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after injection of Pb^{210} with carrier Pb, only 6% of injected Pb^{210} was in the blood cells and approximately 22% in the plasma. The Pb in the plasma fraction left rapidly, less than 2% of the dose remaining after three hours.

Sodium or zirconium citrate injected after carrier-free Pb^{210} did not affect the rate of disappearance of Pb^{210} from the blood, the tissue distribution, or the fraction excreted. In rats receiving 1.03 mg. of Pb as lead acetate labeled with Pb^{210}, zirconium citrate did not affect the immediate rate of disappearance of Pb^{210} from the blood, but it caused more than a threefold increase in the Pb^{210} excreted during the first 24 hours and a decrease in the kidney excretion. The sodium citrate was without effect on blood disappearance rate, tissue distribution, or excretion of the Pb^{210}.

LEAD POISONING IN YOUNG CHILDREN. HUNTINGTON WILLIAMS, EMANUEL KAPLAN, CHARLES E. COUCHMAN, and R. R. SAYERS, Pub. Health Rep. **67**:230 (March) 1952.

Lead poisoning of children caused by ingesting lead from surfaces coated with lead-containing paint is apparently widespread throughout many parts of the nation.

The incidence is high in the city of Baltimore, where it occurs in children of teething age living in old, run-down, rented properties in which lead paint had been used indoors for many years.

Public health education, coupled with a "lead consciousness" on the part of physicians and pediatric clinics of local hospitals, and with a blood-lead laboratory service offered by the city health department, has resulted in a marked increase in case recognition.

It is hoped that the application of principles involving education and the enforcement of measures regulating the use of lead-containing paints will result in material reduction and eventual eradication of child lead poisoning in Baltimore.

SOME OBSERVATIONS ON THE TOXIC PROPERTIES OF 3:5 DINITRO-ORTHO-CRESOL. V. H. PARKER, J. M. BARNES, and F. A. DENZ, Brit. J. Indust. Med. **8**:226-235 (Oct.) 1951.

Dinitro-*o*-cresol is used in agriculture as an insecticide, and the occurrence of deaths among workers has indicated the need for investigation of its toxicity. The possibility of cumulative action, the level of dinitro-*o*-cresol in the blood, and the effects of external temperature, alcohol, and nutritional state were studied on laboratory animals. Near-lethal doses of the compound injected into animals caused prostration and marked increase of respiratory rate. Within four hours the animals either died or recovered. Daily injections of 20 mg./kg. produced no cumulative effect; on the other hand, no tolerance was developed. A single dose of 5 mg./kg. caused no visible signs of poisoning, but hourly injections caused the appearance of characteristic symptoms after the fourth or fifth injection. Death took place in both rats and rabbits after the total dose amounted to 25-35 mg./kg. The number of deaths from injections of 20 mg./kg. was reduced when the animals were kept in a cool (5-10 F.) place. Over 90% of the dinitro-*o*-cresol in the blood was found in the plasma. The time required for the dinitro-*o*-cresol level in the blood to fall to half its initial value after a single injection of 10 mg./kg. was 3 hours in the rabbit, 15 hours in the rat, 20 hours in the cat, and 36 hours in the dog. Between 4 and 10% of injected compound could be recovered in the urine. Alcohol did not affect the severity of the poisoning.

B. H. AMDUR, Cambridge, Mass.

EXPERIMENTAL ASBESTOSIS. W. VON BEHRENS, Schweiz. Ztschr. Path. u. Bakt. (Rev. suisse path. gén. bact.) **14**:275-299, 1951.

Focal fibrosis produced by chrysotile asbestos (fiber length, 5-180 μ) in the peritoneal cavities of mice and in the lungs of rats is the result of a nonspecific foreign-body reaction. The asbestos was not dissolved, nor did it exert any toxic action, and the formation of asbestosis bodies was not observed. The latter could not be induced in vitro. Asbestosis bodies are considered as the product of a nonspecific reaction of certain tissues to filamentous foreign bodies. They do not seem to have any bearing on the pathogenesis of asbestos fibrosis.

...re of 2,000 C. reached in the furnaces, gaseous silica is given off and, in this state, would have a ...ore rapid action on the lung tissue than crystalline quartz. In the case of these smelters ...ere is possibly a complex action by aluminum and amorphous silica. Compensation is not ...t provided for occupational disease of the lungs due to compounds of aluminum, as is done for ...ease due to metallic aluminum, but statutory provision for notification and compensation is in ...paration.

INDUST. HYG. DIGEST [CONDENSED FROM BULL. HYG.].

NEW MANIFESTATION OF ALUMINOSIS. H. MODDER and T. SCHMITT, Deutsche med. Wchnschr. **76**:85-87, 1951.

A clinical investigation of 97 workers in an aluminum-smelting plant disclosed heavy damage ...he lungs of 18 operators of the smelting and alloying department. They had been employed ...average of six years. (Some of the healthy ones had worked 15 and more years.) Clinical ...spiro-ergometric examination showed: aluminosis (8 workers), one with fibrosis; other ...nges caused by aluminum compounds (4); tuberculosis (5). Examination with x-rays ...ealed few characteristic peculiarities in contrast to those found in other types of pneumo...osis of a comparable severity.

CHEM. ABST.

...EUMOCONIOSIS AND SILICOSIS. N. A. VIGDORCHIK, Gigiena i sanit. 1951, No. 1, pp. 20-25.

Review of the available data shows that pneumoconiosis cannot arise from quartz-free dust ...d that there is no mechanism whereby fibrotic changes may take place under the influence of ...artz-free particles. However, some silicate dusts (asbestos, etc.) do cause pneumoconiosis, ...ce they decompose in the body to liberate silica. Toxic dusts, such as fluorides, Be salts, ...silioactive dusts, and Cr salts lead to local toxic effects.

G. M. KOSOLAPOFF [CHEM. ABST.].

Industrial Toxicology

HAZARDS INVOLVED IN PESTICIDE APPLICATION. JULIUS M. COON, Agr. Chemicals **6**:53-55, 1951.

The relative hazards are presented in tabular form. P. CHICHILO [CHEM. ABST.].

NORISODRINE SULFATE: TOXICITY IN INDUSTRIAL USE. R. M. WATROUS and H. N. SCHULZ, Indust. Med. **20**:305-307 (July) 1951.

