# Sir William Osler:

"Listen to the patient; the patient tells you everything."

# Jean-Martin Charcot:

"The patient is a liar."

# Epidemiology of Mesothelioma

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# Outline

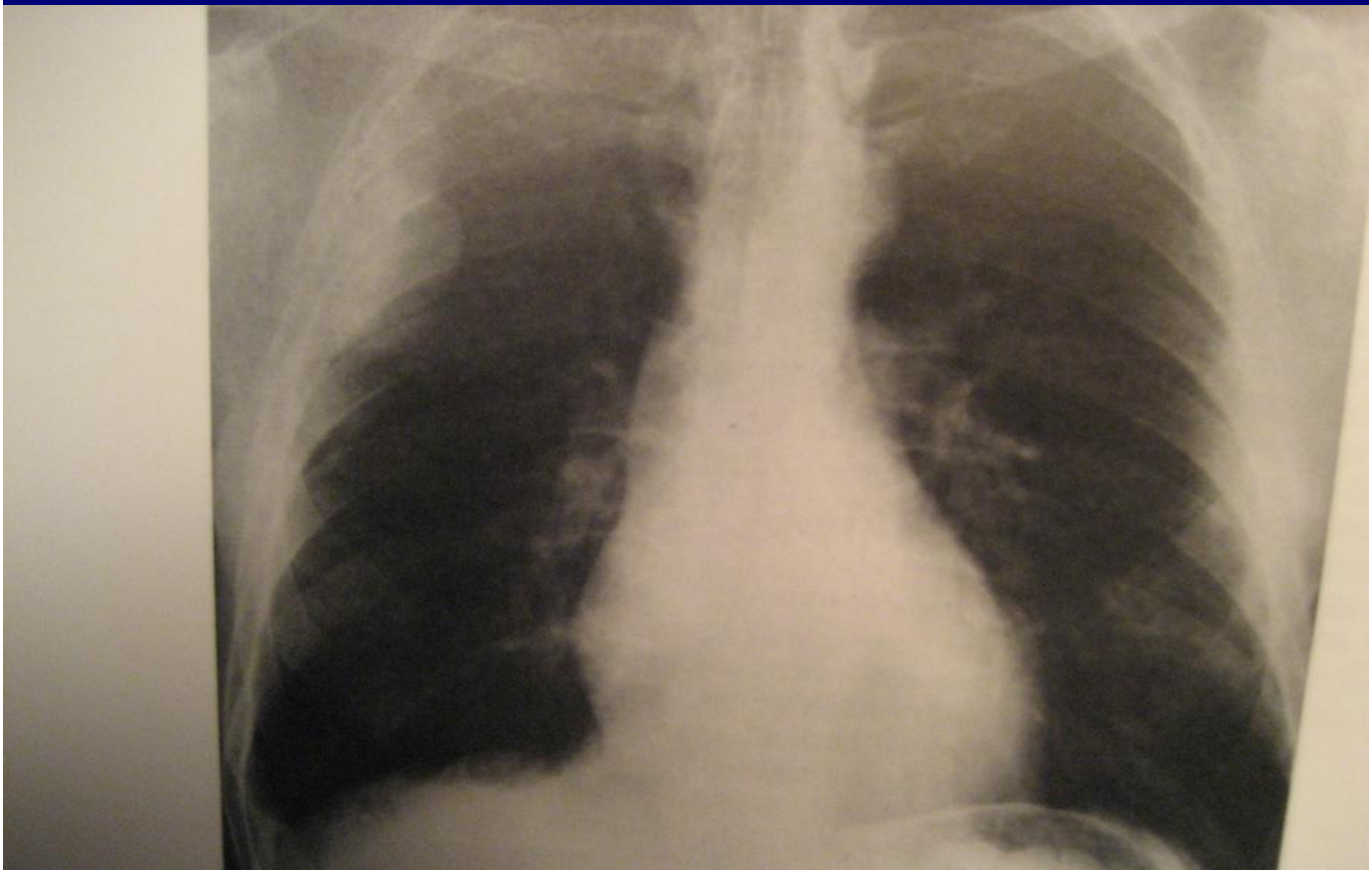
Review of epidemiology of mesothelioma

- Historical context
- Clinical description of disease
- Descriptive epidemiology
- Study issues unique to Minnesota Iron Range

# Clinical History

- Middle-aged gentleman with two-year history as a miner presents with 6-8 week history of right-sided chest pain. Currently a university professor.
- Prior work in the military as jet engine mechanic (1968-72)
- Brake mechanic 1973-75
- Miner from 1975-1979 as “rock crusher”
- Smoked 2 ppd for 10 years
- Exam reveals dullness to percussion right lung along with tenderness T3-6 region

# Miner with Chest Pain



# Differential Diagnosis

Chest Pain and abnormal Chest x-ray:

- Lung cancer with local invasion
- Bone cancer with pulmonary reaction
- Pleural cancer
- Metastatic disease to pleura

# Mesothelioma

- X-ray appearance classic
- Other diagnoses unlikely
- However, lack of criteria for interstitial lung disease and…
- Role of mining???

