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Occupational and Environmental Pulmonary Cancer

With Special Reference to Pneumoconiosis

W. C. Hueper,
National Cancer Institute
National Institutes of Health
United States Public Health Service
Department of
Health, Education, and Welfare
Bethesda, Maryland

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"Do you realize that within the lifetime of men now living, within a hundred years or one-hundred and thirty years at most, all the external conditions under which man lives his life on this earth have been more completely revolutionized than during all the ages of recorded history which preceded."

R. A. Millikan.

Occupational and Environmental Pulmonary Cancer

With Special Reference to Pneumoconiosis

W. C. Hueper

1. Increase in Lung Cancer Frequency.

It is generally recognized that exposure to certain exogenous physical and chemical agents plays an important role in the causation of cancers of the skin. Considering the fact that the respiratory tract may be looked upon as an inverted part of the outer covering of the body and that many of the known or suspected cutaneous carcinogens also are inhaled, it is not surprising that observations made mainly during recent decades have brought to light a rapidly increasing number of environmental and occupational agents which are involved in the development of cancers of the nasal cavity, paranasal sinuses, larynx, and lung. The relative importance of these discoveries is greatly enhanced because of the consistent and spectacular increase in the frequency of cancer of the lung noted during the last 50 years in almost all industrialized countries (Hueper). This rise in the number of deaths from pulmonary cancers has reached in several regions such proportions, that cancer of the lung has replaced cancer of the stomach as the most frequent cause of death from cancer among males (Steiner, Butt and Edmondson; Halpert).

It has lately become a convenient expedient for some investigators to explain away unpleasant things in vital statistics, such as the rising death rate from bronchogenic cancer (Stocks) by changing fashions in certification of causes of deaths, increased awareness of the medical profession of lung cancer, progressive aging of the population and similar half and part truths. However, to the critical observer there exists little if any doubt that an appreciable part of this development is real. The following graphs (fig. 1 and fig. 2) and table (table 1) giving statistical data from this country and abroad support this statement.

Fig. 1. Death Rates for Lung and Larynx Cancer in the United States, 1925 - 1948.

Fig. 2. Lung Cancer Death Rates for England and Wales, 1900 - 1947.

These observations made on official death certificate data are in agreement with the evidence obtained by investigators using autopsy material, Steiner, Butt and Edmondson found at the Los Angeles General Hospital that carcinoma of the lung was noted during the period 1923 - 1927 in 0.6 percent of all autopsies and constituted 4.3 percent of all tumors, while in 1943 to 1946 corresponding figures were 2.3 percent and 11.3 percent. Similarly, Beeler and Iray observed at the Lotterman General Hospital in San Francisco bronchogenic carcinomas in 1.2 percent of all autopsies during the decade 1920 - 1929, whereas they occurred in 2.7 percent in the period 1940 - 1948.

Corresponding observations were recorded by Ochsner and DeBakey; Rosahn; Gowan; Metropolitan Life Insurance Company, and other American investigators (Hueper; Steiner; Bruby and Sweany). The statistical data of Dorn and Potter show that this trend has been in existence since 1914 and has shown a tendency in late years to become less pronounced (table 1).

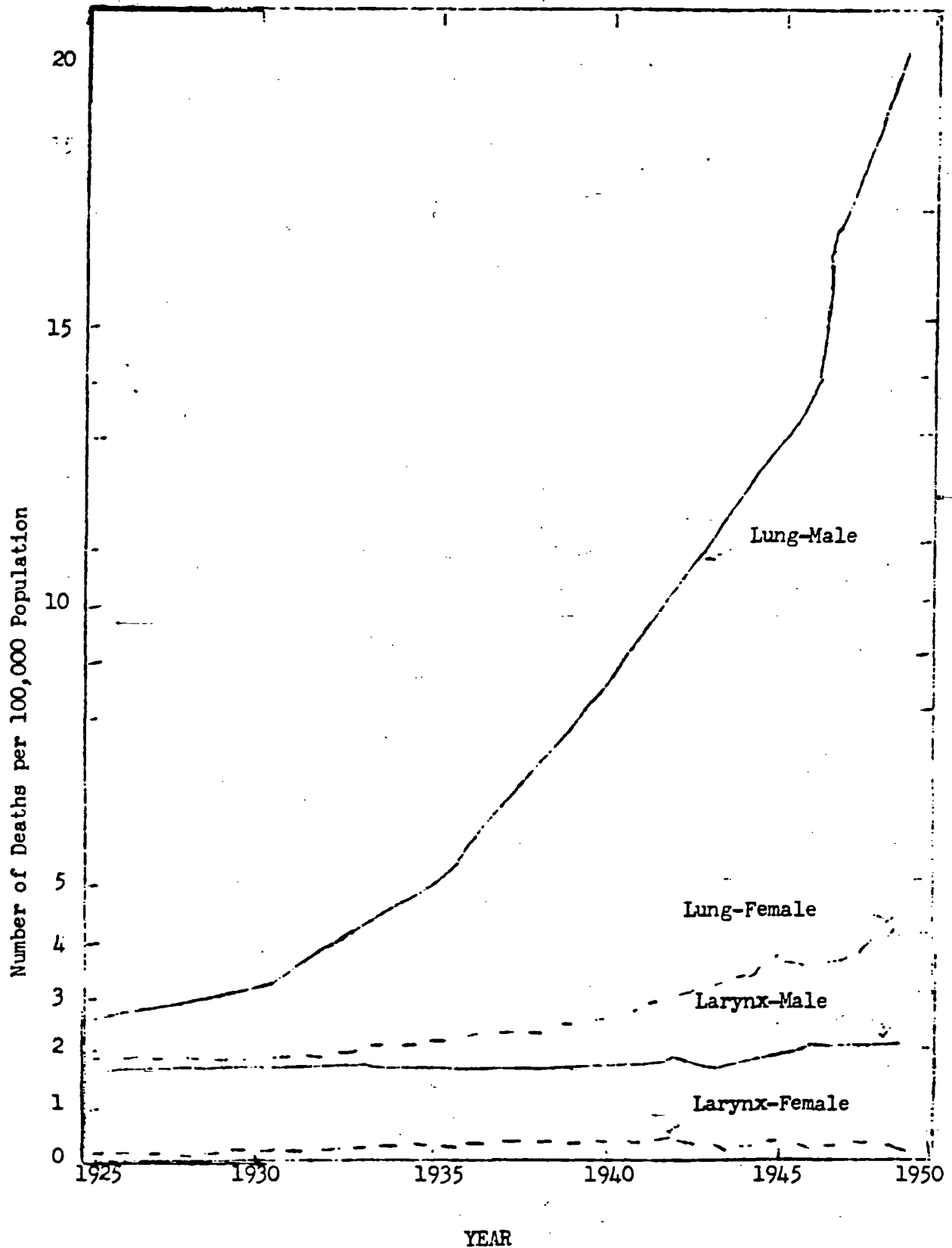
Schinz, Rosin and Sonti reported from Zurich, Switzerland, that the male mortality due to carcinoma of the lung between 1936 and 1944 was 9.8 per 100,000

Table 1.

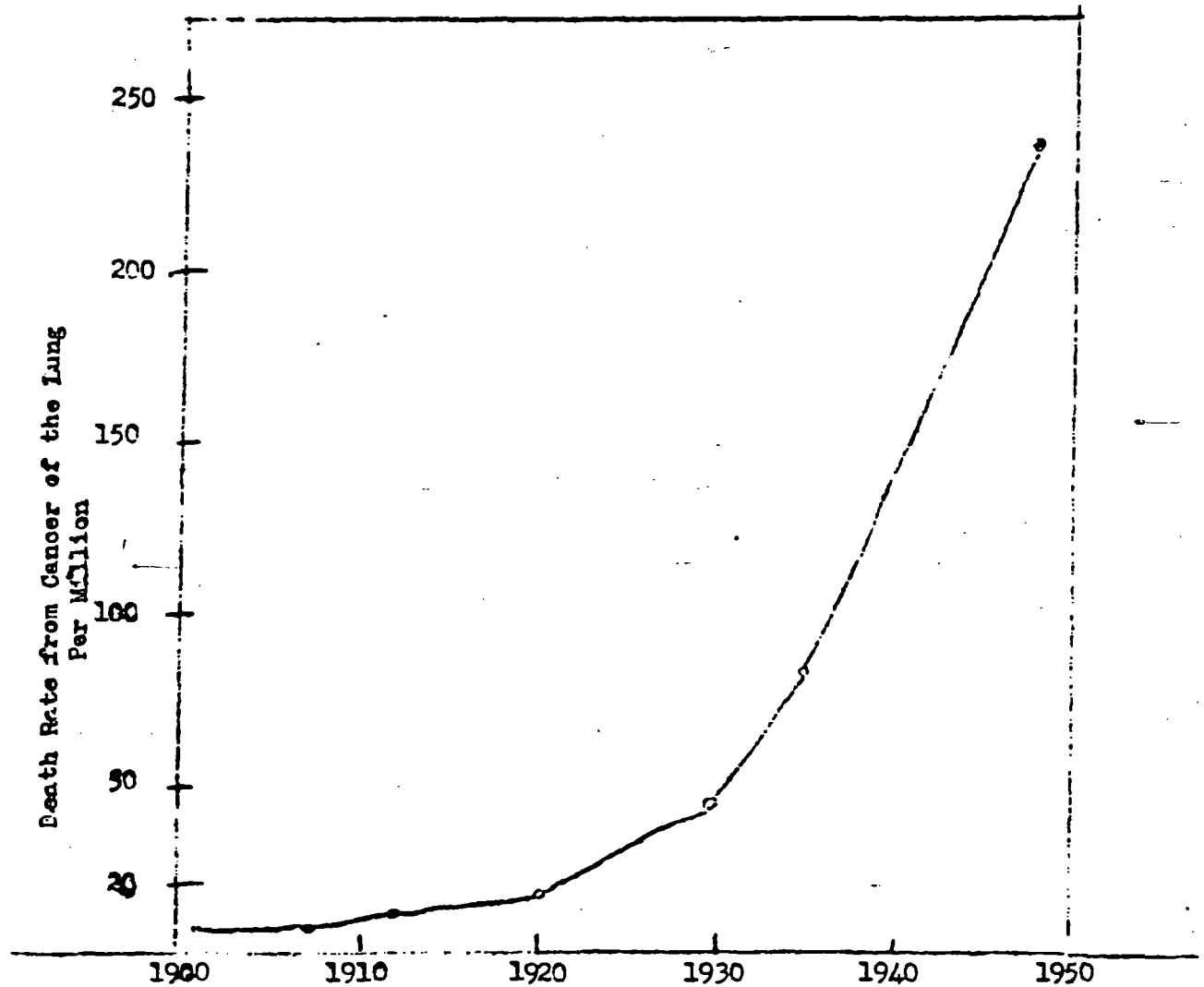
Annual Age Adjusted Increase of Frequency of Lung Cancer Mortality

<u>Dorn</u>	<u>1914-1930</u>	<u>1931-1940</u>	<u>Potter</u>	<u>1933-1944</u>
Males	10.5%	8.5%		5.8%
Females	8.0%	2.5%		2.0%

Trend in Mortality From Respiratory Cancer,
Lung compared with Larynx, by Sex, 1925-1928



Lung Cancer Death Rates
for England and Wales



The rates are based on three year averages for all years except 1947

Doll, R. & Hill, A.B.: Brit. Med. J. 1: 739 (1950)

whereas it was 2.7 per 100,000 from 1896 to 1905. Brandt noted that in Riga, Latvia, the lung cancer incidence rose from 1.5 percent of all cancers found at autopsy in 1901 - 1905 to 10.5 percent in 1921 - 1925. Simross' analysis of the post-mortem material of Goettingen, Germany, yielded similar information, since cancer of the lung constituted 2.6 percent of all cancer in 1906 to 1912, while they were 9.8 percent in 1927 - 1931.

According to a report of von Glinski in 1939, 6.82 percent of all cancers seen at autopsy in Stettin, Germany, involved the lungs. Clammesen evaluating official Danish mortality figures noted an apparent rise in lung cancer among males, whose attack rate increased from 5 per 100,000 in 1931 in Copenhagen to about 25 per 100,000 living in 1945, while the corresponding figures for females amounted to 4 and 7 per 100,000 respectively. The observations of Husted and Billman on Danish post-mortem material confirmed this trend. The investigations of Henschen on the autopsy material of Stockholm hospitals (Sweden) also revealed a progressive increase of lung cancer during the period 1900 to 1946. During the period 1900 - 1909, 1.6 percent of all cancers affected the lungs, during 1910 to 1919 the incidence figure stood at 2.1 percent and had risen to 5.85 percent for the period of 1920 to 1929. In the autopsy material of the St. Erik's Hospital in Stockholm, 9.9 percent of all cancers observed during 1937 to 1946 were located in the lung. While Casole reported in 1927 that among 2,658 necropsies performed in Padua during 1914 and 1925 there were two cancers of the lung (0.07 percent) and among 11,968 autopsies made during 1910 - 1925 in Milan, there were 15 pulmonary cancers (0.13 percent), Fabris noted in 1938, 150 lung cancers among 10,000 necropsies seen in ten years in Venice (1.5 percent).

The statistical studies of Stocks have demonstrated that also in England and Wales there has occurred a phenomenal increase in the frequency of lung cancer during the last several decades (fig. 2). Cancer of the lung in

England and Wales had standardized death rates of 1.1 for males and 0.7 for females during 1901 - 1920 and 10.6 for males and 2.5 for females in 1936 - 1939 which are almost identical with those recorded by Schinz for Zurich. These observations are in a general way confirmed for Great Britain by the studies of Kennaway; Kennaway and Kennaway; Heady and Kennaway; and Cheoseman as well as by those of Bonser. This investigator noted that there was a noticeable increase in the incidence of intrathoracic cancers at post-mortem at the Leeds General Infirmary during 1928 to 1937, following a long period (1891 - 1927) of relatively steady incidence, for which (1894 - 1928) also Passey and Holmes, using post-mortem material of various hospitals, did not observe any significant changes. Heady and Kennaway pointed out that there occurred a ninefold increase of cancer of the lung in men in England and Wales between 1928 and 1947, according to data of death certificates.

The evidence based on death rates from lung cancer and on autopsy observations was confirmed by the results of recent morbidity studies on cancer of the respiratory tract for eight metropolitan centers in the United States (Dorn; Warren; Grodowitz; Cutler; Marcus). The surveys conducted first in 1937 and repeated in 1947, showed for all metropolitan centers a consistent and often considerable increase in the morbidity rates of both cancers of the lung and, to a lesser extent, of the larynx (table 2). The rise in larynx cancer morbidity in the urban areas in the United States demonstrated by the surveys between 1937 and 1947 appears to be definitely more pronounced than the increase of crude larynx cancer death rates per 100,000 in the United States (1930: males, 1.42; females, 9.22; 1937: males, 1.70; females, 0.25) (Jackson and Jackson). These observations on the trend of death rates of larynx cancer in the United States are in relatively close agreement with those made in England and Wales (Kennaway and Kennaway) which stood in 1932 at 4.4 per 100,000 males and at 1.1 for 100,000 females, while they were in

Table 2.

Incidence of Respiratory Cancer, 1937 and 1947
Morbidity Rates for Eight Metropolitan Centers, by Sex
per 100,000 population*

Primary Site and City	Males			Females			Total		
	1937	1947	Percent Increase	1937	1947	Percent Increase	1937	1947	Percent Increase
<u>Bronchus and Lung</u>									
Atlanta	5.0	13.4	168	1.0	5.0	400	2.9	8.9	207
New Orleans	13.1	39.1	198	2.8	4.2	50	7.6	20.8	174
Dallas	5.9	29.0	392	0.5	6.4	1180	3.1	17.2	455
Birmingham	4.5	18.9	320	2.1	3.9	86	3.3	11.0	233
Denver	9.1	21.9	141	4.2	8.1	93	6.6	14.8	124
San Francisco	15.6	34.3	120	3.9	8.1	108	9.8	20.8	112
Chicago	13.3	29.5	122	4.3	7.0	63	8.8	18.0	105
Pittsburgh	9.7	26.1	169	4.9	5.5	12	7.3	15.6	114
Detroit	12.6	32.0	154	2.3	5.7	148	7.5	19.0	159
<u>Larynx</u>									
Atlanta	1.4	4.0	186	0.3	0.3		0.9	2.0	122
New Orleans	11.3	14.9	32	0.4	1.0	150	5.6	7.6	36
Dallas	3.2	5.3	66	1.5	0.4	73	2.3	2.7	17
Birmingham	1.4	4.0	186	0.0	1.3		0.7	2.6	271
Denver	2.0	4.1	105	0.0	0.0		0.9	2.0	122
San Francisco	4.5	8.8	96	0.2	0.8	300	2.4	4.6	92
Chicago	6.7	7.0	4	0.4	0.6	50	3.5	3.7	6
Pittsburgh	4.4	8.0	82	0.4	0.8	100	2.4	4.4	83
Detroit	3.5	6.4	83	0.4	0.3	-25	2.0	3.4	70

*Biometrics Section
National Cancer Institute

1949, 4.1 for males and 1.3 for females.

It is apparent from these data that whatever factors may be responsible for the remarkable rise in the frequency of lung cancer, they have not - or to a much lesser degree - affected the incidence of cancer of the larynx.

If all due and liberal allowance is made for the progressive aging of the population since 1900, for an increased awareness of the medical profession of pulmonary cancer, for improved diagnostic facilities, for better recording systems, and for decreased deaths from other diseases than cancer, there still remains a considerable balance of lung cancers which cannot plausibly be accounted for by these factors. Surely, improvement in the medical proficiency of the pathologic diagnosis of lung cancer can scarcely be advanced as a factor of importance, since the histologic diagnosis of lung cancer is in general not a difficult task and has been practiced with efficiency and competence for many decades in the well-organized pathological institutes of Europe, which serviced the large public hospitals with their sociologically and economically relatively stable patient populations. The numerous objections voiced by Machlin on statistical grounds against the claim of an increase of lung cancers, pertain to only a minor degree to these institutes. Since fundamental changes in the biologic composition and constitution of the population groups involved did not take place within a few decades during which the increase in lung cancer frequency occurred, there remain only alterations in environmental factors related to modern industrialization and living conditions which plausibly might have provided the main causation of this development (Boycott).

2. Geographical Distribution.

The concept that exogenous factors, entering the human environment some 75 to 50 years ago and acting in increasing intensity, are responsible for the recent increase in lung cancers is supported by additional epidemiologic

observations, related to the geographical distribution of pulmonary cancers. The data on the incidence of respiratory cancer, 1937 and 1947, in eight metropolitan centers (table 2) reveal striking differences in the lung cancer morbidity rates of different centers, the extremes being 39.1 per 100,000 population, males, 1947, in New Orleans and 13.4 per 100,000 in Atlanta.

The percentages of increase in frequency for these communities also were far from uniform. Since the most marked discrepancies on these two points occur among metropolitan areas (New Orleans and Atlanta) located in the same part of the country (Southern States), it is most unlikely that differences in the genetic-biologic composition of the populations or fundamental variations in the smoking habit between these populations can be responsible for them. It is, therefore, much more probable that occupational, industrial or other environmental factors related to living conditions account for these regional variations.

Similar variations appear if cancer mortality data for different areas of States are analyzed. When Colorado, for instance, is divided into three regions according to predominating types of occupational activities (eastern part with agriculture, central part with industry, western part with mining and ranching) (fig. 3), it appears that the highest lung cancer death rate exists in the central, industrialized portion (50 per 100,000 male deaths) while the lowest is found in the agricultural area (30 per 100,000), with the western mining regions occupying an intermediary position (32). Seelig and Benignus also demonstrated that lung cancer death rates for 1930 to 1934 were higher in the urban areas than in the rural ones of the forty-eight States.

Similar state-wide discrepancies in the distribution of pulmonary cancer appear, if the lung cancer death rates of the forty-eight States are compared (table 3).

FIG. 3.

