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A Quest Into The Environmental Causes Of Cancer Of the Lung



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Introduction

To be scientifically acceptable, any theory on the etiology of lung cancer must reflect a critical, balanced, and competent analysis of the entire epidemiological, medical, and experimental evidence concerning the types and environmental distribution of and contacts with all known or suspected exogenous agents incriminated in respiratory carcinogenesis for

environmental, occupational, or medical reasons. It is only through such scrutiny that significant and worthwhile information may be obtained as to the relative role which the various individual respiratory carcinogens have played and are playing in the production of lung cancer. The following facts and observations form an important and integral part of such an assessment.

General Epidemiological Considerations

A real, definite, and progressive increase in the frequency of lung cancer started in most industrialized countries around the turn of the century (tables 1-3), that is, at a time when cigarette smoking was still a habit of minor significance (Probst; Berblinger; Grosze, Kahlau; Fischer; Lickint). This rise was first clearly recognized by pathologists of Central Europe during the early 1920's through a study of necropsy data collected during the first two decades of the 20th century and was subsequently confirmed and elaborated upon by biostatistical investigations from America and Europe which mainly used cancer mortality data (fig. 1).

Published records indicate that this development revealed marked variations in the time of onset of lung cancer, in its relative degree of severity, and in its progression rate for different localities and countries. In Germany, for instance, an increase in the incidence of lung cancer was first noted in Saxony and Central Germany only. As late as 1931, Fischer reported that lung cancer represented 11.3 percent of all cancers in Saxony against 6.6 percent in the rest of Germany. In Denmark, according to Clemmesen, a rise in lung cancer frequency was still doubtful during the first three decades of the 20th century and only became

definite after 1930. Similar observations as to a late appearance of this increase were made in Italy. There still exist striking differences in the lung cancer mortality rates of different countries and different regions of the same country (fig. 2). In England, for instance, 25 percent of all cancers in males involve the lung; the corresponding figure for Norway is less than 6 percent.

Similar discrepancies exist for lung cancer morbidity rates for different metropolitan areas in the United States as well as for their relative progression rates (table 4). Another example of the existence of striking regional variations in lung cancer frequency is presented by the remarkable differences in lung cancer mortality rates between urban-industrialized areas and rural districts. This has been demonstrated for England and Wales and for the United States, where lung cancer death rates were found to be consistently higher in urban areas than in rural areas (tables 5-7, figs. 3 and 4). Such observations have been made in Ohio, New York, and Connecticut (Mancuso, McFarland, and Porterfield; Levin, Kraus, Goldberg, and Gerhardt) and were reported from England and Wales by Stocks; Kennaway and Kennaway; Fulton; and Philipps. Stocks reported the comparative mortality ratios for males in

Table 1. Frequency rates of lung cancers in autopsy material (Probst)

Author	Period	Number of autopsies	Total carcinomas	Absolute No.	Lung cancers	
					Percent of all cases	Percent of all autopsies
1852-1900						
Reinhard	1852-76	8,716		5		0.057
Fuchs	1854-85	12,307		8		.065
Wolf	1877-84	4,172		9		.21
Passler	1881-94	9,246	870	16	1.83	.17
Wolf	1885-94	7,228		31		.42
Perutz	1885-97			9	1.27	.10
Marchesani	1887-96	1,946		4		.26
Kikuth	1889-99			10		.07
Feilchenfeld	1895-1900	5,022	511	22	4.3	.24
Riechelmann	1895-1901	7,790	711	27	3.8	.39
Sehrt	1899-1903	1,741	159	3	1.88	.17
Marchesani	1886-1906	3,337		6		.18
1900-1925						
Redlich	1900-05	2,002	496	31	6.3	1.5
Seyfahrt	1900-06				5.1	.67
Karrenstein	1900-07	10,272	934	32	3.42	.31
Kikuth	1900-11			90	3.8	.37
Stachelin	1900-11		566	12	2.1	
Bejach	1904-08		715	20	2.79	
Probst	1906-10	2,739	265	3	1.13	.11
Seyfahrt	1907-13				6.88	.9
Briese	1898-1916	12,971	1,287	60	4.51	.46
Bejach	1908-13	6,808	692	33	4.8	.45
Bejach	1909-12	5,801	586	29	4.95	.5
Marchesani	1906-16	4,754		6		.13
Rau	1909-14	4,816	552	15	2.7	.31
Berblinger	1910-14	2,347	363	8	2.2	.34
Materna	1912-14	866	48	1	2.08	.11
Stachelin	1912-14		218	11	5.0	
Probst	1911-15	3,448	389	13	3.34	.38
Seyfahrt	1914-18				11.23	1.01
Assmann	1912-22					.19
Materna	1915-17	1,667	70	5	7.14	.35
Breckwoldt	1914-19	6,083	554	21	3.7	.36
Rau	1915-19	5,518	580	27	4.8	.49
Berblinger	1915-19	3,280	337	10	2.9	.30
Probst	1916-20	4,989	392	24	6.12	.59
Materna	1918-20	1,609	94	5	5.31	.31
Kikuth	1912-23			146	5.8	.58
Marchesani	1916-22	3,336		10		.3
Stachelin	1915-23		755	38	4.9	
Lubarsch	1920-21		8,301	458	5.4	
Seyfahrt	1919-23				8.75	
Berblinger	1920-24	2,429	287	24	8.3	.99
Materna	1921-23	1,049	75	6	8.0	.57
Breckwoldt	1920-25	6,359	892	26	2.7	.39
Probst	1921-25	3,697	502	36	7.17	.97
Stachelin	1924	749		5	4.9	

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Table 2. Fre

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46-49, with deviations from the average mortality rate set at 100, as follows:

Groups of adjacent towns with over 200,000 occupied dwellings:	
London, East Ham, West Ham, Croydon...	156
Birmingham, Smethwick, Walsall, West Bromwich.....	134
Manchester, Salford, Stockport.....	159
Liverpool, Bootle, Birkenhead, Wallasey...	162
Leeds, Bradford, Halifax.....	132
Sheffield, with 124,000 occupied dwellings.....	135
Newcastle and Gateshead, with 87,000 occupied dwellings.....	114
Aggregate of 6 towns, each with 50,000 to 85,000 occupied dwellings.....	113
Aggregate of 3 towns, each with 40,000 to 50,000 occupied dwellings.....	107
Aggregate of 12 towns, each with 30,000 to 40,000 occupied dwellings.....	104
Aggregate of 13 towns, each with 20,000 to 30,000 occupied dwellings.....	100
Aggregate of 29 towns, each with less than 20,000 occupied dwellings.....	89

In Ohio, for the years 1947-51 (Mancuso, McFarlane, and Porterfield), the standardized

mortality ratios for lung cancer mortality of selected sites among white males 25-64 years of age in urban and rural counties were:

Metropolitan counties (8).....	122.9
Urban counties (7).....	81.8
Rural counties (73).....	68.6

The standard mortality ratio is

$$\frac{\text{Observed deaths}}{\text{Expected deaths}} \times 100.$$

The type of county is defined, according to degree of urbanization, as follows: Metropolitan county—containing cities with 1950 populations of 100,000 or more (91 percent urban); urban—containing cities with 1950 populations of 50,000-100,000 (66.2 percent urban); rural—containing communities with 1950 populations below 50,000 (41.4 percent urban).

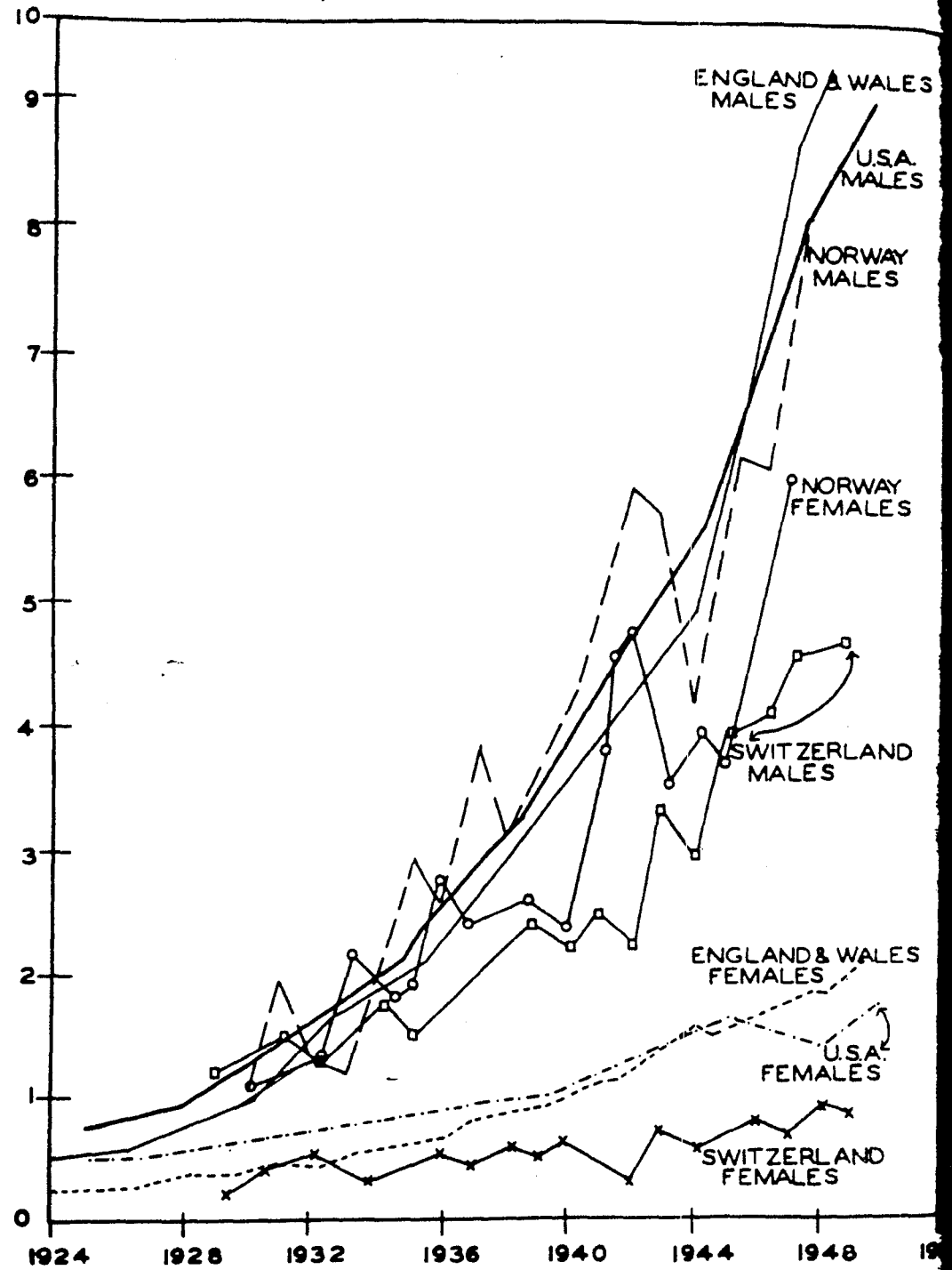
Curwen, Kennaway, and Kennaway only recently recorded fresh evidence supporting earlier observations. The new evidence indicated the existence of positive correlations between population density in England and Wales and mortality from cancer of the lungs

Table 2. Frequency rates of lung cancers in autopsy material of German pathological institutes, 1906-52¹

Author	City	Period	Percentage of lung cancers among all cancers	Sex	
				Male	Female
Fischer-Wasels.....	Frankfurt.....	1906		1.6	0.97
Simross.....	Goettingen.....	1906-12	2.59		
Schairer and Schoeniger.....	Jena.....	1910-14	2.2		
Peters.....	Berlin.....	1913-17	6.2		
Koch.....	Duesseldorf.....	1920-23	3.61		
Gerbe.....	Zwickau.....	1924-27	12.9		
Buschbek.....	Dresden.....	1924-31	19.79		
Dormanns.....	Germany.....	1925-33	13.0		
Simross.....	Goettingen.....	1927-31	9.83		
Peters.....	Berlin.....	1927-31	15.4		
Gerbe.....	Zwickau.....	1928-31	13.0		
Koch.....	Duesseldorf.....	1931-40	12.28		
Weber and Knoll.....	Frankfurt.....	1932	13.9		
Schairer and Schoeniger.....	Jena.....	1932-39	12.0		
Fischer-Wasels.....	Frankfurt.....	1938		12.94	2.38
Koch.....	Duesseldorf.....	1942-45	21.86		
Knorr.....	Leipzig.....	1945-48	13.0		
Emminger and Einsalt.....	Bavaria.....	1945-48		21.4	4.8
Koch.....	Duesseldorf.....	1946-47	26.23		
Fischer.....	Jena.....	1946-48	13.0		
Koch.....	Duesseldorf.....	1948	35.53		
Weber and Knoll.....	Frankfurt.....	1951	28.6		
Kahlau.....	Germany.....	1952		23.4	5.4

¹ From Kahlau.

Figure 1. Comparative trends in respiratory cancer mortality, 1924-50.



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Cancer of the Lung

of males and females and cancer of the larynx of males, but not of females. This relation is even apparent when comparing relative lung cancer death rates in the United States and England with the relative population density in these countries. Whereas, in the United States, with a population of 45 persons per square mile, 1 lung cancer death occurs per 6,600 inhabitants, in England these figures

stand at 755 persons per square mile and 1 cancer death per 3,300 inhabitants.

It has recently been observed that the lung cancer death rate for white males living in the downtown area of Pittsburgh is excessively high—twice the rate for males living elsewhere in the city. It is somewhat uncertain whether this observation carries the same implication as the observations made in Ohio and in England and Wales. Such an interpretation is suggested

Table 3. Lung cancer rates in necropsy material of various German institutes of pathology for the period 1895-1925

Period	Total cancers	Lung cancers	Percent of lung cancers among all cancers	Range	Average
1895-1905	2,801	115	4.1	1.9-6.2	1.9-6.2
1906-15	7,475	283	3.8	2.1-5.0	2.1-5.0
1916-25	15,431	832	5.2	3.0-7.0	3.0-7.0

Figure 2. Age-adjusted death rates for respiratory cancer per 100,000 white males in the United States, 1950. (Lew)

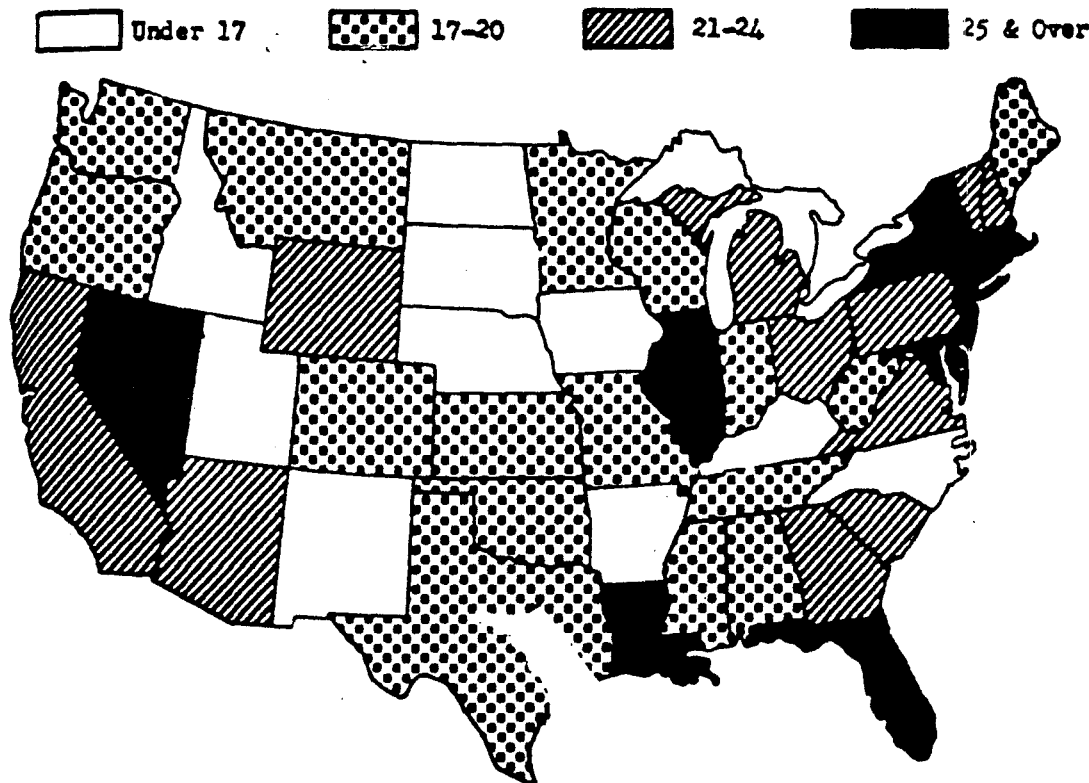


Table 4. Incidence of respiratory cancer, morbidity rates per 100,000 population for 9 metropolitan centers by sex, 1937 and 1947

Primary site and city	Morbidity rates								
	Males			Females			Total		
	1937	1947	Percent increase	1937	1947	Percent increase	1937	1947	Percent increase
Bronchus and lung:									
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	.5	6.4	1,180	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	13.8	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
Larynx:									
Atlanta.....	1.4	4.0	186	.3	0.3		.9	2.0	122
New Orleans.....	11.3	14.9	32	.4	1.0	150	5.6	7.6	36
Dallas.....	3.2	5.3	66	1.5	.4	73	2.3	2.7	17
Birmingham.....	1.4	4.0	186	.0	1.3		.7	2.6	271
Denver.....	2.0	4.1	105	.0	0		.9	2.0	122
San Francisco.....	4.5	8.8	96	.2	.8	300	2.4	4.6	92
Chicago.....	6.7	7.0	4	.4	.6	50	3.5	3.7	6
Pittsburgh.....	4.4	8.0	82	.4	.8	100	2.4	4.4	83
Detroit.....	3.5	6.4	83	.4	.3	-25	2.0	3.4	70

by the fact that the white male inhabitants also had an abnormally high skin cancer death rate (Patno). This is in agreement with the general experience demonstrating the dual role played by many occupational carcinogens, such as arsenicals, coal tar, petroleum derivatives, and radioactive substances in the production of both cutaneous and respiratory cancers.

