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CARCINOGENIC POTENTIAL OF SILICA COMPOUNDS

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"The conflict of living matter and the mineral world" (Policard)(1).

SUMMARY AND CONCLUSIONS

1. Silicate fibers have been shown to produce cancer in man and animals. Cancer of the lung, pleura and peritoneum (mesothelioma), gastro-intestinal system and several other sites may frequently occur. This is now identified as an important public health problem.

2. A variety of such fibers of different chemical and crystallographic structure are active: chrysotile, amosite, crocidolite, anthophyllite, tremolite. These have a number of trace element contaminants.

3. The mass of dust needed to produce disease is small (often less than 0.25-0.50 g in the lungs, in extensive asbestosis), although the number of particles and their surface area are very large. The amount of fibrous silicate dust exposure needed to produce cancer is as little as may occur in the households of asbestos workers or in neighborhoods about asbestos factories.

4. Not all tissues respond to the presence of these fibers with cancer; they may be found in some organs without increased cancer risk. At present the reasons for differences among tissues are not known.

5. Silica (quartz) does not reproduce these carcinogenic effects. Among silica exposed individuals, we have found no mesothelioma, nor increase in gastro-intestinal cancer.

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6. While we have found, as expected, ample evidence of pulmonary fibrosis (silicosis), comparable with the extent of fibrosis with asbestos (asbestosis), there was a far smaller increase of lung cancer. There was thus a dissociation between fibrogenic and carcinogenic potentials of silica and asbestiform fibrous silicates.

Further, silicotic fibrosis was associated with tendency to concomitant tuberculosis. This was not seen with asbestosis.

7. An influence of shape and size of the particles is currently being considered, on the basis of experimental studies. Appropriate human data are presently not available on this aspect of the problem.

INTRODUCTION

Identification of Specific Effect of Silica

At the beginning of this century, there was wide appreciation that inorganic dusts could be detrimental to health, with early death often the fate of knife grinders exposed to flint, metal miners, stone masons and others. This general understanding could be traced back surely to Agricola (1556)(2), and perhaps even to Pliny the Elder (3).

Yet there was dissatisfaction with the generalization "dust" since as Thackrah put it in 1832: "Dust of every kind irritates but not in equal degree" (4). He noted that, in contrast to the stone chippers who generally died before 40, "bricklayers and plasterers' labourers, like asses, never die."

Dusts were indeed indifferent. This was clarified in the first decades of this century and the keen observations made were reviewed by Collis in his brilliant Milroy Lectures in 1915 (5). He pointed to the special effect of crystalline silica, quite distinct from dusts that were found in agricultural work or coal mining, for example. He noted that a variety of dusts might produce "dust-phthisis" or lung scarring, but that only those who inhaled dust with a high concentration of free silica had a greatly increased tendency to die of pulmonary tuberculosis. This observation has been widely confirmed since: that silica-induced disease of the lungs (silicosis) increased the risk of tuberculosis. The identification of this special potential of silica, not found with other dusts, was a brilliant piece of epidemiological deduction and served to establish the clear principle that dusts varied in their biological potential.

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That potential, however, was considered to reside in their fibrogenic effects in the lung. Such fibrogenesis resulted in scarring and very often dust disease of the lungs (pneumoconiosis) was considered synonymous with fibrosis; in later years, effects on the bronchi and air spaces of the lung (bronchitis and emphysema) were also recognized. Various dusts were evaluated in these terms, and calcined diatomaceous earth was considered more hazardous than kaolin because of its much greater tendency to yield lung scarring after inhalation and bituminous coal was regarded as more benign than crystabolite, in the same terms.

The discovery that crystalline silica did not have to be a constituent of dust for scarring to result ("asbestos" included a group of silicates, yet both their dusts and those of finely powered aluminum or beryllium oxide could also cause scarring) did not alter the general stance; fibrosis was the problem.

Initial Identification of Carcinogenic Potential of Silicon Dusts

In the past twenty years, the matter has become more complicated, with the recognition that inhalation of dusts could be associated with effects other than lung fibrosis and that such a wider spectrum of health problems could include serious diseases as cancer. With this recognition has come a widening of our interest in the nature of the dusts involved. We are now concerned, for example, not only with the general class of mineral or extruded silicates, but with particle size to the Ångstrom range, with crystallographic structure, particle surface, trace elements; with shape, acicular or fibrous or granular; with such parameters as piezo-electric effect, potential for intracellular residence and interaction with proteins. The possibility of cancer has focused attention anew on the likelihood of dissemination of fine particles, after inhalation or ingestion, to many parts of the body, and the possibility that such dissemination might result in cancer or other disease in extrapulmonary tissues.

Concern regarding the carcinogenic potential of silicon-containing particles began approximately 40 years ago, with the first reports of cases of lung cancer having been found in two asbestos workers (6, 7). Asbestosis -- the lung scarring which followed the inhalation of asbestos fibers -- had itself attracted much attention by that time, and has continued to. 1. As noted, it represented a group of silicates, rather than free silica-containing dusts; 2. The lung disease it produced was clinically different than that which followed silica inhalation, with the scarring diffuse rather than nodular.

