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Environmental Lung Cancer

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The first evidence indicating the existence of causal relations between environmental factors and the development of cancers of the lung was recorded in 1879, when Haerling and Hesse (66) established the cancerous nature of the lung diseases prevalent among the radioactive ore miners in Schneeberg, Saxony. This discovery of historical importance and great present significance attracted, at its time, little attention because radioactivity was still an unknown fact, and cancers of the lung were comparatively rare before the turn of the century, and, therefore, of little medical interest (Table 1).

TABLE 1. Frequency Rates of Lung Cancers in Autopsy Material, 1852-1900

Author	Period	No of autopsies	Total no carcinomas	Lung cancers	
				Abs no	% of all autopsies
Reinhard	1852-1876	8716	—	5	0.057
Fuchs	1854-1885	12307	—	8	—
Wolf	1877-1884	4172	—	9	0.095
Passler	1881-1894	9246	870	16	0.21
Wolf	1885-1894	7228	—	31	1.83
Perutz	1885-1897	—	—	9	0.428
Marchesani	1887-1896	1946	—	4	0.10
Kikuth	1889-1899	—	—	10	0.26
Felchenfeld	1895-1900	5022	511	22	0.07
Riechelmann	1895-1901	7790	711	27	4.3
Sehr	1899-1903	1741	159	3	3.8
Marchesani	1896-1906	3337	—	6	1.88
					0.17
					0.18

^aReference 140.

When, after World War I, a definite and progressive increase in the relative frequency of lung cancers in autopsy material became apparent (Table II), some thought was given to the possible causes of this phenomenon. Since the widely scattered sources, the topographically irregular appearance, and the relatively short developmental period of these observations did not favor the action of hereditary factors, the main attention in this matter was given to a consideration of various environmental factors which had made their appearance, or undergone marked

changes during the preceding decades. Among the different environmental factors proposed at that time were the numerous cell metaplasia of the bronchial mucosa associated with the influenza epidemic, and pressures to various specific and nonspecific occupational and environ-

TABLE II. Frequency Rates of Lung Cancers in Autopsy Material, 1900-1925

Author	Period	No of autopsies	Total no carcinomas	Abs no	Lung cancers	
					% of all autopsies	% of all autopsies
Reinhard	1900-1905	2002	496	31	6.3	1.5
Seydahr	1900-1906	—	—	—	51	0.67
Karsten	1900-1907	10272	934	32	3.42	0.31
Kikuth	1900-1911	—	—	60	3.8	0.37
Stachew	1900-1911	—	566	12	2.1	—
Probst	1904-1908	—	715	20	2.79	—
Seydahr	1906-1910	2739	255	3	1.13	0.11
Bruege	1907-1913	—	—	—	0.88	0.9
Bruege	1898-1916	12971	1287	60	4.51	0.46
Reinhard	1908-1913	6808	692	33	4.8	0.45
Reinhard	1909-1912	5801	586	29	4.95	0.5
Marchesani	1906-1916	4754	—	6	0.13	—
Rau	1909-1914	4816	552	15	2.7	0.31
Reinhard	1910-1914	2347	363	8	2.2	0.34
Materna	1912-1914	866	48	1	2.08	0.11
Stachew	1912-1914	—	218	11	5.0	—
Probst	1911-1915	3448	389	13	3.34	0.38
Seydahr	1914-1918	—	—	—	11.23	1.01
Assmann	1912-1922	—	—	—	0.19	—
Materna	1915-1917	1667	79	5	7.14	0.35
Brueckwoldt	1914-1919	6083	554	21	3.7	0.36
Rau	1915-1919	5518	580	27	4.8	0.49
Reinhard	1915-1919	3280	337	10	2.9	0.30
Probst	1916-1920	4689	392	24	6.12	0.59
Materna	1918-1920	1609	94	5	5.31	0.31
Kikuth	1912-1923	—	—	146	5.8	0.58
Marchesani	1910-1922	3336	—	10	—	0.3
Stachew	1915-1923	—	755	38	4.0	—
Leharsch	1920-1921	—	8301	458	5.4	—
Seydahr	1919-1923	—	—	—	8.75	—
Reinhard	1920-1924	2429	287	24	8.3	0.99
Materna	1921-1923	1449	75	6	8.0	0.57
Brueckwoldt	1920-1925	6559	892	26	2.7	0.39
Probst	1921-1925	3097	592	36	7.17	0.97
Stachew	1924	749	—	5	4.9	—

(Continued)

mental air pollutants, such as dusts containing silica, soot, smoke, and tobacco; dusts from roads especially asphalted or oiled roads; exhaust fumes of gasoline engines, irritative chemical fumes, vapors, and gases; and war gases. However, no definite or generally accepted conclusions were reached as to the role of these agents in the production of lung cancers and their rise in frequency.

It was not until the third and fourth decade of this century that additional well defined occupational activities and environmental agents were again related to the causation of cancer of the lung and other parts of the respiratory tract: i.e. the nasal cavity, paranasal sinuses, and larynx. Among these additions to the list of environmental respiratory cancers were the lung cancers among chromate manufacturers (1935), of asbestos workers (1935), of arsenic workers (1930), and of coke oven operators (1936), the cancers of the nasal cavity, paranasal sinuses, and lung among copper-nickel smelter workers (1932); the carcinomas of the nasal sinuses among luminous dial painters (1931); the cancers of the nasal sinuses, larynx, and lung among isopropanol manufacturers (1946); and cancers of the larynx and lung among workers exposed to lubricating oil sprays or mists (1936, 1949) (Table III). The most recent and best advertised addition to this list is cigarette smoking.

TABLE III. Occupational Respiratory Carcinogens and Cancers Recorded During Past 75 Years

Agent	Site of cancer	Discovered	Number of recorded cases		
			U.S.A.	Other countries	Total
Arsenic	Lung	1930	7	16	23
Asbestos	Lung	1934	22	66	88
Chromates	Lung	1932	75	65	140
Nickel	Lung	1932	0	84	84
	nares and nasal sinus		0	51	51
Coal Tar	Lung	1936	0	53	53
Petroleum oils	Lung and larynx	1936	7	33	40
	Isopropyl oil		1	0	1
Radioactive chemicals	larynx	1946	4	0	4
	nasal sinus		6	0	6
	Lung		0	625	625
Radioactive chemicals	nasal sinus	1931	3	0	3
	nasal sinus		3	0	3

This impressive evidence on the existence of occupational and environmental respiratory cancers, however, is not generally considered as valid by all parties concerned with such hazards, nor is there any agreement or reliable knowledge as to the relative role which these and other en-

vironmental agents assume in the causation of cancer of the respiratory tract. Thus, the medical director of an important petroleum company recently expressed great skepticism as to the actual merits of the available data on industrial respiratory cancer hazards. He stated, "I have as yet to see a single report in the literature which indicates that the incidence of lung cancer, and I emphasize the word 'incidence,' is higher for any particular industrial group. Even the chromate studies have only shown an increased relative frequency of lung cancer, and hence I feel that until incidence studies have been done, we had better stay away from commenting about lung cancers in industrial workers."

Paralleling this categorical attack on the significance of industry-related environmental and occupational factors in the causation of respiratory cancers is the recent challenge presented by the proponents of the cigarette smoking theory of lung cancer genesis. It is alleged by these investigators, on the basis of statistical evidence, that the great majority of lung cancers—i.e. up to 96%—observed during the last 30 years, as well as the recent rapid rise in lung cancer frequency, are attributable to cigarette smoking and the increase in this habit, respectively (Table IV).

TABLE IV. Statistical Correlations Between Tobacco Smoking and Lung Cancer

Authors	Degree of Smoking Habit Among Lung Cancer Patients (Males)				
	Highly excessive	Very heavy	Heavy	Moderate	Non smokers
					Cigarettes, only, balance pipe and cigars
Schrek <i>et al.</i> (156)	18.3	50.0		12.2	14.6
Wynder and Graham (187)	20.3	30.9	35.2	12.4	1.3
Doll and Hill (42)	5.0	21.0	30.3	38.6	5.1
Breslow <i>et al.</i> (24)	15.3	50.7	19.5	3.5	9.0
Gsell (64)	30.0	37.0	21.0	10.5	2.0
<i>Controls</i>					
Wynder and Graham	7.6	11.5	35.6	30.5	14.6
Doll and Hill	2.1	11.4	30.5	47.1	8.8
Breslow <i>et al.</i>	3.5	34.8	18.8	11.1	30.5

The obvious impression is produced by these far reaching claims that an elimination of the cigarette smoking habit would result, within 15-30 years, in a reduction of the number of lung cancers to a level prevailing before the turn of the century and the advent of the cigarette.

Since the two propositions outlined possess adherents of consequence and are actively and vigorously propagated in both the scientific and lay

press, they deserve serious consideration. The acceptance of either one or both of these allegations is bound to exert a profound influence upon the direction which the control of respiratory cancer hazards will have to take in the immediate future, as well as upon the type of epidemiologic and experimental research work which should be undertaken on this subject during the coming years. Apart from the not unimportant matter of scientific accuracy and validity of these claims, they also pose medicolegal implications of no mean proportions, which are of immediate concern to parties engaged in the prosecution and adjudication of compensation claims. A critical and sober analysis of the evidence available on the causation of respiratory cancers by environmental agents therefore appears to be of some importance and urgency for these reasons, and especially in view of the continued alarming and progressive rise in cancers of the lung in all industrialized countries (Fig. 1).

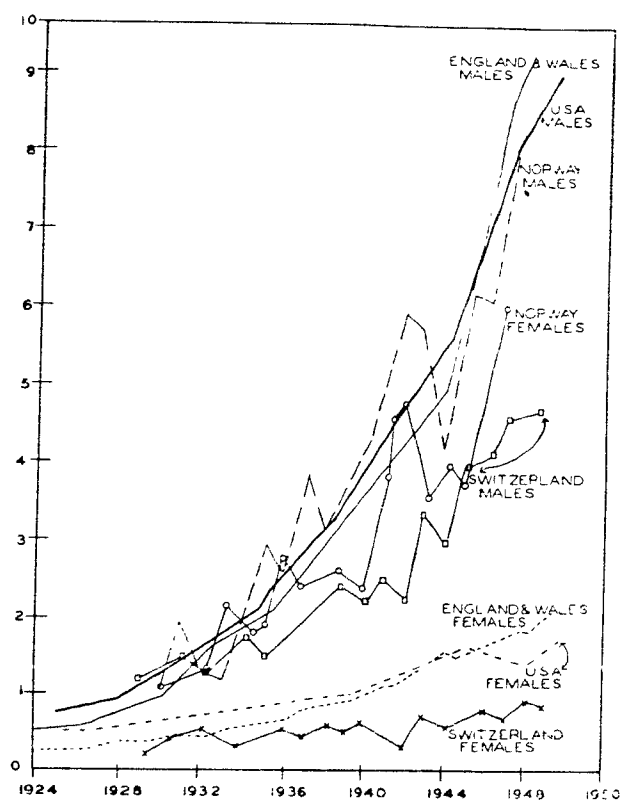


FIG. 1. Comparative trends in respiratory cancer mortality 1924-1950.