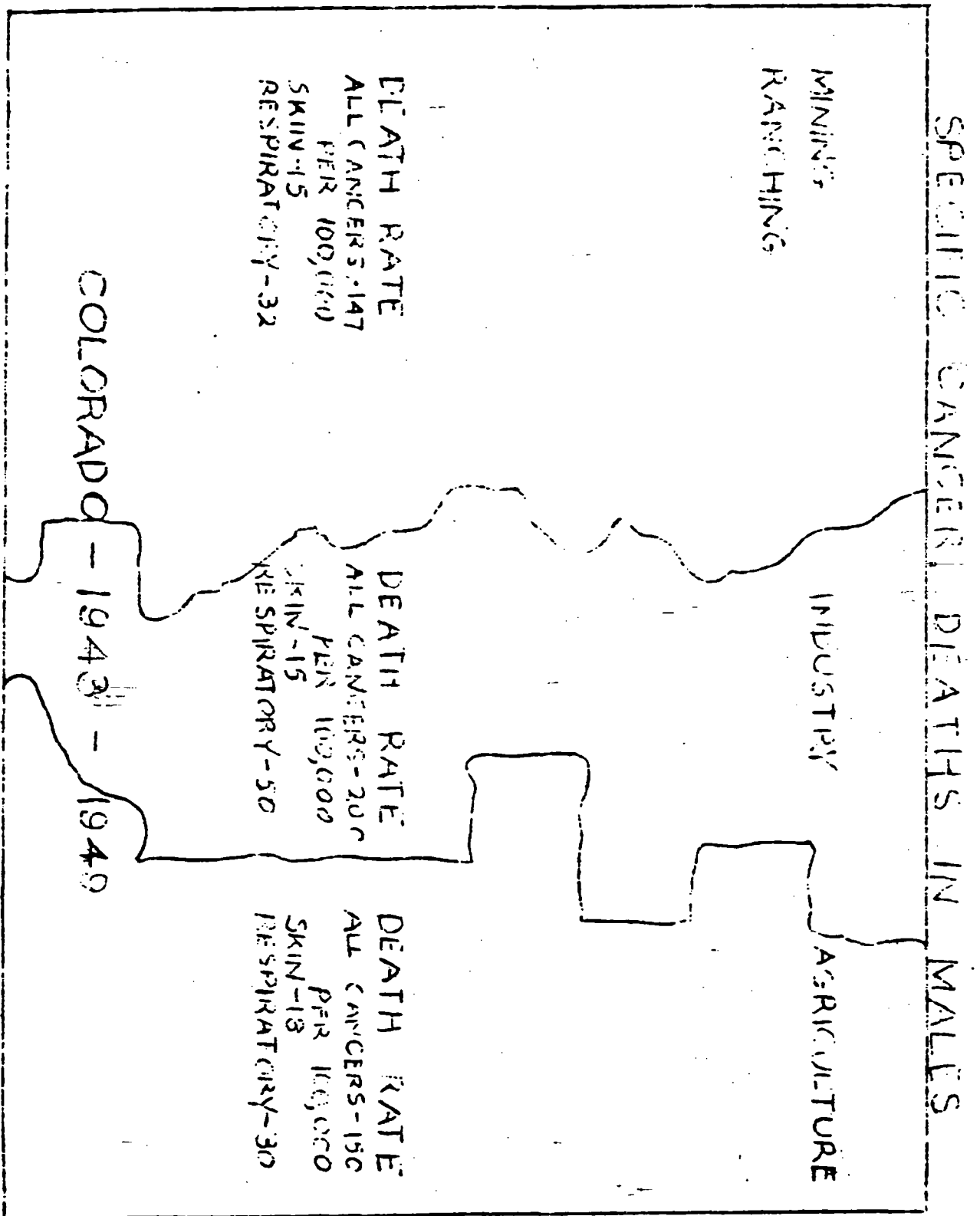


Table 3.

Lung Cancer Death Rates in the 25 States of the United States
in 1946 and 1948
Crude Death
Rates per 100,000

Industrialized States		
State	1946	1948
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	7.9
Pennsylvania	6.7	8.4
Rhode Island	8.7	7.4
States with Regional Industrialization		
State	1946	1948
Florida	5.8	7.4
Louisiana	6.5	8.5
Missouri	7.3	9.4
Montana	10.6	8.8
Nebraska	5.7	8.0
Agricultural States		
State	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 (Rigdon and Kirchoff).

The extremes in deviations of lung cancer death rates between different States were presented by New York with 11.9 per 100,000 deaths as the highest rate and Idaho with 2.9 in 1948. Although the differences are in part explainable by variations in medical care, recording, etc., they are too marked not to be in part at least, real and to represent actual trends.

It is remarkable, moreover, that rates above 7.1 are mainly met in industrial States (Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Ohio, Illinois, Missouri and Michigan) or in States having known cancer-producing industries in some industrialized parts (Montana, Louisiana, Maryland), while the majority of the predominantly agricultural States having relatively low lung cancer rates.

Similarly, Springett reported that the mortality from lung cancer was five times higher in England and Wales than in Norway, while the mortality from larynx cancer in Norway was only one quarter that in England. Fischer, likewise, remarked on the considerable variations of the lung cancer frequency in different parts of Germany, where the highest incidence figures were reported from the densely populated and highly urbanized and industrialized districts of Saxony and the Ruhr Valley (Dissmann).

Stocks; Kennaway; Kennaway and Kennaway; and Fulton also noted in their more recent studies that there was a prevalence of cancers of the lung and larynx in urban areas over rural ones. In urban populations there was, moreover, a lack of influence of social class upon the liability to lung cancer. If the coefficient of number of persons producing one cancer death was set arbitrarily at one hundred for the administrative county of London during 1946 to 1949, it was 233 for rural districts (Kennaway). For cancer of the larynx the coefficients were 100 and 170, respectively. Stocks' statistical analyses of the lung and larynx cancer incidence for different age groups during the periods 1921 to 1930 and 1940 to 1944 revealed that cancer of the

respiratory organs was the certified cause of much higher death rates in urban than in rural areas. In fact, it was shown in 1936 that for cancer of the lung in males there was a steep downward gradient from London through large and small towns to rural areas. While the standardized mortality ratios for cancer of the larynx at ages 35 - 64 for social classes in England and Wales, 1930 - 1932 showed a definite increase toward the lowest social class, cancer of the lung revealed only small and insignificant correlations with the environmental and social indices as expressed by the five social classes used in the evaluation. From studies of the records of the Meteorological Office, however, it appeared that there existed a positive correlation between the lung cancer death rate and sunshine hours for 20 towns investigated. Stocks suggests that the only explanations of these results which seem adequate were that either smokiness of atmosphere is an important factor in itself in producing cancer of the lung, or sunshine is an important factor in preventing its incidence.

In a recent study of Mills on the distribution of respiratory tract cancers in relation to atmospheric pollution in Cincinnati, this author came to the conclusion that in general the cleaner suburbs of the city had low respiratory cancer rates, while the more industrialized, low lying districts had higher rates, and that the rates of respiratory cancer deaths per 10,000 males for a five-year period compared with the average carbon deposit per month in different parts of the city.

3. Atmospheric Pollution.

The topographical distribution pattern displayed by respiratory cancers clearly suggests the action of an environmental agent which is present or operative to a higher degree in urban and industrialized regions than in rural areas. Air pollution from effluents of domestic fireplaces, incinerators, industrial establishments, and carbon black plants, exhaust fumes from gasoline

and diesel engines and coal or oil-fired railroad locomotives, dust from asphalted, tarred and oiled roads and from abrasion of rubber tires (Sharrah), would perhaps best conform with this pattern. The possible causal significance of some or all of the mentioned sources of air pollution has been proposed previously by several investigators (Duguid; McCrae, Funk and Jackson; Klotz; Matz; Katz; Wegelin; Roffo; Seelig and Benignus; Kling, Samssonov and Heros; Oldofredi; Smith, Wm.; Lorentz). Others, however, disclaimed for various reasons, the existence of such connections (Husted and Billmann; Lehmann; Brandt; Fischer; Jaffe; Konrad and Franks; Kennaway and Kennaway; Stocks; Syrek) with lung cancer incidence in England; France; Germany, Poland, Latvia, Russia and Sweden.

The three main sources of potentially carcinogenic air pollution are represented by (a) the specific hydrocarbons which are contained in the combustion and distillation products of carbonaceous matter; (b) arsenicals released as fumes from metallurgical establishments (smelters), and coal-burning furnaces and power plants or as dust following their use as pesticides; (c) radioactive matter present as gases and fumes in the effluents from industrial and military radioactive operations, and radioactive reaction and decay products of atomic energy plants (Smith; Lowry).

a. Domestic soot, which may consist of up to 40 percent of tarry matter (Cohen and Ruston) and which is the chief atmospheric contaminant, contains, according to Goulden and Tipler, 3,4-benzpyrene (300 mg./kg. in a mixed sample) representing one of the carcinogenic agents present in coal tar and shale oil (Berenblum and Schoental). The same carcinogenic chemical has recently been demonstrated in carbon blacks which form a major constituent of automobile tires (Falk and Steiner). It has been estimated that a single automobile tire during its life, produces by friction with the surface upon which it travels, 750 billions of carbon black containing rubber particles

(Sharrah). This does not include the dust created from tarred, asphalted and oiled road surfaces on which the tire was worn. It has been established also that the exhaust of gasoline and diesel engines contains benzpyrene (Waller) and was demonstrated in automobile lubricating oil. It is noteworthy that whilst the particles of coal smoke are distributed over a large range of sizes, Waller found those in the exhaust of internal combustion engines concentrated in a limited range of small sizes. Dust particles of small size are known to undergo maximum retention in the lung.

Recent studies of Waller showed that samples of smoke drawn from the air at eight different towns in England contained benzpyrene. The concentration of benzpyrene rose sharply during the winter, and there was a tendency for the mean annual values to increase with the size of the town. The average benzpyrene concentrations during smog days increased fourfold (from 7.2 mg. per 100 m³ to 32.8 mg.). A large part seems to come, in the opinion of Waller, from domestic fires. Since it has been detected also in the exhaust of combustion engines, some benzpyrene in the atmosphere must come from this source.

While the human evidence concerning the existence of a causal relation between the inhalation of atmospheric carcinogens from soot, rubber tires and engine exhausts and cancer of the lung is suggestive (Schnurer), there exists adequate and valid proof of the carcinogenic properties of soot or carbon black or their benzolic extractives when applied to the skin of mice or inhaled into the lungs of experimental animals. Extracts of dust from the air of eight large industrialized American cities when injected subcutaneously into mice produced sarcomas at the site of introduction (Leiter and Shear; Leiter, Shimkin and Shear).

Mice exposed to the inhalation of soot obtained from a hospital flue stack developed an excessive number of pulmonary adenomas and carcinomas (Seelig and Benignus). Similar results were obtained by McDonald and Woodhouse as well as

Campbell, when mice repeatedly inhaled clouds of soot collected from an English city or swept from tarred English roads. Squamous cell cancer of the bronchi was obtained by Muller in six (6) out of 24 rats painted on the skin with tar over prolonged periods, while Pessano reported similar results in rats exposed to the inhalation of the exhaust of combustion products of petroleum.

b. Extensive pollution of the air with arsenical effluents from metal ore smelters was especially in past decades, a well-recognized fact giving rise to damage to crops and wild and domesticated animals (Hofmann; Prell; Nieberle). It was an unavoidable while usually circumscribed complication of large scale dusting and spraying operations with arsenical pesticides. The contamination of the air of cities with arsenical impurities from the combustion of coal doubtlessly is in general of a much lower order. Goulden, Kernaway and Urquhart recently determined the arsenic content of the air obtained from eight (8) English cities. It was found that there were in one cm. of air, 0.055 micrograms of arsenious oxide. This pollution increased during November to January to 0.104 micrograms. These amounts when inhaled by man over a period of years are considerably below those introduced into the lungs from smoking cigarettes or entering the body when Fowler's solution is taken. Goulden et al. believe, therefore, that the arsenic contained in the air of large cities may have at best a summation effect.

The human epidemiologic evidence on pulmonary cancer caused by an environmental arsenical air pollution is practically non-existent, unless the observations made during recent years in several counties in Montana having copper ore smelters provide what might be considered suggestive evidence (table 4).

c. Contamination of the atmosphere with radioactive material on a regional level near atomic energy plants or occurring at times on a wider scale as the result of massive discharges of radioactive matter following atomic

Table 4.

Lung Cancer Mortality in Several Counties
of Montana, 1947 - 1948

County and Total Population 1940	Major Industry	Number Lung Cancers			Total Cancer Deaths	% Lung Cancer		Annual Lung Cancer Death Rate/100,000	
		Male	Female	Total		Male	Female	Male	Female
Deer Lodge 13,627	Copper Smelting	21	0	21	98	30.8	0.0	145.7	
Silver Bow 53,207	Copper Mining	27	2	29	259	22.6	1.5	48.6	3.9
Cascade 41,999	Copper Mining Smelting	20	5	25	299	12.7	3.5	46.3	12.3
Gallatin 18,269	Agriculture	1	0	1	81	3.0	0.0	5.2	

The estimated crude death rate for lung cancer among white males in the entire United States in 1947 is 10.9 per 10,000 population.

bomb explosions represents a special problem which still needs a great deal of critical investigation for properly assessing the possible creation of cancer hazards to the lung and other organs from prolonged exposures and cumulative effects. The ordinary radioactivity of the air, on the other hand, stems from the gaseous decay products of the small amounts of uranium and thorium distributed throughout the earth's crust. Dawson recently determined the degree of radioactivity of the suspended matter in the air of urban and rural areas in England. The amounts found were small (1/10th to 1/3000th of the lowest amounts considered harmful to man). It appears, therefore, that these common radioactive contaminants of the air do not play any significant role in the production of the ordinary type of human lung cancer. There is thus a certain amount of evidence suggesting the existence of a causal relation between some atmospheric pollutants with the relative distribution of respiratory cancer upon large groups of the general population.

4. Occupational and Professional Distribution, Dusty Trades and Tobacco Smoking Habit.

Numerous attempts have been made also to establish evidence indicating an excessive lung cancer liability for special and restricted population groups related to occupations, trades, professions and habits.

a. Occupational Aspects. A considerable number of investigators recorded failure in attempts to find specific occupational relations to lung cancer incidence (Brockbank; Hollingsworth; Simmross; Haintz; Husted and Billmann; Jaffe; Rice; Rogers; Shennan; Bonser; and others). Others concluded that workers exposed to road dust or nonspecific industrial dusts and fumes displayed an excessive frequency of lung cancer and/or cancer of the larynx (Campbell; Duguid; Ferenczy and Matolcsay; Kennaway and Kennaway; Perrone and Levinson; Rosedale and McKay; Schachter; Singer; Aske-Upmark; Singer; Hampeln; Harvey; Seyfarth; Hudson; Rostoski; Saupe and Schmarl; Schmarl). Silica dust

in particular was mentioned by Weigl; Schmorl and Singer. The basic concept underlying these claims is apparently the still rather wide-spread, although erroneous belief, that cancer may develop on the basis of any nonspecific chronic irritation. Since occupational and experimental cancer research has rather definitely established the fact that carcinogenic properties are possessed by only specific agents of which only a part have also an appreciable irritative action, the above-mentioned assertions as to an alleged carcinogenic action of all and any kinds of dust seem to be conclusions drawn from pre-conceived ideas; and, therefore, are of relatively little scientific value. Street dust does not possess any carcinogenic properties in the opinion of Kikuth; Berblinger, Schmidtman and Probst. The latter cited in support the relative infrequency of lung cancer among policemen, trolleyman, teamsters, chauffeurs, street workers, and street vendors.

Of distinctly greater significance, on the other hand, are the observations made in regard to the increased or decreased frequency of lung cancer among members of certain occupational groups, especially as these data reveal a definite degree of uniformity with which certain worker groups are cited for their excessive liability although the data are coming from different investigators and obtained from different material. The information on this subject is summarized in table 5.

In addition to these occupational groups for which a certain amount of agreement exists, there were mentioned by some investigators, other groups which do not have general support. Versluys noted diamond cutters; Dublin and Graham, engravers; Wynder and Graham as well as BECC 1952, cabinet makers and carpenters; Wynder and Graham, smelter workers; and Versluys, butchers and barmen. A low frequency of lung cancer is recorded for agricultural workers (Kennaway and Kennaway; Versluys) and coal miners (Kennaway and Kennaway; Mason; Versluys; Feil; Schulte; Schulz; Allen).

Table 5.

Occupational Groups with an Excessive Lung Cancer Incidence

Occupational Group	Investigator
Metal workers, welders, metal grinders and polishers, wire makers, tool and die makers, foundry workers, metal moulders, lathe workers, etc.	Borst; Kennaway and Kennaway; Turner and Grace; Mueller; Dublin and Vane; Wynder and Graham; McLaughlin
Cigar manufacturers and tobacconists	Seyferth; Borst; Kennaway and Kennaway; Enger; Versluis; Brinkmann
Engineers; mechanics; machinists, plumbers, etc.	BECC* 1944 and 1952; Gillespie; Turner and Grace; Mueller; Wynder and Graham
Painters, decorators	BECC 1944; Mueller; Dublin and Vane; Fulton Wynder and Graham
Tar workers, road workers, asphalters, paviours, stokers, patent fuel workers, furnace men, foundry laborers, rollers, etc.	Kennaway and Kennaway; Fulton; BECC 1952 Registrar-General (1938), McLaughlin

*Report of British Empire Cancer Campaign.

Recent epidemiologic studies on the frequency of cancers of various sites among the members of different industrial groups in Ohio, conducted by Mancuso, provided another illustration of the existing variations in liability to pulmonary cancer among various large occupational groups (table 6).

These rather crude rates are in general agreement with the observations of other investigators, since they show an elevated lung cancer frequency for workers employed in the ferrous and non-ferrous metal industries and in transportation, and a low lung cancer rate for agriculturists.

Additional evidence suggesting a possible excessive liability of photo-engravers to cancer of the lung was discovered during a recent analysis of the cancer mortality records kept by the International Photo-Engravers' Union - a rather stable occupational group. Among a total of 1520 deaths observed during 1940 to 1949 there were 165 deaths from cancer of all sites, including 45 pulmonary cancers. There were, thus, 2.9 lung cancers per 100 deaths and 28 lung cancers per 100 cancer deaths. The estimated death rate from cancer of all sites for the population of the United States (having the same age composition) during 1946 to 1950 was 133, while the actual number of deaths among members of the International Photo-Engravers' Union for the same period stood at 94. However, there were 27 lung cancer deaths in this group (29%) instead of the estimated 20 (15%). While these observations are in general agreement with those made on photoengravers holding policies with the Metropolitan Life Insurance Company, a recent survey of 684 living photoengravers by chest x-ray examination failed to yield any pulmonary neoplasms (Meyers, Dankmann).

Another possible example of an increased frequency of lung cancer among members of a special occupational group became apparent when the lung cancer frequency among operating and non-operating employees of two major railroads was determined (table 7).

Table 6

Lung Cancer Death Rate per 1,000 Deaths of All Causes for Seven (7)

Industrial Groups in Ohio, 1947 Among 5,309 Male Cancer Deaths

Industry	% Respiratory Cancer
Iron and Steel	2.18
Transportation	2.91
Agriculture	0.82
Rubber and Plastics	2.34
Stone, Clay, Glass	0.66
Non-Ferrous Metal	3.22
Mining and Quarrying	1.53
Total	1.76

Table 7

Lung Cancer Frequency Among Operating and Non-Operating Railroad Workers

Railroad	Period	Total No. Lung Cancers	Lung Cancer Operating RR Workers		Lung Cancers Non-Operating RR Workers		Lung Cancers Unde- termined RR Workers	
			No.	%	No.	%	No.	%
A	1940-1950	29	24	83	5	17		
B	1939-1949	104	59	56	15	15	30	29

The employment ratio of operating railroad workers to non-operating railroad workers of one of the two companies was 1:4. From this ratio it appears that about 75 percent of the lung cancers listed for railroad employees of these two companies occurred among the operating group which represents only 25 percent of the total number of employees. Operating railroad workers included engineers, firemen, conductors, men in the roundhouses and switchmen.

