FILE NAME: State of the Art Literature (SAL)

DATE: 1952

DOC#: SAL054

DOCUMENT DESCRIPTION: Journal Article - Industrial Cancer of the Lungs

Presented at postgraduate course in Medical Aspects of Workmen's Compensation by New York University Post-Graduate Medical School and American Academy of Compensation Medicine, October 22-27, 1951, University Hospital, New York City.

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Industrial Cancer of the Lungs

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THE FIELD of environmental cancer continues to hold out special promise largely because, here, we are dealing with a few specific chemical and physical agents which, it has been demonstrated, can produce cancer under certain circumstances, and at specific primary sites of predilection. In view of how little is known of the etiology of cancer, in general, this cannot fail to be impressive. Unfortunately, the number of environmental carcinogens, so isolated, is very small; and little is known of the physiological and biochemical mechanisms involved. Nevertheless, the mere fact of the absorption into the body of known or suspected carcinogens, of exogenous origin, provides an usual opportunity to study those mechanisms; the processes of detoxification and conjugation, for example, or of storage and excretion. Identification, furthermore, leads to wider knowledge of environmental distribution and the precise conditions of exposure. This in turn provides hope for the development of effective control measures.

Laboratory experimentation has, thus far, brought to the fore approximately 200 chemical substances which appear to be capable of producing cancer in appropriate experimental animals. Very few of these, however, have been shown to be carcinogenic for man. Species specificity plays a prominent role in all animal research; and so, it is not surprising that findings on animals of certain species cannot be directly extrapolated to man. The osteogenic sarcomas, for example, which have been produced in rabbits by beryllium have no counterpart in humans. Mice, which have been exposed to such chlorinated hydrocarbons, as carbon tetrachloride or chloroform; or to certain of the aromatic azo-compounds; or who have been fed selenium, have developed hepatomas never observed in man. When one limits one's inquiry still further to the respiratory tract and more specifically to the lungs, as primary cancer sites, one comes up with a scant few known etiological agents. Many substances are suspect, but at the present time, data in most instances are inconclusive or highly controversial.

Whatever the cause, the incidence of lung cancer is sufficiently high, at present, to constitute a major health problem; possibly a problem in public health or more [illegible]

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COMPENSATION MEDICINE V.4

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health. Lung cancer has been increasing, especially during the last two or three decades, at a rate apparently beyond that of other cancer sites. There is no general agreement as to whether this increase is real and absolute, or merely apparent and relative: and many interpretations have been offered. But it is quite striking that this steady increase has occurred during a period characterized by remarkable technological advances in this country; a period in which increasing numbers of workers are being exposed to a greater number and variety of chemical and physical agents in the industrial environment than ever before. The fact that many of these chemical substances are present in the air of the workroom in the form of noxious dusts, gases, fumes, mists and so forth, has also been duly noted. It is natural enough, therefore, to speculate that perhaps the industrial environment plays an etiological role in this increasing incidence of lung cancer. Indeed, inhalation of air contaminants in general, including smog over cities, is receiving an unusual amount of serious attention at the present time.

Industrial Hygiene Considerations

To those of us who specialize in the field of industrial toxicology, and who are particularly concerned with the physiological and metabolic mechanisms associated with the development of the occupational diseases, industrial lung cancer presents a special challenge, as still another occupational disease. Many and diverse clinical entities are known to result from the inhalation of industrial air contaminants, under certain circumstances. Some of these occupational diseases are characterized by pathology of the upper respiratory passages: others, by lung pathology. It might be useful, therefore, to briefly examine this experience, to see what light it can shed upon the development of lung cancer in industrial workers.

