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Copy from D. V. Stroop for Information of Members and Associates
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ESSO LABORATORIES
Standard Oil Development Company

Medical Research Division

P. O. Box 51
Linden, N. J.

January 15, 1953

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I am attaching a reprint of an article recently
written by Dr. Hueper. I think that this article should be
brought to the attention of all of the members and associates
of the Medical Advisory Committee of the API.

Very truly yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:11k

Encl. - Environmental Cancers:
A Review by Dr. W. C. Hueper
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Environmental Cancers: *A Review*

W. C. HUEPER

(National Cancer Institute, United States Public Health Service, Federal Security Agency, Bethesda, Md.)

Although the knowledge of an environmental causation of human cancer is much older than that of the exogenous origin of infectious diseases, there exists a striking, if not alarming, contrast between the extent to which this information has been put to scientific and practical use in the study and control of these two important groups of diseases. In the attack on the infectious diseases the main efforts were expended on the discovery of the specific causative agents and on their subsequent elimination from the external and internal human environment by appropriate preventive, prophylactic, and therapeutic measures. Interest in the endogenous properties of the host, as represented by heredity, constitution, aging processes, race, and sex, in determining the development and course of infectious diseases did not, as a rule, assume a dominating character. These factors were recognized as having mainly a modifying, but not a causal role, by exerting a certain influence on individual susceptibility to the pathogenic microorganisms and on the course of the disease. The investigation of the anatomic and biologic properties on the various reaction products, particularly those of chronic granulomatous nature, remained usually a less important side issue in devising effective control measures.

The investigations directed against human cancer, on the other hand, paid relatively little attention to the factual evidence of its established environmental causation, but concentrated first on the various morphological aspects of cancer and cancer cells and, more recently, on the biochemical and biophysical properties of cancer tissue. Cancer was, and still is, considered by many investigators a distinct disease entity and is not regarded as an atomic reaction product to a large number of

diverse chemical and physical agents. It has been for the same reason that the rather diffuse etiologic concepts of physiologic aging and heredity have enjoyed a much greater and much more lasting appeal than the much more definite and reliable observations on the diverse exogenous causes of a considerable variety of human cancers.

HEREDITY

Since, in a recent discussion of the age aspects of environmental and occupational cancers (15) the fundamental fallacy of this concept as to the majority of human cancers was discussed in detail, it remains to point out that a similar situation seems to prevail as to the validity of the heredity theory. Conclusions drawn from selectively inbred strains of mice, a notorious biologic artifact without parallel in nature, have been instrumental in giving to hereditary factors an exaggerated and distorted significance as immediate causes of human cancer. While it may be conceded that there exist a few rare cancers which display hereditary tendencies, at least one of them (cancer of the skin in xeroderma pigmentosum) depends in its causation on the primary action of an exogenous agent. Although xeroderma pigmentosum is due to an inherited hypersensitivity to solar radiation prevalent among some inbred family groups, this fact would scarcely justify the conclusion that the ordinary type of solar cancer of the skin is primarily an inherited manifestation of the host organism which is activated by an exposure to solar rays. Such an inversion or perversion of normal reasoning would have to disregard the fundamental fact that without solar radiation there is no cancer, irrespective of the constitution of the individual.

The allegation that hereditary factors based on

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prolonged inbreeding play an important causal role in the production of the lung cancers among miners of radioactive ore in Schneeberg and Joachimsthal (Vesin [39]; Macklin [27]; Lorenz [26]) represents another example of the rather loose speculations which have been advanced to bolster the cause of the heredity theory. Apart from the fact that none of the various proponents has offered any concrete evidence in support of such a claim, any significant degree of inbreeding in a community of about 10,000 inhabitants (Schneeberg) having a railroad station for many years would indeed represent a most remarkable biologic and sociologic feat. This speculation advanced by investigators remote from these operations has no basis in fact according to German investigators.¹

The occasional occurrence of lung cancers in several members of the same family working in these mines certainly cannot be regarded as proof of a hereditary liability. Similar observations of a familial appearance of skin (scrotal) cancers were reported from England during the past century in families of chimney sweeps. Such familial cancers were obviously caused by an occupational or environmental exposure to soot by several members of such families without necessitating the assumption of a common hereditary susceptibility.