It may be mentioned finally that Bourne and Rushin demonstrated the presence of not inconsiderable amounts of chromium (chromite ore and chromates) in the atmospheric air in the immediate environment of a large chromate plant and that Davis recently reported that the use of soluble chromates as corrosion and rust inhibitors in automobiles had led to a yellow discoloration of the snow in Akron, Ohio. In view of the established high lung cancer liability of chromate workers, serious attention must be given during the coming years to possible carcinogenic effects resulting from such atmospheric pollution of the air with chromium containing carcinogens (Hueper). Such observations should not be lightly passed off with the unfounded assurance that it is inconceivable that any hazardous concentrations of chromium or arsenic or other carcinogenic agents might enter the air in the environs of plants (Foulger). Thorough and critical surveys must establish the harmlessness of such contaminations as definite facts before they can be dismissed as potential public health hazards. The occurrence of a not inconsiderable number of "neighborhood cases" of berylliosis caused by plant contamination of the environmental air and associated with at least a potential lung and bone cancer hazard for the victims should represent a very impressive warning against undue complacency.

In view of the demonstration of atmospheric carcinogens (Editorial, Lancet) the serious problem of the possible important role of industrial air pollution in the rise of lung cancers should not be characterized as a subject for "loose and injudicious statements". It is poor scientific judgment if persons

having serious and competent concern with a public health hazard of rapidly growing importance are suspected of "misusing statistics for propaganda purposes" (Lanza).

It is obvious from the evidence available that the incidence of lung cancer prior to 1900, in relation to the frequency of cancer in general, stood at approximately one percent of all cancer. After this period there was at first a gradual increase in the frequency of these neoplasms, followed in many localities studied by a sudden and much more rapid increase, the gradient becoming constantly steeper during the last three decades of this century. One of the characteristic features of this phenomenon is that the development did not start in different cities, countries and continents at the same time but that there were marked differences in the time of onset not only between different countries, but also between different regions and cities of the same country. The development, moreover, was not uniform in degree and intensity in different localities, but evidently affected urban, industrialized areas to a higher extent than rural ones and certain occupational groups more than others (Hueper; Steiner). If the action of environmental carcinogens should mainly account for the striking increase of lung cancer frequency and for its irregular course in different regions and conditions, industrial and industrially related carcinogens would well fit this pattern, since the growth of industrial establishments and the use of their products in the economic life of different countries and communities have greatly lacked uniformity in time, type and extent (Hueper).

b. Tobacco Smoking Habit. Rather far-reaching, if not extravagant, claims recently have been advanced as to the important, if not predominant role which cigarette smoking is alleged to have played in the production of lung cancer and its progressive rise in frequency during the past 50 years. A critical and sober analysis of the evidence offered in support of these

assertions is in order not only for reasons of scientific accuracy but also for medicolegal reasons and especially for determining the direction of future epidemiologic research and of control activities in the field of lung cancer.

A few years after there developed a growing appreciation of the rapid increase of cancer of the lung, smoking of tobacco, particularly, cigarettes, was suspected by some investigators as one of the causes, or the main cause of this phenomenon (Perret; Adler; Wassink, Arkin and Wagner; McCord; Bogen and Loomis; Grace; Thys; Syrek; McNally; Strnad; Joannovic; Berblinger; Hochstaetter; Schoenherr), although such connections were denied by Staehelin and Hintze.

Lickint in 1930, however, was the first to make definite claims in this respect, for which he sought support in the observations of Seyfarth and of Young, Russell, Brownlee and Collis concerning the excessive frequency of lung cancer among restaurant owners and waiters professionally exposed to tobacco smoke. These assertions were repeated by Hoffman; Ferrari; Brockbank; Roffo; Müller; Weigl; and Lehmann, as to the lung, and by Roffo; Herrmann; and Jackson and Jackson as to the larynx. Müller did the first statistical study on the relation of tobacco smoking to lung cancer by comparing the relative intensity of the smoking habit (cigarettes, cigars, pipe) among the members of a series of 86 lung cancer patients with the intensity distribution among a normal control group (table 8).

According to the occupational data given, there were in the cancer series 19 male individuals occupationally exposed to metal dusts and fumes, lubricating oil mist and soot; 12 exposed to soot and automobile exhaust; 11 exposed to ingredients of paints; one (1) exposed to chromates; while of the 10 female cancer cases, three (3) had worked in an ammunition plant and one (1) in a cigarette factory. A possibly significant occupational exposure history thus existed in 43 of the 76 male cases and in perhaps four (4) of the 10 female cases.

Table 8

Degree of Tobacco Consumption Among 86 Lung Cancer Cases and 86 Normal Controls

Degree of Tobacco Consumption	Highly Excessive	Very Heavy	Heavy	Moderate	Non-Smokers
	<u>No. of Cases</u>	<u>No. of Cases</u>	<u>No. of Cases</u>	<u>No. of Cases</u>	<u>No. of Cases</u>
% of Degrees Among Lung Cancer Series	29 (25)	21 (18)	15 (13)	31 (27)	4 (3)
% of Degrees Among Normal Controls	5 (4)	6 (5)	25 (22)	48 (41)	16 (14)

An analysis of the tobacco smoking history of 93 lung cancer patients of Schairer and Schöniger revealed similar statistical correlations, since 29 were highly excessive smokers; 19 very heavy ones; 31 heavy ones; and 11 moderate ones, while three (3) were non-smokers.

While these discussions of a possible causal relation between cigarette smoking and lung cancer first aroused little attention beyond the narrow circle of research workers, the problem started to attract wide attention from the medical profession, public press, industry, and laity after the publication of the papers of Schrek, Baker, Ballard and Dolgoff and of Wynder and Graham in 1950. There followed in rapid succession a number of statistical investigations of this problem from this country and abroad (Levin, Goldstein and Gerhardt; Breslow; Ochsner, DeCamp and DeBakey; Graham; Wynder; Mills and Porter; Dungall; Doll and Hill; Daff and Kennaway; Daff, Doll and Kennaway; Gsell). From the results of these studies the following conclusions were drawn by the different investigators:

Wynder and Graham: Excessive and prolonged use of tobacco, especially cigarettes, seems to be an important factor in the induction of bronchiogenic carcinoma. Among 605 men with bronchiogenic carcinoma, other than adenocarcinoma, 96.5 percent were moderately heavy to chain smokers for many years, compared with 73.7 percent among the general male hospital population without cancer.

Schrek et al.: The correlation between smoking and cancer is probably not due to fortuitous or secondary factors. It seems plausible, therefore, to formulate the hypothesis that there is a direct relationship between cigarette smoking and cancer of the respiratory tract and that cigarette smoking may be a carcinogenic agent. This relatively low percentage of deaths by cancer of the respiratory tract compared to the high percentage of smokers indicates that smoking is, at most, only a weak carcinogenic agent.

Ochsner, DeCamp and DeBakey: There is a distinct parallelism between the sale of cigarettes and the incidence of bronchogenic carcinoma. Because the carcinogenic effect of cigarette smoking does not become evident until after many years of smoking (approximately 20), it is frightening to speculate on the possible number of bronchogenic cancers that may develop as the result of the tremendous numbers of cigarettes consumed in the two decades from 1930 to 1950. If there is a causal relationship between cigarette smoking and bronchogenic carcinoma the deaths per 100,000 population from this cause may be expected to increase from 11.3 to 29.4 by 1970.

(Levin, Goldstein and Gerhardt: These data support the conclusion that lung cancer occurs approximately 65 percent more frequently among males who have smoked cigarettes for 25 years or more than among males who have smoked cigars or pipes for a comparable period, or non-smokers. The data indicate also that pipe and cigar smokers have no higher incidence of lung cancer than non-smokers. The findings suggest, although they do not establish, a causal relation between cigarette and pipe smoking and, respectively, lung and lip cancer.

(Mills and Porter: Among cancers of the respiratory tract from the larynx downward, an abnormally high percentage of cigarette smokers, as well as of pipe and/or cigar users, is found. This group of cancer victims exhibits significantly increased percentages in all forms of smoking.

Doll and Hill: Among the smokers a relatively high proportion of the patients with carcinoma of the lung fell in the heavier smoking categories. Smoking is a factor, and an important factor, in the production of carcinoma of the lung. The risk of developing carcinoma of the lung increases steadily as the amount smoked increases. If the risk among non-smokers is taken as unity and the resulting ratios in the three age groups in which a large number of patients were interviewed (ages 45 - 74) are averaged, the relative risks become

6, 19, 26, 49, and 65 when the number of cigarettes smoked a day are, 3, 10, 20, 35, and say 60 - - that is, the mid-points of each smoking group. Cigarette smoking was more closely related to carcinoma of the lung than pipe smoking. No distinct association was found with inhaling.

It appears from the speculations of Doll and Hill that among the population of Greater London over the age of 45, those who smoke 35 or more cigarettes a day, had a chance of developing cancer of the lung which was fifty (50) times greater than that of non-smokers of similar age. Assuming that these conclusions are essentially correct, it may then justly be argued that an effective control of cigarette smoking offers the means for a far-reaching prevention of cancer of the lung and, possibly, the larynx. The statistical data which form the basis of these conclusions are summarized in table 9. Brunner found among 127 lung cancer patients 75 percent heavy smokers and 9.5 percent non-smokers.

While some of the not inconsiderable differences in the relative percentages of smokers of various degrees are doubtlessly due to the use of different standards in the classification used, this explanation, however, does not hold for the proportion of non-smokers listed by the different investigators. The percentage range for non-smokers is from 1.3 to 14.6 percent for the various lung cancer groups and from 8.8 to 30.5 percent for the control groups. These discrepancies suggest the existence of differences in the basic composition of the human material evaluated. The validity of this concept also is supported by the fact that the various investigators noted rather widely varying proportions of adenocarcinomas in males and females in their respective series. The histologic type of pulmonary cancer is predominantly of the epidermoid variety among males, while a considerable proportion of these tumors among women are of the adenocarcinomatous kind (36.4% in females; 4.5% in males (Gsell); 52% in females; 18% in males (Proc. First Nat. Cancer Conf.); 13.7% in females; 6.7% in males (Mason); 52% in females; 0.6% in males (Wynder and Graham). It was noted also that a history of heavy smoking was less often

Table 9.

Statistical Correlations Between Tobacco Smoking and Lung Cancer

Degree of Smoking Habit Among Lung Cancer Patients (Males)

Authors	Highly Excessive	Very Heavy	Heavy	Moderate	Non-Smokers
Schrek, et al.	18.3	50.0		12.2	14.6 Cigarettes only, balance: pipe & cigars.
Wynder & Graham	20.3	30.9	35.2	12.4	1.3
Doll & Hill	5.0	21.0	30.3	38.6	5.1
Breslow	15.3	50.7	19.5	3.5	9.0
Gsell	30.0	37.0	21.0	10.5	2.0
<u>Controls:</u>					
Wynder & Graham	7.6	11.5	35.6	30.5	14.6
Doll & Hill	2.1	11.4	30.5	47.1	8.8
Breslow	3.5	34.8	18.8	11.1	30.5

- 21 -

elicited from patients with adenocarcinoma than in those with epidermoid carcinoma (Gsell; Wynder and Graham).

The apparent lack of uniformity in the human material analyzed by the different authors is further demonstrated by the appreciable differences in the sex distribution of lung cancers reported at different times, from different regions and by different investigators. The male to female sex ratio fluctuates between 2:1 to 20:1 (Hueper). It is noteworthy, however, that the uniformly observed prevalence of lung cancer among males has, in general, become in recent years even more pronounced than in former decades. This observation strongly militates against a predominant causal role of cigarette smoking in the production of lung cancer, because all previous experience in the field of occupational cancer indicates that given the same type of carcinogenic exposure for both sexes and at the same time an increasing equalization of the intensity of exposure, there occurs a narrowing of the gap in incidence rates of the two sexes and not a widening, which actually exists. This interpretation of the diverging, sex related frequency trends is not fundamentally affected by the statement that the interval between the start of tobacco smoking and the appearance of a lung cancer is between 20 and 40 years (Wynder and Graham; Ochsner, DeCamp and DeBakey; Schrek, Baker and Ballard). Even if women may not have indulged on a large scale in tobacco smoking some thirty years ago, there can be little doubt that the cigarette smoking habit has made during this period much greater strides among women than among men.

The purely statistical approach leading to the assumption of the existence of causal relations between two coincidental events and trends is thus in urgent need of supporting biologic evidence. It is for this reason that the negative statistical correlation between pulmonary cancer frequency and cigarette smoking recently reported by Dungal from Iceland has added relatively little to the basic issues. Dungal pointed out that there were among 1939 autopsies performed during 1939 - 1948 with 417 cancers of all sites only 12 pulmonary cancers (2.9% instead of 10 to 20% in the United States and 12%

in Switzerland), that tobacco, especially of cigarettes was not particularly popular in Iceland until 1939 and that tarring of the roads which had extensively been done since 1920, had not exerted any influence on lung cancer frequency.

Experimental Tobacco Cancer:

Attempts to produce cancers with tobacco tar in experimental animals began many years before even any relation between tobacco smoking and lung cancer was suspected - that is at a time when the claims of a causal relationship between cancer and tobacco smoking was still limited to cancers of the lip, tongue, mouth, and larynx (Martin, Friedell and Rosenthal).

2. Skin Applications of Tobacco Tar:- Macker and Schmincke as well as Helwig using tobacco tar extracts which they applied to the ears of rabbits and the skin of mice, respectively, produced only ulcers with epithelial proliferations, but not cancers. Similarly negative were experiments of Hoffmann, Schreus and Zurhelle who applied denicotinized tobacco tar for 80 days to the skin of mice; and by Cooper, Lamb, Sanders and Hirst who used the same technique for 23 months and observed a single skin cancer. Roffo and Chikamatsu reported the production of cancroids in the ears of a few rabbits after prolonged painting with tobacco tar. These claims were confirmed by experiments of Lü-Fu-hua but cancers of rabbits' ears were seen only when he used simultaneously intravenous cholesterol injections as well as painted the other ear with coal tar. These observations of Lü-Fu-hua on cholesterolized and coal tar treated rabbits were successfully repeated by Schürch and Winterstein who in turn failed to produce skin cancers in mice receiving skin application of tobacco tar and various tobacco tar fractions having different boiling points.

Sugiura subsequently succeeded in producing a solitary squamous cell carcinoma in a mouse painted with tobacco tar distilled at a temperature between 500°-900° C. Tobacco tar distilled between 100° - 500° C. proved to

be noncarcinogenic for mice when applied to the skin. Both distillates were administered in an oily mixture to the ears of rats and rabbits for 52 to 95 weeks without tumor formation. Flory repeated the application of tobacco tar distillates of different boiling points ($130-350^{\circ}\text{C}$); $350-700^{\circ}\text{C}$) as well as of pipe tobacco tar to the ears of rabbits and obtained in a considerable proportion of the animals, papillomas and carcinomatoid tumors, but not carcinomas. Several squamous cell carcinomas were found in mice after the application of these tars.

b. Inhalation of Tobacco Tar Fumes:- The first attempts to produce cancer of the lung in experimental animals by the inhalation of tobacco smoke were made by Mertens using mice which were exposed in glass jars to tobacco smoke injected into these vessels. Among the first set of 125 mice, two (2) developed "lung cancer", but in both instances they most likely were of "spontaneous" origin. When this experiment was repeated no lung tumors were obtained. Likewise, negative were similar experiments of Lorenz et al. when mice inhaled tobacco smoke introduced into a closed container. The strain A mice exposed to tobacco fumes showed the same incidence of spontaneous lung tumors as control animals. In Campbell's experiments in which a similar technique of inhaling tobacco smoke was used, there followed a minor increase of lung tumors in the test series over that of the controls.

A more direct and drastic method for introducing tobacco tar into the lungs of experimental animals was chosen by Poffo who injected this material directly into the lungs of rats and obtained in one (1) rat, four (4) small squamous cell carcinomas.

A critical evaluation of the total experimental evidence permits the conclusion that tobacco tar obtained at various distillation ranges is of very weak if not doubtful carcinogenicity to the skin of mice and produces apparently only carcinomatoid tumors in the ears of rabbits, when applied over long periods

of time. The inhalation of tobacco smoke, released into the atmosphere, by mice failed to produce lung cancers. The unconfirmed positive claims of Roffo have been disregarded in reaching these conclusions.

c. Demonstration of Known Carcinogens in Tobacco Smoke and Tar.

Among the known carcinogenic chemicals which may occur in tobacco smoke or tar carcinogenic aromatic hydrocarbons and arsenicals have to be considered. The carcinogenic aromatic hydrocarbons might be formed during the combustion of the tobacco while arsenicals might occur in only those tobacco tars and fumes which are generated from tobacco containing arsenical insecticide residues.

Although Roffo asserted to have demonstrated 3,4-benzpyrene in tobacco tar by spectroscopic methods, this claim has remained unconfirmed by several very reliable investigators (Schürch and Winterstein; Cooper, Lamb, Sanders and Hurst; Waller).

While the failure to demonstrate 3,4-benzpyrene in tobacco tar does not exclude the possible presence of other carcinogenic chemicals in this material, it nevertheless is an observation which is noteworthy because 3,4-benzpyrene seems to be one of the common carcinogenic combustion products of carbonaceous matter of many kinds.

In view of these negative findings for carcinogenic hydrocarbons in tobacco tar some investigators recently have favored the concept that the alleged carcinogenic effect of tobacco smoke upon the respiratory tract depends at least in part upon the inhalation of arsenic present in the tobacco as an insecticide residue and volatilized during the smoking process (Doll and Hill; Goulden, Kennaway and Urquhart). In fact, rather appreciable amounts of arsenic can be demonstrated in tobacco and in tobacco smoke, especially of the American variety. Gross and Nelson found that the arsenic content of cigarette tobacco of five (5) brands ranged from 9.7 to 36.3 p.p.m., that of cigars from

8.3 to 48.4 p.p.m., and that of pipe tobacco from 26.0 to 50.0 p.p.m. Thomas and Collier noted that the range of the arsenic content of cigarette tobacco was from 35.4 to 114 p.p.m., while that of cigars was 13.2 to 29.5 and that of pipe tobacco 22.7 to 42.8 p.p.m. The reason for the marked variations in different samples and various types of tobacco is undetermined. However, different climatic conditions and methods of cultivation and processing of tobacco in various parts of the United States and the different use to which the various types of tobacco are subsequently put in the production of tobacco goods may have a decided influence in this respect.

In more recent studies of cigarette tobacco by Daff and Nelson, three (3) American brands gave an arsenious oxide content ranging from 25 to 47 micrograms; two (2) English brands had one ranging from 50 to 55 micrograms; eight (8) Turkish brands had one ranging from 0 to 4.1 micrograms; one (1) French brand ranged from 0.5 to 1.5 micrograms; and from a Rhodesian brand, the range was 1.8 to 4.1 micrograms. Popp found that Palatinate tobacco contained 5.1 p.p.m. of arsenic; Macedonian cigarette tobacco 0.7; Java tobacco 0.33; and Brazilian tobacco 4.6. Oliver reported that English pipe tobacco contained 32 p.p.m. of arsenic (as metal); cigarettes 68 p.p.m.; Jamaica cigars, 30 p.p.m.; and Havana cigars, 170 p.p.m.

The observations show that the concentration of arsenic in cigarettes, cigars and pipe tobacco is very variable depending upon the brand as well as upon the country of origin. The tobacco of American derivation, and smoked in the U.S.A., Canada, Norway and England has by far the highest arsenic content (24 to 106 micrograms As_2O_3 per gram of tobacco), while tobaccos grown in the eastern European countries and Turkey have, as a rule, a low arsenic content (0.0 to 4.3 micrograms As_2O_3 per gram of tobacco). This type of tobacco is used in cigarettes made in Austria, France, Poland and Bulgaria.

In adjudging the degree of arsenic hazard which may result from the smoking of arsenic containing tobacco, Daff and Kennaway, Thomas and Collier, and Gross

and Nelson ascertained that between 7.0 and 26 percent of the arsenic present in the tobacco is volatilized and may be inhaled during the smoking process. Remington, however, placed this portion as high as 50 percent. Daff and Kennaway expressed the degree of potential hazard by the following calculation:- "If a person smokes 50 cigarettes with a mean arsenic content of 50 micrograms and 15 percent of this escapes, he has volatilized 0.375 mg. As_2O_3 , which is the amount contained in 0.0375 cc. of Fowler's solution (official dose 0.125 to 0.5 cc.)."

