Industry and Carcinogenesis of the Lung*

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A review of the subject of air pollution reveals two ways in which industry may contribute to carcinogenesis of the lungs: (1) exposure of industrial workers to certain organic or inorganic substances which, after prolonged inhalation, have the power to initiate a carcinomatous process; (2) contamination of the atmosphere around industrial plants by gases, aerosols including particulate matter, noxious fumes, mists and vapors which contain inorganic and organic chemicals which are of a carcinogenic character. This may occur many years after the last contact of the individual with the noxious agent. Occupational lung cancer pertains to inorganic chemicals of the following nature: radioactive ores, asbestos and chromates. In addition, iron derivatives, beryllium, nickel, coal gases and arsenic are probably also in this category.

At this juncture it is fitting to review the various carcinogenic agents known to industry and the evidence upon which this conclusion has been reached. (1) Radioactive ores: cancer of the lung accounts for 50 per cent of the causes of death of the miners of Schneeberg and Jachymov.1 In 1913, Arnstein2 showed that from 1875 to 1912, 276 miners (41.5 per cent) had died of carcinoma of the lung, 64 of tuberculosis, 119 of other lung diseases, and 206 from other causes. He felt other cases had carcinoma of the lung (not diagnosed) and was the first to diagnose squamous-cell carcinoma. In 1935, Lange3,4 found that 60 to 70 per cent of all deaths of miners or pensioners were caused by cancer of the lung and attributed the high incidence of carcinoma of the lung to radioactivity in the rock and air.

Kuschner et al.5 produced bronchogenic carcinoma in rats by implanting pellets plated with radioactive isotope, ruthenium 106, utilizing the pellet implantation technique involving implantation of a cylindrical wire mesh pellet with the above test material (1958).

Cember and Watson6 exposed 16 rats to intratracheal insufflations of radioactive barium sulfate. Two showed severe squamous metaplasia in the lungs; one animal had an area in the bronchus thought to be either premalignant dysplasia or carcinoma in situ; two rats had extensive bronchogenic squamous-cell carcinomas. Recently, bronchogenic carcinoma has been produced in rats breathing or insufflated with radioactive cerium or sulfur.7 It would seem likely therefore, that radioactivity per se is probably the etiologic factor.

(2) Asbestos: the report of the chief inspector7 of factories of Great Britain in 1947 stated that of 235 cases of asbestosis necropsied between 1924 and 1946, 31 (13.2 per cent) were complicated by carcinoma of the lungs or pleura. The figure for silicosis revealed that of 6884 necropsies, 91 cases (1.32 per cent) showed cancer of the lung. In Great Britain necropsies are performed on all industrially exposed individuals. Animal experiments have been negative.8,9

(3) Chromates: Machle and Gregoriou* observed that in 193 deaths of chromate workers representing 11,000 man years of work, 22 per cent died of respiratory tract cancer. It was noted that monovalent ores caused this condition and that neoplastic changes were found in areas close to crystals of chromium. In Germany up until 1939 the total of 39 cases of pulmonary carcinoma were reported to have occurred among 1000 chromate workers in various plants.9 Hueper10 produced carcinoma of the lung in guinea pigs by injecting chromate ore roast subcutaneously into the lung.
These implants gave rise to squamous-cell, round-cell, anaplastic and adenocarcinomatous varieties of lung cancer.

(4) Nickel: the refining of nickel is reported to be associated with a high incidence of carcinoma. However, the clinical evidence is meager and hardly substantiates such a conclusion on the basis of clinical grounds alone. Nonetheless, Hueper has produced lung carcinoma in guinea pigs by exposing them to nickel dust. These animals showed extensive multi-focal adenomatosis, adenocarcinoma and precancerous and cancerous lesions resembling small cellular round-cell carcinoma of man, as well as lesions resembling alveolar carcinoma.

(5) Coal gases: Doll (1952) studied the causes of death among 2,071 male pensioners of a London gas company and found that the number of deaths was approximately double that expected in inhabitants of London of the same age distribution, a rate of 25 cancer of the lung deaths against 13.8 (approximately the same as shown by Kennaway and Kennaway in 1947).

(6) Iron: McLaughlin and Harding found an incidence of 10.8 per cent bronchogenic carcinoma among 149 iron and steel foundry workers. Recently, Faulds has reported an incidence of 8.85 per cent bronchogenic carcinoma in 192 necropsies in Cumberland hematite miners, as compared with an incidence of 1.85 per cent in 2578 necropsies on men over 20 years of age. Soot and pyrolyzing factors could not be excluded as possible causes. Three hundred welders reviewed by McLaughlin and Doig revealed no carcinoma of the bronchus. Experimental studies have not been generally accepted because of discrepancies. The part which iron and iron oxide plays in the high incidence of bronchogenic carcinoma in foundry workers and miners in the iron industry has not been demonstrated conclusively.