"Norisodrine" is a trade mark (Abbott) for N-isopropylarterenol, which has also been called "aleudrin," isuprel,® "isorenin," and isonorin,® and is used principally in the treatment of asthma. In the Abbott Laboratories several cases of toxicity manifested by tremor, apprehension, feeling of tightness in the chest, and nausea were noted. These symptoms were transient and not disabling.

A method for determining "norisodrine" in air is described.

ARNOLD A. LEAR, Boston.

IMPROVEMENT OF PULMONARY FUNCTION FOLLOWING ADMINISTRATION OF ACTH IN CHRONIC BERYLLIUM POISONING. S. R. INKLEY, E. M. KLINE, and W. H. PRITCHARD, J. Lab. & Clin. Med. **36**:840-841 1950.

Three persons had been exposed to beryllium-containing phosphor over periods varying from 32 days to 9 years and had suffered from pulmonary disease of two to five years' duration. Treatment with corticotropin (ACTH) (100 mg. daily) resulted in prompt decrease in cough, dyspnea, and fatigue; smaller doses gave a less striking response. Increases in maximum breathing capacity ranged from 16 to 74%. There was only slight improvement in the chest roentgenograms. It is suggested that the prompt improvement of pulmonary symptoms and function may be due to reduction of both edema and cellular infiltration of the lungs.

ADAPTED FROM BIOL. ABST.

OCCUPATIONAL CANCER HAZARDS IN AMERICAN INDUSTRIES

W. C. HUEPER, M.D.
BETHESDA, MD.

MODERN industry has brought along a considerable number and variety of carcinogenic agents and, no doubt, will bring ever new ones as it develops new methods of production and new products and applies established methods and agents to new purposes. If we look at the long and ever-growing list of known and suspected occupational carcinogenic agents, if we contemplate their widespread existence as industrial wastes contaminating air,[1] water, and soil of the waste-disposal areas of industries, if we consider their presence in many products of daily consumption, we have the general spectrum of the cancer hazards which originate from our modern industrial development. Control measures must be based on the realization of this wide potential scope of carcinogenic contacts. They must concern not only workers engaged in the production or the use of carcinogenic agents but also the population living in the environment of plants with carcinogenic hazards, as well as the general public.[2] It is well to remember that experience with occupational cancer has demonstrated that, given a carcinogenic agent and proper conditions of exposure, the occurrence of cancer among the exposed individuals is merely a question of time. The incidence rate and the length of the latent period depend mainly on the relative potency of the carcinogenic agent present and the intensity of the exposure. The lack of adequate epidemiologic studies and the usually long latent period of exogenous cancer often obscure the appreciation of causal relations between occupational factors and cancer.

A few illustrations as to the distribution of exogenous carcinogenic hazards of industrial origin may be appropriate. For instance, men engaged in the mining and smelting of copper, zinc, and silver ores are exposed to arsenicals. The makers and users of arsenical pesticides that are employed in the form of sprays or dusts suffer a similar exposure, as do patients who receive arsenical medication. Beyond these rather narrow circles of producers and consumers of arsenicals stands that appreciable part of the general population that comes in direct or indirect contact with arsenicals released into the atmosphere with smelter flue dusts or as a result of

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From the National Cancer Institute.

Address presented at a meeting of the Cancer Prevention Committee in New York on June 15, 1949.

Dr. Hueper is Chief, Cancerigenic Studies Section, Cancer Control Branch, National Institutes of Health, Public Health Service, Federal Security Agency.

1. Hartwell, J. L.: Survey of Compounds Which Have Been Tested for Carcinogenic Activity, U. S. Public Health Service, 1941. (371 pp.)

2. Hueper, W. C.: Environmental and Occupational Cancer, U. S. Public Health Reports 1948, Supplement 209. (68 pp.).

large-scale dusting of orchards and cotton fields or from the use of sprays in truck gardens. Arsenicals may enter the human body in drinking water that passed as rain water through arsenic-containing slag heaps of smelters. The consumption of fruits, fruit juices, and wines contaminated with arsenical insecticides affords another source.

In the field of organic chemistry we meet with bladder cancers among producers and handlers of certain aromatic amines, and find that some of these amines are used in the manufacture of pharmaceuticals and that their derivatives are employed as flotation agents in the mining industry and as antioxidants in the manufacture of rubber. Finally, dust and fumes from aromatic-amine operations that have been improperly conducted as to exhaust ventilation may endanger not only workers in adjacent operations but also the population living in the fume zone of the plant. A similar environmental contact with vaporized aromatic amines may result from the burning of emptied containers on open lots within populated areas.

Carcinogenic soot or tar fumes cause cancer of the lungs and skin not only in stokers of coke ovens but also in makers of products for which heated tar and asphalt are used, for example tar paper and asphalt shingles. The possibility must be considered that carcinogenic hydrocarbons of industrial origin may cover as a film the extremely small particles of flue dust and exhausts of petroleum-cracking units. The question has been raised whether a similar hazard exists in concrete factories in which soot-producing diesel engines are used. Carcinogenic soot may also be released into the atmosphere during the manufacture and industrial use of carbon black obtained from oil residues or natural gas or from the burning of waste oils near refineries, causing an occupational and environmental hazard. Carcinogenic oil and tar dusts from oiled or tarred roads present a potential hazard, involving the general population. Similar considerations apply to other carcinogens, such as metallic and radioactive ores.

The recognition of carcinogenic agents and exposures is a prerequisite to a rational and intelligent occupational cancer control. Epidemiologic surveys of plant populations are very important in this respect. Exogenous occupational carcinogens not only excessively increase the cancer incidence rate of one particular organ but may elevate the total cancer incidence rate and primary cancer multiplicity. Likewise, not only workers exposed to aromatic amines show a high liability to bladder cancer, but also workers in gas plants. Thus, specific cancer sites are not necessarily indicative of any particular type of carcinogenic agent. Several agents may exert synergistic action when acting simultaneously or successively, or may independently produce cancer at a certain site.

It may be worth while mentioning here that leukemia may result from low-level, prolonged, and diffuse exposure to x-rays, radioactive agents, or benzol. Nasal sinus cancers have been observed in men exposed to a volatile nickel compound (nickel carbonyl) in the course of nickel refining. Lung cancers have been observed in chromate workers. The use of metals in abrasives and as catalysts in the organic chemical and the petroleum industries as well as the production of metal dusts and mists or vapors in welding, spraying, and polishing operations and in the production of alloys from metal powders may greatly extend the potential scope of occupational metal cancers and may introduce occupational cancer hazards where these are not readily suspected.