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Table 1. X-ray changes in asbestos insulation workers (8)

Onset of exposure years	No.	% Normal	% Abnormal	Asbestosis (grade) 1	2	3
40+	121	5.8	94.2	35	51	28
30-39	194	12.9	87.1	102	49	18
20-29	77	27.2	72.8	35	17	4
10-19	379	55.9	44.1	158	9	0
0-9	346	89.6	10.4	36	0	0
	1 117	51.5	48.5	366	126	50

There were other important features as well. Perhaps the most significant we have come to appreciate has been the long period of clinical latency between onset of exposure and subsequent appearance of x-ray changes. This can be appreciated by review of findings in an investigation of asbestos insulation workers in the New York metropolitan area (8). In 1963, 1 117 of 1 258 such workers were examined. Of the 725 with less than 20 years from onset of exposure most hade normal x-rays (Table 1). It was only after the 20 year point had passed, that abnormalities were commonly seen. We will return to this phenomenon later. A second important finding was the discovery that pleural changes were common among asbestos-exposed workers (9). Unlike other dusts (as coal, silica, beryllium) with which pleural abnormalities are uncommonly seen, the opposite was found to be the case with asbestos. Table 2, recording roentgenographic abnormalities of the pleura among the same 1 117 men, demonstrates that both fibrosis and/or calcification were commonly seen. And when present, they, too, followed the "20 year rule". Few such abnormalities were observed in less than 20 years from onset of work.

Table 2. Roentgenographic evidence of pleural abnormality among 1 117 asbestos insulation workers (9)

Years from onset of exposure	Number examined	Normal pleura	Abnormal pleura Fibrosis	Calcification
40+	121	28	65	70
30-39	194	96	62	67
20-29	77	47	25	8
10-19	379	340	36	5
0-9	346	342	4	0

ASBESTOS CANCER

The first evidence of cancer associated with silicon dust exposure was thus related to asbestos. It remains the most important such cause, by far. Too, lung cancer remains the most common asbestos cancer, although neoplasms of other sites have been identified and, taken together, rival lung cancer in frequency, at least in some circumstances.

Lung Cancer

From 1935 to 1955, additional cases of lung cancer with asbestos exposure were considered, but experience was still limited and the relationship not clarified until a classic investigation by Richard Doll, reported in 1955 (10). He studied the experience of a group of heavily exposed asbestos factory workers employed for at least 20 years. Among the 113 men, 0.8 deaths of lung cancer would have been expected, had their experience been the same as other British men during those years. Instead, 11 such deaths occurred. Although the number of cases was small, the sharp increase in lung cancer deaths provided convincing evidence of a relationship.

Table 3. Expected and observed deaths among 632 N.Y.-N.J. asbestos insulation workers January 1, 1943 - December 31, 1974 (11)

	Exp.[a]	Obs.
Total deaths, all causes	305.20	451
Total cancer, all sites	52.02	200
Lung cancer	12.20	89
Pleural mesothelioma	(b)	10
Peritoneal mesothelioma	(b)	25
Cancer of stomach, esophagus	6.46	20
Cancer of colon	7.64	23
Asbestosis	(b)	37
All other causes	253.18	214

a) 632 members were on the union's rolls on January 1, 1943. 9 died before reaching 20 years from onset of first exposure point. Expected deaths are based upon white male age-specific death rate data of the U S. National Office of Vital Statistics from 1947-1973. Rates were extrapolated 1943-1948 from rates for 1949-1955, and for 1974 from rates for 1969-1973.

b) U S death rates not available, but these are rare causes of death in the general population.

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Since 1955, the importance of lung cancer as a consequence of occupational exposure to asbestos has been amply confirmed. In large series, approximately 20 % of all deaths of asbestos workers have been caused by this neoplasm. In one investigation, the mortality in the New York area was studied. On January 1, 1943 there were 632 men registered as members of this trade's Union in the area. By December 31, 1974, 451 men were deceased. 89 died of lung cancer whereas 12.2 had been anticipated (Table 3)(11).

Dr E.C. Hammond and I are also studying the cancer experience of asbestos insulation workers in the United States and Canada as a whole. On January 1, 1967 there were 17 800 men on the Union's rolls (International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO, CLC). By December 31, 1975, 2 003 men had died (against 1 483.38 expected). 92.28 deaths of lung cancer were anticipated; 427 occurred (Table 4). Similar results have been obtained in other investigations.

The fact that approximately one in five asbestos workers, exposed under conditions which existed in the past, now die of lung

Table 4. Expected and observed deaths among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967 - December 31, 1975

	Deaths	
	Exp.[a]	Obs.
Total deaths all causes	1 483.38	2 003
Cancer, all sites	281.49	867
Lung cancer	92.28	427
Pleural mesothelioma	(b)	52
Peritoneal mesothelioma	(b)	92
Cancer of esophagus	5.77	16
Cancer of stomach	12.71	22
Cancer of colon - rectum	33.87	53
Cancer of larynx	4.45	9
Cancer of oro-pharynx	7.41	17
All other cancers	125.00	179
Asbestosis	(b)	141
All other causes	1 201.89	995

a) Expected deaths are based upon white male age specific mortality data of the U S National Office for Health Statistics for 1967-1974 and extrapolated for 1975.

b) These are rare causes of death in the general population.

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cancer is a critical problem. This is especially true because of the large number of individuals concerned, since the U S Public Health Service has estimated that there are approximately one million men and women in the United States who are currently employed as asbestos workers or who were formerly so employed. To the extent that their conditions of exposure were similar to those of the cohorts studied, and unless treatment results improve, we may look forward to an extraordinary number of asbestos lung cancers in the next 3 to 5 decades (12).

