent aspect of their control lies in their prevention. It is not yet possible to draw up a balance sheet of proportional influence of cigarette smoking and atmospheric pollution though no doubt eventually some such calculation may become a possibility. A number of papers published emphasize the importance of prompt treatment of respiratory infections in chronic bronchitis, and there seems little doubt that the downhill course of the disease is expedited by repetitive severe respiratory infections of any kind. With increasing emphasis on an active therapeutic approach to acute respiratory failure, it has become very important to assess the prognosis of patients with chronic bronchitis and emphysema who are treated for acute respiratory failure. For this reason a three-year follow-up study published by Sukumalchantra, Dinakara, and Williams[90] is of particular interest. Of 43 patients with chronic obstructive pulmonary disease who survived an admission for acute ventilatory failure, about half were alive three years later. The mean age of this group was 62, ranging from 42 to 79. It is to be hoped that other data of this kind will soon be available so that the comparative results of treating acute respiratory failure in terms of eventual prognosis may come to be better understood.

* * *

To those who expect dramatic "breakthroughs" in knowledge in every field of medicine, few of the publications that I have cited may be thought to represent a major advance in understanding. It may be admitted that the rate of progress of knowledge about chronic bronchitis and emphysema is not commensurate with the urgency of the problems posed by these diseases, and yet it is indisputable that the last ten years have seen important advances in understanding; at least the complexity of the probable answers to the simplest questions is beginning to become apparent.

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Senator MUSKIE. Our last witness is Dr. Fredrick Sargent II, dean of the College of Environmental Sciences, University of Wisconsin.

Dr. Sargent, it is a pleasure to welcome you this morning.

We have just said goodby to a noted citizen of Wisconsin, Dr. Young, who was president of the University of Maine, to go to the University of Wisconsin. Your gain is our loss.

STATEMENT OF DR. FREDRICK SARGENT II, DEAN, COLLEGE OF ENVIRONMENTAL SCIENCES, UNIVERSITY OF WISCONSIN, GREEN BAY, GREEN BAY, WIS.

Senator MUSKIE. I understand that you, too, Dr. Sargent, are a member of the National Air Quality Criteria Advisory Committee.

Dr. SARGENT. I am; yes.

Senator MUSKIE. If you will, proceed.

It may be that if you have not finished, I could go to the floor and vote and return, we will take that as it comes.

Dr. SARGENT. All right.

I did not include my credentials in my printed paper. I might say a few words about myself, Mr. Chairman.

I am dean of the College of Environmental Sciences and acting dean of the College of Human Biology at the University of Wisconsin, Green Bay. There I hold the title of professor of human ecology. I am chairman of the human ecology committee of the Ecology Society of America. I have been an active member of a number of committees in the National Academy of Sciences, as well as committees of the Public Health Service; that is, the U.S. National Committee for International Biological Program, the Air Pollution Training Committee, and the National Air Quality Criteria Advisory Committee.

My interest in air pollution is primarily ecological.

The Clean Air Act of 1967—Public Law 90–148, sec. 107b—provides the definition of air quality criteria:

> Air quality criteria * * * reflect * * * scientific knowledge * * * indicating all identifiable effects on health and welfare which may be expected from the presence of an air pollution agent or combination of agents in the ambient air * * *. Such criteria shall include those variable factors which of themselves or in combination with other factors may alter the effects on public health and welfare of any subject agent * * *.

In essence, then, air quality criteria deal with how alterations in the atmospheric environment affect the health and welfare of man.

PUBLIC HEALTH AND WELFARE

For human health and welfare really to be the central issues of air quality criteria, it is most important that they be considered, not in a narrowly oriented text, but in a broadly based frame of reference in which diverse indirect (systems) effects can be accounted for. Accordingly, air quality criteria should become a significant part of an air resource management strategy.

RESOURCE

The atmosphere is a finite resource. Many of its qualities are renewable by natural processes. For example, water evaporates from rivers, lake, oceans, and soil to pass into the air; the moisture returns as rain or snow. Particulate matter such as dust, volcanic ash, and salt from sea spray are dispersed into the atmosphere; eventually they are removed by sedimentation and precipitation. In a biological process driven by solar energy, the green plants and phytoplankton convert atmospheric carbon dioxide into sugars. In this photosynthetic reaction, oxygen is produced and dispersed into the atmosphere.