(7) Arsenic: Lull and Wallach and Osburn of Gwanda showed that mining populations who inhaled arsenic dusts and smelter fumes have a high incidence of lung cancer. Roth of Germany found lung cancer in 12 of 27 or 44 per cent of necropsies performed on vineyard workers who had been exposed to arsenic insecticides and who had urine with high arsenic content.

Vallee and his co-workers in 1960 found no basis for assuming that arsenic caused visceral carcinoma and stated that attempts to induce cancer by painting the skin of experimental animals have been largely negative and the production of arsenical carcinoma in animals has never been demonstrated satisfactorily. However, the clinical and statistical evidence are suggestive of a possible relationship between arsenic and carcinoma of the lung.

(8) Beryllium: Schepers et al. produced neoplasia in rats exposed to aerosols of beryllium sulfate for periods up to six months.

Air Pollution: Hueper lists tar fumes, mineral oil mists, chromium dusts, nickel-carbonyl vapors, arsenic dusts and fumes, asbestos dust, isopropyl-oil vapors and radioactive gases and dust as potential lung carcinogens. He stated that three occupations stand out as having a higher carcinoma rate: those exposed to: (1) hot metal fumes and metal dust, (2) paint, (3) lubricating oils and gasoline fumes.

In addition to acting as occupational carcinogens, inorganic chemicals may play a part in air pollution which is thought by some to be significant. The chief sources of contamination of the atmosphere are industries such as power plants, metallurgical plants, oil refineries, storage tanks for oil, gases and solvents, and the transportation industry including diesel engines, trucks, buses and passenger automobiles. The combustion of coal eliminates small amounts of radioactive materials into the general atmosphere. The amount eliminated by this means, as well as the general increase of radiation on a local and world-wide basis from the fall-out of radioactive atomic debris and from activities of the radiochemical processing industry which have
occurred during recent years apparently do not usually play a part in the process of carcinogenesis of the lung. However, under certain circumstances these factors may contribute to carcinogenesis of the lung, particularly when there is excessive pollution of a small geographic area over prolonged periods of time. Moreover, in the future these factors may be of a great deal more importance if fall-out of radioactive atomic debris and the activities of the radiochemical processing industry are not properly controlled.

Experimental evidence: since 1922 experiments by such investigators as Passey,7 Campbell,7 Leiter, Shimkin and Shear,7 Clemo,7 Kotin and co-workers,8,8 have produced carcinomas in mice painted or injected subcutaneously with ether extracts of household chimney soot; with tars extracted from atmospheric dusts of several large American cities; with tars extracted from industrial smoke; with extracts of exhausts of gasoline and diesel motors; and with oxidation reaction products of aliphatic hydrocarbon atmospheric extracts. Ozonized gasoline in inhalation chambers was utilized by Kotin8 in the induction of alveolar lung tumors in strain A and C57 black mice. On the other hand, according to Hueper,5 compared to the carcinogenic potency of coal tar and aromatic and aliphatic air pollutants, tobacco tars are at most only mildly carcinogenic to the skin of mice. Moreover, inhalation experiments demonstrate the superiority of air pollutants and coal tar dust to cigarette smoke in carcinogenesis.

Epidemiologic Evidence

(1) Urban versus rural factors: a review of the statistics of carcinoma of the lung reveals a preponderant incidence of cases of lung carcinoma in urban areas as contrasted with rural areas. Stocks and Campbell18 estimated that 50 per cent of the cases of lung carcinoma in Liverpool resulted from smoking of cigarettes and 35 per cent resulted from air pollution.

(2) Geography: there are marked variations in the geographic incidence of carcinoma of the lung. In 1955 the lung cancer death rate8 for England was 69.3 per 100,000 for males and 10.6 for females in contrast with a figure of 33.0 and 6.7 respectively for the United States. Yet the cigarette consumption in the United States is far greater, having been estimated as much greater as 2:1.5,25 Immigrants from the United Kingdom to New Zealand29 who are over the age of 30 have a higher incidence of lung carcinoma than the natives. The best explanation of geographic variations is on the basis of an urban factor in carcinogenesis.

