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Chapter 14

# Carcinogenesis of the Lung: Environmental and Host Factors

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Despite the variations in the gross and histopathologic characteristics of *primary cancers of the lung*, virtually all arise from the epithelium of the trachea, bronchi, bronchioles or mucous glands. The direct continuity of the lining of the tracheobronchial tree with the external respiratory environment provides an uninterrupted pathway for the direct contact of environmental carcinogens with the respiratory epithelial cells. One can conclude, therefore, that pulmonary carcinogens are effective in their *environmental, chemical and physical* state in contrast to numerous other carcinogenic agents which require *in vivo metabolic transformation* into their active or proximal form. This existence in the environment or proximal form has greatly facilitated our chemical and physical characterization as well as bioassay of suspect substances. In addition, this nonmetabolized, relatively stable state is compatible with survival for a sufficient interval to appose and ultimately enter the well protected basal layer of cells of the respiratory tract from which cancers arise. These *concepts are crucial to* attempts at elucidating the mechanisms that may be operative in the genesis of *lung cancer*.

In discussing the several factors concerned with an understanding of pulmonary carcinogenesis, one can arbitrarily divide the data into three categories:

*1. Environmental:* the collection and analysis of epidemiologic data as well as the characterization of physical and chemical properties of substances suspected of an etiologic role in lung cancer.

*2. Pathogenetic:* determination of the sequential response of the lung to *environmental agents* with *particular* emphasis on those changes which appear critical to the carcinogenic process.

*3. Pathologic:* histopathologic study of the overt neoplasms to identify characteristics that may be specific reflections of the carcinogenic agents or processes.

I conclude with an attempt to combine the findings from these three areas into a coherent explanation for the genesis of lung cancer.

## ENVIRONMENTAL FACTORS AND PATHOGENESIS

The *major portion of the increase in mortality* from cancer of the lung that has been demonstrated in various parts of the world during the past half-century



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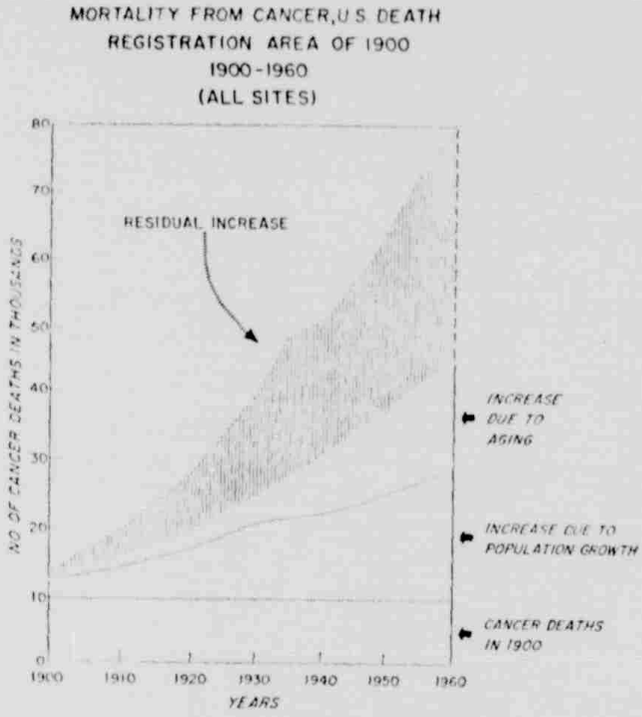



FIG. 118. Mortality from cancer, all sites. The increase in lung cancer represents the largest, single component of residual increase. Sources: *United States Census of Populations*—1910, 1950 and 1960; *Vital Statistics of the United States, Part I*—1940, *Vol. III*—1950, *Vol. II, Part B*—1960.

has been absolute, not merely relative, and is consistent with the introduction of new etiologic influences into the respiratory environment early in the twentieth century (Figs. 118 and 119). The exaggerated incidence has been characterized by:

1. A significant association of a history of cigarette smoking with the risk related in part to the duration and intensity of smoking.[6, 17]
2. A greater liability to the development of lung cancer in urban residents than in rural residents even after correction for smoking.[15]
3. Extreme variations in rates when the countries of the world are compared.[14]
4. A greater frequency of lung cancer in males than in females.[14]

These observations serve the dual purpose of directing attention to specific clinical and experimental studies to identify the responsible mechanisms and serving as benchmarks for determining how much of present knowledge of carcinogenesis can be applied to our understanding of these phenomena. Building on the current state of knowledge, studies have been undertaken to:


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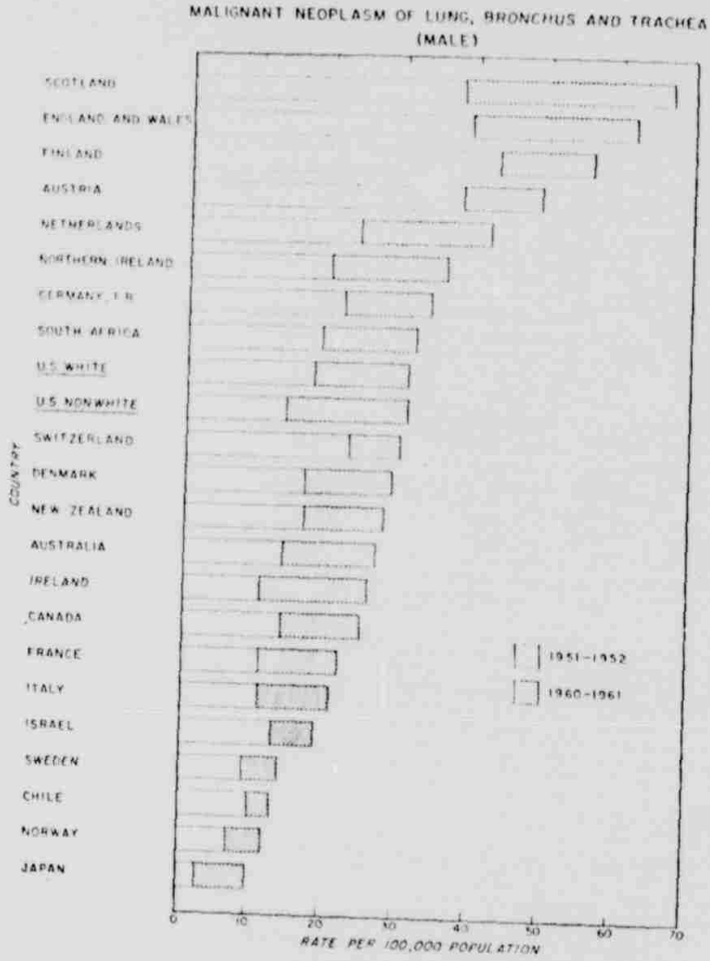



FIG. 119. Age adjusted to death rates for malignant neoplasms of *lung, bronchus, and* trachea. Note variation by country and variation in rate of increase.