In a recent, very illuminating study of the relation of cancer of the lung to tobacco as grown and smoked in different countries, Daff, Doll and Kennaway have unearthed important observations which strikingly demonstrate the complexity of the problem and show "that the arsenic content of tobacco has not provided any simple and exclusive explanation of the association between cigarette smoking and this form of cancer." Analyzing first the data provided by Saglam, Schwartz and Yenerman from Istanbul, Turkey, where for over five (5) decades tobacco was consumed almost wholly in the form of cigarettes and where there have been many heavy smokers among women, they found that there had been a considerable rise in lung cancer frequency during the past 50 years, according to clinical and anatomic-pathologic statistics (increase in clinical material, 12 times, in pathologic material, 4.1 times). However, the male: female ratio changed from 6:1 during 1935 to 1939 to 8:1 during 1949 - 1950, although cigarette smoking has been a habit indulged in by Turkish women for many decades. The tobacco consumption expressed in pounds per head increased from 1.21 in 1925 to 1.9 in 1949. Since the tobacco consumption stood in 1935 at only 1.55 lbs. per head, and in view of the long lag period in the development of lung cancer, it is most unlikely that the increase in lung cancer frequency in Istanbul has any relation either to tobacco consumption or to its arsenic content. This view is supported by the sex ratio which is, like in

many other countries, markedly and increasingly in favor of males, despite the long established smoking habit among Turkish women. Saglan also, therefore, rejected cigarette smoking as a factor in the incidence of bronchial carcinoma.

Another illustration of the apparent lack of significance of arsenic in tobacco in relation to the causation of lung cancer and its recent increase seems to be provided by the autopsy data from Ljubljana, Yugoslavia, provided by Kosir. During the period 1925 to 1939 lung cancer represented 7 percent of all males coming to autopsy with cancer of all sites, and 1.5 percent of all females of the same type, while during 1940 to 1949 these figures stood at 15 percent and 2 percent, respectively. Tobacco is smoked principally in cigarettes of oriental type with a low arsenic content. The increase in lung cancer frequency thus was disproportionately large for males.

The data provided to Daff, Doll and Kermaway on Switzerland by v. Meyenburg have been complemented by those recently given by Gsell.

According to Gsell, there has taken place in recent years a marked increase in the consumption of cigarettes (10-fold between 1924 and 1949) but the main tobacco product consumed in Switzerland had remained the "Stumpen", a medium-sized cigar without a tip. There were 45 Stumpen and cigar smokers and only 30 cigarette smokers among Gsell's 57 cases. The absolute number of lung cancer cases rose in males from 68 in 1905 - 1909 to 2058 in 1945 - 1949 (20.7 times), while the corresponding increase in female cancer deaths was from 59 cases in 1905 - 1909 to 421 cases in 1945 - 1949 (7.1 times). During the same period there occurred a shift of the male: female sex ratio from 2:1 in 1905 - 1909 to 4.9:1 in 1945 - 1949. The lung cancer death rate per million stood in 1931 at 66 for males and at 14 for females, while in 1947 it was 183 for males and 34 for females. The arsenic content of tobacco of Swiss cigarettes was of intermediate order (3.1 to 12.0 micrograms of As_2O_3 per gram). Since during the critical period of lung cancer increase for which Swiss tobacco consumption figures are available (1924 to 1935) the main use of tobacco was in the form of cigars, Stumpen and Toscani, one must assume that the majority of the lung

cancers observed during the years 1940 to 1949 cannot be attributed to the smoking of cigarettes, if smoking at all had any causal connection with their development. That the existence of such a relation is not likely is again attested by the divergent trends in the sex distribution of lung cancer, which according to past experience on this point from the field of occupational cancer would display a tendency toward equalization whenever members of both sexes are exposed to the same environmental carcinogenic agent. That this principle also applies to tobacco smoking is evident from the recent statistical studies of Doll and Hill who ascertained that the risk of developing cancer of the lung is the same in both men and women, apart from the influence of smoking.

The importance of this argument is strikingly illustrated by the information supplied to Daff, Doll and Kennaway by Kreyberg concerning the lung cancer incidence in Norway during the past 20 years. Apart from the fact that deaths from lung cancer were higher in urban than in rural districts of Norway, there occurred during the two decades a definite rise in pulmonary cancer frequency from about 20 in 1930 to approximately 157 in 1948. The rise was more marked in urban areas than in rural ones and affected males to a higher degree than females. While thus the Norwegian experience followed in this respect the usual pattern, it differed fundamentally from it in its sex distribution. During the first six years of the survey period, lung cancers were apparently as frequent in females as in males and thereafter the rise of the rates in females fell somewhat below that of males. This observation permits only one interpretation when analyzed in the light of the existing facts, that the epidemiologic behaviour of lung cancer as to sex distribution was influenced in Norway by probably environmental factors which were not active at all or to the same degree in the other countries investigated. Since the population of Norway has smoked predominantly American made tobacco, this deviation from the common epidemiologic pattern does not support the view that tobacco smoking

in Norway or in any of the other countries was a deciding and important factor in determining lung cancer epidemiology during the past 50 years.

In the various arguments advanced purportedly favoring the cigarette smoking role in the causation and rise of lung cancers much is made of the existing parallelism between the increase of lung cancer frequency and the increased consumption of smoking tobacco, particularly cigarettes, during the last 25 to 50 years. In the graphic presentation of these two developments the relative events of annual rise of lung cancer rates and of tobacco consumption are invariably synchronized, while in fact these events have a distinct heterochronicity because of the long latent period of lung cancer which has been estimated for smokers to range between 20 and 40 years. The lung cancer cases observed in 1950, for instance, therefore have no causal connection with the tobacco consumption of the same year but more likely, if at all, with that recorded for 1920 to 1935. It is evident from this consideration that the so-called "parallelism" as presented by synchronized graph lines gives a definitely distorted expression of any possible hypothetical relation between lung cancer and tobacco consumption (figs. 4 and 5).

Distinctly disconcerting in this respect is also the obvious disagreement of different investigators as to the relative role which cigarette smoking, on the one hand, and the smoking of pipe tobacco and cigars, on the other hand, allegedly play in the causation and rise of lung cancer. While Levin et al. contended that only cigarette smoking but not pipe and cigar smoking reveals a positive statistical correlation, Mills et al. emphasized that all three forms of smoking are equally guilty, while Wynder and Graham; Gsell; and to some degree also, Doll and Hill, assess the individual smoking habit by including all types of smoking. While Doll and Hill contemplated the possibility that pipe smoking may be less lung cancer inducive than cigarette smoking because in their opinion pipe smokers smoke less tobacco than cigarette smokers,

Fig.4.

Comparative Trends in Respiratory Cancer

Mortality 1924 - 1950

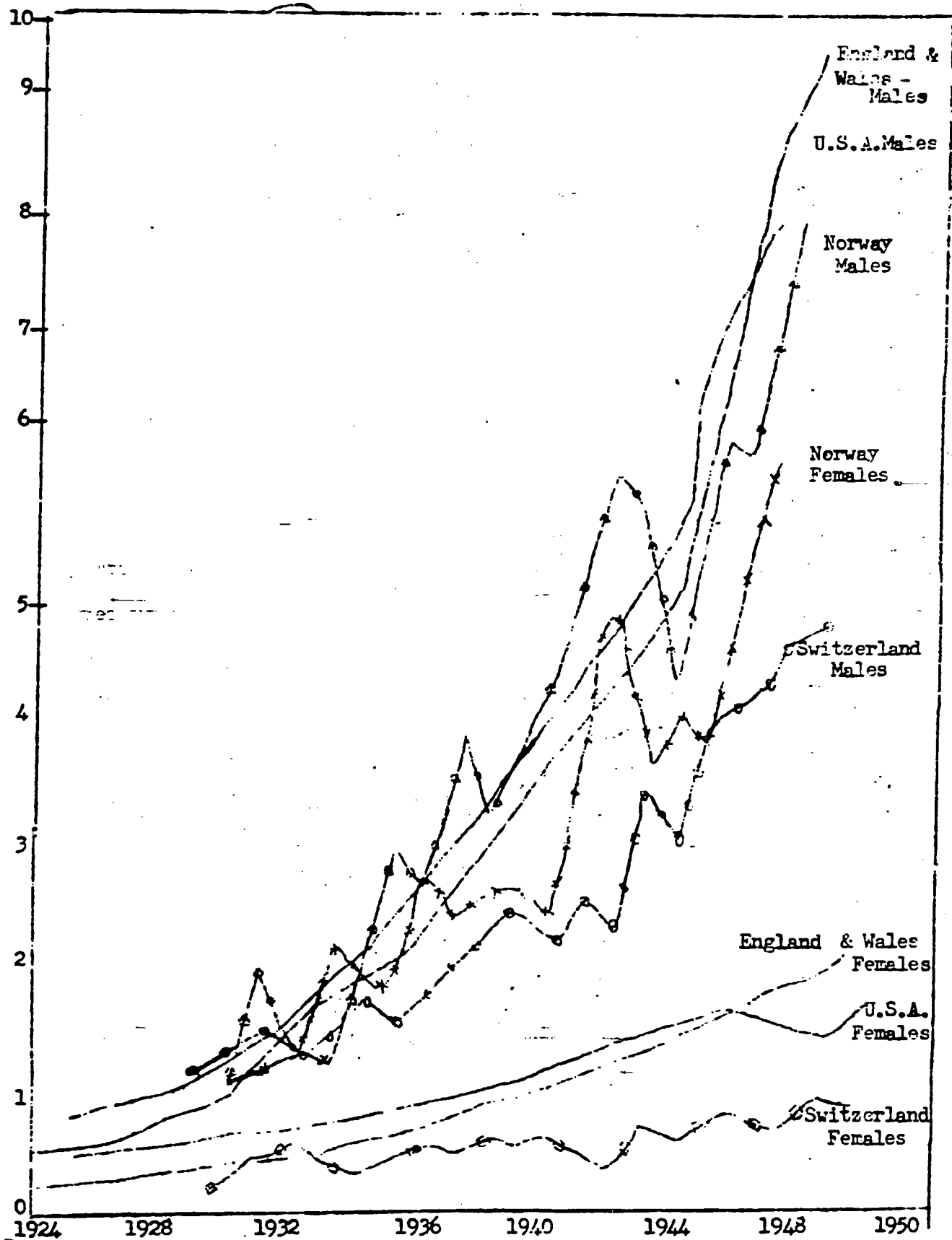
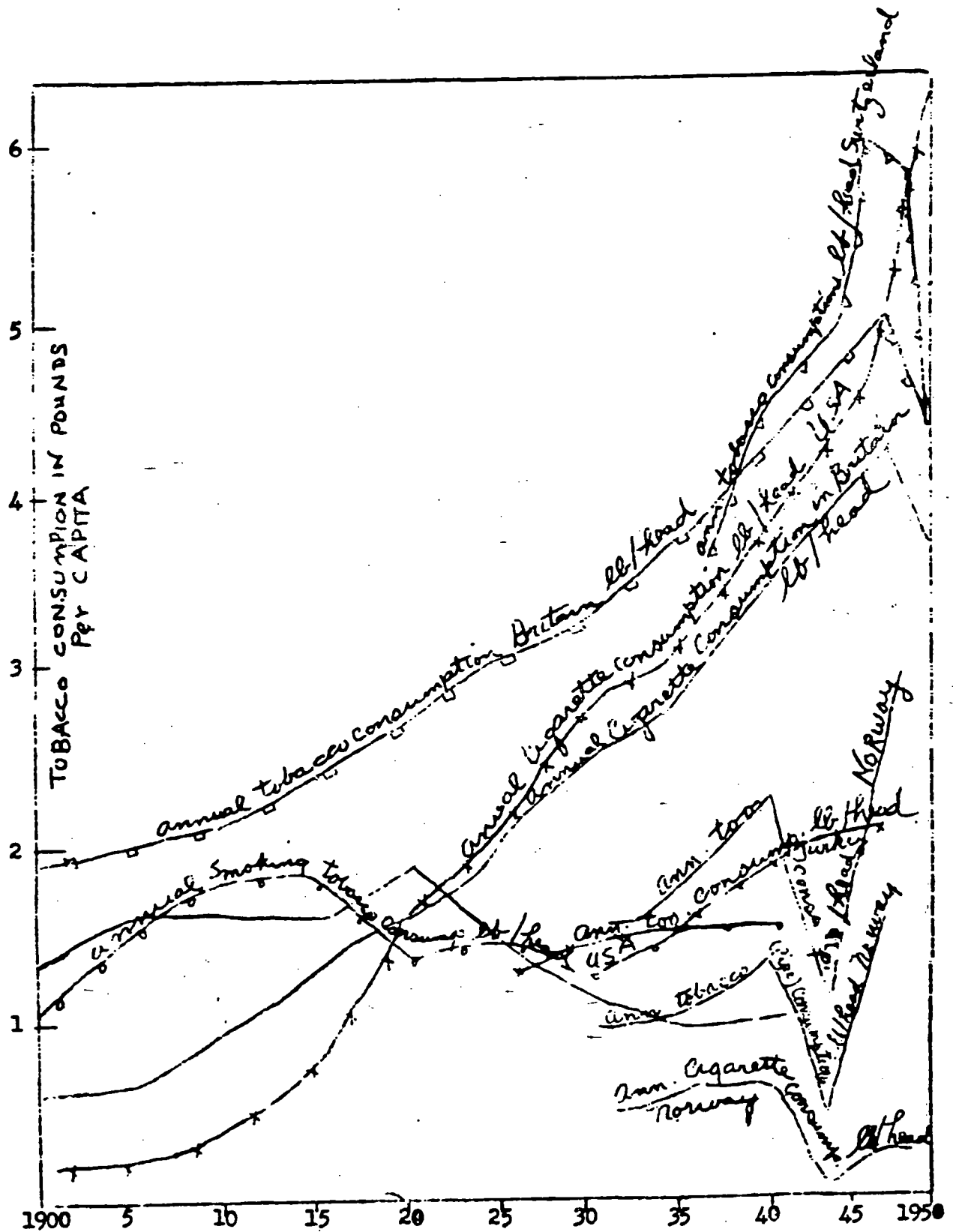


Fig. 5.

Tobacco Consumption per Capita in Pounds



it may be well to consider the fact that many cigarette smokers discard their cigarettes after a few puffs and that, therefore, the assessment of the degree of cigarette smoking may more easily become exaggerated, while that of the pipe and cigar smoker may become underestimated. Gage indeed stated that one study strongly indicated that the average cigarette smoker consumes less tobacco per day or year than a cigar smoker or chewer.

Of undoubted importance seems to be another statement of Doll and Hill in which they note that inhaling of cigarette smoke did not convey any increased lung cancer liability. This is an observation which cannot be reconciled with facts established for determining occupational cancer incidence. Whenever the intensity and duration of exposure to an occupational carcinogen increases, there rises the cancer incidence rate among the exposed population group. There is no plausible reason to assume that the inhalation of allegedly carcinogenic tobacco smoke would be exempted from this rule. The complete lack of even minor increase of laryngeal cancer during the past five decades, although the larynx forms a part of the smoke tract, also militates against the tobacco smoking theory of lung cancer.

It may be concluded that the existing evidence neither proves nor strongly indicates that tobacco smoking and especially cigarette smoking, represent a major or even predominating causal factor in the production of cancers of the respiratory tract and are the main reason for the phenomenal increase of pulmonary tumors during recent decades. If excessive smoking actually plays a role in the production of lung cancer, it seems to be a minor one if judged from the evidence on hand. However, it may be well to remember in this connection, the concluding statement of Doll and Kermaway; that "the study of the relation between the national consumption of tobacco and the national incidence of cancer of the lung has scarcely begun."

5. Cancer of the Lung and Its Relation to Specific Agents.

It should be apparent from the preceding discussion that evidence related to large population groups with exposures to diverse environmental agents with mainly unknown carcinogenic properties gives at best information of only circumstantial value, which may serve as a lead for more specific and detailed subsequent survey studies. The establishment of firm causal connections between environmental influences and the development of cancers of the respiratory system therefore, depends upon the demonstration of definite and significant statistical and causal relations between exposures to specific environmental or occupational agents and/or working conditions and the subsequent appearance of cancers of the respiratory system. It is for this reason that at present the only conclusive evidence on the causal relationship between exogenous factors and cancer of the lung is of occupational origin. In fact, the great majority of the occupational cancers discovered during the present century affect the lung and/or other parts of the respiratory tract (nasal cavity, paranasal sinuses, larynx). While exposure to the so far known respiratory carcinogens occurred in all instances by inhalation, the successful production of lung tumors in experimental animals receiving various carcinogenic chemicals (urethane derivatives, acetylaminofluorene, etc.) through other routes suggests that respiratory carcinogenesis may not be limited also in man to contact with environmental carcinogens by inhalation.

The respiratory carcinogens so far recognized differ greatly in their chemical and physical properties as well as in the physicochemical status in which they come in contact with the respiratory tissue. Some are chemical agents such as various metals or metal compounds (arsenic, chromium, nickel) or minerals (asbestos) or aliphatic organic (isopropyl oil) or aromatic organic compounds (chemical carcinogens in coal tar, pitch, soot, petroleum derivatives). Others exert a carcinogenic effect through physical forces (ionizing radiation),

such as the various radioactive chemicals. They enter the respiratory tract in the form of dust, fumes, mists, vapors and gases. Depending upon the particle size of the dispersed carcinogenic material they may penetrate into different parts of the respiratory tract. If the particles are rather large, they produce mainly cancers in the upper parts (nasal cavity, larynx). They may enter, on the other hand, the deeper portions, such as the bronchi and lung or paranasal sinuses, if they are of very small particle size or take the form of vapors or gases.

The depth of penetration of atmospheric contaminants into the respiratory tract depends moreover on the intensity of exposure and on a possible destructive action of the ciliated epithelial lining and its mucus producing glands of the upper respiratory tract (nose and trachea). Whenever under the influence of an overwhelming or excessively prolonged exposure to pollutants of the air the limit of the protective saturation of the nasal and tracheal mucosa is reached, dispersed particles will penetrate thereafter in increased amounts into the deeper portions of the respiratory conduits.

The relative degree of carcinogenic property of the various respiratory carcinogens depend not only upon their intrinsic carcinogenic potency, but also on the degree of dispersion, their solubility in water and fats, and their direct cytotoxic qualities, all of which influence the action of a particular carcinogen by controlling its penetration into cellular elements and its time of retention and possible permanent deposition in the lung tissues. Since under occupational conditions, exposure to respiratory carcinogens is not infrequently complicated by contact with various noncarcinogenic types of dust, solvent vapors, acid fumes and alkali and oily mists, the primary and direct action of the carcinogens may be modified by an interaction with these concomitant agents or with the anatomic reactions set up by these agents in the lung.

Recent studies of Falk and Steiner and of von Haam, Titus, Shinowara and Caplan, have shown that carcinogenic hydrocarbons (3,4-benzpyrene, pyrene, 20-methylcholanthrene), when adsorbed to the surface of carbon particles, such as those forming the bulk of various carbon blacks (commercial soots), are released only with difficulty by elution with solvents and show within a given time limit a lowered carcinogenic potency when tested in their adsorbed form on mice. It may be assumed that similar conditions prevail when carcinogenic hydrocarbons are adsorbed to the carbon particles of ordinary soot or to particles of silica present in road dust or released as waste catalyst from catalytic cracking towers of oil refineries. Counterbalancing this slowed release, however, is the longer retention of the carcinogenic hydrocarbons when introduced into the lung tissues on the surfaces of chemically rather inert, noncarcinogenic particles.

