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Part I. Environmental and occupational cancer hazards

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Cancer, like all other diseases, is not a mysterious phenomenon of spontaneous creation but the result of the action of definite chemical and physical, animate and inanimate, endogenous and exogenous pathogenic agents. It should therefore be possible to eradicate cancer hazards and cancer by preventive and therapeutic measures. Although both methods will have to be applied to achieve a reasonable degree of cancer control, it is obvious that for humane and economic reasons, the use of effective preventive procedures is preferable to curative procedures.

The prerequisite of prophylactic and preventive measures in disease control is the availability of adequate information on the causes of the disease and on the sources and opportunities of exposure to such causes. Although a recent editorial appearing in the *Journal* of the American Medical Association[55] contains the dogmatic statement that preventive cancer control cannot be practiced by the medical profession because of the prevailing lack of data on the etiology of cancer, the irrefutable fact is that the medical profession at large, which has had access to a great mass of detailed and definite evidence concerning the causes of many types of human cancer (Table I), has shown in the past little inclination to apply this information practically (Samp[206]). Various industrial establishments throughout the world, health departments of many countries, and individual physicians everywhere, on the other hand, have applied for decades this knowledge in haphazard attempts at the preventive approach to cancer control (Hueper[112, 123, 126]; Eckardt[54]; Scott and Williams[212]; Goldblatt and Goldblatt[75]; Bauer[12]; Chiurco[36]).

The numerous human carcinogens of occupational nature are generally recognized because they have been responsible for the occurrence of cancer in various organs and tissues in thousands of human beings and have caused the death of many of them and shall continue to do so for some time to come. Their existence and their significance have found scientific, medicolegal, and legal acknowledgment (Hueper[127]). While the bulk of the diverse factual evidence on environmental causes of human cancer was originally related to occupational cancer hazards, numerous new data acquired during recent decades have made it increasingly obvious that many of the occupational carcinogens to which specific worker groups become exposed during production and processing procedures are subsequently introduced into the general human environment in the form of industrial pollutants of the air, water, and soil and as constituents of many consumer goods and thus are brought in wide contact with members of the general population. Although such general exposures to environmental carcinogens are as a rule less intense than those encountered under occupational conditions, they are often lifelong and under the

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prevailing circumstances frequently unavoidable, i.e., the general public has been placed in the role of a captive population.

This potentially dangerous development associated with the increasing artifactual carcinogenic contamination of the human environment and of goods produced and used in daily living for many years encountered astounding indifference and studied aloofness by many governmental, professional, and private parties engaged in scientific and practical work in cancer. It was only in recent years that a rather rude awakening from this lethargic state resulted from the acute concern of the general public regarding actual and potential cancer hazards related to the following three developments: (1) the growing pollution of the air, water, soil, and foodstuffs with radioactive matter, (2) the increasing introduction of carcinogenic additives and contaminants into the daily food supply and other general consumer goods, and (3) the impressive and progressive rise in the incidence of cancer of the lung during the past 50 years and its probable causal association with the growing pollution of the general and occupational atmosphere with more or less chemically well-defined carcinogenic industrial effluents and with the rapid growth in the degree of personal air pollution through the cigarette smoking habit.

These developments have furnished the factual background for various types of protective legislation enacted during recent years by Federal, state, and municipal legislatures and health agencies relative to the presence and contamination of foodstuffs, drugs, and cosmetics with carcinogenic chemicals, the release of carcinogenic pollutants of the air from industrial plants and the exhausts of automobiles, and the commercial operation of equipment generating ionizing radiation. In fact, the obligatory registration with state authorities of all industrial, commercial, and professional establishments in which ionizing radiation is used and produced, which was introduced during the past decade in several states, fulfills in part a proposal made in regard to all carcinogenic operations some years earlier and still to be accomplished (Hueper[107]).

Considering the fact that at present about 1,100,000 persons with cancer are living in the United States and that about every fourth death of an adult is caused by cancer, cancer of all types and causes displays all the characteristics of an epidemic in slow motion. Through the increasing contamination of the human environment with chemical and physical carcinogens and with chemicals supporting and potentiating their action, the stage is set for the future occurrence of an acute, catastrophic epidemic, which once present cannot effectively be controlled for several decades with the means available (Hueper and Payne[138]; Roth[205]). While the human population has been spared such a general tragedy, in that so far it has remained restricted to relatively small worker groups sustaining exposures to various carcinogenic aromatic amines, arsenicals, and radioactive gases and dust, the distinct possibility of such an event has clearly been demonstrated during the last years by the discovery of a full-blown epidemic of primary liver cancer among the rainbow trout population of American fish hatcheries. This cancer epidemic seems to be causally related to the introduction of carcinogenic ingredients with recently developed commercial feed into this industry (Hueper and Payne[138]).

Prudence decrees that definite restraints be applied to keep the growing man-made carcinogenic contamination of the human environment within reasonable and effectively controlled bounds and to protect the health of the general population, including those who come after us.

Aromatic amino and nitro compounds, azo dyes, and related chemicals

Among the most potent human carcinogens, causing mainly cancer of the bladder, are certain aromatic amines such as naphthylamine, benzidine, and xenylamine. They have elicited cancer of the various parts of

Table I. *Occupational carcinogens, their route of exposure, and their target organs*

General type	*Specific type*	*Route of exposure*	*Target organ*
Chemical carcinogens			
Organic chemicals:	Benzol	Cutaneous, respiratory	Blood-forming organs (leukemia, lymphosarcoma)
Aromatic, polycylic, heterocyclic	β-Naphthylamine, benzidine 4-aminodiphenyl	Respiratory, cutaneous, alimentary	Urogenous organs (bladder, ureter, kidney)
	Auramine		Lung, intestine(?)
	Coal tar, pitch, asphalt, tar oil, creosote oil, anthracene oil, lamp black, lignite, tar, and paraffin oil	Cutaneous, respiratory	Skin, lung
	Synthetic hydrogenated coal oil, tar (Bergius)	Cutaneous	Skin, oral cavity(?)
	Shale oil, and paraffin oil	Cutaneous, respiratory	Skin, larynx
	Petroleum fuel oil, diesel oil, lubricating oil and grease, cutting oil, carbon black, asphalt, tar, coke, crude paraffin oil	Cutaneous, respiratory	Skin, lung
Aliphatic	Isopropyl oil	Respiratory	Nasal sinus, larynx, lung
	Mustard gas	Respiratory	Lung, larynx
Inorganic chemicals	Arsenic	Cutaneous, ingestive, respiratory	Skin, liver, alimentary tract, lung, nasal sinus, larynx
	Nickel	Respiratory	Nasal cavity, nasal sinus, lung
	Iron(?)	Respiratory	Lung
	Chromium	Respiratory	Lung, nasal sinus
	Asbestos	Respiratory	Lung, pleura, peritoneum
Physical carcinogens	Ultraviolet radiation	Cutaneous	Skin
Ionizing radiation	X-Irradiation	Cutaneous, transcutaneous	Skin, connective tissue, bone, blood-forming organs
	Radioactivity (α, β, and γ radiation)	Cutaneous, transcutaneous, respiratory, ingestive, parenteral	Skin, connective tissue, blood-forming organs, nasal sinus, lung, bone, liver
Parasitic carcinogens	Schistosoma hematobium	Cutaneous	Bladder

the urinary tract after exposure in microgram amounts experienced over periods as short as 6 months and have been responsible for a cancer attack rate of practically 100 per cent of the population at risk when no precautionary measures were taken to prevent or reduce severe and prolonged exposure (Hueper[103, 125, 126, 129]; Williams[250]; Mattea[170]; Vigliani and Barsotti[239]; Temkin[233]). β-Naphthylamine has been shown to be so powerful and its occupational cancer hazard so uncontrollable that the production of this carcinogen has been discontinued for some time by large scale chemical manufacturers in England, Germany, Switzerland, and the United States. Supplementing this voluntary action taken by several chemical companies in the United States, the Pennsylvania State Health Department has recently prohibited the further production and commercial use of β-naphthylamine.*

There are over 2,000 cases of occupational bladder cancer from such chemicals

*Jan Lieben: Personal communication, 1961.

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on record. They have occurred among producers of these chemicals, their users in the manufacture of dyes and rubber antitoxidants, and dyers and rubber workers (Hueper[129]; Williams[250]; Baader[9]). More than 500 of these cases have been observed in the United States among employees of seven chemical companies. The actual number of such occupational cancer cases is doubtlessly much higher.

In addition to azo dyes made from these compounds, other aniline dyes which have caused cancer of the bladder among their producers are auramine and fuchsin, the first being a diphenylmethane dye and the second a triphenylmethane dye (Williams[250]; Gross[79]).

The general public has been exposed to carcinogenic amines and to the dyes produced from them because they have been used for many years as certified food, drug, and cosmetic colors (Tables II and III). While some of the dyes, particularly derivatives of the two naphthylamines, have been removed from the certified list during recent years for reasons of "toxicity," others have been retained. Among the decertified dyes are yellow AB and yellow OB, extensively employed for many years for coloring butter, margarine, oils, fats, cheeses, baked goods, medical preparations, and cosmetics (hair oil and pomade). These certified derivatives of β-naphthylamine were shown to contain significant amounts of this carcinogenic dye intermediate as an impurity (Table IV) (Conway and Lethco[43]). A similar fate was decreed for orange SS an α-naphthylamine derivative known as FD & C orange No. 2, shown to be carcinogenic to mice when fed or implanted into the bladder, as well as to the chemically related Food, Drug and Cosmetic dye red No. 32, which has the same basic structure as the carcinogenic compound known as 1-benzeneazo-2-naphthol (Bonser, Clayson, and Jull[18]). Three chemically similar Food, Drug and Cosmetic Dyes, D & C red No. 17, orange No. 4, and red No. 14, have been retained on the certified list of the Food and Drug Administration; so has also a newly admitted dye used for coloring oranges, citrus red No. 2, a close chemical relative of the just-mentioned group of dyes of which some are established carcinogens.

Carcinogenic properties have been demonstrated also for five of the eleven triphenylmethane dyes certified by the Food and Drug Administration. Apart from the fact that producers of the diphenylmethane dye, auramine, and of the triphenylmethane dye, fuchsin, in England and Germany, respectively , developed cancer of the bladder, five of the presently certified triphenylmethane dyes, namely, light green SF, brilliant blue, fast green, Guinea green, and wool violet, have been shown by various investigators here and abroad to elicit sarcomas following repeated subcutaneous injection into rats (Hueper[115, 123]). While this evidence has been judged to be adequate for prohibiting the use of such dyes in foodstuffs in several European countries (Gross[79]; Boyland[23]), the Food and Drug Administration has considered these findings as inadequate evidence for attesting to their oral carcinogenicity and, therefore, has permitted their continued use in American foodstuffs and drinks, although the Delaney Clause does not justify a distinction between oral and subcutaneous car-

Table II. *Some practical uses of certified colors*

Foods	Gelatin desserts, oleomargarine, fats, oils, butter, cheese, bakery products, sausage casings, spaghetti, puddings, frozen desserts, ice cream, maraschino cherries, soft drinks, candies and confections, canned vegetables, pie fillings, oranges, sweet potatoes, etc.
Drugs	Watery and oily solutions, vitamin preparations, tablets, ointments, capsules, etc.
Cosmetics	Toothpastes, soap, suntan oils, skin creams and lotions, hair oil, pomades, shampoos, bath salts, lipsticks, rouges, face powders, nail lacquer, mouthwashes, hair-waving fluids, hair rinses, etc.