Utilization

Man utilizes this resource in two principal ways.

First, he draws upon the air to support the combustion processes of his industrial and transportation systems.

Second, he discharges a large fraction of his gaseous and particulate wastes into the air for dillution and dispersion.

Oxygen production

So far, the biological production of oxygen has kept up with consumption of oxygen by man's technology. There is as yet no evidence that the oxygen content of the atmosphere has begun to decline. Man's use of the atmosphere as a sewer has demonstrated clearly that this resource has a limited capacity for dilution and dispersion. Manmade detritus has begun to accumulate in the atmosphere.

Because of the planetary circulation human airborne detritus can now be found in regions remote from the major aggregations of people and industry. Man's pollution of the atmosphere has global dimensions. While we focus our attention on the acute episodes of air pollution—and I do not for a moment think that we should neglect the implication of these episodes—there has been a concurrent insidious deterioration taking place in the quality of the region of our atmosphere called the troposphere. Because these trends have important implications for human welfare, they must be taken into account in developing air quality criteria.

Several fundamental considerations lead me to this viewpoint.

INTERDEPENDENCE OF ORGANISMS

In the first place, all terrestrial organisms, including man, are absolute dependent upon such qualities of the air environment as temperature, moisture, and oxygen. In the second place, most organisms are dependent one upon the other.

One example this interdependence is the need all organisms have for food. Man is no exception; most of his food derives from other animals or from plants. Those interrelations between organism and environment and between organism and organism are lawful and orderly. In short, they constitute a system, a system which ecologists call an ecosystem.

These considerations suggest that when one thinks of the health and welfare of man, one must develop air quality criteria in an ecological context.

On the other hand, disruptions of air quality may affect human health and welfare directly. These effects include such meteorological phenomenums as heat waves, cold waves, and the sudden changes of weather that occur with the passage of fronts.

Each of these phenomenums extracts its toll of human health in sickness and death. To these natural atmospheric processes man has added pollution. Progressive upward trends are correlated with a mounting morbidity and mortality from respiratory disease. The acute episodes of air pollution are really exaccerbations of the underlying trends; they suggest how air pollution may affect human health if the trends are not reversed.

Weather

What frequently confounds epidemiological analysis is that weather phenomenums which act directly on human health are sometimes phenomenums that also accentuate levels of air pollution. For example, late summer heat waves in Los Angeles are frequently concurrent with episodes of smog. Facts such as these, however, provide ample evidence of how man's health depends upon air quality.

On the other hand, such disruptions may disturb the ecosystem or important components of the system and lead indirectly to appreciable disturbances of human health and welfare. Because of the relative sensitivities of organisms other than man to changes in air quality, it could be that the indirect effects of deteriorating air quality would be more significant than the direct effects.

Air pollution

For example, man depends for his nourishment upon a high biological productivity by plants. Because air pollution acts to reduce quantity and quality of yield from plants, this impoverishment constitutes a significant indirect risk from air pollution to human health.

In the ecosystem, the plant is a key organism, for the solar energy that drives the system is captured by photosynthesis and is stored as sugars, proteins, and fats. This energy is then distributed to various animals in an orderly manner as carbohydrate, protein, and fat.

Ultimately, the energy is lost to space as heat and the nutrients are returned to the soil when the animals and plants die. Soil microorganisms simplify this organic detritus and prepare it for recycling. Thus, the ecosystem is a metabolic system in which energy and nutrients flow from environment through an array of organisms and back to environment.

Food chain

This array of organisms constitutes the "food chain." The several organisms constituting such a chain are linked into what may be thought of as a transactional metabolic network. Each link in this network is critical for the efficient and effective operation of the processes of the ecosystem.

Adaption

Although each organism has capability of adapting to environmental change, the ranges of changes that can be tolerated vary. An environmental change that can be tolerated by one organism may not be tolerable to another. When crucial links in the transactional metabolic networks of the ecosystem are affected, the repercussions may be widespread throughout the system.