Similar modified conditions of exposure are apt to prevail if radioactive gases adsorbed to the surfaces of noncarcinogenic mine dust enter the lung, and are bound to stay in this adsorbed form over a longer period in the lung and, thereby, exert a more pronounced carcinogenic effect upon the lung tissues than when entering these organs as free radioactive gases (radon, thoron). While a few of the respiratory carcinogens cause the development of pulmonary fibrosis and pneumoconiosis (radioactive dust and gases, asbestos, chromium compounds, beryllium, soot and tar fumes), such effects do not accompany the carcinogenic action of others (nickel, arsenic, isopropyl oil, petroleum products).

Consideration also must be given to the possibility that the simultaneous action of pulmonary fibrosis producing dusts or chemical vapors, gases and fumes associated with, preceding or following the action of specific respiratory carcinogens might interfere with the removal from the lungs of inhaled carcinogenic material due to the obliterations of lymphatics and blood vessels

and the formation of fibrous barriers. Such anatomical complications present in the lung again would most likely tend to prolong the action of inhaled carcinogenic agents, and thereby intensify their specific effect on the lung tissues. On the other hand, there exists adequate evidence for the view that established pulmonary fibrosis would hinder to some extent for similar reasons the spread of a cancerous growth within the lung as well as to other tissues.

Fibrogenic pneumoconiosis thus may exert a definite effect on the productive and developmental phases of pulmonary cancer, as well as on its subsequent proliferative phase.

Consideration must further be given to the concept that carcinogenesis by specific agents may be accelerated by the simultaneous action of nonspecific chronic inflammatory processes. Some investigators have proposed that bronchial cancers originate in scars or mucosal pigment perforations produced by the deposition of inhaled dust (Schmorl).

Finally, pneumoconiotic and fibrotic lesions are clinically important from a differential-diagnostic viewpoint, since some of these changes may resemble neoplastic lesions in their symptomatology or they may obscure the presence of such conditions. From the general evidence available on lung cancer it appears, however, that the great majority of these neoplasms are not associated with pneumoconiotic conditions.

Probst pointed out that pneumoconiosis usually is absent in lung cancer. Bauer stated that the inhalation of stone dust as such certainly does not elicit the development of a pulmonary cancer since there exist many industrial operations with definite pneumoconiotic hazards without an increased liability to lung cancer. In the report of the British Empire Cancer Campaign of 1952 the statement appears that pneumoconiosis was present in only one (0.1%) of 325 cases of pulmonary cancer. Olson reported that in a series of 69 cases seen in Boston, pneumoconiosis was present in only 2.9 percent. However, such

observations obviously disregard the rather frequent occurrence of anthracotic and bituminotic pneumoconiotic deposits in the lungs of persons living in industrialized regions. There exists, moreover, the possibility that benign pneumoconiotic conditions elicited by dust of black metallic compounds such as iron oxide or chromite may be mistaken at autopsy for anthracosis. The differentiation between carbon pigments and those of metallic nature requires the use of spodograms or ashed sections. This procedure, however, is not routinely applied.

A. Relation of Inhalation of Metal Dusts and Fumes and of Metal

Pneumoconiosis to Respiratory Cancer.

The chronic dust disease of the lung (pneumoconiosis) caused by the occupational inhalation of dusts and fumes of metal, metal compounds and metal alloys only exceptionally assumes a progressive, fibrogenic character (beryllium). As a rule, metal pneumoconioses are of the so-called benign type; i.e., they cause non-disabling reactions sometimes associated with minor fibrosis around dust particles (subpleural, peribronchial and perivascular tissues). Such "benign" lesions when severe may ultimately lead to a narrowing of the lumens of bronchi and blood vessels and, thereby, in the long run interfere with the proper blood circulation in the lung causing an embarrassment of the right cardiac function. Massive accumulations of so-called inert dusts, moreover, may cause tissue necrosis and the formation of cavities. The pulmonary reactions occurring after inhalation of dusts, fumes or vapors of some metals are mainly of inflammatory and possibly allergic nature (metal fume fever) (manganese, cadmium, zinc, selenium, copper, brass). Both acute inflammatory and chronic fibrosing reactions may be observed with others (beryllium). The metals and metal compounds which deserve consideration in this respect are aluminum, magnesium, beryllium, cadmium, calcium, copper and copper alloys, vanadium, chromium, manganese, nickel, zinc, tin, antimony, mercury, molybdenum,

lead, iron, tellurium, tungsten, titanium, barium, selenium, thallium, arsenic and silver (Greenburg; Hamlin; Silson; Elkins).

Inhalation exposure to these metals may be related to various occupational activities (mining, smelting, casting, polishing, grinding, drilling, powdering, bagging, alloy making and processing, metalizing, electroplating, soldering, welding, metal catalyst production and use, pigment production and consumption (paints, inks, glazes, glass coloring, textile, paper, rubber, plastic and linoleum dyes), spraying, chemical and metallurgical processing, etc.).

The number of workers who are exposed to the various metallic dusts and fumes in American industries is considerable. Bloomfield, Trasko, Sayers, Page and Peyton produced the following estimates (1940) based on the survey of all industries of 10 states and a total of 1,503,204 workers exposed: Lead: 76,743 workers; antimony: 9,735 workers; chromium: 7,976; arsenic: 3,356; mercury: 3,220; cadmium: 3,031; manganese: 2,287; other metals: 220,929; total: 327,277 (22% of worker population surveyed). From additional estimates made by these investigators it can be assumed that approximately the same percentage of industrially employed workers in the rest of the United States has some form of occupational metal dust exposure.

The epidemiologic information on hand indicates that respiratory cancer hazards definitely exist for only a few of the metal dust and fume exposures, that they are potentially present or controversial for others and that for most of them they do not exist. For many, adequate epidemicologic information is not available. Some metals, however, have produced cancers in organs other than the respiratory ones (liver, bone) of experimental animals. Very defective is the information as to the existence or nonexistence of occupational lung cancer hazards for the various metals, metal compounds, types of exposures and industrial operations in which metals with established respiratory cancer hazards are used and produced.

a. Aluminum.

With enormous growth of the aluminum industry, exposure to aluminum dust has become rather widespread during recent decades for various types of industrial workers. During the past decades, it has been proposed and used on a limited basis as an alleged preventive and therapeutic of silicosis (Brown and van Winkle; Berry; Jephcott and Johnston).

While American investigators are, in general, rather skeptical as to the actual existence of an aluminosis (Crombie, Elaisdell and McPherson; Hunter, Millon, Perry and Thompson; Folicard; Ehrismann; Editorial, Lancet), European investigators have described roentgenologic and pathologic changes of diffuse pulmonary fibrosis occurring in workers occupationally exposed to the inhalation of aluminum dust (propeller grinders, reduction furnace workers, aluminum powder workers, aluminum alloy manufacturers (Goralewski; Goralewski and Jaeger; Koelsch; Jaeger and Jaeger; Mödder and Schmitt; Schwallnus and Kleinsorg; Feil; Perry; Filipo; Gerstel; Doese; Kahlau). The recent observations of Wyatt and Riddell on the diffuse pulmonary fibrosis occurring in bauxite workers (Shaver and Riddell; Shaver), tentatively places the blame on the inhalation of amorphous alumina dust or fumes generated during the production of alumina abrasives. It thus may be concluded that a massive and prolonged inhalation of bauxite and possibly also of aluminum oxide dust or fumes may produce fibrotic pulmonary changes (aluminosis).

As to an alleged carcinogenic action of ingested aluminum, first proposed by Odier, it can be stated that such claims have not been confirmed by subsequent investigators (Doese; Bordas; Marie-Amers; Ichok; Bertrand and Serbescue; Blumenthal; Editorial, J.A.M.A.). This negative evidence does not favor the concept of a carcinogenic action of inhaled aluminum dust on the lung tissue, although a final decision of this question must await the result of comprehensive and competent epidemiologic surveys of exposed worker groups for the incidence of respiratory cancers.

b. Magnesium.

The situation as to the inhalation of magnesium dust and its relation to pulmonary neoplasia is similar to that recorded for aluminum. The inhalation of magnesium dust and magnesium oxide fumes in foundries, airplane manufacturing plants, etc. is considered as not particularly harmful although the occurrence of disturbances has been reported (Tuleky; Gariner and Delabont; Ori and Stern; Elkins). The absence of reliable and competent surveys of respiratory cancer incidence among magnesium workers does not permit to render at this time any definite opinion as to the existence of a lung cancer hazard. There is, however, no evidence available for suspecting the occurrence of such complication.

c. Barium.

The development of pneumoconiosis (barytosis) following the inhalation of barium sulfate among workers of barite mills has been reported (Spodini and Elkins; Tuleky; Arrigoni). Nothing is known as to the existence of an excessive liability to lung cancer hazards among the exposed workers.

d. Cadmium.

Contact of the respiratory organs with cadmium vapors, fumes or dust occurs during the smelting of cadmium ores, working up of residues, spraying of cadmium containing paints and pigments, welding of alloys, and other industrial operations (Division of Industrial Hygiene, NIDH) and may give rise to acute pulmonary reactions (edema and hemorrhages; pneumonitis) (Fairhall). The published records do not contain any reference to pulmonary neoplasia as a late effect of prolonged occupational exposure to cadmium fumes, dust and vapors (Greenburg).

e. Calcium.

The deposition of lime dusts in the lungs (calciosis) of lime stone miners, lime burners, marble polishers, gypsum manufacturers, etc. considered as harmless,

gives rise to disseminated foci of peribronchitis and interstitial pneumonia (Teleky). Causal relations to pulmonary cancer from occupational exposures to lime dust are unknown.

f. Cobalt.

Exposure to cobalt dust especially by cobalt ore miners has figured for many years as an alleged cause of cancer of the lung among the Schneeberg miners (Carozzi; Schinz). The increasing use of cobalt in alloys of steel, as a catalyst in the Fischer-Tropsch process of oil production from coal and in the manufacture of iron free magnets and carbide tools and dies has brought a considerable number of workers in contact with cobalt dust (Fairhall, Keenan and Brinton). Granular or conglomerate markings were found in the lungs of such workers upon radiologic examination (Fairhall, Castberg, Carozzi and Brinton). Although Schinz reported the development of a spindle cell sarcoma of the femur in a rabbit which received an intraosseous implantation of powdered cobalt more than three (3) years previously, the survey conducted in 1925 by a special committee of the Labour Office of the League of Nations among workers employed in cobalt mines in other parts of the world (Canada: Cobalt City; Congo: Katanga; Norway: Skuterud; France: Allemont; Czechoslovakia: Dobschina) failed to show any excessive liability of cobalt miners to lung cancer. German investigators, moreover, noted that the high lung cancer frequency in Schneeberg was limited to miners and was absent among the workers employed in the cobalt pigment factory. It may be mentioned, moreover, that the chemical analysis of the lung of a Schneeberg miner who died with lung cancer did not reveal any cobalt (Beyreuther). The evidence on hand supports the view that a carcinogenic action of cobalt upon the lung tissues has not been established and that claims to that effect are not supported by valid evidence.

g. Titanium.

Since the extensive use of titanium and its compounds in paints, steel alloys, cemented carbides, screening smoke and in protective ointments against flash burns is of rather recent date, relatively little information is available as to the existence and type of pulmonary effects produced by the inhalation of dust of metallic titanium and its compounds, mainly titanium oxide. Carozzi thought titanium oxide to be nontoxic because of its chemical inertia. Elina did not observe any pulmonary reactions among workers exposed to titanium oxide dust. However, guinea pigs exposed to this chemical showed after two (2) months an increase of connective tissue of the lung and abundant exudate in the large and medium sized bronchi. Similar observations were made by Lenz (1936) in guinea pigs exposed to the inhalation of clouds of pure titanium oxide, according to Teleky. It seems that under the circumstances, long range epidemiologic studies are indicated for determining whether or not the inhalation of titanium and its compounds may be associated with any lung cancer hazard.

h. Antimony.

Antimony and its compounds are used in considerable quantities in alloys (lead), type metal, bullet cores, pigments in rubber, enamels, paints and textile dyes, bronzing powders and medicinal agents. An appreciable portion of the workers using antimony and its various compounds are exposed to antimony dust and fumes (type setters, metallurgical workers, rubber workers). Irritative symptoms of the upper respiratory tract including perforation of the nasal septum have been reported to occur among these workers (Feil; Shirley; Schwartz and Tulipan). Fairhall and Hyslop stated that antimony metal dust appears to be much more toxic than the dust of other insoluble antimony compounds of industrial importance. They noted, moreover, in connection with industrial exposure to the various antimony dusts, that finely divided antimony

dust can remain suspended in the air longer than would be anticipated with a heavy metal.

None of the few existing studies of antimony dust hazards in industry apparently paid any attention to the possibility of a lung cancer hazard for workers exposed to these chemicals.

1. Beryllium.

Beryllium is a metal which has found significant industrial use only since about 1920. It was not until about 1940 that beryllium and its compounds were extensively employed for numerous purposes and products (beryllium-copper, beryllium-aluminum and beryllium-nickel alloys, glass, phosphors in fluorescent lamps and neon tubes, atomic energy products, ceramics, refractories, x-ray tube windows; vitreous enamel; radio tubes, textile fibres, gas mantles) (Galman; Gardner; Vorwald; Breslin; Hardy; Hyslop, Palmers, Alford, Monaco and Fairhall). 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 (beryllium sulphate, beryllium chloride, beryllium oxide, beryllium fluoride, beryllium carbonate, beryllium manganese silicate, beryllium oxy-fluoride, beryllium silicate, beryllium hydroxide, zinc manganese beryllium silicate) 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 (Gardner; Hardy, Vorwald; Eisenbud, Wanta, Dustan, Steadman, Harris and Wolf; Eisenbud, Berghout and Steadman; Corcoran; Sterner and Eisenbud; Machle, Beyer and Tedbrook; Laskin, Turner and Stockinger; Johnstone, Bruce, Lovejoy, Brothers and Volaquez; Higgins; Vigliani; Wilson; Van Ordstrand, Hughes, DeNardi and Carmooy; Aub and Grier; Shilen, Mellor, Koppenhaver, Cleland, Galloway and Lutz; Hasterlik; Jetter; Ginabat; Van Ordstrand, DeNardi and Schneider; Sander; Kline, Inkley and Tritchard; Fenn; Silson, Benjamin and Wilson; Williams;

Martland, Brodtkin and Martland; Wilson; Machle; Dutra; Morgis and Forbes; Reynolds; Hardy, Bartter and Jaffin; Cass; Pomeranz and Brodtkin; Klemperer; Pascucci; Pyre and Oatway).

Hardy noted as a conservative estimate there occurred up to September 1951 between 300 - 400 cases of acute beryllium poisoning and at least 200 cases of the chronic variety in the United States which resulted in the fluorescent-lamp industry in a mortality of about 25 percent among the ill workers. It is remarkable, moreover, that chronic berylliosis has appeared not only among exposed workers, but also among persons living in the neighborhood of fluorescent lamp factories and inhaling their beryllium 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 (Hardy; Gerrie, Kennedy and Richardson; Kennedy). 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 (Nash, Grier and Freiman; Helwig; Davis and Grimes; Curtis; Large and Stumpe; Gerrie, Kennedy and Richardson; Dutra; Silverman and Erickson; Stokes, Beerman and Ingraham). Beryllium granulomas have also been found in the nose (Kazanjian and Joseph) and in the anterior ocular-structure (Rizzuti).

It is noteworthy that beryllium apparently once inhaled is retained over a long period of time in the human body, since beryllium was detected in the urine up to 10 years after cessation of exposure (Klemperer, Martin and Van Riper) and has been demonstrated in the lungs of rats one 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%)

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, 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; Hoagland and Hood; Dutra, Largent and Roth; Barnes). The preparatory period for the sarcomas was from 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 their pleural cavity and into the paranasal sinuses failed to elicit a single neoplastic response at the site of injection in any one of the 85 animals used within an observation period of two (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 scepticism. The recently reported successful production of bronchogenic carcinomas in the lungs of rats which inhaled over periods of more than one year, dust of soluble and insoluble beryllium compounds (Vorwald), however, makes the appearance of such delayed malignant sequelae in man a distinct possibility.

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 histologic 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 a rather easy proposition. 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, Hall et al.). 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).

k. Selenium

Selenium and its compounds have increasingly been employed by industry during the past two (2) to three (3) decades for various purposes (glass decolorizer, production of ruby glass, glazes, paints, pigments, inks, coloring of plastics, steel and copper alloys, rubber accelerators and antioxidants, photoelectric apparatus, fireproofing of electric cables, insecticide chemicals) (Buchan; Manville). Workers engaged in primary and secondary industries handling selenium containing ores (copper, lead, zinc, pyrites, lime and cement) and selenium products may become exposed to the inhalation of dust and fumes containing metallic selenium, selenium oxide and hydrogen selenide (Smith, M.I.; Dudley and Miller; Dudley; Buchan; Moxon and Rhian).

There may occur an environmental exposure to selenium containing dust in those parts of the United States in which selenium fumes are released from metal ores smelters (Montana, California, Tennessee) (Byers) or where a seleniferous soil exists (Wyoming; South Dakota) (Smith, Franks and Westfall). In addition to toxic manifestations in other organs, especially the liver (Lillie and Smith; Cameron; Smith, Stahlman and Lillie; Fitzhugh, Nelson and Bliss) and nervous system, the inhalation of selenium causes respiratory irritation, with cough, sore throat, and pulmonary edema (Greenburg; Motley, Ellis and Ellis).

There is no recorded evidence indicating that industrial and environmental chronic selenosis produces an increased liability to lung cancer in man and animals, although a prolonged oral administration of selenium to rats resulted in the development of liver adenomas and carcinomas (Nelson, Fitzhugh and Calvery) as well as thyroid adenomas (Seifter, Ehrlich, Hudyma and Mueller).

1. Manganese

Manganese is used chiefly in the steel industry, but also in the chemical, ceramic, glass, dye and varnish industries and in electrotechnics. Cases of poisoning may occur whenever manganese is handled and particularly when manganese dust is produced. Manganese enters the organism mainly through the respiratory passages. While the symptoms of chronic manganism are caused by changes in the central nervous system, pneumonia is a rather frequent reaction among manganese workers and has a high mortality rate (Gärtner; Bander; Voss; Joetten and Reploh; Kahlstorf; Gundel and Heine; Joetten, Reploh and Hegemann; Zanetti; Büttner; Elstad; Büttner and Lenz; Davies; Ehrismann; Vigliani; Fairhall and Neal). Large and numerous deposits of manganese ore dust were found in the lungs (Schopper; Bauer; Boemke) of manganese workers.

There do not seem to exist any data on the lung cancer incidence among manganese workers.

m. Copper

The industrial use of copper, copper compounds and copper alloys (brass, bronze, etc.) has been very extensive for many years and a great number of workers, therefore, are exposed to the inhalation of copper dust and fumes (mines, smelters, foundries, bronze powder operations, parasite repellent applications on hulls of ships, fungicide and insecticides production and use, plating operations, paint production and use, ink manufacture, etc.).

While inhaled copper dust and fumes may elicit irritative symptoms of the respiratory tract, cuprosis is infrequently mentioned as a cause of benign pneumoconiosis (Query; Schietz). Ulcerations of nasal membranes and perforation of the nasal septum have exceptionally been observed among workers of copper plating operations (Barsky). It is noteworthy, however, that copper and brass workers have an highly excessive mortality from pulmonary "tuberculosis" (Hayhurst). Since occupational cancers of the lung as well as cryptogenetic

cancers of this organ not infrequently have masqueraded in the past as tuberculosis of the lung, a thorough and competent clinical and epidemiologic investigation of copper, brass and bronze workers of all types is urgently needed for determining lung cancer morbidity and mortality among members of this occupational group. The recent study of Snegireff and Lombard on the cancer incidence among copper smelter workers is too inadequate and methodologically defective to be of any real value.

n. Tin

Tin is extensively used in alloys, bronze, brass, foil, plate and solder. While tin ores are not mined in the United States, there exist one (1) tin smelter (Texas) and several tin oxide recovery plants.

The inhalation of dust and fumes of tin and tin oxide, especially by furnace tenders, may give rise to the development of a pneumoconiosis (stannosis) which roentgenologically resembles in appearance silicosis and baritosis (Pendergrass and Pryde; Cutter, Faller, Stocklen and Wilson), although anatomically there is an absence of fibrosis (Bartak and Tomecka; Dundon and Hughes). The lungs show a fine network of black lines, which on histologic examination is represented by particulate dark brown and black pigment located in inter-alveolar septa and peribronchical and perivascular tissue.

