Age Aspects of Environmental
And Occupational Cancers

By W. C. HUEPER, M.D.

For many years, age factors have played an important and widely accepted role in theories of cancerigenesis (*9*). Curiously enough the concepts advanced in this matter are related to both ends of the age range. Some investigators adhere to Cohnheim's theory that cancers originate from misplaced embryonic cells. Others are followers of the senescence theory of carcinogenesis and believe that cancerigenesis is in some way closely connected with the physiological changes associated with advancing age. The outlook for achieving a reasonable control of cancer by preventive measures would be dark indeed if either theory proved correct or applicable to all or most types of cancers. It is most unlikely that effective measures can be found to prevent the production of the hypothetical ubiquitary embryonic cell misplacements during fetal life. Likewise, there is little prospect of modifying physiological aging processes in such a way that they would lose their alleged carcinogenic properties.

Fortunately, numerous observations made during the last two decades in the fields of environmental and experimental carcinogenesis tend to minimize greatly the significance of primary age influences in the development of

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malignant tumors and to demonstrate the actual or potential part that exogenous agents assume in bringing about cancerous reactions through a direct or indirect action mechanism (*7, 9*). A revaluation and redefinition of the role of age in the problem of cancer and especially in its environmental aspects appears to be timely and needed.

Relationship of Age to Cancer

Although the majority of cancer deaths in the United States and Europe involve individuals between the ages of 30 and 60 years, there is a progressive and steep rise in cancer incidence, if the incidence rate of cancer is expressed in terms of cancers per 10,000 individuals of identical age (*1, 22*). It is remarkable, however, that the increase in cancer incidence with advancing age is more marked for carcinomas than for sarcomas. Some investigators (*3*) have attempted to reconcile this discrepancy in the age distribution of carcinomas and sarcomas by the hypothesis that connective tissues age faster than epithelial ones. Such a supposition lacks factual support. Observations on experimental and environmental cancerigenesis clearly demonstrate that the histological type of cancer depends upon the tissues to which the cancerigen is applied, or into which it is implanted, or in which it is retained and stored, or for which it possesses a special affinity.

When considering the relationship of age to cancer, there remains the well-established fact that cancers originating from many tissues occur at all ages from the prenatal to the senescence period. Indeed, cancer is the second or

third most frequent cause of death even during the first three decades of life, if deaths from accidents are excluded. Thus among the fatal diseases, cancer ranks high at any age period.

Age Distribution

Additional inconsistencies in the concept of direct age relationships to cancer become apparent when the modal age at death from cancer of different organs is studied (22). According to Holtz, incidence maximums for cancers of the testes, kidney, and suprarenal are found at an age range of 0 to 4 years, for tumors of the bones at 15 to 25 years, for cancers of the testes at 30 to 35 years, for cancers of the brain at 40 to 45 years, for cancers of the female sex organs at 50 to 55 years, for cancer of the skin and abdominal organs at 60 to 65 years, and for cancers of the prostate at more than 70 years. Apart from the fact that certain special types of cancers occur almost exclusively during infancy and childhood (Wilms' tumor of kidney, retinoblastoma, botryoid sarcoma of vagina), cancers of some organs have several age peaks of frequency (cancers of the testes, brain, and blood-forming organs).

While melanomas occur at all ages without any special prominence in any particular decade, except that they are rare in young children, they display a different and unique relationship to age inasmuch as there is a precipitous rise in the capacity of melanomas to metastasize after puberty despite their histological similarity to the usual nonmetastasizing juvenile melanoma (19).

Regional, Sex, and Race Distribution

There are marked variations in the total cancer incidence as well as in the relative incidence of some organ cancers (skin, lung, mouth, stomach, liver) in the populations of different parts of the world and in different regions of the United States. While some such differences can readily be explained by the considerable variations in the average life span in different countries or by certain racial characteristics, or both, they do not reflect primary biological differences related to age. For instance, there are good reasons to believe that the differences in

susceptibility to, and incidence of, cancer of the skin between fair-complexioned and dark-complexioned people are caused by differences in the functional and anatomical qualities of the skin, and that they are not attributable to fundamental variations in some age attributes of the skin of population groups with varying degrees of pigmentation.

