I. THE NATURE AND SCOPE OF ENVIRONMENTAL CANCER HAZARDS

Almost 200 years have passed since the first environmental carcinogen, coal soot, was recognized as the cause of cancer of the human skin. The environmental carcinogenic spectrum composed of accepted, suspected, and potentially carcinogenic agents present in the natural and artificial human environment has grown considerably during the intervening years. Despite the impressive increase therefrom, resulting in the number, diversity, and spread of environmental cancer hazards among the general and especially the industrially employed and urban populations and despite the ready availability of an abundant amount of reliable facts and observations on the causation of human cancers by environmental agents, governmental, private, and professional parties directly concerned with the protection and maintenance of human health have displayed until recently an astounding indifference and aloofness toward this important aspect of the general cancer problem. A partial awakening from this general state of lethargy has, however, occurred during the last decade because of the impact produced by the strong reaction of the general public to widely disseminated information relative to the increasing and probably dangerous contamination of the human environment and of many products of daily consumption with carcinogenic agents.

This rising concern with mainly industry-related environmental cancer hazard was aroused by three recent developments:

1. The growing contamination of air, water, and soil as well as of foodstuffs with radioactive matter from activities in the nuclear energy field.

2. The increasing pollution of the inhaled air with various chemical carcinogens contained in industrial effluents and in automobile exhaust as well as associated with cigarette smoking.

3. The demonstration of a considerable and rising number of carcinogenic chemicals used as intentional and nonintentional food additives and produced in the food because of certain processing procedures as well as employed as ingredients, or present as impurities in drugs, cosmetics, economic poisons, and other consumer goods.

It is significant that, in response to these developments, federal, state and municipal legislatures and public health authorities have enacted laws or issued regulations during the last decade providing increased protection of the general public against cancer hazards resulting from an environmental dissemination of carcinogens in foods, drugs, and cosmetics and in effluents of industrial plants and automobiles. For the first time during the modern industrial era, protective legal measures which, up to that time, had been applied to occupational cancer hazards only were extended to those of general environmental nature. Formal recognition was given thereby to the long neglected fact that many of the known environmental carcinogens initially encountered in certain occupational activities are subsequently being introduced into the general human environment as pollutants of the air, water, and soil and as constituents and impurities of many consumer goods, and are creating through this mechanism a serious public health problem.

While mankind has had contact, during the greater part of its existence on earth, with a number of natural as well as man-made environmental carcinogens such as sunlight, ionizing radiations, arsenicals, infections with *Schistosoma hematobium*, soot, and possibly tobacco products, the human race has had a chance through the thousands of years of exposure to develop against these carcinogens some defense mechanisms in the form of detoxication and chemoimmunity reactions and other protective biologic responses, such as increased pigmentation. Mankind, on the other hand, has not had any opportunities for develop-
ing any reactions of biologic adaptation to the en-
vironmental carcinogens of the modern industrial
era, because of their introduction during a period
of only a few decades. The protection of modern
mankind against the growing number of these
man-made chemical and physical carcinogens
must rely, therefore, entirely on methods and
measures artificially devised.

The extent to which the contamination of the
human environment with new artificial, man-made
physical and chemical carcinogens has progressed
during the past century is strikingly illustrated by
the long list of known, suspected, and potential
human carcinogens, the various routes of contact
with them, the numerous opportunities of expo-
sure to them, the different sites of cancers pro-
duced by them, and the progressive march of occupa-
tional cancers through the individual countries
subsequent to the development of an industrial
economy (Table 1) (4, 17, 22, 56, 68–70, 72, 73).
The presently known spectrum of recognized, sus-
pected, and potential human carcinogens exhibits
a remarkable degree of diversity and complexity
of its component members. It is comprised of se-
veral parasitic and viral organisms, of a growing
number of carbon and silicon macromolecular
polymerized chemicals, of various specific organic
aromatic and aliphatic chemicals, of several metals
and minerals, and of various nonionizing and ion-
izing radiations which exert an actinochemical
action on the chemical constituents of tissues being
exposed to these radiations.

It has often been argued in the past that, be-
cause of the multitude and diversity of carcino-
genic agents, cancers do not represent an anatomic
reaction product of tissues to a specific carcino-
genic agent which retains in its biologic responsi-
siveness and properties a direct relation to the
specific causal agent. The prevailing concept con-
siders cancers as biologic manifestations which de-
velop in response to carcinogenic stimuli and
which assume, once produced, complete biologic
independence from the causal agent, thereby be-
coming disease entities per se. Almost the entire
modern diagnostic and chemotherapeutic research
in cancer control is based on this concept. This
approach is rather surprising and unique in the
annals of medicine and contrasts sharply with the
efforts made in the past for controlling infectious
diseases. These efforts were directed toward influ-
encing the causative agents and their toxic prod-
ucts by biologic and chemical means. It has not
occurred to investigators engaged in such tasks to
attempt the development of curative agents
against these diseases by first obtaining detailed
biochemical information on their anatomic reac-
tion products, such as tubercles and gummas, and
then to use such information for devising chemical
means against some of the biologic mechanisms or
some special constituents found in such circum-
scribed anatomic reaction products, or for develop-
ing diagnostic tests for infectious granulomas, ir-
respective of their specific etiology.

