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Environmental Lung Cancer

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CANCER of the respiratory tract had a relatively minor role in the cancer problem before the turn of the century but has become of major importance because of the rapid rise in the frequency of these tumors during the last three to four decades (Simons; Schinz; Mason; Kennaway; Heady and Kennaway; Clemmesen and Busk; Dorn; Herbut and Clerf; Steiner).[1] In fact, in a few areas death from cancer of the lung threatens to displace cancer of the stomach as the most frequent cause of death from cancer in males. Many investigators consider the recent increase in the frequency of lung cancer as purely apparent, attributable to the marked shift in age distribution of the population, to improvements in diagnostic methods, to greater interest of the medical profession in cancers of the lung, and to a change in the ratio of lung cancers to all cancers because of a reduction of deaths from cancers of other organs.

However, this concept is not shared by some investigators, who feel that at least a part of the increased frequency of lung cancers is due to an alteration in the environmental cancerigenic spectrum, starting some 75 years ago, related to new occupational hazards and newly acquired habits (Halpert). Although critical review of the available evidence does not permit a definite conclusion concerning the general question as to the real or apparent nature of the rise in lung cancers, it provides much circumstantial and conclusive evidence regarding the role which environmental cancerigenic agents apparently play in the causation of these tumors.

Circumstantial Evidence

NUMERICAL Increase of Lung Cancers: Without doubt the rapid prolongation of the average life span has brought in recent decades many more persons into the age group in which lung cancer occurs most often. Since approximately 77% of all lung cancers occur during the ages of 40 to 69 years (Matz), the rise of this age fraction of the population from 18.9% in 1875, to 21.6% in 1900 and 29.9% in 1940 (Sixteenth Census, U.S., 1940), was bound to be reflected in a corresponding increase in the number of lung cancers during the last four decades. However, Dorn as well as Potter, found in their recent statistical analysis of cancer deaths in the United States that there had occurred a consistent rise in the frequency of lung cancer deaths after eliminating the effect of changes in the age composition. Potter stated that this annual increase amounted to 5.8% for males and to 2.1% for females during the years 1933 to 1944. According to Dorn's calculations on this point, the annual percentage increase was 10.5% for males and 8% for females between 1914 and 1931, and 8.5% for males and 2.5% for females between 1931 and 1940. Since almost all lung cancers are fatal, mortality rates and morbidity rates are practically identical.

In view of the observation of this increase in the autopsy material of many large European hospitals which had for many decades an economically rather stable patient population, a consistently high autopsy rate and a competent pathological service, there is little reason to attribute an appreciable portion of this development to improvement in medical service and recording. The consistency and increment of the trend, moreover, would not support such an explanation.

It was noted, on the other hand, that the time of onset and degree of the lung cancer rise varied considerably in different countries (Casolo), and in different parts of the same country (Fischer). This observation seems to exclude the possibility that racial and hereditary factors played an important role. The available statistical evidence suggests, therefore, that any real increase in the frequency of lung cancers if such has occurred, may most likely be ascribed to the action of exogenous factors which en-

[1] Dr. Hueper's references are identified in a detailed and extensive bibliography of which a copy may be obtained by writing him at Cancerigenic Studies Section, Cancer Control Branch, U.S. Public Health Service, National Institute of Health, Bethesda 14, Maryland.

tered the human environment during the last half century. This conclusion receives some support from the fact that the majority of more recently discovered environmental cancerigens cause cancers of the respiratory tract, while those previously established mainly affected the skin.

SEX DISTRIBUTION: There is general agreement that lung cancers are more frequently present in males than females. Since the considerable rise in the occurrence of lung cancers during the past four decades has been accompanied by a definite shift in the sex distribution of the lung cancer in favor of the male sex, the increase in lung cancer incidence seems to depend on agents to which males become exposed more often or more intensely than females and which are essentially unrelated to endogenous, sex conditioned factors.

This conclusion is supported by the fact that the male-female sex ratio of lung cancer exhibits remarkable local differences varying between 2:1 in Sweden (Henschen) to 20:1 in parts of the United States (O'Keefe), while averaging most often 5:1 to 10:1 (Fulton: 7.3:1 in 1610 cases). Clemmesen reported from Denmark that a shift in the male-female sex ratio has occurred there during recent years, after having stood at 5:4 in 1931, it changed to 3:1 in 1945 and is expected to become stabilized at a ratio of 8:1 in the near future.

An exogenous origin of the sex differential of lung cancer is suggested moreover by observations made in connection with occupational cancers of the respiratory tract. Merewether found that the male-female ratio of asbestosis cancer stands at 2.4 to 1. This ratio illustrates the trend toward an equalization of incidence rates of cancer for the two sexes whenever the conditions of exposure to an environmental cancerigen tend to become identical. Highly excessive incidence rates of lung or nasal sinus cancers among males, on the other hand, exist whenever for occupational reasons contact with exogenous cancerigens is restricted to members of the male sex, such as workers in chromate factories, in radioactive mines, and in copper-nickel ore refineries.

HISTOLOGICAL Types: Sex and Age Distribution: Probst stated that, in recent years, there has been a shift toward a more frequent occurrence of epidermoid cancers in pulmonary malignancies of unknown etiology. This observation may be related to the proportionally greater increase of lung cancers among males than females, because squamous cell cancers and round cell cancers predominate in males, while adenocarcinomas are more frequent in females (*Proc. First Nat. Cancer Conf.*). The sex distribution of the various histologic types of lung cancers according to this source, is as follows: Males: 44% epidermoid type, 38% undifferentiated type, and 18% adenocarcinomatous type; females: 11%, 37%, and 52% respectively. While Hollingsworth recorded a similar sex distribution of adenocarcinomas, Mason noted that adenocarcinomas were present in this series in 6.7% of the male cases and in 13.7% of the female cases. Lingskog, on the other hand, reported that adenocarcinomas occurred with equal frequency in both sexes, and that all adenocarcinomas observed were present in individuals below the age of 40.

A similar dependence of adenocarcinoma on the age of the individual was noted in the proceedings of the First National Cancer Conference. The proportion of adenocarcinoma dropped from 30% in the age group 0-49 years, to less than 20% in the age group 60 years and over. There was a corresponding rise in the proportion of epidermoid carcinomas, while the undifferentiated type of cancer seemed to be unaffected by the age factor. Gebauer reported that adenocarcinomas originate in 90% from the secondary and small bronchial branches, while the majority of the undifferentiated and epidermoid cancers develop from the main bronchial branches.

The proportion of the various histologic types of bronchiogenic carcinomas thus appears to differ according to sex and age as well as to their topography in the bronchial system. Their relative sex distribution moreover seems to vary with different investigators and thus with different areas studied. Again, it is not conceivable that such variations in the biologic and anatomic manifestations of lung cancers are due to endogenous causes, while they would find a rather ready explanation in differences of exposure to exogenous agents of various types (Lindskog).

RACIAL Distribution: Although neither Jaffé nor Steiner observed any significant differences in the distribution of lung cancers between whites and Negroes in the Chicago area, other investigators noted that pulmonary cancers are more frequent in whites than in Negroes (Arkin and Wagner; Quick and Brindley; Halpert). Likewise, Khanolkar, reporting on the organ distribution of 3,263 cancers of a Bombay hospital, does not mention lung cancer among the eight types of cancers listed that account for 2,652 cancers evaluated. However, until proper standardization as to age and sex has been made, these observations convey no valid information as to differences in racial susceptibility or special types of exposure to exogenous cancerigenic agents, coinciding with regions populated by different races.

The various kinds of circumstantial evidence evaluated support the concept that environmental factors are involved in the production of cancers of the respiratory tract, especially the lung (Boycott). While the actual extent to which exogenous agents seem to be active in the production of these tumors among the gen-

ral population, and the nature of such agents cannot be deduced from the information available, observations made in the field of occupational cancerigenesis permit a more definite and specific, although also more limited view of these aspects of environmental cancers of the respiratory organs.

