BIOLOGICAL EFFECTS OF ASBESTOS

National Institutes of Health
February 1, 1973

Chairman: David Rall, M.D.
National Institute of Environmental Health Sciences

Environmental Sciences Laboratory
Mount Sinai School of Medicine of
the City University of New York

—

J. Churg, M.D.
E. C. Hammond, Sc.D.
A. M. Langer, Ph.D.
W. J. Nicholson, Ph.D.
I. J. Selikoff, M.D.
Y. Suzuki, M.D.

Program

1.	Introduction	I. J. Selikoff, M.D.
2.	Mineralogy	A. M. Langer, Ph.D.
3.	Disease parameters Lung cancer Pleural and peritoneal mesothelioma Gastro-intestinal neoplasms Other neoplasms Asbestosis and pleural changes	I. J. Selikoff, M.D.
4.	Multiple factor interactions	E. C. Hammond, Sc.D.
5.	Pathology	J. Churg, M.D., Y. Suzuki, M.D.
6.	Environmental contamination Dose-disease response relationships Sources of environmental contamination Asbestos air pollution Asbestos lung burdens	W. J. Nicholson, Ph.D. A. M. Langer, Ph.D.
7.	Projections, 1973-2000 Major unresolved problems	I. J. Selikoff, M.D. E. C. Hammond, Sc.D.
8.	Questions and discussions	

Many of the studies reported are being supported by research program grants from the National Institute of Environmental Health Sciences, ES 00358, ES 00752 and ES 00792 and ES 44812 Career Scientist Award to A. M. Langer.

Participants

Mount Sinai School of Medicine of
the City University of New York.

Jacob Churg, M.D.	Professor of Pathology and Professor of Community Medicine. Director of Laboratories, Environmental Sciences Laboratory.
E. Cuyler Hammond, Sc.D.	Adjunct Professor of Community Medicine (Epidemiology). Vice-President, American Cancer Society and Director, Department of Epidemiology and Statistics.
Arthur M. Langer, Ph.D.	Associate Professor of Community Medicine (Mineralogy). Head, Physical Sciences Section, Environmental Sciences Laboratory
William J. Nicholson, Ph.D.	Associate Professor of Community Medicine (Biophysics). Head, Physics Laboratory, Environmental Sciences Laboratory.
Irving J. Selikoff, M.D.	Professor of Medicine and Professor of Community Medicine. Director, Environmental Sciences Laboratory.
Yasunosuke Suzuki, M.D.	Associate Professor of Community Medicine (Environmental Pathology) and Associate Professor of Pathology.

Outline of Asbestos Mineralogy

1. Asbestos defined: Asbestos is a generic term for 5 varieties of fibrous, hydrated, silicate minerals which possess the following common properties: are separable into thin fibers; are electrical and thermal insulators; may be woven and fabricated into forms easily; are chemically resistant.

Mineral Group	Mineral Species
Serpentine asbestos (1)	Chrysotile
Amphibole asbestos (4)	Amosite
	Crocidolite
	Anthophyllite
	Tremolite

2. Structure:

(A) Chrysotile: (sheet silicate)
- Sheets: silica (tridymite), brucite
- Curvature
- Spiral; concentric growth
- Fibril unit
- Bundle

(B) Amphiboles (chain silicate)
- Silica tetrahedra (units)
- Linking of staggered double chains
- Cation sites (0.40 - 1.40 Å accomodation)
- Anion configuration
- Chemical variation
- Natural occurrence
- Order-Disorder of cations

3. Chemistry: (structural formula)

(A) Chrysotile $(X)_6(Z_4O_{10})\ (O,OH,F)_8\ Mg_6Si_4O_{10}(OH)_8$

(B) Amphiboles $(W,X,Y)_{7-8}(Z_4O_{11})_2\ (O,OH,F)_2$
$(W_{0-1}X_2Y_5)(Z_8O_{22})\ (O,OH,F)_2$ for W=O $_0X_2Y_5$.

Range of Superior Chemical Analyses for Asbestos Minerals

	Chrysotile	Amosite	Crocidolite	Anthophyllite	Tremolite
SiO_2	41.8-42.0	49.47	47.6-56.1	50.1-58.9	54.9-59.5
TiO_2	0- 0.1	0.25	0- [illegible].9	0- 1.2	0- 0.3
Al_2O_3	0.1- 0.5	0.63	0.2- 3.5	0.6- 8.1	0- 4.6
Fe_2O_3	0.2- 1.3	4.15	9.9-20.1	0- 4.5	0- 0.5
Cr_2O_3	0- Tr	0.	0-	Tr-	0-
FeO	0.1- 1.6	35.63	2.3-24.4	0-20.5	0- 0.4
NiO	0- Tr	0.	0-	Tr-	0-
MnO	0- Tr	0.61	0- 1.5	0- 2.5	0- 0.4
MgO	41.4-42.8	6.57	0-15.8	17.6-30.8	21.7-25.5
CaO	0- 0.1	0.52	0- 4.9	0.1- 3.5	11.9-13.1
Na_2O	0- Tr	0.02	4.5- 8.8	0- 0.8	0- 1.3
K_2O	0- 0.1	0.20	0- 2.1	0- 0.2	0- 0.6
H_2O	13.6-14.0	2.33	0- 3.3	1.6- 4.8	0- 2.3

4. Associated Trace Mineral Phases:

(A) Chrysotile:	Serpentine phases (lizardite; antigorite) Magnetite Chromite Brucite (fibrous-nemalite) Talc Magnesite Metallic phases (awaruite) Calcite Olivine, Pyroxenes, amphiboles
(B) Amphiboles:	Amosite (quartz, Fe oxides ± hydrated) Crocidolite (as amosite ± amphiboles) Anthophyllite (talc, chrysotile, ± amphiboles) Tremolite (talc, "serpentine," ± amphiboles)

5. Associated Trace Elements:

(A) Chrysotile:	Ni,Cr,Co,Cu,Mn,Ca
(B) Amphiboles:	(eg. anthophyllite: Ag,Ba,Co,Cr,Cu,Li,Mo,Ni, Sr,V,Zr present in > 10 ppm)
	(eg. crocidolite: Zr,Nb,Th,Ce,Y,La,Ba,V,Ni)

6. Associated Organic Contaminants:

(A) Chrysotile:	Small quantities of oils and waxes
(B) Amphiboles:	Up to 0.3% oils, waxes, amino acids in amosite and crocidolite from So. Africa

7. Surface Properties:

(A) Chrysotile:	Slightly (+) H^+ from surface hydroxyl groups changes with ph and sorbed material.
(B) Amphiboles:	Moderately (-), changes with species, substitution of cations and sorbed surface material. Also different charge at different sites.

General References

Deer, W.A., Howie, R.A. and Zussman, J., 1962, The Rock Forming Minerals: v.2, The Chain Silicates, 329p.; v.3, The Sheet Silicates, 270p., J. Wiley and Sons, N.Y.

Ernst, W.G., 1968, Amphiboles: Crystal Chemistry, Phase Relations and Occurrence: v.1 of Minerals, Rocks and Inorganic Materials, 123p., Springer-Verlag, New York

Mason, B., 1958, Principles of Geochemistry, 310p., J. Wiley and Sons, N.Y.

Speil, S., and Leineweber, J.P., 1969, Asbestos Minerals in Modern Technology: Env. Res. v.2, 166-208.

Asbestos Disease

1. Asbestosis

.This is confined to occupational exposure.

.There is considerable individual variation in response. Some workers may be employed in asbestos trades for more than 40 years and still have normal chest X-rays. In others, as little as 1 day of factory exposure (inadequately controlled) will result in parenchymal or pleural disease decades later.