1. Characterize the exact nature and relevance of the various epidemiologic associations (*e.g.*, spurious, cause and effect, etc.)
2. Identify environmental agents likely to be of etiologic significance and their subsequent bioassay.
3. Elucidate the biologic mechanisms responsible for and compatible with the epidemiologic, clinical and experimental characteristics of lung cancer.
4. Analyze stages in the pathogenesis of the neoplasms to determine the existence of any crucial association between morphogenesis and morphology and specific environmental factors.

The reality of the increase can no longer be seriously questioned. Predicted


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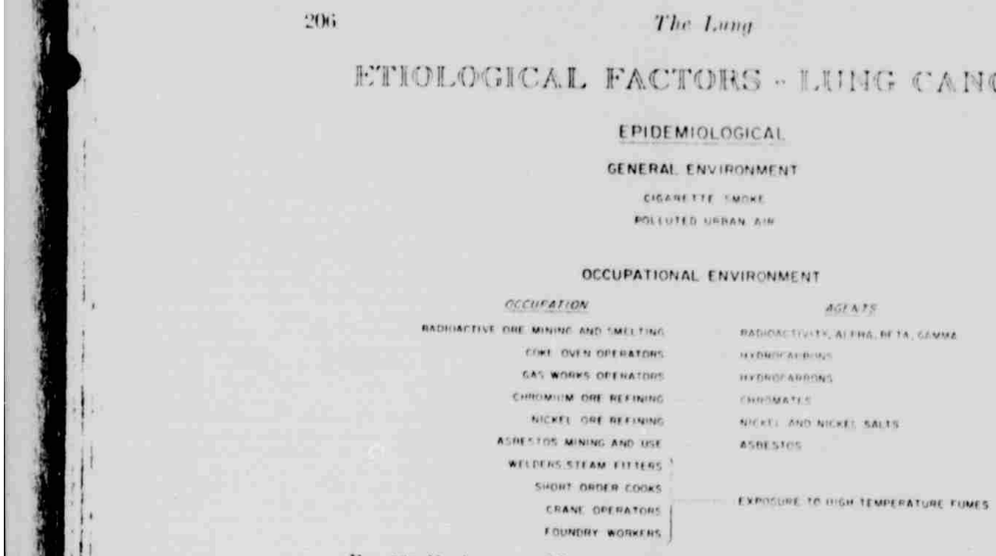



FIG. 120. Environmental factors and agents implicated in the etiology of lung cancer

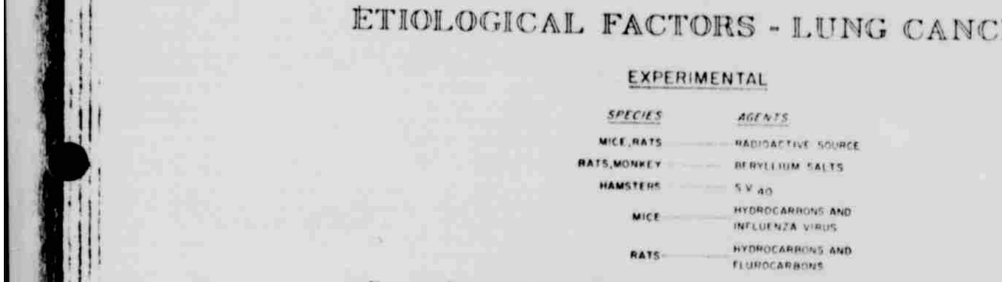



FIG. 121. Experimental studies on carcinogenesis utilizing environmental agents

rates of increase made as far back as 1954[5] have in general materialized, and such possible confounding factors as better diagnosis, increasing awareness and increasing longevity have all had their small influence diluted during the past quinquennium.

Delineation of environmental factors responsible for the increase has focused on three major areas of apparent etiologic significance: cigarette smoking, urban residence and occupational environment, as shown in Figures 120 and 121. Although perhaps the smallest contribution in terms of numbers of cases derives from the last mentioned, the more precisely circumscribed occupational environment, the greater exposure in terms of dose and the restricted nature of the population make this group a rich resource for the study of mechanisms and elucidation of principles. The initiation of carcinogenesis in the respiratory tract can only be postulated on the basis of carcinogen-cell interaction. It therefore becomes necessary to identify a continuum which includes host entry of the

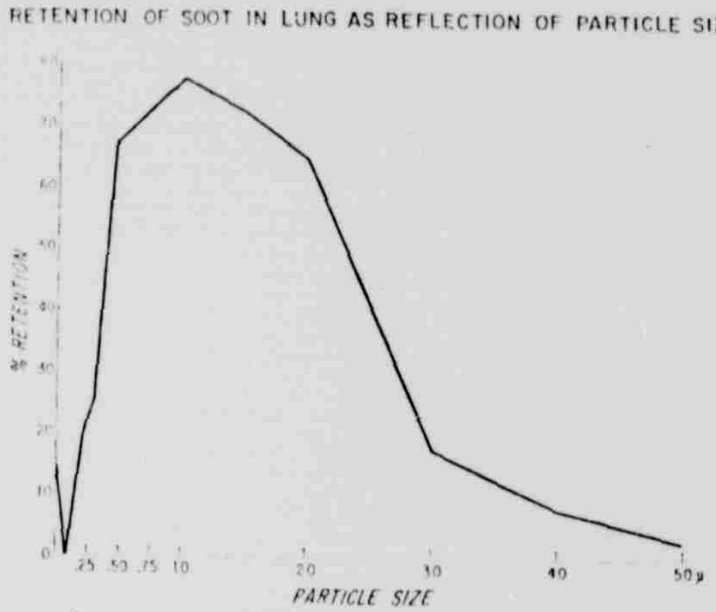



FIG. 122. *Retention of particulate in lung in relation to particle size*

*carcinogen, deposition and retention* on the respiratory mucosa, cellular penetration after passage through the mucous blanket or directly in areas abnormally devoid of mucus and finally intracellular localization. The constellation of factors critically governing this sequence embraces size range of particulates in the respiratory environment, stability of the chemical or physical carcinogens, the integrity of the ciliary mucous barrier and *mode of access to the basal cells*.