Table III. *Recognized or suspected carcinogenic food dyes*

Dye	*Evidence in man*	*Target organ*	*Animal*	*Route*	*Target organ*	*Investigator*
Human carcinogens						
Auramine O (other countries)	Occupational	Bladder				Case; Williams
Magenta, fuchsin (other countries)	Occupational	Bladder	Rat	Oral	Bladder (papil)	Yoshida and associates
Yellow AB (United States)(?) (2-amino-1-naphthol release)	Occupational	Bladder	Dog	Oral	Bladder	Hueper and associates
Yellow OB (United States)(?)	Occupational	Bladder	Dog	Oral	Bladder	Conway and Lethco
Potential human carcinogens						
2-Hydroxynaphthalene compounds						
Sudan I (other countries)	Experiment	Liver	Mouse	Subcutaneous		Kirby and Peacock
Orange SS (other countries)		Connective tissue, intestine	Mouse	Subcutaneous		Bonser
Oil yellow HA (other countries)		Liver	Mouse	Oral		Kirby and Peacock
Sudan IV (other countries)		Liver	Rat, mouse	Oral		Willheim and Ivy; Schmidt; Hackmann
Sudan brown RR (not used)		Liver, stomach, hemato-poietic tissue	Rat	Oral		Hackmann
2-Aminonaphthalene compounds						
Thiazin brown R		Subcutaneous tissue	Rat	Subcutaneous		Hecht
Evans blue (not used)		Liver	Rat	Intra-peritoneal		Marshall
Trypan blue (not used)		Liver, subcutaneous tissue, lymphoid tissue	Rat	Subcutaneous		Gillman; Marshall, Simpson; Brown and Thorson
Black 5410 (other countries)		Subcutaneous tissue	Rat	Subcutaneous		Hecht
Azobenzol compounds						
Butter yellow (other countries)		Liver, bladder	Rat, dog	Oral		Kinosita; Nelson and Woodard
Triphenylmethane compounds						
Light green SF (United States)	Experiment	Subcutaneous connective tissue	Rat	Subcutaneous tissue		Schiller; Gross; Harris; Nelson and Hagan; Hecht
Brilliant blue FCF (United States)		Subcutaneous connective tissue	Rat	Subcutaneous tissue		Nelson and Hagan; Gross

Table III. *Cont'd*

Dye
Fast green FCF (United States)
Azurblue VX (other countries
Guinea green B (United States)
Rhodamine B (other countries)
Rhodamine 6G (other countries)
Fluorescein sodium (not used)
Eosin (water soluble) (other countries)

From Hecht.[88]

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Dye	Evidence in man	Target organ	Animal	Route	Target organ	Investigator
Fast green FCF (United States)		Subcutaneous connective tissue	Rat	Subcutaneous tissue		Nelson and Hagan
Azurblue VX (other countries)		Hematopoietic tissue	Mouse	Oral, cutaneous		Miller and Pybus
Guinea green B (United States)		Subcutaneous connective tissue	Rat	Subcutaneous		Nelson and Hagan
			Rat	Oral		Willheim and Ivy
Rhodamine B (other countries)		Subcutaneous connective tissue	Rat	Subcutaneous		Umeda
Rhodamine 6G (other countries)		Subcutaneous connective tissue	Rat	Subcutaneous		Umeda
Fluorescein sodium (not used)		Subcutaneous connective tissue	Rat	Subcutaneous		Umeda
Eosin (water soluble) (other countries)		Subcutaneous connective tissue	Rat	Subcutaneous		Umeda

From Hecht.[88]

Investigator
Case; Williams
Yoshida and associates
Hueper and associates
Conway and Lethco
Kirby and Peacock
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Nelson and Hagan; Gross

cinogenicity. Through this arbitrary and scientifically unsound interpretation of the concept of "carcinogens," it has been possible to circumvent the application of the law, as represented in the Delaney Clause, to these carcinogenic FD & C dyes.

It is likely that a clarification of some of the legal aspects of these contentions of the Food and Drug Administration may soon be obtained in American courts. These will have to decide whether bladder cancer occurring in 5 workers who had occupational contact with fuchsin and auramine during the production of inks and colored artificial flowers was the result of such exposure.

Mention may be made here that the nitro derivatives of the carcinogenic amino compounds are carcinogenic because they are reduced in the body to the corresponding amino compounds. This observation may be of practical general importance, when effluents of plants manufacturing such chemicals are released into sources of drinking water. Some years ago, one such intermediate, chloronitrobenzol, was recovered from the water of the Mississippi near New Orleans after it had been introduced into the river some 1,000 miles upstream by a chemical plant which converted this chemical into chloronitroanilin, a chemical suspected of being a bladder carcinogen (Hueper[125]).

Other potential sources of cancer to the general population from aromatic amino compounds may be the use of certain brighteners incorporated into detergents, since some of these laundry dyes added to detergents belong to the group of aminostilbenes, of which some members are carcinogenic. Several years ago, a European manufacturer had to remove such an agent from its product when it was found to cause cancer in animals. Cancer of the bladder and liver in rats has also been produced by feeding a phenetidin derivative and synthetic sweetener, phenetylurea, sold in some countries under the name of dulcin (Griepentrog[77]; Fitzhugh and Nelson[62]). It may briefly be mentioned that *o*-tolidine, a benzidine derivative, employed in the folliculinization test, has been shown to be weakly carcinogenic to rats and that one of the recently developed oral antidiabetic chemicals, a sulfonamide derivative, when

Table IV. *Free aromatic amine content of food dyes*

Dye	Batch	Aromatic amine content (p.p.m.)	
		Total aromatic amines	*2-Naphthylamine by chromatographic method*
FD & C yellow No. 3, yellow AB	A	116	84
	B	196	157
	C	193	165
	D	203	175
	E	278	274
	F	1,090	908
FD & C yellow No. 4, yellow OB	G	98	76
	H	95	77
	I	131	108
	J	135	135
S.D.		7.2	10.8

From Conway and Lethco.[43]

fed to rats caused cancer of the bladder (Spitz, Maguigan, and Dobriner[222]). An identical effect was obtained in mice when pellets containing 8-hydroxyquinoline and pyridium were implanted into the bladder. 8-Hydroxyquinoline is used as a spermatocide in many contraceptives and as a bactericidal agent in hair lotions, rectal suppositories, and ointments (Hoch-Ligeti[98]). When fed to rats or intravaginally or intravesically introduced into rats and mice, this chemical elicited local and systemic cancer (Hoch-Ligeti[98]; Boyland and Watson[24]). Pyridium (2, 6-diamino-3-phenylazopyridine) is a red dye employed as a bladder sedative in the treatment of acute and chronic cystitis (Allen colleagues[2]; Boyland and Watson[24]).

While the epidemiologic studies on aromatic aminocancer of the bladder among dye and rubber workers following occupational exposure have definitely established the etiologic importance of these chemicals, the evidence is rather vague as far as the causation of bladder cancer in the general population is concerned. It is impossible with presently available epidemiologic methods to reliably identify specific but generally distributed chemicals in the causation of any type of human cancer. Circumstantial evidence, however, seems to support the existence of such correlations. Bladder cancer rates were elevated up to twice the normal rates of the area in one county and in one city in which there was large scale production and use of carcinogenic aromatic amines for years. Moreover, there has been a moderate increase of deaths in the United States from bladder cancer during the last 10 to 15 years.

In assessing the nature of the causal factors underlying these epidemiologic observations, proper consideration must be given to the fact that the production of cancer of the bladder and other organs by other amino compounds, such as diphenyl methane and triphenylmethane dyes, sulfonamide derivatives, *o*-tolidine, chloronitroanilines, and phenetidin derivatives, extends the potential scope of economic and occupational carcinogens to a large variety of chemicals and thereby extends the possible associated cancer hazard to many additional members of the public.

Miscellaenous organic chemicals

Several additional organic chemicals which are widely used in the human economy and which when administered to experimental animals have produced cancer in various organs deserve consideration as potential human carcinogens. Aminotriazole, of cranberry fame, a weed killer and defoliant, when fed to rats elicits tumors of the thyroid, as reported by Flemming.[69] This herbicide can be purchased in the open market by the general public. Urethane or ethyl carbamate, used especially in the past as a sedative and employed more recently as dope in fish hatcheries, causes tumors of the lung in mice and rats and even reaches their offspring by the transplacental route (Larsen[156]; Klein[148]). It has been incriminated by Balo,[11] because of its former frequent medical use, as one of the causes of the increase in lung cancer. American and Canadian fisheries discontinued its use some time ago because of a possible cancer hazard to women and

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offspring of women working in fish hatcheries and having extensive skin contact with solutions of urethane. The weed killer phenylisopropylcarbamate has been shown to be an effective carcinogen by investigators in the Netherlands (van Esch, van Genderen, and Vink[237]; Hueper[110]), where it was used as an antisprouting agent on potatoes. β-Propiolactone, employed commercially in the plastic industry and being used as a virucide in the preparation of poliovaccine in one European country, is an active carcinogen to the skin of rats and mice. It has been proposed in this country for application as a virucidal and bactericidal space disinfectant in hospitals as well as a soil disinfectant in agriculture (Roe and Salaman[201]; Searle[213]).

The latest addition to this dismal list of environmental carcinogens is safrol, which served for many years as a flavoring agent of soft drinks, especially root beer. It was shown to cause cancer of the liver when fed to rats kept on a normal diet. It is for this reason potentially much more dangerous than the various azo dyes of the butter yellow type which have a similar carcinogenic effect on the rat liver but exert such an action only when the rat is given a riboflavin-deficient diet (Homburger and colleagues[96, 97]).

The advisability of investigating for their carcinogenic properties all of the approximately 300 flavoring agents presently used in the preparation and processing of foods is strongly suggested by the fact that hepatomas develop in rats fed red pepper (capsicum) (Hoch-Ligeti[99]) and senecio alkaloids (Schoental[208]). Since practically all chemicals originally considered to be cocarcinogens have been shown to act as carcinogenic initiators under proper experimental conditions, it is appropriate to note that lemon oil has been found by Roe[199] to be a cocarcinogen.

Special mention may be made by several newly introduced organic chemicals known as nitrosamines. These are industrially used compounds and are capable when fed of eliciting not only cancer of the liver but also cancer of the lung and bladder in rats and hamsters (Druckrey and co-workers[52]; Dontenwill and Mohr[49]; Thomas[235]; Argus and Hoch-Ligeti[7]). This observation demonstrates that cancer of the lung may result not only from inhalation of carcinogens but also from their ingestion. Observations on men occupationally exposed to benzidine who developed not only cancer of the bladder but also cancer of the intestine and lung had suggested such possibilities for some years (Link[158]; Uebelin and Pletscher[236]).

The carcinogenic effects of nitrosamine on the lungs of experimental animals may have additional wide implications because of the suggested carcinogenicity of isonicotinic acid hydrazide in mice (Schwan[211]; Viallies and Casavona[328]). While the development of cancer of the lung from tuberculous scars and cavities has been observed and reported for many decades (Hueper[100]), the greatly increased frequency of such occurrences during recent years poses the problem of whether or not the administration of tuberculostatic and tuberculocidal chemical agents, especially isonicotinic acid hydrazide, may have played in the last decade a specific causal role in this respect.

