222

PLAINTIFF'S
EXHIBIT
SA-98

VOLUME 2 [illegible] NUMBER [illegible]

Occupational Medicine

JULY 1946

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, [illegible] NORTH [illegible] DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION [illegible]

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EXHIBIT
SA98

SIGNIFICANCE OF INDUSTRIAL CANCER IN THE PROBLEM OF CANCER

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THE study of occupational cancer is of eminent significance for the control of human cancer in general. As occupational cancers result from exposure to certain more or less well defined exogenous agents, they represent chance experiments on cancer in man conducted by modern industry on a large scale and thus are human equivalents of experimental cancers in animals.[1] In view of the known differences existing in the susceptibility and reactivity of various species to the numerous recognized physical and chemical cancerigenic agents, industrial cancers possess the great advantage over experimental cancers in animals that they permit the direct study of many of the most important and fundamental aspects of cancer in the human organism, such as the action mechanism of the different physical and chemical carcinogens, the character of the local and systemic reactions associated with the process of cancerization (shifts in the mineral, lipid and vitamin contents of the cells acted on, qualitative and quantitative disturbances in the enzyme and vitamin activity, endocrine function, steroid metabolism, chemoimmunity reactions and metabolization and detoxication of the carcinogenic agents), influence of age, sex and race, hereditary factors, diet, role of periods of exposure and latency and of procancerous and anticancerous mechanisms and the factors responsible for multiplicity of cancers and systemic cancerization.

It is obvious from these considerations that a thorough, extensive and continued investigation of occupational cancers through a study of man exposed to known occupational cancerigenic agents or affected by industrial cancer would be of utmost benefit for a better understanding of the conditions which may cause cancer in man and of the measures which may prevent such developments.

There is a second important reason calling for an appreciably increased interest in the problem of occupational cancer in connection

From the Warner Institute for Therapeutic Research.

1. Hueper, W. C.: Occupational Tumors and Allied Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1942; Cancer in Its Relation to Occupation and Environment, Bull. Am. Soc. Control Cancer 25:6, 1943; Industrial Management and Occupational Cancer, J. A. M. A. 131:738 (June 29) 1946.

with the general problem of cancer. The rapid and enormous growth of modern industry and its vast diversification during the last five decades has been accompanied by a considerable rise in the absolute number and by the appearance of many new types of industrial cancers. This development reflects an important biologic maladjustment of civilized man to his new artificial industrial environment and represents a striking illustration of the momentous role which exogenous environmental agents apparently play in the causation of cancer in general.

Experimental and clinical evidence obtained during the last few years makes it likely that new industrial carcinogenic agents and heretofore unknown types of occupational cancers will be discovered in the next few years in American industries. This development is foreshadowed by recent observations indicating that certain types of industrial cancers which in the past were observed exclusively in European plants have made their appearance in American factories. Moreover, American investigators produced cancer in animals during the last few years by the exposure to carbon tetrachloride, ethyl carbamate, diethylene glycol, beryllium and ergot, i. e., substances extensively used in industry and/or for medicinal purposes.

It seems to be fair to compare present knowledge as to the causation of cancer in man with that available on the causation of infectious disease during the days of Pasteur and Koch. There exist good reasons for assuming that the majority of occupational carcinogenic agents are still unknown and that this applies especially to those occupational carcinogens which have a low potency and which therefore produce a low incidence of cancer not appreciably differing from that seen for the various types of cryptogenetic cancers among the general population.

When these facts and their implications are properly and fully appreciated, occupational cancers are bound to become a public health problem of the first order, which deserves to be seriously and extensively investigated.

I. OCCUPATIONAL CANCER AND CANCER RESEARCH

A. Carcinogenic Agents.—It may be appropriate to recall here that modern cancer research dealing with physical and chemical carcinogens started some thirty years ago as an outgrowth of the study of the causative agents and conditions involved in the production of occupational cancers. Although great strides in knowledge of exogenous carcinogenic agents and their effects on the animal organism have been made since that time, the constantly growing number and diversity of types of occupational carcinogenic agents have raised many new and often still unsolved problems. The existence of wide differences in the physical and chemical properties of the various established or suspected carcinogens suggests that these agents do not exert their specific pathogenic action through the same mechanism. From an analysis of the data at present available on this matter and from theoretic considerations it appears that exogenous carcinogenic factors may elicit malignant growths through one of the following three mechanisms.

In the first group those occupational carcinogens may be found which apparently cause a cancerous cellular transformation by acting directly either in their original form or as metabolites or conjugates on the cellular substrate. The carcinogenic substances contained in tar, pitch, asphalt, soot, mineral oil and related substances, and those represented by certain aromatic amines (betanaphthylamine, benzidine, aniline) perhaps belong to this group of primary carcinogens.

The second group of exogenous carcinogens consists of agents which do not possess any direct carcinogenic properties but which exert such action by changing some normal chemical constituent of the cells or tissue fluids in such a way that it becomes endowed with carcinogenic properties. In view of the long latency period of actinic cancers, excluding the possibility of a direct electronic chromosomal mutation, it seems probable that this mechanism may be active in the development of cancers caused by radiating energy. An indirect or secondary mechanism of cancerization may also be responsible for the occupational cancers observed in workers employed in chromate plants, nickel refineries, asbestos factories and arsenic operations.