Likewise, it is not conceivable that the marked differences in sex distribution of several organ cancers (skin, larynx, lung, bladder, esophagus, lip, tongue, mouth, tonsil, pharynx) represent sex-conditioned variations in the distribution and number of embryonic cell rests or in the time of onset and speed of aging processes of the tissues from which these cancers originate.

The incidence ratio for males and females for cancer of the skin is 4:1, for cancer of the lung from 2:1 to 20:1, for cancer of the larynx 10:1, for cancer of the bladder 5:1, for cancer of the esophagus 10:1. The dilemma in which the protagonists of an age theory of cancer find themselves in this respect is increased by the fact that these ratios are not fixed. They vary in different countries with the changes in environmental conditions, such as the trend toward an equalization or reversal of the sex ratio of cancer of the mouth in India and the Philippines where the chewing of betel nut quids is habitual.

Embryonic Cell Rests and Cancer

The difficulties in attempting to connect age with cancer are accentuated if age concepts are applied to a specific theory, such as Cohnheim's theory. Although some exceptional cancers (Wilms' tumor, and testicular and ovarian teratocarcinomas), usually appearing during the first two to three decades, may be derived from embryonic tissue misplacements, this evidence furnishes little support for the claim that most tumors observed during early life originate from embryonic cell rests (16) or are the result of developmental mechanical disturbances (21), because the typical cancers of adults produced by exposure to exogenous agents are extremely rare in children.

It is a well-established fact that numerous exogenous chemicals introduced into the body

of a pregnant woman can penetrate the placental barrier and act upon the fetus. Theoretically, thus, it is conceivable that a fetus may become exposed to carcinogenic agents entering the fetal circulation from the maternal side (9) and causing cancers during the prenatal or postnatal period. The successful experimental induction of pulmonary tumors in the offspring of mice by a transplacental exposure to urethane administered to the pregnant mouse (11) supports this concept.

Senescence and Cancer

The main argument advanced in support of the senescence theory of cancerigenesis is the statistical relationship between advancing age and rise of cancer incidence. The disturbing existence of different age ranges for the peak incidence of cancers of various organs is explained by the proponents of the senescence theory through the introduction of the concept of heterochronic or disharmonic aging of the various organs, while the appearance of cancers during a comparatively early period of life in which senescent processes are not prominent is regarded as the result of local abnormal precocious tissue senescence occurring on the basis of a congenital constitutional predisposition.

Additional support for the senescence theory is sought by claiming that the length of the latent period of cancers induced by exogenous agents in experimental animals bears a direct relationship to their normal life span, that is, the rate of tissue senescence of a particular species controls the speed of cancer development. Wells contended that from one-fifth to one-tenth of the life cycle of an organism ordinarily is required to produce a malignant tumor.

Since most of the cancers occur in individuals who have entered the "senescent" phase of life, it is only natural that in many instances senescent changes are found in coexistence with cancerous reactions. However, many of these "senescent" changes are not physiological but the result of prolonged exposure to exogenous agents, some of which have cancerigenic properties, such as solar radiation, tar, pitch, petroleum derivatives, arsenicals, and ionizing radiation. Spontaneous as well as exogenously induced cancers in man and animals not infre-

quently develop in a tissue that does not show any so-called "senescent" changes. Pulmonary tumors in mice and aromatic amine cancers in man and dogs illustrate this fact. Finally, cancers are infrequent in certain organs (salpinx, urethra, blood vessels, kidney, testis, heart, bones) at an age period when the atrophying and fibrosing manifestations of advancing age are present.

