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Late Effects of Air Pollution with Special Reference to Lung Cancer

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The Departments of Environmental Hygiene of the National Swedish Environment Protection Board and of the Karolinska Institute have prepared an extensive review on health effects of air pollution, to be used by the Swedish Parliamentary Committee on Energy and the Environment. This report forms the basis for one part of the review, that on late effects. Much of the work on the review, is the result of a team effort involving researchers from numerous organizations.

Introduction

The present report consists of two main parts. One concerns more elementary concepts of relevance for the discussion of late effects in general and the other deals with late effects in relation to air pollution in specific. In the first part, no specific references are given, but the reader is referred to the general references (*1–16*) appearing at the beginning of the reference list.

General Concepts of Late Effects

Cancer

Certain physical, biological and chemical agents have been shown to be capable of inducing cancer. In the following, a number of phenomena associated with the chemical induction of cancer will be reviewed.

From a biological standpoint, chemical induction of cancer can be divided into at least two phenomena, namely initiation and promotion. Two substances which, when applied alone on the skin of mice, do not cause any tumors, can, when applied one after the other, induce a high frequency of tumors. The initiator causes irreversible or in any case very slowly reversible changes in the cell. The promotor, or cocarcinogen, enhances the altered cell's ability to multiply. The promotor is often not carcinogenic at all in itself, not even in very high doses. On the other hand, many carcinogenic substances can serve as initiators in low doses and as both initiators and promotors in high doses. Such substances are termed complete carcinogens.

In contrast to initiation, promotion is a reversible effect. A promotor commonly used in experimental cancer research, especially in studies of the action of skin carcinogens, is croton oil or one of its active components. Sulfur and certain sulfur compounds (possibly sulfur dioxide), aldehydes, phenols, and hydrocarbons (such as dodecane) can serve as promotors. In practice, mixtures of substances, e.g., cigarette smoke, gasoline, and ambient air pollution, contain initiators, as well as promotors and complete carcinogens.

Synergism and antagonism are of importance in the development of cancer. For example, certain polycyclic hydrocarbons which are not carcinogenic at all or are very weak carcinogens have been shown to increase the carcinogenic effect of carcinogenic agents (e.g., cigarette smoke and asbestos). The opposite effect is also known.

The latency period for the development of cancer in humans after exposure to a carcinogenic substance can amount to years or decades.

Chemical carcinogens can also be divided into direct or indirect carcinogens. Direct carcinogens are substances which induce cancer without biotransformation (e.g., certain metal compounds and alkylating agents such as mustard gas and bischloromethyl ether). However, most organic carcinogenic substances have an indirect mode of action, i.e., they are metabolically converted into an active product. Examples of such substances are polycyclic hydrocarbons, such as benzo[a]pyrene

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and nitrosamines. These groups of substances are present among ambient air pollutants.

Different enzymes participate in biotransformation. Many of the enzymes involved in the biotransformation of carcinogenic substances initially have low activity in the body. After the first exposure to the substance, enzyme induction takes place and upon subsequent exposures, a more effective biotransformation may occur. Aryl hydrocarbon hydroxylase (AHH) is an inducible enzyme of great importance for the biotransformation of polycyclic hydrocarbons. The readiness to induce AHH is genetically determined in humans as well as in certain animals. It has been suggested that the risk for bronchial cancer in humans is associated with a high inducibility of AHH in leukocytes.

Different factors are known to influence the site of tumor development, for example the concentration of the carcinogenic substance and the mode of administration. Methylnitrosurea induces brain tumors in rats at low single doses, while tumors in a number of different organs are observed after high single doses. Methyl nitrosamine, which operates by the same proximal carcinogen, induces kidney tumors by single administration of the compound and liver tumors after fractionated exposure or prolonged feeding. Local application of polycyclic hydrocarbons on the skin of mice and rats gives rise to local skin tumors, while subcutaneous injection brings about both local tumors and lung tumors in the mice and intravenous injection breast cancer in rats. Inhalation experiments using only polycyclic hydrocarbons in rodents have not as a rule increased the frequency of tumors in any organ. If, instead, these polycyclic hydrocarbons are administered directly into the trachea or the lung in solid form or absorbed onto particles so that the substances remain for a longer period of time in the respiratory tract, cancer may be induced.

In the context of radiation protection, it is generally assumed that there is a proportionality between radiation dose and response. As regards chemical carcinogenesis the dose–response relationship is often incompletely known, and data on humans do not exist. However, available experiments indicate that there might be a proportionality also for chemical carcinogenesis.

A dose–response relationship can be influenced by many factors. A high vitamin A content in the diet can decrease the cancer response, while a high fat intake can increase this response. Age can be crucial for the frequency of tumors as well as for their latency period. Newborn and young animals are usually several times more susceptible than adult animals. Moreover, carcinogenic substances can pass from mother to fetus and cause cancer in the offspring, both in humans and experimental animals.

Mutations

Mutations can be of several types and in order to be defined as true mutations, they must fulfill two criteria. (1) The number or structure of chromosomes must be altered (chromosome aberrations) or the base sequence, i.e., the sequence of the building blocks in DNA which determine the genetic code, must be altered in a single trait (gene or point mutation). The borderline between these two types of mutations is not strict. (2) The change is so stable that it can be transferred from one cell generation to the next.

Chromosome aberrations can be of several types, i.e., excess or lack of entire chromosomes or parts thereof (unbalanced chromosome aberrations) and exchange of chromosome material within the cell (balanced chromosome aberrations).

Unbalanced chromosome aberrations most often cause a series of adverse effects. Even the smallest chromosome aberration which can be observed in the microscope probably encompasses about a thousand genes. On the other hand, balanced chromosome aberrations generally do not lead to effects, negative or positive. The so-called Philadelphia chromosome which is found in chronic myeloid leukemia might, however, constitute an important exception to this rule.

Point mutations can also be of different types, i.e., exchange, loss or excess of bases. A large number of test systems have been devised by which the number of point mutations can be measured. No such *in vivo* system yet exists for practical application to humans, while there are several mutation systems for human cells in culture.

A directly mutagenic substance must come into contact with the DNA which is well-shielded behind cell and nuclear membranes. Moreover, the substance must react with DNA so that a mutation arises. The risk of mutation therefore depends on the ability of the individual to absorb, metabolize and excrete the mutagenic substance.

A point mutation can cause a change in the structure as well as the function of a protein. There are many examples of structurally abnormal proteins which have totally or partially lost their normal function. Point mutations can also give rise to changes in the nonfunctional parts of a protein molecule and have then no obvious practical consequences (silent mutation).

Mutations which occur in gametes can lead to early fetal death or a genetic disease in the offspring. In the latter case, there is a risk that the

disease will be transmitted to future generations. Dominant point mutations and unbalanced chromosome aberrations are manifested directly in the offspring while recessive point mutations and balanced chromosome aberrations as a rule do not make themselves known until later generations. All individuals are assumed to be carriers of 2-8 so-called recessive lethals. It is also probable that every human gamete normally contains several new mutations but that these are most often silent. About 2–5% of all gametes might have a chromosome aberration. The majority of these will if they become fertilized lead to spontaneous abortions (25–50% of which demonstrate chromosome aberrations) but about 0.5% of all newborn babies have some form of malformation, mental retardation or developmental disorder caused by a chromosome aberration.

The chance that an individual with a genetic disease caused by a mutation will survive and transmit the mutation to future generations depends in many instances on the environment. This chance is greater today than previously since a number of genetic diseases can be treated successfully.

Mutations have occurred throughout history and in all living organisms. The cause of so-called spontaneous mutations is generally not known, but they are probably caused by endogenous events as well as by environmental factors. A large number of the spontaneous mutations are eliminated because of their deleterious effects. A few will remain.

Teratogenic Effects

Fetotoxic effects in the broadest sense refer to structural and functional deviations from normal development. Such deviations can be due to changes which occur before or after conception. The preconceptional changes mainly consist of mutations in gametes. Since these are treated separately, the concept teratogenic effects may in this context be confined to those deviations which appear after conception. The mechanisms behind these latter deviations can be of several types; sometimes they consist of mutations in one or more cells.

A large number of physical, chemical, and biological agents are known to be teratogenic. The effect of such agents depends to a large extent upon the stage during the fetal development at which exposure takes place. Exposure at a very early stage generally leads to fetal death. If it takes place during organogenesis, malformations might occur, and if it takes place after the organ has been formed, the growth of the organ may be affected.

Relationship between Mutagenesis, Carcinogenesis, and Teratogenesis

Several observations indicate that there are similarities in the origin of mutations and cancer and in some cases also of malformations.

Mutations which occur in somatic cells can cause cell death and probably also cancer, although the mechanism by which a normal cell is transformed into a cancer cell has not yet been clarified. There is also evidence that cancer as a rule has a clonal origin, i.e., it is composed of cells belonging to one or more clones.

There is no direct evidence that chemically induced cancer always is preceded by a change in DNA. The good correlation between the carcinogenic and mutagenic effect of some chemicals suggests that there might be a common initial change. All carcinogens are probably also mutagenic, even though complete experimental proof is not on hand for all such substances. However, it is still an open question whether all mutagenic substances are also carcinogenic.

Genetic damage can also be obtained, e.g., by disturbing DNA synthesis and repair.

Teratogenic effects are often relatively unspecific in the sense that they can be obtained by any factor which causes inhibition of cell growth or cell death. Each organ develops during a certain time period and is then susceptible to teratogenic agents. These time periods vary from one organ to another. In humans, the most susceptible period falls during the first months of pregnancy.

Many carcinogenic and mutagenic substances also have teratogenic effects. Some chemicals which have a teratogenic effect in a certain organ during a certain stage of an experimental animal's fetal development will cause tumors in the same organ during a later stage of pregnancy.