.Asbestosis sufficiently severe to be fatal has been seen in our studies in as little as eight years after onset of exposure, but this is most unusual. Death of asbestosis, when it occurs, usually is observed twenty, thirty, forty or more years after onset of work. Three factors generally must be considered in any analysis:

Intensity of exposure
Duration of exposure
Duration from onset of exposure
(Residence time of dust in lungs)

.By and large, significant asbestosis is not seen until at least 20 years from onset have elapsed -- the "20 year rule."

.All varieties of asbestos can produce disease; whether one type is more fibrogenic than another is uncertain.

.Clinical features of note are:

Monosymptomatic disease - dyspnoea
Restrictive lung function pattern; diffusion defects
Fine rales
Finger clubbing
Cough and sputum not prominent, except with smokers
Tendency to serum rheumatoid factor
Cor pulmonale in late stages
Incomplete clinical-X-ray-function correlation

Symptoms or signs are not useful for "early" diagnosis. X-ray and pulmonary function changes vie for early detection of disease, but years may go by before abnormalities become evident. At present, we cannot predict which workers will suffer early and/or severe asbestosis. Appropriate predictive diagnostic techniques do not exist.

.Pleural involvement is an important feature of asbestos disease. Both localized "plaques" or diffuse fibrosis may occur, and calcified plaques are often seen radiologically. When bilateral, they are almost pathognomonic of asbestos exposure; even unilateral calcification is usually reliable for diagnosis, especially when there is no history of tuberculosis, hemothorax, empyema.

Mortality: in cohorts of asbestos workers studied by us, about 7% of deaths were caused by asbestosis with respiratory insufficiency sometimes precipitated by minor pulmonary infection in patient with limited reserve.

Tables (Asbestosis)

X-ray changes tend to be extensive after more than 20 years from onset of work. Findings in 1,117 asbestos insulation workers.

Onset of exposure (yrs.)	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

Pleural changes on X-ray also are notable more than 20 years from onset of work

Years from onset of exposure	Number examined	Normal pleura	Abnormal pleura: Fibrosis	Abnormal pleura: 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

The cardinal clinical symptom - dyspnea - generally obeys the "20 year rule."

Onset of exposure (yrs.)	No.	% Normal	% Dyspnea	Dyspnea (degree) 1	2	3
40+	121	52.1	47.9	26	17	16
30-39	194	70.6	29.4	35	14	8
20-29	77	76.6	23.4	12	3	3
10-19	379	92.6	7.4	27	1	0
0-9	346	98.6	1.4	5	0	0

2. Lung cancer

Important risk begins as early as 10-14 years from onset of exposure, but results in significant number of excess deaths only after 20 years from onset of exposure. Depending upon the nature of the cohort under study, we have found a 5X - 7X increase in lung cancer.

This is the most important cause of death among asbestos workers -- 20% of all deaths are caused by the tumor. All cell types are seen (see Pathology). However, the cancer has some unusual features in asbestos exposure: 2/3 are lower lobe rather than upper lobe; they tend to be peripheral (main bronchus tumors are infrequent; so bronchoscopy tends to have less utility); the pleura is often involved early. Diminished respiratory reserve makes operation less available, and concomitant asbestosis may make radiological diagnosis difficult. The clinical course and prognosis are very much like those in non-asbestos cases.

Lung cancer as a result of environmental asbestos exposure has not yet been explored; it may turn out to be even more important, in terms of number of cases, than environmental mesothelioma. It should be noted that adults in urban areas tend to have asbestos fibers in their lungs (albeit many fewer in number than in lungs of asbestos workers). The significance of the presence of these fibers among cigarette smokers in the general population is not now known. Studies are under way to determine if lung cancer rates are increased among family contacts of asbestos workers, among residents of neighborhoods about asbestos factories, and among workers indirectly exposed to asbestos in the construction industry. Rates will be correlated with asbestos lung burden of individuals in these populations. If rates in these groups are elevated, additional approaches will be necessary to evaluate whether asbestos lung contamination in the general public contributes to its lung cancer risk.

3. Mesothelioma (Diffuse malignant pleural or peritoneal mesothelioma)

Approximately 7% of deaths among asbestos workers are caused by pleural and peritoneal mesothelioma. This is an extraordinary increase, although the exact amount is difficult to calculate, since the incidence in the general population is not known. In the past, the tumor was so rare as not to be separately coded in the International Classification of Causes of Death. Incidence has varied in general autopsy series from 1:1,000 to 1:10,000. In the American Cancer Society's Cancer Prevention Study, 3 of the first 31,652 deaths were listed as caused by mesothelioma. If we assume the tumor was underdiagnosed in the general population by a factor of 2 or 3, then about 1:3,500 deaths was caused by mesothelioma. The contrast with the fate of asbestos workers is striking -- hundreds of times as frequent.

To date, the neoplasm has proven invariably fatal. Duration of life is only infrequently longer than a year after diagnosis -- often less. Among asbestos workers, 2/3 are peritoneal and 1/3 pleural. With environmental exposure, pleural tumors seem more common, although more data are needed before a definitive statement is warranted.

Mesothelioma as the result of indirect occupational exposure occurs. It may turn out to be of greater significance, in terms of total numbers, than that associated with direct occupational exposure. In the construction industry alone, some 4,000,000 workers may have intermittent, low-level exposure from the use of asbestos products (taping joints in dry wall construction, carpenters sawing asbestos-cement sheets, mixing asbestos cement, sanding asphalt-asbestos tile floors, demolition and waste disposal, etc.)

Environmental contamination from factory or mill effluents, or as the result of household contamination by dusts on clothes and shoes of asbestos workers, has been related to mesothelioma. It is not known whether general atmospheric asbestos air pollution (brake lining wear, weathering of asbestos shingles or asbestos cement materials, other end product use) is associated with mesothelioma.

Our knowledge may be summarized as follows:

	Mesothelioma
Exposure	
Direct occupational	- extraordinary hazard
Indirect occupational	- many cases reported
Family contact	- cases known
Neighborhood pollution	- cases known
General community contamination	- ?

4. Gastro-intestinal cancer (stomach, colon, rectum, esophagus)

There is a modest increase of gastro-intestinal tract cancer among asbestos workers (2X - 3X). Whether it also occurs as the result of environmental asbestos exposure has not been studied.

Two observations may be relevant. 1) Among asbestos workers, asbestos fibers are present in the bowel wall long after occupational exposure has ceased. 2) There may be opportunity for asbestos contamination of food and fluids (filtration through asbestos filters; flow through asbestos cement pipes; talc as food additive). The significance of these observations is not known.

Mortality Data

In general, deaths in the asbestos worker cohorts studied may be broadly categorized as follows:

Total cancer	40%
Lung cancer	20%
Mesothelioma	7%
G.I. cancer	8%
Asbestosis	7%

The direct occupational risk is associated with current or prior regular work with asbestos. It has been estimated that 1,000,000 in the United States have or have had such experience.

While the number of individuals presumed to have indirect occupational exposure (or family contact, or neighborhood exposure) is very much larger, the magnitude of their risk of asbestos-associated disease has not yet been determined quantitatively.

The data in the first six tables which follow are derived from the experiences of cohorts of workers with direct occupational exposure and refer only to such groups. Tables 7 and 8 provide some information from 2 series concerning the proportion of environmentally-induced mesothelioma, relative to those occupationally derived.

Table 1

Expected and observed number of deaths among 623 New York-New Jersey asbestos insulation workers, Jan. 1, 1943-Dec. 31, 1971, twenty or more years after onset of first exposure to asbestos.