Latent Period of Cancer

Additional and important evidence against the validity of the senescence theory of cancer is furnished by observations on the latent period of occupational, environmental, and experimental cancers. Willis (22) noted that "We now know that cancer is mainly a disease of the elderly, not because senile tissues are 'predisposed' to cancer, as was once supposed, but because of the usually long latent periods elapsing between the application of carcinogenic stimuli and the development of tumors. Occupational and experimental tumors show that these periods often occupy large fractions of the life spans of the affected animals." The validity of this statement is supported by the data in table 1.

The observations from the field of environmental and occupational cancerigenesis not only

Table 1. Latent periods of occupational cancers

Organ and agent	Average latent period	Range of latent period
Skin	*Years*	*Years*
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 carbonyl	22	6–30
Tar fumes	16	9–23
Ionizing radiation	25–35	7–50
Bladder		
Aromatic amines	11–15	2–40

demonstrate that the basic cancerization process antedates often by many years the time at which the cancer becomes manifest, but they also show that the age at onset of exposure and the intensity of contact with the carcinogenic agent determine the manifestation age.

When children from 4 to 10 years old entered the profession of sweeps in England during the early part of the last century, chimney sweeps developed scrotal cancer at an average age of 30 to 40 years (5). After this practice was discouraged by law and sweeps did not start in the trade before the age of 16, the average age at which scrotal cancer in sweeps was observed rose to from 45 to 50 years at the end of the nineteenth century (4). With the subsequent introduction of improved hygienic conditions and technical procedures reducing the intensity of exposure to soot, the average age of sweeps with scrotal cancer increased to 61.9 years by 1935 (8). The evidence clearly shows that the progressive and considerable increase in the average age of sweeps with scrotal cancer was directly dependent upon the later onset of exposure and on a reduction in the intensity of exposure (12). While sweeps still have a higher liability to scrotal cancer than the general population, the average manifestation age of scrotal cancer in sweeps is now identical with that of scrotal cancers of unknown etiology (table 2).

Table 2. Age distribution of scrotal cancer in chimney sweeps

Years	1892 [1] (cases)	1935 [2] (cases)
25–35	4	1
36–45	7	6
46–55	14	18
56–65	4	33
66–75		28
76–85		17
Average age	45–50	61.9

[1] Butlin (4).   [2] Henry (8).

A similar effect of the age at onset and of the intensity and the duration of exposure to an environmental carcinogenic agent upon the average manifestation age of the resulting cancers is evident in arsenical cancers of the skin. While the average age of skin cancer patients is about 60 years (14), approximately one-third of 115 medicinal arsenical cancers were seen in patients less than 40 years old, and more than 60 percent were not older than 50 years (13). Likewise, the average age of persons with occupational X-ray cancer of the skin is in the age group 41–66 years (9). Occupational cancer of the bladder of chemical or parasitic origin also is characterized by an age incidence which favors the younger age groups below 50 years of age (aromatic amine cancer: 52.8 percent of all cases in individuals less than 50 years old; schistosomiasis cancer: mainly in individuals 30 to 40 years old), contrasted with an age distribution of more than 50 years for 65 percent of all cryptogenetic bladder cancers.

The evidence presented in table 3 shows a shift into younger age groups for skin cancers caused by arsenicals, pitch, paraffin oil, shale oil, and X-radiation, for cancer of the lung induced by tar and ionizing radiation, and for cancers of the bladder produced by beta-naphthylamine and benzidine.

Observations made in experimental carcinogenesis also demonstrate beyond any doubt that the length of the latent period and, thereby, the manifestation age is not dependent upon any senescent changes or on the average life span of a species, but on the intensity of exposure to a carcinogen and to the specific potency of a carcinogen for the particular species. Numerous investigators have shown that young animals react to carcinogenic hydrocarbons as readily as, if not more readily than, adult animals (2, 17, 20, 23).

