

FILE NAME: Kent (KNT)

DATE: 1956

DOC#: KNT103

DOCUMENT DESCRIPTION: Journal Article - The Role of Atmospheric Pollution in the Pathogenesis of Pulmonary Cancer: A Review

Cancer Research
16: 375-393, 1956

The Role of Atmospheric Pollution in the Pathogenesis of Pulmonary Cancer: *A Review**

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*Part of the work reported here is supported by grants from the Field Investigations and Demonstrations Branch, National Cancer Institute, United States Public Health Service, Department of Health, Education, and Welfare, and by a grant from the Ad Hoc Lung Cancer Committee of the American Cancer Society.

INTRODUCTION

A. Lung cancer increase real.—A marked increase in the absolute mortality from cancer of the lung has been demonstrated in various regions of the world during the past several decades (36, 83). Certain epidemiologic aspects of this increase suggest etiologic association with carcinogenic agents presumably introduced into the external environment in the recent past. Of the causal agents advanced, atmospheric pollution (12, 55, 97, 98) and cigarette smoking (7, 15, 28, 30) have been regarded as the two most significant. Lung cancer, in common with all neoplasms, appears unlikely to have but a single initiating and promoting agent concerned with its pathogenesis. Any analysis of the atmosphere as a carcinogenic entity must, therefore, include reference to its possible role as an adjuvant or associative factor to other potential environmental carcinogenic sources. Cigarette smoking, the most often accused of these, will be evaluated in the light of its possible association with atmospheric pollution in the initiation of lung cancer. Sufficient time has elapsed and enough information has been accumulated relating atmospheric pollution to the increase in lung cancer to make a critical review of the data advisable. This report will conclude with a presentation of a suggested theoretical mechanism of human pulmonary carcinogenesis based upon experimental and epidemiologic studies.

Theories of lung cancer pathogenesis, to be valid, should result from a synthesis of responsible epidemiologic, clinical, and pathologic data. Equally significant are supporting data derived from laboratory investigations.

B. Exogenous environment etiologically implicated.

ed.—There is no convincing evidence that an intrinsic biological change might be responsible for the emergence of nonoccupational lung cancer from the status of a medical curiosity at the beginning of the century to a position of major importance at mid-century. In the absence of such data an exogenous source of the carcinogenic agents must be postulated.

These exogenous environmental agents did not become manifest simultaneously throughout the world, as noted by significant differences existing from country to country relative to the time of onset of the increase in lung cancer, the rapidity and intensity of the increase, and variations in the age groups manifesting the peak incidence. These variations are accompanied by similarities which point to the exogenous origin of the causal agent or agents. These include a greater frequency of the disease in urban residents (31, 53, 58, 69, 86, 88, 97, 98) and an intensely exaggerated, almost exclusive increase in males (17, 22, 44, 58, 97). A clinical historical association of heavy cigarette smoking has been reported in a majority of the cases of lung cancer. Sociologic investigations have attempted to associate characteristic histopathologic patterns of pulmonary neoplasms with specific environmental factors. As is evident from the reports of Kirklin *et al.* (59) and Walters and Price (101), the absolute pathologic classification of lung cancers is at present exceedingly difficult. The hazards of establishing cell types and cellular origins are especially marked in relation to anaplastic or so-called oat-cell cancer.

HISTORICAL

A. Nonpulmonary occupational cancer and lung cancers of occupational origin.—Sir Percival Pott (87) first correlated clinical cancer with carcinogenic materials from one source of atmospheric pollution. The local atmospheric pollution incidental to the function of chimneys is self-evident. Whether the sweeping of chimneys carried an increased liability to the development of lung cancer in addition to scrotal cancer is at present undeterminable.

B. Incrimination of atmospheric environment.—Atmospheric contamination as an environmental source of pulmonary carcinogens was first demonstrated when Härtig and Hesse (51) identified the pulmonary disease in radioactive ore miners in Schneeberg as lung cancer. There, of course, the atmospheric pollution was a highly localized one, limited specifically to the occupational environment of the miners. The epidemiologic and pathologic study of the Schneeberg miners resulted in the establishment of environmental lung cancer as

a definite entity. Concepts of latency, the interval between first exposure to the carcinogenic agent and the clinical manifestation of lung cancer, were initially derived from these studies. An increased risk in the development of lung cancer has since been demonstrated to be associated with occupational exposure to nickel (80), chromates (1, 4, 78), and gas-working operations (26).

C. Incrimination of tobacco.—Among the first to describe a correlation between the development of cancer of the lung and factors other than strictly occupational ones was Müller (81) who in 1939 reported a statistical study purporting to show a correlation between smoking and lung cancer. An analysis of the occupational exposure of his subjects in the light of current environmental cancer knowledge indicates that his conclusions of a positive etiologic association are open to question. Following Müller's original report, numerous studies have been undertaken to ascertain any relationships existing between lung cancer and a broader spectrum of environmental factors. A majority of recent investigations noted an association between lung cancer and heavy smoking (47, 72, 89, 104, 105). Numerous investigators have by means of comparative retrospective studies adjudged that heavy cigarette smoking embodies an enhanced risk to the development of lung cancer. The conclusion that this association demonstrates a cause-and-effect relationship has been most eloquently advanced by Hammond and Horn (50), who observed, "For reasons discussed, we are of the opinion that the associations found . . . between regular cigarette smoking and death rates from lung cancer reflect cause and effect relationships."

Contrary opinions have been voiced by other students of the problem, who emphasize that the real increase in lung cancer is markedly less than is generally accepted and thus question whether reported associations between cigarette smoking and lung cancer signify any etiologic implication. Berkson (3) in reviewing the data of Hammond and Horn reported, "My thesis is only that it is unwarranted to conclude from them [data] that a meaningful association already has been proved beyond doubt, as some writers have asserted and as appears to be widely accepted in the United States. Much less do I believe that causation has been established."

EPIDEMIOLOGIC CONSIDERATIONS

A. Limitations of data.—In evaluating the epidemiologic factors relating to this review, certain deficiencies inherent in the available crude data must be considered.

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B. Variations in lung cancer rates among countries.—While great differences continue to exist in several of the preceding factors, an analysis of available epidemiologic data indicates that prior to the early 1930's records for several countries are incomplete, inconsistent, and in many instances inaccurate. Beginning with this period, however, one may with some degree of assurance compare death rates from lung cancer with those recorded in the early 1950's. Though similarities in trend exist in all countries, when the two series of death rates as determined by vital statistics are reviewed, a great disparity can be noted in the specific rates (83). This disparity in actual incidence rates tends to support the thesis that the environmental carcinogenic agent differed in the time of its introduction and varied in its intensity from country to country. Charts 1 and 2 record comparative death rates for a series of countries between the two periods mentioned above.

D. *Variations in age peak incidence and sex incidence.*—Additional convincing supporting evidence for variations in the time of introduction of the carcinogenic agent into the atmosphere can be found when the peak age incidence for lung cancer is compared from country to country as shown in