Circumstantial Evidence Favoring an Environmental Causation of Lung Cancer

Among the various observations favoring an environmental origin of respiratory cancers and its rise in frequency, there may be cited the marked variations in the time of onset of the latter phenomenon, in its intensity and in its progression in different countries, states, provinces, counties, regions, and communities (Tables V and VI, Fig. 2). While

TABLE V. Lung Cancer Death Rates in 25 States and District of Columbia in 1946 and 1948
Crude Death Rates per 100,000

State	Industrialized States	
	1946	1948
Connecticut	85	111
Illinois	81	82
Maryland	65	84
Massachusetts	104	102
Michigan	57	71
New Hampshire	74	101
New Jersey	97	97
New York	102	119
Ohio	60	73
Pennsylvania	67	84
Rhode Island	87	74
States with Regional Industrialization		
Florida	68	74
Louisiana	65	85
Missouri	73	94
Montana	100	88
Nebraska	57	80
Agricultural States		
Alabama	40	51
Arkansas	36	54
New Mexico	26	30
North Carolina	31	40
North Dakota	56	41
Oregon	41	44
South Carolina	36	37
Washington	51	42
Wyoming	49	36

NOTE. The death rates for the year 1946 were taken from "The American Cancer Society, Inc., 1949, Cancer Death Rates for the United States by Sex and Age," and those for the year 1948 were produced by the Department of Health Statistics.

in Norway, less than 6% of all cancers in males involve the lung, the corresponding figure for Great Britain is about 25%. The onset of the rise in lung cancer mortality did not occur in Italy until about 1930 (1910-1925: lung cancer autopsy rate of all autopsies in Padua and Milan 0.07

TABLE VI. *Incidence of Respiratory Cancer, 1937 and 1947*
Males, Rates for Nine Metropolitan Centers, by
Sex per 100,000 Population^a

Primary site and city	Males			Females			Total		
	1937	1947	Percent increase	1937	1947	Percent increase	1937	1947	Percent increase
<i>Bronchus and Lung</i>									
Atlanta	5.0	13.4	168	1.0	5.0	400	2.9	8.9	207
New Orleans	13.1	39.1	198	2.8	4.2	50	7.6	20.8	174
Dallas	5.9	29.0	392	0.5	6.4	1180	3.1	17.2	455
Birmingham	4.5	18.9	320	2.1	3.9	86	3.3	11.0	233
Denver	9.1	21.9	141	4.2	8.1	93	6.6	14.8	124
San Francisco	15.6	34.3	120	3.9	8.1	108	9.8	20.8	112
Chicago	13.3	29.5	122	4.3	7.0	63	8.8	18.0	105
Pittsburgh	9.7	26.1	169	4.9	5.5	12	7.3	15.6	114
Detroit	12.6	32.0	154	2.3	5.7	148	7.6	19.0	150
<i>Larynx</i>									
Atlanta	1.4	4.0	186	0.3	0.3	—	0.9	2.0	122
New Orleans	11.3	14.9	32	0.4	1.0	150	5.6	7.6	36
Dallas	3.2	5.3	66	1.5	0.4	73	2.3	2.7	17
Birmingham	1.4	4.0	186	0.0	1.3	—	0.7	2.6	271
Denver	2.0	4.1	105	0.0	0.0	—	0.9	2.0	122
San Francisco	4.5	8.8	96	0.2	0.8	300	2.4	4.6	92
Chicago	6.7	7.0	4	0.4	0.6	50	3.5	3.7	6
Pittsburgh	4.4	8.0	82	0.4	0.8	100	2.4	4.4	83
Detroit	3.5	6.4	83	0.4	0.3	—25	2.0	3.4	70

^aBiometrics Section National Cancer Institute

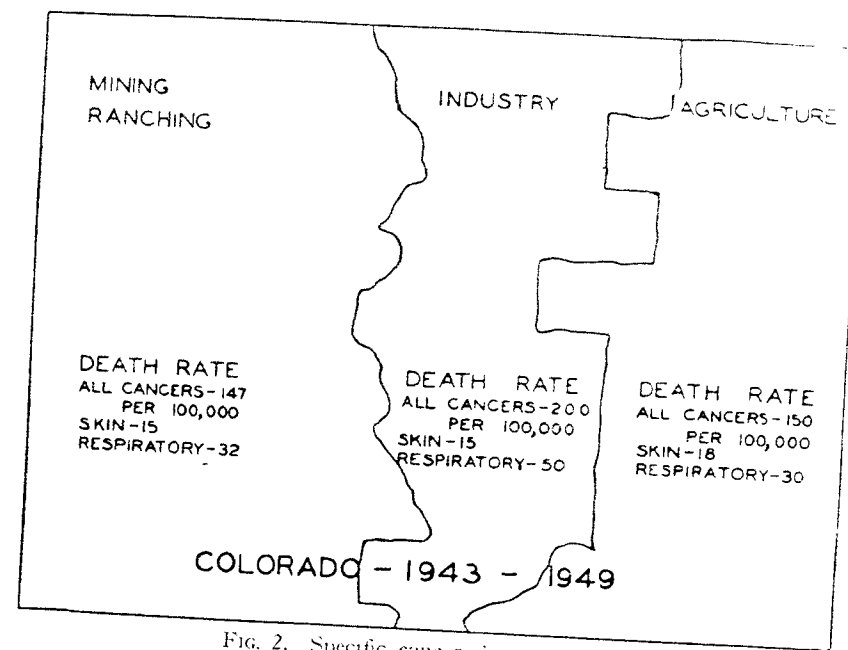


Fig. 2. Specific cancer deaths in males

of these epidemiological findings is indicated by the recent demonstration of 3,4-benzpyrene in the pollutants of the air of several English cities by Waller (180), and of the particulate phase of the air of Los Angeles, California, and of the exhaust of gasoline and diesel engines by Kotin *et al.* (99,100).

TABLE VII. *Lung Cancer Mortality and Population Density*

Groups of adjacent towns over 200,000 occupied dwellings:	
London and Suburban Area	156
Birmingham and Suburban Area	134
Manchester and Suburban Area	159
Liverpool and Suburban Area	162
Leeds and Suburban Area	132
Sheffield with 124,000 occupied dwellings	135
Newcastle and Gateshead with 87,000 occupied dwellings	114
Aggregate of 6 towns with 50,000 to 85,000 occupied dwellings	113
Aggregate of 3 towns with 40,000 to 50,000 occupied dwellings	107
Aggregate of 12 towns with 30,000 to 40,000 occupied dwellings	104
Aggregate of 13 towns with 20,000 to 30,000 occupied dwellings	100
Aggregate of 29 towns with less than 20,000 occupied dwellings	89

^aReference 164

and 0.13%; 1928-1938 in Venice (1.5%). The rise in lung cancer mortality lagged in rural districts of Denmark by ten years behind that of Copenhagen. Stocks (164) found that the local incidence rates of lung cancer in England and Wales during 1921 and 1939, and 1946 and 1948, revealed a general relationship to the extent and density of built up areas as expressions of atmospheric air pollution through smoke from chimneys (Table VII). Similar observations were reported for England and Wales by Kennaway and Kennaway (96) covering the period 1946-1949, and comparing lung cancer mortality rates of Greater London with those of larger towns and rural districts (Table VIII). The etiologic significance

TABLE VIII. *Cancer of Lung and Larynx, England and Wales^a 1946-1949*

Type of community	Lung cancer ratio-number of persons producing one death		Larynx cancer ratio-number of persons producing one death	
	Males	Females	Males	Females
Greater London	100	100	100	100
County borough	129	137	125	55
Other urban districts	160	156	148	59
Rural districts	233	185	170	42

^aReference 96.

This irregular epidemiologic pattern exhibited by lung cancers for different regions and population groups conforms more closely with that shown by industrial developments than with one which might be expected as the result of a carcinogenic action of a single environmental factor, such as cigarette smoking.

This interpretation of the data on the general epidemiologic behavior of lung cancer is supported by evidence on hand on the frequency of these tumors among members of special occupational groups, for some which well defined exogenous carcinogenic contacts are known to exist (Tables IX-XII).

TABLE IX. *Lung Cancer Death Rate per 1,000 Deaths of All Causes for Seven Industrial Groups in Ohio, 1947, Among 5,309 Male Cancer Deaths^a*

Industry	Respiratory cancer
Iron and steel	2.18
Transportation	2.91
Agriculture	0.82
Rubber and plastics	2.34
Stone, clay, glass	0.66
Non-ferrous metal	3.22
Mining and quarrying	1.53
Total	1.76

^aReference 118.

Operating railroad workers inhale carcinogenic polycyclic hydrocarbons contained in the sooty exhaust of diesel engines and coal and oil burning locomotives. The employment ratio of operating railroad workers was 1:4. Thus about 75% of the lung cancers occurred among the operating group representing about 25% of the total number of employees.

Ross (147) recently stated that there occurred during the period 1933 to 1952 an almost tenfold increase in the relative frequency of death from

TABLE X. *Lung Cancer Mortality in Several Counties of Montana 1947-1948^a*

County and total population 1940	Major industry	Number lung cancers		Total cancer deaths	Crude lung cancer		Annual lung cancer death rate 100,000	
		Male	Female		Male	Female	Male	Female
Deer Lodge 13,627	Copper smelting	21	0	21	30.8	0.0	145.7	0
Silver Bow 53,207	Copper mining	27	2	29	22.6	1.5	48.6	3.9
Cascade 41,400	Copper mining	20	5	25	12.7	3.2	46.5	12.3
Goldstream 18,269	Copper smelting	1	0	1	3.0	0.0	3.2	0
None	Agriculture							

^aReference 113. The estimated crude death rate for lung cancer among white males in the entire United States in 1947 is 10.9 per 100,000 population. The workers employed in copper ore mining and smelting inhale dust and fumes of arsenic contained in the ore and released as a by-product during the smelting process.

TABLE XI. *Lung Cancer Frequency Among Operating and Nonoperating Railroad Workers*

Railroad	Period	Total no lung cancers	Lung cancers operating RR workers		Lung cancers nonoperating RR workers		Lung cancers undetermined RR workers	
			No.	%	No.	%	No.	%
A	1940-1950	20	24	83	5	17	---	---
B	1939-1940	104	59	57	15	14	30	20

lung cancer among the members of the Brotherhood of Railroad Trainmen.

Dunner and Hicks (45) recently called attention to two additional specific worker groups, namely boiler scalers and grain dockers, who seemed to have an excessive liability to lung cancer. It may be possible that contact with chromate containing scale, if chromates are used as anti-rusting agents, may account for the observations of boiler scalers. The presence of fungicides or other chemical additives or contaminants may have to be considered in relation to the lung cancer liability of grain dockers.

Conclusive Evidence on Environmental Respiratory Carcinogens

The demonstration of special lung cancer hazards produced by a number of well defined exogenous chemical or physical carcinogens has so far been achieved for only relatively small and circumscribed worker groups. It is well recognized, however, that similar contacts exist for other and often very large industrial groups which either have as yet not been surveyed or about which records of investigations undertaken in the past are not available in published form. Since many of the occupational respiratory cancer hazards extend in some form and to some degree to the general population through contact with industrial wastes released into the atmosphere, with gasoline and diesel engine exhaust, dust from tarred and oiled roads, and the abrasion of rubber tires, or the handling and use of consumer goods (paints, sprays, anti-rusting agents), it can justly be concluded that the actual scope of the environmental respiratory cancer problem may be of a magnitude only faintly discernible from the recorded factual evidence.

General Characteristics of Environmental Lung Cancers

An analysis of the epidemiologic and symptomatic data on environmental respiratory cancers shows that these neoplasms as a group have certain general characteristics.