An additional expression of this urban-rural pattern of lung cancer rates is contained in the recent report of Lew, who found that these rates were 30 to 50 percent higher among industrial policyholders of the Metropolitan Life Insurance Company than among males holding general policies. Lew found, on the other hand, that such differences did not exist for female holders of the two types of policies. He pointed out that industrial policyholders represent, for the most part, urban wage earners and their families in the lower-income brackets and include a high proportion of men engaged in manufacturing, mechanical industries, mining, transportation, and personal service. In contrast, the general policyholders are drawn mostly from middle- and higher-income groups engaged in nonhazardous occupations.

The apparent causal significance of these epidemiological findings has been demonstrated by several investigators. Appreciable amounts of 3,4-benzpyrene have been demonstrated by Waller and Cooper (R. L.) among the air pollutants of English cities; by Kotin and associates in the particulate phase of these atmospheric constituents in Los Angeles, and in the exhaust fumes of gasoline and diesel engines (tables 8 and 9). It has been estimated from these figures by Blacklock, Kennaway, Lewis, and Urquhart that about 16 mg. of 3,4-benzpyrene

Table 5. Cancer of lung and larynx, England and Wales 1946-49 (Kennaway and Kennaway)

Type of community	Lung cancer ratio ¹		Larynx cancer ratio ¹	
	Males	Fe-males	Males	Fe-males
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

¹ Number of persons producing 1 death.

Table 6. Lung cancer death rates in 25 States of the United States, 1946 and 1948, crude death rates per 100,000

State	1946	1948
Industrialized States		
Connecticut.....	8.5	11.1
Illinois.....	8.1	8.2
Maryland.....	6.5	8.4
Massachusetts.....	10.4	10.2
Michigan.....	5.7	7.1
New Hampshire.....	7.4	10.1
New Jersey.....	9.7	9.7
New York.....	10.2	11.9
Ohio.....	6.0	7.3
Pennsylvania.....	6.7	8.4
Rhode Island.....	8.7	7.4

States with regional industrialization		
	1946	1948
Florida.....	6.8	7.4
Louisiana.....	6.5	8.5
Missouri.....	7.3	9.4
Montana.....	10.0	8.8
Nebraska.....	5.7	8.0

Agricultural States		
	1946	1948
Alabama.....	4.0	5.1
Arkansas.....	3.6	5.4
New Mexico.....	2.6	3.0
North Carolina.....	3.1	4.0
North Dakota.....	5.6	4.1
Oregon.....	4.1	4.4
South Carolina.....	3.6	3.7
Washington.....	5.1	4.2
Wyoming.....	4.9	3.9

The death rates for the year 1946 were taken from "The American Cancer Society, Inc., 1949. Cancer Death Rates for each State in the United States by Site," those for the year 1948 were produced by the National Office of Vital Statistics.

Table 7. Lung cancer mortality rates, per 1,000 deaths by sex, in Austria, 1954 (Herbich and Neubold)

Community	Total	Males	Females
Vienna.....	32.7	59.0	7.8
Cities 60,000-1,000,000.....	18.2	31.6	5.0
Cities 20,000-60,000.....	18.4	32.3	3.9
Remainder of Austria.....	10.3	17.3	3.7

Figure 3. Cancer of the lung in males aged 25 years and over, England, 1921-30. Reproduced by permission of the British Empire Cancer Campaign.

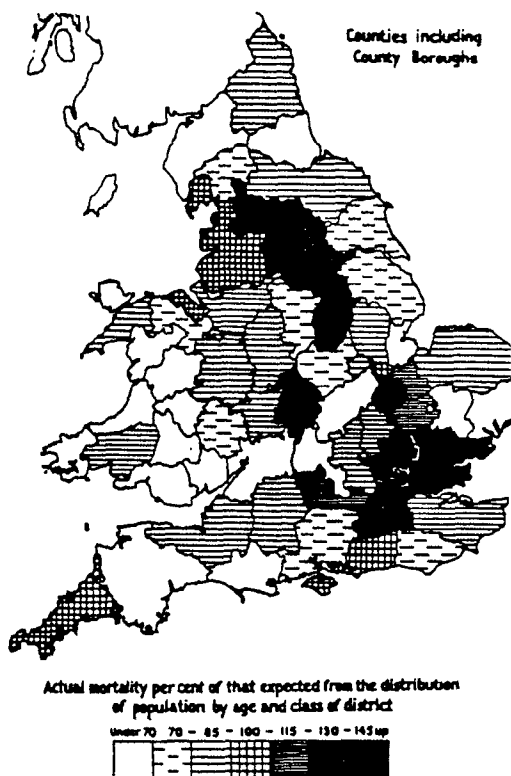


Figure 4. Observed and expected lung cancer deaths in urban and rural Ohio, 1947-51. (T. F. Mancuso)

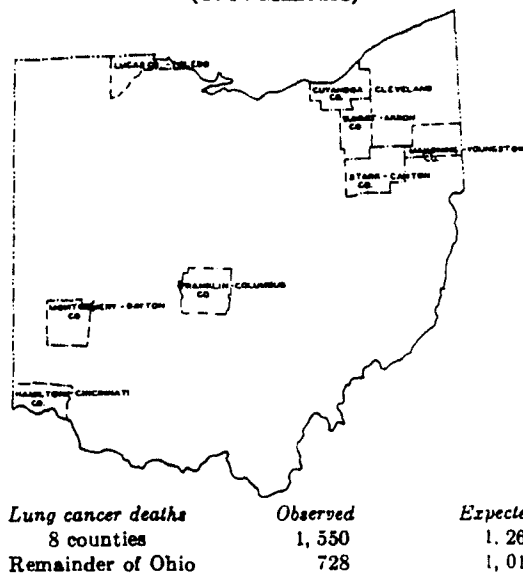


Table 8. Estimated amount¹ of aromatic hydrocarbons in 1-minute samples of gasoline exhaust with varying engine revolution speeds (Kotin)

Revolutions per minute	Pyrene	Compound X	Benz-pyrene	Benz-perylene	Anth-anthrene
500.....	225	289	120	235	153
1,000.....	439	325	61	177	102
1,500.....	507	266	33	60	36
2,000.....	374	142	40	73	27
2,500.....	346	127	25	70	31
3,000.....	121	25	13	85	14
3,500.....	48	5	10	39	15

¹ Quantities are expressed in $\mu\text{gm.}$ at 0 load.

may be inhaled and retained in the lungs from these sources during a lifetime and that this quantity represents approximately 40,000 times the dose (0.4 micrograms) capable of producing cancer in mice upon subcutaneous introduction. It should be emphasized in this connection that 3,4-benzpyrene is only one of the several carcinogenic chemicals isolated from atmospheric pollutants and that, therefore, the actual total amount of atmospheric carcinogens reaching the lung is considerably higher (Falk and Steiner; Kotin and associates). The benzpyrene content of the air was increased fourfold during smog days (Waller).

It is difficult, if not impossible, to reconcile the obvious causal significance of this factual evidence with the claim that such regional, and especially urban-rural, differences in lung cancer

frequency are totally accounted for by differences in the cigarette smoking habits of the two population groups or merely reflect local discrepancies in the diagnostic acumen of urban and rural physicians and in the availability of diagnostic medical facilities.

Such explanations become even less tenable in view of the fact that the annual age-adjusted increase in frequency of lung cancer deaths was higher in 1914-30 than in 1931-44 (table 10), whereas the markedly increased cigarette consumption during previous years should have boosted the annual progression rate above that seen during the earlier period. It has been suggested (Lickint; Hammond) that this paradoxical behavior of progression rates is attributable to the fact that many cigarette smokers did not live long enough to develop a lung cancer because of their precocious death from coronary sclerosis, which also is assumed to be elicited in

Table 10. Annual age-adjusted increase of frequency of lung cancer mortality

Sex	Percent increase		
	1914-30 ¹	1931-40 ¹	1933-44 ²
Males.....	10.5	8.5	5.8
Females.....	8.0	2.5	2.0

¹ Dorn.
² Potter.

Table 9. Estimated amount¹ of aromatic hydrocarbon in 1-minute samples of diesel exhaust with varying load and engine revolution speed and with fuel-injection inefficiency (Kotin)

Revolutions per minute	Load	Condition	Pyrene	Compound X	Benz-pyrene	Benz-perylene	Anth-anthrene
1,000	0	Compression release.....	137	22	146	22	0
	1/4	do.....	267	76	465	42	43
	1/2	do.....	536	175	772	124	223
	3/4	do.....	1,800	640	1,320	610	472
1,200	0	do.....	2,500	639	876	1,265	469
	1/4	do.....	208	0	9	79	4.3
	1/2	do.....	257	0	47	40	24
	3/4	do.....	448	278	437	171	197
1,400	0	do.....	888	488	432	930	320
	1/4	do.....	1,912	614	1,706	976	944
	1/2	do.....	188	0	80	0	20
	3/4	do.....	177	56	78	0	16
	0	do.....	220	76	1,372	368	69
	1/4	do.....	734	337	982	1,071	577
	1/2	do.....	822	346	1,687	944	666
	3/4	do.....					

¹ Quantities are expressed in $\mu\text{gm./min.}$

accounted for by the majority of cases by cigarette smoking. According to statistical evidence. Such an explanation conveniently disposes of an observation challenging the validity of the

some even less tenable. The annual age-adjusted lung cancer deaths were 1931-44 (table 10). Increased cigarette consumption in years should have a death rate above that of 1931-44. It has been suggested that this paradoxical increase is attributable to cigarette smokers who develop a lung cancer death from coronary heart disease to be elicited in

Increase of mortality	
1931-40	1933-44
8.5	5.8
2.5	2.0

Benzo(a)pyrene	Anthracene
22	0
42	43
124	223
610	472
365	469
79	4.3
40	24
171	197
330	320
78	944
0	20
0	16
68	69
71	577
44	666

Table 11. Sex distribution of lung cancer in the United States and selected foreign countries, 1939-1953

Country	Year	Author	Male-female ratio
United States	1953	Dorn	5:1
	1951	Moore	6.6:1
	1947	Humphreys	7:1
	1950	Beeler et al.	11.5:1
	1946	Lindskog	4.5:1
	1951	Carlisle et al.	29:1
	1941	Halpert	14:1
	1951	McBurney et al.	29:1
Mexico	1949	O'Keefe	20:1
	1941	Farberow and Baslow	13.5:1
	1935	Neely	1:1
Norway	1953	Steiner	1:0.7
	1953	Kreyberg	4:1
Sweden	1925	do.	1:1
	1947	Henschen	2:1
Denmark	1931	Clemmesen	5:4
	1945	do.	3:1
Austria	1953	Denk	15:1
	1953	Grosze	6.6:1
Germany	1850-1899	do.	1.8:1
	1900-1919	do.	3.1:1
	1920-1929	do.	3.8:1
	1930-1939	do.	3.8:1
	1940-1949	do.	5.4:1
France	1952	Lemoine	10:1
Canada	1948	Gagnon	8:1
Argentina	1947	Santas	50:1
England	1949	Mason	10:1
	1949	Fulton	7.3:1

1. Mexicans living in Los Angeles.

Table 12. Male-female sex ratio of lung cancers in Germany, 1886-1927 and 1940-50

1886-1927			1940-50		
City	Author	Ratio	City	Author	Ratio
Dresden	Wolf	6.7:1	Dresden	Lickint	15:1
Leipzig	Seyfarth	5.3:1	Leipzig	Knorr	11:1
Do.	Sehrt	2.5:1	do.	Merkel	15:1
Chemnitz	Briese	2.9:1	Zwickau	Gerbe	7:1
Berlin	Wahl	3.7:1	Berlin	Berg	9:1
Do.	Bejach	2.3:1	Potsdam	Hollmann	19:1
Do.	Hanf	3.6:1	Koeln	Breyer	21:1
Do.	Redlich	5.2:1	Muenchen	Anacker	7:1
Koeln	Eichengruen and Essen	4.7:1	do.	Kautzsch	18:1
Muenchen	Fuchs	1.5:1	do.	Frey	24:1
Jena	Bilz	8.0:1	Jena	Kuntzen	49:0
Hamburg	Kikuth	1.8:1	Hamburg	Letzius	12:1

times, in different localities, and in different demographic groups, it is most unlikely that such discrepancies and changes are attributable to fluctuations in the intensity of one single factor, such as cigarette smoking. Instead, they appear to be due to alterations in the type and extent of the action of a broad spectrum of environmental respiratory carcinogens affecting the members of the two sexes to different degrees.

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

1. Males are more extensively employed than females in occupations which produce and use known or suspected atmospheric carcinogens. Also, males 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 in the general atmosphere (effluents of domestic and industrial furnaces, exhaust from gasoline and diesel engines, dust from rubber tires and from 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, 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 proved carcino-

genic atmospheric pollution, while females stay for larger portions of their lives in the cleaner suburban dormitory communities.

These considerations provide substantial support to the concept that local differences in general and occupational industrial air pollutants may more plausibly account for an appreciable portion of the observed differences in attack rates for the two sexes rather than do local variations in their smoking habits.

The doubts as to the unrestricted validity of the cigarette theory are deepened if critical evaluation is made of another dubious link in the chain of claims advanced to bolster this concept. It has been maintained (Graham) that squamous cell carcinomas of the bronchial mucosa are a specific response to cigarette smoking since (a) this histological type of bronchogenic carcinoma was allegedly rare before 1920; (b) it has increased considerably since that date in relative frequency in comparison to other histological types of carcinoma, especially adenocarcinoma; and (c) it is more often found in males than in females.

The facts are as follows: Bronchiogenic squamous cell carcinoma has commonly been found with all known occupational respiratory cancers (table 13). However, many of these agents have also elicited other types of pulmonary carcinomas, such as undifferentiated, round cell carcinomas and adenocarcinomas. Thus, there is no evidence supporting the view that any specific respiratory carcinogen elicits a specific and characteristic type of cancer. A study of lung cancer records of cases observed

Table 13. Histological types of occupational respiratory cancers, according to carcinogenic agent

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	do	4		3	
Chromium	do		2		
Asbestos	do	11	2	2	6
Radioactive gases and dust	do	14	9	7	1
Nickel	Nares and nasal sinus	3		6	
Radioactive gases and dust	do	3			
Isopropyl oil	do			4	