In a third group those exogenous agents are included which have neither primary nor secondary blastogenic properties, but which elicit functional disturbances in certain organs, such as the liver, adrenal glands, pituitary gland and the gonads. The quantitative and/or qualitative functional abnormalities thus produced may lead in turn to the development of endogenous substances or metabolites possessing carcinogenic qualities. The possibility of such a mechanism has not been extensively explored and is mainly speculative, but certain aromatic azodyes may belong to this group of exogenous carcinogens.

It is obvious that adequate information on the sources and types of carcinogenesis not only is essential for determining the scope and effecting the control of environmental cancer and, especially, its occupational variety, but also may bring about a closer connection between the carcinogenesis by the action of exogenous substances with that apparently ensuing from endogenous factors.

B. Sex.—The observations made in occupational cancer in man and its experimental equivalents in animals show unmistakably that any differences in the sex distribution of such tumors are not sex conditioned but are the results of variations in exposure. The great predominance of males among persons affected by occupational cancers is mainly attributable to the fact that industry has employed, until relatively recently, men almost exclusively in such hazardous operations. Only during periods of abnormal strain in the available manpower have women been used on a larger scale in operations involving exposure to carcinogenic agents, such as aromatic amines, tar, pitch, mineral oil, and related substances. The temporary nature of such an employment in addition to the lack of subsequent medical supervision of these women mainly accounts for the fact that in most instances of occupational cancer little information is available as to the incidence and occurrence of such neoplasms in the female sex.

Wherever, on the other hand, occupational carcinogenic agents acted on members of both sexes cancers appeared in both, males and females, according to their relative number exposed and to the degree of exposure sustained. Thus cancer of the skin due to roentgen rays has been seen in men and women. Inversely, operations with carcinogenic hazards in which mainly female workers were present exhibited a prevalence of occupational cancer among women. The occurrence of cancers of the bone among girls working in luminous dial plants exemplified this relation.

These observations on the sex distribution of occupational cancers suggest that environmental factors may play an important role in the causation of the numerous cryptogenetic cancers affecting certain organs (lungs, larynx, gastrointestinal tract and skin) which have extensive contact with exogenous agents, because these cancers occur much more frequently in males than in females.

C. Age and Life Span.—The claim has been repeatedly advanced that an age factor represented by the relative age or the average life span of a particular species has a significant part in determining the degree of susceptibility to carcinogenic agents and the relative speed of tissue cancerization as expressed by the latent period. Clinical and experimental evidence obtained on exogenous occupational and experimental cancers, however, does not lend support to this contention. It is the age at onset together with duration and intensity of exposure which controls the manifestation age of occupational cancers. Depending on these factors industrial cancers have been observed in persons between the ages of 10 and 80 years.

Although the dogma of the parallelism between the biologic dynamics between senescence and cancerization receives some support when comparisons on these points are made between man and mouse, it loses most of its validity when applied to other species and different types of exogenous cancers.

Ultraviolet ray cancer of the skin, for instance, can be elicited without difficulties in mice and in rats, but not in rabbits; cutaneous cancer develops readily in mice after the application of a benzolic solution of methylcholanthrene, but not in rats: the skin of rats and monkeys does not respond with any appreciable speed or permanence to the carcinogenic action of tar, although the skin of mice reacts rapidly, consistently and persistently to this agent with the development of cancer. Thus, regardless of the relative length of their average life spans, certain species are either completely refractory or abnormally resistant to carcinogenic agents which elicit easily in mice carcinogenic responses under equal conditions of exposure.

Observations on occupational cancers in man show, moreover, that in some persons only comparatively short exposure time (six to twelve months) are necessary for eliciting the development of aniline cancers of the bladder or chromate cancer of the lungs. If the aforementioned dogma of the biologic dynamics of cancer genesis in relation to speed of senescence is applied to such cases one is forced to assume that some men apparently possess organs which age in an extraordinarily short time, while others with exposure times of twenty to thirty years undergo senescent changes in slow motion.

Inasmuch as it has been established that different species metabolize carcinogenic agents by different methods into different metabolites, it appears to be more plausible that the observed discrepancies in the speed of tissue cancerization in various species are related to their different special metabolic activities and not to their senescent dynamics as expressed in average spans of life.

It may be noted in this connection that the observation of species-specific differences in the susceptibility to various physical and chemical carcinogens may make it necessary to qualify in the future the term "carcinogen" by adding the species which reacts or react with the development of cancer to a certain "carcinogenic" agent. The importance of this consideration for the testing of occupational carcinogens in animals is obvious.

D. Heredity.—Although it is possible that hereditary factors may determine in part the length of the period of latency and of the time of exposure necessary for eliciting an occupational cancer in the individual case, there is no concrete evidence that a genetic predisposition plays any important role in the incidence of these tumors. The intensity and type of exposure and the potency of the carcinogenic agent involved appear to be the main factors in this respect. Whenever these conditions are favorable to the development of a cancer, there is found an early occurrence, a high incidence and a marked multiplicity of occupational cancers. Thus, aniline cancers of the bladder appear in 30 to 90 per cent of the massively exposed workers. Cancer of the lungs kills 80 per cent of the Schneeberg miners and between 40 and 50 per cent of the Joachimsthal miners exposed to radioactive material. Cancer of the same organ, on the other hand, is found in only 4 per cent of the dead and living chromate workers and in 12 per cent of the asbestos workers who came to autopsy.

