Progress in Medical Research on Air Pollution

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For 3 years the Air Pollution Medical Branch of the Division of Special Health Services has been working in the increasingly more important but relatively unexplored field of air pollution in its specific relation to human health. The work began with a search for and a systematic appraisal of the scattered sources of knowledge, followed closely by tentative explorations into those parts of the problem holding promise of significant findings. Sufficiently successful results of initial activities helped chart the present course of action, which, in turn, points toward ideas requiring emphasis in the future.

THE Public Health Service has been concerned with the health aspects of community air pollution for many years (*1*, *2*). It was not until 1955, however, when Public Law 159 was passed by the 84th Congress, that the subject was accepted as of sufficient importance in itself to merit separate study. The Air Pollution Medical Program of the Division of Special Health Services was set up for this purpose in July 1955.

Specifically, the Air Pollution Medical Program was charged with the responsibility of determining whether or not community air pollution modified health among human populations. The first part of this charge involved the problem of definitions. What is meant by community air pollution? What are health effects? What should be the ultimate goal of the program?

For immediate use, air pollutants were defined as those materials in the community air that were contributed by the acts of man, excluding biological agents and radioactive materials (*3*). It was assumed that a community was an urban aggregation which might well cross political boundaries; it would have a large number of people potentially exposed generally to the same atmospheric air. Health effects were defined as those effects which might result in physiological or pathological changes which could be measured by objective techniques. The ultimate goal was seen early to be the definition of those agents in the air which cause deleterious health effects under specified conditions, so that appropriate steps could be taken to prevent or minimize these effects.

A wide variety of specific information was immediately available. For example, it was known that within the United States mortality rates for certain diseases varied from community to community; that eye irritation in the Los Angeles Basin was associated with the local smog (*4*); and that those who had died during the acute air pollution episodes of London (*5*), Donora (*6*), and the Meuse Valley (*7*) were generally elderly and frequently had preexisting respiratory or cardiac difficulties. From the same episodes and from other data there was evidence that the breathing of irri-

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tants result in changes in respiratory physiology (*8–10*). There was evidence that ozone was toxic (*11–13*) and that rather large amounts were in the air of such areas as Los Angeles (*14*). There was also evidence that oxides of sulfur were present in many urban atmospheres and that they could adversely affect human health. Further, information from Great Britain indicated that observed variations in morbidity and mortality from city to city for some specific diseases were similar in pattern to the known or assumed intensities of air pollution.

A large amount of statistical data offered potentially useful information. But the data needed to be reoriented since they had been compiled for studies or activities unrelated to air pollution. A statistical section was organized in our program to study the application of these data to our purposes.

Two Courses of Action

We pursued two main courses of action. First, studies were designed to measure the health status of a community to determine whether aberrations in health patterns were related to indexes of air pollution. These activities were largely either field investigations or "desk" statistical studies. Second, studies were designed to define the biological or health effects of single or multiple known or suspected constituents of air pollution. These were largely laboratory studies. Thus, the program was divided between epidemiology and laboratory investigations, with certain activities, such as function testing of lungs, falling into both.

For the statistical work we knew that large bodies of data were in the records of vital statistics units throughout the country. Some quick and some more detailed examinations of these data from the viewpoint of specific diseases were essential to see whether any "good leads" were hidden there. Mortality data provide good, solid quantitative figures, but the quality of such data is not as good. For this reason we also needed to examine morbidity records whose accuracy of diagnosis was likely to be of much better quality. The Health Insurance Plan of Greater New York, the Veterans Administration, the Bureau of Old-Age and Survivors Insurance, and others collect extensive morbidity information. While such mortality and morbidity data were more or less readily available, we found practically no records of air pollution levels to which we might relate them. We had either to develop some kind of index of air pollution that could be applicable to any community or to use the limited data from those few localities where some air pollution measurements had been made. It was decided to do both. Air pollution indexes were developed based upon populations, industry, and fuel consumption for all American metropolitan areas. Detailed, although limited, aerometric information is being used in intracity comparisons. The analyses of these measurements are in process.

Epidemiology of Air Pollution

In the program's general responsibility for defining health problems of communities as they may relate to air pollution, we are employing, insofar as possible, the methods of epidemiology. This method originally was developed and applied to deal with communicable disease. In epidemics, an identifiable disease is present in unusual numbers in a given population. It is a relatively simple matter to divide the community into those who do or do not have the disease. When appropriate information has been gathered to describe the differences between these groups, it then becomes possible to investigate how the disease agent was distributed and how it was propagated. The contribution of the external factors of the environment can be estimated and, in some cases, even defined. More recently, the general utility and applicability of the epidemiological method, with various modifications, has resulted in its broad use in the study of mental disorders, home accidents, automobile accidents, heart disease, and even population control.