Pleural Mesothelioma

In the past 20 years, we have had good reason to reflect on the observation that the mesothelial lining of the chest -- the pleura -- could show abnormal changes following asbestos inhalation. In 1953, Weiss (13) reported a primary malignancy of the pleura in an asbestos worker. This warranted interest since pleural mesothelioma had been known to be uncommon. It is difficult to be sure exactly how uncommon it was, since it had not been separately coded in the International Classification of Causes of Death, despite its definition as a separate pathological entity by Klemperer & Rabin in 1931 (14). Review of published autopsy data suggests that it might have occurred in approximately one in 1 000 to one in 10 000 deaths (15).

As with lung cancer, additional case reports followed. The potential association was considerably strengthened by the report of Wagner, Sleggs & Marchand (16). They described 47 cases of pleural mesothelioma derived from the Northwestern part of the Cape Province, South Africa, an area with numerous small crocidolite asbestos mines and mills. The life histories of the individuals provided evidence that 45 of the 47 had had opportunity, decades before, of having been exposed to crocidolite asbestos dust, many in what would now be called "environmental" circumstances. Epidemiological studies soon established that an etiological association existed between asbestos exposure and the subsequent development of mesothelioma; asbestos workers died frequently with mesothelioma while people not known to have worked with asbestos did not (17). Careful experimental studies have confirmed these human observations (18). Thus while we do not exactly know how inhaled asbestos- chrysotile, amosite, crocidolite, anthophyllite -- reaches the pleura, we now know that the fibers do reach this tissue (19), and neoplastic change results.

Peritoneal Mesothelioma

As with primary pleural neoplasms, the first description of an association between peritoneal mesothelioma and asbestos exposure was reported more than 20 years ago (20). Again, additional cases

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soon came to light and, by 1965, it was evident that this neoplasm also had to be added to the list of cancers that could be induced by asbestos (17, 21). Among asbestos insulation workers in the United States and Canada, for example, we have found that 93 of 2 003 deaths 1967-1975 were due to peritoneal mesothelioma, 4.64 % of all deaths (Table 4). Together with pleural mesothelioma, 7.19 % of all deaths in this group of asbestos workers were due to mesothelioma, an extraordinary association for an otherwise rare tumor. In another cohort of asbestos factory workers, it has been projected that 7-11 % of all deaths will be caused by this neoplasm (22), between 100 and 1 000 times what might ordinarily be expected. Experimental confirmation of an asbestos-peritoneal mesothelioma association has also become available (23).

Parenthetically, peritoneal mesothelioma has been found more often than pleural mesothelioma in several asbestos worker cohorts. In contrast, pleural mesothelioma seems much more common following less intimate exposure, as with environmental, family contact or neighborhood exposures (see below).

Gastrointestinal Cancer

In 1964, when analyzing the experiences of the New York metropolitan area asbestos insulation workers, a modest increase in gastrointestinal cancer was found, with 9.71 such neoplasms expected and 29 observed (24), (Table 5). Similar observations have now

Table 5. Expected and observed deaths among 632 asbestos insulation workers New York - New Jersey, 20 or more years after onset of work. January 1, 1943 - December 31, 1962 (24).

	Exp.[a]	Obs.
Total deaths, all causes	196.16	253
Total cancer - all sites	31.44	95
Lung cancer	6.02	42
Pleural mesothelioma	(b)	3
Peritoneal mesothelioma	(b)	1
Cancer of stomach, colon, rectum	9.71	29
All other cancer	15.71	20
Asbestosis	(b)	12
All other causes	164.72	146

a) 9 men died before reaching 20 years from first employment. Expected deaths are based upon white male age-specific death rate data of the U S National Office of Vital Statistics from 1949-1962. Rates were extrapolated 1943-1948 from rates for 1949-1955.

b) Rates are not available, but these are rare causes of death in the general population.

been made by others (25), and we continue to find increased evidence of cancer of the esophagus, stomach, colon and rectum among other cohorts of insulation workers (26). The increase, however, is more modest than that seen with bronchogenic carcinoma or pleural and peritoneal mesothelioma (Tables 3-4).

Oro-Pharyngeal and Laryngeal Cancer

Although experiences are fewer than one would wish, there also appears to be a significant increase in cancer of the buccal cavity, pharynx and larynx. In the 17 800 asbestos insulation workers observed from 1967-1975, observations have been available reflecting 150 975 man-years of experience. 7.41 deaths of cancer of the oro-pharynx, based upon white male age-specific mortality data of the U S National Office for Health Statistics, were expected; 17 occurred. Similar observations have been made with regard to the larynx, where there were 4.4 deaths anticipated and 9 were found (Table 6).

Cancer of the Kidney

For the neoplasms so far considered, direct contact with asbestos fibers following inhalation or ingestion could be assumed, although transport to the pleura or peritoneum might require specific mechanisms such as mechanical penetration or intra-macrophage migration. It has also been of interest to consider whether hematogenous dissemination of the fibers might result in neoplastic disease. We have obtained initial information on the matter. In the same cohort of 17 800 asbestos insulation workers, we have observed 17 deaths of kidney cancer 1967-1975, although only 7.08 were expected (Table 7). This organ, at least, might be sensitive to the presence of disseminated fine fibers.