ENERGY THRIVING ECOSYSTEM

I have noted that the energy driving the ecosystem comes from the sun. This solar energy must traverse the earth's atmosphere before it reaches the region wherein plants and animals reside. The proportion of the total energy, incident at the outer limits of the atmosphere, that ultimately reaches the earth's surface, depends upon how clear the air is.

Clouds and dust in the air reflect some of this incoming solar radiating, preventing it from reaching the surface of the earth. In the past, dust from droughts and ash from volcanoes comprised the principal sources of air pollution from particulate matter. Now man is the chief contributor.

Particulate effects

Vast quantities of particulate matter are discharged into the atmosphere from man's industrial establishment, his cities and his cars, his trucks and trains. During the past several decades, there has been an appreciable increase in atmospheric turbidity, not only in the atmosphere near major cities but in air at places far removed from such metropolitan agglomerations, for example, Davos, Switzerland, and Mona Loa, Hawaii.

What these observations suggest is that the increase in atmospheric turbidity is not localized—not confied to air basins with high pollution potential—but global.

At the same time, there has been an increase in high-level cloudiness along routes of jet aircraft. The jet contrail evolves into sheets of cirrus clouds which cover the sky from horizon to horizon. These clouds act to reflect incoming solar radiation. The lead particles from auto exhaust serve as freezing nuclei and Dr. Vincent Schaefer who demonstrated this phenomenon suggests that such nuclei may contribute to the formation of clouds.

SUGGESTED EFFECTS

What do these trends suggest when viewed ecologically? Reflection of incoming solar radiation could lead to cooling of the earth's atmosphere. Since 1940, the mean global temperature has been falling. Some authorities suggest that manmade dust and other particles are the main factors responsible for this thermal decline.

If the incoming radiation were to be reduced sufficiently, the photosynthetic process in plants could be impaired. Because of the role of the plant in maintaining air quality, a reduction of photosynthesis would have profound effects.

Carbon dioxide

In photosynthesis atmospheric CO_2 is converted into plant carbohydrate; oxygen is released to the atmosphere. The green plants of the land and the phytoplankton of the ocean are the principal producers of atmospheric oxygen.

At the same time these organisms consume atmospheric CO_2—CO_2 which is an end product of metabolic processes of living organisms, of decaying organic detritus, and of industrial processes that consume fossil fuels for energy.

Under these circumstances, atmospheric oxygen would be expected to decline, the biological productivity of the ecosystem would be disrupted, and indirectly man's welfare would be placed in jeopardy.

Air pollution

When to these trends in atmospheric turbidity one adds the direct action of such air pollutants as sulfur oxides, fluorine, and nitrogen oxides on plants and the incursions of man's cities, towns, and roads into the landscape, one cannot help but raise the question, What indirect effects on human health and welfare will accrue?

ECOLOGICAL FRAMEWORK

These thoughts emphasize the need to consider air quality criteria in an ecological framework. Not only is man at risk directly from air pollutants, but, as a consequence of his dependence upon the biological productivity of the ecosystem, he is also at risk indirectly.

Air quality criteria

Air quality criteria constitute but one aspect of an action program designed to restore the qualities of the air environment to configurations that minimize the risks to human health and welfare.

These criteria become the conceptual basis for an air resource management strategy. Such a strategy must constitute a detailed evaluation of the benefits that will accrue to man from restoring air quality against the risks of failure to control the pollution of the atmosphere. The end product of this process of evaluation is a set of air quality standards.

Air quality standards

Air quality standards are both decisions and goals. They are decisions because they represent conclusions about expenditures and adjustments in the way of life man is willing to make to minimize risks. They are goals because time will be required to restore air quality.

AIR RESOURCE MANAGEMENT STRATEGY

Implementing an air resource management strategy—translating air quality criteria into air quality standards and emission standards—is a most complex process. If the strategy is to be ecologically based—and I am convinced it must be—the public must understand the strategy so that they will support the legislation and the economic costs necessary to achieve the standards recommended.

In this process, the universities must exhibit leadership. The scholars of these institutions must work to broaden the public's perception and awareness of the necessity for these programs for managing the air resource.