Conclusive Evidence

RELATION of Lung Cancer to Large Occupational Groups and Non-specific Irritative Chemical Agents: The remarkable increase in the number of lung cancers observed during recent decades induced many investigators to search for possible environmental causes for this development. In considering the various possibilities Kennaway and Kennaway argued that the higher mortality from cancer of the lungs in towns noted by Stocks, the low mortality in agricultural occupations and the absence of a social gradient recorded by Stevenson were compatible with an etiological factor in the air such as coal smoke. Stephens claimed some years previously that the pollution of the air by carbon monoxide from incomplete combustion of coal and gasoline represented a major cancerigenic factor. Oldofredi recently revived this contention and pointed to the high incidence of lung cancer among former members of submarine crews of World War I, when it was exceedingly difficult to control adequately the carbon monoxide content of the air. Campbell's experiments on mice exposed to carbon monoxide, however, failed to show any increased incidence of pulmonary malignancies. Green was inclined to attach a similar significance to the pollution of the air with sulfur dioxide from the burning of sulfur-containing coal and the smelting of various ores.

Other investigators felt that members of outdoor occupations carrying the hazards of dust and fume inhalation, especially dust from tarred roads and exhaust fumes from gasoline engines, were especially likely to develop cancer of the respiratory tract (McCrae, Funk and Jackson; Matz; Schachter; Duguid; Ferenczy and Matolczy; Hutchison). This concept, however, was disputed by others, who pointed out that in some regions (Riga) an increase in lung cancer was observed before any tarred roads were used (Konrad and Franke; Kennaway and Kennaway; Guglielminettia). Knox and Probst pointed out that not the quantity but the quality of dust was important in lung cancerigenesis. A few investigators stated that lung cancer was more frequent among the laboring class than among professions (Brockbank; Weller). There is some evidence indicating that lung cancer is more frequent among the population of industrial areas than among that of rural districts (Fulton; Gerbe). Several large statistical analyses tended to show that some occupations (engineers, mechanics, painters, decorators (Brit. Emp. Cancer Campaign)); painters and furnacemen (Fulton); machinists, foundry workers, metal grinders (Turner and Grace); metal workers, spinners, cigar makers (Borst) exhibit an excessive liability to cancer of the lung.

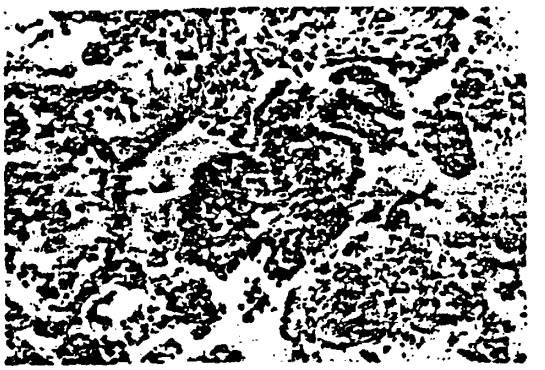
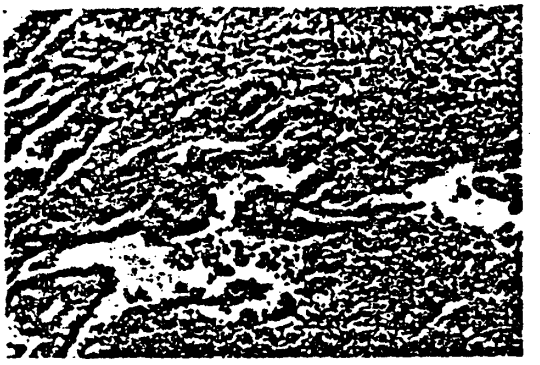


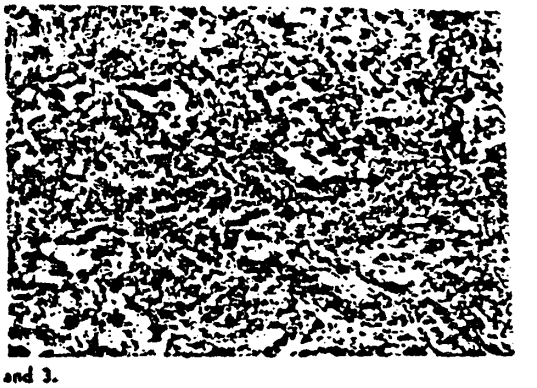
Fig. 1.
Atypical papillomatous epithelial growth in lung with chronic pneumonia such as seen after exposure to irritative chemicals.

From information to be given later in connection with the discussion of recognized cancerigenic agents it is apparent that an appreciable part of the membership of the various occupational groups mentioned, may become exposed to one of the known specific environmental cancerigens (mist of lubricating oils, soot, dust from or pigments of various cancerigenic metals (chromium, nickel, arsenic). It is thus possible or probable that in these instances statistical epidemiologic data reflect real causal relations.

There are, finally, many students of this subject who could not find any relation between special occupations and lung cancer formation (Brockbank; Kennaway and Kennaway; Simmross; Shennan; Rogers; Rice; Husted and Billman; Jaffé; Bonser; Haintz; and others). However, the occupational data on which such statements are based are, as a rule, too inadequate as to specific type and duration of employment and occupational period, which are important because of the long preparatory and latent period of lung cancer to be of any definite value.

A similar conclusion applies to the claims made concerning the etiologic connection between the inhalation of various irritative gases, fumes, mists and dusts of various acids and alkalis (sulfuric acid, hydrochloric acid, nitric acid, ammonia, war gases, formaldehyde) and cancers of the respiratory tract (Fig. 1). While isolated cases of respiratory cancer are bound to occur in occupational groups coming in contact with such agents, the existing epidemiologic evidence does not lend any valid support to a generalization from the observation of a few cases (Koelsch). However, it is worth noting that at least one of the acids mentioned, sulfuric acid, is often contaminated with appreciable amounts of arsenic. This impurity in commercial sulfuric acid has been blamed by





Figs. 2 and 3.
Atypical epithelial proliferations in fibrotic bituminous lung, involving lining of gland-like formations.

Amor for the occurrence of lung and nasal cancers among nickel refinery workers. In view of the absence of reliable epidemiologic studies it is desirable that thorough surveys of operations showing respiratory hazards of the above type be made so as to obtain adequate information on the incidence rate of respiratory cancer among workers exposed to the inhalation of finely dispersed acids, alkalies, and other irritative inorganic and organic chemicals, such as, especially, beryllium and its various compounds, formaldehyde, glycols, isopropyl compounds, carbamate derivatives, organic solvents, phosphors, alloys, paints, insecticide sprays, weed killers, rubber accelerators, and polishes.

There can be little doubt from the evidence presented that data obtained by an evaluation of large occupational groups with varying types and degrees of exposure to irritative agents of non-specific nature yield little definite information concerning a causal relation between occupational activity and cancer of the respiratory tract. Great progress, however, has been made in elucidating such connections whenever epidemiologic investigations were limited to circumscribed groups of workers and populations either exposed to chemical agents of more or less well defined kind or to identical or similar occupational or environmental conditions.

ORGANIC CHEMICALS: The inhalation of coal dust is in general not credited with being inducive to cancer of the lung, since statistical studies conducted in coal miners were negative in this respect (Feil; Jordan; Kennaway and Kennaway; Gerbe; Schulte), and mice and guinea pigs exposed to coal dust did not develop lung cancers (Campbell; Vorwald and Karr).

This innocuousness, however, does not extend to the distillation and fractionation products of coal, oil shale, and petroleum (tar, asphalt, pitch, oil) and their incomplete combustion products, such as domestic, industrial and commercial soots (lamp blacks, carbon blacks, oil blacks, etc.).

