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By W. C. Hueper, M. D.

FEDERAL SECURITY AGENCY

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The National Institutes of Health

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Preface

This study presents a comprehensive review of current knowledge of the environmental causes of human cancer. Dr. W. C. Hueper, whose major interests have been in the fields of environmental and occupational carcinogenesis, has collected and analyzed the most important known facts on this problem, both domestic and from abroad. His summation of the data and his evaluation of their significance, reported in compact and usable form, should be of very real value to everyone concerned with the Nation's health.

The conclusion is inescapable that exogenous agents, particularly of industrial origin, are important factors in the causation of certain types of cancer. It is true that neoplasms of known environmental etiology comprise only a part of the total cancer incidence in the United States. However, the fact that there seems to be a constant though gradual increase in the appearance of these cancers in the general population is swiftly making occupational carcinogenesis a public health problem of very real importance. Epidemiologically, for example, much more needs to be done to reveal additional substances guilty of carcinogenic activities.

It is a problem which admits of no simple solution, as Dr. Hueper makes clear. No one agency, governmental or private, can solve it. Only a carefully coordinated and integrated program of technical and social controls, supported by the cooperative efforts of government, private health organizations, the medical profession, management and labor, can begin to cope successfully with this growing occupational hazard. Such a program deserves the most careful consideration and awareness of everyone concerned with the health of the American people.

Contents

Environmental and Occupational Cancer

By W. C. Hueper, M. D.

Past clinical and experimental efforts toward achieving an effective control of cancer have dealt chiefly with attempts to improve diagnostic methods and therapeutic measures. Without any doubt, this work has had a measurable amount of success.

However, it may be well to remember that the far-reaching control of infectious diseases achieved during the past 75 years has depended to a definite degree on the successful determination and identification of the causative micro-organisms, and on a great deal of extensive and laborious epidemiological study. Recent developments in the field of cancer make it seem likely that there exists a similar interdependence of factors pertaining to etiology and control.

As long as the causative agents responsible for over 99 percent of human cancers remain unknown, and as long as no determined and widespread efforts are made to fill in this serious gap in essential information, there is little hope that rapid progress in the control of cancer can be obtained by rational preventive, prophylactic, diagnostic, and therapeutic measures. The prospects of repeating in the field of cancer the results achieved with the control of infectious diseases are therefore not too favorable, unless some of the methods and approaches used in the latter are applied to cancer research.

Although there are many important and, apparently, fundamental differences between the two groups of diseases, their similarities also are numerous. Data at present available as to the number and types of extrinsic carcinogenic factors suggest that the prospective spectrum of exogenous and endogenous carcinogens may cover a range of agents differing from each other as widely as those composing the spectrum of the pathogenic micro-organisms. The recently discovered species specificity of carcinogenic agents is analogous to the species specific pathogenicity of the micro-organisms causing infectious diseases. The carcinogens, moreover, share with the micro-organisms the marked

differences in pathogenic potency which characterize the various infectious disease agents. Just as, with several of the infectious diseases, the causative infecting agent brings about a sequence of different histological reaction products, reflecting changes in the state of reactivity of the host tissues (as happens with tuberculosis, syphilis, etc.), so extrinsic carcinogens are likely to elicit various histologic responses in the tissues, such as hyperplasias (hyperkeratoses, warts, nodular adenomatoid proliferations), benign tumors (papillomas and adenomas), and cancers.

Furthermore, clinical as well as experimental evidence shows that in both infectious diseases and cancer the sites of the anatomical responses are not only determined by the properties of the particular pathogenic agent involved, but also by the type or route of contact with it. The conditions of exposure which decide the development of tuberculosis of the lungs and of the intestine—inhalation and ingestion, respectively—are fundamentally no different from those which are responsible for the development of cancers of the skin, bones, lungs, etc., after exposure to radioactive material by skin contact, inhalation, ingestion, or parenteral introduction.

An additional resemblance between cancer and the infectious diseases is the fact that the degree of pathogenicity or virulence of the causative agents is only in part an extrinsic quality. It depends to some extent, also, on the intensity and duration of exposure to them. Thus the incidence of bladder cancer among workers in dye plants is highest among those most massively exposed to aromatic amines, and decreases among other operatives in proportion as their contact with these highly potent carcinogens decreases. Epidemiological investigations have shown a similar crowding of tuberculous infections around persons with active and open tuberculosis of the lung.

In other words, the epidemiological pattern of the spread of cancer and of infectious diseases, from foci where causative agents are generated, is essentially identical. For the future control of cancer, this fact is of special importance for several reasons. The progressive march of occupational cancers through all industrialized countries, paralleling the development of modern industries, and the continuous creation of new industrial products of often unknown biological properties, are factors which tend to result in the appearance of an increasing number and variety of extrinsic carcinogenic foci. Since the character of a particular carcinogen as well as the type of exposure to it determines the site of the ensuing cancer, this development may result in the course of time in a change of the quantitative and qualitative aspects of the environmental carcinogenic spectrum, and thereby in the incidence rate of cancer, both as to total numbers and as to sites.

It is evident, therefore, that for an effective future control of cancer

we must determine the causes and directions of the new trends, and institute procedures for their prevention. The repetition of a survey of cancer morbidity in ten different metropolitan areas of the United States, first carried out 10 years ago and being undertaken again this year by the Cancer Control Branch of the National Cancer Institute, assumes special significance in the light of the above considerations.

A second step toward a more adequate epidemiological analysis of cancer was taken recently, with the creation of an Environmental Cancer Section within the Cancer Control Branch. This Section will supplement epidemiological studies with investigations into the extrinsic causative factors of human cancer as they are related to occupation, medicinal agents, diet, climate, customs, habits, geological conditions, and parasitic infections.

A third recent development in this field is the launching by the New York State Occupational Cancer Committee of a project to determine in detail the occupational histories of several thousand cancer patients at the Roswell Park Memorial Institute, at Buffalo, N. Y. These histories are to be analyzed for previous occupational cancer hazards sustained by the patients.

In order to make available a concise and yet comprehensive presentation of current knowledge on the environmental cancer problem, for use not only by cancer specialists but also by the medical profession in general, public health officials, legislatures, social welfare workers, and members of management and of labor organizations, the following paper was prepared. It is based on lectures given before the International Congress on Cancer Research in St. Louis, September 1947; and the postgraduate course of the Department of Occupational Medicine, Yale University Medical School, March 1948. I wish to express my thanks to these organizations for their kindness in permitting me to use the substance of these lectures in this revised form.

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Role of Environmental Agents in Human Cancer Causation

About the time when the microbial origin of infectious diseases was established by Pasteur and Koch, some 75 years ago, the first important data were also made available on the causation of cancer in man by several extrinsic agents. The agents mentioned thus early were arsenic, soot, tar, and crude paraffin oil (*163*). Unfortunately, these basic observations on the etiological significance of inanimate environmental factors in human cancer were not followed up with the same vigor, vision, and persistence as were those relating to the pathogenic animate members of our natural environment. Although a few additional physical and chemical carcinogens were placed during the following decades on the list of causative agents belonging to the modern artificial industrial environment, it was not until isolation of benzpyrene from tar, approximately 20 years ago, that scientific thinking developed an appreciable interest in the causation of cancer by specific extrinsic factors.

Since then a vast amount of experimental cancer research on animals, using numerous newly synthesized carcinogenic chemicals, has been performed. However, this scientifically valuable information has added relatively little to our knowledge of the causation of human cancer (*83*).

Definition and Types of Environmental Carcinogens

Any physical, chemical, or parasitic agent forming a part of our natural or artificial environment that, on proper exposure, directly or indirectly elicits cancerous growths in one, several or all types of human tissues, represents an environmental carcinogen. Although some of these agents, like solar rays, soot, and arsenic, have a practically universal distribution, the occurrence of demonstrable environmental cancers is restricted, as a rule, to regions or to groups of individuals having a particularly intense, prolonged, or otherwise positive contact with these carcinogenic agents. Exposure to these factors is related to a great number of highly diverse environmental conditions, such as oc-

cupational activities, diets, medicines and medicinal devices, cosmetics, wearing apparel, building materials, habits and customs, climate, fauna, contaminants in drinking water, atmospheric air, foodstuffs, and—in recent years—procedures of warfare.

The data supporting an extrinsic, environmental causation of human cancers are of two types. Some of the evidence is of circumstantial character, derived from statistical observations showing definite differences in the incidence rates of cancers. These differences appear in different regions, among different races, sexes, and social and occupational groups, and with different climates, and also are to be noted in marked variations in the relative distribution of cancers upon the different organs in different countries and population groups. The second type of evidence is of a more definite nature, and applies to the environmental tumors proper.

Circumstantial Evidence for Environmental Causes of Cancer

From the large amount of circumstantial evidence indicating the action of extrinsic factors in the production of human cancer, only a few typical and more recent examples will be cited.

Analyzing the recorded cancer mortality among the racially highly mixed population of the United States, Gover found remarkable variations in different sections (*130*). The rates ranged in 1930 from 127 per 100,000 for all cancers of both sexes in Rhode Island to 56 per 100,000 in Arkansas. Similar observations were reported from different parts of Europe (*58*, *62*), where the lower incidence rates are generally recorded from southern countries, while the higher ones were usually found in the northern parts of the continent. The highest cancer mortality was observed in Denmark (*58*).

Although some of these discrepancies are attributable to differences in the quality and quantity of medical service and disease reporting in various parts of Europe and the United States, it is not likely that this factor accounts for them in their entirety, particularly since these regional variations in total cancer mortality are associated with considerable variations in the distribution of cancer of the various organs.

There was, for instance, not only a high rate of cutaneous cancer among both sexes in the Southern States of the United States, but also for all sites of cancer of the buccal cavity among females, and for cancer of the pharynx and mouth among males, in comparison with those found in the Northern States. McDowell noted in 1938 a similar regional distribution of cutaneous cancer in different parts of the

United States, when he recorded an incidence rate of 157 for Atlanta, 129 for New Orleans, 37 for Detroit, 25 for Pittsburgh, and 24 for Chicago (*223*). The incidence rate of cancer of the stomach and of the total digestive tract, on the other hand, was found by Cramer to be higher in the northern sections and in the Pacific coast area than in the west south central and south regions (*62*), while cancer of the lung was relatively high in the northeast and Pacific sections.

Cramer also noted that gastric cancer is most frequent among members of the Caucasian race in Europe and America; but there are wide variations of frequency even within that racial group. In England and Wales gastric cancer accounts for 22.2 percent of the total cancer mortality; in the United States for 42.8 percent of the total cancer mortality; in Holland for 55.5 percent; in Sweden for 60.5 percent; and in Czechoslovakia for 66.0 percent. While gastric cancer is rare among the Javanese, it is as frequent as in European whites among Chinese with European living habits (*31*, *143*). A similar environmental influence is found in connection with primary liver cancer, which is very frequent among Negroes in Africa and among Javanese and Chinese in Java, while its incidence rate among American Negroes does not differ from that found among American whites (*379*, *397*, *133*, *258*, *307*, *70*, *298*, *60*, *211*, *234*).

Additional evidence indicating that environmental factors apparently have a definite influence on the incidence rate of certain organ cancers was recently furnished by Lasch (*200*). He reported striking differences in gastric cancer morbidity rates in various parts of Germany, where for several years an obligatory system of notification was in force. Lasch noted that the incidence rate from 1937 to 1939 was considerably higher in the purely agrarian region of Mecklenburg than in the agricultural-industrial district of Saxe-Anhalt, the industrialized Saar, or urban Vienna. On the other hand, gynecological cancers showed a higher frequency in the latter three areas than in the agrarian district.

The practical absence of penile cancer in Hebrews, its relative rarity in Mohammedans, its moderately high incidence in American Negroes (*357*, *211*), and its very high frequency in Ceylonese, Javanese, and Chinese do not reflect racial susceptibilities. On the contrary, these differences are attributable to hygienic environmental conditions related to frequency of and age at circumcision, the occurrence of phimosis, and similar factors favoring the action of decomposing smegma (*60*, *294*, *163*, *357*).

The marked variations in the localization of cancer in different parts of the oral cavity which have been observed in various parts of India have been attributed to local differences in habits and hygiene (*176*). It is also doubtful that racial or constitutional factors account for the

onsiderable discrepancies in the incidence of lung cancer in different parts of Europe—high in some regions of Germany, England, Switzerland, and low in France and Italy. They are probably caused by local variations in industrial activities, habits, diets, and other environmental conditions (*61*, *163*).

It is generally recognized that racial differences in skin pigmentation are responsible for the higher susceptibility of the skin of fair, blond and blue-eyed persons to cutaneous cancer. Schrek reports that there were 18.4 percent of cutaneous cancers among 10,857 white cancer patients against 1.7 percent of skin cancers among 724 colored cancer patients (*337*). Nevertheless, the environmental origin of skin malignancies is clearly indicated by the sex distribution, as these neoplasms are much more frequent in male whites than in female whites, contrasting sharply with the equal sex distribution observed in colored individuals. There exists no valid reason, however, to attribute the excessive incidence of nasopharyngeal cancers in Chinese to a special racial susceptibility (*368*). It is much more likely that environmental factors of a possibly dietary nature are responsible for this phenomenon.

While sex-conditioned, endogenous carcinogenic factors may be behind some of the remarkable differences in the cancer incidence of the two sexes, there can be little doubt that environmental agents also exert a decided influence. A high incidence in males is found for cancers of several organs which have direct or indirect exposure to extrinsic agents to a remarkable degree. The incidence ratio for males and females for cancer of the skin is 4:1 (*293*); for cancer of the lung 4:1 to 7:1 (*159*, *391*, *271*); for cancer of the larynx 10:1 (*167*); for cancer of the bladder 5:1 (*6*); for cancer of the esophagus 10:1. Cancer of the stomach (*385*) and cancer of the liver (*105*) occur more often in males than in females.

It is also significant that the local distribution of cancers of the skin, and of the gastro-intestinal tract as well, follows a pattern which indicates that an extrinsic carcinogenic agent is most active at certain circumscribed areas favoring intense and prolonged contact, such as the face, the neck and the hands for cancer of the skin, and the physiological narrows and curvatures as well as the presphincter regions of the alimentary tract.

Additional support for these conclusions is derived from studies on the distribution of cancer (social cancer) among the members of certain socio-economic groups (*62*, *175*, *327*). Such a classification divides the population into groups having varying degrees of exposure not only to known environmental carcinogenic agents, such as soot, tar, mineral oil, arsenic, actinic energy, and others of an occupational character, but also to those of a more or less indefinite nature such as

diet. general personal hygiene, wearing apparel. living quarters. and habits.

It is found that cancer mortality increases progressively in each lower economic class for all types of cancers except that of the breast. Kennaway and Kennaway established the principle of higher cancer mortality in the lower economic classes for cancer of the scrotum. and concluded that this type of malignancy is most prevalent in men belonging to a class doing the heaviest type of labor and usually washing least (*175*).