Late Effects of Air Pollution

In this part, late effects of air pollutants are dealt with. Epidemiological as well as experimental evidence from animal studies are reviewed. A systematic treatise of these effects and their associations with air pollution has not been made. Instead the objective has been to concentrate on a few subject areas. Thus the review of epidemiological data is with a few exceptions limited to lung cancer. The discussion of animal data deals partly with evidence from inhalation studies of air pollutants and partly with studies which, despite other administration routes, have been deemed of importance for the understanding of fundamental, particularly quan-

titative, aspects of chemical carcinogenesis.

There is ample evidence that tobacco smoking as well as occupational exposure to carcinogenic substances may give rise to cancer in humans (*17–20*). Substances which have proven to be carcinogenic in occupational exposure include arsenic, asbestos, chromium, nickel, aromatic amines, coal tar, soot, bischloromethyl ether, and vinyl chloride. Furthermore, there are also possibilities for exposure to carcinogenic substances through, e.g., ambient air pollution, food, and water. It has been estimated that 80-90% of all cancers are related directly or indirectly with the environment (*21*). The cancer incidence is steadily increasing in different countries. In Sweden, according to Einhorn and Larsson (*22*), based on the national cancer registry, the number of registered cases of cancer increased during the period 1958 to 1971 from 19,000 to 29,000 per year. They estimated that at a maximum half of this increase could be explained by changes in age distribution and improvements in diagnosis and registration. There is no explanation for the remaining increase during the period.

The most pronounced association with lung cancer has been shown for cigarette smoking which alone or in interaction with other factors causes the major part of all lung cancer. As both tobacco smoke and air pollutants from fossil fuels are combustion products of organic substances, there are many similarities between those types of air pollutants. There is reason to assume that a carcinogenic effect of air pollutants will show up first of all in the lung.

Epidemiological studies have shown increased incidence of lung cancer in urban areas as compared to rural, but this is also true of several other forms of cancer. A recent study in Sweden, where a cohort has been followed for 10 years (*19*), shows an excess urban incidence for cancer of the pancreas, cancer of the bladder, and cancer of the cervix uteri independently of smoking habits. Although these findings deserve attention and should be subject to further research in regard to the possible pathogenesis, data available at present do not make it possible to come up with anything better than a speculative epidemiological evaluation of the role of the general air pollution for the development of forms of cancer other than lung cancer. Therefore, the epidemiological data to be discussed will with few exceptions be limited to lung cancer. The incidence of lung cancer has generally been related to the exposure to certain substances formed or dispersed in the combustion of fossil fuels (polycyclic hydrocarbons and certain metals). It must be pointed out that these substances as a rule can only be considered as indicators of degree of pollution and not necessarily as single causative agents.

As for mutagenic or teratogenic effects, there are simply no epidemiological data available which would make it possible to evaluate a possible association between air pollution and such effects.

Studies on laboratory animals have shown that air pollutants may be carcinogenic. Application of condensates of the particulate fraction in air pollution to the skin of laboratory animals, for example, has given rise to tumors. Particles from a heavily industrialized city like Birmingham, Alabama (U.S.A.), were considerably more carcinogenic than particles from Los Angeles (*23*). A number of potent carcinogenic polycyclic organic substances have been isolated from the particulate fraction. Reviews of carcinogenic effects of such substances have been given by NAS (*23*), IARC (*24*), and EPA (*25*).

A very limited number of experimental inhalation studies are available. Whenever deemed to be of importance for the purpose of the present study they are reviewed. However, they elucidate dose-response relationships only to a very limited extent. Therefore, some data are included from studies where carcinogenic substances are administered via other routes. In the discussion of results from animal studies, extrapolations from high or low doses as well as from animals to humans are taken up.

In Table 1 a number of substances proven or suspected to give rise to late effects in humans or experimental animals are listed.

Lung Cancer and Ambient Air Pollution

Lung cancer has shown a pronounced increase during the last decades, first in men, and now in women. A five times greater incidence is often observed when recent years are compared with the 1940's. The increase in lung cancer in England, U.S.A. and Sweden is shown in Figure 1. The increase is generally considered to depend primarily upon tobacco smoking, chiefly cigarette smoking (*17–19, 54, 55*). An association between lung cancer and smoking has also been observed in smoking monozygotic and dizygotic twins compared with their nonsmoking partners (*56*). The causality of the association between smoking and lung cancer is evident.

The magnitude of the increased risk for lung cancer imposed by cigarette smoking can be taken from several reports and has recently been reviewed (*57*). (Fig. 2). On the basis of Swedish data (*19*) an average male smoker of 1–7 cigarettes a day runs a relative risk of about 2.5 compared to a nonsmoker. The corresponding relative risk for smokers of 8–15 cigarettes a day is about 7, and for smokers of 16 cigarettes or more a day about 11. These relative risks are age adjusted and refer to a

Table 1. Schematic survey of substances in fossil fuels with documented or suspected late effects.

Substance type	Examples of substances	Effect[a]			Source	References
		Carcinogenic	Mutagenic	Teratogenic		
Cyclic hydrocarbons	Benzene	+ a h			Gasoline	(26)
Unsaturated aliphatic hydrocarbons	Ethene		(+)		Oil, gasoline, air pollution	(27)
Halogenated hydrocarbons	Ethylene dichloride[b]		+		Gasoline, air	(28, 29)
	Ethylene dibromide[b]	+ a	+		pollution	(28, 30)
	Methyl chloride		(+)		Combustion of lignin containing materials (plants, wood, peat, lignite)	(28)
Aromatic amines	β-Naphthylamine	+ a h			Coal gas	(31)
	α-Naphthylamine	+ a			Coal gas	(31)
Polycyclic hydrocarbons	Benzo[a]pyrene	+ a h	+	+	General air	(32–34)
	Dibenz[a,h]anthracene	+ a h	+		pollution,	(32, 33)
	Dibenz[a,h]pyrene	+ a h	+		mineral oil, tar, food	(32, 33)
	Acridines and others	+ a				(32)
Aldehydes	Formaldehyde		+		General air	(35)
	Acrolein		+		pollution	(36, 37)
Nitrosamines or substances which form nitrosamines	Dimethylnitrosamine from NO_x	+ a	+		General air pollution	(38, 39)
	Methyl nitrite[c] amines				Many sources, little investigated	
Nitroolefins		+ a			From NO_2 and unsaturated hydrocarbons, air pollution	(40)
Metals and metal compounds	Arsenic	+ h		+ a	Exhaust fumes	(24)
	Nickel	+ a h		+ a	from combus-	(24)
	Cobalt	+ a			tion of coal	(41)
	Chromium	+ a h		+ a	and others	(24)
	Beryllium	+ a		+ a	"	(38)
	Cadmium	(+?) h			"	(24)
	Manganese		+			(42, 43)
	Vanadium		(+?)		Coal, oil	
	Lead alkyls		+		Coal, oil, gasoline	(44)
Radioactive material	^{226}Ra	+ a h	+		Fossil fuels	(45)
	^{228}Ra	+ a h	+			
O_3, peroxides and substances which form peroxides	Ozone	+? a	+		General air pollution	(46) (47)
	Dihydroxydimethylperoxide		+		General air pollution	(48)

[a]a indicates that the effect has been established by animal experimentation; h indicates it has been observed in humans.
[b]Gives rise to vinyl chloride (and vinyl bromide, respectively), which are mutagenic and carcinogenic in rodents and humans.
[c]Methyl nitrite (49, 50) and methyl chloride (51) have been shown to be components of tobacco smoke and should be emitted generally during combustion. Methyl nitrite, which is formed from the reaction between methanol and NO_x, should have a nitrosating effect throughout a wider pH range than does nitrite and therewith is a likely source of nitrosamines. Methyl chloride is alkylating and, based on data on methyl iodide (52), must be considered to be carcinogenic and mutagenic.

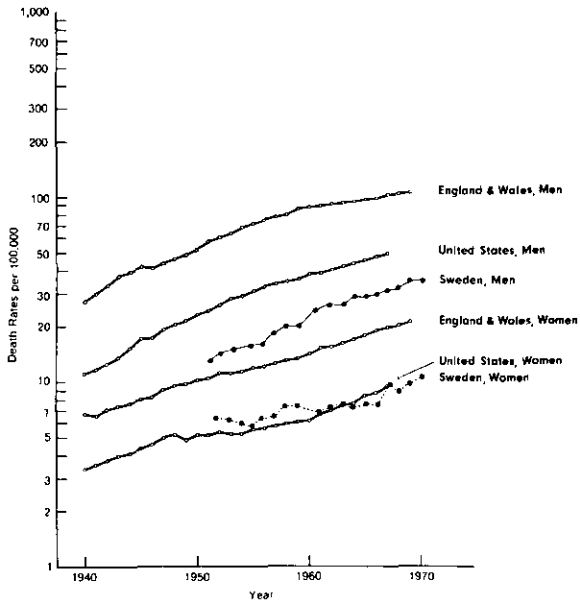

FIGURE 1. Comparison of crude death rates for malignant disease of the respiratory system (ISC 160-164) in United States, England, Wales and Sweden for men and women of all ages. No standardization for age. From Higgins (*53*) except for Swedish data. The Swedish figures for 1952–1957 cover ISC 160–165. The difference can amount to a maximum of a few percent, judging from the findings of recent years.