Even though one cannot now quantitate in detail all the benefits and risks that must be considered in formulating a strategy for air resource management, we must now take steps to initiate the process. There is sufficient evidence now in hand to foresee the serious risks of inaction.

Even though the first steps may be more empirical than desired, waiting for more concrete evidence entails the possibility that changes may be set in motion that are irreversible. The strategy can be refined as more facts accrue.

I suggest this course primarily because of the inevitable delays that characterize taking social action. Yet, even as we initiate such steps, we must realize that it will probably be decades before man sees the benefits of actions taken now. The ecological processes that have been disrupted are simply not easily and rapidly restored.

CONCLUSION

As I conclude this statement, I should like to emphasize what I consider a most important element in the development of an air resource management strategy. That problem is man's perception of himself and his relation to his environment.

As I have stated in BioScience (vol. 17, October 1967, pp. 691–697):

> Man is now educated and trained to have a very parochial view of himself * * *. Now those loyalties must become international and focus on all mankind. Environmental pollution is a problem that confronts all men and all men must be participants in its solution. The realization of this fact is threatening. It requires concern for people beyond one's immediate kin, indeed for people not even born. It symbolizes legal regulation, loss of individual liberty, and invasion of privacy * * *. These are serious matters. They are as important, but inadequately studied, aspects of human adaptability as the physiological regulations that make for biological adaptation. One urgent aspect of strategic planning thus will be to enlarge mans' perspective of his place in, and relation to, the ecosystem in order to assure its continued fitness.

Senator MUSKIE. Dr. Sargent, that bell that just rang about 3 minutes ago is the rollcall, so I do have to leave.

I want to express my very real appreciation for this paper. I think it is the most suitable final paper of its series in the hearings. I think it poses a challenge, the need to move ahead by means of rough approximations that may prove to be inadequate and in some cases excessive, though the former rather than the latter in achievable social action.

I have just one question.

How do you establish threshold limits of polluants which have any relevance at all to a meaningful cause and effect evaluation of the effect upon the ecosystem?

Dr. SARGENT. The way this has to be approached is to examine the effects of air pollutants on the crucial links in the ecosystem. The green plant is a most important crucial link, as I stated in my paper.

Senator MUSKIE. Would you say on that basis that our criteria ought to be such as to eliminate damage to plants?

Dr. SARGENT. I would say they ought to be such as to eliminate damage to the important producing plants, the plants which are sources of nutrient energy for the "food chain."

Senator MUSKIE. It would strike me that that would provide considerable detection in terms of health effects for humans.

Dr. SARGENT. That is correct because the plant in the case of most pollutants is much more sensitive than the human being.

Senator MUSKIE. Dr. Sargent, thank you very much. I hope that we meet again and that we get a chance to discuss this further.

Thank you.

Dr. SARGENT. It has been a pleasure.

Thank you.

Senator MUSKIE. Thank you, sir.

(Questions submitted to Dr. Sargent by Senator Muskie are as follows:)

U.S. SENATE,
Washington, D.C., August 2, 1968.

Dr. FREDRICK SARGENT II,
Dean, College of Environmental Sciences, University of Wisconsin, Green Bay, Wis.

DEAR DR. SARGENT: May I take this opportunity to express my appreciation for your excellent statement on air quality criteria. Your statement was very informative on the medical and scientific evidence available, which can be used to develop air quality criteria, and research needs.

In reviewing the transcript of the hearings, additional questions have arisen. I am transmitting these questions for your response. While some of the questions were touched upon during the course of the hearings, you may wish to expand on your oral responses. Receipt of your comments by August 23, 1968, would assist us in developing further hearings.

Thank you for your assistance and cooperation in this inquiry on air quality criteria.

Sincerely,

EDMUND S. MUSKIE,
U.S. Senator,
Chairman, Subcommittee on Air and Water Pollution.

[Enclosure]

QUESTIONS SUBMITTED TO DR. FREDRICK SARGENT

1. The Air Quality Act of 1967 provides for the development of air quality criteria using the best available medical and scientific evidence. For which atmospheric contaminants, groups of contaminants, or combination of contaminants do you feel there is sufficient scientific and medical evidence to develop air quality criteria?