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While it is not possible to discuss here the full scale of control measures that might or should be applied in the numerous and different carcinogenic operations, it may be advantageous to present general directives and a few specially important considerations.

Since we do not know the minimal effective dose of any of the many occupational carcinogens, it seems obvious that they should be completely eliminated wherever that is practical. This can be done by using or producing suitable noncarcinogenic substitutes. It is usually feasible without creating serious production difficulties to replace benzol by other organic solvents having similar effectiveness. In the case of the highly hazardous beta-naphthylamine it is possible to eliminate the hazard by starting with a sulfonated beta-naphthol which is later aminated and which in a sulfonated form is not carcinogenic. A closed system of production in which all hazardous phases are carried out is another effective method of eliminating cancer hazards in industry. Wherever bulky material is handled, the adoption of a closed system of production may be difficult. Then other means must be found to eliminate or considerably reduce the carcinogenic hazard. The goal may sometimes be obtained by changing from a dry method having a dust hazard to a wet method. Good housekeeping in plants and personal hygiene of the workers are other ways to reduce hazards. Good exhaust ventilation is essential wherever dust, fume, vapor, mist, or gas hazards exist. However, care should be taken that the carcinogenic material is removed from the exhaust air before the wastes are released into the atmosphere and that none of such wastes are blown into adjacent working places and living quarters. Many of the more recently constructed industrial plants are built in such a way that the machinery stands either free or in an open-air shelter, so that any injurious gases, fumes, or vapors may be readily dispersed into the surrounding atmosphere and thereby become harmless through dilution.

While such a system may be suitable for some carcinogenic hazards, it seems to be unsuitable for others, especially for those which are due to agents that are not readily decomposed but accumulate on the ground and in the water and thus may gradually reach dangerous concentrations.

In instances in which the carcinogenic factor represents only a very small portion of the entire product, as in tar, pitch, petroleum derivatives, and similar products, an attempt should be made to develop either production methods through which the production of carcinogenic contaminants is avoided, or, when this is not possible, to remove or destroy the carcinogenic portion in the hazardous product. Until such measures have been developed other procedures are being utilized. In the case of carcinogenic oils or tars, these procedures consist in diluting the oil or tar with noncarcinogenic material so that the carcinogenic potency is lost or reduced to such a low degree that any potential cancer resulting from prolonged and repeated contact with such products has a latent period surpassing the average life span of man.

While such engineering and technical measures are of utmost importance in the control of occupational cancer, the intelligent and ready cooperation of the workers in observing additional precautionary measures when handling carcinogenic material should be obtained. Unless the handlers are informed of the hazards connected with their work, they cannot be expected to follow rules and regulations issued by management. Only when they know and realize the potential risks which

One of the most important attributes of many exogenous carcinogens is their ambivalent properties; i.e., depending on the intensity of action or the dose, they may produce manifestations either in the degenerative, necrotizing, aplasiogenic range or in the hyperplastic, canceroid, leukemoid, cancerous range. In studying a worker population for the presence of a carcinogenic agent, a wide range of abnormal symptoms may be noted representing a diagnostically significant syndrome which I have termed the environmental-carcinogen pattern. Thus, an individual who develops an occupational carcinoma may exhibit not only various types of proliferative, precancerous reactions but, preceding or accompanying these hyperplastic reactions, manifestations which are of the degenerative, atrophic, necrotizing type. Likewise, various members of a worker population exposed to the same carcinogenic agent at different dose levels may display abnormal reactions representing the entire scale of the environmental-carcinogen pattern. Thus, in a benzol operation some workers may suffer from aplastic anemia, others from moderate anemia and leucopenia, a third group may display hyperleucocytosis and polycythemia, while still others may have leukemoid and leukemic reactions. A similar hematic syndrome may be seen in persons exposed to x-rays. Whenever a plant physician observes even parts of such environmental-cancer patterns, he should become alerted to the possibility of a carcinogenic hazard in the operation in which the affected workers are employed.

Other important clues in this respect may be obtained from the demonstration of excessive incidence of cancer in special groups of workers and also from shifts of the sex ratio of cancer incidence. For instance, the male-female ratio of lung cancer incidence is approximately 5:1. Merewether recently reported 31 cancers of the lung associated with asbestosis in a series of 235 cases of asbestosis. There was not only an excessive lung cancer incidence in this group (13.2%), but the male-to-female sex ratio of the cancer cases stood at 2:1.

The histologic type of cancer is as a rule of no significance as a clue concerning an occupational or a nonoccupational origin. However, in the case of lung cancers it appears as if an increasing preponderance of squamous cell and anaplastic cancers over adenocarcinomas favors an occupational or exogenous origin or perhaps more exactly reflects the action of a respiratory carcinogen. Thus, shifts in the ratio of squamous cell cancers to adenocarcinomas of the lung may have an etiologic significance and may indicate not only that an occupational carcinogen is present in a particular operation but that the injurious agent occurs in the form of a gas, vapor, mist, dust, or fume. It is not likely, on the other hand, that the inhalation of dust or mists might elicit cancers in the nasal sinuses, because the narrow passages leading to these cavities would prevent matter of relatively large particle size penetrating into these cavities. However, gases, vapors, fumes, and colloidal dust of carcinogenic property might enter the nasal sinuses.

It is obvious not only that the various types of information mentioned are essential for the discovery of an occupational cancer hazard and for the identification of the causative agent but that they are of utmost importance for the subsequent development of effective preventive and precautionary measures. The acquisition of these data thus forms a part of any sound control program and in fact represents the foundation of it.

carelessness may entail, can they be expected to cooperate intelligently. It seems only fair to industrial users and the general public that a reasonable amount of information about the existence and types of occupational carcinogens is made available to them, so that such hazards cannot be spread or sustained any longer by sheer ignorance of such matters. This does not imply that such information has to make headlines in newspapers, but in a quiet way, preferably through trade circles, pertinent data on recognized, suspected, and potential carcinogenic agents should be distributed, so that the necessary technical and commercial adjustment processes can be initiated and carried out in an orderly fashion without causing any serious disruptions in the industrial, economic, and social pattern.