	1943-1951		1952-1961		1962-1971		Total 1943-1971	
	Exp.	Observ.	Exp.	Observ.	Exp.	Observ.	Exp.	Observ.
Total Cancer: all sites	11.3	28	18.3	57	17.6	104	47.2	189
Lung cancer	1.5	13	3.5	23	5.1	48	10.1	84
Pleural mesothelioma	**	1	**	2	**	5	**	8
Peritoneal mesothelioma	**	1	**	3	**	20	**	24
Cancer of stomach, colon, rectum, esophagus	4.1	7	5.0	18	3.9	16	13.0	41
Cancer all other sites	5.7	6	9.8	11	8.6	15	24.1	32
Asbestosis	**	1	**	10	**	22	**	33
All other causes	65.1	44	89.4	94	78.3	94	232.8	199
Total all causes	76.4	73	107.7	161	95.9	187	280.0	421
Person-years of observation:	3,726		4,406		2,898		11,030	

632 members were on the Union's rolls on January 1, 1943. Seven died before reaching 20 years from first employment. All others entered these calculations upon reaching the 20-year-from-Onset of first exposure point.

Expected rates are based upon age-specific death rate data of U.S. National Office of Vital Statistics from 1949-1967. Rates were extrapolated 1943-1948 from rates for 1949-1955 and for 1968-1971 from rates for 1961-1967.

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

Table 2

Expected* and observed deaths among
17,800 asbestos insulation workers
in the United States, January 1, 1967-December 31, 1971

	Total		Distribution by duration from onset of exposure: Less than 20 years		20 years and more	
	Expected	Observed	Expected	Observed	Expected	Observed
Total deaths	805.63	1,092	178.94	211	626.69	881
Cancer: all sites	144.09	459	26.31	51	117.78	408
Lung cancer	44.42	213	7.03	22	37.39	191
Pleural mesothelioma	**	26	**	2	**	24
Peritoneal mesothelioma	**	51	**	3	**	48
Cancer of stomach	6.62	16	0.97	1	5.65	15
Cancer of colon, rectum	17.51	26	2.51	3	15.00	23
Cancer of esophagus	3.21	13	0.44	1	2.77	12
All other cancers	72.33	114	15.36	19	56.97	95
Asbestosis	**	78	**	5	**	73
All other causes	661.54	555	152.63	155	508.91	400
Number of men	17,800		12,681		5,119	
Person-years of observation	86,300		62,673		23,627	

*Expected deaths are based upon age specific death rate data of the U.S. National Office of Vital Statistics. Rates for 1968-1971 were extrapolated from rates for 1961-1967.

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

Table 4

Expected and observed deaths among 689 asbestos production and textile workers, Jan. 1, 1959 - Dec. 31, 1971

	Observed deaths	Expected deaths
Total cancer (all sites)	72	27.8
Cancer of lung, pleura, trachea, bronchus	35	8.4
Lung cancer	27	+
Pleural mesothelioma	8	‡
Peritoneal mesothelioma	7	‡
Cancer of stomach, colon and rectum	13	5.0
Cancer all other sites	17	14.4
Asbestosis	24	‡
All other causes	103	106.5
Total deaths	199	134.3

+United States data not available but figure should be only slightly less than 8.4

‡United States data not available but these are rare causes of death in the general population.

Table 3

Expected* and observed deaths among 933* amosite asbestos factory workers first employed 1941-1945, and observed to Dec. 31, 1971

	Before 1952		1952-1961		1962-1971		Total, 1941-1971	
	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed
Total deaths	69.98	88	108.27	146	121.24	250	299.49	484
Total cancer: all sites	9.81	15	18.72	44	21.63	84	50.16	143
Lung cancer	1.49	3	3.71	23	6.21	47	11.41	73
Pleural mesothelioma	***	1	***	0	***	2	***	3
Peritoneal mesothelioma	***	0	***	0	***	4	***	4
Cancer of stomach	1.45	3	1.84	4	1.29	4	4.58	11
Cancer of colon, rectum	1.56	2	2.61	5	2.88	8	7.05	15
Cancer of esophagus	0.27	0	0.45	0	0.51	0	1.23	0
All other cancers	5.04	6	10.11	12	10.74	19	25.89	37
Asbestosis	***	3	***	7	***	17	***	27
All other causes	60.17	70	89.55	95	99.61	149	249.33	314

*Expected rates are based upon age-specific death rate data of U.S. National Office of Vital Statistics from 1949-1967. Rates were extrapolated 1941-1948 from rates for 1949-1955 and for 1968-1971 from rates for 1961-1967.

**933 men were employed. In 5 cases, ages were not known and these men have been excluded and from these calculations. 877 men were traced to death or to Dec. 31, 1971. 51 men were partially traced and remain in the calculations until being lost to observation.

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

Table 5

Deaths of lung cancer and pleural mesothelioma among 17,800 asbestos insulation workers in the U.S. and Canada, Jan. 1, 1967-Dec. 31, 1971: relation to elapsed period from onset of work exposure.

		Lung cancer		Pleural Mesothelioma
Years from onset	Expected deaths*	Observed deaths	Ratio	Observed deaths
< 10	0.48	0	--	0
10-14	1.69	4	2.4	0
15-19	4.86	18	3.7	2
20-24	7.55	25	3.3	4
25-29	8.50	41	4.8	7
30-34	6.24	44	7.1	4
35-39	3.53	23	6.5	1
40-44	4.04	24	5.9	3
45-49	3.72	17	4.6	4
50+	3.81	17	4.5	1
Total	44.42	213	4.8	26

*Expected deaths are based upon age specific death rate data of the U.S. National Office of Vital Statistics. Rates for 1968-1971 were extrapolated from data for 1961-1967.

Table 6

Expected and observed deaths of lung cancer among 876 amosite asbestos factory workers, first employed 1941-1945, and observed to Dec. 31, 1971.* Distribution by duration of employment.

Duration of employment	Number of Men	Person-years of observation	Deaths of lung cancer Exp.**	Observ.	Ratio
< 3 months	256	5,869	3.55	13	3.66
3-11 months	294	6,158	3.58	15	4.19
1+ years	326	6,912	4.09	45	11.00
Total	876	18,939	11.22	73	6.51

*This table excludes 57 men. 10 died during first year of employment, 39 could not be traced after the first year, 7 had prior occupational exposure to asbestos and 1 had employment of uncertain duration. 17 men of the 876 were partially traced and remained in the calculations only until lost to observation.

**Expected rates are based upon age-specific rate dats of U.S. National Office of Vital Statistics, 1949-1967. Rates were extrapolated 1941-1948 from rates for 1949-1955 and for 1968-1971 from rates for 1961-1967.

Table 7

Mesothelioma in London Hospital
(Newhouse and Thompson, 1965)

Total patients	76
Occupational asbestos exposure	31
Family contact	9
Neighborhood residence	11
No known contact	25

Table 8

Pleural Mesothelioma: 232 cases in
South Africa Mesothelioma Registry*

Exposure history not available	22
Exposure ascertained	210
Occupational asbestos exposure	102 (48.6%)
Environmental asbestos exposure	76 (36.2%)
No asbestos exposure	32 (15.2%)

*Annual Report 1971. National Research Institute for Occupational Diseases of the South African Medical Research Council, Johannesburg, 1972.

Bibliographical Landmarks in Asbestos Disease

1924 First case report of pulmonary asbestosis (Cooke, 1924).

Not fully accepted at first, reported again in 1927 (Cooke, 1927) when case reports elsewhere confirmed the existence of the disease. In retrospect, Parliament had been notified of the hazard in 1906, when Montague Murray testified concerning fatal pulmonary fibrosis among asbestos textile workers. (Departmental Committee on Compensation for Industrial Disease, 1907).