There is no information as to the incidence of lung cancer among tin workers. None of the so far reported cases of stannosis had such a neoplasia, although one died from cancer of the prostate.

a. Lead

Lead is used as a metal as well as in the form of various compounds for various industrial purposes (pigment in paints, inks, glazes, and enamels, in the manufacture of storage batteries, antiknock agents (tetraethyl lead), insecticides, glass, cable coverings, ammunition, sheet lead, pipes, etc.). During the mining and smelting of lead ores and during the manufacture, processing and

use of the various products workers become exposed to the inhalation of lead dust, fumes and vapors. Chronic lead poisoning is, in fact, one of the most common occupational diseases.

While chronic plumbism as a rule is not characterized by the deposition of lead in the lung nor by the development of fibrosing pulmonary reactions, Black commented on the fact that cancer of the lung had been observed in workers exposed to the inhalation of lead or lead compounds. In support of a possible causal relation between exposure to lead dust and fumes and cancer of the lung, he cited the occurrence of pulmonary cancer in glass workers (Boyd; Gutzeit; Klotz) and type setters and printers (Seyfarth). Rosedale and McKay noted that nine (9) out of 43 persons with lung cancer had been working more or less with lead in one form or another. Black added two (2) cases of lung cancer (linotype worker, metal polisher) to the previously published number of 15 cases of pulmonary cancer in lead workers. He found a chronic fibrous pneumonia in both of his cases.

Because of the close chemical relation between lead and radium and in view of the occurrence of radioactivity in some lots of commercial lead (due to the presence of radium D) he believes that the pulmonary reactions reported represent results of the inhalation of radioactive lead. These allegations have so far remained unconfirmed. Although it may be advisable to ascertain through epidemiologic surveys of various types of lead workers, whether or not there exists an excessive liability to pulmonary neoplasia, it is not likely that such complications of chronic plumbism exist because of the thorough and prolonged study which chronic lead poisoning has been subjected to by investigators of many countries. The reported excessive frequency of lung cancer among painters who are known to be affected not infrequently with plumbism probably has no causal relation to lead exposure because painters, especially spray painters, inhale also other paint constituents, some of which have known carcinogenic properties (zinc chromate, carbon black, etc.).

p. Zinc

Zinc metal and zinc compounds (zinc chloride, sulfide, oxide) are used industrially on a large scale for galvanizing, brass production, alloys, paint pigments, rot-proofing compounds and sheeting,

Inhalation of zinc dust and fumes occurs during smelting, galvanizing, spraying, brass founding, brazing and welding of galvanized iron operations. Such exposures give rise to attacks of metal fume fever. Lehmann stated that volatilized zinc upon cooling forms zinc oxide which in turn is transformed into zinc carbonyl. This is hygroscopic and when inhaled spreads over the surfaces of the respiratory structures, producing a necrotizing effect on the exposed cells. Exposure to fumes of zinc chloride, which is a known corrosive and occasionally still used in the chemosurgical treatment of skin cancers, has resulted in injury to the mucosa of the nasopharynx and respiratory tract (Evans, E. H.).

Whether or not there exists a chronic type zinc poisoning (duBray; McCord and Friedlander), however, is still controversial (Drinker and Fairhall; Hegsted, McKibbin and Drinker; Nuck, Remy and Holtzmann; Gocher). Although the experiments of Nuck et al. on dogs exposed to the inhalation of zinc dust showed that the zinc content of the lung, liver and kidney decreased rapidly after cessation of exposure, the conclusion that such a rapid removal of zinc from the organism precluded the development of a chronic type of zinc poisoning is scarcely acceptable, since many examples of chronic poisoning can be cited which demonstrate that a prolonged retention of a toxic agent is not a prerequisite for the causation of chronic poisoning provided there were contacts with the offending agent over long periods of time. At any rate, it is a well-established fact that under such conditions of exposure a rapid removal of the environmental agent from the site of contact would not preclude the subsequent development of a cancer.

While there does not exist any evidence indicating that an occupational exposure to zinc dust and fumes creates an increased liability to cancer of the respiratory organs, Cristol reported that zinc is present in increased quantities in all malignant growths and that, therefore, a decision should be reached whether this metal might be a carcinogenic agent. In fact, there exists a fair number of observations on the successful production of testicular teratomas in fowl following the intratesticular injection of zinc chloride (Falin and Gromzewa; Falin; Anissimova; Bagg; Bertrand and Vladosco; Falin and Anissimova; Falin and Gromtseva; Ljvruga; Michalowsky). In view of these findings it seems to be desirable to study population groups occupationally exposed to zinc dust and fumes in regard to lung cancer frequency.

q. Vanadium

Vanadium is one of the group of metals which have obtained rapidly increasing importance during the past one (1) to two (2) decades in metallurgical operations. It is mainly used as an alloy in steel and as a catalyst in the production of diamond black, sulfuric acid, phthalic anhydride and benzoic acid.

Exposure to vanadium dust exists in the mining and smelting of vanadium ores. The smelting process is accompanied by the production of dust of vanadium pentoxide (Symanski). The inhalation of this dust has caused among exposed workers pulmonary dust reticulation as well as chronic rhinitis, and bronchitis (Wyers; Balestra and Molfino).

Apart from the fact that vanadium dust apparently is retained in the lung, thereby causing a chronic metal effect upon the lung tissues, its possible carcinogenic relation is complicated by the fact that vanadium ores in this country contain uranium and other radioactive substances. It is for this reason that vanadium ore miners and smelter workers are not suitable subjects for a study of possible carcinogenic vanadium hazards connected with the

inhalation of vanadium dust and fumes. Such future investigations should be conducted on worker groups whose members are not in contact with any known and recognized environmental carcinogen. At present nothing is known concerning any carcinogenic properties of vanadium and its compounds.

r. 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 (iron ore miners, arc welders, grinders, polishers silver finishers, 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 (Greenburg; Pendergrass and Leopold; Jones and Lockhart; Pendergrass, Lane and Ostrum; Doig and McLaughlin; Bohrod; Barrie and Harding; D'Onofrio and Passeri; Sander; Dreessen, Brinton, Keenan, Thomas and Place; Teleky and Gilbert; Humperdinck; Buckell, Garraud, Jupe, McLaughlin and Perry; Balsac and Feil; Lanza; Stewart and Faulds; Boamke; Koelsch; Hamlin; Silson; Teleky). The deposition of iron oxide particles does not elicit in the lungs a progressive and marked fibrosing reaction (Harding, Grout and Davies), unless the inhaled dust contains also silica, producing then a siderosilicosis (Teleky).

The coexistence of siderosis and cancer of the lung has occasionally been observed (Stewart and Faulds, one (1) case; Dreyfus, three (3) cases in watch makers; Vorwald and Karr, three (3) cases in hematite miners; Simons, one (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.

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 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 not likely that exposure to iron dust conveys an abnormal liability to the development of lung cancer. The excessive frequency of this malignant neoplasm among metal workers in general may well be due to exposure to dusts, fumes and vapors of specific carcinogenic metals, such as chromium, nickel, arsenic, and perhaps beryllium, or to mists of lubricating and cutting oils. It may be noted, however, that Warren and Drake when discussing the causation of primary hepatic carcinoma in livers with hemochromatosis stated "Together, primary progressive parenchymal damage to the liver and subsequent deposition of iron in hepatic cells seem to provide a setting for carcinogenesis more effective than simple portal cirrhosis." Whether similar considerations might be applicable to siderosis and cancer of the lung seems to be doubtful in view of the few cases reported so far, in which the two conditions co-existed. However, thorough and comprehensive epidemiologic data on the incidence of lung cancer in workers exposed to iron dust are not available and a definite conclusion on this problem, therefore, must be withheld. The availability of conclusive information on this point appears to be urgent, since 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 (Medicolegal Abstracts).

8. Nickel

Nickel, one of the most industrially important metals, and principally mined in the Sudbury district of Ontario, Canada, finds 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, etc.), electroplating, catalysts, ceramic enamels and colors, pigments in paints and inks, storage batteries, etc. (International Nickel Co.; Friend; Davis).

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 (Sappington; Fischer). While skin contact to nickel and nickel salts not infrequently results in the development of an apparently allergic type of dermatitis (Burckhardt; Wedroff; Weber; Schittenhelm and Stockinger; Müllschitzky; Kolzoff; Cormia and Stewart; etc.), inhalation of the volatile nickel carbonyl has been responsible for an appreciable number of acute and often fatal poisonings (Armit; Amor; Mott; Brezina; Kötzing; Brandeis; Bayer; Krafft; Goldblatt and Wagstaff; Drinker, Fairhall, Ray and Drinker; Hamilton; Royer). 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 (Henderson and Haggard). 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 on 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; Carozzi; Bridge; and Merewether. From 1923 to 1948 inclusive, there were notified with the Chief Inspector of Factories

a total of 47 cases of cancer of the nose and 82 cases of cancer of the lung from the nickel works. By the end of 1948, 46 of the nasal cancer and 72 of the lung cases had died. None of the nasal cases and only two (2) of the lung cases had commenced work in the nickel refinery after 1924 when a reconstruction of the plant had been carried out. The average exposure period for the nasal cancers was 23 years (range, 3-26 years), and for the lung cancers 25 years (range, 1-33 years). No cases of cancer of the larynx have occurred, and only one (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 histologic studies were available in only four (4) cases, three (3) were of the small cell, pleomorphic type, while one (1) was a squamous cell carcinoma.

Similar observations were recently recorded from a Norwegian nickel refinery, where three (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 observed an unusual frequency of respiratory cancers among the workers of the Sudbury nickel ore mines and smelters in Canada,

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

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

The concept of a nickel etiology of respiratory cancers was tested in animals by Campbell, 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 of rats, cancers developed at the site of injection within six (6) to 24 months in about 40 percent of the surviving rats. Among 14 tumors thus produced, 13 were sarcomas and one (1) was a squamous cell carcinoma.

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

No assessment of the degree of occupational nickel cancer hazard can be made from the data available, since the number of workers at risk is unknown. Likewise, no definite opinion can be expressed as to the possible existence and extent of respiratory cancer hazards for persons having for other reasons contact with dust, fumes and vapors containing nickel or its compounds.

t. Chromium

Chromium as a metal, alloy or compound is used for many purposes in industry. It is for this reason that a large number and variety of workers have contact with chromium and chromium compounds and that even restricted groups of the general population may possibly become exposed to these agents in the form of dust, vapor, fumes, mist, liquid and solid (Bourne and Ruskin). Workers most likely to be exposed to chromium and its compounds are acetylene workers, aniline workers, bleachers, blue printers, 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, vulcanisers, waterproofers of textiles and paper, welders, users of chromate anti-rust agents (locomotive attendants and engineers), bitumen and oil refinery workers (U. S. Department of Labor; Sappington; Abraham).

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 anti-rusting agents in automobiles. 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 of 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 in which chromium and its compounds are handled and for which no pertinent published data of any kind exist at the present time (Chief Inspector of Factories, 1947, 1948; Regional and Field Letter OFS; Engelhardt and Mayer; Mayers; Schwartz and Dunn;

Leroux-Robert; Bloomfield and Elum; Feil; Galloro; Ikatsuka and Fairhall; Schrapf; O'Donovan; Deribere; Vaccaro; Goldman and Karotkin; Mancuso; Manciolli; Buess; Winston and Walsh; Harrold, Meek, Collins and Markell; Edmundson; Lieberman; Dixon; Carter; Peroni; Galloro).

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

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 two (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 workers 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, drivers, welder, or manufacturers 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, Druschel and Anders; Bourne and Yee; Buchell 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 pneumoconiotic condition called chromitosis was described by Andrievskaya and Mislavskaya in chromite ore miners and by Lukanin; Letterer, Neidhardt and Klett; and by Mancuso and Hueper in chromate manufacturers. It was produced experimentally in rabbits by Lukanin. Letterer reported ~~chromite~~ chrome-silicosis in a polisher of an iron foundry who inhaled silica and chromium oxide dust.

While the attempts of Gross and Koelsch; and Campbell to produce lung cancer in mice by their exposure to chromate dust were unsuccessful, Schinz and Vollmann, who implanted powdered chromium metal into the femoral cavity of rabbits observed after more than three (3) years, one (1) animal with cancer of the lung and one with cancer of the femur. In a series of pilot experiments recently conducted, guinea pigs, rats and mice were exposed to the inhalation of chromite ore dust at a concentration of 155 gamma per liter of air for five (5) to six (6) hours per day, four (4) days per week, for a total of 18 months, three (3) of the six (6) Wistar rats showed tumors involving respiratory organs. One (1) rat had a squamous cell carcinoma originating in the paranasal sinuses and invading and dislocating the eyeball, two (2) additional rats showed at autopsy, sarcomatous growths involving the mediastinal lymph-nodes and lungs. There was much black pigment within the thickened interstitial tissue. The lungs of three (3) guinea pigs revealed on histologic examination a marked proliferation of the bronchiolar epithelium which often occluded the bronchiolar lumina by the formation of cellular plugs consisting of oval and spindle shaped, hyperchromatic epithelial cells. These cellular masses extended in places into the the adjacent alveolar lumens forming polyps, coatings or solid casts. These changes were widely distributed in the lungs which showed, moreover, a scattering of dark brown to black amorphous pigment located especially in the subpleural zone and within a fibrous and thickened interstitial tissue.

These multicentric proliferative lesions of the bronchiolar epithelium resemble in many respects those recently described by Spain and Parsonnet in a woman and termed by them "minute bronchiolargenic carcinomas." Although the carcinomatous as well as sarcomatous reactions observed in rats and the hyperplastic bronchiolar lesions found in guinea pigs provide suggestive evidence that a prolonged inhalation and pulmonary retention of chromite

dust may have a cancerigenic effect upon pulmonary tissues, this evidence is at present far from being conclusive.

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, Bauke and Alwens; Goldblatt and Wagstaff) and United States (Machle and Gregorius; Gregorius; Baetjer; Hueper, Mancuso and Hueper; Imprescia) 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 (Wackman; Saita; Lecoœur).

Apart from the excessive frequency of lung cancers among chromate workers which according to American observations range from 13 to 31 times the normal, an occupational origin of these cancers is strongly suggested by the shift of the age distribution toward younger age groups. This is particularly striking for the lung cancers present among German chrome pigment workers, since 50 percent of the cancers affected individuals before the age of 40 years when lung cancers of unknown etiology are relatively infrequent. (Table 10).

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; Jonas; Letterer, Neidhardt and Klett; Mancuso and Hueper), Spannagel recently noted a peculiar behaviour of the chromium content of the blood and urine in chromate workers before and after the development of lung cancer. It was found that the normal urinary excretion of chromium ceases in workers with the development of lung cancer

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Table 10.

Age Distribution of Chromium Cancers of the Lung

<u>Years</u>	<u>21-30</u>	<u>31-40</u>	<u>41-50</u>	<u>51-60</u>	<u>61-70</u>	<u>71-80</u>	<u>Total</u>
Cases: 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		

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 two (2) cases (one (1) cancer of the nares (Newman); one (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.

u. Arsenic

Arsenicals represent a by-product or waste product of the smelting of many ores (copper, zinc, silver, cobalt, antimony, iron, bismuth, nickel, tin and lead). Arsenicals are present in the smelter fumes 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 industries. 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 either ingesting arsenicals with foodstuffs contaminated with arsenical insecticide residues or consuming drinking water polluted with arsenicals leached into drinking water supplies from mine and smelter dumps or inhaling arsenicals released into the air from industrial establishments or by small or large scale dusting operations of arsenical pesticides.

(From the published evidence on hand, it appears that environmental and non-occupational 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 of rather recent date that exposure to arsenicals has seriously been considered as a principal causal agent of cancers of the mucous membranes, such as those of the bronchi, stomach and bladder. Indeed, today there exists as yet only highly suggestive but not conclusive evidence linking cancer of the lung with an occupational exposure to arsenical dust. However, in almost all cases of lung cancer for which such claims were made, there existed stigmata of chronic arsenicism in the form of arsenic dermatosis with or without skin cancers. Since the inhalation of arsenical dust and fumes produces rather frequently the development of perforated nasal septa as well as chronic irritative

conditions of the bronchi, thereby creating a symptomatic cancerigenic pattern similar to that seen in chromate workers, the existence of a causal relationship between cancer of the lung and chronic arsenicism appears under such circumstances to be a reasonable conclusion. Chest and x-ray examinations of forty (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 two (2) arsenic smelter workers who died with 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 (4) additional cases of lung cancer in sheep dip workers with arsenic dermatosis noted in one (1) 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 five (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 two (2) cases of lung cancer were observed among 143 cases of medicinal arsenic cancers of the skin (Russell and Klaber), or under occupational conditions whether 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 (1912 - 1923) recorded the occurrence of two (2) additional cases of lung cancers among ten (10) workers of this group having cutaneous cancers. He mentioned, moreover, the presence of cancers of the left foot, abdominal

wall and lung in a furnaceman of a sodium arsenite factory. Analyzing the mortality experience of a sheep dip factory, Hill and Faning found that seven (7) or 31.8 percent of the 22 cancers causing death among members of this group were located in the respiratory organs, while three (3) or 13.6 percent were situated in the skin. There were during the period 1910 - 1943 a total of 75 deaths from all causes. The proportional excess of cancer deaths was mainly attributable to an excessive frequency of cancers of the lung and skin which were confined to workers in the chemical processes and were absent among members of the general group who would be unlikely to be exposed to any specific hazard. Perry, Bowler, Ruckell, 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 epidemiologic investigations on arsenic cancer was made by Snegireff and Lombard studying cancer deaths among employees of several metallurgical plants of unidentified type. Of the total of 105 deaths from all causes recorded during the last 25 years, twelve (12) were due to cancer of all sites and of these, six (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 studies 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 (1) plant surveyed were

caused by cancer of the lung, the observations made in fact confirm a carcinogenic action of inhaled arsenic trioxide upon the tissues of the lung of the exposed workers. The conclusions of the authors seem to be based on wishful thinking and not on a rational evaluation of facts. This interpretation of the data of Snegireff and Lombard is supported by the high incidence of lung cancer among the population of several counties in Montana where copper smelters and mines were operated for many years creating an occupational and environmental pollution of the atmosphere and soil with arsenicals. Prolonged inhalation of arsenical dust and fumes appears to produce an increased liability to cancer of the lung.

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

Comments on Respiratory Metal Cancers

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

Whether or not respiratory metal cancers may develop after the inhalation of other metals represents a problem deserving serious consideration especially where such metals are widely used or have attained major industrial importance only in recent years.

B. Relation of Inhalation of Silicon and Carbon Polymers to Respiratory Cancer

The second group of respiratory carcinogens is composed of chemical agents of rather diverse composition but sharing the characteristic that they may form or occur as linear polymers. The principal evidence suggesting the existence of "polymer cancers" has come from experimental observations. The "so far" known or suspected carcinogenic polymers are either polymerized carbon compounds or silicon compounds (Table 11).

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

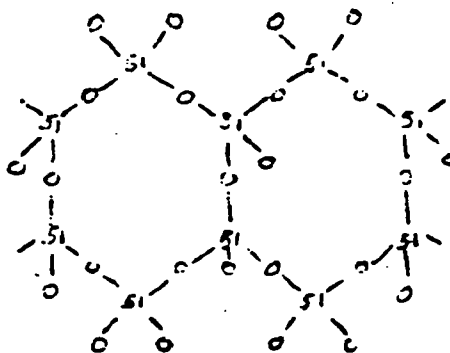
a. Carbon Polymers.

The first experimental evidence apparently representing a carcinogenic effect of a carbon polymer was provided by Turner who obtained in four (4) of nine (9) rats sarcomas at the site of subcutaneously implanted bakelite discs. Bakelite is a phenolformaldehyde polymer. More recently Oppenheimer, Oppenheimer and Stout succeeded in obtaining sarcomas in rats and mice after inbedding subcutaneously various plastic films, namely, cellophane, alcohol-extracted cellophane, a commercial polyethylene, a very pure polyethylene and vinyl chloride film. Sarcomatous reactions were absent following the subcutaneous implantation of linters, surgical cotton, and glass cover slips. Druckrey confirmed these findings on rats which received subcutaneous and intraperitoneal implants of cellophane and of cellophane extracted with boiling benzene. Sarcomas were also obtained by Druckrey in rats which were intraperitoneally injected with a polyamid polymer, namely, ϵ -caprolactam.