Without any doubt, a great deal of educational work has to be done in medical circles so that the members of the medical profession become aware of the existence of occupational cancer hazards and learn to discover and evaluate properly precancerous conditions and thereby aid industrial management in controlling occupational canceration effectively from a medical standpoint. While medical efforts are not likely to reduce in any fundamental fashion existing cancerigenic conditions in industrial plants, they can contribute definitely in alleviating the prognosis of the unfortunate victims.

While much evidently remains to be done in controlling occupational cancer hazards, I do not believe that mankind will succeed in eliminating them completely. As little as this result was obtained in connection with contagious diseases, all of which to some degree are still with us, so will our best efforts fail of entirely eradicating occupational cancers. These will remain with us as manifestations of our self-created modern industrial environment from which we are unable to escape and which we can modify only within certain limits. Though cancer is one of the risks of living, we doubtless shall succeed in reducing these risks to a considerable degree, particularly where they are excessive, for occupational-industrial reasons.

(The two works referred to in Footnotes 1 and 2 are available at a cost of $1 and of 20 cents, respectively, from the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C.)

ABSTRACT OF DISCUSSION

The question was raised as to the feasibility of avoiding the betanaphthylamine hazard by sulfonation. Dr. Hueper stated that the use of sulfonated beta-naphthol as a starting material is a process developed in Switzerland.[3] It has not as yet been employed in the United States. Dr. Hueper also stated that he had noted the use of alpha-naphthylamine in the preparation of pharmaceuticals. He pointed out that commercial alpha-naphthylamine always contains some beta-naphthylamine, which apparently has been responsible for the occurrence of bladder cancer among alpha-naphthylamine producers.

Radioactive materials were considered with reference to the need of long-range planning for disposal of radioactive wastes.

The problem of latency was discussed. Dr. Hueper stated that the latent period of tumors induced by the following materials increases in the order shown: tar, pitch, shale oil, petroleum. It was the consensus that the employment of elderly rather than young persons should be recommended for tasks involving uncontrolled carcinogenic hazards. The view was that the life span of elderly workers would run out before cancer could be induced by the materials to which they were exposed.

3. Müller, A.: Ueber Blasen- und Nierenschädigungen in der Farbstoffindustrie, Helvet. chir. acta 18:1-41, 1951.

LUNG CANCER WITH SPECIAL REFERENCE TO EXPERIMENTAL ASPECTS

WILLIAM E. SMITH, M.D.
NEW YORK

IN A RECENT lecture before this committee, Dr. Hammond [1] presented data to show that the annual death rates for most types of cancer in the United States are stabilized or declining when calculated with allowance for increasing age of the population. He called attention to the fact that the outstanding exception is mortality from lung cancer, which has shown an increase over and above what could be expected as a result of increases in the numbers of elderly persons in our population. Indeed, during the past 30 years, cancer of the lungs has risen from a relatively uncommon tumor to become a major cause of death from cancer in males.

Dr. Gregorius has given us an account of studies conducted by himself and Dr. Machle [2] demonstrating an abnormally high mortality from lung cancer in men engaged in processing chromate ores. Unusually high lung-cancer mortality has also been recorded for miners exposed to radioactive ores in Germany, for nickel-refinery workers exposed to nickel carbonyl, and for both men and women patients with asbestosis in England. These and other suspected sources of occupational lung-tumor hazards have been discussed by Dr. Hueper.[3]

Lung cancers of occupational origin could hardly account, however, for the great number of deaths from this disease. Some leading chest surgeons have felt that their lung-cancer patients were, as a group, unusually heavy smokers, and have directed attention toward the increasing use of cigarettes as a causative factor. Statistical studies of this question will be presented in a following lecture by Dr. Wynder.[4a] Two types of carcinogens have been demonstrated in tobacco smoke: first, tars capable of provoking tumors when painted on the skins of mice [5]; second, arsenic, which is known to elicit cancer of the human skin.[6] The tars are formed

Address presented at a meeting of the Cancer Prevention Committee in New York on Nov. 16, 1949.

Dr. Smith is Assistant Professor, Department of Industrial Medicine, New York University Post-Graduate Medical School.

1. Hammond, E. C.: Trends in Cancer Mortality, A. M. A. Arch. Indust. Hyg., this issue, p. 190.

2. Gregorius, F.: Lung Cancer in the Chromate Industry, A. M. A. Arch. Indust. Hyg., this issue, p. 196.

3. Hueper, W. C.: Environmental Lung Cancer, Indust. Med. **20**:50-62, 1951.

4. (*a*) Wynder, E.: Studies of Lung Cancer in Relation to Smoking, A. M. A. Arch. Indust. Hyg., this issue, p. 218. (b) Sugiura, K., in discussion on Wynder.[4a]

5. Flory, C. M.: The Production of Tumors by Tobacco Tars, Cancer Res. **1**:262-276, 1941.

6. Neubauer, O.: Arsenical Cancer: A Review, Brit. J. Cancer **1**:192-251, 1947.

when the tobacco burns. The arsenic presumably derives from the arsenical insecticides sprayed on tobacco crops.[4b] However, in mice exposed for long periods to tobacco smoke lung cancer has failed to develop.[7]

The air pollution in urban or industrial areas affords another source of widespread exposure to carcinogenic material, but epidemiological studies have failed to establish whether the exposure is significant. Coal tar, known to cause cancer of the human skin, may be responsible for the high incidence of lung cancer reported in stokers of certain types of gas-oven retorts.[8] Studies conducted by the New York City Department of Health showed that up to 176 tons (159.5 metric tons) of solid matter, of which 1520 lb. (690 kg.) were "tar," settled out of the air onto every square mile of Manhattan each month.[9] Extracts of soot collected from the air in Pittsburgh, Chicago, Cincinnati, Youngstown (Ohio), East St. Louis, Chelsea (Mass.), Cambridge (Mass.), and South Charleston (W. Va.) have produced cancer at sites of injection in mice.[10] An increase of the incidence of pulmonary adenomas occurred in the lungs of mice exposed repeatedly to clouds of soot collected from the air of an English city[11] or swept from tarred English roads.[12] On the epidemiological side, the number of lung cancers in the metropolitan area of London was reported to be greater, in every age group, than in rural areas.[13] A similar study conducted in Denmark showed that the number of lung cancers reported in the city of Copenhagen was greater than the number in rural areas.[14a] The Danish authors felt this difference merely reflected better diagnostic facilities in the city, but they subsequently found the incidence of another type of internal cancer (stomach) to be as great in rural areas as in the city.[14b] Aside from the problem of diagnostic facilities, such comparisons of urban and rural populations do not measure only the single factor of air pollution but doubtless reflect other factors, such as differences in occupational exposures or smoking habits. In the United States, information on this

7. Campbell, J. A.: Effects of Exhaust Gases from Internal Combustion Engines and of Tobacco Smoke upon Mice, with Special Reference to Incidence of Tumours of the Lung, Brit. J. Exper. Path. **17**:146-158, 1936. Lorenz, E.: Experimental Studies on Tobacco Smoke, Proceedings National Cancer Conference, Memphis, 1949, p. 203.