Attempts have been made to attribute the high incidence of pulmonary cancer among the Schneeberg miners to a familial hereditary predisposition prevalent among the population of this region. This purely speculative concept has no factual basis and apparently was developed without any reliable knowledge of the actual conditions in Schneeberg concerning the incidence of marriages among close relatives. If an analogy with the genetic background of certain mouse strains showing a comparable incidence of mammary cancer is permissible, one would have to assume that the people of Schneeberg must have propagated by incest for the last three hundred to five hundred years. Such a proposition, however, is obviously outside the realm of science or good sense.

E. Procancerous and Anticancerous Mechanisms.—Recent observations made on occupational and experimental cancers have demonstrated the existence of factors which may enhance or impede the development and growth of cancers. However, a sharp distinction must be made between those agents which act in conjunction with a carcinogen and thus during the process of cancerization and those which influence the growth activities of an established cancer for which the continued action of a carcinogen is unessential. The last-mentioned factors are called procarcinotic when they favor the proliferation and spread of cancer cells and anticarcinotic when they have an antagonistic effect in this respect. Factors of the first group are cocarcinogens when they represent an integral part of a carcinogenic complex, procarcinogens when they aid in the initiation of the transformation of normal into malignant cells and anticarcinogens when they interfere with this process.

A constitutional anticarcinogenic factor is, for instance, responsible for the much higher resistance of the skin of members of the colored races to the carcinogenic action of solar rays than that seen in members of the white race and, particularly, those with light complexion, blue or gray eyes and blond or red hair. Similarly, colored persons are much less susceptible to carcinogenic tar, pitch and mineral oil than are white persons. It is likely that the higher degree of pigmentation of the skin in the colored races and the greater natural oiliness of the skin of Negroes account for these differences.

The assertion was recently made that pneumonoconiosis acts as a cocarcinogen to other factors, such as radiating energy or arsenic, in the development of cancer of the lungs in Schneeberg miners. Inasmuch as nonspecific pneumonoconiosis does not exhibit any demonstrable causal relation to cancer of the lungs and is not essential to pulmonary action of other carcinogens (chromates, nickel carbonyl, tar and arsenic) the alleged cocarcinogenic role of pneumonoconiosis in the cancer of the Schneeberg miners appears to be highly uncertain.

It is interesting to note that the role of all these factors is evidently not a fixed one, but varies with the circumstances. For instance, hyperkeratosis may play in rats a procarcinogenic part in the initiation of cutaneous cancer caused by methylcholanthrene, while it assumes an anticarcinogenic role in the development of cancer of the skin caused by ultraviolet rays. Roentgen rays, rays from radioactive substances and benzene and arsenic are well established carcinogens when acting in small doses over long periods of time, while they are powerful anticarcinotic agents when employed therapeutically in large doses given within a relatively short period.

F. Multiplicity of Cancers.—A multicentric development of cancer is frequent with occupational carcinogenesis. While primary multiplicity of cryptogenetic cancers has been recorded in 0.5 to 3 per cent, this phenomenon has been observed in 15 to 30 per cent of industrial carcinomas (arsenic cancer of the skin, 15 per cent; tar cancer of the skin, 20 per cent; paraffin and oil cancer of the skin, 15 per cent; aniline cancer of the bladder, 25 per cent; roentgen cancer of the skin, 30 per cent). Systemic multiplicity of occupational cancers has been noted in several cases of aniline cancer, in which the bladder and/or the ureters and kidneys were the sites of primary cancers. Exposure to aromatic amines, arsenic, tar and paraffin oil and radioactive substances has been associated in a few instances with hetero-organic multiplicity of cancers, affecting simultaneously or successively organs of different systems, such as the skin, the lungs, the stomach, the bladder, and the kidneys. The excessive frequency of primary multiplicity of occupational cancers is evidently an expression of a relatively powerful carcinogenic stimulation.

The occurrence of hetero-organic multiplicity is of particular interest, as it throws some light on the so-called tissue specificity of certain exogenous carcinogenic agents. It seems to be a general principle that cancerous growths ensue most readily at those sites where the carcinogenic agent is present in an optimal concentration and for the most prolonged period. The site, intensity and length of exposure, the speed of absorption of the carcinogenic agent from the site of primary contact and the organs of deposition, of metabolic conversion and of excretion, in addition to the character of the metabolites formed, represent the factors which determine mainly the location of the carcinogenic responses to a given carcinogenic agent.

These selected illustrations of the more important scientific aspects of occupational cancers may suffice in demonstrating the eminent significance which these tumors have in connection with the general problem of cancer.

II. OCCUPATIONAL CANCERS AS A PUBLIC HEALTH PROBLEM

It is only in rather recent years that industry and public and industrial health organizations have become aware, in this country, that occupational cancers represent a public health and an industrial medical problem deserving serious attention. F. Hoffman complacently noted about this matter in 1928 that the scarcity of recorded industrial cancers in the United States was attributable to the fact that the workers in America are unusually intelligent and susceptible to educational influence, desire to know the truth and facts of a given situation and frequently govern their conduct accordingly. Hoffman added that this observation applied to no particular class of workers more than to those who were connected with the chemical industries in which occupational cancers were unusually frequent in other countries.

A look at the record brings out the following facts: Although the United States has been for several decades the leading industrialized country and has recently accentuated this position through the developments and the outcome of the last war, it is obvious that this country does not equally excel in regard to the study, control, prevention and legislative measures of industrial health hazards, especially those causing occupational cancers. By the end of 1945 only thirty-two states had passed some form of compensation law covering occupational diseases. Since the majority of such laws either contain time limitation clauses as to the filing of compensation claims or apply only to a limited and well defined number of hazardous agents or operations, they provide inadequate or defective coverage against the hazards of industrial cancer.