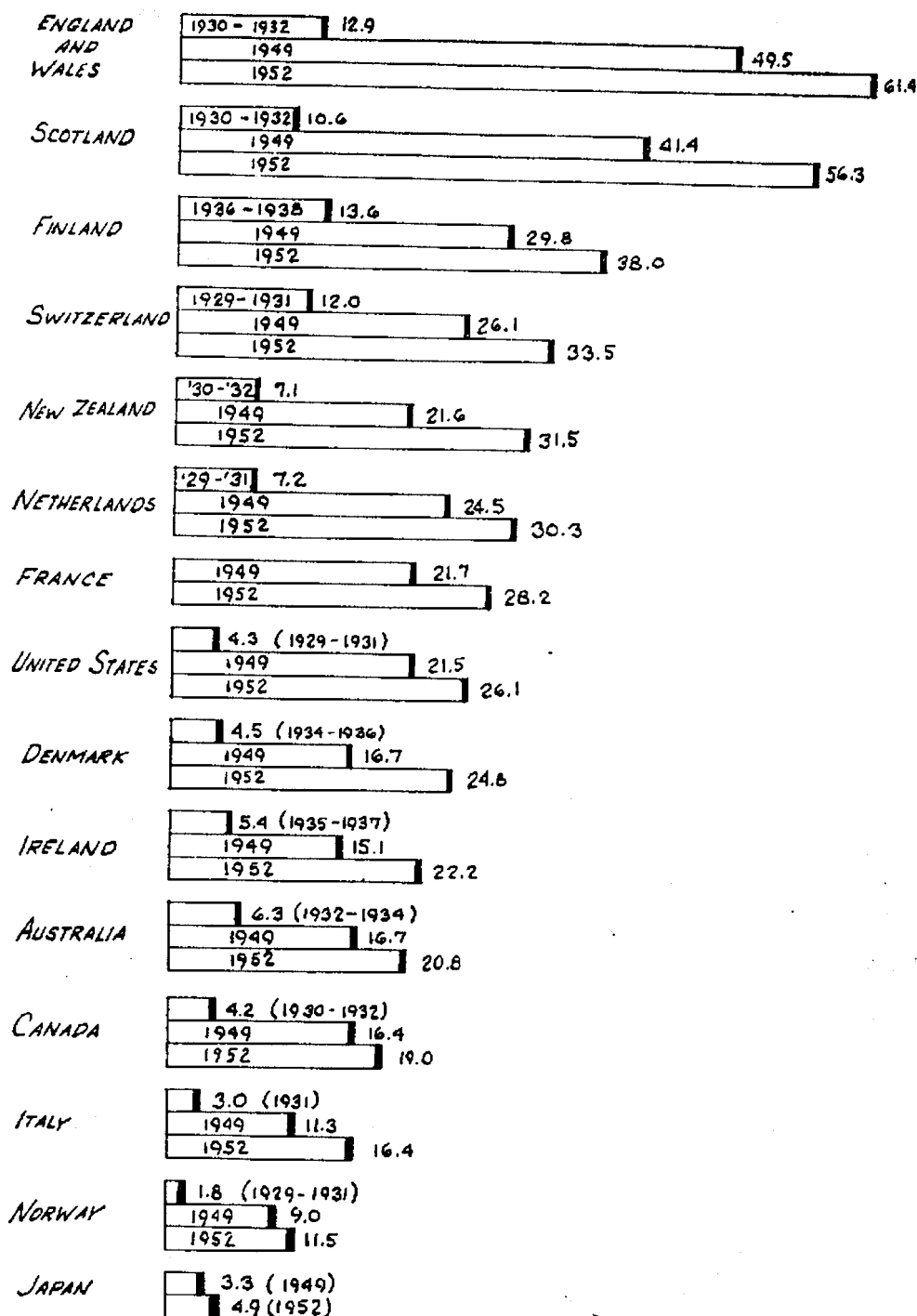


CHART 1.—Death rate for cancer of respiratory system in males (rates per 100,000 deaths). Data obtained from Director-Consultant on Health Statistics, World Health Organization.

Table 1. In those countries with peaks in the earlier decades of life, the introduction of the carcinogenic agent must certainly have been proportionately sooner or in greater concentrations. Further,

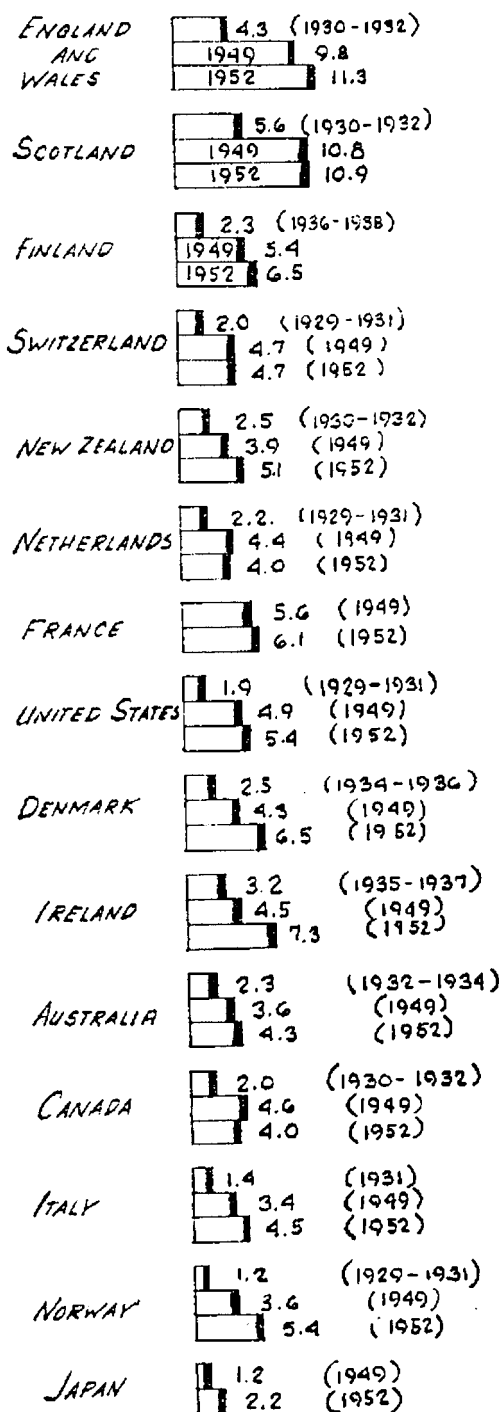


CHART 2.—Death rate for cancer of respiratory system in females (rates per 100,000 deaths). Data obtained from Director-Consultant on Health Statistics, World Health Organization.

differences in urban and rural lung cancer mortality figures may be nothing more than another manifestation of the time of peak incidence. The dose of a carcinogenic agent represents the product of the duration of exposure multiplied by the concentration of the carcinogen. Rural areas differ from urban areas in that pollutants are present in lower concentrations rather than by their complete absence.

TABLE 1
LUNG CANCER INCIDENCE PEAKS BY YEARS
FOR VARIOUS COUNTRIES

	1949		1952	
	Male	Female	Male	Female
Norway	50-59	70 and over	60-64	70 and over
Italy	50-54	55-59	55-59	65-69
England-Wales	55-59	65-69	60-64	65-69
Finland	55-59	60-64	60-64	70-74
Netherlands	55-59	60-64	60-64	65-69
Scotland	60-64	60-64	60-64	60-64
Ireland	60-64	60-64	65-69	60-64
Switzerland	60-64	70-74	70-74	70-74
Japan	60-64	65-69	60-64	65-69
France	60-64	65-69	55-64	65-69
Australia	60-64	60-64	65-69	60-69
Germany	60-64	60-64	60-64	65-69
United States	60-64	65-69	60-64	70-74
Canada	65-69	60-69	65-69	65-69
New Zealand	65-69	65-69	65-69	70-74

TABLE 2
RATIO OF MALE TO FEMALE WITH REGARD TO DEATH RATES FROM CANCER OF THE RESPIRATORY TRACT

	Early 1930's	1951
England and Wales	3.0:1	5.4:1
Scotland	1.9:1	4.3:1
Finland	5.9:1	5.3:1
Switzerland	6.0:1	6.1:1
Netherlands	3.3:1	5.8:1
New Zealand	2.8:1	4.4:1
United States	2.8:1	4.7:1
Denmark	1.8:1	3.9:1
Union of South Africa	3.8:1	3.5:1
Ireland (Republic)	1.7:1	2.7:1
Australia	2.7:1	4.1:1
Canada	2.1:1	4.2:1
Italy	2.1:1	3.5:1
Norway	1.5:1	2.2:1

While there is universal recognition and acceptance of the difference between men and women in liability to the development of respiratory tract cancer, great divergence of opinion exists as to its significance. Changes in the ratio of male to female death rates are shown in Table 2 for the two periods, early 1930's and early 1950's, for various countries. It will be noted that the increase in death rates from lung cancer has been almost exclusively limited to men and that the rate of cancer for women has been relatively constant within countries. It is equally apparent that great varia-

tion can be noted in the increase in the male rate from country to country. Explanations for this disparity on the basis of better and more readily available diagnostic facilities for men, greater susceptibility in men, or an as yet cryptic sex-linkage for lung cancer development are untenable. Lilienfeld (74), however, very recently summarized a preliminary study on nonsexual-site cancers, including lung cancer, by stating that his findings suggested an endocrine-determined susceptibility to these cancers. There remains as probably a more valid explanation for the lower incidence of lung cancer in women a difference in exposure to the environmental carcinogenic agent and perhaps to a very minor degree a difference in response to it. For, in fact, where exposure to identical environments has been recorded, the liability to lung cancer between the sexes is similar (27). In like fashion, Lew (73) found no difference in the lung cancer rates of women policy-holders belonging to the two insurance groups in his study.