Table 6. Deaths of selected neoplasms among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967 - December 31, 1975

Site	Deaths 1.1.67 - 12.31.75 Exp.[a]	Obs.	Ratio
Cancer of buccal cavity and pharynx	7.41	17	2.29
Cancer of larynx	4.45	9	2.90

a) Expected deaths are based upon white male age specific mortality data of the U S National Office for Health Statistics for 1967-1974 and extrapolated for 1975.

Table 7. Deaths of selected neoplasms among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967 - December 31, 1975

Site	Deaths Jan 1, 1967 - Dec 31, 1975 Exp.	Obs.	Ratio
Cancer of buccal cavity and pharynx	7.41	17	2.29
Cancer of larynx	4.45	9	2.02
Cancer of kidney	7.08	17	2.40
Cancer of skin	5.75	10	1.74
Cancer of brain	9.21	13	1.41
Cancer of testis	1.80	2	--
Cancer of prostate	17.70	26	1.45
Cancer of liver and biliary passages	6.62	5	0.76
Cancer of bladder	7.85	8	1.02
Leukemia	11.15	14	1.26
Lymphomas	18.02	19	1.05

Expected deaths are based upon white male age specific mortality data of the U S National Office for Health Statistics for 1967-1974 and extrapolated for 1975.

Other Neoplasms

There is evidence that the presence of asbestos fibers in a tissue is not sufficient, in itself, to necessarily result in neoplastic change. Thus, we have readily observed asbestos fibers in livers of asbestos workers. Yet we did not find any increase in cancer of the liver and biliary passages among the workers under our observation (Table 7). Also, while renal cancer was increased in incidence, this was not true of cancer of the bladder (Table 7). Similarly, there was no significant increase either in leukemia or in lymphomas.

MECHANISMS OF SILICA CARCINOGENESIS

As with cancer in general, we have no clear understanding of the cellular mechanisms which underlie the development of cancer associated with exposure to silicon particulate matter. There is good reason to believe, however, that such an effect is not related simply to the presence of silicon as an element. The reasoning behind this assertion rests upon epidemiological observations.

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Absence of Significant Cancer Effect of Crystalline Silicon Dioxide

Although there have been some differences of opinion concerning whether or not individuals heavily exposed to free silica might have some increased cancer risk, there have been no convincing data that this is so. The matter was not settled, however, because of a number of epidemiological difficulties. Thus, most recorded experience with silica-exposed groups was in the earlier part of this century, when cancer data were not as well defined as they now are, in many places. Also, individuals with heavy silica exposure -- and these were the people one tended to study -- often had severe pneumoconiosis, a reflection of inadequately understood and controlled exposures. Death often supervened before the individual reached an age when cancer was more likely to occur. Finally, the studies tended to be in mining and other non-urban areas and the potential for geographic variability could not be excluded, especially when comparing with the more extensive urban data upon which cancer rates tended to be more reliably set.

We have investigated the question, in view of its considerable theoretical importance. We had the opportunity of investigating the long-term mortality experience of a cohort of tunnel and caisson workers in New York City, who were known to have a risk of silicosis. With the cooperation of Locals 147 and 462 of the Laborers International Union of America, AFL-CIO, we established a cohort of all members of this Union who had been on its rolls for the period 1955-1959, and for at least one year before 1955. There were 932 such men.

In their tunnel work, they were exposed to dusts derived from the rock formations of New York City. The Manhattan Formation of Manhattan Island is known to contain large amounts of quartz, hornblende, biotite and other minerals, in the amphibolite, schists, gneisses and siliceous granulites (27). Chrysotile has not been identified and both hornblende and, less commonly, actinolite have not been identified as bearing a significant risk. Thus, there had been for these men, over the years, opportunity for very significant silica exposure with little identified risk of exposure to asbestiform fibers.

When the 932 men were traced, 294 were found to have died and 638 were alive. Expected and observed deaths are compared in Tables 8-10. There was no increase in cancer. 48.26 deaths were expected in this group, 49 occurred. However, there was some increase in lung cancer, with 13.15 deaths expected and 21 observed. Analysis by attained years from onset of employment indicated that this increase was largely to be found in those men who had reached 30 or more years from onset of exposure, where there were 3.66 deaths of lung cancer expected, and 11 were found. Thus, we have not ruled out some increase in lung cancer associated with heavy exposure to

free silica. However, one cannot be certain that the increase found truly represents an increased risk, since smoking histories were not available for the group during the period of observation and heavy smoking by this group of men could account for the small increase that was seen. Too, we cannot rule out a slight effect resulting from the inhalation of amphibolite dusts, such as hornblende, and actinolite.

Our data contain internal evidence of a silica effect, however. Not only was there a significant increase in deaths due to chronic respiratory disease (11.22 % of all deaths were in this category - Table 11) with the majority due to pulmonary fibrosis (Table 8) but pulmonary tuberculosis was also increased. 2.22 such deaths were anticipated; 11 occurred. Parenthetically, we have not seen increased risk of pulmonary tuberculosis with asbestosis. In the 2 003 deaths of asbestos insulation workers in the United States and Canada, 1967-1975, only 2 were due to pulmonary tuberculosis. In New York City, 1957-1976, we only saw 1 death of pulmonary tuberculosis, among 217 deaths.