The high rates of attack of several environmental cancers rather clearly indicate that heredity evidently plays a relatively insignificant role in their production (cancer of the lung in 75 per cent of miners employed in radioactive mines—Baader [8]; Hueper [16]; cancer of the bladder in almost 100 per cent of dye workers following highly excessive and prolonged exposure to certain aromatic amines—Goldblatt [11]; Mueller [32]; Gross [12]; Hueper [17]; cancer of the skin in 100 per cent of workers with contact with pitch for more than 40 years—Sladden [35]).

It is likely, however, that such an almost complete obliteration of individual inherited or acquired constitutional differences in susceptibility to exogenous carcinogens occurs only in the presence of an overwhelming, high intensity exposure. Whenever groups of individuals become exposed to carcinogens of low potency or sustain exposures of low intensity and duration, there appears evidence indicating variations in the speed and character of the individual responses to the environmental carcinogen. A constitutional influence evidently

controls the susceptibility of different races to solar cancer of the skin, to which light-pigmented individuals are much more liable than dark-pigmented individuals. The effect of this racial difference in reactivity to the carcinogenic action of the ultraviolet radiation from solar sources is reflected not only in a lower incidence of skin cancer in Negroes than in whites, but also in a different topographical distribution of the skin cancers observed in the two racial groups. While skin cancers in whites are mainly located in the skin of the exposed parts of the head, neck, and upper extremities, those observed in Negroes are predominantly situated in the usually covered parts of the body and the lower extremities (31).

Since arsenical cancers not infrequently involve the unexposed parts of the skin, it is reasonable to conclude from the above evidence that the variations in the topographical distribution of skin cancers in whites and Negroes are, in part, due to differences in causal agents active in the production of these cancers.

It is unwise, however, to generalize or overemphasize the role of racial factors in the causation of environmental cancers. Although primary hepatic cancer incidence is high among West African Negroes, their American descendants do not display any such tendency (Berman [5]), indicating thereby that not racial or hereditary factors but environmental factors are underlying the African experience. Likewise, it can be considered as established that the absence of penile cancer among Jews and the high liability of Chinese to this type of malignant tumor do not depend upon race-conditioned constitutional differences, but are mainly the result of differences in personal hygiene, especially the circumcision practiced at an early age by the Jews. There thus exist not only "environmental familial cancers," but also "environmental racial cancers," which have no relation to heredity.

SEX

Differences in the sex distribution of cancers affecting several organs (lip, mouth, larynx, bronchus, skin, and bladder) have given rise to the concept of a sex-conditioned susceptibility to certain cancers. Observations on environmental cancers lend no substantial support to such a theory. Cancer of the lung of unknown origin has a male-female sex ratio of from 4:1 to 24:1, according to various investigators (18). Asbestosis cancer of the lung, on the other hand, displays a male-female sex ratio of 2.4:1, indicating that with an equalization of exposure to a carcinogenic agent there occurs also an equalization of the incidence rates of lung

¹ None of the numerous German workers mentioned in their papers the occurrence of inbreeding in the mining population of the Erzgebirge and Linzbach in answer to a recent inquiry stated that nothing is known among German scientists in this respect.

cancer for the two sexes (Merewether [30]). Likewise, it is most improbable that the male-female sex ratio of 1:1 for Mexican men and women (Steiner, Butt, and Edmondson [37]) living in Los Angeles reflects sex-related factors. It is noteworthy in this respect that the entrance of female mulespinners in the English textile plants was followed after a suitable latent period by the appearance of cancers of the vulva in some of these operators, which fact thereby demonstrates that female mulespinners acquire the anatomic equivalent of the scrotal cancer of their male counterparts (18). While oral cancer is rare in white women, this tumor is rather frequent in Indian women chewing betel quids (Bashford [4]). This bucco cancer of the oral cavity represents 12 per cent of all cancers among Filipino women. For this reason, the sex ratio of oral cancer among Filipinos is inverse to that found among white people inhabiting the temperate zones, where the male-female sex ratio is 3:1 (Maxwell [29]; Vedder [38]).