(a) Soot, Tarry Material Produced by th Incomplete Combustion of Carbonaceous Matte (Coal, Mineral Oil, Natural Gas, Gasoline, Die sel Fuel) (Domestic, Industrial and Commercia Soots): While the cancerigenic action of soo resulting from the incomplete combustion of coa upon the skin is well recognized and best demon strated by the chimney sweep's cancer of th scrotum, the causal relation between the inhalation of atmospheric soot from domestic and industrial sources and lung cancer among the general and industrially employed population i much less definite (Dorn). In fact, cancer of the lung is not unusually frequent among chimney sweeps (Kennaway and Kennaway). Although Schnurer reported that the incidence of lung cancer in a series of 342 necropsies of the Pittsburgh district increased directly with the degree of bituminosis (Figs. 2 and 3) Dorn found in his statistical studies that the lung cancer rate was low in Pittsburgh when compared with that of five other large cities. Experimental studies conducted by Schnurer and Haythorne, and Seelig and Benignus, with the inhalation of smoke from an eggstove or of soot from a hospital flue used as bedding for mice, respectively, were equally inconclusive or unconvincing. On the other hand, there can be little doubt that the soot contained in the air of Pittsburgh and other cities is carcinogenic to mice, since Leiter, Shimkin and Shear and Leiter and Shear could elicit skin cancers in those animals with an extract of soot collected at various localities in the United States. Passey and Carter-Braine found the fraction of household soot boiling over above 250°C most active in this respect.

The question of the possible cancerigenic action from the inhalation of various types of commercial soots prepared from natural gas or oil residues and merchandised as lamp black, oil black, furnace black, gas black, or channel black, has become important in recent years because of the huge production and consumption of these blacks in the rubber industry and for paint and ink manufacture, in the making of

records and because of their use as coloring matter. Some of these blacks have been prepared in late years by the incomplete combustion of oil residues that are obtained from the catalytic cracking process and that possess distinct cancerigenic properties to mice. In addition to the possible lung cancer hazard involving the producers, loaders, shippers, and industrial consumers of such carbon blacks, there may exist a similar hazard for the general population living in the neighborhood of carbon black plants, because during the production of these materials large amounts of soot may be released into the air. A similar environmental cancer hazard may perhaps result from the burning of oil dumps near refineries giving rise to considerable amounts of soot. Little experimental work so far has been done in studying the potential cancerigenic properties of the various commercial soots which, depending upon the production process and raw material used, differ appreciably in chemical and physical respects and especially in tar content (Mantell).

Steinbrueck reported the experimental production of skin cancers in mice painted with black of printing ink. Seelig and Benignus, on the other hand, failed to see any lung cancers in mice exposed to the inhalation of lamp black. Experiments of Miescher and Schwarz, using an ointment containing a benzene extract of oil burner soot applied to the skins of mice, were equally negative. Since the carbon black industry is supporting experimental investigations on the potential pulmonary cancer hazard connected with the inhalation of various carbon blacks, more definite information may soon become available.

(b) Diesel and Gasoline Engine Exhaust: A similar degree of uncertainty exists in regard to the potential cancerigenic properties of the normal and abnormal exhaust products of low compression internal combustion gasoline engines and of high compression Diesel engines in connection with the development of occupational and environmental respiratory cancers (Lorentz; Heilmann; Duguid; Ferenszy and Matolcsy). The contention that the inhalation of exhaust fumes from gasoline and Diesel engines and thus the increased automobile traffic, is causally related to the rise in the incidence of lung cancers in recent decades has been attacked on various grounds.

It was pointed out that the exhaust fumes of these engines when operating perfectly and thereby generating products of complete combustion contain little or no ingredients of potential cancerigenic qualities (Bloch and Widmer; Probst). Mention, moreover, was made of the fact that there does not exist a parallelism between the rise in automobile traffic in different countries and the increase in lung cancer (Lehmann; Konrad and Franck; Syreck), and that occupations particularly exposed to engine exhausts, such as policemen, street cleaners, garage mechanics, and automobile drivers, do not show an excessive incidence of lung cancer (Passey and Holmes; Probst; Katz; Brandt).

Experimental attempts to produce cancer of the skin or of the lung by exposing mice to exhaust gases or to extracts from the fumes of such engines gave negative results (Campbell; Smith; Schmidtmann; Twort and Twort) in the hands of most investigators, although Pessano reported the development of metastasizing cancers of the lungs in rats following prolonged and intense exposure to combustion products of fuel oils.

In evaluating the experimental evidence it may be well to note that the products of exhaust of a well functioning gasoline or Diesel engine differ doubtlessly in many respects from those of an engine with imperfect performance, which generates considerable amounts of soot and other matters of incomplete combustion at high temperature. Since engines with defective combustion are rather frequently met, future attention should be focused on the potential cancerigenic properties of exhaust fumes emitted from imperfectly operating gasoline and Diesel motors, before definite conclusions as to the existence of an environmental and occupational lung cancer hazard from this source can be reached.

(c) Tar Dust and Fumes: The existence of an environmental lung cancer hazard from the inhalation of dust, mist and fumes of tar and tar oils generated during the construction and use of tarred roads has been a matter of considerable speculation, since such a hazard, if present, would be of great practical importance (Brandt; Kling, Samssonov and Heros, and others). However, this concept finds little support from the epidemiologic studies of Lehmann; Husted and Billmann; Fischer, and Kennaway and Kennaway. There was no consistent relation between the lung cancer frequency and the extent of tarred roads in different countries, nor was there any excessive lung cancer incidence among workers especially exposed to the inhalation of tar dust and fumes in several countries (Hugounenq; Husted and Billmann; Müllschitzky).

More recent observations, however, indicate, that the inhalation of hot tar fumes, such as those encountered in the operation of gas generators in connection with the production of illuminating gas and coke, is associated with an increased liability to lung cancer. It was shown that retort workers seem to be especially subject to pulmonary malignancy (Kuroda and Kawahata; Kawahata; Sunderland). According to Japanese experience the gases emitted from the stoking holes contain 0.7% tarry matter. Within a six-year period there came to observation 21 cases of lung cancer among a total of 100 workers employed for more than 10 years. In 14 of the 21 cases the age of the patients was from 35 to 45 years, thus showing a definite

shift into a younger age group than that found for lung cancer in the general population where the majority of cases occurs in the group of from 45 to 65 years. Similar observations have recently been made among gas house retort workers in Canada. Kennaway and Kennaway noted that gas stokers and patent fuel workers, who have a similar exposure to tar fumes and dust have a more than nine-fold incidence rate of lung cancer.

These relatively meager findings in man are repeated by the experimental evidence obtained in mice and other species exposed to tar dust or subjected to cutaneous, intrapulmonary or intravenous administration of tar.

Campbell's experiments showed that mice exposed to dust from tarred roads developed cancer of the skin and of the lungs. Similar experiments of Staufer; Barnewitz; and Bonne, using mice, however, were negative as to the development of lung tumors, although resulting in some of the animals in the development of cutaneous carcinomatosis. Inhalation experiments with dust from tarred roads in which rabbits, guinea pigs and rats were employed were equally unsuccessful in regard to pulmonary tumor formation (Staufer). Intratracheal insufflation of powdered tar into mice, and guinea pigs yielded negative results (Bonne; Schabad). Kimura, on the other hand, using the same experimental method in rabbits and guinea pigs, reported the development of lung cancers in both species. Nakano obtained a similar result in rabbits injected intravenously with a solution of tar in lanolin, while Tedeschi, as well as Simonds and Curtis, observed merely atypical proliferations of the bronchial epithelium of rabbits after repeated intravenous administration of tar. A similar result was obtained after the direct introduction of tar into the pulmonary parenchyma of rabbits (Gerschin and Pigalew). Since none of the so-called carcinomas produced by insufflation, or intravenous or intrapulmonary injection of tar gave rise to metastases, it is doubtful, whether any of the reported atypical proliferations of the bronchial and pulmonary parenchyma were actually malignant.