An identifiable disease or condition is not always evident in these studies. Only recently research has identified a group of organisms called the orphan viruses because they were not known to be associated with a disease. Surveys have shown that many people carry antibodies for these same viruses. Further investigation revealed the disease (*15*).

Those who investigate effects of air pollution on health are in the position of having a large group of potential agents and no specific disease. We suspect that nonspecific effects of air pollution disease now are classed in the catchall of "degenerative disease," or constitute conditions assumed to occur "naturally" in the population. Such conditions would include chronic bronchitis, pulmonary emphysema, and cardiac deaths.

It was necessary to begin our attack upon a broad front and be ready to change direction as information was gained. The pattern of occurrence of chronic bronchitis and lung cancer, on the one hand, and the episodes in Donora and London, on the other, strongly suggested that there were acute effects producing immediate changes in function, even leading to death, and chronic effects demonstrable only after months or years of exposure, or developing long after exposure had ceased. The study of these two phenomena required different approaches with different methods of identifying and quantifying the effects.

Current Developments

Although there is enough evidence to suggest strongly that air pollution can cause many adverse health effects, reliable medical data are not common. Consequently, we have had to search for facts which could withstand careful scrutiny.

The most important known way in which air pollution influences health is that it irritates, and so may possibly damage, membranous surfaces of the body. Our investigations into the recorded acute air pollution episodes show that the primary effects were observed on the respiratory tract with secondary, indirect, effects on the heart. In the Los Angeles area, air pollution appears to have a primary effect upon the eye membranes. The respiratory tract and the eye are particularly susceptible for the obvious reason that they are in contact with the ambient air; and, therefore, these organ systems will receive special attention in this discussion. However, investigations are underway on other matters such as allergy, cancer, and infectious disease. In a field where few guidelines existed we had to create and formulate new techniques on how to measure and evaluate the culpability of air pollution components, how to simulate actual air pollution in test situations, how to measure lung airway resistance, how to employ animal experimental "epidemiology," and how to establish and use air pollution indexes for expressing relative air pollution levels, relative to such elusive factors as intensity, duration, and locale.

Testing of Lung Function

One thing we have needed is a lung function testing method suitable for screening large numbers of people. Through some of our own staff efforts and our support of research at Harvard University, there is now at least one type of testing machine that seems to be suitable for the purpose (*16*). It indirectly measures the airway resistance to expiration. At the Occupational Health Field Headquarters of the Public Health Service a group is complementing the work being done at Harvard. They are considering how to provide the equipment and personnel suitable for testing a large series of people in their own communities and to determine how such procedures should be applied.

In addition, research at the University of Pittsburgh (*17*) and at the University of Cincinnati (*18*) also is concerned with the effects upon lung function of low concentrations of potential irritants. The development of such methods and tests will play an important role in community health studies, such as the current one in Nashville, Tenn. (*19*). Used in conjunction with information about environmental influences within a community, this type of objective medical examination can add significantly to the usefulness and reliability of epidemiological investigations.

Epidemiological Evaluations

There is also the classic type of straightforward epidemiological investigation in the program. The first such study was a reevaluation of the health of the population of Donora, Pa. (*20*) in the light of the 1948 air pollution episode (*6*). Preliminary data indicate that Donora residents who were adversely affected

during the 1948 episode were more likely to have more illness later than were those who apparently were not affected (*20*).

The epidemiological survey of the Detroit-Windsor area, a joint venture by the Governments of Canada and the United States, was begun before 1955. From the data seen thus far, we have been able to deduce some methodological ideas (*21*).

In Nashville (*19*), mentioned above, we are evaluating health patterns in a community where air pollution, when it occurs, is primarily soft coal smoke. The Nashville study has four broad aspects: (*a*) a study of mortality by cause and frequency in relation to place and duration of residence; (*b*) a study from postmortem examinations of carbonaceous dust accumulations in the lungs, also in relation to place and duration of residence; (*c*) a household morbidity survey to find out about acute and chronic disease in relation to place and duration of residence, and in relation, of course, to current air pollution measurements; and (*d*) a study of the influence of measured air pollution upon cardiorespiratory disease patients, including a group with bronchial asthma.

Laboratory and Statistical Studies

Another important approach with bearing on our field of interest is the observation of the effects of airborne irritants upon animals. There often is a high correlation between the effects of an environmental factor upon animals and its effect upon humans.