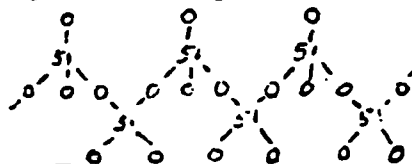
CHAIN AND BAND STRUCTURES OF CANCERIGENIC POLYMERIZED CHEMICALS

I. ASBESTOS; FIBROUS POLYMERIZED SILICATE

CHAIN
STRUCTURE -

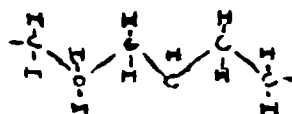


BAND
STRUCTURE -

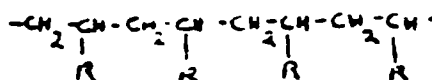


II. CARBON POLYMERS

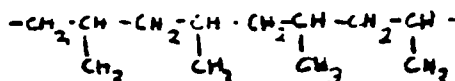
A. POLYETHYLENE - POLYTHENE (POLYETHYLENE FILM)



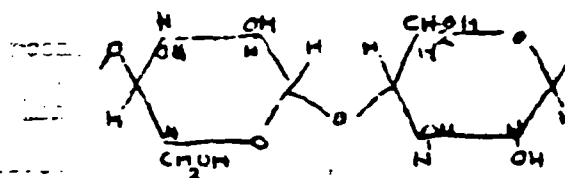
B. POLYVINYL (VINYL FILM)



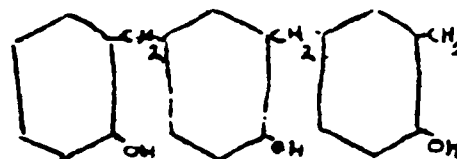
C. POLYPROPYLENE (PROPYLE OIL?)



D. CELLULOSE (CELLULOSE)



E. PHENOL-FORMAL- DEHYDE RESIN (BAKELITE)



Negative results, on the other hand, were noted with Orlen, Nylon and Perlon as well as glass wool.

Additional experimental evidence supporting a cancerigenic role of linear polymers can be deduced from the observation that certain methylolamines, ethylenediamines and epoxides, which readily form linear polymers, possess cytotoxic (canceroclastic) and cancerigenic properties (Elmore, Gulland, Jordan and Taylor; Goldacre, Loveless and Ross; Phillips; Hendry, Rose and Walpole; Hendry, Homer, Rose and Walpole).

Several other industrially important polymers, such as synthetic rubbers, polystyrenes, polymethacrylates, urea-formaldehyde and melamine-formaldehyde resins have as yet not been tested for potential cancerigenic properties.

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

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 seven (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 who worked more than five (5) years in the isopropanol plant. Inhalation

experiments conducted on mice with the various chemicals to which the workers become exposed provided suggestive evidence incriminating isopropyl oil. Since the occurrence of an excessive number of respiratory cancers among isopropanol manufacturers has not been limited to one particular plant, it can be concluded that isopropyl oil, and thus probably polypropylene compounds, represent a human carcinogen.

In an attempt to explain the carcinogenic action of these carbon polymers, Druckrey suggested that they may become bound to cellular proteins by covalence bindings or that low grade polymers may even be incorporated into protein molecules and, thereby, give rise to abnormal proteins, which in turn would be equivalents to the carcinogen-protein complexes established for carcinogenic aromatic amino- and azo-compounds as well as for 3,4-benzpyrene and certain metals (arsenic, chromium, nickel) possessing pronounced allergenic qualities. Perhaps a part of this general reaction mechanism may be represented by the recently reported occurrence of a so-called polymer-fume fever, similar in symptomatology to metal fume fever which in turn resembles anaphylactic shock (Koelsch; Harris).

b. Silicon Polymers

Among the various crystalline, amorphous or colloidal silicates (quartz, asbestos, talc, soapstone, tripoli, diatomaceous earth, silicon carbides, etc.), both asbestos and crystalline silica when inhaled produce specific types of pneumoconioses which in turn allegedly convey an excessive liability to cancer of the lung. Certain silicon polymers thus may display carcinogenic properties similar to those displayed by aliphatic and aromatic hydrocarbon polymers.

I. Silicosis

Since silicotic pneumoconiosis fulfills all the requirements which may be asked from a nonspecific carcinogenic agent acting on the basis of the chronic irritation theory of carcinogenesis, uncomplicated silicotic conditions

(anthracosilicosis, siderosilicosis, etc.) have repeatedly been claimed as favoring the development of lung cancer (Fine and Jaso; Dible; Charr; Klotz and Simpson; Klotz; Schmorl; Andersen and Dible; Rüttner). Isolated cases or small series of cases showing the coexistence of silicosis with cancer of the lung were reported by Allen; Cramer; Dible; Fine and Jaso; Frommel; Harris; Klotz and Simpson; Maxwell; Middleton; Olson; Sladden; Saupe; Swany, Porsche and Douglass; Charr; Gsell; Pancoast and Pendergrass; Vorwald and Karr; Homburger). The total number of such combinations reported from this country and abroad is around 75 cases.

Merewether recently added data of a large series to this evidence. Among 6,884 cases of silicosis which came to autopsy, there were 91 cases associated with cancer of the lung (1.32%), which is practically identical with the incidence rate of lung cancer in the general population. Gloyne, however, obtained on several special groups of workers distinctly higher figures. There were four (4) lung cancers among 78 iron and steel workers (5.1%), nineteen (19) lung cancers among 340 pottery workers (5.6%), nineteen (19) lung cancers among 293 coal miners (6.5%), and eight (8) lung cancers among 90 stone masons (8.9%), who showed pneumoconiosis at necropsy. Strieck, on the other hand, did not see any lung cancers among 186 cases of chalcosis, and Böhm recorded the absence of an increased lung cancer rate among silicotics.

Other investigators, also, have pointed out that cancer of the lung is not more frequent or less frequent among workers exposed to the inhalation of silica dust (anthracite miners, pottery workers, sandstone workers, etc.) than among the general population (Vorwald and Karr; Schulte; Schulz; Saupe; Pancoast and Pendergrass; Olson; Fail; Berblinger). Schulte remarked that the pneumoconiosis present in the coal miners of the Ruhr district seems to provide a poor soil for the development of lung cancer. In view of the fibroblastic proliferation stimulating action of silica, Gardner suggested that if anything, there should be an excess of pulmonary sarcomas, but these have not been reported. Since

in this country alone, over one (1) million workers are exposed to silica dust (Environment and Health) and in view of the fact that silicosis among anthracite and metal ore miners (copper, zinc, silver, gold, etc.) still occurs rather frequently, the available evidence supporting a causal relation between silicosis and cancer of the lung is unimpressive.

A lung cancer once established in a pneumoconiotic lung, according to Allen, on the other hand, is not impeded in its pulmonary as well as metastatic spread by the existing fibrotic blockage of the lymph and blood vessels. It seems that this medicolegally important statement needs further confirmation by other investigators, because it is in disagreement with the observations made and concepts held concerning the retarding influence of organ and stroma fibrosis on the proliferative and metastasizing activities of malignant growths in general.

It may be mentioned in this connection that the inhalation of silica dust and the development of lung cancer by the cobalt ore miners in Schneeberg, Saxony, represents only an apparent exception (Schulz) to the negative conclusions reached. It is not the silicosis of the miners' lungs which is of significance but the possible adsorption of radioactive solids or gases to the silica particles which may be of importance in the production of the lung cancers, because such combinations are likely to prolong the carcinogenic action of the radioactive material upon the lung tissues.

Attempts to produce lung tumors in animals experimentally by the inhalation of silica dust (Vorwald and Karr (guinea pigs, rabbits, rats, chickens, mice, cats); Campbell (mice)) gave essentially negative results. Willis and Brutsaert observed in guinea pigs exposed to silicon carbide after 18 to 31 months multifocal proliferations of the bronchiolar epithelium which seem to invade the adjacent alveoli as small dark cell groups. Since adenomatoid structures have been observed in the lungs of apparently "normal" guinea pigs (Sternberg; Leitch), the significance of Willis and Brutsaert's findings is

remains in doubt.

11. Asbestosis

Asbestos differs from the ordinary giant molecular crystalline silicates not only in its chemical and physical properties, but also in the anatomical aspects of the pneumoconiosis produced by it. In contrast to the tridimensional polymerized silica crystals in which no oxygen atoms are left carrying charges to attract positive ions, asbestos consists of giant fibrous molecules composed of polymerized silico-oxygen 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 (amphibols) 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) Beintker; Wyers; Kruger, Rostoski and Saupe; Vorwald, Durkan and Platt). Canada furnished 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, etc.). Some 35,000 workers are exposed in the United States to asbestos dust (Environment and Health).

It is asserted that inhaled asbestos dust produces asbestosis only if the inhaled fibers are sufficiently long. In the absence of a 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 proteninic or colloidal silicic acid sheath. Whether the iron in the sheaths originates

from the asbestos fibers (Timmermans) or is derived from blood or tissue elements (Vorwald, Durkan and Pratt) 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).

The coexistence of asbestos with cancer of the lung was first reported by Lynch and Smith in 1935 (one case), who recorded later three (3) additional cases (Lynch and Smith; Lynch). Similar observations have subsequently been recorded from this country (Stoll, Bass and Angrist (one case); Holleb and Angrist (two cases); Homburger (three cases)); Canada (Desmeules, Rousseau, Gilroux and Sircis (two cases); Cartier (four cases); Rousseau (one case)); England (Gloyne (17 cases); Harrison (three cases); Merewether (eleven cases); Cureton (one case); Owen (one case)); Germany (Nordmann (two cases); Linzbach and Wedler (one case); Horning (one case); Walz (two cases); Bohne (one case); Domenici (two cases); Bander (one case)). There is, thus, at present a total of 60 cases of asbestosis cancer of the lung on record. To this number must perhaps be added the eight 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.

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 exposure 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 to 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).

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

Table 12.

Age Distribution of Asbestosis Cancer of the Lung

Years	25-34	35-44	45-54	55-64	65-75	Total
Cases	2	11	16	17	5	51

Since lung cancer of unknown etiology occurs rather infrequently before the age of 40, while 26 percent of the asbestos 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 (table 12).

Table 13.

Exposure Time Distribution for Asbestosis Lung Cancers

Excluding Series of Merewether

Years	1-3	4-10	11-20	21 and over	total
Cases	4	6	4	7	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 (table 13).

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 age of noncomplicated cases of asbestosis (128) 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 from 1924 - 1946, 31 cases of coexisting cancer of the lung (13.2 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 16 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.

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

The histologic types of lung cancers observed do not essentially deviate in their relative frequency from those seen in cancers of unknown etiology. There were 22 squamous carcinomas, seven (7) oat cell carcinomas, four (4) anaplastic carcinomas and six (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 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 eight (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; Skull). Kennaway and Kennaway reported that eight (8) lung cancers may be found among 4,000 males of the age range 45 to 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). Asbestotic warts of the skin, on the other hand, are not covered (Oliver, Morand and Brun; Young; Derwitz; Dreessen, et al.).

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 (2) mice. This observation needs to be confirmed before it can be accepted.

Comments on Respiratory Polymer Cancers

While the fundamental concept of "polymer cancers" is a tentative one and needs to be supported by additional evidence, the available data are sufficiently important to require serious attention from both a scientific and practical viewpoint. The rapidly expanding industrial production and industrial and general use of natural and synthetic polymerized substances in plastics, films, rubbers, textiles, etc., brings a considerable part of the working population in direct contact with chemicals of this type. It seems to be advisable, therefore, to study these population groups during the coming decades for the occurrence of cancers, particularly those affecting the respiratory system.

C. Relation of Inhalation of Combustion and Distillation Products of Coal and Petroleum to Respiratory Cancer

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

anthracosis, bituminosis or chronic oil pneumonia.

a. Coal

Severe and prolonged exposures to carbon dust lead to the development of a mildly fibrosing anthracosis even if not complicated by silicosis (Hollman). Some 650,000 workers in this country are exposed to carbon dust.

The inhalation of coal dust, which is mainly carbon without hydrocarbons, is not credited, in general, as a possible cause of cancer of the lung. A low incidence of pulmonary malignancy (38-71) and laryngeal cancer (44-58) (general population 100) was found to be present in coal miners in England and Wales by Kennaway and Kennaway. This observation agrees with similar ones previously mentioned and covering coal miners in Pennsylvania (Allen), in the Ruhr District of Germany (Schulte; Schul), and in Saxony (Gerbe). Gloyne reported, on the other hand, an incidence rate of 6.5 percent of lung cancer with pneumoconiosis (19 cases) among 293 coal miners who came to autopsy. Gough observed a case of lung cancer in one of six (6) coal trimmers dying from anthracosis after an occupational exposure to coal dust for 25 years.

No information is available on the lung cancer incidence among graphite miners and workers inhaling graphite dust and developing a fibrosing, granulomatous type of pneumoconiosis (graphitosis) which shows a tendency to cavitation (Jaffe; Dunner and Bagnall; Dunner; MacMahon; Harding and Oliver; Dassanayake; Ray, King and Harrison). Graphite is one of the allotropic forms of crystalline carbon which is mined in Ceylon and Ontario, and industrially used in lubricants, polishes, electrodes, crucibles, furnaces, lead pencils and electric batteries.

b. Combustion and Distillation Products of Coal

The apparent innocuousness of coal and, possibly graphite dust as respiratory carcinogens, however, is not shared by the incomplete combustion, distillation and hydrogenation products of coal (pitch, tar, soot, creosote oils, anthracene oils, tar oils, and the highly viscous oily and tarry fractions

obtained by the direct hydrogenation of coal employed by the Bergius process). The carcinogenic action of these combustion and distillation products of coal on man and experimental animals has been established beyond any doubt (Henry; Ross; Hieger; Kennaway; Legge; Cook, Hewett and Hieger; Downing; Earle; O'Donovan; Passey; Pott; Woglom; Twort; Teutschlaender; Oliver; Seelig and Cooper; Goulden and Tipler; and many others). Although the bulk of the Casuistic and epidemiologic human evidence of occupational coal tar and pitch cancers has come from England and Germany, it can not 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 according to our own observations 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, brick making, foundries, furnace attendance, railway engine driving, round house operations, pickling of lumber, chimney sweeping, cork brick manufacture, etc.).

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, 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 to a greater degree, also, 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 (Hübner; Gartner and Brauss). Roentgenologic 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 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 dust and fume with an increased liability to cancer of the lung is equivocal. Kennaway and Kenraway 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 Billmann 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 three (3) deaths from lung cancer among 64 deaths of all causes. Menz recently reported that of 93 workers in Swiss gas plants who died during the 1926 to 1946 period, 21 or 22.6 percent died from cancer of all sites, thereby confirming previous English experience that workers of 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), Mullschitzky (tar worker).

This predominantly negative information contrasts sharply with observations made among Japanese generator gas oven workers employed in steel plants and among gashouse retort workers in Canada (Kawahata; Kuroda and Kawahata; Cruickshank). The Japanese investigators found within a six (6) year period, 21 cases of lung cancer among generator oven workers who were exposed to the inhalation of hot tar fumes when stoking the coal. An excessive lung cancer rate was absent among workers employed in other parts of the steel mills. The general incidence of lung cancer among the generator gas workers was five (5) per 1,000 workers employed. Seven (7) of these 21 lung cancers occurred in workers 40 years or younger (33 percent, against 18 percent, in cryptogenetic lung cancers) (Hueper). The exposure time varied from nine (9) years to 23 years, the average being 16.6 years. Similar observations were recently made among Canadian gashouse workers. Of 14 cases of cancer among retort house workers, six (6) were due to cancer of the lung, one (1) to cancer of the larynx and one (1) to cancer of the ethmoid sinuses (57 percent cancers of the upper and lower respiratory tract).

It is likely that similar lung cancer incidence rates may exist among American tar workers. Following a visit with a tar distillery where, among the 300 workers during an eight (8) year period, some 25 skin cancers and more than 80 pitch warts had been observed, there was found one (1) case of lung cancer. Subsequent inquiries made by company officials brought the number of lung cancers in this and other tar operations to six (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 ovens, generator gas plants, gas plants, tar distilleries) seem to have an excessive liability to cancer of the respiratory tract. It is not unlikely that a more thorough and

competent analysis of the death records of other worker groups, which have so far been found to lack such tendencies, might extend the types and number of tar and pitch workers having an abnormally high respiratory cancer rate.

c. 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, 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 (Leitch; Brockbank and Stopford; Scott; Southam; Twort and Fulton; Twort and Twort; Volkmann; Smith, Sunderland and Sugiura; Woodhouse and Irwin; Cruikshank and Squire; Auld; Henry; Schamberg; Hayhurst; Heller; Haagensen; and others). 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).

In addition to skin contact with carcinogenic petroleum derivatives many workers are also exposed for occupational reasons to an inhalation of oil mist or fumes (workers in paraffin pressing operations, certain groups of oil refinery workers, spinners, metal lathe workers, foundry workers, metallurgical workers, printers, etc.). In spite of this established occupational respiratory exposure to petroleum and shale oils, there is not a single case of oil pneumonia among such workers on record, although such conditions have rather frequently been observed after repeated medicinal instillations of mineral oil containing nasal drops (oil aspiration pneumonitis or paraffinoma of the lung) (Schneider; Rossier and Buhlmann; Kaplan; Ikeda; Graef; Gaertner; Cannon and Wash; Cannon; Bodmer and Kallos; Young, Applebaum and

Wasserman; Berg and Burford; and others). In fact, two (2) 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 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 etiologic factors, found that 18 or 16 percent were metallurgical workers exposed to the inhalation of nebulized lubricating and cutting oils, eight (8) were chauffeurs, five (5) mechanics and one (1) was an engineer. They concluded that their observations indicated an excessively high frequency of lung cancer among workers exposed to vaporized or nebulized lubricating oil. While the study of Gafafer and Sitgreaves on cancer morbidity and mortality among the male employees of an oil refining company did not reveal any abnormal liability of the members of the occupational group to cancer of the lung, this judgment may have to be revised at least for certain types of refinery workers according to more recent and scrutinizing observations. Roesch observed three (3) 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.

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, electrode manufacturers, smudge pot operators, phonographic record makers) (Gallie) 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, his 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. (

Comments on Respiratory Aromatic Hydrocarbons

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

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

D. Relation of Inhalation of Radioactive Agents to Respiratory

Cancer

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

It is an established fact that cancers of the skin, connective tissue, 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 epidemiologic and experimental evidence relating an occupational inhalation of radioactive dust and gasses 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, Foot and Wawro; McIntosh; Warren and Spencer; Widmann; Bauer; Bauer and Schraer; Tonges 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 sixteenth 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 (Haerting and Hesse). This judgment was, subsequently, confirmed by Cohnhein; Aucke; Arnstein; Uhlig; Risal; Schmorl; Beyreuther; Rostoski, Saupe and Schmorl; Lange; Neitzel; Döhnert; Baader; Teleky; Hueck; Rostoski and Saupe and Schmorl; Thiele; Weber; Koelsch; Lindemann; Doubrow; 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; Ziel; Sikl; Saupe; Peller; Pirchan and Sikl; Baader; Behounek and Fort.

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 (2) 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 Neitzel in a German technician of a radium laboratory. The cancerous lung was found to be radioactive. Four (4) 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 complication were 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 by the medicinal use of radioactive material arrested in the lung. Mention may also be made in this connection of a report of Martland relating the

occurrence of a cancer of the ethmoid cells in a luminous dial painter, because dial painters not only ingested radioactive material which became deposited in the bones and produced there the development of osteogenic sarcomas, but they also inhaled this matter which, thus, may have produced the carcinoma of the paranasal sinus.