8. Hueper, W. C.: Occupational Tumors and Allied Diseases, Charles C Thomas, Springfield, Ill., 1942, p. 425.

9. Stern, A. C., and others: Report of New York City Air Pollution Survey: III. Sootfall Studies, American Society of Heating & Ventilating Engineering Journal Section, Heating, Piping & Air Conditioning **17**:491-501 (Sept.) 1945.

10. Leiter, J.; Shimkin, M. B., and Shear, M. J.: Production of Subcutaneous Sarcomas in Mice with Tars Extracted from Atmospheric Dusts, J. Nat. Cancer Inst. **3**:155-165, 1942. Leiter, J., and Shear, M. J.: Production of Tumors in Mice with Tars from City Air Dusts, ibid. **3**:167-174, 1942.

11. McDonald, S., and Woodhouse, D. L.: On Nature of Mouse Lung Adenomata, with Special Reference to Effects of Atmospheric Dust on Incidence of These Tumours, J. Path. & Bact. **54**:1-12, 1942.

12. Campbell, J. A.: Cancer of Skin and Increase in Incidence of Primary Tumours of Lung in Mice Exposed to Dust Obtained from Tarred Roads, Brit. J. Exper. Path. **15**:287-294, 1934.

13. Kennaway, E. L., and Kennaway, N. M.: A Further Study of the Incidence of Cancer of the Lung and Larynx, Brit. J. Cancer **1**:260-298, 1947 (refer to p. 292).

14. (*a*) Clemmesen, J., and Busk, T.: On the Apparent Increase in the Incidence of Lung Cancer in Denmark, Brit. J. Cancer **1**:254-259, 1947; (*b*) Cancer Mortality Among Males and Females in Denmark, Cancer Res. **9**:411-414 and 415-421, 1949.

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erimental Studies on Tobacco Smoke,
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Diseases, Charles C Thomas, Spring-

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Engineering Journal Section, Heating,

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1949.

problem has been sought by comparing figures on lung cancer mortality in 13 different cities.[15] The reported rates per 100,000 population ranged from 20.3 to 19.7 in New Orleans, St Louis, and New York. At the bottom of the list stood Detroit and Pittsburgh, with rates of 10.8 and 10. It is noteworthy that the lung-cancer rate was reported as relatively low in Pittsburgh, where an air-pollution problem has long existed. It might also be noted that the highest rates were reported from cities where well-known lung-cancer clinics are located.

As stated earlier, lung cancer is principally seen in males. Such lung tumors as occur in women are generally adenocarcinomas, i. e., tumors composed of cells that bear some resemblance to those that normally line the bronchial passages. In men lung tumors are predominantly anaplastic or undifferentiated or frankly squamous (epidermoid). The squamous cell cancers are composed of cells that resemble skin tissue. Since no such tissue exists in healthy lungs, alteration (metaplasia) must occur in pulmonary epithelium in order to provide cells that could give rise to squamous cell cancers. Patches of squamous cell metaplasia are commonly seen in human lungs that have been the seat of chronic infections or irritations.[16] Squamous cell metaplasia occurs in animals deficient in vitamin A [17] and may be widespread in the lungs of old rats with chronic pulmonary infections,[18] but squamous cell carcinoma is almost unknown in any species of animal other than man. Wells, Slye, and Holmes,[19] in examining 2,865 cases of spontaneous lung tumors in mice, found epidermoid features in only 7. The remainder were adenomas, some of which had undergone cancerous evolution. In 104 cases there were metastases outside the lungs. In 33 cases there were sarcomatous features. The most intensively studied lung tumors of animals, indeed the tumors that have occupied most of the efforts of investigators who have conducted experimental studies of lung tumors, are the pulmonary adenomas of mice. I will have more to say about them later on. There is thought to be a resemblance between them and some human alveolar cell carcinomas, but the latter are not common and I should like to describe now some experimental studies on squamous cell cancers of the lung.

Many attempts have been made to induce lung cancer experimentally in animals, but almost always they have failed or have produced only adenoma. The literature contains many papers claiming success in the experimental induction of lung cancer, but most of these papers refer only to adenomas in mice. In 1924, Möller [20] claimed to have found squamous cell carcinoma in 6 of 24 rats after long-continued painting of tar onto the skin. In view of Passey's subsequent demonstration [18] of the

15. Lanza, A. J.: Health Aspects of Air Pollution, Smoke Prevention Association of America, Chicago 2, 1949 (11 pp.).

16. Niskanen, K. O.: Observations on Metaplasia of Bronchial Epithelium and Its Relation to Carcinoma of the Lung; Patho-Anatomical and Experimental Researches, Acta path. et microbiol. scandinav., Supp. 80, pp. 1-80, 1949.

17. Wolbach, S. B.: Pathologic Changes Resulting from Vitamin Deficiency, J. A. M. A. 108:7-13 (Jan. 2) 1937.

18. Passey, R.; Leese, A., and Knox, J.: Bronchiectasis and Metaplasia in the Lungs of the Laboratory Rat, J. Path. & Bact. 42:425-434, 1936.

19. Wells, H.; Slye, M., and Holmes, H.: The Occurrence and Pathology of Spontaneous Carcinoma of the Lung in Mice, Cancer Res. 1:259-261, 1941.