Exposure to soot in town dwellers was considered an additional important etiologic factor. As cancer of the penis did not reveal a similar socio-economic distribution, they concluded that different causative factors are involved in the production of this neoplasm. The statistical evaluation. moreover, showed that social grading is present with cancer of the skin and of the larynx, is very pronounced for cancers of all sites above the pylorus, but is not observed in the remainder of the alimentary tract.

Ryle and Russell, in their studies of the incidence of skin cancer exclusive of scrotal cancer in England, Wales, Scotland. North Ireland, and Eire (*327*), found that there is no increase in incidence with lowering of social classes in females, while with males a distinct increase is found. Classes exposed to sunlight, soot, and grime showed a high incidence. For example, among men exposed to soot, such as furnacemen, stokers, boiler firemen, and rollers, the rate was 225, against 70 in professional men and white-collar workers. Occupational factors thus appeared to be more important than social class. Indeed. Clemmesen concluded from his analysis of Danish death certificates that it is not improbable that the latency period for the development of cancer varies in different occupational and social groups, depending on the potency of the particular injurious agent, and that this fact may account for the differences in local distribution of cancer in different localities and population groups (*58*).

In the Danish material, for example, there was a low cancer mortality in all agricultural groups and a high one in all industrial groups. The gastric cancer mortality in the industrial group stood at 129 percent, while it was only 57 percent in the white-collar class. Other investigations show that cancers of the lung are excessively frequent in certain varied occupational groups such as engineers, mechanics, painters, decorators, metal grinders, foundry workers, etc., while they are relatively infrequent in clerks and typists (*373*). Although Ryle and Russell maintained that the melanomas are not related to extrinsic factors (*327*), Peller (*288*) noted that white American soldiers and sailors from the Southern States have melanomas less often than

ase from the Northern States, when the number of epitheliomas of the skin are considered, but that this relation is reversed when internal cancers are analyzed.

Additional circumstantial evidence pointing to the action of extrinsic factors in the development of cancers is found in the existence of differences in the local distribution of cancers in certain organ systems, such as the oral cavity (*176*) and skin (*337*) in different regions or racial or occupational groups. Similarly significant are the variations in the incidence of simultaneous or successive multiplicity of cancers during different periods, shifts in sex distribution, and differences in age range (*176*), as well as variations in the absolute and relative frequency of cancers of certain organs. While such fluctuations are usually ascribed to improvements in diagnosis and treatment and, doubtlessly, are due to these factors to some extent, changes in the quantitative and qualitative composition of the environmental carcinogenic spectrum at different times and localities evidently may also play a major role.

The marked increase in the number of lung cancers recorded during the last 40 years from many parts of the globe apparently represents a typical example of the results of such an environmental alteration (*78, 271, 333, 159, 163, 391*). An extrinsic origin of this phenomenon is suggested by the fact that the increase has been more pronounced in males than in females, and that the percentage of adenocarcinomas among the bronchiogenic cancers has been much higher in females (51.7 percent) than in males (14.7 percent), among whom the squamous cell type of cancer predominated (*159*). The present lack of proof that a single extrinsic agent is wholly responsible for this development is not a valid reason against the conception, since it is well known that several agents with highly different physical and chemical properties may cause pulmonary malignancies of occupational origin.

The definite rise in the incidence of leukemia in the United States since 1900 and, particularly, since 1930—94.7 percent during the last 20 years (*328*)—may represent another example of such an environmental change. The rise is not accounted for by differences in age distribution of the population, and leukemia is twice as frequent in whites as it is in Negroes, and more often seen in males than in females. It is more likely that some environmental leukemiogenic agents (benzol, aromatic compounds, tar, actinic energy), which appeared some 40 to 50 years ago and have become increasingly common, are responsible for the rise.

The various data of a circumstantial character which are advanced as favoring a frequent extrinsic causation of human cancers may not be of impressive value when taken separately. However, when seen as

a whole and integrated into a pattern, they provide weighty evidence supporting such a concept. Their validity is greatly strengthened, and the concept itself is made more concrete by the evidence supplied by the various recognized environmental cancers.

Circumstantial evidence for environmental cancer is outlined below:

1. Variations in total and organ incidence for both sexes in different regions.
2. Differences in incidence rate of certain cancers for males and females.
3. Differences of incidence of all and certain organ cancers among various occupational and socio-economical groups and among populations of agricultural, industrial, and urban regions.
4. Differences in the local distribution of cancers in certain organs or organ systems in different regions or population groups.
5. Shifts in organ incidence, sex distribution, frequency of multiplicity, age range during different time periods.

Conclusive Evidence for Environmental Causes of Cancer

The environmental carcinogenic spectrum is composed of agents which vary remarkably in their physical and chemical properties. In only relatively few instances can the origin of environmental cancers be traced to contact with well-defined chemical or physical agents possessing established or suspected carcinogenic qualities, such as arsenic, benzol, aromatic amines, ultraviolet rays, roentgen rays, and rays from radioactive matter.

A second large group of environmental tumors is elicited by exposure to ill-defined mixtures of organic chemicals, the carcinogenic components of which are incompletely known. The members of this second group are tar, pitch, asphalt, soot, carbon black, crude mineral oils, paraffin oils, shale oils, anthracene oil, lubricating and fuel oils, creosote, and bitumen. A substance isolated from tar and crude shale oil, 3,4-benzpyrene, is carcinogenic to mice (*174*, *19*), and is suspected also to be carcinogenic to man.

Still a third group of environmental cancers seem to result from contact with inorganic substances, particularly certain minerals such as chromates, nickel carbonyl, asbestos and, perhaps, beryllium. Several dietary deficiencies involving the protein, fat, vitamin, and iodine metabolism are thought to be responsible for a fourth group of environmental cancers, while a fifth group is composed of neoplasms arising after contact with chemical irritants of unknown nature, such as those contained in betel nut quids, or generated by or associated with *Schistosoma hematobium*.

Listed below are the various groups of environmental carcinogens:

I. Chemical carcinogens.
   A. Organic chemicals.
      Aromatic compounds: tar, pitch, asphalt, soot, shale oil, crude paraffin oil, anthracene oil, lubricating and fuel oils, greases, creosote, lamp black, aromatic amines (betanaphthylamine, benzidine, aniline?), benzol.
      Aliphatic compounds (carbon tetrachloride?).
   B. Inorganic chemicals.
      Arsenicals, chromates, nickel carbonyl, asbestos.
II. Physical carcinogens.
   Ultraviolet rays, corpuscular rays (alpha and beta rays), electronic rays (gamma rays, Roentgen rays).
III. Dietary disturbances involving protein, fat, and vitamin metabolism, and affecting liver, pharynx, and thyroid.
IV. Undefined environmental carcinogens contained in betel quid, khaini, and *Schistosoma hematobium*.

The highly diverse physical and chemical properties of these agents make it improbable that they exert their specific pathogenic action through the same mechanism. From an analysis of the available data and from theoretical considerations it appears that extrinsic carcinogenic factors may elicit malignant growths through one of the following ways.

Some of the agents, such as aromatic amines and the carcinogens contained in tar and related substances, apparently act directly on the cellular substrate, either in their original form or as metabolites or conjugates. This action may be merely catalytic, as only minute amounts of carcinogens of this type may bring about malignant cellular transformations (*285, 62, 343*), or it may arise through interference with the normal cellular enzymatic activity or by combining with macromolecular proteins resulting in the formation of allergens.

A second group of extrinsic carcinogens apparently consists of agents which do not possess direct carcinogenic properties, but which change 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, it seems probable that such a mechanism may be active in their development. A similar indirect and secondary mechanism may also be responsible for the occupational cancers caused by exposure to certain metals (*333*).

A third type of environmental carcinogens may cause quantitative or qualitative functional changes in some endocrine glands or the liver, which respond with the generation of abnormal endogenous carcinogenic products. Cancers of the dietary environmental type may have this origin, as may those produced by hepatoxic agents such as certain azo dyes and chlorinated aliphatic hydrocarbons. It is obvious that the demonstration of the actual existence of such a mech-

anism would not only establish a direct connection between extrinsic and intrinsic carcinogenesis, but would widen at the same time the potential scope of extrinsic agents as producers of human cancer. These considerations are of definite importance because of the recent isolation of cancerigenic substances from normal and neoplastic human tissues, and the occurrence of congenital cancers and cancers in infants (*186, 154, 357, 408, 329, 392, 138*). These latter may be related to the action of extrinsic carcinogenic agents entering the maternal organism during pregnancy and acting on the rapidly proliferating fetal tissues after placental penetration.

Chemical Environmental Carcinogens

Tar and Tar Products, Petroleum and Oil Shale Products

Human contacts with tar, soot, carbon black, pitch, asphalt, crude petroleum, shale oil, creosote, paraffin oil, lubricating and fuel oils, greases, anthracene oil and other distillation and fractionation products of coal, shale, lignite, petroleum and wood apparently cause the majority of environmental cancers in man. The existence of 3,4-benzpyrene in tar (*174*) and shale oil (*20*) probably furnishes only a partial explanation for the carcinogenic action of these and related substances, although Miescher, Almasy, and Zehender recently claimed that the carcinogenic effect of tar on mice shows a simple and direct relationship to its content of benzpyrene (*241*).

Reports from various countries during recent years have supplied a great deal of additional evidence confirming and extending the numerous observations made previously on this subject and reviewed in detail in my treatise on occupational cancers (*163*). English investigators especially have furnished valuable data on the occupational aspects of these cancers and on the relationship between duration and intensity of exposure to the length of latent period and manifestation age (*176, 154, 147, 37, 19, 235*). These studies have again brought out the fact that environmental exposure to these substances is rather widespread and often not readily suspected. Workers such as stevedores, electric brush makers, manufacturers of paper covered electric conduits, slaters, and bricklayers, are subject to it. Kingsbury reported the occurrence of a scrotal cancer in a Tamil engaged in anti-malarial oiling of surfaces of water in India (*179*).

No appreciable reduction in the incidence of tar and oil cancers seems to have taken place in England during the last decade. In 1935 exposure to tar, pitch, mineral oil, and creosote caused 171 epitheliomas; in 1936 the figure was 142 (*120*); and in 1943 it was back at 160 (*235*). Some measure of success in reducing the excessive incidence of cancer

of the skin among workers exposed to Scottish shale oil was obtained by the use of a protective lanolin ointment and the exclusion of red-haired, freckled and fair-skinned workers from employment in operations entailing contact with shale oil (*5, 244*).

Reports from France, Belgium, and the United States on the occurrence of tar and oil cancers are rather meager, but there are good reasons to assume that the number of cases reported represents only a fraction of the cases which actually were observed (*18, 268*).

Firquet and Malter found two cases of skin cancer among 126 Belgian workers exposed to tar and pitch containing on spectrographic analysis 1 to 8 percent of 1.2 benzanthracene and traces to as high as 0.4 percent of 3,4-benzpyrene (*109*). Inasmuch as the incidence of skin cancer in this occupational group did not differ from that seen in the general population, these investigators concluded that the two chemicals mentioned were apparently not carcinogenic to man, a conclusion evidently not warranted by the evidence on hand. In the United States, Schwartz and Tulipan mentioned the occurrence of epitheliomas in 5 out of 100 workers employed in a manufacture of electric conduits covered with pitch impregnated paper (*340*). Chase observed a typical scrotal cancer in a chimney sweep and Klauder found an epithelioma in a paraffin presser (*54, 185*). Although Jonas as well as Schwartz reported the occurrence of numerous cases of creosote burns in workers creosoting wooden blocks and in construction workers handling creosoted lumber, no case of creosote cancer of the skin was placed on record in the United States (*168, 339*).

Although Stewart recently mentioned the occurrence of cancer of the exposed skin, especially the hands and forearms, of grease pit workers in service stations (*358*), Gafafer and Sitgreaves, analyzing the incidence rate of cancer among the employees of an oil refinery, did not find any significant difference from that of the general population (*121*). In view of the carcinogenic action of some lubricating fuel and Diesel oils (*371, 192*), cancerous reactions may result from the accidental injection of such products into the human tissues (grease gun finger, Diesel jet injuries) (*38, 45, 230, 401*).

While the carcinogenicity of wood soot and wood tar present in foodstuffs (smoked meat) and medicinal and cosmetic agents (ointments, hair lotions, eyebrow pencils, etc.) is not certain (*280*), Schock reported from Germany a self-observation on the development of numerous warts of the scalp following the prolonged use of a brilliantine containing petrolatum (*334*). Wood noted a unique case of a bilateral carcinoma of the lung in a patient with lipoid pneumonia caused by the inhalation of mist of mineral oil (*406*).

The role which the inhalation of tar dust and fumes plays in the production of cancer of the lung in man is still unsettled (*257, 254,*

315), despite the experimental evidence that soot obtained from gasoline motor exhaust products and from atmospheric dust causes cancer of the lung after inhalation, or sarcoma of the subcutaneous tissue after injection, in mice and rats (*290, 47, 343*). Although the high incidence of lung cancer among stokers in a Japanese generator plant exposed to the inhalation of hot tar fumes supports such a relationship (*173, 191*), statistical studies of lung cancer mortality rates in the population of various American cities having marked differences in atmospheric soot seem to contradict it, as far as a purely environmental exposure to soot is concerned. The lung cancer rate among males in Pittsburgh was found to be lower than that of any other large city surveyed, with the exception of Denver.

A direct contact with tar, and the inhalation of tarry fumes, in connection with tobacco smoking has been related on the basis of some doubtful evidence to the occurrence of cancer of the lip, oral cavity, tongue, and larynx. (*167, 237*).

It is most likely that tarry combustion products play the major role in the development of cancer of the abdominal skin which accompanies the use of certain heating devices such as the Kangri in Kashmir, the Kairo in Japan, and possibly the Chang in China (*264, 131*). A similar mechanism is evidently responsible for the chutta cancer of the mouth seen among the Northern Cicars of Vizagapatam province in India, who develop cancer of the hard palate due to contact with tar fumes and to burns caused by smoking cigars with the lighted end inside the mouth (*180, 181*). This practice is followed by men and women alike, and is responsible for the fact that cancer of this part of the oral cavity is six times more frequent among the Northern Cicars than it is among the inhabitants of the Bombay region. Another example of a habitual cancer in which contact with soot and grime seems to play the major part is offered by the dhoti cancer, which develops in the region of the loin and the groin as the result of friction and chemical irritation produced by the continued wearing of a loin cloth covering the nether parts of the body. As this garment is not often removed and cleaned, the accumulation of soot from the fireplace, in addition to the decomposition products of unsaturated skin fats (*177*), play the causative role, as it seems also to do in the production of scrotal cancer among the poorer classes in England (*176, 235*).