Perhaps, one of the most striking observations is that the inhalation of these noxious dusts, gases and fumes from the air of the workroom does not necessarily, or even usually, result in injury to the respiratory tract. Indeed, their adverse effects upon the body are often to be found elsewhere. Lead, for example, whether inhaled as dust or fumes, reaches the alveoli of the lungs. But it does not produce lung pathology. It is carried away in the blood stream and causes lead poisoning, a systemic disease. Similarly all industrial solvents enter the body by inhalation, but insofar as we know, their toxicological effects are in areas remote from the respiratory tract. Carbon tetrachloride, for example, has a predilection for the liver and kidneys; carbon disulphide, for the central nervous system; and benzol for the hematopoetic system. Inhalation of beta napthylamine may produce cancer of the bladder, but apparently never of the lungs. Arsenic is of special interest at present in connection with studies on smoking and lung cancer. However, there is no definite evidence, as yet, that inhalation of arsenic is capable of causing lung cancer. It has always been more especially associated only with the cancer of the skin and of the eyelids.

The Pneumoconioses. This group of occupational diseases, as you well know, is characterized by the inhalation into the lungs of foreign dust particles, usually less than 5 microns in size, and the development of characteristic lung pathology. The pneumoconioses are of interest to us here because the dusts involved tend to be irritating; the lung pathology produced is of the chronic type, taking many years to develop; and a fair relationship has been established between pathology and dosage — dosage being measured in terms of the number and size of the dust particles in the air, and the duration of exposure.

Silica and asbestos are of special importance among the dusts which fall into this category. The environmental conditions for their development are essentially similar. Nevertheless, silicosis is not, apparently associated with, or productive of lung cancer, whereas asbestosis very probably is. Is there a chemical difference which accounts for the one being carcinogenic and not the other? Are differences in the physical characteristics of silica and asbestos dust, responsible? We do not know.

Acute and Chronic Irritation. Workers in industry are exposed to air contaminants in the workroom which are far more irritating to the respiratory tract than is either silica or asbestos. Those which do not reach the lungs may, nevertheless, be responsible for severe lacrimation or for varying degrees of local irritation of the nose and throat. Exposures may be continuous or intermittent; concentrations in the air may be high or low. Some air contaminants are highly irritating even in low concentrations. Others are irritating only when concentrations are extremely high. Some are sensitizing agents. In any event, it is of interest that in industry, large numbers of workers have been exposed for a great many years to a variety of chemical air contaminants which are irritants.

In *electro-plating*, for example, long-continued exposure to chromic acid mist may result in ulcerations not only of the nose, but of the skin. Perforation of the nasal septum is a typical finding. Nevertheless, even though large numbers of such workers have suffered from these conditions for a great many years, there appears to be no evidence at present that such lesions ultimately develop into cancer of the nose or cancer of the lungs.

When one goes on to an examination of industrial lung pathology caused by exposure to other highly irritating substances such as *chlorine gas* or *nitrous fumes*, one finds the same apparent lack of any carcinogenic mechanism at work. Continual (or intermittent) exposures to varying concentrations for long periods of time, have caused such conditions as chronic bronchiolitis, alveolitis and bronchitis. Single intense exposures have produced acute bronchitis, pneumonia or even édema of the lungs. But repeated acute and chronic exposures over many years do not seem to have resulted in the development of lung cancer, insofar as we know.

Industrial dusts and gases — such as *flour* or *formaldehyde* — which act as sensitizing agents tend to cause asthma in allergic individuals. Repeated asthmatic attacks, in turn, produce secondary chronic respiratory conditions such as chronic bronchitis, emphysema or bronchiectasis. But again, no relationship has, thus far, been demonstrated between lung cancer and any of these chronic conditions whether of industrial origin or not.

The inhalation of non-toxic dusts, such as *sugar dust or spices* may be highly irritating to the nose and throat because of their chemical reaction with mucous secretions. Even a physiologically "inert" dust, so-called, such as *wood dust*, when continually deposited on the mucous membranes of the nose and throat, tends to cause mechanical interference with ciliary action, and in other ways impairs normal physiological functioning of the upper respiratory tract. And yet, there is no evidence, at present, to indicate that such prolonged exposure is associated with primary respiratory cancer.

The data now available are obviously too limited to warrant any final judgment. However, it would seem that respiratory cancer is not *necessarily*, at any rate, associated with chronic irritation of the respiratory tract resulting from the inhalation of air contaminants in industry.