Exposure Time and Latent Period. In the majority of occupational

TABLE XII. *Occupational Groups With an Excessive Lung Cancer Incidence*

Occupational group	Potential respiratory carcinogens	Investigator
Metal workers, welders, metal grinders and polishers, wire makers, tool and die makers, foundry workers, metal moulders, lathe workers, etc.	Metal dust, lubricating oil mist	Kennaway and Kennaway (96); Turner and Grace (174); Mueller (128); Dublin and Vane (44); Wynder and Graham (187); McLaughlin (122); Breslow <i>et al.</i> (24)
Cigar manufacturers and tobaccoists	Tobacco dust, insecticides, soot	Seyfarth (158); Kennaway and Kennaway (96); Enger (51); Vershys (176); Brinkmann (26)
Engineers, mechanics, machinists, plumbers, etc.	Metal dust, soot, lubricating oil	BECC ^a 1944 and 1952; Gillespie (58); Turner and Grace (174); Mueller (128); Wynder and Graham (187)
Painter, decorators	Metal pigments, coal tar dyes, carbon black, asphalt paints, solvents, vehicles (lacquers, resins, synthetic plastics)	BECC ^a 1944; Mueller (128); Dublin and Vane (44); Fulton (55); Wynder and Graham (187)
Lau workers, road workers, asphalters, pavements, stokers, patent fuel workers, furnace men, foundry laborers, rollers, etc.	Tar and pitch, fumes and dust, soot	Kennaway and Kennaway (96); Fulton (55); BECC ^a 1952; Registrar General (1938); McLaughlin (122)

^aReport of the British Empire Cancer Campaign.

respiratory cancers, the disease is discovered while the individual is still at work; i.e. the exposure time is identical with the latent period. However, there exists reliable evidence gathered from the entire occupational cancer field which proves that the exposure time may be much shorter than the latent period. Therefore, an environmental lung cancer may become manifest many years after exposure to a specific exogenous agent has ceased. An analysis of the final fate of some 150 former chromate workers engaged in chromate production for at least six months, and having passed a latent period of more than four years after discontinuation of their employment, demonstrated that of 25 deaths which have so far occurred in this group, five were caused by cancer of the respiratory tract representing 20% of deaths from all causes. In asbestosis lung cancer the exposure-free interval ranged from several months to 20 years in many cases (182).

From the information available on the length of latent periods for the different types of environmental respiratory cancers, Tables XIII and XIV were prepared which show the interrelations between exposure period and latent period, as well as the years which usually elapse between the onset of exposure and the manifestation of the cancer resulting therefrom.

Attack Rates. The information available on the attack rates of the

TABLE XIII. *Latent Periods of Environmental Respiratory Cancers*

Agent	Lung		Nares and nasal sinuses	
	Average latent period	Range of latent period	Average latent period	Range of latent period
Asbestos	18	15-48	—	—
Chromates	15	5-47	—	—
Nickel	22	6-30	11	3-26
Tar fumes	16	9-23	—	—
Isopropyl oil	—	—	10	6-16
Ionizing radiation	25-35	7-50	25	19-32

*Period expressed in years.

TABLE XIV. *Exposure Time of Environmental Respiratory Cancers*

Agent	Lung		Nares and nasal sinuses	
	Average exposure time	Range of exposure time	Average exposure time	Range of exposure time
Asbestos	20.1	6.0-40 males	—	—
	7.6	0.5-48 females	—	—
Nickel	25	1-33 males	23	3-26

*Time expressed in years.

various environmental respiratory cancers for the populations at risk is defective and inaccurate, with the possible exception of the data on respiratory cancers among chromate manufacturers, isopropyl alcohol makers, and radioactive ore miners. The evidence on hand on attack rates for the various occupational respiratory cancers, moreover, is expressed in terms which cannot readily be brought upon a common denominator. In evaluating the merits of these estimates, consideration, moreover, must be given to the fact that the attack rates are subject to various factors, such as the relative potency of a particular carcinogen, the intensity and duration of exposure, and the accuracy and completeness of records kept especially in regard to former workers who left hazardous operations. The attack rates, therefore, may vary with different groups exposed to the same carcinogen.

The data given in Table XV, therefore, should be regarded as rough approximations designating the magnitude of trends in cancer frequency for special population groups exposed to several particular occupational carcinogens, rather than exact values of incidence, or frequency of respiratory cancers. These attack rates obtained on special worker groups, however, are not applicable to any other worker group which might be exposed to the same agents, nor to the general population which has active respiratory contact with some of them in a mitigated form.

Age and Sex Distribution. Occupational respiratory cancers often follow the general pattern of occupational cancers by exhibiting a trend toward a shift to younger age groups than those characteristic for cryptogenetic cancers of the respiratory organs. It seems that the age at onset of exposure as well as the intensity and duration of exposure in addition to the potency of the carcinogen account for this phenomenon (Table XVI).

A characteristic and significant shift in age distribution of occupational respiratory cancers is demonstrable for lung cancers produced by chrome pigments, tar fumes, and ionizing radiation.

The great majority of occupational respiratory cancers recorded involved males, because only males were employed in the hazardous occupations. The only exception to this observation is offered by the asbestosis cancers of the lung, which affected in a series of 52 cases—for which sex data are available—37 males and 15 females, representing a male-female ratio of 2.5:1 (general ratio 5:1 to 10:1). Equalization of carcinogenic exposure, as represented by asbestosis for the two sexes, thus resulted in a trend toward equalization of liability to lung cancer. These observations which can be duplicated for other carcinogens and sites also do not favor the concept of a sex-related susceptibility to lung cancer.

TABLE XV. Respiratory Cancer Attack Rates by Environmental Carcinogens

Agents	Site of cancers	Incidence in population at risk	Percent of all cancer deaths	Attack rates	
				Morbidity rate	Mortality rate
Per 100,000					
Aromatic hydrocarbons					
Coal tar fumes	Lung	500:100,000	45%		
Petroleum oils	Lung	2000:100,000	55%		
Carbon and silicon polymers	Paranasal sinuses	10:100		134.5 (normal 65)	(13.2-20% asbestos autopsied (0.8-2.4% normal))
	Larynx				
Isopropyl oil	Lung				
Asbestos					
Metals					
Arsenic	Lung				1457 males (10.9 normal)
Chromates	Lung			(42x normal)	146,338
Nickel	Nares Paranasal sinuses Lung	329:100,000 574:100,000		(20x normal)	
Ionizing radiation					
Radioactive ores	Lung				(50-80% of all deaths)

TABLE XVI. Age Distribution of Environmental Lung Cancers

Agent	10-30		31-40		41-50		51-60		61-70		71 & Over	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	
Asbestos	2	4	6	12	11	21	16	32	14	31		49
Chromates	1	1	11	13	22	24	34	38	21	23	1	90
Chrome pigments	-	-	5	60	3	30	1	5	1	5	-	10
Tar fumes	-	-	7	33	12	57	1	5	1	5	-	21
Ionizing radiation	6	5	30	27	38	33	29	26	10	9	-	113
Controls	99	6	222	12	444	24	609	34	356	21	62	1792

The marked and growing predominance of males among lung cancer victims seems largely to be due to the following factors:

1. Males are more extensively employed than females in occupations where known or suspected atmospheric carcinogens are produced and used, and work more consistently and over longer periods of their lives in such occupations.

2. Males predominate in outdoor occupations, especially in urban areas, where they become exposed to carcinogenic pollutants contained in the general atmosphere (effluents of domestic and industrial furnaces, exhaust of gasoline and diesel engines, dust from rubber tires, and asphalted and oiled roads).

3. Males more often than females perform heavy physical labor requiring deep and frequent respiratory movements facilitating the penetration of carcinogenic air pollutants into the distal portions of the respiratory tract, and thereby increasing the frequency and degree of exposure.

4. Males more often than females work through the entire span of their occupational life within urban areas with proven carcinogenic atmospheric pollution, while females to a greater degree than males, stay for larger portions of their lives in the cleaner suburban dormitory communities.

Histologic Types of Occupational Respiratory Cancers. Although the information available on the histologic types of occupational respiratory cancers are quite defective, it is apparent from the data on hand, that among the respiratory cancers recorded as of occupational origin, various histologic types occur, and that there does not exist any relation between a specific etiologic factor and the histologic type of carcinomatous response (93). The numerical relations between the various histologic types of occupational respiratory cancer elicited by different environmental carcinogens are presented in Table XVII.

Carcinomas composed of several histologic types were repeatedly observed [squamous cell-adenocarcinoma with asbestosis (114); six combinations of squamous cell and round cell carcinomas (Schneeberg cancers) (154)].

TABLE XVIII. *Histologic Types of Occupational Respiratory Cancers*

Agent	Organ	Squamous cell carcinoma with or without cornification	Round cell or oat cell carcinoma	Anaplastic or polymorphic carcinoma	Adenocarcinoma
Tar fumes	Lung	3	—	—	2
Nickel	Lung	4	—	3	—
Chromium	Lung	—	2	—	—
Asbestos	Lung	11	2	2	6
Radioactive gases and dust	Lung	14	9	7	1
Nickel	Nares and nasal sinus	3	—	6	1
Radioactive gases and dust	Nares and nasal sinus	3	—	—	—
Isopropyl oil	Nares and nasal sinus	—	—	4	—

It may be mentioned that a multifocal origin of various occupational respiratory cancers (asbestos, ionizing radiation) has been reported by several investigators. This observation may be interpreted as reflecting the marked severity of occupational exposures since multicentric carcinogenic developments are rather commonly observed under the abnormal and extreme exposure conditions practiced in experimental carcinogenic studies.

Causal Mechanisms. Biochemical Reactions of Respiratory Carcinogens. Apart from the rather diffuse causal concepts such as heredity, cell misplacement, and chronic irritation, there have been obtained during recent years data on specific chemical interreactions of respiratory carcinogens with constituents of the host organism. It seems that all of these reactions are common either to several or all of the known respiratory carcinogens and therefore may furnish a scientifically sounder basis for future investigations into the nature and different phases of the actual chemical local and systemic, humoral, cytoplasmic, and nuclear changes which ultimately result into cancerous cellular transformations.

Sulfhydryl Inactivation. During the past two decades various investigators have shown that several carcinogenic substances act upon

sulfhydryl groups, and thereby cause an inactivation of sulfhydryl activated enzymes and disturbances in the cellular redox metabolism (67, 84, 146), and that chemical carcinogens may be inactivated by combining with or inducing oxidation of sulfhydryl groups (33, 67). Such effects have been demonstrated for split products of 2-methylaminoazobenzene (139) as well as for 3,4-benzpyrene (27), and were demonstrated by Hueper *et al.* (88), for ionizing radiation acting upon biologic growth promoting material (embryo extract). Arsenicals are known to combine with and accumulate in tissues rich in sulfhydryl groups (epidermis, hairs, nails).

There thus exists some evidence that certain exogenous carcinogens which produce cancers of the respiratory tract inhibit the metabolic action of free sulfhydryl groups and/or may cause enzymatic and oxidative disturbances. The extensive industrial use of nickel and chromium as catalysts, and the inhibiting action of beryllium on alkaline phosphatase provide evidence suggesting other action mechanisms of carcinogens upon enzymatic activities. There exists, moreover, the possibility that through a direct chemical action these carcinogens may bring about the production of abnormal endogenous substances, such as for instance steroids by an oxidative effect of chromates on cholesterol (53).

