

Recent Results in Cancer Research

Fortschritte der Krebsforschung

Progrès dans les recherches sur le cancer

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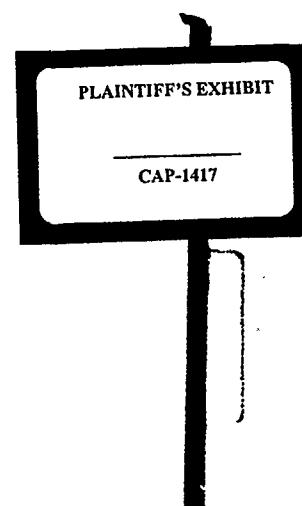
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A. Nonspecific Industrial Irritants

The "chronic irritation theory" of carcinogenesis proposed by Virchow around the middle of the past century forms the scientific basis for the often-repeated claim that the inhalation of nonspecific irritative air pollutants, especially those encountered in certain industries and occupations, represents a significant cause of cancers of the respiratory system.

In support of such allegations, it is argued that any air pollutant (dust, fume, mist, vapor, gas) exerting a prolonged but nonspecific irritating effect upon the respiratory mucosa would stimulate in this tissue epithelial proliferations and metaplasias which ultimately would lead to cancerous developments (SCHIMORI; HAMPERL; SUEFARTH; DUGUID; BROCKBANK; KREYBERG; STAEMMLER) and that, therefore, people employed in "dusty" work were more liable to develop lung cancers than people with "open-air" occupations and "housework" (KREYBERG). In agreement with such statements are the observations that there seems to exist, according to statistical studies, a positive association between previous respiratory diseases of chemical or parasitic nature (chronic bronchitis, chronic fibrosing pneumonia, bronchiectasis, tuberculosis, influenza, etc.) and the subsequent appearance of lung cancers (RÖSSE; WOODRUFF and NAHAS; FINKE; CASE and LEA; CAMPBELL and LEE; CUNNINGHAM; NASSAU and WALTER).

In fact, chronic inflammatory processes in this organ system, especially chronic bronchitis, regardless of their infectious or chemical etiology, have been proposed as furnishing the principal basis for subsequent cancerous developments in the lung (PASSEY; LÖHR and WAGNER). The existence of such correlations has been advocated particularly in England, where industrial air pollution, chronic bronchitis and cancer of the lung are most prevalent (NATIONAL SURVEY; STOCKS; PEMBERTON FAIRBAIRN and REID; BURGESS and SHADDICK; CAMPBELL and LEE; KUSCINER), although BRETT recently was unable to demonstrate any statistically significant associations between lung cancer and previous respiratory disease. A similar conclusion regarding the existence of interrelations between chronic fibrosing processes of the lung, regenerative bronchiolar epithelial proliferations in their periphery and the subsequent development of pulmonary cancers from such lesions is incorporated in the concept of scar cancers of the lung proposed by RÖSSE; FRIEDRICH; LÜDERS and THEMEL; and others. BALO, JUHASZ and TEMES suggested that a part of the recent increase in lung cancer might be attributable to the formation of lung cancers around pulmonary infarcts, since there has been a rise in embolic processes during recent years due to the increase in cardiovascular diseases. Since STANTON and BLACKWILL failed to induce experimentally cancers of the lung near infarcted areas unless a specific carcinogenic chemical was also administered, it is unlikely that scar formation as such predisposes to the development of lung cancers and that for this reason the

concept of traumatic cancers of the lung has any scientific and medicolegal validity (HUEPER). This interpretation of the available evidence is supported by the following specific observations.

Pneumoconiosis

Chronic fibrosing processes in the lungs of benign or progressive character are often the result of an occupational inhalation of foreign materials in the form of particles or droplets, which are in part retained in the lung (STOFER). While some investigators have claimed that such exposures and their anatomic sequelae might ultimately lead to the development of pulmonary cancers, this concept is not supported by the majority of the epidemiologic facts on hand for most of these conditions (anthracosis, aluminosis, silicosis, barytosis, resinosis, suberosis, byssinosis, etc.) (TELEKY; KOELSCH; HUEPER). There is so far only a single case on record in which a cancer of the lung developed in a worker who had suffered from bagassosis (ONUGBO). The most comprehensive and convincing data on the absence of such associations exist for the two most common pneumoconiosis, namely, anthracosis and silicosis.

a) Mineral Dust Pneumoconiosis

a) Anthracosis

Various epidemiologic studies of the frequency of lung cancers among coal miners often affected with anthracosis which were conducted in several countries have shown that members of this population group have not an excessive liability to this type of cancer, and that in fact their lung cancer mortality rate, as a rule, is lower than the standard rate for the entire population and is similar to that of the rural population, which generally is the lowest of all occupational and socio-economic groups investigated (KENNAWAY and KENNAWAY; JAMES; DYER; FEIL; VIKSTUYS; GRABE; SCHULZ; ALLEN; SCHULTE). The bronchitis rate for coal miners, on the other hand, was found to be highly excessive (STOCKS). Anthracosis which is a nonprogressive type of pneumoconiosis, therefore, does not exert any demonstrable favorable influence on the induction of pulmonary cancer.

b) Silicosis

Silicosis has been in the past and to somewhat lesser extent still is a rather common occupational disease occurring among members of several large worker groups, such as especially hard rock miners, foundry workers, anthracite miners, stone masons and granite cutters. The relationship of silicosis to cancer of the lung covers three aspects (HUEPER; WEISSMAN).

A. The occurrence of large densities observed on x-ray film of the chest in individuals suffering from tuberculosilicosis may be mistaken for carcinoma of the lung.

B. It has remained controversial whether silicosis favors the development of lung cancer, hinders it, or does not exert any influence on this process.

C. Since the exposure to several established or suspected occupational respiratory carcinogens (radioactive substances, iron, arsenic) is complicated in some occupations by a simultaneous contact with silica, the role of silica and silicosis on the action of

the specific carcinogens and on the cancerization process, respectively, has remained a subject of dispute.

The difficulties not infrequently encountered in the clinical diagnosis of cancer of the lung, whenever chronic inflammatory conditions prevail in this organ, are common experience and are likely to be aggravated in the presence of a tuberculosilicosis (KIRGIN; SCHAUTZ and KLEIN; BRADSHAW and CHODOFF). A definite diagnostic decision in some such cases may be possible only through an autopsy. The degree of diagnostic uncertainty which may be created under *in vivo* conditions may be judged by the fact that the diagnosis of cancer of the lung was found either to be incorrect or not justified by the clinical evidence presented in approximately 40% of several hundred cases in which cancer of the lung was listed on the death certificate as the cause of death. Epidemiologic studies on the association of silicosis and carcinoma of the lung based solely on clinical criteria have evidently only limited scientific value and may even yield misleading information.

Under the influence of the theory incriminating chronic irritation as a major cause of cancer through stimulating a typical regenerative cell proliferation, silicosis was considered by various investigators as a condition favoring through mechanical, physical or chemical irritation, the development of lung cancer (ADAMO; MOREL *et al.*; PIAZZA; GROSSE; EHRLHARDT; BOSSI; TAKEDA *et al.*; AHLENDORF; ASTORRI; FINE and JASO; DIBLE; ANDERSON and DIBLE; KLOTZ and SIMPSON; KACUGNO and CARTA; SCHAUTZ and KLEIN; CHURCO; DIKSITEN; PUCCINI; GHISLANDI and FINELLI; KLOTZ; KIKUCHI and KODAMA). In support of this claim, SCHAUTZ and KLEIN as well as PUCCINI and DIKSITEN, cited the occurrence of epithelial metaplasias in the bronchial mucosa of individuals with silicosis coexisting with bronchogenic carcinoma. They asserted that the development of such precancerous changes in the bronchial mucosa were stimulated by the chronic bronchitis which according to these authors is regularly associated with even minor silicotic pulmonary changes. PAUL, on the other hand, noted a very low incidence of chronic bronchitis (0.1%) in Rhodesian copper miners among whom silicosis is prevalent. A similar connotation has the observation of CHATGIDAKIS who reported that the enlarged bronchial glands with excessive mucous secretion and dilated ducts found among white South African gold miners with silicosis was a phenomenon commonly seen also among elderly male non-miners. These lesions, therefore, were regarded by him as causally not related to the silicotic state.

In contrast to KAHILAU, who contended that only minor silicotic lesions furnish a favorable soil for subsequent cancerous developments, SCHAUTZ and KLEIN claimed that the close topographic relation between fibrotic silicotic scarred areas in the lung and carcinomas of this organ indicated the existence of positive associations between the two conditions. This concept of silicosis carcinoma of the lung proposed in recent years again by ROESSELE and BALO, is closely related to the concept of cancer of the lung forming in the marginal areas of old tuberculous and syphilitic scars and of infarcts.

It is possible that pulmonary scars with their locally disrupted vascular supply and their phagocytic accumulations may indeed favor the development of cancers from the surrounding tissue because of their tendency to arrest and store foreign matter which is either inhaled or after ingestion or parenteral introduction has entered the circulating blood (HUEPER). Since such substances retained in and around

pulmonary scars may possess carcinogenic properties, such as soot, the occurrence of cancerous reactions near fibrous silicotic nodules is conceivable provided that an associated exposure to some specific carcinogen takes place (RACUNO and CARTA). The carcinogenic effect under such circumstances would not depend upon any nonspecific irritative action of silica or be the result of some mysterious deviation of regenerative cellular proliferations but would be the result of some secondary and independent carcinogenic exposure for which the silicotic scar tissue acts in the role of a localizing and preparatory focus.

The bulk of the available epidemiologic evidence on the association of silicosis and lung cancer supports the view of a mere coincidental role of silicosis in this combination. Several large statistical analyses performed on autopsy material derived from several occupational groups with silicosis hazard confirm this conclusion (Table 1), which is, moreover, shared by many experienced investigators (VORWALD

Table 1. Frequency of Carcinoma in Lungs with Silicosis

Author	No. of Silicotic Lungs at Autopsy	No. of Carcinomas of Lung in Series	Percentage of Lung Cancers
KLOTZ, 1932	50	4	8.00
GOLDING, 1946	270	—	0.70
SPOFFORD, 1952	170	3	1.20
	81	1	1.80
	383	7	4.54
FINE and JACO, 1938	22	1	4.54
MURKIN, 1950	210	4	1.90
FRUEHLING <i>et al.</i> , 1953	186	10	5.37
JACCHER, 1948	256	12	4.68
SLADDEN, 1933	60	2	3.33
RUBINER, 1949	2204	32	1.50
SWEENEY <i>et al.</i> , 1936	40	1	2.50
FINLAND, 1949	804	4	0.50
JAVENNE	358	7	1.95
VORWALD and KURN, 1935	1438	10	0.73
MITTMANN, 1959	5951	440	8.80
BECKER, 1958	439	13	3.00
Total	12,922	551	3.11

and KARR; SCHULZ; SCHULTE; KENNAWAY and KENNAWAY; MEREWETHER; FAULDS; MITTMANN; FRUEHLING and OPPERMAN; BRAUN; JAMES; MULLER; MARCHAND-ALPHAND; CUALLACCI, NADIRAS and MULLER; ALLEN; RUETINER; SCHOGGI; BERLINGER; WEDLER; FISCHER; FISCHER-WASELS; HOLSTEIN; STAEHMLER; JOHNSTONE; CHARR; WAETJEN and others).

The concept that silicosis may even exert a certain protective effect against the development of lung cancer, especially during advanced stages of the disease, has found several proponents because they could show, that an inverse relation seems to exist between the grade of silicosis and the relative liability to cancer of the lung (SPORN-LEIN; SCHOGGI; MITTMANN; BAUER; MEKLEJOHN). Additional support for this claim is received by observations made by ROSTOSKI and SAUPE on SCHNEIBERG miners, since cancers of the lung among these miners were recorded by DONSER, FAULDS and STEWART; and FAULDS to exist for the silicotic changes and lung cancers seen in English hematite miners (Table 2).

Table 2. Distribution of Lung Cancer in Relation to Grade of Silicosis (MITTMANN) (1950-1957)

	Minimal Silicosis	Light Silicosis	Medium Silicosis	Severe Silicosis	Total
<i>Silicosis with Lung Cancer</i>					
Cases	165	154	81	40	440
Percentage	37.5	35.0	18.4	9.1	
<i>Silicosis without Lung Cancer</i>					
Cases	1,515	1,769	1,480	1,187	5,951
Percentage	25.5	29.7	24.9	19.9	

The available data on the age distribution at death of individuals suffering from silicosis and cancer of the lung are rather scanty and do not reveal any striking or significant changes from the ordinary age distribution of lung cancer (Table 3), unless

Table 3. Age Distribution at Death from Silicosis Lung Cancer

Years	30-39	40-49	50-59	60-69	70 & over	Total
Cases	1	7	16	12	1	37

the observations of FRUEHLING *et al.* can generally be applied. These authors recorded an average age of 53.36 years at death for silicotics with lung cancer, while this age stood at 62.87 for individuals with lung cancer without silicosis. It is proposed that the silicotic complication accounts for this distinct shift into an earlier age group. It does also not appear that the distribution pattern of histologic types of lung cancers found in coexistence with silicosis presents any deviations from the norm (Table 4). Lung cancers in silicotics likewise seem to be located more often at the

Table 4. Histologic Types of Lung Cancers in Silicotics

Squamous (cell) Carcinoma	Round- and Oval Cell Carcinoma	Adeno-carcinoma	Total
16	20	1	37

hilum and in the upper lobes than in the lower lobes, where the majority of asbestosis cancers are situated.

Attempts to produce cancers of the lung in experimental animals (mice, guinea pigs) by exposing them to dust of silica or silicon carbide, respectively, have yielded equivocal results since adenomatoid formations in both species occur also on a "spontaneous" basis (CAMPELL; WILLIS and BRUTSAERT). Of more definite significance in regard to carcinogenic properties of quartz, a macromolecular silicon oxide, are the experiments of DRUCKERY and SCHMAEHL. These investigators observed the development of four (4) sarcomas in the abdominal cavity in 29 rats intraperitoneally implanted with finely powdered quartz sand, and interpreted this result as an indication of a weakly carcinogenic action of quartz. Sarcoma formation apparently did not occur in rats following a subcutaneous deposition of quartz sand and after an intraperitoneal and subcutaneous implantation of powdered glass, indicating

thereby that a chronic mechanical irritation alone does not provide a carcinogenic stimulus (HUEPER and PAYNE; DRUCKREY and SCHMAHL; HUEPER).

From the evidence on hand it appears that a well developed or advanced silicosis does not seem to furnish a favorable soil for the subsequent development of cancer of the lung. It is likely that any extensive fibrosis and hyalinization is likely to interfere with an adequate action of chemical carcinogens which might be embedded in such an oligocellular or acellular matrix. There exists, moreover, the possibility that any microcarcinomas formed in such an ill-vascularized tissue may find it difficult to proliferate or to survive especially in the face of a progressive fibrosis, such as that characterizing silicosis. Whether or not the concept of KAILAU, that an incipient silicosis provides a more suitable soil for carcinogenesis deserves further consideration as a part of the general problem of carcinogenesis occurring in the vicinity of pulmonary scars (or BIASI).

b) Vegetable and Animal Dust Pneumoconiosis

Among the numerous occupational activities associated with an inhalation of dusts of vegetable and animal matter (cotton, hemp, sisal, cork, sugar cane, wood paper, silk, wool, animal hair, feathers, shellac), some of which give rise to progressive fibrosing pneumoconioses (byssinosis, bagassosis, etc.), only tabacosis has been related by epidemiologic evidence to cancer of the lung, while the possibility of such associations deserves consideration for shellac pneumoconiosis.

a) Tabacosis

Because of the numerous claims made especially during recent years concerning carcinogenic chemicals present not only in tobacco smoke but also in processed tobacco leaves and responsible for the induction of cancers of the respiratory system and of the oral cavity, it is noteworthy that several decades ago dust of tobacco leaves inhaled during the cultivation, harvesting and curing was incriminated on statistical grounds of causing cancer of the lung in cigarette makers (ENGER; ROTTMANN; BRINKMANN; KOUWENAR; KOELSCH; SEYFARTH). In commenting on such claims, LEHMANN noted that persons engaged in the tobacco trade are usually heavy smokers, and that this habit is more likely to be the causative mechanism than the inhalation of tobacco dust.

Since more recent epidemiologic studies on the frequency of lung cancer among American workers employed in cigarette factories have failed to show any excessive liability to lung cancer for these individuals, the supposition of LEHMANN lacks factual evidence. It is moreover a reasonable suspicion that the chewing of tobacco leaves, particularly when forming a part of the betel nut quid and khaini quid furnishes the main carcinogenic principle responsible for the high incidence of cancer of the oral cavity prevalent among populations in South-East Asia. Apart from any natural carcinogens present in tobacco leaves, consideration also must be given to the fact that such leaves are contaminated frequently with arsenical and chlorinated hydrocarbon pesticide residues and with soot from burnt wood or heavy petroleum oils used during the curing process.

It is at present uncertain whether any of these materials or some others are responsible for the excessive frequency of lung cancer among English grain dockers (DUNNER and HICKS).

β) Shellac Pneumoconiosis

In view of the repeatedly reported abnormally high lung cancer incidence among painters (MÜLLER; DUNLAP and VANE; FULTON; WYNDER and GRAHAM), it is of interest that the inhalation of shellac used in lacquers and varnishes and often applied with a spray gun, may elicit a chronic indurative and progressive fibrosing pneumonitis (HIRSCH and RUSSEL). After purification, shellac consists mainly of hydroxy acids of aromatic and aliphatic hydrocarbons joined together by lactone and various internal ester linkages. While it will be wise to include shellac in any assessment of cancer hazards to the lung among painters and cabinet makers, members of these trades sustain occupational exposures to various additional respiratory carcinogens, such as chromates, nickel, arsenic, carbon black, aniline dyes used as pigments, solvents and paint removers of coal tar and petroleum derivation, etc. which presumably are more carcinogenic than shellac, if such should be the case.

c) Chronic Chemical Pneumonitis and Bronchitis

Similarly negative epidemiologic observations exist concerning causal relations between various types of chemical pneumonitis and the liability to bronchial cancers in individuals thus affected (acid workers, alkali workers, cement workers, synthetic fertilizer producers, manganese and cadmium smelter workers, epoxy resin producers, etc.), although some workers in such occupations (acid workers, alkali workers, cement workers) develop perforated nasal septa through the corrosive action of the inhaled dust or mist. They thus display exposure stigmata similar to those seen in workers with occupational contact to several specific chemical dusts and fumes implicated in the production of cancers of the respiratory tract (arsenicals, chromates) (KOELSCH). The negative evidence on such association available for alkali workers refutes the allegation of MORGAN that the respiratory cancers observed in nickel refinery workers are attributable to the inhalation of alkali dust generated in the calcining process.

There is likewise no valid epidemiologic evidence supporting the claim that workers exposed to fumes and mists of mineral acids have an excessive liability to respiratory cancer. The large scale use of such acids (sulfuric acid, hydrochloric acid, nitric acid, fluoric acid, etc.) for a large variety of industrial operations resulting in an occupational exposure of many workers to these agents has not yielded any incriminating evidence (KOELSCH; KIKUTH; LICKINT; ADELHEIM). These observations are not only of practical but also of scientific importance, because these agents have been accused of arresting the ciliary movement of the bronchial epithelium thereby decreasing the natural forces of resistance of this tissue to the action of inhaled carcinogens (KUSCHNER; FALK, TREMER and KOTIN).

B. Specific Industrial Respiratory Carcinogens

The evidence concerning an etiologic role in the induction of cancers of the respiratory organs is a great deal more reliable, definite, and comprehensive, on the other hand, for a number of specific occupational respiratory carcinogens. Many of them are, moreover, introduced into the general atmosphere in the form of industrial and industry-related effluents and enter the home environment in the form of consumer goods and economic poisons (Table 5).

Table 5. Recognized Occupational Respiratory Carcinogens

Agents	Site:			
	Lung	Larynx	Nose	Nasal Sinuses
Arsenic	+	+	+	+
Asbestos	+	+	+	+
Chromium	+	+	+	+
Nickel	+	+	+	+
Isopropyl Oil	+	+	+	+
Mustard Gas	+	+	+	+
Coal Tar	+	+	+	+
Mineral Oil	+	+	+	+
Radioactive Chemicals	+	+	+	+

1. Significance of Specific Industrial Carcinogenic Irritants

Although the knowledge of specific industrial carcinogenic agents affecting the skin dates back to almost 200 years, the recognition of occupational carcinogens

Table 6. The Time Table of Discoveries of Occupational Cancers

Name of Agent	Date	Discoverer	Target Organ	Type of Contact
<i>Chemicals-Organic</i>				
Coal Soot	1775	POTT	Skin	Occupational
Coal Tar (lignite)	1876	VON VOLKMAN	Skin	Occupational
Coal Tar (bitumen)	1892	BEHL	Skin	Occupational
Coal Tar (Anthracite)	1910	ZWEIF	Skin	Occupational
Coal Tar (tumes)	1936	KAWAHATA	Lung	Occupational
Creosote Oil	1920	O'DONOVAN	Skin	Occupational
Anthracene Oil	1908	OLIVER	Skin	Occupational
Paraffin Oil (Shale)	1876	BEHL	Skin	Occupational
(Petroleum)	1910	SCHLIMBERG	Skin	Occupational
Petroleum Coke	1890	DEWILLIE and GUERMONDIZ	Skin	Occupational
Lubricating Oil (Petroleum)	1930	HELFER	Skin	Occupational
(Shale)	1910	WILSON	Skin	Occupational
Benzene	1928	DELORE and BORGOMANO	Skin	Occupational
Hydrogenated Coal Oil (Berghius)	1960	SIXTON <i>et al.</i>	Bone Marrow	Occupational
Isopropyl Oil	1947	NALE and HURPER	Skin, Mouth, Nasal Sinus, Larynx, Lung	Occupational
Mustard Gas	1959	YAMADA	Larynx, Lung	Occupational
<i>Chemicals-Inorganic</i>				
Arsenic	1822	PARIS	Skin	Occupational
Asbestos	1887	HUTCHINSON	Skin	Medicinal
Chromates	1930	SAURE	Lung	Occupational
Nickel	1935	LYNGE and SMITH	Lung	Occupational
Radioactive Chemicals	1932	PRILL-ALWINS and GREENELL	Lung	Occupational
Radioactive Chemicals	1894	UNNA	Nasal Cavity and Sinuses, Lung	Occupational
Ultraviolet Rays	1902	FRUEN	Skin	Occupational
Röntgen Rays	1879	HÄRING and HESS	Skin, Lung	Occupational

acting upon the organs of the respiratory system is only 35 years old, despite the fact that some of these respiratory carcinogens had been known for many decades

to cause skin cancers. The pace of discovery of respiratory carcinogens of industrial derivation has been accelerated during recent years and has resulted in the establishment of a list of suspected and potential chemical carcinogens, some of which doubtless will subsequently be found to be carcinogens to the human respiratory organs (Table 6).

a) Classification of Occupational Respiratory Carcinogens

Depending on the amount and quality of evidence incriminating occupational environmental agents in the causation of cancers of the respiratory system, these etiologic factors can be classified into the following three groups:

- Recognized respiratory carcinogens
- Suspected respiratory carcinogens
- Potential respiratory carcinogens

1. Recognized respiratory carcinogens are those agents for which the available medical, epidemiologic, pathologic and experimental evidence is adequate for establishing reliably causal relations between occupational exposures to such agents and the subsequent development of cancers of the respiratory system in man.

The following agents fulfill such requirements:

- Arsenicals (inorganic)
- Asbestos
- Chromates and Chrome Pigments
- Nickel
- Isopropyl Oil
- Mustard Gas
- Coal Tar
- Mineral Oil
- Radioactive Substances

Since occupational cancers are non-intentional experimental cancers obtained in man, they should be assessed in regard to their etiologic significance on the same level as evidence obtained in experimental animals. They in fact provide even more weighty evidence than experimental animals as far as the existence of specific human cancer hazards is concerned because they demonstrate the carcinogenic effectiveness of particular environmental agents in the species man. This consideration is specifically applicable in adjudging arsenicals as recognized human carcinogens despite the equivocal nature of the experimental evidence on hand.

2. Suspected Respiratory Carcinogens are those agents for which the human evidence is at present not entirely conclusive although the available experimental evidence support directly or indirectly the existence of causal reactions of such agents to the development of cancers of the respiratory system in man.

Environmental Agents which belong to this group are:

- Beryllium
- Benzidine
- Iron Oxide
- Soot — Incomplete Combustion Products of Carbon, Petroleum, Wood, Gas
- Chemicals Contained in Gasoline and Diesel Engine Exhausts
- Thermic Tobacco Derivatives (Tobacco Combustion Products and Volatilized Normal and Arrefactual Constituents).

Table 7. Suspected and Potential Respiratory Carcinogens

Agents	Species	Route	Lung	Skin	Subcut. Tissue	Bone	Bladder	Liver	Kidney	Hemat. Tissue	Miscellaneous
Iron	Man	Respiratory	+								
(Iron-polymer Complex)	Man, Rat										
Beryllium	Rat	Respiratory	+								
	Rabbit	Intravenous									
Carbamate	Mouse	Parenteral									
	Rat	Oral									
Dimethylaminostilbene	Rat	Oral	+								
	Rat	Oral	+								
Benzidine	Man	Respiratory	+								
	Rat	Oral									
Nitrosamines	Guinea pig	Oral	+								
	Rat	Oral	+								
Acetylaminofluorene	Rat	Oral	+								
	Rat	Oral	+								
Isoniacid	Man	Subcut.	+								
	Mouse	Oral	+								
Diesel & Gasoline	Man	Respiratory	+								
Motor Exhaust	Man	Respiratory	+								
	Mouse	Respiratory	+								
Oxidized Vaporized Gasoline	Mouse	Respiratory	+								
Atmospheric Soot	Mouse	Respiratory	+								
	Man	Respiratory	+								
4-nitroquinoline-1-oxide	Rat	Subcut.	+								
	Rabbit	Respiratory	+								
Silicosis, Bagassosis	Man	Respiratory	+								
	Man	Respiratory	+								
Tobacco Tar	Mouse	Subcut.	+								
	Mouse	Subcut.	+								
Aliphatic and Aromatic Epoxides	Mouse	Subcut.	+								

3. Potential Respiratory Carcinogens are those agents for which the incriminating evidence is predominantly restricted to observations made in experimental animals exposed to these agents being components of local or general human environments incriminated by suggestive epidemiologic evidence in man (Table 7).

Environmental Agents included in this group are:

Carbamates

Nitrosamines

Isoniacid

Carbon Polymers (PVP, PVA, Polymethane, Epoxy Resins, Carboxymethyl-cellulose, etc.)

Oxidized aliphatic and aromatic hydrocarbons (epoxides and peroxides) generated in heated vegetable oils and animal fats and by photooxidation of evaporated gasoline

Silicosis

Byssinosis, Bagassosis and related Organic Pneumoconioses

Acetylaminofluorene

Table 8. Cancers in Non-Respiratory Organs Elicited by Occupational Respiratory Carcinogens

Agents	Route of Contact	Connective Tissue	Skin	Liver	Hematopoietic Tissue	Bones	Alimentary Tract
Arsenic	Cutaneous Oral		+				+
	Respiratory						
Coal Tar	Cutaneous		+				
Mineral Oil	Cutaneous Parenteral	+	+				
	Oral						+
Radiation	Cutaneous	+	+				
Chemicals	Oral Parenteral			+	+	+	

b) Route of Exposure

While the majority of respiratory carcinogens enter the respiratory tract as pollutants (dust, fumes, spray, mist, vapor, gas) of the inhaled air, a few may apparently become active on the pulmonary tissue when introduced into the body of man or animals through non-respiratory routes, i.e., by ingestion, penetration of the skin, or parenteral introduction (arsenicals, benzidine, nitrosamine, acetylaminofluorene; carbamates), or even by transplacental penetration (ethyl carbamate). Some of the carcinogenic atmospheric pollutants are rather stable (chromates, nickel, arsenic, radioactive substances, asbestos), whereas others are changed and inactivated by chemical and photochemical reactions to which they are subjected in the air (polycyclic aromatic hydrocarbons, such as 3,4-benzpyrene). Climatic conditions and associated non-carcinogenic pollutants (particulate and gaseous) influence the quality and quantity of the atmospheric carcinogenic spectrum and its individual components.

Although some of the respiratory carcinogens have been constituents of the human environment for thousands of years, most of them are products of modern industrialism and all of them have been polluting the air to an increasing degree during the past century. Three fundamental types of respiratory exposure to these carcinogens can be distinguished:

1. Occupational exposure to specific carcinogens in specific industrial operations. Since the degree of exposure is, as a rule, more severe under these conditions than under any other ones, incidence rates of respiratory cancers among some of the exposed worker groups are also higher than those noted from any other types of exposure. All recognized respiratory carcinogens are involved in the production of occupational respiratory cancers and have, moreover, furnished the bulk of the epidemiologic evidence incriminating exogenous agents in the production of respiratory and nonrespiratory cancers in man. "... first discovery of occupational cancers of the lung dates back as early as 1879 when the high incidence of lung cancer among Schneeberg miners was traced to, at that time, non-definable occupational factors.

An occupational contact with carcinogens is not necessarily restricted to workers who produce, process or handle directly such agents but not infrequently exists also for workers employed only temporarily in such operations (maintenance and repair men) or who work near such operations, such as yardmen, truckers, packers and loaders, or who are employed in other jobs near carcinogenic operations carried on in the same room or building or in nearby buildings.

2. Atmospheric pollutants of local and general distribution provide the second type of exposure to respiratory carcinogens. Carcinogens disseminated in the general atmosphere originate from various chemical and radioactive effluents emitted from smokestacks, chimneys of plants, houses, and ships, from exhaust pipes of automobiles, buses, trucks and railroad locomotives, from dust of oiled, asphalted and tarred roads, from radioactive fallout of atom bomb explosions and from chemical fallout of pesticide drift. Local carcinogenic effluents may be found within the vicinity of plants in which carcinogenic materials are produced, used, processed, and handled and along the roads on which they are trucked. Locally restricted air pollution of carcinogenic nature may be connected with the use of chromates and carcinogenic mineral oils in air conditioning equipment and of anticorrosive chromates in the water of steam heating plants of homes and office buildings, with the employment of asbestos in insulating material in homes and the use of carcinogenic pesticides and herbicides in homes and on lawns. Local or general types of carcinogenic respiratory exposure are connected with the dietary consumption of foodstuffs contaminated with arsenical pesticide residues or other carcinogenic contaminants of foodstuffs.