As the pathogenesis is detailed, the multidisciplinary approach to studying the *factors enumerated and their evolution* becomes evident, and hopefully a model for carcinogenesis of the lung will evolve with specific application as well as identification of principles.

## Physical Factors

Carcinogenic agents enter the respiratory tract as particulates *either in a pure* state or adsorbed on inert nuclei. The dynamics of their passage through the *arborizations of the tracheobronchial tree* and the pattern of deposition and retention underlie three observations fundamental to an understanding of their mechanism of action.

1. Particle size, which determines to a major degree the extent to which penetration of the tracheobronchial tree will occur, is critical in the range 125 Å to 2.5 $\mu$ (Fig. 122). Those larger than 2.5 $\mu$ are for the most part arrested in the nose, accessory nasal sinuses, pharynx and oral cavity, assuming they gain entry into the host at all. At *the other extreme, a lesser but still significant* segment of exceedingly small particles (less than 125 Å) remains suspended in *tidal air* except for the minuscule particles that are precipitated by Brownian


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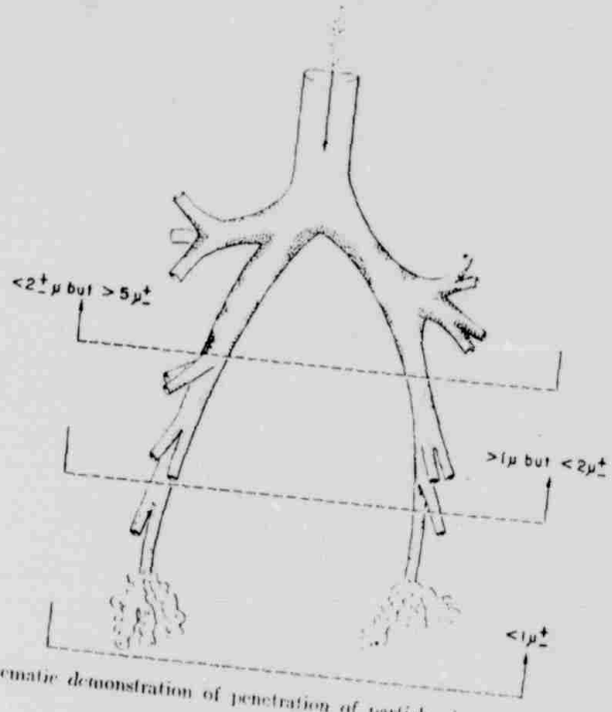



FIG. 123. Schematic demonstration of penetration of particles in tracheobronchial tree in relation to size.

movement. The pulmonary retention of particulate matter in relation to size is maximum at 1.0 $\mu$ and falls off sharply for sizes larger than 2 $\mu$ and smaller than 0.25 $\mu$. In our studies, maximum deposition has been shown to occur in the segmental bronchi and beyond. Particle size also influences the rate and extent of elution of carcinogenic agents from particles on which they are adsorbed either in the macrophages or in their free state on the respiratory epithelium.[22, 10]

2. Impingement of particles with resultant maximum effect occurs at arborizations, *e.g.*, miniature carinas throughout the tracheobronchial tree, and it is at these sites that alterations in the functions of the ciliary mucous apparatus are most intense and prolonged.[33] The relation of particle size to depth of penetration and site of maximum initial effect is shown in Figure 123.

3. The abnormal retention and accumulation of carcinogenic particles is thus facilitated, especially in bronchi of small caliber, in which a peribronchial and peribronchiolar inflammatory response further interferes with physiologic mechanisms of defense. Ultimately, it is these sites that are among the first to show changes. The effect of irritant aerosols on particle movement is shown in Figures 124 and 125.[11] The response is initially a transitory one, with recovery following cessation of exposure. However, depending on the intensity and repeti-

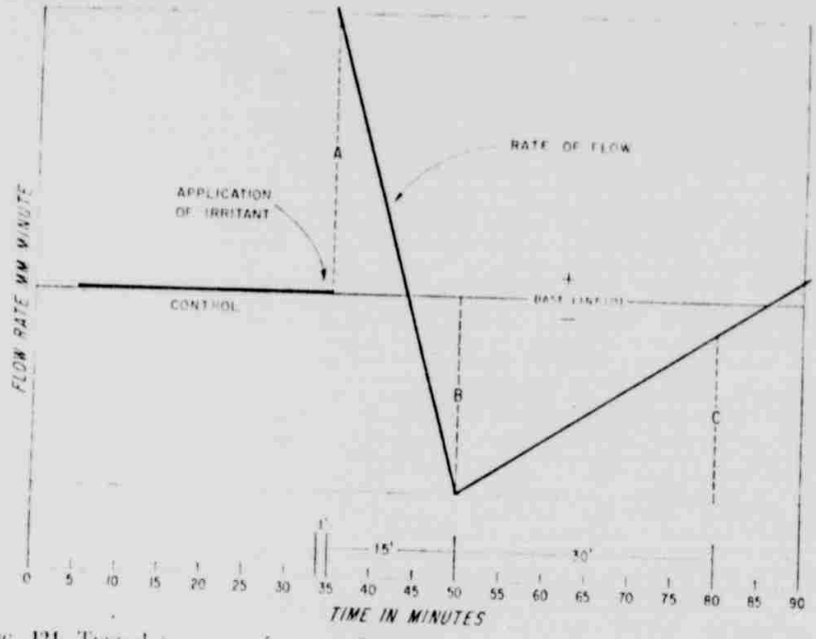



FIG. 121. Typical response of mucus flow following exposure to irritants. Inhibition is preceded by transient initial stimulation and followed by recovery.

tion of exposure, total cessation of movement can follow, and ultimately the site may develop morphologic abnormalities and neoplastic transformation.

How may the experimental observations and principles described be operative in experimental pulmonary carcinogenesis and what evidence is there that similar mechanisms function in man? More specifically, how is the protected target layer of basal cells assaulted structurally as well as physiologically?

