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Occupational and Environmental Cancers of the Respiratory System

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With 48 Figures

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PLAINTIFF'S EXHIBIT
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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 KENNAWAY; SCHINZ; RAPOSO; LIPSCHUTZ; HUEPER and ITAMI; HUEPER and PAYNE; BOUTWELL BARONI, VAN ESCH and SAFFIOTTI). The recent production of liver cancers in rainbow trout fed carbasone 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

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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

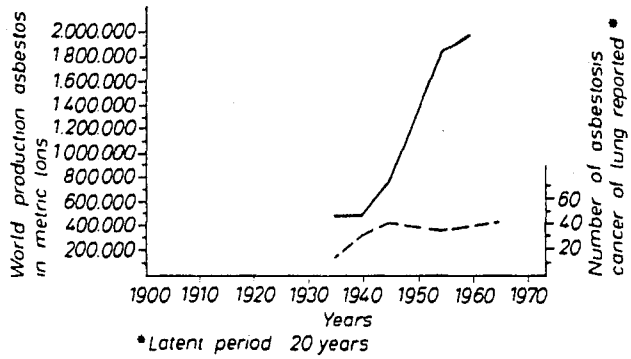


Fig. 4. World production of asbestos and asbestosis carcinoma of the lung

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 band-like structure or a chain-like structure (Fig. 5) (PARKES). 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 cancerigenic when implanted into rats (HUEPER).

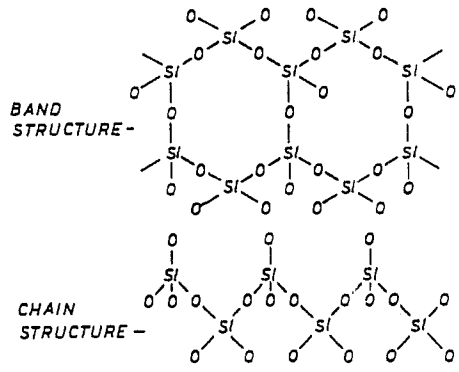


Fig. 5. Asbestos; fibrous polymerized silicate

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

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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: Lung, Pleura, Peritoneum

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

Compounds of Economic Importance	Operations and Products with Contact to Asbestos for Producers, Processers, Users, Consumers, Pesidents	Population Groups with Occupational and Environmental Exposure to Asbestos
Chrysotile, Amphibole, Amosite, Crocidolite Tremolite Containing Magnesium, Aluminium, Calcium, Iron, Silica	Asbestos rock mining, loading, shipping, crushing, milling; *asbestos spinning, weaving,* mixing, cutting, pressing, molding, plastering, cementing, spraying of steel construction, undercoating of automobiles, insulating pipes, etc. clothes, cloths, sheets, blankets, curtains, brake linings, yarns, cords, ropes, twines, ribbons, artificial snow, filler in rubber goods, plastics and roof coatings, filter cloths, filter pads, filter paper, artificial wood, tiles, shingles, card boards, wall boards, partitions, panels, paper, clutch facings, clapboard, 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	*Occupational Groups:* *Asbestos rock miners, loaders truckers, crushers, millers; asbestos spinners, weavers;* electrical appliance and wire manufacturers, masons, carpenters, heating equipment workers, rubber workers, shingle 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 *brake-lining producers, asbestos felt insulation worker,* asbestos sound insulation worker, asbestos insulator, pipe coverer, *asbestos tube wrapper,* 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.

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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 (DEMY), 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 GLOYNE.

Although some investigators still maintain that asbestosis is a rather rare occupational disease, the actual known facts are quite different (HUEPER). 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 (TOTTEN and GROSS; THOMSON; WAGLER, MÜLLER and ANSPACH; WEBSTER; KIVILUOTO; NEWHOUSE; CORDOBA, TESLUK and KNUDTSON), affected in part also with carcinoma of the lung and mesothelioma of the pleura (NEWHOUSE).