There are three ways that animals may be used in such investigations. First, wild and domestic animals may be examined for the effects of naturally occurring pollution. The following are cited as two examples of the many reports demonstrating this approach. Informed that the health of chickens was adversely affected by air pollution in the Los Angeles area, we supported a field study of this phenomenon. Because the results were inconclusive, the experiment is now being repeated under well-controlled conditions. Research conducted at the University of Southern California has shown that both the fertility of mice and the survival rate of newborn mice are reduced by long-continued parental exposure to inhalation of low concentrations of synthetic air pollution of the Los Angeles type (*22*).

The second way is to expose the animals under experimental conditions to single pollutants or multiple pollutants whose composition is more or less known. Of two such experiments being carried out at Vanderbilt University (*23*) the first is to determine exactly where in the respiratory tract the common air pollutant, sulfur dioxide, impinges to cause its effect. The second is to observe one series of animals exposed over a lifetime to sulfur dioxide at known low concentrations and another series exposed to bituminous coal smoke.

A third way of using experimental animals is to establish colonies of different species and strains under controlled conditions, and let them live out their lives in typical, urban areas where they would be exposed to the same atmosphere as that breathed by the human inhabitants. Simultaneously, observations would be made of a group of control animals for which the air is appropriately cleaned to remove the pollutants. We are currently financing such a study at Wayne University (*24*).

In statistical studies, the work is divided broadly into a study of records of past mortality by cause and past morbidity by cause in relation to environmental factors, including, of course, air pollution. At the same time our statistical unit is looking into recent and current frequency of causes of death and the frequency of illness. In both instances efforts have been concentrated on those clinical entities which might be causally related to air pollution.

The first report to come from our statistical unit was Comparative Mortality Among 163 Metropolitan Areas of the United States—102 Causes of Death (*25*).

The morbidity data for the current retrospective studies were collected from the Veterans Administration records of veterans receiving disability pensions and from records of persons enrolled in the Health Insurance Plan of Greater New York. From such data we have been able to make a preliminary estimate of the possible biological significance of only a small portion. Certain respiratory tract diseases appear to be frequently associated with

intense urbanization and, by inference, probably with intense air pollution.

To study specific diseases and body reactions believed to be associated with air pollution, the nature of the irritant action must be considered. While ophthalmologists for many years have used irritant materials to stimulate healing of some types of eye ulcers, experimental animals exposed to sublethal levels of ozone (a respiratory tract irritant) have developed pulmonary fibrosis. In both of these reactions, we have examples of the tissue-stimulating properties of certain air pollution components which in one case were beneficial to the organism and in the other harmful.

Nitro-Olefins

Theoretical considerations based on available data have indicated that, under the peculiar circumstances that may at times exist in the air of the Los Angeles Basin, nitro-olefins may be produced in that atmosphere (*26*, *27*). However, the presence of these compounds has thus far not been demonstrated, probably because of their labile nature. Despite this failure, we considered it important to study the noxious properties of the nitro-olefins. In investigations at the University of Miami to test their toxicity, 18 nitro-olefin compounds have proved to be highly damaging to animals, however they are administered (*28*). With high dosages, deaths occurred so rapidly that only acute congestion of all vital organs was found. When the specific stress factors of high temperature and humidity were added, deaths of the animals occurred even earlier. This confirmed other toxicological studies reporting that biological stress produced in any one of a number of ways, including physical exertion, intensified the effect of poisons (*29*). So far this investigation at the University of Miami has also confirmed some of the earlier toxicological studies of nitro-olefins. Our investigator at the University of Miami is now ready to begin long-term exposures to nitro-olefins in low concentrations, simulating what, it is believed, may occur in community air.

An adventitious observation was made in the early phases of the study of the nitro-olefins. The researchers found that their own eyes were strongly irritated when they handled the compounds or even when they examined the animals that had been treated with them. They, therefore, tried the effect of low concentrations on themselves, and found that at levels of air concentrations theoretically approximating those in the air of the Los Angeles Basin they again experienced symptoms of eye irritation (*30*). These experiments on eye irritation were repeated by an investigator working in Los Angeles, using a different technique; again, it was observed that eye irritation occurred with exposures to low concentrations of the nitro-olefins.

Ozone, Sulfur Oxides, and Aerosols

Other laboratory studies on the mechanism of action of known irritants have been pursued at the Occupational Health Field Headquarters. Most important were those involving ozone, a gas that has its effect in the deeper parts of the lung. Experimental animals exposed to concentrations lower than those previously considered injurious suffered fatal pulmonary edema (*31*). Animals repeatedly exposed to quite low, safe-concentration levels developed resistance to later exposures known to be toxic (*32*). It is possible that such a protective mechanism may be of importance in protecting man's lungs from injury under natural conditions. Exploration of the nature of this protective action has not been successful, so far. The phenomenon may be related to the fact that, in the test tube at least, ozone reacts with protein to form a new specific antigenic agent (*33*). If such a reaction actually occurs between ozone and the surface proteins in the human respiratory tract, it may explain why some resistance to later exposure occurs.