Protein Conjugations. Following the successful artificial conjugation of aromatic chemicals and related carcinogens with proteins through azo-, or isocyanate-, or carbanido-linkages and the production of carcinogen-hapten specific immune bodies in the serum of animals injected with such synthetic antigenic complexes (34, 54, 80, 102, 144), attempts were made to demonstrate similar but spontaneously formed carcinogen-protein complexes in the tissues of animals exposed to carcinogens. Fieser (53) suggested that carcinogenic polycyclic hydrocarbons might combine with cell proteins by the opening of an S = S linkage. While the actual existence of protein carcinogen combinations was first shown in connection with hepatoma producing aminoazo dyes (125, 126), Miller (125) succeeded also in demonstrating the formation of protein bound derivatives of 3,4-benzpyrene in the epidermal fraction of mouse skin. It is likely that arsenicals combine with protein bound sulfhydryl groups, and thereby form arsenic-protein complexes which may give rise at times to allergic reactions. The not infrequent occurrence of allergic dermatoses in workers exposed to two additional respiratory metallic carcinogens, namely chromium and nickel, suggests the formation of corresponding protein complexes through linkages of these metals with the carboxyl-, hydroxyl- or sulfhydryl-groups of the amino acids. In fact, recent investigations of Lorscheur (108), as well as Hueper, Johnson and Grogan (90) on

animals injected with mixtures of chromium and nickel compounds in protein solution, have resulted in the production of metal specific antibodies. Attempts at demonstrating similar antibodies in the serum of chromate manufacturers, several of whom had been operated on for cancer of the lung, gave equivocal results. Of the positive precipitin reactions observed in these experiments with human material, antigens prepared with trivalent chromium (chromium acetate) gave, in general, more consistent and stronger reactions than those obtained with antigens containing hexavalent chromium (potassium chromate). Associated studies of Grogan and Oppenheimer (62) on trivalent and hexavalent chromium compounds dissolved in human plasma and tested for the presence of metal protein complexes by the techniques of dialysis, moving boundary, and paper electrophoresis, and light scattering phenomena, provided chemical evidence supporting the immunochemical observations.

Mention also may be made in this connection of the statement of DeNardi *et al.* (37) to the effect that the pulmonary granulomatous reactions seen in berylliosis are attributable to the formation of beryllium protein complexes eliciting an allergic reaction. These more recent observations on the formation of protein complexes by polycyclic hydrocarbons and metals possessing carcinogenic properties lend support to the chemo-allergic mutation theory proposed by Hueper (82) in connection with the development of bladder cancers in dye workers exposed to certain aromatic amines (beta-naphthylamine, benzidine (121)).

Recent studies of English investigators (65, 70), have furnished a new and intriguing concept as to possible combinations of carcinogens with tissue proteins through the postulated formation of cross linkages between carcinogenic chemicals and the macromolecular fibers of chromosomes. This hypothesis was evolved from evidence obtained in the study of carcinogenesis by nitrogen mustards, di-epoxides, polyethyleneimines, and related compounds. In view of the fact that one of the various means by which these substances may exert their specific action in the cells is through polymerization, it is assumed that polymerized epoxide chains might interreact with proteins or nucleoproteins of chromosomal origin, by cross linkage with multipoint attachment, and thereby cause mitotic aberrations. The initial reaction of one of the epoxide groups of monomeric molecules, with the cell component also may start a process of polymerization by being followed by a self-condensation of the free epoxide groups into a polyethenoxy structure.

These concepts are of interest to respiratory carcinogenesis for several reasons. They may have direct application to the development of pulmonary cancers in connection with occupational exposures to silicon

and carbon polymers, namely, asbestos and isopropyl oil (containing polypropylenes and/or isopropyl epoxides (43, 86)). Since it has been shown experimentally that at least one epoxide (1,2,3,4-diepoxybutane) is carcinogenic (71), the observations of Kotin *et al.* (90) concerning the presence of carcinogenic unsaturated aliphatic epoxides in the atmosphere of Los Angeles gain increased importance as to the nature of possible carcinogenic air pollutants in urbanized areas.

Additional potential extensions of cross linking carcinogenic polymers in relation to pulmonary carcinogenesis may result from the proposed medicinal use of polyvinyl alcohol and methylmethacrylate balls for the extraperiosteal plumbage of the pleural cavity for insuring a permanent collapse of the lung because of pulmonary tuberculosis (83, 186). Mention may also be made of the fact that two large molecular polymers, namely, polyvinyl pyrrolidone and dextran, which have recently been introduced as plasma extenders, are in part arrested in the pulmonary capillaries and enter the capillary endothelial lining and interstitial perivascular tissue, thereby creating intimate contact with pulmonary structures. These medicinal uses of various natural and synthetic polymers are of potential significance because of the demonstration of carcinogenic effects (43, 135, 190) produced in mice and rats following an intraperitoneal and subcutaneous implantation of a considerable number of chemically closely related polymers, such as cellophane, polyethylene, polyvinyl chloride, Nylon, acrylic resin, polyamide (E-caprolactam), Teflon, and Silastic. Although there are no observations indicating whether or not these findings in animals may apply to man, it appears to be wise to keep all industrial workers, who may have respiratory contact with fumes, vapors, and dust of these and related polymers in the production and processing of synthetic plastics and textile fibers, under close medical surveillance for a possible development of respiratory cancers. These precautions are also indicated because of the use of some known or suspected chemical carcinogens (nickel carbonyl, aromatic amines) as catalysts and/or antioxidants or curing agents in the manufacture of these polymers (methacrylate plastics, synthetic rubber; epoxyresins).

Because of the similarity of the cytologic alterations, especially chromosomal fragmentation and bridge formation at anaphase, produced by the various aliphatic carcinogens studied by Hendry *et al.* (70, 71) and Haddow (65) to those elicited by ionizing radiation, their action has been called "radiomimetic." It is interesting to note in this connection that ionizing radiation may stimulate depolymerization of macromolecular polymers as well as the formation of cross linkages between polyethylene chains. Whether such effects are active in the production of pulmonary

and nasal sinus cancers in workers exposed to radioactive dust and gases, however, is speculative (179).

The various observations and hypotheses discussed in relation to the possible biochemical changes underlying environmental respiratory carcinogenesis suggest that all agents seem to interact by some mechanism with proteins or nucleoproteins and produce, thereby, abnormal proteins. The significance of these proteinic alterations to the cancerization process, however, is undetermined.

Specific Respiratory Carcinogens and Cancers

The respiratory carcinogens so far recognized differ greatly in their chemical and physical properties as well as in the physicochemical status in which they come in contact with the respiratory tissue. Some are chemical agents, such as various metals or metal compounds (arsenic, chromium, nickel), or minerals (asbestos), or aliphatic organic (isopropyl oil), or aromatic organic compounds (chemical carcinogens in coal tar, pitch, soot, petroleum derivatives). Others exert a carcinogenic effect through physical forces (ionizing radiation), such as the various radioactive chemicals. They enter the respiratory tract in the form of dust, fumes, mists, vapors, and gases. Depending upon the particle size of the dispersed carcinogenic material they may penetrate into different parts of the respiratory tract. If the particles are rather large, they produce mainly cancers in the upper parts (nasal cavity, larynx). They may enter, on the other hand, the deeper portions, such as the bronchi and lung or paranasal sinuses, if they are of very small particle size or take the form of vapors or gases.

METALS. Nickel. Nickel, one of the most industrially important metals, and principally mined in the Sudbury district of Ontario, Canada, finds many uses (alloyed with iron, copper, chromium, aluminum, cobalt, and molybdenum) employed in the manufacture of stainless steel, heat resisting steels, forgings, casts, wires, sheets, structural shapes, tubing, rods, bars, strips, etc.), electroplating, catalysts, ceramic enamels and colors, pigments in paints and inks, storage batteries, etc.

Exposure to nickel fumes and nickel dust of metallic nickel and its compounds or to nickel carbonyl vapors is, therefore, frequent for industrial workers of many types and in many operations.

The first report concerning the occurrence of an excessive number of cancers of the nasal passages (nasal cavity and paranasal sinuses) and of the lungs among workers on the Clydach plant of the International Nickel Company located at South Wales, England, was made by Grenfell (61) in 1932, although the first appearance of these neoplasms among the

nickel refinery workers was noticed in 1924 (9). Subsequent reports dealing with these cancers were made by Stephens (162), Amor (4), Cooper (32), Carozzi (29), and Merewether (124). From 1923 to 1948 inclusive, there were notified with the Chief Inspector of Factories a total of 47 cases of cancer of the nose and 82 cases of cancer of the lung from the nickel works. By the end of 1948, 46 of the nasal cancer and 72 of the lung cases had died. None of the nasal cases and only two of the lung cases had commenced work in the nickel refinery after 1924, when a reconstruction of the plant had been carried out. The average exposure period for the nasal cancers was 23 years (range, 3-26 years), and for the lung cancers 25 years (range, 1-33 years). No cases of cancer of the larynx have occurred, and only one cancer of the nasopharynx was observed at Clydach.

The nasal cancers involved the turbinates, nasal septum, and paranasal sinuses (ethmoids). Of these the majority were of the undifferentiated cell type (six), some showed a squamous cell character (three), while columnar cell carcinomas were uncommon (one). Of the lung cancers, of which histologic studies were available in only four cases, three were of the small cell, pleomorphic type, while one was a squamous cell carcinoma.

Similar observations were recently recorded from a Norwegian nickel refinery, where three cases of lung cancer were seen (109). In one of these cases a squamous cell carcinoma was associated with sarcoid lesions.

Goldblatt and Wagstaff (60) mentioned that so far cancers of the respiratory tract have not been noted among the workers employed at the German nickel refinery at Ludwigshafen, nor has there been observed an unusual frequency of respiratory cancers among the workers of the Sudbury nickel ore mines and smelters in Canada.

Amor (4) pointed out that the majority of individuals employed at Clydach, who developed respiratory cancers, were not exposed to the inhalation of nickel carbonyl, but to that of nickel matte dust, or dust from the nickel matte roaster (109). More recent data communicated by Morgan (127) confirmed this observation, although exposure to nickel carbonyl vapors had occurred more frequently among the affected workers than apparent from the data previously given by Amor. The relatively high incidence of cancer of the nasal cavity, indeed, suggests that a rather coarse particulate dust readily arrested at the region of the turbinates may have been active in the production of cancers at this particular site, while nickel containing vapors or a very small particulate dust most likely account for the cancers of the lung and nasal sinuses.

As to the causative agent, various theories have been advanced. Amor

avored the concept that the inhalation of mist from arsenic containing sulfuric acid used in the refining process was the active carcinogenic agent. It is most unlikely that this is correct because the nickel refinery workers do not suffer from perforated nasal septa, and display no evidence of chronic arsenicism, such as dermatosis and cutaneous cancers, which almost always have accompanied the occurrence of lung cancer among workers exposed to arsenical dusts or fumes.

Amor (4) stated that the refined nickel-copper ores are free from radioactive matter. The respiratory cancers observed among nickel refinery workers thus are not identical in etiology with those seen in miners employed in the radioactive mines of Schneeberg and Joachimsthal.

Workers employed at the roasters, in the nickel carbonyl operation and at other parts of the plant, on the other hand, become exposed to the inhalation of dust, fumes, or vapors containing nickel. Nickel is the common denominator for all of them. It thus is most probable that the respiratory carcinomas observed among nickel refinery workers are reaction products to more or less finely dispersed nickel particles or vapors. There is no evidence available, however, which indicates that the inhalation of nickel in particulate or vaporized form is accompanied by pulmonary changes of a pneumoconiotic nature.

The concept of a nickel etiology of respiratory cancers was tested in animals by Campbell (28), who exposed mice to the inhalation of powdered nickel matte, and observed that these animals had a lung tumor incidence significantly higher than that of the unexposed control mice. The recent experiments of Hueper (85) seem to demonstrate more conclusively the carcinogenic properties of metallic nickel. When pure metallic nickel powder was implanted into the femoral and pleural cavities and in the subcutaneous tissue of rats, cancers developed at the site of injection within 6 to 24 months in about 40% of the surviving rats. Among 49 tumors thus produced among a total of 175 rats, 48 were sarcomas, and 1 was a squamous cell carcinoma (Figs. 3, 4).