A new bread emulsifier, named polyoxyethylene(8)stearate, when fed to rats produced bladder stones and cancer of the bladder (Fitzhugh and associates[63]; Hueper and Payne[139]). By invoking the by now obsolete concept that chronic irritation of nonspecific type is a recognized cause of cancer (Fitzhugh and associates[63]; Food Protection Committee[65]), it has been argued that the chemical was merely causing the production of bladder stones and that these stones in turn, through the mechanism of chronic mechanical irritation, were the real and primary cause of cancer of the bladder. The scientific merits of this interpretation become evident from the fact that some years ago the Food and Drug Administration banned the use of diethylene glycol as a humectant of tobacco because, like polyoxyethylene(8)stearate, it caused blad-

der stones and bladder tumors in rats when fed (Fitzhugh and Nelson[63]; Hueper and Payne[139]). It is noteworthy that diethylene glycol is one of the constituents or impurities contained in this new bread emulsifier.

Among the various additional organic chemical carcinogens which have been introduced during recent years into human economy and which so far have displayed carcinogenic properties in experimental animals only, special mention may be made of several hepatotoxic chlorinated hydrocarbons used as solvents, such as carbon tetrachloride and chloroform (Edwards and Dalton[56]), or as pesticides, such as DDT and Aramite (Fitzhugh and Nelson[64]; Sternberg and colleagues[224]). All of them when fed have produced cancer of the liver in rats, mice, and dogs. Aramite proved to be the most powerful carcinogen of this group. The Food and Drug Administration has set a zero tolerance limit on Aramite in foodstuffs which are handled in interstate commerce. Since this carcinogenic pesticide can be bought in the open market and because its use is subject to little, if any, control by intrastate agencies, protection of the general consumer against any cancer hazard related to this carcinogenic pesticide has remained defective.

Natural and synthetic estrogens when administered in adequate doses to experimental animals of several species have caused cancer in many organs, e.g., uterus, breast, kidney, and blood-forming tissues. They thus fulfill the conditions generally associated with the definition of carcinogens. It has remained controversial or uncertain whether they exert a similar carcinogenic effect upon the uterus and breast of man in general or of certain hormonally predisposed members of the human race, such as women with breast cancer and cancer of the corpus uteri. These hormonal agents are administered under more or less controlled conditions for medical reasons to both men and women. They are used without any controls in cosmetics and are implanted in pellet form or given as feed additives to cattle and fowl and thus may subsequently reach the general consumer in food (Hueper[115, 122, 123]). Potential cancer hazards from the introduction of estrogenic chemicals into consumer goods present a public health problem deserving serious study for occupational reasons (producers of estrogens and estrogenized cosmetic and pharmaceutic preparations and animal feed) as well as for patients and consumers of estrogens.

The voluntary arrangements made several years ago by the Federal government with the industrial producers of estrogens and their commercial users in the production of food animals lacked the force of law and thus could be violated at will. The Food and Drug Administration, therefore, has recently prohibited the implantation of estrogen pellets into food animals. In view of the present overabundance of the American food supply and because of the growing tax burden imposed on the general citizen for storing excess foodstuffs and for enforcing regulations pertaining to it, a continuation of the past practice of administering stilbestrol to food animals not only appears to be economically unsound but, more importantly, also creates for the consumer a needless potential cancer hazard.

This critical attitude toward estrogens in foods and general consumer goods, such as cosmetics, should be adopted, although natural estrogens are physiologically important products and despite the fact that the physiologic nature of estrogens has been cited by commercially interested parties as an argument in advocating the continued uncontrolled use of these chemicals in cosmetics and in the production of food animals. The intrinsic fallacy of this argument becomes apparent if one considers that exposure to ultraviolet radiation in physiologic doses is beneficial and essential to the maintenance of life. This fact, however, does not provide any rational basis for considering indiscriminate, unnecessary, uncontrolled, and excessive exposures to this actinic energy as a harmless procedure, because ultraviolet rays have distinct carcinogenic effects on the skin of Caucasians.

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The production of cancer of the liver, bladder, lung, skin, and other organs with various cyclic, polycyclic, heterocyclic, and aliphatic hydrocarbons used as flavoring agents, herbicides, solvents, sedatives, antisprouting agents, emulsifiers of food, contraceptives, and disinfectants in experimental animals provides further evidence on the growing contamination of the general economy with potential human carcinogens (Hueper[123]).

Polycyclic aromatic hydrocarbons and carbonaceous combustion and distillation products

There exists abundant valid evidence from observations made on members of various occupational groups in many countries that prolonged exposure of the skin to combustion and distillation products of coal, oil shale, lignite, and petroleum, such as coal tar, tar oils, pitch, carbon blacks, soot, lignite and shale oils and paraffins, petroleum cooling, lubricating, and fuel oils, tars, asphalts, and waxes, has been responsible for cancer of the skin, including the scrotal sac and the vulva. The scrotal cancer of the English chimney sweeps identified in 1775 was the first occupational cancer recognized (Pott[198]), while the skin cancer observed in 1876 among German lignite tar distillery workers represents the first occupational cancer attributable to products of modern industrialism (Volkmann[241]). Some 3,000 cases of occupational skin cancer caused by the various products mentioned have so far been placed on record from different countries, especially England (Henry[91, 92]; Passey[192]; Schürch[309]; Teutschländer[234]; Butlin[30]; Berenblum[14]; Hueper[111, 126]; Hueper and Payne[137]; Brockbank and Stopford[28]; Eckardt[54]; Cruickshank and Squire[42]; Gilman and Vesselinovitch[73]; Hueper and Cahnmann[133]).

The great majority of such cases occurring in American industries such as oil refineries, coke oven operations, gas plants, coal tar distilleries, creosoted lumber factories, and tar paper operations have not been made a matter of published record and, therefore, are one of the reasons for the distorted statistics on occupational cancer incidence in this country (Heller[94]; Hueper[112, 126, 127]). Occupational and medical observations as well as experimental findings indicate that tars obtained by the distillation of wood or vegetable matter are carcinogenic to the skin of man (Shirokov[216]; Sulman and Sulman[227]; Neve[184]; Hueper and Payne[136]; Kuratsune and Hueper[153, 154]; Hueper[123]). Such tars contain 3, 4-benzpyrene (Table V), although in much smaller amounts than coal soot and coal tar.

Recent evidence obtained in mice and rats extends the incriminating evidence to the synthetic oils and tars produced by the indirect and direct hydrogenation of coal by the Fischer-Tropsch and Bergius processes. The Bergius oils were shown to cause occupational cancer and keratoacanthoma of the skin and oral mucosa in man (Hueper[111, 114]; Sexton[214]). Cutaneous contact by members of the general population with such carcinogenic materials in consumer goods probably accounts for only a small fraction of the skin cancer observed.

Where hydrocarbon products might be involved in the causation of skin cancer in

Table V. *3,4-Benzpyrene concentrations in pyrolysis products*

Source	*3,4-Benzpyrene (γ per 100 Gm.)*
Soot, domestic (Gouldon and Tipler[76])	30,000
Soot, coal (Kuratsune[152])	1,200-5,600
Soot, wood (Kuratsune[152])	170-3,600
Charred matter from biscuit (Kuratsune[152])	1.1-7.2
Coffee soot (Kuratsune and Hueper[153])	20-44
Condensed smoke from cigarettes (Cooper and Lindsay[39])	0.91 per 100 Gm. of cigarette
Condensed smoke from cigars (Cardon and colleagues[33])	11-70 per 100 Gm. of cigar

From Kuratsune and Hueper.[153]

the general population, one might suspect undue contact with such household goods as floor wax, shoe polish, lubricating oil used in workshops and for servicing automobiles and motorized equipment, pesticide sprays containing methylated naphthalenes, coal tar and carbon black paints, and soot from fireplaces (Hueper[123, 127]).

Carcinogenic hazards to parts of the alimentary tract may result from the frequent ingestion of insufficiently refined mineral oils of various derivation taken for laxative purposes. Boyd and Doll[21] found that individuals habitually taking mineral oil laxatives had a statistically higher attack rate of intestinal cancer than persons using other laxatives. A similar connotation have the scattered observations on the occurrence of cancer of the lung in individuals using mineral oil nasal sprays or drops and on the development of carcinomas and sarcomas in tissues injected for cosmetic or prosthetic purposes with waxes or paraffins obtained from the distillation of lignite or petroleum (Hueper[123]).

Since mineral oils and waxes free from demonstrable amounts of known carcinogenic polycyclic aromatic hydrocarbons have elicited cancer in experimental animals when injected parenterally,* failure to isolate and identify known specific carcinogenic chemicals from waxes and paraffins does not at present provide valid evidence ensuring the safety of such products when used in consumer goods. Attempts have recently been made to present cancer produced in the subcutaneous tissue or bladder of mice and rats around implants of "pure" paraffin as foreign body reactions of nonspecific nature or to equate them with the sarcomas elicited by plastic films and to disregard the distinct probability that they are specific effects of carcinogens of unknown type contained in paraffin. Such arbitrary interpretations not only unduly favor industrial interests at the expense of the health of the general consumer but also ignore the fact that crude waxes are potent carcinogens to the human skin (Hendricks and colleagues[30]). The paraffins and microcrystalline waxes which caused cancer in these tests were used for impregnating food containers, for coating confections, fruits, and vegetables, such as citrus fruit, apples, and cucumbers, and for removing feathers from fowl.

A possible carcinogenic hazard to the human consumer from the ingestion of carcinogenically active paraffins and waxes is suggested by the observations of Falk, Kotin, and Miller,[151] who reported that 3, 4-benzpyrene and 1, 2, 5, 6-dibenzanthracene added to dairy wax are eluted within 55 hours from the coating of test tubes prepared with such waxes into the milk and cream placed in the lumina. Brief mention may be made here of the fact that various detergents, or certain constituents of household detergents, made from petroleum chemicals have exerted a definite cocarcinogenic effect upon the action of carcinogens applied to the skin of mice or proposed for use as food additives. These include Tween 60, intended for use as an emulsifier, and dodecane and dodecyl benzol, present in the raw material from which household detergents are manufactured (Shubik[217]; Hueper[130]; Eckardt[54]). Whether these agents have similar promoting effects on the carcinogenic action of coal tar, petroleum oils, and similar carcinogenic products when in contact with human tissues is still undetermined but has become a matter of serious concern. It is suspected that an accidental contact with such chemicals might account for some of the "acute traumatic" cancer in skin previously sensitized by exposure to submarginal doses of a carcinogen.

Recent experimental observations indicated that effluents from oil refineries release carcinogenic wastes into public waters which, at some distance from the source of water pollution, may serve as supplies of drinking water to large metropolitan areas (Hueper and Ruchhoft[132]; Borneff and Fischer[19]). It is undetermined whether a prolonged consumption of such water con-

*P. Shubik: Personal communication, 1962.

Table VI. *Lung c*

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Kawai and colleague
Doll[45]
EDCO

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Table VI. *Lung cancer death ratios of coke oven and gas retort workers*

Author	*Country*	*No. of cases*	*Mortality rate*	*Year and occupation*
Kawahata[143]	Japan	21	500.0	1933-1937: gas retort workers, Yahata Steel Works
Kawai and colleagues[144]	Japan	10		1946-1960: gas retort workers, Yahata Steel Works
Doll[45]	England	97	284.0	Gas stokers, coke oven chargers
			202.0	gas production men
EDCO	United States	12	784.0	1946-1960: coke oven workers
		23	148.7	gas plant workers
			10-25	other employees

stitutes a cancer hazard to the general public.