Because of the past failure to obtain, by the
application of this biologic concept of cancer, any re-
liable specific diagnostic test for cancer and any
effective chemotherapeutic agent against cancer-
ous tissue, one is left wondering whether it is not
appropriate and timely to put to work in this re-
search the many facts and observations on envi-
rornmental carcinogenesis and cancers, and to re-
turn to those scientific principles which brought
success to the control of infectious diseases. The
advisability to explore more fully the potentialities

<table>
<thead>
<tr>
<th>Country</th>
<th>Discoverer</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Rehn</td>
<td>1892</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Scheller</td>
<td>1903</td>
</tr>
<tr>
<td>Great Britain</td>
<td>Ross</td>
<td>1918</td>
</tr>
<tr>
<td>Russia</td>
<td>Rosenbaum &amp; Gottlieb</td>
<td>1926</td>
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<td>Austria</td>
<td>Schüller</td>
<td>1928</td>
</tr>
<tr>
<td>United States</td>
<td>Ferguson et al.</td>
<td>1934</td>
</tr>
<tr>
<td>Italy</td>
<td>di Minio</td>
<td>1936</td>
</tr>
<tr>
<td>Japan</td>
<td>Nagayo &amp; Kinosita</td>
<td>1940</td>
</tr>
<tr>
<td>France</td>
<td>Billiard-Duchesne</td>
<td>1946</td>
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of the etiology-specific concept of cancer for its
diagnosis, prophylaxis, and treatment is suggested
by the many similarities existing between the
spectra of environmental carcinogens and of
pathogenic microorganisms.

Both major systems of disease-producing agents
include a wide range of different component mem-
bers varying markedly in their degree of potency
or virulence among each other—i.e., from produc-
ing a 100 per cent attack rate in the population to
the risk of affecting only a fraction of it or the ex-
ceptional individual. There exist, moreover, definite
and epidemiologically important differences in
their pathogenicity or their carcinogenicity, re-
spectively, for different species, strains, races, and
individuals of the same race or strain.

This observation on the significance of the host
reaction for the occurrence of a carcinogenic re-
response has led to the contention that the host rela-
tionship might be more important in this respect
than the carcinogen proper and that, therefore, a
control of cancer hazards might be achieved by
modifying in the right direction the constitutionally conditioned reaction of the host organism to the carcinogen. It may be pointed out in this connection that despite distinct congenitally or acquired constitutional differences among equally exposed individuals, the realization of a cancerous reaction or of a tissue response to an infectious agent, like the tubercle bacillus, is fundamentally determined by the action of the pathogen. Without the primary action of the pathogen the host reaction is immaterial. Past experiences with constitutionally conditioned or genetic diseases have, moreover, shown that their control is most difficult. There is also no sound scientific reason in support of the recently revived, speculative allegation that, in contrast to pathogenic microorganisms, environmental chemical carcinogens are not primary carcinogens but act in the process of carcinogenesis merely as agents triggering the specific action of genes or even viruses. The entire symptomatic pattern of manifestations associated with primary carcinogens but act in the process of carcinogenesis merely as agents triggering the specific action of genes or even viruses. The entire symptomatic pattern of manifestations associated with carcinogenesis militates against the validity of such a concept.

Additional similarities between environmental carcinogens and pathogenic microorganisms are related to the fact that both are capable under certain conditions of eliciting chemo-specific allergic reactions, indicating thereby symptomatically the occurrence of an interaction of the two types of pathogens with proteins of the host organism. The degree of response, as well as the site of reaction in the host for both pathogens, depends to some extent on the particular route of contact, on the intensity and duration of exposure, and on the modifying influences which other exogenous factors, such as diet or chemotoxic manifestations, might exert on the realization and type of tissue changes resulting. Finally, it may be noted that man is in contact throughout his entire lifetime not only with a variety of microorganisms (some with known pathogenicity to man) without developing from all exposures and in all instances an infectious disease, but also to diverse chemical and physical carcinogens acting on him from various sources and at different times and failing to elicit during his lifetime, in most instances, a cancerous response of some tissue. It seems that the total effective carcinogenic burden of an individual thus is, in part, determined by the various factors mentioned; to another part it seems to depend upon the degree of synergistic, antagonistic, or indifferent interaction of the various carcinogens and upon their interplay with noncarcinogenic endogenous and exogenous factors acting in the host organism. Similar interrelationships are operating in determining the activity of pathogenic microorganisms, such as, for instance, tubercle bacilli, in the host organism.

From these considerations it may, therefore, appear wise to pattern the future attack on environmental cancer hazards on the principles and methods of investigation and the concepts of biologic mechanisms employed in past studies of the causation and the control of infectious diseases.

II. FUNDAMENTAL ASPECTS OF ENVIRONMENTAL CARCINOGENESIS

It is one of the fortuitous and fortunate by-products of the recent emergence and growing appreciation of environmental cancer hazards as major public health problems that many of their scientifically and practically important but often ill defined and badly understood facets were placed into sharper focus. The immediate need for considerably increased and comprehensive investigations on many fundamental and applied aspects of the environmental cancer problem became rather painfully apparent during the recent hearings of several Congressional Committees (11–16) which led to the inclusion of the Delaney cancer clause into the laws enacted in relation to health hazards from food additives and food and cosmetic colors. The various points of dispute which arose at these occasions illuminated the large gaps in factual knowledge on environmental cancers in man and on carcinogenesis by environmental agents in experimental animals and demonstrated the appreciable uncertainty which exists regarding some of the most important scientific concepts on these subjects.

DEFINITION OF A CARCINOGEN

During these discussions, as at other occasions, difficulties were encountered in arriving at a generally acceptable definition of a carcinogen. Although a definition of this basic aspect of environmental carcinogenesis which fulfills all scientific requirements does not exist at the present time, it is nevertheless possible to devise a definition which is satisfactory for most scientific conditions and which is practical and applicable for medicolegal purposes.

Carcinogens may be defined as chemical and physical agents which are capable, under proper conditions of exposure, of producing in animals, including man, cancers which would not occur without the intervention of these agents. Carcinogens thus do not merely produce a significant increase in cancer incidence when administered at any dosage level, by any route of administration, and to any species or strain, but elicit cancers lo-
ated ordinarily at sites associated with induced carcinogenesis. This rather inclusive definition of a carcinogen which is applicable also to so-called conditional (Steiner) (75), (Nau) (57), functional (Hueper) (38, 38), hormone-dependent (Morris) (39), and indirect carcinogens avoids the difficulties connected with the use of definitions containing more or less arbitrary restrictions.