There was one finding already mentioned in another context that was rather disturbing. When animals breathed sublethal concentrations of ozone daily over a period of months, they developed scarring in the lungs (*34*).

Investigators working on lung-function testing have found that oxides of sulfur (gases produced by burning sulfur contained in small but significant amounts in many fossil fuels) caused increased airway resistance (*8*). This, it was observed, occurs with air concentrations

found on occasion in some urban communities. It has also been demonstrated that a derivative of sulfur dioxide, sulfur trioxide, in equal concentration is even more irritating than the dioxide (*9*). Both gases are produced when fossil fuels are burned. Finally, it was shown that the effect of sulfur dioxide, and of certain other irritant gases, is markedly enhanced by the presence of a solid or liquid aerosol which by itself may not be irritating (*35*). Aerosols of this type, of course, also commonly appear in the air, especially in urban communities. Irritating gases are not all necessarily enhanced by aerosols; the nature of the aerosol itself also is of significance (*36*, *37*). We are currently studying the possible mechanisms of this phenomenon. The thesis that the effect of an irritant gas on the lung is enhanced by the simultaneous presence of an aerosol, however, is not accepted by all investigators, but the preponderence of medical opinion favors it. Since it is impossible to conceive of natural air without the presence of an aerosol of some type, the matter may indeed be significant.

Tissue, Cell, and Enzyme Studies

Necessarily our studies of the action of these noxious agents on the body began at the primary level. Knowing that the body's response to membrane irritation would evoke a series of protective mechanisms that would mask the effect, we determined that one of the better ways to study membrane irritation would be in isolated cells and cell groups. We are promoting such an activity at Baylor University. Using a mixture probably containing nitroolefins as one of the toxicants, data thus far show that such air pollution adversely affects muscle contraction and leucocyte metabolism in special preparations (*38*). This continuing work has as its ultimate purpose the elucidation of the effect of such air pollutants upon the enzyme systems that are modified to produce these end reactions.

In line with these explorations, we also employed the tissue culture technique which is relatively unexplored for toxicological studies. This technique is applied to the study of cell preparations, generally of human origin, for changes in growth, reproduction, and metabolism. An authority in the field of tissue culture studies at the University of Nebraska undertook the project for us. Using tissue cultures about which a great deal is known (fibroblasts, cancerous cervical epithelial cells, and liver cells), the investigator showed that low concentrations of sulfur dioxide stimulate cellular activity; high concentrations of the gas are lethal (*39*). The effects of sulfur dioxide, nitrogen dioxide, salts of these acid gases, gasoline, and ozone are under continuing investigation.

Work on the causes and nature of eye irritation has progressed slowly. Research in California has produced some significant findings and it is now generally agreed among authorities that although the eyes of susceptible persons in Los Angeles become irritated when certain air pollution constituent levels are high, there are no objective changes in the eyes (*40*). In addition, the occurrence of eye irritation under experimental conditions is statistically associated with the presence in the air of a group of chemicals that include the nitroolefins, as mentioned (*41*).

Explorations at the Occupational Health Field Headquarters show that another body system may be affected by irritation from air pollution. While exploring the mechanism involved in the development of pulmonary edema from ozone, previously described, it was shown that there was a simultaneous decrease of certain enzymes including alkaline phosphatase in the affected lung tissue (*42*). A search was then made for the alkaline phosphatase level in the circulating blood as possibly being a more convenient indicator of lung injury. Again, the enzyme level was found to be altered. In the present state of knowledge we have not been able to extrapolate these findings to the human. But, if we should succeed in doing so, we may be able to detect the degree of lung injury simply by testing a blood sample.

Cardiorespiratory Disease

At the University of Cincinnati, a detailed study of house-bound cardiorespiratory patients revealed that the diffusion of vital gases across the respiratory membranes into the blood was adversely affected by peak levels of urban air pollution in the Cincinnati area (*18*). This

may indeed be significant. At the University of Pittsburgh attempts are underway to test the effects of irritant gases upon the lung function of experimental animals in which cardiorespiratory disease has been previously produced artificially (*17*).

In this connection, a Los Angeles pulmonary physiologist, during periods of high air pollution, has placed patients with known lung disease at the Samaritan Hospital in a special room where only cleaned air is allowed to enter. After a period of a few hours, these people show appreciable improvement in the function of their lungs, and so in their well-being.