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. DEMY recently noted: "One would think that would be enough, but medical obtuseness, industrial coyness, and labor's timidness 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, HOFFMANN, 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 smell 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 (MITCHELL). Asbestosis is relatively common among asbestos workers

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of various occupations. MEREWETHER 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 BOHLIG, JACOB and MUELLER, more than 33% of the approximately 10,000 German asbestos workers show signs of asbestosis (1960). BOEHME, 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 5% among individuals employed less than 3 years and 79% among those exposed for over 10 years. Data from Finland and Sweden by WEGELIUS 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 presence 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 asbestotics 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; EGBERT and GEIGER; HOLLEB and ANGRIST; HOMBURGER; LYNCH and SMITH; LYNCH and CANNON; LYNCH and PRATT-THOMAS; ISSELBACHER, KLAUS and HARDY; O'DONNELL and MANN; O'DONNELL; STOLL, BASS and ANGRIST; TELISCHI and RUBENSTONE; MANCUSO; SELIKOFF, CHURG and HAMMOND; DYSON and TENTRALANCE; CORDOBA, TESLUK and KNUDSON (Three (3) cases of carcinoma of the lung with asbestosis in shipyard workers under investigation by HUEPER and PAYNE were omitted).

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

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

Great Britain: GLOYNE; SMITH; CURETON; OWEN; HUGH-JONES and HEARD; ELWOOD and COCHRANE; BUCHANAN; KEAL; MEREWETHER; DOLL; BONSER, FAULDS and STEWART; KENNAWAY 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 Asbestotics: Reported Cases*

Country	Number	Sex	Age	Exposure Time	Latent Period	Lag Period	Site	Histological Type
USA	88	M 87 F 1	37—69 Av. 50	5—48 Av. 23	6—36 Av. 23	1—30	LL 29 UL 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 Av. 11		A 2
England	149	M 107 F 32	32—76 Av. M 55.2 F 44.6 Av. 54	1—45 Av. 16	16—45 Av. 23	9—20 Av. 3	LL 4 UL 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		LL 22 UL 4	S 12 R 11
Finland	1							
Italy	3	M 2 F 1	46—54 Av. 49	17—26 Av. 29				S 1
France	2	M 1	53	10			LL	S 1
Switzerland	1	M 1	62	7	24	17	LL	A 1
Total	240	M 197 F 41	32—76	1—45	4—45	1—30	LL 53 UL 7	S 45 R 40 A 19

LL = Lower Lobe.
UL = Upper Lobe.
S = Squamous-Cell Carcinoma.
R = Round-Cell Carcinoma.
A = Adenocarcinoma.

Germany: LINZBACH and WEDLER; WELZ; WEDLER; BOHNE; BOEMKE; JACOB and BOHLIG; BOHLIG and JACOB; BOEHME; WERBER; BOHLIG, JACOB and MUELLER; HORNIG; KÖNIG.

Italy: PORTIGLIATTI-BARBOS; FRANCIA and MONARCA; ROMBOLA

France: HUREL, 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 laggers, cement mixers, packers, boiler coverers, 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 asbestotics to develop cancers of the lung were gathered from autopsies. Although this material is a selective one, its signi-

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ficance 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). KÖNIG 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%. CORDOBA *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
MEREWETHER . . .	Males	222	48	22
	Females	143	17	12
	Both	365	65	17.8
WYERS		115	17	14.8
DOLL		105 (asbestos workers)	18	17
GLOYNE		121	17	13.2
O'DONNELL and MANN		40	20	50
LYNCH		40	5	8.3
BECKER				14—15
WEDLER		92	15	16
BOEHME	Both	31	11	36
	Males	17	12	71
	Females	14	2	14
Controls				
BECKER (males over 20, average age at death, 61 years)			4	
(silicotics)			3.6	
MEREWETHER (6,884 post mortems on silicotics, 91 lung (cancers) (average age at death, 59.4 years)			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). SELIKOFF *et al.* noted that a lung cancer rate of 6 to 7 times the normal rate prevails among insulation workers.