Table 8. Causes of death among 932 New York City tunnel workers, 1955-1972

	Exp.	Obs.	Ratio
Total deaths, all causes	225.76	294	1.30
Cancer, all sites	48.26	49	1.02
Lung cancer	13.15	21	1.60
Cancer of esophagus, stomach, colon-rectum	11.13	10	0.90
Cancer of larynx	0.79	3	--
Cancer of oro-pharynx	1.71	1	--
Cancer of pancreas	2.77	5	--
Cancer of kidney	1.14	2	--
Cancer of all other sites	17.57	7	0.40
Pulmonary disease, total	9.02	50	5.54
Pulmonary tuberculosis	2.22	11	4.95
Pneumoconiosis, fibrosis	--	20	--
Other chronic respiratory disease	--	13	--
Pneumonia, influenza	6.80	6	0.88
Accidents, violent deaths	11.67	39	3.34
All other causes	156.81	156	0.99

Table 9. Causes of death among 932 New York City tunnel workers, 1955-1972, by attained years from onset of employment

	<10			10-19			20-29			30 +		
	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio
Total deaths, all causes	16.31	18	1.10	58.42	66	1.13	90.27	112	1.24	60.77	98	1.61
Cancer, all sites	2.07	2	--	11.93	7	0.59	19.67	18	0.92	13.60	22	1.62
Lung cancer	0.53	1	--	3.29	2	--	5.47	7	1.28	3.66	11	3.01
Pulmonary disease, total	--	1	--	--	10	--	--	19	--	--	20	--
Pulmonary tuberculosis	0.30	0	--	0.70	4	5.71	0.89	4	4.49	0.33	3	--
Pneumoconiosis, fibrosis	--	0	--	--	2	--	--	8	--	--	10	--
Other chronic disease	--	1	--	--	0	--	--	5	--	--	5	--
Accidents, violent deaths	1.86	8	4.30	4.12	14	3.40	3.77	14	3.71	1.91	3	--
All other causes	12.08	7	0.58	41.67	35	0.84	65.94	61	0.93	44.93	53	1.18

	Total		
Total deaths, all causes	225.76	294	1.30
Cancer, all sites	48.26	49	1.02
Lung cancer	13.15	21	1.60
Pulmonary disease, total	--	50	--
Pulmonary tuberculosis	2.22	11	4.95
Pneumoconiosis, fibrosis	--	20	--
Other chronic disease	--	13	--
Accidents, violent deaths	11.67	39	3.34
All other causes	163.61	156	0.95

Table 10. Causes of death among 932 New York City tunnel workers, 1955-1972, by number of years worked

	<10			10-19			20-29			30 +		
	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio
Total deaths, all causes	59.30	66	1.11	90.96	93	1.02	61.53	105	1.67	13.96	30	2.22
Cancer, all sites	12.04	8	0.66	19.33	14	0.72	13.60	18	1.32	3.29	9	2.74
Lung cancer	3.18	4	--	5.24	5	0.95	3.80	8	2.11	0.93	4	--
	Total deaths	No.	%	Total deaths	No.	%	Total deaths	No.	%	Total deaths	No.	%
Total respiratory disease	66	3	4.55	93	23	24.73	105	18	17.14	30	6	20.00

	Total		
Total deaths, all causes	225.76	294	1.30
Cancer, all sites	48.26	49	1.02
Lung cancer	13.15	21	1.60
	Total deaths	No.	%
Total respiratory disease	294	50	17.01

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Table 11. Deaths of chronic respiratory disease and tuberculosis among 932 tunnel workers, 1955-1972

Duration of employment (years)	Total deaths in category	Chronic respiratory disease		Pulmonary tuberculosis	
		Number	%	Number	%
<10	66	1	1.52	1	1.52
10-19	93	12	12.90	7	7.53
20-29	105	15	14.29	2	1.90
30+	30	5	16.66	1	3.33
	294	33	11.22	11	3.74

We may conclude, with reasonable confidence, that silica does not lead to cancer, merely because of its elemental nature, nor because of its potential for fibrosis.

CURRENT PERSPECTIVES

The main outlines of the occupational asbestos cancer problem were largely defined by the mid-1960s. It was clear that exposure to asbestos could constitute an important hazard.

Taken by itself, this would be an important enough problem. However, the further dimension of wide community concern was added as the result of several critical observations made at about the same time.

First, Thomson, Kaschula & MacDonald demonstrated in 1963 that asbestos bodies were to be frequently found at autopsy among individuals in the general population (29). This observation was extended shortly thereafter by the demonstration that asbestos fibers were also to be found in the lungs of urban dwellers (30). While it was understood that these observations only demonstrated previous exposure to asbestos, and carried no necessary prognostic significance concerning disease hazard, there was unease with the finding that fibers, which could in some people (asbestos workers) at some exposure levels (occupational exposures) cause serious neoplastic disease, were also present in the very large majority of urban residents, albeit at much lower concentrations (31).

The second observation that attracted attention was that of Kiviluoto, who demonstrated that pleural calcification was to be found frequently among residents living about an asbestos mine and mill in Finland (32). Pleural calcification was appropriately interpreted only as indicating prior exposure, decades before, to asbestos air pollution from the mine and mill and, again, not

necessarily indicating, as a consequence, a substantial environmental cancer hazard. Still, the pleural reaction evidenced by the radiological changes demonstrated that non-occupational community exposure to environmental asbestos contamination could result in at least one tissue change (pleural calcification). The possibility existed that other changes (neoplasm) might result.