It is noteworthy, on the other hand, that the cutaneous application of tar to mice was followed by the appearance of adenocarcinomas of the lung (Murphy and Sturm; Koose and Cordes; Lynch; Schabad; Watson and Mellanby; Campbell; Samssonow; Puccinelli). Pucinelli as well as Möller obtained, with the same method, lung cancers in rats. These remote cancerigenic effects of cutaneously applied tar on the lung suggest the possibility that in man also cancer of the respiratory tract may result from contact with environmental cancerigens by other than the respiratory route.

(d) Tar Fumes from Tobacco Smoking: The tobacco smoking habit provides an additional environmental source through which tarry material in the form of hot fumes comes in contact with the tissues of the respiratory tract. In view of the existing tendency to relate the recent increased frequency of lung cancers to the action of a single, widely distributed cancerigenic agent, it was to be expected that some investigators would point to the parallelism between the phenomenal growth in the cigarette smoking habit and the rising incidence of cancer of the respiratory tract during the last three to four decades (Bogen and Loomis; Schürch and Winterstein; Hruby and Sweany; Roffo; McNally; Lickint; Müller; Arkin and Wagner; Ferrari; Mertens; Ochsner, Dixon and DeBakey; Fulton; Grace; Hoffman; Schrek; Baker; Ballard and Dolgoff; Wynder and Graham; Jackson and Jackson; Hermann and others). While some of these investigators (Roffo; Wynder and Graham) went so far as to attribute the chief responsibility for the development of lung cancer to cigarette smoking, others claimed that the inhalation of tobacco smoke is merely one of the factors that is involved (Hoffman).

In analyzing the statistical evidence advanced in support of these contentions, it becomes apparent that in no instance have occupational or environmental exposures to the various known or suspected cancerigenic agents been considered. The complete exclusion of these factors when investigating tabagism must lead to serious errors. It is, moreover, evident that the present trend in the sex ratios of lung cancer and of cigarette smoking run in opposite directions—that is, while the sex ratio of lung cancer becomes more heavily weighted in favor of the male sex, that of cigarette smoking doubtlessly favors increasingly the female sex. The claim of Roffo that the spectrographic examination of tobacco tar demonstrates the presence of cancerigenic aromatic hydrocarbons, such as 3,4 benzpyrene, has not been substantiated by Cooper, Lamb, Sanders and Hirst, and Schürch and Winterstein. It is obvious, on the other hand, from measurements of the temperatures obtained in pipes, cigars and cigarettes during the smoking process that temperatures are reached (400° to 700°C) which might cause the production of aromatic compounds of cancerigenic nature through thermo-cracking (Flory; McNally; Cooper, Lamb, Sanders, and Hirst).

Attempts to produce cancer of the lung in mice by the inhalation of tobacco smoke have failed (Lorenz, Stewart, and Daniel). The results of cutaneous applications of tobacco tar to the skin of mice and rabbits have been contradictory. While Roffo claimed rather uniform and consistent cancerigenic action of various tobacco tars in mice and rabbits, the great majority of other experimentalists either obtained only carcinomatoid growths in the ears of rabbits and an occasional skin cancer in mice (Cooper, Lamb, Sanders and Hirst; Campbell; Flory; Lu-Fu-Hua; Schürch and Winterstein; Chihamatsu) or no tumors at all (Bogen and Loomis; Hoffmann; Schreus and Zurhelle; Mertens).

It appears from the evidence reported that at the present time only suggestive epidemiologic data exist connecting the inhalation of tar fumes in tobacco smoke and thereby the smoking habit with the development of lung or larynx cancer in man (Hueper). It is unlikely, moreover, that this type of respiratory contact with a variety of vegetable tar plays a dominant role in the production of lung cancer, since experimental observations place tobacco tar at best among the weak exogenous cancerigens.

It is essential in any consideration of this question to take cognizance of the fact that all tobaccos grown in the European and American countries are apt to be contaminated with residues of arsenical insecticides. The smoking of such a tobacco, therefore, would entail the inhalation of arsenical vapors or fumes which by themselves seem to represent a respiratory cancer hazard.

Although the exposure to tobacco dust does not entail contact with tarry combustion products of tobacco, mention is made in this connection of the claim that the inhalation of tobacco dust (tobacco workers, cigar makers, tobacco dealers) creates an increased liability to lung cancer (Seyfarth; Krompecher; Heilmann; Behla; Benda; Ferenczy and Motolcsy; Brinkmann; Enger; Langbein; Borst; Jaeger and Kolb; Rottmann; Koelsch; Wacher and Schmincks; Lickint). Lehmann, however, pointed out that persons engaged in the tobacco trade are, in general, heavy smokers. The entire statistical evidence as to a lung cancer hazard from tobacco dust is unreliable and requires confirmation before such allegations can be entertained seriously.

(e) Petroleum and Shale Oils: Inhalation of processed mineral oil mists and fogs occurs for occupational as well as medical reasons. The question, therefore, has arisen as to whether such exposures may result in the production of cancers of the respiratory tract. Kennaway and Kennaway stated that there exists a relatively high incidence of laryngeal cancer in mule spinners who, during their work, inhale a mist of cancerigenic shale oil used in lubrication of the spindles. While the use of mules has long been discontinued in the United States in textile manufacturing using fibers of vegetable, animal or synthetic chemical origin, mules are still employed in asbestos mills for the production of asbestos threads having a minor addition of other fibrillar material (cotton, rayon). Southam noted that mule spinners exposed to a spray of shale oil occasionally develop not only cancer of the scrotum but also of the stomach and lung. Scott, on the other hand, stated that he had not seen a single case of lung cancer in shale oil workers, of whom those employed in the press rooms of paraffin departments may become exposed to the inhalation of oil fogs. Roesch reported a case of triple cancer (lung, skin, stomach) in a paraffin worker of a lignite oil operation. An inhalation hazard from lubricating oil mist and fog (cutting oil) has been incriminated in the excessive incidence of lung cancer among French turners, millers, planers, mechanics, and fitters (Huguenin, Fauvet and Bourdin; Touraine and Bour; Kling, Samssonow and Héros). Statistical data cited previously indicate that painters who are exposed to the inhalation of mists from petroleum fractions used in paints have an excessive lung cancer incidence rate. No information on this point is available in regard to printers and construction workers who spray impure paraffin (Humperdinck; Meyer-Brodnitz) and in workers in match and water-proofed paper factories using impure paraffin for impregnation.

While there does not exist any information on the pulmonary effects of oil mists and fogs (nebulized oil) in experimental animals, Schabad, Campbell, Twort and Lyth; and Kling, Samssonow and Héros reported an increase of lung tumors in mice following the cutaneous application of shale oils and lubricating oils of petroleum derivation. There was, however, no direct correlation between the degree of cutaneous cancerigenicity of these oils and the extent of pulmonary tumorigenesis.

(f) Isopropyl Oil: The only aliphatic chemical that may be involved in the development of cancer of the nasal sinuses and of the lung when inhaled as a vapor is apparently isopropyl oil which is a crude product of the manufacture of isopropyl alcohol. Although neither the actual existence of these occupational respiratory cancers nor the nature of the causal agent is as yet entirely established, the observations made in two plants known to us are of sufficient significance to deserve further study. If confirmed these findings would open a large new field of environmental chemical agents (straight chain and cyclic aliphatic hydrocarbons) that would require intensive scientific and epidemiologic investigations for evidence of potential cancerigenic properties.

INORGANIC CHEMICALS: Observations made during rather recent years in the occupational field indicate that respiratory exposure to inhaled dusts, fumes, vapors and gases of various metals or metal compounds seems to convey an excessive liability to cancer of the respiratory system.