(3) Sex: there is a marked preponderance of lung carcinoma among men as pointed out in the figures given above. Smoking habits do not adequately account for this difference, particularly in view of the greatly increased incidence of smokers among women at this time. Advocates of the smoking theory explain this by postulating that the present female population has not had adequate exposure to cigarette tars over a long enough time to reflect on the figures and by predicting that in the future this incidence will increase greatly. However, men work in environments in which they are exposed much more frequently to suspected cancer hazards, whereas women live in cleaner and more protected areas. Ian MacDonald30 pointed out that while the proportion of women smokers has increased from less than 5 per cent to 40 per cent, lung cancer has emerged as a disease of males, from an earlier ratio of 2:1 to about 6:1 at present.

(4) Correlation with exposure to 3,4 benzopyrene: Stocks and Campbell18 showed that the 3,4 benzopyrene content of air filtrates gave a 1:10 ratio of rural to urban area. The actual amount of 3,4 benzopyrene in cigarette smoke is very minute and probably plays little part unless one invokes the theory of co-carcinogens, and synergism. The correlation here is far better for air pollution than for cigarette smoking.

(5) Tobacco: as previously noted, the correlation between tobacco consumption
and the incidence of carcinoma of the lung in various countries is not good. Moreover, among non-smokers in England it has been demonstrated that the incidence of carcinoma of the lung is higher in the urban than in the rural areas.

(6) Social status: Cohart of New Haven found lung carcinoma 40 per cent greater among the poor than among other socio-economic groups. This suggests environmental pollution as playing a part in the high incidence among lower socio-economic status individuals.

**Conclusions**

1. There is excellent evidence, both clinical and experimental, that bronchogenic carcinoma may be induced by the inhalation of certain mineral dusts.
2. The number of cases of bronchogenic carcinoma induced by the inhalation of inorganic metals in certain hazardous occupations is relatively small and in no way accounts for the recent rapid rise in the incidence of this type of neoplasia.
3. Experimental evidence reveals the ability of certain organic substances such as coal tar, aromatic and aliphatic hydrocarbons and ozonized gasoline to induce carcinogenesis in experimental animals.
4. The greater incidence of bronchogenic carcinoma in urban than in rural communities suggests the possibility that industrial atmospheric pollution by organic and inorganic chemical substances may play an important part in the increasing incidence of bronchogenic carcinoma throughout the world.

**Conclusiones**

1. Hay una evidencia excelente tanto clínica como experimental de que el carcinoma bronquigénico puede provocarse por la inhalación de ciertos polvos minerales.
2. El número de casos de carcinoma bronquigénico que puede provocarse por la inhalación de ciertos metales inorgánicos en ciertas ocupaciones peligrosas es relativamente pequeño y de ninguna manera tiene importancia para explicar el reciente aumento en la incidencia de este tipo de neoplasma.
3. La evidencia experimental revela que ciertas substancias orgánicas son capaces de provocar carcinogénésis en los animales de experiencia y tales substancias son el alquitrán del carbón, los hidrocarburos aliílicos y aromáticos y la gasolina ozonizada.
4. La mayor incidencia del carcinoma bronquigénico en el medio urbano en comparación con el rural sugiere la posibilidad de que estas substancias que polucionan la atmósfera sean orgánicas o inorgánicas pueden desempeñar un papel creciente en la incidencia del carcinoma bronquigénico en todo el mundo.

**Resume**

1. Il semble évident tant au point de vue clinique qu’expérimental que le cancer bronchique peut être provoqué par l’inhalation de certaines poussières minérales.
2. Le nombre de cas de carcinomes des bronches provoqués par l’inhalation de métaux inorganiques dans certains métiers est relativement petit, et ne peut pas être cause de l’accroissement récent et rapide de ce type de néoplasie.
3. L’expérimentation révèle la possibilité de provoquer le cancer chez les animaux de laboratoire à l’aide de certaines substances organiques comme le goudron, les hydrocarbures aromatiques et aliphatiques et l’essence ozonisée.
4. La plus grande fréquence des cancers chez les habitants des villes que chez de la campagne fait penser qu’il est possible que la pollution atmosphérique par des substances chimiques, organiques et inorganiques, joue une part importante dans l’accroissement de la fréquence du cancer des bronches à travers le monde.

**Zusammenfassung**

1. Es gibt ausgezeichnete Anhaltspunkte sowohl in klinischer als auch in experimenteller Hinsicht dafür, daß ein Bronchialcarzinom durch die Inhalation bestimmter Mineralstaubarten verursacht werden kann.
3. Experimentelles Beweismaterial zeigt das Vermögen bestimmter organischer Substanzen wie Kohlenteer, aromatischer und aliphatischer Kohlenwasserstoffe und ozonisierten Benzin, bei Versuchstieren eine Krebsentstehung zu bewirken.

**Complete reference list will appear in the reprints.**