The third observation was that of Wagner and his colleagues who brought the matter a step further by demonstrating that, at least in some environmental circumstances, such a result (mesothelioma) could occur (16).

These three findings, taken together, raised the question whether asbestos neoplasia might be a much wider and more pervasive problem than an occupational hazard alone. Observations since have amplified these concerns.

Family-Contact (Conjugal) Disease

An important contribution was made by Newhouse & Thompson in 1965 (33) when they described nine cases of mesothelioma among individuals whose only known contact with asbestos was presumably by virtue of their residence within households of asbestos workers. Investigations have shown that such situations provide ample opportunity for exposure, with contamination of a household by dust brought home on the workmen's shoes, clothes, hair, etc. By 1975, Anderson and his colleagues collected 33 reported cases of household-contact mesothelioma and added 4 that they had seen (34).

Household contact mesothelioma may well turn out to be an uncomfortably common problem in the future. In a current investigation in our Laboratory of the wives and children who resided with asbestos factory workers during their period of employment 1941-1954, approximately one-third of family contacts (wives, children) examined 1975-1976 had radiological abnormalities on chest films, of the type characteristically seen with asbestos exposure (parenchymal fibrosis, pleural fibrosis, pleural calcification). These chest film abnormalities were generally limited in extent and not accompanied by symptoms such as dyspnea. Nonetheless they indicate that asbestos exposure was common in the workers' households, to the extent necessary to result in, in many cases, radiological change (34). The ultimate fate of these people cannot now be predicted. Nevertheless, there is some concern, especially since four instances of mesothelioma have already been found.

Neighborhood Exposure

The general observations of Wagner, Sleggs & Marchand (16) and Newhouse & Thompson (33) have already been referred to. Other reports have since appeared, including those of McEwen and her colleagues (35), and Greenberg & Lloyd Davies (36). That the problem

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might be more wide-spread than initially believed is suggested by recent observations in Turkey (38).

Cases of neighborhood disease can and do occur; what is not now known, however, is whether these are likely to be frequent, or uncommon.

Bystander Disease

Harries, in 1968, reported 5 cases of pleural mesothelioma at the Royal Navy Dockyard in Devonport (38). None was in an asbestos worker; trades were listed as welder, laborer, shipwright, boiler-maker, fitter. This called attention to the possibility that men working in the same areas as those in which asbestos work was in progress, could also be exposed to the same dust, to a significant extent. While they might be "bystanders" in one sense, they were not, in another. Further experiences confirmed the initial observations. By 1973, 55 cases of mesothelioma had been recorded at Devonport. Only 2 were in asbestos workers, while 53 were among men in other trades at the shipyard (39).

Dose-Disease Response

An important difficulty in evaluating the quantitative relationship between amount of exposure and subsequent risk of asbestos-disease has been the long period of clinical latency between onset of effective exposure (i.e., the amount necessary to cause disease) and subsequent appearance of such disease, including asbestosis and cancer. Since few measurements were made in the 1920s, 1930s and 1940s, and virtually none in relation to work exposure of individuals with whom we were later concerned in the 1950s, 1960s and 1970s, it has been difficult to correlate quantitative measurements of exposure and risk of disease. Some measurements have been available for risk of asbestosis and more general, but perhaps more pertinent, evaluations have been made for cancer risk. The latter include two useful sets of observations.

Newhouse & Thompson analyzed 76 cases of mesothelioma in the files in the London Hospital (33). As expected, 31 cases had history of having worked with asbestos. However, 45 did not. Of these, 9 had presumed exposure resulting from residence within households of asbestos workers and 11 had lived within a half-mile of an asbestos plant in London. Although no quantitative dose-disease response relationships could be derived from these data, since the population bases from which they were derived were not known, it was nevertheless proposed that an exposure gradient was demonstrated.

Recently, more direct information has become available. Among the 933 workers employed in an amosite asbestos factory during World War II, employment was limited for some, and prolonged for others. Beginning in 1941, a number worked for as little as a day or a week, some for 1-3 months (often, while waiting to go into military ser-

vice) and still others worked for the full 13 years until the plant closed in 1954. Some information exists that exposures were poorly controlled, with levels often reaching 50 fibers/ml or more. It was found, by the end of 1974, that the lung cancer risk of this group of workmen was considerable, with 12.45 such deaths expected and 83 observed (Table 12). Closer analysis, however, showed that the extent of this risk varied with the duration of exposure (and, therefore, "dose"). The mortality ratio of observed to expected deaths was, for example, 3.87 for those with three months work or less, while those with one or more years of exposure showed a mortality ratio of 10.56 (Table 13) (11).

Table 12. Deaths among 933[a] workers employed in an amosite asbestos factory, starting five years from onset of work 1941-1945 to December 31, 1974 (11)

	Deaths 1946-1974		
Cause of death	Exp.	Obs.	Ratio
All causes	285.62	483	1.69
Cancer - all sites	50.10	157	3.13
Lung cancer	12.45	83	6.67
G.I. cancer	12.05	24	1.99
Pleural mesothelioma	(b)	5	....
Peritoneal mesothelioma	(b)	5	....
"Asbestos" cancer	24.50	117	4.78
Other cancer	25.60	40	1.56
Asbestosis	(b)	28	....
All other causes	235.52	298	1.27

a) Expected deaths are based upon white male age-specific death rate data of the U S National Office of Vital Statistics, 1949-1972. Rates were extrapolated for 1946-1948 from rates for 1949-1955 and for 1973-1974 from rates for 1968-1972.

