

FILE NAME: International Harvester (INTH)

DATE: 1953

DOC#: INTH052

DOCUMENT DESCRIPTION: Conference Presentation - Cancer of the Lung-A
Critical Presentation

800 ACS - 2345
227

MS - American Cancer Society
Meetings - Miscellaneous

Dear Karl -

*I think it would be well for your group to send a "Monitor"
to this meeting*

Paul

American Cancer Society
47 Beaver Street
New York 4, N. Y.

Attached: Correspondence with
Dr. Brewster S. Miller,
Director, Professional
Education Section,
American Cancer Society

Annual Meeting - Scientific Session

CANCER OF THE LUNG: A CRITICAL EVALUATION

Hotel Commodore
New York, N. Y.
November 3 - 4, 1953

November 3, 1953

**I. IS LUNG CANCER ON THE INCREASE: - EVALUATION OF PRESENT DAY
EVIDENCE**

Harold F. Dorn
National Institutes of Health, Bethesda

Discussion:

Daniel Horn
American Cancer Society, N. Y.

II. ETIOLOGY: OCCUPATIONAL AND ENVIRONMENTAL ASPECTS

(1) The Place of Tobacco in the Etiology of Lung Cancer

Ernest L. Wynder
Memorial Cancer Center, N. Y.

E. Cuyler Hammond
American Cancer Society, N. Y.

Discussion:

Alexander Gilliam
National Cancer Institute, Bethesda

H. B. Parmele
P. Lorillard Company, Jersey City

**(2) The Current Status of Air Pollution Studies in the Etiology of Lung
Cancer**

Paul Kotin
University of Southern California
Los Angeles

(3) The Experimental Production of Lung Tumors

NOTE: Dr. Brewster S. Miller, Director, Professional Education Section, ACS, invited Mr. Hammer to participate in a discussion of remarks by Doctors Hammond and Wynder (above) - declining letter attached, giving permission to be read at the Meeting.

Howard B. Andervoot
National Cancer Institute, Bethesda

Harry S. N. Green
Yale University, New Haven, Conn.

Discussion:

William E. Smith
New York Univ. - Bellevue Medical Ctr., N. Y.

Hermann Lisco
Argonne National Laboratory, Illinois

(4) Potential Occupational Factors:

William E. Smith
New York University - Bellevue Medical
Center, N. Y.

Discussion:

(a) Chromates

Willard Machle
National Research Council, Wash., D. C.

Seward E. Miller
U. S. Public Health Service, Wash., D. C.

(b) Arsenicals Coal-tar
derivatives

W. C. Hueper
National Cancer Institute, Bethesda

(c) Beryllium

Arthur J. Vorwald
Saranac Lake, N. Y.

(d) Radioactive dust

Merrill Eisenbud
U. S. Atomic Energy Commission, N. Y.

(e) Asbestos

Kenneth M. Lynch
Medical College of South Carolina
Charleston

(f) Genetics

Walter E. Heston
National Cancer Institute, Bethesda

(5) The Geographic Considerations in the Lung Cancer Problem

Harold L. Stewart
National Institutes of Health, Bethesda

III. CONTROL: DETECTION ASPECTS

(1) Dividends and Defects of the Mass Survey Method in Detecting Lung
Cancer

Lewis Guiss
Los Angeles, Calif.

Seam

Cancer of the Lung
An evaluation of the
Problem

1956
ACS

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CANCER OF THE LUNG

AN EVALUATION OF THE PROBLEM

Proceedings of the Scientific Session
Annual Meeting
American Cancer Society, Inc.
November 3-4, 1953

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55-11610

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THE EXPERIMENTAL PRODUCTION OF LUNG TUMORS

Harry S. N. Greene, M.D.
Yale University School of Medicine
New Haven, Connecticut

I have several series of experiments concerned with the experimental production of lung cancer to report. These experiments involve a technique different from the standard procedure in as much as transplants of embryonic tissue rather than the tissue of the adult animal is used as a test material.

The desired tissue or organ is removed from a half-term mouse, impregnated with the material to be tested, and transplanted somewhere in adult individuals.

The eye, the brain, or the subcutaneous space offer adequate sites for inoculation. When this technique is utilized with known carcinogens, such as methylcholanthrene or dibenzanthrene, cancer is produced with great rapidity and in high incidence. Moreover, cancer is produced in embryonic organs that, in their adult state, appear to be resistant to the carcinogenic action of the substance.

As a control, transplants of embryonic mouse lung were obtained halfway through gestation and transplanted to the subcutaneous space of the axilla of adult mice. The animals were killed two months after transfer for microscopic study. Sections showed normal lung tissue made up of expanded alveoli and bronchi. Epithelialization of alveoli, commonly referred to as a pulmonary adenoma, occurred with high frequency in all transplants.

The most common tumor produced in lung transplants with methylcholanthrene is an epidermoid carcinoma. Typical epidermoid carcinoma different from the ordinary human carcinoma of the lung in its high degree of keratin occurs

regularly thirty to forty days after transfer of embryonic mouse lung containing a single crystal of methylcholanthrene.

Sarcomas also occur in these transplants with some frequency. They grow rapidly and obliterate all normal lung structures. Mixed tumors, that is, carcinosarcomas, are also common.

The tumors occur in almost 100 per cent of the transplants and are apparent within thirty to fifty days after transfer. They are true cancers. They grow on transfer, metastasize, and are heterologously transplantable.

It would seem that this technique might be of some value in the testing of substances thought to be carcinogenic; and this has been done. Because of the frequent occurrence of cancers in lungs that show asbestosis, asbestos was one of the materials tested.

Fragments of embryonic mouse lung were impregnated with asbestos fibers and transplanted to the subcutaneous space of more than 150 adult animals. Small groups were killed at intervals for histologic study, but the majority of animals were held for as long as nine months.

At the end of this period the transplants were all examined histologically. All showed asbestosis but in no instance whatsoever was any indication of cancer found.

Typically, the transplant showed a diffuse fibrosis quite unlike the fibrosis that occurs in degenerating lung tissue. Giant cells containing asbestos fibers as well as typical asbestosis bodies were common. It is to be emphasized again that, despite the fact that all the transplants showed asbestosis, none of them showed cancer.

A similar series of experiments was carried out utilizing beryllium. Again a large series of animals were used and again the animals were held as long as nine months. Typical beryllium granulomas were found in the lungs but in no case whatsoever was there any indication of neoplasia.

Finally, a series of experiments was carried out utilizing

a variety of tobacco products. These included extracts of pipe tobacco, cigarette tobacco, cigarette papers, and tar from pipes. More than three hundred animals were used and the majority were held for as long as a year.

At the end of that time the transplants were studied histologically and in no instance whatsoever was there any indication that the materials used were carcinogenic. Before concluding, I should like to make one point with reference to the experimental production of cancer in animals.

This concerns the fact that human lung cancer is a biological entity, and, before experimental cancer in animals can be considered a counterpart of the human disease, a similar biological character will have to be demonstrated.

Study of transplants also shows the difference in biological behavior between human lung cancer and human carcinomas of similar morphological type obtained from other parts of the body. The comparison here is made on heterologous transplantability.

Heterologous transplantability is a measure of the phase of development of the tumor concerned. It means that a tumor is in a late phase of development---that it is metastasizing.

The results of transfer of a series of epidermoid carcinomas obtained from sites other than the lung were similar to those with other material obtained directly from the operating room.

About half of the tumors were transplantable heterologously. In other words, about half of the tumors obtained from the operating room are in a late phase of development and are metastasizable and the other half are in an early stage of development and are not metastasizable.

Examination of our figures has shown that wherever the tumor was heterologously transplantable, the patient died within a short period of time. In contrast, when the tumor was not heterologously transplantable and the operation was adequate, the patient survived.

The point to be made then is that, at the time of clinical

discovery and operation in epidermoid carcinoma in parts of the body other than the lung, about half of the tumors are in an early phase of development.

However, there was a complete reversal of this picture in the case of lung cancer. In a series studied in our laboratory every single one was heterologously transplantable. I emphasize again that this tumor tissue was obtained at the time of clinical discovery and at the time of clinical discovery every single one of the tumors was transplantable to alien species, which means that every single one of the tumors was in a late stage of development and was metastasizable.