Figure 5. Annual

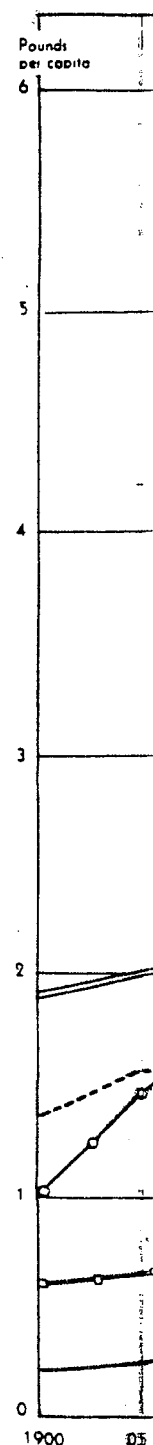
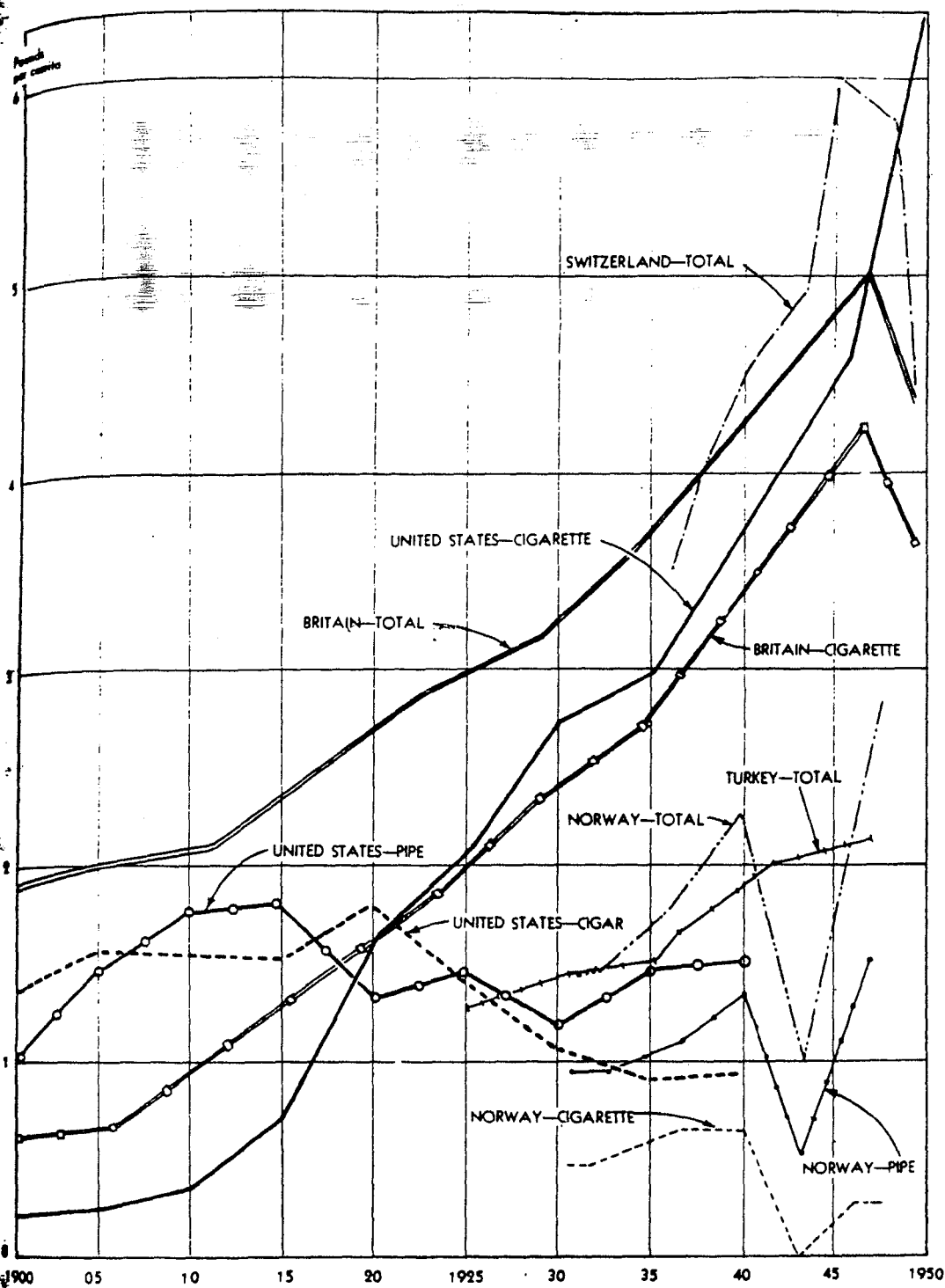


Figure 5. Annual tobacco consumption in pounds per capita, Great Britain, Norway, Switzerland, Turkey, and the United States, 1900-50.



before 1920, or even before 1900, readily establishes the fact that during those years squamous cell carcinomas of the bronchi were by no means rare occurrences (Wolf, 1895—8 squamous cell

Table 14. Consumption of tobacco in pounds per head-year, New Zealand and United Kingdom, 1900-1950 (Eastcott)

Year	Pounds of tobacco per head-year	
	New Zealand	United Kingdom
1900.....	2.3	1.95
1910.....	2.69	2.22
1920.....	3.59	2.99
1930.....	3.28	3.31
1940.....	3.87	3.97
1950.....	5.36	4.22

carcinomas among 15 lung cancers; Probst, 1927—25 percent squamous cell carcinomas between 1905 and 1918; Watsuji, 1903—23 percent squamous cell carcinomas between 1892 and 1899; Adler, 1912—approximately 40 percent squamous cell carcinomas among 181 lung carcinomas collected from the literature with adequate histological data; Proc. First Nat. Cancer Conf., 1949—44 percent squamous cell carcinomas in males; 11 percent in females.

While adenocarcinomas are more frequent in females than in males, they also are more frequent in young persons than in old ones (Lindskog; Proc. First National Cancer Conf., 1949). The evidence on hand scarcely supports the contention that adenocarcinomas are of endogenous causation (Lickint) or that they have an etiology differing from that of squamous cell carcinomas (Kreyberg). The male-female sex

Table 15. Average death rate per year per million persons (males) from cancer of the lung, 1932-53, New Zealand compared with England and Wales (Eastcott)

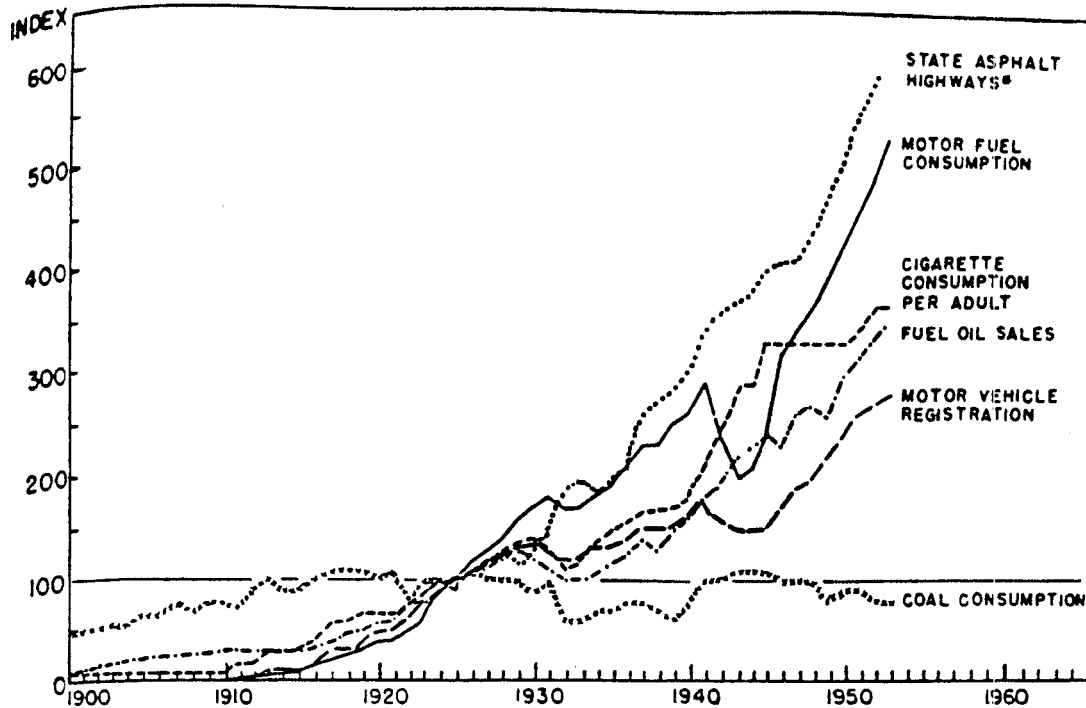
Period	Country	Age				
		35-44	45-54	55-64	65-74	75 and over
1932-36.....	New Zealand.....	13	87	158	204	62
1937-41.....	do.....	33	108	235	283	213
1940-41.....	England and Wales.....	126	424	802	715	448
1942-46.....	New Zealand.....	46	168	466	635	326
1942-46.....	England and Wales.....	132	466	1,072	1,032	527
1947-51.....	New Zealand.....	43	287	732	1,014	735
1947-51.....	England and Wales.....	166	781	1,682	1,857	1,073
1952-53.....	New Zealand.....	61	305	1,027	1,456	1,110
1952-53.....	England and Wales.....	175	858	2,171	2,650	1,688

Table 16. Observed and expected mortality from cancer of the lung according to place of birth, New Zealand or the United Kingdom (Eastcott)

Place of birth	Observed deaths	Expected deaths	Age at entry to United Kingdom			
			Under 30		30 and over	
			Observed deaths	Expected deaths	Observed deaths	Expected deaths
New Zealand.....	632	721.8				
United Kingdom.....	369	279.9	201	229.2	168	139.5

NOTE: The significance of the difference between observed and expected deaths in the two countries is $p < 0.001$.

Figure 6. Trends in selected environmental factors, United States, 1900-53 (Hammond).



ratio of lung cancer (1:0.7) among Mexicans living in Los Angeles, as well as the ratio of 2.5:1 for asbestosis cancers (Merewether), do not support the view that women have any hormonal protection against the action of environmental respiratory carcinogens if identical conditions of exposure prevail.

The claim that squamous cell carcinoma of the bronchi is in any specific way related to cigarette smoking thus may be laid to rest, since no special histological type of bronchiogenic carcinoma bears any consistent connection with any of the recognized respiratory carcinogens.

Finally, it may be mentioned that there does not exist any parallelism between the annual per capita consumption of tobacco in different countries and their respective pulmonary cancer death rates (Herbich and Neubold; Gilliam) (fig. 5). It has been calculated that the English lung cancer rate is apparently double that of the United States, although the English smoke 30 percent fewer cigarettes per capita than Americans. This interesting and perhaps significant observation, which fails to support the

validity of the cigarette theory, is disposed of by its proponents by assuming that exposure to cigarette tar is less severe for Americans who do not smoke cigarettes to the very end than for English smokers who, for economic reasons, indulge in this questionable habit.

Recent epidemiological studies of Eastcott in New Zealand provided the most important data on this point. It was found that the relative consumption of tobacco in pounds per head-year for the population of New Zealand and the United Kingdom revealed an inverse relation to their lung cancer death rates (tables 14 and 15).

Eastcott, moreover, found when comparing the observed number of lung cancer deaths with the expected number for native New Zealanders of British extraction and for immigrants from the United Kingdom that the immigrant group meets with a much higher incidence of bronchiogenic cancer than would be expected on the basis of equity, suggesting that the immigrant has an increased susceptibility to lung cancer (table 16).

The chances of dying of cancer of the lung are 30 percent higher for all United Kingdom

lung, 1932-53,

5-74 75 and over

204	62
283	213
715	448
635	326
032	527
14	735
857	1,073
436	1,110
650	1,688

place of birth,

from

and over

Expected deaths

139.8

ries is $p < 0.001$.

er of the Lung

immigrants, but for those who were 30 years of age or more on entering New Zealand, the risk is 75 percent higher, according to Eastcott. Differences in habits of tobacco smoking are unlikely to contribute to this picture, in the opinion of Eastcott.

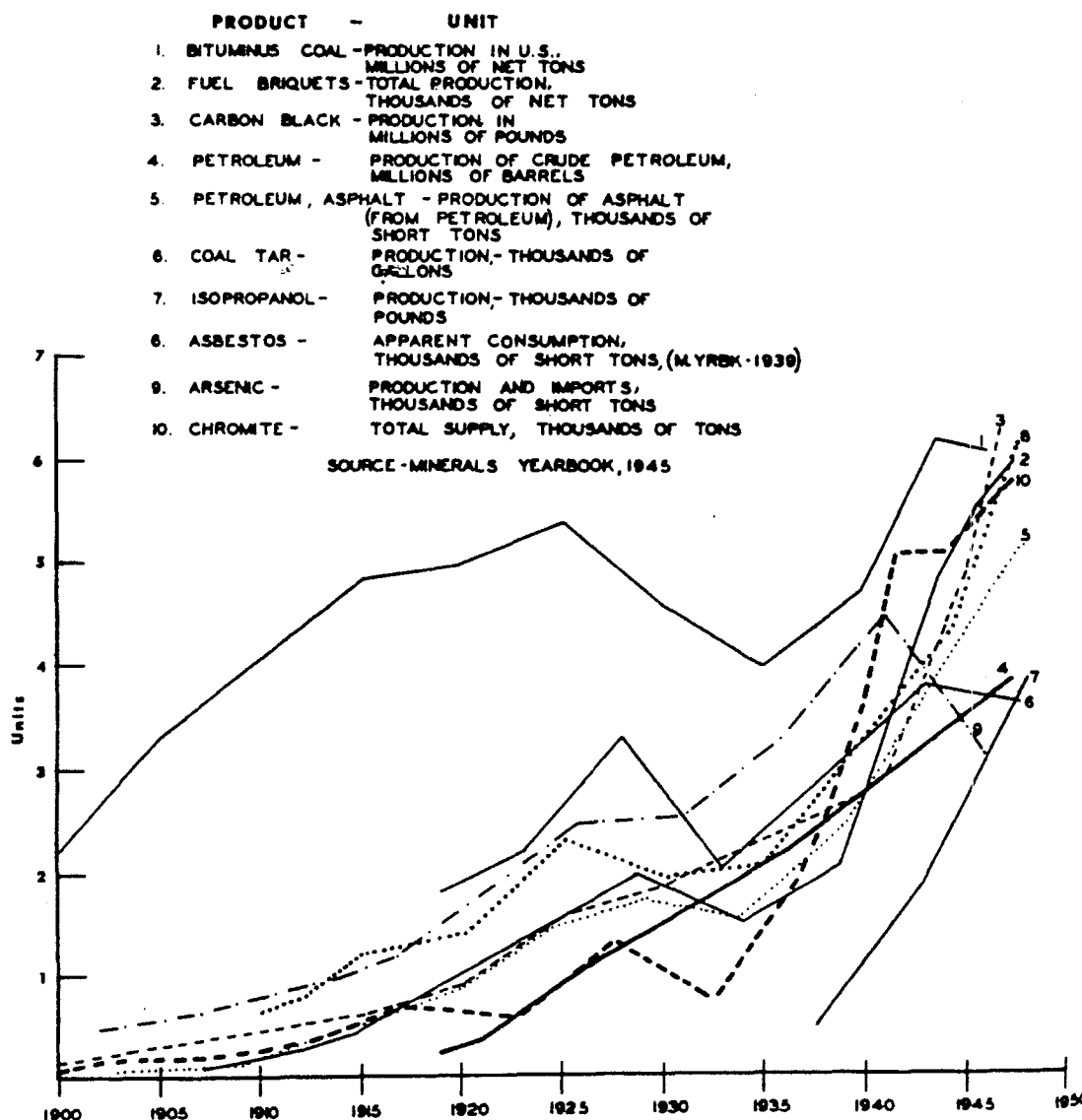
Herbich and Neubold pointed out that there did not exist any consistent proportional frequency between cigarette consumption and

lung cancer mortality for Upper Austria and Kaernten, on the one side, and for Steiermark and Tyrol, on the other side, although in all four provinces there prevailed approximately the same per capita consumption of cigarettes. These authors suggested that the high lung cancer mortality among the people living in the marginal regions of the northern slope of the Alps might be related to climatic-atmospheric

conditions, winds, which air of Vienna Alpine region.

Similar conditions prevailing in lung cancer Midlands and Neube cancer most communities where there are fumes from dust and from the inhabitants remote from rise in lung increase in construction.

Figure 7. Rise in annual production or consumption of cancer-related industrial chemicals between 1900 and 1948.



The contribution by epidemic evidence of rates of cancer as well as the specific and number of well-defined

Epidemiology of Industrial

Epidemic lung cancer groups and existence of persons with cancer of striking type. list some of responsible

Table 17 for seven

Public Health

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conditions and to the direction of prevailing winds, which bring the industrially polluted air of Vienna into the valleys of the northern Alpine regions.

Similar observations on the influence of the prevailing winds upon the relative frequency of lung cancers in different areas of the English Midlands were reported by Stocks. Herbig and Neubold, moreover, found that the lung cancer mortality rates were twice as high in communities located along main highways, where the atmosphere was polluted with exhaust fumes from gasoline and diesel motors and the dust and fumes of asphalted roads, than among the inhabitants of villages and towns situated remote from such traffic arteries. In fact, the rise in lung cancers follows more closely the increase in consumption of motor fuel and the construction of asphalted highways than the

consumption of cigarettes (fig. 6. Hammond; fig. 7, Hueper) and is similar to the increase in production of other cancer-related chemicals.

It is apparent from the numerous observations and facts of general environmental nature cited that there exists an impressive amount of circumstantial evidence of different character and from various sources which strongly suggests that several, if not many, environmental factors acting in varying degrees and combinations cause or contribute to the development of pulmonary cancers and are involved in their recent rise in frequency. Much of the evidence on hand, particularly the irregular epidemiological pattern of lung cancer, points to an important role which industry-related factors and the growth of modern industry may have assumed in these respects.

Occupational Evidence and Respiratory Carcinogens

The concept that environmental factors cause or contribute to pulmonary cancers is supported by epidemiological, medical, and experimental evidence obtained from analysis of lung cancer rates of various occupational population groups as well as by studies of lung cancers and their specific and different causal agents present in a number of restricted worker groups and in well-defined industrial operations.

Epidemiological Data on Large Industrial Groups

Epidemiological studies on the frequency of lung cancer among members of large industrial groups and trades have brought to light the existence of marked variations in the liability of persons engaged in different occupations to cancer of the lung. Tables 17-19 supply striking illustrations of these differences and list some of the factors which may possibly be responsible for them.

Table 17, which lists lung cancer death rates for seven industrial groups in Ohio, shows a

striking difference between the rates for agricultural laborers and for employees in the nonferrous metal industry, with rates for transportation workers occupying a position directly behind the rates for nonferrous metal workers. It seems to be characteristic of inhabitants of agricultural areas to rank first in death rates from cutaneous cancer and last in rates for pulmonary cancer. This is in accordance with the relationship between solar radiation and

Table 17. Lung cancer death rates per 1,000 deaths from all causes for 7 industrial groups in Ohio, 5,309 males, 1947 (Mancuso)

Industry	Death rate
Nonferrous metal.....	3.22
Transportation.....	2.91
Rubber and plastics.....	2.34
Iron and steel.....	2.18
Mining and quarrying.....	1.53
Agriculture.....	.82
Stone, clay, glass.....	.66
Total.....	1.76

skin cancer and the relationship between low concentrations of carcinogenic air pollutants and lung cancer.