1931 Industrial survey showed high prevalence of asbestosis in asbestos textile factories in Great Britain (Merewether, 1931).

Similar prevalence in U.S. asbestos textile industry was found in PHS study (Dreessen, et al, 1938).

1935 A case of lung cancer with asbestosis was reported and etiological association suggested (Lynch and Smith, 1935).

Despite numerous similar case reports, the possibility of a chance association could not be avoided and the question remained open.

1953 1954 An instance of pleural mesothelioma, and one of peritoneal mesothelioma, in association with asbestosis, were reported (Weiss, 1953; Leichner, 1954).

Again, these random cases, and others reported elsewhere in the next several years, did not prove an etiological relationship; the possibility of a chance association remained, although the frequent linking with asbestos of this otherwise rare tumor (see Wagner, et al, 1960) was striking.

1955 Lung cancer risk of asbestos factory workers clearly established by epidemiological study (Doll, 1955).

Careful epidemiological study, going beyond lung cancer, showed U.S. factory hazard as well (Mancuso and Coulter, 1963).

1955 Pleural calcification emphasized as radiological accompaniment of asbestosis (Jacob and Bohlig, 1955).

Extraordinary incidence in asbestos workers later demonstrated (Selikoff, 1965). Pleural calcification may occur in 50% of experienced asbestos workers against 1 in 1,000 general hospital admissions.

1960 Environmental asbestos disease suggested by two brilliant studies. Each took advantage of clinical asbestos "marker."

Pleural calcification was found to be common in neighborhood about an asbestos mine and mill (499 of 6,312 x-rayed). (Kiviluoto, 1960.)

Numerous cases of pleural mesothelioma reported in asbestos-rich area of South Africa. On inquiry, many had had no occupational exposure but, rather, potential environmental contact (Wagner, Sleggs and Marchand, 1960). This study also did much to establish asbestos-mesothelioma relationship.

1961 Physiological defect in asbestosis clarified as restrictive disease without important obstructive airway component (Bader, Bader and Selikoff, 1961).

1962 Experimental mesothelioma produced by intrapleural instillation of asbestos (Wagner, 1962).

More recently, this model has been well used to investigate important variables (Stanton and Wrench, 1972). Lung cancer has also been induced (Gross, 1967).

1963 Wide environmental contamination suggested by frequent presence of "asbestos bodies" in lungs of routine autopsies (Thomson, Kaschula and MacDonald, 1963).

This was soon confirmed in many cities of the world. The concept derived from these observations was that lungs of urban dwellers are regularly contaminated by asbestos. This was disputed. It had long been known that a number of fibers other than asbestos could also be coated to give similar appearance. It was proposed that, unless one was certain of the nature of the core, non-specificity be signaled by calling these structu "ferruginous bodies" (Gross, Cralley and de Treville, 1967). The matter was not resolved until 1971 (See Langer, et al).

1964 Asbestos disease described as common among insulation workers, drawing attention to the construction industry, which uses 2/3 of asbestos in U.S., and the potential for much wider environmental contamination than that derived from factories (Selikoff, Churg a Hammond, 1964).

1964 Gastro-intestinal cancer found three times as frequent as expecte in cohort of asbestos workers (Selikoff, Churg and Hammond, 1964) Confirmed in later studies.

1965 Epidemiological investigations established mesothelioma as a comm occupational risk (Selikoff, Hammond and Churg, 1965).

Peritoneal mesothelioma was now emphasized in these and oth studies (Enticknap and Smither, 1964).

1965 Potential significance of environmental asbestos disease highlig by report of mesothelioma among family contacts and residents ab an asbestos plant (Newhouse and Thompson, 1965).

1968 Spectrum of asbestos disease further widened by description of m thelioma among shipyard construction workers with a history of i direct exposure to asbestos decades before (Harries, 1968).

Again, mesothelioma was used as a "marker." The problem of -cer as a consequence of asbestos contamination of constructi work sites and shipyards (carpenters, plumbers, electrician masons, laborers, etc.) may turn out to be more important t direct asbestos work (many millions versus hundreds of thou Lung cancer as well as mesothelioma may be involved (Fletch

1968 Multiple factor effect demonstrated. In addition to direct carcinogenic and fibrogenic action, asbestos multiplied the lung cancer potential of cigarette smoking (Selikoff, Hammond and Churg, 1968). Asbestos workers who smoke cigarettes have eight times greater risk of dying of lung cancer, as cigarette smokers who do not work with asbestos, and ninety times the risk of men who neither smoke nor work with asbestos.

1970 Soils naturally contaminated with asbestos-bearing geological formations may expose agricultural populations (Burilkov and Michaelova, 1970) and provide some measure of "natural background" of environmental asbestos contamination.

1971 Chrysotile asbestos in lungs of New Yorkers demonstrated by electron microscopy (Langer, Selikoff and Sastre, 1971). Biological potential of such contamination not now known.

1972 Asbestos air pollution may be responsible, at least in part, for lung contamination of urban dwellers (Nicholson, Rohl and Ferrand, 1972; Selikoff, Nicholson and Langer, 1972). Air samples, studied by electron microscopy, uniformly showed asbestos present in each of 47 U.S. cities. Levels were well below those of asbestos worksites, however.

1972 Environmental causes of mesothelioma stressed by analysis of cases in South Africa (South African Medical Research Council, 1972). 36% of 210 cases were considered the result of environmental exposure to asbestos, 49% were occupational in origin and 15% had no history of asbestos exposure.

Bibliographical References

1. Bader, M.E., Bader, R.A. and Selikoff, I.J. Pulmonary function in asbestosis of the lung; an alveolar-capillary block syndrome. Amer. J. Med. 30:235, 1961.

2. Burilkov, T., Michailova, L.: Asbestos content of the soil and endemic pleural asbestosis. Environ. Res. 3:443-451, 1970.

3. Cooke, W.E. Fibrosis of the lungs due to the inhalation of asbestosis. Brit. Med. J. 2:578-580, 1929.

4. Cooke, W.E. Pulmonary asbestosis. Brit. Med. J. 2:1024-1025, 1927.

5. Departmental Committee on Compensation for Industrial Disease. London. H.M.S.O., 1907. pp. 127-128 of minutes of evidence.

6. Doll, R. Mortality from lung cancer in asbestos workers. Brit. J. Industr. Med. 12:81-86, 1955.

7. Dreessen, W.C., Dallavalle, J.M., Edwards, T.I., Miller, J.W. and Sayers, R A Study of Asbestos in the Asbestos Textile Industry. (Public Health Bullet No. 241) Washington: U.S. Government Printing Office, 1938. 126 pp.

8. Enticknap, J.B. and Smither, W.J. Peritoneal tumours in asbestosis. Brit. J. Industr. Med. 21:20-31, 1964.

9. Fletcher, D. A mortality study of shipyard workers with pleural plaques. Brit. J. Ind. Med. 29:142-145, 1972.

10. Gross, P., deTreville, R.T.P., Toker, E.B., Kaschak, M. and Babyak, M.A. Experimental asbestosis. The development of lung cancer in rats with pulmonary deposits of chrysotile asbestos dust. Arch. Environ. Health 15:343-355, 1967.

11. Gross, P., Cralley, L.J. and deTreville, R.T.P. "Asbestos" bodies: their nonspecificity. Amer. Industr. Hyg. Ass. J. 28:541-542, 1967.