These and other similar observations indicate that the differences in the sex ratio of certain cancers of unknown origin are apparently not due, in the main, to hormonal factors but rather reflect variations in the types and intensity of exposure to environmental carcinogens affecting members of the two sexes to a different degree for reasons of occupations, habits, customs, clothing, hobbies, and general living conditions.

EPIDEMIOLOGIC PATTERN

The type of the epidemiologic pattern of environmental cancers depends less on certain constitutional factors of the population studied (heredity, race, sex, age) than on the composition, as well as the type, intensity, and duration of action of the agents constituting the environmental carcinogenic spectrum to which they have been exposed. The physical and chemical carcinogens exert their disease-producing effect, just like the pathogenic micro-organism, whenever and wherever they operate under proper conditions of exposure and irrespective of the special type of contact (occupational, medicinal, dietary, habitual, environmental, etc.) present.

The general soundness of this concept is attested by the following observations. The appearance of occupational cancers in the various industrialized countries has closely followed the spread of certain industries. This sequence of events is well illustrated by the chronologic and geographic appearance of bladder cancer among dye workers in different countries following the establishment of aniline dye industries (Table 1).

Additional support for the concept proposed is

derived from the demonstration of a centrifugal spread and scatter pattern of occupational cancer hazards from the focus of original production of carcinogens in basic industries through processing and consumer industries to the ultimate handler and general consumer of the finished products. This pattern becomes apparent in the occurrence of skin and lung cancer among the producers of tar and pitch in gas plants and coke ovens, the appearance of similar cancers among tar refinery workers, roofers, road construction workers, cork brick manufacturers, and other members of secondary industries and trades handling and using tar and pitch. An identical chain of environmental cancers among successively exposed population groups exists in regard to arsenicals, which have

TABLE 1
CHRONOLOGIC AND GEOGRAPHIC APPEARANCE OF
BLADDER CANCER AMONG DYE WORKERS
IN DIFFERENT COUNTRIES (17)

Country	First year reported	Author	Total no. recorded up to 1951
Germany	1895	Rehn	Approximately 350
Switzerland	1905	Schedler	190
Great Britain	1918	Ross	300
Russia	1926	Rosenbaum and Gottlieb	71
Austria	1932	Schueler	(2)
United States	1934	Ferguson <i>et al.</i>	250
Italy	1936	di Maio	90
Japan	1940	Nagayo and Kinoshita	(7)
France	1946	Billiard-Duchesne	41

elicited cancers among miners of arsenic-containing ores, smelter workers, manufacturers of arsenical insecticides, users and consumers of foodstuffs and drinking water contaminated with such arsenicals, as well as individuals receiving arsenicals for medicinal reasons (Hueper [16]; Neubauer [33]; Arhelger and Kremen [2]; Butzengeiger [8]; Hill and Faning [14]; Arguello, Tello, Macola, and Manzano [1]).

Occupational cancer hazards also display a cancer distribution pattern which shows the highest attack rates among the population groups employed within the immediate vicinity of the carcinogenic industrial foci and gradually decreasing attack rates among population groups increasingly remote from it and thus less intensely and frequently in contact with carcinogenic agents. A good illustration of this concentric distribution pattern of occupational cancers is offered by the aromatic amine bladder cancers. The bladder cancer incidence rate, according to past experience, was highest among intermittently but intensely exposed maintenance and repair men who were followed in decreasing order by operators regularly

employed in the manufacture of beta-naphthylamine and benzidine, these by truck drivers, yard men, chemists, engineers, and supervisors who have irregular and mitigated exposures. Whether or not "neighborhood cases" of aromatic amine cancers actually occurred among the population residing or working within the fume and waste disposal zone of aromatic amine operations is still doubtful and controversial (Mueller [32], Hueper [17], and Gross [12]). Since, according to Gehrmann, Foulger, and Fleming (10), workers employed in a building formerly used for the production of beta-naphthylamine have an occupational bladder cancer hazard from contact with the minute amounts of the chemical volatilized from impregnated building material, neighborhood cases of this occupational cancer may conceivably occur among persons living near aniline dye plants with defective loading, shipping, and waste disposal arrangements for beta-naphthylamine and benzidine.