Aromatic Amines

The possible production of cancer of the urogenic organs by exposure to aromatic amines and aniline dyes has attracted continued attention during the past few years (*68, 305, 313, 265, 6, 52, 227, 362, 55*). New cases of bladder cancer in dye workers have been reported from sev-

al countries, including Switzerland, Italy, France, England, and the United States. Both Slotkin and Maguigan noted such tumors in dye workers of Buffalo's chemical plants (*348*, *227*). Recent clinical observations finally seem to have established the carcinogenic properties of benzidine, about which there existed some doubt. While betanaphthylamine is generally recognized as a potent carcinogen, alphanaphthylamine seems to be noncarcinogenic, and aniline has remained in the controversial column. A great deal of uncertainty also exists in regard to related aromatic amines, such as phenylbetanaphthylamine, which is used for the prevention of aging in vulcanized rubber (*57*, *92*). It is significant in this respect that Rosenthal-Deussen noted the occurrence of hemorrhagic cystitis among girls employed in a fly-glue factory in which homologues of aniline were used in the preparation of the glue, and that Koelsch recorded similar symptoms in English ammunition workers handling aniline, o-, m-, and p-toluidine, and xylidine (*314*, *188*).

It is likely that the incidence of bladder cancer might rise if a therapeutic practice originally advocated by Henschen in 1937 and recently endorsed by Allemann should find general acceptance. Henschen advised the treatment of bladder cancers by oral medication with betanaphthylamine which he and Allemann believe to be a form of biological chemotherapy for cancers of this organ (*6*, *148*).

On the experimental side, the work of Bonser and of Maguigan and Dobriner has confirmed the previous investigation of Hueper and co-workers by producing cancer of the bladder in dogs by ingestion of commercial as well as pure betanaphthylamine (*32*, *227*, *163*). Maguigan and Dobriner (*227*), however, failed to cause such tumors in dogs by the administration of benzidine, though it evoked hepatomas and leukemias in rats. Slotkin announced that the first successful experimental production of aniline cancers had been brought about by Sahr in 1905, in dogs and rabbits. The animals developed bladder neoplasms 3 months after ligation of the ureters and exposure to benzidine and betanaphthylamine fumes. These results have been confirmed by Slotkin (*348*).

Experimental observations indicate that other aromatic chemicals are capable of producing bladder tumors: o-aminoazotoluene (*407*, *275*); 2-acetylaminofluorene (*13*): o-toluidine (*252*) and 2,3-azotoluene (*361*). Stroembeck's experiments on rats, incidentally, seem to settle a controversy of long standing, as to whether the carcinogenic substances elicit neoplastic responses by direct contact with the vesical mucosa as urinary constituents, or reach this tissue by the hematogenous route (*361*). Stroembeck implanted a segment of the bladder of rats into the liver, and then administered 2,3-azotoluene. While tumors developed in the bladder stump, the transplants in the liver

remained normal, indicating thereby that the carcinogenic agent is contained in the urine.

Benzol

Additional evidence of a leukemiogenic action of benzol has been recorded during recent years (*91, 216, 142, 382, 164, 301, 289, 272, 236*). The widespread exposure of workmen in industry to benzol is evident from recent reports (*402, 75, 165, 356, 341, 196, 116, 9*). It is significant in this respect that Duvoir, Fabre, Fabre, and Derobert (*84*) were able to demonstrate benzol in the bone marrow of two men who died from chronic benzol poisoning 14 and 20 months, respectively, after cessation of exposure to this chemical. Other observations suggest that chronic exposure to benzol may be responsible for the development of polycythemia vera (*247, 142*). Kirschbaum and Mixer did not succeed in verifying the previous claims of deLignac, that mice exposed over several months to benzol develop leukemia (*184*). Finally, it may be noted that Meyer observed the occurrence of acute leukemia in a patient with subchronic naphthalin poisoning and that Rolland saw the development of an acute leukemia in a workman handling naphthol (*238, 310*). Experimental evidence indicates that tar and several synthetic aromatic carcinogens are capable of eliciting leukemic responses in mice (*184, 118, 119, 193, 212, 239, 149, 170, 100, 204*).

Arsenic

Among the inorganic chemicals, arsenic has enjoyed for years a doubtful role as a carcinogen, although next to soot it is the oldest substance related to the development of occupational cancer (Paris, 1825). Kennaway recently relegated this claim to the realm of cancer mythology and was seconded by Boyland (*174, 34*). Schwartz asserted that contact of arsenicals with the skin does not cause cutaneous malignancies, but that the ingestion of these substances is essential (*339*).

While Henry was uncertain whether or not to accept as of arsenic origin a scrotal cancer in a sheepdip worker handling sodium arsenite, he conceded that such an etiology might exist for 3 cases with medicinal (i. e., oral) exposure to this chemical, and mentioned 13 additional cases which he suspected might have the same causation (*147*). It is interesting to recall, in this connection, that Richerand reported the presence of scrotal cancer in arsenic workers as early as 1815, and that Bayle noted them in 1833 in lead workers, according to White (*396*). Although White did not consider these reports reliable, it may be worth noting that Tamponi recently mentioned the development of ulcers of the scrotal skin in certain Sardinian workers who used a spray containing sodium arsenite for combatting grasshoppers

964). Negishi recorded the occurrence of arsenic poisoning in lead-workers (*860*), and Schaerrer reported arsenic cancers of the skin in silver miners (*332*).

Additional cases of occupational cancer through contact with arsenical spray or fumes from smelters have been recorded in America (*112, 366*), Japan (*245*), England (*269, 104, 296, 55*), and Germany (*287, 146, 29*). While none of these cases showed scrotal lesions, this fact scarcely represents a valid reason for denying such a localization, especially if the conditions of exposure and of personal hygiene should favor a cancerous development at that site. Although Gross considered the incidence of industrial arsenic cancer as low (*136*), there is no doubt that arsenical occupational dermatoses and hyperkeratoses among various types of workers (loaders and packers of arsenicals, cotton field workers, vineyard workers, workers in arsenic plants) are not uncommon (*335, 231, 172, 117, 53*).

Despite the controversial evidence in regard to industrial arsenical cancer of the skin, its occurrence on a medicinal basis appears to be firmly established (*166, 375, 384, 300, 286, 15, 325, 281, 337, 248, 308, 326, 9, 106, 316, 147, 129*). In view of the recent claim of Merewether (*235*) that nobody could relate the development of a melanomatous malignancy to an exposure to an extrinsic agent, mention may be made of an observation of Rothman and Felsher (*316*), who reported the occurrence of a malignant melanoma on the basis of a medicinal arsenical leukomelanoderma.

Strong evidence recently has accumulated, according to Hunter (*164*), indicating that exposure to arsenicals may predispose to the development of cancer of the lung. In support to this claim he revived the theory of the arsenical origin of the lung cancers in the miners of Schneeberg and Joachimsthal. The occurrence of cancer of the lung in persons with cutaneous evidence of chronic arsenic poisoning in connection with industrial or medicinal exposure was reported for nine cases (*36, 235, 147, 248, 287, 129*). Similar claims have been made in regard to the causation of bladder cancer.

In view of the rare development of hyperkeratoses and cancer in persons exposed to arsenicals—none among 12,321 orchardists known to be in contact with lead arsenate (*259*), and none among the arsenic eating mountaineers of Tyrol and Styria (*273*)—Wile considered other predisposing factors to be essential (*398*). The experimental evidence of the carcinogenicity of arsenicals is meager, and is merely suggestive (*309, 163*). It is possible that the relatively short lifespan of the mice used prevented the arsenicals from taking proper effect, or that the more rapid and effective excretion of arsenicals through the hair in furred animals is responsible for the present unsatisfactory experimental results.

Chromium

Chromate cancer of the lung is another of the metal cancers which deserves special attention because of its rather recent discovery and the obscure nature of its causative mechanism (*338*, *207*). Although Stewart recently asserted that the statistical evidence supporting the claim of an occupational origin of these tumors was "filamentous," (*358*), this contention is not borne out by the actual data available. Kennaway commented on the extremely high incidence of lung cancer among the chromate workers at Griesheim (*174*), apparently referring to a previous statement of Gross (*136*), who had placed the incidence rate of lung cancer as high as 40 percent for the worker population of some plants.

From the official information available, there were in Germany up to 1939 a total of 39 cases of lung cancer among approximately 1,000 chromate workers employed in several plants for a sufficiently long time to be affected (*163*). The incidence of lung cancer among the chromate workers, living and dead, was thus 4 percent, according to noncorrected figures, and was in all probability higher. This is at least four times the normal rate for the general adult population. Recent observations indicate, moreover, that the occurrence of these cancers is not restricted to German operations, as similar cases have been observed in American chromate plants (*224a*).

Cancers developed mainly in workers employed in and around chromate and bichromate operations, where exposure to chromate dust was present (*7*, *136*, *137*). Workers affected were employed in the grinding and mixing of ores, in the oxidation of chromite to chromate, and in the transformation of monochromate to bichromate. Chromium pigment workers, clerks, glazers, drivers and locksmiths working transitorily in and around such operations were also affected. The length of exposure varied from 7 to 47 years, and the age of workers with manifest lung cancers from 29 to 69 years. Kennaway's recent statement (*174*) that the relatively advanced age of these workers indicated a comparatively mild cancerous stimulus, despite the high incidence of lung cancer among those exposed, is therefore open to question.

The actual extent of this cancer hazard cannot be properly evaluated at this time for lack of reliable data. However, it may be considerable. Chromium ores, which are mined in South Africa, Turkey, Greece, and the Philippines, are extensively used for the production of armor plate, projectiles, gun carriages, axles, springs, cutlery, and other steel goods; as an alloy of manganese, cobalt, tungsten, vanadium, and nickel; for the manufacture of high-speed tools, exhaust valves, turbine blades, roller bearings, and pump rods; in stainless steel processing; for pigment making in inks, paints, glass, and

enamels; as oxidizers in aniline dye production; as mordants and tanning agents; for bleaching fats and oils; and for the plating of metal parts (*380*).

The only experimental evidence available is that offered by Schinz, who implanted metallic chromium in the thighs of rabbits and observed in some which survived for more than 4 years a few sarcomas at the site of implantation and some lung carcinomas (*333*).

Nickel Carbonyl

The occurrence of cancer of the nasal sinuses and of the lung in copper-nickel refinery workers in South Wales may represent another example of metal cancer, with nickel or nickel carbonyl as the active agents. The South Wales refineries use nickel ores mined at Sudbury, Canada, and subject them to the Mond process, which uses nickel carbonyl in the separation of copper from the nickel (*24*). This concept is disputed by Amor (*8*), who claims that none of the workers who come in contact with nickel carbonyl suffer from any diseases of the respiratory tract. He believes that arsenic is the carcinogen responsible for these cancerous manifestations in the respiratory organs, because such reactions have not been seen among workers in Canadian refineries using the same ores and the same procedures, except that sulfuric acid is not employed for the extraction of copper. It is not possible at this time to comment on these claims without knowing the length of time that the Canadian plants have been in operation. As the average latent period of these cancers is 22 years, the apparent absence of nasal and pulmonary cancers among the Canadian workers may simply be due to a time factor.

Up to 1939 there were 34 cancers of the nasal cavity and sinuses, mainly the turbinates and ethmoids, and 24 cancers of the lung (*55*). An analysis of the death certificates issued in South Wales showed that 36, or 34.2 percent of the 105 cancers of the respiratory organs which occurred between 1907 and 1934 among the population of the district in which the nickel refineries are located were in copper-nickel refinery workers. The attempt made by Campbell to produce lung cancer in mice by the inhalation of nickel dust gave inconclusive results (*47*).

Beryllium

The development of sarcoid granulomas in the lungs of workers exposed to the inhalation of beryllium dust represents the most recent addition to the list of blastomatous and blastomatoid reactions to metals in man (*122, 197*). Lanza collected 20 to 25 such cases in a plant manufacturing fluorescent lamps. Gardner mentioned a total of about 100 cases with pulmonary reactions to beryllium. Of these

he considered about 60 as being genuine. The relatively large number of cases observed within a comparatively short time indicates the possible extent of this industrial hazard (*155, 400, 381, 229, 353, 201, 65*), and reflects the wide use beryllium has found in industry in recent years. The metal is used as an alloy with copper, aluminum, magnesium, nickel, iron, and silver. It is used in fluorescent lamps as a phosphor. It is found in radio tubes, incandescent lamps, electric heating elements, and in phosphorescent compositions such as luminous indicators. Refractories, particularly certain types of crucibles, contain it, as do vitreous enamels, gas mantles, and certain textiles. It may also be a part of the process of producing atomic energy.

The actual causation of these pulmonary reactions in the human lung is unknown. However, there is some indication that other factors besides beryllium are at work. Experiments on dogs, rabbits, guinea pigs, white rats, and white mice did not result in pulmonary proliferative responses when zinc beryllium oxide or other mixed phosphors, such as strontium, barium, and cadmium, were administered by inhalation or injection. On the other hand, rabbits injected intravenously with zinc beryllium silicate and insoluble beryllium oxide almost invariably developed highly malignant sarcomas of the bones within 5 to 7 months (*122*). These tumors closely resembled those caused in the bones of luminous dial painters by radioactive matter.

Asbestos

Another one of the more recently discovered occupational cancers which may belong to the metal group is the cancer of the lung in asbestos workers. Asbestos consists of polymerized silicon oxide molecules which form long chains laterally interconnected by weak metal ion links (iron, magnesium, aluminum, caesium). Since 1935 a total of 23 cases of asbestos cancer of the lung has been reported by American, English, and German investigators (*221, 222, 128, 406, 162, 260, 96, 188, 393, 390, 158, 214, 160, 28, 330*). Wedler (*390*) noted that there were 14 cases of lung cancer among a total of 92 autopsies on asbestosis patients. Four of the cancers were present in females, the rest were in males. They ranged in age from 35 to 75 years, and the exposure time from 3 to 27 years. It is noteworthy that the manifestation age of asbestos cancer is relatively young.

The asbestos industry in the United States employed some 19,000 workers in 1944 (*347*). More than 10,000 of these were exposed appreciably to asbestos dust (*197*). Despite this high percentage of exposed individuals, the incidence of asbestosis is low (*347*). This information contrasts strongly with that available from Germany, where Boehme, studying 132 out of 500 workers in an asbestos factory, found radiological evidence of asbestosis in 29 percent (*27*). The

ncidence of this complication increased with the length of exposure. Asbestosis was present in 5 percent of workers employed for less than 3 years, 18 percent of those employed from 3 to 5 years, 56 percent of those working from 5 to 10 years, and 79 percent of those exposed for over 10 years.