12. Harries, H.M. Asbestos Hazards in Naval Dockyards. Ann. Occup. Hyg. 11:135-145, 1968.

13. Jacob, G and Bohlig, H. Roentgenological complications in pulmonary asbestosis. Fortschr. Röentgenstr. 83:515-525, 1955.

14. Kiviluoto, R. Pleural calcification as a roentgenologic sign of non-occupational endemic anthophyllite-asbestosis. Acta. Radiol. Suppl. 194:1-77, 1960.

15. Langer, A.M., Selikoff, I.J. and Sastre, A. Chrysotile asbestos in the lungs of persons in New York City. Arch. Environ. Health 22:348-361, March 1971.

16. Leicher, F. Primarer Deckzellentumor des Bauchfells bei Asbestose. Arch. Gewerbepath. u. Gewerbehyg. 13:382-392, 1954.

17. Lynch, K.M. and Smith, W.A. Pulmonary asbestosis III: Carcinoma of lung in asbesto-silicosis. Amer. J. Cancer 24:56-64, 1935.

18. Mancuso, T.F. and Coulter, E.J. Methodology in industrial health studie The cohort approach, with special reference to an asbestos company. Arc Environ. Health 6:210-226, 1963.

19. Merewether, E.R.A. The occurrence of pulmonary fibrosis and other pulmonary affections in asbestos workers. J. Industr. Hyg. 12:198-222, 23 257, 1930.

20. Newhouse, M.L. and Thompson, H. Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. Brit. J. Industr. Med. 22:261-269, 1965.

21. Nicholson, W.J., Rohl, A.N. and Ferrand, E.F. Asbestos air pollution in New York City. In: Proc. Second Int'l. Clean Air Congress, Ed. Englund, H.M. and Berry, W.T. Acad. Press, New York, 1971 pp.136-139.

22. Selikoff, I.J. The occurrence of pleural calcification among asbestos insulation workers. Ann. N.Y. Acad. Sc. 132:251-367, 1965.

23. Selikoff, I.J., Churg, J. and Hammond, E.C. Asbestos Exposure and Neoplasia. J.A.M.A. 188:22-26, 1964.

24. Selikoff, I.J., Churg, J. and Hammond, E.C. Relation between exposure to asbestos and mesothelioma. New Eng. J. Med. 272:560-565, 1965.

25. Selikoff, I.J., Hammond, E.C. and Churg, J. Asbestos exposure, smoking and neoplasia. J.A.M.A. 204(2):106-112, April 1968.

26. South African Medical Research Council. Annual Report 1971 of the National Institute for Occupational Diseases. Johannesburg, 1972.

27. Stanton, M.F. and Wrench, C. Mechanisms of Mesothelioma Induction with Asbestos and Fibrous Glass. J. Nat. Cancer Inst. 48:797-821, 1972.

28. Thomson, J.G., Kaschula, R.O.C., MacDonald, R.R.: Asbestos as a modern urban hazard. S. Afr. Med. J. 7:77-81, 1963.

29. Wagner, J.C., Sleggs, C.A., Marchand, P.: Diffuse pleural mesothelioma and asbestos exposure in North Western Cape Province. Brit. J. Industr. Med. 17:250-271, 1960.

30. Wagner, J.C. Experimental production of mesothelial tumours of the pleura by implantation of dusts in laboratory animals. Nature 196:180-181, 1962.

31. Weiss, A. Pleurakrebs bei Lungenasbestose, in vivo morphologisch gesichert. Medizinische 3:93-94, 1953.

Table 2

Expected and observed deaths among 17,800 U.S. and Canada asbestos insulation workers, Jan. 1, 1967-Dec. 31, 1971*

	Total		No history of cigarette smoking**		History of cigarette smoking		Smoking habits not known	
Number of men Jan. 1, 1967	17,800		2,066		9,590		6,144	
Person-years of observation	86,300		10,163		46,615		29,522	
	Expected deaths	Observed deaths	Expected deaths	Observed deaths	Expected deaths	Observed deaths	Expected deaths	Observed deaths
Cancer all sites	144.09	459	19.92	33	79.58	265	44.59	161
Lung cancer	44.42	213	5.98	2	25.09	134	13.35	77
Pleural mesothelioma	***	26	***	2	***	17	***	7
Peritoneal mesothelioma	***	51	***	9	***	29	***	13
Cancer of stomach	6.62	16	0.95	1	3.60	8	2.07	7
Cancer of colon, rectum	17.51	26	2.52	4	9.53	14	5.46	8
Cancer of esophagus	3.21	13	0.44	0	1.80	7	0.97	6
Asbestosis	***	78	***	4	***	45	***	29
All other causes	661.54	555	92.67	36	356.67	286	212.20	233
Total deaths	805.63	1,092	112.59	73	436.25	596	256.79	423

*Expected deaths based upon age specific U.S. mortality rates for white males disregarding smoking. Lung cancer estimates based upon U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163.

**Included 609 men who smoked pipes or cigarettes.

***United States data not available, but these are rare causes of death in the general population.

Pathology of Asbestos-Associated Disease

Asbestos enters the human body via two principal routes: the respiratory tract and the gastrointestinal tract.

Respiratory tract

Asbestos dust consists mainly of fine, needle-like fibers, ranging in length from a few hundred microns to considerably less than one micron. The dust is easily inhaled and smaller fibers are carried to the most distant segments of the lung -- respiratory bronchioles and alveoli -- where they become trapped. Some of the fibers remain in situ; others are taken up by macrophages and carried into the alveolar septa and the lymphatic vessels, and from there to the regional lymph nodes and to the subpleural lymphatics. Asbestos fibers are able to penetrate into the pleural space; either because they have sharp ends and are quite rigid, or because they are carried by macrophages.

Fate of asbestos fibers:

Some fibers slowly dissolve at a rate dependent upon the type of asbestos. Some are coated by iron-protein compound and thus probably neutralized. Both of these are very slow processes. In other instances, fibers remain in situ apparently little altered. In either case, asbestos has time to exert injurious effect on the cells of the lung. Its toxicity probably depends not only upon its chemical composition but also upon its physical properties (e.g. size and shape of fibers, piezoelectric properties) and its ability to concentrate various, often toxic, substances on its highly adsorbent surfaces.

Pulmonary fibrosis (asbestosis):

Minor degrees of injury can be repaired. Considerable concentration of asbestos is needed to produce widespread irreversible damage. Injury and death of cells and their replacement by connective tissue leads to pulmonary fibrosis. This at first is limited to the septa, but eventually destroys the alveoli and bronchioles while some of the remaining air spaces become dilated. Within the fibrosed areas variable numbers of asbestos fibers and bodies can be found. The function of the lung, gas exchange, is much reduced. Pneumonia is a frequent and sometimes fatal complication, because of poor ventilation and poor clearance of the affected lung tissue.

Plaques represent localized areas of pleural thickening. Though they can occur in various pulmonary diseases, they are particularly frequent in asbestosis and are more often found on the parietal than on the visceral pleura.

Right sided heart failure is another frequent complication of severe asbestosis. It is caused by obliteration of a large part of the pulmonary vascular tree, leading to pulmonary hypertension and to cardiac overstrain.

Malignant tumors:

Pulmonary asbestosis is relatively less frequent now than it was 30 years ago, when the danger of inhaling asbestos was less widely appreciated. However, another serious complication appears many years after asbestos exposure, namely, malignant tumors. The exposure is very often light and limited in time causing only slight or moderate pulmonary fibrosis. However, 20 or 30 years later a large proportion of exposed people develop either pulmonary carcinoma or pleural or peritoneal mesothelioma.