Whether or not nickel assumes a carcinogenic role for cancers of other organs and following exposures by other routes is unknown. It may be mentioned, however, that Araki and Mure (5) demonstrated by spectrographic methods, nickel in human and animal cancers of various types and sites. The nickel content ranged from 6.273 mg. kg. of fresh tumor tissue to 0.2 mg. kg.

No assessment of the degree of occupational nickel cancer hazard can be made from the data available, since the number of workers at risk is unknown. Likewise, no definite opinion can be expressed as to the possible existence and extent of respiratory cancer hazards for persons having for

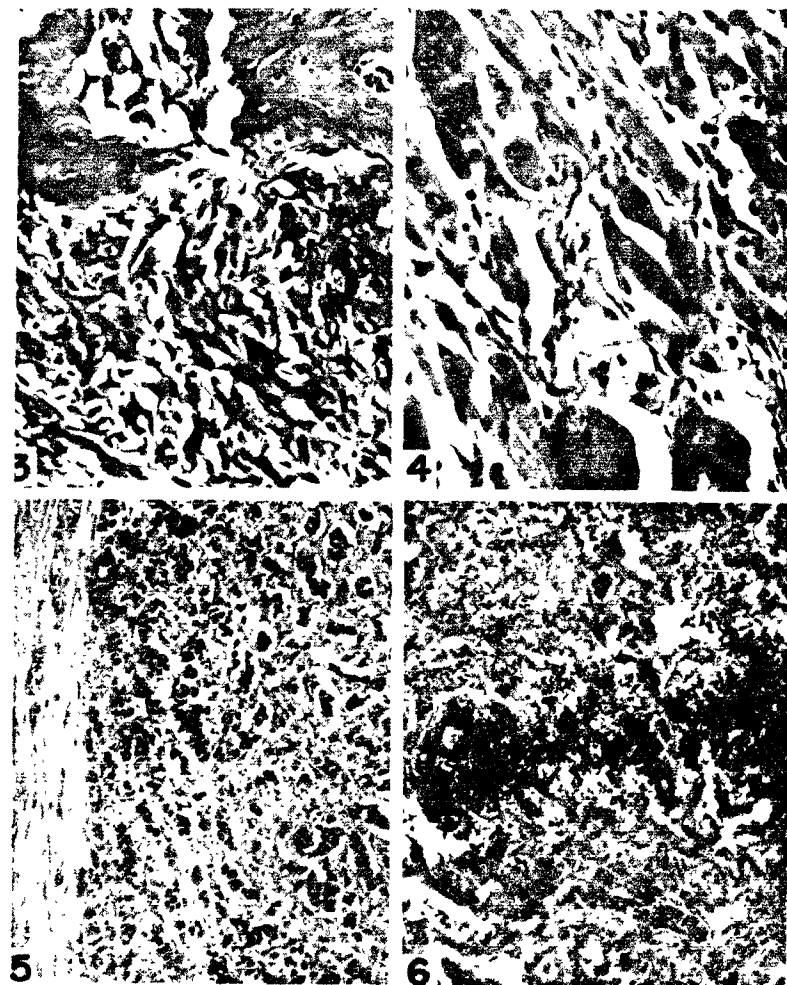


FIG. 3. Osteogenic sarcoma in the thigh of a rat injected with powdered metallic nickel into the femoral vein.

FIG. 4. Myoblastic sarcoma in the thigh of a rat injected into the femoral cavity with powdered metallic nickel.

FIG. 5. Round cell carcinoma of the lung in a chromate manufacturer.

FIG. 6. Massive deposition of chromite ore dust in the lung of a chromate manufacturer.

other reasons contact with dust, fumes, and vapors containing nickel or its compounds.

Chromium. Chromium as a metal, alloy, or compound is used for many purposes in industry. It is for this reason that a large number and variety of workers have contact with chromium and chromium compounds, and that even restricted groups of the general population may possibly become exposed to these agents in the form of dust, vapor, fumes, mist, liquid, and solid (22). Workers most likely to be exposed to chromium and its compounds are acetylene workers, aniline workers, bleachers, blueprinters, chrome workers, chromium platers, chromate manufacturers, chromite miners, crayon makers, dye workers, electroplaters, enamel workers, glass and pottery frosters, glass colorers, pottery glazers, artificial flower makers, battery makers, linoleum workers, paint makers, ink makers, painters, photographic workers, photoengravers, polishers, printers, rubber workers, steel workers, tannery workers, vulcanizers, waterproofer of textiles and paper, welders, users of chromate antirust agents (locomotive attendants and engineers), bitumen and oil refinery workers, plastic manufacturers, vegetable oil processors.

The observation of apparently occupation connected cancers of the respiratory organs, especially the lung, has been limited so far to two types of operations, the production of chromates from chromite ore and the manufacture of certain chromium pigments (zinc chromate, barium chromate, lead chromate). In these operations both water soluble and insoluble chromium compounds are inhaled by the exposed workers. The chemical nature of the actual carcinogenic agent which is responsible for the excessive liability of chromate and chromium color workers to cancer of the lung is still controversial. Although all investigators believe that some chromium compound or compounds are causally involved, it has remained uncertain whether the compounds suspected are hexavalent or trivalent, water soluble or insoluble, monochromates, or dichromates. Water soluble chromium compounds (monochromates, dichromates, and zinc chromate) are most often incriminated. Mancuso and Hueper (119) recently pointed out that it may be more likely that carcinogenic effects are elicited by chromium compounds which are either not soluble in water or only slightly so, because such chemicals when inhaled as dust would be retained and deposited in the lung and thus exert a prolonged effect upon the pulmonary tissues. Such chromium compounds present in a chromate plant would be represented by chromite ore and its early conversion products preceding the formation of monochromates. These little water soluble trivalent chromium compounds occur in the material present in mixers and roasters, and are contained in the slag which usually is stored for future use in the yard area of the plants.

It is definitely surprising that an excessive liability to lung cancer has been established so far only for chromate workers in Germany and the United States (11, 39, 92, 116, 119), and in chrome pigment workers in Germany (9, 10, 63, 104, 130). Bidstrup (19) found a single case of lung cancer upon x-ray examination of the chest of 321 chromate manufacturers employed for more than 10 years in English plants, while no data exist on this point in regard to chromate producing or consuming plants in other countries, such as Switzerland, Italy, and France.

Apart from the excessive frequency of lung cancers among chromate workers which according to American observations range from 13—31 times the normal, an occupational origin of these cancers is strongly suggested by the shift of the age distribution toward younger age groups. This is particularly striking for the lung cancers present among German chrome pigment workers, since 50% of the cancers affected individuals before the age of 40 years when lung cancers of unknown etiology are relatively infrequent.

With the exception of two cases [one cancer of the nares (133); one cancer of the maxillary sinus (60)], the lung was the exclusive site of respiratory cancers observed among chromate workers. The total number of these cancers is at present around 140 cases from all sources. None has been reported as originating from nasal septum ulcers (Fig. 5).

Chromium pneumoconiosis seems to accompany the development of cancer of the lung in chromate and chrome pigment manufacturers. It is uncertain, however, whether the pneumoconiotic plays an essential or modifying role in the specific cancerization process or whether it is merely a phenomenon of coincidental coexistence (Fig. 6).

While the attempts of Gross and Koelsch (63), and Campbell (28) to produce lung cancer in mice by their exposure to chromate dust were unsuccessful, Schinz (153) and Vollmann (177), who implanted powdered chromium metal into the femoral cavity of rabbits, observed, after more than 3 years, one animal with cancer of the lung and one with cancer of the femur. In a series of pilot experiments recently conducted, guinea pigs, rats and mice were exposed to the inhalation of chromite ore dust at a concentration of 155 γ /liter of air for 5-6 hours day, 4 days/week, for a total of 18 months. 3 of the 6 Wistar rats showed tumors involving respiratory organs. One rat had a squamous cell carcinoma (Fig. 7) originating in the paranasal sinuses and invading and dislocating the eyeball, two additional rats showed, at autopsy, sarcomatous growths involving the mediastinal lymph nodes and lungs. There was much black pigment within the thickened interstitial tissue. The lungs of three guinea pigs revealed on histologic examination a marked proliferation of the

bronchiolar epithelium which often occluded the bronchiolar lumina by the formation of cellular plugs consisting of oval and spindle shaped, hyperchromatic epithelial cells. These cellular masses extended in places into the adjacent alveolar lumens forming polyps, coatings or solid casts. These changes were widely distributed in the lungs which showed, moreover, a scattering of dark brown to black amorphous pigment located especially in the subpleural zone, and within a fibrous and thickened interstitial tissue (Fig. 8).

Arsenic. Arsenicals represent a by-product, or waste product of the smelting of many ores (copper, zinc, silver, cobalt, antimony, iron, bismuth, nickel, tin, and lead). Arsenicals are present in the smelter fumes past decades, as insecticides, fungicides, and vermicides (sheep and cattle dip, grasshopper bait, rat poison) as well as a herbicide, especially for clearing railroad rights of way. Arsenicals are applied as sprays to orchards and vineyards, and are dusted from airplanes upon cotton, corn, soybean, and potato fields. They are employed as wood preservatives, in the manufacture of glass, lead-base alloys, dyestuffs, bronzing, and paint pigments, and medicinal and cosmetic preparations.

While the causal role which arsenic plays in the production of cancers of the skin on the basis of chronic arsenicism of occupational, medicinal, or environmental origin has long since been firmly established, it is of rather recent date that exposure to arsenicals has seriously been considered as a principal causal agent of cancers of the mucous membranes, such as those of the bronchi, stomach, and bladder. Indeed, today there exists as yet only highly suggestive but not conclusive evidence linking cancer of the lung with an occupational exposure to arsenical dust. However, in almost all cases of lung cancer for which such claims were made, there existed stigmata of chronic arsenicism in the form of arsenic dermatosis, with or without skin cancers. Since the inhalation of arsenical dust and fumes produces, rather frequently, the development of perforated nasal septa, as well as chronic irritative conditions of the bronchi, thereby creating a symptomatic cancerigenic pattern similar to that seen in chromate workers, the existence of a causal relationship between cancer of the lung and chronic arsenicism appears under such circumstances to be a reasonable conclusion. Chest and x-ray examinations of 40 workers employed in an arsenic smelter revealed a mild degree of pneumoconiosis (152).

Although Saupe himself did not discover any evidence of lung cancer among the workers studied—even though they often were afflicted by hyperkeratoses of the skin and perforated nasal septa—he cited the autopsy

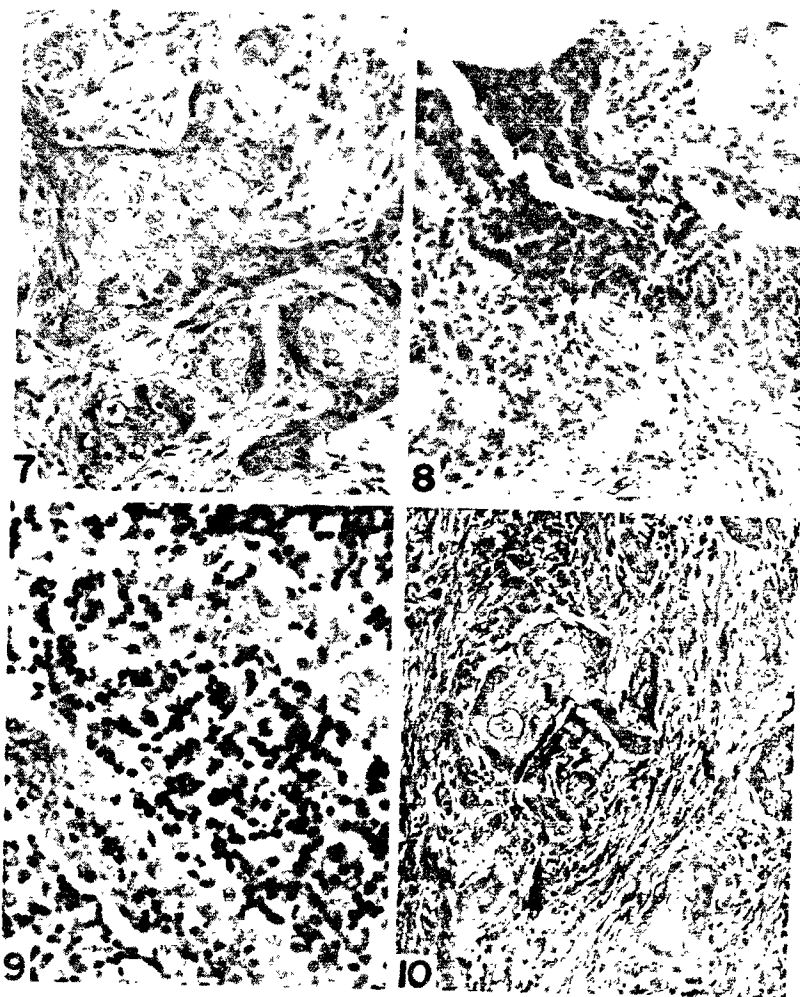


FIG. 7. Squamous cell carcinoma originating in the nasal sinus of a rat inhaling for 18 months chromite ore dust of a particle size below 4 μ .