Nordmann and Sorge (*267*) exposed mice to inhalation of asbestos dust for from 6 to 9 weeks. Of the surviving animals, 20 percent developed squamous cell carcinoma originating from the bronchial mucosa. Other epithelial growths in various stages of development were present in 42 to 57 percent of the animals, in addition to diffuse or nodular fibrosis of the lung. The histological character of the cancers (squamous cell carcinoma instead of adenocarcinoma of the spontaneous type) and the histogenetic derivation of the tumors (bronchial mucosa instead of alveolar epithelium of the spontaneous type) support a specific causation of these reactions by inhaled asbestos dust.

Potential Chemical Environmental Carcinogens

Experimental evidence obtained during the last few years indicates that perhaps only a small part of the total number of existing environmental carcinogens is known, and that entirely new types of agents may be discovered. This is foreshadowed by the work of American investigators, who found that selenium, diethylene glycol, carbon tetrachloride, chloroform, ethyl carbamate and ergot are capable of producing tumors of the lung, liver, bladder, or nervous tissue, in mice or rats. It is interesting to note that several of these substances are aliphatic compounds, which are not ordinarily credited with possessing carcinogenic properties. However, the possibility that aliphatic chemicals or their cyclic condensation products may exert such an action in man is suggested by recent observations in the field of occupational carcinogenesis. The fact that environmental cancers can be produced by metals or aliphatic compounds seems to call for a great deal more attention to these agents than has been given in the past.

Selenium, which has found extensive use in industry during recent years, is the cause of the so-called alkali disease among cattle in those parts of the United States where the soil contains excessive amounts of the substance. Cirrhosis of the liver and hepatomas were produced in rats which were fed selenium (*262*). Male rats fed 1, 2, and 4 percent of diethylene glycol developed stones in the bladder after 32 weeks, and papillomatous bladder tumors in one-third of those tested. One of these tumors was carcinomatous (*262*).

The hepatocarcinogenic action of chlorinated aliphatic hydrocarbons such as carbon tetrachloride and chloroform, which are used as anesthetics in medicine and as cleaning fluids and solvents in industry.

offers another example of the incompletely explored spectrum of environmental carcinogens (*95, 93, 102, 94, 101*). While there is no information as yet on hepatic malignancies in man resulting from cirrhosis of the liver caused by an exposure to these substances, ample evidence is available to show that these chlorinated hydrocarbons represent a considerable industrial hazard, and have occasionally given rise to liver injuries (*80, 190, 87, 360, 74, 163*).

Of considerable significance is the discovery of the carcinogenic action of urethane (ethyl carbamate) on the lungs of mice. When urethane was administered with the drinking water or by subcutaneous or intraperitoneal injection once a week for not more than 4 weeks, the incidence of lung cancers rose from a normal level of 5 percent to 80 percent within 4 months of observation (*263, 149, 150, 199*). Propyl-, butyl-, and iso-amyl-carbamates were relatively ineffective in this respect. Inasmuch as mice and other small laboratory animals are much more sensitive to the pharmaco-dynamic actions of urethane than are dogs and men, it is possible that there may be similar specific differences in its carcinogenic effect. It is significant, however, that ethyl carbamate exhibits an ambivalence concerning cancer which is similar to that shown by other carcinogens such as roentgen rays, radioactive substances, arsenic and benzol. Like these, it is not only capable of eliciting cancerous growths, but also of inhibiting them. Urethane, when given repeatedly over a period of several months to patients with myeloid or lymphoid leukemia, produces a transitory reduction in the number of leucocytes and in the size of the spleen and lymph-node resembling that caused by the administration of roentgen rays or benzol (*284*).

Another hint at the carcinogenic potentialities of our modern environment is offered by the fact that rats treated over a period of several months with ergot developed neurofibromas in the ear (*262*). This observation is of special interest, since no direct evidence of any environmental causation of tumors of the nervous system has as yet been put on record. That such a causative mechanism is possible is indicated by the fact that animal tissues react with the development of gliomas and gliosarcomas when synthetic aromatic hydrocarbons are implanted. Nervous tissue is thus shown to be susceptible to these agents. Moreover, the appearance of a glioma in the brain of a rat fed 2-acetylaminofluorene, a chemical developed as an insecticide (*403*), demonstrated the possibility of an indirect contact of the brain with a cancer producing environmental agent (*217*). This action may perhaps depend on certain chemical affinities of the nervous tissue, similar to those possessed by bone marrow for benzol and of bony tissue for radioactive substances.

There are without doubt other environmental exposures which may

involved in the causation of cancer in man. In view of the role which estrogens play as cocarcinogens in the production of mammary cancer in mice, including those of the male sex (*193*), and of the alleged but still unproved similar effect in women, the recent observation of swelling of the breasts, due to a proliferative glandular hyperplasia, in male workers engaged in the production of stilbestrol, is of distinct interest (*331*, *110*). The subsequent appearance of mammary cancers in such workers would provide positive proof of the existence of such relations, since cancers of the breast are rarely met with in human males. The ratio of male to female mammary cancer is 1 to 88 (*281*). Suggestive evidence supporting such interrelations was provided recently by Abramson and Warshawsky, who observed the development of a mammary cancer in a man who received over prolonged periods a dose of diethylstilbestrol (1 mg. daily, for a total of 1,097 mg.) in the treatment of cancer of the prostate (*1*).

Physical Environmental Carcinogens

Ultraviolet Rays

The concept of the causation of cancer of the exposed parts of the human skin and lower lip by the ultraviolet portion of the solar spectrum has, during recent years, received additional support from epidemiological, occupational, sexual, racial, and experimental observations (*293*, *26*, *363*, *99*, *14*, *163*, *216*). Since not only chronic solar or chemical dermatitis and cancer, but also the so-called senile keratoses, are absent or very rare in colored persons, it is probable that these precursors of cutaneous cancer in the skin of white persons are at least in part the result of exposure to injurious environmental influences (*352*).

The actual causative mechanism of solar cancer has remained as obscure as that of other actinic cancers. It is not likely, however, that these neoplastic reactions ensue from a sudden, physically induced, cellular mutation, because of the long latent period usually observed. Whether or not the photochemical production of endogenous carcinogenic chemicals through a direct action of ultraviolet rays upon certain cellular components (sterols, aromatic protein complexes, pyrimidines) might be responsible for these cancers is still uncertain, as attempts to isolate a chemical carcinogen from irradiated tissue have been unsuccessful (*359*, *153*).

Discussing the practical importance of solar cancer for members of the white race, Blum (*25*) noted that even if a carcinogenic action of solar rays on the human skin is granted, there is no cause for alarm. Under most severe conditions of exposure, only two-tenths of 1 percent

of the population develop skin cancers. It is not thought that the solar cancer hazard would necessitate the exclusion of the fair-skinned members of the white race from colonizing the tropics, since adequate protective measures are available, and since the existing hazard is so small. This conclusion receives some support from the considerably lower incidence of solar cancer among the female part of a population in sunny, dry regions. Probably this is due to the fact that women take better care of their skin and are more prone to apply protective measures, and also to the fact that they undergo less exposure for reasons of sport and occupation.

Roentgen Rays and Radioactive Substances

The danger of cancer formation through exposure to corpuscular energy (alpha and beta rays) and electronic energy (gamma rays and roentgen rays), which was previously restricted to relatively small groups of individuals, has reached considerable proportions through the scientific, military, and civilian use of atomic energy, with its numerous radioactive fission products (*193*, *206*, *79*, *49*, *90*, *378*, *377*, *111*, *169*, *389*, *261*, *254*, *255*, *399*, *88*, *404*, *270*, *35*, *251*, *312*, *303*, *39*). Uhlmann pointed out in 1942 that despite the improvements in roentgen apparatus and technique many injuries are still caused by actinic burns (*374*). He saw 70 such cases in 3 years in the Tumor Clinic of Michael Reese Hospital, Chicago. While about half of these injuries were present in physicians, only five were found in roentgenologists. The others were general practitioners and specialists of other branches of medicine handling roentgen equipment and radium. He believes that physicians in general are not sufficiently familiar with the techniques of using such devices and with the proper precautions to be observed.

The indiscriminate use of electronic energy during the First World War resulted in many burns with their frequent carcinomatous sequelae, which are said to follow in 25 percent of all chronic radiodermatitis cases. Evidence is accumulating that the industrial and medical use of roentgen rays and radium during World War II was not entirely free from similar complications, despite the increase in knowledge of protective measures essential to their use. Drinker recently noted (*80*) that the misuse of X-ray equipment in the hospital of one Maritime Commission shipyard forms an unwholesome chapter in our war history, and that in other shipyards where roentgen rays and radium were employed for the inspection of weldings and castings proper precautions were observed only after some struggle with the physicists in charge and the managements.

Additional evidence on occupational, medicinal, and cosmetic radiation injuries and cancer has been reported during recent years (*295*,

208, *346*, *161*, *67*, *171*, *48*, *146*, *225*). McMahon et al recorded what might be the first human case of sarcoma formation following a diagnostic intravenous injection of thorotrast 12 years previously (*225*). Hatcher reported the occurrence of bone sarcomas following the irradiation of tuberculous joints with large doses of roentgen rays and radium, and collected 24 such cases having a median latent period of 6 years (*146*).

New evidence was advanced supporting the leukemiogenic action of small doses of electronic energy in man, similar to that seen previously in mice (*163*, *149*, *182*, *119*). Ulrich found that the incidence of leukemia among American radiologists is eight times that of the average physician (*376*). A 3.9 percent mortality from leukemia was reported among 205 radiologists who died between 1935 and 1944, against 0.44 percent among 34,626 physicians dying during the same period. Using similar statistical materials, March (*376*) noted similar relations over a period of 15 years (8 cases of leukemia in American radiologists, with 23 additional cases recorded in the world literature). Correlations of the incidence of leukemia among American physicians with that of the white male population in general revealed that leukemia is 1.7 times more frequent among the former (*150*). Similar evidence was found in the Decennial Supplement, part IIa, Occupational Mortality, Report of the Registrar-General of England and Wales, 1931. It is interesting to note that Warren observed one case of monocytic leukemia, following a preliminary leukopenia and anemia, among those Japanese exposed to atom bomb radiation (*389*).

No fundamentally new or important information has been recorded during the last few years in regard to the causation of lung cancers among the cobalt miners in Schneeberg and the uranium miners in Joachimsthal, although the significance of this problem has greatly increased. If reports from these regions are correct, these mines as well as those previously abandoned in adjacent territory are being worked with high intensity for radioactive ores. Other pitchblende-containing mines in Canada and the Congo have been mined for atomic fission materials at a greatly increased rate since the end of the war. Search for similar ores is carried on in many lands for the same purpose.

Such activities entail exposure to the inhalation of radioactive dust and gases, a hazard which may extend, if proper precautions are not taken, to the neighboring population. Similarly, populations surrounding atomic energy plants may be exposed to radioactive fumes and waste waters. In view of these facts, it seems urgent that definite information be obtained whether the lung cancers of the Schneeberg-Joachimsthal miners are caused by radioactive energy (*163*), or by

other substances present in the ores, such as arsenic (*8*), nickel (*333*), chromium (*136*), or at least in part by concomitant silicosis (*218*).

Campbell's experiments on mice inhaling a pitchblende dust containing no arsenic and practically no radium gave inconclusive results as to the development of lung cancers (*47*). Lorenz, Heston, Deringer, and Eschenbrenner exposed mice to a long-continued irradiation with gamma rays (8.8 r gamma per 8 hours—definitely higher than that to which the Schneeberg miners are subjected), and found that lung tumors increased over 50 percent above the normal level (*219*). In view of the marked differences in exposure, these investigators concluded that the Schneeberg cancers are apparently not of radioactive origin. However, inasmuch as the degree of exposure to radioactive materials varies greatly at different times and in different mines at Schneeburg, this conclusion cannot be accepted without distinct reservations. On the other hand, experiments of a similar nature performed on mice by Rajewski, Schraub, and Kahlau (*302*), resulted in a larger increase in the incidence of lung tumors, but they cannot be regarded as reliable because of improper experimental conditions as to age and selection of animals.

Henshaw (*149*) and Henshaw and Riley (*151*) produced leukemic conditions, in addition to skin cancers, in mice exposed to small amounts of X-rays as well as to pile radiation. Furth (*119*) observed not only leukemic conditions but also ovarian cancers in female mice after a generalized radiation. Osteogenic sarcomas were produced in animals by the intradermal injection and oral feeding of 25 to 100 gamma of radium (*82*, *103*) and by the insertion of mesothorium into the bone marrow of rabbits (*338*). Brues (*40*) obtained bone tumors in animals exposed to various uranium fission products from a chronic reacting pile. The length of the latent period of these tumors was a function of the dose. Petrov and Krotkina (*292*) furnished proof of their observations, reported several years ago, on the development of carcinoma of the gall bladder in guinea pigs following the implantation of radium.

Dietary Carcinogens

A great deal of experimental evidence relates dietary conditions to the development of cancer in animals (*46*, *253*, *297*, *321*), such as the effect of caloric restriction on the incidence of cancer (*365*, *323*, *324*, *198*, *322*); the influence of members of the vitamin B complex (riboflavin, inositol, choline, biotine), amino acids (cystine), avidin, and various oils, on the susceptibility or resistance of the liver in rats to the carcinogenic action of certain aromatic azo-compounds (*44*, *124*,

57, 272, 187, 342, 205, 242, 43) ; the effect of cystine and lysine on the incidence of spontaneous cancers in the mouse (*394, 134, 240, 395*) ; and the possible production of carcinogenic products through the development of oxidated oils as the result of overheating animal and vegetable fats and lipoids (*291, 17, 16*).

While these experimental observations have no counterpart as yet in the production of human cancers by environmental agents, there are several environmental cancers in man in which dietary factors apparently play a definite while indirect role.

Cancer of the Pharynx

In those parts of Sweden and Finland located within the Arctic Circle, the main diet throughout the year consists of reindeer meat and salt fish. Only during the short summer are green vegetables available. As a result of this unbalanced, vitamin-deficient diet, a symptom complex appears, mainly in women, which is termed the Plummer-Vinson syndrome. During the course of the deficiency state hyperkeratoses of the oral and nasopharyngeal mucosa develop, which ultimately lead to the appearance of cancer of the nasopharynx (*4, 2, 249*). Ahlbom found this syndrome in 65 percent of 123 women with cancer of the mouth, pharynx, and esophagus (*4*).

Liver Cancer

The second member of this group is the primary cancer of the liver which occurs, apparently on the basis of certain dietary deficiencies, among African Negroes, particularly Bantus, employed as miners in the gold mines of Witwatersrand near Johannesburg, and also in Javanese and Chinese. The excessive incidence of these cancers, which are relatively rare among whites and also among colored people enjoying European-American living standards, has been known for a number of years (*343, 21, 31*), and has been attributed variously to some special racial susceptibility, to endemic parasitic infection, or to nutritional deficiencies (*174, 21, 317*).