It is obvious that several physiologically active hormones and nutrients such as estrogens, iron, cobalt, and, possibly, selenium must be considered according to this definition as carcinogens. Their carcinogenic properties may become manifest if these substances are produced in or introduced into the organism in abnormal amounts or under abnormal circumstances, such as those prevailing at times under occupational, medicinal, or dietary exposures, or created under experimental conditions. Since the physiologic nature of these chemicals has been advanced as an argument against their role as carcinogens and has been used for supporting the demand that they be exempted from any legal restrictions as food additives and contaminants, it may be pointed out that chemicals of animate and inanimate origin occurring in and produced by nature are in no way superior to or different from those made by man in carcinogenic respects (ultraviolet and ionizing radiations, arsenicals, chromium, nickel, asbestos, ergot alkaloid, senecio alkaloids, chili, crude petroleum, viruses).

The claim has recently been advanced by several investigators (Eckardt [19], Bonser 1) that sarcomas produced in rats at the site of the subcutaneous introduction of test materials of any kind represent by themselves not adequate proof for the carcinogenicity of the substances eliciting such cancers. Such allegations have become, during recent years, of more than purely scientific importance, because they have been employed to discredit the carcinogenic significance of several chemicals (dyes, plastics, paraffin, etc.) which elicited cancers in rats and which are present in consumer goods. The legal objections against their use as food additives were thereby removed in some instances. The Food and Drug Administration, U.S. Department of Health, Education and Welfare, for instance, adopted this concept some time ago in its interpretation of the legal significance of the substances eliciting such cancers. Such allegations have become, during recent years, of more than purely scientific importance, because they have been employed to discredit the carcinogenic significance of several chemicals (dyes, plastics, paraffin, etc.) which elicited cancers in rats and which are present in consumer goods. The legal objections against their use as food additives were thereby removed in some instances. The Food and Drug Administration, U.S. Department of Health, Education and Welfare, for instance, adopted this concept some time ago in its interpretation of the legal significance of the substances eliciting such cancers.

It can scarcely be maintained that the objections raised against the carcinogenic significance of tissue responses produced by chemicals in the connective tissue of rats should be limited to connective tissue located in the subcutaneous area. They cannot plausibly be applied to other mesen-
chymatous or epithelial tissues of the rat, such as epidermis, muscle tissue, mucosal epithelium of the bladder and liver, for which, in part, similar differences in species-specific susceptibility to carcinogens have been noted. Despite the need for additional information on these aspects of environmental and experimental carcinogenesis, it would be most unwise to deny that the formation of subcutaneous sarcomas in rats following a subcutaneous deposition or repeated introduction of some test material is not an indication of the carcinogenic property of the chemical tested (Hueper and Payne [39, 40]; Hueper [32, 33, 36]).

The adoption of such a thesis as a matter of scientific policy and experimental practice would indeed lead to an abandonment of the subcutaneous route of administration of test materials in all species. Since such a procedure has practically been suggested in a recent treatise (Publ. 749) (23) on technics suitable for the experimental evaluation of carcinogenic hazards from the use of food additives prepared by the Food Protection Committee, it is appropriate to emphasize that such advice is scientifically unsound and practically operating in favor of the inclusion of carcinogens into the general food supply as advocated by some representatives of the food processing industries as well as by some of their scientific sympathizers and consultants.

Closely related to the controversy of carcinogenic properties, in general, of environmental chemicals is the dispute whether or not the demonstration of carcinogenic responses in animals or man from chemicals applied to the skin or injected into the subcutaneous tissue represents a valid or probable indication that the test material may exert a similar effect upon the other tissues of contact in the host organism, especially when it is either inhaled, such as cigarette smoke, or ingested, such as food additives. In fact, the demand has been made to distinguish between universal carcinogens, such as ionizing radiations and possibly 2-acetylaminofluorene, capable of producing cancers in all types of tissues upon proper exposure, and carcinogens whose specific action is limited to certain tissues and organs and whose local action depends in part on the route of introduction of the carcinogen, in part upon special tissue affinities. The majority of the known carcinogenic chemicals, therefore, would evidently belong to the latter class, although most of them have not been adequately tested in this respect. The designation of a chemical as a carcinogen, according to this concept, would have to be specified and complemented by the additional information on the particular species, strain, tissue, and route of introduction in which and by which the carcinogenic property of the test material became manifest.

Because of the highly defective information available on the target organ of the carcinogenic action of chemicals tested in animals by various routes, the adoption of such a classification of carcinogens and, particularly, its practical application for the determination of potential cancer hazards in man is unwarranted at this time. Under the prevailing conditions decisions based on the above principles would reflect mainly lack of pertinent factual information and would not be derived from concrete positive or negative evidence obtained from properly designed experiments.

There exist only some fragmentary data concerning such relationships which are useful in these respects.

Observations in man and animals indicate that agents causing cancer of the skin, such as arsenicals, mustard gas, and radioactive chemicals, may when inhaled produce cancer of the lung. Arsenicals and radioactive chemicals and possibly also mineral oils, when ingested, may elicit cancers of the digestive tract, such as the liver and the intestine or of other nondigestive organs, such as the bones, respectively. Whereas benzidine, 4-amino-diphenyl, and several of its derivatives which are bladder carcinogens to man and dogs, when subcutaneously injected into rats, have given rise to the development of carcinomas of the intestine, evidence is lacking whether or not a similar effect can be produced in rats or in other species when such chemicals are fed, although it is suspected that benzidine may elicit, under occupational conditions of exposure in man, not only bladder carcinomas but also carcinomas of other organs, such as the intestine and lung. Since, under such circumstances, benzidine penetrates the skin, is inhaled, and is ingested, it is not possible to state whether such multifocal effects are attributable to the introduction of benzidine through one or several of these routes.