(a) Arsenic: While cancer of the skin through medicinal, environmental, or occupational contact with inorganic or organic arsenicals has become a well recognized fact, (Hueper; Neubauer), cancer of the respiratory organs following exposure to arsenical dust, fumes or spray or after medicinal ingestion of arsenicals represents a sequela of more recent observation and of less firmly established nature. The total number of lung cancers after medicinal or occupational exposure to arsenicals stands at present at 13 cases with one additional case listed as

LUNG CANCER MORTALITY IN SEVERAL COUNTIES OF MONTANA, 1947-1948

County and Total Population 1940	Major Industry	Number Lung Cancers		Total Cancer		% Lung Cancer		Annual Lung Cancer Death Rate/100,000	
		Male	Female	Total	Deaths	Male	Female	Male	Female
Deer Lodge 13,627	Copper Smelting	21	0	21	98	30.8	0.0	145.7	
Silver Bow 53,297	Copper Mining	27	2	29	259	22.6	1.5	48.6	3.9
Cascade 41,999	Copper Mining Smelting	20	5	25	299	12.7	3.3	46.3	12.3
Gallatin 18,269	Agriculture	1	0	1	81	3.0	0.0	5.2	

The estimated crude death rate for lung cancer among white males in the entire United States in 1947 is 14.9 per 10,000 population.

cancer of the larynx. Two of these cancers occurred after medicinal use of arsenicals (Semon; Montgomery and Waisman; Russell and Klaber), the other followed after occupational exposure to dust of arsenical pesticides, (manufacture and use) (sheep dip manufacturers, vineyard workers) or smelter fumes (Merewether (four cases); Hopkins and Studdiford (one case); Saupe (two cases); Frommel (one case); von Pein (one case); and Faning (five cases of lung (three apparently identical with Merewether's), one case of larynx). In the majority of the lung cancer cases of apparently occupational origin there co-existed cutaneous lesions characteristic of chronic arsenicism.

The cancers of the respiratory tract observed by Hill and Faning among sheep dip manufacturers represented 31.8% of all cancers observed in this group (engineers, packers, chemists).

These occupational observations are of distinct environmental importance, since reports from Germany have related serious arsenical injuries in domestic and wild animal life living within the fume zone of silver and lead smelters to arsenic containing fumes released into the air from these plants (Prell). Nieberle also reported from the same region the endemic occurrence of adenocarcinomas of the nasal sinuses in a flock of sheep, and stated that "a certain connection of this disease with the locality and with an injury by arsenic can scarcely be excluded."

Similar environmental and industrial health conditions may exist in this country for those parts where arsenic containing flue dust or arsenical insecticides have been and/or are released into the air in appreciable quantities. Recent observations made in regard to the lung cancer incidence in certain counties in Montana where huge quantities of arsenical fumes in past years entered the air from copper smelting operations may be of significance in this respect (Lull, Wallach). Mortality and morbidity records for the years 1947 and 1948 revealed that 30.8% (21 cases) of all male cancer deaths (total cancer 98 deaths) were listed as due to cancer of the respiratory tract in Deer Lodge County where about 25% of the population (13,627) is engaged in smelting of copper ores containing 0.5% arsenic, and where from the past industrial history of this region an occupational as well as environmental arsenic hazard may be assumed to exist.

In the adjacent Silver Bow County where extensive copper and zinc mining activities are carried on, the proportion of lung cancer deaths to cancer deaths was 22.6% (27 cases) for males and 1.5% (two cases) for females (total number of cancer deaths 259, total population 53,207). There was in contrast in the adjoining Gallatin County which is agricultural in character and which has a population of 18,269, one male lung cancer death, while again in Cascade County with a population of 41,999 and with copper-arsenic ore mining and smelting activities the proportion of lung cancer deaths to all deaths from cancer was 12.7% for males (20 cases) and at 3.5% (five cases) for females, with a total number of 299 cancer deaths. These observations are of only limited value since they cover too short a period of time, too small a number of cases, and no detailed data on the occupational and environmental aspects of the individual lung cancer cases. However, the high frequency of lung cancer in counties where arsenic contamination of the environment is known to exist is of sufficient importance to call for a thorough and extensive study of the presence of a potential arsenic lung cancer hazard in all those regions in which existing occupational and environmental conditions warrant such investigations.

Such epidemiologic studies are especially indicated because of the difficulties encountered in the production of arsenic cancers in experimental animals and because of the complete lack of any investigations of the pulmonary cancer aspects of arsenic hazards by experimental methods (Neubauer; Hueper).

(b) Asbestos: There occurs respiratory contact with three different types of silica compounds, namely, inorganic crystalline or amorphous silicates, organic silicones and asbestos. Since silicotic pneumoconiosis is characterized by a chronic granulomatous inflammatory re-

action, and thus seems to fulfill remarkably well the basic requirements of the chronic irritation theory of cancerigenesis, several investigators have incriminated this frequent type of occupational pneumoconiosis in the development of cancer of the lung (Fine and Jaso; Anderson and Dible; Charr; Klotz; Dible). There are in fact some 50 cases on record in which cancer of the lung or larynx and silicosis were co-existing (Dible; Fine and Jaso; Klotz and Simpson; Maxwell; Sladden; Middleton; Sweany, Porsche and Douglass; Vorwald and Karr; Allen; Sokoloff; Pancoast and Pendergrass; Simons; Schnurer; Charr; Harris). However, the great majority of investigators have come to the conclusion that there does not exist any causal relation between silicosis and pulmonary or laryngeal malignancy (Vorwald and Karr; Allen; Feil; Harris; Pancoast and Pendergrass; Saupe; Schulte; Schülz; Berblinger). Schulte and Schulz noted that coal miners in the Ruhr district, among whom silicosis is frequent, have no unusual frequency of lung cancer, while Allen recorded a similar observation for the coal miners of Pennsylvania. Corresponding negative observations were made by Vorwald and Karr on individuals who came to necropsy with silicosis at the Saranac Laboratory and have been reported by the Miner's Phthisis Medical Bureau of South Africa based on studies made among the South African gold miners in the Johannesburg district.

These conclusions are supported by the results of experimental investigations, in which mice, rats, guinea pigs, rabbits, chickens and cats were exposed to the inhalation of silica dust (Campbell; Vorwald and Karr; Willis and Brutsaert).

A fundamentally different situation, on the other hand, seems to prevail in regard to the causal relation between asbestosis and cancer of the lung. Because the recognition of asbestosis as a special form of pneumoconiosis is of rather recent date, the analysis of 18,280 death certificates for cancer of the lung and larynx in males from England and Wales from 1921 to 1932 did not reveal any cases of lung cancer in asbestos workers (Kennaway and Kennaway). Since 1935, however, an appreciable number (55) of cases of asbestosis complicated with cancer of the lung have been recorded from England, Germany, Canada and the United States (Lynch and Smith; Lynch; Lynch and Cannon; Egbert and Geiger; Gloyne; Wood; Horning; Welz; Wedler; Nordmann; Merewether; Luton and Champfix; Linzbach and Wedler; Dominici; Baader; Homburger; Holleb and Angrist; Desmeules, Rousseau, Giroux and Sirosis; Cureton) (Figs. 4, 5 and 6).

The proportion rate of lung cancer in persons with asbestosis who came to necropsy stands between 13 and 15%. The exposure time ranged from three to 27 years (average 15 years).

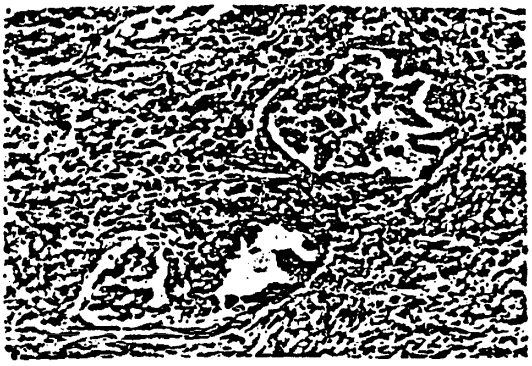


Fig. 4.
Atypical glandular epithelial formations in fibrotic and chronically inflamed lung with asbestosis bodies within desquamated epithelial cells located within lumen of cystic gland-like formations.