The dietary theory has found an increasing number of supporters in recent years, as these cancers developed on the basis of a cirrhosis. Since it had been shown that cirrhosis of the liver in experimental animals (*30, 140, 66, 86, 26*) follows certain dietary deficiencies (protein and vitamin B complex), and since it is known from human observations that cirrhosis of the liver is a frequent precursor of primary cancer of the liver, a dietary origin for these cancers in the ill-nourished colored people was suspected. This concept recently received weighty support from the clinical, pathological, and experimental studies of a group of South African scientists (*125, 126, 127*),

who succeeded in producing cirrhosis of the liver, as well as primary cancers of that organ, in rats fed the deficient diet (mealie pap and sour milk) consumed by the Bantus. Similar observations were reported by Copeland and Salmon (*61*), who elicited cirrhosis and carcinoma of the liver in rats fed a diet deficient in choline. The animals developed not only tumors in the liver, but also primary cancers in other internal organs, including the lungs.

It will be important to watch for the possible development of these and other types of dietary cancers among the starving people in various parts of the globe, especially as the available diet is often deficient in proteins, fats, and vitamin B complex, and in view of the fact that primary cancer of the liver is uncommon among white Europeans. Another location which may yield additional confirmation is Trinidad, where the laborers employed in the oil fields have a diet which is grossly deficient in vitamins A and B (*85*).

Cancer of the Thyroid

The excessive incidence of carcinoma of the thyroid in regions with endemic goiter due to iodine deficiency in the soil, drinking water, and foodstuffs represents the third example of an environmental cancer in man on the basis of dietary imbalances (*386*). These cancers usually originate from adenomatous nodular goiters, and have their experimental counterparts to some extent in the thyroid hyperplasias and adenomas produced in rats when given a diet of rapeseed or one containing thiourea (*299*, *135*, *22*). In 2 of 30 rats given thiourea the resulting thyroid tumors were metastasizing carcinomas. This malignant transformation of thiourea-treated thyroids can be enhanced by the simultaneous administration of 2-acetyl-aminofluorene (*22*). The possible implications of these observations in rats as to the potential hazards connected with a prolonged thiouracil treatment of toxic goiter in man are obvious.

Indefinite Environmental Carcinogens

The last group of cancers to be listed has a well-established relation to environmental agents which are of ill-defined character.

Schistosomiasis Cancer of the Bladder

Although the excessive incidence of bladder cancer among the inhabitants of Egypt and the causal relation of this neoplasm to an infection with Schistosoma hematobium has been known for many years (in fact, it is the oldest recognized environmental cancer), it still

seems to be rather common among the fellahs of the Nile Valley. Ward recently observed 130 cases of bladder cancer in a Cairo hospital; most of them were associated with schistosomiasis. Twenty-two of his patients were under 30 years of age (*387*). This is only one of many environmental cancer observations, incidentally, which indicate that senile changes have very little connection with the causation of many cancers.

Afifi has stated his doubts of the actual existence of causal relations between vesical schistosomiasis and bladder cancer (*3*). However, he also cited data from autopsy records obtained by Sorour in two Egyptian hospitals which seem to support such relations. Sorour found 85 cases of cancer of the bladder, or 23.3 percent of the total of 254 cases of cancer seen in 5,924 post mortem examinations. This incidence rate is about 10 times the normal rate for bladder cancer (*350*).

While a schistosomiasis infection has repeatedly been connected with development of primary cancer of the liver, especially in the Chinese, such a relation has not been observed in Egypt. It seems to be losing ground increasingly in other parts of the world where schistosomiasis occurs (*143*, *226*).

The repeated occurrence of schistosomiasis in veterans of World War II, who acquired the infection while serving abroad in areas where the disease is endemic (*368*, *291*, *250*), possibly may result in the development of bladder cancer in some of these former soldiers in years to come.

Betelnut Cancer of the Mouth

While in general the habit of betel-nut chewing is undoubtedly the cause of the excessive incidence of cancers of the oral cavity observed in certain parts of India and the Philippine Islands, there is evidence that the composition of the buyo quid is an important factor. Eisen found, for instance, that this habit does not lead to mouth cancers among the inhabitants of New Guinea and adjacent islands (*97*). Khanolkar also reported that there were considerable variations in the incidence of oral cancer in different parts of India, despite widespread adherence to the betel nut chewing habit (*176*). Khanolkar is inclined to agree with Somervell (*349*), who noted that the oral cancer incidence is high in those parts of India in which the quid contains a strong variety of tobacco in addition to the usual ingredients. Woelfel, Spies, and Cline (*405*) suggested that the essential carcinogenic factors might be furnished from the betel leaves by certain allyl phenols and isomeric propenyl compounds which dimerize under the influence of sunlight and form stilbenols.

Khaini Cancer of the Lower Lip

Cancer of the lower lip (Khaini cancer) is the most common oral cancer among natives of Bihar in northwestern India. It apparently results from the irritation caused by the placing of a pinch of rubbed tobacco mixed with lime in the groove between the front teeth and the lower lip (*177*). The composition of this mixture resembles that of the buyo quid inasmuch as it also contains tobacco and lime. These observations receive some support from a report of Friedell and Rosenthal (*277*) on the etiologic role of chewing tobacco in cancer of the mouth and from claims made by German investigators (*278, 279*) in regard to the carcinogenic effect of tobacco dust on the lungs of cigar makers and sorters.

Cancer of the Scalp

Carcinoma of the scalp is frequent among Mohammedans in Northern India who shave their heads with blunt razors, thereby causing frequent abrasions and infections. Similar observations have been reported among the Mohammedans of North Africa.

Thermic Cancer

The not infrequent development of cancers in accidental wounds and scars resulting from burns is a recognized observation, although the causative mechanism involved is still obscure. The carcinogenic action of thermic rays acting over a long period of time, however, is open to question. The occurrence of cutaneous cancer on the shins of English railroad engineers, allegedly caused by the heat from the firebox, furnished the basis for such claims. Warniek (*388*) recently revived this concept by reporting the development of a cancer of the face in a fair-skinned, red-haired man employed as a roller in a rolling mill where he was exposed to excessive radiating heat. Mattenci (*232*) contended from an analysis of 93 cases of skin cancer that basal cell cancers are elicited by infra-red rays, while squamous cell cancers are due to ultraviolet rays.

In commenting on his case, Warniek noted the small number of reports concerning the appearance of basal cell cancer in workers exposed to heat rays (*388*). Inasmuch as heat waves carry a relatively small amount of energy, it is not likely that they would exert profound effects on the chemical structure of the various cellular components, and thereby contribute to the causation of endogenous carcinogens. Proper consideration moreover must be given to the fact that workers exposed to radiating heat are also usually in contact with the tarry combustion products of coal or oil.

Extrinsic Co-, Pro- and Anti-carcinogenic Factors

A great deal of work has been done in recent years on the various cocarcinogenic, procarcinogenic and anticarcinogenic factors of local and systemic nature, active in and influencing experimental carcinogenesis (*321*, *285*, *19*, *365*, *210*). However, there is very little definite information in this connection on environmental cancers, even though such data are of considerable importance in regard to the conditions influencing local incidence, individual susceptibility, epidemiology, and development of effective preventive and prophylactic measures (*346*).

The postulated causative role which physical or chemical trauma is supposed to play in the production of accidental cancer has for many years been of special scientific and medicolegal interest. The problem has been the subject of a great deal of experimental work, particularly in recent times, and contradictory results have been obtained. Many investigators obtained negative answers as to the positive effect of trauma of various kinds on different types of carcinogenesis (*41*, *71*, *73*, *72*, *220*, *283*, *320*). Others found that physical or chemical traumas seemed to favor the development of cancer in prepared soil (*195*, *372*, *306*, *19*, *163*, *62*, *213*, *56*, *69*, *115*, *203*, *274*, *304*, *311*, *319*, *367*). The practical significance of the relation between trauma and cancer has again become of increased importance because of the present and future medicolegal adjudication of claims derived from war injuries (*189*, *89*, *209*, *59*, *81*, *107*, *249*).

The knowledge that several environmental carcinogens, such as roentgen rays, radioactive substances, benzol, and arsenic, possess bivalent properties in regard to the development and destruction of ncer has led several investigators to attempt the development of a biochemical or biophysical treatment of cancer by extending this principle to other carcinogens. It was thought that the administration either of small amounts of a known environmental or experimental carcinogen, or of a carcinogen of low potency, or of a chemical noncarcinogen possessing a structure closely resembling that of a carcinogen, might counteract the development or further growth of a cancer of known or unknown etiology (*336*). This type of reasoning has during recent years received important support from the successful application of structural blockage to the chemotherapy and immunotherapy of infectious diseases, as well as to the action mechanism of various vitamins.

Thus Henschen and Allemann proposed the treatment of bladder cancer by the intravesical or intravenous administration of betanaphthylamine (*6*, *148*). It may be possible that the antagonistic action of estrogens on the growth activities of prostate cancer depends on such a mechanism (*141*). Some experts have suggested that one way

to prevent the more malignant cancers of the internal organs would be to elicit skin cancers, biologically less malignant and more easily cured, by physical or chemical means (*11, 12, 238*).

On the experimental side, an antagonistic action between chemical carcinogens of high and low potency when applied to the skin of mice has been reported (*194*). Hashida has recorded the anticarcinogenic properties of certain aniline dyes in the production of liver cancer by o-aminoazotoluene (*144*). Haddow, Harris and Kon, as well as Boyland, concluded from similar experiments that a structural similarity between potent carcinogenic and inhibitory compounds may be involved in the antagonistic action (*141, 34*). Additional experimental evidence supporting such a correlation exists (*354, 33*).

Although the practical therapeutic application of the principle of ambivalence has given permanent curative results only in connection with roentgen rays and radioactive substances, the various observations thus far made in this field are of sufficient promise to justify an extensive study of specific chemical anticarcinogens.

Causative Mechanisms

Among the considerable variety of carcinogenic agents already known or suspected, the viruses and virus-like pathogens are conspicuously absent. Since the "milk factor" has been classified among the viruses by some observers, it is not impossible that future studies may demonstrate the presence of such "ready-made for action" carcinogens in human cancers. Suggestive evidence in this direction is presented by the occasional development of cancer of the penis on the basis of condylomata acuminata which have an established virus causation. It can be anticipated that with the increasing identification and characterization of extrinsic carcinogens, an intelligent systematization of such agents will be developed, which will equal that now existing for the microbial human pathogens. But before this information can become fully useful, it is essential that the present and future information on the causal genesis of cancer be adequately supplemented with data on its formal genesis. Due to the present inadequate state of knowledge of this aspect of the problem, one can only advance hypotheses derived from the correlation of a number of isolated observations, most of which are related to experimental and spontaneous cancers in animals.

It has been found in recent years that not only cancers in fish, reptiles, and birds, but also a few papillomatous tumors in mammals, such as the Shope cotton tail papilloma, are caused by animated proteinic matter, the so-called viruses (*178, 139, 355, 113, 114, 344, 285, 318, 60*).

These agents possess antigenic properties (*224*). A similar claim has been made by Taylor (*366*) in regard to the agent responsible for and isolated from mammary cancer of the mouse. Specifically, the "milk factor" involved in and essential for the production of this tumor has been identified as a virus of macromolecular, proteinic nature (*23*, *10*, *383*, *42*) which acts as an antigen and produces antibodies when injected into rabbits (*132*). It seems to be established that it is normally transmitted from the mother to the offspring through the milk, and that this transmission is accomplished most readily during the first 12 days of postfetal life. This covers the period when the milk consists of a mixture of actual milk and blood serum called colostrum, and when the intestinal mucosa of the young mice has an abnormal permeability which permits the penetration of macromolecular material (*246*). It is thus possible that the milk factor is not actually a virus, but merely a large, pathogenic and antigenic protein molecule which causes during the early part of postfetal life a chemical sensitization that cannot become manifest until the shock organ, the mammary gland, has been transformed under the stimulus of estrogens into a reactive medium (*76*, *77*).

The possible importance of macromolecular carcinogen-protein complexes in the formal genesis of cancerous growths is apparent from the work of Creech et al. (*63*, *64*), with substances of this nature prepared by the isocyanate method of coupling aromatic carcinogens with proteins. Hoffman-Osterhof (*156*), emphasized the possible significance of such complexes as important links in the process of carcinogenesis by pointing out that amino groups of proteins couple readily with quinones and that quinones are formed in the body from aromatic amines and related substances (*123*), and thus become the source of allergic reactions. Similarly, the sulfhydryl group of the protein molecules may provide an avenue for the combination of these macromolecules with extrinsic carcinogenic chemicals, such as arsenic (*123*, *108*). The recent inability of Mayer (*233*) to prevent the proliferation of epithelial cells exposed to aromatic amines by the administration of pyribenzamine can scarcely be considered a valid reason for denying the absence of an allergic reaction in the development of such proliferative responses to specific stimuli. Timofiew and Schewtschenko (*370*) also asserted that the development of precancerous conditions in the lung is related to special allergens acting on the blood, epithelium and mesenchyme, and denaturing tissue proteins.

It is interesting therefore that Miller and Miller (*243*) found in the livers of rats treated with the hepatocarcinogen *p*-dimethylaminobenzene a macromolecular cell constituent which was probably a protein conjugated with the dye. This dye could only be recovered

by the digestion of the protein fraction of the complex and could not be extracted with solvents. As this dye complex was present in the liver cells only, Miller and Miller felt that it had an important place in the production of the liver cancers. This conclusion received support from the investigations of Gillman and Gillman (*126*) on primary cancer of the liver in Bantu Negroes. These researchers demonstrated in the liver and blood of such individuals a macromolecular, abnormally large, iron-containing protein, whose presence they related to the carcinogenesis of the liver.

When Spencer mentioned, in his dissertation on tumor immunity (*351*), the potential role of macromolecular substances in the cancer process and concluded that the possibilities of an immunologic approach to the cancer problem had not been exhausted, he pointed cancer research in a direction which offers hope and promise.

Occupational Factors in Growth of Cancer Incidence

Occupational Carcinogenic Agents

The great majority of cancers which can be traced to an occupational origin in modern times have resulted from carcinogens which entered industrial processes during the past 50 years or less. Table 1 presents all the known or commonly suspected chemical, physical and parasitic carcinogens of occupational importance.

The recent experimental production of cancers in animals by other agents of industrial significance, such as chlorinated aliphatic hydrocarbons, urethane, selenium, and beryllium, has demonstrated their potential carcinogenic properties. Consequently, it may be assumed that a more intensive study of the effects of industrial environmental factors will reveal some or many additional occupational carcinogens.

The physicochemical properties of the agent, the type of contact of the worker with it, and the reaction of the organism to it, i. e. particularly its metabolization, excretion, and fixation in certain organs, determine the site of the resulting neoplasm. It is for these reasons that different occupational carcinogens elicit cancers in the same organ, and the same carcinogen may cause the development of tumors in different organs. Table 2 briefly summarizes the existing known conditions and interrelations.