Synergistic Action of Chemicals and Drugs — Both in industrial toxicology and in medical therapeutics, one encounters the familiar phenomenon of synergism. Exposure to a single substance, in amounts which are completely innocuous, may become toxic when this is combined with a dose of another toxic substance which, would have been equally safe, if given alone. This principle has been well established both for experimental animals and for man, as you well know.

And yet, as a practical matter, it is all too often overlooked that workers in the course of a long life, are exposed to multiple physical and chemical agents in their environments both in and out of industry. The principle of synergism is operative here as elsewhere — however frustrating this may be to the research workers in the field of occupational caner.

Differences in Susceptibility Differences in individual susceptibility to disease pervades all of clinical medicine. It is a familiar phenomenon in the occupational diseases and in environmental cancer. Among persons doing essentially the same work, some, apparently, get lead poisoning or develop cancer while their co-workers do not.

Age and sex differentials are not well understood, in general. But in the field of lung cancer, there are indications that there may be significant shifts both in age and sex incidence when exogenous carcinogens are responsible. Thus, while the incidence of lung cancer is higher for men than for women, in the general population, this relative sex incidence may apparently be significantly altered in situations where women have the same occupational exposures as the men. Similarly, the incidence of occupational lung cancer appears to affect a somewhat younger age group than that characteristic for the population as a whole.

Safe Dosage and Prevention Since toxicity is, in general, a function of dosage — where dosage is measured in terms of intensity and duration of exposure — the occupational diseases are amenable to control by well established industrial hygiene techniques. For that reason, it has been useful to develop safe standards [illegible] potentially toxic substances in industry. These are know as Maximum Allowable Concentrations (M.A.C.). While allergy, synergism and some other matters, which we need not go into here, present complications, these standards have proved invaluable for the prevention of occupational diseases. They are constantly being improved and extended as new scientific data become available.

It is unfortunate, therefore, that equally convenient and simple relationships between dosage, toxicity and carcinogenicity do not seem to exist in the field of environmental cancer. It is not helpful to know that a chemical substance is toxic because this does not apparently indicate anything as to its carcinogenicity and vice versa. Lead has already been cited as a toxic chemical which is not carcinogenic. Beta napthylamine, conversely, is carcogenic but has never been known to produce systemic poisoning. And so, the maintenance in a factory workroom of Maximum Allowable Concentrations will not necessarily insure safe working conditions, if a potential carcinogen happens to be present.

It has recently been suggested that there *is* a critical dose for each carcinogen of exogenous origin; and that cancer will ultimately develop once this dose has been reached, whether as a result of a single exposure or cumulative absorption over a period of time. But even could such dosage be accurately determined one would still, for purposes of prevention, face the formidable problems created by the fact that cancer may take a great many years to develop; that it may also develop after a relatively short exposure; and that there may be a lag of years between the pertinent exposure and the development of the cancer.

Known And Suspected Carcinogens

Let us, now, turn to a consideration of specific factors in the industrial environment which are known to produce lung cancer, or which are suspect and under investigation.

1) *Organic Chemicals*

Among the organic chemicals, none, thus far, has been definitely shown to be capable of producing lung cancer. Many are still under investigation, but the data now available are inconclusive and contradictory.

The products of incomplete combustion of coal have been studied, as well as its various distillation and fractionation products. These studies have included such substances as tar, asphalt, pitch, oil, lamp blacks, carbon blacks and various types of soot. Thus far, the results in all cases have been either negative or inconclusive insofar as cancer of the respiratory tract is concerned.

Soot has always been of special interest because it was responsible for the classical scrotal cancer of chimney sweeps. These boys must have inhaled considerable soot in the course of their work; and yet, no suggestion has come to us to the effect that they also developed lung cancer. Perhaps the diagnostic techniques of those days were too inadequate. For that reason, special interest attaches to a statistical study made by Dr. Dorn of the relation of lung cancer to atmospheric soot from domestic and industrial sources. In this study he found the incidence to be *low* in Pittsburgh as compared with five other large cities.

Commercial soots prepared from natural gas and oil residues are also under investigation. The carbon black industry is now supporting experimental research in this field and further data of interest may be forthcoming in the near future.

