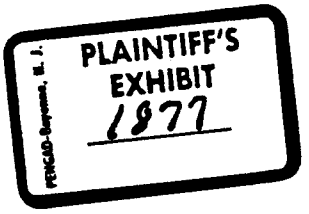
Hueper

Occupational Medicine



VOLUME 2
1946

14907

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

CONTENTS OF VOLUME 2

JULY 1946. NUMBER 1

AUGUST 1946. NUMBER 2

SEPTEMBER 1946. NUMBER 3

SIGNIFICANCE OF INDUSTRIAL CANCER IN THE PROBLEM OF CANCER

W. C. HUEPER, M.D.
NEW YORK

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 car-

cinogens 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 non-carcinogenic 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, chem-

ists, 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.