FIG. 8. Massive proliferation of the bronchiolar epithelium in a guinea pig exposed for over 18 months to chromite ore dust.

FIG. 9. Anaplastic carcinoma of the nasal sinus in an isopropanol manufacturer.

FIG. 10. Squamous cell carcinoma with asbestos bodies in the lung of an asbestos textile worker.

observations previously made by Schmori (154) on two arsenic smelter workers who died with cancer of the lung (170). Four additional cases of lung cancer in sheep dip workers with arsenic dermatosis noted in one of these were reported by Merewether (123), while Hopkins and Van Studdiford (79) observed in a farmer living near a cotton field sprayed with insecticides, arsenical dermatosis, epitheliomas, and cancer of the lung. The occurrence of 5 cases of lung cancer (79, 123), among only 24 individuals suffering from occupational arsenical dermatosis and epitheliomas caused Neubauer (132) to wonder whether this is mere coincidence, because only two cases of lung cancer were observed among 143 cases of medicinal arsenic cancers of the skin (150), or under occupational conditions, whether the irritation of the respiratory tract by arsenical dust was responsible for the phenomenon.

Henry (72), commenting on the occurrence of skin cancers among sheep dip workers (1910-1923), recorded the occurrence of two additional cases of lung cancers among ten workers of this group having cutaneous cancers. He mentioned, moreover, the presence of cancers of the left foot, abdominal wall, and lung in a furnace man of a sodium arsenite factory. Analyzing the mortality experience of a sheep dip factory, Hill and Faning (74) found that 7, or 31.8%, of the 22 cancers causing death among members of this group were located in the respiratory organs, while 3, or 13.6%, were situated in the skin. There were during the period 1910-1943 a total of 75 deaths from all causes. The proportional excess of cancer deaths was mainly attributable to an excessive frequency of cancers of the lung and skin which were confined to workers in the chemical processes and were absent among members of the general group who would be unlikely to be exposed to any specific hazard. Perry, Bowler, Buckell, Druett, and Schilling (137) concluded from the clinical evidence obtained that after many years of exposure to arsenicals these sheep dip workers may develop a squamous cell carcinoma in the bronchus.

The most recent addition to epidemiologic investigations on arsenic cancer was made by Snegireff and Lombard (161) studying cancer deaths among employees of several metallurgical plants of unidentified type. Of the total of 109 deaths from all causes recorded during the last 25 years, twelve were due to cancer of all sites and of these, six were located in the lung. The investigators concluded from this evidence that "there are indications that biologically the human race made the adjustment to arsenic in the environment and that only rarely, when associated with other contributing endogenous factors such as systemic disease, or possibly factors such as radiation, it may be capable of upsetting the biological equilibrium;" and further "that the handling of arsenic trioxide in the industry

does not produce a significant change in the cancer mortality of the plant employees; hence other factors in addition to arsenic must be considered significant in the causal relationship to cancer." In view of the fact that 50% of all cancer deaths among employees of one plant surveyed were caused by cancer of the lung, the observations made in fact confirm a carcinogenic action of inhaled arsenic trioxide upon the tissues of the lung of the exposed workers. This interpretation of the data of Snegireff and Lombard is supported by the high incidence of lung cancer among the population of several counties in Montana where copper smelters and mines were operated for many years creating an occupational and environmental pollution of the atmosphere and soil with arsenicals. Prolonged inhalation of arsenical dust and fumes appears to produce an increased liability to cancer of the lung.

However, the existence of such connections should be acknowledged only when there existed at some time, clinical and if possible, histo- and biochemical evidence of chronic arsenicism. In view of the absence of any such evidence associated with chronic arsenicism among the nickel refinery workers affected by cancers of the nasal cavity, paranasal sinuses and lung, among excessive tobacco smokers with cancer of the larynx and lung, it is most unlikely that exposure to arsenic dust, fumes, and vapors plays any role in the production of respiratory cancers in members of these population groups.

Beryllium. Beryllium is a metal which has found significant industrial use only since about 1920. It was not until about 1940 that beryllium and its compounds were extensively employed for numerous purposes and products (beryllium-copper; beryllium-aluminum, and beryllium-nickel alloys; glass; phosphors in fluorescent lamps and neon tubes; atomic energy products; ceramics, refractories; x-ray tube windows; vitreous enamel; radio tubes; textile fibres; gas mantles).

Hardy (68) noted as a conservative estimate that there occurred up to September 1951 between 300-400 cases of acute beryllium poisoning and at least 200 cases of the chronic variety in the United States which resulted in the fluorescent lamp industry in a mortality of about 25% among the ill workers. It is remarkable, moreover, that chronic berylliosis has appeared not only among exposed workers, but also among persons living in the neighborhood of fluorescent lamp factories and inhaling their beryllium effluents (49, 50).

It is noteworthy that beryllium apparently once inhaled is retained over a long period of time in the human body, since beryllium was detected in the urine up to ten years after cessation of exposure (97) and has been demonstrated in the lungs of rats one year after the inhalation

of beryllium oxide (46) as well as in their bones (13, 165) where it may replace calcium. Experiments of Aldridge, Barnes, and Denz (2), moreover, have shown that beryllium ions react rapidly with certain tissue proteins and form complexes with plasma proteins when introduced into the blood. These complexes protect the beryllium from being precipitated by phosphate ions.

Gardner (57) in 1946 reported the production of osteogenic sarcomas in rabbits injected intravenously with insoluble beryllium containing powders (beryllium phosphate, zinc beryllium silicate). Other investigators subsequently confirmed these results with the same and other beryllium compounds (beryllium oxide, beryllium silicate, metallic beryllium) introduced into rabbits by the intravenous or respiratory routes (160, 14, 76, 129, 75, 47, 13). The preparatory period for the sarcoma was from 11-24 months. Commenting on the successful production of osteogenic sarcomas in rabbits after inhalation of beryllium oxide, Dutra, Largent, and Roth (47) noted the fact also that the bones of persons dying with berylliosis contained not inconsiderable amounts of beryllium. Barnard (12) and Dutra *et al.* (47) suggested that osteogenic sarcoma from compounds of beryllium "might possibly be another industrial hazard."

In 1948, Hueper (87) proposed that the sarcoid pulmonary manifestations of berylliosis might be followed by outright malignant lesions in the lungs. The recently reported successful production of bronchogenic carcinomas in the lungs of rats which inhaled over periods of more than one year, dust of soluble and insoluble beryllium compounds (178) makes the appearance of such delayed malignant sequelae in man a distinct possibility.

Comments on Respiratory Metal Cancers. The evidence presented demonstrates that some metals and metal compounds when inhaled as dusts, fumes, mists, or vapors are capable of producing cancers in various parts of the respiratory tract. Pneumoconiotic changes precede and accompany such developments when chromium compounds are inhaled, while such lesions have not been reported following the inhalation of nickel compounds and are apparently of minor nature after the inhalation of arsenicals. Although the respiratory introduction of beryllium compounds leads in animals to the development of progressive granulomatous pneumoconiotic alterations which may become complicated in rats by bronchiogenic carcinomatous manifestations, no such malignant sequelae has been reported as yet in human berylliosis.

Whether or not respiratory metal cancers may develop after the inhalation of other metals represents a problem deserving serious consideration

especially where such metals are widely used or have attained major industrial importance only in recent years.

RELATION OF INHALATION OF SILICON AND CARBON POLYMERS TO RESPIRATORY CANCER

The second group of respiratory carcinogens is composed of chemical agents of rather diverse composition, but sharing the characteristic that they may form or occur as polymers. The principal evidence suggesting the existence of "polymer cancers" has come from experimental observations. The so far known or suspected carcinogenic polymers are either polymerized carbon compounds or silicon compounds.

Cancers of the respiratory tract in man seem to be causally related to both varieties of polymer carcinogens.

Isopropyl Oil. Through the recent discovery of cancers of the paranasal sinuses, larynx, and lung among isopropanol manufacturers, the occurrence of carbon-polymer cancers has probably been extended to man. Isopropyl oil, i.e., the crude liquid from which isopropyl alcohol is distilled, and which is a slightly turbid, viscous liquid, turning, upon standing, slowly into a brownish to blackish tarry material, contains polypropylene compounds as well as propylene ether which may be oxidized into propylene peroxide and propylene epoxide having a tendency to polymerize. Polypropylene, merchandised as Opponol K, is used commercially as an oil for cable filling.

Workers employed in isopropanol manufacture have been exposed to the inhalation of vapors, mist, and dust of isopropyl oil, escaping from leaky pipe connections, defective pumps, and gaskets, or spilled on the floor at the occurrence of breaks in pipelines and during repairs on pipes, pumps, and stills. Weil, Smyth, and Nale (183) reported that between 1928 and 1950, a total of seven neoplasms affecting various parts of the respiratory tract [nasal sinuses (four), larynx (two), and lung (one)] came to observation among 71 employees or in 8.4% who worked more than five years in the isopropanol plant (Fig. 9). Since the occurrence of an excessive number of respiratory cancers among isopropanol manufacturers has not been limited to one particular plant, it can be concluded that isopropyl oil, and thus possibly polypropylene compounds, represent a human carcinogen.

Asbestosis. Asbestos differs from the ordinary giant molecular crystalline silicates, not only in its chemical and physical properties, but also in the anatomical aspects of the pneumoconiosis produced by it. In contrast to the tridimensional polymerized silica crystals in which no oxygen atoms are left carrying charges to attract positive ions, asbestos consists

of giant fibrous molecules composed of polymerized silico-oxygen tetrahydra which are arranged in chains or bands. Canada furnishes about 75% of the world production of asbestos. Canadian asbestos, because of its long fibers, is especially suitable for textiles.

The co-existence of asbestos with cancer of the lung was first reported by Lynch and Smith (115) in 1935 (one case), who recorded later three additional cases (114, 115). Similar observations have subsequently been recorded from the United States (77, 78, 93, 166); Canada (30, 38, 149); England (36, 59, 69, 124); Germany (9, 20, 21, 81, 106, 134, 184). To this number must perhaps be added the eight cases of cancer of the lung complicated by asbestosis which Kennaway and Kennaway (96) discovered in an analysis of the death certificates of males registered between 1921 and 1938, and the series recorded by Wyers (188).