20. Möller, P.: Carcinoma pulmonaire primaire chez les rats pie hadigeonnés

frequency of extensive squamous metaplasia in the lungs of old rats I am inclined to doubt that the changes described by Möller were carcinoma. In 1939, Nordmann and Sorge[21] exposed mice to repeated inhalations of asbestos dust. The particle size was not stated, but asbestos fibers were found in the lungs. Out of an original 100 mice, ill-defined epithelial changes were thought to have resulted in the lungs of 9 animals, squamous cell metaplasia in 6, squamous cell carcinoma in 1, and adenocarcinoma in 1. The first lesion interpreted as "cancer" was found after 240 days, at which time 10 animals survived. The authors' statement that cancer had been produced in 20% of the animals has been quoted as experimental evidence for the carcinogenicity of asbestos dust. Actually, the photograph which was offered to illustrate the one "squamous cancer" almost certainly represents merely squamous cell metaplasia, and the only other tumor asserted to be a cancer, an "adenocarcinoma," is not illustrated and is a type of tumor that can arise spontaneously from the common mouse adenoma. In my opinion, therefore, the experience described by Nordmann and Sorge does not afford evidence that asbestos dust is capable of provoking tumors. On the contrary, it would appear to demonstrate that asbestos dust did not provoke lung tumors under the conditions of test employed.

The first indubitable experimental production of a squamous cell carcinoma of the lung was accomplished in 1937 by Andervont,[22a] who coated threads with dibenzanthracene and drew them through the chest walls of mice. He cut each thread where it emerged from the body wall and thus left a piece in the lung. By successfully transplanting the growths serially into new hosts, Andervont established the truly neoplastic nature of a squamous cell cancer induced in this way.

Coal tar injected through the chest wall[23] into rabbit lungs and instilled intratracheally into mouse lungs[24] failed to evoke cancer, though the intratracheal method is said to have yielded an adenocarcinoma in a guinea pig.[25] Methylcholanthrene in olive oil injected intratracheally into rats evoked sarcomas but not carcinomas,[26] but a Finnish author, Niskanen,[16] claimed that he had observed squamous cell carcinomas in rat lungs after intratracheal injection of dibenzanthracene in olive oil. His photographs suggest that at least one lesion may have been neoplastic rather than merely metaplastic, but none were transplanted, and the claim that they were in fact cancers must be viewed with some reservations. Intrapulmonary injection of the powerful pure carcinogens methylcholanthrene, benzpyrene, dibenzanthracene, and 9,10-dimethyl-1,2-benzanthracene dissolved in paraffin provoked sarcomas and adenomas in mouse lungs but completely failed

21. Nordmann, M., and Sorge, A.: Lungenkrebs durch Asbeststaub im Tierversuch, Ztschr. Krebsforsch. **51**:168-182, 1941.

22. Andervont, H. B.: (*a*) Pulmonary Tumors in Mice, Pub. Health Rep. **52**:1584-1589, 1937; (*b*) **53**:1647-1665, 1938; (*c*) **54**:1519-1524, 1939.

23. Garschin, W. G., and Pigaleff, I. A.: Experimentelle Untersuchungen über atypische Epithelwucherungen: Atypische Epithelwucherungen in den Lungen bei Entzündungen, die durch intrapulmonale Steinkohlenteerinjektionen hervorgerufen werden, Ztschr. Krebsforsch. **33**:631-653, 1931.

24. Bonne, C.: Ueber Geschwülste bei Teertieren, Ztschr. Krebsforsch. **25**:1-22, 1927.

25. Kimura, N.: Artificial Production of Cancer in the Lungs Following Intrabronchial Insufflation of Coal-Tar, Japan M. World **3**:45-47, 1923; cited by Garschin and Pigaleff.[23]

26. Valade, P.: Recherches sur l'activité cancérigène du méthylcholanthrène, Bull. Assoc. [illegible] 26:452-460, 1937

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to elicit any carcinomas.[27] Campbell[12] showed that mice exposed to inhalation of sweepings from tarred roads had an increased incidence of pulmonary tumors, but in the absence of evidence to the contrary these tumors must be presumed to have been simply adenomas. It is noteworthy that carcinomas appeared on the skin of some of the animals in Campbell's dust chambers. Similarly, as mentioned earlier, inhalation of tobacco smoke has failed to produce carcinoma in the lungs of mice, although tars extracted from tobacco smoke have elicited cancer from the skin.[5]

In my own experience, carcinomas have been induced from lung tissue removed from mouse embryos and implanted along with olive oil solutions of methylcholanthrene[28a] or dibenzanthracene[28b] into the thigh muscles of adult animals of an inbred strain. With the use of this procedure (the "tissue-transplant technic") lung tissue has yielded squamous cell, transitional cell, anaplastic, and alveolar cell carcinomas, and the neoplastic nature of each of these types of growths has been established by successful transplantation. These experiments were conducted with a view to studying early changes, and it was found that the carcinogens quickly induced squamous cell metaplasia from the pulmonary epithelium. Some of the tumors were frankly keratinizing epidermoid cancers, but others, composed of cells piled up in several or many layers, showed flattening of cells in the upper layers but stopped short of keratinization. These were the "transitional cell carcinomas." Still others had even less marked squamous cell characteristics. All, however, preserved their distinctive patterns on being transplanted to other hosts. The findings serve to demonstrate that neoplastic change can supervene in cells at different stages of metaplasia. This concept would account for the different types of cancer seen in response to the same carcinogenic chemical.

In contrast to the diversity of tumor types evoked by these chemical carcinogens stands the histological uniformity of virus-induced tumors. Adenocarcinomas of the mouse breast and the breast adenomas that precede them have an extraordinarily uniform appearance. They are due to a virus, though hormonal and genetic factors are needed for their evolution. It would not be surprising if the adenomas of mouse lungs, which also have an extraordinarily uniform appearance, were some day shown to have a virus causation, though chemical and genetic factors are already known to influence their number. Let us turn now to a consideration of these tumors.

That pulmonary adenomas of mice are true neoplasms is established by the metastases that are occasionally found in distant organs[19] and by the growth of the adenomatous tissue when transplanted to new hosts.[22c] They arise from the walls of alveoli[29] and are discrete, compact nodules composed of cuboidal cells lining narrow, tortuous channels and arranged in a single layer on a delicate stroma. The incidence of these tumors varies greatly among different strains of inbred mice.

27. Rask-Nielsen, R.: Types of Tumours in the Lungs of Strain Street Mice Following Direct Application of Large Doses of Four Different Carcinogenic Hydrocarbons, Brit. J. Cancer **4**:117-123, 1950.