Accordingly, we found that all of the patients shortly died. I emphasize again that these were small tumors, many of them much smaller than the epidermoid carcinomas of other regions of the body.

A point to be emphasized here is that human lung cancer is a biological entity, and it is essential that experimental tumors in animals be shown to possess analogous properties before they can be considered counterparts of the human disease.

In conclusion, then, techniques that have produced cancer in high incidence and with great rapidity with known carcinogens have failed to produce cancer with asbestos, beryllium, and tobacco.

Secondly, the identity of the experimental lung cancer produced by methylcholanthrene with the human disease is in doubt in as much as these tumors fail to show the same biological character as is manifested by human lung cancer.

DISCUSSION--The Experimental Production of Lung Tumors

William E. Smith, M.D.

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It seems to me that two main factors impress one in thinking about experimental studies directed toward lung cancer.

One is that we should be studying tumors that are as comparable as possible to the disease as it is seen in man. The fact is that the great majority of studies on lung tumors in animals, valuable though they have been, have centered around the study of pulmonary adenomas in mice. These adenomas are different from the great majority of lung tumors in man.

A second point is that very little has been done with inhalation techniques. As we have listened to the speakers this morning, we have heard of a number of substances that are thought to have something to do with cancer of the lung in man. These substances enter the lungs by inhalation.

We have induced carcinomas, histologically very similar to carcinomas seen in human lungs, by transplanting embryonic mouse-lung tissue into the leg muscles of adult mice together with methylcholanthrene, dibenzanthracene, or benzo(a)pyrene. In our experience these tumors have grown with great rapidity when transplanted to new hosts.

The majority of these tumors have been transitional-cell carcinomas but we have also seen frankly keratinizing epidermoid carcinomas. Both these types of tumors preserve their histological characteristics on transplantation.

I think that what we have learned is that the neoplastic change can supervene in cells at different stages in the course of metaplasia. Once the neoplastic change occurs, the cell is fixed in that stage of metaplasia.

One serious shortcoming of these tests, carried out with implants of lung tissue, succeeded in producing tumors of the sort seen in human lung, whereas direct injection of carcinogen

materials into the lung has usually elicited either adenomas or sarcomas. Perhaps this difference is due to the fact that when the tissue is transplanted its lymphatic and vascular supply is disturbed, and the carcinogen put with it can then remain in prolonged contact with the tissue; whereas, when the carcinogen is introduced into the normal lung, it may pass through it and be carried off somewhere else so that it lacks time to act on the pulmonary epithelium.

This focuses our attention on the manner in which test material is presented to the lung. This may be crucial in experiments designed to learn whether some selected material can produce cancer in the lungs.

Reference

Smith, W. E.: Lung cancer with special reference to experimental aspects. (Proc. Cancer Prevention Committee.)
A. M. A. Arch. Indust. Hyg. 5:209-217, 1952.

POTENTIAL OCCUPATIONAL FACTORS IN LUNG CANCER

William E. Smith, M.D.
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In contrast to some other forms of cancer, lung cancer is not a complete mystery. There are some situations in which causes of the disease have been recognized.

The first instance in which a cause of lung cancer was recognized goes back to the experience of men in the German and Bohemian uranium mines. For many years cancer of the lung had been observed with striking frequency in miners in the German uranium mines. In one autopsy series, 40 per cent of the miners who died, died with cancer in their lungs. In the 1930's, medical officers for the mines across the border in Czechoslovakia conducted a study to learn whether such a problem existed in their mines. More than three hundred of their miners were examined fluoroscopically. Not one case of lung cancer was detected. Nevertheless, in the decade in which that study was made, eighty-three of the Czech miners died, and more than forty of them had cancer in their lungs.

This experience teaches us two important lessons. One is that some factor in the environment can enter the lungs and there produce cancer. The second is that a radiological survey can fail to detect an occupational lung-cancer hazard.

The next instance in which a cause of cancer of the human respiratory tract was recognized came from the experience of a nickel refinery in Wales. The medical officers there had recorded the occurrence of fifty-two cases of cancer of the nasal sinuses in men in this particular plant and ninety cases of cancer of the lung. The occurrence of this large number of cancer cases in the respiratory system left no doubt that some occupational factor was involved. When the jobs of the men who had these respiratory-tract cancers

were studied, it was found that the majority had worked in a part of the plant where the nickel ores were treated with sulfuric acid to extract copper. The acid used was a grade that contained arsenic. The ores themselves were rich in arsenic. Both arsenic and nickel were present in the dust in the room where the calciners for this operation were located.

In 1921, the plant shifted to a grade of acid free of arsenic and, in 1924, rebuilt the calciners to decrease dust and fumes. There has been no case of nasal-sinus cancer in that plant in any man whose employment has dated since 1924. Here we have an instance in which an occupational lung-cancer hazard has been brought under control. And here we have a third important lesson, namely, that some forms of cancer may be amenable to sanitary-engineering measures designed to minimize exposure to hazardous materials.

In recent years, an occupational lung-cancer hazard has become apparent in the chromate industry. Dr. Machle was to be here today to describe his studies on this problem. Since he is unable to be here, I should like to mention some of his findings, which were published a few years ago.

Dr. Machle and Dr. Gregorius conducted their study at the request of the six major chromate-producing plants in the United States. They found that there had been a total of 193 deaths in the chromate plants they studied; sixty-six of these were due to cancer, forty-two of them to cancer of the respiratory system.

For a group to control this experience they turned to the records of the Metropolitan Life Insurance Company, finding that among 733 deaths of industrial-policy holders 115 had died of cancer and ten had died of cancer of the respiratory tract. There was thus a difference between the 63.6 per cent cancer of the respiratory tract found in the deaths that had occurred in the chromate plants and the 8.7 percent in the control group.

As they examined the experience in the individual plants, they found that in one there had been fifty-five deaths, nineteen of them from cancer. Eighteen of those nineteen cancer

ten were due to cancer of the respiratory system. In another plant there had been thirty-seven deaths, ten of them due to cancer of the respiratory system. Lung cancer was a prominent cause of death in other chromate plants that they studied. However, there was one interesting exception.

This was a plant in which there had been thirty-three deaths. Over the years, people in industry die just as people die everywhere else. In that particular plant, thirty-three men had come to the end of their lives, but not one had cancer in his respiratory system. This group stood out as being different from the experience in the other plants. A study was then made to learn if there was something different about this plant.

This study showed that the plant in which there was no lung-cancer problem received the chromates in solution, whereas the plants that had a problem were those processing the ore. Attention was therefore focused on this latter phase of the operation as presumably the phase that presented the hazard. Here we have an example of an important principle in industrial medicine, namely that occupational hazards do not afflict all personnel within a particular industry but only those individuals engaged in certain processes. Identification of these processes permits intelligent design of methods for control of the hazard. This matter will be discussed later today by Dr. Seward Miller.

Let us turn now to another topic. A few years ago, the Chief Inspector of Factories in Great Britain published figures showing that over the last twenty years his office had received reports of 128 cases of asbestosis in men and that lung cancer had been found in twenty-two of these cases. In the same period had been 107 cases of asbestosis. Lung cancer therefore present in a much smaller percentage of the cases of asbestosis than everinastosis in a percentage that was about one per cent of the lungs.

There is a very interesting comparison between the percentage of lung cancer in asbestosis and the percentage of lung cancer in the general population. In the general population, the percentage of lung cancer is about one per cent. In the asbestosis population, the percentage is about one per cent. This is a very interesting comparison, and it is one that is worth noting.

identically the same as the figure for lung cancer in the general population as calculated from the Registrar-General's death certificates for England and Wales.

These data led the Chief Inspector to conclude that there was an occupational lung-cancer hazard among individuals, especially males, who developed asbestosis. He attempted to learn whether this impression might have arisen because the people who developed asbestosis had lived longer than the individuals who had developed silicosis and thus had more opportunity to live into the "cancer age." But this was not true. The individuals with asbestosis had died earlier than the silicotics.

I visited the Chief Inspector about three years ago at a time when he had records of thirty-one cases of coexistent asbestosis and lung cancer. At that time, I had the opportunity to visit the medical officers of the plants from which these cases had come, and to visit Dr. Gloyne at Oxford and the laboratory of Dr. C. V. Harrison in London, the pathologists who had examined these lungs. I was able to find out something about twenty of the thirty-one cases. The majority were squamous-cell or oat-cell tumors.