Nonferrous metal workers, on the other hand, often have contact with dust, fumes, and vapors of some carcinogenic metals, such as chromium and nickel, or with arsenicals which are impurities in many nonferrous metals (copper, zinc, silver). Transportation workers are exposed to the exhaust from gasoline and diesel engines, petroleum lubricants, and dust from asphalted roads. The relatively high death rates of workers employed in the rubber and plastics industry may possibly be attributable to the use of coal tar, petroleum oils, and tars, furnace black, mineral pigments of carcinogenic chemicals, and aromatic amino-antioxidants used in the production of rubber and plastics.

The actual discrepancy in the lung cancer liability between operating and nonoperating railroad workers is even greater than is appar-

ent from the figures listed in table 18. The employment ratio of operating to nonoperating railroad workers in one of two large railroad companies was 1:4. From this ratio, it appears that, on the basis of the crude, nonstandardized (sex, age) figures presented, about 75 percent of the lung cancers in railroad employees occurred among the operating group, which supplied only 25 percent of the total number of employees. Operating railroad workers included engineers, firemen, brakemen, conductors, switchmen, and roundhouse personnel, that is, workers exposed to the inhalation of coal soot and oil fumes from diesel engines and fuel and lubricating oils, which contain carcinogenic polycyclic hydrocarbons.

Dunner and Hicks recently called attention to two additional worker groups, boiler scalers and grain dockers. In the experience of Dunner and Hicks, these workers showed an excessive liability to cancer of the lung. Twen-

Table 18. Frequency of lung cancer among operating and nonoperating railroad workers

Railroad	Period	Total lung cancers	Type of railroad worker					
			Operating		Nonoperating		Undetermined	
			Number	Percent	Number	Percent	Number	Percent
A-----	1940-50	29	24	83	5	17	-----	-----
B-----	1939-49	104	59	57	15	14	30	29

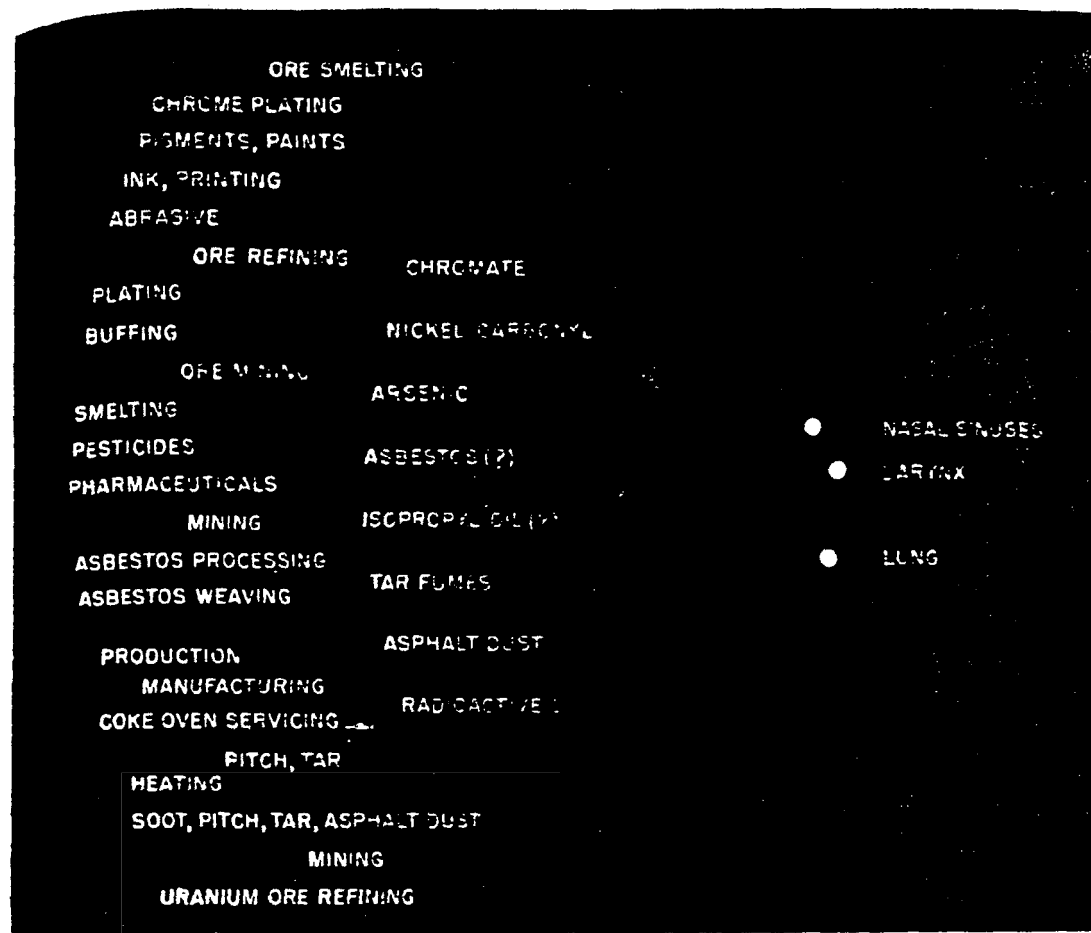
Table 19. Occupational groups with excessive incidence of lung cancer

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; Turner and Grace; Müller; Dublin and Vane; Wynder and Graham; McLaughlin; Breslow and associates.
Cigar manufacturers and tobacco-nists.	Tobacco dust, insecticides, soot....	Seyfarth; Kennaway and Kennaway; Enger; Versluys; Brinkmann.
Engineers, mechanics, machinists, plumbers, crane operators in smelters, etc.	Metal dust, soot, lubricating oil....	BECC ¹ 1944 and 1952; Gillespie; Turner and Grace; Müller; Wynder and Graham.
Painters, decorators.....	Metal pigments, coal tar dyes, carbon black, asphalt paints, solvents, vehicles (lacquers, resins, synthetic plastics).	BECC ¹ 1944; Müller; Dublin and Vane; Fulton; Wynder and Graham.
Tar workers, road workers, asphalters, paviours, stokers, patent fuel workers, furnace men, foundry laborers, rollers, etc.	Tar and pitch fumes and dust, soot.	Kennaway and Kennaway; Fulton; BECC ¹ 1952; Registrar-General (1938); McLaughlin.

¹ Report of the British Empire Cancer Campaign.

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Figure 8.



ty-four lung cancer cases were found among 5,000 dock workers at Hull, England, of whom 2,500 were exposed to grain dust. There were 10 boiler scalers with lung cancer. With the exception of 1 boiler scaler, none had any radiological evidence of pneumoconiosis and only 5 had a slight degree of pneumoconiosis upon histological examination. No lung cancers were observed among dockers who were not exposed to grain dust. It may be possible that boiler scalers sustain a carcinogenic exposure to chromate-containing scale, if chromates were used as antirusting agents, or that these workers sustain a pulmonary deposition of iron oxide. Whether specific vegetable matter or some carcinogenic contaminant of the grain, such as residues of chemical fungicides or other processing or preserving agents, account for

the abnormally high frequency of lung cancer among grain dockers is at present a matter for speculation.

Mention also may be made of the recent observation of Faulds on the excessive frequency of pulmonary cancer among English iron ore workers employed in mining activities at two different locations. Necropsies performed on these miners during 1932-53 showed a lung cancer incidence of 9 percent (192 necropsies with 17 lung cancers), while post-mortem examinations done on 2,378 males of comparable age who were not employed in these mines revealed that only 44, or 1.85 percent, had primary lung cancers. It is remarkable that there did not exist any parallelism between the degree of pulmonary fibrosis observed in the iron miners and their liability to lung cancer

(degree of fibrosis in cancerous lungs, 1 plus; in tuberculous lungs, 2 plus; in fibrotic lungs without cancer and/or tuberculosis, 3 plus). The absence of a positive correlation between pulmonary fibrosis and lung cancer was noted when the evidence on lung cancer among the radioactive ore miners of Joachimsthal and Schneeberg was analyzed (Hueper). Although the actual causal factor responsible for the lung cancer among iron ore miners remains to be determined, it may be mentioned that Levin and his co-workers recently recorded a positive statistical correlation between an occupational exposure to iron oxide and heat and cancer of the lung.

The studies of Breslow, Hoaglin, Rasmussen, and Abramson 518 histologically proved cases of lung cancer in California suggested the existence of an increased liability to lung cancer for members of the following occupational groups: welders, sheet metal workers, steamfitters, boilermakers, crane operators, and nonferrous metal smelter workers, that is, individuals who are exposed to metal dusts and fumes; oilers, oil field workers, wipers, and marine engineers, who have contact with oil fumes, mists, and sprays; asbestos workers; construction and maintenance painters, who inhale vapors or various organic solvents, resins, lacquers, plastics, and rubber, as well as finely dispersed inorganic and organic pigments (chromium, nickel, copper and arsenic compounds, carbon black, aniline dyes); and commercial cooks exposed to fumes and mists of overheated vegetable and animal fats and mineral pan greases.

A recent study of the causes of death of the members of the International Photoengravers Union raised the suspicion of an excessive lung cancer liability for members of this occupational group.

From the different lung cancer death rates listed for the various occupational groups, it is obvious that the total number of workers possibly exposed to occupational carcinogens of known or still unknown nature is evidently very large and comprises workers employed in basic and processing industries, construction, transportation, services, trades, laboratories, and professions (fig. 8). It is, on the other hand, equally clear that the quantity and quality of

information available on the occupational aspects of lung cancer causation are deplorably defective because of an absence of extensive and prolonged analyses of lung cancer deaths among various industrial groups for specific causal factors. The evidence on hand nevertheless is adequate for demonstrating that the wide variations in lung cancer frequency apparently existing between different industrial population groups are attributable to differences in more or less well-definable occupational exposures and not to differences in cigarette smoking habits.

Occupational Respiratory Cancers and Carcinogens

Conclusive evidence of the existence of exogenous carcinogens and environmental respiratory cancer hazards is provided by the epidemiological, medical, and experimental data concerning occupational respiratory cancers. A general view of the occupational respiratory cancer panorama, including causal agents, and organs affected is presented in table 19.

Scope of Environmental Lung Cancer Hazards

An indiscriminate acceptance of the figures given in table 20 as reflecting the actual scope of these identified and recognized respiratory cancer hazards, however, would be seriously misleading, despite views expressed by several protagonists of the cigarette theory (Ringertz; Wynder and Graham; Levin; and others). Although a definite demonstration of specific occupational lung cancer hazards has so far been made for only relatively restricted worker groups, the evidence on hand is not only unequivocal but also indicates that other worker groups exposed to the same causal agents or subjected to identical or similar working conditions are subject to the same hazards. In contrast to the apparently low carcinogenic potency of the suspected, but unidentified, agent presumably contained in tobacco smoke, the occupational respiratory carcinogens are evidently highly potent, as shown by their high respiratory cancer attack rates (table 21).

Since environmental carcinogens have been shown to produce cancers wherever they operate in adequate intensity and duration, and considering the fact that many of the occupational

respiratory cancer related general and justly be assumed to represent the cause of cancers among nation, especially highly industrial

Table 20. Occupa

Agent
Arsenic..... Asbestos..... Chromates..... Nickel..... Coal tar..... Petroleum oils..... Isopropyl oil..... Radioactive chemi..... Total..... Carcinog..... Aromatic hydrocarb..... Coal tar fumes..... Petroleum oils..... Carbon and silicon..... Isopropyl oil..... Asbestos..... Metals: Arsenic..... Chromates..... Nickel..... Ionizing radiation: Radioactive ores..... Public Health Mo

Occupational respiratory carcinogens occur as industry-related general atmospheric pollutants, it may justly be assumed that these pollutants represent the cause of a significant portion of lung cancers among members of the general population, especially those who live and work in highly industrialized areas.

The approximate scope of occupational exposures to the various respiratory carcinogens may be estimated from data supplied by Bloomfield and his co-workers. From a survey of 1,503,204 workers employed in all industries of 10 States, it was found that 7,976 were exposed to fumes and dusts of chromium compounds and

Table 20. Occupational respiratory carcinogens and cancers recorded during past 75 years, their causes, sites, and numbers

Agent	Site of cancer	Year discovered	Number of recorded cases		
			United States	Other countries	Total
Arsenic.....	Lung.....	1930	7	16	23
Asbestos.....	do.....	1934	22	74	96
Chromates.....	do.....	1932	75	65	140
Nickel.....	do.....	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.....	Lung.....	1946	1	0	1
	Larynx.....		4	0	4
	Nasal sinus.....		6	0	6
Radioactive chemicals.....	Lung.....	1879	0	625	625
	Nasal sinus.....	1931	3	0	3
Total.....			125	1,001	1,126

Table 21. Respiratory cancer attack rates, by environmental carcinogens

Carcinogen	Sites of cancers	Incidence in population at risk	Attack rates		
			Percent of all cancer deaths	Rate per 100,000	
				Morbidity	Mortality
Aromatic hydrocarbons:					
Coal tar fumes.....	Lung.....	500:100,000	45		
Petroleum oils.....	Lung.....	2,000:100,000	55		
Carbon and silicon polymers:					
Isopropyl oil.....	{ Paranasal sinuses, larynx. }	10:100		134.5 (normal 6.5)	
Asbestos.....	Lung.....				(13.2-20 percent asbestosis autopsied (0.8-2.4 percent normal)).
Metals:					
Arsenic.....	Lung.....				145.7 males (10.9 normal.)
Chromates.....	Lung.....			(42× normal)	146-338
Nickel.....	{ Nares, paranasal sinuses. }	329:100,000			
	{ Lung..... }	574:100,000		(20× normal).	
Ionizing radiation:					
Radioactive ores.....	Lung.....				(50-80 percent of all deaths).

3,356, to fumes and dusts of arsenicals. For industrial workers of all 48 States, respiratory health hazards existed from the inhalation of dust, fumes, mists, and vapors for 35,000 individuals employed in asbestos operations, in 33,000 having contact with arsenicals, in 240,000 inhaling various types of metal dust, and in 2,500,000 having cutaneous, respiratory, and ingestive exposures to various combustion and distillation products of coal tar, pitch, creosote oil, soot, and to petroleum fuel oils and lubricating oils, greases, and cooling oils, to name a few.

The highly defective state of knowledge concerning the actual number of occupational respiratory cancers is, moreover, demonstrated by the fact that information on the existence and number of such cancers in specific industrial operations with recognized respiratory cancer hazards is distinctly spotty, not only as to data available from different countries but also concerning those on hand from identical operations of the same country. The following observations may illustrate this point.

The existence of an excessive liability to cancer of the lung from an inhalation of coal tar fumes by retort attendants of gas and coke oven plants has been established by a few reports from Japan, Canada, and England. Apart from these isolated data, no others are available for similar operations from these or any other highly industrialized countries (Germany, United States, France, Italy, Poland, Russia). Likewise, there is no official record available concerning the occurrence of respiratory cancers among carbon electrode makers and attendants in aluminum manufacturing plants, where workers become exposed to dust and fumes from the pitch and petroleum asphalt in the electrodes, and where, according to information available from four different countries, tar and asphalt cancers of the skin have been observed as the result of such contacts.

It is, moreover, surprising that data on the occurrence of lung cancers among producers and users of arsenical insecticides have been reported almost exclusively from Europe, although the United States has been for many years the main producer and consumer of these products. Similarly, reports as to the existence of respiratory cancer hazards from an occupational inhalation of mists and fogs of lubricating

and cooling oils have so far totally originated from Europe, despite the fact that American industries offer ample opportunities for identical exposures, that an excessive liability to lung cancer has been noted for paraffin pressers employed in oil refineries, and that the survey of one oil company has shown that there was a marked predominance of operating refinery workers among the lung cancer victims of this particular organization.

Finally, attention may be called to the fact that the entire evidence as to the existence of lung cancer hazards for radioactive-ore miners has come from the observations made in Schneeberg and Joachimsthal. However, mining of uranium ores has been carried on for 10 to 20 years in the Congo, Canada, and the United States and extensive milling operations of the African ores have been conducted in Belgium for many years without any official record of similar respiratory complications among the workers employed.

Additional incompleteness of the existing records on occupational respiratory cancers may be related to the possibility that pulmonary cancers may have their causation from agents entering the body by an extraréspiratory route. While all known respiratory carcinogens are of environmental origin and are inhaled as air pollutants, there exists some suggestive occupational, medicinal, and experimental evidence indicating that agents introduced by other routes may be effective in eliciting lung cancers. Several cases of lung cancer are on record which developed after an oral administration of arsenicals and which appeared in individuals with arsenical dermatoses and skin cancers (Neubauer). Lung cancers also have been observed in some aniline dye workers suffering from primary occupational bladder cancer (Müller) following prolonged cutaneous, ingestive, and respiratory exposure to dusts and vapors of certain carcinogenic aromatic amines. The possible scientific and practical significance of these findings is suggested by the experimental observation of lung cancers in 10 percent of rats given the potent carcinogen, 2-acetylaminofluorene by an extraréspiratory route (Biel-schowsky). A cutaneous as well as parenteral introduction of coal tar and several polycyclic hydrocarbons as well as of urethane resulted in

a precocious number of pulmonary cancers.