# Asbestos Historical Perspectives

- 1906-Montague Murray describes “asbestosis”
- 1924-Cooke publishes “asbestosis”
- 1930-Merewether describes asbestosis in English textile workers
- 1935-Lynch and Smith describe lung cancer in patient with asbestosis
- 1946-Fischer and Drinker studied pipe covering on ships
- 1946-ACGIH set standard at 5 mppcf
- 1955-Doll described lung cancer in asbestosis patients
- 1960-Wagner describes mesothelioma in S. African miners from crocidolite exposure
- 1964-Selikoff describes asbestosis, lung cancer and mesothelioma at < 5mppcf

*Brit. J. industr. Med.*, 1960, **17**, 260.

# DIFFUSE PLEURAL MESOTHELIOMA AND ASBESTOS EXPOSURE IN THE NORTH WESTERN CAPE PROVINCE

BY

J. C. WAGNER, C. A. SLEGGS, and PAUL MARCHAND

*From the Pathology Division, Pneumoconiosis Research Unit of the Council for Scientific and Industrial Research, Johannesburg, West End Hospital, Kimberley, and the Department of Thoracic Surgery, University of the Witwatersrand and Johannesburg General Hospital*

(RECEIVED FOR PUBLICATION APRIL 24, 1960)

Primary malignant tumours of the pleura are uncommon. Thirty-three cases (22 males, 11 females, ages 31 to 68) of diffuse pleural mesothelioma are described; all but one have a probable exposure to crocidolite asbestos (Cape blue). In a majority this exposure was in the Asbestos Hills which lie to the west of Kimberley in the north west of Cape Province. The tumour is rarely seen elsewhere in South Africa.