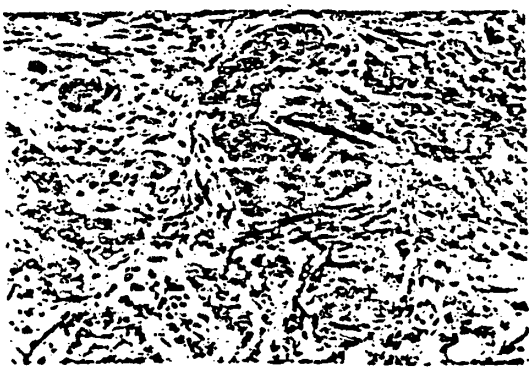


Fig. 5.
Squamous cell cancer of lung with asbestosis bodies adjacent to epithelial cell pegs.

Fig. 6.
Combination of atypical glandular formations and squamous cell carcinoma in asbestotic lung.

The latent period after cessation of exposure was from 10 to 12 years. Multiple cancers were found in several cases, and both male and female workers were affected. The male-female sex ratio, according to Merewether is 2.4:1, while the mean age is about 52 years. Although Warren rather recently maintained that the con-

Age Distribution of Asbestosis Cancer						
Age:	30-40	41-50	51-60	61-70	71-80	years
Cases:	2	7	6	1	1	

It is noteworthy that the manifestation age of asbestos cancer is relatively young.

Exposure Time of Asbestosis Cancer						
Exposure:	1-5	6-10	11-15	16-20	21-25	26-30 years
Cases	2	3	2	3	5	1

nection between asbestosis and lung cancer is of coincidental nature, the actual existence of a causal relation appears to be very likely (Lecoeur; Koelsch; Saita; Hueper; Teleky; Editorial); Gross).

The reason for the different behaviour of silica and asbestos in regard to pulmonary cancerigenesis is unknown. The various metallic constituents of asbestos may possibly play a role.

While the experiments of Vorwald and Karr performed on guinea pigs that were exposed to asbestos dust gave negative results, those conducted with mice by Nordmann and Sorge apparently yielded positive results, since a few of the animals surviving the inhalation of asbestos dust sufficiently long showed at autopsy pulmonary lesions interpreted as squamous cell cancers of bronchiogenic nature. All spontaneous pulmonary tumors occurring in mice, on the other hand, are of glandular type and alveolar origin.

(c) Chromium: Another member of the group of respiratory metal cancers is the cancer of the lung observed in the manufacture of chromates and chromium pigments (zinc chromate). While the first two cases of chromate cancer of the lung were observed in 1914 in Germany (Lehmann), it was not until 1936 that their number had become sufficiently large for establishing definitely the causal relation between exposure to chromate dust and lung cancer in German chromate plants (Alwens and Jonas; Alwens, Bauke and Jonas; Bauke and Alwens; Baader; Gross and Koelsch; Gross; Pfeil; Teleky; Bauer; Carozzi; Koelsch; Lecoeur; Saita; Staemmler; Teutschlaender; Kennaway and Kennaway). While the exposure in the chromate plants was to dust of chromite ore and of monochromate and bichromate salts of sodium or potassium, the respiratory contact in the chromium pigment manufacture which resulted in lung cancer was in all cases (eight) to zinc chromate (zinc yellow) (Gross and Koelsch). Baader noted moreover that there were nine cases of lung cancer on record among workers of the chromate consuming industries in Germany.

The more recent observations of similar nature among American chromate workers cover so far only chromate manufacturing operations. In neither country is there any information available as to the existence of lung cancer hazards for workers employed in chromium plating operations, in the manufacture of inks and paints, in printing, painting, dyeing, dye

Fig. 7.
Round cell carcinoma of the lung in a chromate worker with black chromite deposits in adjacent lung tissue.

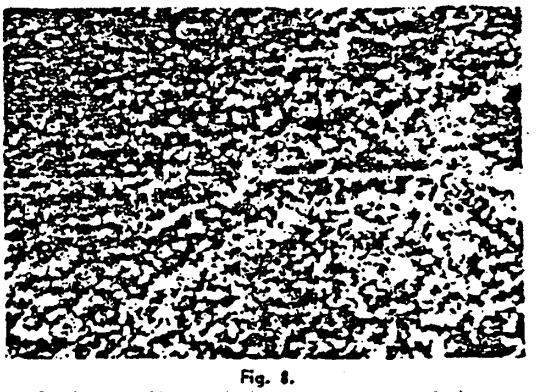


Fig. 8.
Spodogram of lung with chromite pneumoconiosis showing the black chromite deposits within the white mineral skeleton of the ashed lung section.

making establishments, and in the production and processing of metallic chromium and chromium alloys. It is remarkable that, according to Goldblatt and Wagstaff, the English chromate industry apparently has remained free from these respiratory cancer hazards. Gross estimated that the chromate lung cancer incidence rate among the approximately 1,000 effectively exposed German workers stands at 3.9%. It appears to have risen in more recent years to about 5%, since Baader placed the total number of chromate cancers in Germany at above 50.

No similar figures are available from this country. However, the epidemiologic studies of Machle and Gregorius have shown that the lung cancer incidence rate among American chromate workers is from 10 to 40 times that of a comparable industrial group, or an average of 16 times the expected rate. A recent analysis of the final fate of some 150 former chromate workers engaged in chromate production for at least six months, and having passed a latent period of more than four years, demonstrated that of 25 deaths that had so far occurred in this group, five were caused by cancer of the respiratory tract (20%) (Figs. 7 and 8).

AGE DISTRIBUTION OF CHROMATE CANCERS OF THE LUNG

21-30	31-40	41-50	51-60	61-70	71 and above	Years	Total	Mean
1	5	10	15	14	0	German	48	
0	6	12	16	7	1	American	42	51.7
1	11	22	34	21	1	Total	100	

The age distribution of the chromate cancers is practically identical (Kennaway and Kennaway) with that seen in a series of 1,514 lung cancers of unknown etiology that was analyzed by Matz.

EXPOSURE PERIOD OF CHROMATE CANCERS OF THE LUNG

4-10	11-20	21-30	31-40	41 and above	Years	
10	15	8	12	1	German	15 years
10	22	8		2	American	16.6

The total number of observed cases of chromate cancer of the lung from both the United States and Germany is now well above 100, since additional cases have been discovered after the above figures were reported.

Although ulcers and perforations of the nasal septum are frequently observed in chromate workers, there is only one case of carcinoma of the nares in a chromate worker on record (Newman).

The statement of Machle and Gregorius that apparently the monochromate only is cancerigenic does not seem to be supported by observations made in German plants where in Leverkusen 10 cases and in Uerdingen 14 cases were found among workers in dichromate plants. Such a selectivity of monochromate is, moreover, scarcely conceivable from a biochemical viewpoint since both monochromates and bichromates are readily ionized in the body. Whether chromite ore dust represents a cancerigenic factor in chromate workers is still an open question although it may produce a chemical pneumoconiosis (Lukanin). Likewise it is uncertain whether chromium plays an essential role in the production of other human cancers, although Dingwall and Beans some 15 years ago demonstrated spectroscopically chromium in various human cancers.

The exposure of rabbits and cats for several months to chromite and chromate dust present in a chromate factory did apparently not elicit any cancerous responses (Lukanin). The implantation of metallic chromium into the marrow cavity of the femur of rabbits (Vollmann), on the other hand, gave rise in animals surviving for more than three years to cancers at the site of deposition and in the lung (Schinz).

(d) Nickel: The occurrence of cancers of the nares, nasal sinuses and of the lung among workers in Clydach, South Wales, engaged in processing Canadian coppernickel matte of the Sudbury mines by the Mond nickel carbonyl process was first observed in 1924 (Baader). During the following 15 years several reports on the continued appearance of such cancers were made by various investigators (Grenfell; Cooper; Stephens; Bridge; Amor; Merewether). Up to 1939 there were recorded with the Chief Inspector of Factories 34 cases of nasal sinus cancer and 24 cases of cancer of the lung. These figures have risen to 47 cases of cancer of the nose and 82 cases of cancer of the lung for the period of 1923 to 1948 (Merewether). No similar observations have been made or recorded so far from German, Canadian and American nickel refineries using the same process.