## Epithelial Response

The ciliary mucous apparatus is a highly sensitive component of the respiratory epithelium, and its physiologic maintenance appears to be chiefly under parasympathetic control, although numerous factors, serotonin among others, also affect its function.[9, 13, 21] Under ambient conditions, irritant gases and particulates occurring in cigarette smoke, polluted urban air and certain occupational environments can alter the rate of ciliary action and mucus secretion as well as the chemical and physical properties of the latter. An essentially similar effect can be seen as part of the response to certain bacterial and viral infections of the lung. The crucial aspect of the response is slowing or cessation of mucus flow both as a result of interference with ciliary action and qualitative and quantitative variations in the mucus secretion.[8] The net effect of this response is the enhanced retention of particles as shown in Figure 126. These physiologic responses have a morphologically demonstrable counterpart when the insults are repetitive. The sequence is schematically shown in Figures 127 to 129. Repre-

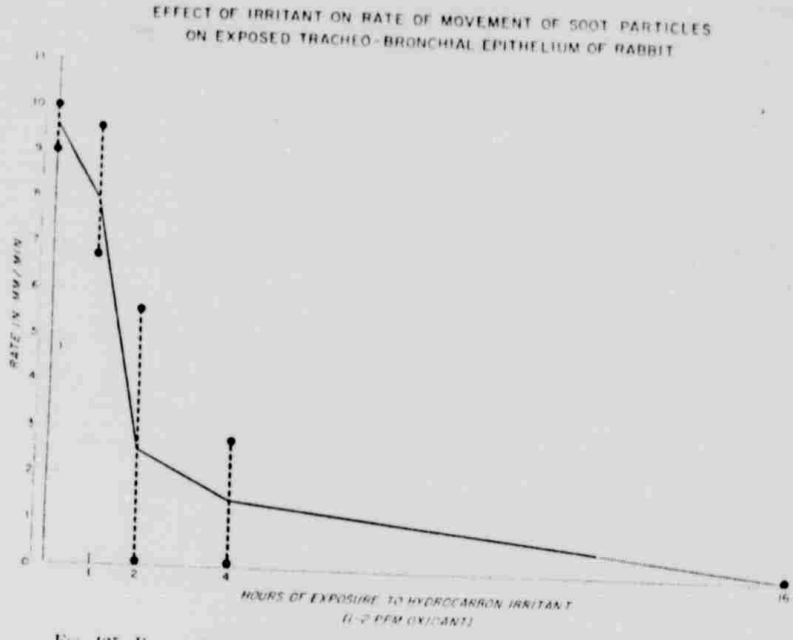



FIG. 125. Progressive inhibition of particle movement under *in vitro* conditions.

sentative histologic sections demonstrating the sequence *in vivo* are shown in Figures 130 to 133. As can be noted, the initial effect of aerosols is limited to the superficial cells with changes characterized by marked hypersecretion followed by desquamation down to, but not including, the basal cells. Because the cells of the basal cell layer are the required targets for carcinogen action, the sequence of desquamation and regeneration in the presence of a carcinogenic stimulus creates an optimal environment for malignant transformation. First, apposition between carcinogen and basal cell can occur, and, second, proliferation associated with the stimulus for tissue repair is conducive to carcinogenic response. Repetition of this sequence can lead to abnormal repair with the progression of lesions from hyperplasia to metaplasia to metaplasia with atypical changes (Figs. 134 and 135) and ultimately cancer. The importance of injury and repair in the carcinogenic process has received confirmation in several studies. Stanton and Blackwell[32] were able to induce squamous carcinomas of the lung in rats through a combination of mechanically induced pulmonary infarcts and the injection of methylcholanthrene. The neoplasms were observed at the margins of the infarct where tissue repair was in progress, and they concluded "that the carcinomas were derived from regenerating epithelium frequently converted to keratinized squamous epithelium by the carcinogen." Kotin and Wiseley[21] produced inflammatory and proliferative lesions of the lung in mice by sequential


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EFFECT OF EXPOSURE OF RABBITS TO IRRITANT (HYDROCARBON PEROXIDES) ON RETENTION OF INHALED SOOT (HOURS) (WITH AND WITHOUT RECOVERY)

| | IRRITANT EXP. | ROOM AIR (RECOVERY) | SOOT EXP. | ROOM AIR (RECOVERY) | SOOT IN LUNG (mg.) | |
|---|---|---|---|---|---|---|
| (1) | 0 | 0 | 1 | 0 | 3.7 | (1) |
| (2) | 1 | 0 | 1 | 0 | 7.9 | (2) |
| (3) | 1 | 0 | 1 | 24 | 5.4 | (3) |

*1 CONTROL
2 ANIMAL NO. 1
3 ANIMAL NO. 2

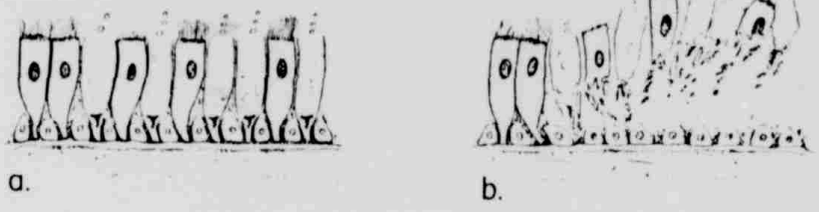
| | IRRITANT EXP. | ROOM AIR (RECOVERY) | SOOT EXP. | ROOM AIR (RECOVERY) | SOOT IN LUNG (mg.) | |
|---|---|---|---|---|---|---|
| (1) | 0 | 0 | 1 | 0 | 1.1 | (1) |
| (2) | 1 | 4 | 1 | 0 | 7.4 | (2) |
| (3) | 1 | 8 | 1 | 0 | 5.2 | (3) |
| (4) | 1 | 24 | 1 | 0 | 2.0 | (4) |

*1. CONTROLS

FIG. 126. Effect of exposure to irritants on quantitative retention of inhaled soot particles in lung.

infection with influenza viruses. Squamous cancers resulted when exposure to carcinogenic hydrocarbon aerosols was superimposed on the influenzal infection (Figs. 136 to 139). Kuschner, Laskin, Cristofano and Nelson[24] were able to induce squamous cancers by implanting pellets of methylcholanthrene in the bronchi of rats. They observed that their success was probably due to the traumatic procedure involved which rendered the epithelium more susceptible to action of carcinogens.