Pulmonary carcinoma associated with asbestos exposure has a predilection for the lower lobes (in contrdistinction to the general population where it is more common in the upper lobes), but otherwise it is similar in its rate of growth, metastases and histologic structure. Pulmonary fibrosis, if present, may mask early lesions and make recognition difficult.

It can be demonstrated experimentally that asbestos is a carcinogen, though in the lung its carcinogenic potential is very weak. Of the people exposed to asbestos, only those tend to develop carcinoma who also smoke cigarettes, but the combination of asbestos and smoking produces strikingly high incidence of malignancy. (See multiple factor effect data.)

Pleural mesothelioma arises from the lining cells of the pleura, the mesothelial cells. It is less common than carcinoma, but in those exposed to asbestos it is at least 100 times as common as in the gener population. Smoking apparently has no effect upon its incidence. Mesotl tends to grow along the pleural surfaces encasing the lung in a thick layer of tumor tissue, but it may also invade the lung and produce distant metastases. It comes in a variety of histologic patterns, the most characteristic of which combines features of carcinoma and sarcoma (biphasic tumor). Cells of mesothelioma, as well as the normal mesothelial cells, secrete material rich in acid mucopolysaccharides. Experimentally mesothelioma can be produced by intrapleural injection of asbestos.

Gastrointestinal tract

Part of inhaled asbestos may be expectorated and swallowed, or asbest may be carried into the mouth by contaminated food on fingers. It ca be demonstrated experimentally that asbestos fibers lodge in the wall of the stomach and intestine and may penetrate into the peritoneal cavity. In limited studies to date, no excess of tumors has been obs in the gastrointestinal tract of animals fed asbestos, but in man car oma of stomach and large intestine is more frequent in those exposed asbestos than in the general population. The incidence of mesotheli of the peritoneum is strikingly increased after asbestos exposure. M thelioma can be produced in animals by intraperitoneal injection of asbestos. Peritoneal mesothelioma tends to grow along the peritonea surfaces, but it also produces large solid or nodular masses. Histo logically, it is very similar to pleural mesothelioma.

Asbestos Dose-Disease Relationships

Only limited data are available on asbestos dose-disease relationships. Few dust counts were taken 20, 30, or 40 years ago and those done usually reflected the presence of other dusts, silica, talc, mica, etc., along with asbestos. Materials, production techniques, and control equipment have changed significantly and current conditions cannot be used to evaluate past exposures.

Some data, albeit scanty, are available on the asbestos exposure of insulation workmen and a group of workpeople in an integrated asbestos manufacturing complex. These exposure data, which are only semiquantitative, can be related to excellent mortality information (Table 1 and Table 4 of Asbestos Disease section) As a result of past occupational exposures of about 10 to 20 fibers (longer than 5μ) per milliliter of air nearly 40% of the deaths of these workpeople can be attributed to their work environment.

No data are available on the asbestos dose-disease relationship at lower exposure levels. While any asbestos disease present in other than occupational circumstances will be at a significantly reduced intensity, the large number of people at risk give rise to serious concern. In addition to the 250,000 workpeople directly exposed to asbestos by virtue of their job, 5,000,000 are exposed indirectly in their occupations. Their asbestos exposure may be 10 to 1000 times less than the exposures which produced the current catastrophic occupational asbestos disease experience. At these lower exposures, if the percentage of deaths related to asbestos is, hypothetically, even 100 times less than direct occupational, 40,000 individuals may be affected. In environmental circumstances with 200,000,000 people potentially exposed, an additional tenfold reduction in asbestos associated disease would still leave 80,000 individuals affected.

Dose-response data are urgently required for other than direct occupational asbestos exposures. Analysis of the mortality experience and asbestos exposure of workpeople indirectly exposed is important. Indirect methods of assessing past air levels, such as the analysis of settled dust, can be helpful in the study of populations environmentally exposed. Autopsy lung tissue burdens of asbestos provide an especially useful method of assessing past exposures.

Analytic methods will require electron microscopic techniques. Most asbestos fibers present in the air, even in occupational circumstances, are not visible by light microscopy. In many circumstances, positive identification of single asbestos fibers can only be accomplished by electron microprobe techniques.

Sources of Environmental Contamination

Indirect occupational exposures to asbestos have been documented as causal... disease in a wide variety of trades in the shipbuilding and ship repair in... Mesothelioma is now observed, at an increasing rate, in other than asbesto... workers -- in plumbers, welders, electricians, carpenters, pipe fitters, ... The exposures of these other workmen may come from simply working in the vi... of asbestos application or from brief periods when asbestos must be removed ... pipes or fittings before their own work can be done.

Similar exposures are common throughout the construction industry, especial... during the past ten years. Since 1960 spray fireproofing of steelwork with asbestos containing materials has produced extensive contamination through... construction sites with men of all trades exposed. Over 4,000,000 workmen ... employed in the building industry. Their numbers alone create serious con... for their potential risk.

A variety of indirect occupational exposures can occur whenever asbestos i... widely used. Many electric utility employees are exposed during repairs of boilers or turbines. Chemical plants make extensive use of asbestos insul... material on high temperature pipes and vessels as well as incorporating the... into some of their products. For example, in one chemical plant we have ... the transport of asbestos from a warehouse area, through the plant, to the ... of use exposed unnecessarily every production employee.

Family exposures constitute an insidious form of asbestos exposure. The du... workmen's clothing (see Figure 1e) serves as a ready source of contaminatio... the employee's home. We readily find fibers of asbestos and other insulat... material in the settled dust of asbestos clothes have been implicated in th... deaths of wives of factory workmen. Moreover, children's play clothes wash... with a father's asbestos laden overalls are likely to become contaminated ... fiber and provide a continuing asbestos exposure to the child. (This cro... tamination of garments has been found to occur during the dry cleaning of a woman's coat containing asbestos fiber.)

The magnitude of average asbestos air levels in these family exposures is n... known. In fact the variability of the exposure precludes accurate definiti... However, these family exposures can be virtually eliminated by proper use of change rooms, shower facilities, and laundry facilities which should be avai... able to all asbestos workpeople. At the present time only a limited number ... work sites have adequate change rooms and few, if any, special laundry faci... ties exist in the asbestos industry. Such laundry facilities must, of cours... be well controlled as mesothelioma has been found among dry cleaning and laundry employees.

Environmental exposures range from ubiquitous, virtually continuous, low lev... concentrations derived from a wide variety of commonly used products to the... from short term "pathological" uses of asbestos with extremely high concentr... tions of limited duration. Examples of the former are airborne asbestos fr... the erosion products of brake linings, residence near a factory with inadeq... emission controls, asbestos in water systems, and asbestos in beverages and food products.

It is estimated that 40,000,000 pounds of asbestos is incorporated into brake linings each year. While high temperatures may alter much of the fiber during use, hundreds of thousands of pounds of asbestos can enter the environment annually from this source. Definitive data on the asbestos air concentrations from motor vehicle brake usage are lacking. However, in some very limited studies, asbestos levels two or three times background were observed at sites of extensive braking.

Water systems have been found to contain concentrations of asbestos in excess of 10 micrograms per gallon. The source of this water contamination is ill defined but it could arise from geological erosion, rain cleansing of the air, or pollution from human use of asbestos.

Asbestos filters have often been used in the food, beverage, and drug industry. Studies in our laboratory have demonstrated that erosion of the fibers from the filters occurs and the products can become contaminated.

Some very questionable uses of asbestos that have given rise to significant environmental exposures include the open transport and dumping of asbestos waste, the use of asbestos in paper mache and cement art material which is mixed dry by children, the incorporation of asbestos into consumer fabrics, and any procedure which can generate uncontrolled asbestos aerosols (such as spray fireproofing).