3. Habitual exposure to carcinogenic air pollutants of a personalized type, which in contrast to the two previously mentioned ones is voluntary, is associated with the smoking of tobacco, especially in the form of cigarettes. Similar voluntary exposures to the inhalation of respiratory carcinogens may be connected with the spraying or nebulizing of hair lotions and hair lacquers containing carcinogenic ingredients, such as 8-hydroxyquinoline, cresote, arsenicals, and various carbon polymers, such as polyvinyl pyrrolidone and polyvinyl alcohol. A voluntary type of carcinogenic exposure is associated also with the consumption of arsenicals and mineral oils for certain medicinal reasons. A similar iatrogenic mechanism may account for the

marked and increasingly often reported cancers in tuberculous lungs of patients treated with antituberculous chemicals (isoniacid).

It is apparent from this classification of exposure types that during recent decades technologic developments have spread respiratory carcinogens originally mainly active among members of restricted occupational groups not only to ever larger and more general industrial worker groups but also have disseminated such in part highly potent agents through industrial and industry-related wastes from occupational environments into local and general environments where they have contact with the population particularly its urban and industrialized components.

2. Occupational Respiratory Cancer and Smoking

During the past decade numerous investigators have attempted by comprehensive biostatistical studies and experimental investigations to determine the relative causal role which cigarette smoking allegedly plays in the induction of cancer of the lung, larynx and several non-respiratory organs such as the oral cavity, esophagus, stomach and bladder, and has contributed within the last 50 years to the alarming rise in frequency of lung cancers. A rather modest effort has been made during this period, on the other hand, of ascertaining equally comprehensive and pertinent information on the same etiologic and epidemiologic aspects of respiratory carcinogenesis as they apply to the various recognized environmental carcinogens which, in part are evidently not only considerably more potent than those apparently present in cigarette smoke but which have also much more prolonged and intense contact with large portions of the general population. An exposure to such atmospheric factors often lasts 24 hours a day and starts with the most susceptible neonatal age period and lasts throughout the entire life-time. This quantitatively and qualitatively disproportionate etiologic information on respiratory carcinogens available for these factors has tended to produce a distorted assessment of the relative significance of the various carcinogens in etiologic and epidemiologic respects and has interfered with the development of an over-all balanced programmatic approach to an effective prevention of respiratory cancer hazards of all types and from all sources.

This interpretation of the prevailing situation is supported by the following observations. Critical analyses of the causal environmental background of the excessive incidence of lung cancers among chromate workers, employees in asbestos plants and trades, and radioactive ore and hard rock miners, have demonstrated that such phenomena could not be attributed to cigarette smoking as a predominant etiologic factor, but were due to occupational exposures to specific chemicals (BIDSTRUP and CASE; SELIKOFF, CIURG and HAMMOND; WAGONER *et al.*; PARSONS, DE VILLIERS, BARTLETT and BECKLAKE). Symptomatic and epidemiologic evidence supporting this view in connection with lung cancer in chromate workers is contained in the reports of ALWENS *et al.*; FISHER; and GAFAER *et al.*

ALWENS *et al.*, in an early publication on the subject of chromate cancers of the lung, pointed out that an abuse of tobacco could not be demonstrated in most of his patients. GAFAER *et al.* recorded that 81.1% of the chromate workers with lung cancers and that 79.4% of the foundry workers used as controls had been smokers. These investigators noted, moreover, that the white chromate workers smoked more heavily than the colored ones.

On the other hand, the lung cancer liability of the colored workers was considerably higher (80-fold of standard rate) than that of the white workers (40-fold increase); in the brief report of FISHER, mention was made of the fact that among the 38 chromate producers with lung cancer, two (2) were non-smokers, three (3) smoked pipe and/or cigar, three (3) smoked less than one pack of cigarettes per day, nineteen (19) smoked between 1 and 1½ packs per day, and five (5) smoked two (2) packs.

The most valid analysis on this matter has been provided by BIDSTRUP and CASE who came to the following conclusion: "Thus even if the smoking habits of the chromate workers were so changed from those of the general population that all of them fell into the category of heavy smokers, the increase of carcinoma of the lung that then would be expected would not satisfactorily account for the increase which we have observed. In fact, we have no reason to believe that their smoking habits are different from those of the general population, and an explanation based on a hypothesis of altered smoking habits would need to be supported by satisfactory evidence of such alteration before it could be seriously considered".

The recent allegation of OTTELL that lung cancers in chromate workers were found only in individuals who smoked cigarettes thus appears to be an expedient subterfuge and skillful device helpful to industrial management for escaping their legal and moral obligations toward their employees and the human society. Such fanciful contentions have obviously no scientific basis in fact and belong to the pseudoscientific propaganda emanating during the last decade to an increasing degree from some scientific guardians of commercial interests.

According to KATYNGRO, workers breathing the air of a Norwegian gas plant inhale during a 40-hour-work-week, an amount of 3,4-benzopyrene which is equivalent to that present in 5,000 cigarettes (200 to 730 micrograms per 100 cfm of air) (ECKARDT). The general population of London, which has one of the highest worldwide lung cancer rates, sustains a daily exposure to 3,4-benzopyrene inhaled with the polluted air which corresponds in degree to an amount of this chemical present in 5 packages of cigarettes (SAWICKI *et al.*).

SELIKOFF, CHURG and HAMMOND commenting on this aspect in connection with their study of an excessive liability to lung cancer in asbestos cement workers came to the following conclusion: "From this we may conclude, that even if all our asbestos workers had smoked a pack or more of cigarettes a day (and, indeed, from our sample we know they did not), and if exposure to asbestos were of no significance, then their lung cancer death rate would have been about 3.4 times as high as the rate in the general US male population. Clearly, the smoking habits of the asbestos workers cannot account for the fact that their lung cancer death rate was 6.8 times as high as that of white males in the general population."

The epidemiologic and etiologic evidence on hand justifies the conclusion that occupational cancers of the respiratory system, like those of other organs and tissues, doubtlessly escape proper recognition and recording in many, if not most cases. They are included under these circumstances either among the cancers of so-called "spontaneous" or more correctly, "cryptogenic" origin or are attributed during more recent years to cigarette smoking as the allegedly most important, most wide-spread and most universal environmental carcinogen.

It should be obvious that any wide acceptance of such scientifically unsound and socially irresponsible claims concerning the principal role of cigarette smoking in the

causation of cancers, especially respiratory cancers, would paralyze not only a legitimate and urgently needed pursuit into the various environmental factors inducing such cancers, particularly the many industry-related pollutants of the urban air, but has provided already effective legal arguments before civil courts and compensation boards for denying justified claims for compensation of occupational respiratory cancers to the victims of such hazards as well as to their widows and orphans (HUEPER and CONWAY; HUEPER; HUEPER, KOTIN, TABOR, PAYNE, FALK and SAWICKI).

3. Epidemiology of Occupational Respiratory Cancers

The distinct caution which should be exercised at present in quantitating the relative role which individual factors or groups of factors assume in the causation of respiratory cancers and in their marked rise in frequency is indicated by the prevailing inability of assigning any reliable figures to the number of occupational respiratory cancers as well as to their industry-related environmental counterparts induced by atmospheric pollutants. Despite the definite shortcomings of the available epidemiologic data for both groups of respiratory cancers, the available evidence nevertheless clearly indicates that occupational and industry-related industrial factors are distinctly more important than this is conceded by the proponents of the cigarette theory, which is moreover defective in several important biologic characteristics of environmental carcinogenesis.

The highly fragmentary nature of the presently available epidemiologic data on occupational respiratory cancers is documented by the following facts:

Existing epidemiologic information is restricted to data obtained from surveys of relatively small industrial operations or special moderately sized and specialized industries with highly excessive respiratory cancer risks. No country possesses any large scale, systematized and current information on such matters for entire, large industries producing, processing, handling and using one or several of the known respiratory carcinogens and employing sometimes thousands, if not millions of workers sustaining occupational contact with these carcinogens to varying degrees and durations. Such conditions, for instance, exist in the United States for the steel and iron industries, for the power industry, petroleum industry, metal ore smelting and refining industries, metallurgical industries, chemical and rubber industries, plastic industries, asbestos industry, nickel and chromate industries, transportation, shipping, railroad and aviation industries, and paper and textile industries.

Even where some fragmentary epidemiologic data exist they scarcely ever cover those workers who have left for some reason the hazardous occupation and often have become employed in other companies or industries, while having carried along their specific occupational cancer liability to their new jobs (BIDSTRUP and CASE; HUEPER). Since work in many such operations is objectionable to the workers employed because it is dirty and inductive to toxic effects, the labor turnover is frequently considerable creating thereby a large number of effectively exposed workers escaping proper surveillance for their delayed cancerous manifestations.

Rarely any attempt has been made to ascertain the number of occupational respiratory cancers which occurred previous to the discovery of the cancer hazard in an

industrial operation. It is intriguing to speculate about the number of lung cancer which were elicited in chromate producers in a plant which at the time of the discovery of this hazard showed a lung cancer frequency of 40 times the standard rate among white workers and 80 times such a rate among colored workers, considering the fact that this plant had been engaged in this type of manufacture for over 5 decades. It is also provocative to contemplate the medical diagnosis of the cause of death for workers dying from a pulmonary ailment after being employed in an asbestos brake lining factory, before it was found upon post mortem examination of such workers that 50 per cent of those who came to autopsy with the diagnosis of asbestosis were also suffering from cancer of the lung. Additional experiences with the peculiar nature of present-day industrial and public health practices on occupational respiratory cancer hazards are contained in the discussion of the various specific respiratory carcinogens (coal tar, petroleum oils, radioactive ores, etc.). They throw a revealing light on a recent comment made by a high medical official of the U.S. Public Health Service in regard to the evidence pertaining to environmental lung cancer hazards as they relate especially to cigarette smoking when he asserted that no additional research is anymore necessary for the establishment of the facts (July 27, 1965).

The distinct inadvisability of adopting a public health policy of the blocked mind toward the disconcerting problem of lung cancer etiology with its many complex aspects awaiting satisfactory solution is further demonstrated by the numerous observations indicating the action of occupational and industry related environmental agents in the causation of these tumors in industrialized as well as economically underdeveloped societies.

Several comprehensive epidemiologic studies on the frequency of lung cancer among members of different socio-economic classes and of large occupational or industrial groups have demonstrated the existence of definite differences in the rela-

Table 9. Standardized Mortality Ratio¹ at Ages 35-65 in Each Social Class from Cancer of Various Sites
Decennial Supplements 1921 and 1931 (Registrar General)

Social Class	1921-1923					1931-1932				
	I	II	III	IV	V	I	II	III	IV	V
All sites	80	92	99	96	123	83	92	99	102	114
Lip	30	50	70	140	170	—	56	68	147	183
Tongue	48	73	95	100	165	78	60	98	110	143
Tonsil	25	88	94	106	163	(86)	6	93	97	147
Pharynx	89	78	100	160	161	(76)	83	99	87	130
Oesophagus	76	91	104	88	130	74	87	98	94	130
Stomach	60	82	100	106	130	55	83	98	111	122
Upper alimentary canal	58	80	99	102	140	63	80	97	109	129
Lower alimentary canal	105	105	100	93	98	98	103	102	100	95
Larynx	72	96	93	96	135	60	81	98	90	143
Skin	63	73	100	120	150	(59)	75	95	116	133
Lung	100	109	97	79	124	107	96	101	91	112

¹ Registered percent of calculated deaths.

tive liability of such members to contract cancers of the lung (REGISTRAR GENERAL; STOCKS; COHART; MANGUSO and COULTER; HERDAN; CLEMMISEN and NIELSEN;

GRAHAM, LEVIN and LILINTHAI; KENNAWAY). While the criteria used by the English investigators represent somewhat arbitrary groupings of the surveyed population on socio-economic and occupational characteristics reflecting a decreasing scale of income as well as types of occupation, American and Danish investigators have

Table 10. Standardized Mortality of Males in 1949-53 by Social Class and in Farm and Mine Workers for Lung and Bronchitis

Social Class	SMR at Ages 20-69					PMR at Age 65 & over				
	I-II	III	IV-V	Farm	Mine	I-II	III	IV-V	Farm	Mine
Lung and Bronchitis	82	107	104	55	79	95	105	99	47	55

The specification of the social classes and sub-classes is as follows:

Class I Professional and similar occupations

II Intermediate

III Skilled occupations

(i) Mineworkers

(ii) Transport workers

(iii) Clerical workers

(iv) Armed forces

(v) Others in III

IV Partly skilled occupations

(i) Agricultural workers

(ii) Others in IV

V Unskilled occupations

(i) Building and dock labourers

(ii) Others in V

Table 11. Lung Cancer Death Rates in 3 Districts of Connecticut (Griswold)

District	Occupational Character	Standard Lung		Cancer Rates Both
		Males	Females	
Naugatuck Valley Area.	Rubber, metal, machinery, chemical	85.02	14.87	48.01
Northeast Area	Textile, paper, agriculture	69.24	21.69	45.01
Rural	Agriculture	30.60	17.35	15.00
	Industry, agriculture	85.02	14.87	50.54
		38.65		26.53

Table 12. Standardized Incidence Ratios in United States Cities and Standardized Mortality Ratios in England and Wales for Cancers of Lung and Bronchitis Among Men (BUELL, DUNN and BRESLOW)

Primary Site	Ten United States Cities 1947, Standardized Incidence Ratios by Income Class (All Ages)					England and Wales, 1949-1953, Standardized Mortality Ratios by Social Class (Ages 20-64)				
	I	II	III	IV	V ²	I ³	II	III	IV	V ⁴
Lung, bronchitis	67	78	99	118	134	81	82	107	91	118

¹ High income. ² Low income. ³ Professional workers. ⁴ Unskilled workers. Source: - U.S. data from DORN and CUTLER, England and Wales data from Registrar-General's report.

employed rent and income or residence in different quarters of a community as a gradient, which in turn also reflects differences in occupational activities of the groups, in addition to living habits, medical care, and social activities. There is general agreement in these studies that relative lung cancer liability exhibits a distinct social class gradient (Tables 9, 10, 11, 12 and 13) (GRISWOLD; BUTLI, DUNN and BRESLOW).

Table 13. *Socioeconomic Distribution by Region of Cancer of the Lung in New Haven, 1935-1949* (E. M. COHART)

Region	Male Cases			Female Cases			Total Cases		
	Observed	Expected	Ratio of O to E	Observed	Expected	Ratio of O to E	Observed	Expected	Ratio of O to E
I	52	58.77	0.88	11	16.97	0.62	66	75.74	0.87
II	58	68.85	0.84	11	16.77	0.66	69	83.62	0.81
III	125	107.38	1.16	31	22.26	1.39	156	129.64	1.20
Total	235			53			291		

The circumstantial epidemiologic evidence supporting a major role of occupational factors in the induction of respiratory cancers is provided by statistical analyses of lung cancer rates in large industrial worker groups and of members of various occupations and trades. (MANCUSO; MORRISON; BRISLOW; LEW; REGISTRAR GENERAL;

Table 14. *Mortality from Lung Cancer and All Causes, Specific Occupations With Significantly Divergent S. M. R.'s for Lung Cancer in California Men, Ages 20 to 64, 1949 to 1951*

Social Class	Occupation		Lung Cancer Deaths		All Causes S. M. R.	
	Observed	Expected	Observed	Expected	S. M. R.	S. M. R.
Lung Cancer S. M. R. Above 100	I	11	6.3	175	107	
	II	12	6.4	188	100	
	III	108	74.7	145	89	
	III	44	32.1	137	122	
	III	27	18.5	146	110	
	III	20	15.4	188	145	
	IV	29	11.6	250	225	
	V	11	3.8	289	272	
	V	16	7.4	216	139	
	IV	44	24.4	180	184	
	IV	11	5.6	196	106	
	V	155	118.7	131	162	
	Laborers (not farm or mine)					
Lung Cancer S. M. R. Below 100	I	1	4.8	21	30	
	I	4	10.9	37	89	
	I	1	5.8	17	72	
	II	4	12.5	32	64	
	II	92	140.5	65	82	
	III	80	98.7	81	82	
	III	33	47.1	70	78	
	V					
	V					
	Other specified laborers (mainly gardeners)					

¹ N. e. c., not elsewhere classified.

KENNAWAY and KENNAWAY.) The data presented in the several Tables (Tables 14, 15, 16, 17 and 18) prepared by various investigators in different countries on the

lung cancer death rates of members of various occupations trades, professions and industries illustrate this point. Such fluctuations in the relative liability to lung cancer

Table 15. *Cancer Mortality by Occupation; Persons Insured Under Ordinary Policies — Special Studies: Occupations with Probably Higher-Than-Average Death Rates from Cancer* (E. A. LEW)

Occupational Group	Deaths from Cancer	Ratio of Actual Deaths from Cancer to Expected Deaths Measured by Mortality Ratio $\pm$ Probable Error %	Period Covered by Study
Waiters in hotels, restaurants, and club	14	125 $\pm$ 22	1915-1927
Waiters in hotels, restaurants, and clubs (male, no liquor served)	32	200 $\pm$ 24	1925-1936
Cooks, hotel, restaurant, and domestic	13	136 $\pm$ 25	1915-1927
Cooks in hotels, restaurants, and clubs	23	123 $\pm$ 17	1925-1936
Domestic cooks	10	200 $\pm$ 42	1925-1936
Hotel keepers, etc. (not at bar)	78	176 $\pm$ 13	1915-1927
Guards, watchmen, and doorkeepers, exclusive of those at penal institutions	22	233 $\pm$ 33	1915-1927
Janitors and sextons	24	125 $\pm$ 17	1915-1927
Stationary firemen	22	131 $\pm$ 19	1925-1936
Brick and stone masons	11	150 $\pm$ 30	1915-1927
House painters and varnishers	31	173 $\pm$ 21	1915-1927
Grinders of metals	11	220 $\pm$ 44	1925-1936
Furnacemen and puddlers in iron and steel works	11	172 $\pm$ 35	1915-1927
Blacksmiths	20	150 $\pm$ 22	1915-1927
Tailors (ages 40 and over)	33	150 $\pm$ 16	1915-1927
Semiskilled operatives in clothing manufacture (ages 40 and over)	18	175 $\pm$ 20	1915-1927
Spinners, weavers, and winders in cotton mills	22	165 $\pm$ 23	1925-1936
Initiated men (Army, Navy, Marine Corps)	12	160 $\pm$ 31	1925-1936
Laborers in nonhazardous occupations	18	180 $\pm$ 28	1925-1936
Section and track foremen on railroads	11	247 $\pm$ 49	1915-1927
Proprietors, foremen, and semiskilled workers in production of nonalcoholic beverages	14	300 $\pm$ 53	1915-1927
Junk and rag dealers	18	175 $\pm$ 28	1915-1927

Table 16. *Lung Cancer Death Rates per 1,000 Deaths from All Causes for 7 Industrial Groups in Ohio, 1947* (MANCUSO)

Industry	Death Rate
Nonferrous metal	3.22
Transportation	2.91
Rubber and plastics	2.34
Iron and steel	2.18
Mining and quarrying	1.53
Agriculture	0.82
Stone, clay, glass	0.66
Rate for all industries listed	1.76

among such diverse population groups cannot justly be attributed to differences in the biologic constitutional composition of their membership to contract cancer of the

lung. They can only be ascribed to quantitative and qualitative variations in the exposure conditions to mainly still unidentified environmental and occupational respiratory carcinogens.

Additional evidence on differences in occupation-related differences of lung cancer mortality rates have been recorded by WYNDER and GRAHAM; BERNET; POCHÉ, MITTMANN, and KNELLER; TURNER and GRACE, and others. It appears

Table 17. Standard Mortality Rates of Malignant Neoplasms of the Respiratory System in Occupational Classes in Scotland (MORRISON)

Occupational Code No.	Occupation	SMR: Above 150
160-164	Platers, riveters, shipwrights	183
231-249	Electrical apparatus makers, electricians	170
131, 132	Moulders	162
589	Masons and stone cutters	161
134-138	Foundry workers, etc.	157
681	Dock laborers	150
912	Crane drivers	132
600-609	Painters, decorators	Below 70
019, 021, 029	Farm workers	25
010, 011, 018, 020	Farmers, etc.	27
110-119	Foremen & overlookers in metal manufacture	54
013-015	Market or other gardeners	56
620-629	Managers or industrial undertakings other than managers of office departments	69

Table 18. Mortality from Lung Cancer and All Causes. Standardized Mortality Ratios by Major Occupation Groups in California Men, Aged 20 to 64, 1949 to 1951

Number	Major Occupation Group	Lung Cancer		All Causes S. M. R.	Occupation Repeating Ratio ¹	
		Deaths	Actual S. M. R.		Number	Ratio
1	All reported occupations	151	99	96	24/18	133
3	Professionals, etc.	269	84	90	17/17	100
3	Managers, etc.	97	76	83	14/14	100
4	Clerical, etc.	152	86	82	22/23	96
5	Sales	567	103	97	92/82	112
6	Craftsmen, etc.	278	120	95	36/47	77
7	Operatives, etc.	202	105	93	44/55	80
8-9	Service workers	203	110	109	33/32	103
11	Laborers	111	119	142	11/6	183
2	Farmers	61	94	93	4/10	40
10	Farm laborers		54	90		

¹ Number on death certificate divided by number according to occupational history. Histories were obtained by interview with hospitalized lung cancer patients who were subsequently traced on routine state death records (BRESLOW).

from these studies that workers employed in the metallurgical industry, painters, decorators, and mechanics are distinctly more often affected by lung cancer than farmers and agricultural laborers as well as coal miners. There is no evidence not is

it conceivable that such variations in lung cancer frequencies for different worker groups are in any way causally associated with demographic differences in cigarette smoking habits. This argument is applicable with equal force to the etiologic factors responsible for the occupational lung cancers of women working in smoke filled kitchens or inhaling smoke from braziers who develop lung cancer at a high rate, such as the Mexican women in Southern California (STEINER; BUECHLEY, DUNN, LINDEN and BRISLOW) or at a rather young age, such as the Bantu women in South Africa (HURWITZ).

4. Pluripotentiality of Respiratory Carcinogens

Respiratory carcinogens display to a remarkable degree pluripotential properties. This phenomenon is in part due to the fact that carcinogenic agents inhaled with the environmental air come in contact not only with the mucosal lining of the respiratory tract, but invariably also with that of the alimentary tract by being swallowed with the saliva and nasal secretion, as well as with the epidermis of the skin. The observation of cancers in non-respiratory organs in individuals exposed to atmospheric carcinogens, therefore, should serve as a warning of simultaneously existing cancer hazards to the respiratory system. The experiences obtained in the past with the discovery of occupational lung cancer hazards related to previously recognized skin carcinogens furnishes an adequate illustration in support of such correlations. It can be expected that this pattern of multiple target organs of respiratory carcinogens applies also when presently available observations are restricted to the respiratory organs. It is remarkable therefore that this biologic principle generally valid for occupational carcinogens does not hold apparently for exposures to cigarette smoke. Despite the fact that there exist definitely many more heavy cigarette smokers than coal tar workers and cobblers who have developed cancer of the fingers and hands from exposure to carcinogenic tar and pitch, cancers of the fingers often deeply brown stained by a prolonged and intense contact with cigarette tar have not been observed in chain smokers. A similar discrepancy exists regarding the apparent absence of cancer of the lip in cigarette smokers whose labial mucosa is constantly bathed in the tarry juice oozing from the tip of the cigarette. Lip cancers, on the other hand, have been recorded in tar workers as well as in fishermen keeping the tarry threads and the tar contaminated needle used during the repair of nets between their lips (HUEPPE). It is improper to invoke as an explanation for such differences in action between cigarette tar and coal tar a hypothetical variation in tissue susceptibility especially since cigarette tar is capable of inducing cancer of the skin in mice, and as claimed, is present in a concentrated form in the butt of cigarettes.

5. Carcinogenic Symptom Complex

All known respiratory carcinogens elicit in man in addition to cancers in different part of the respiratory system also a complex of symptoms which in part is characteristic for a particular carcinogen and which reflects its toxic action on the respiratory mucosa as well as other tissues.

Arsenic: Perforated nasal septum, bronchitis, metaplastic changes in bronchial mucosa, chronic dermatitis, melanosis of the skin, leukoderma, hyperkeratosis of palms and plantar surfaces, neuritis, cirrhosis of the liver, obliterative arteritis in lower extremities, multiple cancers of the skin, liver, lung, esophagus, etc.

Asbestos: Asbestos warts of the hands and forearms, bronchitis, progressive fibrosis of lung of diffuse character and involving lower lobes first, focal emphysema, adenocystic degeneration of bronchi, thickening and calcification of pleura, asbestos bodies in sputum, squamous cell metaplasia of bronchial mucosa, atypical carcinosis of abdominal cavity, peritoneal mesothelioma, mesothelioma of pleura, carcinoma of lung.

Chromates: Chronic dermatitis with chrome holes (indolent ulcers) on hands and forearms, perforated nasal septum, chronic rhinitis, chronic ulcerative bronchitis, chronic laryngitis, chromitosis of lung, chronic chemical pneumonitis, chronic ulcerative gastritis and colitis, cancer of lung.

Nickel: Chronic dermatitis, chronic bronchitis, chronic chemical pneumonitis, adenocystic degeneration of bronchioli, chronic rhinitis, carcinoma of nares and paranasal sinuses.

Radiopaque Chemicals: Chronic bronchitis, radiation pneumonia, anemia and leukemia, hypoplastic and hyperplastic changes in bone marrow, cancer of lung, cancer of nasal sinuses.

Coal Tar: Chronic dermatitis, tar warts, melanoderma, cornified horns on exposed skin, chronic rhinitis with loss of sense of smell and taste, bituminosis of lung, chronic bronchitis, papillomas and cancers of skin, cancer of lung.

Mineral Oil: Chronic dermatitis, melanoderma, warts, papillomas, chronic chemical pneumonitis (lipoid pneumonia), cancer of the skin at sites of principal exposure (hands, forearms, face, neck, scrotum, feet, lower extremity), cancer of the larynx, cancer of the lung.

Crude Isopropanol: Chronic sinusitis, nasal polyps, cancer of the larynx, nasal sinuses, lung.

Mustard Gas: Chronic dermatitis, chronic rhinitis, laryngitis, and pneumonitis, emphysema, bronchiectases, cancer of the lung, larynx and nasal sinuses.

These etiology specific symptom complexes represent in part exposure stigmata. They occur in many but not all individuals with these occupational cancers. Their appearance may precede often by many years the manifestation of the cancer.

6. Sex Distribution

With the exception of asbestos cancers of the lung and cancers of the nasal sinuses after exposure to radioactive gases or dust in luminous dial painters, the occurrence of all other occupational cancers of the respiratory system has been limited so far to members of the male sex. This sex distribution reflects and is the result of the exclusive employment of males in the various occupations with respiratory cancer hazards. Whenever females were equally exposed to occupational respiratory carcinogens, they exhibited a liability to cancer comparable to that seen in males.

7. Occupational "Neighborhood" Cancers

Recent observations on individuals living in the vicinity of industrial operations with occupational respiratory cancer hazards (coal tar fumes, chromate fumes, asbestos dust, beryllium dust) (FARKET; GROSS; WAGNER *et al.*; KIMURA; SARUTA *et al.*; FERSHTUDT; BOURNE and RUSHIN; WALTERS; WEBSTER; THOMSON; EISEN-NUD *et al.*), have revealed that industrial respiratory cancer hazards were spread into the immediate environment of plants in which such chemicals were produced or handled and were found along the roads on which industrial carcinogens were transported. Characteristic pulmonary lesions (asbestosis, berylliosis) were found in environmental residents as well as in consumers using such materials in their household and also in animals living in such environments (NIEBERLE; WEBSTER, KIVILUOTO). Industrial carcinogens thus have produced not only endemic "neighborhood pneumoconioses and cancers" but presumably also nonoccupational "household cancers of the lung".

As the result of general intraplant contaminations of the air, occupational lung cancers have been seen, moreover, in workers who were not directly employed in carcinogenic operations but were engaged only temporarily in such operations for repair and maintenance work or were employed in adjacent buildings, or did yard work in the vicinity of such buildings (GROSS) or performed work of non-carcinogenic nature, but were brought in direct contact with carcinogenic chemicals handled by other workers in the same operation (SELKOFF *et al.*). The existence of such "occupational association" exposures has rarely been considered in past epidemiologic investigations on an occupational causation of cancer in man.

Equally important in this respect should prove more comprehensive epidemiologic studies on the scatter pattern of occupational respiratory cancers in worker populations, as well as in the general population, along the lines of the known "traffic pattern" of specific carcinogens. Such studies should start with the original production operations of the carcinogens. They should follow them through the consuming industries and trades and finally be applied to the home environment of the ultimate public consumer as well as to the local and regional general environment. The ultimate consumer becomes exposed to these agents not only when they are present as ingredients, impurities and contaminants of consumer goods but also when they pollute water, air, soil, fauna, and flora (HUEBER, KIVILUOTO; WAGLER; MUELLER and ANSPACH; NEWHOUSE).

8. General Periplant Dissemination

The existence of respiratory cancer hazards in the immediate intraplant and extraplant environment has been demonstrated by the presence of several types of respiratory carcinogens in such areas. The spread of occupational cancer hazards in accordance with their known "traffic pattern" has also been proven. It stands to reason therefore that a similar, while mitigated effect, of the various occupational and industry-related respiratory carcinogens present in the general air, especially of cities and industrialized regions, accounts for a significant portion of the respiratory cancers occurring in the general population. There are good reasons for assuming that

industrial atmospheric pollutants are responsible in part, not only for the alarming increase of lung cancers during recent decades but also for the distinctly higher lung cancer rates in urban populations over rural ones (COMMINGS; HAMPELIN; HUEPER; KOTIN and FALK; STOCKS; STOCKS and CAMPBELL; HAMMOND; CURWEN, KENNAWAY and KENNAWAY; PYBUS).