There were 37 males and 15 females among the 52 cases for which information on sex was available. The male: female ratio is thus 2.5:1, which represents a marked shift toward the female side when compared with the usual sex ratio of 5:1 to 10:1 for lung cancers of unknown etiology. Equalization of carcinogenic exposure as represented by asbestosis, for the two sexes, thus resulted in a trend toward equalization of liability to lung cancer.

Additional support for a causal relation between asbestosis and cancer of the lung is derived from the fact that Merewether (124) found among 266 cases of asbestosis observed from 1924-1946, 31 cases of co-existing cancer of the lung (13.2%), while there were 91 cases of lung cancer with an average age of 59.4 years among 6,884 cases of silicosis (1.32%), which came to autopsy. Wedler (182) noted that asbestosis cancer of the lung occurred in 14 cases or 16% of 92 cases of asbestosis on which necropsies were performed, whereas the normal rate of lung cancer in autopsy material was estimated to be 2-6%. (Table XVIII-41a).

The histologic types of lung cancers observed do not essentially deviate in their relative frequency from those seen in cancers of unknown etiology. There were 22 squamous carcinomas (Fig. 10), 7 oat cell carcinomas, 4 anaplastic carcinomas, and 6 adenocarcinomas.

The evidence on hand has convinced the West German Government to make asbestosis cancer of the lung a compensable disease (169).

Comments on Respiratory Polymer Cancers. While the fundamental concept of "polymer cancers" is a tentative one and needs to be supported by additional evidence, the available data are sufficiently important to require serious attention from both a scientific and practical viewpoint. The rapidly expanding industrial production and industrial and general use of natural and synthetic polymerized substances in plastics, films,

TABLE XVIII Causes of Death Among Male Asbestos Workers Compared with the Mortality Experience of All Men in England and Wales^a

Cause of death	No. of Deaths		Test of significance of difference between observed and expected (Value of P)
	No. observed	Expected on E. and W. rates	
Lung cancer ^b	11	0.8	< 0.000001
Other respiratory diseases (included pulmonary tuberculosis) and cardiovascular diseases:			
with mention of asbestosis	14	—	} > 0.001
without mention of asbestosis	6	7.6	
Neoplasms, other than lung cancer	4	2.3	} < 0.1
All other diseases ^c	4	4.7	
All causes	39	15.4	< 0.000001

^aR. Doll

^bIncluding one case with pulmonary tuberculosis

^cIncluding two cases (benign stricture of esophagus and septicemia) in which asbestosis was present, but was not thought to have been a contributory cause of death

rubbers, textiles, synthetic plasma expanders, etc., brings a considerable part of the working population in direct contact with chemicals of this type. It seems to be advisable, therefore, to study these population groups during the coming decades for the occurrence of cancers, particularly those affecting the respiratory system.

RELATION OF INHALATION OF COMBUSTION AND DISTILLATION PRODUCTS OF COAL AND PETROLEUM TO RESPIRATORY CANCER

The third major group of recognized, suspected, or potential occupational respiratory carcinogens is composed of substances containing specific carcinogenic aromatic hydrocarbons, and being derived from the incomplete combustion, distillation, catalytic cracking and hydrogenation of coal, petroleum, shale, natural gas, and similar carbonaceous matter. The carcinogenic hydrocarbons are especially contained in the higher boiling fractions of coal tar, pitch, creosote oil, anthracene oil, soot, carbon black, fuel oils, lubricating oils, and crude paraffin oils. The inhalation of dusts and mists of these materials results in their partial retention in the lung and in the production of anthracosis, bituminosis, or chronic oil pneumonia.

Combustion and Distillation Products of Coal. The apparent in-

nocuousness of coal and possibly graphite dust as respiratory carcinogens, is not shared by the incomplete combustion distillation and hydrogenation products of coal (pitch, tar, soot, creosote oils, anthracene oils, tar oils, and the highly viscous oily and tarry fractions obtained by the direct hydrogenation of coal employed by the Bergius process). Recent observations made among generator gas oven workers in Japan, Canada and England (35, 41, 95, 96) indicate that an exposure to coal tar fumes produces an excessive liability to lung cancer. The Japanese investigators found within a 6-year period, 21 cases of lung cancer among generator oven workers, who were exposed to the inhalation of hot tar fumes when stoking the coal. An excessive lung cancer rate was absent among workers employed in other parts of the steel mills. The general incidence of lung cancer among the generator gas workers was 5/1,000 workers employed. Seven of these 21 lung cancers occurred in workers 40 years or younger (33%, against 18% in cryptogenetic lung cancers). The exposure time varied from 9 years to 23 years, the average being 16.6 years. Similar observations were recently made among Canadian gashouse workers. Of 14 cases of cancer among retort house workers, six were due to cancer of the lung, one to cancer of the larynx and one to cancer of the ethmoid sinuses (57% cancers of the upper and lower respiratory tract).

It is likely that similar lung cancer incidence rates may exist among American tar workers. Following a visit with a tar distillery where, among the 300 workers during an 8-year period, some 25 skin cancers and more than 80 pitch warts had been observed, there was found one case of lung cancer. Subsequent inquiries made by company officials brought the number of lung cancers in this and other tar operations to 6 cases of cancer of the lung. Similar exposures exist for the carbon electrode workers in aluminum production plants, where workers have developed cancers of the skin as the result of contacts with petroleum "carbon" tar fumes.

From the evidence available, it appears that the inhalation of tar fumes sustained by workers of certain operations (coke ovens, generator gas plants, gas plants, tar distilleries) seem to have an excessive liability to cancer of the respiratory tract. It is not unlikely that a more thorough and competent analysis of the death records of other worker groups, which have so far been found to lack such tendencies, might extend the types and number of tar and pitch workers having an abnormally high respiratory cancer rate.

Petroleum and Shale Oil. In addition to skin contact with carcinogenic petroleum derivatives many workers are also exposed for occupational reasons to an inhalation of oil mist or fumes (workers in paraffin pressing

operations, certain groups of oil refinery workers, spinners, metal lathe workers, foundry workers, metallurgical workers, printers, etc.). In spite of this established occupational respiratory exposure to petroleum and shale oils, it was only recently that two or three cases of occupational oil pneumonia among such workers were placed on record, although such conditions have rather frequently been observed after repeated medicinal instillations of mineral oil containing nasal drops (oil aspiration pneumonitis, or paraffinoma of the lung). In fact, two cases of cancer of the lung apparently developing on the basis of a medicinal mineral oil pneumonia have been described (151, 185).

The occupational evidence available or published on this aspect is rather scanty and in part controversial. Kennaway and Kennaway (96) found a relatively high ratio of laryngeal, but not of pulmonary cancer in mule spinners, who inhale a spray of carcinogenic shale oil lubricating the spindles. Southam (167) noted that mule spinners occasionally develop multiple primary cancers involving the stomach or the lung in addition to cancers of the skin. Scott (157), on the other hand, stated that he had not observed a single case of lung cancer among shale oil workers.

Huguenin, Fauvet, and Bourdin (91) who analyzed a series of 112 lung cancers for possible etiologic factors, found that 18 or 16% were metallurgical workers exposed to the inhalation of nebulized lubricating and cutting oils, eight were chauffeurs, five mechanics, and one was an engineer. They concluded that their observations indicated an excessively high frequency of lung cancer among workers exposed to vaporized or nebulized lubricating oil. While the study of Gafafer and Sitgreaves (56) on cancer morbidity and mortality among the male employees of an oil refining company did not reveal any abnormal liability of the members of the occupational group to cancer of the lung, this judgment may have to be revised at least for certain types of refinery workers according to more recent and scrutinizing observations. Roesch (145) observed three primary cancers (skin, stomach, and lung) in a paraffin worker. Touraine and Bour (171) also attributed the development of pulmonary cancer among certain worker groups to lubricating oil mists. Such exposure conditions may account also for the excessive lung cancer mortality among male metal grinders observed by Turner and Grace (174).

In one large American oil refinery, the employees of the paraffin pressing operation showed not only a highly excessive incidence of scrotal cancer and furnished 43.8% of all cancers recorded among all workers, but also 56% of all lung cancers, although they represented about 12% of the total worker population.

Since oil soot as a waste or commercial product has been found to be

carcinogenic and to contain known carcinogenic hydrocarbons, a thorough and competent survey of occupational groups particularly exposed to the inhalation of soot (operating railroad personnel, stokers, carbon black manufacturers, rubber, paint and ink makers, painters, soot burners, printers, diesel engine drivers, electrode manufacturers, smudge pot operators, phonographic record makers) is an urgent necessity.

Comments on Respiratory Aromatic Hydrocarbons. At the present time, exposure to tar, pitch, asphalt, heavy fuel oils, lubricating and cutting oils, soot from domestic furnaces, incinerators, industrial power plants, oil refineries, steel plants, metal smelters, carbon black factories, oil dumps, and smudge pots, as well as to the effluents of diesel and gasoline engines represents the most widespread occupational and environmental contact with carcinogenic material.

Since our civilization and economical life has been built around the production and use of the basic carbonaceous substances and their derivatives, it does not seem feasible to attain complete protection against exposure to these carcinogenic chemicals with the preventive and prophylactic engineering and sanitary measures practical and economical at the present time. There is, however, no doubt that a great deal remains to be done in this respect and that we are still rather far removed from having the maximal amount of possible reduction in exposure to the respiratory cancer producing hydrocarbons contained in the various carbonaceous substances mentioned.

RELATION OF INHALATION OF RADIOACTIVE AGENTS TO RESPIRATORY CANCER

Up to some ten years ago, occupational exposure to radioactive agents was limited to relatively small groups of industrial and professional workers [miners and refiners of radioactive ores, industrial and medical consumers of radioactive substances (gas mantle manufacturers, luminous dial painters, radio tube makers, physicists and their assistants, radiologists and their assistants)]. Since the advent of successful atomic fission and the ready production of synthetic radioactive substances, the number and variety of individuals who have occupational contact with radioactive matter have rapidly and greatly increased [uranium and thorium ore miners, smelters and refinery workers, atomic energy plant employees, military personnel, agricultural, biologic, medical, chemical metallurgic, oil, pharmaceutical, and other industrial research workers employing radioactive isotopes, as well as operators handling directly or indirectly such materials or technical devices giving off ionizing radiation (radioactive

static eliminators), sewage disposal workers, paper, and textile manufacturers, etc.]

The "mala metallorum" causing death at an early age of the miners in the ore mountains of Saxony was first described by Agricola (1) during the early part of the sixteenth century, and was subsequently mentioned by other investigators. However, it was not until 1879 that its malignant neoplastic character was correctly recognized (66) (Fig. 11). This judgment was subsequently confirmed (6, 8-10, 18, 23, 25, 40, 98, 103, 105, 131, 143, 148, 154, 170, 175, 181). Although the miners of the uranium ore mines in Joachimsthal (Czechoslovakia) also were suffering from a fatal lung disease similar to that observed among the cobalt ore miners in Schneeberg, Saxony, it was not until 1926 that the cancerous nature of the pulmonary disease among these miners was recognized (111). Additional confirming evidence was provided later by Beutel (17); Ziel (189); Sikl (159); Saupe (152); Peller (136); Pirchan and Sikl (138); Baader (10); Behounek and Fort (16).