All of the twenty cases whose records I had the opportunity to see had been employed in the industry prior to 1932. In 1932, modern exhaust ventilation equipment had been installed to reduce dust hazards in the plants in which these cases had occurred. Ten of the other eleven patients that were on record had been employed at an even earlier time, and I did not attempt to locate their records. In the cases that had appeared, the "latent period" between beginning of employment and appearance of cancer averaged about sixteen and a half years. In 1950, eighteen years had passed since the ventilators were put in, and only one case of lung cancer had been recorded among men whose employment had begun since the installation of ventilators in 1932.

This question of asbestosis and lung cancer will be discussed in detail this afternoon by Dr. Kenneth Lynch.

Quite recently, the Archives of Industrial Hygiene carried some interesting data published by Weil, Smyth, and Nale. These authors reviewed the medical records of a chemical

On the basis of the vital statistics reports of the United States, they expected approximately 13.5 per cent of the deaths to be due to cancer. Actually, only 13.2 per cent were due to cancer. Nevertheless, upon analysing the cancer deaths by site, instead of finding the expected rate of 9.6 per cent attributed to cancer of the respiratory tract, they found a substantially higher figure, namely 14.7 per cent. The excess was traced to a group of men engaged in the production of isopropyl alcohol. Among seventy-one men engaged in this work, there had been three cases of cancer of the ethmoid sinus, one of the sphenoid sinus, one malignant papilloma of the vocal cord, one case of benign papilloma of the vocal cord, and one case of cancer of the lung.

From this experience, it would appear that an occupational tumor hazard might exist for these men. But what could the offending material be? The purpose of the process was to manufacture isopropyl alcohol, but many other materials were handled as starting materials, intermediates, or by-products. These various materials were studied on animals at the Mellon Institute in Pittsburgh. Tumors of the lung were produced in mice by one of these materials, isopropyl oil. Isopropyl oil is a complex mixture, and the exact nature of the agent remains to be defined.

Environmental lung-cancer hazards have been indicated in some other occupations, for example in situations involving exposure to coal-tar fumes, as will be discussed today by Dr. Hueper.

In closing, I should like to note that occupational tumor hazards apply to relatively small groups of men. They could not begin to account for the large number of lung-cancer cases that occur. They have, however, an important lesson to teach us in that they show that agents from the external environment may enter the respiratory tract and there produce cancer. The attention is thus focused on the need for study of potentially carcinogenic materials to which large numbers of men may be exposed.

I have given you a discussion of studies in laboratory animals on lung cancer, and a discussion of our studies on the effects of coal-tar fumes on the lungs of humans.

operating conditions.

Reference

Smith, W. E. : An evaluation of claims for occupational factors in cancer of the lungs. Acta, Union internat. contre cancer 9:476-484, 1953.

DISCUSSION--Potential Occupational Factors in Lung
Cancer

CHROMATES

Seward E. Miller, M. D.
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I should like to discuss the portion of Dr. Smith's paper dealing with chromate production with respect to lung cancer.

Since 1890 there have been occasional reports in the European literature on lung cancer associated with exposure to chromates. In this country Dr. W. C. Hueper called attention to this and reviewed the literature in 1942.

In 1947 and 1948 Dr. W. Machle and Dr. F. Gregorius were employed by the chromate producers to study the incidence of lung cancer among workers in seven chromate-producing plants. They studied the health records of these employees, which were available from numerous sources, and went back ten to fifteen years when such records were available. A report of this study was published in Public Health Reports for August 27, 1948, and showed, among other findings, that 21.8 per cent of all deaths in the chromate industry were due to cancer of the respiratory system. This is sixteen times the expected 1.3 per cent, while the crude death rate for cancer of the lung was twenty-five times the normal.

In 1948 the chromate-producing industry requested the Public Health Service to undertake a complete medical and environmental study of the industry in the United States. The study followed the traditional medical, epidemiological, environmental, analytical, statistical pattern developed by the Public Health Service during the past forty years. In 1953 the Public Health Service completed and published the report of this comprehensive clinical and environmental study.

My discussion of the factors responsible for cancer among chromate workers is based on this study. I will present briefly the manufacturing process, some morbidity and mortality data, observations on working environment, and some remarks on a possible etiologic factor.

The Manufacturing Process. Briefly, this consists of roasting the finely ground chromite ore with soda ash or with a soda-ash and lime mixture, to produce a water-soluble chromium compound, sodium chromate, which is converted by acidification and crystallization into crystalline sodium bichromate. Soluble materials other than chromates and bichromates occur in the chromate and bichromate liquors. By-products such as alumina, sodium sulfate, and sodium vanadate may be recovered from these liquors.

The process may be divided into two general phases known in industry as the dry end and the wet end. The dry end of the process may be subdivided into segments of operation referred to as milling, roasting, and leaching. The wet end may be divided into segments of operation referred to as neutralizing, treating, and concentrating. Although these processes are the same, basically, throughout the industry many modifications are prevalent. Thus, mix proportions are different; the extent to which residue is recycled varies; methods of roasting and leaching differ; methods of concentration vary; and many differences exist in minor procedures.

Morbidity and Mortality Data. Analysis of the sick-benefit--association records in the chromate-producing plants shows that the annual number of cases of sickness and nonindustrial injuries per 1000 white males was 116 for chromate workers as compared with 108 for a large group of other industrial workers. For each specific cause of illness except cancer the chromate worker had frequency rates that were not greatly different from other workers; cancer with a rate of 7.1 per 1000 white male chromate workers compared with 0.7 for workers in other industries stands out as markedly in excess for chromate workers.

During the nine-year period from 1940 through 1948 the average annual death rate per 100,000 males, aged 15 to 74 years, for all causes was 1503 for chromate workers and 928 for the corresponding male population of the United States; for all causes except cancer the death rates were 924 and 797, respectively.

For cancer the actual number of deaths of chromate workers was approximately four and a half times the number that would have been expected had the cancer rates for all males in the United States prevailed. When cancer of the respiratory system was observed separately for chromate workers, there were nearly twenty-nine times as many deaths found as were expected.

The respiratory cancer deaths showed a ratio of actual to expected number of 14 for whites and 80 for colored. On the other hand, cancer of all other sites was about what would be expected for whites; the ratio of actual to expected number of deaths was 1.14. For colored the ratio was 0.67 indicating that the deaths were actually less frequent than expected.

The Working Environment. The excess morbidity and mortality among workers in chromate production led to an examination of the working environment for possible etiological factors. Such basic operations as crushing, grinding, roasting, leaching, granulating, neutralizing, filtering, concentrating, drying, and packing are common to many industries, and there is no evidence that these operations as such involved any particular health hazards. It appears reasonable, therefore, to surmise that the high prevalence of cancer may be related to exposure to some substance or substances characteristic of this industry. The primary raw materials utilized in the industry are chromite ore, soda ash, lime, sulfuric acid, fuel oil, water, and air. Except for the chromite ore, all of these substances are encountered in many other industries that, so far as is known, have no unusual prevalence of lung cancer. Consequently, one must consider chromite ore and its derivatives as being primarily responsible for the pathological effect. Most investigators of this problem have reached the same conclusion and there appears to be general agreement that chromite ore or with one or more of its compounds is

definitely implicated.

Machle and Gregorius suggested that the carcinogenic compounds of chromium were the monochromates. In our study we developed and wish to introduce for consideration a new and hitherto unexplored possibility: the acid-soluble water-insoluble derivatives of chromite ore. In the working environment an appreciable portion of the total chromium was found to be present in an acid-soluble water-insoluble state indicating the presence of a form or forms of chromium that are dissimilar to either insoluble chromite ore or the water-soluble, hexavalent chromium.

These acid-soluble compounds are produced in the roast and remain principally in the residue. Consequently they are present in appreciable amounts wherever roast or residue is encountered, which would include most of the dry end of chromate production. Where ore is crushed, these acid-soluble compounds would not be present. However, where residue is crushed and recirculated, these acid-soluble water-insoluble compounds are encountered.