General experimental experience indicates that the respiratory and digestive systems of rodents are apparently less susceptible to the action of various human and experimental carcinogens than those of man. Because of the distinct limitations to be placed upon the value of results obtained by the introduction of test materials through these routes in experimental animals, it appears to be most unwise, if not dangerous, to attach any decisive importance as to their significance to human cancer hazards on a negative outcome of tests in which the alimentary and respiratory routes were employed. At the present state of our knowledge on these phases of experimental carcinogenesis the
apparent inability of a chemical given by mouth to produce cancers in experimental animals does not justify the conclusion that such a chemical does not exert such an effect in man and thus is not a dietary carcinogen.

As long as these and other methodological uncertainties concerning the identification of carcinogens prevail, it is advisable, as a matter of wise precaution, to exclude as far as possible all environmental carcinogens from contact with man so as to avoid any subsequent epidemic-like occurrence of cancers attributable to an indiscriminate decision made 10-30 years ago.

Criteria of Cancer

It is doubtless correct that the majority of cancers occurring spontaneously or induced in man and animals fulfill the various criteria of cancer developed on an empirical basis and generally accepted as characteristics of malignant neoplasms. It has been known, on the other hand, that exceptions to these rules are not infrequent. The histologic differential diagnosis between a squamous-cell carcinoma of the skin and a keratoacanthoma, both recently observed in workers having contact with hydrogenated coal oils (Sexton) (74), is often difficult or impossible. This distinction can be made at times only on the basis of the subsequent benign or malignant course which a particular tumor assumes. Clinical experiences in coal tar workers and aromatic amine workers also have shown that polyposus growths of the skin and of the bladder mucosa, respectively, presenting the gross appearance of cancerous reactions, may regress spontaneously (false positives) (Hueper; Goldblatt [25]). Ulcerative lesions in the skin of monkeys produced by the prolonged application of coal tar and exhibiting, upon histologic examination of biopsy material, the characteristics of epidermoid cancers likewise may ultimately heal, despite the continued application of the carcinogenic material. These observations evidently indicate that the histologic demonstration of malignancy is not always proof of the biologic malignancy of a neoplastic lesion.

Another striking and rather frequent exception from the criteria characterizing cancers is represented by basal-cell carcinomas of the skin, which may develop following an occupational or environmental exposure to sunlight, coal tar, and arsenicals. Basal-cell cancers of the skin do not produce metastases and thereby lack one of the most important properties of malignant growths. It may be pointed out in this connection that an appreciable number of environmentally important carcinogens (asphalt, coal tar, uranium, nickel, chromates, shale oil, hydrogenated coal oils, coffee soot, 3,4-benzpyrene), when subcutaneously or intramuscularly introduced in rats and mice, will produce cancers only at the site of administration but often do not form metastases, although they show extensive infiltrative and destructive growth and often a high degree of anaplasia (Hueper and co-workers [92, 35, 36, 39, 40, 63]).

These observations have distinct scientific and medicolegal importance since Brunner (7) recently demanded that the designation of "sarcoma" should be withheld from the malignant mesenchymatous neoplasms which develop around subcutaneous implants of various plastics because of their low tendency to form metastases. Since the majority of cancers of the bladder produced in man and dogs by contact with carcinogenic aromatic amines do not form metastases in regional lymph nodes or remote organs, the absence or low tendency of such manifestations of discontinued cancerous growth cannot be considered as a scientifically sound reason for assigning to such neoplasms a special position and for placing them among the noncancerous growths. The carcinogenic nature of the chemicals causing these cancers would be denied by such a decision.

During recent years repeated attempts have been made to relate specific histologic types of cancers to a specific etiologic agent (Hueper) (34). It was, for instance, contended that all or most squamous-cell carcinomas of the lung were due to exposures to cigarette smoke and that adenocarcinomas were of a different etiology. It may be pointed out here that abundant observations with various specific occupational respiratory carcinogens attest to the fact that the same agent may elicit different histologic types of lung cancer. Experiences gained with various environmental carcinogens tested on animals have also demonstrated the absence of correlations between these two aspects. Recent reports based on a detailed, if not minute, histologic and histochemical analysis of lung cancers observed in this country, such as Los Angeles, and abroad, such as Japan and Italy (Kreyberg) (46), have, moreover, shown that the increase in lung cancers affected in these areas mainly the adenocarcinomatous variety.

Because of these irreconcilable discrepancies it may, therefore, be wise to investigate the possibility that variations in the general and local histologic type of cancers may depend upon the speed with which a cancer develops from the tissue of origin and with which it grows later in various parts. It seems to be reasonable to assume that a cancer which develops rapidly from a tissue exposed to a carcinogen and not, or little, damaged
by this agent would duplicate the original tissue from which it is derived—i.e., for instance, glandular tissue in the bronchial mucosa. If, on the other hand, a cancer originates from a tissue which has undergone for some time chronic, reparatory, and metaplastic alterations, it is likely that the cancer would reflect in its structure the metaplastic tissue from which it is derived. Such conditions may prevail whenever a bronchiogenic carcinoma develops from metaplastic areas of the bronchial mucosa affected by chronic inflammatory processes of chemical, bacterial, or viral nature. Similar correlations apparently prevail in determining the predominant histologic type of cancers of the bladder attributable to exposures to aromatic amines and to *Schistosoma hematobium* infections. The aromatic amino cancers originating from a bladder mucosa which usually does not display any chronic inflammatory reactions are, as a rule, of the transitional-cell type. Cancers of the bladder appearing in individuals suffering from chronic Schistosomiasis of this viscus associated with severe inflammatory and leukoplakic reactions, on the other hand, are predominantly of the squamous-cell type.

The histologic type of a particular cancer, therefore, seems to be the combined result of the relative potency of the carcinogenic action and the reactive status of the host organism.