Often asbestos exposures occur as a result of fiber contamination of other products. Talc often coexists with varieties of asbestos and the use of cosmetic talcum powders can produce a significant asbestos exposure. In some foreign "talcum powders" the material may contain substantial amounts of anthophyllite asbestos. Industrial talcs, especially, are liable to be contaminated as a major source of such talc coexists with extensive deposits of asbestos.

Individuals doing home repairs may occasionally have short term exposures, often unsuspected. Gypsum spackle compounds used to seal wallboard joints or patch plaster often contain asbestos in amounts up to a few percent by weight. The sanding of such material, when dried, can generate high concentrations of asbestos. An insidious such exposure is that to individuals in urban areas whose apartments have been rehabilitated under lead control programs. Here, wallboard is typically installed over the lead contaminated paint. Spackle is applied to the joints and sanded with the result that asbestos dust rather than lead may contaminate the household.

Over 3000 uses of asbestos have been documented. Many of these products are produced safely and can be used safely. The production and use of others, however, can easily give rise to significant human exposures. Only constant vigilance by industry, by government, by research scientists, and by consumers will assure their eventual safe use.

Asbestos Air Pollution

Ambient air levels of asbestos range from approximately 10^{-10} gm/m^3 to over 10^{-7} gm/m^3. Thus, asbestos may constitute only 0.0001 percent to 0.1 percent of the particulate matter present in a given air sample. Moreover, the asbestos found in the ambient air includes both micron-size fibers and numerous individual fibrils which may be agglomerated with a variety of other material present in the air sample.

These considerations preclude the possibility of quantitative analysis of such ambient air samples by light microscopy, bulk spectroscopic techniques, or X-ray diffraction. The agglomeration of the asbestos with other materials and the presence of many sub-light microscopic fibers render light microscopy ineffective. Moreover, the unique identification of small optically visible fibers is not always possible, even using a petrographic microscope. Any bulk analysis method attempted to date has failed because of the presence of the much greater quantity of other inorganic and mineral material.

The only effective analysis method has required the use of electron microscopic techniques and involves the following steps:

1. collection of the air samples on membrane filter paper,
2. low temperature ashing of the collected material to remove the filter material and other organic matter,
3. dispersion of the residue by grinding or use of ultrasonic energy,
4. fixation of the dispersed residue in a nitrocellulose film which is mounted on an electron microscope grid, and
5. scanning at 40,000 X magnification using electron microscopy to determine the mass of asbestos originating from a prescrib fraction of the initial sample.

The dispersion procedure has been found necessary as large frag ments of other inorganic material obscure the presence of asbesto which often exists in fibril form attached to other particles. I fortunately, this procedure allows only the mass concentration to be determined and information on the size distribution of the fil is lost.

One hundred eighty-seven samples from 49 United States cities, collected by the National Air Pollution Control Administration during 1969 and 1970, were analyzed at the Environmental Science

Laboratory. The following table gives the range of values obtained from quarterly composites of biweekly 24 hour samples.

Chrysotile asbestos content of ambient air samples collected by NAPCA in 49 United States cities.

Fiber range in nanograms/ m^3	No. of samples in range
0.1- 0.9	61
1.0- 4.9	102
5.0- 9.9	12
10.0-19	9
20 -49	2
50+	1
Total samples	187

Results were also obtained from a series of single 8 hour samples collected in New York City by the Department of Air Resources at 12 sites of their sampling network.

Chrysotile content of ambient air in New York City by borough

Sampling Locations	Number of Samples	Asbestos air level in 10^{-9} grams/m^3	
		Range	Average
Manhattan	7	8-65	30
Brooklyn	3	6-39	19
Bronx	4	2-25	12
Queens	4	3-18	9
Staten Island	4	5-14	8

Sampling about construction sites where extensive spraying of asbestos-containing fireproofing material was taking place shows this procedure to contribute significantly to asbestos air pollution. In some instances chrysotile asbestos levels approximately 100 times "background" were observed.

Chrysotile asbestos concentrations near spray fireproofing sites

Sampling Location	Number of Samples	Asbestos air Level in 10^{-9} g/m^3	
		Range	Average
1/8-1/4 mile	11	9 -375	60
1/4-1/2 mile	6	8 - 54	25
1/2- 1 mile	5	3.5- 36	18

Asbestos Lung Burdens

Examination of human tissues may provide information as to the intensity of fiber exposure; fiber type (involving mixed exposure); fiber distribution; and fiber alteration in vivo.

The amount of tissue examined in the search for asbestos fibers is related to the degree of exposure (occupationally exposed vs. the "general population," or "non-exposed") and the materials available for study. Little material is required for the identification of fibers in tissue from individuals with "heavy" asbestos exposure. Here, histologic sections are quite adequate. However, in cases where small amounts of asbestos are likely to be encountered, bulk tissue will significantly increase fiber yield, greatly reduce time of fiber search, and yield results with increased statistical validity.

Histologic sections may be prepared for fiber analysis by a number of methods. The technique selected is based upon the type of instrumentation which will be used in fiber localization and identification. The following technique is now used routinely in the preparation of tissues for examination with electron beam instruments; it is called the carbon-extraction technique (Pooley, 1972; Langer, et al, 1972b). The preparation involves:

1. the ashing of a 5-8 micron thick, unstained, histologic section mounted on a glass slide;

2. impregnating the relict tissue in a water-soluble plastic (poly-Vinylalcohol);

3. "peeling" the hardened plastic, and the incorporated ashed tissue, from the slide;

4. inverting the relict tissue and depositing a thick carbon coat onto the inverted surface;

5. dissolving the plastic from the carbon sheet (which now includes the relict tissue and the inorganic particles), and;

6. placing the carbon film onto appropriate substrates for examination in an electron beam instrument (EM copper locator grids are best for this purpose).

The bulk tissue technique is the KOH digestion method as outlined in Langer, et al (1971)

1. Dried lung tissue is digested in a 5% KOH solution while being heated at 90°C for a 4-hour period;

2. Several cycles of washing and centrifugation of the residue are required for the complete removal of digested materials and the KOH;

3. The residues are then dispersed in triple-distilled water by sonification and a small amount pipetted onto an appropriate electron microscope substrate.

4. After drying, the grid is scanned in a transmission electron microscope at a magnification of 42,000 X. The scan is made across the diameter of the field and the fiber density converted into mass.

The major advantage in using such a method is the concentration of particles from masses of tissue greatly in excess from what one would normally encounter in a histologic slide. The major disadvantages are the time required for a single specimen scan and the instrument commitment to such an analysis.

Some estimates of lung burden have been made. In one study of lung residues obtained from 28 people who died in New York City we estimated that their lungs contained chrysotile concentrations on the order of micrograms to tenths of milligrams quantities (several hundreds of millions of fibrils). However, that study produced conservative estimates on the basis of technique of preparation (sample loss) and enumeration (direct on EM screen). In another study of 100 additional cases from the "general population," a more controlled procedure produced lung burden estimates which exceed several 10's of milligrams. We have compared these values with those obtained in the analysis of tissues from workmen exposed to asbestos occupationally. Here the number of fibers per lung is on the order of hundreds of billions, and the calculated mass may be as high as 5 gms/lung. Indirect occupational exposure to fiber results in lung burdenslying between the general population and occupational exposure levels.

Some observations of importance are:

1. Histologic sections are adequate for particle evaluation in cases of intense exposure; however, bulk tissues give best results in cases from the general population.

2. Exposure intensities may be qualitatively evaluated in unknowns.

3. Sub-light microscopic fibers far exceed those seen by light microscopy in number in all cases and tissues studied thus far.