28. Smith, W. E.: (*a*) The Neoplastic Potentialities of Mouse Embryo Tissues: V. The Tumors Elicited with Methylcholanthrene from Pulmonary Epithelium, J. Exper. Med. **91**:87-104, 1950; (*b*) The Tissue Transplant Technic as a Means of Testing Materials for Carcinogenic Action, Cancer Res. **9**:712-723, 1949.

29. Grady, H., and Stewart, H.: Histogenesis of Induced Pulmonary Tumors in Strain A Mice, Am. J. Path. **16**:417-432, 1940.

In the A strain of mice, these tumors are found in 77% of virgin females by 16 months of age and in 71% of males by 14 months. The C57 black strain, by contrast, has an incidence of less than 1%. One might inquire whether the tendency to develop pulmonary adenomas is passed on through the mother as in the case of the tendency to develop adenomas of breast tissue, in which a virus is transmitted in the milk. Bittner [30] has made an experiment which provides data on this point. He found that mating C57 males with A females, or C57 females with A males, gave in each instance progeny with a high incidence of pulmonary adenomas, comparable to that of the A strain. The pulmonary adenomas, therefore, do not appear to be associated with a virus transmitted in the manner of the mammary adenoma virus.

Intravenous or subcutaneous injection of carcinogenic hydrocarbons or even painting of such hydrocarbons or of coal tar onto the skin increases the incidence of pulmonary adenomas in proportion to their spontaneous incidence in the strains selected for test, as shown by Lynch [31] and Andervont.[22b] Elaborate statistical studies have shown that the incidence of pulmonary adenomas in response to graded intravenous doses of a carcinogen is so sensitive a measure of response that this method has been advocated as a means for biological assay of carcinogenic materials.[32] Heston has shown that the ability of pure-line mouse strains to produce adenomas spontaneously [33] or in response to intravenous dibenzanthracene [34] is inherited by multiple factors, for F1 hybrids of A mice outcrossed to three other strains differed in their yield of adenomas, the hybrids tending to be intermediate in this respect to their parent strains.

Intravenous, intraperitoneal, subcutaneous, or oral administration of urethan increases the incidence of adenomas. The number of adenomas is proportional to the dose of urethan.[35] In limited groups of animals studied by British workers, urethan evoked tumors when instilled intranasally,[36] and after intraperitoneal injection it caused more tumors in a strain (R III) with a moderate spontaneous incidence than in a strain (C57) with a low spontaneous incidence of adenomas.[37]

Urethan differs remarkably from the polycyclic hydrocarbon carcinogens not only in its small molecular size, solubility in water, and rapid excretion but in that

30. Bittner, J. J.: Spontaneous Lung Carcinoma in Mice, Pub. Health Rep. **53**:2197-2202, 1938.

31. Lynch, C. J.: Influence of Heredity and Environment upon Number of Tumor Nodules Occurring in Lungs of Mice, Proc. Soc. Exper. Biol. & Med. **43**:186-189, 1940.

32. Shimkin, M. B., and McClelland, J. N.: Induced Pulmonary Tumors in Mice: IV. Analysis of Dose Response Data with Methylcholanthrene, J. Nat. Cancer Inst. **10**:597-604, 1949.

33. Heston, W. E.: Inheritance of Susceptibility to Spontaneous Pulmonary Tumors in Mice, J. Nat. Cancer Inst. **3**:79-82, 1942.

34. Heston, W. E.: Genetic Analysis of Susceptibility to Induced Pulmonary Tumors in Mice, J. Nat. Cancer Inst. **3**:69-78, 1942.

35. Larsen, C., and Heston, W.: Induction of Pulmonary Tumors in Mice by Anesthetic Agents, Cancer Res. **5**:592, 1945.

36. Selbie, F. R., and Thackray, A. C.: Lung Adenomas Induced by Urethane in CBA Mice, Brit. J. Cancer **2**:380-385, 1948.

37. Cowen, P. N.: Some Studies on the Action of Urethane on Mice, Brit. J. Cancer **1**:401-405, 1947.

no matter what its route of administration it produces tumors selectively in the lungs,[38] and these tumors are all histologically identical. So sensitive is mouse lung tissue to urethan that when pregnant mice are given this compound, pulmonary adenomas develop in their offspring.[39] In experiments conducted by Peyton Rous and me,[40] adenomas were found in the lungs of baby mice three days after their birth from mothers given urethan subcutaneously during pregnancy. This unprecedented rapid evolution of tumors argues that urethan acts by some method different from that of a conventional primary carcinogen. Histological studies provide some ground for thought as to what this mechanism may be. Tiny nests of cells resembling adenoma cells were occasionally observed in serial sections of lungs of young mice from untreated mothers.[40] I have recently seen a small but indubitable adenoma in the lungs of a "normal" 10-day-old C mouse and a much larger one in the lungs of a "normal" 30-day-old mouse of the A strain. In view of these findings of adenomatous-like islands and even frank adenomas in the lungs of such young individuals of the C and A strains, which have, respectively, a moderate and a high spontaneous incidence of adenomas in old age, it became important to examine the lungs of young individuals of the C57 strain, which have a very low incidence of adenomas.[41] In serial sections of lungs from month-old C57 animals, I have thus far not found cell groups that could be regarded as early adenomas. The data available, though limited, are consistent with the hypothesis that chemical induction of pulmonary adenomas depends on stimulation of specific cells possessed in differing numbers by different individuals. Whether the presence of these cells reflects the action of a virus remains to be discovered.

Claims have been made for the demonstration of a virus in pulmonary adenomatosis of sheep. This disease ("jaagsiekte") has assumed epidemic proportions in sheep in some parts of the world. It is a more diffuse process than the pulmonary adenomas of mice, but the cells have the same appearance, Niels Dungal,[42] in Iceland, has reported the following results in experiments with it: The disease was seen to develop in healthy sheep housed above sick sheep. A diseased sheep was made to breathe through a 20% glycerin-saline solution, and 5 cc. of this solution was introduced intratracheally into each of three lambs, in two of which the disease developed. The breath of one of these, collected in glycerin-saline, was filtered through graded collodion membranes (0.9), and the filtrate was injected into the right lungs of four mice. These mice were killed four months later, and one had what was considered "jaagsiekte" of both lungs. These experiments suggest that a virus is responsible for pulmonary adenomatosis in sheep, but the finding of adenomatosis in only two lambs on an island where the disease is endemic and in

38. Urethan also damages the liver and induces liver tumors (Jaffe, W. G.: Carcinogenic Action of Urethane on Rats, Cancer Res. 7:107-112, 1947).