This situation deserves serious consideration, as the enormous and rapid expansion of the industrial activities engendered during the war was not infrequently carried on under unfavorable conditions, such as inexperienced management and workers, emergency construction of plants and use of hazardous substances under the pressure of war without the possibility of instituting proper precautions. It stands to reason that the chances of exposure to occupational carcinogens faced by the industrially employed population of this country were increased by these circumstances during the last few years. The results of such exposures in the form of cancers, however, will not become manifest before ten to thirty years hence in the majority of persons thus exposed, that is, at a time when many workers have taken up employment of very different types and most of the women workers have abandoned their industrial activities and either returned to or taken up housework. It is obvious that the industrial origin of many of the then occurring occupational cancers will not be correctly recognized, and this will be particularly true in regard to occupational cancers developing in former industrial employees of the female sex, unless the knowledge concerning and the interest in the occupational genesis of cancer become considerably more widespread among the members of the medical profession than is the case at the present time.

As industrial cancers are not notifiable diseases in most of the states and as American industries have shown so far great reluctance in placing their cases of occupational cancer on record, there exist in this country only incomplete data as to the actual number and variety of these disease conditions, their causes and the agents and operations responsible for their development. This evident lack of proper appreciation of the importance of industrial cancer in the United States stands in sharp contrast to the unrestricted and wide publicity which these tumors have received for many years in other industrialized countries, such as England, Germany and Switzerland, in which industrial cancers are compensable and notifiable industrial diseases and from which for this reason relatively reliable and complete official information concerning them is available.

In view of the continued ignorance concerning the causation of the great majority of cancers occurring among the population in general it is regrettable that no competent and extensive investigations exist in regard to the possible role which industrial or related exogenous agents might play in the causation of some of these tumors. The demonstration of such a relationship, if it exists at all, will not be an easy task, as it is likely that any carcinogenic substances which might be inadvertently contained in the numerous articles of daily use possess a potency of relatively low order. There is, moreover, no good reason to assume that such agents are numerous and enjoy a wide distribution, as the majority of the definitely identified chemical carcinogens are rather specific, representing usually only a few compounds among a large group of noncarcinogenic related derivatives

The first step for an effective future control of the hazards of industrial cancer in this country should be a comprehensive and thorough survey of all industries producing or handling known or suspected carcinogenic agents, including those occurring in the form of contaminants, by-products or waste products. Wherever cases of definite or suspected industrial cancer are found the following data should be obtained: type of operation; character of carcinogenic agent or agents; absolute and relative number of workers affected; sites, types, length and intensity of present and previous exposures to carcinogenic agents; local and general precancerous symptoms and reactions; latency period; organ or organs involved; incidence of multiplicity and histologic types of cancers; age, constitution, sex and race of persons affected; diagnostic, preventive, prophylactic and therapeutic measures taken and sociologic, sanitary and technical aspects (physical, chemical, engineering).

If occupational cancers should be found among the workers of a certain operation in one plant and should be absent apparently among those of a similar operation somewhere else, efforts should be made to ascertain any underlying differences (type and intensity of exposure; sex, race and rate of turnover of labor; details of manufacturing processes; type of precautionary measures; length of time operations were established; raw products used; intermediary and by-products generated; climate, and diet).

Special attention should be paid in this connection to those American industries which have apparently remained free or almost free from occupational cancers, although numerous cases have been reported from similar establishments in other countries (pulmonary and nasal cancers in nickel refinery workers and pulmonary cancers in chromate workers, asbestos workers and arsenic workers). A thorough restudy of the potential cancer hazard to manufacturers and handlers of arsenicals seems to be especially indicated, as recent observations made by clinicians in this country and in Europe as well as governmental data from England show that not only an alimentary and therefore mainly habitual and medicinal exposure to arsenicals, but also a respiratory and cutaneous contact, which is prevalent in industry, may cause the development of cancers of the skin and the internal organs (lungs, alimentary tract). It is not probable that any occupational cancers of the skin or lungs and leukemias would be found at this time among the many persons who came in contact during recent years with radioactive gases and dust, because a much longer latency period is required in general before such complications become manifest. However, all persons who have sustained such exposures should remain under close medical supervision for the next twenty or thirty years.

There can be no doubt that an evaluation of the data obtained in such a survey will permit conclusions which can be translated into definite research problems of an experimental or clinical nature and into useful recommendations for medical, sanitary, technical and legal measures.

An effective control of occupational cancers requires the close and harmonious cooperation of many and diverse parties (physicians, chemists, physicists, engineers, biologists, public health officials, law making and enforcing agencies and industrial management). If such collaboration can be obtained, the great majority of industrial cancers known today may disappear within the next twenty to thirty years from the list of industrial diseases. The continued occurrence of occupational cancers, on the other hand, represents a challenge not only to the intelligence but also to the social conscience of human society, because industrial cancers may be compared with a biologic bomb having a delayed time fuse which may be placed in the body of the victim without his knowledge and realization and which may display its deadly effect many years later when the conditions connected with its introduction are often forgotten.

... treatment and continued in 8 cases for more than two months is convincing evidence that the remission was induced rather than spontaneous. It should be remembered, however, that if treatment is continued for more than eighteen months and then discontinued, the resultant remission might well be a natural one.