Exhaust gases from diesel and gasoline engines have very naturally come under suspicion. But here again, investigations as to the incidence of lung cancer among persons heavily exposed, such as policemen, street cleaners, garage mechanics and automobile drivers, have all been negative.

Crude mineral oil and tar are still in the doubtful category. Inhalation of aerosols of processed mineral oil and shale oil; fumes from creosote and anthracene oil (3, 4 benzpyrenes) and particularly crude paraffin oils or the heavier fuel oils are all under suspicion at present. They are being investigated, but no conclusive data are available thus far. Special attention is being given to tar fumes in tobacco smoke. Isopropyl oil, inhaled as a vapor, in connection with the manufacture of isopropyl alcohol, is the only chemical in the aliphatic group that is suspect as a cause of lung cancer.

2) *Inorganic Chemicals*

Asbestos. The relation of asbestos to lung cancer, long suspected, has received new confirmation from the 1949 Annual Report of the Chief Medical Inspector of Factories in England. During the period from 1924 to 1946 inclusive, 235 deaths were reported either caused by asbestosis or in which asbestosis had been established at necropsy. Cancer of the lungs or pleura was found in 31 of these cases or 13.2 per cent. This is very high compared with a general incidence of 1 per cent for cancer of the lungs among all adults examined at necropsy in England. Moreover, the sex distribution seemed also to suggest the presence of an occupational carcinogen. The histologic character of the cancers — squamous cell, instead of adeno-carcinoma — and their histogenetic derivation, in that the bronchial mucosa was involved rather than the alveolar epithelium, was interpreted to indicate the presence of a specific exogenous carcinogenic agent as the etiological factor: in this instance, inhalation of asbestos dust.

The development of cancer of the lungs is believed to be more directly related to asbestosis, the disease, than to the inhalation of asbestos dust per se. Differential diagnosis by X-ray between asbestosis and lung cancer presents all of the difficulties one would anticipate. It has been suggested that cytological examination of the bronchial secretions might well be included in periodic examinations of workers exposed to asbestos dust, whenever clinical or X-ray evidence suggests the possibility of a precancerous lesion. Careful histological studies of lung tissue, postmortem, in all such cases would also provide valuable data.

It has been estimated that 20,000 workers are now employed in asbestos-producing industries in this country and Canada.

Nickel Carbonyl—Exposure to nickel carbonyl in the nickel works in England has also been the subject of special investigation and report by the Chief Medical Inspector of Factories. In a review of the incidence of nose and lung cancer between the years 1923 and 1948, inclusive, he found 47 cases of cancer of the nose, and 82 cases of cancer of the lungs among these workers. The average duration of exposure before the development of cancer was 23 years for the nose cases, and 25 years for the lung cases. The average length of time between diagnosis and death was short: and by the end of 1948, 46 of the nasal and 72 of the lung cases had died. The precise causative agent has not yet been identified and the matter continues to be under active investigation. However, there is no comparable experience in this country.

The Chromates The etiological role of the chromates in the production of lung cancer has been pretty well established in this country in the last few years: and these findings have confirmed previous European experience.

In 1948, at the request of the chromium-producing industry, Drs. Machle and Gregorius made a study of deaths from cancer of the respiratory tract from 1937-1947, in five chromium-producing plants. Dr. Mancuso, the year following, examined the records of all employees who had worked one year or more between 1931 and 1949 in a chromate-producing plant in Ohio. Dr. Baetjer then reviewed all of the European and American experience, and reported on a study of her own in which she analyzed the records of two hospitals in Baltimore located near a chromate-producing plant. In each of these studies the incidence of lung cancer among the chrome workers was significantly high.

A total of 112 case reports, were thus collected, of cancer of the respiratory tract among workers exposed to chrome. Of these, 100 worked in the chromate-producing industries; 11 in the manufacture of chrome pigments; 2 in other industries. Sixty-three of the cases occurred in Germany, 57 in the United States, and 1 each in Switzerland and England. The chemical substances believed to be responsible are the hexavalent chromium compounds, particularly Na and K monochromate or dichromate; and zinc chromate, inhaled as dusts.