Pattern and

If a map of concentration of pollutants were prepared, it would exhibit a sort of the general atmospheric pollution pattern, with the general atmospheric pollution pattern superimposed. It stands to reason that the exposure pattern is an important influence on the character and incidence of various respiratory carcinogens with a geographical scatter and spread of carcinogenic production factors.

The following factors may be distinguished:

1. General exposures to environmental hydrocarbons, incomplete combustion, and industrial exhaust fumes, abrasion products from asphalt, arsenicals, compounds of burned coal, metal smelter use of arsenical radioactive materials from the soil, and the atmospheric explosions.

2. Special exposure to

a precocious appearance and an increased number of pulmonary tumors in mice.

Pattern and Types of Respiratory Cancer Hazards

If a map of the distribution and relative concentration of the different carcinogenic air pollutants were prepared for a given area, it would exhibit a sort of crazy quilt pattern to which the general atmospheric pollutants would furnish the overall background color, varying in depth between darker urban areas and lighter rural districts. Other types of carcinogenic atmospheric pollutants having a more circumscribed field of distribution would appear as irregularly arranged and variously sized and shaped spots and islands of different colors superimposed upon the general background. It stands to reason that such locally differing exposure patterns are bound to exert an important influence upon the epidemiological character and incidence rates of pulmonary cancers of various regions; each one of the various carcinogens would produce its own epidemiological scatter pattern showing a diminishing spread of cancers from multiple carcinogenic production foci.

The following three main types of exposure to environmental atmospheric carcinogens may be distinguished:

1. General environmental atmospheric exposures to certain aliphatic and polycyclic hydrocarbons released into the atmosphere as incomplete combustion products of domestic and industrial and ship fuels, as parts of the exhaust fumes of gasoline and diesel engines, as abrasion products of rubber tires, and as dust from asphalted and oiled roads; exposure to arsenicals contained in the mineral ash and soot of burned coal and in the effluents of certain metal smelters, and related to the large-scale use of arsenical pesticides; and exposure to radioactive material either naturally released from the soil and from bodies of water or polluting the atmosphere as the result of nuclear explosions.

2. Special and locally restricted atmospheric exposure to carcinogenic pollutants of the air

exists in the vicinity of nonferrous metal smelters releasing in their effluents and from their slag heaps fumes and dust containing nickel, arsenicals, chromium compounds, and beryllium. Similar exposure exists in the vicinity of carbon black plants, oil refineries, tar distilleries, gas plants, and similar industrial establishments producing large amounts of soot or other polycyclic hydrocarbon containing effluents, and in the vicinity of radioactive ore mills and atomic energy plants.

The individualized type of air pollution connected with the smoking of tobacco, with its suspected carcinogenic hazard to the lung in the special form of cigarette smoking, may be included in this type of exposure to atmospheric carcinogens.

3. During the last 75 years, an increasing number of specific chemical and physical agents have either definitely been recognized or are strongly suspected of being responsible for the appearance of cancers of the nares, paranasal sinuses, larynx, and lung among members of certain occupational groups. These specific occupational exposures are associated with the inhalation of coal tar and pitch fumes and dusts, mists and fogs of petroleum derivatives, soot, vapors of isopropyl oil, that is, the crude liquor from which isopropyl alcohol is distilled; arsenic, nickel, chromium compounds, asbestos, and ionizing radiation. Since the available evidence establishes such carcinogenic connections with only some, but not with all, inhalants, such as silica or coal dust, it is apparent that carcinogenic activities are not associated with all atmospheric pollutants.

Occupational Respiratory Cancers

The respiratory cancers of recognized or strongly suspected occupational origin are important, not only as industrial disease manifestations but also as prototypes of etiologically and topographically identical cancers affecting workers in other, similarly hazardous occupations as well as of those cancers involving an indefinite portion of the general population sustaining for environmental reasons contacts with the same industry-related carcinogens.

Dusts or mists composed of particles having a diameter below 4 microns, on the other hand, penetrate into the deeper parts of the respiratory system and therefore are mainly responsible

It was not until the third and fourth decades 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, that is, the nasal cavity, paranasal

Exposure to metallic nickel carbonyl vapor in industrial workers conditions. While salts not infrequently of an apparent inhalation of have been responsible for acute and of monary manifestation of alveolar exudation into the pleural cavity and pulmonary hemorrhage to the toxic action of nickel carbonyl upon the

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).

Specific Carcinogens

Inorganic Chemicals

NICKEL

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

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. While skin contact to nickel and nickel salts not infrequently results in the development of an apparently allergic type of dermatitis, inhalation of the volatile nickel carbonyl has been responsible for an appreciable number of acute and often fatal poisonings. The pulmonary manifestations (congestion, desquamation of alveolar epithelium, fibrinous acellular exudation into alveolar spaces, bronchial mucosal hemorrhages) are apparently attributable to the toxic action of finely dispersed nickel formed from the disintegration of nickel carbonyl upon the pulmonary structures. Krafft

suggested that these reactions are the result of a nickel allergy having the lung as its shock organ.

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 of the Clydach plant of the International Nickel Company, located at South Wales, England, was made by Grenfell in 1932, although the first appearance of these neoplasms among the nickel refinery workers was noticed in 1924 (Baader). Subsequent reports dealing with these cancers were made by Stephens; Amor; Cooper (E. H.); Carozzi; Bridge; and Merewether. From 1923 to 1948 inclusive, there were reported to 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 workers with nasal cancer and 72 of those with lung cancer had died. None of the patients with nasal cancer and only 2 of the patients with lung cancer 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 cancer patients was 23 years (range, 3-26 years), and for the lung cancer patients, 25 years (range, 1-33 years). No cases of cancer of the larynx have occurred, and only 1 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 (6), some showed a squamous cell character (3), while columnar cell carcinomas were uncommon (1). Of the lung cancers, of which histological studies were available in only 4 cases, 3 were of the small cell, pleomorphic type, while 1 was a squamous cell carcinoma.

Similar observations were recently recorded from a Norwegian nickel refinery, where 3 cases of lung cancer were seen (Løken). In one of these cases a squamous cell carcinoma was associated with sarcoid lesions.

Goldblatt and Wagstaff 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 reported an unusual frequency of respiratory cancers among the workers of the Sudbury nickel ore mines and smelters in Canada, although several cases of nasal sinus cancers were recently seen in one Canadian nickel plant.

Amor 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 (Løken). More recent data communicated by Morgan confirmed this observation, although exposure to nickel carbonyl vapors had occurred more frequently among the affected workers than was 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 favored the concept that the inhalation 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 (Hueper).

Amor 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 in 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, 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 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 subcutaneous tissue of 175 rats, cancers developed at the site of injection in 50 of them.

Whether or not nickel assumes a carcinogenic role for cancers of other organs and following exposures by other routes is uncertain. It may be mentioned, however, that Araki and Mure demonstrated, by spectrographic methods, nickel in human and animal cancers of various types and sites. The nickel content ranged from 6.273 mg. per kilogram 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 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, liquids, and solids (Bourne and Rushin). Workers most likely to be exposed to chromium and its compounds are acetylene workers, aniline workers, bleachers,

blueprinter, chromate, on makers, workers, gers, potters, battery makers, ink makers, photo workers, s canizers, v welders, u railroad en stallations.

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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, waterproofers of textiles and paper, welders, users of chromate antirust agents in railroad engines, automobiles, steam heat installations, and bitumen and oil refinery workers.

An environmental atmospheric contamination with chromium compounds may result from the release of chromium-containing industrial wastes of chromate plants and of oil refineries using a chromium-containing silica catalyst for the catalytic cracking of oils. An environmental spread of chromates may also follow the use of such compounds as antirusting agents in automobiles and for anticorrosive coating of airplanes. Since many of the industrially used chromium compounds exert a corrosive action on tissues, skin contact and/or inhalation of such agents results in the development of chrome ulcers of the skin and nasal septum which in turn provide definite proof of an existing health hazard. Commenting on the appearance of such manifestations among workers in new industries using chromium compounds, the Chief Inspector of Factories of England and Wales remarked in his report of 1944 that "the control of old hazards in new industries is of interest to others as well as to the student of industrial health, for it would seem that in many cases the hazard is not recognized until damage to tissue has been done, when old principles have to be relearned and adapted to new uses."

This reflective observation seems to be quite appropriate when contemplating the possible existence of respiratory cancer hazards for individuals employed in the numerous industrial operations for which no pertinent published data of any kind exist at the present time.

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 manu-

facture 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 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 are 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.

Supporting this concept as to the chemical nature of the carcinogenic chromium compounds is the fact that workers as well as animals exposed to the inhalation of chromite ore dust have not only a high chromium content of the lungs but also an excessive blood chromium level (Mancuso and Urone). Recent experiments on rats which inhaled finely powdered chromite ore dust showed that after 18 months a chromium level of 13.0 and 17.0 gamma, respectively, in 100 cc. of blood was found in 2 rats studied. This finding, moreover, definitely establishes the fact that a fraction of the chromium contained in chromite ore is solubilized in the pulmonary tissues and discharged into the blood.

Additional support of a causal role of trivalent compounds may be derived from the observation that 10 of the 20 chromate workers with lung cancer reported on by Alwens and Jonas in 1938 were not employed within the manufacturing buildings or were repair men or maintenance workers (blacksmith, glazier, driver, welder, or manufacturer of sulfuric and hydrochloric acid, produced in a nearby building). While all of them probably had some exposure to chromates, it is likely that their contact with chromite ore dust or with dust from the slag heaps containing more or less "insoluble" chromium compounds was much more pronounced (Mancuso; Urone and Anders; Bourne and Yee; Buckell and Harvey).

As the result of the retention of "insoluble" chromium compounds in the lung tissues, there develops a blackish spotty pigmentation and a spotty fibrous thickening of the peribronchial and interstitial tissue where the chromium dust particles are deposited. This pneumonconiotic condition called chromitosis was described by Andrievskaya and Mislavskaya in chromite ore miners, and by Lukanin; Letterer, Neidhardt, and Klett; and Mancuso and Hueper in chromate manufacturers. It was produced experimentally in rabbits by Lukanin. Letterer reported a chrome silicosis in a polisher in an iron foundry who inhaled silica and chromium oxide dust.

While the attempts of Gross and Koelsch and of Campbell to produce lung cancer in mice by exposing them to chromate dust were unsuccessful, Schinz and Vollmann, who implanted powdered chromium metal into the femoral cavity of rabbits observed after more than 3 years, 1 animal with cancer of the lung, and 1 with cancer of the femur.

It is definitely surprising that an excessive liability to lung cancer has been established so far only for chromate workers in Germany (Pfeil; Alwens and Jonas; Teleky; Carozzi; Gross and Koelsch; Alwens, Bauke and Jonas; Lehmann; Martineck; Gross; Koelsch; Alwens and associates; Goldblatt and Wagstaff) and in the United States (Machle and Gregorius; Gregorius; Baetjer; Hueper; Mancuso and Hueper; Imprescia; Division of Occupational Health, U. S. Public Health Service) and in chrome pigment workers in Germany (Baader; Gross and Koelsch; Letterer, Neidhardt and Klett). Bidstrup 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, ranges from 13 to 31 times the normal frequency of lung cancers among the general male population, 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 percent of the cancers affected individuals before the age of 40 years, when lung cancers of unknown etiology are relatively infrequent (table 22).

The quantitative data on the chromium content of various organs and blood of persons with chromium lung cancer have been reported by several investigators (Alwens and Jonas; Let-

terer, Nieder Hueper). Sp behavior of th and urine in c the developm that in chron excretion of el ment of lung blood chromi confirmed, th importance in respects.

With the e the nares (2 maxillary sin lung was the observed am number of th 125 cases fr reported as ulcers.

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Table 22. Age distribution of cases of chromium cancers of the lung, according to type of worker

Type of worker	Age (years)						Total
	21-30	31-40	41-50	51-60	61-70	71-80	
American chromate	0	8	16	19	10	1	54
German chromate	1	3	7	14	12	1	38
German chrome pigment		5	3	1	1		10

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1	54
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1	10

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terer. Niedhardt and Klett; Mancuso and Hueper). Spannagel recently noted a peculiar behavior of the chromium content of the blood and urine in chromate workers before and after the development of lung cancer. It was found that in chromate workers the normal urinary excretion of chromium ceases with the development of lung cancer while simultaneously the blood chromium level becomes elevated. If confirmed, this observation may have distinct importance in causal, metabolic, and diagnostic respects.

With the exception of 2 cases—1 cancer of the nares (Newman) and 1 cancer of the maxillary sinus (Goldblatt and Wagstaff)—the lung was the exclusive site of respiratory cancers observed among chromate workers. The total number of these cancers is at present around 125 cases from all sources. None has been reported as originating from nasal septum ulcers.

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

ARSENIC

Arsenicals represent a byproduct 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 and slag heaps. They are extensively produced and used, especially during 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 (Mote). Arsenic and its compounds constitute, according to "Environment and Health," a health hazard for 35,251 workers employed in American in-

dustries. This definitely is a very conservative estimate of the number of exposed workers, considering the long, although incomplete, list of different occupations entailing contact with arsenicals given by Chamberlain. The estimate, moreover, does not include the rather considerable number of persons who are exposed to arsenicals for purely environmental reasons by ingesting arsenicals with foodstuffs contaminated with arsenical insecticide residues, by consuming drinking water polluted with arsenicals leached into drinking water supplies from mine and smelter dumps, or by inhaling arsenicals released into the air from industrial establishments or by small- or large-scale dusting operations of arsenical pesticides.

From the published evidence, it appears that environmental and nonoccupational contacts with arsenicals have been responsible in recent decades for the majority of cases of chronic arsenicism and cutaneous arsenical cancers (Neubauer; Hueper; Arguello; Tello; Macola and Manzano; Butzengeiger; Baader; Nieberle; Hofmann; Prell; Holmquist; Montgomery and Waisman; Cannon; Arhelger and Kremen; Straube; Bohnenkamp; Hanser and Simon; Gonnet; and many others).

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 rather recently 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. The inhalation of arsenical dust and fumes induces 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. Under such circumstances, the existence of a causal relationship between cancer of the lung

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and chronic arsenicism appears to be a reasonable conclusion. Chest and X-ray examinations of 40 workers employed in an arsenic smelter revealed a mild degree of pneumoconiosis (Saupe).

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 observations previously made by Schmorl on 2 arsenic smelter workers who died from cancer of the lung (Teleky). Frommel briefly mentioned the occurrence of a cancer of the lung in a taxidermist who used an arsenical powder for dusting the pelts of animals. Four additional cases of lung cancer in sheep dip workers with arsenic dermatosis noted in one of these were reported by Merewether, while Hopkins and Van Studdiford 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 (Merewether; Hopkins and Van Studdiford) among only 24 individuals suffering from occupational arsenical dermatosis and epitheliomas caused Neubauer to wonder whether this is mere coincidence, because only 2 cases of lung cancer were observed among 143 cases of medicinal arsenic cancers of the skin (Russell and Klaber), or whether under occupational conditions the irritation of the respiratory tract by arsenical dust was responsible for the phenomenon.

Henry, commenting on the occurrence of skin cancers among sheep dip workers (1910-23), recorded 2 additional cases of lung cancers among 10 such workers who had cutaneous cancers. He mentioned, moreover, the presence of cancers of the left foot, abdominal wall, and lung in a furnaceman in a sodium arsenite factory. Analyzing the mortality experience of a sheep dip factory, Hill and Fanning found that 7, or 31.8 percent, of the 22 cancers causing death among members of this group were located in the respiratory organs, while 3, or 13.6 percent, were situated in the skin. There were during the period 1910-43 a total of 75 deaths from all causes among workers in this factory. 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 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 epidemiological investigations on arsenic cancer was made by Snegireff and Lombard in studies of 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, 12 were due to cancer of all sites, and of these, 6 were located in the lungs. 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 studied 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 percent of all cancer deaths among employees of one plant surveyed were caused by cancer of the lung, the observations made in fact strongly suggest 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 cancers 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 (table 23).

However, the existence of such connections

Table :

County and population

Deer Lodge, 13
Silver Bow, 53
Cascade, 41.49
Gallatin, 18.26

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Table 23. Lung cancer mortality in several Montana counties, 1947-48 (Lull and Wallach) ¹

County and total population 1940	Major industry	Number lung cancers		Total	Total cancer deaths	Percent lung cancer		Annual lung cancer death rate 100,000	
		Male	Female			Male	Female	Male	Female
Deer Lodge, 13,627	Copper smelting ²	21	0	21	98	30.8	0.0	145.7	0.0
Silver Bow, 53,207	Copper mining ²	27	2	29	259	22.6	1.5	48.6	3.9
Cascade, 41,499	Copper mining, smelting ²	20	5	25	299	12.7	3.5	46.3	12.3
Callatin, 18,269	Agriculture	1	0	1	81	3.0	0	5.2	0

¹ Personal communication of unpublished data.² The estimated crude death rate for lung cancer among white males in the entire United States in 1947 was 10.9 per 100,000 population.³ The workers employed in copper ore mining and smelting inhale dust and fumes of arsenic contained in the ore and released as a byproduct and waste product during the smelting process.

should be acknowledged only when there existed at some time clinical and, if possible, histological 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, and 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.