Evidence supporting a radioactive origin of the lung cancers among these two groups of miners was provided by the observation of lung cancers among employees of radium refineries and radium laboratories. Löwy (111) reported the occurrence of two such cases among the workers employed in the laboratories of the Joachimsthal mines, where the ores are refined and the purified material is tested. One of the cases had chronic radiodermatitis, leukemia, and lung cancer. A similar observation was recorded by Teleky (170) and Neitzel (131) in a German technician of a radium laboratory. The cancerous lung was found to be radioactive. Four cases of lung cancer have recently been observed, according to Baader (10), among the workers employed in the radium ore processing plant in Belgium, where the occurrence of such complications were previously said to be absent (117). Perhaps the development of a bilateral alveolar carcinoma of the lung in a woman 16 years after the intravenous injection of 75 cc. of thorotrast may also supply suggestive evidence by the medicinal use of radioactive material arrested in the lung. Mention may also be made in this connection of a report relating the occurrence of carcinomas of the paranasal sinuses in three luminous dial painters. The dial painters not only ingested radioactive material which became deposited in the bones and produced there the development of osteogenic sarcomas, but they also inhaled this matter (7).

The attack rate of lung cancer among the Schneeberg miners has consistently been between 75 and 80% since 1879, while that of the Joachimsthal miners has been stated to range from 40-50%, although this incidence rate may be too low considering the recent statement of Baader

(10) who noted that during the period 1930-1943, a total of 180 cases of lung cancer were acknowledged as compensable occupational diseases and that in 1929 there were only 323 miners employed at Joachimsthal. Considering the fact that the exposure and latent period of lung cancer in Joachimsthal miners ranges from 13-23 years, it may justly be assumed that these lung cancer cases originated in a miner population of approximately 300-400 members working at these mines between 1920 and 1930. The exposure and latent period at Schneeberg is stated to vary from 15-18 years for the majority of the cases, but to be occasionally as short as seven years (10, 142).

Measurements of the radioactivity of the Schneeberg and Joachimsthal mines have demonstrated that in both places, mine air and dust have an excessive degree of radioactivity surpassing many times the maximal tolerance dose [Joachimsthal 30 times (15, 16, 103, 112, 136, 141, 163, 172)]. Similar, if not even more serious exposure conditions exist in most of the mines situated on the Colorado Plateau where uranium ore miners inhale not only radon, but its solid daughter elements and excrete polonium in the urine (31, 168).

Kahlau and Rajewski (94) and Schraub and Kahlau (155) subjected mice to the inhalation of radon. Many of the animals developed bronchial lesions characterized by an atypical epithelial lining as well as pulmonary adenomas (in 7 of 12 mice of the test series, against one in the control series). While they concluded from this evidence that the radioactive origin of lung cancers in Schneeberg and Joachimsthal miners was confirmed, it seems to be advisable to consider the evidence obtained by these investigators as highly suggestive but not conclusive because great variations in the incidence rate of lung tumors occur among different groups of mice belonging to nonbred strains.

Similar observations have been reported by Lorenz, Heston, Eschenbrenner, and Deringer (110) as well as by Henshaw, Riley, and Stapleton (73). These investigators found that mice exposed to ionizing whole body radiation revealed in addition to leukemia and ovarian tumors an increase in the number of pulmonary neoplasms. Of greater significance in this connection are the findings of Lisco and Finkel (107), who found in rats inhaling an aerosol of radioactive cerium, metaplastic, and neoplastic proliferations of the bronchial epithelium. Similar results were obtained with plutonium brought into the lungs of rats. Since uranium ore miners inhale not only radon and radium dust, but also uranium which may be retained in the lungs, Hueper, Zuefle, Link, and Johnson (89) injected metallic uranium powder dispersed in lanolin into the pleural and femoral cavities of rats and obtained sarcomas at the sites of injection.

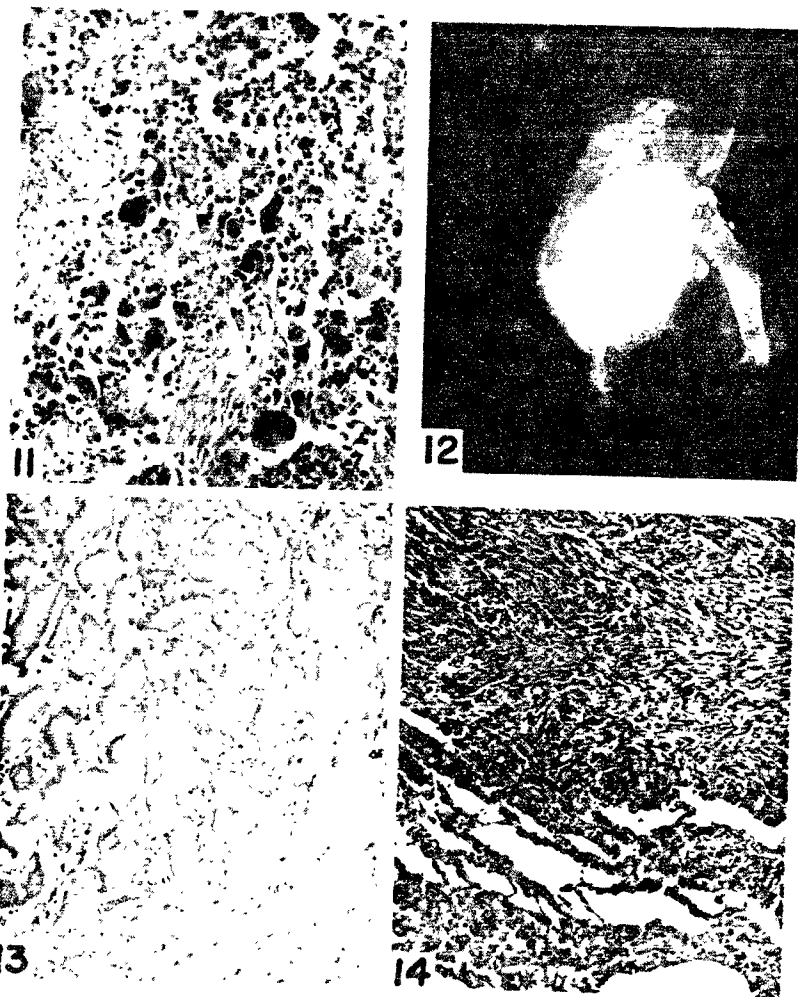


FIG. 11. Anaplastic carcinoma of the lung of a cobalt ore miner of the radioactive mines at Schneeberg, Saxony.

FIG. 12. X-ray picture of a bone forming sarcoma of the femur of a rat following the intrafemoral deposition of powdered metallic uranium, visible in clumps in and around the tumor.

FIG. 13. Bone forming sarcoma of the femur of the rat shown in Fig. 12. The tumor formed metastases in the lung.

FIG. 14. Spindle cell sarcomatous metastasis in the lung of a rat with a primary sarcoma of the thigh developing after the intrafemoral deposition of powdered metallic uranium.

tion in 13 or 24% of the 60 rats used (Figs. 12, 13, 14). Evidence thus produced shows that focal accumulations of uranium which is an alpha-radiation emitter may exert a cancerigenic action upon the surrounding tissues, but it does not discriminate between the influence of metal toxicity *per se* and radioactivity in the genesis of these lesions.

From a critical evaluation of the epidemiologic, clinical, and experimental evidence available, it appears that a prolonged inhalation of radioactive gases and or dust may elicit in man pulmonary cancers (52, 120). In commenting on the production of lung cancer by atmospheric carcinogens, an editorial (*Lancet*, 1952) (48) remarked, "radioactivity of Joachimsthal mines is stated to be thirty times the tolerance dose. It is scarcely surprising, therefore, that in the past more than half the miners died of lung cancer." It stands to reason that this effect on the lungs of workers will prevail wherever similar conditions of exposure to radioactive gases and dust exist.

Comments on Respiratory Radioactive Cancer. The rapidly growing production and use of radioactive material, and, thereby, conditioned increased potentiality of inhalation of radioactive gases and dust for certain occupational groups and possibly, also, for parts of the general population determine the scope and significance of respiratory cancer hazards which may result from such exposures. Since the attack rate of lung cancer from this source is very high, according to past experience with miners of radioactive ores, a competent assessment of the degree of exposure to radioactive dust, mist, and gases by worker groups and neighborhood population is essential wherever radioactive material is produced or handled. The available information supports the view that the simultaneous inhalation of siliceous dust, causing the development of a silicosis in individuals mining or processing radioactive ores, does not represent a condition which favors the production of lung cancers, or fundamentally modifies their course once they have become established (86).

Summary and Conclusions. The reported evidence leaves no doubt that there exist an appreciable number of well defined chemical and physical agents which are responsible for the occurrence of cancers of the lung and other parts of the respiratory tract among members of certain occupational groups. The epidemiologic data available on these occupational respiratory cancers indicate that some of them possess a high carcinogenic potency. Since environmental contact with these agents also exists for members of other and in part, very large occupational groups as well as for the population in general, especially its urban component, it can justly be assumed that such exposures account for an undetermined number of respiratory cancers occurring among them. The validity of

this conclusion is supported by the statistical and epidemiologic data recorded on the relative frequency of cancer of the lung among different countries, states, regions, communities, urban and rural areas, and large occupational groups. The problem of occupational respiratory cancer, therefore, is not of speculative nature but a widely recognized and well established reality, which deserves serious consideration not only by members of the medical profession and of public health agencies, but also by the representatives of industrial management and labor. The general evidence as to the recording of occupational cancers as well as the rather recent discovery of most of the respiratory carcinogens make it likely that the scope of the industry related lung cancer problem is much larger than indicated by the number of cases as yet reported and the types of carcinogens so far recognized. Epidemiologic data and medical considerations, moreover, do not support the view that the causation of lung cancer and its recent phenomenal rise in frequency are attributable to the action of one single environmental factor and its recent entrance into the human environment, respectively. It seems rather that various factors have been responsible for these developments and have contributed to different degrees to these events in different population groups and at various times. An effective future containment of the environmental respiratory cancer hazards depends upon the widest dissemination of the existing data as well as on the acquisition of additional information by adequately conducted surveys supported by properly integrated experimental work.

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Problems Arising From a Study of Tumor Host Relations

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To refreshen your memories, and perhaps add something to clarity, I would like to define and discuss tumor-host relations for the purpose of this paper. We regard tumor-host relations (or, in the older terminology, "systemic effects of tumors") as those changes produced in tissues, remote from the tumor, in which no evidence of metastatic malignant cells is found. These effects may be anatomical or biochemical in nature. We have added more recently that they should be divorced from the effects of inanition and anemia.

As our knowledge of tumor-host relations increases, and some understanding is obtained of the mechanism of their production, we may be able to talk about primary and secondary effects. For example, the involution of the thymus gland seems to be secondary to an increased activity of the adrenal (9). Thus adrenal hyperactivity would be classed as a primary effect and the thymus involution as secondary. But it is probable that the hyperfunctional adrenal is due to increased pituitary activity. The adrenal then becomes secondary and the thymus tertiary. It may be that the introduction of the terms primary and secondary would be useful in organizing the expanding body of our knowledge, but they will be only relative terms, to be discarded as progress is made.

The study of tumor-host relations may be classified into three approaches to the problem: (a) the description of different types of effects produced by the tumor, a routine, but necessary catalogue; (b) attempts to understand how these effects are produced in the complexities of the mammalian organism; and (c) defining the prime cause of the effects. Sufficient is now known of (a) so that more work and information are needed about (b) and (c), particularly about the latter. There is evidence to support the concept that some material is released into the blood stream from the tumor (1, 21), or on the other hand that some component necessary for the normal function of tissues is abstracted from the blood by the tumor (30). No one has produced a typical tumor bearing rat by the chronic administration of a tumor extract.

A final word about specificity—anyone who works in the field is aware that none of the effects described to date are specific for cancer; indeed if this were so the basis for a diagnostic test for cancer would be established! It is probable that the literature on diagnostic tests for cancer has yielded more to the tumor-host studies than to cancer diagnosis (7).