Increasing evidence is accumulating from various countries indicating that frequent and prolonged consumption of such foodstuffs as meats and fish smoked for purposes of preservation may increase liability to cancer of the alimentary tract, especially the stomach. Chemical analyses of such smoked foods have shown that 3,4-benzpyrene originally present in the smoke is not only demonstrable on the outer surface of such smoked meats, sausages, and fish but is found also in the meat proper. This penetration of carcinogens from the covering material of foodstuffs into the food proper is thus similar to the transfer of carcinogens noted when carcinogenic hydrocarbons contained in the coating of waxed containers are taken up by the contents, i.e., the milk and cream, or when 3,4-benzpyrene is retained by oysters living in waters contaminated with carcinogenic ship fuel oil (Hueper[123]; Kuratsune and Hueper[153]; Hueper and Cahmann[133]).

In some of the oldest successful experimental demonstrations of the carcinogenicity of tarry material, tar produced by the exposure of cholesterol, bone, human tissue, yeast, and rice brain to high temperatures was employed by Kennaway.[146] Subsequent experiments on charred foodstuffs by American and Japanese investigators have extended these observations on the production of carcinogens by such food processing procedures to other foods (Kuratsune[152]).

Table VII. *Rates of lung cancer frequency in selected occupations in England with exposure to fumes, gases, and dust from coal tar, petroleum oils, and combustion products of motor fuel*

Occupation	*Lung cancer rate*
Workers in gas plants	129
Workers of gas retorts	284
Producers of gas	202
Crane operators in gas plants	138
Superintendents of gas plants	136
Printers	119
Chimney sweeps	119
Asphalt workers	164
Street cleaners	169
Drivers of automobiles	149

From Kennaway and Kennaway.[147]

There can be no doubt that the consumption of meat or fish broiled over an open fire and exposed thereby not only to contamination with carcinogenic soot but also to the development of carcinogens in the charred surface layers carries a cancer hazard corresponding to that related to the ingestion of smoked foodstuffs and is also associated with the addition of carbon black, a type of commercial soot, to foodstuffs (Nau and colleagues[181]). Until several years ago, carbon black was used in the manufacture of imitation caviar in Germany.

Medical and epidemiologic evidence acquired during the last 30 years in Canada, England, and Japan incriminates occupa-

Table VIII. *Relation of density of population in urban areas in England to lung cancer rates from 1946 to 1949*

Urban area	Mortality rate
Groups of conurbations with more than 200,000 inhabited houses:	
London, East Ham, West Ham, Croydon	156
Birmingham, Smethwick, Walsall, West Bromwich	134
Liverpool, Bootle, Birkenhead, Wallasey	164
Manchester, Salford, Stockport	159
Leeds, Bradford, Halifax	132
Sheffield, with 124,000 inhabited houses	135
Newcastle and Gateshead, with 87,000 inhabited houses	114
Groups of cities each with 50,000 to 85,000 inhabited houses	113
Groups of three cities each with 40,000 to 50,000 inhabited houses	107
Groups of twelve cities each with 30,000 to 40,000 inhabited houses	104
Groups of thirteen cities each with 20,000 to 30,000 inhabited houses	100
Groups of twenty-nine cities each with less than 20,000 inhabited houses	89

From Stocks.[229]

tional inhalation of coal tar fumes in the development of cancer of the lung in coke oven and gas retort workers and in individuals employed under similar exposure (Tables VI and VII). The existence of similar causal relations has been demonstrated for workers exposed to the inhalation of fogs, mists, and sprays from crude paraffin oil, cooling oils, and lubricating oils encountered by workers engaged in paraffin pressing operations of oil refineries, in textile spinning, and in metallurgic plants (Hueper[134, 137]). It is noteworthy that a recently published report on the occurrence of scrotal cancer among paraffin pressers of one American oil company does not include the complete data of coexisting lung cancer and that similar observations on the excessive frequency of lung cancer among operating employees of another American oil company have been withheld from publication for as many (10) years. The recent statement of Hendricks and colleagues[89] that "there is no evidence to suggest any relation between inhalation of oil mist and lung cancer" is not supported by facts available but not reported. It should also be mentioned for the record that no published data are available on the frequency of cancer of the lung or skin among the many workers employed for decades in American steel plants, coke oven operations, tar distilleries, and gas works and exposed to coal tar, although the United States possesses by far the largest industrial establishments of this kind in the world.

The presence of excessive lung cancer rates has recently been reported for inhabitants of several fishing villages on the Baltic coast, where smoking of fish is carried on as a home industry (Voitelovich and associates[240]).

These observations on the excessive liability to cancer of the lung of workers exposed to distillation and combustion products of coal and petroleum provide an important clue to etiologic factors operative in the remarkable rise of lung cancer among urban populations in all advanced countries during the past 60 years and particularly in metropolitan and highly industrialized regions (Hueper[112, 117, 119, 124, 134]). Chemical analyses on the exhaust of gasoline and diesel engines have shown that

Table IX. *Lung cancer death rates in three districts of Connecticut*

District	Occupational character	Standard lung cancer rates		
		Males	Females	Both
Naugatuck Valley area	Rubber, metal, machinery, chemicals	85.02	14.87	48.01
Northeast area	Textile, paper, agriculture	69.24	21.69	45.01
Rural	Agriculture	30.60		15.00
Area by occupation	Industry	85.02	17.35	50.54
	Agriculture	38.65	14.87	26.53

From Griswold.[78]

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Table X. *3,4-B*
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English cities

City	Medi of
London	
Sheffield	
Leicester	
Burnley	
Bilston	
Cannock	
Hull	
Bristol	

From Waller.[244]

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	Standard lung cancer rates		
	Males	*Females*	*Both*
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	85.02	14.87	48.01
	69.24	21.69	45.01
	30.60		15.00
	85.02	17.35	50.54
	38.65	14.87	26.53

they release, particularly under urban conditions of traffic and when exposed to excessive stress and defective maintenance, considerable amounts of carcinogenic hydrocarbons in the air (Tables VIII, IX, and X). In addition to the significant observations on population groups occupationally exposed to carcinogenic hydrocarbons contained in fumes, soot, mists, and gases, chronologic, epidemiologic, and chemical data on urban air pollution and lung cancer incriminate this development as an important, but not the only, factor operating in the rise and causation of cancer of the lung. The activity of a variety of factors in occupational pulmonary carcinogenesis is evident from the wide fluctuations in lung cancer mortality rates among members of large industrial worker groups (Mancuso[167]; Morrison[179]) (Tables XI and XII) and the number of recognized respiratory human carcinogens (Table XIII).

Table X. *3,4-Benzpyrene content in the particulate phase of air pollutants of English cities*

City	*Median annual concentration of 3,4-benzpyrene in air (μg per 100 cu. M.)*	*Smog days*
London	4.6	
Sheffield	4.2	17.3
Leicester	2.9	
Burnley	2.7	
Bilston	2.7	
Cannock	1.9	
Hull	1.8	
Bristol	1.3	

From Waller.[244]

Since cigarette smoke condensate contains minute amounts, not only of various carcinogenic polycyclic aromatic hydrocarbons but often also of volatilized arsenical pesticide residue as well as cocarcinogenic chemicals, such as phenols, the personalized type of air pollution in the form of cigarette smoking contributes to and aggravates the carcinogenic exposure of the respiratory mucosa associated with the inhalation of carcinogens of organic and inorganic nature present in the general and occupational atmosphere (Doll[45, 46]; Wynder[253]; Hammond and Horn[86]). Recent statistical studies carried on in the United States, France, and Denmark have, moreover, linked cigarette smoking to an excessive liability to cancer of the bladder (Clemmesen[37, 38]; Denoix[44]). While such correlations may be demonstrable on an individual basis, they fail to become evident when lung and bladder cancer rates of American cities are compared, i.e., there is no parallelism between the levels of lung and bladder cancer rates for individual cities. These observations may be of some significance because such a parallelism exists when state death rates for lung cancer are compared with those for heart disease, which also has been connected with cigarette smoking (Table XIV). Whether such statistical associations are mainly attributable to the influence of cigarette smoking, however, is doubtful, because numerous additional exogenous and endogenous agents exhibit relations to arteriosclerosis and neoplasia (Table XV) (Hueper[108]).

Of the various recognized and suspected respiratory carcinogens, those produced by the incomplete combustion of carbonaceous matter and by the distillation of coal and mineral oil appear at present to possess the greatest importance because of their wide distribution in the human environment.

Mustard gas

The occasional delayed appearance of cancer of the lung and larynx in soldiers poisoned by gas in World War I was reported during the first two decades after that conflict (Hueper[106]); more recent epidemiologic analyses on the frequency of lung cancer among English and American veterans yielded suggestive statistical evidence supporting the existence of a causal relation between gas poisoning sustained in 1917 and 1918 and lung cancer development decades later in individuals who sustained such chemical trauma to the respiratory tract (Case and Lea[34]; Beebe[13]). The occurrence of cancer of the lung and larynx

Table XI. *Lung cancer death rate per 1,000 deaths of all causes for seven industrial groups in Ohio in 1947 among 5,309 cancer deaths in men*

Industry	*Respiratory cancer*
Iron and steel	2.18
Transportation	2.91
Agriculture	0.82
Rubber and plastics	2.34
Stone, clay, and glass	0.66
Nonferrous metal	3.22
Mining and quarrying	1.53
All industrial groups	1.76

From Mancuso.[167]

among Japanese producers of mustard gas recorded during the last decade has provided more definite confirmation in man (Yamada and colleagues[254]). This is, moreover, supported by experimental observations on the production of cancer by sulfur and nitrogen mustards in mice. These findings provide one of several illustrations of the carcinogenic action of carcinostatic chemicals used in human and experimental cancer therapy (estrogens, urethane, arsenic, alkylating agents, benzol, 4-nitroquinoline-*N*-oxide, x-radiation, radioactive chemicals).

Isopropyl oil

Cancer of the paranasal sinuses, larynx, and lung first noted by Nale and Hueper[112, 186] in 1946 among producers of isopropyl alcohol in one American factory was found subsequently in several other similar plants in the United States (Eckardt[54]). The occupational origin was thereby established beyond any reasonable doubt. The evidence on hand strongly suggests that some constituent present in the viscous crude liquor from which isopropyl alcohol (isopropyl oil) is distilled, and not the alcohol as such, is responsible for the cancer. This suspicion is supported by the results of studies on experimental animals conducted by Weil, Smyth, and Nale[249] with the cooperation and guidance of Hueper.