Chronic Bronchitis

In addition to studying the nature of air pollutants, their effects on specific organ systems, and the method of evaluating their effects upon community health, we hope to observe the relationship of air pollution to specific diseases. At the California State Department of Public Health, investigations currently are underway on the effect of air pollution on the natural history of the diffuse clinical syndrome called chronic bronchitis (*43*).

Studies of the natural history of chronic bronchitis have been strongly influenced by experience in Great Britain (*44*). Air pollution in the British Isles, associated primarily with weather and use of relatively low-grade solid fuel, has been a subject of concern for years. The episode in London in December 1952 (*5*), to which some 4,000 deaths were attributed, led to intensive epidemiological study. Some significant concepts stem from these current investigations.

For some time chronic bronchitis has held a high place among the causes of death in Great Britain (*44*), certainly much higher than in the United States. Without going into the attempts to consider all the possible variables that may explain the reasons for the difference, it is the consensus of enlightened British medical opinion that they do, in fact, have a high frequency of this disease and that its occurrence is very likely associated with air pollution. In contradistinction to our predicament, they have identified a disease entity which they can relate to their air pollution.

In effective liaison with the British investigators (*45*), we are currently trying to clarify the reasons for the difference between their frequency of chronic bronchitis and ours. Prevailing judgment among qualified people is that the frequency of this disease in the United States has been increasing in recent years.

Bronchial Asthma

Bronchial asthma has also received considerable attention, but the results of several investigations are far from conclusive. A study in Pasadena, Calif., under the auspices of the California State Department of Health, involved a preliminary survey of the occurrence of asthmatic attacks in relation to certain air pollution variables (*46*). The results indicated that there was a doubtful association between certain high air pollution levels and occurrence of asthmatic attacks. This finding was unexpected, to say the least. Observations among asthmatic patients in the Nashville study may be useful in clarifying the matter (*19*).

One of the newest aspects of the Air Pollution Medical Program is designed to investigate the size of the health problem caused by airborne allergens of vegetative and related origins. Seasonal hay fever, it is estimated, attacks between 1 and 2½ million people in the United States; bronchial asthma is said to affect from ½ to 3½ million persons. We are also obtaining data on the degree of disability that these illnesses cause and their cost to the Nation in loss of working ability.

The concept that simple chemical substances may combine with body proteins to form a new substance which may be allergenic has played an important role in establishing our concern with airborne allergens or allergen precursors. Such precursors, simple chemical substances, may well be present in polluted air. We discussed briefly how ozone combined with proteins experimentally resulted in the formation of a new antigenic agent (*28*). The significance of that observation is enhanced by a report received a few years ago from the U. S. Army in Japan (*47*). It appeared that in and about Yokohama some persons of the Army of Occupation and members of their families developed symptoms of bronchial asthma on certain days. This was deemed to be due to

material discharged into the air from industrial operations. From the data supplied, the specific causative mechanism is not known. It cannot be ignored, however, that reports of this nature are rare. A few reports in the medical literature (*48–50*) have directed attention to an allergic response to sulfur dioxide in air; however, it is perplexing that despite the fact that sulfur dioxide is present in the air of so many urban communities, the reports are so rare. If the matter were looked into thoroughly, more reports might be forthcoming.

Respiratory Infections

Although infectious diseases are primarily the concern, in the Public Health Service, of the National Institute of Allergy and Infectious Diseases and of the Communicable Disease Center, our program has been probing the possibility that air pollutants may modify airborne infectious agents; they also may be a factor when exposed human tissue becomes vulnerable to infection. Early studies by others have suggested that airborne chemicals destroy some airborne bacteria and might, therefore, actually reduce the possibility of air-transmitted disease of the respiratory tract. What was not considered in those early studies was the possibility that air pollutants would alter the body membrane surfaces to make them susceptible to infection. A few years ago, researchers at Johns Hopkins University studied the occurrence of pneumonia in mice exposed to coal smoke and then to pneumococci (*51*). The data indicated that pneumonia did not occur more frequently in mice exposed to smoke. However, another investigator, working at the Armour Research Foundation under Air Force auspices, exposed animals to low concentrations of ozone prior to their exposure to airborne organisms, and found that pneumonia infection was of greater frequency in the exposed animals (*52*). We are currently supporting research at the University of California on the influence of ozonized gasoline fumes upon the pneumonia rate in mice, exposed also to a virulent pneumococcus (*53*).