128 workers were omitted from these calculations: 33 had prior asbestos exposure; 38 died in the first five years after onset of employment. 49 were not completely traced; and eight had other asbestos employment after the five year from onset point.

b) U S death rates not available but these are rare causes of death in the general population.

Table 13. Expected and observed deaths subsequent to first year after onset of employment among 870 amosite asbestos factory workers first employed 1941-1945 and observed to December 31, 1973.

	3 months or less			3-11 months work			1 year + work		
	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio
Total deaths, all causes	99.75	112	1.12	94.34	170	1.80	110.55	216	1.95
Cancer, all sites	16.92	28	1.65	16.29	46	2.82	18.99	81	4.27
Lung cancer	4.13	16	3.87	4.00	16	4.00	4.64	49	10.56
Pleural mesothelioma	n.a. a)	0	--	n.a.	2	--	n.a.	2	--
Peritoneal mesothelioma	n.a.	0	--	n.a.	1	--	n.a.	4	--
Cancer stomach	1.46	1	0.68	1.47	3	2.04	1.73	5	2.89
Cancer colon, rectum	2.38	4	1.68	2.27	7	3.08	2.67	5	1.87
Asbestosis	n.a.	1	--	n.a.	2	--	n.a.	23	--
All other causes	82.83	83	1.00	78.05	122	1.56	91.56	112	1.22
		249			294			327	
Number of workers	5 747			6 305			7 061		
Person-years observation									

This table excluded 63 men. Ten died during first year of employment, 34 could not be traced after the first year and 19 had prior occupational exposure to asbestos. Of the 870 men, 18 were partially traced and 16 had subsequent asbestos work. These remained in the calculations until lost to observation or until onset of subsequent asbestos work. Expected deaths are based upon white male age-specific death rate data of the U S National Office of Vital Statistics, 1949-1971. Rates were extrapolated for 1941-1948 from rates for 1949-1955 and for 1972-1973 from rates for 1967-1971.

a) U S death rates not available but these are rare causes of death in general population.

There is reason to believe that the dose-disease response relationships for the several kinds of asbestos disease do not necessarily follow the same patterns. Pleural mesothelioma, for example, may occur at levels of asbestos exposure below those necessary to yield radiologically evident asbestosis. At the moment, there is inadequate information to warrant judgment concerning dose-disease response relationships for lung cancer. We know a good deal about lung cancer incidence with more intense occupational exposure, but population-based studies have not yet been completed with regard to lung cancer incidence among individuals with less than intense exposure, as in family or neighborhood circumstances. There is little knowledge concerning dose-disease response patterns for gastrointestinal cancer, since this has only been investigated among occupationally-exposed groups.

Despite these variables, it appears clear that, taken as a whole, there is an important dose-disease response gradient for asbestos cancer, with disease much more likely to occur with heavier exposure and less likely to occur with less intense exposure.

Dose-Induction Period

Just as higher doses are associated with greater likelihood of asbestos cancer, there also seems to be substantial variation in the time of appearance of the neoplasms that result, according to the dose received. Initial information in this regard has begun to appear. While it still requires conformation, it is suggested that with brief (albeit intense) exposure, excess cancers will appear but that increased risk will not be observed for some time. Thus, again among the amosite factory workers, we have found statistically significant increased risk of lung cancer 15 years after onset of employment among workers with five or more years of work experience. In contrast, among those with a month or less of employment, an increased ratio of observed to expected deaths of lung cancer was not observed until 30 or more years had passed.

Comparatively few data are so far available for mesothelioma, but I would expect that this will also be found for these neoplasms, as well.

Period of Clinical Latency

Laced through the discussions in the foregoing has been the clinical importance of the period of clinical latency in asbestos disease. Quantitative information is now becoming available to document this perspective, and to emphasize the fact that one can hardly expect to be able to fully evaluate the effects of asbestos exposure without the opportunity for adequate duration of observa-

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tion. Tables 14-16 analyze the experiences of asbestos insulation workers in the United States and Canada, with regard to time of death of lung cancer, pleural and peritoneal mesothelioma, in relation to the elapsed period from onset of work experience. It will be seen that no mesotheliomas were seen in less than 15 years from onset of exposure and comparatively few in less than 20-25 years from onset. Similar observations obtained for lung cancer.

With but few exceptions, serious risk begins after 20 years from onset, and continues from that point on.