9. Carcinogenic Potency and Attack Rates of Industrial Respiratory Cancers

The high carcinogenic potency of most industrial respiratory carcinogens is reflected in the highly excessive attack rates of respiratory cancers affecting various parts of this system (nares, paranasal sinuses, larynx, bronchi) according to observations in various circumscribed and usually severely exposed worker populations (Table 19). This fact receives additional support from the evidence that the carcinogenicity of these agents is not in doubt.

Table 19. Attack Rates of Occupational Respiratory Carcinogens

Chemical	Site of Cancer	Incidence in Population in Risk	% of All Cancer Deaths	Mortality Rate per 100,000	Mortality Rate per 100,000
Arsenic	Lung	—	—	—	145.7 males (10.9 normal)
Asbestos	Lung	—	—	12 × normal	(13.2–50.0% of all autopsies on asbestotics) (1 normal)
Chromium Nickel	Lung, Nares, Paranasal Sinuses	329:100,000 574:100,000	—	42 × normal 20 × normal	146–338
Radioactive Chemicals	Lung	—	—	—	(50–80% of all deaths)
Crude Isopropanol	Paranasal Sinus	10:100	—	134.5 (normal 6.5)	—
Coal Tar	Larynx	500:100,000	45%	—	—
Mineral Oil	Lung	2,000:100,000	55%	—	—

gens involved are capable of producing in most instances, cancers in several organs and in several species when introduced into experimental animals by the same or different routes.

10. Age Distribution

It is a well-established experience in occupational and experimental chemical carcinogenesis that optimal exposures to potent carcinogens sustained at an early adult period of life often lead to a shift of the age peak of cancers produced into an earlier period of life than that seen with the same type of cancer found in the general population which is often less intensely exposed to same agents.

The data recorded indicate that there is a distinct shift toward younger age groups demonstrable only for cancers of the lung induced by exposures to diatomates and chrome pigments and to radioactive chemicals (Table 20). Most occupational lung

Table 20. Age Distribution of Occupational Cancers of the Lung, Nose, Larynx, and Pleura in Percentage of Total Number

Years	0–29	30–39	40–49	50–59	60–69	70 and over	Total number of cases
Carcinogen	1.2	3.6	22.2	45.7	21	6	81
Arsenic	0	6.6	19.0	32.0	21.3	3.2	122
Asbestos	0	23	31	23	23	0	40
Chromium	0.8	15.7	25.5	33.3	22.5	2.2	102
Nickel	0	1	6	50	41	2	75
Nose	0	0	0	41	55	4	20
Coal Tar	0	9	24	20	25	22	58
Mineral Oil	0	0	0	58	42	0	12
Mustard Gas	0	5	15	47	33	0	19
Radioactive Chemicals	7	36	27	19	11	0	83
Controls General	6	12	24	34	21	3	1,702
Silicosis	0	2	21	43	32	2	100

cancers do not differ in this respect from those allegedly caused by excessive cigarette smoking and seen in the general population.

It is likely that the absence of a distinct shift in the age distribution of the majority of industrial respiratory cancers is related to the fact that the age of onset

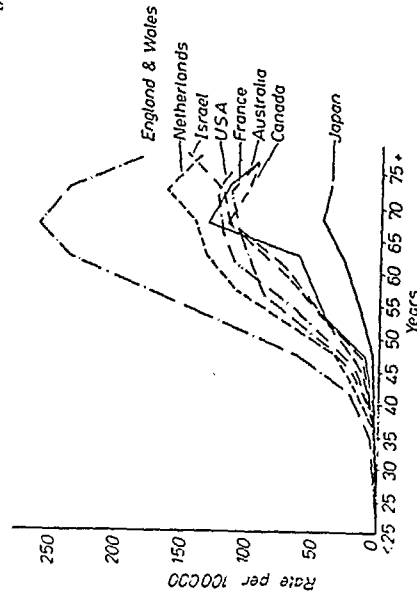


Fig. 1. (A. J. Pincus)

of exposure to the occupational carcinogen is, as a rule, at an adult age and that the degree of exposure to the various carcinogens is not sufficiently high for shortening significantly the length of the latent period. Observations on chimney sweep cancer of the scrotum (HURPER) and on occupational aromatic amino cancer of the bladder

(GOLDBLATT and GOLDBLATT), on the other hand, indicate that the age at entrance into a hazardous occupation determines to a demonstrable degree the age of manifestation of the cancer. Since PHILLIPS recently recorded a shift of the age-peak of pulmonary cancers in the English population by one decade, into a younger age group than that seen in other Western countries, it seems to be unlikely that such a

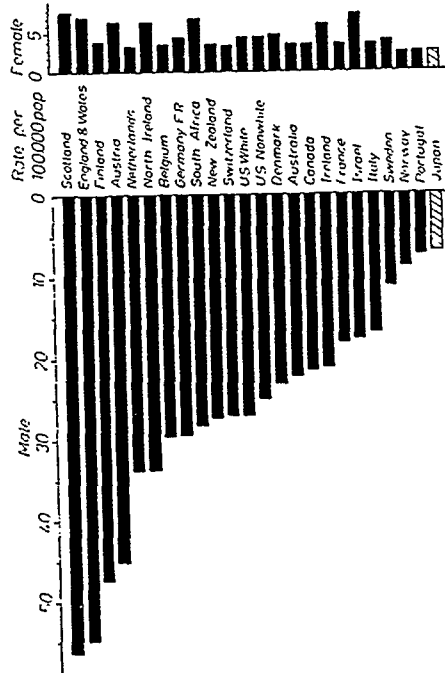


Fig. 2. Malignant neoplasm of lung and bronchus rates 1956-1957 (M. SUGI)

Table 21. Observed and Expected Death Rate of Lung Cancer According to Place of Birth
A. New Zealand and Great Britain (D. F. EASTCOTT, 1956)

Birthplace	Observed No. of Deaths	Expected No. of Deaths	Age at Time of Immigration from Great Britain	
			Under 30 years of age	Over 30 years of age
New Zealand . . .	632	721.8	201	168
Great Britain . . .	369	279.8	229.2	139.8

B. Lung Cancer Death Rates Among White Males in South Africa, 1947-1956, per 100,000 (G. DEAN)

Country	Age Periods	
	51-60 Years	65+ Years
South Africa:		
Native Male Whites . .	50	112
British Immigrants . . .	112	172
Others	67	152
England and Wales, 1951 .	135	219

shift can justly be attributed to any intensification of exposure to carcinogenic respiratory agents for occupational and habitual reasons occurring during the last 50 years, but is more likely due to enhanced pollution of the atmosphere with carcinogenic chemicals which were inhaled to an increasing degree during this period starting with an early age (Fig. 1). The age shift thus is the result of a progressively intensified and

extraordinary exposure of the children of England to carcinogenic air pollutants. This phenomenon evidently accounts also for the greater part of the unusually high lung cancer rates among the English population (See) (Fig. 2) as well as for the excessively high pulmonary cancer liability of British immigrants to New Zealand, South Africa and the United States (EASTCOTT; DEAN; MANCUSO) (Tables 21, 22 and 23).

Table 22. Death Rates of Lung Cancer in Male Immigrants, 25-64 Years of Age
Per 100,000 Population in Ohio
(T. F. MANCUSO)

Population of	Death Rate	Immigrants in Cuyahoga County from	Death Rate
Cuyahoga County 1947-1951, Native White Americans	28.75	All Foreign Countries 1947-1951	38.11
England and Wales, 1950	55.48	England and Wales 1947-1951	31.75
Italy, 1951	16.26	Italy, 1947-1951	18.61

Table 23. Inhalation of 3,4-Benzopyrene in Urban and Rural Regions
(SAWICKI et al., 1960)

Estimated Amount of Bp Inhaled by a Male Non-Smoker Living in	Micrograms per Year
Missouri State Forest	0.1
San Francisco	14.0
Detroit	110.0
London	320.0

11. Latent Period

The average length of latent period of occupational cancers of the respiratory tract ranges from 10 to 30 years (Table 24). It may be much shorter in some cases

Table 24. Latent Period of Occupational and Environmental Cancers of the Lung

(Carcinogenic) Chemical	Average Latent Period in Years	Range of Latent Period in Years
Asbestos	18	15-21
Chromates	15	5-47
Nickel	22	6-30
Coal Tar Fumes . . .	16	9-23
Ionizing Radiations	15-35	7-50

and considerably longer in others. While often the length of the latent period is equal to the exposure period, the exposure time may be much shorter than the latent period and after cessation of exposure to a carcinogen may be followed by a symptomless "lag" period of several months to many years. In some cases of asbestos carcinoma of the lung, for instance, the exposure time was only six months, while the first evidence of a pulmonary cancer in an asbestotic lung appeared in these individuals some 10 to 15 years later. In most cases of asbestos mesothelioma of the pleura, on the other hand, the average latent period was 30 to 40 years which included a lag period of some 20 years. Similar observations on a much delayed appearance of

occupational and industry-related lung cancers have been made among chromate producers and among individuals living near asbestos mines and mills (HUEPER; WALTER; WAGNER *et al.*). It is obvious that workers once exposed adequately to an occupational respiratory carcinogen carry their excessive liability to an occupational cancer along into later life and into occupations which may be free from such hazards.

12. Histologic Types

Claims have recently been advanced that specific etiologic factors, such as cigarette smoke, determine the histologic type of lung cancers (KREYBERG). Hence, it should be emphasized that adequate and reliable experiences with a variety of occupational respiratory carcinogens attest to the histologic nonspecificity of the ensuing cancerous responses (HUEPER). These carcinogens induce pulmonary carcinomas of any types in man and experimental animals. In fact, they may elicit in the same lung multicentric cancers of different histologic type and, in animals, also sarcomas (Table 25). The reasons for such different histologic responses of the bronchial mucosa are

Table 25. *Histologic Types of Lung Cancers in Man Induced by Several Occupational Carcinogens*

Carcinogen	Histologic Types of Lung Cancers			Total Number
	Squamous Cell Cn.	Round-Cell Cn.	Adeno Cn.	
Arsenic	19	24	4	47
Chromium	46	66	11	123
Asbestos	45	40	19	104
Silica (Control)	16	20	1	37
Ionizing Radiation	14	16	0	30
Coal Tar	3	0	2	5
Nickel (Nares)	3	13	0	16
Mustard Gas	11	8	0	19
Controls-Males (DORN and CUTLER)	29.3%	61.2%	9.5%	100%

obscure, although it is conceivable that adenocarcinomas are more likely to evolve from the adenocystic bronchial proliferations commonly found in asbestotic lungs, while squamous cell carcinomas probably develop from focal squamous cell metaplasias. The observations on the histologic types of occupational pulmonary cancers do not support the allegation that adenocarcinomas have a genetic origin and thus differ fundamentally in etiology from their squamous cellular or round cellular counterparts (KREYBERG).

C. Specific Occupational Cancers and Their Environmental Counterparts

The preceding critical appraisal of the characteristics of occupational respiratory carcinogens has demonstrated definitely that occupational respiratory cancers can be induced by a variety of chemical agents. Occupational respiratory cancers and their

industry-related and etiologically identical environmental and medicinal counterparts provide conclusive evidence of the polyetiology of respiratory cancers. The data presented have shown moreover that some of the occupational respiratory carcinogens are widely distributed in the general atmosphere especially in urban and industrialized regions and in some metropolitan communities, such as London and New York, contaminate the air and therefore are inhaled by their residents in amounts considerably higher than those inhaled by the majority of smokers and reached only exceptionally by the most heavy smokers. It has been noted also that the carcinogenic potency of many of the occupational respiratory carcinogens is distinctly higher according to human and experimental evidence than that demonstrable for cigarette smoke even when applied as a tar condensate under most severe experimental conditions. While pluripotential carcinogenic properties of cigarette smoke has been deduced from circumstantial statistical evidence on man, these qualities have been established beyond any doubt in man and animals for various occupational carcinogens. Human experience with the majority of the occupational respiratory carcinogens indicates furthermore that these agents are capable of inducing cancers in different parts of the respiratory tract, including the nasal cavity and nasal sinuses. The latter parts so far have as yet not been incriminated as susceptible to the alleged carcinogenic action of cigarette smoke. There exists also adequate clinical and experimental evidence which demonstrates that cancers of the lung and nasal sinuses follow not only by an inhalatory introduction of respiratory carcinogens but also upon an ingestive and parenteral one. More recent observations on the carcinogenic action of a large series of nitrosamines by DRUCKREY and associates, and others, have brought out the fact that the chemical structure of these compounds and others, which are widely used in industry directs their action toward specific target organs, including the lung and nasal sinuses for some of these substances.

With these facts on hand, it is rather surprising that the results of the numerous recent statistical analyses on the causation of lung cancers and their remarkable increase during recent decades either have totally failed to obtain evidence incriminating to any significant degree occupational carcinogens and their environmental counterparts in such matters or have relegated them to a minor and negligible role (Surgeon General's Report on Tobacco and Health). The misleading and deceptive argument that the epidemiologic evidence in support of the cigarette theory of lung cancer is even more conclusive than that which supported the contagious causation of smallpox when prophylactic measures were introduced reveals more crusading fervor than sound and sober medical judgment, since smallpox are due to a well defined and single infectious agent, while respiratory cancers are attributable to a considerable number of different causal agents. Because lung cancer rates are continuing to rise despite the various measures adopted to reduce the consumption of cigarettes, it may be proper to consider the introduction of preventive and protective measures against the various additional and factually proven causes of respiratory cancer.

The following detailed descriptions of the various recognized, suspected and potential occupational respiratory cancer hazards should provide sufficient and valid evidence for justifying a widening of the medical, public health and technologic approaches aimed at a preventive control of cancers amenable by past experience in industry to such measures.

1. Arsenic

Sites of Arsenic Cancers: Recognized: Skin, Lung, Liver; Suspected: Mouth, Esophagus, Larynx, Bladder.

Exposure Stigmata: Dermatitis, Neuritis, Arteritis, Gastroenteritis, Liver Cirrhosis; Laryngitis, Perforated Nasal Septum, Blandinitis, Anemia.

Compounds of Economic Importance (tri- and pentavalent): Arsenic metal and alloys, Ores of Silver, Gold, Copper, Tin, Lead, Cobalt, Nickel, Antimony, Iron (Pyrite), Realgar, Orpiment, Arsenic acid, Arsenious acid, Arsenic trioxide, Arsenic pentoxide, Sodium arsenite, Calcium arsenate, Copper arsenate, Lead arsenate, Cupric Acetoarsenite (Paris Green), Cupric arsenite (Scheele's Green), Schweinfurt Green, London Purple, Wollman's salt, Arsenic (Arsenurated Hydrogen), Arsamlic acid, Cacodylates, Arphenamines, Lewistite, etc. Trypsamine; Carbosone; Stovarsol.

Operations and Products with Contact to Arsenic for Producers, Processors, Users, Consumers, Residents: Copper alloy; lead shot; dust, fumes, mist, vapors in and around metal ore smelters and refineries; dust and water draining off slag heaps of mines and smelters; water from arsenic containing rock; pigments in paints, ink, glazes, glass, soap, and dyes of textiles and paper; decolorizer of glass; mordant; preservative of wood, pelts, fur hides; delairing agent of pelts; herbicide; antipruritic agent; pesticide (cattle and sheep dip, grasshopper and mosquito bait, insecticide of potato beetle, Japanese beetle, cotton boll weevil, codling moth, gypsy moth); amebicide, algicide, rodenticide; gas purification by Thylax process; war gases (Lewisite, etc.); hair lotion; animal feed additive; pharmaceuticals (tonics, antianemic preparations, Fowler's solution, Donovan's pills, Asiatic pills, cacodylates, arphenamines, caustic ointments, etc.).

Population Groups with Occupational and Environmental Exposure to Arsenic Occupational Groups: Airplane pilots, arsenic roasters, artificial flower makers, book binders, bronze workers, cannery workers peeling fruit treated with insecticides, citrus fruit orchard workers, cotton plantation workers, cut-glass workers, dyers, dyestuff makers, electroplaters, enamellers, farmers, fur handlers and preparers, galvanizers, gardeners, glass mixers, glass sprayers and dustiers, Japan makers, jewelers, lead factory workers, insecticide makers, insecticide manufacturers, gold refiners, ink manufacturers, manufacturers of arsenic, copper, zinc, silver, lead ores, oil linoleum color workers, lithographers, miners of arsenic, copper, zinc, silver, lead ores, oil cloth manufacturers, oil refinery workers, paper (colored) makers, paper platers, paper hangers, paper printers, felt and hair factory workers, pencil (colored) makers, pharmaceutical workers, photographers, poison bait makers, pottery decorators, pottery plant glaze dippers and mixers, printers, pyrites burners, rubber tire manufacturers, rubber wax makers, pounders, mordant mixers, rubber pressors, rubber tire manufacturers, sealing wax makers, seamstresses handling fabrics dyed or treated with arsenicals, sheep dip manufacturers, smelter workers, sulfur burners, sheep wool cutters, sulfuric acid workers, stevedores, tannery workers, taxidermists, textile printers, tinner, tobacco processors, velvet makers, winery workers, vineyard workers, war gas manufacturers, wire drawers, wood preservers, wax goods manufacturers, arsenical pigments, weed killer producers, wire drawers, wood preservers, wax goods manufacturers, zinc mixers, zinc smelter chargers, felt hat carriers, ferro-silicon workers.

Non-occupational Groups: Residents in vicinity of metal smelters and of orchards, fields and woods dusted and sprayed with arsenical pesticides; individuals consuming drinking water and foodstuffs contaminated with arsenical algaecide and insecticide residues; individuals smoking tobacco with arsenical residue; and inhaling arsenical air pollutants from burnt coal; veterans with war gas poisoning; patients given prolonged treatments with arsenical preparations (anemia, psoriasis, syphilis, trypanosomiasis, etc.); inhabitants of rooms with arsenic containing wall paint or wallpaper.

The world production of arsenic in 1955 was 37,000 short tons of which 10,800 were produced in the U.S.A. and of which were used 18,000 tons.

Arsenic and its compounds are widely distributed in nature and are practically ubiquitous. For this reason arsenic is found in traces in most inanimate and animate matter. Exposure to arsenicals from non-occupational sources is therefore common and accentuates that from occupational ones. The wide spread use of arsenicals as

pesticides and herbicides as well as of feed additives furnishes and additional avenue of human contact because of the thereby conditioned contamination of foodstuffs with residues from such materials. Inorganic and organic arsenicals are moreover employed for various medicinal uses in tonics, antianemics, amebicides, and spirocheticides. Arsenicals are moreover released into the air and bodies of water with the effluents of non-ferrous metal smelters and of coal burning furnaces. Since exposures from these sources often complicate occupational contacts with arsenicals, a brief listing of data regarding quantities of arsenic in various environmental media is presented.

a) Non-occupational Sources of Exposure to Arsenicals

a) Atmospheric Urban Pollutants

DART and KENNAWAY (1950) and GOULDEN, KENNAWAY and URQUHART (1952) recorded the following information on the arsenic content of the air of several English communities

Beckton (London)	0.132 micrograms As ₂ O ₃ per cbm of air
Bilston	0.075
Mandchester	0.073
Liverpool	0.068
Sheffield	0.065
County Hall (London)	0.058
Hull	0.054
Bristol	0.037

While the effluents from the stacks of one copper smelter in U.S.A. were said to emit only about 10 per cent of the arsenic originally present in the flue dust and fumes, the balance being retained by electrostatic precipitators, in a second American smelter about 50% of the arsenic was released into the general atmosphere from the stacks. The arsenic content of soot of English factories was given by SOWDEN (1927) to be 500 ppm, while SILVERSTEIN (1962) noted that 0.015 to 0.100 mgm. of arsenic was contained in one cbm of air.

β) Water Pollutants

The arsenic content of sea water was found to be 0.0006 to 0.03 ppm, whereas that of water of estuaries into which industrial wastes are being drained was 0.14 to 1.0 ppm (VALLEE, ULMER and WACKER, 1960). The development of dietary arsenic cancers of the skin in persons consuming fresh water contaminated industrially or naturally with arsenic was observed when the water contained the following amounts: Reichenstein, Silesia: 1.22 mg. per 100 cc. (GEYER, 1898); Cordoba (Argentina): 0.28 to 5.45 mg. per 100 cc. (ARGUELLO *et al.*, 1938; TELLO, 1951); Taiwan (China): 0.8 to 2.5 ppm (How and YEH, 1963). For comparison it may be stated that the maximal official dose of FOWLER's solution contains 5 mg. As in 0.5 cc.

γ) Foodstuff Contaminants

The maximal allowed concentration of arsenic in vegetables and fruits in the United States is 1.4 mg. As₂O₃ per kg. and stands at 2.65 mg. per kg. of animal tissue. Seafood has naturally a relatively high arsenic content varying between 3 mg. of As/kg for oysters and 174 mg. for prawns.

Arsenic in fruits and vegetables is mainly derived from pesticides residues and, locally, also in part from chemical fallout of smelters, pesticides factories and similar establishments. Milk, meat, liver, eggs, etc. may retain some of the arsenic contained in organic arsenical feed additives.

d) Soil Contaminants

SMALL and McCANTS reported that the soil from farmland not treated with arsenical pesticides in North Carolina had an arsenic content of 1 to 5 ppm., while it stood at 2.8 ppm. after arsenic application. Crops raised on such a soil translocated arsenic from the soil into roots and stems of crops.

e) Tobacco Contaminants

While the arsenic content of human food is usually regulated by law, that of tobacco is not. Arsenical pesticides have been used freely on tobacco crops for several decades in most countries. Smoking tobacco therefore contains arsenic in amounts which have varied from 2 parts per million to 170 ppm. depending upon the type of tobacco tested and the year of examination. Arsenic in cigarette tobacco has been considered by some investigators to represent a significant factor in the causation of lung cancer among smokers (DAFF and KENNAWAY; HOLLAND *et al.*; SATTERLEE; and others).

There are numerous reports on the occurrence of acute and chronic arsenic poisoning from contact with arsenic from non-occupational sources (HUTCHER). Such effects have not remained restricted to man but have been observed also in domesticated and wild animals, especially when exposed to arsenic containing smelter fumes (cattle, sheep, horses, goats, hogs, bees, deer, foxes, hares, fish) (PRILL; KAY; NIENHUIS; HUTCHER; HARRIS and SWAIN) (Germany, Canada, U.S.A., France, Japan).

b) Arsenicals as Carcinogens

During recent years several American industrial investigators challenged the widely held conclusion that arsenicals are definite human carcinogens inducing cancers in the skin and various internal organs, including those of the respiratory tract (SNEIGIRTF and LOMBARD; VALLER, ULMER and WACKER; JOINSTONE and MILLER; FROST; ECKARDT). This allegation has been applied not so much to the causation of cancers of the skin from a medicinal use of inorganic arsenicals, as to the existence of such associations particularly in regard to cancers of internal organs following contact with inorganic arsenicals for occupational reasons. There exists a voluminous literature on occupational, medicinal, dietary and environmental arsenic cancer effecting mainly the skin and less often other organs (NEUBAUER; HUTCHER; HUTCHER and CONWAY), refuting definitely such unfounded contentions. Some uncertainty still exists regarding a carcinogenic effect of organic arsenicals mainly used for medicinal purposes and as feed additives. Since organic arsenicals produce toxic symptoms identical with those elicited by inorganic arsenicals, it would be surprising indeed if the two types of arsenicals should differ in carcinogenic respects. In fact, several reports have indicated several medicinally used organic arsenicals as being responsible for the development of multiple cancer of the skin (NEUBAUER). The high incidence of uterine cancer among Danish prostitutes was tentatively also related to the arsenical antisyphilitic treatments often received by these individuals. A similar suspicion has

been entertained regarding an arsenical causation of the oral and pulmonary carcinomas found in the presence of syphilis (DÖRKEN).

There is no established carcinogenic dose for arsenicals. The German winners with dietary arsenic cancers analyzed by ROTH who developed multiple cancers of the skin, liver, lung and other organs ingested over a twelve year period a total of 53,682 mgs. of arsenic at an average (minimum 18.6 mgm.; maximum 88,764 mgm.). NEUBAUER noted a variation of arsenic intake in individuals with medicinal arsenic cancers involving mainly the skin which ranged from 190 mgm. to 121,000 mgm. The average was about 28,000 mgm. Little valid information exists regarding the minimal exposure time of arsenic cancers (NEUBAUER; ROTH; KOVLSCH; CURRIE).

c) Respiratory Arsenic Cancers

The development of cancers of the respiratory system has been noted following an occupational, medicinal and dietary introduction of inorganic arsenicals by inhalation and ingestion (ROTH; CALMAN; SEMON; WILLIAMSON; MONTGOMERY; SOMMERS and McMANUS; DANHOLT and FOSS; HOPKINS and SUNDHOLM; RUSSELL and KRAMER; and others). In an appreciable percentage of these cases their occurrence was preceded or associated with the appearance of additional primary cancers in other organs, especially the skin. They were often but not always accompanied by the presence of symptoms of chronic arsenic poisoning, thereby establishing to some extent their arsenical origin (DOTE).

Epidemiologic studies on the frequency of lung cancer in workers occupationally exposed to arsenicals are available for insecticide producers (HILL and FANNING), copper smelter workers (SNEIGIRTF and LOMBARD; LULL and WALLACH), winners using arsenical insecticides (ROTH), nickel refinery workers (ROCKSTROM) and gold miners (OSBURN) (Table 26, Fig. 3). Additional cases of 1 : cancer in similarly

Table 26. Lung Cancer Mortality in Several Counties of Montana 1947-1948 (LULL and WALLACH)

County and Total Popul- ation 1940	Major Industry	Numbers Lung Cancers		Total Cancer Deaths	Percent Lung Cancer		Annual Lung Cancer Deaths Rate per 100,000		
		Male	Female		Male	Female	Male	Female	
Deer Lodge 13,627	Copper Smelting	21	0	21	98	30.8	0.0	145.7	0
Silver Bow 53,207	Copper Mining	27	2	29	259	22.6	1.5	48.6	3.9
Cascade 41,499	Copper Mining Smelting	20	5	25	299	12.7	3.5	46.3	12.3
Callahan 18,269	Agri- culture	1	0	1	81	3.0	0.0	5.2	0

The estimated crude death rate for lung cancer among white males in the entire United States in 1947 is 10.9 per 100,000 population.

The workers employed in copper ore mining and smelting inhale dust and fumes of arsenic contained in the ore and released as a by- and waste-product during the smelting process. The copper ores mined in Montana contain about 5 per cent of arsenic.

exposed workers are listed in Table 27. There is moreover a certain likelihood that the excessive liability of hard rock miners in the Rocky Mountains, recently reported

by WAGNER *et al.* are attributable in part to the arsenic content of the ore dust inhaled by them. The apparent lack of similar observations among Swedish copper miners and millers handling arsenic containing ores (RINGEIZ; FORSSMAN; HOLMQUIST) is perhaps due to the fact that such mining operations in Sweden started only in 1928. Information on the occurrence of arsenic cancers among metal miners in Mexico and Chile is lacking (AMBLUX *et al.*).

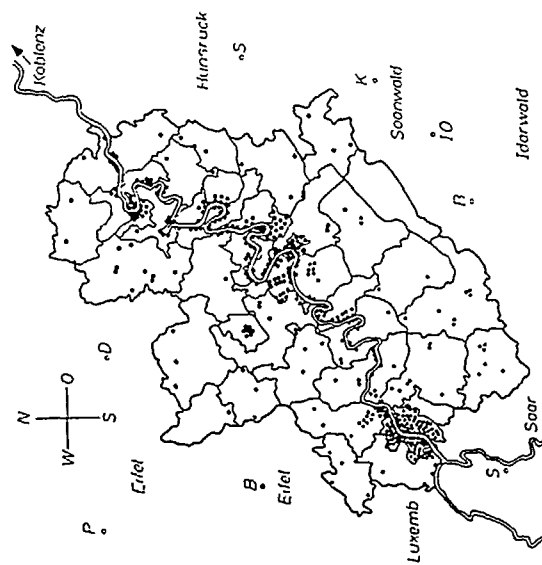


Fig. 1. Moselle from Trier to Cöchem. Regional distribution of cases of lung cancer (Rott).

Table 27 lists a total of 155 cancers of the lung probably or definitely attributable to an occupational contact with arsenicals. Arsenical dermatoses coexisted in 82 cases and cancers of the skin in 17 cases. The exposure period which often was equivalent to the latent period varied widely and ranged from 3 to 45 years. The lag period varied between 8 and over 10 years. The occurrence of arsenic cancers of the respiratory organs was not entirely restricted to members of the male sex, since Rott mentioned their occurrence in seven female vintners, who died with clinically diagnosed bronchiogenic carcinoma. In addition to 155 cancers of the lung, there were reported 3 cancers of the larynx and 2 cancers of the nasal sinuses.