A small amount of the residue is suspended in the leach liquor and thus enters the wet-end processes. Additional residue and roast reach the wet-end portion of the plant as air-borne dust. These two sources together with basic chromium sulfate, in some instances, probably account for such acid-soluble water-insoluble chromium as was found in the workroom air in the wet end of the plants. It appears likely that most of the residue carried over with the leach liquor is removed with the sodium sulfate. Acid-soluble water-insoluble chromium originating from subsequent processing is predominantly basic chromium sulfate.

Some pertinent observations on the etiological aspects of these acid-soluble, water-insoluble compounds are: Sufficient work-history data were obtainable in ten cancer cases so that they could be correlated with their working environment. Of these ten cases, seven had work histories indicating prolonged exposure to appreciable amounts of the acid-soluble water-insoluble form of chromium found in the roast and residue. Two cases had work histories in which the sole occupation was kiln operator or kiln-building laborer. Both of these occupations have to do with the roasting.

One case had a work history that indicated exposure to chromic acid, sodium bichromate, and the acid-soluble water-insoluble chromium but not to roast or residue.

All of the cancer cases were exposed to the hexavalent chromium compound, since this form is distributed throughout the entire plant.

No cases occurred among men with work histories showing prolonged exposure to high concentration of chromite ore.

Now, in conclusion, although the agent responsible for cancer found in this industry was not determined by the study, attention was directed to the acid-soluble water-insoluble chromium compounds as of possible etiological importance. Research is now being carried out in at least two institutions attempting to evaluate the carcinogenic properties of this suspect.

Discussion of Potential Occupational Factors in Lung Cancer

ARSENICALS; COAL-TAR DERIVATIVES

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Paralleling the rise in the frequency of lung cancers during the past five decades is the increase in the number of respiratory carcinogens discovered during the same period and polluting the occupational and general environment of industrialized mankind (Fig. 1).

Some of these agents had previously been known for their carcinogenic action on the skin. Others, particularly some of the metals, apparently exert their specific action on the tissues of the respiratory tract exclusively. In agreement with observations made on the topographical localization of cancers in other duct systems of the body, respiratory cancers of environmental origin are preferably occupying sites where either the flow of the inhaled polluted air is interfered with, i.e., the normal narrows of the respiratory tract, such as the regions of the nasal turbinates and the larynx; or its bifurcations; or where the respiratory tract forms dead-end sacculations in which inhaled carcinogenic matter may accumulate and condense, such as the paranasal sinuses and the bronchiolar regions of the lung. The traffic pattern of the pollutants in the respiratory tract thus corresponds to the distribution pattern of respiratory cancers elicited by atmospheric carcinogens.

While the role of arsenicals in the production of cancer is well established on the basis of chronic arsenicism of occupational, dietary, and environmental origin, the role of arsenicals in the production of lung cancer is only recently established, it is of rather recent date. The exposure of arsenicals has seriously been considered as a potential general agent of cancer of the lung (Fahnestock, 1954). The role of arsenicals as an only highly suggested agent in the production of lung cancer of the lung is still a matter of controversy. However

Table 1
ENVIRONMENTAL CARCINOGENS PRODUCING CANCERS
OF THE RESPIRATORY TRACT AS WELL AS OF THE
SKIN

Carcinogens	Type of contact	Organ affected
Arsenicals	Cutaneous	Skin carcinoma
	Alimentary	(Basal-cell cancer Squamous-cell cancer)
Chromates	Respiratory	Lung carcinoma
	Respiratory	Lung carcinoma
Chrome pigments?		
Nickel carbonyl?	Respiratory	Nasal-sinus carcinoma Lung carcinoma
Asbestos?	Respiratory	Lung carcinoma
Radioactive chemicals	Cutaneous	Skin carcinoma and sarcoma
	Alimentary	Bone sarcoma
	Respiratory	Lung carcinoma
	Systemic	Leukemia and lympho-sarcoma?

in almost all cases of lung cancer for which such claims were made, there were present stigmata of chronic arsenicism in the form of arsenic dermatosis with or without skin cancers. Such associations must be considered as etiologically significant, because similar relationships exist for cancers of the lung and of the skin attributable to exposures

Table 3
LUNG-CANCER--DEATH RATE FOR SEVERAL INDUSTRIAL
GROUPS IN OHIO, SHOWING THE HIGHEST RATE FOR NON-
FERROUS METAL WORKERS

Industry	% respiratory cancer
Iron and steel	2.18
Transportation	2.91
Agriculture	0.82
Rubber and plastics	2.34
Stone, clay, glass	0.66
Nonferrous metal	3.22
Mining and quarrying	1.53
Total	1.76

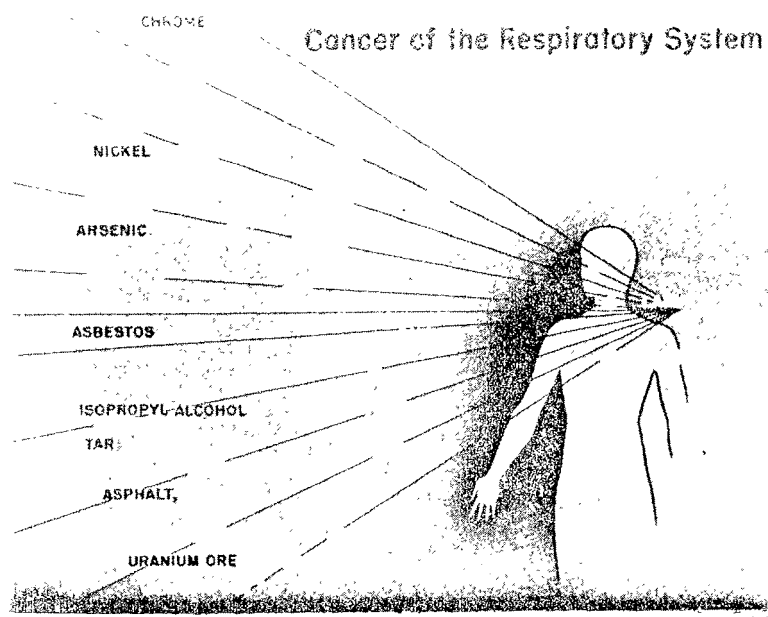


Fig. 1. The spectrum of the known and the suspected respiratory carcinogens.

to coal tar, soot, petroleum derivatives, and radioactive substances. They thus seem to reflect a common exposure pattern to environmental carcinogens, the target organ of which varies with the physicochemical status of the agent and the main route of contact with it.

The total number of arsenic lung cancers showing this symptom complex and being thus representatives of the etiological entity, "arsenic cancer" comprises eight cases

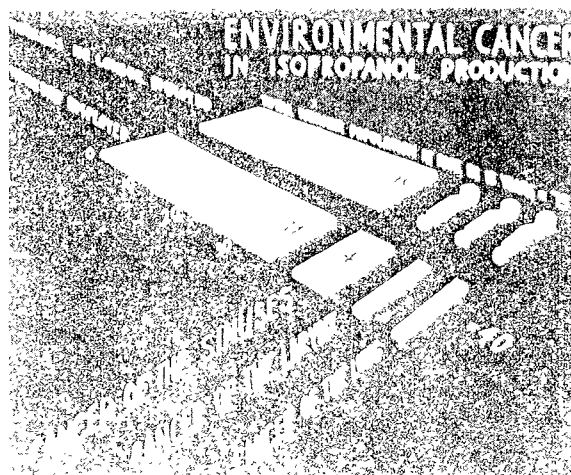


Table 2
LUNG-CANCER--MORTALITY RATES IN SEVERAL COUNTIES IN MONTANA WITH AND
WITHOUT ENVIRONMENTAL AND OCCUPATIONAL ARSENIC HAZARDS

County	Industry	No. lung cancer			Total cancer deaths	% lung cancer		Lung-cancer-death rate per 100,000	
		Male	Female	Total		Male	Female	Male	Female
Deer Lodge 13,627	Copper smelting	21	0	21	98	30.8	0.0	145.7	0.0
Silver Bow 53,207	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	3.5	46.3	12.3
Gallatin 18,269	Agriculture	1	0	1	81	3.0	0.0	5.2	

Table 6
LUNG-CANCER FREQUENCY AMONG OPERATING AND NONOPERATING RAILROAD WORKERS
SHOWING A PREPONDERANCE OF LUNG CANCER FOR THE OPERATING RAILROAD WORKERS
EXPOSED TO AN INHALATION OF COAL AND OIL SOOT