4. Asbestos bodies, objects visible by light microscopy and often used as an index of asbestos exposure, only partially and only in some occupational cases reflect the lung burden of asbestos.

5. Chrysotile asbestos is the most common sub-light microscopic fiber in human tissues, most often occurring in the fibril form.

References

Langer, A.M., 1970, Electron microprobe analysis (study of asbestos fibe and bodies from lung tissue): In Laboratory Diagnosis of Diseases Cause by Toxic Agents, F.W. Sunderman and F.W. Sunderman, Jr., Eds., W.H. Gree St. Louis, Mo., Chap. 14, p. 126-136.

Langer, A.M., Rubin, I.B., and Selikoff, I.J., 1972, Chemical characterization of asbestos-body cores by electron microprobe analysis: Jour. Histochem. and Cytochem., v. 20, no. 9, p. 723-734.

Langer, A.M., Rubin, I.B., Selikoff, I.J., and Pooley, F.D., 1972b, Chemi characterization of uncoated asbestos fibers from lungs of asbestos work by electron microprobe analysis: Jour. Histochem and Cytochem., v.20, n p. 735-740.

Langer, A.M., and Pooley, F.D., 1973, Identification of single asbestos fibers in human tissues; In Proceedings Intl. Agency for Res. on Cancer; Biol. Effects of asbestos, Lyon, 1972, C. Wagner, Ed., Paper 19, in pres

Langer, A.M., Selikoff, I.J., and Sastre, A., 1971, Chrysotile asbestos the lungs of persons in New York City: Arch. Env. Health, v. 22, p. 348

Langer, A.M., Baden, V., Hammond, E.C., and Selikoff, I.J., 1971, Inorg fibers, including chrysotile, in lungs at autopsy: preliminary report: Inhaled Particles III, Proceedings of the Conf. Brit. Occup. Hyg. Soc. I 1970, W.H. Walton, Ed., Unwin Bros., Surrey, England, v. 2, p. 683-694.

Langer, A.M., Ashley, R., Baden, V., Berkley, C., Hammond, E.C., Mackler A.D., Maggiore, C.J., Nicholson, W.J., Rohl, A.N., Rubin, I.B., Sastre, A., and Selikoff, I.J., 1973, Identification of asbestos in human tissu Jour. Occup. Med., v. 15, (March) in press.

Ehrenreich, T., Mackler, A.D., Langer, A.M. and Selikoff, I.J., 1973, Indentification and Characterization of Pulmonary Dust Burden in Pneumoconiosis: In Laboratory Diagnosis of Diseases Caused by Toxic Agents., Applied Seminar on Clinical Pathology of Respiratory Diseases, Sunderman, F.W., Ed., in press.

Pooley, F.D. (1972) Electron microscope characteristics of inhaled chrysotile fiber. Brit. Jour. Industrial Med., 29, 146-153.

Pooley, F.D., Oldham, P.D., Chang-Hyum, Um, & Wagner, J.C. (1970) The detection of asbestos in tissues. In Pneumoconiosis Proc. of the Intl. Conf., Johannesburg, 1969, H.A. Shapiro, Ed., Capetown, Oxford Univ. Press, 108-116.

Timbrell, V., Pooley, F.D., & Wagner, J.C. (1970) Characteristics of res able asbestos fibers in Pneumoconiosis Proc. of the Intl. Conf. Johannes 1969, H.A. Shapiro, Ed., Capetown, Oxford Univ. Press, 120-125.

Problems and Perspectives

The shipyard mesothelioma question epitomizes the spectrum of difficulties now posed by the asbestos problem.

Background: Scientists have been sensitized to look for prior asbestos exposure, however brief, whenever mesothelioma is seen and, conversely, to watch for the occurrence of mesothelioma whenever an individual has had asbestos exposure. This sensitization perhaps explains the increasing uneasiness with which recent British publications have been received in this country. Starting in 1968, a series of papers has appeared reporting numerous mesotheliomas among individuals currently or previously employed in British shipyards. It is noteworthy that few of these people had been asbestos workers; they had merely been employed in the same yards (as carpenters, electricians, boilermakers, riggers, pipefitters, caulkers, etc.) in which a relatively small number of other men (generally insulators or "laggers") had been working with asbestos. Their shipyard employment had, in most instances, started thirty or so years before the onset of mesothelioma.

These British data are of interest to us because their shipbuilding and shiprepairing industry was rejuvinated about five years before ours; 1935 to our 1939-1940, and their mesothelioma experience could presage similar disease in this country.

U.S. shipyard employment 1940-1945: Between the two world wars, approximately 75,000 men and women were employed in our shipyards at any one time. The vast expansion of the industry in World War II led to rapid growth of the workforce, which reached a maximum of 1,750,000 in the fall of 1943. Altogether, 4,500,000 men and women worked in our shipyards at some time 1940-1945. Given their age distribution in those years, about 3,000,000 are alive. Needless to say, few of these WW II shipyard workers are currently employed in this occupation (which numbers 225,000). They are working at a host of other trades or professions and many only dimly remember the shipyard interludes in their lives, thirty years ago.

Shipyard mesotheliomas: As in Britain, mesotheliomas are now being seen in this country in individuals who, in WW II, were employed in one or another capacity in shipyards -- men and women who had worked for six weeks, six months, two years. When lung tissue is examined, asbestos fibers and fibrils are readily found (by electron microscopy), in numbers considerably larger than the relatively scant contamination found among urban dwellers generally. Apparently, the mineral fibers inhaled 30 years ago have remained intact, in most instances, at least. The individual's exposure may have been six weeks -- that of the lung parenchyma 30 years.

The mesotheliomas being seen are both pleural and peritoneal, with a preponderance so far of the former. As a rule, there have been no X-ray changes of concomitant asbestosis -- it would seem that asbestos exposure insufficient to result in radiologically evident asbestosis

may still be enough to induce mesothelioma. Cases have been seen in former shipyard electricians, tinsmiths, engineers, riggers, boiler-makers, carpenters, laborers, etc. Parenthetically, the U.S. Navy accepts responsibility (in terms of compensation) for cases of mesothelioma among individuals who had worked in its yards in WW II, provided there has been no subsequent asbestos exposure, deeming itself the "last employer." These are random cases and it is not known how many are occurring, nor what proportion of the 3,000,000 former shipyard workers will develop mesothelioma. 7% of shipyard insulatic workers die of this disease; it is highly unlikely that those indirec exposed will reach this level, although it is conceivable. Those th occur will be seen over the next twenty years.

We have no way at the moment of predicting which individuals will develop mesothelioma, nor have we means of "early" diagnosis (at a time when the tumor is presumably still localized). Therapy has been palliative; cure eludes us.

What is to be done? Many groups are concerned with approaches to th asbestos problem, as to others; labor unions, industry, NIOSH, EPA, DOL, for example, are concerned with development of engineering cont administrative standards and clinical surveillance. Scientists at N and elsewhere can augment and extend these efforts, utilizing a rang of disciplines from epidemiology to cell biology.

1. Can we inactivate the fibers presently in the lungs of shipyard workers? Can we "defuse" their asbestos lung burden before disease supervenes? There are some leads in this regard.

2. Can we develop serological or other means of predictive value? Early diagnosis?

3. Develop understanding of pathogenetic mechanisms, at the interface between "mineral matter and the living world."

4. Successful treatment of mesothelioma; worthy task for the Natio Cancer Plan.

Progress in these areas will be of value across the whole spectrum asbestos disease, from occupational groups to environmental exposur from the asbestos worker to the urban dweller with, currently, asbc lung contamination. In addition, it is likely that biological conc of fundamental value will be added to scientific understanding.