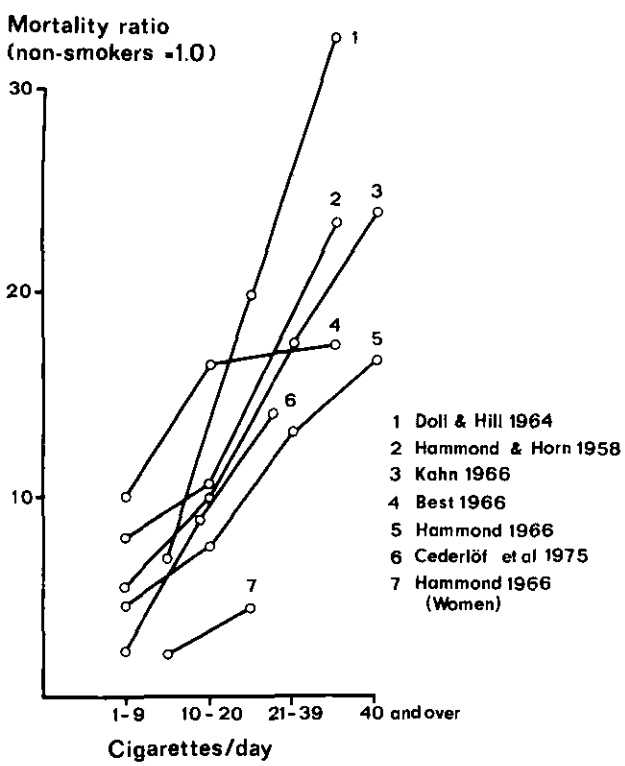

FIGURE 2. Risk ratios for cigarette smokers over nonsmokers in different studies (*57*).

population group with an age range from 16–69 years. Assuming linearity and a male population, where 50% were and had long been 10-cigarette-a-day smokers, roughly three-fourths of all lung cancer cases, or about 285 per 10^6 person-years, could be ascribed to the smoking alone or, quite possibly, to smoking in interaction with other substances. Corresponding calculations based on 20 cigarettes a day would explain 85% of the lung cancer cases. These calculations should be looked upon as rough estimates giving an indication of the clearly dominating role of smoking for the development of lung cancer.

Not only smokers are exposed to smoke from cigarettes. A large number of nonsmokers may daily participate in "passive smoking," when they take part in meetings in rooms with insufficient ventilation, or in gatherings at restaurants or private homes. This problem was discussed (*58*) at a workshop on Environmental Tobacco Smoke Effects on the Nonsmoker.

It was estimated that a nonsmoker who spends 5 hr daily in poorly ventilated rooms will be exposed to about 2.5–5 mg particulate matter from cigarette smoke. It can also be estimated that smoking one single cigarette will result in an exposure of 15–25 mg for the smoker.

A large number of investigations have been carried out to study the association between ambient air pollution and lung cancer. Several of those, all showing an increased incidence of lung cancer in urban areas compared with rural areas, have been reviewed (*59*). The association of lung cancer incidence to urbanization is evident from the Swedish Cancer Registry (Fig. 3). In comparing the incidence of lung cancer in urban as against rural areas it must be borne in mind that urban populations differ in many respects from rural populations (*19, 62*). For example, there are not only proportionally more smokers but also more heavy smokers residing in cities (Table 2).

Considering the fundamental importance of the smoking habit, investigations of the dose–response relationship between air pollution and lung cancer are difficult to evaluate unless the effect of smoking is carefully controlled. It should here be pointed out that standardization only for the current amount of smoking may not be enough as differences in exposure time may be of paramount importance. Studies on nonsmokers only might be indicative but hardly conclusive as air pollution might act more severely in interaction with smoking.

Other respects in which rural and urban dwellers might differ are occupation and the probability of becoming afflicted by contagious diseases, factors which may be of importance for lung cancer. They may also differ as to mobility, genetic composition,

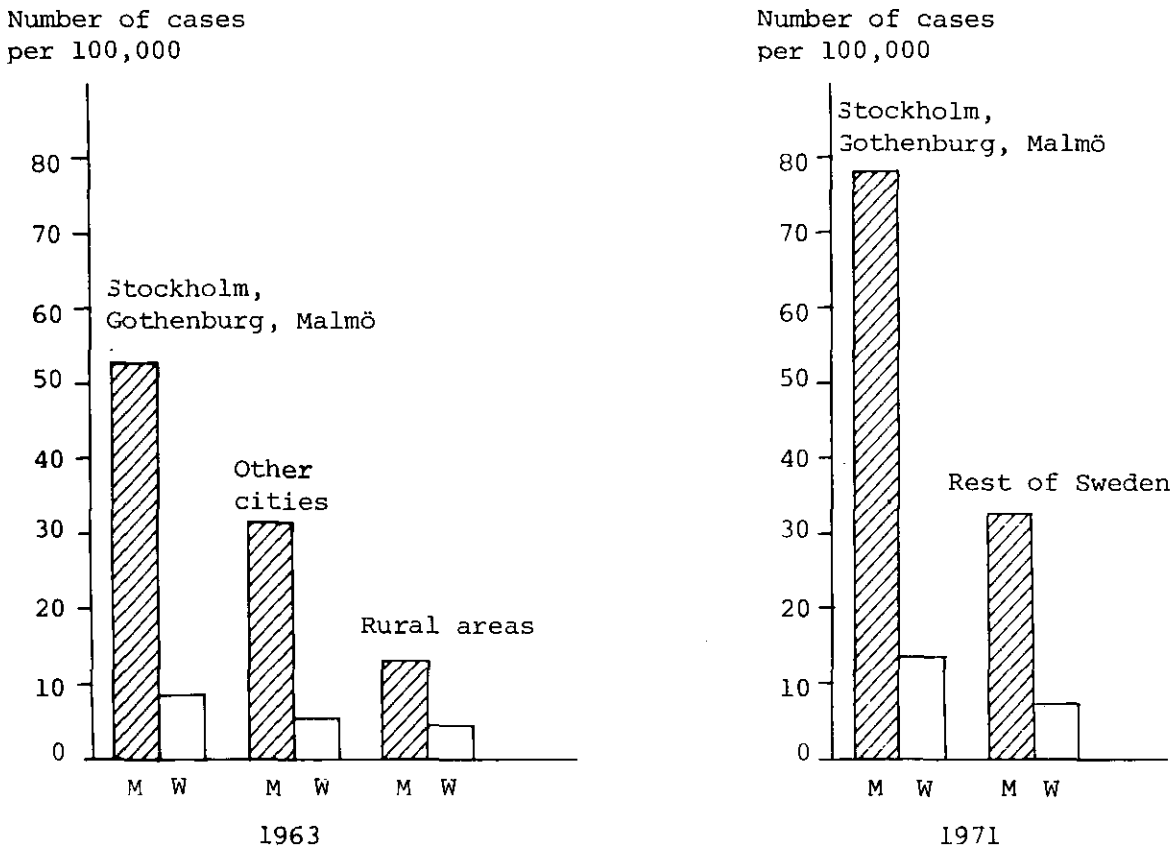

FIGURE 3. Age-adjusted incidence rate of lung cancer in 1963 and 1971, distributed by sex and place of residence. Data from the Swedish Cancer Registry (*60, 61*).

Table 2. Distribution into different smoking categories of males aged 18–69 living in rural areas, towns, and the metropolitan areas Stockholm, Gothenburg, and Malmö.[a]

	Rural areas	Towns	Stockholm Gothenburg, and Malmö
No. of cases	8207	7746	5173
Smoking history			
Never smoked, %	38	27	22
All current smokers, %	53	63	66
All cigarette smokers, %	28	40	50
Cigarettes only smokers, %	14	19	28
≥ 16 cgt/day	2	5	10
8-15 cgt/day	4	7	11
1-7 cgt/day	7	7	7

[a]Data of Cederlöf et al. (*19*).

socio-economic conditions and degree of crowding.

For an evaluation of the association between air pollution and lung cancer, one may first turn to prospective studies. In these, a cohort of individuals is followed for several years. Information on their smoking habits, occupation, and place of residence is gathered at the start. Only a few such studies exist, none of which provides detailed information on a sufficient number of relevant variables. A relatively large number of retrospective studies have been carried out. Smoking habits and place of residence have been compared in patients with lung cancer and control groups. Retrospective studies encounter difficulties in developing properly comparable groups of subjects. In addition, there are some studies on migrant population groups, and a few regression studies.

According to findings on the association between cigarette smoking and lung cancer, the disease has a latency period that may average 3-5 decades. There is no reason to believe that the latency period for lung cancer caused by air pollutants should be shorter. Difficulties in evaluating possible associations between air pollutants and lung cancer thus will arise if there has been migration from one place to another.

No studies yet published take into account all of the factors of potential importance for the development of lung cancer. Attempts to relate lung cancer directly to air pollutants, and even more so to

specific air pollutants, must therefore be somewhat uncertain. At any rate, it seems obvious that general air pollution is proportionately a small factor for lung cancer compared to tobacco smoking (*17, 53–55, 63*). Even so, NAS (*23*), based to a great extent on evaluations by Carnow and Meier (*59*), is of the opinion that air pollution can contribute to 10–20% of the lung cancer incidence in heavily polluted urban areas. Quantitative aspects of this question will be discussed in a later section.

Prospective Studies. Hammond (*64*) presents a follow-up of his extensive work from 1959 in which more than one million male and female volunteers had been followed. The main objective was to look at the health effects of smoking. His data concerning the association between urbanization and lung cancer cover a 6-yr period and are limited to men who had been residing at the same place for at least 10 yr at the beginning of the investigation. Table 3 shows the observed and the expected number of lung cancer deaths after standardization for age and smoking habits. A separation is also made between persons having and not having an occupation where exposure to dust, fumes, gases, or x-rays may have occurred. If place of residence is not considered, the relative lung cancer mortality of men with occupational exposure to dust etc. was 1.09, as opposed to 0.96 for men without such exposure. In the large metropolitan areas, corresponding values were 1.23 and 0.98, respectively. Men occupationally exposed to dust and the like and living in urban areas with high or intermediate levels of benzene soluble particles show a ratio of 1.33–1.35 compared to 1.13 in cities with low exposure to such substances. Farmers show a ratio of only 0.81. Persons who are not occupationally exposed to dust or fumes show substantially smaller differences, if indeed any can be observed at all. However, farmers show a low ratio here as well, 0.76.

