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ETIOLOGICAL PROBLEM IN HUMAN LUNG CANCER

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IN 1950, 18,313 deaths were attributed to lung cancer in the United States among 1,379,151 from all causes in a population of nearly 160,000,000 people.[11] A survey in 1947 and 1948 by the National Cancer Institute in ten American cities reported (crude) pulmonary cancer-mortality rates per 100,000 white population of 15.4 in Birmingham, 15.5 in Pittsburgh, 15.9 in Dallas, 18.3 in Detroit, 18.6 in Chicago, 21.8 in Philadelphia, and 22.5 in New Orleans; in three cities in which the figures for whites and nonwhites were combined, the rates were 8.9 in Atlanta, 14.8 in Denver, and 20.8 in San Francisco.[15] It is not known to what extent these large differences are real but, in any event, the mortality is sizeable.

The risk can be expressed in another simple form. Of every 100 babies born in this country, nearly two will ultimately develop lung cancer, mostly between 50 and 80 years of age. In any disease having such a small attack rate and only after so long a time, recognition of the etiological factors is extremely difficult, especially if they are multiple, if only intermittently present, and if the long interval from birth to disease represents the induction time from cumulative effects. The problem is quite different from that in an acute disease, such as measles, in which nearly 100 per cent of persons are attacked, usually within the first ten years of life, shortly after exposure to the etiological agent, and by an agent that has multiplied and that is present when the disease is manifest.

The problem of the etiology of lung cancer is greatly complicated by the probability that there are multiple factors. The occasional tumors that occur in childhood (see reference 16 for references) are hardly attributable to the same agents as are those found in uranium and cobalt miners or in asbestos-, chromate-, nickel-, tar-, and other special worker groups.[10]

The great majority of individual cases are now not explained by any recognized exposure or other factors, and they are designated "spontaneous"—an obvious absurdity in a physical universe. Many recent lines of investigation have opened the possibility of accounting for this group. However, the numerous leads have increased the apparent complexity of the problem. The current situation resembles that of "pneumonia" in about the year 1883, when its numerous etiological agents were just beginning to be separated out and identified by the single-bacterial-colony technique, the use of Koch's postulates, and epidemiological methods. Reliable methods for proving the importance of suspected agents are, however, not yet available in lung cancer.

The recent identification of 3,4-benzpyrene, a potent carcinogenic agent, and other aromatic polycyclic hydrocarbons in soots and carbon blacks[5, 7] assumes importance in view of the global pigmentation of human lungs by anthracotic materials and the demonstration of this compound in atmospheric dusts[12, 22] and in a human lung.[16] Likewise, the discovery of these carcinogens in other common atmospheric contaminants, such as the fumes of internal-combustion engines,[13, 21] asphalts,[9] and rubber tires and other products,[6] provides additional possible sources for etiological agents having a wide distribution. The statistical association between the use of tobacco and lung cancer[3, 4, 8, etc.] presents another possibility, which is greatly strengthened now that a carcinogen, 3,4-benzpyrene, has been identified in the tar of cigarette smoke.[1, 2]

In view of the plethora of possible agents, one concept of the current etiological situation in the United States may be outlined about as follows (Table 1).

From this annual total of approximately three quarters of a billion man-years of exposure to possible sources of agent only about 20,000 lung cancers occur each year. It is not known whether these few persons develop the disease because their pulmonary cells have the highest susceptibility to neoplastic transformation, because they have had the greatest exposure to causative agents, or because these factors are combined. Neither is it known whether the effects of these and other hypo-

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TABLE 1

HUMAN PULMONARY EXPOSURE TO ESTABLISHED AND HYPOTHETICAL CARCINOGENS

Approximate number of persons being exposed annually to:	
3,4-benzpyrene and other carcinogens in soots	160,000,000
3,4-benzpyrene and other hydrocarbons in engine exhaust fumes.	160,000,000
3,4-benzpyrene and other hydrocarbons in asphalts, etc.	160,000,000
3,4-benzpyrene and other carcinogens in rubber products, such as tires, etc.	160,000,000
Possible carcinogens in tobacco products	85,000,000
asbestos	?
chromates	?
nickel	?
other unrecognized agents	?
Total annual man-yr. of exposure, approx.	725,000,000
Total annual lung cancers, about	20,000

thetical chemical agents are, in whole or in part, additive; mutually inhibitory; synergistic; summatable to other unmentioned and, perhaps, nonspecific factors; or whether they operate in still other ways.[17]