2. The Air Quality Act of 1967 provides for the re-issuance of air quality criteria as new medical and scientific evidence becomes available. What types of studies would be useful to confirm or refine air quality criteria?

3. As a member of the National Air Quality Criteria Advisory Committee, would you care to comment on how the committee operates?

4. There has been discussion of special risk or susceptible population groups. What in your opinion is their relevance to public health policy?

(The response by Dr. Sargent was not available for this printing and will appear in Volume III which will be published at a later date.)

Senator MUSKIE. Before we recess the hearings I would like to include for the record a statement with an attachment I have received from Ralph Wands, Director, Advisory Center on Toxicology, National Research Council.

(The statement follows:)

NATIONAL RESEARCH COUNCIL, NATIONAL ACADEMY OF
SCIENCES, NATIONAL ACADEMY OF ENGINEERING,
ADVISORY CENTER ON TOXICOLOGY,
DIVISION OF CHEMISTRY AND CHEMICAL TECHNOLOGY,
Washington, D.C., June 14, 1968.

Hon. EDMUND S. MUSKIE,
Chairman, Subcommittee on Air and Water Pollution,
U.S. Senate,
Washington, D.C.

DEAR SENATOR MUSKIE: In response to your invitation of May 27 to testify to the Subcommittee on Air and Water Pollution, I regret that I am unable to appear personally but perhaps the following comments will be helpful, particularly in connection with item IV of the outline of your hearings.

As you know, the National Academy of Sciences is a private, cooperative society of distinguished scholars in scientific or engineering research, dedicated to the furtherance of science and its use for the general welfare. Its charter, an Act of Incorporation passed by the U.S. Congress and signed by President Lincoln on March 3, 1863, calls upon the Academy to serve as an official advisor, upon request and without fee, to the federal government on any question of science or technology. A subsidiary body, the National Research Council, was organized in 1916 at the request of President Wilson and now serves as one of the primary mechanisms whereby the scientific and technical expertise of the country can be brought to bear upon problems of national import.

The Committee on Toxicology of the National Research Council was organized in 1947 to make assistance available to federal agencies on problems of toxicology arising within their organizations. Full time professional staff support for this Committee was provided in 1957 with the establishment of what is now known as the Advisory Center on Toxicology. The federal agencies who sponsor the activities of the Committee an Center are identified and organized by an interagency memorandum of agreement between Army, Navy, Air Force, Atomic Energy Commission, National Aeronautics and Space Administration, National Center for Air Pollution Control, and the Coast Guard. This agreement provides for annual fiscal support of the Center by means of a contract between the Academy and the Office of Naval Research utilizing funds transferred to this account by the sponsoring agencies.

The responsibilities of the Advisory Center on Toxicology are basically those of providing a central source of information and technical staff to support the Committee on Toxicology in advising the sponsors on scientific and technical questions relating to the health hazards to military and civilian personnel arising from the toxic properties of materials of interest to the sponsoring federal agencies.

For many years the activities of the Committee on Toxicology have included responding to requests from some of the sponsoring agencies for recommended concentrations of air contaminants in confined spaces. Initially these were related to problems of design and operational requirements for nuclear submarines. More recently they have also involved manned spacecraft. It is important to note that these are intentional, continuous, long-term exposures of carefully selected men under close medical surveillance.

Recommendations of acceptable concentrations for brief exposures to highly toxic contaminants have also been made by the Committee for use in planning emergency procedures in the event of spills of such materials as liquid rocket propellants. It should be noted that these are only applicable to on-site personnel who have undergone some selection and who are also subject to medical surveillance. The emergencies are considered to be rare in the lifetime of an individual.

In arriving at the foregoing recommendations, the Committee has developed a philosophical basis for its approach to these problems. This was formalized in a pamphlet issued in 1964 by the Committee entitled "Basis for Establishing Emergency Inhalation Exposure Limits Applicable to Military and Space Chemicals". This is now out of print but a photocopy is enclosed for your consideration. Using such criteria the Committee is able to review the available toxicological information to arrive at a recommendation which, in their judgement and combined experience, safely meets the criteria. Quite often, the available information is inadequate so that the recommendation, if any is made, is tentative and appropriate research is urged. The Committee frequently reviews its recommendations and revises them when justified in the light of new knowledge.