Lung Cancer

The increase in the frequency of lung cancer throughout the world in recent years has stimulated universal interest. The most recent data point to cigarette smoke as a major factor. Cigarette smoking notwithstanding, some statistical studies have shown that the cancer rate is higher in urban areas with high air pollution levels than in rural areas with low air pollution levels (*54*).

It is generally accepted that the air can carry materials capable of acting as carcinogens. Acceptance of this belief is based in great part on work done with experimental animals. Industrial experience has shown that the air inside certain factories contains some carcinogens. It is not difficult, then, to understand that many of these same agents are released into the community air. Furthermore, such well-known experimental carcinogens as benzpyrene have been found in community air (*55*), as well as in exhaust gas from the internal combustion engine (*56*, *57*). Research conducted at the University of California at Berkeley has shown that such polycyclic hydrocarbons can be produced by combustion of even some of the simplest straight-chain hydrocarbons under suitable conditions (*58*).

Some epidemiological investigations of the lung cancer problem in Great Britain show that there is an association between urban living, frequency of lung cancer, and the presence in the air of certain polycyclic hydrocarbons already known to be carcinogenic for experimental animals. Preliminary statistical evaluation of certain American mortality data in our own program bears out the association between air pollution and lung cancer.

Currently in progress, in the second year of a 3-year job, is an investigation of the carcinogenic potential of the particulate matter collected in nine cities in the United States (*59*). For these nine cities there are relatively wide variations in lung cancer frequency.

Mucosal Changes in Air Passages

In considering the relationship of cancer of the lung (or possibly of other organs) to air pollution, some people deny a possible causal connection between the two because, they say, the amount of potential carcinogenic material in the air is too small to be biologically active. Although we can see no immediate resolution to the controversy on this matter that would

be acceptable to all, we do keep in mind that there are airborne materials which may act as adjuvants, enhancing the potential injurious effect of even small amounts of such carcinogenic agents. One of these adjuvant factors is the ability of some airborne compounds to remove and thus activate the carcinogenic polycyclic compound sometimes found adhering to an inert particle (*60*). Similarly, airborne irritants, because they can slow the rate of removal of potential carcinogens from lung airways, enhance the contact time between the carcinogens and susceptible epithelium (*61*). Finally, airborne irritants cause some denudation of the surface layers of the lining of the air passages, thus exposing the deeper, more susceptible layers to contact with potential carcinogens (*62*, *63*).

Some investigators have shown that airborne irritants, at least those from cigarette smoke, cause appreciable changes in the epithelial lining of the airways of the human lungs (*64*). These investigators believe that the changes are directly related to cancerous developments. Regardless of whether or not cancer is so related, it is still important that such irritation causes severe changes in the anatomy and in the functional activity of the human air passages.

The air passages naturally get primary attention in considering the relation between air pollution and cancer; but other tissues and organs also may be affected. A preliminary review of our statistical studies on the frequency of cancer of the esophagus and stomach reveals an association similar to that between air pollution and lung cancer. This finding may be related to some experimental observations wherein it was noted that animals exposed to various dusts showed an appreciable amount of dust in the intestinal tract (*65*). This finding also fits, to a certain extent, the occurrence of symptoms of stomach irritation that occurred in some of the recorded episodes of acute air pollution (*6*).

In the closing months of 1958, it appears that we can say definitely that several important and significant findings have emerged from our research on air pollution and its effects on man. Although further study is required in virtually all fields, it is obvious that we have uncovered some very promising leads.

Future Emphasis

Analyzing the progress of our program, we have reached the conclusion that during the next few years we can achieve the best results by concentrating research on five principal subjects:

1. The relationship of air pollution to variation in the geographic distribution of death and disease, by cause.
2. The association between air pollution and the functions of the respiratory system.
3. The association between air pollution and cancer and cardiovascular diseases.
4. The effects of specific air pollutants, singly and in combination, in accordance with the varying chemical and physical properties.
5. The fringe areas of air pollution health research.

Locale and Disease

In regard to the first, we have long known that there are important mortality differences among nations, among continents and, to some extent among ethnic groups. Only recently, however, have we begun to appreciate the fact that there are important differences in mortality among cities and that most of the differences may occur even among different areas within a city. There is now no doubt that urbanization exerts an effect on health. The higher the degree of urbanization, the more prevalent do some diseases become. We know, of course, that among the many variables that may contribute to these differences are the following: climate, socioeconomic status, ethnic or genetic composition, food and water supplies, availability of medical care, and the pattern of customs in medical diagnosis. Despite these other variables, however, we are convinced that air pollution is without doubt an important factor among the many potential causes of geographic variations in mortality and morbidity.