Rusch and Baumann noted that the latent period of ultraviolet-ray cancer in mice was 3.5 months if the daily period of exposure was 60 minutes. It was increased to 9 months when the exposure period was reduced to 10 minutes. Rabbits and guinea pigs, on the other hand, have proved refractory to the carcinogenic action of ultraviolet rays. The latent period of bladder cancer in dogs fed betanaphthylamine daily is from 18 to 24 months, while it rises to 5 years if the feeding of the chemical is discontinued after 6 months. Fieser and co-workers (6) found that the average latent period of skin cancer in mice varied with different carcinogenic hydrocarbons. It was 2.5 months

for methylcholanthrene, 3.5 months for 3,4 benzpyrene, and 7 months for 1,2,5,6 dibenzanthracene when these chemicals were tested under standardized conditions. Hueper observed that hairless rats, which have a normal life span of about 360 days and a markedly keratotic skin, were definitely less susceptible to the carcinogenic action of ultraviolet rays than normal albino rats having an average life span of 555 days, while both strains were refractory to methylcholanthrene in a benzolic solution applied to the skin.

Additional evidence militating against the fundamental importance of age factors in the production of many human cancers is provided by observations on the epidemiology of penile cancer. The large-scale Jewish experience with circumcision on the eighth day of life indicates this procedure affords complete protection against a subsequent development of penile cancer, and the studies of Schrek and Lenowitz (15) on circumcised American white persons and Negroes suggest that circumcision performed during the first 6 years has a similar protective effect. Circumcision at a later age

(6 to 35 years), on the other hand, does not result in any significant difference in the incidence of penile cancer between circumcised and noncircumcised individuals. Since the interval between circumcision and the appearance of penile cancer ranges from 8 to 40 years with an average interval of 23 years (10), it is evident that the specific cancerigenic exposure in penile cancer apparently takes place during the first 10 to 15 years of life.

The high death rate of cancer of the lung among miners of radioactive ores, which stands at some 70 percent of all deaths for the Schneeberg miners and at some 40 percent for the Joachimsthal miners, cannot be attributed to the existence of a "preferential" type of aging among these population groups. The progressive rise in the incidence of pitch warts and cancers among English pitch workers from 17 percent of the workers after 1 to 5 years of exposure to 100 percent after more than 40 years of exposure (18) provides an additional illustration of the lack of importance of senescent changes in the causation of occupational cancers.

Table 3. Age distribution of occupational cancers

Organ and agent	10–30		31–40		41–50		51–60		61–70		71 and over		Total number
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Skin													
Arsenic	10	8. 7	28	24. 3	35	30. 4	24	20. 9	17	14. 8	1	0. 9	115
Pitch	6	5. 1	14	12. 2	34	29. 6	38	33. 1	20	17. 3	3	2. 7	115
Tar			6	7. 5	14	17. 5	15	18. 7	32	40. 0	18	16. 2	80
Paraffin			6	5. 9	30	28. 8	38	34. 8	29	27. 6	3	2. 9	106
Shale oil			12	17. 8	22	32. 3	23	33. 8	6	8. 9	5	7. 3	68
Solar radiation	2	. 9	8	3. 6	24	10. 7	58	25. 8	76	33. 8	56	25. 0	224
X-radiation			18	51. 4	. 9	26. 1	6	17. 1	0	0. 0	1	2. 9	35
Control	13	1. 8	74	10. 4	125	17. 6	165	23. 2	174	24. 5	157	22. 2	709
Lung													
Asbestos			2	11. 8	7	41. 2	6	35. 3	1	6. 0	1	6. 0	17
Chromate	1	1. 0	11	11. 0	22	22. 0	34	34. 0	21	21. 0	1	1. 0	100
Tar			7	33. 3	12	57. 1	1	4. 8	1	4. 8			21
Ionizing radiation	6	5. 3	30	26. 7	38	33. 6	29	25. 7	10	8. 7			113
Control	99	5. 8	222	12. 2	444	24. 5	609	33. 6	356	19. 6	62	3. 4	1, 792
Bladder													
Aromatic amine	8	3. 8	40	19. 0	63	30. 0	81	38. 6	17	8. 1	1	. 5	210
Control	2	. 8	21	8. 1	59	22. 7	85	32. 8	63	24. 2	29	9. 4	259

Conclusions

Numerous observations made in connection with cancers in general as well as especially with environmental and occupational cancers indicate that neither embryonic cell rests nor senescing tissues play an important or essential role in the development of malignant neoplasms.