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

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respectively. While BOHLIG *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: Number observed	Number of Death: Expected on England and Wales rates	Test of Significance of Difference between Observed and Expected (Value of P.)
Lung cancer [1]	11	0.8	< 0.000001
Other respiratory diseases [2] and cardiovascular diseases:			
With mention of asbestosis	14	—	< 0.001
Without mention of asbestosis	6	7.6	
Neoplasms, other than lung cancer	4	2.3	> 0.1
All other diseases [3]	4	4.7	
All causes	39	15.4	< 0.000001

[1] Including 1 case with pulmonary tuberculosis.
[2] Including pulmonary tuberculosis.
[3] Including 2 cases (benign stricture of esophagus and septicaemia) in which asbestosis was present but was not thought to have been a contributory cause of death.

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: Observed Deaths	Total: Expected Deaths	White Males: Observed Deaths	White Males: Expected Deaths	White Females: Observed Deaths	White Females: Expected Deaths
Lung, bronchus, trachea (162, 163)	18	5.29	14	5.11	4	0.18
Peritoneum (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 BOHLIG *et al.* contain a dilution factor which a priori may negate and defeat the purpose and validity of such studies (HUEPER).

While BOHLIG *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

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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 BOHLIG *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 BOHLIG *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 director of the Industrial Hygiene Foundation (DR. BRAUN), the medical officer of the Thetford 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 asbestotics among the population group 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

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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 (HUEPER). 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 (JACOB and BOHLIG). 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.

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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 bronchioli which contain in their lumens asbestos bodies. Asbestos textile worker



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

mas represent an unusually high percentage among asbestosis cancers (18% adenocarcinomas, 43% squamous cell carcinomas and 39% round-cell and anaplastic carcinomas). Also combinations of adenocarcinoma and squamous cell carcinoma have repeatedly been reported (Table 35) (BOHLIG, JACOB and MUELLER; 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; BOEMKE). Although similar, while usually less marked, mucosal lesions are found in association with other occupational carcinomas

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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 adenomatus 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 body embedded in the carcinomatous tissue in a textile worker

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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	per cent	Number	per cent	Number	per cent
Asbestos Series	45	43	40	39	19	18
Controls (DORN and CUTLER)						
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 (CARTIER; MANCUSO and COULTER; BOHLIG; JACOB and MUELLER; KÖNIG; LEICHER; WEDLER; WEBSTER; OWEN; SELIKOFF, CHURG and HAMMOND; WAGNER; WAGNER *et al;* ENTICKNAP and SMITHER; SLEGGS, MARCHAND and WAGNER; DOLL; WEISS; KEAL; BONSER FRANCIA and MONARCA; THOMSON; FOWLER; SLOPER 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	Lag Period	Site	
Germany	7	M 5	40—69	4—42	31—42	2—28	Pleura	6
		F 2	Av. 57	Av. 21	Av. 13	Av. 13	Peritoneum	1
Canada	2	M 2	65	10			Pleura	2
England	9	M 1	35—60	1—23	14—25	10—15		
		F 8	Av. 50	Av. 9	Av. 19	Av. 13	Peritoneum	9
USA	3	M 3	50—52				Pleura	1
							Peritoneum	2
Italy	1	M 1	46	17	30	13	Pleura	1
South Africa								
Occ.	16	M 15	36—68				Pleura	16
Res.	17	F 1	Av. 45				Pleura	17
		M 7	31—63					
		F 10	Av. 49					
Total	55	M 34	31—68	4—42	19—35	2—28	Pleura	43
		F 21	Av. 52	Av. 14	Av. 28	Av. 13	Peritoneum	12

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).