SHUGART and LOMBARD noted seven deaths from lung cancer among American copper ore smelter workers in a total of 18 deaths from cancer of all sites. OSBURN recorded 19 lung cancers among 34 cancers of all sites observed among African gold ore miners (Negroes), i.e., a frequency rate of lung cancers among African Negroes which is threefold that of American males. Rott reported that lung cancers were found in 42 per cent of German vintners who came to autopsy with symptoms of

chronic arsenic poisoning. He compared this figure with that of 44.4 per cent of lung cancer noted by BRIDGEMAN and FORT obtained in an autopsy series of uranium miners of Joachimsthal. Rott, moreover, pointed out that the lung cancer rate among German vineyard workers of the Moselle valley applied to a rural and agricultural population which as a rule has a low lung cancer rate. The 45 lung cancers described by ROCKSWOLD occurred among a plant population of nickel refiners averaging 111 workers during the years 1932 to 1953. These and other observations

Table 27. Occupational Arsenic Cancers of the Lung, Larynx and Nasal Sinuses

Lung	Sites and Numbers			Exposure Period	Occupation	Author, Year
	Larynx	Nasal Sinuses	Cervical Glands			
7					Copper Smelter	SHUGART and LOMBARD, 1951
19	1	1		5	Gold Ore Miner	OSBURN, 1957
9		9	4	17	Pesticide Producer	DEBONNE and HAMMILL, 1952
1				36	Vineyard Worker	BAUER, 1958
19	1	2	19		Cobalt Smelter Worker	KARL, 1959
2					Vineyard Worker	ROTT, 1956, 1958
1					Arsenic Smelter Worker	SARANT, 1928
1					Farmer	MONTGOMERY and WATSON, 1941
1				43	Arsenic Worker	CRUICK, 1917
2				37	Pesticide Worker	BENNETT <i>et al.</i> , 1939
17				20	Copper Ore Miner	AKIZAKI, 1960
8		6		3	Vineyard Worker	HILL, 1956
45		45		8-45	Nickel-Cobalt Ore Smelter Worker	ROCKSWOLD, 1959
5	1				Pesticide Producer	HILL and FANING, 1948
2					Sheep-dip Producer	HILL, 1934
4				37-43	Sheep-dip Producer	MAREWELL <i>et al.</i> , 1944
1		1			Vineyard Worker	V. PLAS, 1943
1					Vineyard Worker	LANGELOTT, 1950
8					Vineyard Worker	KOTISCH, 1958
1					Furrier	FRANZ, 1927
2		1	1		Pesticide Sprayer	HILL <i>et al.</i> , 1961
155	Total					

justified the recognition of occupational arsenic cancers of the lung before German courts, when they were brought to litigation (LIEBIGOTT; MEESSEN; BAUER; von PLIN). The recently reported occurrence of three cases of lung cancer associated with cutaneous arsenic dermatosis among French wine growers indicates the general applicability of this concept (LATARJET).

Arsenic cancers of the lung involve, according to KORTSEN, more often the upper lobes than the lower ones and resemble in this respect pulmonary cancers of unknown causation. The age distribution of individuals at time of death from arsenic cancer of the lung exhibits a moderate shift toward younger age groups (Table 28).

Table 28. Age Distribution of Arsenic Cancers of the Lung

Year	0-29	30-39	40-49	50-59	60-69	70 and over	Total
Cases	1	3	18	37	17	5	81
Percent	1.2	3.6	22.2	45.7	21	6	

The distribution of histological types of lung cancers of occupational arsenic causation did not differ fundamentally from that found in cancers of this organ in general (Table 29).

Table 29. Histological Types of Lung Cancers of Arsenical Etiology

Squamous Cell Carcinoma	Basoid Cell Carcinoma	Adeno-Carcinoma	Total
19	24	4	47

In two cases of KORTSEN, two primary carcinomas were present in the same lung which differed in their histologic structure. Considering the fact that at times different parts of the same carcinoma of the lung may exhibit carcinomatous structures of differing morphology, such observations made in multicentric pulmonary cancers are not unusual. One of KORTSEN's cases had moreover a cancer of the larynx and a cancer of the skin, while the second one was associated with a cancer of the skin. Combinations with 1 to 4 cancers of the skin were recorded for 6 of 16 bronchiogenic carcinomas of the lung seen by KORTSEN in German winners, who had also cirrhosis of the liver. Similar heteroorganic multiplicity of arsenic cancers, some involving the lung, has been reported also after a medicinal administration of arsenicals.

There is evidence that both trivalent and pentavalent inorganic arsenicals possess carcinogenic properties. Pentavalent arsenic is reduced in the body to the trivalent form. Although some uncertainty still remains concerning the carcinogenic potency of organic arsenicals of the two valencies. The occurrence of only few cutaneous cancers usually of multicentric type has been related to such compounds (arsphenamines, cacodylates). Such an action must be anticipated since organic arsenicals are metabolically degraded in the body with the release of arsenic (NIEBAUER). An oral or respiratory occupational exposure to either type of arsenical, therefore, should be considered as significant in constituting a lung cancer hazard.

Little reliable and valid information is available concerning the minimal dose and minimal duration of exposure to arsenicals required for causing a cancerous reaction in any organ, including those of the respiratory system (NIEBAUER; KORTSEN; CURTIS). As a rule, like with other occupational cancers, contact with the carcinogenic agent was prolonged in arsenic cancers of the respiratory organs, extending over many months or years. Exposure, on the other hand, did not need to be continuous but was often intermittent. Because arsenic is relatively readily excreted through various channels from the body (Table 30), this fact is important

for medicolegal and diagnostic reasons. Chemical analyses for arsenic in the urine, hairs, nails, etc. performed years after arrest of contact, therefore, may not show amounts of arsenic above the "normal" level, which, on the other hand, may vary within a wide range because of the common environmental exposure to arsenicals

Table 30. Arsenic Content of Biological Materials of Man

Material	Arsenic Content	Material	Arsenic Content
Urine (1961)	0-60 mg per 100 grams	Blood	0-60 mg per 100 grams
Serum (1941)	24-77 mg per 100 grams	Hair	150-520 mg per 100 grams
Cause and Gans (1949)	25-88 mg per 100 grams	Nail	200-900 mg per 100 grams
Pruss (1950)	0-900 mg per 100 grams	Skin	10-160 per liter
Bondy et al. (1923)	0-900 mg per 100 grams	Milk	0-200
Schubert and Schubert (1958)	0-900 mg per 100 grams	Urine	30
Cox (1925)	0-900 mg per 100 grams	Urine	46-200
Schubert (1943)	0-900 mg per 100 grams	Urine	13-330
Kennedy and Schaeffer (1951)	0-900 mg per 100 grams	Urine	5-8
Savitsky and Page (1952)	0-900 mg per 100 grams	Urine	60-65
L.A.M.A. (1912)	0-900 mg per 100 grams	Blood	8
Washington, D.C., Residents	0-900 mg per 100 grams		
Tunsted and Myers (1935)	0-900 mg per 100 grams		

Excreted Arsenic

Pruss (1961)	140 mgm. per 100 grams	Blood	140 mgm. per 100 grams
Javorn (1950)	209 ppm	Hair	209 ppm
L.A.M.A. (1912)	564	Nail	564
Savitsky (1962)	80-190 micrograms per 100 cm ³	Urine	80-190 micrograms per 100 cm ³
Kortsen (1940)	5-550	Urine	5-550
Tunsted and Myers (1935)	100 or more indicates poisoning	Urine	100 or more indicates poisoning
Pinto and McGill (1953)	300 or more indicates poisoning	Urine	300 or more indicates poisoning
Kortsen (1940)	820	Urine	820
Bondy et al. (1923)	150	Urine	150
Pruss (1950)	120 per gram	Urine	120 per gram
Causton et al. (1939)	100 per liter	Urine	100 per liter
	670-3111	Urine	670-3111
	300 to 106,700 per 100 gm	Skin	300 to 106,700 per 100 gm
	150,000	Skin	150,000
	1000 per kg	Hair	1000 per kg
	3000 per kg	Nails	3000 per kg

Arsenic is retained in bones (Boos and Werny, 1935).

from many natural and manmade sources including footstuffs, cigarette smoke and air (TILLO; HOIMANN; GOULDIN, KENAWAY and URQUIART; FOOD STANDARDS COMMITTEE; EDITORIAL; ARGILLO, TELLO, MACOLA and MANZALO; ARHILGER and KREMLIN BAILLY; BAILLY, KENAWAY and URQUIART; BOHNERKAMP; BUTZINGFELDER; DALL and KENAWAY; JOLAND et al.; JIAVERI; PINTO and MCGILL; SATTERLEE).

KOELSCH stated that a daily intake of 3 to 4 mg. of arsenic causes the development of chronic arsenic poisoning. In analogy with observations made on many human and experimental carcinogens, it may be assumed that the carcinogenic dose of arsenic is well below this level and that, therefore, the demonstration of symptoms of chronic arsenic poisoning are not essential and obligatory for concluding on an arsenical causation of a respiratory cancer.

The etiologic significance of arsenic in the production of occupational respiratory cancers is supported by the following evidence:

1. The occupational history demonstrates an exposure to arsenicals.
2. The clinical symptoms of a chronic arsenicosis (melanosis, hyperkeratoses especially of the trunk, palmar and plantar surfaces; solitary and multiple cancers of the skin, cirrhosis and cancer of the liver, perforated nasal septum, chronic bronchitis, toxic neuritis, neurovascular disorders) in many individuals with respiratory cancer having such an occupational history provide medical evidence of the toxic and carcinogenic effects of the exposures sustained. Such symptoms represent prodromal and, in part, precancerous and cancerous manifestations as well as occupational stigmata of an arsenic cancer syndrome observed in single individuals and groups of individuals exposed to arsenicals.
3. Respiratory cancers in individuals with such a history and syndrome have developed respiratory cancers following an exposure of adequate intensity and duration, and after lag- and latent-periods conforming with observations made with other recognized occupational cancers of the respiratory system.
4. The demonstration of excessive amounts of arsenic in the excreta, blood, hair and nails of individuals belonging to such occupational groups when performed during such exposures or soon after their cessation, provides factual evidence of the biologic effectiveness of such contacts.
5. The unusually high frequency of multicentric cancers affecting either the same organ or different organs observed in individuals after occupational, medicinal and dietary exposure to arsenicals, supplies additional evidence of the primary carcinogenic action of this chemical.
6. A similar connotation must be ascribed to the predominant localization of arsenic cancers in the organs of primary contact or of secondary metabolism and excretion or of prolonged deposition.
7. In view of the abundant and reliable evidence in man, the past failure of producing unequivocally cancers in experimental animals does not furnish any valid evidence against the conclusion that arsenic is a human carcinogen.

d) Experimental Arsenic Cancer

Despite frequent attempts to induce cancer in experimental animals (mice, rats, chickens, rabbits) by the administration of various arsenicals by various routes (cutaneous, oral, parenteral), a reliable and consistently repeatable production of experimental arsenic cancers has not been achieved as yet (LEITCH and KENNEDY; SCHIMZ; RAPOSO; LINSCHUTZ; HUEBER and TRAMI; HUEBER and PAYNE; BOUTWILL BARONI, VAN EICH and SAFHOTTI). The recent production of liver cancers in rainbow trout fed carbazon by HALVER and ASHLEY, if confirmed, may provide, however, this long sought evidence.

2. Asbestos

a) Technologic Data

Among the many chemicals inhaled by inhabitants of modern industrialized and chemicalized countries for environmental and occupational reasons asbestos plays a rapidly increasing role because of the phenomenal growth of the asbestos mining and consuming industries and the therewith connected great rise in the use of consumer

goods containing asbestos in some form (Fig. 4). Asbestos is a complex magnesium-silicon polymer containing varying amounts of aluminum and iron oxide. The bulk of the asbestos commercially used (95%) is chrysotile which is mined in Canada; U.S.A.; U.S.S.R.; South Africa and many other countries. Chrysotile has an iron content ranging from 0.1 to 11.0 per cent and a magnesium oxide content ranging

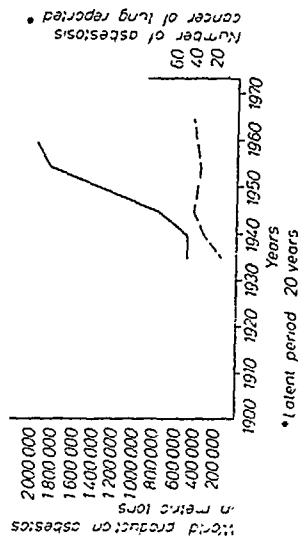


Fig. 4. World production of asbestos and asbestos carcinomas of the lung

from 39 to 44 per cent. Crocidolite mainly mined in South Africa, on the other hand, consists of sodium iron silicate which contains from 34 to 44 per cent iron oxide and from 1 to 7 per cent magnesium oxide. The different types of asbestos vary also in their fibrillar structure among each other. While chrysotile felts when in contact with water, blue Cape asbestos (crocidolite) retains its fluffy consistency and therefore its insulating qualities. The fibrillar polymerized molecule of asbestos assumes either a hand-like structure or a chain-like

structure (Fig. 5) (PARKER). During

recent years organic silicones of polymerized nature have been produced synthetically, such as Silastic, which is a polymerized dimethyl siloxane. They are used as lubricants, coating agents, and rubber. When silastic latex is vulcanized for its conversion into rubber, it assumes a sponge structure. Experiments with implants of silastic latex and rubber have shown that this material is carcinogenic when implanted into rats (HUTCHER).

Detailed data on the origin, production and industrial application of asbestos are contained in the monographs of ROSATI and of SINCLAIR.

The rapid growth in employment in the asbestos industry and the phenomenal increase in the number of products in which asbestos is used is well illustrated by data

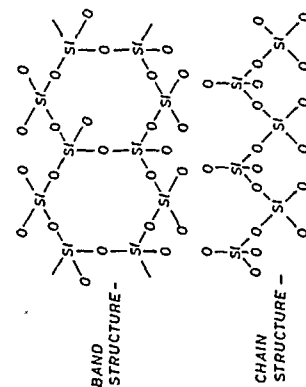


Fig. 5. Asbestos; fibrillar polymerized silicate

supplied by LEATHART and SANDERSON. The number of workers employed in the English asbestos industry stood in 1935 at 10,000 persons. It had risen to 18,700 by 1958. While the amount of asbestos cement products expressed in tons was 105,720 in 1930, it had increased to 461,700 by 1958. While 2070 tons of cement insulation was used in 1930, this figure stood at 42,500 in 1958. About 2200 tons of asbestos were used for asbestos brake lining in 1935, while approximately 10,000 were employed in the production of brake lining in 1958.

The number of persons employed in the American asbestos industry was estimated to be in the neighborhood of 35,000 workers around 1950, according to governmental statistics. Considering the marked increase in the use of asbestos since that time, the total employment figure should be at present in the U.S. close to 100,000.

Sites of Asbestos Cancers: Recognized: Lungs, Pleura, Peritoneum

Exposure Stigmata: Chronic fibrosing pneumonia involving first lower lobes (asbestosis), asbestos bodies in sputum, asbestos warts of skin (fingers.)

Components of Epidemiologic Importance	Occupations and Products with Contact to Asbestos for Producers, Processors, Forces, Consumers, Residents	Population Groups with Occupational and Environmental Exposure to Asbestos
Chrysotile, Amphibole, Amosite, Crocidolite Tremolite Containing Magnesium, Aluminum, Calcium, Iron, Silica	Asbestos rock mining, loading, shipping, crushing, milling; <i>asbestos spinning, weaving,</i> mixing, cutting, pressing, molding, plastering, cementing, spraying of steel construction, under- coating of automobiles, insulating pipes, etc. clothes, cloths, sheets, blankets, curtains, brake linings, yarns, cords, ropes, twines, ribbons, goods, plastics and roof coatings, filter cloths, filter pads, filter paper, artificial wood, tiles, shingles, card boards, wall boards, partitions, panels, paper, clutch facings, claphoard, pipe coverings, pipes, insulation blocks, insulation jackets, gaskets, pump packings, electric wire insulation, structural heat insulation, facings of acoustical building materials, catalyst supports in sulfuric acid production, putties	<i>Occupational Groups:</i> <i>Asbestos rock miners, loaders</i> <i>truckers, crushers, millers; asbestos</i> <i>spinners, weavers;</i> electrical appliance and wire manufacturers, masons, carpenters, heating equipment workers, rubber workers, dingle and tile manufacturers, building material manufacturers, filtering material manufacturers, molders of asbestos products, asbestos-asphalt makers, putty manufacturers, asbestos cement makers, asbestos paper cardboard and <i>brake-lining</i> <i>producers, asbestos felt insulation</i> <i>worker, asbestos sound insulation</i> worker, asbestos insulator, pipe coverer, <i>asbestos tube wrapper,</i> asbestos cork insulation worker; construction workers, automobile makers, garage attendants

Nonoccupational Groups:

Residents in vicinity of asbestos
processing, asbestos cement and
textile mills inhaling plant
effluents polluted with asbestos
dust and individuals living and
working along roads on which
asbestos is trucked; inhabitants of
houses with asbestos insulation.

b) Epidemiologic Data on Asbestos and Carcinoma of the Lung

Since cancers of the lung, pleura and peritoneum are directly related to occupational and environmental exposures to asbestos dust and to the development of asbestotic reactions in the lung, the delay encountered in the discovery of asbestosis in modern times and the difficulties in its diagnosis represent important features in the epidemiology of asbestos cancers. Despite the fact that the use of asbestos as a textile fiber and the knowledge of asbestosis date back to antiquity (DIWY), it was rather recent that this occupational pneumoconiotic hazard was rediscovered (MURRAY, 1900). The first cases of asbestosis complicated by pulmonary carcinomas were described several decades later (1933) by LYNCH and SMITH and by GLOYNIE.

Although some investigators still maintain that asbestosis is a rather rare occupational disease, the actual known facts are quite different (HARRIS). The enormous increase in the production and industrial use of asbestos during recent decades has been followed by a growing number of reports on the occurrence of occupational asbestosis observed in many countries (United States, Canada, Mexico, Great Britain, France, Germany, Belgium, Switzerland, U.S.S.R., Sweden, Denmark, Finland, Italy, South Africa). Epidemiologic and pathologic evidence obtained during the last few years moreover indicates that exposure to asbestos of a non-occupational basis may have become quite common, because asbestos bodies and mild to severe asbestosis have been observed rather frequently in individuals without demonstrable occupational contact with asbestos (FORTIN and GROSS; THOMSON; WAGNER, MÜLLER and ANSPÄCH; WINTER; KIVIMÄKI; NIEMINEN; (ORIOVA, TISLIK and KESKINEN), affected in part also with carcinoma of the lung and mesothelioma of the pleura (NIEMINEN).

The published records on asbestosis have remained rather defective for various reasons. Without any doubt a considerable number of cases of occupational asbestosis have been and still are incorrectly diagnosed as chronic pulmonary tuberculosis, silicosis, chronic fibrosing pneumonia and similar chronic pulmonary diseases. The diagnosis of asbestosis may be missed entirely during lifetime and this condition is then only discovered at autopsy (KÖNIG; THOMSON). Morbidity data on asbestosis based on clinical diagnoses only therefore tend to underestimate the frequency of this occupational disease.

Such diagnostic difficulties are sometimes accentuated by undesirable practices in the bona-fide recognition of asbestosis and of any cancerous lesions associated with it. DIWY recently noted: "One would think that would be enough, but medical bluntness, industrial coyness, and labor's timidity unwittingly hoodwinked the law in a Department of Labor investigation in Canada, in 1912. The Commission could find no occupational damage in 600 asbestos workers. Even in 1918, HARRIS, in a U.S. Labor Bureau Statistics Bulletin, assured the insurance companies that the early deaths among asbestos workers were due to tuberculosis. It is a pretty exercise in medical history to consult textbooks of pathology from 1910 to 1930. They are uniformly blank on asbestosis. And even today, the descriptions smelt of library paste."

The former astounding lack of medical and epidemiologic information has changed for the better in recent years, although it has remained rather defective in some countries (MARCHALL). Asbestosis is relatively common among asbestos workers

of various occupations. MERRITT and PRICE noted in 1930 that 95 or 26.2% of 363 out of a total of 2,200 asbestos workers medically examined in England showed evidence of asbestosis. According to BOHIG, JACOB and MUELLER, more than 33% of the approximately 10,000 German asbestos workers show signs of asbestosis (1960). BOHIG, on the basis of radiologic evidence, obtained on 132 German asbestos workers, arrived at an attack rate of asbestosis of 29%. The rate increased with the duration of employment, being 50% among individuals employed less than 3 years and 79% among those exposed for over 10 years. Data from Finland and Sweden by WIKARIUS and NORO on 476 and 167 workers, respectively, recorded a frequency of asbestosis in members of these groups of 30 and 65%, respectively, following the discovery of the first case of occupational asbestosis in Sweden as late as 1953 (AHLBORG and HANSSON). Among 31 Danish workers employed for over 20 years in asbestos work, 9 exhibited signs of asbestosis (30%) (FROST *et al.*). ALVARADO *et al.* recorded the occurrence of asbestosis in 6 out of 8 Mexican asbestos workers studied. While LANZA stated in 1936 that between 1928 and 1936 only 12 deaths from asbestosis among about 10,000 exposed asbestos workers were recorded in the U.S.A., and that the Metropolitan Life Insurance Company was notified during the period of 1924 to 1936 that asbestosis was a contributory cause of death in 17 of its policy holders, LYNCH and CANNON published observations made between 1931 and 1948 on 40 cases of asbestosis seen at autopsy among workers employed in one medium-sized textile plant. An identical number of asbestosis cases were seen between 1940 and 1960 by O'DONNELL and MANN at post mortem examinations of patients coming from a small town with a large asbestos brake lining plant. It should be obvious from even these fragmentary data that asbestosis is still a frequent and often fatal occupational disease among workers of many countries, even if comprehensive and long-term medical and pathological studies on the large and growing worker populations having occupational contact with asbestos dust are lacking.

Since the prevalence of asbestosis has usually been considered the prerequisite for the subsequent development of a carcinoma of the lung or of a mesothelioma of the pleura or of the peritoneum, these deficiencies in the available information tend to impair a clear demonstration of the real scope of the existing associations between the two conditions. A second difficulty encountered in reliably assessing the extent and degree of lung cancer hazards of asbestosis is represented by the fact that there has occurred in the past a confusing duplication in reporting cases of asbestosis cancers. In the following (Table 31) an attempt has been made to eliminate this error as far as possible by critically analyzing the various published reports, relating to asbestos carcinoma of the lung.

The reports of the authors were evaluated in the preparation of this table:

United States: ANDERSON and CAMPAGNA; ECHERT and GIGER; HOLLEN and ANGRIST; HOMBERGER; LYNCH and SMITH; LYNCH and CANNON; LYNCH and PRATT-TOMAS; ISSELBACHER, KLAUS and HARDY; O'DONNELL and MANN; O'DONNELL; STOLL, BASS and ANGRIST; TILUSCH and RUENSTON; MANGUSO; SHUKOFF, CHURG and HAMMOND; DYSON and TINTALANCE; CORDOBA, TISLOR and KNUDSON (Three cases of carcinoma of the lung with asbestosis in shipyard workers under investigation by HUELER and PAYNE were omitted).

Canada: DESMULES, ROUSSEAU, GIROUX and SIROIS; LUTON and CHAMPTIN; CARTIER; ROUSSEAU; BRAUN and TRUAN (34 unpublished cases of asbestosis car-

cinoma of the lung in asbestos miners of Quebec and studied histologically between 1940 and 1955 by VORWALD and SCHIFFERS at the Saranac Laboratories have not been included).

Great Britain: GLOYNE, SMITH; CURLTON; OWEN; HUGH-JONES and HARRIS; ELWOOD and COCHRAN; BUCHANAN; KEAL; MEREWETHER; DOLL; DONNER, FAULDS and STUART; KINNAWAY and KENNAWAY (cases recorded by WYERS were omitted because they were apparently included in listings of MEREWETHER of 1947 and 1955).

Table 31. *Carcinomas of the Lung in Asbestos: Reported Cases*

Country	Num. in	Sex	Age	Exposure Time	Latent Period	Last Period	Site	Histological Type
USA	88	M 87 F 1	37-69 Av. 50	5-48 Av. 23	6-36 Av. 23	1-30	L.L. 29 U.L. 10	S 18 R 18 A 9
Canada	10	M 10	48-65 Av. 57	2-33 Av. 22.5	14-34 Av. 25	4-16		A 2
England	149	M 107 F 32	32-76 Av. M 55.2 F 44.6	1-45 Av. 16	16-45 Av. 23	9-20 Av. 3	L.L. 4 U.L. 1	S 16 R 24 A 3
Germany	58	M 44 F 7	35-79 Av. 52	3-34 Av. 28	4-40 Av. 28		L.L. 22 U.L. 4	S 12 R 11
Finland	1							
Italy	3	M 2 F 1	46-54 Av. 49	17-26 Av. 29			L.L.	S 1 S 1
France	2	M 1 F 1	53	10			L.L.	A 1
Switzerland	1	M 1	62	7	24	17	L.L.	A 1
Total	240	M 197 F 41	32-76 Av. 54	1-45 Av. 23	4-45 Av. 23	1-30 Av. 3	L.L. 53 U.L. 7	S 45 R 40 A 19

L.L. = Lower Lobe.

U.L. = Upper Lobe.

S = Squamous-Cell Carcinoma.

R = Round-Cell Carcinoma.
A = Adenocarcinoma.

Germany: LINZBACH and WADLER; WELZ; WEDLER; BOHNE; BOEMKE; JACOB and BOHIG; BOHIG and JACOB; BOHME; WARRER; BOHIG, JACOB and MUELLER; HORNIC; KÖNIC.

Italy: PORTIGLIATTI-BARUOS; FRANCA and MONARCA; ROMBOLA
France: HUELL, LAGUILLAUME, CHAMPEIX and JACQUEMENT
Finland: NORO

Switzerland: CHAUVET

The individuals affected by asbestosis cancer of the lung were asbestos miners, millers, crushers, loaders, sorters, grinders, cleaners, pipe fitters, cement mixers, packers, boiler covers, mattress fillers, weavers, spinners, and cement workers.

The epidemiologic-statistical data supporting the existence of causal relations between exposure to asbestos dust and the subsequent development of asbestosis of the lung and carcinoma of the lung are in part derived from observations of post mortem material in part they are obtained by population studies. The first and still most frequent data indicating an excessive liability of asbestosis to develop cancers of the lung were gathered from autopsies. Although this material is a selective one, its signi-

fiences as evidence supporting such a liability is attested by the consistency of the evidence showing a highly excessive frequency of lung cancer in individuals with asbestosis in all countries in which such studies were made (Table 32). KOSMIN in a recent publication noted a lung cancer rate for male asbestotics of 46.1% against one in the general autopsy series of 11.6%, and one for female asbestotics of 21.7% against one in the general autopsy material of 2.1%. CORONA *et al.* found that 33% of their series of 20 cases of occupational asbestosis had lung cancer, and WAGNER placed it at 20%. In an analysis of 549 cases of asbestosis recorded between 1924 and

Table 32. Frequency of Cancers of the Lung in Autopsies of Asbestotics

Author	Sex	Number of Autopsies of Asbestotics	Number of Lung Cancers	Percentage of Lung Cancers
MILGROM . . .	Males	222	48	22
	Females	143	17	12
	Both	365	65	17.8
WYERS		115	17	14.8
DOLL		105 (asbestos workers)	18	17
CHESSE		121	17	13.2
OTTONS and MANN		40	20	50
LASNET		40	5	8.3
BECKER		92	15	16
WILKIN	Both	31	11	36
BONNIE	Males	17	12	71
	Females	14	2	14
<i>Controls</i>				
BECKER (males over 20, average age at death, 61 years) (silicotics)		4		
MILGROM (6,884 post mortems on silicotics, 91 lung cancers) (average age at death, 59.4 years)		3.6		
		1.32		

1962 in England, BUCHANAN noted 99 carcinomas of the lung among 364 males with asbestosis and 22 such cancers in 185 female workers with this disease. Even in the methodologically rather crude epidemiologic survey of white male employees of selected asbestos products plants conducted in U.S.A. by ENTERLINE these workers had a respiratory cancer rate of 193.3.

An identical connotation as to an excessive incidence of carcinoma of the lung among asbestos workers and especially among workers with asbestosis, have the results of the epidemiologic studies of DOLL in England (Table 33). The association of lung cancer to employment in asbestos was 15-fold that of the standard population. In a similar study conducted on the worker population of an American asbestos brake lining plant, MANCUSO and COULTER obtained identical evidence confirming the occurrence of an excess of deaths from lung cancer (Table 34). SLUKOFF *et al.* noted that a lung cancer rate of 6 to 7 times the normal rate prevails among insulating workers.

The scientific value of these observations was recently challenged by BONNIE, JACOB and MULLER and by BRAUN and TRUEN in investigations on the morbidity from lung cancer among asbestos workers in Saxony and in the Province of Quebec,

respectively. While BONNIE *et al.* maintained that the lung cancer morbidity rate of all German asbestos workers is not higher than that of a comparable general population (between 5 and 6 per 10,000), it is most doubtful whether this calculation reflects the actual conditions prevailing. Experiences made on the epidemiology of occupational cancers of various types have clearly shown that the anatomic reactions to such hazards, as a rule, become manifest only in long-term workers who have sustained a prolonged and often severe exposure or in individuals for whom, following cessation of exposure, an adequate latent period elapsed which usually extended over

Table 33. Causes of Death among Male Asbestos Workers Compared with the Mortality Experience of all Men in England and Wales (DOLL)

Cause of Death	Number of Death		Test of Significance of Difference between Observed and Expected (Value of 1.5)
	Number observed	Expected on England and Wales rates	
Lung cancer ¹	11	0.8	0.000001
Other respiratory diseases ² and cardiovascular diseases:			
With mention of asbestosis	14	7.6	0.001
Without mention of asbestosis	6	2.3	0.1
Neoplasms, other than lung cancer	4	4.7	
All other diseases ³	4	15.4	0.000001

¹ Including 1 case with pulmonary tuberculosis.

² Including pulmonary tuberculosis.

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

Table 34. Observed and Expected Deaths Due to Lung Cancers, 1940 through Mid-1960 Among a Cohort of White Male and Female Employees of Company C at Some Time in 1938 or 1939, Ages 25-64 Years at Death

Site	Total		White Males		White Females	
	Observed Deaths	Expected Deaths	Observed Deaths	Expected Deaths	Observed Deaths	Expected Deaths
Lung, bronchus, trachea (162, 163)	18	5.29	14	5.11	4	0.18
Peritonum (158)	3	0.10	2	0.08	1	0.01

(Medical Survey in an American Asbestos Brake Lining Plant)

10 to 25 years. Unless proper methodologic precautions in the collection and evaluation of epidemiologic data are taken, data of the type used by BONNIE *et al.* contain a dilution factor which a priori may negate and defeat the purpose and validity of such studies (ENTERLINE).