It has been suggested that thiouracil could not induce a relatively long remission because it produces in the gland a hyperplastic but functionally inefficient state. It has been recognized that a hyperplastic state of the thyroid can exist in a patient experiencing a relatively permanent remission of his thyrotoxicosis. This has been demonstrated by the structure of the remnant of the thyroid gland after thyroidectomy by Rienhoff [10] and Branch. They examined sections of the thyroid gland removed several months after thyroidectomy and found the characteristic evidence of stimulation of the thyroid. Even though this state of hyperplasia persists, Preston and Thompson [11] concluded that a single thyroidectomy may accomplish control of the toxic state sufficiently to avoid subsequent operations in 85 per cent of the patients.

Treatment with thiouracil has the same effect as thyroidectomy, at least temporarily. This is accomplished by reducing the function of the thyroid tissue by interference in the iodine concentration and oxidation process of the gland. It is entirely possible that the hyperplastic state of the thyroid induced by thiouracil changes to a state of normal involution after a variable time. Evidence in support of this is to be found in the report of Shirer and Cohen,[12] who observed a normal morphologic picture in a thyroid gland removed from a patient previously treated unsuccessfully for seven months with thiouracil.

Further evidence of the active effect of thiouracil in producing a more permanent change in thyroid function is found in the case reported by Barr,[7] and in 1 observed in our series in which a thiouracil induced picture of myxedema recovered slowly over a period of six months after treatment with thiouracil was discontinued.

In our opinion this evidence indicates that thiouracil does more than iodine in that it produces a change in the thyrotoxic state which persists after the administration of the drug is discontinued.

CONCLUSIONS

Thiouracil may be used in about one third of the thyrotoxic patients only as preoperative treatment, since these patients possess nodular goiters which might develop a malignant condition. Another 7 per cent of the total number will require thyroidectomy on account of complications which occur during thiouracil therapy. The most serious of these complications to be kept in mind is agranulocytosis.[8] About 15 per cent of the patients with thyrotoxicosis will leave the physician's care for personal reasons of the patient, which are in some instances related to difficulties encountered in thiouracil therapy.

In the remaining 45 per cent of the total group, made up of those with toxic hyperplastic goiter, thiouracil therapy may be discontinued at the end of a little over an average of ten months with the prospect that 60 to 80 per cent of the patients will experience a relatively persistent drug induced remission. For this selected group, at least during the period of observat[ion] which has continued to date, this result is as satisfact[ory] as that of subtotal thyroidectomy. The majority [of] patients with thyrotoxicosis, however, must be trea[ted] by surgical means. Those receiving thiouracil m[ust] continue treatment with the drug for indefinite perio[ds]. For these reasons surgery is still the treatment of choi[ce] in the management of this condition. Thiouracil [is] superior to iodine, however, as it is more specific [in] its action and induces a more complete and permane[nt] remission in patients with this disorder. In the trea[t]ment of selected cases of thyrotoxicosis, therefore, thi[o]uracil treatment must be considered as a form of therap[y] which has promise, and ultimately it may prove to b[e] as satisfactory as thyroidectomy in this group of patient[s].

10. Rienhoff, cited by Fitz.[3]
11. Preston, F. W., and Thompson, W. O.: Persistence and Recurrence of Toxic Goiter Following Subtotal Thyroidectomy, Arch. Int. Med. 69:1019 (June) 1942.
12. Shirer, J. W., and Cohen, M.: The Effects of Thiouracil on the Thyroid Gland, Ann. Int. Med. 23:790 (Nov.) 1945.

INDUSTRIAL MANAGEMENT AND OCCUPATIONAL CANCER

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The term "occupational cancer" applies to malignant tumors which originate in persons during the course of and as the result of the regular and usually prolonged exercise of certain occupational activities which entail contact with some exogenous, physical or chemical carcinogenic agent acting in proper intensity. Occupational cancers are in general elicited by specific factors which form an integral part of the ordinary working conditions and thus are not the result of some unforeseen, accidental injury sustained while at work.

Although a few of the cancers so far recognized as of occupational origin have been known or have existed without correct recognition prior to the advent of the modern industrial era, such as the soot cancer of the chimney sweeps and the cancer of the lung of the cobalt and uranium miners in Schneeberg and Joachimsthal, the great majority of occupational cancers appeared after the start of the present industrial development and as a result of it. During the last century there occurred not only a constant rise in the absolute number of these malignant growths but also a decided increase in the types of organs affected by them, in the number of exogenous occupational agents involved in their production and in the variety of manufacturing establishments in which workers were afflicted with them.

An analysis of the available data on occupational cancer has shown that the type of the resulting tumor, the length of the latent period preceding its manifestation, the organ affected and the age of the person involved depend on the character of the carcinogenic agent, the type and intensity of exposure and the age of the person when the first exposure takes place. The soot cancer of the scrotum found in chimney sweeps, for instance, was observed some hundred and twenty-five years ago even in children, since boys as young as 4 years were used in England at that time for cleaning chimneys. The exposure to the carcinogenic soot during this operation was severe, and the degree of cleanliness among these unfortunate youth was very low. When, during the middle of the last century, the English government repeatedly raised the age limit of the apprentices of this trade, there followed a gradual rise of the age range at which the scrotal cancers appeared among chimney sweeps. At the same time the institution of better hygienic conditions and the improvement of working tools and of chimney construction reduced

From the Warner Institute for Therapeutic Research.

the degree of exposure to soot. As the result of these changes the scrotal cancer of chimney sweeps in England now appears at the same age as that found in members of the general population affected by cancer of the scrotum of unknown etiology. Only the increased incidence of this particular type of tumor among chimney sweeps has remained as evidence of the action of an occupational carcinogenic agent.