IRON

The extensive production and use of various types of iron and of diverse iron products offers frequent opportunities for the inhalation of dust and fumes of iron and its various alloys and compounds by iron ore miners, arc welders, grinders, polishers, silver finishers, and metal workers.

The resulting red or black siderosis caused by pulmonary retention of Fe_2O_3 or of $\text{Fe}_3\text{O}_4 \cdot \text{H}_2\text{O}$, respectively, is considered an inert form of pneumoconiosis which does not cause disability and which at least in part seems to be reversible. The deposition of iron oxide particles does not elicit in the lungs a progressive and marked fibrosing reaction unless the inhaled dust also contains silica, producing then a siderosilicosis.

The coexistence of siderosis and cancer of the lung has occasionally been observed (Stew-

art and Faulds, 1 case; Dreyfuss, 3 cases in watchmakers; Vorwald and Karr, 3 cases in hematite miners; Simons, 1 case in a blaster of iron casts). It may be mentioned, moreover, that Kennaway and Kennaway reported a 2.25-fold incidence of pulmonary cancer among metal grinders and that Turner and Grace as well as Campbell noted an excessive frequency of lung cancer among metal workers.

The most recent contribution to the problem of siderotic cancer of the lung was furnished by Faulds, who noted that among 192 iron ore miners coming to necropsy between 1932 and 1953 there were 17 lung cancers (8.85 percent). Ehrhardt and G  thert, on the other hand, noted that red siderosis of the lung does not produce a special predisposition to lung cancer.

The uncertainty existing in this respect is further illustrated by statistical data provided by J. W. Brower, Deputy State Registrar, Minnesota Department of Health, on the number of deaths from lung cancer among iron ore miners residing in St. Louis and Itasca County (total number of miners, 13,313) against that of residents of Minnesota (population base, 2,982,483). There prevails a consistently higher lung cancer death rate for iron ore miners for the 5-year period than that noted for Minnesota residents (table 24).

Experimental studies on animals exposed to iron oxide and hematite, respectively, gave contradictory results as to the production of lung tumors. While Vorwald and Karr, using guinea pigs and rats, failed to obtain lung cancers with

Table 24. Deaths due to cancer of the lung among iron ore miners and residents of Minnesota, (Brower) 1950-54

Year	Number of deaths		Death rate per 100,000	
	Minne- sota resi- dents	St. Louis- Itasca County miners	Minne- sota resi- dents	St. Louis- Itasca County miners
1950.....	328	5	11.0	37.6
1951.....	289	4	9.7	30.0
1952.....	329	12	11.0	90.1
1953.....	367	8	12.3	60.1
1954.....	345	6	11.6	60.1

hematite dust. Campbell reported an increase in the number of lung tumors in mice exposed to iron oxide over that of the control series.

When the available evidence is viewed critically, it is still uncertain whether an exposure to iron dust conveys an abnormal liability to lung cancer. Although Warren and Drake recently concluded that the development of primary carcinoma of the liver as a sequela of hemochromatosis apparently depended in part on the intracellular deposition of iron, such considerations may not necessarily be applicable to pulmonary siderosis and cancer.

However, thorough and comprehensive epidemiological data on the incidence of lung cancer in workers exposed to iron dust are not available. Hence, a definite conclusion on this problem must be withheld. The availability of conclusive information on this point appears to be urgent, in view of the suggestive evidence recorded by Faulds and because of the fact that damages have been allowed in the past by court action in at least one case of cancer of the lung, in the production or aggravation of which the inhalation of steel dust was alleged to have played a significant role.

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 fibers, gas mantles). It is evidently for this reason that untoward effects in persons exposed to the inhalation of dusts and fumes of beryllium and its various compounds have been recognized only during the last decade. These manifestations were of both acute and chronic nature as far as the respiratory organs were concerned (acute beryllium pneumonitis, chronic pneumoconiotic granulomatosis, berylliosis). Some investigators used the term "sarcoid" in describing the histologically peculiar, pulmonary manifestations. 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-containing effluents (Eisenbud, Berghout and Steadman; Eisenbud, Wanta, Dustan, Steadman, Harris, and Wolf).

Similar observations on occupational berylliosis were reported from Germany, Italy, England, Russia, and Canada. Not infrequently, similar granulomatous lesions have been observed in other parts of the body after the usually traumatic introduction of beryllium dust, especially of beryllium phosphors from broken fluorescent tubes. The skin of the fingers and hands was the most frequent extrapulmonary location of these reactions. Beryllium granulomas have also been found in the nose and in the anterior ocular structure.

It is noteworthy, that beryllium apparently once inhaled is retained over a long period of time in the human body, since beryllium has been detected in the urine up to 10 years after cessation of exposure (Klemperer, Martin, and Van Riper) and has been demonstrated in the lungs of rats 1 year after the inhalation of beryllium oxide (Dutra, Largent, Cholak, Hubbard and Roth) as well as in their bones (Stokinger, Steadman and Root; Barnes), where it may replace calcium. The skeleton retains the bulk of the beryllium in the body (50-80 percent) if the inhaled aerosols are soluble compounds, such as beryllium sulfate and beryllium fluoride; the lungs retain the bulk of beryllium if the compounds are insoluble, such as beryllium oxide. Experiments

of Aldridge, shown that certain tissue plasma prot blood. These from being p

The metabolites obtained from fact that Gas tion of osteo intravenously ing powders. lium silicate, quently conf and other oxide, beryll introduced in respiratory r Sissons; Hoag Largent, and period for the

Comments osteogenic se of beryllium noted the fa dying with b able amount following co years, consid been exposed pounds of throughout fact that cas been reported of poorly sol eventuate in sumably, the would be co rabbits, and over a period whether per beryllium ar

Barnard a coma from possibly be far, only rab opment of administrative direct introd into the fem cavity, and

beryllium products, the windows, and fibers, gas in the reason that used to the in-beryllium and been recognized these manifestations of chronic pneumoconiosis. Some "sarcoid" in the lung, pulmonary ble moreover, appeared not only so among persons of fluorescent beryllium. Berghout and Hustan, Stead.

national beryllium, Italy. Not infrequently lesions have been found in the body after inhalation of beryllium phosphors from the skin of the man. Frequent reactions have been found in the structure. In apparently long period of beryllium 10 years after, Martin, and demonstrated in the inhalation of beryllium, Cholak, in their bones (Barnes). The skeleton in the body of aerosols are beryllium sulfate. The beryllium compounds are in the experiments

of Aldridge, Barnes, and Denz, 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.

The metabolic peculiarities of beryllium compounds obtain special importance in view of the fact that Gardner 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 (Sissons; Barnes, Denz and Sissons; Hoagland, Grier and Hood; Nash; Dutra, Largent, and Roth; Barnes). The preparatory period for the sarcomas was 11-24 months.

Commenting on the successful production of osteogenic sarcomas in rabbits after inhalation of beryllium oxide, Dutra, Largent, and Roth noted the fact also that the bones of persons dying with berylliosis contained not inconsiderable amounts of beryllium. They came to the following conclusions: "During the last 20 years, considerable numbers of persons have been exposed to dusts of poorly soluble compounds of beryllium in various industries throughout the United States. Despite the fact that cases of cancer of this type have not been reported, it is possible that the inhalation of poorly soluble compounds of beryllium may eventuate in osteogenic sarcoma in man. Presumably, the incubation period of such tumors would be considerably longer in man than in rabbits, and observations may be required over a period of years before it will be known whether persons who have been exposed to beryllium are prone to have such tumors."

Barnard also suggested that osteogenic sarcoma from compounds of beryllium "might possibly be another industrial hazard." So far, only rabbits have responded with the development of osteogenic sarcomas following the administration of beryllium compounds. The direct introduction of powdered beryllium metal into the femoral cavity of rats, into the pleural cavity, and into the paranasal sinuses failed to

elicit a single neoplastic response at the site of injection in any 1 of the 85 animals used within an observation period of 2 years (Hueper).

When in 1948 Hueper proposed that the sarcoid pulmonary manifestations of berylliosis might be followed by outright malignant lesions in the lungs, this suggestion was received with a great deal of skepticism. The recently reported successful production of bronchogenic carcinomas in the lungs of rats which, over periods of more than 1 year, inhaled dust of soluble and insoluble beryllium compounds (Vorwald), however, makes the appearance of such delayed malignant sequelae in man a distinct possibility, especially as several cases with coexisting berylliosis and cancer of the lung have recently been observed (Kahlau). In view of the established occupational as well as general environmental occurrence of human berylliosis, it may be pointed out that the discovery and identification of this pneumoconiosis was definitely facilitated by the distinctive and definitive histological features of the disease. If these manifestations should be followed by the development of cancers of the bones and lungs, the establishment of causal relations between a previous exposure to beryllium and the subsequently appearing cancerous reaction would appear to be rather easy.

The studies on the toxicity and carcinogenicity of beryllium compounds indicate that the toxic and cancerous manifestations are to be considered as responses to the action of beryllium itself and not as the result of the associated anions of its acidic salts (Stokinger, Sprague, and Hall). In considering possible future carcinomatous developments in persons with previous exposure to beryllium, some consideration also may be given to the toxic effect exerted by beryllium on the liver leading to the development of cirrhosis and to an impairment of the metabolic and detoxicating function of this organ (Aldridge, Barnes, and Denz; Hoagland, Grier, and Hood).

Organic Chemicals

COMBUSTION AND DISTILLATION PRODUCTS OF COAL

The apparent innocuousness 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 highly viscous oily and tarry fractions obtained by the direct hydrogenation of coal employed by the Bergius process). The carcinogenic action of these combustion and distillation products of coal on man and experimental animals has been established beyond any doubt. Although the bulk of the casuistic and epidemiological human evidence of occupational coal tar and pitch cancers has come from England and Germany, it cannot justly be assumed that American-made coal tars, tar oils, creosote oils and pitches differ fundamentally in their carcinogenic properties from those manufactured abroad. The exposures sustained by the numerous types of American workers in a great variety of occupations and operations do not seem to differ from those found for their European colleagues, nor are the carcinogenic effects on the skin of these workers at variance with European observations.

However, in addition to skin contact with these products of processed coal, there exists for some groups of workers a considerable exposure to these agents in the form of dust or fumes (tar distilleries, tar paint, shingle, roofing paper, paper conduit, and battery case manufacture, gas works, coke oven operations, road construction and repair work, roofing, brickmaking, foundries, furnace attendance, railway engine driving, roundhouse operations, pickling of lumber, chimney sweeping, cork brick manufacture, electrolytic metal production, and so on).

Since the high boiling fractions of synthetic oils produced by the direct hydrogenation of coal through the Bergius process have been shown to be highly carcinogenic to the skin and/or subcutaneous tissue of mice and rats, respectively, certain types of workers manufacturing and using such products and inhaling fumes or mists of these carcinogenic petroleum and tar oil substitutes may have a special lung cancer hazard. Manufacturing plants using the Bergius process have been operative for some 20 years in Germany and have recently been constructed by several industrial concerns in the United States.

Not only the environmental, but also to a greater degree, the occupational inhalation of dust, soot, and fumes produced by the incomplete combustion of coal results in the development of a "soot lung," called bituminosis,

which is characterized by the deposition of finely dispersed carbon particles contaminated with hydrocarbons normally contained in coal tar in the interstitial lung tissue. Roentgenological changes may appear in the lungs after many years of exposure to high concentrations of soot in the air inhaled. While the pulmonary deposition of small to moderate amounts of soot in the lungs, such as is commonly found in inhabitants of industrialized regions, does not elicit any appreciable fibrous proliferations, massive storage of soot particles in the lung tissues may finally be associated with an increase of the interstitial connective tissue and with pseudoglandular formations of peribronchial alveoli.

The human evidence relating exposure to coal tar and pitch dust and fumes with an increased liability to cancer of the lung is not extensive and is in part controversial.

The human evidence relating exposure to coal tar dust and fumes with an increased liability to cancer of the lung is equivocal. Kennaway and Kennaway stated that "coal tar in the atmosphere, whether derived from roads, domestic chimneys, or any other source, does not cause an exceptionally high incidence of cancer of the lung." A similar statement was made by Hugounenq and by Husted and Biilmann in regard to the liability to cancer of the lung for workers employed in the tar industry and in the construction and maintenance of tarred roads. McLaughlin did not find any lung cancer among 3,059 foundry workers subjected to clinical and X-ray examinations, although there were 3 deaths from lung cancer among 64 deaths from all causes. Menz recently reported that of 93 workers in Swiss gas plants who died during the 1926-46 period, 21, or 22.6 percent, died from cancer of all sites, thereby confirming previous English experience that workers in tar and pitch operations have an excessive liability to cancer in general. Isolated observations of lung cancer in workers exposed to the inhalation of tar fumes were made by Koelsch (blacksmith, tar worker), Rodenacker (briquette factory worker), and Müllschitzky (tar worker).

In an analysis of lung cancer deaths among members of different occupational groups for the years 1933-38 Kennaway and Kennaway, on

the other hand (100) lung cancer following occupation: gas stokers, 28; crane operators, 136; printers, asphalt workers, 129; and automobile mechanics, 129; moreover, a number among employees.

Additional evidence is provided by the observation of lung cancer in generator gas plants and among workers in Canada and England. Kawabata: Crude oil investigators found cases of lung cancer among workers who were exposed to hot tar fumes. Lung cancer is also employed in other general incidence of generator gas plants employed. So occurred in workers (33 percent among lung cancers) varied from 9 to being 16.6 years recently made workers. Of 14 cases, 6 were cancer of the ethmoid sinus, upper and lower.

It is likely that rates may exist. Following a visit to 25 skin cancer cases had been observed during an 8-year study of lung cancer. company officials reported cancers in this cases of cancer.

From the evidence of the inhalation of certain occupational plants, gas plants

the other hand, noted that an above-average (100) lung cancer frequency existed for the following occupations: gashouse workers, 129; gas stokers, 284; gas producers, 202; gasworks crane operators, 138; gasworks superintendents, 136; printers, 119; chimney sweeps, 119; asphalt workers, 164; metal polishers, 174; painters, 129; tanners, 141; street cleaners, 169; and automobile drivers, 149. They recorded, moreover, a ninefold increase of lung cancer among employees of a Canadian gas plant.

Additional supporting information was provided by the observations made among Japanese generator gas oven workers employed in steel plants and among gashouse retort workers in Canada and England (Kawahata; Kuroda and Kawahata; Cruickshank; Doll). 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 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 per 1,000 workers employed. Seven of these 21 lung cancers occurred in workers aged 40 years or younger (33 percent against 18 percent in cryptogenetic lung cancers) (Hueper). 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, 6 were due to cancer of the lung, 1 to cancer of the larynx, and 1 to cancer of the ethmoid sinuses (57 percent were 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 to a tar distillery where some 25 skin cancers and more than 80 pitch warts had been observed among the 300 workers during an 8-year period, there was found 1 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.

From the evidence available, it appears that the inhalation of tar fumes sustained by workers of certain operations (coke oven, 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. A recent observation of lung cancer in a worker exposed to heated pitch and asphalt points to another source of occupational pulmonary tar cancer of definite practical importance (Patch).

PETROLEUM, SHALE OIL, AND NATURAL GAS

The carcinogenicity of certain high boiling fractions of petroleum and oil shale, as well as of the combustion products of some of these petroleum derivatives, such as oil shale and natural gas, have definitely been demonstrated not only on experimental animals but also on workers developing cancers of the skin after prolonged contact with these agents. Known carcinogenic chemicals, moreover, have been isolated from these petroleum derivatives as well as their combustion products (Berenblum and Schoental; Fischer, Priestley, Eby, Wanless and Rehner; Falk, Steiner, Goldfein, Breslow and Hykes; Waller; Rehner; Kotin and associates.)

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, and so on). In spite of this established occupational respiratory exposure to petroleum and shale oils, there are on record only three cases of oil pneumonia among such workers, although such conditions have rather frequently been observed after repeated medicinal instillations of mineral oil containing nasal drops (oil aspiration pneumonia 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 (Wood; Sante).

The occupational evidence available or published on this aspect of cancer of the lung is rather scanty and in part controversial. Kennaway and Kennaway found a relatively high

ratio of laryngeal but not of pulmonary cancer in mulespinners, who inhale a mist of the carcinogenic shale oil lubricating the spindles. Southam noted that mulespinners occasionally develop multiple primary cancers involving the stomach or the lung in addition to cancers of the skin. Scott, on the other hand, stated that he had not observed a single case of lung cancer among shale oil workers.

Huguenin, Fauvet and Bourdin, who analyzed a series of 112 lung cancers for possible etiological factors, found that 18, or 16 percent, were metallurgical workers exposed to the inhalation of nebulized lubricating and cutting oils. 8 were chauffeurs, 5 were mechanics, and 1 was an engineer. Huguenin and his associates 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 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. Rösch observed three primary cancers (skin, stomach and lung) in a paraffin worker. Touraine and Bour 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.

There is, moreover, some evidence available indicating that the inhalation of mists or fogs of certain processed petroleum oil fractions also conveys an increased liability to cancer of the lung. During a recent survey on cancer incidence among employees of a large oil refinery, the surprising observations were made that there was not only a highly excessive incidence of scrotal cancer among employees of the paraffin pressing department but that incidence of cancer of the lung was also excessive. Paraffin pressers, who represent about one-tenth of the total employed worker group, furnished 56 percent of the lung cancer observed.