Those ascribing a predominant initiating and promoting role to cigarette smoking offer as an explanation the almost universal onset of smoking in women two to three decades later than in men, and as a corollary they postulate a future rise in the lung cancer rates in women. They neglect to consider that fewer opportunities exist in the instance of women for daily industrial and urban exposure to carcinogenic air pollutants. Women only to a very limited degree in the past have worked in manufacturing installations, have driven in heavy traffic to and from work, and have performed heavy manual labor in dirty polluted environments. Rather, they formerly spent most of their time in residential areas within cities or semi-rural suburban communities. A note of caution appears necessary in interpreting any future rise in female lung cancer rates. Perhaps even more dramatic than the increase in smoking that has occurred in women during the past several decades has been their entry into the previously almost exclusively male business, industrial, and occupational domain. The implications of this are clear.

E. Interpretation of epidemiologic data for selected countries by local investigators.—The interpretations by investigators of their data, which were freely utilized in compiling Charts 1 and 2 and Tables 1 and 2, are important and will be discussed by countries.

Denmark: Clemmessen (14, 15, 17) and his co-workers reported the increase in mortality from lung cancer as beginning approximately in 1931. This increase was most marked in Copenhagen, and a progressively lower incidence was noted in provincial towns and rural areas. Rather than re-

flecting a true difference in the risk in the development of lung cancer, he ascribed the different rates to a delay of 8 years in the onset of the carcinogenic influence in provincial towns and 10 years in rural areas. This conclusion followed an analysis of incidence rates for successive cohorts. The cohort studies further indicated that a 2-decade period of exposure was necessary for the carcinogenic effect to become clinically manifest. He placed the introduction of etiologic agents into the environment during the period between 1900 and 1910. He could find no reason to assume any carcinogenic influence due to atmospheric pollution but rather correlated the increased development of lung cancer with heavy cigarette smoking.

Norway: Kreyberg (68, 69), in reporting the increasing incidence of lung cancer in Norway, noted a seven-fold increase in men and a four and a quarter-fold increase for women in lung cancer between the years 1930 and 1950. In analyzing the phenomenon of lung cancer in Norway, he detected the first evidence of a rise in approximately the middle 1940's with a progressive increase occurring since then. He concluded from a detailed analysis of his data that the panorama of lung cancer increase is not as yet perceptible in true rural districts in Norway, which continue to have the same distribution, histological type, and sex ratio as presented by Oslo a few decades ago. In parallel with Clemmessen, he demonstrated a progressive decrease in lung cancer incidence with decreasing urban community size. He concluded on the basis of a review of 235 cases that the new development (lung cancer increase) was as yet not manifest in truly rural districts. On the other hand, the increase was definitely established in all types of urban settlements. In spite of a decreasing incidence in progressively smaller towns, he noted that the urban predominance was a reflection of an essential urban factor other than smoke and fumes from industry, since towns of identical size had similar rates independent of the degree of industrialization. By applying the 20-year exposure or latency period, the onset of the rise may be postulated as having begun between World War I and the middle 1920's.

Sweden: Specific death rates for lung cancer from Sweden, as reported by Henschen (52), show a pattern of lung cancer increase dissimilar from that of either Norway or Denmark. This increase has been at a slower rate than that noted in either Norway or Denmark, with the over-all incidence figures being more nearly akin to those of the Netherlands (60). Worthy of special comment is the fact that the sex ratio in Sweden differs significantly from that of Denmark and Norway.

United States: Dorn (31, 32) noted that the

in the development of different rates of the carcinogenic effect placed the introduction of the environment and 1910. He reported the increase in lung cancer in Norway, and a four and one-half fold increase in lung cancer in analyzing the data, he detected approximately the increase occurring in lung cancer in true rural districts have the same sex ratio as in the city. In parallel with a progressive decrease in lung cancer mortality on the basis of development, it is not manifest in all types of increasing incidence, he noted that the decline of an acute and fumes of industrial size had degree of industrial exposure or may be postulated after World War I and

lung cancer in men (52), show dissimilar from this increase noted in either rural incidence or those of the industrial comment is given differs significantly in Norway. He noted that the

mortality from cancer of the lung in the United States in both white and nonwhite populations is greater in males than in females, and the divergence is becoming more marked with the passage of time. The increase shows a progressive acceleration from 1930 to 1952. A study of cancer morbidity data for the years 1937 and 1947 in nine metropolitan centers shows incidence differences and variations in the rate that can be explained only by environmental variations. The increase in lung cancer in the United States is present in all ages, with the peak age incidence occurring between the ages of 60-65.

It has been postulated that the increase in lung cancer incidence in the United States became clinically manifest in 1920. By assuming the 20-year period of exposure postulated by Clemmesen, we see that 1900 represents the time of introduction of carcinogens into the environment. This parallelism of the time of onset in the United States with that of Denmark is pointed out by Dorn, who further noted that the incidence rates for males in Copenhagen in the 1943-47 period are surprisingly similar to those for the United States in the 1947-48 period. A primary difference observed was that the maximum incidence in the Danish data occurred between the ages of 55-59, or about 5 years earlier than in the United States. The similarity between Denmark and the United States is even more remarkable in females.

Hoffman and Gilliam (53), in studying the geographic distribution of lung cancer mortality in the United States, showed that cancer mortality is greater in towns than in rural areas among all age, race, and sex groups. It is of interest to note that they used the standardized mortality ratio (S.M.R.) of the Registrar General of England and Wales in reporting their data.

Rigdon and Kirchoff (88) in a more limited geographic study reported an increased incidence of lung cancer in urban residents. They felt that they had correlated the presence of lung cancer with the availability of medical diagnostic facilities and with low patient-doctor ratios. They summarized their findings in saying that "... in our opinion the data available today do not justify the conclusions that the increase in the frequency of cancer of the lung is the result of cigarette smoking. The statement that carcinoma of the bronchus has actually increased in frequency is in our opinion open to question."

England: Stocks (96, 97) showed that for the years 1920-30 there was a marked increase in cancer of the lung in Great Britain, an increase that was real, progressive, and ever accelerating. The distribution of mortality due to lung cancer showed a positive association with the density of

population and maleness. Death rates in the largest towns were more than twice as high as in the country districts. Subsequent studies in 1946-49 and 1952-54 verified this difference in urban-rural mortality. Curwen, Kennaway, and Kennaway (22) in studying cancer of the lung concluded that "... fresh evidence to support earlier findings that mortality from cancer of the male and female lung is positively correlated with population density." Following an analysis over a prolonged period of the same source material as Stocks, they concluded that "the Standard Mortality Ratio (S.M.R.) for cancer of the lung in both sexes, and of the larynx in males, increases with increasing urbanization, that is to say, is greater in the County Boroughs than the Urban Districts, and in the Urban Districts than the Rural Districts. Cancer of the female larynx shows exactly the reverse relationship."

"These trends apply equally when the figures are analyzed according to the separate regions, but there are differences between the regions, which may or may not be due to differences in degrees of urbanization undetected by the classification we have used."

More recently, Stocks and Campbell (98) undertook a study for the purpose of evaluating the lung cancer death rates among smokers and non-smokers in relation to air pollution. He summarized his findings with the statement: "The absolute urban excess is much the same in each smoking group, suggesting that an 'urban' factor is added to the effects of smoking." He further noted, "Differences in smoking habits of the populations can account for only a small fraction of the contrast in total rates, and it is estimated that about half the Liverpool deaths of men from lung cancer arise from cigarette smoking and about three-quarters of the remaining half are due to a factor which is only slightly present in the rural area...."

France: Denoix and Gelle (25) report a regular increase in lung cancer as far back as records exist. The evolution has been regular with no acceleration being demonstrated at any given point. Further, the increase in morbidity is shared by all ages. The over-all death rate from lung cancer in males has increased 30 per cent during the years 1949-52. The actual rate is close to that of the Netherlands and Denmark, all three of which are significantly lower than those for the British Isles.

Australia: Fowler (42) reported a uniform increase in the rate of lung cancer of 7.7/100,000 per year for males and 4.6 for females. He emphasized that, though the rate of increase differs from that of other countries, the exponential pattern is the same. The increase may be presumed to have begun in 1930, with a fragmentary increase occurring in the previous two decades.