Deposition and impingement in the arborizations of the respiratory tract are governed by physical laws of particle movement. It is of interest that, under experimental conditions, particle deposition and retention occur more readily in the more distal segments of the tracheobronchial tree. At first, this observation appeared incompatible with the clinical and pathologic observation that primary



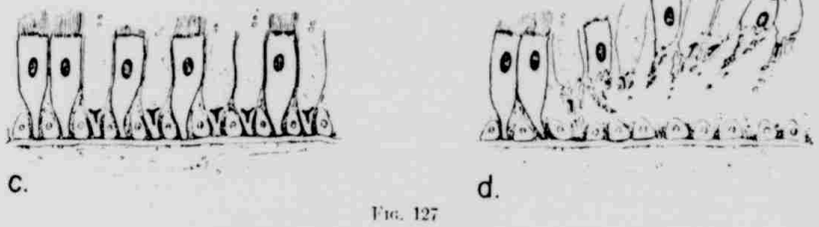
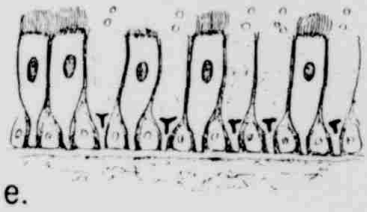




Fig. 127



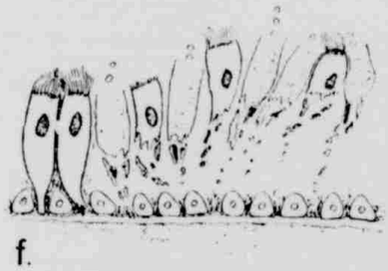
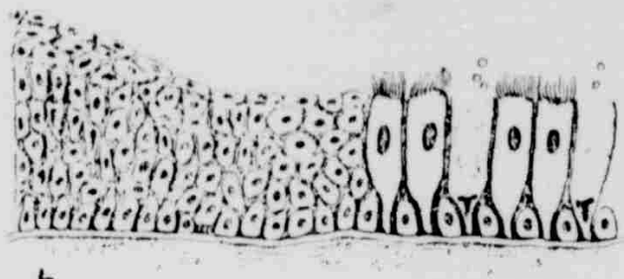



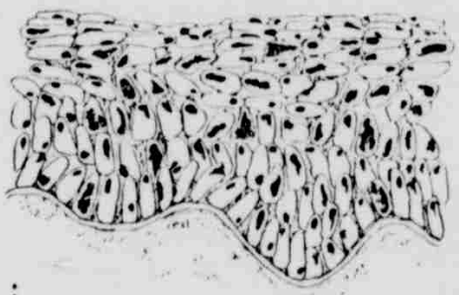




Fig. 128



h.



i.

FIG. 129

FIGS. 127 to 129. *Schematic* representation of progression of changes following exposure to environmental aerosols. Sequential response starts with increase in mucus secretion with slowing of rate of mucus flow followed by superficial epithelial desquamation and regeneration of epithelium. Repetitive cycles can lead to basal cell hyperplasia and squamous metaplasia, and theoretically to development of neoplasia in the presence of carcinogenic stimuli.

bronchia, carcinomas originated chiefly in the mainstem bronchi. This belief, however, was based primarily on studies using necropsy material and understandably included a majority of cases in which tumor size was great and point of origin was difficult to ascertain. Recent reports by Rigler,[30] by Garland, Beier, Coulson, Heald and Stein[12] and by Meyer and Liebow,[27] however, seriously question the validity of the concept that most primary lung cancers are hilar or central in origin.

### Pathologic Aspects

Having achieved an experimental model in which sequential changes are consistent with the theoretical requirements for pulmonary carcinogenesis, clinical relevance clearly is measured by the actual findings in man. In a prodigious study of the changes in the bronchial epithelium in relation to smoking and lung cancer, Auerbach, Stout, Hammond and Garfinkel[2] and Auerbach and Stout[1] described a series of changes characterized by loss of cilia, increase in the number of cell rows and the presence of atypical cells in the thickened epithelium. Their findings suggested a progression of changes from initial goblet cell hyper-

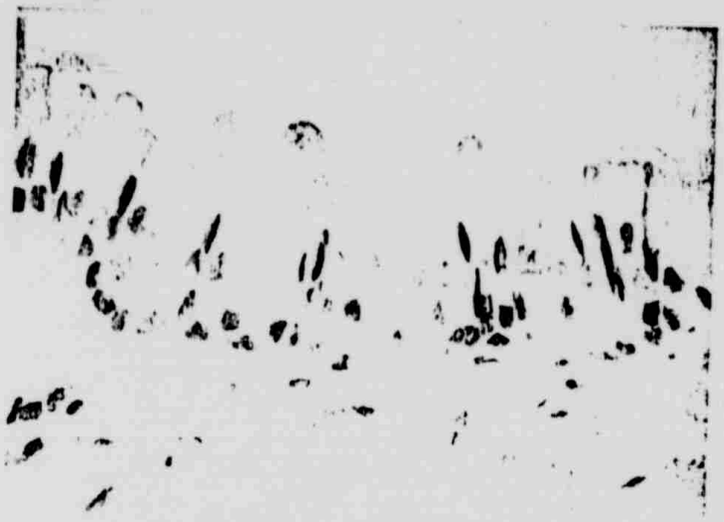


FIG. 130. Stage of marked increase in mucous secretion with mucous droplets demonstrable in lumen. (× 250.)



FIG. 131. Pooling of mucus in bronchial epithelium, with compression of nuclei, beginning obliteration of cell membranes and thick static mucous stream overlying epithelium. Particle movement virtually entirely inhibited at this stage. (× 250.)


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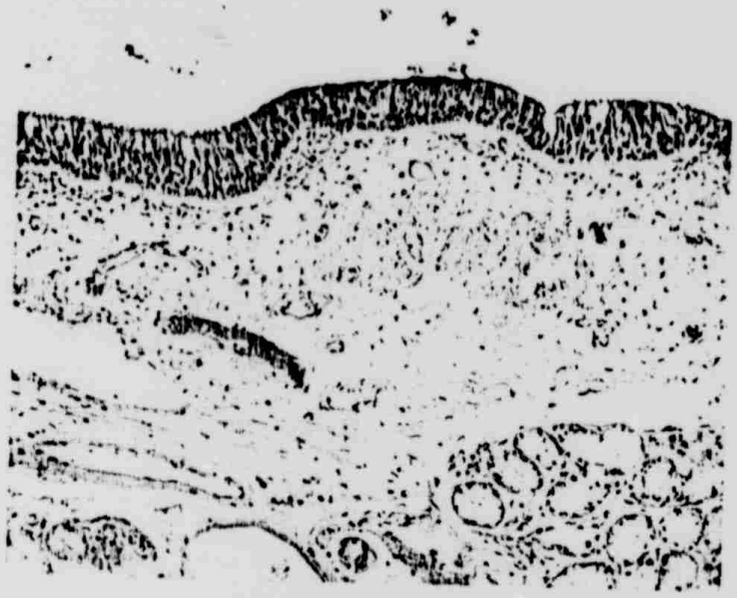


FIG. 132. Focal area of hyperplasia between two areas of ciliated epithelium. This is presumably a site of impingement. (× 125.)