39. Larsen, C. D.: Pulmonary Tumor Induction by Transplacental Exposure to Urethane, J. Nat. Cancer Inst. 8:63-70, 1947.

40. Smith, W. E., and Rous, P. R.: The Neoplastic Potentialities of Mouse Embryo Tissues: IV. Lung Adenomas in Baby Mice as Result of Prenatal Exposure to Urethane, J. Exper. Med. 88:529-554, 1948.

41. The studies of lungs from A and C57 mice were carried out at the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine.

42. Dungal, N.: Experiments with Jaagsiekte, Am. J. Path. 22:737-759, 1946.

one mouse precludes a firm conclusion at present. In sheep the disease is often complicated by pneumonia, but in mice it occurs quite free of inflammatory changes.[20]

After various infections of the human lung, notably interstitial pneumonias associated with viruses, alveoli may become lined with cuboidal cells. It is not known whether this condition is in any way related to the so-called "alveolar cell" carcinoma, which presents a somewhat similar histologic aspect. If the patient has died in the course of what is thought to have been an "atypical" pneumonia and alveoli are seen lined with cuboidal cells, particularly where the mesenchymal structure of the alveolar walls is thickened ("interstitial pneumonitis"), the change is considered a response to infection. With this picture in mind, let us turn to lungs which are the seat of widespread change of this sort, notably those studded with nodules of such tissue, occasionally metastasizing to other organs. These are the "alevolar cell" (terminal bronchiolar) carcinomas,[43] or, as some pathologists have termed them, pulmonary adenomatosis. Here, more readily than in the cases mentioned above, one finds alveoli lined by cuboidal cells without any underlying interstitial pneumonitis. One is therefore inclined to believe that the epithelial change is primary and not merely an incidental response to inflammation. However, pneumonitis is usually observed somewhere in such lungs: the patients may come under observation or die after a febrile illness, and it is difficult to judge whether pneumonitis preceded or was superimposed on the adenomatosis. Only 20 cases of this terminal bronchiolar cell carcinoma have been seen at Memorial Hospital in the last 20 years.[43] Hence, they constitute only a small part of the over-all lung-cancer problem.

In man, another type of adenoma is considered to arise from the bronchial mucous glands and may have both endodermal and mesodermal components, laying down cartilage and bone.[44] Such mixed tumors are thought to arise from neoplastic change in cells still possessing "embryonal" potentialities for development. Sarcomatous elements are sometimes found in spontaneous [19] or transplanted [22e] pulmonary adenomas of mice.

SUMMARY AND CONCLUSIONS

The pulmonary adenoma of mice has been the type of lung tumor most amenable to experimental study and as such it has occupied the attention of most experimenters engaged in the study of lung tumors. It would appear, however, that the pulmonary adenoma of mice represents a specialized situation with limited bearing on the types of tumors that account for the great majority of cases of lung cancer in human beings. Carcinomas more nearly resembling those common in man have been produced from mouse lung by the tissue-transplant technic, but this is a very artificial procedure that can at best serve merely as a screening technic for testing substances suspected of having something to do with lung cancer.

In reviewing experimental studies, an outstanding fact is that cancer of the lungs (aside from adenoma) has never been conclusively produced in any animal

43. Smith, R.; Knudtson, K., and Watson, W.: Terminal Bronchiolar or "Alveolar Cell" Cancer of the Lung. Cancer 2:972-990, 1949.

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by any material to which the animal was exposed by inhalation. The hazards presented by materials suspected to cause cancer of the human lungs are inhalation hazards. My chief conclusion, therefore, is that we are singularly ill-equipped for experimental study of one of the chief problems of human cancer. Recognition of deficiencies may lead to their remedy. It is, for example, noteworthy that potent carcinogenic hydrocarbons instilled or injected into the lungs in solution in oil or in soft paraffin have almost invariably failed to elicit tumors (carcinomas) of the tissue (epithelium) lining the surface of the respiratory tract but have instead caused tumors (sarcomas) of the deeper tissues. These facts argue that carcinogens which are presented to the lungs in solution pass readily through the thin surface tissue and affect the underlying structures. Indeed, when the normal lymphatic drainage of the lung is disturbed, as happens in the tissue-transplant technic referred to above, then solutions of carcinogens readily elicit carcinomas from pulmonary epithelium. These considerations may explain why carcinomas were obtained by Andervont when he inserted into the lungs threads coated with dibenzanthracene, for the chemical then existed as crystals, and it may be presumed that some crystals were arrested by portions of the lining epithelium. In the planning of experiments on lung cancers, large rewards may therefore be anticipated from careful consideration of the physical state in which test materials are presented to the lungs. Industrial physicians and hygienists are well aware that the particle size of noxious dusts plays a large role in determining the site of tissue reaction in the lungs. Thus, the small particles in siliceous dusts pass through the alveolar walls and exert their pathologic effects on the deeper tissues, whereas the larger fibers of asbestos are arrested in the terminal air spaces and produce a wholly different pathologic picture. The known facts gleaned from experimental studies of silicosis and asbestosis may prove of much value in future inhalation studies of materials suspected to cause cancer of the lungs.

In closing, let us note again that undifferentiated, anaplastic, or squamous cell cancers compose the majority of lung cancers seen in man. Attention should therefore be directed toward materials or conditions leading to dedifferentiation or metaplasia of pulmonary tissue. Chronic pulmonary infections, vitamin-A deficiency, and polycyclic hydrocarbon carcinogens have been mentioned above as provoking metaplasia, but only the polycyclic hydrocarbons have induced neoplasia. The following four sets of conditions might then be formulated:

1. An agent may evoke metaplasia but not neoplasia.
2. An agent may evoke both metaplasia and neoplasia.
3. Metaplasia evoked by an agent of either of the above types may be converted to neoplasia by an agent that may or may not possess the ability to evoke a primary metaplastic change.
4. Neoplastic cells, once evoked, may be influenced to grow by cocarcinogenic agents related or unrelated to the evoking agents.

Such a set of possibilities lends itself to experimental investigation and may afford a framework for analysis of groups of chemicals handled in plants having an unusually high incidence of lung cancer.