New Zealand: Eastcott (38) in analyzing his data was cognizant of the role that immigration to New Zealand played in the modification of his sample. By integrating this factor into his epidemiologic data, he concluded that immigrants from Great Britain to New Zealand are affected by their former environment and that this effect is related to the length of exposure to that environment. The exclusive effect demonstrated was in relation to lung cancer and was established as prior urban residence. He noted, "The chances of dying of cancer of the lung are 30 per cent higher for all United Kingdom immigrants, but for those who are 30 years of age or more on entering New Zealand, the risk is 75 per cent higher. . . . Differences in habits of tobacco smoking are unlikely to contribute to this picture."

Iceland: Dungal (34) in 1950 concluded that the rarity of lung cancer in Iceland was associated with a slow rate of increase in the cigarette smoking habit throughout his country. He felt that atmospheric pollution would play little, if any, role in any future increase in lung cancer. He predicted that a rise in the lung cancer rates would become manifest between 1960 and 1965 if smoking were chiefly responsible for its initiation. In a more recent report (35), he noted a beginning rise in incidence. Though the number of cases is too few to permit any epidemiologic conclusion, he relates the cases to heavy smoking on the part of older people in whom "lung cancer is now beginning to crop up."

F. Racial differences in lung cancer rates.—A study of racial differences in the susceptibility to lung cancer is indicated especially in terms of the guidance it can provide for future studies. Steiner *et al.* (95), in a study of the necropsy records at the Los Angeles County General Hospital, reported, "For present purposes it may be stated that in Mexicans the incidence of lung cancer was as high in women as in men, and that the incidence in the latter equalled that in caucasoid men." Hoffman and Gilliam (53) reported a lower lung cancer rate in Negroes and summarized their findings: "The total rates for the white population are considerably higher than those for the nonwhite, but the difference is more pronounced among males than among females." In marked contrast, Duchon (33) in South Africa found no increased incidence in Caucasians when contrasted with the Bantu native that could not be explained by difference in longevity. Warwick and Phillips (102), in a study of cancer among the Canadian Indians, detected no differences in incidence they could attribute to race. Finally, Sitbon (92) in Algeria reported no racial variations in the incidence in lung cancer.

The foregoing data permit of no conclusion other than indicating a need for future intensive studies.

G. Socio-economic differences in lung cancer rates.—Numerous investigators have been impressed with the variations in cancer incidence on the basis of the socio-economic status of different population groups. In applying this criterion to patients with lung cancer, Clemmessen and Nielsen (16) noted a significant acclivity in the incidence of lung cancer in the male population of the poorer classes in Copenhagen. Kennaway (57), in reviewing the data relating to cancer in the publications of the General Register Office, could not discern any influence of social class upon the liability to lung cancer. He did, however, emphasize ". . . the very considerable effect of urban conditions which suggest some carcinogenic factor to which all classes are exposed." Very recently, Cohart (19) in a limited study paralleled the findings of Clemmessen and Nielsen and concluded, "The incidence of lung cancer was more than 40 per cent greater among the poor than among other socio-economic classes. Unless it is assumed that cigarette smoking is inversely related to socio-economic status, an assumption that probably cannot be supported in fact, then it is reasonable to conclude that important environmental factors other than cigarette smoking exist that contribute to causation of lung cancer." Density of population, proximity to industrial installations, atmospheric pollution, poor socio-economic status, and increased liability to lung cancer constitute a configuration repeated frequently in epidemiologic studies on lung cancer.

H. Occupational lung cancer.—The significance of occupational respiratory cancers resides not only in their role as an important group of industrial diseases but also as denotations of environmental lung cancer truly secondary to atmospheric pollution. They, therefore, should serve as guideposts for the study of lung cancer in relation to air pollution of a general rather than occupational type. Specific pulmonary carcinogens which have been identified in the occupational environment include nickel and chromium, as unequivocal examples of inorganic chemicals, and combustion and distillation products of coal and petroleum, as examples of organic chemicals. The data incriminating radioactive substances have been referred to previously. Though there is no unanimity of opinion, Doll (29), Weil and his co-workers (104), Perry *et al.* (85), and Bonser and her associates (6) have reported highly suggestive data associating increased lung cancer rates with exposure to asbestos, isopropyl oil, arsenic, and iron, respectively.

Worthy of comment is the paradoxical situation relating to chromates and beryllium. While little question exists as to the increased pulmonary cancer incidence associated with exposure to chromates, extensive attempts to induce experimental pulmonary cancers in a broad spectrum of mammalian species have been uniformly unsuccessful (2). Conversely, beryllium, which has but a questionable association with increased lung cancer rates in those occupationally exposed, has been used to produce bronchogenic carcinomas in the lungs of rats (99). The experimental corroboration

interpretation. Attempts to relate increasing lung cancer rates with increasing tobacco consumption, though falling into a broad and variable pattern, may be considered relatively successful. Comparable analyses with respect to motor fuel consumption, increase in asphalt highway mileage, fuel oil sales, and motor vehicle registration show an even more pronounced relationship. It should be noted that a uniform and perhaps critical deficiency in all these associations is the gross failure to correlate the data with the period of introduction of the carcinogen into the environment rather than with

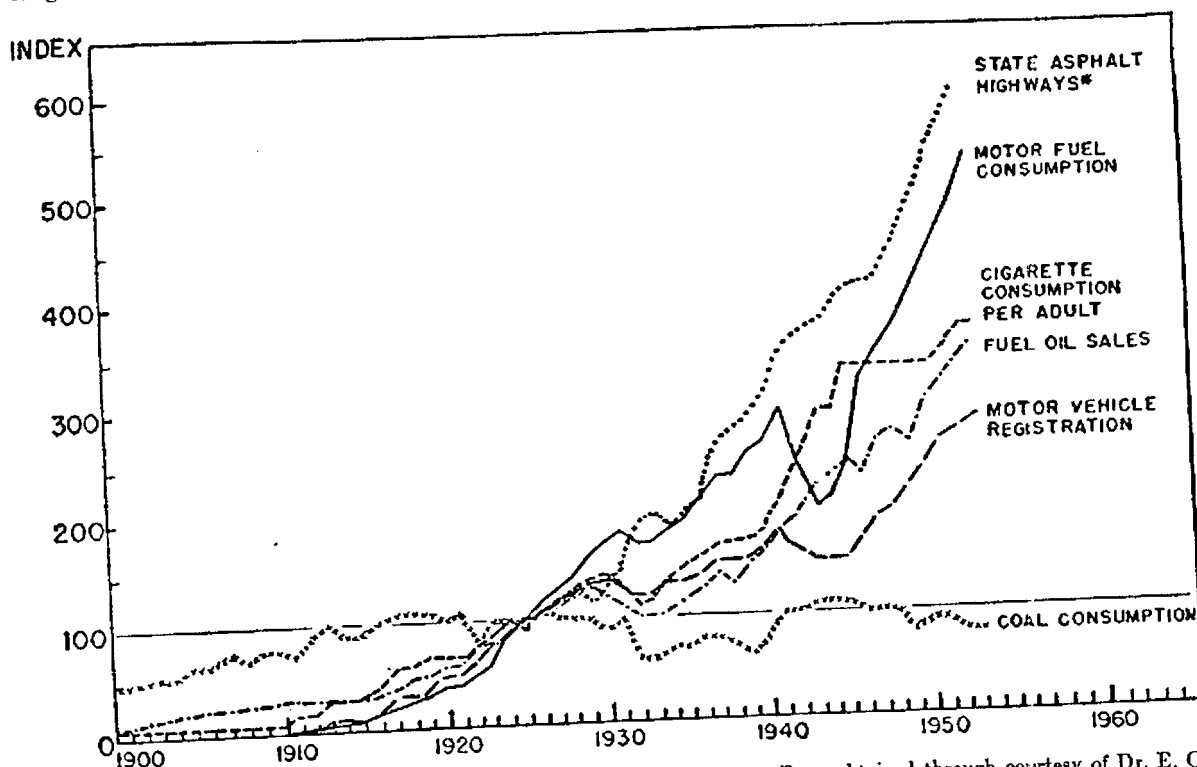


CHART 3.—Trends in selected environmental factors, U.S., 1900-1953 (1924-26 = 100). Note: Cigarette consumption per adult reflects entire population rather than that segment

which smokes. Data obtained through courtesy of Dr. E. C. Hammond.

of radioactivity as a pulmonary carcinogen has been reported following the development of bronchogenic carcinomas in rats (75).