Benzol

Benzol, a product of the distillation of coal tar as well as a petrochemical, is widely used in chemical manufacture and is a frequent constituent or impurity of organic solvents and degreasing agents. While its toxic, aplasiogenic effect upon the blood-forming tissues represents its main health hazard, observations of the last three decades have established benzol as a leukemogenic agent capable of causing both myeloid and lymphoid leukemia in individuals who usually are exposed to it for occupational reasons (Browning[27]; Hueper[112, 126]; Kähler and Merker[142]). It may be noted that these hematic reactions to benzol are not, as claimed, leukemoid responses representing agnogenic myeloid hyperplasia (Hueper[112]). An anemic phase

Table XII. *Standard mortality rates of malignant neoplasms of the respiratory system in occupational classes in Scotland*

Occupational code No.	*Occupation*	*SMR*
		Above 130
160-164	Platers, riveters, shipwrights	183
231-249	Electrical apparatus makers, electricians	170
131, 132	Moulders	162
589	Masons and stonecutters	162
134-138	Foundry workers, etc.	161
681	Dock laborers	157
912	Crane drivers	150
600-609	Painters, decorators	132
		Below 70
019, 021, 029	Farm workers	25
010, 011, 018, 020	Farmers, etc.	27
110-119	Foremen and overlookers in metal manufacture	54
013-015	Market or other gardeners	56
620-629	Managers of industrial undertakings (other than office departments)	69

From Morrison.[179]

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Table XIII. *Respira*

Material
Metals and minerals
Arsenic
Chromium
Nickel
Asbestos
Beryllium(?)
Iron oxide(?)
Radioactive chemica
Organic chemicals
Coal tar
Petroleum oils
Incomplete combust products of carbo matter (soots, gas and diesel engine hausts, tobacco f etc.)
Crude isopropyl alc
Mustard gas
Oxidation and poly tion products of a compounds of vol gasoline(?)

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Occupation	SMR
	Above 130
riveters, wrights	183
cal apparatus ers, electricians	170
ers	162
s and stonecutters	162
ry workers, etc.	161
laborers	157
drivers	150
rs, decorators	132
	Below 70
workers	25
rs, etc.	27
en and over-ers in metal ufacture	54
t or other leners	56
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may precede the subsequent development of leukocytotic, eosinophilic, and basophilic reactions which are followed by leukemoid manifestations ultimately assuming the character of definite leukemia (Hueper[101]). The maturation arrest characterizing the response of the bone marrow under such conditions has many morphologic similarities to the myeloid reactions produced by ionizing radiation and accompanying the chemoallergic agranulocytotic effects elicited by an appreciable number of synthetic drugs usually of aromatic chemical nature. These have been introduced into medical practice during the past 50 years. Because of the evidence noted, patients surviving such agranulocytotic drug reactions (Hueper[126]) should be invesigated for delayed leukemogenic manifestations.

Table XIII. *Respiratory carcinogens*

Material	Organ affected
Metals and minerals	
Arsenic	Lung, larynx, paranasal sinuses
Chromium	Lung, nasal cavity, paranasal sinuses
Nickel	Lung, nasal cavity, paranasal sinuses
Asbestos	Lung, pleura, peritoneum
Beryllium(?)	Lung
Iron oxide(?)	Lung
Radioactive chemicals	Lung, paranasal sinuses
Organic chemicals	
Coal tar	Lung, larynx(?)
Petroleum oils	Lung, larynx(?)
Incomplete combustion products of carbonaceous matter (soots, gasoline and diesel engine exhausts, tobacco fumes, etc.)	Lung, larynx(?)
Crude isopropyl alcohol	Lung, larynx, paranasal sinuses
Mustard gas	Lung, larynx
Oxidation and polymerization products of aliphatic compounds of volatilized gasoline(?)	Lung(?)

Table XIV. *Crude death rates per 100,000 for arteriosclerotic heart disease and cancer of the lung in selected states*

State	Deaths from heart disease (1950)	Deaths from lung cancer (1948)
Connecticut	288.6	11.1
Massachusetts	298.2	10.2
New York	322.5	11.9
Illinois	236.2	8.2
New Hampshire	316.0	10.1
Alabama	130.4	5.1
New Mexico	85.4	3.0
Wyoming	135.6	3.9
South Carolina	118.8	3.7
North Dakota	168.2	4.1

Arsenic

During recent years, various American investigators have challenged the validity of the widely held conclusion that arsenicals are human carcinogens (Eckardt[54]; Frost[67]; Johnstone and Miller[141]). It should be emphasized, the lack of proper occupational and environmental observations on arsenic cancer from American sources notwithstanding, that the global epidemiologic and medical evidence available and published on carcinogenic manifestations in various organs elicited by arsenicals following medicinal, occupational, and dietary exposure is ample and adequate for establishing the conclusion firmly (Hueper[112, 127]; Neubauer[183]; Sommers and McManus[220]; Roth[204, 205]; Tello[232]; Rockstroh[203]; Henry[92]; Hill and Faning[95]).

The endemic occurrence of arsenic cancer of the skin among population groups consuming drinking water polluted from industrial and natural sources with arsenic and showing cutaneous stigmas of chronic arsenic poisoning has been recorded in Germany, Argentina, and Taiwan. The dermatologic literature of many countries contains an appreciable number of case reports on the occurrence of often multicentric carcinomas of the skin in patients given arsenical preparations for various reasons (Neubauer[183]). The site distribution differs characteristically from that found in cancer

Table XV. *Exogenous and endogenous agents possessing tumorigenic and arteriosclerotogenic associations*

Agent	*Arteriosclerotic manifestations*	*Carcinogenic manifestations*
Exogenous agents		
Arsenic	Endarteritis (Raynaud-like vasospastic disease) Periarteritis nodosa	Carcinoma of skin, liver, and lung
Asbestos	Fibrosing pulmonary arteriosclerosis with asbestosis	Carcinoma of lung, pleural, and peritoneum
Beryllium	Fibrosing pulmonary arteriosclerosis with berylliosis	Carcinoma of lung (rat), and bone (rabbit); sarcoid granuloma of lung and skin
Schistosomiasis	Parasitic pulmonary venosclerosis and fibrosing arteriosclerosis	Carcinoma of bladder
Ergot alkaloid	Fibrosing peripheral arteriosclerosis and "thromboangiitis obliterans"	Neurofibroma of ear (rat)
Nicotine	Fibrosing endarteritis, thromboangiitis obliterans, coronary sclerosis(?)	Adrenal adenoma (rat)
Ultraviolet radiation; vitamin D	Calcifying arteriolsclerosis (rat)	Carcinoma and sarcoma of skin and orbit (rat and mouse); carcinoma of skin
Ionizing radiation	Fibrosing endarteritis	Cancer of skin, bone, lung, hematopoietic tissue, liver, etc.
Endogenous agents		
Epinephrine	Fibrosing arteriosclerosis	Pheochromocytoma, (epinephrine production, hypertension)
Natural and synthetic estrogens		Cancer of uterus, breast, etc., (mice, rats, and man)
Hyperestrinism	Antiatheromatogenic effect	
Hypoestrinism (oophorectomy)	Atheromatosis	
Thyroid hormone Hypothyroidism	Atheromatosis	Adenoma and carcinoma of thyroid; adenoma of hypophysis
Parathyroid hormone Hyperparathyroidism	Calcifying arteriosclerosis	Parathyroid adenoma, carcinoma
Hepatic functional deficiency (cirrhosis nutritional impairment, choline deficiency)	Atheromatosis	Adenoma and carcinoma of liver; gynecomastia
Macromoleculoses		
Lipoproteins	Atheromatosis	Carcinogenic action of cholesterol(?); carcinogen-carrying action of cholesterol(?)
Hyperlipoproteinemia Hypercholesterolemia		
Lipoidoses	Reticuloendotheliosis; arterial amyloidosis	Myeloma
Hyperproteinemia and heteroproteinemia		
Waldenström's disease		Sarcomas of lymphoid and reticuloendothelial origin
Glycogenosis		
Exogenous Carbohydratic Macromoleculosis		
Polyvinyl alcohol		
Polyvinyl pyrrolidon		
Carboxymethylcellul		
Dextran and iron de		

From Hueper.[108]

of the skin elicited by cutaneous carcinogen conforms to the topogr cancerous cutaneous l the arsenic cancer syn observation of isolate cancer in other organs after occupational, m mental contact with a in copper ore miners and arsenical insecti users (Hueper[125, 126]; R and Lombard[219]; Osbu ing[95]) during past dec of a severe epidemic o cer affecting the skin liver, and other orga vineyard workers suff arsenic poisoning whic occupational use of ars the drinking of wine co

Table XVI. *Topograph cancer of the skin*

Region	*En*
Face, nose, and neck	
Hands and arms	
Feet and legs	
Haired parts of skin	
Nonexposed skin	

From Hueper.[112]

Table XV. *Cont'd*

Agent	*Arteriosclerotic manifestations*	*Carcinogenic manifestations*
Glycogenosis	Atheromatosis	Glioma, adenoma of skin, rhabdomyomatosis of heart
Exogenous Carbohydratic Macromoleculosis		
Polyvinyl alcohol	Atheromatogenic effect	Carcinogenic effect (rat)
Polyvinyl pyrrolidone	Atheromatogenic effect	Carcinogenic effect (rat)
Carboxymethylcellulose	Atheromatogenic effect	Carcinogenic effect (rat)
Dextran and iron dextran	Atheromatogenic effect	Carcinogenic effect (rat, mouse, hamster)

From Hueper.[108]

of the skin elicited by other environmental cutaneous carcinogens (Table XVI) but conforms to the topographic pattern of non-cancerous cutaneous lesions associated with the arsenic cancer syndrome. Following the observation of isolated cases or groups of cancer in other organs, especially the lung, after occupational, medicinal, or environmental contact with arsenicals, particularly in copper ore miners and smelter workers and arsenical insecticide producers and users (Hueper[125, 126]; Rockstroh[203]; Snegireff and Lombard[219]; Osburn[190]; Hill and Faning[95]) during past decades, the occurrence of a severe epidemic of hetero-organic cancer affecting the skin, respiratory tract, liver, and other organs among German vineyard workers suffering from chronic arsenic poisoning which resulted from the occupational use of arsenical pesticides and the drinking of wine contaminated with the residue has brought the cancer hazard from arsenic into sharp focus (Rockstroh[203]; Roth[204, 205]) (Table XVII).

Rockstroh[203] reported the occurrence of 45 cases of lung cancer among members of a plant population averaging 111 workers during the years 1932 to 1953. Roth[205] found in eighty-two autopsies of vineyard workers with symptoms of chronic arsenic poisoning performed during the period of 1950 to 1959, 61 individuals with one or several cancers, often involving not only the skin but also internal organs (74.4 per cent). In 44 of these cases, the cancer was situated in the respiratory tract (nasal sinus, larynx, tracheobronchial tree, lungs) (53.65 per cent). In 4 of these instances of lung cancer, bilateral cancer of the lung was present, and in 1 a carcinoma of the larynx and in 1 a carcinoma of the tongue were present, in addition to cancer of the skin.