While BONNIE *et al.* conceded from their calculations that the lung cancer expectancy of one thousand workers with asbestosis and a more than 20-year employment in the industry showed a ten-fold increase over standard rates (50 per 10,000), they attempted to minimize the obvious significance of this finding by arguing that the observed number of lung cancers in this group should not be applied to the actual number of 1,000 asbestoses but instead to a hypothetical number of

3,300 cases which they assume have asbestosis. As pointed out before, such a supposition scarcely reflects the real conditions. It is likely from past experience with occupational cancers of the lung that a competent comprehensive post mortem study of the added number of 2,300 cases would increase considerably also the number of asbestosis cases showing a coexisting carcinoma. The argument of *Boulic et al.* therefore is incorrect and misleading especially as it must be suspected that the number of observed lung cancers in this series understated their actual number.

If *Boulic et al.*, moreover, noted in confirmation of their negativistic concept that asbestosis cancers of the lung have not been reported from South Africa, they labor evidently under a serious lack of pertinent information on the subject.

Even more serious objections must be raised against the scientific merits of the claims made in this matter by *BRAUN* and *TRUAN* who studied asbestos miners and millers in the Province of Quebec, Canada. Some importance must be attached to the fact that the project reported by *BRAUN* and *TRUAN* was to be undertaken under the aegis of the National Cancer Institute of Canada (Annual Report, NCI Canada, 1955—56) according to the "consensus of opinion" arrived at a meeting of the statistician of the National Cancer Institute of Canada, the medical director of the Johns-Manville Corporation, the medical officer of the Industrial Hygiene Foundation (Dr. *BRAUN*), the medical officer of the Theford Mines and other medical and technical personnel. After this initial arrangement the industrial sponsors of the project apparently abandoned this cooperative scheme and proceeded independently, being financially aided through contributions from various asbestos plants in the U.S.A.

According to the data published, this study was based on a survey of about 6,000 individuals employed by the asbestos industry in the Province of Quebec. While there is a break down as to the degree of dust exposure and the number of individuals in each of three graduated groups, no data are offered as to the duration of exposure to asbestos dust for the individuals contained in these groups. Although there is a statement as to the number of smokers and non-smokers, the report is totally devoid of any information concerning the number of asbestoses among the population groups analyzed. No information is available regarding the number of long-term workers and their relative liability to lung cancer. No mention is made in the report in regard to the autopsies which have been performed on members of this cohort who died during the period surveyed. This aspect appears to be particularly important, since *BRAUN* and *TRUAN* professed that only nine (9) "proven" cases of lung cancer were discovered to have occurred in the cohort analyzed. This is a rather surprising observation since during a somewhat longer period than that covering the survey, a histopathologic study of lungs from dead asbestos workers from Quebec by pathologists of the Saranac Laboratory under the sponsorship of industrial management, revealed a total of 34 cases of asbestosis cancers of the lung. It should be obvious from this observation that the epidemiologic investigation of *BRAUN* and *TRUAN* contains most likely only a fraction and possibly a minor fraction, of the cases which actually occurred, and that a thorough and critical analysis of the surveyed worker group for clinical and pathologic evidence of asbestosis and cancer of the lung would have yielded a result quite different from the reported one.

The conclusions reached by *BRAUN* and *TRUAN* concerning an absence of an excessive liability to lung cancer among Quebec asbestos workers are even incorrect

if proper epidemiologic procedures are applied to their data as reported. While the statement of *BRAUN* and *TRUAN* that the annual rate of deaths from lung cancer in the asbestos cohort for the years 1950 to 1955 is only slightly higher than the rate for the inhabitants of the Province of Quebec would be correct under these conditions, this statement represents a peculiar type of statistical acrobatics which tends to obscure the real incriminating evidence on hand by using a highly biased population group as a "normal" standard.

It is a well known fact that urban populations in all industrialized countries have a decidedly higher lung cancer death rate than that prevailing for inhabitants of rural regions (*HU-ME*). Since the asbestos mines are situated in rural areas of Quebec and are not located within the fume zones of Quebec and Montreal where a high lung cancer rate prevails (*Montreal rate 32.3*), the lung cancer death rates of the asbestos miners which stands at 33.8 per 100,000, has to be compared with the rates present in rural counties of the Province of Quebec, which, according to the data provided on this point by *BRAUN* and *TRUAN*, stands at 9.4 and 9.8. The method of establishing the absence of a significantly higher lung cancer liability for asbestos miners used by *BRAUN* and *TRUAN* is, therefore, patently incorrect, grossly misleading, and results in obscuring the actual existence of an excessively elevated lung cancer rate for members of this worker group when proper standards of comparison are used.

While such statistical manipulations may benefit industrial interests, they are neither original nor singular and have been applied repeatedly in the past to other occupational cancers, such as amine-cancers of the bladder and lung cancers from the inhalation of radioactive gases and dust. They have never been successful in the long run in obscuring the correct facts and have always been detrimental to public health and scientific and general morals.

It must be maintained on the basis of the evidence provided by *BRAUN* and *TRUAN* that the members of this worker group have indeed an excessive liability to cancer of the lung in accord with all other information available on this subject from many additional sources throughout the world. Although cancer of the lung does not seem to be the most frequent fatal complication of asbestosis, it is evidently sufficiently frequent for elevating the lung cancer rate of asbestos workers as a group and therefore is a serious sequela of exposure to asbestos.

c) Clinicopathologic Relations

The diffuse pulmonary fibrosis characteristic for asbestosis and distinct from the nodular fibrosis in silicosis, starts usually in the lower lobe, where radiographic studies may reveal a thickening of the pleura and a bunching of the small bronchi with their ends turned back (*JACON* and *BOULIC*). The close causal relation between asbestosis and cancer of the lung is demonstrated by the fact that asbestosis cancers affect more often the lower lobes than the upper lobes (53:7) in contrast to the general type of lung cancer which involves more frequently the upper lobes.

Associated with this etiologically significant topographical peculiarity of asbestosis cancers are the various equally important metaplastic, precancerous and cancerous changes of the bronchial and bronchiolar epithelium which precede and accompany the development of lung cancers in asbestotic lungs.

In the fibrotic matrix of such lungs, the mucosa of the usually non-stenosed bronchi and bronchioli shows multicentric atypical epithelial foci as well as squamous cell metaplasias. Bronchioli are often distended to adenocystic formations exhibiting the above-mentioned metaplastic changes and containing in their lumens desquamated epithelial cells and asbestos bodies. Adjacent to such metaplastic and precancerous lesions, the fibrous matrix may contain multicentric cancerous formations with or without asbestos bodies in the neoplastic parenchyma and stroma (Figs. 6 to 10). The high frequency of atypical adenomatoid and adenocystic bronchiolar lesions found in asbestotic lungs appears to account for the fact that adenocarcino-

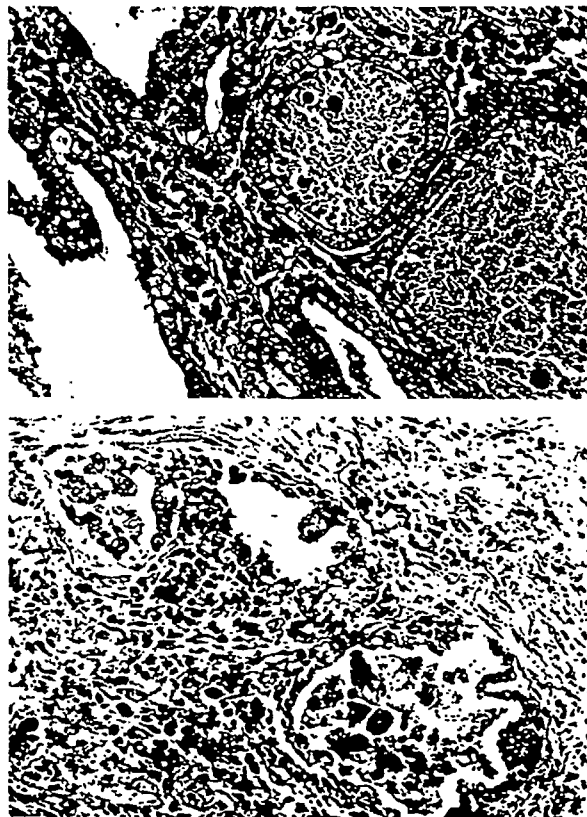


Fig. 6. Asbestotic fibrosis of the lung showing cystically distended bronchiole which contain in their lumens asbestos bodies. Asbestos textile worker.

Fig. 7. Marked adenocystic transformation of bronchiole in the asbestotic lung of an asbestos textile worker.

mas represent an unusually high percentage among asbestosis cancers (18% adenocarcinoma, 43% squamous cell carcinoma and 39% round-cell and anaplastic carcinomas). Also combinations of adenocarcinoma and squamous cell carcinoma have repeatedly been reported (Table 35) (BOULIC, JACOB and MULLER; LYNCH and SMITH). The commonly multicentric and widely distributed occurrence of the metaplastic changes in the bronchial mucosa of asbestotic lungs furnishes a plausible reason for the reported relatively frequent development of multicentric carcinomas in such lungs (GLOYNE; LYNCH and SMITH; BORMKE). Although similar, while usually less marked, mucosal lesions are found in association with other occupational carcinomas

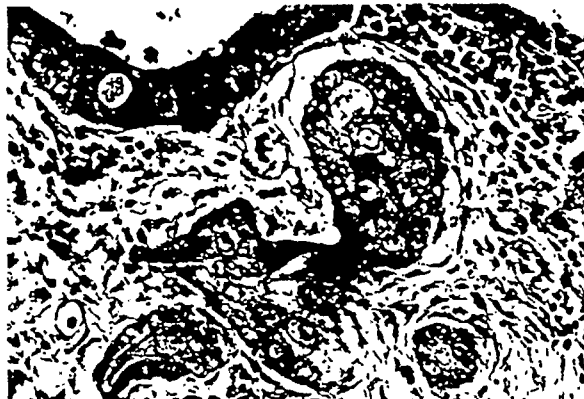


Fig. 8.



Fig. 9.

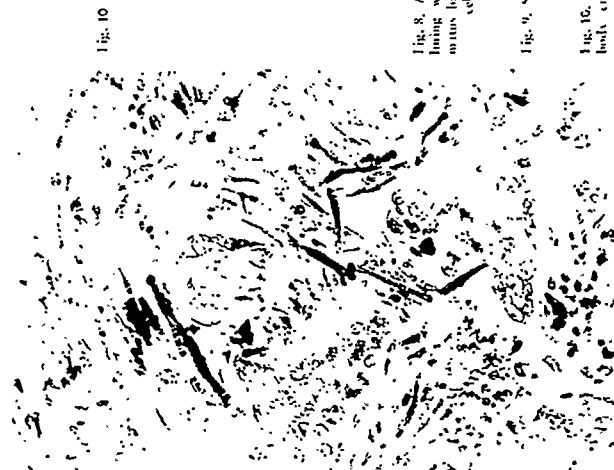


Fig. 10.

Fig. 8. Asbestotic fibrosis in the lung of an asbestos brake lining worker with atypical cellular lining of an adenomatous bronchiolar cyst and islands of metaplastic squamous cells, suggesting beginning carcinomatous changes.

Fig. 9. Squamous cell carcinoma and adenocystic bronchioli in the lung of an asbestos textile worker.

Fig. 10. Squamous cell carcinoma with numerous asbestos bodies embedded in the carcinomatous tissue in a textile worker.

of the lung (chromate, nickel), they are even less commonly encountered in lungs harboring the "spontaneous" variety of carcinoma.

The distinctive topographical distribution of asbestos carcinomas in the lower lobes as well as several special histopathologic properties of these neoplasms mentioned relate their development to the presence of asbestos and the pathologic changes incited in the lung by this mineral.

Table 35. *Distribution of Histologic Types of Pulmonary Carcinomas in Asbestotic Lungs*

	Squamous Cell Carcinoma		Round Cell and Undifferentiated Carcinoma		Adenocarcinoma	
	Number	percent	Number	percent	Number	percent
Asbestos Series	45	43	40	39	19	18
Controls (Dons and Curcio)						
Males		29.3		61.2		9.5
Females		13.6		59.7		26.7

d) Epidemiologic Data on Mesotheliomas of the Pleura and Peritoneum

Recent observations made in Germany, Great Britain, the United States, Canada, Italy, and South Africa strongly suggest that asbestosis is causally related also to the development of mesotheliomas of the pleura and peritoneum (CARTER; MANGUSO and COURTIER; BOHME; JACOB and MULLER; KÖNIG; LIECHT; WIEDER; WIEHNER; OWEN; SILIKOFF; CHURG and HAMMOND; WAGNER *et al.*; ENTICANAP and SMITH; SLIGGS, MARCHAND and WAGNER; DOLL; WEISS; KLAU; BONSER; FRANGIA and MONARCA; THOMSON; FOWLER; STOPER and WARNER). It is noteworthy that the occurrence of mesotheliomata in South Africa is restricted to the miners of the crocidolite (blue Cape asbestos) mines and to residents living in these mining districts (Fig. 11), either near asbestos mining operations or along the routes on which the

Table 36. *Mesotheliomas of the Pleura and Peritoneum in Asbestotics*

Country	Number	Sex	Age	Exposure Time	Latent Period	Long Period	Site
Germany	7	M 5 F 2	40-69 Av. 57	4-42 Av. 21	31-42 Av. 13	2-28 Av. 13	Pleura Peritoneum
Canada	2	M 2	65	10			Pleura
England	9	M 1 F 8	35-60 Av. 50	1-23 Av. 9	14-25 Av. 19	10-15 Av. 13	Peritoneum Pleura
USA	3	M 3	50-52				Peritoneum Pleura
Italy	1	M 1	46	17	30	13	Pleura
South Africa	16	M 15 F 1	36-68 Av. 45				Pleura Pleura
Res.	17	M 7 F 10	31-63 Av. 49				
Total	55	M 31 F 24	31-68 Av. 52	4-42 Av. 14	19-35 Av. 28	2-28 Av. 13	Pleura Peritoneum

asbestos was trucked (WAGNER). The occurrence of mesotheliomas in asbestos workers of many other countries indicates, however, that also chrysotile is capable of inducing these mesotheliomatous growths (Table 36).

The rather late discovery of these neoplastic sequelae to occupational and environmental exposure to asbestos may be attributable to three reasons. Although pleural mesotheliomas have been considered by some investigators as pleural extensions of pulmonary carcinomas, the recent observations on mesotheliomas in asbestos workers show definitely that such pleural neoplasms may develop in the absence of carcinomatous growths in lungs with relatively minor asbestotic changes. Pleural and especially peritoneal mesotheliomas found in asbestos workers have moreover suffered

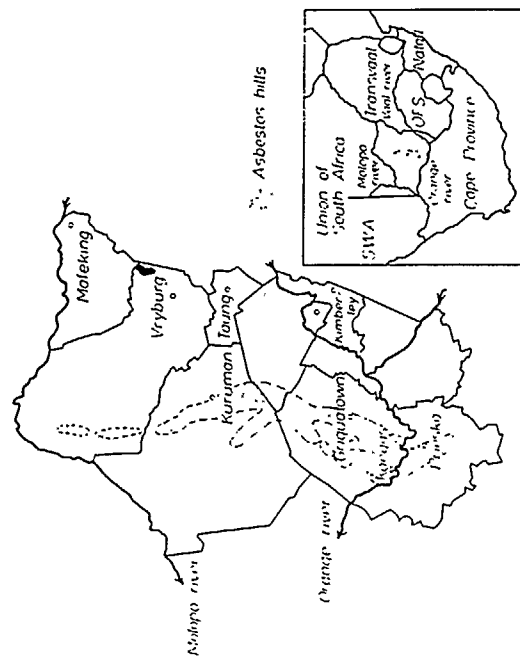


Fig. 11. Map of Grapaland west asbestos fields.

from diagnostic misinterpretations, i.e. they have not infrequently been diagnosed as adenocarcinomas of some glandular organ because of their frequent adenomatoid components. The third reason for their late discovery is connected with their long latent period, which often extends between 30 and 50 years and which may include a lag period of several decades. From a diagnostic and etiologic standpoint, it is important that the occurrence of asbestos bodies in cases of mesotheliomas was restricted to the lungs (Figs. 12 and 13).

It is interesting to note that among the 11 intrathoracic cancers recorded by Köning from Hamburg, 4 were pleural mesotheliomas. He noted moreover that among the extrapulmonary cancers found in 36 asbestotics 3 were peritoneal mesotheliomas. These observations may be of historical as well as etiologic significance, because the German shipbuilding industry was the first industry which soon after the turn of the last century introduced the use of blue Cape asbestos, for which up to that time no commercial use had been found.

The conclusion that definite causal relations exist between exposures to asbestos, the presence of asbestos bodies in the lungs and the subsequent development of meso-

theliomas of the pleura and peritoneum is supported by the fact that mesotheliomas, which ordinarily are rather rare tumors, represent, according to present observations, 15.1 per cent of all pulmonary cancers found in asbestotics, while this percentage stands for pulmonary cancers in general at about 4% (WATHER). It is, moreover, significant that the number of mesotheliomas observed among a restricted population group specifically exposed in South Africa has been rising rapidly during recent years and that a similar epidemiologic phenomenon has occurred in workers of the English asbestos industry (WAGNER).



Fig. 12. Natural tumor deposits in the interstitial tissue of the lung of asbestos worker.

Fig. 13. Mesothelioma of the peritoneum of this worker showing rounded nodular formations in a scarred matrix.

e) Age Distribution of Asbestosis Cancers

It is noteworthy that asbestosis carcinomas of the lungs do not share with some other occupational respiratory cancers the frequently observed shift of the age distribution into younger age groups (Table 37). In fact, the mean age at death of

Table 37. Age Distribution of Asbestosis Carcinomas of the Lung

	Age in Years										Total
	40	50	60	70	80	90	100	110	120	130	
No.	6	10	8	28	23	47	39	32	26	5	4
%	222	12	444	21	609	31	356	21	62	3	1,792
Asbestos Series											
Control (Lung)											

asbestotics without lung carcinoma was 44.2 years (males 49.2 years, females 38), while that of asbestotics with lung cancer was 52.1 years (males 55.2, females 44.6) (MURPHY). Severe asbestosis seems often to kill before there is time for the development of a lung cancer.

The age distribution of pleural and peritoneal mesotheliomas seen in asbestotics and in individuals with occupational and environmental exposure to asbestos dust exhibits in comparison to the asbestosis carcinomas of the lung a distinct shift into younger age groups.

Table 38. Age Distribution of Mesotheliomas of the Pleura and Peritoneum

	Age in Years										Total
	40	50	60	70	80	90	100	110	120	130	
No.	9	23	13	31	9	23	9	23	9	23	40
%											

In the absence of reliable data on the age distribution in a sufficiently large control group of the general variety of mesotheliomas, it is uncertain whether the observed age shift has any etiologic significance.

f) Sex Distribution of Asbestosis Carcinomas of the Lung

In his first report on the sex distribution of asbestosis cancer of the lung based on a total of 31 cases and published in 1947, MURPHY noted a male-female sex ratio of 2.4:1 which contrasted significantly from the normal ratio of about 10:1 prevailing in recent decades. Assuming that all other conditions were equal, it could be concluded that with an equalization of a carcinogenic occupational exposure for male and female asbestos workers there resulted a tendency toward an equalization of a specific cancer hazard for the two sexes.

In a subsequent report by MURPHY published in 1955 and comprising 65 cases of occupational asbestosis cancer of the lung, the male-female sex ratio had risen to 3:1 (48 males, 17 females). This figure stands at 4:1 (194 males, 41 females) for the collective series of 235 cases recorded in this study. It seems, therefore, that the sex distribution, like the age distribution, is still in flux and displays a tendency toward a "normal" level (BOITAT, JACON and MURPHY). The apparent lower liability to female asbestos workers to develop cancers of the lung may be related to work in safer jobs.

However, as long as reliable information is lacking on the total number of asbestos workers of both sexes, their age distribution, their length and type of employment in asbestos occupations, and their degree and duration of exposure to asbestos dust, any definite conclusions on these points should best be kept in abeyance.

g) Anticarcinogenic Action of Asbestos

PETER and others asserted that an antagonism or inverse relation exists between the development of cancers of the skin and that of internal organs in population groups exposed to cutaneous carcinogens. BOITAT *et al.* recently claimed that a similar antagonistic relation seemed to be present between the relatively high liability to cancer of the lung, which represented 85% of all cancer deaths in the worker popula-

tion furnishing 57 lung cancers, and the rather low cancer attack rate for other organs (10 cases). Apart from the fact that the validity of *Pittet's* thesis has been disputed by many investigators, especially those familiar with general cancer attack rates noted in various worker groups occupationally exposed to various carcinogens as well as in animals treated with physical and chemical carcinogens (coal tar, petroleum oils, polycyclic aromatic hydrocarbons, ionizing radiation) (*Hutter*), the observation on which *Bohrer's* claim is based was not confirmed by the results of the cohort study of *Mancuso*. The expected total cancer death rate of the population group analyzed was 27.74, the observed one stood at 55. Although the abnormally high lung and peritoneal cancer rates contributed the main share to the excess, there was no distinct diminution in the incidence of cancer of other sites in this group. The brain tumor rate was even increased. It would be unreasonable to assume by applying *Pittet's* thesis in reverse that a carcinogenic action of asbestos on the pulmonary tissues protected the skin against a cancerous transformation of the cutaneous asbestos warts (*Dewert*; *Driessen et al.*; *Chivier*, *Morand* and *Brun*), which are as invariably benign as their silicotic counterparts (*Crossland*). Whether asbestososis have an elevated cancer incidence of abdominal organs is still doubtful (*Mancuso* and *Goulter*; *König*; *Suttorf*; *Churg* and *Hammond*).

h) Synergism in the Production of Asbestosis Cancers

Bohrer et al. recently emphasized the important role which other occupational and environmental carcinogenic air pollutants, such as those contained in cigarette smoke, to which asbestos workers become exposed may assume in the causation of cancer of the lung. While it may be conceded that a synergistic action of several carcinogens has been demonstrated in experimental animals, such an effect between several carcinogens is by no means consistent. It may indeed be totally lacking or be of antagonistic nature (*Hutter*). At any rate this concept should not be advanced for minimizing the fundamental carcinogenic importance of asbestos in the production of lung cancers and should not be offered or accepted as a valid medical argument against awarding compensation in litigations on asbestosis cancer of the lung. *Suttorf et al.'s* findings did not support any significant accentuating role of cigarette smoking on asbestos carcinoma of the lung.

i) Exposure Time and Latent Period

In common with other occupational cancer hazards asbestosis cancers of the lung display an exposure time covering a wide range. These fluctuations reflect not only the importance of the intensity and duration of exposure but also the significance and the reaction of the host organism to the carcinogen in determining the occurrence and developmental speed of a carcinogenic response. A similar commutation is carried by the length of the latent period. Exposure time and latent period observed in asbestosis cancers, therefore, follow the general epidemiologic-biologic pattern of occupational cancers.

k) Experimental Production of Cancers with Asbestos

Attempts to produce cancers in experimental animals by the inhalation or parenteral introduction of asbestos have yielded contradictory results. *Nonnmann* and

Sorge, who exposed mice to asbestos dust by inhalation and *Schmitt* who injected asbestos subcutaneously and intraperitoneally into rats, reported the development of cancers in the lung and subcutaneous tissue, respectively. Similar experiments by *Vorwald*, *Durkin* and *Pratt*; *Lyons*, *McIver* and *Cain*; *Wagner*; and *Hutter*, employing mice, rabbits, rats, guinea pigs, monkeys, and dogs gave, on the other hand, negative results, when various types of asbestos were inhaled or implanted parenterally. *Pracock* and *Pracock*, who injected asbestos into the axillary air sac of White Leghorn fowls observed carcinomas developing from the wall of the sacs in two of 30 chickens surviving for periods of a year or more. *Wagner* succeeded in the production of pleural mesotheliomas in rats intrapleurally injected with powdered South African asbestos, and *Smith*, *Müller*, *Churg* and *Suttorf* were equally successful in hamsters receiving asbestos by the same route. They found drysoite and amosite effective in this respect.

The experimental evidence obtained favors the view that asbestos is not only carcinogenic to man but also to several animal species.

l) Causative Mechanism of Asbestos Carcinogenesis

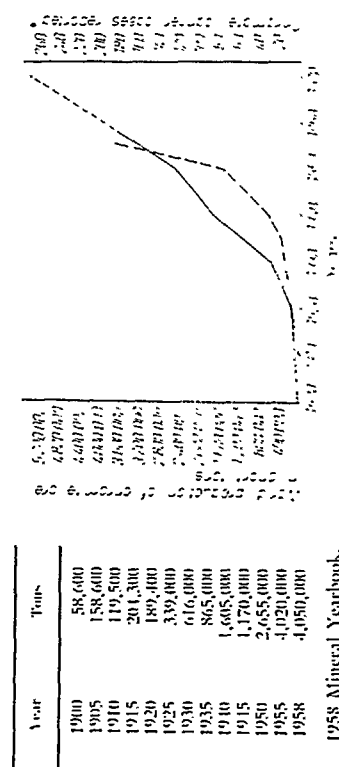
Efforts to elucidate the carcinogenic mechanism active in the production of cancers in the lung and mesothelial tissues have yielded several in part contradictory concepts. Some investigators have proposed that the development of carcinomas in the asbestotic lung is a non-specific neoplastic reaction to chronic inflammatory and fibrosing processes favoring an unlimited regenerative proliferation of bronchial epithelium. Since such chronic irritative responses are minimal in the majority of the lungs of individuals suffering from asbestos mesotheliomas and since asbestos bodies have not been discovered within these tumors, this chronic irritative concept of asbestos carcinogenesis evidently is not applicable to asbestos mesotheliomas.

Observations on the decrease of particle size of asbestos bodies observed with the elapse of time after cessation of exposure by *Künin* and by *Knox* and *Blattin* suggest that asbestos particles, especially drysoite, to a lesser degree crocidolite, are decomposed in the lungs and that some degradation product of asbestos might furnish the carcinogenic stimulus. This concept receives support from observations made by *Hutter* in connection with the carcinogenic action exerted by various nanomolecular carbon and silicon polymers. It was shown in these experiments that some of these polymers were degraded especially when implanted as sponges into the abdominal cavity of rats. The implantation of polyurethane foam resulted in the development of sarcomas and of adenocarcinomas of the intestine as well as of peritoneal mesotheliomas. The neoplasms contained flaky degradation products of the sponges implanted. In an appreciable number of these animals the sponges were completely absorbed. These findings point to the operation of a chemical mechanism as the principal carcinogenic avenue in asbestos carcinogenesis.

Since asbestos bodies are surrounded by an iron-protein complex sheath and because most types of asbestos contain iron in appreciable amounts, the possibility of a specific carcinogenic action of iron was considered. The reported excessive frequency of lung cancer in English and French hematite miners and foundry workers was cited in support of this concept. It was also pointed out that *Hammond* and *Horsing* had suggested that the iron in the carcinogenic iron-dextran complexes represented the actually active carcinogenic principle and not the dextran. Apart

during this period rose by 70%, while that employed for the manufacture of chromium compounds for chemical uses increased by only 20%. These technologic and commercial observations are of importance in the assessment of the past, present and future scope of occupational and environmental cancer hazards associated with exposures to chromium and chromium compounds. The data indicate that with the rapid recent rise in the production and use of chromium and its compounds and alloys in the human economy (DANKSMAN; WATSON) and the thereby conditioned greater occupational and environmental exposure to these agents, there may follow during the next decades a distinct and progressive increase in the number of chromium cancer affecting mainly parts of the respiratory system among members of many special

Table 39. World Production of Chromite Ore in Shott Tons from 1900 to 1958
P. J. THOMPSON and B. B. MITCHELL



1958 Mineral Yearbook, Vol. I, p. 316, U.S. Government Printing Office, 1959.

Fig. 11. Chromite ore production and chromium cancers of lung.

worker groups as well as of the general population (Fig. 14). Cancer hazards to this type may be related to occupational contacts encountered during the production, processing and industrial use of these agents. They may be associated with environmental exposures to chromium-containing industrial effluents contaminating the air, water and soil and after secondarily being transferred to agricultural products and meats, also the human food supply, and they may result from contact with chromium-containing constituents and pollutants of general consumer goods (GROSS; HUPFER). While these industrial developments have been accompanied in many operations by a reduction in the intensity of exposure to chromium-containing dust, fumes and vapors through the introduction of improved production methods and of protective measures, there has not occurred lately any appreciable decrease in the duration of occupational exposure to these agents and, doubtlessly, there has taken place during the same period a remarkable increase in the number of exposed individuals engaged in old and new activities and practices providing contact with, in part, new chromium compounds and alloys. There were employed in the American Navy Shipyards in 1960 about 2,000 zinc chromate spray painters among a total of approximately 60,000 workers. During World War II about 6,000 spray painters worked in the aviation industry in southern California.

Chromium

b) Epidemiologic Cancer Aspects

The first observation which aroused the suspicion concerning the existence of a cancer hazard to the lung in workers exposed to chromates was made in 1911 and 1912 in two workers engaged in Germany in the production of alizarin which required the use of chromates as oxidizing agents (PITEL).

