Environmental Causes of Lung Cancer

By W. C. HUEPER, M.D.

TO BE SCIENTIFICALLY acceptable, any theory on the etiology of lung cancer must reflect a critical, balanced, and competent analysis of the entire epidemiological, medical, and experimental evidence concerning the types and environmental distribution of and contacts with all known or suspected exogenous agents incriminated in respiratory carcinogenesis for environmental, occupational, or medical reasons. It is only through such scrutiny that significant and worthwhile information may be obtained as to the relative role which the various individual respiratory carcinogens have played and are playing in the production of lung cancer. The following facts and observations form an important and integral part of such an assessment.

A large amount of factual and circumstantial evidence of epidemiological, clinical, pathological, and experimental types incriminates a number of general environmental and specific occupational air pollutants in the causation of cancer of the lung. Exposure to these agents exists for considerable parts of the population in general as well as for large groups of industrial workers. Epidemiological observations on hand indicate that only a part of the environmental agents which may cause lung cancer are known. However, an appreciable number of them have been identified, such as dusts and fumes of nickel, chromium compounds, arsenicals, asbestos, coal tar, soot, vapors or mists of

Dr. Hueper is head of the Environmental Cancer Section of the National Cancer Institute, Public Health Service, chairman of the Cancer Prevention Committee of the International Union Against Cancer, and a past president of the American Society for the Study of Arteriosclerosis. He is the author of more than 200 publications on environmental cancer and related subjects, including the book "Occupational Tumors and Allied Diseases," published in 1942.

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Readers wishing the data in full may purchase copies of the monograph from the Superintendent of Documents, Government Printing Office, Washington 25, D. C. A limited number of free copies are available on specific request to the Public Inquiries Branch of the Public Health Service. Copies will be found also in the libraries of professional schools and of the major universities and in selected public libraries.

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isopropyl oil, certain cancer-producing petroleum derivatives, and radioactive ores and gases. Significant amounts of recognized cancer-producing chemicals, moreover, have been demonstrated in the exhaust of gasoline or diesel engines and in the atmospheric pollutants of English and American cities. They are contained also in the dust of asphalted roads and in the carbon black constituting a considerable component of automobile tires. The number, variety, and amounts of cancer-producing contaminants of the general and occupational environment have grown during recent decades with the development of modern industry and the increased use of industry-related products. Numerous epidemiological observations strongly suggest that industry-related factors have played an important causal roll in the rise of lung cancers in the industrialized countries of the Western World observed during the last 50 years.

Epidemiology

The general epidemiological evidence supporting this concept is as follows: While a real, definite, and progressive rise in lung-cancer frequency has been noted since the turn of the century, this development revealed marked variations in its time of onset, in its relative degree, and its progression rate in different countries and localities. In some countries, a rise in lung cancer death rates did not become apparent until after 1930 (Denmark, Norway, Italy). In others, and particularly in highly industrialized countries (Germany, Switzerland, England), this change was demonstrable soon after 1900.

English, German, Austrian, and American observations show consistently and significantly higher lung cancer death rates for inhabitants of urban-industrialized areas than those prevailing for rural areas.

Industrial life insurance male policyholders coming from low-income groups and engaged in manufacturing, mining, transportation, and other occupations with possible and often specific respiratory health hazards were found to have lung cancer rates which were 30 to 50 percent higher than those present for general policyholders, mainly composed of white-collar workers and the self-employed.

There was not only a marked irregularity in the progression rates of lung cancer deaths and morbidity for 10 different metropolitan areas in the United States, according to surveys made in 1937 and 1947, but the annual lung cancer death progression rates in the United States were higher for 1914–30 than for 1931–44. Allowing a 20-year latent period, one would expect that the progression of the death rate in recent years would be much higher than in the early period, if cigarette smoking would represent a major causal factor in the rise of lung cancer frequency.

Considering the remarkable variations in the male-female sex ratio at different times, in different localities and different demographic groups ranging even during recent years from 1:1 to 50:1, it is most unlikely that such discrepancies and changes are attributable to fluctuations in the intensity of one single factor, such as cigarette smoking, but appear to be due to alterations in the type and extent of action of a broad spectrum of environmental carcinogenic agents affecting the members of the two sexes to different degrees. Men are for occupational and environmental reasons more intensely and consistently exposed to a variety of known environmental cancer-producing atmospheric pollutants than women.