Another prospective study is one on a Swedish series by Cederlöf et al. (*19*). This study is built upon a 10-yr follow-up of a stratified probability sample covering about 55,000 persons, nearly equally divided between men and women, all of whom were between 18 and 69 years of age in 1963. Information on smoking habits, place of residence,

Table 3. Observed and expected number of lung cancer deaths by place of residence and by occupational exposure to dust, fumes, gases or x-rays, adjusted for age and for smoking habits, confined to men who had lived in same neighborhood for last 10+ yr.[a]

	Occupationally exposed to dust, fumes, etc.			Not occupationally exposed to dust, fumes, etc.		
Place of residence[b]	Observed no.	Expected no.	Ratio	Observed no.	Expected no.	Ratio
Total, all male subjects	576	530.5	1.09	934	979.7	0.96
Metropolitan area, pop. > 1,000,000	165	134.1	1.23	281	285.7	0.98
City	92	69.1	1.33	168	158.3	1.06
Town or rural	73	65.0	1.12	113	127.4	0.89
Metropolitan area, pop. < 1,000,000	166	145.4	1.14	271	280.5	0.97
City	92	83.3	1.10	170	184.0	0.92
Town or rural	74	62.1	1.19	101	96.5	1.05
Nonmetropolitan area	245	251.0	0.98	382	413.5	0.92
Town	102	104.9	0.97	200	199.1	1.00
Rural	143	146.1	0.98	182	214.4	0.85
Los Angeles, Riverside, and Orange Counties, Calif.	30	21.9	1.37	38	39.6	0.96
Rural (farms)	63	77.6	0.81	71	92.9	0.76
No. of cities						
8, High particulates (130-180 $\mu g/m^3$)	45	32.9	1.37	66	73.9	0.89
11, Moderate particulates (100-129 $\mu g/m^3$)	21	18.8	1.12	39	49.5	0.79
14, Low particulates (35-99 $\mu g/m^3$)	48	37.4	1.28	110	100.1	1.10
9, High benzene-solubles (8.5-15.0 $\mu g/m^3$)	28	21.0	1.33	52	51.5	1.01
10, Moderate benzene-solubles (6.5-7.9 $\mu g/m^3$)	44	32.7	1.35	65	75.1	0.87
12, Low benzene-solubles (3.4-6.3 $\mu g/m^3$)	33	29.2	1.13	76	81.8	0.93

[a]Data of Hammond (*64*).

[b]The term "metropolitan" has been defined as an area (county) with at least 1 city of > 50,000 inhabitants; "town" means a place with a population between 2,500 and 49,999 persons; "rural" refers to an area with < 2,500 persons. The word "city" is used for cities with at least 50,000 inhabitants.

and income was obtained via a questionnaire survey in 1963. Data on mortality and cause of death were taken from the registry of the Central Bureau of Statistics. The information on smoking is detailed, while residence is classified crudely into three groups depending upon whether the respondents at the beginning of the investigation lived in one of the three cities Stockholm, Gothenburg, or Malmö, in smaller towns or in rural areas. The role of urbanization is seen in Table 4. In nonsmokers the number of lung cancer cases is very small, but no evidence of an urbanization effect is seen. Among smokers an association between lung cancer and urbanization is observed. Lung cancer thus is more common among cigarette smoking men residing in the large cities (Stockholm, Gothenburg, or Malmö) compared to men residing in towns, which in turn had more lung cancer than the men in the rural areas. This trend is statistically significant for the groups "all cigarette smokers" and "cigarette only smokers."

Retrospective Studies. Lung cancer patients' smoking habits and place of residence have been studied in a number of retrospective investigations; comparisons have been made with various samples from a normal population. Extensive studies of this nature have been carried out in the U.S.A. (*65, 66*) as well as in Japan (*67*).

Haenszel's (*65, 66*) investigations covered a sample of 10% of the total lung cancer deaths in 1958–1959 in the U.S. For purposes of comparison, a representative sample covering about 25,000 men and 35,000 women over 35 years of age was studied. Table 5 presents the Standard Mortality Ratio for men and women and for different categories of smokers. It is seen that for both men and women there is an excess mortality associated with urbanization. This can be observed among smokers as well as among nonsmokers. The effect of smoking is clearly the most important cause of lung cancer in this study, just as in others in which it has been examined.

Hitosugi (*67*) used a similar technique. He performed a questionnaire survey to find out smoking habits and place of residence of lung cancer patients residing in three areas having differing levels of air pollution. Hitosugi found a clear association between smoking and lung cancer, but he also found an association between levels of air pollution and lung cancer in male smokers but not in male nonsmokers. The picture is unclear for women. The results are given in Table 6 which shows the frequency of lung cancer in relation to smoking and air pollution. The division into the three areas is based on measurements of particles, sulfur dioxide and benzo[a]pyrene. In the high, intermediate and low exposure areas, the levels of benzo[a]pyrene were given as about 80, 30, and 25 ng/m^3, respectively.

A retrospective study from Ireland was reported by Wicken (*68*). He compared smoking and residential patterns of persons who had died from lung cancer with those who had died from other causes. Information was gathered via interviews with relatives of the deceased. An association with smoking, but also with degree of urbanization, was obtained. Persons residing in central Belfast were at two to three times the risk of developing lung cancer as persons living in rural areas. Smokers of 20 cigarettes and more a day ran a risk about 20 times that of nonsmokers. Higgins (*53*) studied cancer mortality in the U.S. and England during the period 1940–1970 and discussed its association with smoking habits and air pollutants. In the U.S., a steady increase of lung cancer has taken place among both

Table 4. Mortality per 10,000 person years from lung cancer (ISC = 162) as underlying cause among nonsmokers and age-adjusted risk relative to standard group among smokers by smoking group; urban-rural residence considered in all cases.[a]

		Rural		Town		Cities	
Sex	Smoking history	Rate/10,000 person-yr[b]	No. deaths	Rate/10,000 person-yr[b]	No. deaths	Rate/10,000 person-yr[b]	No. deaths
M	Never smoked	1.6	5	1.0	2	0.0	0
	All current smokers	4.9	30	5.9	34	7.7	33
	All cigarette smokers	2.5	9	6.1	18	9.5	28
	Cigarette only smokers	1.6	3	6.1	10	7.8	15
	≥ 16 cgt/day	7.0	2	17.3	6	6.5	5
	8-15 cgt/day	2.7	1	5.5	3	10.6	7
	1-7 cgt/day	0.0	0	1.5	1	4.6	3
F	Never smoked	1.6	12	1.0	6	0.3	1
	Cigarette only smokers	0.0	0	2.4	3	4.9	5
	≥ 16 cgt/day	0.0	0	0.0	0	0.0	0
	8-15 cgt/day	0.0	0	6.3	2	11.0	4
	1-7 cgt/day	0.0	0	0.8	1	2.2	1

[a]Data of Cederlöf et al. (*19*)

[b]Smoker figures give risk relative to standard groups, standard group for the age-adjustment: nonsmokers, rural residents.

Table 5. Standardized lung cancer (ISC = 162, 163) mortality ratios (SMR) for white men (1958) and women (1958-1959) with number of deaths observed, by rate of tobacco use, for selected residence classifications (only persons residing in the same place throughout their entire lives).[a]

Sex	Residence classification	SMR[b]				Observed deaths			
		Never smoked	Occasional or ex-cigarette smoker, pipe or cigar smoker[c]	Regular cigarette smoker: ≤ 1 pack daily	Regular cigarette smoker: > 1 pack daily	Never smoked	Occasional or ex-cigarette smoker, pipe or cigar smoker[c]	Regular cigarette smoker: ≤ 1 pack daily	Regular cigarette smoker: > 1 pack daily
M	Persons with only one exposure residence	13	36	122	486	38	169	481	482
	Urban	18	46	138	548	27	123	330	369
	Rural	8	23	98	355	11	46	151	113
F	Persons with only one exposure residence	75	76	205	647	230	17	80	33
	Urban	90	81	216	700	163	13	63	28
	Rural	54	66	170	500	67	4	17	5

[a]Data from Haenszel et al. (*65, 66*).

[b]SMR = standard mortality ratio, adjusted for age by the indirect method = 100 for U. S. white males, age 35 and over, 1958, or U. S. white females, age 35 and over, 1958-1959.

[c]Pipe or cigar smokers, men only.

Table 6. Age-standardized lung cancer death rate per 100,000 (age 35-74) by the amount of smoking and by the extent of air pollution.[a]

	Age-standardized death rate/100,000					
	Men			Women		
	Low pollution level	Intermediate pollution level	High pollution level	Low pollution level	Intermediate pollution level	High pollution level
Nonsmoker	12.0	5.2	3.5	4.6	8.1	3.5
1-14 cgt/day	10.4	16.7	19.1	19.9	19.4	13.6
15-24 cgt/day	12.8	24.6	28.1	14.5	39.6	28.9
≥ 25 cgt/day	37.1	18.6	38.8	0	0	0
≥ 15 cgt/day	19.1	23.5	30.8	12.7	37.0	18.2

[a]Data of *Hitosugi (67)*.

men and women and in virtually every age group (Figs. 4 and 5). The increase among women is dramatic. Higgins explains the trends in the U.S. by smoking habits. As far as England is concerned, the lung cancer incidence among women has been on the increase, but among men it has declined or remained stable in all age groups except the oldest (Fig. 6). Higgins does not consider the decline, which begins as early as the 1950's, a result of reduced smoking. He points instead to the dramatic reduction in air pollution. As further support for the hypothesis that air pollution plays a role, he refers to the fact that the greatest reduction in both lung cancer rates and pollution has taken place in London, where efforts to combat air pollution have been the strongest. For comparison, age-specific male lung cancer rates for Sweden are given in Figure 7. In summary, however, it has to be pointed out that it is not clear what role the decrease in air pollution may have played.