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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

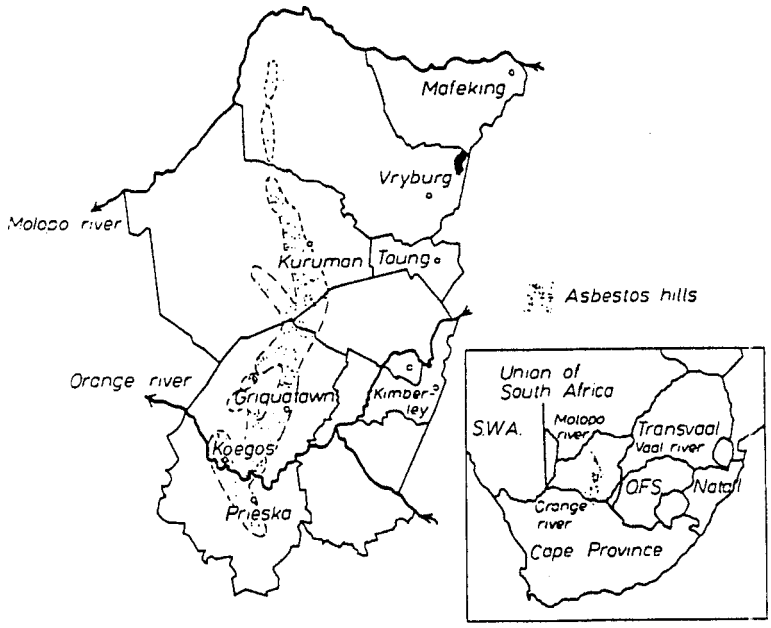


Fig. 11. Map of Griqualand west asbestos fields

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 KÖNIG 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 subquent development of meso-

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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% (WALTHER). 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. Scattered minor deposits in the interstitial tissue of the lung of asbestos bodies in an asbestos worker with a mesothelioma of the peritoneum



Fig. 13. Mesothelioma of the peritoneum of this worker showing pseudoglandular formations in a sarcomatoid 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												
	10–30		31–39		40–49		50–59		60–69		70 and over		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Asbestos Series			10	8	28	23	47	39	32	26	5	4	122
Control (HUEPER)	99	6	222	12	444	24	609	34	356	21	62	3	1,792

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60–69		70 and over		Total
o.	%	No.	%	
32	26	5	4	122
56	21	62	3	1,792

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) (MEREWETHER). 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								
	30–39		40–49		50–59		60–69		Total
	No.	%	No.	%	No.	%	No.	%	
Cases	9	23	13	31	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, MEREWETHER 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 MEREWETHER 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 (BOHLIG, JACOB and MUELLER). 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

PELLER 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. BOHLIG *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-

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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 PELLER'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) (HUEPER), the observation on which BOHLIG'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 PELLER'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 (DEWIRTZ; DREESSEN *et al.*; OLIVIER, MORAND and BRUN), which are as invariably benign as their silicotic counterparts (CROSSLAND). Whether asbestotics have an elevated cancer incidence of abdominal organs is still doubtful (MANCUSO and COULTER; KÖNIG; SELIKOFF; CHURG and HAMMOND).

h) Syncarcinogenesis in the Production of Asbestosis Cancers

BOHLIG *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 (HUEPER). 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 medicolegal argument against awarding compensation in litigations on asbestosis cancer of the lung. SELIKOFF *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 of the reaction of the host organism to the carcinogen in determining the occurrence and developmental speed of a carcinogenic response. A similar connotation 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. NORDMANN and

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SORGE who exposed mice to asbestos dust by inhalation and SCHMAHL who injected asbestos subcutaneously and intraperitoneally into rats, reported the development of cancers in the lung and subcutaneous tissue, respectively. Similar experiments by VÖRWALD, DURKAN and PRATT; LYNCH, MCIVER and CAIN; WAGNER; and HUEPER, 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. PEACOCK and PEACOCK, 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 suceeded in the production of pleural mesotheliomas in rats intrapleurally injected with powdered South African asbestos, and SMITH, MILLER, CHURG and SELIKOFF were equally successful in hamsters receiving asbestos by the same route. They found chrysotile 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 nonspecific neoplastic reaction to chronic inflammatory and fibrosing processes favoring an unlimited regenerative proliferation of bronchiolar epithelium. Since such chronic irritative reponses 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 KÜHN and by KNOX and BEATTIE suggests that asbestos particles, especially chrysotile, 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 HUEPER in connection with the carcinogenic action exerted by various maromolecular 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 HADDOW and HORNING had suggested that the iron in the carcinogenic irondextran complexes represented the actually active carcinogenic principle and not the dextran. Apart