As a general rule, occupational cancers arise at those sites where the particular carcinogen has the most prolonged and intense contact with the tissues. Thus ultraviolet rays, roentgen rays, and radioactive substances, acting externally upon the skin, cause the development of cancers at the exposed parts, i. e., face, neck, and hands. Arsenicals, on the other hand, which are fixed by the sulfhydryl groups of the epidermis and hair follicles, may develop cancers also in unexposed parts of the body. Ingested radioactive matter that is fixed in the bones causes sarcoma of the bones and leukemias starting from the bone marrow. The leukemiogenic action of benzol, which may be ingested or inhaled, is due to the fixation of the chemical in the fat tissues of the bone marrow.

Table 2. *Recognized and suspected occupational carcinogenic agents showing organ systems affected*

[Classification: E—Established; D—Doubtful]

Substance	Organ or system	Class
Aniline and derivatives	Bladder, ureter, kidney	D
Anthracene, crude	Skin	E
Aromatic organic chemicals	Liver	D
Arsenic	Skin	E
	Liver	D
	Respiratory system	D
	Eyelids	E
Asbestos	Respiratory system	D
Asphalt	Skin	E
	Eye	E
Benzidine and derivatives	Bladder, ureter, kidney	D
Benzol	Blood forming organs	E
Benzol derivatives	Blood forming organs	D
Burns, thermic	Skin	E
Chlorinated aliphatic hydrocarbons (?)	Liver	D
Chromates	Respiratory system	E
Creosote	Skin	E
	Lip	E
	Eye	E
Mineral oil, crude	Skin	E
	Lip	D
	Respiratory system	D
	Eye	E
Naphthylamine, beta	Bladder, ureter, kidney	E
Nickel carbonyl	Respiratory tract	D
Oil shale	Skin	E
Paraffin oil, crude	do	E
Pitch	do	E
	Lip	D
	Bladder	D
	Eye	E
Radiant heat (?)	Skin	D
Radioactive substances	do	E
	Lungs	E
	Blood forming organs	E
	Bone	E
Roentgenrays	Skin	E
	Blood forming organs	E
	Subepithelial connective tissues	E
	Eye	E
Sodium nitrate, crude	Skin	D
Soot	do	E
	Bladder	D
Spindle oil	Skin	E
Tar	Lip	E
	Skin	E
	Respiratory system	D
	Bladder	D
	Blood forming organs	D
	Eye	E
Ultraviolet rays	Skin	E
	Eye	E

Table 1. *Classification of occupational carcinogens*

[E—Established; D—Doubtful]

Organ system	Classification	Remarks
Skin and its appendages:		
Anthracene, crude	E	
Arsenic	E	
Asphalt, artificial	E	Dependent on ingredients.
Burns, thermic	E	
Mineral oil, crude	E	
Oil shale	E	Varies with geographic origin.
Paraffin oil, crude	E	
Pitch	E	
Radiant heat (?)	D	
Radioactive substances	E	
Roentgen rays	E	
Sodium nitrate	D	Occurs in Chile only.
Soot	E	
Spindle oil	E	
Tar	E	
Ultraviolet rays	E	Not recognised as occupational.
Alimentary system:		
Aromatic organic chemicals	D	Hepatic tumors in laboratory animals only.
Arsenic	D	Increased incidence of liver carcinoma following cirrhosis.
Chlorinated aliphatic hydrocarbons (?).	D	
Creosote	E	Lip only.
Mineral oil, crude	D	Do.
Pitch	D	Do.
Tar	E	Do.
Respiratory system:		
Arsenic	D	
Asbestos	D	
Chromates	E	
Mineral oil mists	D	
Nickel carbonyl	D	
Radioactive substances	E	Lung cancer among miners and laboratory workers.
Tar fumes	D	
Urogenous organs:		
Benzidine	D	Including some derivatives.
Naphthylamine, beta	E	
Pitch	D	In agricultural workers in infested areas.
Schistosoma	E	
Soot	D	
Tar	D	
Blood-forming organs:		
Benzol	E	
Radioactive substances	E	
Roentgen rays	E	
Tar	D	
Mesenchymatous tissues:		
Radioactive substances	E	Bone.
Roentgen rays	E	Skin sarcomas, bone
Eye and its adnexae:		
Arsenic	E	Lids only.
Asphalt	E	
Creosote	E	
Mineral oil, crude	E	
Pitch	E	

Table 2. *Classification of occupational carcinogens*—Continued

Organ system	Classification	Remarks
Eye and its adnexae—Continued		
Roentgen rays	E	
Tar	E	
Ultraviolet rays	E	
Nervous system	------	None recorded.
Endocrine glands	------	Do.

The excretion of carcinogenic aromatic amines or their metabolic derivatives is responsible for the production of cancers of the bladder, where the carcinogenic urine may act over prolonged periods on the vesical mucosa. This accounts for the fact that only rarely do such cancers develop in the renal pelvis or the ureter, through which the urine usually passes without delay.

The inhalation of carcinogenic fumes, mists, vapors, gases, or dusts, which may become precipitated or fixed in the linings of the respiratory conduits and sinuses, accounts for the appearance of cancers of the bronchi and nasal sinuses in workers exposed to radioactive dusts and gases, chromate dusts, nickel carbonyl vapors, asbestos and arsenic dust and tar fumes.

Evidence Supporting an Occupational Origin of Cancer

Inasmuch as occupational cancers do not differ fundamentally from those elicited by similar or different medicinal or environmental agents, or from those of unknown etiology, the proof that a particular case or type of cancer is of industrial origin rests on evidence of varying types and significance.

Statistical Evidence

An excessive incidence of a certain type of cancer among a group of workers engaged in a definite operation or exposed to some physical or chemical agent during their normal activities has often been the first indication that an occupational agent was involved in the production of these neoplasms. However, this excessive appearance of a particular type of tumor is, as a rule, limited to groups of workers having more or less intensive and prolonged contact with occupational carcinogenic agents, and is therefore often not demonstrable for the entire worker population of a plant, or even reflected in the incidence rate of this type of cancer among the population of a community or a region. Statistical investigations that include indiscriminately large and occupationally heterogeneous groups of workers

having widely differing degrees of exposure—many of them none at all—render not only incorrect but misleading results.

Thus, cancer of the bladder has been observed in up to 100 percent of those workers who had had severe and prolonged contact with betanapthylamine and benzidine. However, when the incidence rate of bladder cancer was determined within the worker population of plants in which these industrial neoplasms were observed, the rate was approximately the same as that noted among the patient population of a large urological clinic. Cancer of the lung occurs in about 80 percent of the cobalt miners of Schneeberg and in approximately 50 percent of the uranium miners of Joachimsthal, yet there is no excessive frequency of this cancer found among the workers handling the cobalt ores in the manufacture of pigments, or among the general population of these regions when the actual miners are excluded from consideration.

It has recently been maintained that there is no evidence of an excessive incidence of lung cancer in workers with asbestosis, as the clinical examination of 20,000 asbestos workers did not reveal a single case of lung cancer. The fact is that the diagnostic distinction between asbestosis and cancerous lesions in members of this occupational group must be difficult at times. Actually, the roentgenologic examination of such a number of individuals in the general population would reveal one or more cases of cancer of the lung. A total of 23 such cases in association with asbestosis has been found by the much more reliable method of post mortem examination, thus indicating the likelihood that asbestos may under certain circumstances be carcinogenic.

The scrotal cancer of the chimney sweeps and mule spinners, the cancer of the fingers and hands of the radiologists, the cancer of the nasal sinuses and lungs of the nickel refinery workers, and the bronchiogenic cancer of the chromate workers are other examples of occupational cancers having statistically significant incidence rates.

Relation to Medicinal and Environmental Cancers

Whenever the occupational factors are known, observations made with the same agents when they form for other reasons a part of the human environment may be helpful in deciding the question of a possible occupational cause of cancer. Arsenic cancer of the skin, for instance, has been observed in an appreciable number of individuals who ingested this chemical over prolonged periods either in the form of medicine, or as a contaminant of drinking water or wine. Roentgen-ray cancer of the skin is a not uncommon late complication of excessive therapeutic irradiation. Epitheliomatous growths have been observed repeatedly after the use of vaseline or tar in cosmetics.

Precancerous Lesions

Several industrial carcinogenic agents elicit precancerous reactions which are characteristic to a certain extent of the causative agent, and which represent various transitional stages between the original normal state of the tissues and the carcinomatous end result.

Table 3. *Description of precancerous occupational lesions*

Precancerous lesions		Etiologic agent
SKIN:		
Alopecia:	Spotty loss of hair.	Arsenic, radioactive substances, X-rays.
Atrophy:	Skin grossly thinned and glistening in patches, associated with keratotic areas.	Pitch, tar, asphalt, radioactive substances, radiation (including ultraviolet rays).
Eczema:	Dry seborrheic patches on skin.	Arsenic, asphalt, pitch, soot, tar.
Keratosis:	Flat, discrete, scaly area on skin with raised pearly borders. Usually on parts of skin exposed to carcinogen, but may occur in unexposed parts, particularly about sweat glands, with arsenic.	Anthracene, arsenic, asphalt, creosote, crude mineral oil, paraffin, pitch, sodium nitrate, soot, tar, radioactive substances, radiation (including ultraviolet rays).
Hyperkeratosis:	Rough, fissured keratotic plaques with small, hard, wart-like horns, usually on hands and soles. May become nodular and ulcerate.	
Verrucae:	Form of hyperkeratosis.	
Ulceration:	Breakdown of keratotic lesions.	
Leukoderma:	Absent pigmentation alone.	Anthracene, arsenic, asphalt creosote, crude mineral oil, paraffin, pitch, tar, radioactive substances, radiation (including ultraviolet rays).
Leuko-melanoderma:	Patchy increased and absent pigmentation of skin. Most common in areas of highest pigmentation, and may involve oral mucosa.	
Melanoderma:	Increased pigmentation alone.	
Scleroderma:	Dry, scaly, parchment-like skin, with enlarged pores, associated with leukomelanoderma.	Crude mineral oil, paraffin oil, radioactive substances, radiation.
NASAL PASSAGES:		
Papillomas: Polyps:	Develop in antrum ethmoid cells, and turbinates.	Nickel carbonyl.
BLADDER:		
Hemorrhage: submucosal:	Varying size with telangiectasis. Located mainly in trigone and about ureteral orifices.	Aniline, benzidine, b-naphthylamine and derivatives.
Papillomas:	Polypous or villous, pedunculated or sessile, often multiple about trigone and ureteral orifices.	
EYES:		
Papillomas:	Pedunculated, develop mainly on lids, occasionally on eyeball.	Arsenic, asphalt, creosote, crude mineral oil, pitch, tar, radiation (including ultraviolet rays).
BONES AND BONE MARROW:		
Blood dyscrasias:	Hyperplastic, hypoplastic, aplastic, or hemolytic anemia. Thrombocytopenic purpura with spleen not markedly enlarged. Transitory leukopenia, monocytosis.	Benzol and derivatives, radioactive substances, radiation.
LUNGS:		
Pneumoconioses: Chronic Pneumonia:	Bituminosis, asbestosis, "lipoid" pneumonia, chronic chemical pneumonia, arsenical dermatosis, chromate ulcer of hands, perforated nasal septum (chromate, arsenic).	Asbestos, arsenic, tar, soot, oil, mist, chrome salts, chrome pigments, nickel carbonyl.
Blood dyscrasias:	See bones and bone marrow (above).	Radioactive substances, radiation.

These include hyperplasias, hyperleucocytoses, carcinomatoid, and sarcomatoid atypical proliferative responses, and leukemoid reactions. Hyperkeratoses, warts, and epithelial cornified horns are seen in chronic dermatoses caused by exposure to arsenic, tar, mineral oil, and related substances, and roentgen rays and radioactive substances. Hyperleucocytoses and leukemoid changes have been noted in individuals exposed to benzol, roentgen rays and radioactive energy. Sarcomatoid lesions (chronic radiation osteitis and periosteitis) seem to be the precursors of the osteogenic sarcomas found in chronic radium poisoning.

Although many of these precancerous manifestations regress spontaneously if the exposure to the causative occupational agent ceases, some of them are followed by or transformed into malignant growths. The appearance of such reactions in workers exposed to an agent which has been shown to be carcinogenic in some species of animals therefore represents a warning signal that should not be disregarded.

For this reason the occurrence of sarcoid granulomas in the lungs of beryllium workers should arouse suspicion as to their significance and ultimate development, especially as Gardner has demonstrated carcinogenic properties for several beryllium compounds in experiments with rabbits (*122*). Similar considerations should cause the various chlorinated aliphatic hydrocarbons, such as chloroform and carbon tetrachloride, to be viewed as possible carcinogens. These hydrocarbons are known to produce liver degeneration and cirrhosis in man, and have been shown to elicit hepatocarcinomas in mice.

Significance of Experimental Cancers

The experimental reproduction of occupational cancers in animals through their exposure to those agents apparently responsible for their appearance in man is considered usually to be a conclusive link in the chain of evidence. On the other hand, failure to repeat human experience experimentally in animals has sometimes thrown more or less serious doubts on the validity of the occupational evidence. This situation has been complicated further in late years by the demonstration of species specificity for certain carcinogens in relation to experimental animals.

Cancer of the skin, for instance, can be consistently produced with carcinogenic tar in mice and rabbits, with distinct difficulty in rats and dogs, and not at all in monkeys. Ultraviolet ray cancer of the skin is elicited readily in mice and rats, but all efforts to produce it in rabbits have failed. Although the occurrence of arsenic cancer of the skin in men is generally accepted, its reproduction in mice, rats, rabbits, dogs, or fowls has not yet been accomplished unequivocally. The experimental reproduction of bladder cancer by the administration of

betanapthylamine was unsuccessful in mice, gave controversial results in rabbits, and was consistently accomplished in dogs. The prolonged introduction of benzidine, the second occupational agent responsible for the development of bladder cancers in man, into dogs did not result in similar responses in their bladders, while it caused leukemia and cancer of the liver in rats.

Such divergent reactions of different species to the various occupational carcinogens apparently have their basis in the existence of fundamental differences in the metabolism of the various species. These observations are by no means unique in biology. They have their analogies in the often striking species specific differences in the reactivity to numerous chemicals and drugs, as well as in the pathogenicity of micro-organisms. Although the application of observations made in experimental cancerology to man is subject to limitations similar to those obtained in experimental pharmacology and microbiology, there can be no doubt that they are equally informative and valid when derived from a suitable species.