Another major factor determining the character of the epidemiologic pattern of occupational cancers is represented by their latent period, which in turn depends upon the relative potency of a particular carcinogen, its physicochemical properties (solubility, dispersion, chemical reactivity

latent period. Apart from individual differences in susceptibility, these irregularities in the intensity of exposure to environmental carcinogens mainly account for the wide range of latent periods recorded for environmental cancers (Table 2).

The target organ of environmental carcinogens depends on various factors. Special tissue affinity of benzene to the fat tissue contained in hematopoietic organs thus seems to account for its exclusive leukemogenic action. The intensity of ex-

TABLE 2
LATENT PERIODS OF ENVIRONMENTAL
AND OCCUPATIONAL CANCERS

Organ	Agent	Av. latent period (years)	Range of latent period (years)
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
Lung	X-radiation	7	1-12
	Asbestos	18	15-21
	Chromates	15	5-47
	Nickel	22	6-50
	Tar fumes	16	2-25
Bladder	Ionising radiation	15-35	7-50
	Aromatic amines	11-15	2-40

and affinity, etc.), the physicochemical and co-carcinogenic or anticarcinogenic properties of its vehicle or its associated agents, the route of contact, the intensity of the individual exposures, their rhythm, and the total duration of exposure. These factors, which have a distinct influence upon the incidence rate of cancers among exposed population groups, also exert a definite influence upon the length of the latent period. With decreasing intensity of exposure there occurs a reduction in the incidence of cancers and a lengthening of their

TABLE 3
SITE OF CANCER AND ROUTE OF EXPOSURE

Type of contact	Carcinogenic agent	Site of cancer
Cutaneous	Arsenic	Skin
	Coal tar, pitch, soot, asphalt	
	Creosote oil, anthracene oil	
	Petroleum asphalt, coke, tar	
	Petroleum oils (high boiling)	
	Shale oil, crude paraffin oil	
	Lignite oil and paraffin oil	
	Ultraviolet radiation	
	X-radiation, radioactive chemicals	
	Benzene	
Respiratory	Arsenic dust	Hematopoietic tissues
	Chromium compound dust and fumes	Lung
	Nickel dust and vapors	Lung, nasal cavity and sinuses
	Asbestos dust	Lung
	Beta-naphthylamine, benzidine dust and vapors	Bladder
	Coal tar fumes	Lung
	Petroleum oil mist	Lung
	Isopropyl oil vapors*	Nasal sinuses, larynx, and lungs
	Radioactive dust and gases	Lung
	Arsenic	Skin
Ingestion	Radium, mesothorium	Bone

* Isopropyl oil is the crude liquor from which isopropanol is obtained by distillation (40).

posure to some environmental carcinogens also seems to determine the distributory mechanism of the resulting cancers. The relatively high frequency of heterotopic multiple primary cancers observed among dye workers with cancers of the urogenous tract as well as other organs (lung, stomach, intestine, prostate—Mueller [32]; Hueper [16]) seems to be due to an unusual hematogenous spread of the carcinogenic hydrocarbons ordinarily mainly excreted through the urine (Bonser [7]). The principal reason for the appearance of cancers in various organs, however, represented by the route of exposure (Table 3).

Epidemiologic and demographic studies carried out during the past two decades have demonstrated the existence of marked and significant variations in the total incidence of cancer as well as in the organ, sex, age, and race distribution of cancers in different countries, regions and popula-

differences in the intensity of carcinogens mainly at periods re-

l carcinogens tissue affinity ed in hemato- for its exclu- sivity of ex-

EXPOSURE

Site of cancer
Skin

Hematopoietic tis-
sues

Lung
Lung

Lung, nasal cavity,
and sinuses
Lung
Bladder

Lung
Lung
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Lung
Skin
Bone

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carcinogens also mechanism of vely high fre- imary cancers cancers of the organs (lung, ller [32]; Hue- usual hematog- hydrocarbons igh the urine for the appear- is, however, is re (Table 3).

studies carried s have demon- and significant cancer as well as distribution of ns and popula-

tion groups. While a part of such variations is due to differences in the age distribution of the various population groups surveyed as well as in the quality of medical care and of medical recording of diseases, there remains for many of these discrepancies in rates of regional cancer incidence no other plausible explanation than the differences in exposure to environmental carcinogenic factors (Table 4).