Railroad	Period	Total number lung cancer	Operating RR workers		Lung cancer Nonoperating RR workers		Undetermined RR workers	
			number	%	Number	%	Number	%
A	1940-1950	29	24	83	5	17	--	--
B	1939-1949	104	59	57	15	14	30	29

Table 4
LUNG-CANCER-DEATH RATIOS FOR COKE-OVEN AND
GAS-RETORT WORKERS

Author	Country	No. cases	Mortality rates
Kawahata	Japan	21	500
Doll	England	97	284 (gas stokers, coke- oven chargers) 202 (gas-producer men)

of which five were found among a series of twenty-four occupational arsenic cancers. This proportion of lung cancers is high considering the fact that only two pulmonary cancers

Table 5
OCCUPATIONAL GROUPS WITH AN EXCESSIVE LUNG
CANCER INCIDENCE

Occupational group	Investigator
Metal workers, welders, metal grinders and polishers, wire makers, tool and die makers, foundry workers, metal moulders, lathe workers, etc	Borst; Kennaway & Kennaway; Turner & Grace; Mueller; Dublin & Vane; Wynder & Graham; McLaughlin
Cigar manufacturers and tobacconists	Seyfarth; Borst; Kennaway & Kennaway; Enger; Versluys; Brinkmann
Engineers, mechanics, machinists, plumbers, etc.	BECC* 1944 & 1952; Gillespie; Turner & Grace; Mueller; Wynder & Graham
Painters, decorators	BECC 1944; Mueller; Dublin & Vane; Fulton; Wynder & Graham
Gas workers, road workers, ropemakers, gasworkers, stokers, cement workers, furnace workers, etc.	Kennaway & Kennaway; Fulton; BECC 1952, Registrar-General (1938), McLaughlin

* British Empire Cancer Campaign

were found among 143 medicinal arsenic cancers of the skin. In addition to this more or less conclusive evidence, there exist a number of observations of circumstantial nature, supporting the existence of arsenic cancers of the lung. Hill and Faning noted that seven cases, or 31.8 per cent of all cancers occurring among arsenical sheep-dip manufacturers, affected the lung. Snegireff, surveying cancer deaths among copper-smelter workers recorded that in one smelter six out of twelve cancer deaths involved the lung. Also Schmorl reported the occurrence of two lung cancers among arsenic smelter workers. Similar implications have epidemiological data on lung-cancer mortality in several counties in Montana (Table 2; see page 92). The annual lung-cancer death rate per 100,000 males in Deer Lodge County, where for many decades extensive smelting operations of arsenic-containing copper ores were carried out and considerable amounts of arsenical fumes were released into the atmosphere, stands at 145.7, while it is 5.2 for the neighboring agricultural Galatin County and 10.9 for white males of the United States. An arsenical background may also be responsible for the elevated lung-cancer death rate found among nonferrous metal workers in Ohio, since arsenical impurities are commonly contained in such metals, particularly copper, zinc, and tin, and may enter the plant air as fumes and dust (Table 3). The available evidence indicating the existence of arsenic cancer of the lung is thus substantial, although perhaps not entirely conclusive. A total of some 35,000 American workers are said to be employed in operations with potential arsenical health hazards. Many additional persons of the industrial and general population may have effective arsenical contacts, especially when using arsenical pesticides and herbicides or handling material with insecticide residues or living in areas where arsenicals are released into the air as industrial waste or for pest control. The potential general scope of this hazard thus may be considerable. However, the extent to which such exposures are actually effective in producing cancer of the lung or any other organ is largely undetermined.

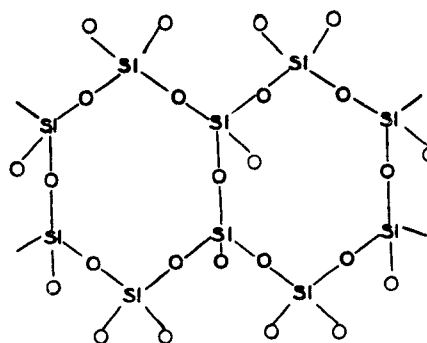
These considerations also apply to some degree to lung-cancer hazards related to an environmental or occupational inhalation of incomplete combustion products of coal, such as coal-tar fumes, pitch dust, and soot (Table 4).

Observations made among gas-retort workers and coke-oven operators show rather conclusively that individuals inhaling excessive amounts of coal-tar fumes acquire a high liability to cancer of the lung. Similar exposures exist for tar distillers, coal-tar paint manufacturers and painters, paper conduit makers, roofers, road-construction and -repair workers, blast-furnace attendants, and carbon-black manufacturers, processers, and users. The lung-cancer death rate of Japanese generator gas workers of a steel plant stood at 500 per 100,000 employees, while it is 40 per 100,000 American males age 25 or more. Canadian observations made among retort-house workers indicated that 57 per cent of all cancer cases involved the respiratory tract (six of them the lung, one the larynx, and one the ethmoid sinus). Although no corresponding data are available from United States plants, there is no sound reason for assuming that the identical exposures existing in such establishments have not identical results. There is no basis for assuming that American coal tar is not carcinogenic, because adequate evidence exists as to an excessive incidence of skin cancers among workers of several processing and consuming factories, using gas-house and coke-oven tars in this country.

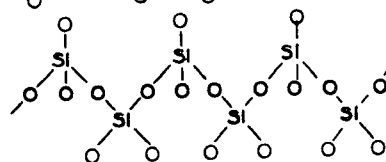
Additional support for an occupational origin of lung cancer from inhalation of coal-tar fumes and soot is furnished by the excessive incidence of these cancers found among tar workers, asphalters, paviours, stokers, patent-fuel workers, furnace men, foundry workers, rollers, and other occupational groups with similar tar and soot contacts, according to English statistics (Table 5). That a pollution of the atmosphere with soot from industrial and domestic furnaces may casually be related to the regional variations in lung-cancer incidence is suggested by the fact that the highest lung-cancer death rates in the United States are found in the densely populated and industrialized States, while the lowest rates prevail in the predominantly agricultural States. State-wide occupational cancer surveys recently conducted in several States also consistently show definitely higher lung-cancer death rates in urbanized and industrialized regions than those noted in rural areas. Similar observations were made in England and Wales, where the lung-cancer death rate in London is two and a half times that of the rural districts, as well as in Germany, where the highest lung-cancer death rates are found in the highly urbanized and densely populated areas of the Ruhr Valley, Silesia, and Berlin. The

I. ASBESTOS; FIBROUS POLYMERIZED SILICATE

CHAIN STRUCTURE -

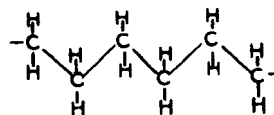


BAND STRUCTURE -

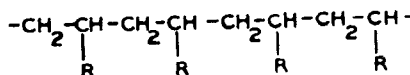


II. CARBON POLYMERS

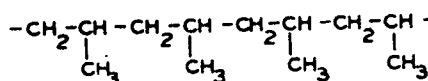
A. POLYETHYLENE — POLYTHENE
(POLYETHYLENE FILM)



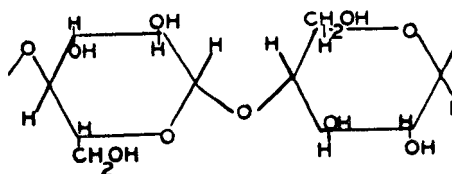
B. POLYVINYL
(POLYVINYL FILM)



C. POLYPROPYLENE
(ISOPROPYL OIL?)



D. CELLULOSE (CELLOPHANE)



**E. PHENOL-FORMAL-
DEHYDE RESIN
(BAKELITE)**

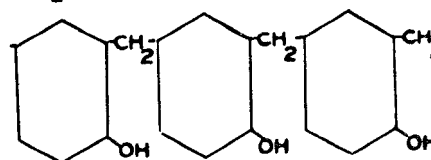


Fig. 4. Structural formulas of carcinogenic polymerized carbon and silicon compounds.

demonstration of carcinogenic hydrocarbons, particularly 3, 4-benzpyrene, in the soot of American and English cities where coal furnishes the principal fuel provides a rational basis for these regional differences in lung-cancer frequency.