While the mechanisms are not known, certain observations were made which are of interest:

1) Most cases were found to be primary bronchiogenic carcinomas. In a few instances, the upper respiratory tract or the oral region were involved. The incidence of cancer in other tissues was not high.

2) In some cases, an exposure of four years appeared to be sufficient. In most cases, however, a great many years of exposure were necessary. In some instances there was a latent period of variable duration between leaving the exposure and the development of the cancer.

3) The intensity of exposure could not be evaluated in these cases. Presumably, however, in years gone by, this type of work was very dusty.

4) Lung cancer in these workers showed a somewhat younger age distribution than that for nonoccupational lung cancer.

5) There was no indication that persons exposed to chromates in other occupations were more than normally liable to cancer of the respiratory tract.

In New York State there is exposure to chrome and its compounds in a variety of industries: In the mining and extraction of chrome ore, which is ferrous chromite; in the manufacture of chrome pigments, including zinc and lead chromates; in chrome-plating operations, where there is exposure to chromic acid and chromic acid mist; in the leather industry where chromium sulphate and sodium bichromate are used in tanning. Photo-engravers are exposed to ammonium bichromate and also to asphalt. Since both of these substances are under suspicion, the Division of Industrial Hygiene decided to make a special study of these workers.

In photo-engraving, the copper plates are coated with a thin light-sensitive film of gelatin and ammonium bichromate, and the plate is then exposed to light behind a negative. The penetration of light through the transparent areas of the negative, causes the formation of a water-insoluable chromium-gelatin film, which is resistant to acid. The parts not exposed to light remain soluble and are washed off. Prior to etching all large surfaces, which are gelatin-free and which would ordinarily have to be eaten away, are coated with an asphalt paint, which is resistant to acid. After the plates have been etched in a ferric chloride solution, these areas are reamed out with the aid of rotary electric cutting tools.

An unselected series of 681 photo-engravers were X-rayed in cooperation with the chest clinic of the New York City Department of Health. No pulmonary neoplasms were found. The matter is still under investigation.

3. *Radiation*

Exposure to radiation is on the increase not only in industry but in hospitals and research laboratories everywhere. Radium dial painting is booming again as a result of industrial expansion for defense. The examination of metal castings for flaws by the use of radium and X-ray has become routine in foundry operations. Radioactive cobalt is being used increasingly for this purpose at present. The fluoroscope has not only made its way into retail shoe stores, but is used in many industries as an examing device for the detection of misplaced nails in shoe manufacture; for examination of metal inserts in plastics; for the detection of foreign bodies in packaged foods, and so on. Radioactive static eliminators are utilized to prevent fires in dozens of industries and operations. These include publishing houses, plastic fabric manufacture, teletype machine installations, etc. Radioactive isotopes are stepping out of the expert hands of technical personnel, in research laboratories, and are now finding their way into the hands of lay workers, not at all familiar with the potential hazards to health which are involved; nor with the precautionary measures which are essential for safety.

Wherever there is radioactive dust in the workroom air — however invisible to the naked eye one is presented with a known etiological agent in the production of lung cancer. There is, as yet, very little information as to what constitutes a "safe" dust count; or how much radioactive dust one might, in general, anticipate in specific operations. Too few dust counts have, as yet, been made to provide this basic experience. However, standards for radon gas in the air of the workroom, emanating from radioactive materials present there, have been established; also for radon in the expired air of individual workers. Taking of the air samples is not too difficult. But these samples must be sent to highly specialized radiation laboratories for analysis, and this is fairly expensive.

In such plants there is usually simultaneous exposure to various types of external radiation. This type of exposure will not produce lung cancer; but adequate lead shielding and other control measures are nevertheless essential for the prevention of cancer elsewhere in the body.

Research

It is quite apparent that industrial lung cancer; indeed, the whole field of environmental cancer has been barely scratched, and that there is still a great deal of pure speculation current, despite all efforts to establish the facts.