**Causative Mechanisms**

The various theories developed through the years concerning the causative mechanisms by which chemicals of various types interact with constituents of the cell in the cancerization process have been, in part, of a generalized and, by necessity, rather diffuse type, such as the chronic irritation theory, the somatic mutation theory, the allergic theory, the Warburg's theory of anoxic fermentation, the hypotheses concerning the role of free radicals, peroxides, and sulfhydryl groups, and the postulate of the activation of abnormal carcinogenic genes or specific viruses by carcinogenic chemicals. Other theories are of more restricted nature applying to some specific type of carcinogenic chemical, such as the polycyclic aromatic compounds—i.e., the Pullman electronic theory; and some structural characteristics of the members of these chemical groups, as well as of some carcinogenic aromatic amines—i.e., the formation of ortho-hydroxymetabolites. Whereas some of the general type theories have also been used for explaining the action of carcinogenic metals, such as the sulfhydryl theory and the hypothesis on the formation of intracellular protein complexes, only Warburg's theory of cellular anoxia and the theory on the formation of protein complexes have so far been offered in an attempt to account for the development of polymer cancers (Hueper) (37), if one disregards the recently advanced speculative assumption that some mysterious and nonspecific forces emanating from the surfaces of implanted plastic films are responsible for the neoplastic phenomena observed (Nothdurft [59]; Oppenheimer et al. [62]).

Apart from the purely scientific benefits ensuing from a better understanding of the causative mechanism or mechanisms of carcinogenic agents, the availability of such information would be of distinct advantage for distinguishing between carcinogenic and none carcinogenic environmental chemicals and would facilitate the development of more efficient, more reliable, and faster screening procedures. At the present time none of the various theories is of any real value for this purpose.

It is also probable that an adequate knowledge of the causative mechanism of environmental carcinogens would help in the development of etiologically specific diagnostic procedures and of rational and effective prophylactic and therapeutic measures. Since some of these carcinogens are recognized human allergens, such as the various metals, and others are known to form complexes with cellular proteins (various azodyes, quinones formed from carcinogenic aromatic amines, carcinogenic polycyclic aromatic hydrocarbons) (Hueper [29, 30]; Mayer [48]; Miller and Miller [49]; Heidelberger et al. [27]; and others) and thereby may become antigens, a comprehensive experimental exploration of a chemo-specific allergenic mechanism of environmental carcinogenesis seems to be worth while. Experimentation with none carcinogenic chemicals structurally similar to carcinogenic chemicals for testing the usefulness of structural blockade as a prophylactic measure and for determining the importance of specific spatial configuration and qualitative and quantitative structural factors for the interaction of exogenous and endogenous agents in the cancerization process offer an additional promising approach for advancing the control of environmental cancer hazards and cancers.

Important facets in these efforts, which depend in part upon a more exact and detailed information on the causative mechanism of carcinogens, are associated with the selection of the proper animal species suitable for the screening of chemicals for carcinogenic properties and with the extrapolation of observations made in animals to man in both qualitative and quantitative respects.

The decisive significance which specific metabolites, formed by some species but not by others, possess in determining the occurrence as well as
the site of a carcinogenic response has been strikingly illustrated by the role which ortho-hydroxy-derivatives of certain carcinogenic aromatic amines, such as β-naphthylamine, 4-aminodiphenyl, and benzidine, play in the production of bladder cancers in man and dogs, and in the absence of such neoplastic reactions in mice and rats in which these metabolites are essentially absent. The development of cancers at other sites in these species, when given the aromatic amines mentioned, on the other hand, indicates that these species apparently produce metabolites which have alterations in carcinogenic properties and relative potency of several chemicals which result from a shift in the position and the relative length of their sidechains (polycyclic aromatic hydrocarbons: benzpyrene, dibenzanthracene) and occur subsequent to the introduction of fluorine into the ring (aromatic amino compounds) (Miller and Miller) (49).

The increased reliance of the modern economy on products of the chemical industry and the growing awareness of the carcinogenic nature of some of its products make an early acquisition of an adequate knowledge of the basic factors underlying, modifying, and controlling chemical carcinogenesis an urgent necessity. The availability of sufficient factual data which may serve as guides for avoiding the development of carcinogens in the production of new chemical compounds would protect the chemical and related industries against engaging in research which might prove to be needlessly costly, when it inadvertently leads to the development of carcinogenic compounds.

**Potency of Carcinogens and “Safe” Dose**

The emphasis which has recently been placed upon the determination of the absolute and comparative potency of carcinogens in experimental animals, for the purpose of making educated decisions about the safety of chemicals, is a reflection of the increased awareness of the potential health risks associated with chemical exposure. Understanding the potency of carcinogens is crucial for evaluating the potential for cancer risk and determining safe levels of exposure. This is essential for both regulatory purposes and for informing the public about the safety of chemicals in their daily lives.

<table>
<thead>
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<th>Chemical</th>
<th>Man</th>
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</tbody>
</table>

Additional advantages would accrue from such knowledge, not only to the study of the environmental cancers but also to the future development of noncarcinogenic economically important chemicals by industry, if the reason were known for the
guesses at their so-called “safe dose” to man, has resulted in uncovering the many methodological difficulties existing in this respect and in demonstrating the distinct lack of fundamental facts for arriving at a “safe dose” which is safe for the great majority of members of the human populations at risk—i.e., mainly the general public and the general consumer of industrial goods.

Abundant experimental experience has clearly shown that the absolute tumor yield, as well as the length of the latent period for carcinogenesis by a particular carcinogen, may vary in wide limits not only among different species but even among different strains of the same species and among the two sexes of the same strain, although identical conditions of exposure are being used. Almost 100 per cent of dogs, for instance, developed bladder cancer within 2 years when given optimal doses of β-naphthylamine by mouth, whereas only about 10 per cent of mice fed this carcinogen showed, within this period, cancers of the liver (Bonser et al. [5]; Hueper et al. [41]). Another carcinogenic aromatic amine, namely, 2-acetylaminofluorene, administered orally to rats, elicited cancers in various organs (liver, intestine, ear duct, lung, etc.) in most of the treated rats within a year (Bielschowsky et al. [3]; Morris et al. [54]), whereas dogs given this chemical by the same route required for the development of cancers of the bladder and of the liver a minimum exposure period of over 5 years (Morris and Eyestone) [55].