The four (4) 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 because of an insufficiently long exposure and latent period (Love). The argument that these workers were, in part, not directly concerned with radioactive material carries, on the other hand, little weight, as they had, doubtlessly, at times, environmental contact with such 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 above ground, as well as 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 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 (2) 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, although this incidence rate may be too low considering the recent statement of Baader who noted that during the period 1939 to 1943 a total of 180 cases of lung cancer were acknowledged as compensable occupational diseases and that in 1929 there were only 323 miners employed at Joachimsthal. Considering the fact that the exposure and latent period of lung cancer in Joachimsthal miners ranges from 13 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 to be occasionally as short as seven (7) years (Baader; Rajewsky, Schraub and Kahlau).

The total number of Schneeberg miners who have 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 - 1943). An appreciable number of these miners died at a relatively early age from lung cancer as evident from the data given in table 14, showing 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 Lorensen; Lange; Rajewsky; Stocklasa). Humphris suggested that the recent introduction of pneumatic drills into these mining operations 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 (Schmidtman; Lowy; Campbell; Döhnert; Kahlau;

Rajewsky, Schraub and Kahlau). Schmidtman obtained neither pneumoconiosis nor pulmonary cancer in animals exposed for two (2) years to the inhalation of Schneeberg mine dust collected from drill holes. Campbell, on the other hand, reported that mice inhaling dust of Czechoslovak pitchblende displayed a significantly increased number of pulmonary tumors. In experiments of Döhnert and 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, therefore, difficult. Kahlau and Rajewski, 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 pulmonary adenomas (in seven (7) of 12 mice of the test series against one (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 non-inbred strains.

However, some observations contradicting this conclusion have been reported by Lorenz, Heston, Eschenbrenner and Beringer 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 little, if any, increase in the number of pulmonary neoplasms. Of greater significance in this connection are the findings of Lisco and Finkel, who found in rats inhaling an aerosol of radioactive cerium, metaplastic and neoplastic proliferations of the bronchial epithelium. Similar results were

obtained with plutonium brought into the lungs of rats. Since uranium ore miners inhale not only radon and radium dust, but also uranium which may be retained in the lungs, Hueper, Zuefle, Link and Johnson 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 66 rats used. Evidence thus produced shows that focal accumulations of uranium which is an alpha-radiation emitter may exert a cancerigenic action upon the surrounding tissues, but it does not discriminate between the influence of metal toxicity per-se and radioactivity in the genesis of these lesions.

From a critical evaluation of the epidemiologic, clinical and experimental evidence available, it appears that a prolonged inhalation of radioactive gases and/or dust may elicit in man pulmonary cancers (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 thirty times the tolerance dose. It is scarcely surprising, therefore, that in the past more than half the miners died of lung cancer." It stands to reason that this effect on the lungs of workers will prevail wherever similar conditions of exposure to radioactive gases and dust exist. The excessive suicide rate observed in the past among the miners in Joachimsthal (Sikl) reflects aptly 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 (1936, 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 lungs with cancer. Because of the relatively slow course of the pulmonary tumors, they 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. Ziefl in 1935 reported that marked silicosis among these miners is quite frequent and that ashed lungs contain large amounts of silicon oxide. Pirchan and Sikle, 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 lungs carrying cancer, and there were single cases of outspoken silicosis combined with cancer; but on the whole, silicosis was not a prominent feature in cases of cancer, on the other hand, the lungs most heavily affected with silicofibrosis being generally free from malignant growth. Behounek and Fort noted that pneumoconiosis was recorded as 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 roentgenologic evidence of pulmonary silicosis. However, silicosis was of minor degree among the seven (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 Schneeberg and Joachimsthal. Whether it has an antagonistic effect upon the cancerization process or modifies the course of the established cancer remains problematical.

Finally it may be mentioned that these lung cancers vary a great deal in histologic structure, 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 pattern set by all other occupational cancers. The same environmental carcinogenic agent is capable of eliciting a great variety of cancers, although all of them originate from the identical tissue matrix.

Comments on Respiratory Radioactive Cancer

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

A. Relation of Vegetable Dust Pneumoconioses to Cancer of the Respiratory Tract

An appreciable number of occupational activities of varied types are associated with an exposure to vegetable dust (tobacco, cotton, hemp, sisal, sugar cane, wood, paper). Some such contacts elicit pneumoconiotic changes. Inhalation of cotton dust given off in preparing the cotton for spinning and weaving causes a progressive fibrosis of the lung in reaction to the inhaled and retained cotton fibers (byssinosis) (Bolen; Thiry; Caminita, Baum, Neal and Schneider; Lanza). Pulmonary fibrosis, likewise, may follow upon a prolonged exposure of dust generated from the handling of sugar cane residue used for the production of fiber board (bagassosis) (Manas; Gerstl, Trager and Szczepaniak; Casteleden and Hamilton-Paterson; Silson; Lanza). The possibility of a carcinogenic action of these vegetable fibers on the lung tissues has apparently not been considered nor have any cases of lung cancer among such workers been reported.

The inhalation of dust from dried tobacco leaves, on the other hand, has received some attention in this respect, although the actual existence of a fibrosing tobacco pneumoconiosis (tabacosis) is controversial (pro: Zenker; Boemke; Palitsch; contra: Long; Gross; Krueger, Rostoski and Snape; Pencoast; Miller and Landis; Landis, Funk, Smyth and Miller). In considering these claims, it should be noted that workers handling dried tobacco leaves not only have contact with the powdered vegetable matter of the tobacco leaf, but also inhale silica containing soil dust, nicotine, arsenical insecticide residues, and soot from the drying and curing procedure secondarily contaminating the leaves (McCormick, Smith and Marsh).

The claim that persons exposed to the inhalation of tobacco dust exhibit an excessive liability to lung cancer is partly based on epidemiologic evidence among German and Indonesian tobacco workers and cigarette manufacturers (Enger; Rottmann; Seyfarth; Brinkmann; Kouwenaar; Koelsch), in

part it is supported by observations made in connection with the high incidence of oral cancer among population groups indulging in the chewing of quids containing tobacco (betel quid-chewing tobacco (lit. Hueper; Wynder; Friedell and Rosenthal; etc.)). Although the evidence supporting a carcinogenic effect of inhaled tobacco dust upon the respiratory tract is at present only mildly suggestive, the strong evidence of such an action on the oral mucosa when tobacco is chewed, is an indication that serious efforts should be made to establish reliable factual evidence whether or not similar relations exist when tobacco dust is inhaled and acts upon lung tissue. Such investigations appear to be especially urgent, in view of the fact that recent experimental observations indicate that alkaloids as well as aliphatic polymers derived from cellulose possess carcinogenic properties.

P. Relation of Animal Dust Pneumoconioses and of Fibrosing

Pulmonary Parasitic Diseases to Cancer of the Respiratory Tract

Nothing is known whether workers engaged in the production, processing and cleaning of silk, wool and hair, and the various goods, made from these animal fibers, and thus, exposed to varying degrees to the inhalation of these proteinic macromolecular polymers have any excessive liability to cancer of the lung. While the occurrence of cancers of the skin among textile workers using such fibers has occasionally been reported, the causation of these lesions has justly been attributed to contact with carcinogenic lubricating oils.

In view of the repeatedly reported abnormally high lung cancer incidence among painters, it is of interest to mention briefly that the inhalation of shellac, a basic constituent of various lacquers, and oil and spirit varnishes extensively used in industry as finishing substances and often applied as a spray, has resulted in the development of a chronic indurative progressive fibroblastic pneumonia (Hirsch and Russell). Shellac is a natural

resin of insect origin and before purification contains lac dye and wax. Most of these impurities except wax are removed in processing the shellac. Some evidence favors the view that the component resins of the original lac are bound together in a complex form or a weak chemical linkage (Bhattacharys). This relationship is destroyed during purification and the pure lac resin consists of hydroxy acids of the aromatic and aliphatic series joined together by lactone and various internal ester linkings.

Although painters and cabinet makers are exposed during their occupational activities to many other chemicals, some of known carcinogenic nature (solvents, oils, resins, plastics, pigments, waxes, paint removers), it may be wise to include shellac in any future considerations of the possible causes of the excessive liability of members of this occupational group to lung cancer.

Among the various parasitic infections of the lung which are associated with localized or diffuse fibrosing changes in this organ, tuberculosis stands in first place. In fact, during past decades, pulmonary tuberculosis, particularly tuberculous cavities and bronchiectases, were regarded by some investigators as a frequent cause of cancer of the lung (Ewing; Kraft; Fried; Derischanoff; Larson; Moore and Neal; Moore and Schmeisser; Ssipowsky; and others). The coexistence and possible causal, antagonistic or fortuitous relationship of tuberculosis and cancer of the lung has been the subject of numerous investigations (Hueper; Marx; Cohen; Munteau and Amon; Schwartz; Robbins and Silverman; Hambly). The possibility of a causal relationship was suggested because cancer seems to develop with unusual frequency in tuberculous lesions of the skin (lupus) (lit. Hueper). The great majority of investigations, however, does not support the contention that the various chronic inflammatory and fibrosing processes associated with pulmonary tuberculosis causes or favors the development of cancer of the lung (Fried; Brymalski and Sweany; Attinger; Olson; Hambly; Vinson; Symmers; Walzer; and

others (see lit. Hueper)) and indicates that the coexistence of these two conditions is fortuitous. This conclusion is supported by the fact that cancer of the lung has become in recent years much more frequent, while pulmonary tuberculosis, during the same period, has shown an opposite trend. Cancer of the lung, on the other hand, is of great importance for differential diagnostic reasons, since the number of cases in which tuberculosis and cancer of the lung coexist appears to be increasing (Gerstl, Warring and Howlett). Cancer of the lung may symptomatically simulate pulmonary tuberculosis (Siltzbach; Bergmann, Shatz and Flance; Hembly).

The causal relationship between schistosomiasis of the bladder and cancer of this organ is a generally acknowledged fact. Less certain is an etiologic connection between cancer of the colon and rectum and schistosomiasis of these organs. Although schistosomiasis of the lung is not infrequently observed in regions in which this parasitic disease is endemic (Egypt; North, Central and South Africa; Central and South America; West, East and South Asia) (Erfan; Gelfand; Mainzer; Shaw and Ghareeb; ~~Cawston~~ Wright, et al.; Clark and Graef; Koppisch), the ultimately developing pulmonary cirrhosis apparently has not given rise to cancer of the lung as far as the published records indicate.

The available evidence, thus, apparently shows that the inhalation of animal fibers or the presence of parasites and their metabolic products in the lung does not result or favor the development of cancer in this organ. It cannot be maintained, however, that the quantity and quality of data existent on this subject should make this conclusion definite.

G. Relation of Various Bacterially or Chemically Induced Chronic Inflammatory Processes to Cancer of the Lung

Although many noxious gases, vapors and fumes do not accumulate in the lungs on prolonged exposure, they may elicit chronic inflammatory processes

of more or less diffuse or localized character (chronic bronchitis, bronchiectases, chronic chemical pneumonia, cavitation). Occasionally, such exposures and their anatomic effects upon parts of the respiratory tract have causally been related to cancers subsequently developing in the injured and inflamed tissues.

Birkholz asserted that a laryngeal carcinoma was caused by an inhalation of benzine-petroleum vapors over a period of three (3) years. Commenting on a similar claim of Nikoloff that the inhalation of benzene vapors was responsible for the production of a pulmonary carcinoma, Koelsch stated that benzene and its homologues do not exert a specific carcinogenic effect upon the lung tissues. It is, however, uncertain whether or not this statement applies without any exceptions to all organic solvents and solvent vehicles, since some of these agents have elicited cancers when applied to the skin of mice. Although repeated exposures to formaldehyde fumes, such as those sustained by manufacturers of certain plastics, embalmers, makers of certain deodorizers, may cause chronic bronchitis (Wyss) and despite the fact that formaldehyde has recently been shown to be a mutagen (Auerbach), there does not exist any valid evidence indicating that this chemical also is a respiratory carcinogen.

Claims have repeatedly been advanced concerning carcinogenic effects produced by the inhalation of alkali and acid fumes upon various parts of the respiratory tract (larynx, lung) (Kikuth; Hunermann; Betke). A highly doubtful significance of such isolated occurrences is indicated by the fact that Koelsch did not find a single case of lung cancer when studying large series of manufacturers of inorganic acids (sulfuric, hydrochloric, nitric acid) and large scale industrial users of these chemicals (chemical, metallurgic, and graphic industries). Likewise, there is no evidence that the pneumo-fibrosis observed in a high percentage of Italian sulfur miners causing

peribronchial as well as micronodular fibrotic lesions associated with bronchiectases increases the liability to cancer of the lung.

Following the first World War the alleged carcinogenic action of war gas poisonings has played a conspicuous role among speculations as to the cause of the rising number of respiratory cancers. Poisonings by chlorine, phosgene, diphosgene, dichlorethyl sulfide, and diglycol chloride was considered one of the major causes in this development by Kikuth; Spamer; Brockbank; Matz; Denker; and others. Koelsch conceded that a few cases of lung carcinoma exhibited a doubtful etiologic relation to war gas injuries. Although the chronic effects of acute war gas poisonings were oblitative bronchiolitis and bronchiolar metaplasia, a connection between cancer of the lung and war gassing was lacking in the series of pulmonary cancers reported by Berblinger; Probst; and Simons. Since some of the war gases contained arsenic, while derivatives of mustard gas have recently been shown to possess carcinogenic properties for experimental animals, a final decision on the existence of such connections must at present be held in abeyance.

The relative infrequency with which other chronic inflammatory and cicatricial pulmonary lesions, especially bronchiectases, of nonspecific, and in part traumatic nature, appear as alleged direct or indirect causes of bronchogenic carcinomas (Schwyter; Friedrich; Rössle; Mangelsdorff; Woodruff and Nahas; Weller; Plazy; Gouriou and Germain; Dahlmann; Wells and Cannon; Pilgersdorfer; Luckow; Gomez; Fischer-Wasels; Fischer and Fenster; Gillespie; Bourret and Fraisse; Rospide; Konwaler and Reingold; and others), indicates that chronic irritation (Berenblum) as such does not represent a direct and primary cause of cancers of the respiratory tract. The validity of this general conclusion is apparent from the total evidence presented.

It may be concluded that pneumoconioses of benign or progressive type as well as pneumofibroses resulting from the inhalation of noxious gases,

vapors and fumes not retained in the lungs or from bacterial or parasitic pulmonary infections of occupational or non-occupational origin do not exhibit a consistent causal relationship to cancer of the lung.

Wherever cancer of the lung appears to be etiologically connected with the inhalation of chemical dusts, fumes, mists, vapors and gases, such relations are highly selective and specific. Since pulmonary cancers are also elicited by chemical agents which do not produce any appreciable fibrosing reactions in the lung, it is most unlikely that these pulmonary changes represent an essential primary part in the causative mechanism of pulmonary neoplasia. It is quite evident that the irritative and carcinogenic properties of respiratory carcinogens are neither identical nor closely interrelated, and that in this respect, these agents behave like those which cause cancer of the skin. Only a few of the skin irritants are also cutaneous carcinogens.

While observations in other fields of human and experimental carcinogenesis indicate that acute or chronic inflammatory processes might set off or accelerate a cancerization process initiated by a specific agent, there is no evidence available indicating that such an action is exerted by pneumoconiotic reactions upon the development of lung cancer. The average latent periods of occupational respiratory cancers is about the same for cancers elicited by all respiratory carcinogens investigated, regardless of whether they have pneumoconiotic qualities or not.

Chemoallergic reactions, however, may be active in the production of both fibrosis and/or cancer by some of these agents. The evidence on hand does not permit a definite conclusion whether the action of a pneumoconiotic agent or the presence of a pneumofibrosis accentuates or impairs the action of a respiratory carcinogen or has no influence whatsoever on it. It is, likewise, uncertain whether a progressive pneumoconiosis favors or impedes

the intrapulmonary and metastatic spread of an established environmental or cryptogenetic cancer of the lung, although the general evidence available on this point would support a hindering effect.

H. Methodologic and Medicolegal Aspects

It has recently been asserted that air pollution is not a serious or critical menace to public health (Lanza). The evidence presented does not support the correctness of such a view. The industrial hygienist accustomed to think in terms of toxic concentrations of chemicals in the atmosphere should become better acquainted with the often subtoxic or metatoxic concentrations in which carcinogens can and do act effectively. The possibility of delayed untoward effects by the prolonged inhalation of atmospheric pollutants appears to be especially likely, whenever such pollutants exert a cumulative effect or are readily retained in the body and, thereby, able to perform their insidious work over long periods of time. The long, symptom free latent periods sometimes extending from 15 to 20 years after cessation of exposure to an environmental carcinogenic agent are striking and convincing proof and demonstrations of this fact. This consideration applies not only to industrial products and wastes, but with equal force also to the large number of environmental poisons (pesticides, herbicides, chemical additives to foodstuffs, cosmetics, and sanitary household goods) with which large parts of the general population come in daily contact. The recent demonstration of cumulative storage of DDT, which when given in excessive amounts to rats, has produced hepatic tumors, in the fat tissue of unexposed members of the general population, provides an apt illustration of the possible existence of health hazards from such sources (Pearce, Kattson and Hayes).

While it may be difficult in many instances to supply absolute scientific proof, which will satisfy even the biased sceptic, of relationship between air contaminants and damage to health (Best), particularly cancer of the

respiratory organs, such proof can be obtained if competent personnel, adequate funds and facilities are made available. Past efforts made in this respect were scarcely extensive nor always competent.

Environmental carcinogens behave very much like pathogenic microorganisms in producing disease phenomena in only a fraction of the total population at risk. As a rule, the number of persons affected depends directly on the relative potency of the carcinogenic agent and on the intensity and duration of exposure to it by the individuals composing the group. While naturally susceptible individuals seem to succumb first and in the presence of a weakly acting carcinogen may be the only persons affected, the attack rate may practically reach 100 percent of the exposed population, if a carcinogen is highly potent and the exposure to it very severe and prolonged.

Consideration, also, must be given to the fact that in contrast to the almost simultaneous affliction of large numbers of persons by infectious diseases during epidemics, environmental and occupational cancers exhibit in this epidemiology a distinctly endemic pattern, i.e. the existence of an environmental or occupational cancer hazard becomes apparent only if effectively exposed and, therefore, restricted population groups are analyzed for the occurrence, number, site, age and sex distribution of cancers observed among its members over periods of not less than five (5) to 10 years. The inclusion of a large number of unexposed or little exposed individuals who did not exhibit at any time the specific stigmata of an effective contact, invariably leads to a dilution and possible obliteration of the actual positive evidence (Hueper; Hueper and Mancuso). Whenever occupational cancers are consistently associated with other disease phenomena affecting the same organ and producing symptomatically similar lesions such as cancer of the lung and pneumoconiosis, reliable epidemiologic evidence depends upon the availability of pathologic diagnoses (biopsies, autopsies) for all cases included in the group evaluated.

Chest x-ray studies and cytologic data from sputum examination are under such circumstances of only limited value.

It is obvious that an efficient and reliable study of respiratory cancer hazards occurring in industry is a complex undertaking requiring not only competent investigators and adequate facilities but also a comparatively unusual amount of financial support. A proper appreciation of the actuality and scope of the problem among interested parties is of rather recent date and so far only a few research institutions have devoted a part of their work to a study of industrial respiratory cancer hazards. The Trudeau Laboratories have pioneered in this field and occupy a leading place. Because of the rapidly increasing importance of respiratory cancers as public health problems, the National Cancer Institute has provided through special cancer control grants, financial assistance to three (3) universities (University of Pittsburgh, University of Utah and University of Southern California) for the establishment of research facilities for epidemiologic and experimental studies of environmental cancer, particularly cancers of the respiratory tract caused by occupational and environmental air pollutants. It is hoped that these units may become within a few years, organizations totally independent from governmental support and may provide interested private parties as well as local health agencies with additional privately controlled special laboratories, staffed by cancer research specialists competent and experienced in highly diverse and difficult aspects of environmental cancer research. It may be hoped that with the passing of time, an effective and reasonable control of environmental respiratory cancer hazards may be achieved, which may prove satisfactory and fair to all parties concerned

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