Migrant Populations. A number of investigations on emigrants from England to New Zealand (*69*), South Africa (*70, 71*) and U.S.A. (*72*) show that the frequency of lung cancer among emigrants is lower than among Englishmen remaining in their native country but higher than among those born in the new country. This finding has been interpreted as showing the long-term effects of air pollutants in the native country. One of the difficulties in the evaluation of these data is that it is not known to what extent the emigrants differ from the populations used for comparison.

Regression Studies. There are studies where correlation and regression techniques have been used in attempts to clarify the effects of various air pollution indices on the incidence of lung cancer (*59, 73, 74*). In 1960, the World Health Organization (*75*) recognized that air pollution might be a possible cause of lung cancer and that this should be further investigated. Stocks (*73*) reported on associations

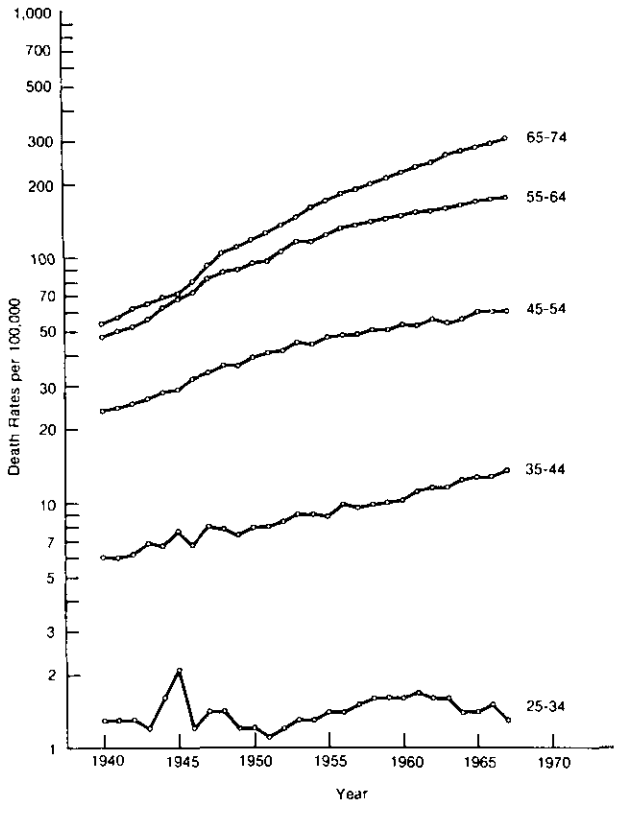

FIGURE 4. Death from cancer of the respiratory system (ISC 160-164) for white men of various ages in United States from 1940 to 1967 (*53*).

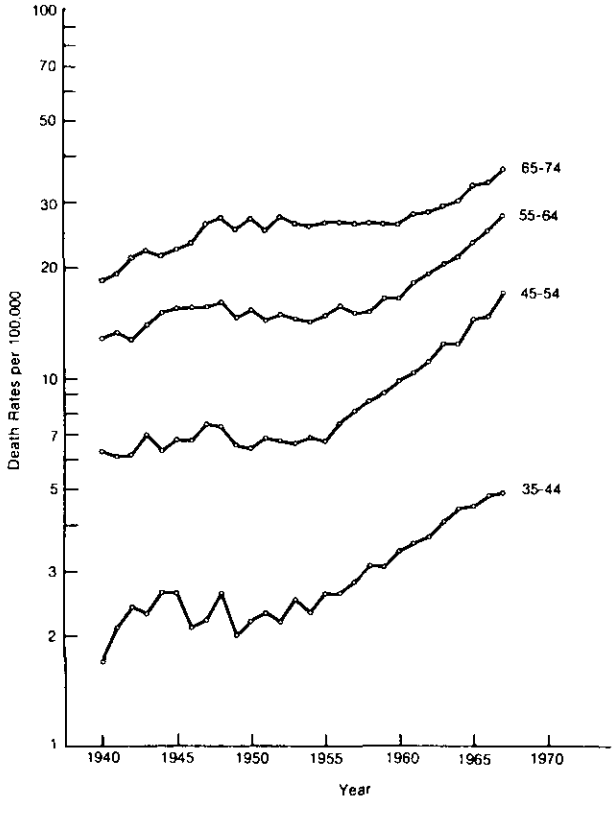

FIGURE 5. Death from cancer of the respiratory system (ISC 160–164) for white women of various ages in United States from 1940 to 1967 (*53*).

between smoking, air pollution and lung cancer on the basis of data from Belfast, Dublin, Helsinki, Oslo, Copenhagen, Liverpool, Wales, and Wrexham (England). Smoking habits were obtained by interviews, and air pollution, including benzo[a]pyrene, was measured at all eight locations. The results showed associations between the lung cancer rate and air pollution as well as smoking. In the same report Stocks relates cancer incidence data from 19 countries to the mean annual per capita consumption of solid and liquid fuel, and smoking as measured by the annual cigarette consumption per adult at five points in time between 1939 and 1957. Stocks found "notable correlations" between the lung cancer rate and both smoking and solid fuel consumptions but not for liquid fuel use.

A study by Carnow and Meier (*59*) merits special attention, as the authors arrive at quantitative estimates in regard to the simultaneous effects on the lung cancer rate of both smoking and air pollution, the latter indexed by the content of benzo[a]pyrene in ambient air. Their quantitative estimates were adopted as criteria by the National Academy of Sciences' Committee on Biological Effects of Atmospheric Pollutants (*23*).

The analysis was partly based on aggregate data from each of the 48 contiguous states of the United States. Cigarette sales per person over 15 years of age (1963) and average exposure to benzo[a]pyrene were taken as independent variables.

The multiple regression analysis was performed for males and females, whites and nonwhites, within four 10-year groups between 35 and 75 years of age as well as on age-adjusted data. The regression coefficient for benzo[a]pyrene for white males was found to be similar for each age-specific group as well as for the age-adjusted totals. The results suggest that an increase in urban pollution associated with an average benzo[a]pyrene concentration of 1 ng/m^3 corresponds to an increase of 5% in the lung cancer death rate.

Carnow and Meier (*59*) also re-evaluated Stocks' data from 19 countries (*73*). The multiple regression analysis suggests an increase in male lung cancer deaths at 20% per metric ton of coal burned per capita.

In discussing the model of analysis, the authors expressed their belief that the method is subject to

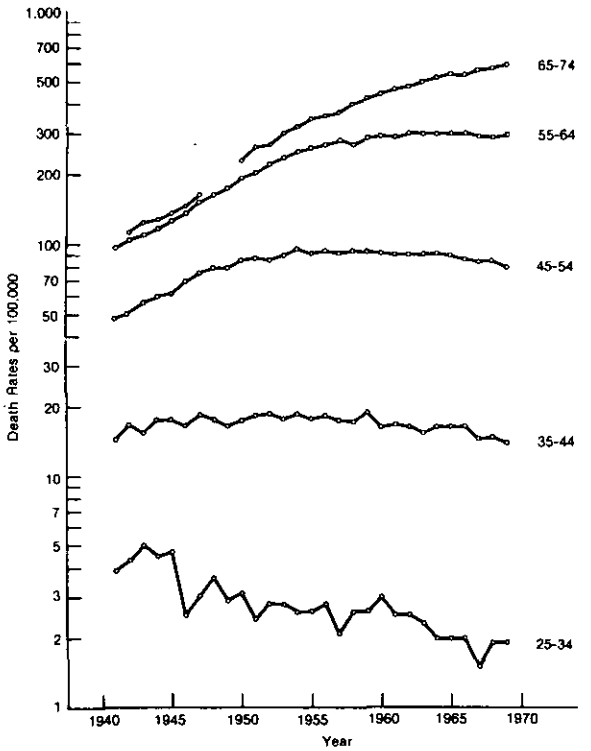

FIGURE 6. Death from cancer of the respiratory system (ISC 160–164) for men of various ages in England and Wales from 1941 to 1969 (*53*).