The experimental evidence at present available in support of a carcinogenic action on the part of many of the suspected occupational agents is often inadequate, controversial, or completely lacking. The prevailing preference for mice in this type of work is in part responsible for this situation. The secretiveness and the restrictions with which occupational cancers are often surrounded has moreover discouraged any extensive experimental study of these tumors. While adequate experimental evidence exists as to the production of cancers of the skin by tar, mineral oils, and related substances, ultraviolet rays, roentgen rays, and rays from radioactive matter, the evidence is inadequate and controversial on experimental arsenic cancer of the skin. Reliable experimental observations indicate the carcinogenic action on the respiratory tract of tar and, quite recently, of radioactive gases. The evidence for such respiratory cancers is defective, however, as to chromates and asbestos, and is entirely lacking for arsenicals and nickel carbonyl. The carcinogenic action of betanaphthylamine on the bladder has been established by the experiments of several investigators, while experimental evidence as to benzidine and several other suspected agents in this organ, such as tar, dyes, and arsenic, is missing. Osteogenic sarcoma and leukemia have been reproduced reliably in animals by the use of radioactive matter and roentgen rays, while controversial evidence only exists as to the leukemiogenic action of benzol.

Conflicting results in animal experimentation are doubtlessly caused in part by the use of different strains or species, and by variations in experimental conditions (diet, solvent of agent, intensity and duration of exposure, particle size of agent inhaled, anatomical peculiarities of

ecies used). They may also be due to the administration of suspected materials of different composition, and therefore of varying carcinogenic properties. For example, tar produced in high temperature retorts from coal is usually carcinogenic, while tar coming from low temperature retorts possesses such qualities to a lower degree or not at all. Wood tar, frequently employed for medicinal purposes, is usually noncarcinogenic. Some crude mineral oils containing originally aromatic substances are carcinogenic, while mineral oils coming from other fields and having a different composition are not. However, even these may acquire such properties if they are subjected to high-temperature and high-pressure distillation, as aromatic compounds are generated under these conditions from aliphatic ones. Oils obtained by the distillation of shale have proved to be carcinogenic in Scotland and Germany, unless they are subjected subsequently to special processing. Asbestos, likewise, not only differs in physical respects but also chemically, particularly in regard to its metallic components.

Physicochemical Investigations

Many attempts have been made to isolate the actual carcinogenic factors from the tumor tissue, blood, or excretions of individuals or animals with cancers elicited by occupational agents, and thus to provide the most convincing evidence of their etiology. However, most efforts in this direction have failed. It has been possible to recover chromium from the tumor tissue of chromate workers, radioactive matter from the lung cancers of the Schneeberg miners and from the osteogenic sarcomas of dial workers, and arsenic from the neoplastic tissue of the skin of persons exposed to this chemical. However, the metabolite of betanaphthylamine, 2-amino-1-naphthol, appearing in the urine, is not definitely carcinogenic, and extracts from cancers caused by roentgen rays were noncarcinogenic.

Whether or not this course of events will be changed by the recent discovery of Ekman and Stroembeck (*98*), remains to be seen. These investigators isolated toluidines or para-substituted derivatives of meta-toluidine from the urine of rats with bladder tumors resulting from the administration of aromatic azo-compounds, and produced bladder papillomas in other rats given the isolated substances. Their observations seem to be of special importance as to the causation of bladder tumors in men, since they succeeded in obtaining considerable amounts of primary aromatic amines, some of which might be present in oxidized form, from the urine of patients with "nonoccupational bladder" cancer.

Summary of Evidence of Occupational Carcinogenesis

It is apparent that much of the evidence by which cancerigenesis is connected with occupational activities is circumstantial, and that only in a relatively few types of occupational cancers is definite and specific evidence available. Despite these shortcomings in kind, the sum total of the statistical, clinical, and experimental evidence is of sufficient weight to justify the definite acceptance of the occupational origin of most of the cancers listed.

This scientific recognition of the occupational etiology of certain cancers does not automatically, in most instances, imply a medicolegal acceptance of such interrelations, with all their important economic and social implications. However, the resistance usually encountered on the medicolegal front has been partially overcome, at least abroad, for cancers of the skin caused by tar, pitch, oils and their derivatives, arsenic, roentgen rays, and radioactive substances; for cancers of the lung resulting from radioactive material and chromates; for cancers of the bladder caused by aromatic amines; and for osteogenic sarcomas elicited by radioactive substances.

The other industrial cancers previously mentioned have not yet been generally included among the compensable occupational diseases, even in Europe. At present they enjoy a sort of probationary status in that they are recognized in some countries, while not in others. Since occupational carcinogens probably will continue to be used by industry and to cause occupational cancers, there is little doubt that most of the cancers of this doubtful group will reach compensable status as and when the number of cases increases, and the importance of occupational cancers is more generally appreciated.

Occurrence and Incidence of Occupational Cancers in the United States

It is not possible to give any definite information on the types of occupational cancers occurring in the United States, nor are there any even approximately accurate and reliable data on the actual number of occupational neoplasms to be found in this country. Industrial management, labor, legislative bodies, public health organizations, and the medical profession are all responsible in varying degrees for this condition. The information available represents not what actually exists, but what has been recorded or is conceded.

Cancer of the Bladder

Cancer of the bladder in dye workers has been part of the American industrial scene since 1932—that is, some 15 years after the start of

large-scale production of aromatic amines for the manufacture of dyes. Approximately 100 cases of this occupational cancer were recorded up to 1938 from one American chemical concern. No additional information on this subject has been made a matter of public information since that time, except for a brief communication regarding the occurrence of such cancers among the workers of another chemical company in 1947.

From information available, it appears that a total of about 200 cases of occupational cancer of the bladder have been observed during the last 20 years among the workers in three chemical organizations, including both producers and consumers of betanaphthylamine and benzidine. No information has been published on this problem by any of the many other chemical manufacturing plants or by plants using those chemicals or their close derivatives, including the rubber and pharmaceutical industries.

However, assuming that the actual number of bladder cancers with this causation were five times the recorded figure, or 1,000 cases, only a very small fraction of the total would be represented, since about 100,000 bladder cancers were reported in the 20-year period surveyed (1928–47). Thus, only 1 out of every 100 cases could be attributed to occupational contact with the aromatic amines on the basis of the above assumption. Doubtlessly additional and important exogenous and endogenous factors are involved in the causation of bladder cancer.

Skin Cancer

Occupational cancers of the skin resulting from contact with solar rays, roentgen rays, rays from radioactive material, tar, pitch, mineral oil, lubricants, soot, and arsenicals, have been reported in this country since 1900, when the first cases of roentgen cancer were placed on record. This was followed in 1910 by the description of five cases of tar epitheliomas, and in 1932 by a report of two cases of industrial arsenic cancer. However, as long ago as 1906 Hyde (*276*) had commented on the comparatively high frequency of cancer of the skin among outdoor workers in the dry and sunny regions of the Middle West. With the exception of the skin cancers of suspected solar origin, which many investigators consider to be the most prevalent type of this malignancy, an astonishingly small number of occupational cancers of the skin has been placed on record in the United States. There are 71 tar and pitch cancers, 62 grease and oil cancers, 45 roentgen cancers, and 18 arsenic cancers. Needless to say, the majority of the tar and oil cancers have not been reported, while the long latent period of arsenic cancer may account in part for the small number of reported cases with arsenical causation.

No incidence figures are available on cancer of the hands and fore-

arms occurring in grease pit workers of service stations recently mentioned by Stewart (*358*). Since high-pressure, high-temperature fractionation and cracking of oil by hydrogenation is being used to an increasing degree in the modern petroleum industry, and inasmuch as the tendency toward the formation of cyclic compounds of potentially carcinogenic properties is thereby enhanced, the above-mentioned possibility deserves serious attention during the coming years. Although the industrial use of oil shale and bitumen for the production of oil, gas, and related products is at present of minor importance in this country, the situation may undergo a fundamental change in the near future as a result of the rapid exhaustion of our natural oil reserves. If proper precautions are not then taken to prevent the manufacture and use of carcinogenic shale oils, occupational cancers of the skin may appear at a rate similar to that found among the shale oil workers and mule spinners in England and Scotland.

Respiratory Cancers

No official records exist in this country as to the occurrence of cancers of the lung and nasal sinuses in workers exposed to the inhalation of gases and fumes containing radioactive matter, arsenicals, nickel carbonyl, and tar. However, Lynch and Smith reported in 1935 the first American case of primary carcinoma of the lungs associated with asbestosis (*222*). Since then 8 additional cases have been reported from this country, out of a total of 23 cases from England, Germany, and the United States. In view of the sarcoid nature of the granulomatous lesions seen in beryllium workers, it may be mentioned that there is on record a single case of co-existent pulmonary asbestosis and sarcoidosis (*347*).

It is definitely too early for pulmonary malignancies to occur in workers who have had contact with radioactive dusts and gases during the mining and processing of radioactive ores for the production of radium and atomic energy, since operations in which this type of exposure may have taken place have been carried on in this country for an insufficient length of time to cover the usual latent period of these tumors. As for arsenic, the reports of the chief inspector of factories in England have mentioned repeatedly during the last few years the appearance of cancers of the lung in workers exposed to the inhalation of arsenical dusts and fumes (*36*, *55*). There is consequently need for detailed study of this field in the United States, because of the extensive exposure to arsenic to which large parts of the industrially employed as well as the general population in certain regions of the country are liable. These investigations might throw some light on the remarkable increase in the mortality rate for lung cancer, which more than doubled between 1933 and 1945—from 4 to about 9 percent

of all cancer deaths—and which shows marked variations in various regions of the country.

Cancer of the lung in chromate workers, which so far has been reported from Germany only, has definitely appeared in the United States (*224a*). The interest in this cancer on the part of those concerned with chromate production has been considerable during recent years. No definite information is available on the presence or absence of cancer of the nasal sinuses and of the lungs in workers in American nickel refineries using the carbonyl process, although an appreciable number of such cancers has been reported from South Wales.

Industrial osteogenic sarcoma in dial painters applying radioactive material represents the only occupational neoplasm observed exclusively in this country. No new cases have been placed on record since their first epidemic-like appearance some 15 years ago (*229*).

Leukemias

Leukemic reactions in persons exposed to benzol or radioactive energy have been observed in this country. There are six cases of occupational benzol leukemia, occurring in painters, workers in can factories, shoe-manufacturing plants, artificial-leather factories and rotogravure printing establishments. Other workers employed in the same factories and also exposed to benzol have shown hyperleucocytoses or leukemoid reactions. Similar observations have been made in individuals coming in contact with radioactive energy, in whom leucocytotic and preleukemic conditions, as well as leukemia, have been observed. The first American case of an occupational radiation leukemia was reported in 1929 by Stewart (*358*). Since then two additional cases have been recorded, and several statistical studies on the excessive incidence of leukemia among radiologists have provided support for the concept of an occupational radiation leukemia. Thus, a potential leukemic hazard exists for all persons exposed to radiation while working with atomic energy for military, industrial, or scientific purposes, and handling radioactive matter in the radio and textile and other industries using radioactive static eliminators.

Problems in the Control of Occupational Cancer

It is obvious from the foregoing that occupational cancer presents an increasingly serious health problem in the United States (*282*), as it does wherever industrial processes proliferate and men and women are brought into intensive and prolonged contact with occupational carcinogens. Nevertheless the subject has attracted relatively little attention from industry, labor, public health bodies. or the medical profession. Sufficient data have been accumulated, it is believed, to indicate the extent of the problem and to call for aggressive control procedures on the part of the various sectors of our society mentioned.

Factors Responsible for Lack of Interest

Industrial Management

The limited publicity which occupational cancers and their causative agents have been given has left considerable portions of industrial management in complete ignorance of the existence of such sequelae to certain industrial activities. Furthermore, the general uncertainty prevailing in regard to the etiology of cancers in general tends to create a reaction of scepticism concerning the mechanism of their actual occurrence. Thus the reluctance of some members of industrial management to accept any claims as to the presence of occupational carcinogenic hazards in their plants and operations is a natural reaction of persons not adequately informed on the biological peculiarities of occupational cancers, especially their long latent period.

Furthermore, the not infrequent absence of reliable and convincing statistical data on the occurrence and incidence of occupational cancers, as well as the existence of improperly prepared and, therefore, misleading statistical evidence, favor the development of a negative reaction among members of industrial management.

A second factor which tends to interfere with a wider knowledge of the incidence of occupational cancers is the apprehension of industrial management that an unrestricted public recording and scientific dis-

ussion of these neoplasms might result in undesirable publicity to the organizations involved in such hazards, and might thus impair the sale of their products. It is feared, moreover, that such publicity might cause the institution of expensive and sometimes unwarranted compensation suits; that it might necessitate the costly rebuilding of existing plants; and that it might require the introduction of extensive and complicated technical, sanitary and medical precautionary measures, which might possibly hinder production, alarm workers, and cause considerable outlay over prolonged periods. Although the financial burden connected with such measures would not represent a serious obstacle to their adoption by management, as the cost can be passed on to the consuming public, an uneven application of such regulations in different States would result in unbalancing the competitive field and thus would be objectionable.

There is also the possibility in management's mind that a greater degree of publicity on occupational cancers might result in the passage of laws and and regulations requiring a closer and more stringent governmental supervision of plant operations and of treatment of workers.

Labor and Labor Organizations

Although neither labor nor management is always aware of the carcinogenic hazards connected with certain occupational activities, it cannot be said that labor always adopts readily the preventive and prophylactic measures prescribed by management for labor's protection against hazards already recognized. Such an attitude toward precautionary measures is dictated in part by the common human negligence toward everyday injurious agents not causing readily apparent disease manifestations, and in part by the fact that such measures may cause some physical inconvenience to the workers, or may interfere with their productivity and thereby their income. For instance, periodic cystoscopic examinations for workers in certain dye plants cause them a definite degree of discomfort. For this reason, their importance as a prophylactic measure may not always be properly appreciated by the workers concerned. The relatively high incidence of precancerous chronic roentgen dermatitis observed among radiologists indicates that this indifference to a known carcinogenic hazard is not limited to workers without a proper education in biology and medicine.

Another example of the same attitude is often shown by workers who leave occupations in which they sustained dangerous exposure to carcinogenic agents and who neglect later on to remain under medical supervision, even when regularly urged to do so by their former employers. The excessively long latent period involved in the devel-

opment of some of the industrial neoplasms makes such supervision an essential if the disease is to be discovered in time; and yet workers only too often forego medical examinations which could save them from the worst manifestations of cancer, or even prevent its appearance.

The absence of reliable and adequate information on the significance and scope of the occupational cancer hazard, as well as an insufficient appreciation of the extent of that hazard on the part of officials of labor organizations, seems to be responsible for the fact that, so far, these leaders generally have evinced only an occasional interest in the problem, and have exerted little effort to impress either workers or management with its urgency.

Legislative Bodies

It is obvious that the adequate protection of workers against occupational cancer hazards, and of the general population against environmental industrial carcinogens, depends to a large extent on the existence and enforcement of proper laws covering the many facets and special conditions of this complex problem.