As previously mentioned, the cases of occupational lung cancer recorded thus far are too few to affect materially nation-wide incidence figures. Nevertheless, neighborhood contamination and general atmospheric pollution with these substances is well documented. Additional details referring to these factors will be discussed subsequently.

I. Résumé.—An unbiased analysis of the epidemiologic data reviewed here clearly shows that at this time the data are capable of more than one

the increase in lung cancer rates. In other words, the role and importance of the latency period are either overlooked or minimized. If the latent period is regarded as being approximately two decades in duration, reference to Chart 3 will show that not only does the rise in lung cancer follow more closely factors other than tobacco, but in addition the increase in these environmental factors is more capable of correlation with the latent period. Hueper (55) has similarly shown that a parallelism exists between the increased production of cancer-related chemicals and the rise in lung cancer (Chart 4).

ENVIRONMENTAL CARCINOGENIC AGENTS

A. *Occupational respiratory carcinogens.*—Considerable basic information has been derived from a detailed study of established respiratory carcinogens in occupational environments. First and most obvious is a broadening of the spectrum of environmental carcinogens capable of producing pulmonary cancer.

Second, opportunities for specific documentation of initial exposure time to these agents and their concentrations are possible by referring to industrial records or vital statistics. Latency periods have been shown to vary from less than 10 years to as much as 50 years for the various accepted occupational cancerigenic agents. Regardless of the particular agent studied, the average

cancers have been identified in nickel workers. As noted by Hueper (55), "Carcinogenic dusts consisting mainly of coarse particles are mainly arrested in the nares where they cause cancer of the turbinates. The nasal cancers observed among copper-nickel matte refinery workers inhaling the coarse dust of the roasters illustrates this interrelation." The bronchogenic cancers found in coke-oven and gas-retort workers, and among those exposed to chromates, represent instances of occupational exposure to aerosols, dusts, vapors, or mists of a particle size sufficiently small to permit penetration into the arborization of the tracheobronchial tree.

Failure in this report to detail the association between increased liability to lung cancer in asbes-

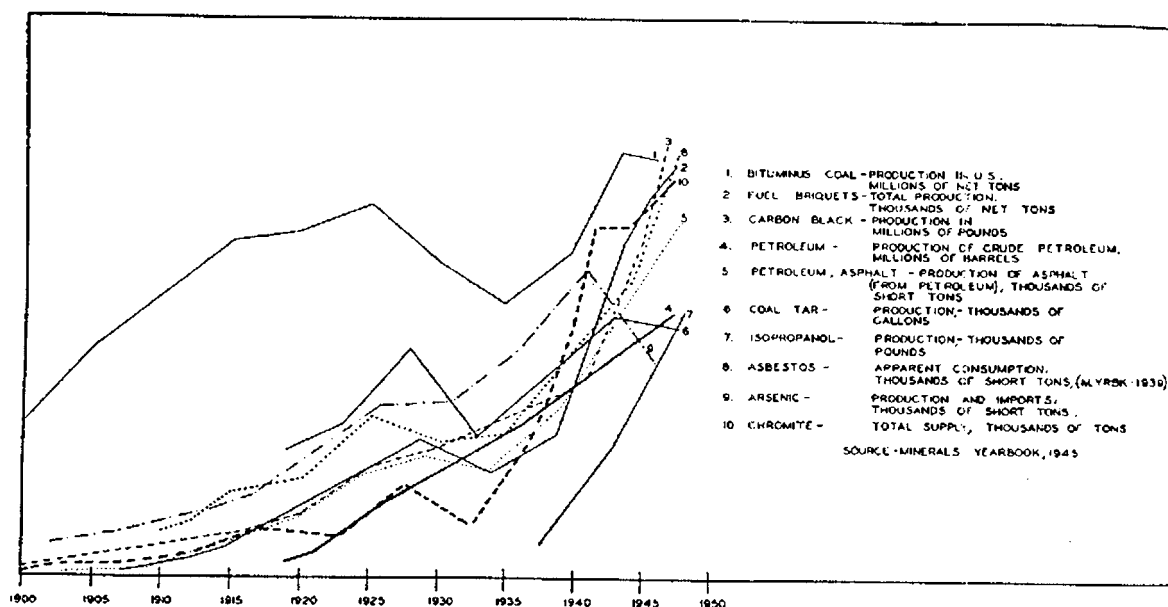


CHART 4.—Rise in annual production or consumption of cancer-related industrial chemicals between 1940 and 1948. Data obtained through the courtesy of Dr. W. C. Hueper.

latent period invariably falls in a 15–25-year time period (55). This is not unanticipated in view of our knowledge that many of these agents in larger doses are sufficiently toxic so as to produce morbidity or mortality well in advance of the time necessary for clinical cancer to develop. As a result, exposure to quantitatively small amounts would appear to be the necessary antecedent for any cancer development.

Third, the development of neoplasms in selective sites of the respiratory tract provides information on the significance of the physical state of the chemical carcinogens. Perhaps foremost among the physical factors is the size of the particulate matter of the carcinogen per se or the carrier on which it is adsorbed. Nasal cancers as well as pulmonary

workers, workers exposed to isopropyl oil, and those in contact with arsenic should not be interpreted as minimizing the importance and validity of the data. Rather, the conclusions to be derived from the data are similar to those already discussed. The reader is referred to the comprehensive and excellent review of Hueper in *Recent Developments in Environmental Cancer* (54) for a critical study of the newer data relating to occupational cancer.

B. *Sources of carcinogenic atmospheric pollutants.*—Of the carcinogenic materials present in the atmosphere, certainly those resulting from the incomplete combustion of organic matter are most universally distributed. Soot, a clinically recognized cutaneous carcinogen from the time of Sir

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Percival Pott (87), is a major component of the smoke formed and emitted into the atmosphere following the partial combustion of solid, liquid, and gaseous fuels. Compounds introduced into the atmosphere from these sources belong primarily to the group of aromatic polycyclic hydrocarbons. A typical carcinogenic representative of this group is 3,4-benzpyrene. Although the gradual shift from solid to liquid or gaseous fuels throughout the world has resulted in quantitative variations in the pollutants emitted into the air, qualitative changes have been minimal. Additional sources of these complex aromatic compounds include the tars and asphalt used for road surfacing. The increase in mileage of asphalt-topped roads has already been referred to in Chart 3. Added to this source of carcinogenic materials is the carbon black introduced into the air secondary to rubber tire wear, tear, and degradation.

An ever expanding and increasing source of emission of carcinogenic hydrocarbons into the atmosphere is liquid fuel used in internal combustion engines. Gasoline engines represent the most universal type of motive power in urban areas, and diesel fuel engines power our buses, trucks, railroad locomotives, and electric power facilities to an ever expanding degree. Not only are large amounts of the known carcinogen, 3,4-benzpyrene, introduced into the air by the combustion of petroleum fuels, but the reaction products of non-combusted gasoline in their aliphatic, nonaromatic, polycyclic state possess experimental carcinogenic potency (63, 67).

Supplementing these compounds there are emitted into the atmosphere measurable concentrations of inorganic materials demonstrated to be occupationally associated with increased liability to lung cancer development. Included would be heavy metals, light metals, and inorganic dusts.

Quantitation of a known carcinogenic substance obtained from an atmospheric pollution source was first reported in 1949 by Goulden and Tipler (46) who, by means of fluorescence spectroscopy, identified 3,4-benzpyrene in a representative sample of chimney sweep's stock in a concentration of 300 mg/kg of soot.

C. *Known and suspected carcinogenic agents in the atmosphere.*—Waller (100) sampled the atmosphere at ten different sites in several cities in Great Britain and demonstrated the presence of 3,4-benzpyrene in the air. The highest concentration of 4.5 $\mu\text{g}/100$ cubic meters was obtained in London, and the lowest noted was in Bristol, with 1.3 $\mu\text{g}/100$ cubic meters measured there. A mean concentration of 2.6 $\mu\text{g}/100$ cubic meters was obtained for all sites studied. The concentration in London

was half again as great during the winter as it was during the summer, and during foggy weather the concentration was over 4 times that on clear days. While the amount of benzpyrene retained in the lungs is, of course, impossible to assess at present, he calculated the respiration of approximately 12 mg. of benzpyrene during an average 70-year life span. Blacklock, Kennaway, Lewis, and Urquhart (5), following an analysis of the carbon content of human lungs, estimated that approximately 16 mg. of benzpyrene may be inhaled during a life-time. It should be noted that the primary atmospheric source of these compounds in Great Britain is from combustion of coal, with as yet undetermined amounts contributed by vehicular exhausts.