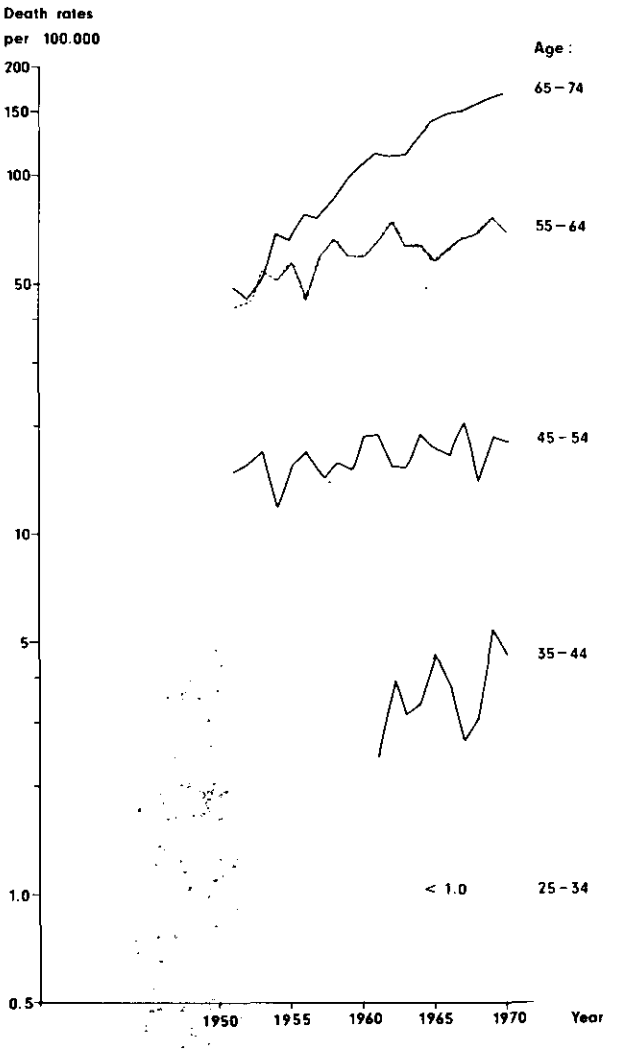

FIGURE 7. Death from cancer of the respiratory system (ISC 162–163) for men of various ages in Sweden from 1951 to 1958.

severe limitations. They pointed out a variety of circumstances that might have influenced the overall assessment of the results. They concluded, however, "It appears both reasonable and prudent to take as a working hypothesis the existence of a causal relation between air pollution and pulmonary cancer death rate at the rate of a 5% increase for each increment of pollution as indexed by 1 benzo[a]pyrene unit." They further concluded, "This hypothesis leads to the estimate that a substantial reduction in the pollution of highly urban environments would lead to a corresponding reduction in death rate from cancer of the lung (e.g., a reduction of air pollution corresponding to a reduction of benzo[a]pyrene concentration from about 6 μg/1000 m^3 to around 2 μg/1000 m^3 might reduce the death rate by about 20%). Similar benefits might be expected in all smoking categories." It should be pointed out that this statement, both as put forth by Carnow and Meier (*59*) and as adopted almost verbatim by NAS (*23*), evolved in the context of the need for policy decisions and is not to be taken as a proof that either air pollution or benzo[a]pyrene must be causally related to the effects as seen in the regression equation (*76*).

The following points deserve further consideration, viz., the validity of the measures used, the appropriateness of the regression analysis model and the limitations on making generalized predictions on the basis of the regression function.

One key question in regard to the validity of the exposure measures, i.e., tobacco consumption, and air pollution as indexed by benzo[a]pyrene, asks how meaningful are averages as estimates of individual exposure within heterogeneous aggregates composed of subgroups that may differ widely in regard to racial, ethnic, socioeconomic, and other cultural patterns. For example, in certain states women, young people or blacks may make up more of the buyers than in others. Tobacco consumption goes in parallel with industrialization, and even though tobacco sales may be the same today in two different states, this does not mean that the expo-

sure over time has been the same. The time of exposure may have been more extended in a state with industrialization originating from long ago in comparison to a "younger state." If the tobacco exposure on an average has been longer in states with higher benzo[a]pyrene averages, i.e., indicating a higher degree of urbanization, such a bias could certainly explain to some unknown extent an "effect" of air pollution as expressed in the benzo[a]pyrene regression. There are also problems with the state averages of benzo[a]pyrene. As the original data were unpublished, only guesses can be made, but it seems likely that peak concentrations and low-level concentrations may also distribute differently between states with about the same average.

There is a problem of whether benzo[a]pyrene is the most appropriate overall index of air pollution. This practice seems mainly to stem from the fact that it is held to be carcinogenic and also relatively easy to measure in ambient air. Different compositions of air pollution may, however, be reflected in similar benzo[a]pyrene contents. It is therefore not specific as an index but might serve as a general indicator of urbanization, a factor which evidently correlates to socioeconomic, occupational, racial and cultural distributions. It seems inevitable that a general "urbanization index" signifies variations that are only partly referable to the impact of air pollution exposure.

The multiple regression model of course cannot do anything more than estimate a mathematical relationship between the lung cancer rate and the two independent variables, whatever they stand for.

Evidence from sampling studies indicates that the relation between number of cigarettes smoked per day and the cancer rate is approximately linear, except possibly for very low consumption (Fig. 2). There is no reason to believe that the carcinogenic effect of air pollution should be otherwise.

The data presented in the Carnow-Meier paper will give a coefficient of multiple correlation of 0.48, corresponding to an explainable total variance of about 23%. Partialization of the total correlation reveals a correlation of 0.43 for the smoking variable and 0.22 for the benzo[a]pyrene variable. However, more than ¾ of the total variation of the cancer rate is in this analysis not explained by the variables in question.

As the "unexplained" variation is made up by the deviation between observed and expected values for the 48 states, it is of interest to see how the departures from expectation distribute geographically. In Figure 8 the dark areas denote the 12 states where the cancer rate was appreciably higher than expected (upper quartile), while the unshaded areas denote 12 states where the observed values were appreciably lower than expected (lower quartile). The lightly shaded areas denote the remaining 24 states. Blot and Fraumeni (*74*) studied lung cancer mortality in the United States (1950–1969), using county data developed by Mason and McKay (*77*). They found increased rates among males in counties where paper, chemical, petroleum, and transportation industries were located. They also stated that these associations were not attributable to urbanization, socioeconomic factors, or manufacturing operations. Neither smoking habits nor air pollution measurements were taken into account. The geographical distribution of the lung-cancer rate found in their study is strikingly similar to what is revealed by Figure 8.

Although the analysis of the data from the 48 states can be questioned, it does reveal, on a large population, yet another suggestive relation between urganization and lung cancer incidence. However, so many uncertainties remain in interpreting the regression analyses that it seems fair to await further research before using them as a basis for quantitative assessments in regard to air pollution.

A few last remarks should be made about the possibilities of generalized prediction. If one argues that no reliable basis for quantification has been established, then prediction would of course be impossible. On the other hand, even if the regression equations could be argued to have given reliable estimates of the relationship of lung cancer to air pollution, prediction would still be difficult. Benzo[a]pyrene in itself may only be in a small way responsible for the cancer incidence. One could theoretically assume that two kinds of air pollution, A and B, have increased concurrently during industrial development and urbanization over the years. Air pollution A may contain a strong carcinogenic substance X, but only insignificant amounts of benzo[a]pyrene. B may contain high levels of benzo[a]pyrene but only limited amounts of substance X. As A and B are strongly correlated, benzo[a]pyrene would be a good index of the existence of substance X. One can further assume that substance X is the true cause of the greater part of the lung cancer cases, while benzo[a]pyrene contributes only to a small extent. In this case, a decrease of air pollution B would result in lower benzo[a]pyrene values but would not appreciably affect the lung cancer rate, since air pollution A would still be present. This reasoning is relevant not only for a possible association between benzo[a]pyrene and lung cancer but also for any case in which a substance is believed to be a valid indicator of a toxic action.

In addition to the studies discussed above, sev-

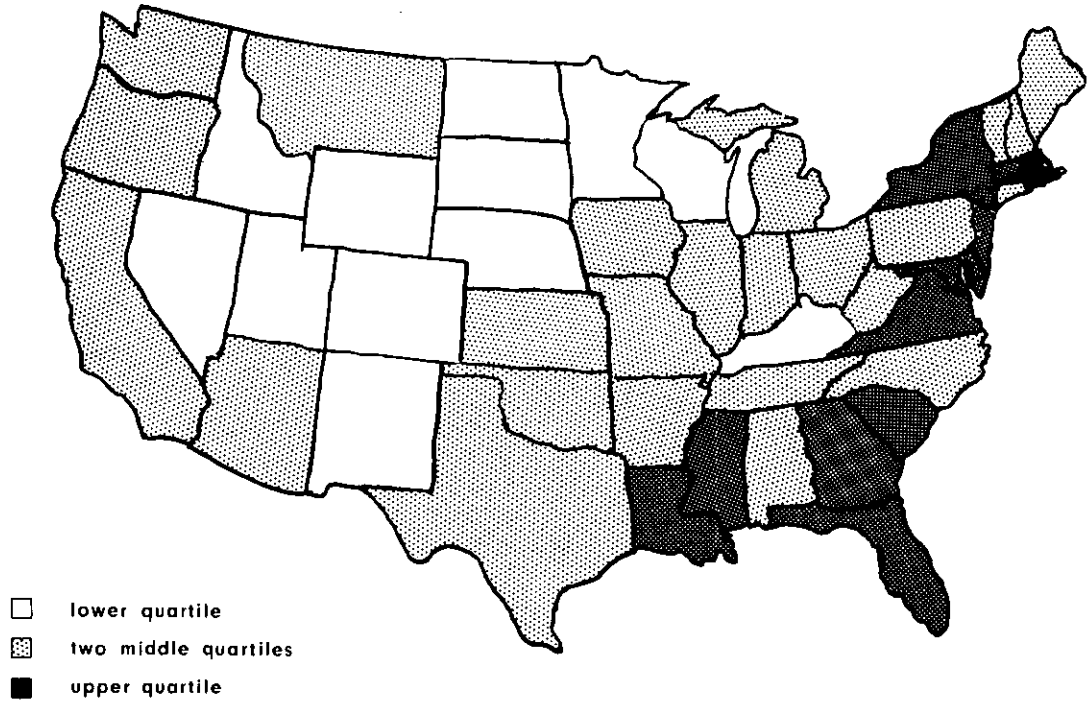

FIGURE 8. Distribution of deviations between observed lung cancer rate and an expected rate based on the Carnow-Meier multiple regression function.

eral regression-type investigations of the association between air pollution and lung cancer have been published. Some of the results have been used for predicting health effects from fossil fuel based energy production. Quite often the studies were carried out on earlier published data, which makes it difficult to judge the limitations inherent in the data sample and the assumptions underlying the regression model.