plasia to metaplasia, metaplasia with atypism and ultimately carcinoma *in situ* and invasive cancer. Their data support the epidemiologic observation of a dose response to environmental agents (smoking). It is of interest that in a reverse comparison, *i.e.*, man to the experimental model, they emphasized the similarity of changes including "hyperplasia and other changes in the bronchial epithelium of mice."[3] Indistinguishably, histologic counterparts can be identified in both man and experimental animals. The significance of hyperplasia and metaplasia both in experimental animals and man is not completely understood. The observation of metaplasia in both has again focused attention on the significance of metaplasia as a stage in the genesis of cancer. In both man and animal, we believe that there are morphologic criteria which serve to distinguish preneoplastic from so-called nonspecific metaplasia with a high degree of reliability. Metaplasia occurring in the absence of a carcinogenic stimulus as denoted by hypovitaminosis A, chronic irritation, certain bacterial infection as in bronchiectatic cavities and viral infections of the myxovirus type have not been shown to progress to neoplasia in experimental models. The metaplasia seen classically in response to carcinogenic stimuli can at a given level frequently herald the oncoming cancer, as shown in controlled laboratory studies. In essence, metaplasia of specific types carries greater risk of malignant transformation within the framework of dose dependent response.


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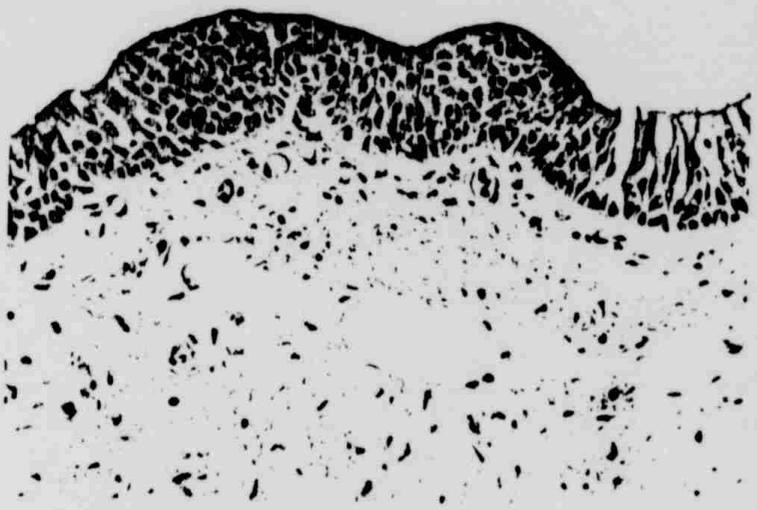


FIG. 133. Area of squamous metaplasia immediately adjacent to ciliated bronchial epithelium. (× 250.)



FIG. 134. Marked thickening of hyperplastic epithelium immediately adjacent to ciliated area. (× 125.)


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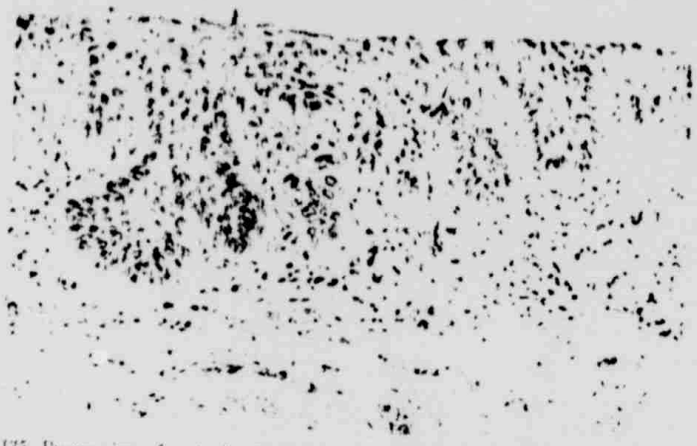


FIG. 135. Progression of metaplastic change with beginning *downgrowth* and pleomorphism of cells. (× 125.)

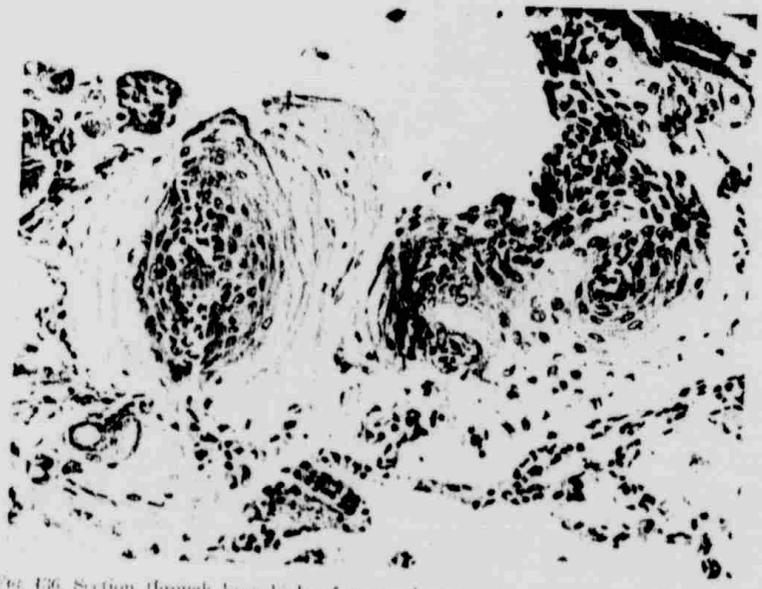


FIG. 136. Section through bronchiole of mouse lung showing areas of keratin production and pearl formation. Note thickening of bronchiolar epithelium adjacent to squamous nest. × 250.)

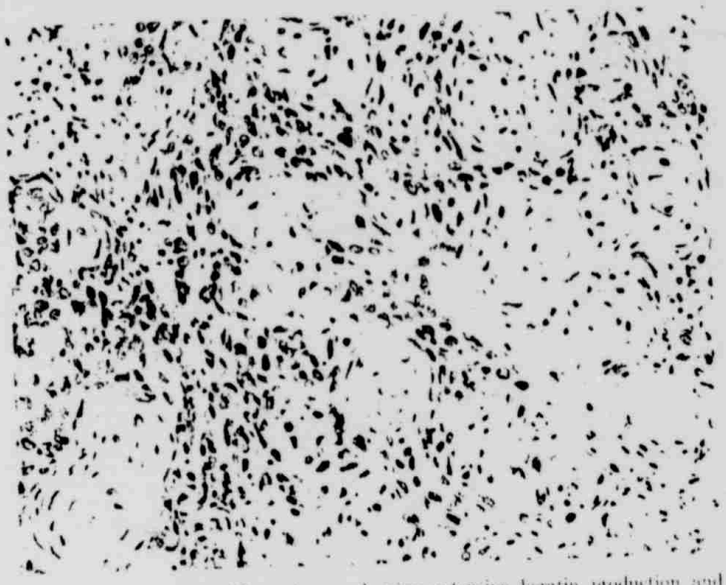


FIG. 137. Area of epidermoid carcinoma showing extensive keratin production and pearl formation. (× 125.)