Kotin (64) and his associates studied the Los Angeles atmosphere and demonstrated a presence of 0.84 mg. of 3,4-benzpyrene per million cubic feet of atmosphere. In marked contrast with London, this carcinogen could be attributed almost entirely to the exhaust products of gasoline and diesel engines. A detailed study of gasoline and diesel engine exhausts revealed quantities estimated up to 120 μg . of benzpyrene in 1-minute samples of gasoline engine exhausts and up to 1.7 mg benzpyrene/minute from diesel engine exhausts (65, 66). In comparing the ratio of pyrene to benzpyrene in the atmosphere with that at the vehicular exhaust source, Falk and his co-workers (40) noted a reversal of the ratio, with benzpyrene being present in greater concentration than pyrene in the atmosphere. This phenomenon was explained through study of the survival of various polycyclic aromatic hydrocarbons in the atmosphere. Compounds were tested in their pure state and while adsorbed on soot and following exposure to washed air and smog. In all instances benzpyrene was significantly more stable than was pyrene. In fact, it was virtually indestructible in the dark. Cooper and Lindsey (20) emphasized the ubiquity of atmospheric pollution following analysis of 1 kg. of freshly fallen snow in Hertfordshire, England. The snow contained 1–2 μg . of pyrene and traces of 3,4-benzpyrene and anthanthrene.

Clemons and Miller (18) divided the city smoke they collected into three fractions. The presence of 3,4-benzpyrene was detected in one of these fractions.

The spectrum of carcinogenic agents present in the atmosphere has very recently been broadened following the report of Kotin and Falk. Following skin painting in C57BL mice and following inhalation in strain A mice and C57BL mice (63, 67), they found the oxidation products of aliphatic hydrocarbons to be carcinogenic. The implications of the pulmonary neoplasms induced with these

agents will be discussed. The chief source of aliphatic materials in the atmosphere is unburned gasoline.

Mention should be made of the presence of arsenic in the atmosphere. The sources would include primarily the burning of fuels and secondarily insecticide use and metallurgical sources. Goulden (45) and his co-workers measured the arsenic content of the atmosphere at eight sites in England during the winter and summer. They computed from their data that approximately 0.5 mg. of arsenic as arsenic trioxide would be respired during the course of 1 year. While this amount is low, its possible role in association with other known carcinogens should be kept in mind.

The concentration of metals in the atmosphere has been determined by investigations of the Stanford Research Institute (93) for Los Angeles and by Chambers and his co-workers (13) for several other American cities. The amounts present, especially of chromium and nickel, are minimal. As in the case of arsenic, however, possible additive or synergistic effects with hydrocarbon carcinogens should not be forgotten.

Perhaps the most controversial of atmospheric factors of theoretical carcinogenic significance are those relating to ionizing radiation. In a comprehensive study of radioactive material in the atmosphere carried out in London, in Manchester, and in the country at Rothamsted, Dawson (24) concluded that no considerable difference existed between urban and rural districts. Day-to-day variations were marked and could be related to the activity of the atmosphere in terms of wind velocity: "The more stationary the air, the greater the activity." At all times amounts present were exceedingly small in comparison with the lowest concentration considered harmful to man.

D. Biologic demonstrations of carcinogens with atmospheric pollutants.—Biological demonstration of carcinogenicity with materials which are frequent sources of air pollution was successfully undertaken by Passey (84), who in 1922 reported the production of experimental cancers in mice following painting with ether extracts of household chimney soot. Campbell (11) similarly produced skin tumors in mice following painting with tars extracted from chimney soot. Leiter (70, 71) and his co-workers reported the development of subcutaneous sarcomas in mice injected with tars extracted from the atmospheric dusts of several American cities. The extracted tars were injected in amounts varying from 21 to 71 mg. suspended in 0.25 cc. of tricapylin. More recently, Kotin and his co-workers reported the production of skin

cancers in C57BL mice following painting with extracts of Los Angeles atmosphere and materials collected from the exhaust of gasoline engines and diesel engines (64-66).

The preceding representative examples of skin tumor production in mice, coupled with analytical studies previously mentioned, provide direct biologic evidence of carcinogenic materials belonging to the aromatic polycyclic hydrocarbon group of compounds in several pollution sources and in the atmosphere per se. The traditional carcinogenicity of these compounds is well known. In 1955 Kotin and his co-workers reported the successful production of skin tumors in mice using aromatic polycyclic hydrocarbon-free atmospheric extracts (61). The samples used for the tumor production consisted of oxidation products of aliphatic hydrocarbons formed in the atmosphere in accordance with the theory as developed by Haag-Smit (48, 49) and since confirmed by others (103). He postulated a primary photochemical reaction between oxides of nitrogen (a product of internal combustion engine exhaust) and organic molecules: alcohols, aldehydes, ketones, acids, and hydrocarbons, both as emitted from vehicular exhaust and as introduced into the atmosphere through the volatilization of uncombusted gasoline. Ozone forms as a result of a radical chain reaction. While less is known about the reaction products other than ozone, the ozone itself is known to react spontaneously with unsaturated molecules which also are present in gasoline engine exhaust and unburned gasoline. The reaction products consist of an aerosol which was used for skin painting.

The products of this subsequent reaction (ozone plus hydrocarbon) occurring in the atmosphere are more completely understood than those of the primary free radical reaction. This reaction is instantaneous and produces an ozonide which in the presence of moisture gives rise to a variety of peroxides. These compounds result in aldehydes and acids. The peroxides react subsequently with aldehydes and acids, producing peracids which then react with unsaturated hydrocarbons to yield epoxides. A simplified schematic representation of these reactions is shown in Chart 5. It should be noted, however, that many additional side reactions take place simultaneously, reducing the yield of these compounds. The tumor yield with these compounds was less than that observed with atmospheric extracts containing aromatic polycyclic hydrocarbons.

The broadening of the spectrum of carcinogens in the atmosphere with these agents is of special significance in that their entry into the environ-

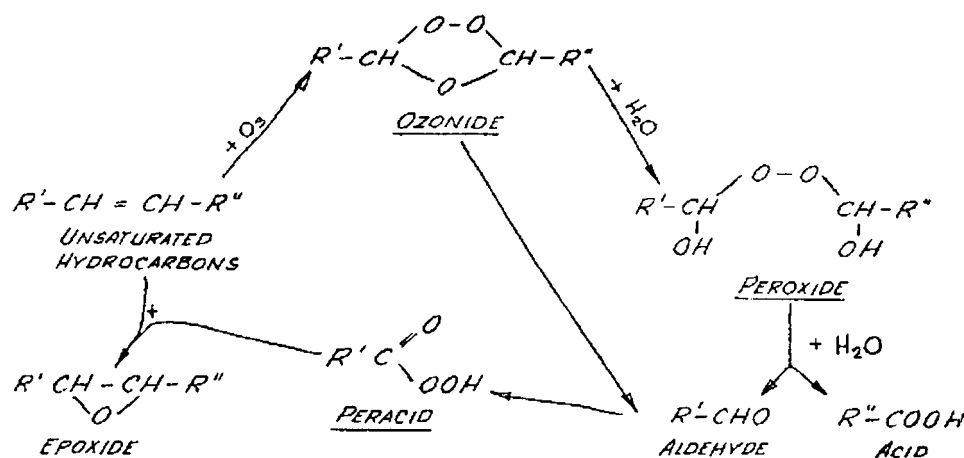
ment is compatible with their action as initiating or promoting agents in the increasing incidence of cancer of the lung.

Attempts to induce or increase the yield of pulmonary tumors by inhalation experiments were first reported by Campbell (8-10), who exposed mice in inhalation chambers to resuspended sweepings of dust from tarred roads. In addition to the development of cutaneous tumors, he noted a higher incidence of pulmonary tumors in his test mice than in his controls.