Recent experiments with a number of hexavalent chromium salts have shown that the physical properties, i.e., the degree of water solubility of the individual compounds, control both the tumor yield and the length of latent period (Table 3).

The relative biologic availability of carcinogens when in contact with the host organism, therefore, influences the potency of a carcinogen by controlling either the relative amounts of carcinogen released within standard periods from depots or by determining the length of time it stays in contact with the tissues at any one site because of its excretion or removal rate.

### TABLE 3

**CANCEROUS RESPONSES AT THE SITES OF IMPLANTATION OF SEVERAL CHROMIUM COMPOUNDS IN THE THIGH MUSCLE AND PLEURAL CAVITY OF RATS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Cumulative total of cancers/numbers of survivors; ratio at months after start</th>
<th>Latent period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0-3</td>
<td>4-6</td>
</tr>
<tr>
<td>Chronic chromate</td>
<td>1.M.</td>
<td>0/34</td>
<td>11/22</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>8/23</td>
<td>15/13</td>
</tr>
<tr>
<td>Calcium chromate</td>
<td>1.M.</td>
<td>0/32</td>
<td>5/25</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>1/30</td>
<td>16/10</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>15/16</td>
<td>17/9</td>
</tr>
<tr>
<td>Strontium</td>
<td>1.M.</td>
<td>0/28</td>
<td>2/26</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>1/33</td>
<td>9/20</td>
</tr>
<tr>
<td>Barium chromate</td>
<td>1.M.</td>
<td>0/34</td>
<td>0/33</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>0/31</td>
<td>0/30</td>
</tr>
<tr>
<td>Lead chromate</td>
<td>1.M.</td>
<td>0/34</td>
<td>1/28</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>0/34</td>
<td>0/32</td>
</tr>
<tr>
<td>Sodium dichromate</td>
<td>1.M.</td>
<td>0/26</td>
<td>0/33</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>0/24</td>
<td>0/21</td>
</tr>
<tr>
<td>Chromite roast</td>
<td>1.M.</td>
<td>0/34</td>
<td>0/32</td>
</tr>
<tr>
<td>Zinc yellow</td>
<td>1.M.</td>
<td>0/33</td>
<td>1/32</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>0/33</td>
<td>7/23</td>
</tr>
<tr>
<td>Chromium acetate</td>
<td>1.M.</td>
<td>0/34</td>
<td>0/33</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>0/34</td>
<td>0/32</td>
</tr>
<tr>
<td>Sheep fat</td>
<td>1.M.</td>
<td>0/34</td>
<td>0/32</td>
</tr>
<tr>
<td></td>
<td>1.P.</td>
<td>0/34</td>
<td>0/32</td>
</tr>
</tbody>
</table>
From the results of recent experiments undertaken for comparing the relative carcinogenic effectiveness on mice of a potent carcinogen, 3,4-benzpyrene, when standardized amounts were administered subcutaneously in a single injection with that obtained when the same total amount of carcinogen was given by repeated monthly injections, it appeared that the effects produced depended not only on the amount administered but also on whether it was given in a single dose or in multiple doses. The carcinogenic response under these conditions increased when the total dose was administered in increments (Chart 1).

Of distinct significance in regard to the determination of carcinogenic potencies was also the observation of a plateau effect seen in mice given 3,4-benzpyrene by single injection after an optimal quantitative exposure had been reached. In contrast, there was a continued rise in the cancer yield with a progressive increase in the total dose of carcinogen injected when it was given in fractionated doses (Payne and Hueper [65]). Since a low-level, recurring exposure to a carcinogen, according to these findings, is more hazardous than a single exposure to the same total amount, and because man sustains, as a rule, the first type of yield with a progressive increase in the total dose of carcinogen administered, subcutaneously in a single injection after an optimal quantitative exposure had been reached, it was found that the number of demonstrable urinary metabolites increased with an increase in the dose of the dye given and that there occurred a shift in the quantitative relations between the chemically different metabolites under these experimental conditions. In view of the fact that the chemical character and the relative quantity of individual metabolites of urinary carcinogens seems to influence the carcinogenic response produced in the bladder by some of the known carcinogenic amines, it is probable that purely quantitative factors may decisively influence not only the outcome of experimental potency studies but also the degree of cancer hazard from such chemicals in exposed human populations. These observations, moreover, illuminate the frequently raised problem concerning the existence of marked differences in the susceptibility to environmental carcinogenic agents by different members of the general population, since it consists not only of so-called normal individuals but also of a considerable proportion of metabolically abnormal ones who may possess a reactivity to carcinogens different from that of the normal group.

The importance of the reactive status of the host organism in determining the potency of environmental carcinogens and, consequently, any calculation which one might dare to make in regard to a “safe dose” has recently received added attention by the demonstration of a greatly increased susceptibility of newborn mice to carcinogenic polycyclic aromatic hydrocarbons (Pietra et al. [66, 67]). Since previous experiences with a transmitted malignant exposure of the maternal milk to their offspring resulting in an early appearance of pulmonary tumors in the young has a similar connotation, experimental potency determinations with prospective application to man must take these observations into proper consideration. In fact, infants and children, if these findings in animals should apply also to man, would be particularly vulnerable to prolonged exposures to rather small and perhaps minute doses of environmental carcinogens present in foodstuffs, including the maternal milk, in the air, and in drinking water. Because of their prospective long lifespan, infants also face the additional liability of a long latent period, usually necessary for weak carcinogenic exposures to result in manifest tumor formation. There is an additional health hazard from such intrauterine exposures of the
from cutaneous contact with hydrogenated coal products produced by the Bergius process (Hueper [3] and Sexton [74]), and with respiratory contact to mustard gas (Heston [28]; Case and Lea [7]; Beebe [2]; Yamada et al. [76]). The experimentally induced occurrence of cancers in animals by the use of a chemical with economic importance should thus furnish an adequate justification for conducting comprehensive epidemiologic investigations on population groups exposed to this agent for exploring the existence of a similar environmental cancer hazard to man.