The various lung cancer-causing agents elicit lung cancers of various structural types. No special type of lung cancer is characteristic for any special carcinogenic factor. None of the main structural types was rare at any time or has any exclusive connection with cigarette smoking.

There does not seem to exist any parallelism between the lung cancer death rate and the per capita consumption of cigarettes for different countries. In fact, the rise in lung cancer death rates parallels as closely, or even more closely, the rise in production and/or consumption rates of motor fuel, coal tar, petroleum products, and several carcinogenic metals and minerals, or the construction of asphalted roads, than that of cigarettes.

Industry-Related Factors

Occupational and epidemiological investigations present additional circumstantial evidence

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in support of industry-related factors as important causal agents in the production of lung cancer.

An analysis of lung cancer frequency among members of seven large industrial groups lists nonferrous metal workers with the highest rate, followed by transportation workers, while farm laborers have the lowest rate. Other investigations indicate that workers exposed to soot from coal- or oil-burning furnaces or powerplants, to metal fumes and dusts or arsenicals, have excessive lung cancer death rates. Included in these occupational groups are operating railroad workers, engineers, stokers, chimney-sweeps, oilers, furnacemen, mechanics, welders, polishers, patent fuel workers, marine engineers, wipers, foundry workers, gashouse workers, tar workers, road workers and asphalters, sheet-metal workers, boilermakers, crane operators, smelter workers, molders, boiler scalers, lathe workers, iron ore miners, grain dockers. Since the total number of members of such occupational groups is considerable, it cannot be maintained that occupational cancer hazards account for only an insignificant portion of the total lung cancer deaths. It is, moreover, evident that abnormal occupational lung cancer hazards seem to exist only for certain groups of workers and that for this reason they must be related to exposures to definite, specific, and identifiable substances. There is scarcely any likelihood that such occupational differences in lung cancer liability are attributable to fundamental differences in cigarette smoking habits between members of the various occupational groups.

Occupational Groups

Occupational cancers of the respiratory organs (lung, larynx, nasal cavity, and nasal sinuses) provide conclusive evidence of the existence of industry- and occupation-related respiratory cancer hazards for members of well-defined worker groups having contact with specific agents.

Such respiratory cancer hazards have been demonstrated for retort workers of gas manufacturing plants and coke ovens, for workers employed in crude paraffin oil pressing operations, for isopropanol manufacturers, for nickel refinery workers, chromate manufacturers and chrome pigment handlers, for arsenical insecticide producers and users, for asbestos workers, and radioactive ore miners. The lung cancer attack rates for members of these occupational groups are many times those found for the general population of same age and sex. While the great majority of the victims of occupational respiratory cancer are males, because only males are employed in most of these hazardous occupations, whenever females also were employed, such as in the asbestos industry, and have the same type and a similar degree of exposure, there is a trend toward an equalization of the lung cancer attack rates for the two sexes.

Exposures to occupational respiratory cancer-producing agents are sometimes characterized by a typical symptom complex involving not only the respiratory organs but also other tissues and organ systems. The symptom complex related to coal tar cancer provides a striking illustration of the value of this type of medical evidence in support of a specific etiology of a lung cancer.

Medical evidence amply attests to the fact that contact of the skin with coal tar pitch, asphalt, soot, creosote, and tar oils has been responsible for several thousand cases of occupational cancer of the skin, scrotum, and lip. There are, moreover, important cutaneous stigmata characteristic of occupational contacts with these products. These manifestations form a well-defined symptomatic coal tar cancer pattern consisting of chronic dermatitis, comedones, folliculitis, hyperpigmentations of the skin, leukoderma, cutaneous atrophies, warts, papillomas, cornified horns, and light hypersensitivity. Since respiratory exposure to coal tar fumes always entails also cutaneous contact with this material, pathological symptoms from both the cutaneous and respiratory systems combine in the composition of the symptom complex elicited by exposure to coal tar and related problems.