The striking differences in the lung cancer morbidity rates in metropolitan centers located in the same part of the country militate against the concept that such local discrepancies can justly be attributed to variations in medical care and recording, or to differences in the biologic composition and hereditary properties of the populations concerned, or to the predominant action of a single etiologic environmental factor, especially cigarette smoking (Wynder and Graham [41]). The local variations as well as the consistent increase of lung cancer morbidity rates must be ascribed to a combination of exogenous factors affecting, to differing degrees, the various population groups as well as the two sexes surveyed. Since the known environmental lung cancers have a latent period ranging usually from 10 to 25 years, it may be concluded that the rising trend of lung cancers is attributable to changes in the environmental carcinogenic spectrum which started around the turn of the century and the effects of which are becoming increasingly evident (Hueper [18]). Supporting this concept is the fact that the majority of environmental and occupational cancers discovered during the last 25 years involve cancers of the respiratory tract (cancers produced by chromium compounds, nickel, arsenicals, asbestos, coal tar, petroleum oils, isopropyl oil, radioactive substances) (21, 28).

In the conduct of epidemiologic studies on environmental cancers certain important precautions have to be observed, if misleading, incorrect, or inconclusive results are to be avoided (Hueper [17]; Downing [9]). It is essential to survey as far as practicable the total effectively exposed population, and to exclude from membership in the actually exposed population group all those individuals who have merely an "administrative" adherence to it. In a survey of environmental cancers among oil refinery workers, for instance, it is scientifically not permissible to include office personnel, sales people, and other white-collar workers, unless they sustain real contact within the refinery area to suspected or recognized carcinogenic agents for occupational reasons. Similarly, whenever, within an industrial population to be surveyed, only a restricted group is shown to have

a carcinogenic hazard, figures on incidence must be calculated for this group only, and not for the total plant population, since the latter procedure results in an undue dilution of positive evidence and thereby in distorted epidemiologic information. The limited occurrence of bladder cancer to relatively small and restricted groups of dye workers (10), the excessive liability to scrotal cancer limited to workers employed in paraffin pressing operations in oil refineries (34), and the increased liability to lung cancer among persons with asbestosis—and not among all persons employed in asbestos operations—provide pertinent illustrations of this point.

TABLE 4

LUNG CANCER MORBIDITY RATE, 1937 AND 1947, FOR
RESIDENTS OF EIGHT METROPOLITAN CENTERS
PER 100,000 POPULATION*

City	MALES		FEMALES		TOTAL	
	1937	1947	1937	1947	1937	1947
Atlanta	5.0	13.4	1.0	5.0	2.9	8.9
New Orleans	13.1	39.1	2.8	4.2	7.6	20.8
Dallas	5.9	29.0	0.5	6.4	3.1	17.2
Birmingham	4.5	18.9	2.1	3.9	3.3	11.0
Denver	9.1	21.9	4.2	8.1	6.6	14.8
San Francisco	15.6	34.3	3.9	8.1	9.8	20.8
Chicago	13.3	29.5	4.3	7.0	8.8	18.0
Pittsburgh	9.7	26.1	4.9	5.5	7.3	15.6

* Supplied by Biometrics Section, National Cancer Institute.

An analysis of the population "at risk" should include not only workers presently employed for a sufficiently long period, so as to cover the minimal latent period of the average occupational cancer (5 years), but also all formerly employed workers dead or alive who left the industry, plant, operation, or trade group fulfilling this condition. The inclusion of large groups of short-term employees with insufficient exposure and latent period into the surveyed group also introduces a serious dilution factor which causes misleading or inconclusive results (23, 36).

Since the occurrence of environmental cancers rarely has the character of an epidemic, but as a rule appears as an endemic, it is necessary to conduct epidemiologic studies as long-term investigations, which means the analysis of data covering periods of at least 5 years. Negative results obtained from short-term investigations comprising periods of 1 or 2 years give, at best, inconclusive results if not incorrect ones (6).

In view of the long latent period of environmental cancers it is necessary to restrict occupational cancer surveys to plants which have been in operation for at least 10 years, unless a large portion of the workers in their employ has previously been employed in similar operations elsewhere.