Table XVI. *Topographic distribution of solar, arsenic, and roentgen-induced cancer of the skin*

Region	*Environmental solar cancer (%)*		*Arsenic cancer (%)*		*Occupational roentgen-induced cancer (%) (Hueper)*
	Roffo	*Tello*	*Dietary (Tello)*	*Medicinal and occupational (Neubauer)*	
Face, nose, and neck	95.00	77.73	8.57	12.21	4.76
Hands and arms	3.07	1.43	6.27	46.61	84.52
Feet and legs	0.52	0.01	4.43 (10.70)		0.00
Haired parts of skin	1.02	21.33	80.73	41.18	10.72
Nonexposed skin	0.39				

From Hueper.[112]

Table XVII. *Occupational arsenic-induced cancer of the lung, larynx, and paranasal sinuses*

Incidence by site					Exposure period (yr.)	Occupation	Author and year of publication
Lung	Larynx	Nares and nasal sinuses	Coexisting keratoses	Skin cancer			
7						Copper smelter worker	Snegireff and Lombard, 1951
19			1			Gold ore miner	Osburn, 1957
	1				5	Pesticide producer	Derobert and Hadengue, 1952
9			9	4	17	Vineyard worker	Braun, 1958
1					36	Cobalt smelter worker	Krug, 1959
19	1	2	19	9		Vineyard worker	Roth, 1956, 1958
2						Arsenic smelter worker	Schmorl, 1928
1				1		Farmer	Montgomery and Waisman, 1941
1					43	Arsenic worker	Currie, 1947
2					37	Pesticide worker	Bridge and colleagues, 1939
17					20	Copper ore miner	Akazaki, 1960
8			6		3-8	Vineyard worker	Hess, 1956
45			45		8-45	Nickel-cobalt ore smelter worker	Rockstroh, 1959
5	1					Pesticide producer	Hill and Faning, 1948
2						Sheep dip producer	Henry, 1934
4					37-43	Sheep dip producer	Merewether, 1944,
1			1	1		Vineyard worker	versus Pein, 1943
1				1		Vineyard worker	Liebogott, 1950
8						Vineyard worker	Koelsch, 1958
1						Furrier	Frommel, 1927
2			1	1		Pesticide sprayer	Hueper, 1961

There were, moreover, 5 cases of esophageal cancer, 8 hemangiosarcomas of the liver, 1 cholangiocarcinoma, and 1 renal carcinoma present in Roth's series. The latent period of these cases was up to 50 years. Roth[205] concluded from these catastrophic late effects of chronic arsenic poisoning that arsenic is a highly dangerous carcinogen which produces cancer in various organs and tissues. He emphasized also that the combined occurrence of multiple cancer of the skin and of internal organs should be considered suspect of arsenical causation. It is significant that 7 of the instances of arsenic cancer observed by Roth[204] were found in female vintners. Occupational arsenic cancer thus exhibits an exposure-dependent sex liability similar to

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	Currie, 1947
	Bridge and colleagues, 1939
	Akazaki, 1960
	Hess, 1956
	Rockstroh, 1959
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	Liebogott, 1950
	Koelsch, 1958
	Frommel, 1927
	Hueper, 1961

ıes. He emphasized also occurrence of multiple and of internal organs ed suspect of arsenical ıificant that 7 of the in- cancer observed by in female vintners. Oc- cancer thus exhibits an t sex liability similar to

that noted in cancer of the lung among English asbestos workers and in cases of scrotal and vulvar cancer of English mule spinners.

Although the wide distribution of arsenic in many natural and industrial products precludes elimination of contact of the human population with arsenic, the available evidence strongly supports the view that any needless exposure to arsenic should be avoided and should be proscribed by proper laws where indicated.

Asbestos

Asbestos is a complex and chemically variable fibrous silicon polymer consisting of silicon, magnesium, aluminum, sodium, and iron oxides. The iron oxide content may range from 0.1 to 11 per cent for chrysotile to some 39 to 44 per cent for blue Cape crocidolite in which Harrington[84] recently demonstrated traces of 3,4-benzpyrene. Since the first discovery reported in 1935 on the coexistence of asbestosis and carcinoma of the lung in American and English textile workers (Lynch[164]; Gloyne[74]), it has become increasingly evident that the inhalation of asbestos fibers, especially when it results in the development of asbestosis (Murray[180]), creates an excessive liability to the subsequent appearance of a carcinoma of the lung, which not infrequently may be of multicentric origin, being derived from the multifocal adenomatoid and metaplastic bronchiolar and bronchial epithelial lesions commonly found in such lungs.

The first and still most frequent data indicating excessive liability of asbestotics to develop cancer of the lung were obtained from postmortem observations. Although this material is selective, the significance of the evidence obtained from it is attested to by the consistency of its character, as shown by studies from different countries and occupational groups (Table XVIII). During recent years, the autopsy observations have been confirmed by Doll[48] in statistical studies on the lung cancer mortality experience of English asbestos workers and by Mancuso* on American employees of an asbestos brake lining plant (Table XIX). The scientific value of these observations was recently challenged by Bohlig, Jacob, and Müller[17] and by Braun and Truan[26] in investigations on the morbidity from lung cancer among asbestos workers in Saxony and in the Province of Quebec, respectively. While Bohlig, Jacob, and Müller[17] maintained that the lung cancer morbidity rate of all German asbestos workers is not higher than that of a comparable general population (between 5 and 6 per 10,000), it is doubtful whether this calculation reflects the actual conditions. The epidemiology of occupational cancer of various types has clearly shown that the anatomic reactions to such hazards, as a rule, become manifest only in long-term workers who have sustained prolonged and often severe exposure or in individuals for whom, after cessation of exposure, a latent period elapsed which extended over 10 to 25 years.

Unless proper methodologic precautions in the collection and evaluation of epidemiologic data are taken, data of the type used by Bohlig, Jacob, and Müller contain a dilution factor which a priori may negate and defeat the purpose and validity of such studies (Hueper[127]). More serious objections must be raised against the scientific merits of the claims made in this matter by Braun and Truan,[26] who studied asbestos miners and millers in the Province of Quebec. According to the data published, this study was based on a survey of about 6,000 individuals employed by the asbestos industry in Quebec. There is an analysis of the degree of dust exposure and the number of individuals in each of three graduated groups, but no data are offered on the duration of exposure to asbestos dust. Although there is a statement on the number of smokers and nonsmokers, the report is devoid of information on the number of asbestotics in the population group analyzed. No information is available regarding the number of long-term workers and their

*T. F. Mancuso: Personal communication.

relative liability to lung cancer. No mention is made in the report on autopsies which have been performed on those who died during the period surveyed. This is particularly important, since Braun and Truan[26] professed that only 9 "proved" cases of lung cancer were discovered to have occurred in the population analyzed. This is a rather surprising observation since during a somewhat longer period than that covering the survey, a histopathologic study by the pathologists of the Saranac Laboratory, under the sponsorship of industrial management, on lungs from dead asbestos workers from Quebec revealed 34 cases of asbestosis cancer of the lung.

The conclusions reached by Braun and Truan[26] concerning an absence of an excessive liability to lung cancer among Quebec asbestos workers are incorrect even if proper epidemiologic procedures are applied to their data as reported. While the statement of Braun and Truan[26] that the annual rate of deaths from lung cancer in the asbestos group for the years 1950 to 1955 is only slightly higher than the rate for the inhabitants of the Province of Quebec would be correct under these conditions, this statement represents statistical acrobatics which tend to obscure incriminating evidence on hand by use of a highly biased population group as a "normal" standard. It is a well-known fact that urban populations in all industrialized countries have a decidely higher lung cancer death rate than that in rural regions (Hueper[117, 134]). Since the asbestos mines are situated in rural areas of Quebec and are not located within the fume zones of Quebec and Montreal, where a high lung cancer rate prevails (Montreal rate 32.3), the lung cancer death rate of the asbestos miners, which stands at 33.8 per 100,000 has to be compared with the rates present in rural counties of the Province of Quebec. According to the data provided on this

Table XVIII. *Frequency of cancer of the lung in autopsies of asbestotics*

Author	*Sex*	*No. of autopsies of asbestotics*	*Incidence of lung cancer*	*Percentage of lung cancer*
Merewether[174]	Male	222	48	22.0
	Female	143	17	12.0
	Both	365	65	17.8
Wyers[252]		115	17	14.8
Doll[48]		105 (asbestos workers)	18	17.0
Gloyne[74]		121	17	13.2
O'Donnell and Mann[188]		40	20	50.0
Lynch[164]		40	5	8.2
Becker[22]				14.0-15.0
Wedler[248]		92	15	16.0
Boehme[16]	Male	17	12	71.0
	Female	14	2	14.0
	Both	31	14	36.0
Total		909	171	18.4
Controls				
Becker: men over 20; average age at death 61 years (silicotics)				4.0
Merewether: 6,884 postmortem examinations on silicotics; 91 instances of lung cancer; average age at death 59.4 years				3.6
				1.32

Table XIX. *Obse*
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	16.0
	71.0
	14.0
	36.0
	18.4
	4.0
	3.6
	1.32

Table XIX. *Observed and expected deaths due to lung cancer, 1940 through mid-1960, among a cohort of white male and female employees of company C at some time in 1938 or 1939 (ages 25 to 64 years at death)**

Site	Total		Men		Women	
	Observed deaths	Expected deaths	Observed deaths	Expected deaths	Observed deaths	Expected deaths
Lung, bronchus, and trachea[162, 163]	18	5.29	14	5.11	4	0.18
Peritoneum[158]	3	0.10	2	0.08	1	0.01

*T. F. Mancuso: Personal communication.

point by Braun and Truan,[26] their conclusion is patently incorrect and grossly misleading and results in obscuring the existence of a markedly elevated lung cancer rate for members of this worker group.

The causal relation between asbestosis and cancer of the lung is demonstrated by the fact that asbestosis cancer affects more often the lower lobes than the upper lobes (53:7) in contrast to the general type of lung cancer which involves more frequently the upper lobes. Associated with this etiologically significant topographic peculiarity and frequent multicentric occurrence of asbestosis cancer are the various equally important metaplastic adenocystic precancerous and cancerous changes of the bronchial and bronchiolar epithelium which precede and accompany the development of cancer in asbestotic lungs (Hueper[119, 124, 125]). The coexistence of asbestosis and lung cancer has been reported from the United States, Canada, England, France, Germany, Italy, Switzerland, and Finland in asbestos miners, millers, crushers, loaders, sorters, grinders, cleaners, pipe laggers, cement mixers, packers, boiler coverers, mattress fillers, weavers, spinners, and cement workers.

Recent observations in Germany, Great Britain, the United States, Canada, Italy, and South Africa strongly suggest that asbestosis is also causally related to mesothelioma of the pleura and peritoneum (Cartier[32]; Mancuso*; Bohlig, Jacob, and Müller[17]; Leicher[157]; Wedler[248]; Koenig[149]; Doll[48]; Keal[145]; Wagner, Sleggs, and Marchand[243]; Sleggs, Marchand, and Wagner[218]). It is noteworthy that the frequent occurrence of mesothelioma, which is ordinarily a rather rare cancer, in South Africa has been restricted to the residents of the blue Cape asbestos districts and to workers and miners having occupational contact with this particular type of South African asbestos. Many of the nonoccupational victims of this neoplastic disease as children had played on asbestos dumps, had visited the mills and mines, and had lived near such establishments or along the roads on which the asbestos was transported and where the ground was contaminated with asbestos dust (Wagner, Sleggs, and Marchand[243]).

The evidence on hand indicates that both carcinoma of the lung and mesothelioma of the pleura and peritoneum may develop subsequent to and as the result of inhalation of asbestos dust and that such cancerous sequelae may appear after an exposure to asbestos mined in different parts of the world and differing in chemical composition. Asbestosis of the lung does not have to be well developed, according to more recently obtained evidence, in order to be a prerequisite for the development of cancerous sequelae. In fact, pleural and peritoneal mesothelioma has been observed in patients showing only a minimal amount of usually locally restricted asbestosis.

Beryllium, cobalt, and selenium

Various experiments with beryllium compounds have demonstrated that these

*T. F. Mancuso: Personal communication.

result of a specific carcinogenic action of the chromium contained often in such materials; observations on cancer incidence among stainless steel producers and processers which might provide a clue in such matters are not available.