Occupational cancers, essentially the products of modern industrialization, are relatively recent phenomena. Consequently, they have not yet become the subject of established and intelligent legislative procedures in most countries. Furthermore, even those countries which have laws dealing with occupational cancers have not always made sure that they are adequate. Most of them are more or less defective in insuring reasonably safe working conditions in factories, workshops and laboratories producing, using, or handling carcinogens.

Compensation laws covering carcinogenic occupational hazards, for example, often apply only to some of the agents, or to defined operations in which contact with these agents exist. Often they do not take proper account of the long latent period following exposure, and thus eliminate a great number of justified claims.

Criminal codes should take cognizance of the fact that the willful and undue exposure of an individual to a carcinogenic occupational agent for personal gain by another party is for all practical purposes equivalent to an attack with a deadly weapon with a delayed action mechanism.

Departments of Public Health, Industrial Hygiene, Cancer Control and Labor

The manifest dearth of reliable and adequate information on occupational cancers, the defective nature of existing laws applying to these neoplasms, and the lack of sufficient appropriations for their study, have prevented various governmental agencies concerned with this

dustrial hazard from becoming sufficiently active. Official statistics on the problem are, therefore, highly incomplete in most countries. The situation is somewhat better, however, in countries which have made occupational cancers notifiable diseases, and in which governmental inspection of factories and workshops has been instituted.

Medical Profession

The medical profession in general has been slow in the past to appreciate properly the causative role which the prolonged and unobtrusive action of extrinsic physical and chemical agents may play in the production of many chronic and often etiologically still obscure degenerative diseases, such as arteriosclerosis, arthritis, and cancer. It is therefore not surprising that most physicians have scarcely begun to learn about the carcinogenic properties of occupational agents. Occupational data in the histories of cancer patients are consequently either completely lacking or of little scientific value.

It is not enough to record, for instance, that a patient was a mechanic or a chemical worker at the time a cancer became manifest. On the contrary, it is essential to ascertain his complete occupational history in relatively great detail for as much as some 20 years before the discovery. The appropriate occupational risks must be looked for in the earlier work experience of men afflicted with cancer of possibly industrial origin. Such tedious inquiries, however, are not being made today, even in hospitals predominantly handling cancer patients. It is obvious, moreover, that any such inquiries, and any intelligent deductions from them on the relation of the data obtained to the existing cancer, can be made only by persons possessing a genuine knowledge of industrial conditions, industrial carcinogenic hazards, and occupational cancers. At present, this type of specialized information is possessed only by a relatively small number of members of the medical profession.

Public Health and Industrial Problems

Incidence and Causation

To date, some 8,000 cases of occupational cancer caused by a large number of definitely recognized or strongly suspected carcinogens of physical, chemical or parasitic character have been observed in workers engaged in a great variety of occupational activities. These cancers have affected many organs and tissues. Their localization in different parts of the body has depended in part on the type of contact with a particular agent, in part upon its physicochemical qualities

and the reactivity of the organism. The fact is thus established that extrinsic agents connected with the occupational activity of man are capable of eliciting cancerous growths in human tissues irrespective of any physiologic or pathologic senile changes or hereditary influences.

Number of Carcinogens

The number and variety of occupational carcinogenic agents have been increasing steadily and rapidly during the past 60 years (table 1) and, at the same time, the number and types of carcinogenically hazardous operations have increased at a rate paralleling the degree of expansion and diversification of industrial activities during the same period.

Variety of Carcinogenic Mechanisms

The marked discrepancies in the physicochemical properties of the different recognized and suspected occupational agents indicate that they exert their specific carcinogenic effect on the tissues by different mechanisms. Some seem to possess properties of direct cellular cancerization; others elicit such reactions in an indirect way either by causing endogenous carcinogenic substances in the tissues with which they come into contact, or by eliciting metabolic disturbances in internal organs, such as the liver or endocrine glands, which then generate endogenous carcinogenic substances. It is evident therefore that cancers of apparently endogenous origin may actually have a primary extrinsic causation.

Defects in Statistical Determination

The demonstration of an occupational origin of cancers depends mainly on statistical evidence, which often shows an excessive incidence of a certain type or types of cancers in a restricted group of workers. Inasmuch as recent analyses of the incidence rate and manifestation age of occupational cancers have shown that these factors depend on the potency of the carcinogen, the intensity and duration of exposure to it, and the age of onset, it is obvious that statistical methods will miss all those occupational cancers which do not differ in their incidence rate and manifestation age from their prototypes of unknown etiology in the general population. The existing evidence therefore suggests that at present only the most potent and obvious occupational cancers and carcinogens have been discovered, while those of low incidence rate caused by carcinogens of low potency have not yet been recognized.

This conclusion is supported by the fact that, so far, occupational cancers have not been demonstrated in either the gastro-intestinal tract or the nervous system. The cells of the alimentary tract obviously come in direct contact with a host of extrinsic factors; those of the nervous system react readily to a great number of them following their resorption into the organism. On general grounds, therefore, it is highly improbable that two entire organ systems should be totally immune to extrinsic carcinogens, including those of occupational origin. These considerations add to the evidence indicating that the number of occupational cancers is appreciably higher, and their variety as to sites and types definitely greater, than is suggested by recorded figures.

Probability of Increase in Occupational Cancers

The abnormal character of some of the industrial activities of recent years makes it probable that there will be a rise in the number and types of occupational cancers during the next decades, as happened under similar conditions after the First World War. Evidence again is accumulating that under war pressure, plants were built and manned by men inadequately familiar with the occupational carcinogenic hazards inherent in many of their operations. It is possible that such hazards were, in the main, avoided in the construction and operation of American plants and laboratories handling radioactive substances. However, the final evaluation of this problem cannot be made until some 10 to 20 years have elapsed, and a detailed and thorough study of cancer incidence among the large number of former employees of these plants has been made. The elaborate precautionary measures taken in these operations, on the other hand, do furnish a striking illustration of the seriousness of the occupational cancer hazard as applied to a fairly limited industrial activity and to an agent which can be traced with comparative ease.

A second factor growing out of World War II which may bring about an increase in the incidence of occupational cancers during the coming years is the dislocation of many industries, particularly abroad. This is due partly to the destruction or dismantling of many factories and partly to the construction of plants in certain countries which formerly had different types or little industrial production, and thus were not experienced in the control of operations using carcinogenic occupational agents. This means that the bad record, carcinogenically speaking, which resulted from the hurried development of large-scale chemical industries during and following World War I may be repeated.

Chance of Exposure Widespread

The scope of the occupational cancer problem is made even more apparent when the types and numbers of persons potentially exposed to occupational carcinogens is realized. These agents may affect workers in basic industries producing, using and handling raw materials and semifinished goods possessing carcinogenic properties; in consuming industries, workshops, trades and professions using the output of the basic industries; and in transport and merchandising organizations engaged in packing, loading, shipping, and selling industrial goods with carcinogenic properties. They also may have an adverse effect on that part of the general public which consumes such goods, or which comes in contact with carcinogenic industrial wastes discharged into the air, water, or soil. The chain of events whereby an occupational carcinogen may be transformed into a medicinal or environmental one is readily demonstrable with substances such as tar or arsenic. The general existence of these various interrelations is shown by the appearance of the various occupational cancers in different countries following the establishment of industries producing the carcinogens.

Need for Study

The scientific study of occupational cancers, precancerous conditions, and causative agents offers a unique opportunity for ascertaining the nature of extrinsic agents which are carcinogenic to man, and to investigate in the human being the local and systemic reactions elicited by such agents during the preparatory and manifestation periods of the cancerization process. The study of occupational cancers also permits the determination of the role which associated environmental, hereditary, and constitutional factors play in the susceptibility to occupational carcinogens in man. In addition, it makes possible the development of specific or nonspecific preventive, prophylactic and therapeutic measures, many of which might be applicable to human cancer in general.

Control of Occupational Cancers

An effective, rational control of occupational cancers depends on accurate knowledge of the causative agents, and on the institution and strict enforcement of adequate preventive and prophylactic measures. This goal may be approached through the following methods and procedures.

Elimination or Control of Occupational Carcinogens

Exposure to carcinogens in industry should be eliminated wherever possible, or at least reduced to the technically feasible minimum. This can be achieved by designing buildings and machinery to prevent the escape of dust, fumes, mists and vapors (the closed system of production); by the institution of efficient exhaust ventilation; by maintaining a high level of good housekeeping; by disposing of carcinogenic wastes with suitable precautions; and, when necessary, by the isolation of a carcinogenic operation from the rest of the plant. Exposed workers should be furnished with suitable protective clothing, gloves, masks, and similar safety devices. The degree of unavoidable contact should be further reduced by the installation and enforced use of proper sanitary measures, such as special eating quarters, washing and bathing facilities, and separate lockers for street clothes and work attire. Workers should be familiarized through lectures repeated at regular intervals with the type of carcinogenic hazard present, so as to obtain their willing cooperation in the enforcement of the various precautionary measures. Repairs after accidents during which an increased exposure to the carcinogenic agent is likely to occur, and the repair and cleaning of machinery and pipelines, should be performed by specially trained and protected teams.

Measures designed to reduce contact with occupational carcinogens are of great value, as observations made in connection with several occupational cancers and with experimental cancers of animals have shown that a decrease in the degree of exposure results in a lengthening of the latent period, thus possibly delaying the manifestation of a cancer even beyond the average span of human life.

Medical Examinations

Since the practical importance and general appreciation of occupational cancer hazards is bound to grow during the coming years, employers would be wise to determine in preplacement examinations the applicant's complete occupational history, for ascertaining any previously sustained exposure to occupational carcinogenic agents. In view of the usually long latent period of occupational cancers, this procedure represents an expedient safeguard against subsequent compensation claims for such disorders originating from exposures sustained by the claimant before entering the employment of the party sued. Applicants for clerical jobs should be included, as it is not uncommon that persons formerly employed in production and laboratory work may later change to white collar jobs.

Medical supervision and periodic medical examinations should be

maintained not only during the time of employment in a hazardous operation, but for some 15 to 20 years beyond the end of employment, thus providing medical observation of the exposed workers for the entire latent period of occupational cancers. It may be advisable to establish for this purpose a number of industrial cancer detection clinics, staffed by physicians experienced in the occupational background of precancerous and cancerous manifestations, and provided with technical assistants trained to cover the various non-medical aspects of occupational cancer which would be required for the efficient operation of such clinics.

Periodic medical examinations should be made not only of those workers who are regularly employed in operations with carcinogenic hazards, but also of those who may enter such operations at irregular intervals, such as repairmen, guards, truckers, shippers, supervisors, and chemists and physicists of control departments and laboratories, as well as of those who are working within an effective range of such operations (fume zone) such as yard workers. The frequency of periodic medical examinations should be increased with the age of the exposed employee and with the length of his employment in the hazardous operation. The type of medical examination should be properly adapted to the special kind of carcinogenic hazard existing.

Frequent spectrographic examinations of the urine of workers in contact with aromatic amines for the presence of these substances and of their metabolic derivatives should be practiced in plants producing or handling such products. Annual or semi-annual cystoscopic examinations are highly desirable wherever workers can be persuaded to submit to these procedures. Inasmuch as bladder cancers are not infrequently symptomatically silent (especially as to the presence of hematuria) until they have reached an advanced stage, cystoscopic examinations afford the only efficient diagnostic means for the discovery of bladder cancers in dye workers while they are still in a precancerous or early cancerous stage. Whether or not the frequent cytologic study of urinary sediment with the Papanicolaou method may be of additional help in this respect remains to be determined.

In periodic studies of the blood of workers exposed to actinic energy and benzol, special attention should be paid to the presence of hyperleukocytotic reactions and to excessive increases of monocytes. Roentgen films of the chest should be made at one-year intervals for all workers exposed to the inhalation of radioactive substances, tar fumes, arsenical dust, chromate dust and fumes, nickel carbonyl vapors, mists of mineral oils, asbestos dust, and beryllium compounds. Similar studies of the nasal sinuses are indicated for workers employed in operations entailing inhalatory contact with nickel carbonyl. These tests might well be supplemented by periodic cytologic examinations

of the sputum and of the nasal discharge, particularly where chronic inflammatory conditions of the respective air conduits exist.

Inspections

The adoption of a system of regular inspection of all plants using, handling or producing industrial carcinogens by government inspectors is desirable. Such a system has been used successfully for a number of years in England, in connection with occupational cancer control. Factory inspectors would be charged with checking on the presence of carcinogenic agents in plants and workshops, with enforcing regulations covering the handling, storing, and use of such agents, with supervising the protection of workers exposed to them, and with approving methods of disposal of carcinogenic wastes. While the last-mentioned aspect has recently received some prominence in connection with the disposal of radioactive waste products, an indiscriminate discharge of carcinogenic chemical wastes represents a distinct potential hazard to the health of the factory and general populations, and thus deserves serious attention.

Labeling and Packaging

Mechanical devices capable of producing carcinogenic actinic energy should carry proper warning labels, and should be furnished with explicit instructions as to suitable protective measures. Carcinogenic chemicals should be packed in strong, leakproof containers to eliminate any danger to loaders, shippers and other persons handling them during transport, storage, merchandising or use. The containers should be constructed in such a way that they can be emptied without hazard to the workers performing the task and to those employed nearby. Such requirements are particularly applicable to highly potent occupational carcinogens, such as betanaphthylamine and radioactive substances. Carcinogenic material containers should carry prominent labels with appropriate warnings.

Licensing of Establishments

Factories, workshops, laboratories and other establishments producing, handling or using carcinogenic materials should be obliged to register with departments of labor and/or public health, and to obtain special operating licenses. This would aid in establishing the supervision of plants by factory inspectors, and would act as an educational measure by familiarizing the managers of such operations with the potential carcinogenic properties of the substances and devices used in their establishments.

such a compilation of information should include all presently and formerly employed female workers. The availability of such data is an important prerequisite to the determination of the scope of the occupational cancer problem, and for the preparation of effective controls.

Education

All available means of education and information should be used to spread knowledge and understanding of the occupational cancer problem among the various parties directly or indirectly concerned with it. One of the aims of such education should be to create among the various groups a spirit of cooperation essential for combatting successfully the occupational cancers that form an important part of the general cancer problem.

Research

Inasmuch as occupational cancers are of direct concern both to industry and to government, the financial support and actual undertaking of research on these disorders may be accomplished best if the two would coordinate their efforts, and establish an active exchange of the experiences of their respective investigators. Only thus can the far-reaching ramifications of this complex problem be explored effectively and economically.

Such cooperative efforts are particularly important in the study of the epidemiology of occupational cancers, in the discovery and identification of new carcinogenic agents and of the types of exposure involved, and in the development of applicable control measures. The fruits of investigations thus jointly carried out will not only reward management and labor, but will also aid in the ultimate conquest of the problem of cancer in general.

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