The Committee has also been involved in questions of exposure of the public to air contaminants. An example of this is its report dated March 1, 1966 to the

Air Force and Public Health Service titled "Air Quality Criteria for Beryllium and its Compounds". You are already aware of this report as it was submitted in the testimony of Colonel A. F. Meyer to the Subcommittee on Air and Water Pollution during its hearings in 1966 on S. 3112.

In recent months the Committee has received requests for recommendations of acceptable concentrations for brief exposure of the public to air contaminants such as might arise from military and space operations from many of the sponsoring agencies. The Committee is, of course, aware that Congress has assigned responsibility for such matters to the Secretary of Health, Education, and Welfare. Accordingly, the Committee is planning a conference on these questions which will involve representatives of the Secretary in order that the scientific judgement of the Committee can be made available most effectively.

The foregoing is intended to provide an understanding of the nature and extent of the activities of one entity within the National Academy of Sciences that relate to Air Quality Criteria. If additional specific information is desired, please let us know.

Respectfully submitted.

RALPH C. WANDS, *Director.*

[Enclosure]

BASIS FOR ESTABLISHING INHALATION EXPOSURE LIMITS APPLICABLE TO MILITARY AND SPACE CHEMICALS

Prepared by the Ad Hoc Committee:
Henry F. Smyth, Jr., *Chairman*
Theodore F. Hatch
Keith H. Jacobson
Moreno L. Keplinger
Frank Princi (deceased)

Revised and approved by the Committee on Toxicology:
Arnold J. Lehman, *Chairman*
William G. Frederick
Horace W. Gerarde
Herbert E. Stokinger
John A. Zapp, Jr.

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL,
WASHINGTON, D.C.

PREFACE

The introduction of new chemicals for military and space application has created the need for establishing Emergency Exposure Levels for both occupational and non-occupational groups. Methods which have been proposed in the past for deriving short-term exposure levels such as mathematical modifications of existing Threshold Limit Values, have not been completely satisfactory since they have not taken into consideration conditions of exposure which differ from industrial patterns, or the body systems involved when individuals are exposed to high concentrations of toxic materials.

Since no authoritative source exists for establishing Emergency Exposure Levels, the Committee on Toxicology of the National Research Council, at the request of the Sponsoring Agencies of the Advisory Center on Toxicology, has, with the assistance of an ad hoc Committee, attempted to develop a rationale upon which such levels might be promulgated. The conclusions and recommendations of these Committees are set forth in this report, with the hope that they will serve as a guide to those concerned with this important problem.

HARRY W. HAYS,
Director, Advisory Center on Toxicology.

I. THRESHOLD LIMIT VALUES

The Committee regards The Threshold Limit Values promulgated by the American Conference of Governmental Industrial Hygienists as sound guides to acceptable concentrations of airborne toxicants for exposure of humans in industry. To a considerable extent the values are validated by monitored experience. They are equally applicable to any situation essentially equivalent to that of industrial exposure, i.e., where mature persons, generally in good health, working in groups under supervision, are subjected to contaminated

atmospheres of substantially constant concentrations, for not more than eight hours a day, on five days of each week.

The Committee recognizes that exposures to toxicants often deviate from the industrial pattern. It is aware of the specious rationale of using a factor representing the ratio of exposure periods to convert a particular Threshold Limit Value to a number thought to be a guide for acceptable non-occupational exposure patterns. Experience has proven that this rationale is wrong and cautions that reliance upon it may result in serious injury.

For these reasons, any standards for exposure patterns differing from the industrial pattern must be promulgated independently of the threshold limit, after detailed study of the conditions of exposure and of the toxicological data, and should represent the consensus of a body of experienced toxicologists. Each substance requires individual study.

II. PREDICTABLE SHORT-TERM EXPOSURES

A. Occupational

There are situations where practical operation appears to require the acceptance of the possibility or the certainty that humans will be exposed briefly to very high concentrations of airborne toxicants. It is taken for granted that the concentrations and durations of exposure can always be estimated in advance by calculation, or by measurements on a mock-up. Standards for acceptable short-term exposures are needed to determine whether the risk of practical operations is acceptable, whether the humans must work at all times and perhaps at reduced efficiency in protective equipment, whether means must be found to remove humans completely from vulnerable locations or whether the operation must be altered to reduce human exposures to a more tolerable level.