Because of the small number of cases and the newness of this finding no serious attention was paid to it, especially since its significance as an industrial cancer hazard was denied by LUTMANN and KOLLSCH. However, 25 years later, ALWINS, BAUKL and JONAS and subsequently GROSS and other German investigators reported the occurrence of lung cancers in a considerable number of workers employed in the manufacture of chromates or having, for other reasons, contact with chromate dust and fumes in such plants and plant areas. It became soon apparent that also the producers of chrome pigments (zinc chromate, barium chromate and lead chromate) exhibited an excessive liability to lung cancer (GROSS and KOLLSCH). The entire evidence recorded on the occurrence of these respiratory occupational cancer hazards in Germany up to 1952 was reviewed by SPANNAGEL in 1953, who collected a total of 86 lung cancers and four (4) nasal sinus cancers among German chromate and chrome pigment workers (PITEL, LUTMANN; TILLEY; KOLLSCH; ALWINS and BAUKL; ALWINS, BAUKL and JONAS; ALWINS; GROSS and ALWINS; GROSS; GROSS and KOLLSCH; BAUKL; RINCK; ASANG; FISCHER-WASSEL; CADOTSCH; LUTMANN, NIMMARD and KUTTI). Among the workers thus affected were not only chromate producers but also workers with intermittent contact to effluents of such operations (GROSS), such as truckers, glaziers, locksmiths, welders, workers employed in buildings located within the fume zone of chromate operations and suffering in part from perforated nasal septa (GROSS) (hydrochloric acid and sulfuric acid workers); chrome pigment producers (GROSS; BAUKL; LUTMANN *et al.*; FISCHER-WASSEL); a polisher of aluminum casts treated with sodium bichromate (ASANG), and a spray painter (BAUKL). A larynx cancer of somewhat doubtful association to an exposure to chromic acid occurred in a galvanizer (CADOTSCH). Recent unpublished observations of HUPFER and of PAYNE and HUPFER established the occurrence of lung cancers in cutters of scrap metal painted with chrome yellow who were employed in a shipyard and in spray painters applying chrome yellow paints as an anticorrosive coating to airplanes. Five cancers of the lung were observed in 1962 in American chrome pigment workers who had been employed in a chromate plant (HUPFER) which formerly had been found free from such occurrences (MACHLE and GRIGORIUS).

The first case of lung cancer in a chromate producer in the U.S.A. was recognized in 1946 as the result of a litigation (HUPFER). When subsequently upon suggestion of HUPFER, the American chromate producing industry conducted a survey among workers employed in seven plants, 42 additional cases were discovered (MACHLE and GRIGORIUS). These studies and others performed thereafter (BARTNER; MANCUSO and HUPFER; BURTON, FRASER and KOVINE; JARRIS; GARAFIA *et al.*; HUPFER; FISCHER and KUTTI) provided definite proof that workers engaged in the manufacture of chromates exhibited also in American plants a highly excessive attack rate of cancer of the lung. Subsequent similar epidemiologic investigations made in England by BINSTROP and by BINSTROP and CASE revealed the existence of similar connections for English chromate workers.

These observations came some 60 years after the initial finding by NIWMAN of an adenocarcinoma of the turbinates in a chrome pigment worker in Scotland. During recent years reports on the occurrence of isolated cases of cancers of the lung and nasal septum in chromate producers have been published from other countries (Italy, Czechoslovakia, U.S.S.R.) (VIGHANI and ZURLO WACKMANN; PORTUGIATI DI-BARROSI; BARBORIK, NANSULAN, ORAL, SHINALOVA and HOSHINO; GIUSIUKO).

In fact, it has become likely from clinical and experimental findings that the carcinogenic action of chromium may not entirely be limited to the respiratory system, but may extend under special conditions to other tissues such as the skin and bones. WELZ recorded the occurrence of a squamous cell carcinoma of the skin of the forearm in a graphic workers suffering from a chronic chrome eczema, while STRAUPIER and McDONALD noted the development of bone sarcomas in individuals following the nailing or plating of bone fractures. The occasionally observed development of cancers around bullers and shell fragments embedded in various tissues, including the lung and nasal sinuses, may possibly be attributable to a carcinogenic action of chromium contained in such materials (BLUMHUIS), since implants of various chromium compounds into rats and mice gave rise to the development of sarcomas of different types (HUTNER; HUTNER and PAYNE; PAYNE). The following table (Table 40) presents a summary of the cases of industrial chromium cancer reported from various countries.

Table 40. Cancers of the Respiratory System in Industrial Producers, Processors, and Users of Chromates, Chrome Pigments, and Other Chromium Compounds

Country	No. of Cases	Site of Cancer						Location in Lung					
		Lung	Larynx	Nares	Nasal Sinuses	Upper Lobe	Lower Lobe	Right	Left	Right	Left	Right	Left
Germany . . .	93	89	1		3	14	9	16	8	6	6	4	4
U.S.A.	77	76			1	12	5	6	3	6	6	4	4
England . . .	13	12											
Italy	3	2		1									
Czechoslovakia	1	1											
Total	187	180	1	1	5	26	14	22	11	12	12	8	8

It should not be assumed that the number of cases listed in this Table represent even approximately the number of cases of chromate cancers which actually occurred among workers employed in plants and operations and inhaling chromium containing air pollutants. While American, German, U.S.S.R., and South-African investigators (GALATIER *et al.*; KORTSCH; LUKANIN) noted that chromite ore dust inhaled during the mining and the processing of ore into refractory bricks and cement has not produced a lung cancer hazard, this statement is of uncertain validity because of the absence of acceptable large scale epidemiologic investigations on worker groups thus exposed and the high rate of labor turnover among such workers. The trivalent chromium of finely powdered chromite ore, moreover, is transformed by the action of atmospheric oxygen into a water soluble hexavalent chromium (GROGAS) and thus becomes biologically active. Experiments of HUTNER, moreover, have shown that chromite ore dust inhaled by mice and deposited in their lungs is solubilized, mobilized and demonstrable in the blood.

It appears from observations made in man exposed to chromite ore dust that similar changes apparently take place in the human lung since chromium could be demonstrated in the blood, urine and tissues of individuals thus exposed (MANCUSO and HUTNER).

Apart from the epidemiologic surveys made on rather small worker groups engaged in the manufacture of chromates in Germany, U.S.A. and England, there is a complete lack of similar studies on the many and much larger worker populations who have respiratory contact with hexavalent and trivalent inorganic and organic chromium compounds and with metallic chromium and alloys, such as especially chrome platers, stainless steel makers, welders, metal cutters and spray painters. Even the available epidemiologic studies performed on members of the chromate producing industries in the three countries mentioned yielded only fragmentary information, since they did not include a comprehensive analysis of former workers employed in their plants, who can be expected to have developed at least in part, cancers of the respiratory organs while employed later on in other jobs. The data provided by SPANNAGEL and others on the length of the lag period elapsing between the cessation of exposure and the appearance of the first symptoms of a respiratory cancer illustrate the significance of such epidemiologic relations (Table 41).

Table 41. Length of Lag Period of Chromate Cancers of the Lung

Years	1	2	3	5	6	10	11	15	16	20	21	30	Total
Cases	16		8		19		3		1				49

In an analysis of HUTNER conducted on 154 former chromate producers employed in a Mid-Atlantic State of the U.S.A. who had been engaged at this work for a minimum of 6 months and who had left the chromate plant at least four years prior to the investigation, it was found that among 20 deaths which had occurred in this group, four (4) were due to cancer of the lung, one (1) to cancer of the maxillary sinus; one (1) to cancer of the colon and one (1) to leukemia. The respiratory cancer death rate in this group which thus accounted for 25 per cent of all deaths, indicates clearly that an excessive liability to cancer of the respiratory system persists for individuals after exposure to chromium has ceased for many years (Fig. 15). It is, therefore, important that SPANNAGEL succeeded in obtaining data on the cause of death in only a part of the former employees of several German chromate plants which had stopped operation many years prior to the time of this investigation. HUTNER and CAST were confronted with similar difficulties in their studies on English chromate producers, since they were unable to ascertain the fate of 217 of 333 former workers of the 723 chromate workers still alive. GAFFNER *et al.* also emphasized the fact that the number of recorded deaths from respiratory cancer among American chromate producers recorded in their survey was minimal for the following reasons:

1. Deaths of employees who were not members of a sick benefit association were not included.
2. Persons who worked in chromate but left the industry prior to their terminal illness were not included.
3. Members who died over a year after onset of disability due to cancer were not included.

4. Several members who had a clinical course consistent with the presence of cancer of the respiratory tract were not included because cancer was not recorded on their death certificates.

5. Some members whose deaths were not recorded as cancer died without a complete medical examination or biopsy.

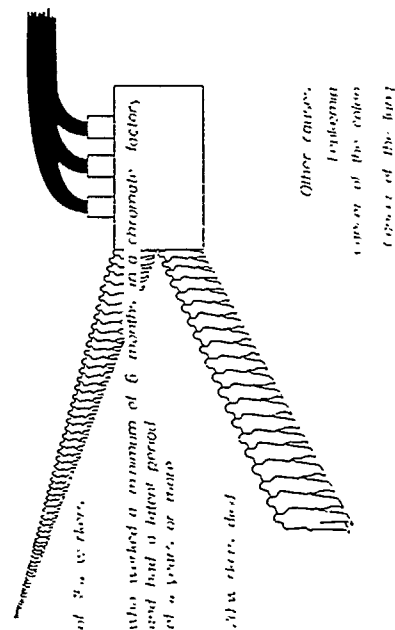


Fig. 15. Environmental cancer

Since work in chromates appears to be objectionable in many respects there is a rather large labor turnover in such plants. Impresciti estimated an annual labor turnover of from 40 to 50% in a chromate plant employing about 400 workers. GARATTE noted that 38.6 per cent of all workers (37.5 for whites, 41.8 for colored) had worked less than 5 years in chromate operations. In two plants surveyed by them less than 7% of the white workers had been employed there for 20 years or longer. Also BARTER stated that no information on a delayed occurrence of lung cancer was available in her study of the chromate plant in Baltimore for the many workers who had left over a 15 to 20-year period. The deficiencies in the epidemiologic data produced thereby are bound to lower possibly considerably the lung cancer attack rates calculated from the available information because of the omission of the undetermined number of lung cancers which doubtlessly developed among former chromate workers whose cause of death remained obscure.

Because of these limitations in the available epidemiologic data, the various statements made concerning the incidence and frequency of chrome cancers of the respiratory organs represent at best well considered approximations or are mere educated guesses. All of them are nevertheless definitely indicative of the existence of highly excessive lung cancer rates among chromate producers and chrome pigment makers (Table 42). GARATTE stated that up to 40 per cent of the employees in chromate plants in Germany developed lung cancers. Estimating that among approximately 2,000 chromate workers who had been employed in German plants between 1880 and 1948, a minimum of 86 lung cancers had occurred, SPANNAGEL noted a morbidity ratio of 43:1 for chromate workers. MACARTHUR and GRIGORIUS found that 21.8 per cent of all deaths among American chromate workers were attributable

to occupational factors and that the ratio was 16 times the standard one of 1.3%. The range of the ratio for different plants was from 1.3 times to 31 times. The crude death rates from lung cancer for members of this occupational group stood at from 18 to 50-fold the standard rate and averaged 25-fold. MANCUSO and HOFMEYER estimated a lung cancer rate among American chromate workers to be about 15 times the normal rate, while BARTER noted that the lung cancer rate in chromate workers was 28 times the standard of the employed male population of Baltimore 18 years and older (34 times for whites, 18 times for colored). GARATTE *et al.* concluded from the results of their survey that nearly 29 times as many deaths as were expected were found among American chromate workers.

Table 42. Comparative Frequency Rates of Lung Cancer in Chromate Workers of U.S.A., Germany and England

Country	Frequency		Lung Cancer per 100,000	
	Expected	Observed	Chromate Workers	General Population
United States	1.9	31.9	470.8	16.7
Germany	1	43		
England	1.3	7		

They noted, moreover, that a racial comparison of respiratory cancer deaths showed that the ratio of actual to expected number was 40 for whites and 80 for colored. It should not be concluded from this observation that colored individuals possess a racially conditioned higher susceptibility to lung cancer. The difference in lung cancer rates noted by GARATTE *et al.* for whites and colored individuals employed in chromate operations is attributable to the fact that colored workers are usually employed in the dirtier operations and, therefore, sustain the more severe exposure to the carcinogenic agent. The validity of this reasoning is supported by the observations made by GARATTE *et al.* on the time of first occurrence and on the frequency of nasal septum perforations among members of the two racial groups (Table 43).

Table 43. Time of Appearance and Frequency of Nasal Septum Perforations in White and Colored Chromate Producers in U.S.A. (GARATTE *et al.*)

Time of Employment	Number of Workers	Percentage of Perforated Nasal Septa	
		All Workers	Colored
0-6 months	41	2.4	0
6 months to 3 years	117	39.3	31.5
3-10 years	370	55.4	44.3
10 years and over	369	69.6	61.0
Total	897	56.7	49.3
			76.6

Most investigators agreed that the excessive liability to cancer among chromate workers was restricted to cancers of the lung (MACARTHUR and GRIGORIUS; BUNSTRUP and CAST; GARATTE *et al.*) and did not extend to other organs exposed to chromates (skin, alimentary tract), although chromate workers exhibit frequently inflammatory

and ulcerative reactions in these organ systems. TITUS, on the other hand, has suggested that an occupational cancer hazard in chromate workers might extend to the alimentary system. So far only the occurrence of ulcerative lesions in the stomach and intestine has been reported (BUNN; RIND; MOSINGER and FROSTING). There is no evidence in support of the view that the development of a cancer of the lung in chromate workers lowers their liability to cancers in any other organ (GALEHR; BARTER; MACHUL and GRIGORIUS).

c) Special Aspects

The exposure time preceding the development of respiratory cancers in chromate workers exhibited, according to the various assessments, wide variations depending apparently upon differences in exposure conditions as well as upon fluctuations in the individual susceptibility. It was noted, however, that the exposure time of chrome pigment workers developing lung cancer was distinctly shorter than that of the chromate producers (GROSS) (Table 44). This phenomenon may perhaps be due to the

Table 44. Length of Latent Periods for Cancers of the Lung in Chromate Workers

Years	3	5	6	10	11	20	21	30	31	40	41 and over	Total	Average length
All cases	2	25	79	15	17	8	176	24 years					
Pigment workers	1	1	1	1	1	7	15 years						
U.S.A. workers	1	11	23	11	1	2	49	17 years					

fact that the yellow pigments mainly involved in this respect, particularly zinc chromate, possess higher carcinogenic potency than the chromium compounds encountered in chromate operations (HUTNER and PAVONI).

The entire range of exposure times noted in the 131 cases for which data were available extended from 2 to 47 years with 60% of them falling in the 6- to 20-year range. The existence of marked variations in the length of effective exposure periods is in accord with similar observations recorded for other occupational cancers. Most of the long exposure periods noted are most likely merely incidental because they are identical with the latent periods observed in these cases. Whenever relatively short exposure periods were followed by a longer lag period, it may be assumed that the intensity of exposure may have been quite severe, or the inhaled material was rather water insoluble, therefore was retained in the lungs over long periods of time and was gradually released from its intrapulmonary depots. It is also possible that in a particular exposed individual some special exogenous or constitutional additional factor of local or systemic nature was operative which favored and accentuated the action of the inhaled carcinogen. It is, for instance, conceivable that the irritative respiratory effect of inhaled acid fumes in German acid workers developing chrome cancers of the lung acted in such a capacity (neighborhood cases), since it is likely that the concentration of the carcinogenic air pollutants must have been rather low in the atmosphere of the acid operations.

A similar connotation have the distinct fluctuations in the length of the latent period which varied in the individual cases from a minimum of three (3) years to a maximum of 58 years. About 70 per cent of all cases had a latent period extending from 11 to 30 years.

The relative length of the latent period in the individual cases may be taken as reflecting the intensity of exposure, the carcinogenic potency of the particular chromium compound or compounds to which the individual became exposed, and his reactivity as a host.

d) Histologic Types of Chrome Cancers of the Lung

While four (4) nasal sinus carcinomas observed in chromate workers were all squamous cell carcinomas, those affecting the lung exhibited a degree of variation which roughly corresponded with that seen in "spontaneous" cancers of this organ. This observation offers a good illustration of the fact that there does not exist any definite relationship between any particular carcinogenic agent and any specific histologic type of cancer (Table 45).

Table 45. Histologic Types of Pulmonary Carcinomas in Chromate Workers

Types	Squamous Cell Carcinomas	Round, Anaplastic and Undifferentiated Cell Carcinomas	Adenocarcinomas	Total
No. of cases	46	66	11	123

In two American cases, two different types of carcinomas coexisted in the lungs. Since one of these double cancers affected the pleura (BARTER) and was of an undifferentiated type, the possibility must be considered that it might have been a meso-

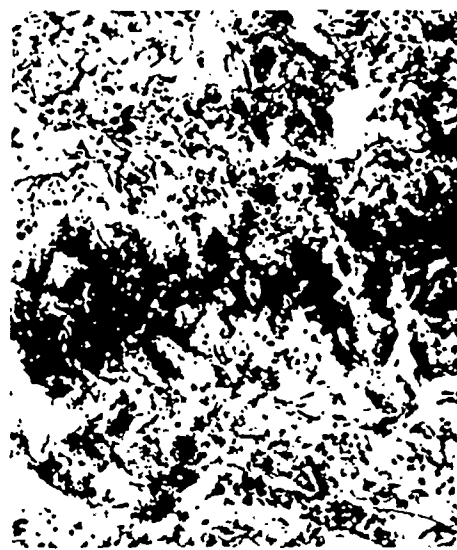


Fig. 16. Massive deposits of black chromate ore dust in the lung of a chromate producer

thelioma of the pleura. There is no sound scientific reason for assuming that the adenocarcinomas are not of occupational origin but result from embryonic malformations (ALWIS). A study of the various histologic intrapulmonary changes preceding the development of lung cancers elicited in man and experimental animals show

clearly the multiple potentials of the lung tissue accounting for the development of cancers of the different types which were observed sometimes in the same lung.

Chromate producers exhibit often the manifestations of a chronic sinusitis, chronic ulcerative rhinitis, chronic laryngitis, chronic tracheitis and chronic bronchitis, which



Fig. 17. Numerous fine reflecting particles in the perivascular tissue of the lung of a chromate worker located within a black pigmentary deposit seen under polarized light



Fig. 18. Large intrabronchial polyp with focal squamous cell metaplasia

at times may assume an ulcerative character (SPANNAGEL, MACHLE and GRIGORIUS; MASCUSO). The lungs of chromate producers who are exposed to the inhalation of chromite ore dust show at autopsy often varying degrees of black spotting. These pigmentary deposits which resemble in appearance anthracotic lesions, however, do



Fig. 19. Fibrous desmoplastic pneumonitis with adenocarcinoma transformations of bronchiole in a chromate producer

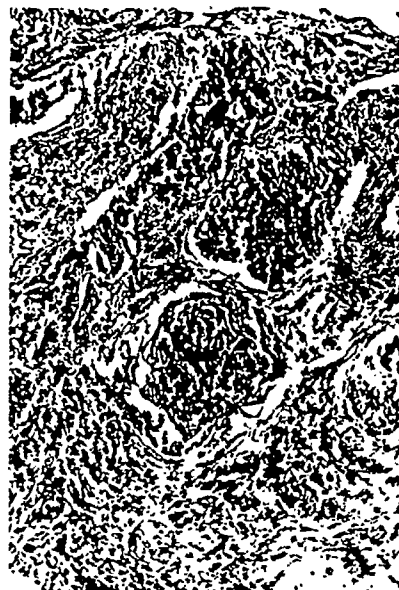


Fig. 20. Minute, small cell carcinoma in the lung of this worker

not disappear, as anthracotic deposits do, in incinerated sections because of their mineral character. In polarized light they show numerous, small, white reflecting crystalline granules (Figs. 16, 17). The bronchial lumens contain often purulent material, while the bronchial mucosa may form polypous formations covered by a hyperplastic stratified columnar epithelium with localized squamous cell metaplasias (Fig.

18). The retention of toxic chromium-containing dust may give rise to the development of some degree of interstitial fibrosis (chromiosis) (MARGISO and HUPPER; RINGS; LITTEBER; BAADER; LUKANIN; LITTEBER, NICHOLSON and KLUFT; ANDRIEVSAYA and MISLAVSKAYA). In severe conditions of pulmonary chemotoxic-

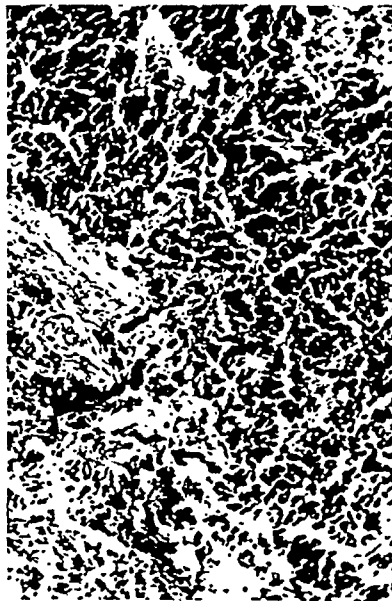


Fig. 21. Small round cell carcinoma of the lung in a chromate worker with black pigment in the fibrous tissue surrounding the tumor mass.

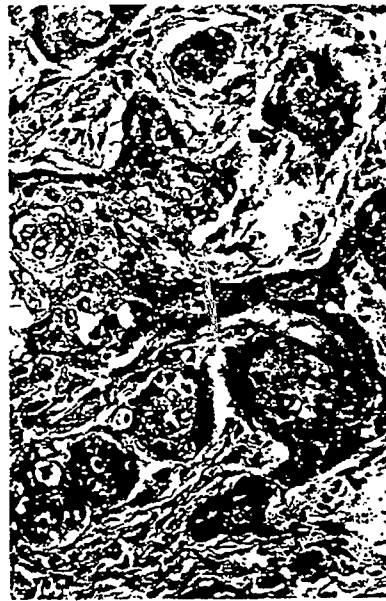


Fig. 22. Squamous cell carcinoma of the lung in a chromate worker.

cosis, there occurs a multiepisic transformation of the bronchioli. Such lesions at times may be complicated by multifocal proliferations of small hyperchromatic bronchiolar epithelial cells producing the impression of miniature carcinomas (Figs. 19 and 20). Such precancerous lesions of glandular, small cellular and squamous cell nature evidently form the basis for the various histologic types of carcinomas subsequently developing (Figs. 21 and 22) (HUTNIK). The irrelevancy of the nature of a pul-

monary carcinogen in such matters was clearly shown in a series of experiments in which rats were intrapleurally implanted with various chromium-containing materials (chromite ore roast, chromic chromate, calcium chromate, etc.). The bronchial mucosa responded to the carcinogenic stimulus of chromium with the development of cancers of different histologic types (HUTNIK; HUEBER and PAYNE). In some ani-

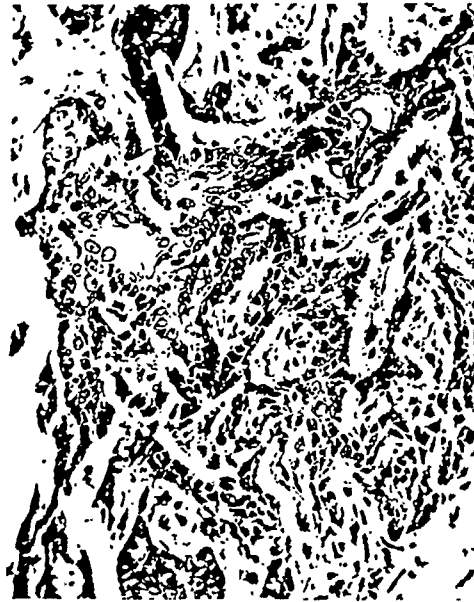


Fig. 23. Squamous cell carcinoma of the lung of a rat following an intrapleural deposition of chromic chromate.

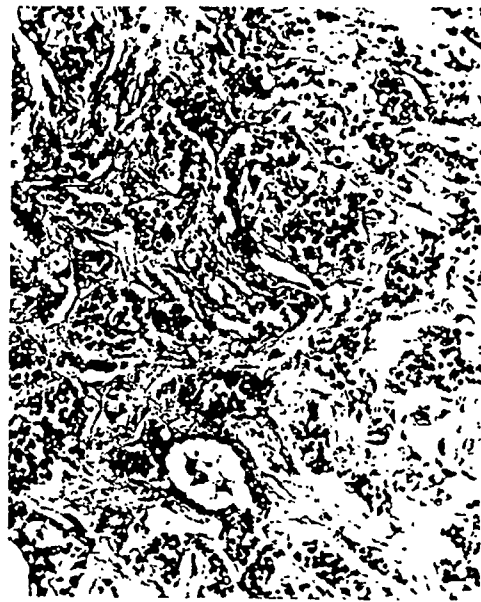


Fig. 24. Adenocarcinoma of the lung of the white rat.

mals several cancers of two or three different types coexisted in the same lung (squamous cell carcinoma, adenocarcinoma and sarcoma) (figs. 23, 24, 25) together with corresponding precancerous lesions.



Fig. 25. Ovarian, sarcoma of the lung of the same rat

c) Clinical Aspects

Chromic cancers of the lung in contrast to asbestos cancers, do not exhibit in their location any special preference to any particular part of the lung. Of 93 cases for which some information was available on this point, forty (40) were situated in the upper lobes, 33 in lower lobes and 20 in the region of the hilum.

None of the various symptomatic manifestations observed in chromate workers (perforated nasal septum, chronic bronchitis, unilateral enlarged density of the hilar region and thickening of the peribronchiolar structure in x-ray pictures of the lungs, pneumoconiosis, etc.) can be considered as a precancerous lesion characteristic for chrome cancer of the lung. These and other symptoms (chrome holes and chronic eczema of the skin, gastric ulcers, chronic ulcerative colitis and chronic sinusitis) represent merely stigmata of an occupational exposure to irritative chromium compounds. The survival time of the majority of chrome cancer patients did not exceed one year after the discovery of the tumor (SPANNAGEL; GALATIER *et al.*; BAETJER), although recently a few cases (3 out of 7) have survived a pneumonectomy for more than six (6) postoperative years (FISHLER).

f) Chromium Content of Tissues, Blood and Urine

Since chromium has become an almost ubiquitous element through its widespread use in modern industry and industrial products and the contamination of air, water, and soil with chromium and its subsequent introduction into the human food supply,

the blood, urine and tissues of man often contain small amounts of chromium. Considerable quantities of this metal, on the other hand, have been demonstrated in the urine, blood and tissues of chromate producers and other industrial workers processing and using chromium metal and chromium compounds (Tables 46 and 47)

Table 46. Concentration of Chromium in Body Tissues With and Without Known Exposures to Chromium (A. BAETJER)

Tissue	Range of Chromium Concentrations, Reported in Tissues from Chromium Workers	
	Micrograms/100 g. Wet Tissue	Range of Chromium Concentrations, Reported in Tissues from Chromium Workers
Lungs	0 - 33	130 - 9,887
Lung tumors	0 - 33	0 - 1,658
Metastatic tumors	0 - 33	2 - 100
Tracheobronchial lymph nodes	0 - 1	12 - 7,590
Bronchus	0 - 1	95 - 386
Trachea	0 - 1	0 - 32
Nasal septum	0 - 33	287
Larynx	0 - 33	21
Kidney	0 - 9.6	0 - 211
Liver	1 - 11	0 - 159
Spleen	0 - 98	0 - 91
Abdominal lymph nodes	1 - 4	4 - 80
Stomach	0 - 5	4 - 11
Intestines	10	4 - 5
Bladder	0 - 33	3 - 226
Heart	0 - 8	0 - 20
Muscle	0 - 8	0 - 19
Pancreas	21	8 - 36
Thyroid	43	24 - 53
Adrenal	0 - 41	5 - 76
Brain	0 - 4	0 - 5
Bone	5	0 - 292
Cartilage	0 - 4	6
Hair	0 - 4	1
Skin	0 - 4	31
Aorta	0 - 4	5

(BAETJER; MANCUSO and HURTER; SPANNAGEL; GAFAHER *et al.* and others) with the analytical methods developed by SPANNAGEL; DRONE and ANDERS; CAHMAN and BISH. It is of interest that in chromate producers the by far largest amounts of chromium were found in the normal parts of carcinomatous lungs especially their hilar regions, and that the carcinomatous portions contained distinctly smaller concentrations. This is explainable by the fact that chromium containing pollutants cannot be inhaled and be deposited in the newly formed carcinomatous tissue. Chromium can practically get into such parts only when the cancer invades the structures of the lung already containing chromium deposits.

SPANNAGEL, commenting on the normally occurring excretion of chromium by the healthy human organism with the urine stated that an increase of the blood chromium level above 20 gamma per 100 cc. should arouse the suspicion of the existence of a bronchial cancer in the individual studied. Since the observations of MANCUSO on exposed, temporarily unexposed and former chromate workers have revealed the

occurrence of marked variations in the chromium blood level and a retention of an excessive level many months after cessation of exposure, it is at present perhaps wiser to consider such observations mainly as evidence of a marked and prolonged exposure to chromium containing air pollutants.