According to Amor, the average employment period for the nasal sinus cancer cases was 19.4 years (range: 6.0 to 30.0 years) and that of the lung cancers 21.4 years (range 7.0 to 32.0 years). The average exposure time to dust was 11.3 years for the nasal sinus cases (range 3.0 to 26.0 years) and 11.6 years for the lung cancer cases (range 1.0 to 33.0 years). With a few exceptions all workers who developed nasal or pulmonary cancers had entered employment before 1924 (Merewether). The average age at death was 51.0 years for the nasal cancer cases (range: 36.0 to 66.0 years) and 53.0 years for the lung cancer cases (range: 48.0 to 66.0 years).

As to the causative agent, Amor emphasizes that only one case has been observed in a worker who had contact with nickel carbonyl, while all others had been exposed to arsenic-containing dust originating from commercial sulfuric acid contaminated with arsenic and used for the extraction of copper. The absence of similar cancers among the nickel refinery workers in Canada is explained in the opinion of Amor therefore by the fact that in Canada the sulfuric acid extraction process is not used.

The concept of an arsenical origin of these respiratory cancers, however, is not supported by the apparent absence of arsenical dermatoses and cancers of the skin among the affected nickel refinery workers. Such manifestations rather regularly accompany the cancers of the lung in arsenic workers and thus represent a part of the environmental arsenic lung cancer pattern. There is, moreover, no evidence from any other source that the industrial use of commercial sulphuric acid usually containing arsenical impurities has given rise to cancer of the respiratory tract. Exposure to arsenical dust, while having frequently caused ulceration and perforation of the nasal septum, has not given rise to nasal cancers.

The cancers of the nares and nasal sinuses in the nickel workers involved the middle turbinates and the ethmoids and were histologically of squamous, undifferentiated or papillary columnar cell types. One columnar cell cancer involved the nasopharynx. The four pulmonary cancers that were studied histologically were of small round cell or squamous cell types.

The inhalation experiments conducted by Campbell on mice exposed to arsenic-containing nickel dust obtained as concentrated matte from the Mond Company gave results of doubtful statistical significance, since the ratio of lung tumors in the test series and in the controls was 14:8. It is uncertain whether these experiments actually duplicate the conditions of exposure

sustained by the workers in the nickel refineries, since the nickel-copper matte manufactured in Canada and used in England contains only minute amounts of arsenic. The origin of the arsenic, according to Amor, is not from the matte but from the sulfuric acid used.

Since cancers of the respiratory tract seem to continue to occur in English nickel refinery workers, there is sufficient indication to investigate thoroughly their causal aspects by epidemiologic and experimental methods for practical as well as scientific reasons. Definite information should be obtained whether these cancers are of arsenical causation as claimed by Amor or are attributable to the inhalation of nickel carbonyl vapors and thus represent a separate type of metal cancer. A study of the respiratory cancer incidence in workers engaged in nickel plating, manufacture and use of nickel pigments and alloys, and in the polishing of nickel may aid in clarifying the presently controversial etiologic aspects of the cancers occurring among the copper-nickel refinery workers.

PHYSICAL AGENTS: (a) X-radiation: Despite the large number of persons whose lungs have been subjected to intensive irradiation by x-rays for medicinal reasons (cancer of the breast or lung), there is not a single case of medicinal x-ray cancer of the lungs on record. Chronic radiation pneumonitis, on the other hand, has been of relatively frequent occurrence. Apart from the extensive hyalinizing and fibrosing changes characterizing this process, there occurred swelling and transformation of the alveolar epithelium into cuboidal and columnar cells and cellular monstrosities, and stratification, giant cell formation and squamous cell metaplasia of the bronchial epithelium (Bauer and Schaer; Warren and Spencer; Warren and Gates; Widmann; McIntosh and Spitz; Leach, Farrow and Foote; Jacobsen; Freid and Goldberg; Bauer). Engelstad produced similar reactions in the pulmonary parenchyma and bronchial epithelium of rabbits without obtaining cancerous responses. Warren and Gates reported corresponding acute lesions in rats.

The development of a squamous cell cancer of the larynx on the basis of a chronic x-ray injury produced by 86 x-ray treatments given for a skin disease of the neck was reported by von Eicken.

(b) Radiation of Radioactive Substances: There are only two cases on record in which prolonged inhalation of radioactive gases and dust by a laboratory technician and a chemist engaged in the production of medicinal radium preparations or in the manufacture of luminous paint, respectively, (Tonges and Kalbfleisch; Kalbfleisch; Belt; Doenecke) caused fatal fibrosis of the lungs. The high incidence of pulmonary cancer among miners in Schneeberg and Joachimsthal where radioactive ores are mined

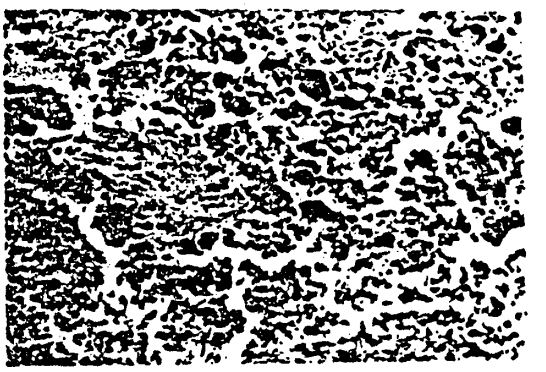


Fig. 9.

Highly anaplastic carcinoma in a Schneeberg miner showing many grotesque cells which are commonly seen but not specific for an irradiated mucosal lining.

and the air in the mine ducts contains radioactive gases and dust strongly indicates that a prolonged exposure to these agents is causally related to the occurring pulmonary malignancies (Weber; Uhlig; Thiele, Rostoski, Saupe and Schmorl); Thiele; Stocklasa and Penkava; Stocklasa; Schmorl; Scheffler; Rostoski and Saupe; Rostoski, Saupe and Schmorl; Rajewski; Neitzel; Ludewig and Lorensen; Lorenz; Lindemann; Lange; Koelsch; Hueck; Hopmann; Beyreuther; Agricola; Aucke; Arnstein; Baader; Bauer; Epstein; Henckel; Härtung and Hesse; Fischer-Wasels; Teleky; Doubrow; Peller; Saupe; Behounek and Fort; Czechoslovakian Commission; Ziel; Woldrich; Tschelnitz; Sickl; Behounek; Pirchan and Sickl; Löwy; Humphries; Beutel and Woldrich) (Fig. 9).

Work in radium laboratories may represent an additional source of occupational cancer of the lung through inhalation of radioactive gases and dust. Three cases of this type have been observed in chemists (Neitzel; Löwy). Martland, moreover, reported the occurrence of a carcinoma in a nasal sinus in a luminous dial painter, who sustained a similar exposure. It is apparent from the discussion of Evans and Goodman that a similar respiratory hazard may exist for employees of mesothorium refineries and thorium mantle factories, who inhale thoron, since the degree of atmospheric radioactivity in such plants was found to be in quantitative agreement with the experiences in Schneeberg and Joachimsthal mines (40 to 600 x 10^{-11} curies of thoron per liter of air in thorium operations against 40 to 1800 x 10^{-11} curies in Schneeberg mines and 80 to 560 x 10^{-11} curies in Joachimsthal mines). Since Bryan and Silverman recently pointed out that electrostatic eliminators covered with a gold film containing either polonium or radium present an industrial inhalation hazard by contamination of the air with fine particles containing radioactive material, the possible development of pulmonary cancers in workers engaged in operations where

these devices are used (textile, paper) might ll be kept in mind. Most of the recent in- tigators of the Schneeberg and Joachimsthal ung cancers agree that their radioactive cau- sation can be considered as almost definitely established.