The absence of published reports on the occur-

rence of occupational cancers in an industry having known or suspected cancer hazards is no assurance that a serious occupational cancer problem in these establishments is nonexistent. Perhaps the most notorious example that can be cited as an illustration of such occurrences is represented by the long delayed discovery of the lung cancers among uranium miners of Joachimsthal. Although the existence of a high lung cancer incidence among the Schneeberg miners was established in 1876, despite repeated inquiries made by German investigators with the various governmental authorities under whose jurisdiction the uranium mines in Joachimsthal located nearby on the southern slope of the Erzgebirge were operated, it was not until some 50 years later that the high frequency of lung cancers among this group of similarly exposed workers was recognized. Until that time (1926), the century-old practice of mistaking lung cancers of the Joachimsthal miners for pulmonary silicosis or tuberculosis was continued. Likewise, associated pathologic conditions sometimes may operate in obscuring the co-existence of an occupational cancer. This danger exists, for instance, for asbestosis cancer of the lung, unless a thorough necropsy study is made.

CARCINOGENESIS

An analysis of the action mechanism of the various recognized, suspected, or potential human carcinogens supports the viewpoint that the majority of cancers develop at sites where, for some reason, the most intense or most prolonged exposure to the carcinogen takes place. The following types of mechanisms determining the distribution of environmental cancers may be distinguished.

a) *Cancers developing at sites of primary contact.*—To this group belong the cancers of the skin resulting from cutaneous exposures to substances such as coal tar, petroleum oils, creosote oil, soot, and similar combustion and high temperature distillation products of carbonaceous matter, as well as to ultraviolet and ionizing radiations; moreover, the cancers of the nasal cavity, nasal sinuses, larynx, and lung elicited by the inhalation of arsenicals, chromium, and nickel compounds, (beryllium?), asbestos, isopropyl oil, tarry matter, and radioactive gases and dusts. The cancers of the connective, bony, and hematopoietic tissues following exposure to penetrating ionizing radiation may be included in this group of primary contact cancers.

b) *Cancers developing at sites of selective deposition.*—Arsenical cancers of the skin, osteogenic sarcomas following ingestion of radium and/or

mesothorium, leukemia following contact with benzene, (thyroid carcinoma following radioactive iodine medication, leukemia subsequent to radioactive phosphorus medication, osteogenic sarcoma following inhalation of beryllium compounds?) may be included in this group.

c) *Cancers developing in organs with special functional or toxic affinity for carcinogens.*—Representatives of this group are almost exclusively caused by carcinogens of potential importance as far as humans are concerned and thus have been observed mainly in experimental animals. Cancers of this type are the tumors of the liver developing following exposure to various azo dyes, aminofluorene compounds, chlorinated hydrocarbons and selenium, the cancers of the breast and uterus subsequent to an excessive exposure to estrogens, and cancers of the thyroid following the prolonged administration of thiouracil derivatives.

d) *Cancers developing in organs of excretion of carcinogens.*—Cancers of the bladder, ureter, and kidney observed in individuals and experimental animals having cutaneous, ingestive, and respiratory contact with certain aromatic amines and azo compounds due to the presence of carcinogenic material in the urine belong to this group.

e) *Cancers developing on the basis of functional abnormalities due to certain dietary deficiencies and representing a type of indirect or secondary environmental carcinogenesis.*—Cancers of the hypopharynx and of the liver noted among population groups subjected to a diet deficient in vitamin B complex and protein as well as cancer of the liver in rats kept on a choline-deficient diet are members of this group.

f) *Cancers of the young resulting from a transplacental penetration of carcinogens.*—There exists so far only experimental evidence in support of such an exposure route in the demonstration of the development of pulmonary tumors in the offspring of pregnant mice given urethan near term (Larsen [25]; Klein [24]). Whether or not a similar mechanism may be active in the production of congenital cancers or cancers developing during infancy and early childhood appears to be a worthwhile subject of investigation in view of these findings.

While it is not likely that exogenous agents are the only factors responsible for human cancers, the increasing number and widening variety of environmental carcinogenic agents suggest that they seem to be operative in a much larger proportion of cancers than is recognized or realized at present. It appears from the evidence available that the study of environmental cancer hazards and cancers offers not only the most

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