Seelig and Benignus (90, 91), in one of two experiments, used chimney soot as an inhalant for Buffalo strain mice and reported an 8 per cent primary pulmonary tumor yield in contrast with a 2

of exposure and ending with the 52d week. At all intervals the number of tumor-bearing mice, the number of multiple tumor-bearing mice, and the total tumors in the test chamber were significantly greater than those in the control chamber. Kotin further has demonstrated the production of pulmonary tumors in C57BL mice exposed to a similar atmosphere of ozonized gasoline.¹

Bronchogenic cancers, apparently of the type seen clinically, have thus far been produced experimentally only in rats. Vorwald (99) exposed rats for over 1 year to an atmosphere containing soluble and insoluble beryllium salts and noted the development of true bronchogenic neoplasms. Dutra (37) produced osteogenic sarcomas in ex-



UNDERLINED COMPOUNDS ARE
SUSPECTED OF CARCINOGENICITY

CHART 5.—Schematic representation of oxidation reactions of aliphatic compounds

per cent yield in their controls. In a second experiment they adsorbed gas-work tar onto carbon black for inhalation by C57BL mice. No pulmonary tumors were produced in the test mice.

McDonald and Woodhouse (77) exposed mice of apparently indifferent strains to dust obtained from city thoroughfares and to dust collected from the air-purifying system of a hospital adjoining an industrial area. While they reported that they were unable to show the striking increase in their test mice that Campbell reported in a similar experiment, they did show an exaggerated production of pulmonary adenomas in their test mice.

Kotin and Falk (63) reported an exaggerated incidence of pulmonary tumors in strain A mice exposed to an atmosphere of ozonized gasoline. They removed mice from the inhalation chamber at 4-week intervals, beginning with the 24th week

per experimental animals exposed to an atmosphere containing beryllium oxide. Lisco and Finkel (75) observed neoplastic changes in the bronchial epithelium in rats exposed to an aerosol of radioactive cerium. The carcinogenic powers of ionizing radiation for tissues other than the lung are well known.

DISCUSSION

A. *Epidemiologic considerations in interpretation of pathogenesis.*—The epidemiologic data relating to lung cancer as reviewed here show marked contradictions. The inconsistencies appear to be wholly irreconcilable if but a single initiating and promoting agent were to be regarded as being responsible for the increasing incidence of lung cancer. Of the two suggested major etiologic factors, cigarette smoking alone appears the least

¹ P. Kotin, unpublished data.

capable of adaptation to the panorama of lung cancer as it is currently manifest. The limitations of the tobacco concept of etiology are evident in studies showing differences in lung cancer rates on the basis of socio-economic status. Geographic studies singling out urbanization as the exclusive variable in groups with contrasting lung cancer rates cast further doubt on the validity of the major role assigned to tobacco in pulmonary cancer. The urban-rural difference in incidence could very possibly, in one or even several countries, be a manifestation of difference in smoking habits. It is unlikely, however, that peoples with different cultures, economics, and mores should have identical smoking habits and patterns. More readily tenable is the hypothesis that urban-rural differences are a true reflection primarily of the difference in the cleanliness of the atmospheric environment. Data already referred to in the text as a basis for this observation are available from epidemiologic studies made in Norway (68, 69), New Zealand (38), the United States (31, 32, 43, 44, 55), and Denmark (14-17). These data emphasize differences in urban-rural cancer rates and the greater incidence in the low socio-economic groups. Clemmessen interprets differences in rural-urban incidences as evidence of difference in the onset of exposure to the carcinogenic agent. A more likely explanation would be that the concentrations of carcinogens in the atmosphere in rural areas are lower as a result of fewer sources of atmospheric pollution and dilutions of the pollutants carried to the country by winds from the city. Accepting differences in urban-rural rates as a function of atmospheric pollution, one can readily reconcile the parallelisms noted between lung cancer rates and density of population and degree of urbanization. Not the least significant of the epidemiologic considerations concerned with atmospheric pollution are the documented instances of occupational lung cancer. The parameters of the exposure and the response of the host are defined within measurable limits. Sex differences in lung cancer rates are not irreconcilable with the concept of atmospheric pollution as a major etiologic factor. The contrasting social and economic roles of men and women result in a more prolonged exposure to a greater concentration of polluted atmosphere on the part of men.

The conviction that air pollutants possess the ability to initiate and promote pulmonary cancer in no way precludes the role of other possible factors. Stocks and Campbell (98) in their recent study of the combined effect of smoking and air pollution on lung cancer death rates demonstrated an urban-rural ratio of 9:1 for nonsmokers residing

in Liverpool as compared with those living in adjacent rural areas. At every level of smoking intensity, Liverpool rates exceeded the rural rates. As smoking increased, the disparity progressively decreased to a level where the difference approached a factor of less than two. They concluded that a dual role now appears to be tenable as a working hypothesis for the guidance of future studies. Since not all residents in any area smoke and the very method of smoking varies from individual to individual, attempts to correlate lung cancer incidences with tobacco consumption on a per capita basis in any given population group denote a type of epidemiologic gerrymandering. In a given community, however, a constancy in exposure to atmospheric pollution or lack of exposure can be related to residence site, occupation, and duration of these two.

The inconsistencies and the irreconcilable factors in the epidemiologic data make it amply apparent to this reviewer that the contributions of laboratory data will be of ever increasing significance in the ultimate revelation of the mechanisms and etiologies of lung cancer.

B. Role of chemical and physical factors in pathogenesis.—Of equal significance to the epidemiologic data are the chemical and physical data relating atmospheric pollution to the pathogenesis of lung cancer. The demonstration of 3,4-benzpyrene in urban atmospheres has been successful wherever undertaken. On the basis of current knowledge, the concentration and the atmospheric survival of this carcinogen are sufficiently great to postulate a biological effect in humans. The recent demonstration by Kotin and his co-workers of the carcinogenicity of oxidation products of aliphatic hydrocarbons has made the incrimination of the atmosphere more certain. The ubiquity of gasoline, the most common source of these compounds, combined with the temporal aspects of the introduction of liquid fuels permits of epidemiologic integration as well.

The combination of carcinogenic aromatic polycyclic hydrocarbons, oxidation products of aliphatic hydrocarbons, and known occupational carcinogenic agents which pollute the atmosphere warrants suspicion of the atmosphere as a factor in the pathogenesis of human lung cancer. Complete ignorance of any possible additive or synergistic effects they may manifest and the absence of exactitude of dosage in man make their diligent study imperative.

The presence of 3,4-benzpyrene in the combustion products of tobacco has been reported. Cooper and Lindsey (21) recovered 4 μ g. of this carcinogenic agent from the smoke of 500 cigarettes. This

concentration is less than that noted in the atmosphere in terms of total amounts respired by those exposed. It is clear that the alleged cause-and-effect relationship ascribed to smoking cannot currently be predicated on the presence of 3,4-benzpyrene in tobacco smoke. Assuming that the average total of inspired air measures up to 7,500 cubic meters per year as calculated by Stocks (98), the average resident of Liverpool, whether smoker or nonsmoker, would inhale 450 μg . of benzpyrene. This does not take into account the other presumably carcinogenic materials in the air.

Physical factors play a significant role in the deposition of particulate matter in the respiratory tract. The per cent retention of particulate matter in the lung on the basis of particle size is shown in Charts 6 and 7. Dautrebande (23) correlated the location of particulate deposition with specific sites in the tracheobronchial tree. The particle size of the carcinogenic material in the Los Angeles atmosphere as measured by Kotin¹ and others is wholly consistent with penetration and settling out of these particles distal to the trachea. The relative absence of primary tracheal carcinoma is not an indication of local tissue immunity but rather reflects the failure of particles to settle out. Those particles capable of settling out on the tracheal mucosa are identical in size with those trapped in the nose, epipharynx, and accessory

nasal sinuses. Particles of smaller size down to approximately 0.25μ settle progressively distally in the arborization of the bronchi. Those less than 0.25μ remain suspended in tidal air until a sufficiently miniscule size is reached so that Brownian movement can produce precipitation.