Table 47. *Concentration of Chromium in Blood and Urine as Reported in the Literature* (A. BAI FIER)

Investigator	Degree of Exposure to Chromium	Blood Concentration of Chromium in Micrograms/100 g of Blood	Urine Concentration of Chromium in Micrograms/Liter of Urine
GRAY	No exposure	r.h.c. 20.0 plasma 14	
GUSTAFSSON	No exposure	3.5 12.0	
SPANGLER	No exposure		0 16.3
	Occasional exposure		Ave 18.2 (Max 76.8)
	Chromate workers	8 580	Ave 78.2 (Range 0 to 832)
U.S.P.H.S.	White chromate workers	4.0	43.0
	Colored chromate workers	6.0	71.0
AMMONS	No exposure	0 2.02 trace to 32.7	None
	Chromate workers		0 10.0
MAYER	Slight exposure	0.5 17.0	0 380.0
	Chromate workers during exposure		
	74 days after end of exposure	1.0 16.4	8.0 51.0
	66 days after reemployment	2.0 13.5	
	Former chromate workers	0.9 10.0	0 20.0
	Chromate planters		1.5 20.0
UNION and MAYER	Chromate workers	Blood clot 0.6 9.1 Serum 0 0.8 C.B. 0.3 4.7	
	Chromate workers 74 days after cessation of exposure	Dichlorinated serum 0.3 4.4 Fluorin 0.3 4.4	
PASCALI et al.	Chromate plating industry	C.U.R. Plasma 3.7 4.6 2.6 3.9	(0 2,880 micrograms/day)
	No exposure		
BONNET et al.	Chromate worker during exposure	14.0 1.7	51.2
	Chromate worker 5 years after low exposure	3.0 0	3.6
	Chromate worker 23 years after exposure	5.4 2.0	0
	Chromate worker	2.2 0.6	0

b) Atmospheric Neighborhood Pollution

In view of the observation of several intraplant neighborhood cases of chrome cancers of the lung in a German operation attesting to the high carcinogenic potency of certain chromium compounds, it is of importance to note that there exists a car-

cinogenically perhaps not insignificant pollution of the air in the neighborhood of chromate producing plants and of other chromium using and processing establishments, which involves in part larger urban areas (Bourne and Russum; BATTI, KAPLAN and COUCHMAN; TAYLOR and WARREN) (Fig. 26). According to the observations of BATTI *et al.* the concentrations of chromium in the air of Baltimore fluctuated with the activity of a chromate producing plant located in the city. They were highest in the afternoon and lowest in the 2 hours before major operations began in

Table 48. *Concentrations of Chromium in the Urban Air Near Chromate Producing Plants*

Author	Concentration in $\mu\text{g}/\text{m}^3$	Distance from Plant
Bourne and Russum	0.12 0.06 0.001	100 ft 2,000 ft 10,000 ft
BATTI et al.	0.0001 minimum 0.018 maximum	700 ft

Table 49. *Chromium Content of the Atmosphere in Selected American Cities 1953-1957* Sanitary Engineering Center, USPHS

Cities	Chromium in micrograms per cubic meter of Air	
	Maximal Value	Minimal Value
Baltimore	0.290	0.023
Pittsburgh, Louisville, East Chicago, Denver	0.100	0.200
Average American City	0.0002	0.010

Table 50. *Concentrations of Chromium in the Air of Different Areas of Chromate Producing Plants*

Country	Author	Operations	Cr in $\mu\text{g}/\text{m}^3$
France	SPANGLER	Chromite Ore Crusher Sodium Chromate Borelling	8.0 0.16
Germany		Chromite Ore Crusher Furnace	0.44 0.60 0.35
U.S.A.	MAYER and COUCHMAN	Kids and Mills Packing	0.01 2.8 2.0 21.0
	GRATZ et al.	General Area Mill Room Potash Production	0.003 1.0 1.07 0.17

the plant each morning. Whether such pollutions may give rise to the creation of industry-related environmental cancer hazards for individuals working and living in the dust and fume zones of such establishments is at present unknown and remains to be determined.

The actual existence and the potential degree of such an environmental industry-related lung cancer hazard depends not only on the absolute amounts of chromium polluting the general atmosphere in the vicinity of such plants, but also in the chemical type and biologic availability of the chromium pollutants (MANCUSO and

Table 31. Comparison of Average Chromium Concentrations of Chromium in British and American Chromium Factories (M. Buckell and D. G. Harvey)

Phase in Process	General Description	Sample Points	British (concentrations in mg./c.c. m.)		American (concentrations in mg./c.c. m.)	
			Average (c.c.)	Range	Average (c.c.)	Range
1	Pre-reaction phases: mainly insoluble chromium (chromite) (lime and ash)	Near mixers only	2-14 (3)	3-27	0-005 (3)	0-01
2	Reaction phase: Discharge end of furnace; by frit hopper during discharge by wash tanks during emptying of frit		0-17 (9)	0-660	0-029 (10)	0-146
3	Reaction phase: continued; extraction (filtering)	By wash tanks before, during and after flooding; filtering out of extracted frit; running off monochromate liquor	0-057 (6)	0-214	0-009	4-13
4	Formation of dichromate (liquor)	By acidifier tanks	0-014 (7)	0-094	0-056 (8)	0-175
				0-0002		0-005

HUEPER; GARNER *et al.*; HUEPER and PAYNE) which determine their carcinogenic reactivity. The following data on the concentration of chromium found in the urban air near such plants and on the amounts and types of chromium present within various areas of chromate plants may help to place this problem into proper perspective. Consideration must here be given to the fact that the minimal carcinogenically effective concentration of chromium in the air is unknown (BAETJER) (Tables 48 and 49).

h) Atmospheric Intraplant Pollution

The following two tables (Tables 50, 51) present the atmospheric conditions prevailing in British and American chromate producing plants in greater detail and illustrate at the same time the carcinogenically important variations in the types of chromium compounds present in different parts and with different activities of these plants (BUCKELL and HARVEY; GARNER *et al.*). The threshold limit value for chromic acid and chromates (as CrO_3) for 1961 has been set at 0.1 mg./cub. m. of air (BALL *et al.*). While this value may represent a concentration at which under ordinary circumstances of occupational exposure, toxic health hazards are not encountered among the great mass of workers, they definitely do not constitute a measure by which industrial carcinogenic hazards can be determined, especially since it is well known that the carcinogenic dose of many chemicals is distinctly lower than their minimal toxic dose.

i) Chromate Carcinogenesis and Smoking Habits

At various occasions doubts have been voiced concerning the real causal role of chromium compounds in the production of cancers of the respiratory organs (LITTMAN; OLTU). OLTU in fact only recently alleged that cancers of the lung develop only in those chromate producers who smoke cigarettes and that the carcinogens present in cigarette smoke act specifically and synergistically on the cellular changes elicited in the bronchial mucosa by the irritative action of the inhaled chromium compounds. ALWENS in an early publication on the subject of chromate cancers of the lung pointed out that an abuse of tobacco could not be demonstrated in most of his patients. GARNER *et al.* recorded that 81.1% of the chromate workers with lung cancers and that 79.4% of the foundry workers used as controls had been smokers. These investigators noted, moreover, that the white chromate workers smoked more heavily than the colored ones and that, on the other hand, the lung cancer liability of the colored workers was considerably higher than that of the white workers. In the brief report of FISHER, mention is made of the fact that among the 38 chromate producers with lung cancer, two (2) were non-smokers, three (3) smoked pipe and/or cigar, three (3) smoked less than one pack of cigarettes per day, nineteen (19) smoked between 1 and 1½ packs per day and five (5) smoked two (2) packs.

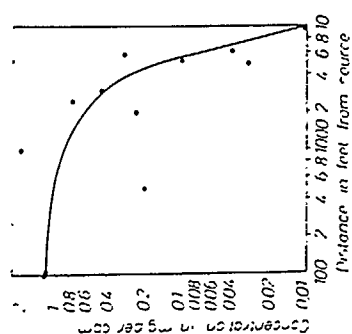


Fig. 26. Chromium content of the air in the vicinity of a chromate plant (Buckell and Harvey)

This evidence also does not support the dogmatic statement of O'LELL concerning an exclusive role of cigarette smoking as a cause of lung cancer in chromate workers. The most valid analysis on this matter has been provided by BIRSKOP and CAST: who came to the following conclusion: "Thus even if the smoking habits of the chromate workers were so changed from those of the general population that all of them fell into the category of heavy smokers, the increase of carcinoma of the lung that then would be expected would not satisfactorily account for the increase which we have observed. In fact, we have no reason to believe that their smoking habits are different from those of the general population, and an explanation based on a hypothesis of altered smoking habits would need to be supported by satisfactory evidence of such alteration before it could be seriously considered."

k) Experimental Production of Chrome Cancers

Attempts of GROSS; SHIMKIN and LITTEK; BARTJER *et al.*; SUTHER and BARTJER; and HURPER to produce cancers in rabbits, guinea pigs, rats and mice by the inhalation of powdered chromite ore, chromite ore roast, yellow chromium pigments (mixture of lead chromate, barium chromate and zinc chromate) and green chromium oxide



Fig. 27. Ulcerative squamous cell carcinoma of the snout of a rat exposed to chromite ore roast dust

yielded negative results except that rats exposed to chromite ore and with chromite ore roast developed ulcerative squamous cell carcinomas of the skin of the snout (HURPER and PAYNE) (Fig. 27).

While an intratracheal introduction of basic potassium zinc chromate and of barium chromate into mice proved likewise unsuccessful in eliciting bronchial carcinomas (BARTJER *et al.*), HURPER and PAYNE using the same procedure on rats which

were insufflated with suspensions of strontium chromate, calcium chromate and zinc chromate in gelatin solution, obtained pulmonary sarcomas in two rats out of 79 intratracheally injected with calcium chromate and one (1) rat out of 49 given by this route, strontium chromate. The total tumor yield was nevertheless disappointing in view of the high carcinogenic potency of the chromates employed when introduced into rats by the intrapleural and intramuscular routes (Table 52). PAYNE subsequently

Table 52. Cancerous Responses at the Sites of Implantation of Several Chromium Compounds in the Tibia Muscle and Pleural Cavity of Rats

Compound	Route as Rats	Number of Cancers at Site	Percent Cancer Yield	Minimal Latent Period
Chromite	IM	30	86	7
Chromate	IM	34	97	7
Calcium	IM	10	29	7
Chromite	IM	28	80	7
Sintered Calcium	IM	13	37	6
Chromate	IM	21	60	6
Sr chromate	IM	16	46	6
Chromite	IM	17	50	6
Barium	IM	0	0	
Chromate	IM	2	6	14
Lead	IM	3	9	16
Chromate	IM	3	9	16
Sodium Dichromate	IM	0	0	
Chromite Roast	IM	1	3	19
Residue	IM	8	23	12
Zinc	IM	16	45	5
Yellow	IM	22	65	6
Chromite	IM	1	3	16
Acetate	IM	1	3	
Silicop	IM	0	0	
Fat	IM	0	0	

demonstrated that also mice subcutaneously injected with calcium chromate and sintered calcium chromate developed cancers, after HURPER had shown that chromite roast intrapleurally introduced into rats elicited sarcomas and carcinomas of the lungs and of the mediastinal tissues.

A contradictory outcome was recorded when powdered metallic chromium was implanted into the femoral cavity of rats, dogs and rabbits, by HURPER and by VOLLMANN and by SCHUSZ. Whereas rats kept for two (2) years and dogs observed for eight (8) years following such procedures did not develop any tumors at the site of metallic deposits, SCHUSZ observed in three (3) out of twenty (20) rabbits with intravenous chromium deposits in the femur, the development of sarcomas after a minimal latent period of 4 years. Since these tumors, however, did not involve the sites of the implants but were found remote from them (2 in the chest, one (1) in the bony pelvis), it is uncertain whether they actually represent reaction products to chromium.

The histologic examination of the cancers observed in the thighs and chests of rats and mice receiving implants of the various chromates demonstrated that chromium is a carcinogenic agent capable of eliciting cancers from various tissues and of different

types (Fig. 28). Sarcomas apparently derived from fibrous tissue, bony tissue, muscle tissue and myxomatous tissue were observed, as were carcinomas of squamous cell



Fig. 28. Modified squamous cell carcinoma in the lung of a rat intrapleurally implanted with calcium chromate.

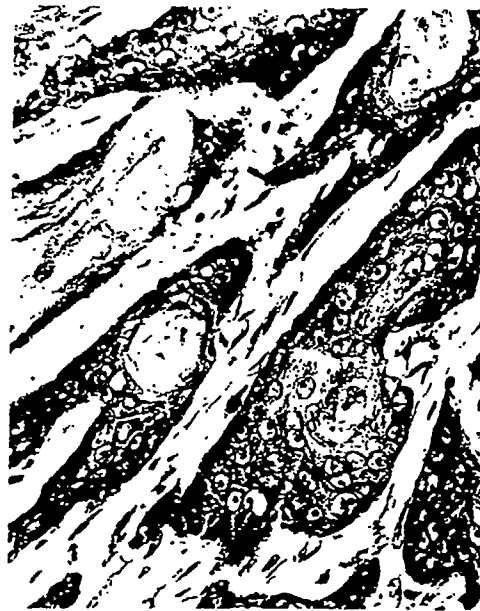


Fig. 29. Combined squamous cell carcinoma of the lung in a rat with an intrapleural implant of calcium chromate.

type, round-cell type and glandular type involving the lung often combined with various adenocystic and metaplastic bronchiolar lesions and at times associated with

sarcomatous tumors occurring in the same lung or in the form of carcinosarcomas, such as those occasionally seen also in man (Petry *et al.*) (Figs. 28, 29, 30, 31, 32, 33).



Fig. 30. Adenocarcinoma with squamous cell transformations in the lung of a rat given lead chromate intrapleurally.



Fig. 31. Adenocarcinoma of the lung in a rat after intrapleural administration of strontium chromate.

It is noteworthy, moreover, that the lungs exposed to these chromium compounds and thus involved, showed distinct chronic inflammatory and fibrosing changes which

were similar to those reported to occur in rats following a respiratory introduction of chromic oxide and zinc chromate (MAMMANN and PHILIP, BISTE *et al.*).



Fig. 32. Carcinosarcoma of the lung in a rat following intrapleural deposition of chromic chromate



Fig. 33. Osteogenic sarcoma with squamous cell next to the lung of a rat implanted intrapleurally with chromic chromate

1) Causative Mechanism of Chromium Carcinogenesis

As long as the exact carcinogenic role of chromium in the production of cancers of the respiratory organs of chromate producers and similarly exposed workers re-

mained uncertain, various concepts were advanced concerning the causal agent active in their production, i.e., whether these cancers were elicited by trivalent or hexavalent chromium compounds, by monochromates or dichromates, by water soluble or insoluble derivatives, by chromite ore, intermediary roasting products or chromium metal, or by chromium in all these forms under proper conditions of exposure (GROSS; BALTIJR; MACHLE and GREGORIUS; GAFAR *et al.*; MANCUSO and HUIPER; HUIPER and PAYNE). Even the possibility was considered that chromium in any form was causally not related to the development of the lung cancers, but was attributable to respiratory contact with other constituents of the chromite ore, such as iron and vanadium, or to exposure to incomplete combustion products of the fuel (coal, fuel oil, gas) extensively used in the roasting process of the ore, and representing the cause of lung cancer occurring among workers inhaling such products for occupational reasons (coke oven workers, gashouse workers).

The two last mentioned possibilities could be dismissed as relevant for the following reasons. Cancer of the lung had been observed among chromium pigment makers who had no respiratory contact with incomplete combustion products of carbonaceous fuel. Investigations of CAMMANN, moreover, had shown that 3,4-benzpyrene could not be demonstrated in chromite ore roast, where it would be likely to occur as an impurity, if this aromatic polycyclic hydrocarbon would occur or would be stable under the condition present in the roasters. This aspect was subsequently re-investigated by PAYNE who found that the addition of hexavalent chromate phosphate and of chromate roast residue to 3,4-benzpyrene before this chemical was subcutaneously injected into mice, reduced because of their oxidative action on 3,4-benzpyrene, its carcinogenic potency as evidenced by a decrease in the tumor yield and a lengthening of the latent period.

As a by-product of this investigation, PAYNE moreover, demonstrated that the leaded roast residue retains some carcinogenic potency for rats, since out of two series of 35 rats each, one implanted intrapleurally with the residue, the other implanted intramuscularly, three developed intrathoracic sarcomas and one (1) an intramuscular sarcoma, respectively. The pollution of the intrapleural and extrapleural air with roast residue, therefore, may create a cancer hazard for workers and residents of the dust zone.

The experimental observations of HUIPER and PAYNE, made on a series of hexavalent and trivalent chromium compounds showed definitely that chromium as such when present in a biologically available form accounts for the carcinogenic potency of chromium derivatives, and that the degree of biologic availability as reflected by their relative degree of water solubility determines the relative potency of a particular compound.

The various findings on the type of chromium compounds and the tissue reactions of degenerative, fibrosing, hyperplastic, metaplastic, precancerous and cancerous nature elicited by them indicate that chromium is capable of producing cancers of the lungs and other tissues without the intervention of any additional factor considered essential for preparing the tissues exposed to chromium compounds for their carcinogenic action as suggested by KUSENBER and NELSON. It appears also from the experimental evidence available that both trivalent and hexavalent chromium compounds possess carcinogenic properties contrary to the opinion of SPANNAGEL who held that trivalent chromium is noncarcinogenic because it cannot be oxidized in the

body into biologically active hexavalent chromium. The studies of HUIJER and GROGAN demonstrated that this concept is not correct inasmuch as trivalent chromium may operate as a depot chromium in the body which is gradually transformed into hexavalent chromium through the oxidative action of biologic processes. It thereby may become of distinct carcinogenic importance since it can exert a prolonged effect on the tissues in the vicinity of such depots. Such an action may extend long after an occupational exposure to chromium has ceased. The relative low carcinogenic effect of sodium chromate upon rats under experimental conditions may not adequately reflect its potency under occupational conditions inasmuch as occupational exposures may involve relatively smaller and, therefore, necronically little effective doses of sodium chromate. Under such circumstances of contact the carcinogenically important proliferative effect of chromium on tissues may dominate over its necrotizing one and thereby enable the development of a cancer, especially since the corrosive hexavalent chromium ion is reduced finally in the cells into the less active trivalent one (GROGAN; BAUTJER *et al.*).

Because chromium is an eminently allergenic substance giving frequently rise to the development of chromium dermatitis (cement workers, locomotive engineers (anticorrosive in water), metallurgical workers (antirusting agent in cutting oils), leather manufacturers (MORRIS), HUIJER suggested in 1942 as a part of the allergic theory of carcinogenesis that immunochemical processes related to the formation of chromium-protein complexes might play a significant role in the carcinogenic process initiated by chromium. Similar thoughts were advanced by SCHINZ and UHLINGER. Subsequent investigations carried out by GROGAN and OPPENHEIMER and by GROGAN in further pursuit of this concept demonstrated the *in vitro* formation of such complexes by both trivalent and hexavalent chromium compounds with egg albumin and human plasma proteins. BAUTJER, DAMRON and BUDACZ also showed that cationic as well as anionic chromium brought in contact with lung tissue is bound in such a way that it became insoluble in saline extractants, while CLARK found in *in vitro* experiments that both trivalent and hexavalent chromium compounds denature blood plasma albumin. It is likely that such complexes may possess antigenic properties, since ISHIKAWA succeeded in producing chromium specific antibodies in rabbits by the repeated intramuscular injection of potassium bichromate, potassium chromate, chrome alum and chromium carbonate (LOISELIER and SAUVAGE). Although EDMUNSON stated that chromate producers suffering from perforated nasal septa and chrome ulcers show negative patch tests for potassium bichromate, some preliminary experiments with antisera produced in rabbits by the repeated intra-abdominal injection of egg albumin-chromate complexes and tested on blood sera of chromate workers with and without lung cancers, gave results which suggested the presence of immunochemical reactions to chromium in some of the workers investigated (HUIJER and PAYNE). More comprehensive and exact studies of this type, therefore, may yield results important for diagnostic and therapeutic reasons.

m) Preventive Measures

The serious nature of the respiratory cancer hazards connected with the production, processing and industrial use of chromium compounds and possibly also of metallic chromium and its alloys provide sufficient reasons for the institution of adequate preventive and prophylactic technologic, industrial-hygienic and medical

measures for obtaining the maximal possible protection of the workers employed in such operations as well as of the general population working and residing in the vicinity of such plants.

n) Technologic Measures

The objective of all technologic measures is the maximal reduction of the dissemination of chromium containing dust, fumes and mist in the air of work rooms and of the plant area. Precautionary measures to this end should be applied not only within the buildings and to the production, processing and packaging procedures, but also to the handling of the waste products released into the atmosphere from the stacks and into public waters as well as to the storage and disposal of the finely powdered sludge. The entire operation starting with the unloading of the powdered chromite ore to the packaging of the finished goods should be carried on as far as possible in enclosed machinery preventing the escape of dust, fumes and mist into the plant environment. Whenever such measures are technologically not practical, operations with remaining environmental contaminations should be established in facilities separate from the protected operations, so that the contaminants can be restricted to such areas and can be controlled and removed by other procedures, such as exhaust ventilation, vacuum cleaning and washing of floors, walls and ceilings with water. Chromium-containing matter should be removed from effluents by proper scrubbers and electrostatic precipitators so as to prevent a carcinogenic contamination of the plant environment. The effectiveness of control measures should be ascertained at frequent intervals by determinations of the chromium content of the air. SPANNAGHIL stated that the presence of 0.1 mg. of chromium per dm. of air does not create any toxic hazards, although it still might cause a carcinogenic hazard. A chromium content of 2.5 mg. to 6.5 mg. of chromium/dm. causes, according to SPANNAGHIL, severe reactions in individuals working in such an atmosphere. Good housekeeping for preventing accumulation of spillage and dusts is an essential practice for safe plant operation.

It is advisable to incorporate the following principles and considerations in the control program and practices of chromate producing and processing plants.

- a) All operations should be carried on as far as possible in closed systems that can receive routine servicing, lubrication and cleaning without being opened.
- b) The filling of loading and condensation tanks should be controlled by automatic devices preventing any accidental overflow of chromate solutions.
- c) Cleaning of floors should be done by washing with water and not by sweeping with broom, so as to prevent the production of dust.
- d) All pipes, ducts, rafters, ledges, etc. where dust may accumulate should be grouped in such a way that they can be boxed in, since the dust accumulating under ordinary conditions of construction on these parts cannot be removed without liberating considerable amounts of dust into the air, and removing this dust is technically difficult to accomplish.
- e) Walls should be constructed of smooth, washable material, such as glazed brick, so that they can be cleaned easily with water.
- f) The spilling of chromates or chromate containing wastes on the floors should be kept at a minimum at all times. This material should be washed away immediately whenever such spillage has occurred.

e) The bagging of chromate should be performed under an exhaust hood which covers both the filling and weighing apparatus and the sewing arrangement so that the small cloud of dust issuing from the bag when it is compressed is removed into the exhaust system. It may be advisable, moreover, to have the bags rest on a movable common grate on which they slide without lifting and through which any spillage drops on a pan continuously rinsed with water.

h) Floors at various levels within large sheds should be constructed of iron grating or of smooth hard concrete or tile.

i) Especially hazardous operations should be separated from the rest of the operations by placing them in special compartments or even separate buildings.

j) All precautionary measures should be, as far as possible, of technical and mechanical nature, since workers do not seem to be inclined to use individual safety devices. Good housekeeping within the plant and safe disposal of hazardous wastes together with adequate engineering of the production machinery are the keystones to effective control of the cancer hazard.

Workers employed in operations in which a certain pollution of the air and cutaneous and ingestive contact remains unavoidable should be provided with adequate protective devices, such as proper work clothes frequently cleaned, gauntlets, respirators, goggles, etc. which must be inspected for defects and operation at frequent intervals. Since a complete removal of all potential and actual cancer hazards is difficult if not impossible in such operations, only workers at least 35 years of age should be employed there. Through preemployment examinations, all applicants with a history of respiratory diseases, especially chronic bronchitis, chronic sinusitis, tuberculosis, hay fever, etc., gastrointestinal disturbances, liver and kidney ailments and chain smokers should be excluded.

f) Medical Prophylactic Measures

Workers should be kept under close medical surveillance. The following measures are indicated in carrying out such a policy.

1. Periodic x-ray examination in intervals of 4 months for all workers exposed including foremen and supervisors, i.e., of all persons entering hazardous operations routinely or frequently during the course of their occupational activities. Yard workers, repairmen, truckers, clerks working in offices, laboratory personnel and medical dispensary employees, exposed to chromate dust from adjacent operations, also should undergo these examinations.
2. Whenever clinical evidence suggests the presence of a bronchogenic tumor, bronchoscopy should be performed for obtaining a biopsy and, if possible, a sample of bronchial secretion should be collected for cytologic study for the presence of tumor cells and for spectroscopic examination for its chromate content (qualitative and quantitative).
3. In all cases with chronic bronchial "irritation" the sputum should be examined repeatedly for cancer cells with the Papanicolaou method.
4. It may be advisable to check on the presence and degree of exposure to chromates by performing periodic chemical or spectroscopic analyses of the urine and blood of workers employed there for presence and amounts of chromates, as well as cytologic sputum examinations.

Records should be kept over a period of decades on the operating conditions of such plants, on the results and methods of examinations of air and water contamination, on accident insurance and compensation commission data for future reference and evidence.

For prophylactic and therapeutic purposes an attempt should be made of removing chromium stored in the tissues from the body. Whether the use of chelating agents, such as edathamine, may prove useful in this respect remains to be seen (MALOFF; HAYTM).

Cancers of the lung, larynx, nasal cavity and paranasal sinuses occurring in chromate producing and processing workers should be considered as results of occupational exposures and should be considered compensable occupational diseases (MAGR; WORTH and SCHULTZ; HOSCHKE). It is of distinct public interest if such cancers, whenever they are suspected or recognized as being due to occupational exposures to chromium and chromium compounds, are made notifiable to governmental health and labor authorities. Such regulations when adequately enforced would provide the proper factual basis for correcting undesirable and harmful plant practices, for establishing sources of preventable environmental contaminations with a potent carcinogenic agent and for instituting adequate precautionary and preventive measures, on employment and medical histories of workers including former and retired workers, whenever needed. The system of obligatory notification of chromium cancers could, moreover, be employed for activating proper compensation procedures by compensation boards whenever indicated, for obtaining proper economic protection for victims of occupational chrome cancers.

4. Nickel

a) Technological Aspects

Nickel and nickel compounds are relative newcomers among the metals used in the human economy. It was first isolated as late as the year 1751. The beginning of an industrial production of nickel dates back as little as about 150 years ago. The bulk of the present day nickel ore used for numerous metallurgical and chemical purposes is mined in Sudbury, Ontario, Canada. Smaller amounts are obtained in the U.S.S.R., Cuba, New Caledonia and Norway (DAVIS). Smelting of nickel ores is carried on in many other countries such as the U.S.A., England and Germany, and often entails in the refining process the production of nickel carbonyl (Mond process). Nickel metal is extensively employed in nickel-plating manufacture of stainless steel and Monel metal, in the production of storage batteries, for metal-spraying operations, for submicron nickel powder production and use, and in the production of various alloys. Nickel carbonyl is used in the manufacture of acrylic resins as a carbon monoxide transfer agent, and as a catalyst in various chemical industrial processes, such as the cracking of bitumen and hydrogenation processes of animal and vegetable oil (INTERNATIONAL LABOUR OFFICE; INTERNATIONAL NICKEL COMPANY; ABRAM; MILLER *et al.*; SAPPINGTON). Nickel compounds are employed as pigments in inks, enamels, glazes and paints. The total world production of nickel stood in 1950 at about 150,000 metric tons. An organic nickel compound has recently been introduced as an antiknock agent and is used as such as an additive to gasoline.

10. Petroleum — Mineral Oil — Wax — Asphalt — Petroleum Carbon — Carbon Black — Methylated Naphthalene — Combustion Products — Shale Oil and Derivatives

a) Technological Aspects

Mineral oils and related products, such as waxes, tars, asphalts, and pitches, can be obtained by the distillation and fractionation of various natural raw products, such as petroleum, oil shale, bituminous coal, natural asphalts, and hydrogenated coal (HUEFNER; GOLDBLATT and GOLDBLATT; PAGE *et al.*; LJUNSKY). Since these raw products vary according to their derivation among each other as well as among members of the same group in their chemical composition, and because this quality is distinctly influenced for their derivatives by the types of processing procedures used, the great majority of these products lacks any definite chemical uniformity and standardization. Nevertheless, the general rule can be applied that derivatives which have been obtained by the application of high temperatures resulting in the formation of cyclic compounds (AULD) or are the result of cracking processes (HOLT *et al.*) contain polycyclic aromatic hydrocarbons, some of which are recognized and potent chemical carcinogens to man and animals (HIGGER and WOODHOUSE; TWORT and FULTON; EBY, PRIESTLEY, REINER and HALE; SHUBIK, SAGGIOTTI, LJUNSKY, PUTRA *et al.*; LJUNSKY, DOMSKY and RAHA; EICHNORFF and TITSCHACK; TENNENS, THOMAS and MUKA).

Although it has been claimed that only such products having a high boiling point are carcinogenic, human and experimental observations definitely show that also derivatives distilling over at a boiling point below 700 °C, such as methylated naphthalenes, may possess carcinogenic properties (SHUBIK and SAGGIOTTI; HUEFNER and CAINMANN; ANDERVONT; POEL; HORTON, DRYMAN and TROSSLIT; KOTIN, FALK and THOMAS; LUSHBAUGH; LUSHBAUGH and HACKETT).

In fact, there exists an increasing amount of evidence incriminating not only aromatic components of mineral oils and related chemicals in the production of cancers, but also aliphatic chemicals such as paraffins, aliphatic epoxides (ozonized gasoline) and nitro olefins (SHUBIK, SAGGIOTTI, LJUNSKY *et al.*; KOTIN, FALK and McCAMMON; KOTIN, FALK and THOMAS; KOTIN and FALK; JULSRUD; DEICHMANN).

The carcinogenic properties of these materials is being attested by numerous reports relating the development of cancers of the skin, including scrotal skin, in various types of worker groups having an occupational contact with them (lubricating oil, paraffin oil, cooling oil, waxes, fuel oil, asphalt and coke of stills, plasticizers in tiles, fillers in rubber, electrode component, etc.) as well as in several species of experimental animals to which they were applied or injected (HENDRICKS, BERRY, LIONE and THORPE; LIONE; SOUTHAM and WILSON; HENRY; WADE; ECKARDT; HOLT; PAGE *et al.*; SMITH and SUNDERLAND; CRUICKSHANK and GOURVITCH; CRUICKSHANK and SQUIRE; AULD; BROCKBANK; SQUIRE, CRUICKSHANK and TOHLEY; FIRE; GILMAN and VESSELINOVITCH; MASTROMATTEO; SPINK; BAYNES and TOMLINSON; HUEFNER and PAYNE; SIMMERS; HUEFNER and CAINMANN; STANBRUCK and CARL; WYNDER; SUNDERLAND, SMITH and SUGURA; TWORT and TWORT; VOSMAE; COOK, CARRUTHERS and WOODHOUSE; WOODHOUSE; LJUNSKY *et al.*; WADE; MACKENNA and HORNER). The great majority of the occupational oil cancers of the skin were reported from Great Britain. Not more than 10% of the observations originated from the United States despite their much more extensive production and use and a

greatly higher production of petroleum derivatives in the U.S.A. than in Great Britain. As a partial explanation of this astounding phenomenon, reference may be made to a remark of ECKARDT who stated that "the carcinogenicity of cutting oils is of such a low degree that good personal and industrial hygiene practices should eliminate any cancer hazard associated with these materials". The perhaps industrially unpleasant fact nevertheless exists — despite this admonition of taking rather lightly possible cancer hazards from such agents — that cancers of the skin from occupational contact with cutting oils have been observed in American metallurgical establishments. They regrettable, however, have not been made a matter of public record although such effects were demonstrated also in experimental animals (HUEFNER and PAYNE). Litigations regarding such cases were rather settled out of court. The occurrence of skin cancers in man and experimental animals from exposure to cutting oils, on the other hand, has been reported by Canadian investigators (MASTROMATTEO; GILMAN and VESSELINOVITCH).