We started late in the field of epidemiology because of conceptual and operational difficulties, the necessity to acquire basic statistical data, and the unfulfilled hope that our initial laboratory investigations would provide information and directions that might simplify the human studies. Much of the required demographic data has now been acquired.

What are the principal results thus far of our epidemiological studies, preliminary though they may be?

1. There is evidence that the people who were affected by the air pollution episode in Donora in 1948 have more sickness and a higher mortality rate later than their fellow townsmen of similar ages who were not affected.

2. There is evidence that death rates for certain causes increase directly with degrees of urbanization. Specifically, these causes include cancer of the lung, cancer of the stomach and esophagus, and arteriosclerotic heart disease and certain other heart conditions.

3. Short-term increases in air pollution exposures cause changes in the lung function of persons with chronic cardiorespiratory impairments, and this effect may be delayed for 3 or 4 days after exposure. Exposure to "filtered air" may relieve these symptoms.

Admittedly, these findings are not as definitive or comprehensive as we would like them to be. We feel, however, that they are sufficient to justify the more intensive studies now underway, and those planned for the next few years. This means that we shall continue direct operational support of statistical analysis of morbidity and mortality data, community surveys (such as those at Nashville and Donora), and morbidity investigations similar to those on chronic bronchitis and bronchial asthma in California.

Irritants and Breathing

The second major subject has to do with the effect of air pollution on man's breathing ability. The effects found thus far are essentially those resulting from irritation. The important findings include the following:

1. Irritant gases, such as sulfur dioxide and ozone in amounts similar to those in community air, have an adverse effect upon man's ability to breathe.

2. Continuous or repeated inhalation of ozone scars the lung tissues of animals.

3. Exposure to ozone disturbs the alkaline phosphatase levels in the body, which may indicate that other changes in enzyme and metabolic activity are occurring.

4. Irritant gases cause pulmonary edema and affect enzyme systems and other physiological mechanisms.

5. Inhalation of some irritant gases mixed with certain aerosols that are usually considered physiologically inert increases the adverse effects of the gases.

6. On the other hand, repeated inhalation of small quantities of ozone, and possibly other gases, appears to result in a significant degree of increased resistance to the acute effects of ensuing heavier exposures.

These findings have resulted in the main from experimental exposures of animals. Their extension to human beings poses obvious difficulties of varying degrees, and in a few instances, efforts of such extension have already begun. We expect to continue to support and carry out the significant leads by the following: (*a*) evaluating pulmonary function; (*b*) continuing research grants in basic and applied pulmonary physiology; (*c*) direct investigations of effects on animals exposed to irritant pollutants; and (*d*) research contracts to groups using basic and applied physiological techniques. Although the basic laboratory work involving biochemistry, enzymes, and tissue cultures has shown promise, the findings can not yet be extended to man. Because of the basic nature of this research it is best supported by the research grant mechanism.

Cancer and Heart Disease

Our third major subject includes lung cancer, and possibly other cancers, as well as cardiovascular diseases.

No one can deny that heart disease and cancer are two of the important diseases in this country today. Together, they account for 54 percent of all deaths (*66*). Lung cancer, although accounting for only 1.8 percent of deaths (*66*) has been increasing rapidly in recent decades. Statistical studies relate this increase in lung cancer to cigarette smoking. A similar association has been shown with heart disease mortality, which, although less startling in percentages, is even more impressive in total numbers of deaths. What light, if any, have studies on air pollution thrown upon the causes of these diseases?

1. There is evidence that death rates for certain causes of death increase markedly with urbanization. Specifically, these causes include cancer of the lung, trachea, and bronchus, cancer of the stomach and esophagus, arteriosclerotic heart disease, and myocardial degeneration. The increase of lung cancer with population density persists even when the degree of cigarette smoking is held constant (*54*).

2. Fragmentary evidence of the distribution of cancer mortality within cities appears to be at least partially related to the distribution of air pollution intensity.

3. Certain air pollutants found in our cities are known to be experimentally carcinogenic for animals. Chemical analysis has disclosed many other potential carcinogens in air; these may also be carried by particulate matter deep into the lung.

Admittedly, these findings taken together would justify devoting our entire resources to following them up. However, the total air pollution budget of the Public Health Service, slightly less than $4 million, with about $1.5 million available for health studies, has powerful allies in the current annual Public Health Service appropriation for heart research ($46 million), and for cancer ($75 million). Consequently, the air pollution program is directed to encouraging those with technical and financial resources to undertake epidemiological and laboratory studies on environmental stresses in the community in general, and on air pollution in particular. For example, cooperation with the National Cancer Institute was arranged to determine the carcinogenic potential of air pollution particulate samples collected from nine cities by the National Air Sampling Network. The protocol was developed jointly with the National Cancer Institute and the Air Pollution Engineering Program. The Air Pollution Medical Program paid part of the cost of the first year. The National Cancer Institute assumed the total cost for the second year.