That soot generated by the incomplete combustion of petroleum derivatives, such as diesel oil, lubricating oil, and industrial and domestic fuel oil, collected from the atmosphere of a large metropolitan area also contains carcinogenic hydrocarbons was reported this morning. This observation carries the similar implications as to the existence of an environmental lung-cancer hazard for the population living under such conditions. The exposure to these carcinogenic atmospheric pollutants is evidently intensified under conditions of smog. Waller in England noted a four-fold increase of the benzpyrene content of the air during smog days. The potential occupational importance of these observations is indicated by recent studies on the lung-cancer frequency among operating and nonoperating employees of two large railroads operating mainly with diesel engines (Table 6; see page 92). It was noted that 75 per cent of the lung cancers were found among the operating railroad workers; i. e., engineers, firemen, conductors, brakemen, roundhouse men, and switchmen who are exposed to the inhalation of oil soot and who represent about 25 per cent of the total number of railroad employees. The crude death rates from lung cancer for operating and nonoperating railroad workers thus show a ratio of 16:1.

There is, moreover, some evidence available indicating that the inhalation of mists of certain processed petroleum-oil fractions also conveys an increased liability to cancer of the lung. During a recent survey on the cancer incidence among employees of a large petroleum refinery, which was mainly conducted by one of our larger oil companies for ascertaining the scrotal-cancer rates among workers employed in the paraffin pressing operation, the surprising observation was made that these workers had not only a highly excessive scrotal-cancer rate (312 per 100,000 against the normal 3.15) but that this rather small group of workers of the refinery-worker complement furnished not only 40 per cent of all the cancers recorded in the entire group but also 63 per cent of the lung cancers. The paraffin pressers constituted a group of some 353 men, among a total of

population of about 2500, the rate for lung cancers in paraffin pressers is many times the normal rate. It is interesting to note in this connection that the series of eighty-six lung cancers analyzed by Mueller in 1939 for the importance of cigarette smoking contained twenty-one individuals who were occupationally exposed to petroleum oils or their combustion products. Similarly Huguenin et al. noted that eighteen of 112 lung cancer cases studied were subject to the inhalation of nebulized lubricating and cutting oils. This observation leaves no doubt that certain processed petroleum oils are carcinogenic to man upon skin contact and in a nebulized form produce lung cancers upon their intrapulmonary introduction.

Brief mention may be made in this connection of the experimental demonstration of carcinogenic properties in several high boiling fractions of American shale oils and in oils obtained by the Bergius process of direct hydrogenation of coal as well as by the Fischer-Tropsch process of secondary hydrogenation of carbon monoxide formed from coal. Since so far only the production and consumption of Bergius oils have found industrial use in this country during recent years, no data exist on the occurrence of cancers in man from such sources.

During the past decade, observations on the excessive incidence of cancers of the nasal sinuses, larynx, and lung were made among manufacturers of isopropyl alcohol produced from certain gaseous by-products of petroleum refining (Fig. 2). A total of twelve such cases have so far been recorded, seven of them involving the nasal sinuses, four the larynx, and one the lung (Fig. 3). (For Fig. 3 and Figs. 5 to 12 see pages 300 to 302 .) It was calculated that the incidence rate of cancer of the nasal sinuses and larynx for this occupational group was 134.5 per 100,000 against a normal rate of 6.3 and that the incidence of these two cancers exceeded the expected incidence 21.3 times. The causative agent is apparently a volatile constituent of the crude liquor from which the isopropyl alcohol is distilled. It seems to be an impurity contained in the liquor, such as mesitylene, isopropyl peroxide or epoxide, or polypropylenes. The presence of polymerized propylenes and of isopropyl peroxides and epoxides, which rather readily form polymers in the crude isopropanol liquor, is particularly intriguing because of the production of cancers in

in rats following the unplantation of a number of synthetic polymers, such as bakelite, cellophane, polyethylene, polyvinyl chloride, polytetrafluoroethylene, polyhexamethylenediamine adipate, and polysilicone (Fig. 4). It is, therefore, not unlikely that the cancers of the lung associated with isopropyl-alcohol manufacture and with exposures to asbestos may belong to this new class of polymer cancers elicited by carbon and silicon polymers (Fig. 5).

The occurrence of cancers of the nasal cavity, nasal sinuses, and lung among workers employed in Wales in the refining of Canadian copper-nickel matte accounted for forty-seven cancers of the nose and eighty-two cancers of the lung by 1948. According to recent reports from Norway, cancers of the lung have appeared also among the workers of a Norwegian nickel refinery (three cases), and it seems that several cases of nasal cancers have recently been seen among the workers of a similar operation located on the North American continent. While it was for many years uncertain whether nickel was the causal agent involved, the recent successful production of cancers in rats following the intrasosseous implantation of powdered nickel showed conclusively the causal role of this metal in the production of the occupational cancers of the respiratory tract in man. Occupational exposure to nickel in this country is rather extensive (Figs. 6, 7, 8). The use of nickel carbonyl as a catalyst in the production of polyacrylate plastics represents the most recent addition to the long list of occupational exposures to nickel.

In contrast to the successful production of cancers in experimental animals by nickel implants, this method to yield cancers at the site of deposition failed with chromium and chromite ore. Only suggestive results were obtained in rats and guinea pigs inhaling a fine particulate chromite ore for many months (Figs. 9, 10).

The subcutaneous and intrasosseous introduction of metallic uranium, on the other hand, was followed by the development of sarcomas in a significant number of rats (Fig. 11, 12). There is thus experimental evidence indicating that the accumulation of deposits of uranium in the body is a causal agent in the production of tumors. This observation is of importance in view of the high likelihood

of European uranium miners to develop cancer of the lung. Cancer of the lung among members of this occupational group has accounted for from 50 to 75 per cent of all deaths in Schneeberg and Joachimsthal's radioactive cobalt and uranium mines. In the Joachimsthal area alone, 180 cases of occupational lung cancer were compensated during a period of four years, 1939 to 1943, although the number of miners employed in 1929 totaled about 330. Since several thousand workers are at present employed in similar operations on the Colorado Plateau, it is necessary for physicians to know that in this particular group of miners the chief health hazard is represented by cancers of the lung and not by silicosis or some other form of pneumoconiosis.

The rapid increase of interest in and awareness of environmental and occupational cancer hazards including those relating to the respiratory system has been encouraging. While we are still in the early stages of their recognition and control, a promising beginning has been made in this direction. Of the fifteen different American industries that have shown an active interest in the study of occupational cancer hazards during the last five years, eleven were concerned with agents producing cancers of the respiratory tract (coal tar, petroleum, isopropanol, carbon black, chromate, arsenic, nickel, beryllium, uranium, asbestos, tobacco). Meetings, such as we have today, are most valuable in clarifying controversial issues, in adding to defective information, and in disseminating competent knowledge among the various parties concerned with the study and control of an increasingly important cancer hazard.

The following conclusions can be drawn from the total evidence available:

1. Our modern industrial environment contains a number of potent respiratory carcinogens of widely differing chemical nature.
2. Effective exposure to these agents exists not only for limited occupational groups, but in part also for the general population.

Table 7

LUNG CANCER MORBIDITY RATES FOR EIGHT METROPOLITAN AREAS SHOWING THE MARKED RISE IN CANCER FREQUENCY DURING THE DECADE, 1937-1947, THE CONSIDERABLE VARIATIONS IN REGIONAL LUNG-CANCER MORBIDITY, AND THE APPRECIABLE DIFFERENCES IN THE REGIONAL RATES OF PROGRESSION

City	Males		Females		Total	
	1937	1947	1937	1947	1937	1947
Atlanta	5.0	13.4	1.0	5.0	2.9	8.9
New Orleans	13.1	39.1	2.8	4.2	7.6	20.8
Dallas	5.9	29.0	0.5	6.4	3.1	17.2
Birmingham	4.5	18.9	2.1	3.9	3.3	11.0
Denver	9.1	21.9	4.2	8.1	6.6	14.8
San Francisco	15.6	34.3	3.9	8.1	9.8	20.8
Chicago	13.3	29.5	4.3	7.0	8.8	18.0
Pittsburgh	9.7	26.1	4.9	5.5	7.3	15.6

1. The lung-cancer attack rates vary in different population groups with the relative potency of the individual agents and the intensity and duration of contact with them.