It is recognized that both occupational and non-occupational exposures can occur at predictable intervals when they can in no sense be considered to be accidents. An example is the static test-firing of samples of production batches of rocket propellants. There is no justification for submitting individuals to any appreciable risk in a predictable exposure. Advance provisions should be made to control the exposure of employed individuals by means of limitations on quantities and distances, by physical security, and by personal protective equipment. The goal of control should be good industrial hygiene practice. This is not yet codified specifically for short-term exposures, although informed toxicologists will find many Threshold Limit Values which are applicable without numerical change.

B. Non-Occupational

In view of the wide range of individual susceptibilities embraced among the inhabitants to a variety of chemicals, the Committee recommends that predictable single and repetitive short-term exposure of residential communities to potentially harmful concentrations under peacetime circumstances should be prevented through adequate safeguards. The standards to be followed should be in accord with good environmental health practices, and where they exist, to standards of good community atmospheric pollution control.

III. UNPREDICTABLE EXPOSURES

The Committee recognizes the existence of two additional categories of short-term exposure situations. In the first category, brief occupational exposure is a possibility, it is not avoidable, its time of occurrence is not predictable, nor is its eventual occurrence a certainty. Such an exposure would be considered an accident and a rare event in the life of any one individual. In this category there is often justification for exposing individuals to some degree of risk. The Committee encourages the promulgation of lists of acceptable concentrations to assist in the advance planning of installations where such exposures may occur, and to establish working rules for these installations. In order to emphasize the accidental nature of the brief exposure which is recognized as unavoidable, it is recommended that the promulgated values shall be designated Occupational Emergency Exposure Limits or an equivalent phrase in keeping with the connotation of unpredictable accident.

In the second category is a possible, but unpredictable, non-occupational brief exposure, such as may occur in a residential area in the vicinity of an operational or test facility. For such situations where exposures are unavoidable, the Committee recommends that Non-Occupational Emergency Exposure Limits be

promulgated. These might be quantitatively identical with Occupational Emergency Exposure Limits for certain substances.

IV. DEFINITION OF EMERGENCY EXPOSURE LIMIT

It is the opinion of the Committee that the sensory comfort of the exposed person is not a necessary concern in determining an Emergency Exposure Limit Value. It is recommended that values selected shall be defined in essentially the following terms:

The Emergency Exposure Limit for short-term exposure to an airborne contaminant is a concentration which, when inhaled for a specified single brief period, rare in the lifetime of an individual, is believed not to result in a period of disability or interfere with the performance of his assigned task. In no event shall the value so selected produce danger from flammability of combustible aerosols, or result in substantial impairment of vision or visibility, or the ability to breathe.

V. RARE IN THE LIFETIME OF AN INDIVIDUAL

It appears impossible to interpret existing toxicological data in support of any short-term standard other than a single exposure of a previously unexposed individual. Therefore, it is recommended that each installation adopt working rules to assure that no person will be allowed in a position where a second exposure is possible until he has been authorized to do so by the responsible physician.

VI. SAFETY FACTORS

Standards, threshold limits and tolerances are customarily promulgated with values which include some safety factor. This allows for some uncertainty in interpretation of experimental data, in estimation of the exposure of the population to be protected, and some individual variation in resistance. The magnitude of the safety factor may or may not be public knowledge, and it may be different for different substances in the same list. The differences in safety factors may have a rational basis, such as the nature of the injury caused by exceeding the standard, or they may be empirical.

The Committee sees more danger than value in the incorporation of an arbitrary safety factor into Emergency Exposure Limits. The limits are intended to guide the informed specialist. It is believed that he can do a more competent job in protecting people if he is furnished with a limit which, in the best judgment of a group of toxicologists, is the greatest concentration justified by the experimental evidence, provided the absence of any arbitrary safety factor is made generally known. This realistic limit would be analogous to the strength of materials data which the structural engineer uses in designing. The safety factor is applied in his operation of design, in proportion to the precision with which stresses to be withstood are known to the designer.