Animal Studies

The fourth subject deals with the effects of different air pollutants. All our previous experience indicates that the chemical and physical nature of substances are important in determining their biological effects. We have not devoted much effort to studying the effects of specific substances, largely because our air sampling information indicates that, as an acute problem, the community levels found are too low, and that as a long-term problem it is not possible to isolate effects due to one substance from those due to others. We have, however, promoted research work on the effects of mixtures of pollutants and especially those that generally simulate the type of pollution in Los Angeles. Some of the significant leads that stem from those studies are the following:

1. Certain nitro-olefins believed on theoretical grounds to be present in Los Angeles air may be among the factors that irritate eyes. Synthetically prepared nitro-olefins have been found to be highly irritating and rapidly fatal to animals in acute exposures. At concentrations believed possibly extant in Los Angeles air at times, they cause eye irritation in man.

2. There is diminished oxygen uptake and decreased growth of micro-organisms exposed to simulated Los Angeles type of air pollution.

3. The fertility of experimental mice and the survival rate of newborn mice seem to be reduced by the artificial Los Angeles type of air pollution.

The Los Angeles area has made great strides in controlling its original sources of air pollution. The most important remaining uncontrolled source of pollution in Los Angeles is said to be the internal combustion engine. Because of special budgetary considerations we expect to be able to expend a large sum during the next fiscal year on the study of automobile exhaust gases and their toxicity. These studies will be based in part upon a research facility that will generate, monitor, and analyze various types of light-irradiated exhaust gases and will then feed them to exposure chambers designed to study the effects on vegetation, microorganisms, and small experimental animals.

Fringe Areas of Research

Our fifth subject, the fringe areas, includes those problems which appear to be of primary concern to researchers who are not in air pol-

lution work. One example is that of the inhalational allergies. This subject is divisible into two aspects. First, the familiar plant pollens, causing hay fever and similar reactions. Second, the question of whether or not chemical conditions in air can cause allergic reactions in some susceptible people.

Another example in this fringe area is the effects of air pollutants which reach the gastrointestinal tract. If our pilot studies of such questions indicate the serious possibility of important findings, we are prepared to follow through.

Long-Range Goals

We have described a blueprint for the near future. These are the things we are doing now or will be doing during the next 2 or 3 years. Medical research in air pollution from the long-range aspect, we believe, will be the following:

First, we think we shall some day return to the consideration of effects upon cells and tissues. Methods will eventually be developed whereby we will be able to extrapolate the observed effects to intact animals and to human beings. Controlled exposures of isolated cells and of tissues will then be a screening device.

Second, we expect that we shall develop realistic maximal permissible concentrations, based on reliable studies and adaptable to the industrial and meteorological conditions of a given city.

Third, we think that the public health engineer and the public health physician will participate much more in studies of community ecology, in planning and zoning programs, and the like. The advantages and disadvantages of alternative proposals may be evaluated, not only in aesthetic and economic terms, but with reference to present and future effects upon the health of the community.

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New Laws Affecting Health Activities

The following legislation affecting health was passed by the 85th Congress during its second session:

P. L. 85–544 authorizes the Surgeon General of the Public Health Service, for fiscal years 1959 and 1960, to make training grants totaling $1 million annually to schools of public health (H. R. 11414).

P. L. 85–664 extends the Hospital Survey and Construction Act for 5 years (H. R. 12628).

P. L. 85–589 amends the Hospital Survey and Construction Act to permit applicants to obtain loans in place of grants for the construction of hospitals and related facilities (H. R. 12694).

P. L. 85–777 extends for 3 years the Health Research Facilities Act, which authorizes $30 million annually for research construction grants (H. R. 12876).

P. L. 85–840, among other Social Security Act amendments, increases by $5 million each the annual appropriation authorizations for three State grant programs administered by the Children's Bureau: maternal and child health, crippled children, and child welfare (H. R. 13549).

P. L. 85–908 provides for White House Conference on Aging in 1961 and authorizes Federal financial aid for preparatory State conferences (H. R. 9822).

P. L. 85–926 provides for grants of up to $1 million to institutions of higher learning to expand educational opportunities for mentally retarded children through teacher training and other programs (H. R. 13840).

P. L. 85–929 amends the Food, Drug, and Cosmetic Act to prohibit chemical additives in food that have not been pretested for safety (H. R. 13254).