The experimental work of Hueper and Payne[118, 135, 140, 193, 194] on rats and mice has definitely established the carcinogenic properties of chromium when present in a biologically available form. The epidemiologic as well as experimental evidence attesting to the carcinogenic properties of chromates (Alwens[4]; Gafafer and colleagues[70]; Fisher[61]; Bidstrup and Case[15]) refutes the allegation that the high incidence of lung cancer in chromate workers is attributable to cigarette smoking (Oettel[187]).

In contrast to asbestosis cancer of the lung, which preferably is situated in the lower lobes, that evoked by chromates is located more frequently in the upper lobes and thus follows the general pattern of distribution of cancer of the lung.

Lung cancer attack rates ranged in different American plants from 13 to 80 times normal. Negro workers exhibited a higher lung cancer attack rate than white workers because they were usually employed in jobs with greater intensity of exposure to chromate dust and fumes. It is for this reason also that Negro chromate producers develop nasal septum perforations earlier and at a higher rate than white workers (Table XXI). After cessation of exposure to this occupational carcinogen, former chromate producers retain their excessive liability to cancer of the lung (Hueper[117]). The available incidence rate of lung cancer among members of this worker group, therefore, is too low. Since the labor turnover in this occupation is rather high and many workers leave employment before they develop lung cancer (Gafafer and colleagues[70]; Baetjer[10]; Bidstrup and Case[15]), an appreciable number of such cancer cases are not recorded. It is noteworthy that so far, no epidemiologic studies on lung cancer rates have been made in any country on chrome platers, chrome pigment spray painters, metal cutters and smelter workers handling stainless steel and metal parts coated with anticorrosive chrome paint, and welders, although the occurrence of isolated cases of lung cancer in individuals after a period of employment in these occupations has been observed. It may be worthwhile, moreover, to explore lung cancer rates in residents of and individuals working in buildings in which chromates are used as antirusting agents of the water in steam-heating and air-conditioning plants and are released into the air. Because of the lack of any reliable data on large population groups having respiratory and ingestive contact with chromates, the actual extent of cancer hazards from chromium is at present undetermined.

Table XXI. *Time of appearance and frequency of nasal septum perforations in white and Negro chromate producers in the United States*

Time of employment	*Number of workers*	*Percentage of perforated nasal septa*		
		All workers	*White*	*Negro*
0-6 mo.	41	2.4	0	11.1
6 mo.-3 yr.	117	39.3	31.5	64.3
3-10 yr.	370	55.4	44.3	74.8
10 yr. and over	369	69.6	64.0	93.1
Total	897	56.7	49.3	76.6

From Gafafer and coauthors.[70]

Iron

Recent epidemiologic investigations on the frequency of lung cancer among members of occupations with pulmonary siderosis (boiler scalers, hematite miners, foundry workers) reported from England and France suggest that the presence of siderosis confers on the lungs an increased liability to development of cancer (McLaughlin and Harding[171]; Faulds and Stewart[58]; Harding and Massie[83]; Faulds[57]; Monlibert and Hayange[177]; Braun and coauthors[25]) (Table XXII). Isolated cases of lung can-

cer coexisting with siderosis previously recorded had been suspected as being caused by related conditions (Hueper[126]). Warren and Drake[246] had incriminated the iron contained in the liver with hemosiderosis as the carcinogen active in the production of liver cancer often found associated with this condition. Whether or not the development of sarcoma of the subcutaneous connective tissue and of the reticuloendothelial tissues of mice, rats, and hamsters repeatedly injected with an iron-dextran complex is attributable to the iron content (Haddow and Horning[82]; Haddow[81]; Richmond[202]) is uncertain since rats injected intrapleurally with finely powdered, pure iron obtained by the degradation of iron carbonyl did not exhibit any cancerous responses (Hueper and Payne[140]; Gilman[71]), while rats injected subcutaneously with several dextrans developed reticulum cell sarcoma (Hueper[120]).

Since many industrial workers are exposed to the inhalation of iron oxide, particularly when oxygen is used in the manufacture of steel, the problem of occupational lung cancer resulting from such exposure urgently deserves study. Similar attention should be extended to the carcinogenic effect of the medicinally and parenterally administered iron-dextran complex, since this carcinogenic agent is being used in the management of a noncancerous disease, anemia, and since it is now a well-established medical principle to avoid carcinogenic procedures such as irradiation in the therapeutic management of benign diseases for which effective noncarcinogenic therapeutic procedures and agents are available.

Nickel

After the initial report of Stephens[223] on the excessive occurrence of cancer of the nasal cavity, paranasal sinuses, and lung among workers in the nickel matte refineries at Clydach, Wales, publications on the same subject by Amor,[5] Morgan,[178] Doll,[47] and Williams[251] from England and by Loken[162] of Norway, as well as observations subsequently made among Canadian nickel smelter workers, have confirmed the original findings (Table XXIII). The continued development of these types of cancer and their occurrence in different countries despite the cessation many years ago of the use of a sulfuric acid free from significant amounts of arsenic makes it most unlikely that arsenic inhaled with sulfuric acid fumes during the refinery process represents the real cause of this respiratory cancer as still maintained by Morgan.[178] This old assumption was unlikely a priori since the workers developing this occupational cancer did not exhibit symptoms of chronic arsenicosis and the cutaneous cancer which so strikingly acompanied much of the respiratory cancer found in workers with bona fide contact with arsenicals.

The production during recent years by several investigators of sarcomas and carcinomas in mice, rats, and guinea pigs after a parenteral introduction of metallic nickel powder or nickel salts or after the inhalation of powdered nickel and nickel carbonyl has provided adequate experimental evidence incriminating nickel as the carcinogenic agent (Hueper[109, 113, 118, 140]; Sundermann and associates[231]; Sundermann and Sundermann[230]; Hatem[85]; Gilman[71];

Table XXII. *Siderosis of lung and cancer of lung in English hematite miners and iron foundry workers*

Author	*Occupation*	*No. of autopsies*	*Incidence of lung cancer*	*Percentage*
McLaughlin and Harding[171]	Iron foundry workers	149	16	10.8
Faulds and Stewart[58]	Hematite miners	180	17	9.4
Harding and Massie[83]	Boiler scalers	12	3	20.0
Faulds and Stewart[58]	Controls	2,220 (over 30 years)	45	2.0

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Table XXIII. *Comparis observed and expected among nickel workers*

Period	*Organ*	*Incidenc canc* *Ex-pected*
1938-1947	Nose	0.066
1948-1956		0.082
1938-1947	Lung	2.600
1948-1956		5.900

From Doll.[47]

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Incidence of lung cancer	Percentage
16	10.8
17	9.4
3	20.0
45	2.0

Gilman and Ruckenbauer[72]; Mitchell and colleagues[176]). It is remarkable that up to now, occupational nickel cancer has not been placed on record from the United States although this country is one of the principal industrial consumers of this metal, its alloys, and its compounds.

Carbon and silicon polymers and plastics

The repeated demonstration of cancer formation in mice, rats, and hamsters at the site of subcutaneous, intraperitoneal, and retroperitoneal implantation of water-insoluble carbon and silicon plastics and their occurrence in the reticuloendothelial tissues after a parenteral injection of solutions of water-soluble polymers or after their subcutaneous and intra-abdominal deposition in powdered form not only has created important practical problems relating to the possible existence of cancer hazards associated with the medical, cosmetic, and dietary uses of such chemicals in man but also has been followed by a lively controversy

Table XXIII. *Comparison between observed and expected incidence of cancer among nickel workers*

Period	Organ	Incidence of cancer		Ratio of No. of expected to observed cases of cancer
		Expected	Observed	
1938-1947	Nose	0.066	16	1:242
1948-1956		0.082	13	1:159
1938-1947	Lung	2.600	36	1:13.8
1948-1956		5.900	39	1:6.7

From Doll.[47]

regarding the type and specificity of the causative mechanism operating in the production of these polymer cancers (Oppenheimer and co-workers[189]; Druckrey and Schmähl[50, 51]; Nothdurft[185]; Alexander and Horning[1]; Haddow and Horning[82]; Hueper[116, 120, 121]; Lusky and Nelson[163]).

The adoption of the view by the majority of investigators in this field that a nonspecific physical mechanism eliciting nonspecific biologic effects in the tissue surrounding plastic implants, especially films, is involved in utimately causing cancerous tissue changes (Nothdurft[185]; Oppenheimer and associates[189]; Alexander and Horning[1]) has serious implications concerning the validity of the long-held and well-supported concept regarding the specificity of chemical carcinogens. Through the extension of this concept to the cancerous responses elicited by other parenterally introduced and chemically "inert" substances, e.g., food dyes and dairy waxes, this concept may also exert a dangerous influence on restrictive public health practices previously considered sound by providing scientifically dubious justification for the continued use of carcinogenic chemicals in products of general human consumption, especially foodstuffs. This situation has been complicated and worsened as far as the application of the results of bioassays on carcinogenic chemicals to man is concerned by the allegation that sarcoma evoked by plastics implanted into the subcutaneous tissue of rats merely reflects an "abnormal" carcinogenic reactivity of the connective tissue of rats to practically any type of physical or chemical trauma and, therefore, is of no real significance in relation to possible cancer hazards from such macromolecular or particulate chemicals in man (Oettel[187]; Food Protection Committee[66]; Hueper[120]).

A critical appraisal of the various observations cited and arguments advanced in support of such far-reaching claims not only demonstrates their scientific defects concerning carcinogenesis from implanted or injected carbon and silicon polymers but also refutes the contention that cancer induced in subcutaneous tissue of rats and mice by the repeated introduction of chemically inert matter is without corollary and without significance as to the carcinogenic potency of these materials in man when they are administered by the same or other routes (Hueper[130]). In fact, recent experi-

mental observations made with polyurethane foams implanted into the subcutaneous tissue and the peritoneal cavity of rats have shown that the carcinogenic action of these polymers is evidently of chemical origin, that under proper experimental conditions they are capable of evoking not only sarcoma but also carcinoma, and that they are carcinogenically active in the form of sheets, foams, and powders. It should be evident from these and other findings that it is definitely premature to abandon the chemical theory of polymer carcinogenesis and substitute for it the rather nebulous concept of a physical surface mechanism. Whether or not such macromolecular chemicals will also prove to be carcinogenic to man will be seen when an adequate latent period after their parenteral implantation or injection into man for surgical and cosmetic reasons has elapsed in a sufficient number of individuals. Attention should also be extended to the possible occurrence of late cancerous complications, possibly resulting from occupational and nonoccupational inhalation of plastic dusts and fumes and of solutions of polymers, especially those used in hair sprays.

Ultraviolet radiation

Comprehensive epidemiologic observations made on the skin cancer rate among peoples living in regions with a dry, sunny, warm climate (southwestern and southern United States, Argentina, Australia, South Africa) where exposure to the ultraviolet rays of sunlight is prolonged and intense throughout the year attest to the fact that these nonionizing rays elicit carcinoma (epidermoid carcinoma, basal cell carcinoma) of the exposed parts of the skin, including lips, and that fair-complexioned Caucasians are most susceptible to their carcinogenic action (Peller[195]; Molesworth[175]; Phillips[197]) (Table XXIV). According to more recent observations, it appears that such exposures may also incite the development of melanoma (Texas, Australia, South Africa) (Lancaster[155]; McGovern and Mackie[173]). Members of the oriental race are definitely less affected by solar cancer of the exposed skin (Allison and Wong[3]), and American and African Negroes are more or less totally resistant unless they are albinos; the latter exhibit a frequency and topographic distribution of skin cancer identical with that seen in fair-complexioned white people (Shapiro[215]). Individuals with hereditary hypersensitivity to solar rays develop xeroderma pigmentosum and skin cancer during childhood which cause death early in life in 100 per cent.