Table 14. Deaths of lung cancer among 17 800 asbestos insulation workers in the United States and Canada, January 1, 1967 - December 31, 1975. Distribution by attained years from onset of work

Attained years from onset of work	Number of men	Man years of observation	Deaths of lung cancer Exp.[a]	Obs.	Ratio
10	8 189	25 974	0.65	0	--
10-14	8 527	26 361	2.54	6	2.36
15-19	9 402	31 203	7.89	29	3.68
20-24	8 306	27 754	15.20	55	3.62
25-29	5 768	17 616	18.13	87	4.80
30-34	3 077	10 016	15.71	96	6.11
35-39	1 657	4 496	9.46	59	6.24
40-44	977	2 845	7.17	37	5.16
45+	1 362	4 710	15.53	58	3.72
All men	17 800	150 975	92.28	427	4.63
20 years	12 683	83 538	11.08	35	3.16
20+ years	11 470	67 437	81.20	392	4.83

a) Expected deaths are based upon white male age-specific mortality data of the U S National Office for Health Statistics for 1967-1974 and extrapolated for 1975.

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Table 15. Deaths of pleural mesothelioma among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967 - December 31, 1975 Distribution by attained years from onset of work

Years from onset of work	Number of men	Man years of observation	Total deaths	Deaths of pleural mesothelioma: Number	Deaths/1000 person years	Percent all deaths
10	8 189	25 974	50	0	0	0
10-14	8 527	26 361	77	0	0	0
15-19	9 402	31 203	180	2	0.03	1.11
20-24	8 306	27 754	289	4	0.14	1.38
25-29	5 768	17 616	343	15	0.85	4.37
30-34	3 077	10 016	298	9	0.89	3.02
35-39	1 657	4 496	201	8	1.78	3.98
40-44	977	2 845	176	3	1.05	1.70
45+	1 362	4 710	389	10	0.21	2.57
All men	17 800	150 975	2 003	51	0.34	2.55
20 years	12 683	83 538	307	2	0.02	0.65
20+ years	11 470	67 437	1 696	49	0.73	2.90

Table 16. Deaths of peritoneal mesothelioma among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967 - December 31, 1975 Distribution by attained years from onset of work

Years from onset of work	Number of men	Man years of observation	Total deaths	Deaths of peritoneal mesothelioma: Number	Deaths/1000 person years	Percent all deaths
10	8 189	25 974	50	0	0	0
10-14	8 527	26 361	77	0	0	0
15-19	9 402	31 203	180	3	0.10	1.67
20-24	8 306	27 754	289	3	0.11	1.04
25-29	5 768	17 616	343	15	0.85	4.37
30-34	3 077	10 016	298	17	1.70	5.70
35-39	1 657	4 496	201	14	3.11	6.97
40-44	977	2 845	176	15	5.37	8.52
45+	1 362	4 710	389	26	5.52	6.68
All men	17 800	150 975	2 003	93	0.62	4.64
20 years	12 683	83 538	307	3	0.04	0.98
20+ years	11 470	67 437	1 696	90	1.33	5.31

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Table 17. Death of lung cancer and mesothelioma among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967 - December 31, 1975, by smoking habits

Smoking habits	Man-years of observation	Deaths/1 000 man-years of observation		
		Lung cancer	Pleural mesothelioma	Peritoneal mesothelioma
History of cigarette smoking	81 316	3.50	0.38	0.73
No history of cigarette smoking	17 909	0.33	0.39	0.83
Never smoked	12 756	0.31	0.16	0.71
Pipe and/or cigar	5 153	0.39	0.97	1.16
Unknown	51 750	2.62	0.25	0.37

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Multiple Factor Interactions

In 1967, the observation was made that lung cancer risk among asbestos workers seems to be largely concentrated among those workers who also had a history of cigarette smoking. On January 1, 1963, among the 370 survivors of the original cohort of 632 men who were members of the Insulation Workers' Union in the New York metropolitan area on January 1, 1943, there were 87 men who had no history of cigarette smoking, and 283 with such history. By 1967, 2.98 deaths of lung cancer were anticipated among the cigarette smokers; 24 occurred. On the other hand, not one death of this neoplasm was seen among the 87 non-smokers, despite the fact that, among those who died, much asbestos was found in their lungs. Thus. there was evidence that lung cancer among these asbestos workers was not due to asbestos alone -- none of the non-smoking asbestos workers died of lung cancer -- nor to the smoking alone, since only three or so such deaths would have occurred among men of the same age in the general population. The combination of the two, smoking plus asbestos, was associated with the extraordinary increase in observed over expected deaths. It was calculated that asbestos workers who smoked cigarettes had approximately 92 times the risk of dying of lung cancer, compared to men who neither smoked nor worked with asbestos, and it was proposed that asbestos greatly increased the lung cancer risk of cigarette smokers (40).

This observation has now been amply confirmed. Asbestos workers who have no history of cigarette smoking are not likely to die of lung cancer. While their risk may be greater than non-smokers in general (without occupational exposure to asbestos) since the risk of the latter is comparatively low, even increasing it threefold would not result in a very important hazard, overall. Among cigarette smoking asbestos workers, on the other hand, the already high risk associated with cigarette smoking, when multiplied by asbestos, results in the extraordinary hazard of lung cancer that has been observed.

Parenthetically, neither pleural mesothelioma nor peritoneal mesothelioma is associated with cigarette smoking, among asbestos workers. These risks are present in both cigarette smoking asbestos workers and those without such history (Table 17).

Ingestion of Asbestos

To this point, evidence concerning asbestos disease hazard has been associated with inhalation of the dust. Little is known concerning hazard of ingested asbestos, although the problem has been brought to sharp attention with the contamination of Lake Superior by asbestos content mine waste (41). Also contamination of public water supplies by erosion from asbestos cement pipe systems is being investigated.

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