The difficulties in pin-pointing the responsible agent or factors in individual human lung cancers are great. If, for example, a serial number, beginning with number 1 and going through to 20,000, were assigned to each of the lung carcinomas as they show up on January 1 and thereafter of any year, the etiological problem would be that of determining in case number 1 the relative importance of each factor in the list given and of others as yet unknown. The same problem would present itself in case number 2 and in each succeeding subject to number 20,000. In no two cases, probably, would the responsible agents, their proportions, and their sources be exactly the same.

It is possible that further investigation will show that one or several agents predominate in some, or even in a majority of, cases. The demonstration of this fact would be easier if none of the agents were chemically unique. 3,4-Benzpyrene found in a lung with cancer might have come from one or several sources, the identification of which would be difficult or impossible. The chemically unique carcinogens in Table 1 were, consequently, the first to be recognized. Extracts of human lungs tested for carcinogenic activity, with no attempt at fractionation of the components,[20] have yielded evidence of activity of the degree emphasized by Kennaway as of importance in human cancer.

FIG. 1. Comparison of an experiment in carcinogenesis (curve "A"), in which 100 per cent of animals developed tumor in two years, with human lung cancer (see text).

In experimental carcinogenesis, it is possible, by varying the carcinogen, its dosage, the species and strain of animal, the tissue exposed, and other factors, to achieve high (up to 100 per cent) or low (5 per cent) tumor yields in a few months. Despite the ability rigidly to control the experimental conditions, the interpretation of the results is sometimes difficult.[19] Having exerted its effects, the carcinogen may be absent in that chemical form when the tumor appears. Furthermore, the presence of an agent known to be carcinogenic does not necessarily prove that it will induce or has induced a tumor or even that it is biologically active. The inactivation of 3,4-benzpyrene by adsorption to carbon particles[18] may explain why the inhalation of approximately 200 μg. per year of this chemical[1] does not result in a greater number of human lung cancers. The effects of 150 μg. per year of 3,4-benzpyrene in cigarette tars[2] may also be mitigated by this phenomenon of biological inactivation. If 160,000,000 people living in an environment of carcinogenic agents develop only 20,000 lung cancers each year, important protective factors must be in operation.

The human etiological problem is difficult not only biologically and chemically but also epidemiologically. This is illustrated by Fig. 1. Curve "A" represents an experiment in which 100 per cent of the animals injected with a carcinogen developed tumor within two years. Interpretation of the results of this magnitude may be extremely difficult if several agents have been combined. In contrast, the curve for lung cancer in a human population followed for eighty years would be represented at the level of 2 per cent, a point so near the base line that it cannot even be demonstrated by the scale used in Fig. 1. Nevertheless, as was recently pointed out by Kennaway, this is the order of magnitude in which it is necessary to think in human cancer etiology. It is the difficult level of causative factors that the statistician and epidemiologist, the geneticist, and the chemist must work with, separate, and identify in lung cancer. Of course, the epidemi-

ologist uses other techniques by which he hopes to simplify the analysis.

Having come this far, it may be permissible, and desirable, to speculate a bit further about the problem in the eventual control of lung cancer by prevention. Here there is an encouraging analogy, in principle, provided by experimental carcinogenesis. This is to the effect that it is not necessary to withhold a carcinogenic agent completely to prevent a cancer, but only to reduce the exposure below a certain threshold level. If the small risk that man has to lung cancer represents the combination of highest susceptibility plus greatest dosage, the problem of prevention becomes one of a further slight reduction in exposure by withholding a part of the presently acting agent or agents. This would become a logical consequence of successful efforts identifying and assigning correct roles to each agent.

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