However, not all occupational cancers have followed such a favorable development. Whenever the managers of new plants and their medical advisers have neglected to profit, in the construction and operation of their establishments, from the adverse experiences previously had by other manufacturers in the same fields, there has appeared some ten to fifteen years later a renewed, acute and sometimes epidemic-like occurrence of occupational cancers in these industries. Such a course of events is exemplified by the incidence of cancers of the urinary bladder in workers of the aniline dye industry. These tumors were first observed in 1895 in German dye works and were later found among the chemical workers of other countries, such as Switzerland, Italy, England, Japan and the United States. The time of appearance of cancers of the bladder of this origin followed closely the time of large scale development of chemical industries in the countries mentioned. Thus the first cancers of the bladder in chemical workers of this country were noted in 1932, that is, approximately fifteen years after the American dye industry had reached large proportions. Within the short period of six years thereafter almost 100 cases of this industrial cancer occurring in men of relative youth were placed on record from a single chemical concern, attesting to the presence of a relatively massive exposure of the workers to the causative agents—that is, betanaphthylamine and benzidine. The full significance of this incidence figure becomes apparent from the fact that there were only about 300 cases of this particular occupational cancer reported, according to the statistics of the German government, from the entire German chemical industry within a period of forty years, that is, from 1895 to 1935. Although no authentic data are available as to the occurrence and the incidence of tumors of the bladder among the workers of other American chemical concerns, the existence of such cases is known.

Cancers resulting from contact with radiant energy—that is, the rays from radioactive substances and roentgen rays, illustrate strikingly the influence which the type and intensity of contact exert on the formation of the ensuing tumor. It appears that the inhalation of radioactive gases or radioactive dust causes cancer of the lung, such as that sustained by miners in Schneeberg and Joachimsthal, whereas the local action of radioactive and roentgen energy on the skin causes the development of cancers of the skin, such as those seen in radiologists, roentgenologists, their assistants, and in x-ray tube manufacturers, physicists and engineers. The ingestion of radioactive matter, on the other hand, causes the development of cancers of the bones, such as those observed several years ago in girls who applied luminous paint to dials. However, in more recent years cancers of the blood, known as leukemias, have been noted in increasing number among physicians and radium chemists exposed frequently to relatively small doses of roentgen rays or rays from radioactive matter. These deleterious effects on the blood-forming tissue have their cancerous equivalents in the leukemias observed among persons exposed to benzene. This organic solvent, like roentgen rays and rays from radioactive matter, causes a destruction of the blood-forming tissue and results in a fatal anemia when acting in large doses, but it may elicit leukemic responses when acting in small doses and in suitable intervals on the blood-forming tissue.

In most cases of industrial cancer, experimental research on cancer has succeeded in demonstrating the specific carcinogenic agent involved by using these agents to reproduce similar tumors in animals. Definite proof of carcinogenic properties have thus been obtained for arsenic, tar, pitch, soot, crude mineral oil, crude paraffin oil, anthracene oil, shale oil, some fuel and lubricating oils, creosote, benzene, aromatic amines, ultraviolet rays, roentgen rays and rays from radioactive substances. In recent years, however, cancers of the lung have been noted among workers in chromate plants, nickel refineries and asbestos-manufacturing establishments. These tumors are either suspected or recognized as being of occupational origin. An interesting feature of these cancers is represented by the fact that the cancers of the lung in chromate workers were observed only in several German plants, while the cancers of the lung in nickel refinery workers were found exclusively in English plants where the nickel carbonyl process was used. Although the same process is employed in some nickel refineries located in Canada and the United States, cancers of the lung have not been noted among the workers employed here if full credence can be given to the meager information available on this matter. Cancer of the lung in asbestos workers, on the other hand, has been reported from Germany, England and the United States. The actual causative agent in the production of cancers of the lung in chromate, nickel and asbestos workers is still unknown.

The rapid increase in the number of recognized and suspected agents causing industrial cancers which have occurred during the last forty years makes it more likely that new and heretofore unsuspected carcinogenic agents of an industrial nature will be discovered during the coming years. Such a development is foreshadowed by observations made during recent years by American investigators. It was found that cancers of the liver developed in mice exposed to carbon tetrachloride, a commonly used organic solvent. The inhalation of ethyl carbonate (urethane), which is employed for anesthetic purposes, resulted in the appearance of cancers of the lung in mice. Tumors of the bladder were formed in rats fed diethylene glycol, which is one of the newer widely used organic solvents. Tumors of the peripheral nervous tissue were seen in the ears of rats to which crude ergot, a drug extensively used in obstetric practice, had been fed over long periods.

Occupational carcinogenic agents produce cancers in numerous organs. Cancers of the skin are elicited by contact with arsenicals, tar, pitch, soot or carbon black, crude mineral oil, lubricating oil, shale oil, crude paraffin oil, anthracene oil, solar and ultraviolet rays, roentgen rays and rays from radioactive substances. The number of industrial cancers of this organ runs into several thousands. Cancers of the nasal passages have been noted after occupational exposure to chromates, nickel carbonyl and radioactive substances. Cancers of the bronchi and lung have been traced to an industrial exposure to arsenicals, chromates, nickel carbonyl, soot, tar, asbestos and radioactive substances. Cancers of the lip have appeared following contact with tar and after prolonged exposure to solar rays, while cancers of the mouth and of the tongue seem to be etiologically related to an industrial contact with tar and arsenicals. Cancers of lowed occupational exposures to aromatic amines such as naphthylamine, benzidine and aniline and occasionally to tar and arsenicals. Cancers of the blood, called leukemias, have resulted from contact with benzene, roentgen rays and rays from radioactive substances. The latter are also responsible for the occurrence of cancer of the bones.