2. The recent rise in lung-cancer frequency seems to be due to agents that started to enter our environment some seven or five years ago and that since then have become increasingly active, although the existing, marked variations in regional lung-cancer frequency indicate that the local effectiveness of these agents differed apparently greatly in quantitative and qualitative respects (Table 7).

3. It is most unlikely that any single factor played a generally predominant role in bringing about the startling increase in lung-cancer frequency.

4. Lung cancer is like any other type of human cancer, and is not a single entity but a collection of diseases differing etiologically and to some extent also symptomatically, showing certain resemblances in their regional distribution.

7. The proper appreciation of these facts and their relationships may help in stimulating the exploration of more etiologically specific approaches to an effective preventive, diagnostic, and therapeutic control of cancer in man.

DISCUSSION- Potential Occupational Factors in Lung
Cancer

ASBESTOS

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President, Medical College of South Carolina
Charleston, South Carolina

I trust that the appearance of this subject and a speaker to the subject will not go too far in dignifying the possible position of asbestos or asbestosis in the questions that we all have about the background of carcinoma of the lung. In the abysmal ignorance in which we reside in this important territory, however, I assume that it is justified to keep before us such questions as we may justify for further study until we learn more of the answers.

In an autopsy series that produced for special study forty-nine cases from workers in an asbestos manufacturing plant who were shown to have demonstrable deposits of asbestos in the lungs, there was associated carcinoma of the lung in four instances. Immediately, of course, it must be noted that both figures are too small for very serious statistical types of calculation; however, this gives an incidence of 8.2 per cent.

The series has been partially published heretofore and may now be brought up to date. To it may now be added nine cases of asbestosis that have been gathered since the last report in 1947. One of these nine had associated bronchogenic carcinoma. In addition, there has been one case of carcinoma of the lung confirmed by a bronchial biopsy in a clinical case of asbestosis, that is, one diagnosed clinically and showing asbestosis bodies in the sputum.

In the calculation of incidence of carcinoma of the lung, in cases of asbestosis in this series were limited to those that showed definite or advanced fibrosis of the lungs, of which there were thirty-five cases, the rate would, of course, be higher—44 per cent. The general incidence of carcinoma of the lung in the hospital autopsy series concerned was

1.5 per cent during the same period and in the same age range as the cases of asbestosis. That is the circumstance that brings this to attention: the difference between the anticipated and the actual incidence, even though the series is small.

On the basis of pathological study, these forty-nine cases showing asbestos deposits in the lungs have been divided into groups, using the degree of lung fibrosis as the main criterion of the stage of the disease. All of the lung carcinomas were in cases of at least moderate and usually of advanced fibrosis, showing the usual characteristics of the disease asbestosis.

Since the first report of the occurrence of carcinoma of the lung associated with asbestosis was made by us in 1934, a number of other reports have been published, some by compilation, I think. Dr. Smith has called attention to the British statistics reported by the Chief Medical Inspector, Dr. Merewether, but I believe that Dr. Merewether gathered together reports that had been made by others as well as his own observations. In 1947 he noted that at least thirty-one instances of carcinoma of the lung had occurred in 235 cases of asbestosis, giving an autopsy incidence there of 13.2 per cent.

Homburger reported that, in his autopsy service from 1918 to 1938, there were forty-five cases of carcinoma of the lung, an incidence of 1.08, which is similar to the general incidence in our service; there were eight cases of asbestosis encountered in that series with associated pulmonary carcinoma in four---again sufficient to call attention to itself, but again dealing in small numbers.

Stoll, Bass, and Angrist referred to a report by Wyers in 1949 recording 115 cases of asbestosis, among which there were 14.8 per cent with associated carcinoma of the lung, this being similar to Dr. Merewether's figures.

Now, obviously, none of these reports nor their sum total, as a matter of fact, can be accepted as conclusive proof that inhalation of asbestos dust or contraction of the pulmonary disease, asbestosis, predisposes to the occurrence of cancer of the lung. However, the established fact that

competent observers working in widely separated locations have encountered the two diseases in the same individuals in such a conspicuous way maintains the question as one of importance and worthy of our attention and of further investigation.

Unfortunately, the problem does not lend itself well to experimental study. As yet, no definitely analogous carcinoma of the lung has been experimentally produced by any comparable exposure. In fact, bronchogenic carcinoma in man has no reported counterpart in other animals.

Apparently the only claimed production of cancer of the lung by exposure of experimental animals to inhalation of asbestos dust, published by Nordmann and Sorge in Germany, is so subject to question that it can hardly be credited. They reported one instance of experimental occurrence of carcinoma of the lung from exposure of small animals to asbestos dust. The correctness of that observation is subject to question, while the metaplasia of epithelium, which they also attributed to the same exposure, may also be questioned as to etiology.

Our own experimental studies, now extending over several years, with the assistance of the National Cancer Institute, have not reached any concluding stage. They have not produced anything spectacular up to the present time, and, as we knew when we started out, all of us are more or less behind the eight ball in setting up an experiment that may provide an analogous situation to that from which carcinoma in man may come.

From an analysis of the problem, then, as it still stands, it appears that the available evidence on whether asbestosis may play an etiological role in the occurrence of carcinoma of the lung is not conclusive but that it does support the suspicion sufficiently to require continued investigation; at least, the available evidence does not allay that suspicion. That makes it sufficient.

In view of the importance of such a question, and assuming that suspicion warranted, perhaps it is also permissible to ask a sort of some apparently pertinent circumstances and questions. While we do have knowledge of

certain carcinogenic substances, such as have been discussed here today, having such an influence under certain more or less artificial conditions, there is actually meager evidence that such factors play any considerable part in the natural occurrence of malignant neoplastic disease in man.

In passing, it may be noted that nothing comparable to asbestos, the material asbestos, is included among the reported causes of experimental cancer. Also, while in recent times we have tended to veer away from the long-enduring belief in low-grade chronic disease of structure and function-disturbing kind as an etiological background for cancer, actually we have not produced sufficient evidence to discard the old theory.

Perhaps it may be asked why silicosis has not been discussed in comparison to asbestosis in the question of the occurrence of carcinoma of the lung. Dr. Smith referred to that, however, out of a study also made by Dr. Merewether, I think, in Great Britain, in which the incidence of carcinoma of the lung in a large series of cases of silicosis was not comparable to that in asbestosis. The only other study of which I am aware is that of Klotz who, in a similar number of autopsies in his service, found a very similar ratio of carcinoma of the lung in fifty cases of silicosis to that which we found in our cases of asbestosis. He also had in his service a very similar general incidence of carcinoma of the lung, about 1.17 per cent. That is apparently the only comparable study of silicosis except the one mentioned by Dr. Smith this morning.

However, it would not necessarily be good to draw close comparison between silicosis and asbestosis, for the materials themselves are not the same either physically or chemically, and apparently the manner in which they cause damage of the lungs is not the same. Therefore, although both of them are chronic fibrous diseases of the lung, there is not necessarily any reason why they should behave alike in reference to carcinoma of the lung.

In conclusion I wish to mention that we have encountered an additional case of bronchogenic carcinoma associated with advanced asbestosis. This will be reported in detail in another paper.

DISCUSSION FROM THE FLOOR

Chairman Pendergrass: This symposium is now open for discussion.

Dr. Martin Friedrich: I should like to call to the attention of the physicians gathered here a very interesting and valuable geographic study that was performed in 1911 by a medical student, C. E. Green. He toured practically all the cities and hamlets of England, Ireland, Scotland, Wales, parts of France, and parts of Germany and very definitely established that the incidence of cancer at that time, even with their diagnostic methods and techniques, ran about one case in seven in some towns and hamlets that were in a secluded hill or valley or on a knoll or along sharp hills; whereas, in adjoining towns two, three, or five miles away, with the people in the same types of industries, with the same types of food and other habits, the incidence ran from one case of cancer in forty-four to one in fifty-four.

He then traced the habits of these people, the methods of heating their homes, and he found that coal was the common fuel used. He noted a few exceptions, however, in valleys where the incidence of cancer was extremely low and, as with the people in Iceland, these people burned peat. Again, there was one exception---a city, town, or hamlet where the people were burning peat and yet the incidence of lung cancer was as high as in coal-burning towns. On analysis the peat in that particular site showed as high a sulfur content as in the coal used in other towns. In the peat-burning valleys where cancer was very low, the peat had a very low sulfur content.