Since 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; carbon electrode manufacturers and users in aluminum plants; smudge pot operators; phonograph record makers) is an urgent necessity. The negative conclusions reached by Ingalls as the result of a survey of the carbon black industry are based on evidence of dubious merits, because only 79 of the 677 evaluated workers have been employed for 10 years or more in the industry. Since the majority of known occupational lung cancers have an average latent period of over 10 years, Ingalls' conclusions are actually based on 79 living and active workers. It stands to reason that an analysis of the death records of former carbon black workers may have told a different story, especially if the diagnoses were based on autopsy findings. Such investigations would also add to our knowledge as to the existence, extent, and type of bituminosis which might be expected to exist in workers inhaling finely dispersed soot particles.

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 exposure to the effluents of diesel and gasoline engines, represents the most widespread occupational and environmental contact with carcinogenic material. The specific carcinogenic agents contained in these carbonaceous matters are certain specific aromatic hydrocarbons, which not infrequently are attached to carbon particles giving rise, when inhaled, to bituminosis or anthracosis; or they are constituents of oily matter which, when inhaled and retained in the lungs, cause oil pneumonia or paraffinoma of the lung.

Since pure anthracosis is not causally related to cancer of the lung, the pneumoconioses accompanying respiratory carcinogenesis by aromatic hydrocarbons do not play a primary and essential role in this process, although the pneumoconioses may lower the intensity and

prolong the duration of the carcinogenic chain.

Since our civilization has been built around basic carbonaceous materials, it does not seem complete protection against carcinogenic chains by prophylactic measures is practical and adequate. There is, however, much that remains to be done. We are still rather ignorant as to the maximal amount of exposure to the respiratory carbonaceous substances which

Carbon

Recent studies by Homer, Rose, and Wagoner have shown a new and interesting combination of linkages between chemicals and chromosomes. From evidence of carcinogenesis by nitroethylenimines, in view of the fact that by which these specific action, it is assumed that chains might mucoproteins and linkage with m by cause mitotic action of one meric molecule may start a process followed by a epoxide groups.

These concepts with respiratory reasons. Since Druckrey and shown that various poly-

prolong the duration of the effect of the specific carcinogenic chemicals on the lung tissues.

Since our civilization and economic 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.

Carbon and Silicon Polymers

Recent studies of English investigators (Hendry, Homer, Rose, and Walpole; Hendry, Rose, and Walpole; Haddow) have furnished a new and intriguing concept as to possible combinations of carcinogens with tissue proteins through the postulated formation of cross linkages between certain types of carcinogenic chemicals and the macromolecular fibers of chromosomes. This hypothesis was evolved from evidence obtained in the study of carcinogenesis by nitrogen-mustards, diepoxides, 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 mucoproteins 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 polyetheneoxy-structure.

These concepts are important in connection with respiratory carcinogenesis for several reasons. Since Oppenheimer and associates; Druckrey and associates; and Zollinger have shown that a parenteral implantation of various polymerized plastics (cellophane,

polyethylene, polyvinyl chloride, polymethyl methacrylate, polyamide, Teflon, and others) into rats and mice are followed by the development of sarcomas at the site of deposition, there exists the possibility that the inhalation of vapors, mists, and dusts of the monomers and polymers of these and related chemicals for occupational reasons may create a respiratory cancer hazard to man.

The more immediate importance of these concepts, however, lies in their application to the production of occupational respiratory cancers by a silicon polymer, asbestos, possibly also by a carbon polymer contained in isopropyl oil (polypropylene or propyl epoxide). The probability of such an action mechanism, moreover, is supported by observations of lung cancers among Japanese mustard gas manufacturers.

ASBESTOS

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 tetrahedra which are arranged in chains or bands (Parkes). Depending on the origin of asbestos, the fibrils may be short or long. Italian, South African, and Australian asbestos (amphibils) consists of fibrillar or radiating crystals of calcium-magnesium silicate or sodium iron silicate (40 percent iron oxide). Canadian, Russian, German, and French asbestos is hydrated magnesium silicate, which contains small amounts of iron oxide (5.75 percent). Canada furnishes about 75 percent of the world production of asbestos. Canadian asbestos, because of its long fibers, is especially suitable for textiles.

Depending on its physical characteristics, asbestos finds numerous uses (textiles, filter material, building material, gaskets, insulating material, adsorbants, and so on). Some 35,000 workers in the United States are exposed to asbestos dust.

It is asserted that inhaled asbestos dust pro-

duces asbestosis only if the inhaled fibers are sufficiently long. In the absence of fibrous structure, the dust is said to be inert (Wyers; Vorwald, Durkan, and Pratt). Since the larger fibrils are arrested in the bronchioles (Gardner), the granulomatous reactions form peribronchiolar fibrous cuffs with giant cells and asbestos bodies. These have a fibrillar core and an iron staining proteinic or colloidal silicic acid sheath. Whether the iron in the sheaths originates from the asbestos fibers or is derived from blood or tissue elements is still controversial. These two observations deserve special mention because of the apparent dependence of cancerous changes in the lungs of asbestos workers upon the presence of asbestosis and in view of the possibility that the proteins of the lung tissue may specifically interreact with free groups of the filamentary asbestos molecules (Druckrey and associates).

The coexistence of asbestosis with cancer of the lung was first reported by Lynch and Smith in 1935 (1 case). They later recorded 3 additional cases (Lynch and Smith; Lynch). Similar observations have subsequently been recorded from this country (Stoll, Bass, and Angrist, 1 case; Holleb and Angrist, 2 cases; and Homburger, 3 cases); from Canada (Desmeules, Rosseau, Gilroux, and Sirois, 2 cases; Cartier, 4 cases; Rousseau, 1 case); from England (Gloyne, 17 cases; Harrison, 3 cases; Merewether, 31 cases; Cureton, 1 case; Owen, 1 case), and from Germany (Nordmann, 2 cases; Linzbach and Wedler, 1 case; Horning, 1 case; Welz, 2 cases; Böhme, 1 case; Domenici, 2 cases; and Baader, 1 case).

Thus, there is at present a total of 80 cases of asbestosis cancer of the lung on record. To this number must perhaps be added the 8 cases of cancer of the lung complicated by asbestosis which Kennaway and Kennaway discovered in an analysis of the death certificates of males registered between 1921 and 1938. Eleven additional cases of asbestosis cancer of the lung in workers in two English plants were recently reported by Doll, who felt from his statistical analysis that there exists a definite causal relation between these two conditions (table 25).

Merewether noted that the mean age of males with asbestosis cancer of the lung was 55.2 years (range 22-72) and that their mean expo-

sure time was 20.1 years (range 6-40), while the mean age of female cases was 44.6 years (range 32-71) and their mean exposure time was 7.6 years (range 0.5-48). However, in many cases there elapsed a long exposure-free interval ranging from several months to 20 years before the lung cancer became manifest (Wedler; Wyers).

The age distribution of asbestosis cancer of the lung was:

Age (years)	Cases of lung cancer
25-34.....	2
35-44.....	11
45-54.....	16
55-64.....	17
65-75.....	5
Total.....	51

Since lung cancer of unknown etiology occurs rather frequently before the age of 40 and since 26 percent of the asbestosis cancers appeared before the age of 44, it seems that there exists a moderate shift toward younger age groups for cancers associated with asbestosis of the lung.

The exposure time for asbestosis lung cancer, excluding the series of Merewether, was:

Exposure time (years)	Cases of lung cancer
1-3.....	4
4-10.....	6
11-20.....	4
21 and over.....	7
Total.....	21

The exposure time of this series covers a wide range (1-23 years), indicating that type and intensity of exposure to asbestos as well as perhaps an individual susceptibility to asbestosis play an important role in determining the development of this pneumoconiosis and thereby the possibility of a secondary carcinomatous sequela in the lung.

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.

It is of importance to note that the mean

Table 25. Causes

Lung cancer¹.....
Other respiratory².....
With mention of
Without mention
Neoplasms, other³.....
All other diseases³.....

All causes.....

¹ Including 14

² Including pu

³ Including 2

not thought to hav

age of 128 non-
was only 44.2
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Hueper; Gross
Linzbach and
Welz; Doll).

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Table 25. Causes of death among male asbestos workers compared with the mortality experience of all men in England and Wales (Doll)

Cause of death	Number of deaths		Test of significance of difference between observed and expected (value of P.)
	Number observed	Expected on England and Wales rates	
Lung cancer ¹	11	0.8	<0.000001
Other respiratory diseases ² 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	
All other diseases ³	4	4.7	>0.1
All causes	39	15.4	<0.000001

¹ Including 1 case with pulmonary tuberculosis.

² Including pulmonary tuberculosis.

³ Including 2 cases (benign stricture of esophagus and septicaemia) in which asbestosis was present but was not thought to have been a contributory cause of death.

age of 128 noncomplicated cases of asbestosis was only 44.2 years (Merewether). One may conclude from this observation that some of these individuals apparently died from asbestosis before their lung cancer had a chance to develop (Linzbach and Wedler).

Additional support for a causal relation between asbestosis and cancer of the lung is derived from the fact that Merewether found, among 266 cases of asbestosis observed during 1924-46, 31 cases of coexisting cancer of the lung (11.65 percent), while there were 91 cases of lung cancer with an average age of 59.4 years among 6,884 cases of silicosis (1.32 percent) which came to autopsy. Wedler noted that asbestosis cancer of the lung occurred in 14 cases, or 15.2 percent 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 percent.

Lanza, Vorwald, Warren, and Cartier are all quite skeptical as to the actual existence of an excessive liability of individuals with asbestosis to lung cancer, and Cureton and Homburger are undecided on this question. Other investigators, however, favor this concept or consider the existence of a causal relation as highly probable or established (Kennaway; Merewether; Teleky; Nordmann; Hueper; Gross; Lecoeur; Smith; Saita; Wegelin; Linzbach and Wedler; Stoll, Bass, and Angrist; Welz; Doll).

The histological types of lung cancers ob-

served do not deviate essentially in their relative frequency from those seen in cancers of unknown etiology. There were 22 squamous carcinomas, 7 oat cell carcinomas, 4 anaplastic carcinomas, and 6 adenocarcinomas. In view of the fact that one of the Norwegian cases of nickel cancer of the lung was associated with pulmonary sarcoidosis, it may be mentioned that Skavlem and Ritterhoff reported the combination of an asbestosis with a sarcoidosis of the lung which, however, was not complicated by a carcinoma.

Attempts have been made to refute the claim of a causal relation between asbestosis and lung cancer by determining the frequency of pulmonary cancer among the total worker population of the asbestos industry (Cartier; Vorwald). Such a procedure is bound to give misleading results. It is quite immaterial how many workers employed in the industry develop lung cancer, since an undetermined portion of these workers doubtlessly sustains either no exposure or only a low intensity exposure and thus does not develop asbestosis of the lung, which is the prerequisite for the subsequent cancerous development. Asbestosis must be considered as the essential stigma of an effective exposure. It is, moreover, necessary to know the sex and age distribution of the worker population studied and evaluated as well as to know the duration of employment and exposure. A marked labor turnover in the industry is not conducive for obtaining reliable information on

the actual number of lung cancers and asbestosis cases which may result from effective exposures. For these reasons, no definite conclusions can be drawn from the observation of Cartier, noting 8 cases of lung cancer among 4,000 workers studied for 10 years, especially as the frequency of asbestosis among effectively exposed workers increases with the duration of exposure (Böhme). Kennaway and Kennaway reported that 8 lung cancers may be found among 4,000 males of the age range 45-64 years.

The evidence on hand, at any rate, has convinced the West German Government to make asbestosis cancer of the lung a compensable disease (Tabershaw).

The experimental approach to the problem has so far given equivocal results. Vorwald and Karr, using guinea pigs which were exposed to asbestos dust, obtained negative results. Nordmann and Sorge employed mice for this purpose and claimed to have produced bronchiogenic carcinomas with pulmonary fibrosis in two mice. This observation needs to be confirmed before it can be accepted.

ISOPROPYL OIL

Through the recent discovery of cancers of the paranasal sinuses, larynx, and lung among isopropanol manufacturers, the occurrence of carbonpolymer cancers has probably been extended to man. Isopropyl oil—the crude liquid from which isopropyl alcohol is distilled and which is a slightly turbid, viscous liquid, slowly turning, upon standing, 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 reported that, between 1928 and 1950, a total of 7 neoplasms affecting various parts of

the respiratory tract (nasal sinuses, 4; larynx, 2; and lung 1) came to observation among 71 employees, or in 8.4 percent of those who worked more than 5 years in the isopropanol plant.

Five additional cases were observed in another isopropyl alcohol plant, making a total of 12 cases, 7 of which involved the nasal sinuses, 4 the larynx, and 1 the lung. It was calculated that the incidence rate of cancer of the nasal sinuses and larynx for the second group was 134.5 per 100,000, against a normal rate of 6.3, and that the incidence of these cancers exceeded the expected incidence 21.3 times.

From the evidence available it is likely that these cancers as well as those associated with asbestosis belong to the new class of "polymer cancers."

MUSTARD GAS

The alleged carcinogenic action of war gas poisoning figured prominently in the speculations as to the cause of the increase in lung cancers observed during the early 1920's (Kikuth; Brockbank; Klotz; Derischanoff; Hünemann; Reiche). Residuals of warfare gassing were noted by Matz in 10 out of 138 cases of pulmonary cancer among American World War I veterans. Four out of 64 cases of lung cancer, recorded by Brockbank, were gassed badly during this war. Macklin noted that war gas poisoning occurred in 5 percent of 164 cases of lung cancer among males, while it was present in only 2 percent of soldiers without this disease. Koelsch conceded that a few cases of lung cancer exhibited a doubtful etiological relation to war gas injury, which was claimed to have caused also two cancers of the larynx (Spamer; Tilley). No distinction was made at that time as to the particular chemical nature of the various gases used during World War I.

These contentions found little acceptance at that time. From a carcinogenic viewpoint, special interest has to be attached to the various arsenic-containing gases, especially Lewisite, and to mustard gas (dichlorethyl sulfide). The arsenical war gases, when inhaled, theoretically may not only cause nonspecific chemical damage to the respiratory tissues but also may produce there a specific delayed carcinogenic reaction.

such as that seen with these gases belong to the group.

A possible cause of gas upon the hand, may be a radiomimetic effect that demonstrates animals exposed to mustards of all kinds. According to the concepts, the cause of these cancers is possibly active.

During the 1920's bronchiogenic cancers were observed among employees of the Manufacturing Chemicals Company, Lewisite and Y-gas workers was 30 percent. All three cases of poisoning due to Y-gas (Yamada, Hiro) were observed. These observations of carcinomatous exposure to mustard products deserve attention.

While the function of these "polymer cancers" is a topic supported by available data are sufficient to attract attention from the viewpoint. The production and natural and synthetic and cross-linking rubbers, resins, brings a considerable variation into direct type. It seems that study these products coming decades particularly the system.

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Up to some extent sure to radioactively small groups of workers active ores, in

such as that seen exceptionally after skin burns with these gases. Cancers of such an origin belong to the group of arsenic cancers.

A possible carcinogenic action of mustard gas upon the bronchial mucosa, on the other hand, may be related to its cross-linking and radiomimetic effect, and may be identical with that demonstrated to exist for experimental animals exposed to several sulfur- and nitro-mustards of aliphatic and aromatic nature. According to the mentioned theoretical concepts, the causative mechanism operative in these cancers resembles in some respects that possibly active in polymer cancers.

During the last few years, three cases of bronchiogenic carcinoma and 3 cases of larynx cancer were observed among long-term employees of the Japanese Army Poison Gas Manufacturing Plant on Okuno Island, where Lewisite and Yperite were made. One of these workers was 30 years old and a second, 53 years old. All three suffered from chronic war gas poisoning due to contact with mustard gas (Yamada, Hirose, and Miyanishi). In view of these observations, the distinct probability of carcinomatous effects upon the lung following exposure to mustard gas or chemically related products deserves serious consideration.

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 a practical viewpoint. The rapidly expanding industrial production and industrial and general use of natural and synthetic polymerized substances and cross-linking chemicals in plastics, films, rubbers, rosins, adhesives, textiles, and so on, brings a considerable part of the working population into 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.

Radioactive Chemicals

Up to some 10 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, smelter and refinery workers, atomic energy plant employees, military personnel, and agricultural, biological, medical, chemical, metallurgic, oil, pharmaceutical, and other industrial research workers employing radioactive isotopes, as well as operators handling directly or indirectly materials or technical devices giving off ionizing radiation, such as radioactive static eliminators (Silson; Berman and Ernest; Bryan and Silverman), sewage disposal workers, paper and textile manufacturers, and so on.

It is an established fact that cancers of the skin, connective tissue, and bone and blood-forming organs have resulted from excessive exposures to radioactive substances affecting the organism or parts of it by various routes. There exists a great deal of highly suggestive, if not conclusive, epidemiological and experimental evidence relating an occupational inhalation of radioactive dust and gases to the development of pulmonary cancers. Although excessive medicinal and occupational exposure to ionizing radiation (radium, X-radiation) alone may produce in man and experimental animals a fibrosis of the lungs (Kalbfleisch; Doenecke; Belt; Bergmann and Graham; Engelstad; Warren and Gates; Leach, Farrow, Foote and Wawro; McIntosh; Warren and Spencer; Widmann; Bauer; Bauer and Schraer; Tönges and Kalbfleisch; Freid and Goldberg), occupational exposure to radioactive dust and gases has often been complicated by simultaneous inhalation of dust containing various metals (chromium, nickel, iron, arsenic, cobalt) as well as silica. Pulmonary cancers observed among radioactive-ore miners, therefore, have been complicated in an appreciable number of cases by silicosis of a minor to moderate degree.