The exposure time necessary for eliciting cancerous reactions in exposed workers varies greatly with the type and potency of the carcinogenic agent, with the intensity of exposure and with the susceptibility of the individual. The range is from six months to three to four decades, while the average exposure time is from five to fifteen years. In most instances occupational cancers appear in a younger age group than that found for the same cancer of unknown etiology in the general population. Age and sex factors do not, as a rule, play any role in the production of industrial cancers. The incidence rate of these tumors shows decided variations not only for the different carcinogenic agents but also for the different operations and is directly proportional to the potency of the carcinogenic agent and the intensity and length of exposure. Cancer of the bladder thus affects from 30 to 90 per cent of the severely exposed dye workers, while cancer of the lung kills from 75 to 80 per cent of the cobalt miners of the Schneeberg mines. Carcinogenic agents eliciting occupational cancers of the skin, on the other hand, have a lower morbidity and mortality rate because the precancerous changes of the skin preceding the appearance of the tumors gives ample warning, as a rule, of the threatening malignant condition, while the ready accessibility of the skin to therapeutic measures enhances the prognosis of cure. It is of a certain importance from an industrial point of view that the skin of colored workers is less susceptible to the cancerigenic action of solar rays and of tar, pitch and similar substances than that of white, and especially of fair-skinned, workers.

The total number of occupational cancers placed on record is small when compared with the large number of cancers of unknown etiology. It is obvious, however, that the latter group contains an undetermined number of cancers of occupational origin, as many of them either are not properly recognized or are not made a matter of public information.

Although today a great deal of evidence on the causes of occupational cancer and the conditions under which it develops is available, relatively little effort has been made to spread this knowledge among parties who are vitally concerned with this information, namely the managers and physicians of industrial concerns, although they carry the main load of controlling this preventable type of cancer. This situation is the more deplorable because the present rapid development of industry tends to extend the hazards of the known industrial carcinogenic agents while at the same time creating new ones which may cause the appearance of cancers ten to twenty years hence, unless concerted efforts are made in time to discover and control such dangers by appropriate countermeasures. It is essential that industry should devote considerably more effort than heretofore to determining the cancerous or noncancerous nature of such of its numerous products as may be suspected on general grounds of cancerigenic properties. As occupational cancers are chance experiments on cancer in man, conducted by modern industry on a large scale, which render direct, reliable and conclusive information as to the cause and mechanism of human cancer, the investigative study of these conditions deserves a great deal more consideration than it has been given in the past. The experience gained from the study of occupational cancer, and especially of its causative mechanism and its prevention and control, should prove of great value in the future in fighting cancer in general at its source; that is, it should aid in the elimination of the causes of cancer before they are capable of initiating the malignant growths. In waging this campaign it should be realized that a well planned, systematic and, probably, prolonged attack must be launched if worth while results are to be expected. However, I am convinced that with the necessary perseverance and determination this battle against occupational cancer in particular and against cancer in general can be won, if every one concerned aids in the effort.

If industry can be persuaded to finance the foundation and maintenance of an organization exclusively devoted to the study of the causation and control of industrial cancers, not only will industry be the main beneficiary of this move, but also it will greatly advance the fight against cancer in general, which is of direct concern to every one, unless it is forgotten that every tenth adult dies from this disease.

RECOMMENDATIONS FOR THE CONTROL OF OCCUPATIONAL CANCER

1. Plant management officials, industrial workers and members of the medical profession must be made increasingly aware of the fact that numerous agents of our new industrial environment possess carcinogenic properties.

2. Construction and chemical engineers should design buildings, machinery and apparatus with this hazard in mind—that is, they should try to favor the closed system of production, the installation of adequate exhaust ventilation, the use of building material which does not absorb carcinogenic substances, the avoidance of nooks, crevices and ledges where carcinogenic dust can be deposited, and the employment of wall and floor covering that can be thoroughly and repeatedly cleaned with water and steam used in connection with cleansers.

3. Adequate provision must be made for the removal of carcinogenic material from waste gases, fumes, waters, dust and the like before these waste products are released into the air, public waters or other channels affording the contact of the general population with carcinogenic industrial wastes.

4. Carcinogenic material must be packed in leakproof containers.

5. Similar appropriate protective technical measures should guard the persons handling roentgen rays and radioactive substances from being exposed to deleterious quantities of radiant energy.

6. These measures must be sufficiently extensive to protect also persons working or living in the immediate environment where physical or chemical carcinogenic agents are handled.

7. Whenever the use of carcinogenic material in industry cannot be eliminated by the use of substitutes, workers should be protected from contact with carcinogenic agents by suitable protective clothing, gloves, masks and the like and by the enforced observance of adequate hygienic measures, such as the use of washing facilities, showers and special rooms for storing street clothes and for taking meals and frequent changes of working clothes.

8. Frequent and experienced medical supervision of the workers exposed to carcinogenic material is impera-

tive for effective control of the hazard. This supervision must also extend to workers who have left the employment after having been exposed to carcinogenic agents for a sufficiently long time or who have been shifted to noncarcinogenic operations.