C. *Significance of experimental laboratory data in pathogenesis.*—As suggested above, the inconsistencies and contradictions in the epidemiologic data placed increasing responsibility and emphasis on the laboratory for the elucidation of etiologic

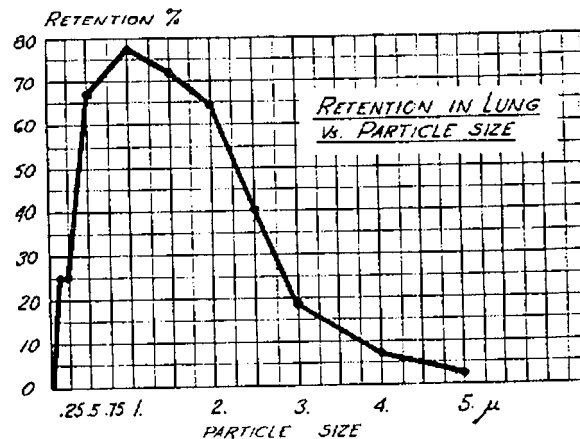


CHART 6.—Per cent retention of particulate matter in lung in relation to particle size.

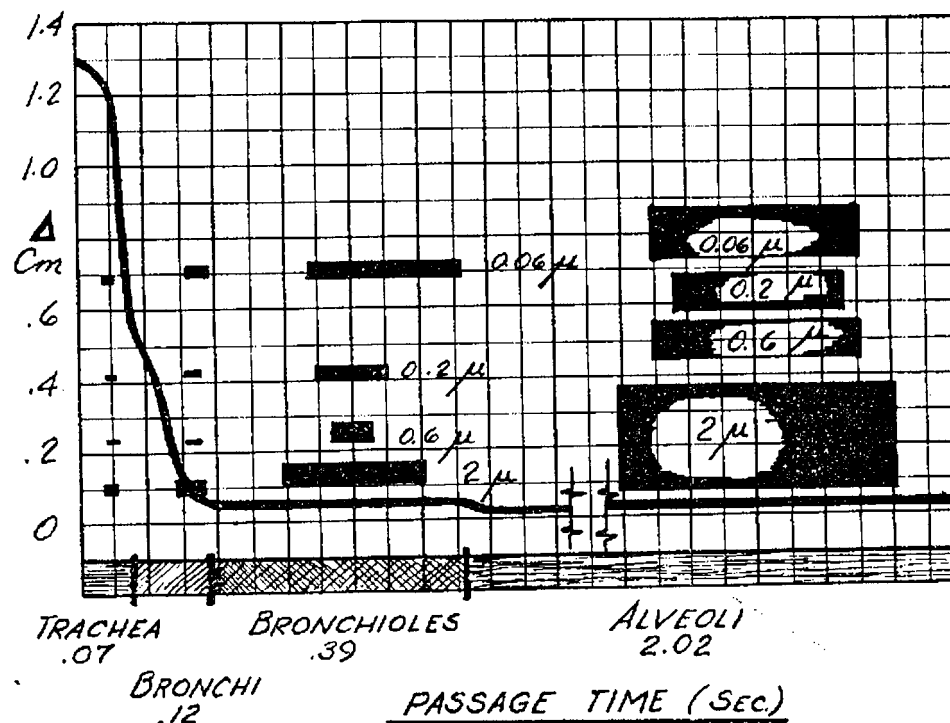


CHART 7.—Anatomical pattern of deposition and time of passage of particulate matter in relation to particle size (after Dautrebande).

agents and mechanisms for lung cancer development. The chemical demonstration of carcinogenic agents in the environment and their successful use for the production of tumors in experimental animals do not prove or even especially strongly suggest a like relationship in the instance of man. When, however, a demonstrable parallelism exists between epidemiologic data and laboratory findings, greater significance accrues to both. Medical history is replete with examples in which laboratory findings have been proved ultimately to have their counterpart in the human experience. Exceptions have been very few.

D. *A theoretical mechanism for the pathogenesis of lung cancer.*—By means of integrating laboratory findings and experimental data, the author has arrived at a theoretical mechanism for the pathogenesis of lung cancer. In spite of the presence of soot in the atmosphere for many centuries and its association with cutaneous cancer, it is only within the last several decades that lung cancer has become a problem of epidemic proportions. Skin cancers as occupational responses to soot have long been known. It has been noted by Steiner (94) and Falk and Steiner (41) that carcinogenic hydrocarbons adsorbed on soot are biologically ineffective until they are separated by elution from the soot particles. It has been postulated that in the case of the skin, sebaceous secretions provide the necessary polar substances for the elution of the carcinogenic materials. Experimentally, Kotin and his co-workers (62) have demonstrated poor elution powers for the mucous secretions in the respiratory tract. However, the introduction of aliphatic polar compounds into the atmosphere makes available an environmental source of an eluting agent capable of entry into the respiratory tract.

The simultaneous respiration of the carcinogen-laden soot and the eluting agent provides a mechanism for biological activity of the carcinogen. This mechanism is unlikely to occur when soot alone is breathed.

Aliphatic hydrocarbons and their oxidation products in the air were further incriminated in the pathogenesis of cancer when it was shown that they could induce both skin cancers and alveolar carcinomas in mice. Cutaneous cancers resulted from the painting of mice, and lung tumors were produced by inhalation. The dual capacity shown for these compounds makes them suspect on a laboratory basis. When the laboratory data are considered along with epidemiologic data, it is apparent that these aliphatic materials were introduced into the atmospheric environment at a time consistent with their having etiologic significance.

In addition to the eluting role and carcinogenicity demonstrated for these aliphatic materials, they have been shown to be potent irritants for the respiratory mucosa. In common with other atmospheric irritants introduced secondary to industrialization, these materials transiently affect the respiratory mucosa by interfering with ciliary activity and normal mucous secretion. The interference with these normal resistance factors permits the accumulation of particulate matter at selected sites in the tracheobronchial tree as shown by Kotin. The sites are chiefly at bifurcations and angulations in the respiratory arborizations. This accumulation allows prolonged residence of particles on the respiratory epithelium. The elution of carcinogens is facilitated, as has been demonstrated by analytical procedures. Diffusion of intact soot particles occurs into the respiratory epithelium, as has been demonstrated by electron microscopy. A study of the respiratory epithelium in lungs obtained at necropsy from unselected cases shows that the most common sites of metaplasia are similar to those in which soot accumulates in experimental animals.²

In essence, it has been demonstrated that carcinogens have become significant in the pathogenesis of pulmonary cancer within the past half-century in spite of their atmospheric presence for several centuries. This transformation may be attributed to (a) the atmospheric presence of carcinogens in a size range consistent with their respiration and retention within the lung; (b) the introduction into the atmosphere of polar substance capable of eluting adsorbed carcinogens from soot particles following their deposition in the respiratory mucosa; (c) interference with the normal defensive mechanisms of the bronchial epithelium by abnormally affecting ciliary motion and mucous secretion; (d) the introduction of cancerogenic nonaromatic polycyclic hydrocarbon agents into the air. Included in this group are aliphatic hydrocarbons and their oxidation products, metals, inorganic dusts, and probably macromolecular substances.

Any conceivable role of tobacco smoking in the pathogenesis of lung cancer appears to this reviewer to be at the level of a nonspecific irritant or eluting agent for previously deposited carcinogenic agents. There is at present no convincing evidence that tobacco possesses the necessary qualifications for the initiation and promotion of lung cancer.

CONCLUSION

Pulmonary cancer in common with all neoplasms may be properly regarded as having several

² D. Tatter, E. M. Butt, and P. Kotin, unpublished data.

factors concerned with its initiation and promotion.

A review of the factors relating atmospheric pollution to lung cancer both on the epidemiologic and experimental levels warrants its incrimination as one of the dominant agents etiologically associated with the increase in mortality from lung cancer now being reported in various regions of the world.

Other agents, including the frequently accused excessive use of tobacco, appear to be capable of playing only a secondary role in the increase in lung cancer rates. They may conceivably act as promoting agents so that in the presence of a prepared or initiated soil they can act either synergistically, as additives, or as cocarcinogenic agents.

Refinements in both epidemiologic and laboratory data are indicated as are the new methodologies for the study of the phenomenon of lung cancer.

ACKNOWLEDGMENTS

The assistance of Dr. Hans L. Falk is gratefully acknowledged in relation to the chemical phases of this review.

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It is noted that carcinogenic agents in the past half-century have been present for a long time. The presence of carcinogenic agents in the atmosphere with their respiratory system; (b) the inhalation of substances from soot, the respiratory system, normal epithelium by and mucous cancerogenic agents into the respiratory system, hydrocarbons, metals, inorganic molecular sub-

Looking in the light of this, the irritant or carcinogenic evidence qualifications for lung cancer.

With all the foregoing several published data.

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