Only one American oil company has chosen to publish its more recent experiences on the occurrence of cancers of the scrotal skin in paraffin pressers (HENDRICKS, BERRY, LIONE, and THORPE; LIONE and DINHOLM) and has done this only after a delay of ten years when the paraffin pressing process for obtaining waxes had been replaced by the solvent process, although wax cancers have been known for many years (DAVIS; LONGMUIR; HUEFNER). Since similar conditions of exposure to carcinogenic oils from which crude or "slack" wax is pressed have prevailed in other oil companies, according to reliable observations, it stands to reason that some such cancers must have occurred also in employees of these companies. Whether many of the victims of these occupational petroleum wax cancers received compensation for having contracted an often fatal occupational paraffin oil cancer, appears to be doubtful because of the statutory time clause which limits the making of such claims. It is also symptomatic of the general policy adopted in the management of information on such matters that the very extensive experimental data on carcinogenic properties of petroleum products obtained at a Midwestern university under the sponsorship and with the financial support for the American Petroleum Institute during twelve years of research, have not been published in printed form but seem to be considered still as "privileged information" if ECKARDT's philosophy in such matters should have been adhered to. The observation on oil cancers has suffered the same fate, which was assigned to a similar study on coal tar cancer hazards, which was conducted at the same university during the same period, and which was carried out under the sponsorship of a group of coal tar producers who had been stimulated by HUEFNER to engage in such research in 1950.

A disconcerting amount of human and experimental evidence attests to a carcinogenic effect of fully-refined hard, soft and liquid paraffin products not only on animal tissues but also on human tissues when applied to the skin, ingested, inhaled, implanted into the lumen of the urinary bladder, or parenterally injected (COLONN; SCHICK; SCHIMMEL and RITTIG; BOYD and DOLL; HUEFNER; DRUCKREY, SCHIMMEL and PRUSSMANN; NEUKOMM; SHUBIK *et al.*; BONSER, BOYLAND, BUSBY and CLAYSON; BONSER, CLAYSON, JULL and PYRAH; QUERY; MEIGS; BONSER, CLAYSON and JULL; POTTER and ROBERTSON; IRVING, GUTMANN and LARSON). SHUBIK *et al.* reported the presence of 1,2,5,6-dibenzanthracene in fully refined paraffins used for the coating of milk containers, and PROKHOROVA and ZNAMENSKY recorded the

demonstration of 3,4-benzpyrene in paraffins of Russian make. While petroleum waxes meeting certain physicochemical specifications are permitted in the food industry of the U.S.A., the two Russian investigators recommended that the foodstuff industry should be subject to controls in regard to the use of such waxes. The experimental production of cancers in the subcutaneous tissue of mice receiving implants of pellets of fully refined paraffin in which such impurities of carcinogenic aromatic hydrocarbons were not demonstrable with the most sensitive available methods — indicates that a carcinogenic effect of paraffin seems to depend on both aromatic and aliphatic chemical constituents of crude, semi-refined and fully-refined waxes.

Apart from the various contacts which human population groups have with these carcinogenic agents for occupational and economic-environmental reasons, such exposures may occur also because of the pollution of some natural media with native petroleum oils. Such petroleum oils and the polycyclic aromatic hydrocarbons contained in them have been demonstrated in the sediments of the Gulf of Mexico (WHITEHEAD and BREGER; SMITH; BAKER; MULIK and EIDMANN) as well as in South African asbestos (crocidolite) (HARINGTON), and in manganese nodules of the western North Atlantic (THOMAS and BLUMER). These findings indicate a rather wide range of natural occurrence of polynuclear hydrocarbons related to natural types of mineral oils and their prolonged preservation in strongly oxidized sediments over many thousands of years. Natural crude petroleum, moreover, has seeped in and contaminated in some areas of the United States, local drinking water supplies. Petroleum and mineral oils from natural sources, as well as from dumping ship fuel oil and escape of engine exhausts into ocean, lake and river waters, especially in or near harbor areas, has been polluting to an increasing degree all bodies of water within or near industrialized countries (CAHNMANN and KURATSUN; HUEFER).

It is noteworthy in this connection that non-processed natural bitumen or asphalt, such as that mined from the "asphalt lake" in Trinidad, has not displayed any carcinogenic properties in man (ZELIO) and experimental animals (HUTVIG), although crude natural petroleum oils, particularly those rich in aromatic compounds, have induced cancers when applied to the skin of mice and rabbits (HIEBER and WOODHOUSE; TWEED and FULTON) and may have been involved in the causation of skin cancers in oil field workers (SCHWARTZ, TULIPAN and BIRMINGHAM).

Carcinogenic constituents of mineral oils and derivatives are emitted into the air in numerous occupational activities where they are used in the manufacture of numerous products (rubber, plastics, steel, linoleum, etc.) or as lubricants, coatings and as fuels. They are present in automobile exhausts and in the effluents of oil refineries and filling stations.

Exposure to various types of petroleum products is rather widespread for the populations of industrialized countries for both occupational and environmental reasons (dietary, cosmetic, medicinal, atmospheric, aquatic, sanitary, etc.) (HUEFER). They form constituents of polishes, paints, pesticide preparations, paper and food container coatings, printing materials, water repellents of brick walls and textiles, lubricants, fuel oils, and many other products used in plants and homes (Division of Air Pollution; HENDRICKS).

b) Epidemiology

Occupational respiratory contact with these products may be due to an inhalation of oil fogs, mists and sprays, such as those encountered under occupational condi-

tions in paraffin pressing sheds, metal lathe operations, spraying of pesticide preparations, investment casting, high pressure lubrication, diesel jet testing, paraffin oil spraying of brick construction, textile spinning, and printing, and complication also exposures to combustion products in automobile and diesel engine exhausts (JONTS; TUNICI *et al.*; HUMPHRECK; MYLER-BRODIN). A habitual and occupational inhalation or ingestion of mineral oil containing nasal and laryngeal sprays creates a similar respiratory contact with paraffin oils and also may cause an oil pneumonia (FOX and BIGHAM; PROUHIT *et al.*; JAMPOUS *et al.*; SANTI; WOOD). While it has often been asserted that the ingestion of such oils for laxating purposes may lead to an aspiration of such oils into the lungs and thereby to the development of an oil pneumonia, it is more likely that the oil droplets retained under such conditions in the lungs enter the body through resorption by the intestinal mucosa from where they are transported into the blood of the vena cava inferior, the thoracic duct and the pulmonary arterial system. Here they are retained finally within the pulmonary capillaries (DANIEL, FRAZER, FRENCH and SAMMONS; HUEFER; MEYERS and GRIFITTI; SCHNEIDER; EDITORIAL) and thereby give rise to inflammatory and possibly cancerous reactions.

Lung and larynx cancer hazards from occupational exposure to finely dispersed or nebulized oil in the inhaled air have been recorded by HUGUENIN, FAUVET and BOURDIN for metallurgical workers, chauffeurs, garage mechanics and engineers. KENNAWAY and KENNAWAY noted a relatively high ratio of laryngeal cancers, but not of pulmonary cancers, in mulespinners having contact with shale oil and showing a high attack rate of cancers of the skin, especially the scrotum and vulva. Southam mentioned that mulespinners developed occasionally multiple primary cancers involving the lung and stomach in addition to the skin. ROISCH observed a combination of three primary cancers (skin, lung and stomach) in a paraffin presser; TOURAIN and BOUK also attributed the development of cancer of the lung in members of some occupations to their inhalation of lubricating oil mists. Such exposures may account also in part for the excessive lung cancer mortality among male metal grinders observed by TURNER and GRACE. A similar observation concerning a special liability to cancer of the lung by metal turners, mechanics, fitters and wood workers was reported by BERNDT. From an epidemiologic analysis of the relation of occupation to cancer of the lung in Japan, TSUCHIYA concluded that the only occupational group showing a higher risk to lung cancer were workers exposed to petroleum products.

Additional suggestive evidence on such relationships involving an occupational exposure to oil mist was advanced by HUGUENIN, FAUVET and BOURDIN, and HUGUENIN, FAUVET and MAZABRAUD. The epidemiologic analysis of employees of a large Public Utility Company by CHRISTIAN also provided evidence in support of the view that an inhalation of oil mists and fumes created an excessive liability to lung cancer since substation operators exposed to oil fumes from interruptors, had a lung cancer rate of 433 per 100,000, chauffeurs had one of 238 and mechanics one of 215, while the average rate was 35.4.

Respiratory exposures to mineral oil fogs, mists and fumes are doubtlessly sustained by workers employed in automobile service stations and garages (FREDDIE), in rolling mills using the cold reduction of steel strip (JONTS), in iron casting operations and steel plants (LARKSON) where mineral oil baths are employed for quenching purposes; in asbestos-cement plants where mineral oils are used as molding oils (UNGE-

nigrescent); in textile spinning establishments (EICKHOFF); in manufactures of roofing felt (GOLDFIELD and MCANULTS), in industrial establishments in which mineral oil is used as an air filtering agent in air conditioning equipment (HICURT), and in large-scale spraying of pesticide preparations which are dispensed in methylated naphthalene. It is interesting to note that EICKHOFF could not detect any special cancer hazard from contact with mineral oils in German textile workers. Drinker even ventured the opinion that there was no scientific support for apprehension on the breathing of oil mists, either from machine shop work or from insecticide spraying where a gasoline-type vehicle is the vehicle.

While HENDRICKS *et al.* recently concluded from a review of the literature and from their own observations in oil refineries that "there is no evidence to suggest any relation between the inhalation of oil mist and lung cancer" and that paraffin preservers do not show an excessive liability to lung cancer, it is noteworthy that the existence of such causal associations are clearly demonstrated among the workers of one of the refineries included in the study of HENDRICKS *et al.* as evident from the data of Table 68 (HOLT).

Table 68. Comparison of Lesions Among Pressmen with 10 Years or More Service with the Normal Male Population Using Adjusted Rates for Both the Pressmen and the Normal Population (HOLT *et al.*)

Site of Lesion	Adjusted Rate per 100,000*		% of Total Lesions	
	Normal Population	Pressmen	Normal Population	Pressmen
Lung	30	271	7.3	13.3
Stomach	68	407	16.3	20.0
Intestines	35	135	8.7	6.6
Rectum	34	135	8.3	6.6
Seratum	0.15	1080	...	53.0

According to HOLT, the probabilities of the observed cancer cases occurring in the normal population were as follows: Lung: One in 10,000; Stomach: Five in 10,000; Seratum: Less than 3 in ten trillion. These findings are in general agreement with those made in another oil refinery in which a survey revealed that of 19 cases of lung cancer occurring among the total number of employees of all types, 17 cases involved workers engaged in manufacturing processes and only two (2) affected white collar workers, although their ratio was 1:2.

Apart from the fact that cancers have developed at times from cosmetic paraffins present in various human organs (BAUER, BAADER, SCHMACHIL and REITER), such developments have been reported occasionally also as sequelae of medicinal oil pneumonia (WOON; SANTÉ). The recent observations of BONSER *et al.* on the development of cancers of the bladder in rats with intravesically placed paraffin pellets and of similar neoplasms in the bladder of mice equally treated (MEIGS) and the production of subcutaneous sarcomas around paraffin implants in mice (SITOUK *et al.*) give convincing testimony of the carcinogenic properties possessed by even fully refined paraffin waxes and paraffin oils. They support the view that the inhalation of such products in nebulized form should create a serious respiratory cancer hazard to the millions of workers employed in many industries, and different occupations, and exposed to oil mists, fogs and sprays (HURPER and PAYNE).

Of even more serious and general significance in this respect is the inhalation of exhaust fumes emitted from gasoline motors and diesel engines, since such effluents contain not only often unburned fuel in the form of oil droplets but also appreciable amounts of newly created carcinogenic combustion products. The atmospheric pollution with these carcinogenic constituents of the exhausts of automobiles, busses and trucks as well as of many types of industrial machines and airplane motors, is responsible for a considerable fraction of the rapidly increasing smog formation in all metropolitan areas (KOTIN and FALK; LYONS; KATZ; COMINS; COOPER; WALLER; COMINS and LAWTHIER; WYNDER; MULLS; FITTON).

During recent years repeated attempts have been made to minimize the cancer hazards to respiratory organs which might result from the release of diesel engine exhaust into the air of workshops as well as of the general environment, by claiming that such effluents while being toxic, do not contain any carcinogenic polycyclic aromatic hydrocarbons if the operation of a diesel engine is well adjusted (COMINS, WALLER and LAWTHIER; COMMITTEE ON MEDICAL SCIENCE, EDUCATION, and RESEARCH). Support for this general allegation has been provided by the failure of several experimental investigations in obtaining skin and lung cancers in mice or rabbits, respectively, which were either painted with diesel engine exhaust soot or inhaled it (MITTLER and NICHOLSON; SCHMIDTMANN).

Such assertions should not be accepted as valid for the following reasons. Since the type of exhaust released from diesel engines depends upon the type of engine and the fuel supplied to it as well as on the conditions under which an engine is operated (availability of oxygen, workload), there probably does not exist any typical diesel pollution (BATTIGELLI). The ideal operating conditions used for demonstrating the carcinogenic innocuousness of diesel engine exhaust do not exist under many "normal" conditions of operation of diesel engines and many of these engines are not kept in proper working condition. This is visibly apparent from the frequent release of dark black soot from the exhaust pipes of diesel trucks. Such soot does not contain only carbon but also carcinogenic polycyclic aromatic hydrocarbons (KÜHN; SULLIVAN and CLARY; BATTIGELLI; KOTIN, FALK and THOMAS; CLEMO). The carcinogenic chemicals present in the diesel engine exhaust therefore, can be expected to be present whenever a diesel engine is subjected to excessive strain usually caused by an overload or when it is operated in an environment with limited oxygen supply (mines, tunnels) (WALLER, COMINS and LAWTHIER; HOLT; CROOK; SULLIVAN and CLARY). Such pollutions are likely to exist also in inadequately ventilated diesel engine test rooms and repair shops (CALIANTI).

While the available human evidence does as yet not definitely establish whether an occupational inhalation of diesel engine fumes has solely been responsible for the production of lung cancers in man, the carcinogenic constituents in their exhaust certainly would tend to aggravate the total load of inhaled carcinogenic chemicals in all individuals exposed to such atmospheric pollutants. Diesel engine exhausts thus may significantly contribute to the development of lung cancers among members of such population groups. The epidemiologic studies by KAPLAN and by RATTLE on the lung cancer liability of operating railroad workers in the United States and in England have led these investigators to the conclusion that the lung cancers observed among these railroad workers did not have any apparent causative relationship to diesel fume inhalation. The statistical methods used by KAPLAN and the control

groups chosen by him to prove this claim, however, are of a type which destroys any scientific value of the conclusions reached by KAPLAN from his data. The negative evidence by KAPLAN, moreover, is refuted by observations published by HUIJER on this subject, who found that 75% of all lung cancers among railroad employees of two large American companies were found among operating railroad workers who constituted only 25% of the total number of employees. KAPLAN's findings also disagree with the data obtained by ROSS from an analysis of the rapid growth of the lung cancer rate among members of the Brotherhood of Railroad Trainmen between 1935 and 1952 (Table 69) (10 fold).

Table 69. *Incident of Cancer other than of the Lungs from Insurance Records of the Brotherhood of Locomotive Engineers, Brotherhood of Locomotive Firemen and Engineers, and Brotherhood of Railroad Trainmen*

Year	Deaths from Cancer other than that of the Lungs Firemen (per 50,000) (per 100,000)	Engineers (per 50,000) (per 100,000)	Total
1942	77	164	241
1943	79	161	240
1944	88	190	278
1945	74	176	250
1946	92	215	307
1947	91	229	320
1948	70	200	270
1949	85	240	325
1950	77	206	283
1951	87	230	317
1952	81	238	319
Totals	901	2,249	3,150
Increase Cancer (less lung) com- paring 1942-1953	5.19%	45.12%	6.67%
Increase Cancer (less lung) com- paring 1942-1951	12.99%	40.24%	45.33%
Average Increase of Cancer (less lungs) for 10 years, 1942-1951, incl.	6.49%	22.56%	14.67%

January 25, 1954, E. S. ROSS, M.D., Chief Medical Director, Brotherhood of Railroad Trainmen.

Chemically similar exposures are sustained by petroleum asphalt workers, road construction and repair workers, tile makers, carbon electrode manufacturers and users, and many others who inhale petroleum asphalt dust and fumes with demonstrated carcinogenic properties (LOCKHART; MALY and MADALA; HUIJER and PAYNE; SIMMONS).

Such pollutions with carcinogenic hydrocarbons generated by the incomplete combustion of gasoline and motor oil may recently have been intensified by the introduction of possibly carcinogenic additives, such as lead naphthenate, carbon tetrachloride, 1:1:1-trichloroethane, etc. to gasoline (BALDWIN, CUNNINGHAM and

PRATT; DOOLEY). A similar observation was made also in regard to additives used in cutting oils which, when applied to the skin of mice, induced cancer formation (GILMAN and VESSI LINOVIICH).

Finally, attention may be called to types of exposure to petroleum products which may create respiratory cancer hazards for workers employed in tobacco sheds in which tobacco leaves are cured by exposing them to the heat and soot generated by the burning of carcinogenic residual fuel oils, or for workers in and residents of quarters which are heated with stoves and burners using kerosene or petroleum oil as fuel (DIKUS), or for agricultural laborers employed in or living near orchards and vegetable fields protected against cold spells by the burning of old rubber tires and fuel oil in smudge pots, by the production of large amounts of soot. The failure to produce skin cancers in mice (MITSCHER and SCHWARZ) treated with a concentrated benzol extract of oil soot from a domestic oil burner in an ointment base cannot be considered as a competent type of experimental study since the maximal duration of the experiment was only 272 days and was, therefore, insufficient for covering even half of the minimal latent period of a bona fide carcinogenic bioassay on test materials of the type used (HUIJER and CONWAY; HUIJER and PAYNE; KURATSUNE and HUIJER).

The numerous observations on the causative role of polycyclic aromatic hydrocarbons present in various carbonaceous materials widely used for the production of heat and energy in the human economy and discharged often into the air of work rooms and communities without any consideration of the possible and even actual respiratory cancer hazards created thereby, deserve serious attention by all public health agencies if any rational prevention of respiratory cancers is to be attempted (SULA).

11. Ionizing Radiations

a) Technological Aspects

Exposure of man to ionizing radiations (alpha-, beta-, and gamma rays) occurs from natural as well as man-made sources. Natural radiations act either from external sources, such as cosmic radiation and radiations arising from radioactive elements present in the crust of the earth and as potassium 40 and carbon 14 in organic matter, including foodstuffs. Radioactive matter present in the atmosphere in the form of gas (radon) or dust may be inhaled or ingested and may consist of natural elements or, if the product of atomic nuclear operations, may be of man-made origin. X-radiation or Roentgen-radiation generated by many devices such as cathode tubes, x-ray tubes, electron guns, x-ray diffraction apparatus, radioactive static eliminators, television tubes and radar apparatus, is essentially a product of man-made activities.

While all living matter, including man, has been exposed since time immemorial to usually minor doses of natural ionizing radiations from external sources and has withstood such influences without any apparent major biologic injury, this situation has undergone, since the turn of the century with the discovery of radioactive chemicals and x-radiation, and particularly since the more recent development of atomic energy during the last 20 years, fundamental changes. During this period, health hazards and especially cancer hazards to man from contact with radioactive chemi-

The observation of a cancer of the lung in a laboratory technician, 23 years old, who had worked with DDT for nine years previously (RANDE) and in a chemist-entomologist who had been engaged for a number of years in the development of DDT preparations (LUTHER) suggest the possibility that these hepatocarcinogenic agents when inhaled in sufficient quantities over an adequate length of time might exert also a carcinogenic effect upon the respiratory organs. For this reason, it seems to be advisable to undertake epidemiologic studies on producers and the industrial and agricultural users of chlorinated hydrocarbons inhaling these chemicals in the form of dust, mists, suspensions and gases sustaining identical types of exposure for their relative liability to cancer of the respiratory organs.

f) Formaldehyde

Since formaldehyde is a mutagen (AUBRACH) and because GARCIN and SCHABAD (1935) produced atypical proliferations of the bronchial epithelium in mice following the introduction of formalin, the suspicion has prevailed that the inhalation of formaldehyde vapors might lead to the development of lung cancer in man (bakelite makers, undertakers, histologic technicians, wrinkle proofers of clothing, etc.) (FISHER, KANOF and BIONDI; GLASS; HENSON; LUTZ; BOURNE; and SUTHERLAND). Some experimental support of such a suspicion may be deduced from observations of WATANABE and SUZUMOTO, who obtained subcutaneous sarcomas in rats following the subcutaneous injection of urotropin, a formaldehyde releasing urinary antiseptic. Experiments of HORTON, TYE and STRUMER who subjected mice to the inhalation of gaseous formaldehyde, did not result in the production of pulmonary tumors although the tracheal and bronchial mucosa of such animals showed hyperplastic and atypical metaplastic changes which, however, did not progress to an invasive cancer. In contrast, some of the mice subjected to repeated inhalation of an aerosol of coal tar developed squamous cell cancers of the bronchi. Formaldehyde vapors applied simultaneously with the inhalation of aerosol of coal tar did not hasten or potentiate tumor formation in the lung.

There is not sufficient experimental and human epidemiologic evidence indicating that exposures to formaldehyde vapors constitute a significant and actual lung cancer hazard.

g) Natural and Man-Made Polymers

Several isolated observations suggest that an occupational and habitual inhalation of various natural and man-made carbon polymers might causally be related to the development of cancer of the lungs. The coexistence of bagassosis and lung cancer was reported by ONUCINO. KOTIN and FALK recorded two cases of lung cancer in workers exposed to fiberglass and plexiglass dust or fumes generated during the synthesis and manufacture of these products. Fragments of the polymers were present in the tumor tissue. BRISLOW, studying the role of different occupational factors in pulmonary carcinogenesis, found that deep-fat frying cooks had a statistically excessive liability to lung cancer. It may be of significance that fatty acids undergo polymerization when subjected to high temperature and oxidation and that such fats contained material which when injected into rats displayed carcinogenic properties. The demonstration of carcinogenic qualities in various aliphatic diepoxides when applied to the skin of mice furnishes additional evidence that polymerization products might be

involved in the cancerization process elicited by some chemicals since diepoxides exhibit a tendency to polymerize and to influence the degree of polymerization of chemicals with which they come in contact (HENDRY, HOMER, ROSE and WAPPORT; WILU, CONDRA, LAUN and SYRUEGL; ORRIS, VAN DOUREN and NELSON; HINE, GUZMAN, COURSEY, WILLINGTON and ANDERSON; KOTIN and FALK). Since HIRI *et al.* found in tests on animals that two epoxy-resins possessed carcinogenic properties, it may be pertinent to point to the excessive attack rate of lung cancer in painters (PIRE; WYNDER). Mention also may be made in this connection of the local and systemic carcinogenic effects elicited in rats by parentally introduced carboxymethyl cellulose, polyvinyl pyrrolidone and several dextrans (NELSON; HOFFER), since these and similar water-soluble polymers are widely used as active ingredients in hair lacquers and have induced in some individuals (beauticians especially) multifocal granulomatous reactions in the lungs (LIDELSTON; BERGMANN, ELANCF, CRUZ, KLAN, ARONSON, JOSH, and BLUMENFELD; BRUNNER, GIOVACCHINI, WYATT, DUNLAP and CALANDRA; BERGMANN; BRUNNER; DRAZZI, NELSON, NEWBURGER and KELLY; DYAN; DOYLE; CARES).

1. The spreading practice of deep-fat frying for commercial and home purposes and the thereby conditioned exposure of cooks, kitchen personnel and housewives to fumes and mists of repeatedly heated and oxidized fats which have undergone polymerization, provides an urgent indication to survey employees of commercial deep-fat frying operations for their relative liability to cancers of the respiratory organs.

This type of respiratory exposure may also be present as a part of the carcinogenic hazards connected with charcoal broiling of meats and fish, although the major part of carcinogenic exposures is probably connected here with the inhalation of carcinogenic combustion products of coal or wood and of burned meat and fish.

2. Employees in beauty parlors and women and men applying frequently to their hair and without precautions, nebulized hair lacquers furnish another group of people in need of comprehensive and critical epidemiologic analysis for occupational and habitual lung cancer hazards.

3. A third class of individuals who should be analyzed in this direction are the large and diverse groups of industrial producers, processors, and users of water-soluble and insoluble, solid and liquid plastics inhaling dusts, fumes, and mists of various natural and man-made polymers and developing in part as the result of such exposures, irritations of the lung (chemical pneumonia) or pneumoconioses.

D. Prevention and Control of Occupational Respiratory Cancer Hazards

The evidence presented establishes definitely the fact that numerous man-made and man-used respiratory carcinogens have been introduced into the human environment during the past 150 years and that they are responsible not only for a rapidly growing number of occupational cancers of the lung, pleura, larynx, nasal cavity and paranasal sinuses, but evidently also play a significant role in the causation of such cancers in the general population through their direct or indirect, local and general

spread into the atmosphere, especially of urban and industrialized regions. Since cancers of the respiratory system are still among the least therapeutically controlled malignant tumors and have alarmingly increased in frequency during the last 60 years, they represent an important problem for applied cancer prevention.

A practical approach to occupational respiratory cancer control by preventive and prophylactic measures has to include two aspects representing different problems of technology, public health, and law. The primary, but not always principal hazard affects the various types of workers engaged in the production, processing, handling, transportation, shipping, consuming and using of such carcinogenic materials. It is obvious that this group of workers includes often a considerable number of individuals who are not ordinarily and readily suspected of having such contacts. Many of them, moreover, are being exposed to such agents while working either on other jobs within the plant area or while handling such products, usually intermittently, in transit (stevedores, truckers, shipping clerks, laundresses, salesmen, delivery men, etc.). There can be little doubt that under ordinary circumstances, occupational exposures to respiratory carcinogens go often unnoticed for the vast group of individuals listed. They are usually also not subjected to any control measures. Cancers resulting from such contacts for these reasons do, as a rule, not become causes of compensation procedures even if existing occupational compensation laws would apply to occupational diseases contracted under such circumstances.

The second and often much larger group of individuals exposed to occupational or industrial respiratory carcinogens, comprises the persons who have contact with these agents following their dissemination in the immediate environment of industrial establishments (fume zone), i.e., persons who work, live, play or attend school near such plants and later in life and often after a lag period of many years, develop the so-called "neighborhood cancers". A variety of these cancers are represented by those which occur in individuals living or working near the roads of transportation of carcinogenic materials and inhale, therefore, the dust from roads accidentally contaminated with such materials or reside along roads paved with slags containing carcinogenic residues (asbestos, radioactive chemicals, nickel, etc.). An additional group of persons having environmental exposures to respiratory carcinogens consists of members of the household of workers who have occupational contact to carcinogens and who bring home their dusty and dirty work clothes for cleaning, and thereby spread contact with such carcinogens to other members of the household ("household cancers"). The definite demonstration of such respiratory "neighborhood" and "household cancers" is of rather recent date and has remained limited essentially to only two types of carcinogens (beryllium, asbestos). Their recognition was facilitated by the fact that these carcinogens produce pulmonary changes of etiologically characteristic nature. While the environmental dissemination of respiratory carcinogens has been made the subject of some control legislation, it is doubtful whether any number of these cancers appearing in members of the general population from such events has ever been made the subject of litigation or of criminal prosecution.

A preventive control of occupational respiratory cancer hazards can be achieved by either eliminating the carcinogenic agent from the work environment, i.e., by discontinuing its further production and use, or by employing production and handling procedures which preclude any contact of workers with the hazardous material. The practical application of the first mentioned method of control which obviously is

the most effective one, encounters often distinct difficulties because of the unavoidable need for many of the carcinogenic products mentioned, such as chromium, nickel, carbonaceous fuel, etc. It is, moreover, obvious that such procedures would always result also in the closure of the plant and thereby in the loss of employment of the workers involved. Safety, therefore, is sought under such circumstances with unemployment through elimination of the hazardous jobs.

A similar result is likely to occur in many instances if hazardous occupational exposures to respiratory carcinogens are controlled by the introduction of safer and more effective technologic production measures. Such procedures usually are associated with the introduction of extensive automation which again results in a reduction in labor force. The use of and insistence on technologic preventive measures against respiratory cancer hazards, as against any other industrial cancer hazards thus create serious social and economic repercussions for the workers employed in such operations. The safety obtained under such circumstances for the workers retained in their jobs is, moreover, rarely absolute. There usually remains some unavoidable degree of hazard for such workers. Unless special precautions are taken, it is also possible that the use of effective preventive measures within a plant may result in a more marked pollution of the periplant environment, i.e., air, soil and water, through a more massive release of plant wastes with exhaust air and waste water. It is obvious from these considerations that also a control of respiratory cancer hazards by technologic means is available only for a price. It is up to human society to decide whether or not it is willing and able to pay the entire price or whether it prefers to make a compromise at some level of partial safety which does not endanger its present economic existence, but which at the same time provides only incomplete and probably not maximally possible safety.

It is apparent, moreover, from the preceding discussion that in any attempt to secure relative protection against occupational and industry-related respiratory cancer hazards, human society is faced with the practical and moral problem that such efforts might result in the substitution of one social inequity by another one and that the enforcement of justice thereby might become a two-faced measure. Any attempt at improving radically this complex situation and to unravel the complicated relationships will confront mankind with the perplexing dilemma of finding new means for promoting progress and prosperity without human sacrifice and for restraining those of its members who continue to adhere to the old principle of dubious morality that the ultimate purpose of organized mankind is the accumulation of physical, monetary assets and not the acquisition of moral values and the protection of the well-being of its individual members as well as of mankind as whole.

References

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