FIG. 138. Area of epidermoid cancer with pulmonary artery showing attenuation of one side of vessel wall with infiltration by cancer cells and tumor thrombus. (× 75.)


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| | C57 BLACK | SURVIVORS | TUMOR-BEARING ANIMALS: PULMONARY ADENOMA | TUMOR-BEARING ANIMALS: SQUAMOUS CELL CARCINOMA LUNG |
|---|---|---|---|---|
| CONTROL | 450 | 330 | 28 | 0 |
| HYDROCARBON AEROSOLS | 450 | 231 | 45 | 0 |
| FLU | 450 | 270 | 12 | 0 |
| FLU & HYDROCARBON AEROSOLS | 450 | 328 | 16 | 33 |

FIG. 139. Tumorigenic response in mice exposed to hydrocarbon and influenzal infection

Equally consistent with experimental laboratory findings are the observations of Auerbach and his associates[1-3] that the most common site for epithelial changes are at bifurcations of the tracheobronchial tree. He concluded that "in all four parts of the bronchial tree the percentage of sections with various epithelial changes was higher in sections with than in sections without 'definite bifurcations.' This was true of both patients dying of lung cancer and those who smoked 1 package or more a day and who died of other causes."[2] Finally, the regression of lesions as noted in human subjects with a history of cessation of smoking has a laboratory counterpart in animals removed from a carcinogenic environment into either washed air or the ambient atmosphere.

The histologic characteristics of the neoplasms of the lung are of particular significance because numerous studies suggest a relationship between environmental experience and histopathologic classification. Kreyberg[25] in his monograph has advanced the concept that lung tumors fall into one of two large groups: group I, epidermoid carcinomas and small cell anaplastic carcinomas and, group II, adenocarcinomas, bronchioloalveolar carcinomas, carcinoids and mucous gland tumors. He observed that group I cancers are "environmental cancers" in the sense that they are the types predominantly seen in males, urban residents, cigarette smokers and those occupationally exposed to nonradiation carcinogenic experiences. He further noted that they constitute by far the greatest segment of lung cancers associated with increasing incidence of the disease. In contrast, group II adenocarcinomas were referred to as "endogenous tumors" as they apparently have not increased in measurable quantities during the period rise in incidence. The sex ratio of tumors in this group is low, and they occur almost equally in rural and urban areas, and a significant influence of cigarette smoking cannot be established. He concluded that, if indeed they are environmental in origin, etiologic agents have not significantly increased of late, and males and females appear to be equally responsive to the carcinogenic stimulus.

Herman and Crittenden[19] in a review of the distribution of primary lung carcinomas in relation to time as determined by histochemical techniques concluded that in their series the proportion of group I epidermoid and undifferentiated carcinomas to group II adenocarcinomas for men is decreasing. This was in contrast to the ratios reported by Kreyberg[25] and others. The differences in classification depend both on technic and interpretation. Although resolution

of the differences has not been fully accomplished, it is clear from all studies that epidermoid carcinomas show an unequivocally strong association with environmental experience. More specific evidence of a relation of etiology to histologic characteristics may be found in the group of occupational lung cancer associated with exposure to ionizing radiation. This first observation of a possible association between a specific environmental factor and the type of cancer followed the identification of primary lung cancers as the cause of death in a high percentage of the miners of radioactive ores in Schneeberg.[18] Originally, the small cell cancers were regarded as lymphosarcomas. Recently Wagoner, Archer, Lundin, Holaday and Lloyd[31] in a study of radiation as the cause of lung cancer among uranium miners reported that pathologic studies have shown that the tumors are predominantly undifferentiated small cell tumors. As these authors note, it was of interest that, in Japan, chronic exposure of factory workers to a radiomimetic agent, mustard gas, has also produced a marked excess of tumors of the same organ (lung), of the same locale within that organ (central) and of the same histologic type (anaplastic small cell).[19]

## GENERAL CONSIDERATIONS

A review of carcinogenesis in the lung would be incomplete were it limited exclusively to the interaction of environmental carcinogenic agents with the respiratory tract. For lung cancer, as with all neoplasms, as yet undefined systemic factors appear operative in determining such parameters as susceptibility to the action of carcinogenic agents and the natural history of overt neoplasms. General observations have been made in many areas which appear to have relevance to the pattern of lung cancer.

### Migratory Populations

In his studies of cancer mortality among the foreign born in the United States, Haenszel[11] has shown a striking alteration in liability to lung cancer among migrants. Differences in mortality from cancer of the lung and bronchus were observed when native and foreign born were compared, as shown in Figure 140. The effect was most marked in males, and for several countries the shifts in mortality rates were upward, whereas in others a significant reduction in risk was observed. In either event, the changes were always in the direction of the rates of the United States. This observation has significant pathogenetic implications. First, it strongly suggests that recent events can significantly govern the time of clinical appearance of the neoplasm. Second, it re-emphasizes the influence of environmental factors perhaps up to the period of overt neoplasia. Third, it supports the concept that endogenous metabolic factors may be critical in determining risk.

### Factors Affecting Sexual Differences

The sexual difference in the incidence of lung cancer has been a subject of great concern. With the passage of time, it is apparent that part of the lower incidence in women is in all likelihood the result of lesser exposure to cigarette smoke and also of a lesser experience with urban polluted air. Despite the be-