Against the existence of causal and direct age relationships to cancerigenesis the following facts may be cited:

1. Only carcinomas but not sarcomas exhibit an incidence rate that significantly increases with age.

2. Cancers of different organs have widely varying age peaks covering the entire life span. Several organ cancers have two or even three distinct age peaks.

3. The distribution of cancers by sex, race, and regions displays a pattern that cannot be reconciled with a uniformly operating age factor.

4. The well-established occurrence of occupational cancers during childhood, the experimental transplacental induction of lung tumors in mice, and the consistent development of occupational and experimental cancers by exogenous carcinogens at predeterminable sites and after predictable periods of exposure strongly indicate that embryonic cell rests account for only the exceptional cancer and that senescent tissue changes are unimportant.

5. Many of the so-called senescent changes in tissues allegedly providing the prepared soil for cancer represent the result of prolonged exposures to specific environmental or occupational cancerigenic factors.

6. Numerous observations on environmental, occupational, and experimental cancerigenesis prove that a long latent or preparatory period precedes the appearance of cancers following an effective exposure to a carcinogenic agent. It is mainly for this reason that the majority of such cancers are observed during the later part of life.

7. The validity of this concept is supported by the fact that the length of the latent period is dependent upon the intensity and duration of exposure to a carcinogenic agent and to its relative carcinogenic potency.

8. The manifestation age of environmental and occupational cancers is directly related to the age at onset of the cancerigenic exposure.

9. The excessive frequency of cancers of certain organs among members of special professions and occupations also suggests that factors other than physiological aging are responsible for the causation of these neoplasms.

The evidence presented supports the view that cancer development in organs or tissues having early, frequent, and prolonged contact with exogenous agents is in most instances not directly or indirectly related to age factors. It appears possible, however, that organ cancers, which may be the result of functional or hormonal disturbances, may, in part, be dependent in their genesis on the action of age factors, because changes in the internal environment associated with and resulting from organic functional impairments and imbalances occur with advancing age.

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Dr. Knutson Appointed Chief Dental Officer

Dr. John W. Knutson was named the new chief dental officer of the Public Health Service by Surgeon General Leonard A. Scheele early in June. Chief of the Division of Dental Public Health until then, Dr. Knutson succeeded Dr. Bruce D. Forsyth on the latter's conclusion of a 4-year tour of duty as chief dental officer.

A member of the commissioned corps of the Public Health Service since 1934, Dr. Forsyth has been assigned to Federal Security Agency Region I in Boston as regional dental officer for the Public Health Service. In his new capacity, Dr. Forsyth will act as dental consultant for the New England area.

Also a commissioned officer since 1934, Dr. Knutson joined the Public Health Service in 1931. He served as dental clinician at Public Health Service hospitals in Chicago, and Norfolk, Va., during his early career. From 1938 to 1940, Dr. Knutson was assigned to the National Institutes of Health, Public Health Service, to conduct research in dental caries. For the next 4 years, he conducted demonstration studies and laboratory research in dental health at the Minnesota State Department of Health. He became chief of the dental section, State Relations Division of the Bureau of State Services, in 1944, where he acted as dental consultant to State health authorities until his appointment as chief of the Division of Dental Public Health in 1949.

Dr. Knutson's predecessor, Dr. Forsyth, served as chief dental officer at various Public Health Service posts between 1934 and 1948, including the U. S. Reformatory at El Reno, Okla., and Public Health Service hospitals and clinics in New York, Fort Worth, Tex., and Washington, D. C.