VII. LIMITATION OF SHORT-TERM

The effect of brief inhalation of a substance is determined by a number of factors. These include the basic mechanism of injury, the individual resistance of the exposed man, and the concentration-time-effect relations of the substance at the target site in the body, the latter being markedly influenced by physical exertion.

The ranges of possible variations in these dynamic processes lead to considerable uncertainty in predicting concentrations and individual responses. These uncertainties are of such a magnitude that there is little physiological or practical significance to Emergency Exposure Limits for an exposure period of less than ten minutes, and therefore the Committee does not encourage the development of such limits for shorter periods of time.

It is possible that an Emergency Exposure Limit may be needed to protect a man through automatic instrumental monitoring of his exposure. It is the impression of the Committee that suitable reliable instrumentation can be devised, but that it is not now available for most substances. In such a situation it may be thought by some that rapid changes in ambient concentrations justify the promulgation of Emergency Exposure Limits for exposures as brief as one or two minutes.

It should be pointed out that if conditions are expected to result in rapid changes in ambient concentrations, one can expect concentration gradients to

be steep in a spatial sense. A man's exposure under these conditions cannot be monitored unless the sample is drawn from the exact location of his nose. This calls for the wearing of a harness and trailing a sampling hose, restricting freedom as much as if the man were fully protected by an air-supplied helmet. The Committee concludes that the practical use which could be made of Emergency Exposure Limits for periods briefer than ten minutes would so restrict a potentially exposed man as to defeat the purpose of the limits.

VIII. TOXICOLOGICAL DATA REQUIRED TO PROMULGATE AN EMERGENCY EXPOSURE LIMIT

Emergency Exposure Limits for many substances cannot be promulgated without performing new experimental toxicological studies. Whether new studies are needed, or existing data are utilized, the minimum information required will be the same.

A. One should know beyond reasonable doubt the identity of the most sensitive target organ or body system whose integrity is menaced by short inhalations of the substances, and at what level effects on this target are insignificant.

B. One must have time *vs.* concentration response data extending in both directions beyond the time intervals for which limits are to be promulgated, and sufficient observations to verify complete reversibility of effect. Data upon two species, one a non-rodent mammal, are recommended as an absolute minimum.

C. Certain exposure data for orientation purposes are essential in estimating the emergency limits. These can often be obtained from accidental exposure during commercial development of a substance by appropriate evaluation of the exposure.

SUMMARY AND RECOMMENDATIONS

1. No mathematical modification of Threshold Limit Values will produce tolerances which are sound guides to acceptable short-term exposures. Such tolerances must be promulgated for one substance at a time, as the consensus of a body of experienced toxicologists. The Committee on Toxicology of the National Research Council does not condone the use of lists which use mathematical modifications of threshold limit values on an overall basis.

2. a. Predictable short-term occupational exposures which are not accidents should be controlled to the standards of good industrial practice.

b. Predictable single and repetitive short-term non-occupational exposures which are not accidents should be controlled in accord with good environmental health practices, and where they exist, to the standards of good community atmospheric pollution control.

3. In brief short-term exposures which are possibilities at an unpredictable time, rare in the life of any individual, Occupational and Non-Occupational Emergency Exposure Limits are proper guides to determine what concentration can be accepted.

4. The Emergency Exposure Limit for short-term exposure is a concentration which, when inhaled for a single specified brief period, rare in the life of an individual, is believed not to result in a period of disability or interfere with the performance of his assigned task.

5. "Rare in the life of an individual" implies that no person will be allowed in a position where a second exposure is possible until he has been authorized to do so by the responsible physician.

6. The Committee recommends that Emergency Exposure Limits which are established should not incorporate arbitrary safety factors.

7. The Committee is reluctant to encourage the development of Emergency Exposure Limits for an exposure of less than ten minutes.

8. It is possible that Emergency Exposure Limits for some substances, can be promulgated on the basis of existing toxicological data, but new observations will be required for other substances. The Committee's recommendations on the minimum data are presented.

Senator MUSKIE. This concludes this series of hearings. There will be further hearings at times to be announced later.

(Whereupon, at 11:55 a.m., the subcommittee adjourned.)

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