A similar connotation has the observation of any epidemic-like appearance of cancers in animals, especially if they are food animals and if they become exposed to environmental factors, particularly dietary constituents, which are identical with or similar to those introduced into the human food supply. While the occasional appearance of cancers in domesticated and wild animals, including fish exposed to human carcinogens, such as radioactive matter, petroleum oils, and arsenicals, had previously been reported, the scope of such environmental pollutions to animals and man was demonstrated by the recent observation of an epidemic of primary liver cancer among rainbow trout kept in hatcheries throughout the country (Hueper and Payne; 2 Rucker, Yasutake and Wolf [71]). It was found that such cancers occurred in animals as young as 6-7 months old and affected about 80-90 per cent of brood trout kept for over 3 years. The evidence indicated that the carcinogenic agent active in the production of these liver cancers was evidently highly potent and apparently acted upon the very young animal. A preliminary assessment of the circumstances under which this epidemic has made its appearance suggests that a dietary factor (arsenical amebicides, sulfoxamides, oxidized fatty acids, antioxidants, vitamin, and protein imbalances, etc.) is to be implicated, which is contained in or associated with the processed fish feed introduced into the industry some years ago.

This tentative explanation is made rather probable because of the fact that various chemicals introduced into animal and human foodstuffs and dietary deficiencies have been shown to elicit primary cancer in experimental animals (chlorinated hydrocarbon pesticides, such as DDT and Aramite; fungicides, such as thiourea and thiourea derivatives and thioacetamide; the sweetening agent, phenyl urea [Dulcin]; the flavoring agent, safrol; the food contaminant, selenium; the pesticide, arsenic; several food dyes, oil orange E; oil yellow HA, butter yellow; and dietary methionine and protein deficiencies). Since some of the various dietary ingredients mentioned are not only present in many of the foodstuffs used for human consumption but are also stored in the human body and thus capable of exerting a prolonged and progressively accentuated action, the occurrence of a
Preventive Medicine, March 1961, Dr. Thomas F. Mancuso, Chief, Industrial Hygiene, Ohio Dept. Health, Columbus, presented before the Meeting of the American Academy of Ohio.

The fact that the eminent carcinogenic role of benzidine and its analogs is well recognized in epidemiologic studies on occupational cancers in the United States is also responsible for the fact that the eminent carcinogenic role of benzo(a)pyrene in the causation of cancers of the bladder, which is generally recognized throughout the world, has been challenged by some American investigators (Eckardt [40]) who followed in this respect the lead given some years ago by Gehrmann [24].

Through such practices the false impression is supported that occupational cancers are uncommon (Eckardt [41]; Oettel [61]) and that, for this reason, this particular but highly important kind of environmental cancer is only of limited importance as a public health problem. The fact is that according to world-wide experience the study of occupational cancer hazards deserves greatly increased attention not only because they elicit important and often fatal industrial diseases, but also because the special circumstances related to exposures to carcinogenic agents present for occupational population groups greatly facilitate the demonstration of the action and sometimes of the character of an industrial carcinogen. Such a carcinogen, through its subsequent introduction into the general human environment, might also represent an environmental carcinogen which then has usually a rather diffuse distribution and possibly widely scattered carcinogenic effects not readily shown by available epidemiologic methods. Epidemiologic studies on occupational cancer hazards, therefore, may provide the key to the recognition of environmental cancer hazards.

Retrospective epidemiologic studies are indicated for the multitude of occupational population groups whose members have been exposed for many years to the various known carcinogens. Such studies are especially indicated whenever the available evidence for a particular carcinogenic hazard has remained totally or mainly restricted to non-American sources, such as cancers in hematite miners and foundry workers, in nickel smelter workers, in employees of asbestos mines, mills and textile plants, in miners of arsenic-containing ores, arsenic smelter workers, and insecticide makers and users, in uranium ore miners and millers, chemical and pharmaceutical producers and users of various aromatic amino- and nitro-compounds and whose users in industry (particularly rubber plants and processing and preparation of foodstuffs), makers of synthetic estrogens and the producers and users of estrogenized animal feeds, employees of oil refineries and carbon black and carbon electrode plants, and workers on gas retorts in gas plants and coke ovens, as well as the numerous industrial users of coal tar and pitch.

Prospective epidemiologic investigations are needed for the even more numerous occupational populations engaged in the manufacture and use of the many potential human carcinogens for...
which, at present, any type of human evidence is lacking. Retrospective and prospective epidemiologic studies can most profitably be pursued at present on worker groups of great stability (long-term employment) who are employed in factories located in rather small communities and representing their main local industrial establishment.

Such surveys on human populations undertaken for the discovery and assessment of occupational cancer hazards should be supplemented by long-term surveys on wild and domesticated animals living on the ground and in bodies of water in the vicinity of industrial operations with carcinogenic hazards, since industrial effluents released into the air and into bodies of water near such plants may contain carcinogens which may elicit carcinogenic responses among such animals. In fact, observations of cancers among these animals may serve as early warning signs of the existence of an industry-related environmental cancer hazard to man breathing the air, drinking the water, and eating the plants and fruits grown in the soil polluted with carcinogenic chemical dirt from nearby industrial plants, and means of motorized transportation. The reported more frequent occurrence of lung cancer in dogs living in urban areas in the U.S.S.R. than in those of rural regions, if confirmed, furnishes a good illustration of such correlations, especially since they would point to the importance of carcinogenic factors in urban air pollutants as significant agents in the causation of this particular type of cancer (Leake [47]; Hueper [31]; Hueper et al.).