Table XXIV. *Incidence of skin cancer per 100,000 population in six urban areas*

Author	*City*	*Rate*	*Percentage rate for white males for all cancer*
McDowell[172]	*Northern area*		
	Detroit	24	12.3
	Chicago	25	12.5
	Pittsburgh	37	16.0
	Southern area		
	New Orleans	129	26.0
	Dallas-Ft. Worth	140	
	Atlanta	157	38.5
	Birmingham		43.3

Cities by region and race	*Incidence of skin cancer per 100,000 population*	
	Male	*Female*
Peller[195] North	23	18
South	116	70
West	41	34
All white	38	28
Negro	5	4

It seems that the amount of pigment present, the relative thickness of the epidermis, especially its cornified layer, and the quantity and possibly also the quality of sebum produced act as natural protective factors which determine the observed variations of susceptibility to solar cancer of the skin among members of different races. It has remained uncertain whether the carcinogenic action of ultraviolet radiation is

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	Male	Female
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entirely a physical phenomenon which is elicited by rays between the wave length of 2,900 to 3,341 Å or whether it is a photochemical phenomenon and thus fundamentally a manifestation of chemical carcinogenesis. Studies by Blum[31] have shown that the effect exerted by repeated exposure to ultraviolet radiation is cumulative and largely irreversible. The experimental production of ultraviolet carcinoma and sarcoma of the skin of albino and pigmented mice and rats is readily accomplished, especially in those parts of the skin which have a sparse hairy coat (feet, ears, and eyelids). The wrinkled, thick, and cornified skin of hairless rats of the rhinoceros type, however, appears to be refractory to the carcinogenic action of ultraviolet rays (Hueper[104, 106]).

Ionizing radiation (irradiation, radioactive chemicals)

Among the numerous exogenous carcinogens, ionizing radiation seems to be the only universal carcinogen, i.e., capable of producing cancer in all species, known so far. Although it has remained undetermined whether the carcinogenic action is the result of a physical effect upon cell constituents or represents a radiochemical effect upon cellular chemical components, the general biologic characteristics of cancer evoked in man and animals by ionizing radiation, i.e., length of latent period, cumulative effects of repeated exposures, precancerous alterations in tissues, ambivalent reactions in tissues (atrophy, degeneration, necrosis-hyperplasia, atypical carcinomatoid and leukemoid reactions, cancer), are identical to those observed with cancer elicited by chemical carcinogens. The reported appearance of cancer involving the skin or the blood-forming tissues after a single and relatively brief exposure to ionizing radiation seems to favor the chemical theory of radiation carcinogenesis since the circumstances accompanying the response resemble closely those seen in chemical carcinogenesis associated with a depot effect from a carcinogen.

While α-ray and β-ray emitters have produced cancer in animals, the carcinogenic action of these rays on man, while likely, is not definitely established.

Cancer of the skin on the basis of chronic radiodermatitis has been observed after occupational, medicinal, and cosmetic exposure to x-rays and γ-rays. Cancerous sequelae have appeared in the skin with chronic radiodermatitis in 10 to 33 per cent of cases (Hueper[125]). Sulzberger and associates[226] have noted that chronic radiodermatitis of the human skin did not develop as long as the total dose of ionizing rays remained below 1,400 r. In fact, skin receiving ionizing radiation within this range exhibited a lower incidence of cutaneous cancer, according to their observations, than untreated skin of control cases. Since a plausible explanation for this paradoxic behavior of irradiated and nonirradiated skin is lacking, a competent and comprehensive re-examination of the problem of the minimal effective carcinogenic dose of ionizing radiation to the skin is indicated.

Cancer of the bone has been seen after transcutaneous irradiation of the tissues overlying the bones for benign conditions in the overlying soft tissues and has been noted in painters of luminous dials after an ingestion of radioactive chemicals (Martland[169]; Aub and associates[8]). Numerous experimental results confirm these human observations. It was possible to produce osteogenic sarcoma by x-irradiation of the bones, by implantation of radioactive chemicals into bones, and by feeding those radioactive chemicals which are "bone seekers" (Schuerch and Uehlinger[210]; Hueper and associates[131]).

Cancer of the lung in radioactive cobalt ore miners in Schneeberg, recognized in 1879, represents the first occupational cancer of the lung placed on record (Hueper[126]; Lorenz[160]; Peller[191]). The occurrence of similar cancer among pitchblende miners in Joachimsthal noted in 1926 furnished important evidence supporting a radioactive cause of this cancer (Loewy[161]). Recent epidemiologic studies, initiated in 1948 by

Table XXV. *Latent periods of occupational cancer*

Organ and agent	*Average latent period (yr.)*	*Range of latent period (yr.)*
Skin		
Arsenic		
Medicinal	18	3-40
Occupational	25	4-46
Tar	20-24	1-50
Creosote oil	25	15-40
Mineral oil	50-54	4-75
Crude paraffin oil	15-18	3-35
Solar radiation	20-30	15-40
X-radiation	7	1-12
Lung		
Asbestos	18	15-21
Chromates	15	5-47
Nickel	22	6-30
Tar fumes	16	9-23
Ionizing radiation	25-35	7-50
Bladder		
Aromatic amines	11-15	2-40

Hueper among the uranium ore miners in the Colorado Plateau and subsequently assumed and continued by other investigators, have yielded data indicating that a similar lung cancer hazard apparently exists for members of this worker group (Archer and colleagues[6]). Since experimental studies on the production of pulmonary cancer in rats instilled with radioactive material intratracheally have demonstrated that inhaled radioactive dust and gases can produce carcinoma of the lung, there is scarcely longer any doubt concerning the radioactive origin of lung cancer in man (Lisco and Finkel[159]; Cember and Watson[35]). It is apparent that the cancer hazard to the lung for such workers in mines and mills is high, since about 70 per cent of all deaths among the miners of Schneeberg were due to lung cancer, while this percentage stood at 45 per cent for the miners in Joachimsthal.

Whether intravenously administered thorium dioxide solution may have caused cancer of the lung in some cases is at present somewhat doubtful. On the other hand, it is established that thorium dioxide directly injected for diagnostic purposes into the maxillary sinus has given rise in 3 cases to carcinoma of the mucosal lining (Hueper[128]). There are on record 4 cases of squamous cell carcinoma of this sinus among luminous dial painters who inhaled radon and thoron (Aub and associates[8]).

Human and animal evidence obtained mainly during the last decade has established the fact that a causal relation exists between leukemia in man and animals and radiation sustained by exposure to radium and Thorotrast and by contact with occupational and therapeutic x-rays and radioactive chemicals generated during the explosion of the atom bombs on Hiroshima and Nagasaki (Heyssell and colleagues[23]; Cronkite, Moloney, and Bond[41]; Warren[245]; Hueper[102, 112]; Peller and Pick[196]; Watanabe[247]; Court Brown and Doll[40]; Furth and Furth[68]). It is still uncertain whether or not exposure to ionizing radiation of the fetus in utero may result in subsequent development of a leukemic reaction during infancy. The appearance of a leukemic reaction in exposed individuals has been preceded in some instances by a primary aplastic phase followed by a secondary hyperplastic phase characterized by leukocytosis, monocytosis, erythrocytosis, and finally leukemoid reaction. The minimal latent period of leukemia resulting from the atom bomb was 3 years, while the average latent period of occupational radiation leukemia, especially that found among physicians and radiologists, was 7 to 19 years. Such variations in the length of the latent or induction period of radiation leukemia are well within the range of fluctuations observed with other environmental cancer (Table XXV) and are dependent in part on the relative potency of the particular carcinogen, in part on the intensity and duration of exposure to it, and in part on variations in individual susceptibility.

There has been an increase in the frequency of leukemia in several countries and regions during recent decades. While this

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phenomenon has been attributed by some observers to effects from radioactive fallout, there is at present inadequate evidence in support of such a contention because there is no reliable information on the minimal leukemogenic dose of ionizing radiation. Moreover, the introduction of many chemicals possessing a myelotoxic and especially agranulocytogenic action into industry, medicine, and the human economy make it likely that some of these chemicals might possess leukemogenic properties and thus have contributed to the observed rise in leukemia.

Exposure to ionizing radiation has been incriminated in the production of cancer of other organs and tissues. The former diagnostic use of Thorotrast thus has been responsible for the occurrence of carcinoma and sarcoma of the liver, kidney, maxillary sinus, lung, and breast, into which the thorium dioxide was either injected or in which it was retained (Suckow and associates[225]; Feine and Leonhardt[59]). No information is available on the occurrence and site distribution of cancer among the workers and residents of those areas in Brazil and India in which monazite sand containing thorium is found and mined.

While the diagnostic use of radioactive iodine has given rise to the occurrence of cancer of the thyroid, it has not as yet been established whether an identical effect has followed upon an exposure to radioactive iodine generated by the explosion of nuclear material or released during accidents of nuclear power plants and incorporated secondarily into human foodstuffs, especially milk. It is likewise uncertain whether radioactive phosphorus administered in the therapeutic management of polycythemia has caused or contributed to the development of leukemia observed not too infrequently as a late complication of this myeloid disorder.

Summary

The growth of an environmental carcinogenic spectrum composed of recognized, suspected, and potential human carcinogens of chemical, physical, and parasitic nature should provide an impressive warning to all concerned with the maintenance and protection of the health and well-being of mankind to exert all possible effort to develop methods and facilities by which sources of production, channels of dissemination, routes of exposure, prospective and actual target organs and tissues, and number and types of individuals exposed to natural and man-made carcinogens can be more readily and reliably identified.

Since most environmental carcinogens have been introduced into the human ecology with the advent of the industrial era and because man has therefore had insufficient time to develop any defensive adaptation reactions to the numerous synthetic components of the environmental carcinogenic spectrum, it is essential that, where possible, human contact with environmental carcinogens be totally eliminated or, whenever such a stringent measure appears impractical or impossible, reduced to a minimum with respect to degree, frequency, duration, and number of persons exposed. Needless and reckless introduction of carcinogens into consumer goods, water, air, and soil is bound to lead to an epidemic of environmental cancer the course of which, once set in motion, will resist the prophylactic or protective anticarcinogenic measures now available.

While the presently available methods of identifying carcinogenic agents are admittedly slow and not totally adequate, experimental observations and their implications in man demand that first and dominant consideration be given to the protection of the community against actual or potential cancer hazards. In such a decision, the health and life of the general public should receive the benefit of doubt without any reservation.

The determination of carcinogenic properties in weak carcinogens and of the type and degree of cancer hazards to man created by them, especially as far as chemical carcinogens are concerned, may present considerable difficulty because their action

may be direct or indirect and may be primary or secondary, as well. For these reasons, the control of cancer hazards from chemical carcinogens may prove to be much less readily attainable than that of radioactive carcinogens.

Toxic properties of chemicals are unrelated to their carcinogenic ones. Chronic toxicity tests, therefore, do not yield any reliable information or any possible carcinogenic qualities of the chemicals tested.

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