Dr. C. Harold Steffee, National Cancer Institute: I should like to add two comments on the experimental aspects of the relationship of chromates to lung cancer. For the past two years I have been fortunate in being associated with Dr. Anna Baetjer in her project on the relationship of hexavalent chromate dust to bronchogenic carcinoma. As with asbestos, nickel, and various other metals, the project suffers from the fact that there is no regularly producible tumor of animals that can be considered analogous to human bronchogenic carcinoma. In most of the experiments a mixed chromium

material, which simulated the dust exposure of humans in the chromate-producing plants, has been employed. This contained the hexavalent and trivalent chromium compounds that occur in the production of sodium chromate from chromite. In other experiments zinc and barium chromates have been used. These materials have been administered to mice, rats, guinea pigs, and rabbits by the intratracheal, intrapleural, intravenous, or inhalation routes. Studies have also been made using the embryo-lung transplant technique in mice. In none of these experiments have we succeeded in producing bronchogenic tumors or in increasing the number of alveologenic tumors in Strain-A mice.

There is one encouraging result that should be mentioned. In all of the strain-A mice and in half of the Swiss mice given zinc chromate intratracheally, we have observed an epithelial investment of the alveolar walls that is, as nearly as I can tell, comparable to that observed by Dr. Vorwald in his beryllium-inhalation experiments in the rat. Dr. Vorwald demonstrated the beryllium lesions here this afternoon. We have not seen any tumors in the animals we have studied to date, but these chromate experiments are being repeated and extended.

Chairman Pendergrass: Is there any other discussion or question?

Voice: I am wondering whether Dr. Stewart could comment on the geographical distribution of lung cancer in the United States?

Chairman Pendergrass: Dr. Stewart, will you answer that question?

Dr. Stewart: The man that is most capable of doing that is Dr. Harold Dorn, if he is in the audience. He knows more about cancer in the United States than anybody I know.

Chairman Pendergrass: Dr. Dorn? (No response.)

Dr. Stewart: I think the main features of the difference in the distribution of cancer in the United States were brought out in Dr. Hueper's paper; that is, Atlanta is certainly a low area; New Orleans is high; San Francisco is high. I am

really not capable of commenting on the variations in other parts of the country, but there are variations.

Chairman Pendergrass: Dr. Hueper, will you elaborate on that, please?

Dr. Hueper: If we go into the agricultural states we end up with lung-cancer--mortality rates of anywhere between 35 and 45. There are two interesting exceptions. There is a high lung-cancer--mortality rate in California, which one might explain by industrialization. The outstanding state is Nevada, however. Nevada has a high lung-cancer--mortality rate and I can't think of anything that would cause that. It is an interesting state to study.

New Orleans is also an interesting region to study. I cannot think of any industry there that might be responsible for the high lung-cancer--morbidity rate of 39.1 per 100,000. I don't know why it is that way, but such communities or such regions should be very profitable to study to find something about the environmental causes of cancer in man and in the United States particularly.

Chairman Pendergrass: Do you think the Ochsner Clinic might account for it?

Dr. Hueper: No. Only residents are counted and not transients.

Dr. Nandi: I am from Burma. I have been rather interested in the incidence of cancer as shown by Dr. Stewart in the slides a little while ago. The figure of 0.2 per cent was put down for Thailand. In the Far East our pathological studies are very incomplete. The autopsies that we do and the clinical examinations show that our figures on cancer of the lung are by no means so high as you will find in the United States, Austria, and England.

Now we have to remember one thing. That is the question of tobacco. You heard earlier in the morning from Dr. Wynder that the tobacco that is smoked is smoked in a different fashion than you smoke in this country. It is not so much in the form of cigarettes but through a pipe that goes through a

pipe and whether that has got anything to do with the dilution of the tobacco smoke and has any bearing on the carcinogenic factor in the lung we do not know.

Secondly, there is the question of air pollution. Now air pollution, of course, is by no means so great as in this country. At the same time we have to remember that in our part, dust is a very, very serious problem, especially in the Middle East and probably in India and Burma.

The question of cooking was mentioned. Most of the women spend their time cooking and we can't say that our incidence of cancer is so high. At the same time I must apologize, as I said at the very beginning, that our pathological studies are so very incomplete that it would be rather difficult to draw any conclusion. I do suggest that it is a study that is worth while and I request that the American Cancer Society devise some means so that something may be obtained in that regard.

Chairman Pendergrass: I should like to ask Dr. Stewart whether the longevity of individuals living in Thailand is comparable to that in the United States. Is that an explanation for the low factor of cancer incidence?

Dr. Stewart: I think it is a factor. These figures that I presented are really not based on morbidity studies as we know them in this country, for example. They are based on a series of autopsies and surgical specimens and clinically diagnosed cases.

Now in Thailand, certainly before 1922, they had very good pathological studies. Dr. Ellis, who is Professor of Pathology at Jefferson Medical College, went over there and stayed for many, many years. The Dean of the medical school and Professor of Radiology there was a classmate of mine, and I have seen a good deal of him since that time and he is quite an up-to-date fellow. He certainly knows cancer of the lung very well.

Recently Dr. Vellios spent a year there. He was trained by Bob Moore in St. Louis, and he published his figures on cancer in Thailand in the journal CANCER in this country. It

was from that series that I extracted that figure of 0.2 per cent.

Dr. Paul Lawson is probably in the audience here and he has just come back from Thailand where he spent a year and he tells me that the old autopsy records were destroyed during the war. However, he confirms the prevailing opinion that cancer of the lung is considerably less frequent in Thailand than it is in this country and in a good many other countries.

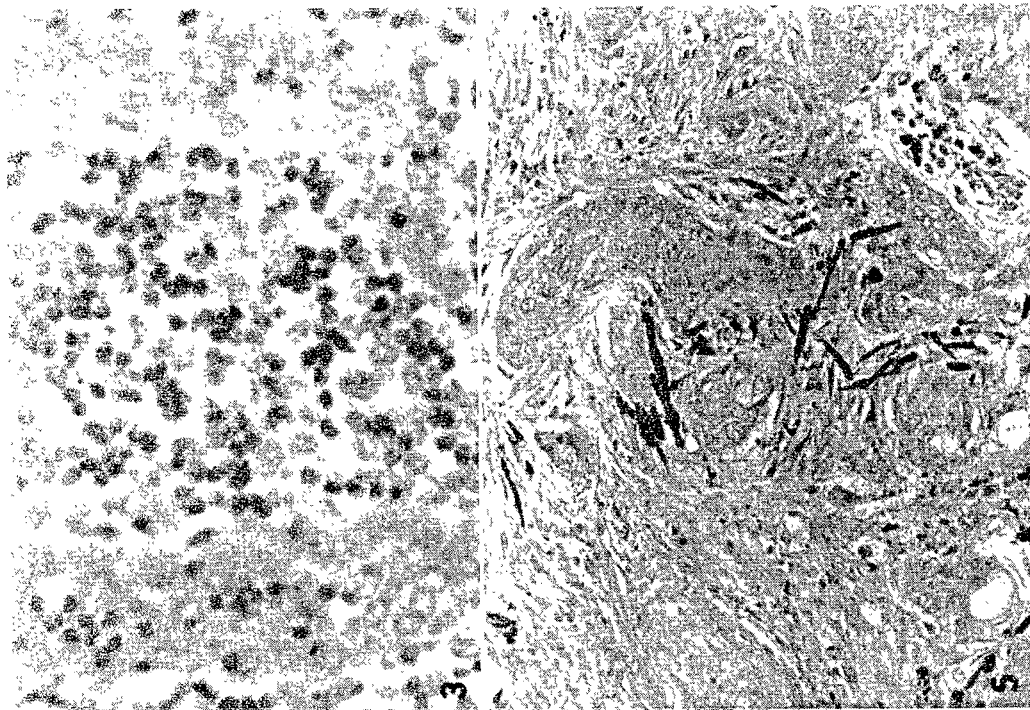


Fig. 3 An pleomorphic carcinoma of the chondrosarcoma of the sinus of an asbestosis worker

Fig. 5 Sarcoid carcinoma of the lung with asbestos bodies



Fig. 6 Epithelioid carcinoma of the lung of a rat containing clumps of metallic bodies