Lave and Seskin (*78*) used data from Stocks (*79, 80*) to explain the lung cancer mortality rate by population density and the amounts of either suspended particles, or precipitated matter as air pollution indices. Using data from Ashley (*81*) they also regressed lung cancer mortality on population density, or either smoke or sulfur dioxide contents in ambient air as a measure of air pollution. In other contexts (*45, 82*), the gross mortality rate was analyzed with the same methods.

Although different indices of air pollution have been used, the regression results can be roughly compared as the different indices are correlated with each other in the observations made. If the indices are translated into each other, the regression coefficients for lung cancer mortality on air pollution generally agree within a factor range of 2–5, giving some evidence that, from a purely statistical point of view, the results of the individual studies may not be artifacts. However, this still does not prove that air pollution, or any of its constituents, causes lung cancer. The consistency is rather to be expected because of the correlation that exists between different indices of air pollution. Moreover, in the regression analyses discussed above, as well as in the majority of others, the smoking factor was not controlled but omitted in the regression model. Such regression estimates cannot be used for prediction of health effects.

Lung Cancer in Special Exposure Situations

Occupational Exposure to Particulate Polycyclic Organic Matter. There are no epidemiological studies on humans exposed only to benzo[a]pyrene or other polycyclic organic compounds. A number of studies, however, show that workers exposed to tar and soot (which contain benzo[a]pyrene) have an increased incidence of lung cancer. Bringing together data from Lawther, Commins, and Waller (*83*), Doll et al. (*84*), and Lloyd (*85*) makes it possible to examine questions of dose–response. In these papers as well as in a NIOSH criteria document for occupational exposure to coke oven emissions (*86*) references are

given to pertinent literature up to that time. Recently the findings of an increased lung cancer incidence in workers at coke ovens have been further confirmed (*87, 88*).

Gas and coke oven workers exposed to polycyclic organic matter, as measured by benzo[a]pyrene, show as compared to the general population a considerably increased risk of developing lung cancer which cannot be accounted for by differences in smoking habits. It is not possible, however, to state whether the increased risk is due to exposure to benzo[a]pyrene or to other polycyclic hydrocarbons occurring together with benzo[a]pyrene.

In two recent publications, attempts have been made to quantify dose–response relationships implied by the data just discussed (*23, 89*). The NAS report (*23*) concluded that the dose–response relation found "lacks plausibility, because a dose increment of two orders of magnitude—from about 10 μg/1,000 m^3 benzo[a]pyrene to 1,000 μg/1,000 m^3—hardly increases the lung cancer mortality ratio of the average British gas worker relative to the urban dweller." Pike et al. (*89*), taking into consideration differences in exposure time, calculated that the average British gas worker was exposed to a benzo[a]pyrene concentration equivalent to 400 ng/m^3 benzo[a]pyrene in ambient air. This exposure had given rise to an extra risk corresponding to a rate of 160 lung cancer cases per year per 100,000 persons. They assumed a strictly proportional effect, implying that each ng/m^3 benzo[a]pyrene would cause 0.4 extra lung cancer cases per 100,000 persons per year.

In summary, long-term exposure to particulates of tar and soot, containing polycyclic organic matter including benzo[a]pyrene, has given rise to a considerable increase in lung cancer incidence in British gas workers as well as U. S. coke oven workers. Considerable underestimates of the risk can be obtained if the conclusions based on industrial exposures are used for the general population which includes especially susceptible individuals, such as old and sick persons. One crucial question is whether the benzo[a]pyrene in a gasworks can be considered as an index of risk for carcinogenicity in the same way as benzo[a]pyrene in urban air. To date, there does not seem to be sufficient evidence to answer this question with certainty. Another important question is whether a linear extrapolation to low level exposures is appropriate. The results from the different smoking studies (Fig. 2) may speak in favor of a rather linear relation between dose (a mixture of carcinogenic substances including benzo[a]pyrene) and lung cancer within a wide dose range. The question of extrapolation to low doses will be discussed below, taking into account evidence from animal data as well.

Exposure to Certain Metals. It is well-known that arsenic is carcinogenic for man, as evidenced by the development of skin cancer after medication or unintentionally high exposure via drinking water (*90–92*). Evidence is also accumulating that exposure to arsenic, alone or in combination with other substances, via air may give rise to lung cancer (*93, 94*). As for dose–response relationships, no hard data exist. However, as early as 1948, in a factory where sodium arsenate was produced, Hill and Faning (*95*) found excess deaths due to respiratory cancer in workers exposed to arsenic. The average air concentration of arsenic ranged from 254 to 696 μg/m^3. Pinto and Nelson (*93*) stated that exposure to 100 μg arsenic trioxide/m^3 in a smelter for 25 years or less had not caused an increased incidence of respiratory cancer.

Several studies (*96–98*) have shown that exposure to hexavalent chromium may lead to lung cancer. There is some evidence that lung cancer has occurred after long-term exposure to about 0.5 mg/m^3 of chromium.

Industrial exposure to cadmium has been associated with an increased incidence of lung cancer as well as of cancer of the prostate (*99–101*). The evidence for a causal association regarding lung cancer is very weak and that regarding cancer of the prostate is not conclusive. The International Agency for Research on Cancer (*26*) has stated the following in their evaluation: "Available studies indicate that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man. In addition, one of these studies suggests an increased risk of respiratory tract cancer."

As for nickel, there is abundant evidence of an excess of cancer of the nasal cavities and of the lung among workers in nickel refineries (*26*). High concentrations of nickel compounds with low solubility, such as the oxide and subsulfide, have been suspected of being the causative agents, together with nickel carbonyl vapor. It has not been shown that soluble nickel salts can cause cancer.

Experimental Studies

Exposure of the Lung to Carcinogenic Substances Present in Ambient Air Pollution. This survey is confined to carcinogenic substances which have been administered to animals via inhalation, intratracheal instillation, or implantation into the airways. The latter methods have been included because so few inhalation experiments have been performed and because they show the importance

of the method of administration. The pattern of deposition after inhalation and intratracheal instillation differs (*102*).

Inhalation experiments have been carried out with polycyclic hydrocarbons in pure form, but not in a single case has an association between exposure and an increase in cancer frequency been demonstrable (*103*). Such an association has been shown, however, under special experimental conditions. When benzo[a]pyrene and dimethylbenzanthracene in a suspension of carbon particles (India ink) in a colloidal protein solution were given to rats intratracheally, a high frequency of lung tumors (including squamous cell carcinoma) was observed (*104, 105*). Yanisheva (*106*), using the same method, found a doze–response relationship between benzo[a]pyrene and lung tumors. Doses down to 0.1 mg, divided into 10 subdoses, brought about an increase in cancer frequency.

The reason that benzo[a]pyrene and dimethylbenzanthracene together with India ink produced such high incidences of tumors may be that these particles increase the retention of these substances (*107*). High frequencies of tumors, including squamous cell carcinoma, have been found in studies using intratracheal instillation of benzo[a]pyrene in doses down to 15 mg when mixed with iron oxide particles (*108, 109*).

Kuschner (*110*) implanted cylinders (1 × 5 mm) of cholesterol mixed with benzo[a]pyrene and methylcholanthrene in various concentrations in the bronchi of rats. The same technique was used to administer radioactive substances, which then also gave rise to squamous cell carcinoma. A linear association was found provided that the dose was expressed on a logarithmic scale and the frequency of squamous cell carcinoma on a probit scale.

Rats were exposed to 10 mg/m^3 benzo[a]pyrene and about 10 mg/m^3 SO_2 1 hr/day, 5 days/week (*111*). After 98 weeks, two of 21 rats had acquired squamous cell carcinoma. Another group of rats was also exposed to 10 mg/m^3 benzo[a]pyrene and 10 mg/m^3 SO_2 1 hr/day but given an additional 30 mg/m^3 SO_2 6 hr/day, 5 days/week. In this group, five out of 21 rats had developed squamous cell carcinoma after 98 weeks. These experiments suggest that a combination of benzo[a]pyrene and sulfur dioxide can be carcinogenic for animals.

Mice were exposed to artificial smog (ozonized gasoline), whereupon increase of alveolar tumors was reported (*112*). In a later experiment in which mice were exposed to artificial smog and during the same exposure time infected repeatedly with influenza virus, an increased frequency of squamous cell carcinoma was observed (*113*). Nettesheim et al. (*114*) also found an increase in the frequency of lung tumors (adenoma and adenocarcinoma) in mice exposed to artificial smog (ozonized gasoline). Infection with influenza virus 2 weeks prior to inhalation of the artificial smog reduced tumor frequency.

Mice which inhaled calcium chromate particles throughout their entire lifetime developed two to four times as many lung adenomas as control animals (*115*). In an inhalation study, three out of 15 guinea pigs exposed to calcium dichromate and sodium chromate, at an average of 3–4 mg chromium trioxide/m^3, developed adenoma. An intratracheal instillation of the same substances in guinea pigs did not result in cancer (*116*). Intratracheal instillation of a chromate mixture, corresponding to 0.04 mg chromium trioxide, did not induce any tumors in mice (*117*), while inhalation of calcium chromate was reported to have induced squamous cell carcinoma in rats (*103*).

In inhalation studies, nickel dust gave rise to cellular changes in the lung of rats and guinea pigs (*118*) but lung cancer was observed in only one of 42 guinea pigs. In both experiments, the animals inhaled 15mg/m^3 nickel particles of less than 4 μm for 6 hr/day, 4–5 days/week up to 21 months. Ottolenghi et al. (*119*) exposed rats to 1 mg/m^3 of nickel sulfide for 78 weeks and observed them for another 30 weeks. They found a higher frequency of lung tumors, including cancer, in the exposed rats (14%) compared with the controls (1%). Altogether 400 animals were included in the study. In an inhalation study on rats with nickel carbonyl in concentrations between 0.03 and 0.06 mg/l. air for 30 min three times per week for one year, cellular changes in the bronchi of all 72 animals were found after a period of 30 months. Four animals showed some form of tumors (*120*).