9. A nationwide survey by skilled investigators should be made to determine the actual scope of the problem of industrial cancer. Representatives of management, industrial physicians, members of the Public Health Service and of departments of industrial hygiene and possibly also representatives of the workers should participate in such a survey.

10. Precancerous and cancerous industrial diseases should be made notifiable to the departments of industrial hygiene of the various states.

11. Adequate compensation laws for occupational diseases should be passed for the protection of both management and workers against excessive awards or inadequate compensation, respectively, for claims that result from the production of occupational cancers.

12. Government inspectors should examine all industrial plants at regular intervals to determine whether or not they meet the essential safety requirements necessary for minimum protection of the workers against the hazards of industrial cancer.

13. An institute for the study of industrial cancer should be founded and should be attached to or coordinated with one of the existing large cancer research centers, in order to provide for proper integration of the results obtained by such investigations with those produced by cancer research in general. Such an organization would serve industry for consultative and investigative purposes on matters of occupational cancer.

14. A committee composed of industrial physicians, cancer research workers, industrial physicists, chemists and engineers, compensation lawyers, members of the Public Health Service and of state departments of industrial hygiene, representatives of industrial management and union officials should be created, whose members should act as a body of consultants and special experts to the Institute for the Study of Occupational Cancer.

Art and Anatomy.—Among the great artists who engaged in dissection were Michael Angelo, Raphael and Albrecht Dürer. Greatest of all was Leonardo Da Vinci (1452-1519). This gifted and versatile artist, a man centuries ahead of his time in original ideas, who visualized aviation and modern methods of warfare and who discussed many problems of engineering which were later put into practice, also made discoveries in anatomy, such as the maxillary sinus and the moderator band of the heart. He was the first to demonstrate the ventricles of the brain by wax injections and to depict correctly the fetus and its membranes within the uterus. Originally he set out to study the bones and muscles in their relation to art, but his interest grew, and he pursued his investigation of the deeper parts, the viscera, the brain, the blood vessels and especially the heart. He intended to publish a great work on anatomy in collaboration with Marco Antonio della Torre of Pavia, but this project was abandoned owing to the death of his co-worker. It is only within recent years that the value of Leonardo's contribution to anatomy has been fully appreciated. He made hundreds of sketches and manuscript notes, many of which are preserved in the Royal Library at Windsor and have only recently appeared in print. This apostle of naturalism in art must also be regarded as a leading pioneer in anatomy.—Guthrie, Douglas: A History of Medicine, Philadelphia, J. B. Lippincott Company, 1946.

Clinical Notes, Suggestions and New Instruments

ACUTE SYPHILITIC NEPHROSIS SUCCESSFULLY TREATED WITH PENICILLIN

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The nephrotic syndrome is defined as a clinical symptom complex characterized by profuse proteinuria, hypoalbuminemia and edema without serious renal insufficiency or hypertension. It may be seen in a variety of conditions and has been observed in connection with acute syphilis.[1]

REPORT OF CASE

History.—J. Y., a white man aged 31, was first admitted to University Hospitals July 18, 1945 with a chief complaint of generalized edema and genital ulcerations of approximately one week's duration.

In the early part of June 1945 several superficial lesions developed in the coronal sulcus of the penis. These gradually enlarged, with subsequent ulceration. July 2 he was seen by one of us (L. G. S.), who made the diagnosis of chancroid of the penis and started the patient on sulfathiazole two tablets four times daily. This was continued until July 6, when the result of the serologic test for syphilis drawn at the first interview was reported as strongly positive. On July 7 he was given 0.04 Gm. of oxophenarsine hydrochloride (Mapharsen) intravenously, with no immediate reaction. However, eight to twelve hours later he had a shaking chill and temperature elevation to 104 F. Within twelve hours the patient was again symptom free. July 10 another injection of 0.02 Gm. of oxophenarsine hydrochloride was given intravenously, without ill effect. He returned on July 15 and at that time had moderate edema of the face, legs, penis and scrotum and complained of general malaise, anorexia and low back pain. No urine examination was done at this time. On July 17, when he was seen again, the edema of the face, legs, penis and scrotum was more severe. The urinalysis revealed 4 plus proteinuria and an occasional red blood cell. On July 18 the edema was less severe and the urine contained only an occasional red blood cell. He was then referred to University Hospitals for study.

Physical Examination.—The temperature was 37 C. (98.6 F.), pulse rate 82, respiratory rate 18, blood pressure 124/72, weight 78.1 Kg. He was well developed and well nourished. He did not appear to be in distress. There were no abnormalities of the skeletal system. The mucous membranes were of normal color with no abnormal lesions. There was slight facial edema, especially noticeable about the eyes. There was no apparent edema of the upper extremities. There was moderate pitting edema of the sacrum, external genitalia, thighs and legs. The skin was normal in color and texture, with no abnormal lesions. There was a well defined, firm, freely movable nontender lymph node in the right inguinal region measuring 2 by 2 cm. There were two smaller lymph nodes similar in character in the left inguinal region. There was no other lymphadenopathy.

There was moderate periorbital edema. The conjunctivas were pale. The corneas and scleras were normal. The pupils were equal and regular, measured 4 mm. and reacted normally

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The work described in this paper was done under a contract, recommended by the committee on medical research, between the Office of Scientific Research and Development and the Western Reserve University.

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