It is for these reasons that the radioactive genesis of the cancers of the lung noted among these miners as well as among uranium and

radium refinery workers has been doubted by some investigators, who felt that one of the various nonradioactive metals or the silicosis represented the main causal or an important contributory agent (Schinz; Lorenz; Schmorl; Rostoski and Saupe) or that the available evidence did not provide absolute proof of a radioactive genesis (Lacassagne). Several investigators felt that the lung cancers among the radioactive-ore miners in Schneeberg and Joachimsthal were principally attributable to a hereditary predisposition created by inbreeding of the mining population (Macklin and Macklin; Lorenz; Vesin).

The "mala metallorum" causing death at an early age of the miners in the ore mountains of Saxony was first described by Agricola during the early part of the 16th century and was subsequently mentioned by other investigators (Henckel; Scheffler; Thiele). However, it was not until 1879 that its malignant neoplastic character was correctly recognized (Härtig and Hesse). This judgment was, subsequently confirmed by Cohnheim; Aucke; Arnstein; Uhlig; Risel; Schmorl; Beyreuther; Rostoski; Saupe and Schmorl; Lange; Neitzel; Döhnert; Baader; Teleky; Hueck; Rostoski, Saupe, and Schmorl; Thiele; Weber; Koelsch; Lindemann; Doubrov; Brandt; Brezina. 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 (Löwy). Additional confirming evidence was provided later by Beutel and Waldrich; Ziel; Sikl; Saupe; Peller; Pirchan and Sikl; Baader; Behounek and Fort; and Teleky.

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 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 and by Neitzel 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, among the workers employed in the radium ore processing plant in Belgium, where the occurrence of such complications was previously said to be absent (Maisin, citing Delaet). 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 that lung cancers may originate from radioactive material used medicinally, when such materials become arrested in the lung.

Mention may also be made in this connection of a report of Martland relating the occurrence of cancer in the ethmoid cells in a luminous dial painter, and of two additional cases reported by Aub. Evans, Hempelmann, and Martland. Dial painters not only ingested radioactive material which became deposited in the bones and produced osteogenic sarcomas, but they also inhaled this matter which, thus, may have produced the carcinoma of the paranasal sinus.

The four cases of cancer of the lung recently reported in an industrial population at an atomic pile site, however, are definitely not causally related to any specific radioactive exposures sustained by the workers concerned. In these cases exposure and latent period were insufficiently long to cause lung cancer (Love). On the other hand, the argument that these workers were, in part, not directly concerned with radioactive material carries little weight. Doubtlessly, they had at times environmental contact with such a material when the meteorologic conditions were unfavorable for the ready dispersal of radioactive wastes at this particular operation.

In favor of an occupational and radioactive origin of the lung cancers among the Schneeberg and Joachimsthal miners is, moreover, the fact that the excessive liability to pulmonary neoplasia is limited to the workers employed underground and is absent among the workers employed aboveground, and among the population at large of Schneeberg and Joachimsthal, including the employees of the cobalt pigment plant using the Schneeberg ores (Bauer; Schmorl).

An excessive lung not been found an Johann Georgens have a low radioactive, no valid evidence of arsenic-, chromium containing ores at a rate even remaining among the two ra

The attack rate at Schneeberg mine between 75 and 80% of the Joachimsthal range from 40 to incidence rate in recent statement during the period of lung cancer was considerable diseases among 323 miners employing the fact that period of lung cancer ranges from 13 to assumed that these in a miner population 400 members were 1920 and 1930. 5 at Schneeberg is years for the majority to be as short Schraub, and Ka

The total number died from cancer 1939, according to approximately 40 Joachimsthal miner has reached 225 number of these at a relatively early data given in table the definite shift

Measurements at Schneeberg and demonstrated that, in have an excessive passing many times (Joachimsthal 3 Behounek and F. Lorensen; Lange. It was suggested of pneumatic di

An excessive lung cancer attack rate, also, has not been found among the miners of the nearby Johann Georgenstadt region, where the mines have a low radioactivity. There is, furthermore, no valid evidence on record that miners of arsenic-, chromium-, nickel-, and bismuth-containing ores are affected by lung cancers at a rate even remotely approaching that seen among the two radioactive ore miner groups.

The attack rate of lung cancer among the Schneeberg miners has consistently been between 75 and 80 percent since 1879, while that of the Joachimsthal miners has been stated to range from 40 to 50 percent. However, this incidence rate may be too low, considering the recent statement of Baader, who noted that during the period 1939-43, a total of 180 cases of lung cancer were acknowledged as compensable 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 to 23 years, it may justly be assumed that these lung cancer cases originated in a miner population of approximately 300 to 400 members working at these mines between 1920 and 1930. The exposure and latent period at Schneeberg is stated to vary from 15 to 18 years for the majority of the cases, but occasionally to be as short as 7 years (Baader; Rajewsky, Schraub, and Kahlau).

The total number of Schneeberg miners who died from cancer of the lung between 1879 and 1939, according to available records, stands at approximately 400, while the number of Joachimsthal miners who fell victim to this disease has reached 225 (1926-43). An appreciable number of these miners died from lung cancer at a relatively early age as is evident from the data given in table 19 (page 16), which shows the definite shift toward younger age groups.

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 (Peller); Behounek; Behounek and Fort; Tschelnitz; Ludewig and Lorenser; Lange; Rajewsky; Stocklasa). It was suggested that the recent introduction of pneumatic drills into these mining opera-

tions aggravated the hazard by increasing the production of fine particulate dust containing solid radium.

Repeated attempts have been made to produce cancers of the respiratory tract in experimental animals exposed to the inhalation of radium emanation and/or radioactive mine dust (Schmidtmann; Löwy; Campbell; Döhnert; Kahlau; Rajewsky, Schraub, and Kahlau). Schmidtmann obtained neither pneumoconiosis nor pulmonary cancer in animals exposed for 2 years to the inhalation of Schneeberg mine dust collected from drill holes. Campbell, on the other hand, reported that mice which inhaled dust of Czechoslovak pitchblende displayed a significantly increased number of pulmonary tumors. In experiments of Döhnert and of Hueck, mice were placed in cages within the mines. Some mice developed moderate chalicosis, while pulmonary and mediastinal tumors (adenomas, round cell sarcomas), in addition to an occasional squamous cell metaplasia of the alveolar epithelium, were seen in an "abnormally" high percentage of the exposed animals. However, the actual number of affected animals was small, and the interpretation of the results as to their significance was therefore difficult.

Kahlau and Rajewsky, Schraub, and Kahlau subjected mice to the inhalation of radon. Many of the animals developed bronchial lesions characterized by an atypical epithelial lining as well as by pulmonary adenomas (in 7 of 12 mice of the test series, against 1 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 noninbred strains.

Additional, mildly suggestive observations have been reported by Lorenz, Heston, Eschenbrenner, and Deringer as well as by Henshaw, Riley, and Stapleton. Both groups of investigators found that mice exposed to ionizing whole body radiation revealed, in addition to leukemia and ovarian tumors, some increase in the number of pulmonary neoplasms. Of

greater significance in this connection are the findings of Lisco and Finkel, who found metaplastic and neoplastic proliferations of the bronchial epithelium in rats inhaling an aerosol of radioactive cerium. 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 injected metallic uranium powder dispersed in lanolin into the pleural and femoral cavities of rats and obtained sarcomas at the sites of injection in 13, or 24 percent, of the 54 rats surviving the minimal latent period of 6 months. 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 epidemiological, clinical, and experimental evidence available, it appears that a prolonged inhalation of radioactive gases and/or dust may elicit pulmonary cancers in man (Martland; Evans). In commenting on the production of lung cancer by atmospheric carcinogens, an editorial (*Lancet*, 1952) remarked, "radioactivity of Joachimsthal mines is stated to be 30 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. The excessive suicide rate observed in the past among the miners in Joachimsthal (Sikl) aptly reflects the human misery produced if such hazardous working conditions are permitted to persist.

While there thus can be little, if any, doubt of the principal role of ionizing radiation in the production of lung cancers among radioactive ore miners and similarly exposed occupational groups, some comments on the possible significance of pneumoconiosis in eliciting or modifying this effect may be indicated.

Reports on the occurrence of pneumoconiosis among the miners in Schneeberg and Joachimsthal are contradictory. While Schmorl as well as Rostoski, Saupe, and Schmorl in their early

reports (1926, 1928) noted that Schneeberg miners suffer from more or less intense anthracosilicosis and that this condition was causing or favoring the development of the bronchial cancers, Rostoski and Saupe stated in 1930 that pneumoconiosis was usually not very extensive in cancerous lungs. Because of the relatively slow course of the pulmonary tumors, Rostoski and Saupe felt that pneumoconiosis may slow the intrapulmonary growth of the tumors. Hueck, on the other hand, remarked that silicosis does not represent a precancerous condition for the Schneeberg lung cancers. Some of the miners had silicosis but not lung cancer, while others had lung cancer but not silicosis.

Similar discrepancies seem to prevail concerning the Joachimsthal miners. Ziel in 1935 reported that marked silicosis among these miners is quite frequent and that ashed lungs contain large amounts of silicon oxide. Pirchan and Sikl, on the other hand, maintained that no pneumoconiosis could be found, in spite of an abundance of pneumatic drilling, and that pneumoconiosis has no role in the production of the lung cancers. This opinion was shared by Löwy. Sikl, in his most recent communication on the subject, stated that some degree of fibrosis suggestive of silicotic origin could, of course, be seen in the cancerous lungs, and there were single cases of marked silicosis combined with cancer. On the whole, however, silicosis was not a prominent feature in cases of cancer; on the other hand, the lungs most heavily affected with silicofibrosis were generally free from malignant growth. Behounek and Fort noted that pneumoconiosis was recorded as the cause of death in only 8.2 percent of 63 miners who came to autopsy between 1929 and 1938. This statement contrasts strikingly with the observations made by Saupe during a chest X-ray study of 398 Joachimsthal miners conducted in 1939. He found that 43.4 percent of these miners presented roentgenological evidence of pulmonary silicosis. However, silicosis was of minor degree among the 7 miners who were suspected of having pulmonary neoplasms.

Although the data are in part contradictory, it seems that silicosis does not play any significant role as a direct or contributory cause of cancer of the lung among the radioactive-

ore miners in Joachimsthal. Whether it has a cancerizing effect is the question of the established fact.

Finally, it must be noted that lung cancers vary a great deal in their course. Many are of the rounded type, while a few are of the spindle type. The radioactive miners in this respect are no different from other occupational groups.

The rapidly increasing incidence of lung cancer among radioactive miners mentioned, marked by the limited working population of the radioactive mines, represents a problem of serious proportions. It is a cancer from which no one is immune. To the past experience of the radioactive miners, therefore, the degree of active contamination in the neighborhood and operation of the mines, active effluent controls, are urgent measures for the health of the community.

The complete analysis of the data and experimental evidence leaves no doubt that occupational general population contacts with radioactive materials are a serious problem.

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the established cancer remains problematical.
Finally, it may be mentioned that these lung
cancers vary a great deal in histological struc-
ture. Many were squamous cell carcinomas;
others, round cell or anaplastic carcinomas;
while a few were of adenocarcinomatous type.
The radioactive lung cancers, thus, follow in
this respect the general pattern set by all
other occupational cancers.
The rapidly growing production and use of
radioactive material and the thereby condi-
tioned, markedly increased exposure of some
limited worker groups as well as the general
population to gases, dusts, and mists containing
radioactive matter of long half-life doubtlessly
represents a potential respiratory cancer hazard
of serious proportions. The attack rate of lung
cancer from such sources is very high, according
to past experience with miners of radioactive
ores. Therefore, a competent assessment of
the degree of exposure to atmospheric radio-
active contaminants for worker groups and
neighborhood populations of radioactive plants
and operations, and the continuous and strict
supervision concerning the amounts of radio-
active effluents emitted from such establish-
ments, are urgently necessary for safeguarding
the health of these individuals.

Comments and Conclusions

The comprehensive panoramic view and
analysis of the total epidemiological, medical,
and experimental evidence available on exog-
enous respiratory carcinomas and carcinogens
leave no doubt of the fact that not only large
occupational population groups but also the
general population have definite and prolonged
contacts with one or several of these agents.

For most of these agents, adequate conclu-
sive proof of their carcinogenicity is provided
by epidemiological, medical, and experimental
data. One of several specific carcinogenic

Table 26. Latent periods of environmental respira-
tory cancers, in months (Hueper)

Agent	Cancer of—			
	Lung		Nares and nasal sinuses	
	Average latent period	Range of latent period	Average latent period	Range of later 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

Intensive studies also are needed for deter-
mining whether, through radioactive fallouts,
the inhalation of highly radioactive dust par-
ticles diffusely settling in the bronchial mucosa
and producing there minute foci of high inten-
sity radiation may elicit delayed cancerous
reactions. Since radiation cancers, like other
occupational cancers, have a long latent or
induction period (table 26), it is essential that
all possible precautions be taken against en-
vironmental contamination with radioactive
matter to prevent a possibly permanent con-
tamination of the human environment with
dangerous amounts of radioactive matter.

related to a specific industrial operation. Epidemiological, medical, and experimental data concerning these respiratory carcinogens attest their high carcinogenic potency under occupational conditions, particularly when acting on humans. It is therefore reasonable to assume that inhalation of the same agents, in a mitigated form as air pollutants, by the general population is responsible for a considerable portion of the lung cancers attributable to such contacts.

If this coherent and logical picture presented by the evidence supporting the various occupational respiratory cancers and, especially, the coal tar fume cancer of the lung, is compared with that available for the cigarette smoke lung cancer, even upon superficial examination, several additional serious defects and inconsistencies not previously pointed out become apparent.

It is surprising to note the absence of positive statistical associations between lung cancer and cigarette cough, although this latter symptom is clinically characteristic of chronic chain smokers. Despite the fact that the lips and oral mucosa are constantly bathed in the tarry liquor oozing from the tip of the cigarettes and despite the contact of these parts with the smoke coming from the cigarettes, there is no consistent statistical association with cancer of these parts. The assertion that no tarry material exudes from the cigarette tip is belied by the evident fact that chronic cigarette smokers are observed to have brown-stained fingers. There is, on the other hand, not a single record available of cancer of the fingers attributable to cigarette tar. Such cancers of the fingers would be equivalent to the numerous cases of coal tar cancers of the hands for which records are available.

In an attempt to provide an explanation for this discrepancy in the carcinogenic behavior between coal tar and cigarette tar, Lickint resorted to the speculative assumption that cigarette tar possesses a special tissue specificity so that the skin of the first three fingers, although impregnated with cigarette tar, is "immune" to its carcinogenic action.

It also would be medically unsound to conclude upon a sort of racially conditioned tissue immunity for explaining the observation of

Lipschitz, who reported in 1931 that the autopsy records of a large Jewish hospital in Warsaw, Poland, showed a lung cancer frequency of 8.9 percent of all cancers for Jews against a frequency of 15.3 percent for non-Jews, especially in view of the fact that Eastern Jews are particularly prone to develop thromboangiitis obliterans, which has the best established causal relations to tobacco smoking.

The claimed absence of a positive association between lung cancer and the habit of inhaling cigarette smoke also is inconsistent with the rule that the incidence rate of occupational cancers increases with the intensity of exposure to a carcinogen. The medical considerations on cigarette smoke cancer of the lung thus reveal a number of serious and fundamental defects and contradictions.

The best that can be said about the experimental evidence on hand regarding carcinogenic properties of tobacco tar is that it indicates the carcinogenic agents in some cigarette tars through the use of hyperreactive animals. There is no evidence that these observations of the skin of a strain of selectively inbred mice have any equivalent in man. Thus the practical importance of these observations as to cancer of the human lung is at present uncertain, especially since Passev, in recent experiments on mice painted for 16 months with tobacco tar, was unable to elicit a single cancer of the skin.

From these considerations, it is apparent that any final decision concerning the relative role of cigarette smoking in the causation of cancer of the human lung should be kept in abeyance until a great deal of additional and more valid, and especially medically conclusive, evidence becomes available. The data on hand make it unlikely that cigarette smoking represents a major factor in the production of lung cancer and in its recent phenomenal rise in frequency. For these reasons, it would be most injudicious mainly to base the future preventive control of lung cancer hazards on a theory of such doubtful scientific merits and to concentrate the immediate epidemiological and experimental efforts on this apparently overpropagandized concept. The apparent wisdom of such an attitude is readily apparent from the fact that not only a great deal of the circum-

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stantial epidemiological evidence but also practically the entire factual and conclusive evidence available on specific exogeneous causes of respiratory cancers indicates that these cancers are either of occupational origin or points to industry-related factors. Not only large occupational groups but also the members of the general population have contact with these agents in various forms and intensity.

Finally, it may be noted that the evidence on hand justifies the viewpoint that, in arriving at a judgment (Baader; Lickint) in any medico-legal dispute requiring the assessment of liability for the development of a respiratory cancer, any evidence incriminating specific occupational factors should be given preference over that possibly provided by a cigarette smoking history.

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