In my opinion, the medical evidence supporting a major role of cigarette smoking in the causation of lung cancer, on the other hand, is inadequate. It is surprising to note the absence of positive statistical associations between lung cancer and cigarette cough, although this latter symptom is clinically characteristic of chronic chain smokers. Despite the fact that

the lips and oral mucosa are constantly bathed in the tarry liquor oozing from the tip of the cigarettes and despite the contact of these parts with the smoke coming from the cigarettes, there is no statistical association with cancer of these parts.

The claim that no tarry material exudes from the cigarette tip cannot be taken seriously, considering the well-known fact that chronic cigarette smokers have notoriously dark-brown-stained fingers. There is, on the other hand, not a single case of cancer of the fingers attributable to cigarette tar available, which would form the equivalent to the numerous cases of coal tar cancers of the hands placed on record. Such a lack of confirmatory medical evidence cannot conveniently be disposed of by assuming a specific "immunity of the skin of the first three fingers" to tobacco tar.

The claimed absence of a positive association between lung cancer and the habit of inhaling cigarette smoke also is inconsistent with the rule that the incidence rate of occupational cancers increases with the intensity of exposure to a carcinogen. The medical considerations on cigarette-smoke cancer of the lung thus reveal a number of serious and fundamental defects and contradictions.

Carcinogenicity of Industrial Agents

Experimental investigations have furnished ample proof of the carcinogenicity of many of the agents involved in the production of human respiratory cancer of occupational origin.

Such an experimental evidence is available for coal tar, pitch, soot, various mineral and petroleum oils, nickel, and radioactive substances. For the carcinogenic action of constituents of coal tar there exists for instance, a large mass of experimental observations made on various species, such as mice, rats, rabbits, dogs, and chickens. Specific carcinogenic polycyclic hydrocarbons, moreover, have been isolated from coal tar and pitch, soot, mineral oils, and carbon black, and such findings have been confirmed by various investigators.

The experimental evidence concerning a carcinogenic action of tobacco tar, on the other hand, is remarkably uncertain. There exists a considerable discrepancy in the observations made by various investigators as to its carcinogenic action on mice and rabbits. While the majority either did not find any or a very mild carcinogenic effect when tobacco tar was applied to the skin of mice or rabbits, two groups of investigators reported remarkable results in this respect. It is rather disconcerting that the latest of these reports made only a year ago could not be confirmed by subsequent investigators using a similar technique and time of application of the tobacco tar to the skin of mice.

The best that can be said about the experimental evidence on hand regarding carcinogenic properties of tobacco tar is that it indicates the presence of mildly carcinogenic agents in cigarette tar through the use of hyper-reactive animals. There is no evidence that these observations of the skin of a strain of selectively inbred mice have any equivalent in man. Thus the practical importance of these observations as to cancer of the human lung is at present uncertain.

Conclusions

1. The total epidemiological, clinical, pathological, and experimental evidence on hand clearly indicates that not a single one but several if not numerous atmospheric pollutants are to a great part responsible for the causation of lung cancer.

2. The available data do not permit any definite statements as to the relative importance of the various recognized respiratory carcinogens in the production of cancers in the general population. Additive, cumulative, and synergistic effects of several of such agents are a distinct possibility.

3. Observations on occupational respiratory cancers, on the other hand, indicate that in restricted occupational groups exposed to well-defined and highly potent respiratory carcinogens all or most of the respiratory cancers found are attributable to one single carcinogenic air pollutant.

4. The widespread presence of industry-related atmospheric pollutants of recognized carcinogenic properties suggests that the recent alarming rise in lung cancer frequency espe-

cially among males may in part be causally related to the local and general development of modern industry and the use of its products.

5. While it is possible that cigarette smoking has played a contributory role in this respect, the total evidence available if critically evaluated does not favor the concept that cigarette smoking represents a major factor.

6. Since extensive and expensive efforts are required for obtaining an effective preventive control of the existing respiratory cancer hazards, rigid measures should be taken to discourage the introduction of new atmospheric air pollutants of carcinogenic type, especially if they are of the general environmental variety which are most difficult to control.