Nitroalkenes, the so-called nitroolefins, can be present in ambient air pollution. The only nitroolefin which seems to have been tested with regard to possible carcinogenic effects is nitrohexene (*40*).

Dose–Response Studies. Dose–response relationships with regard to cancer have been observed for only a few substances or groups of substances. In no case are data based on inhalation studies. Some of the substances or groups of substances which have been studied are polycyclic hydrocarbons, among them methylcholanthrene, dibenzanthracene, and benzo[a]pyrene. Of these, at least the two latter are present as ambient air pollutants as a result of incomplete combustion of organic material. Another well studied group of substances consists of the nitrosamines, of which at least one, dimethylnitrosamine, is present in low concentrations in ambient air pollution (*121*).

Dose–response studies regarding polycyclic hy-

drocarbons have been performed on rodents with single subcutaneous injections of doses from 1 μg up to 4 mg per animal. All animals given injections of 4 mg benzo[a]pyrene developed tumors, while only a few percent did so when given a dose of about 0.06 mg. Concerning dibenzanthracene, a dose of about 1 μg gave a tumor frequency of a very few percent (*122*). This study also shows that tumor frequency is related to dose.

This as well as other studies on the same substances (*123, 124*) shows that also at low doses the dose–response relationship does not deviate significantly from a straight line (*125*). Before it can be generally established that the dose–response relationship is indeed linear, further studies are needed, especially on the lower dose ranges. Given a linear association between cancer frequency and dose, the probability of inducing tumors per dose unit is constant and independent of dose.

Mantel and co-workers (*126–128*) have used a mathematical model to extrapolate from high to low doses. The model is based upon a fitting of the probit for the incidence of cancer to a straight line as a function of the logarithm for dose. The model implies that the estimated risk per dose unit within the very low dose range will be essentially lower than it would be in an ordinary linear extrapolation. Their theory has been criticized by, among others, Hoel et al. (*129*) and Crump et al. (*130*), who consider the latter type of extrapolation to lower doses to be most correct.

The data discussed above have been obtained via single administrations of the carcinogenic substances in various doses. However, it is known that dividing a single dose into small doses and giving them at intervals can increase tumor frequency. For instance, a single injection of 0.5 mg benzo[a]pyrene resulted in cancer at the site of injection in 25% of exposed mice while the same dose divided into 12 subdoses administered at monthly intervals produced tumors in about 70% (*131*). Similar results have been obtained in other studies on polycyclic hydrocarbons (*132*). These results cannot be explained by an accumulation of benzo[a]pyrene in the organism nor by a permanent induction of the activating enzyme. It is known that aryl hydrocarbon hydroxylase, the enzyme which activates benzo[a]pyrene to become the carcinogenic product, halves its activity in the hamster embryo cell *in vitro* within hours after induction (*133*).

The average latency period between the administration of carcinogenic substances and the emergence of the tumor becomes shorter and shorter as the dose increases, but not proportionally so (*125*). Druckrey (*134*) has made calculations based upon other researchers' studies of polycyclic hydrocarbons and his own studies on nitrosamines in rodents. The author stated that these data, in line with corresponding data on radiation-induced cancer (*125*) pointed to the latency period in the induction of cancer being inversely proportional to the dose raised to the power of ⅓. This means that a thousandfold reduction of the dose gives about a tenfold increase in the mean latency period. However, in practice it is not possible to calculate a dose which is so low that the mean latency period would exceed the expected lifetime, especially since the variation of the latency period within an exposed group increases more and more as the dose is successively reduced.

With regard to chemically induced mutations—just as is the case for radiation-induced mutations—experimental data indicate that the dose–response curve is linear, even for low doses (*135*). Many chemical substances give a drastically increased mutation frequency when the doses exceed a certain threshold (*136–138*), which likely stems from a disturbance in DNA repair.

Dose–response relationships for teratogenic effects of both chemical substances and ionizing radiation have been studied to only a limited degree and are therefore insufficiently known. As a rule, only small groups of animals have been used, and the doses have been relatively high. Extrapolation to lower dose levels is hence not possible.

Extrapolation of Experimental Data to Human Beings. When it comes to extrapolating data on late effects from experimental systems to human beings, the knowledge is quite limited. The mechanism of action for the development of carcinogenic effects is likely to be the same for humans as for animals, even though there are differences in uptake, biotransformation, distribution and elimination which can have a decisive influence upon the magnitude of the risk. A substance which is carcinogenic in animals nonetheless should reasonably be regarded as potentially carcinogenic in humans as well (*26*). All substances which have been shown to entail an increased risk of cancer in humans have been observed to be carcinogenic in animal experiments, with the possible exception of arsenic. A special problem concerns increased rates of chemically induced tumors normally occurring spontaneously in an experimental animal. In this case, there may exist a difference in the mechanisms of action for initiation of new tumors as opposed to stimulation of a spontaneous tumor (*139*). IARC does however consider that a substance which significantly increases the frequency or shortens the latency period for spontaneous tumors implies a potential risk for humans.

The possible finding that a low incidence of human cancer is caused by air pollutants would not contradict the postulation that, as a whole, a large number of cancer cases can have been caused by air pollutants. For practical reasons, it has been impossible to work with large series of animals in experiments. Accordingly, when an animal experiment fails to show an increase in cancer frequency, this does not exclude the possibility that such a risk can indeed exist and would have been disclosed had only the number of animals been large enough. If a strain of mice has a spontaneous cancer frequency of 0.1% and the goal is to have a 95% chance to discover a doubling of the cancer frequency at a 5% significance level, more than 30,000 animals are needed both in the control group and the exposed group.

The uncertainty in a quantitative evaluation increases even more upon extrapolation from the experimental model to the human exposure situation, the reasons for which have been given in part above. In animal experiments, one substance is administered at a time. A human being, during an entire lifetime, is exposed to many initiators or promotors in both the general and the working environments. Moreover, experimental animals are normally inbred, rendering them genetically homogeneous. The experiments begin when all animals are of the same age and body weight. Stress factors, food, drink, biological rhythm etc. are likewise rather uniform. Such uniform conditions do not exist in a human population. Furthermore, the variation in susceptibility may be considerable.

Evaluation

A large number of reports are available concerning associations between lung cancer and urbanization. The mere finding that lung cancer in urban areas is higher than in rural areas does not in itself prove that general air pollution caused the increase. Air pollutants in cities do contain higher concentrations of carcinogenic substances, including benzo[a]pyrene and other polycyclic hydrocarbons, which have caused lung cancer in animal models and in certain cases also in humans. Urban dwellers, however, also differ importantly from rural dwellers with regard to several other potentially harmful exposure factors.

The increased incidence of lung cancer in urban areas as compared to rural areas depends in part on differences in smoking habits. An effect of urbanization has remained even after attempts to control for smoking habits, but these attempts may have been inadequate, as has been pointed out above. Moreover, it has not been possible to take into account all other potentially harmful influences. Therefore, it is at present not possible to provide epidemiological proof that air pollution per se causes an increase in lung cancer incidence and much less to ascribe an observed increase to a specific substance. At the same time, the failure to verify a causal hypothesis in a strict sense does not justify a conclusion that air pollution is causally unrelated to lung cancer. The association found and the occurrence of carcinogenic substances in urban air make it reasonable, and definitely prudent, to conclude that part of the association is causal. From the point of view of preventive medicine, primacy should be given to cigarette smoking but the role of air pollution must be of considerable concern as well. Even if the excess risk ratio of lung cancer due to ambient air pollution is assumed to be as low as 1.05–1.10, it would nonetheless lead to 100–200 cases per year in Sweden, where the annual incidence is about 2,000 cases. On a global basis the numbers would be extremely large even if the ratio were still smaller. What has been said here refers to lung cancer. As already mentioned in the introductory remarks, an urban factor has also been associated with other forms of cancer which would add to these numbers should air pollution be one of the causative factors. This question has not been possible to evaluate.

A central question in experimental research with carcinogenic substances is the shape of the dose-response curve at low concentrations. This question is open, but, in keeping with a conservative judgment, it seems reasonable to assume a linear relationship, which would imply that "safe" concentrations do not exist.

Appendix 1

Persons Participating in the Preparation of the Document on the Health Effects of Air Pollution to be Used by the Swedish Parliamentary Committee on Energy and the Environment

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Environmental Hygiene, Karolinska Institute and National Swedish Environment Protection Board; Bo Holmberg, Division of Toxicology, National Board of Occupational Safety and Health; Jan Lindsten, Department of Clinical Genetics, Karolinska Hospital; Magnus Piscator, Department of Environmental Hygiene, Karolinska Institute; Ragnar Rylander, Department of Environmental Hygiene, University of Gothenburg; Per Strangert, Research Institute of the National Defense; Stefan Sörensen, Department of Environmental Hygiene, National Swedish Environment Protection Board; Lennart Tomenius, Department of Environmental Hygiene, National Swedish Environment Protection Board; and Torbjörn Westermark, Department of Nuclear Chemistry, Royal School of Technology.

During the work continuous contacts have been maintained with Lars Lindau, Division of Air Pollution of the National Swedish Environment Protection Board, Bo Lindell, National Swedish Institute of Radiation Protection, Yngve Hagerman, Chemistry Department at the National Board of Occupational Safety and Health, and Lars Högberg, Secretary of the Parliamentary Committee on Energy and the Environment.

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