A critical evaluation of the evidence advanced in favor of other factors, such as silica, arsenic, bismuth, chromium, nickel and cobalt, shows that little or no factual and valid evidence supports such claims. Perhaps the most objectionable contention that has been put forward in this respect is the speculation that the lung cancers among the Schneeberg and Joachimsthal miners are the result of inbreeding and thus of hereditary predisposition (Macklin). The facts are quite different. The majority of the Schneeberg miners reside in Schneeberg, a community of some 10,000 inhabitants located at the end of a railroad branch line, and thus are living in a remote but not isolated mountain region of Saxony, which has been for many years the most densely populated state of Germany. Even a limited type of inbreeding that would be remotely comparable to the hereditary and abnormal conditions created in inbred strains of mice is scarcely conceivable under such circumstances. A study of the names of 53 miners listed by Härting and Hesse supports this conclusion, since there were 44 different names in this group. Duplications existed seven times, triplication and quadruplication once each. This degree of repetition of names is not unusually high and is plausibly explained by the fact that in some instances several members of the same family were probably employed in the mines. The occurrence of "familial" cancer under such conditions is not due to heredity but due to identity of exposure to an environmental cancerigen. Similar circumstances of exposure to soot have been in past decades the reason for the appearance of scrotal cancer among several members of the same family engaged as chimney sweeps in England. To introduce the concept of heredity into such a picture is totally unjustifiable and merely acts to obscure or confuse rather clearly established facts of environmental cancerigenesis.

There were approximately 400 cases of lung cancer among the Schneeberg miners between 1876 and 1939, while 42 cases of this disease came to observation among the Joachimsthal miners during 1929 to 1938 (Peller). It appears from the epidemiologic studies made that between 75 and 80% of the deaths among the Schneeberg miners and from 47 to 50% of the deaths of the Joachimsthal miners were caused by cancer of the lung.

The recorded age distribution clearly demonstrates a shift toward the younger age groups in individuals dying from lung cancer following exposure to radioactive dust and gases.

The period of exposure ranged for the majority of the Schneeberg miners from 20 to 50 years, but was occasionally as short as seven years. The exposure time of the Joachimsthal miners was from 13 to 23 years.

AGE DISTRIBUTION OF LUNG CANCERS IN RADIOACTIVE ORE MINERS

20-29	30-39	40-49	50-59	60-69	70 and over	Total	
6	28	21	30	8	0	0	83 Schneeberg
	3	17	9	2	0		31 Joachimsthal

No information is available on the occurrence of lung cancers among the miners employed in the Katanga mines in the Congo, which are open pit mines, in the Canadian mines at the Great Bear Lake region and in the vanadium-uranium mines in the Rocky Mountain area (Warschwaski; Mainsin).

It seems to be characteristic of the Schneeberg and Joachimsthal lung cancers that many of them are of the small cellular or highly anaplastic type, which accounts for the fact that they were first diagnosed as sarcomas. The topographical restriction of these cancers to the lung suggests that the cancerigenic agent mainly responsible for these tumors occurs either in the form of a dust or is adsorbed to the surface of dust particles, because cancerigenic vapors or gases in the absence of dust seem to cause cancers of the lungs as well as of the nares and nasal sinuses (nickel, carbonyl and isopropyl oil workers).

While the experiments of Schmidtmann and Löwy aimed at the production of pulmonary cancers in mice exposed to radioactive dust and gases were negative, subsequent ones conducted by Döhnert, Rajewski, Schraub and Kahlau; Lorenz, Heston, Eschenbrenner and Deringer gave suggestive results. Of definitely more conclusive character are the observations reported by Lisco and Finkel who obtained malignant pulmonary tumors in rats exposed to an aerosol of radioactive cerium.

The greatly and rapidly increasing production and uses of radioactive substances of natural and synthetic character for research, industrial and military purposes that has taken place during the last 25 years in this country have brought along exposures to radioactive material for an appreciable number of individuals. The conditions of such contacts are of a quality and order that the appearance of cancers of the respiratory organs in some members of this group must be anticipated.

Comments

THE data presented permit the conclusion that some of the cancers of the respiratory tract are attributable to the inhalation of a number of more or less well defined chemical or physical agents.

Although the total number of these respiratory cancers is relatively small when compared with the total number of cancers of this organ system, the proved environmental origin of these tumors lends strong support to the great amount

of merely circumstantial evidence indicating that environmental factors play a significant role in the production of pulmonary, nasal and laryngeal malignancies.

The available information on the recognized and suspected respiratory carcinogens, moreover, suggests that the known numbers of environmental respiratory cancer represent only a fraction of the actual ones, since existing epidemiologic studies on this point are highly defective.

Although all known environmental cancers have followed upon the inhalation of exogenous cancerigens present in the form of dust, fume, mist, fog, vapor or gas, serious consideration should be given to the possibility that some or many cancers of the respiratory tract may be due to agents entering the organism through the alimentary or cutaneous route and being either excreted through the respiratory organs or having special metabolic or chemical affinities to these tissues.

The past history of the discovery of environmental respiratory cancers has shown that the first indication of their existence is usually presented by the occurrence of a crowding of such tumors among members of restricted occupational groups. Industrial physicians and specialists in pulmonary diseases might, therefore, make valuable contributions to the etiology and epidemiology of respiratory cancers by investigating thoroughly the entire occupational history of their respiratory cancer patients for evidence of a previous exposure to an environmental cancerigen. Special attention should also be given to all those patients who enter medical care with the diagnosis of tuberculosis or silicosis or both and who have been employed in industries where they became exposed to various cancerigenic metals, such as arsenic, uranium ores, chromates, nickel, asbestos, and bituminous substances. The history of occupational respiratory cancers offers several vivid examples of occupational lung cancers mistaken for many years for tuberculosis or silicosis.

Future studies of environmental pulmonary cancerigenesis might well include proper consideration of local atmospheric conditions for air pollution with cancerigenic agents.

In view of the long latent period of environmental respiratory cancers which ranges from five to 40 years and because of the fact that these cancers may develop many years after cessation of exposure to the cancerigenic exogenous agent, it is essential that arrangements are made for the medical supervision and control of effectively exposed persons to extend beyond the period of employment. Likewise, it is pertinent that detailed employment and exposure data in addition to name, birth date and place, and social security number are recorded and kept for all persons who had effective exposure to environmental respiratory cancerigens, so as to ascertain in future investigations reliable and valid epidemiologic evidence on the existence and extent of cancers of the respiratory tract. While such procedures will prove to be tedious, and expensive, they will amply repay all efforts by improving the health of our people not only through prevention of environmental cancerigenesis, but through resultant fundamental contributions to the etiology of human cancer.

The experiences made in connection with environmental respiratory cancers suggest that the regional variations in lung cancer among the general population may be attributable to locally restricted quantitative and qualitative differences in the environmental cancerigenic spectrum.

Likewise, the evidence related to environmental lung cancers indicates that the increased frequency of these tumors observed during recent decades is apparently not caused by the appearance of one new environmental cancerigen related to occupation or habits, but rather reflects the action of several or many cancerigens.

He Says He Did It To Save Money

ILLINOIS' Governor Stevenson on December 28 ordered the liquidation of the Bureau of Industrial Hygiene in the State Department of Public Health, on recommendation of the Schaefer Commission to Study State Government. The commission pointed out that "one of the more obvious cases of overlapping and duplication of activities" between separate state agencies existed in the competing activities of the bureau and the Industrial Hygiene Unit of the Department of Labor's Division of Factory Inspection. The governor ordered the bureau liquidated by next June 30, the end of the present biennium. The Bureau of Industrial Hygiene currently employs 16 persons and has a biennial appropriation of $133,735. The commission's report recommended and the governor directed that the facilities of the health department's central laboratory be made available to the Department of Labor to review findings made in the course of its inspections.