In the etiology-specific interpretation of such statistical data, when applied to cancer of the lung in man, it appears wise to consider the proved polyetiology of many cancers, including lung cancers, as well as the probability that several carcinogenic and co-carcinogenic factors might combine in eliciting a cancerous response. The results of recent epidemiologic and pathologic observations have revived the former interest in the relation of tuberculosis and cancer of the lung. In view of the fact that the oral administration of the sedative, urethan (Jaffé [42]) and of the tuberculostatic isonicotinic acid hydrazid (Mori et al. [52]) resulted in an excessive development of pulmonary adenomas in mice, it may be indicated to investigate with statistical methods the possible role which the various types of medications administered for different reasons to persons with tuberculosis of the lung may have played in the development of cancers in tuberculous lung (Baló [1]).

In the interpretation of the statistical data obtained from epidemiologic studies of occupational groups it is unrealistic to adopt the concept that "It is scientifically unsound to attribute a given type of cancer to an occupation unless it can be established with statistical significance that the incidence of this type of cancer among employees is higher than in the general population, or in an employee group comparable in all other characteristics except the occupation" (Eckardt [19]). Such decisions do not depend entirely on the outcome of statistical investigations but require also the application of sound medical judgment concerning the symptomatic and pathologic manifestations noted in members of worker groups suspect of being subjected to an occupational cancer hazard. Individuals exposed to benzol and ionizing radiations, for instance, exhibit a hematic syndrome reflecting strikingly the ambivalent aplastic and hyperplastic effects, including leukemia, produced by these agents upon the blood-forming tissues. Since the entire range of such reactions can be elicited with these agents in experimental animals there can exist no reasonable scientific doubt concerning the causal relation between contact with benzol and ionizing radiations and the subsequent development of leukemia, despite the fact that the presently available epidemiologic data may not be entirely sufficient to support such a conclusion. The objections raised lately by several commercially interested parties to further consider arsenicals as human carcinogens because of the absence of adequate epidemiologic and experimental evidence in support of such a concept, held for many years by numerous competent and experienced dermatologists and industrial physicians, also totally disregard the characteristic symptomatic pattern of chronic arsenic poisoning presented by the type, sequence, and location of cutaneous changes preceding the development of cancers of the skin, lung, and liver often seen in individuals who were exposed to arsenicals for occupational, medicinal, and dietary reasons.

A serious shortcoming of the presently available epidemiologic-statistical methods is related to the fact that the information obtained by such procedures usually relies on the demonstration of abnormalities in the quantitative pattern of the cancer panorama found in the population group examined, i.e., as a rule an incidence rate of a certain type of cancer which is excessive in relation to that found in a standard or control population. However, conclusions drawn from such comparisons are subject to the vagaries of the so-called "stand-
ard” cancer rates, since these vary within rather wide limits for different population groups according to region and occupation. If one should give full credence to the claims of the advocates of the cigarette theory of lung cancers, they vary for these cancers also according to the prevalence and intensity of the smoking habits observed by the members of the particular population group analyzed which, in turn, are alleged to determine their predominant histologic variety. “Standard” cancer rates thus are rather arbitrary values, which, when indiscriminately and improperly applied, might obscure the demonstration of an occupational cancer hazard.

An example of such an obliterated correlation is being offered by the gradual disappearance of the formerly marked discrepancy in lung cancer incidence rates between English coke oven and gashouse workers exposed to an inhalation of coal tar fumes and the English population in general, becoming lately exposed to an increasing degree to carcinogenic constituents present in industrial air pollutants and in automobile exhaust (Hueper [31]; Doll [18]). Similar objections apply to the validity of data on cancer incidence in so-called normal control groups, which can also be selected in such a way that they may or may not differ fundamentally from the test group as far as cancer rates are concerned, although they are apparently chosen by the generally accepted rules. The decision concerning the absence or presence of an occupational cancer hazard among members of a test population, therefore, should not entirely depend on the demonstration of an excessive cancer incidence rate, because this rate, for the reasons given, may be within the limit of “standard” values, despite the existence of a distinct occupational cancer hazard.

Because of the ambivalent effects elicited by many carcinogens, such as ionizing radiations, benzol, estrogens, urethans, and others, it appears to be important that considerable epidemiologic research be conducted on the carcinogenic relations of various chemotoxic disease manifestations characterized by degenerative manifestations, such as aplastic anemia, agranulocytosis, liver degenerations and necroses, functional and anatomic thyroid hypoplasias, and cutaneous atrophies, which represent either direct chemotoxic reactions or chemoallergic responses.

The rapidly growing industrial, dietary, cosmetic, and medicinal use of macromolecular chemicals, such as especially plastics and water-soluble carbon and silicon polymers, which have displayed carcinogenic properties in experimental animals, also seems to justify the organization of a registry of patients who received parenteral implants of such plastic materials for a subsequent epidemiologic assessment of possible late carcinogenic sequelae around such implants appearing some 10–30 years after such deposits were made. As a matter of wise precaution, such studies may also be extended to persons wearing plastic dentures, since it is important to ascertain whether or not a prolonged mucosal contact with such plastics might be related to a delayed formation of cancers in the oral cavity.

This brief outline on the facts, the concepts, and the many unsolved and controversial problems of environmental carcinogenesis and cancers has served its purpose if it has conveyed adequately the message that the field of environmental cancer research represents not only one of the most important facets of cancer research but, at the same time, also one of the most rewarding and immediately useful ones. With the availability of increased funds and increased interest in these aspects of cancer control especially by prophylactic and preventive measures, it may be hoped that the foreseeable future may see perhaps a repetition of the successes which this approach brought to the control of communicable diseases.

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