The difficulties which are hindering progress are not immediately apparent, but become quite clear as soon as intensive work is begun. Most important, perhaps, is the fact that a worker's occupation at the time he develops cancer, or dies of it, is rarely the etiological factor. The cause may be found in some previous occupation which he had some 10, 15 or 25 years earlier — an occupation difficult to ascertain at the time of his present illness or death, and difficult to evaluate. For, any investigation, at this later date, will usually reveal environmental conditions very different from those to which he had been exposed, so many years before. The further fact that rapid technological advances are the order of the day in industry; and that labor, in this country, is highly mobile, presents many serious stumbling blocks to the research worker, at every turn.

The New York State Occupational Cancer Committee tried to overcome these obstacles by interviewing some 4,000 cancer patients at the Roswell Park Memorial Hospital where accurate clinical and pathological diagnoses were available. In these interviews, a serious attempt was made to obtain a detailed occupational history, going back to the patient's first job. Each such occupation was then evaluated, by specialists in the field of industrial hygiene, in order to ascertain, as accurately and as completely as possible, *all* of the environmental factors to which *each* patient had been exposed in the course of his working life. Since each patient was found to have had about 4 or 5 different jobs, on an average; and numerous abnormal elements were involved in the working environment of each job, the number of variables which were inevitably introduced into the study was such as to make our statisticians shudder. And yet, these variables are inherent in any effort to get at the facts and they cannot be ignored.

There are a few industries, such as chromate manufacture, for example, or the manufacture of aniline dyes, where one or more active carcinogenic agents so dominate the industrial environment as to highlight the fact of the high incidence of cancer among those workers. It is not sufficiently appreciated, however, that this probably represents one of the more exceptional situations in industry. By and large, the environmental characteristics of a particular industry, a particular process or even a particular workroom are not necessarily, or even usually, pathognomonic for that industry, process or workroom. Many of the same abnormal environmental factors, in different combinations, are to be found in a great variety of totally unrelated industries and occupations. For that reason, statistical correlations between a given primary cancer site and specific industries or occupations are not necessarily fruitful. Until some practical method has been developed for the identification and isolation of these common denominators in the industrial environment and statistical correlations prepared on the basis of these data, there is good reason to believe that the etiological components of this environment will largely continue to elude the research worker.

There is, however, one practical contribution which can be made by almost every practicing physician whether in his office, in the outpatient department or in the hospital; and that is to take a careful occupational history on *all* patients whether they are suspected of having cancer or not and to record successive occupations on subsequent visits. More than that, social welfare services can contribute by providing for a good occupational history on all Forms to be filled out by applicants. This would include applications for Workmen's Compensation, Unemployment Insurance, Placement, Sickness Insurance, and any other type of social security. Labor Unions' sickness records could similarly include this type of information. Aside from the fact that social security numbers on death certificates are now beginning to make it possible to go back and learn something of the cancer patient's previous work, records along the lines above indicated are nowheres to be found at the present time. If conscientiously compiled from now on, however, a vast source of information would become available during the next 15 or 20 years, as to the occupational exposures of persons who ultimately develop cancer. Whether this vision of future benefits is sufficiently inspiring to overcome natural resistance to undertaking additional work, in the present, is the big question mark.

The great value and limitations of research work with experimental laboratory animals, as a method of developing leads for the detection of carcinogenic agents in the industrial environment, are too well known to this audience to warrant more than passing mention.

Summary and Conclusions

There has been striking increase in the incidence of lung cancer; and because this has largely coincided with advances in technological progress in this country, there is a very natural suspicion as to cause and effect. Of the many organic and inorganic chemical and physical agents which are suspect, and under investigation at the present time, only a few have been [illegible] cated as causative agents in the production of industrial lung cancer: The chromates, nickel carbonyl in English nickel factories, radioactive substances, and probably asbestos.

An effort was made to evaluate the role of both chronic and acute irritation, in the production of industrial lung cancer, by reviewing what is known of some of the more familiar occupational diseases which are characterized by chronic and acute pathology of the upper respiratory passages and the lungs. No necessary relationship could be demonstrated. However, a final determination must await the development of far more precise and complete data than are now at hand.

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