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from the fact that a carcinogenic action of iron in man and experimental animals has not been established as yet by these observations, the well known lack of carcinogenic developments around iron deposits of old hemorrhages definitely discourages the acceptance of the iron concept of asbestos carcinogenesis (HUEPER). The same reluctance should apply to the suggestion that the protein-iron complex might be related to a specific immuno-chemical reaction as an essential phase in asbestos carcinogenesis (Editorial).

The recent demonstration of HARINGTON and of HARINGTON and SMITH that small amounts of a strongly fluorescent oil containing small amounts of 3,4-benzpyrene can be eluted with cyclohexane from several sorts of asbestos, has posed the question whether asbestos cancers might not be attributable to a slow release of carcinogenic polycyclic aromatic hydrocarbons from the surfaces of asbestos particles inhaled and retained in the lungs. It was shown that the minute amounts of 3,4-benzpyrene attached to crocidolite can readily be removed from the asbestos by serum. HARINGTON and SMITH demonstrated moreover that 3,4-benzpyrene can be adsorbed by crocidolite, chrysotile and coal dust from which it could readily be eluted subsequently by serum to much the same extent. Only crocidolite, to a lesser degree amosite, but not chrysotile were found to contain an oil with 3,4-benzpyrene, which was present in amounts ranging from 4.9 to 0.2 micrograms per 100 grams of fiber for the various specimens examined. While the absolute amounts of 3,4-benzpyrene adsorbed to asbestos fibers seem to be rather small to be significant carcinogenically, it may be unwise to dismiss these findings as unimportant, because the experiments of SHABAD and of SAFFIOTTI *et al.* with carcinogens adsorbed to carbon particles and iron oxide particles, respectively have demonstrated the carcinogenic effectiveness of such preparations on the lungs of experimental animals. However, if such a combination of asbestos with carcinogenic polycyclic aromatic hydrocarbons should be shown as being a potent combination, such a finding would not exclude a direct carcinogenic effect of asbestos, because chrysotile which lacks, according to HARINGTON, any carcinogenic chemical contamination nevertheless appears to be carcinogenic to man and experimental animals.

Finally, mention must be made of the proposal to regard asbestos carcinogenesis as a manifestation of the formation of cancers by the surface forces of polymer plastics (NOTHDURFT; OPPENHEIMER *et al.*). An application of this hypothesis, mainly based on speculations, to asbestos cancers appears to be unjustified, since asbestos exerts its carcinogenic action as a fine particulate powder, which, according to the proponents of this hypothesis, represents a physical state in which polymerized plastics are carcinogenically inactive.

3. Chromium

Sites of Chromium Cancers: Recognized: Lung, Nasal Cavity
Suspected: Stomach, Larynx

Exposure Stigmata: Dermatitis, Cutaneous "Chrome Holes", Ulcerated and Perforated Nasal Septum, Laryngitis, Tracheitis, Bronchitis, Chronic Fibrosing Pneumonia, Chronic Gastritis, Indolent Intestinal Ulcers

Compounds of Economic Importance (Di-, Tri- and Hexavalent)

Chromite ore, Chromium metal, Chromium alloys (Iron, Nickel, Cobalt), Chromium oxide, Chromium trioxide, Chromous Chloride, Chromic chloride, Chromyl chloride, Chromic nitrate, Chromium oxychloride, Chromium boride, Chromium carbide, Ammonium chromate,

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