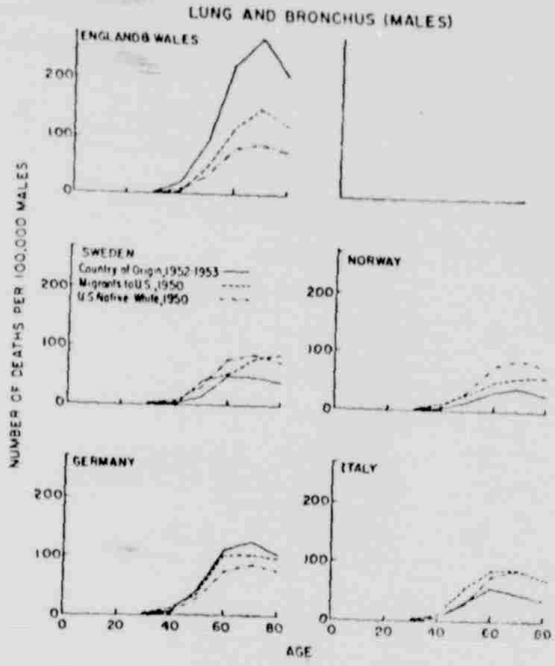



FIG. 110. *Age-specific mortality from cancer of the lung among migrants in comparison with United States native Caucasians and population in countries of origin.*

lated increasing incidence currently observed in women, it is obvious that part of the variation in the magnitude of risk is related to endogenous factors. This is supported by the observation of Haenszel and Taeuber[16] who, in their study on the lung cancer mortality of Caucasian females, noted that there was no evidence that regular use of cigarettes and residence in urbanized areas combined to produce risks higher than those expected from the sum of the two separate effects. Whether this result implies that the observations were too crude to measure lower levels of carcinogenic exposure among women, which leaves open the possibility that exposures for women remain below the threshold values required to produce interaction, or reflects a true sex difference in carcinogenic response remains uncertain. Haenszel and Taeuber further observed that there are sexual differences in cancer incidence of extrapulmonary sites so that a similar variation in lung cancer incidence represents neither a new nor a unique biologic situation.

Steroidal differences may in part account for male-female differences in liability. An association between adrenocortical hyperactivity in men and increased liability to lung cancer was noted in the chemical studies of Werk and Sholiton.[35] Williams and Sommers[36] also reported a greater incidence of adrenocortical hyperplasia in lung cancer patients than in controls. It is of particular interest

that there have been several reports recently of Cushing's Syndrome in association with bronchogenic carcinoma. There is increasing evidence that an androgenic factor may also in fact be of significance in the development of bronchogenic carcinoma. Sommers,[31] in studying host factors in fatal human lung cancer, concluded that "host endocrine changes with established epidermoid carcinomas usually included an inferred pituitary-adrenocortical hyperfunctional state." Studies on the absorption of particulate matter into epithelial cells of the respiratory tract strongly indicate that in the presence of androgens the rate of intracellular localization is greater than under the influence of estrogens. Willis,[32] in reviewing the Transactions of the Pathological Society of London for the years 1881 to 1900, felt that only eight of 34 cases of carcinoma of the lung were accurately diagnosed. More pertinent, however, is his observation that the male-female ratio in the 34 cases was 3.5:1. This ratio is essentially similar to that reported in much larger and more recent series of cases.

## Metabolic Factors Modifying the Response to Carcinogenic Polycyclic Aromatic Hydrocarbons (PAH)

Epidemiologic studies on occupational and general environmental cancer following exposure to PAH almost uniformly show an irregular pattern of incidence in populations exposed to essentially similar carcinogenic environments. Studies by others as well as ourselves have shown that carcinogenesis is dependent on the persistence of unmetabolized hydrocarbons at the site of administration or elective localization. Under physiologic conditions, the hepatobiliary system is the primary site of metabolism and systemic elimination of PAH. Experimental studies have shown that metabolites of carcinogenic hydrocarbons are remarkably less carcinogenic or totally noncarcinogenic when contrasted with their parent hydrocarbons.[1] Any interference with metabolism, therefore, is likely to be reflected in abnormal persistence of the parent carcinogen with a resulting prolonged carcinogenic effect. The rate of excretion and the characteristics of metabolites of PAH, including the carcinogen, benzo(a)pyrene, were reported by Falk, Kotin, Lee and Nathan.[7] In mice and rats with induced minimal liver injury, there is a delay in the appearance and a reduction in the amount of metabolites in the bile. This, in turn, is reflected in an increase in the carcinogenic response of mice to a constant dose of benzo(a)pyrene.[23, 28] It is suggested that host variations in the ability to metabolize carcinogenic PAH may be one factor in the explanation of the variations in response to environmental carcinogens. Epidemiologic studies have shown that an enhancement of the increased risk to the development of cancer of several sites (oral cavity, pharynx, esophagus and lung) after exposure to PAH is associated with a history of regular alcohol ingestion.[20, 38, 39] This exaggerated risk is particularly notable in populations exposed to recognized sources of carcinogenic PAH, such as polluted urban air, cigarette smoking and certain occupational environments. An explanation advanced for the possible role of alcohol is that of either a carcinogen acting directly on the target cells or a cocarcinogen acting as a promoting agent. An alternative possibility may be that interference with


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hepatic function incidental to regular ingestion of alcohol may result in a decrease in the ability of the liver to metabolize carcinogenic hydrocarbons.

## CONCLUSIONS

In considering carcinogenesis in the lung, it is necessary to synthesize epidemiologic, clinical and experimental factors. Epidemiologically, the following observations must be kept in sight: (1) the relatively low attack rate; (2) the long induction period; (3) the disappearance of the responsible agent or agents from the neoplastic site at the time of tumor appearance; (4) the frequently long interval between cessation of exposure and tumor appearance.

The first two items strongly suggest either the action of a weak carcinogenic stimulus or the almost universal existence and effect of host resistance factors. The complex environment to which man is exposed is consistent with laboratory observations that multiple factors may act in combination to induce lung cancer. Although recognition and acceptance of the concept that multiple factors are concerned with the initiation and promotion of lung cancer pose particularly complex problems to the experimentalist, epidemiologic data provide several leads. Attempts to pursue these have been described. The growing experimental data suggesting a role for viral agents in the pathogenesis of experimental neoplastic disease direct us to studies utilizing both oncogenic and nononcogenic viruses alone and in combination with chemical carcinogens. The production of epidermoid carcinomas of the lung in hamsters by Rabson, Branigan and Legallais[29] using polyoma viruses provides a model for studying the effect of environmental agents. The role of endogenous factors in modifying host entry, metabolism of carcinogens and systemic elimination must also be actively pursued.

Epidemiologically, a reduction in lung cancer incidence may be properly anticipated as a result of reducing or eliminating the concentration of any of the environmental factors discussed. It is our belief, however, the predictions as to the extent of reduction when only one of the factors is eliminated are meaningless in the light of the multiplicity of factors described. It is wholly unwarranted to anticipate a reduction in lung cancer rates equal to the fraction showing a statistical association with any environmental factor or specific carcinogenic agent. The proper evaluation of the contribution of any agent to the pathogenesis of lung cancer will be possible only in terms of its relation to the action of other significant environmental influences.

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