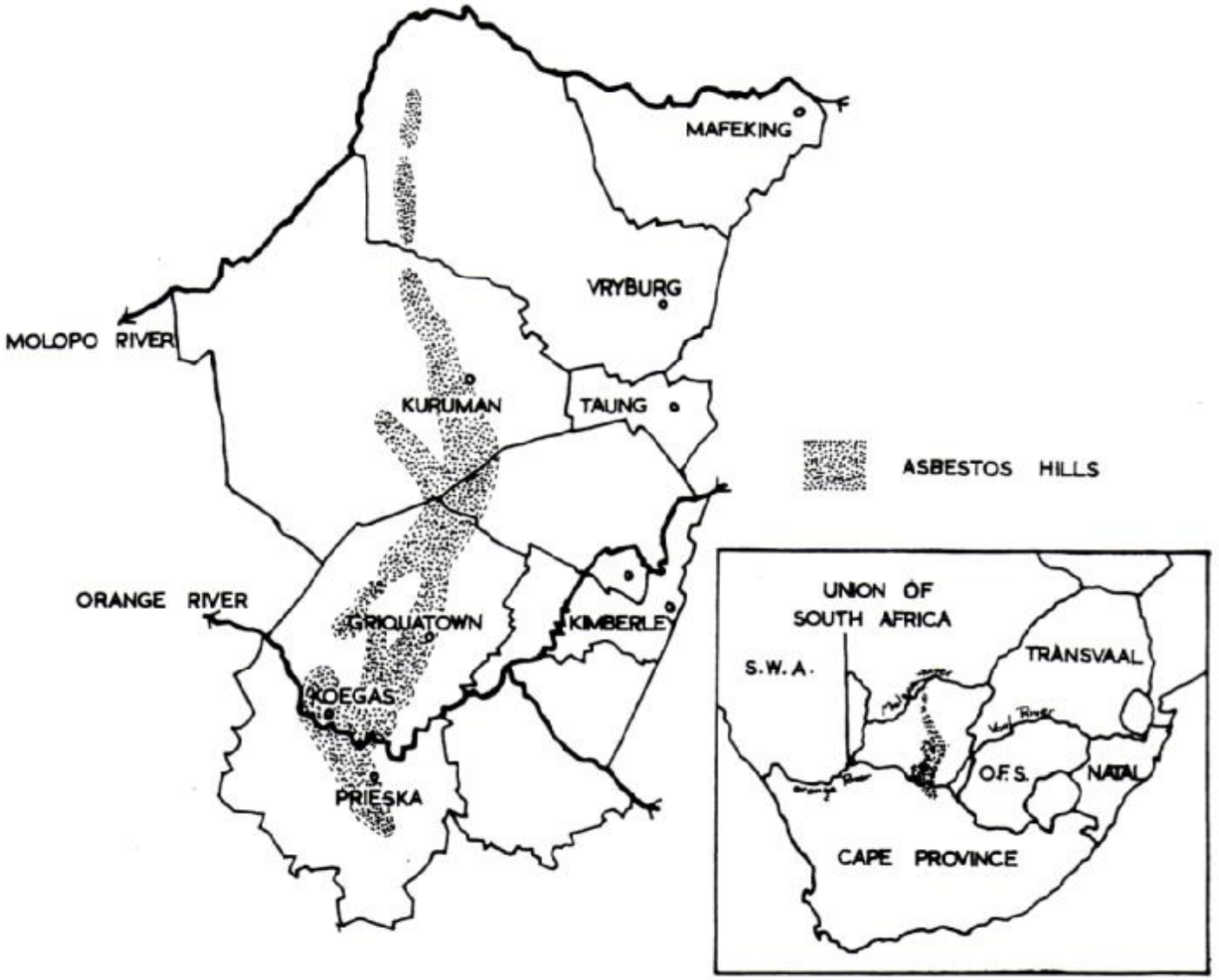



FIG. 1.—Map of Griqualand West asbestos fields.

TABLE 3

DIFFUSE PLEURAL MESOTHELIOMA: ASSOCIATION WITH ASBESTOS

| (1) Case No. | (2) Year of Birth | (3) Age at Diagnosis | (4) Race | (5) Sex | (6) Born on Asbestos Fields | (7) Asbestos Exposure | (8) Diagnosed on Biopsy | (9) Necropsy | (10) Histological Evidence of Asbestosis | S (i |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1920 | 36 | B | M | + | Other history unknown until came to the Witwatersrand at the age of 23 | − | + | + | |
| 2 | ±1913 | ±42 | MXD | M | + | Mined asbestos from 1930-33; left area at the age of 27 | − | +* | − | |
| 3 | 1902 | 53 | B | F | + | Lived whole life in a location near an asbestos mill | + | − | − | |
| 4 | 1896 | 58 | W | F | + | Lived on asbestos fields until the age of 5; worked in asbestos warehouse 1916-20 | + | − | − | |
| 5 | 1925 | 31 | B | M | + | Spent all his working life in the vicinity of mines | − | +* | − | |
| 6 | 1903 | 53 | W | F | + | Lived all her life in the vicinity of mines | + | − | − | |
| 7 | 1920 | 36 | W | M | + | Lived all his life in the vicinity of mines; worked as a miner | + | − | + | |
| 8 | 1894 | 63 | MXD | F | + | From the age of 24 lived in a village serving local mines; often visited mines; watched cobbing outside houses | + | − | − | |
| 9 | 1905 | 52 | MXD | M | + | Whole life spent near mines, digging wells | + | − | − | |
| 10 | 1909 | 49 | W | M | + | Lived at the mine from age 7-17 years; played on dumps and in mine as a boy; returned to assist from age 21-25 | + | − | − | |
| 11 | 1898 | 60 | MXD | M | + | Whole life spent near mines; miner 1931-33 | + | + | + | |
| 12 | 1910 | 48 | B | M | + | Lived near mines until the age of 17; miner 1927 | + | − | + | |
| 13 | 1909 | 50 | W | F | + | Lived near mine until the age of 21; played with fibre as a child | + | − | − | |
| 14 | 1918 | 40 | B | M | + | Whole life spent near mines; miner 1938-41; played on dumps as a child | + | + | + | |
| 15 | 1916 | 42 | W | F | + | Daughter of Case 22; lived at mine until age of 20; went to school near cobbing sheds | + | − | − | |
| 16 | 1896 | 60 | W | M | + | Went to school near mines; transported asbestos 1914-16 | + | − | 0 | |
| 17 | 1911 | 48 | MXD | F | + | Lived on major wagon route till age of 15; several subsequent visits | + | − | − | |
| 18 | 1920 | 38 | B | M | + | Whole life in the vicinity of the mines; miner 1945-58 | + | + | + | |
| 19 | 1922 | 37 | MXD | M | + | Family lived at mine; miner 1938-1959 | + | − | + | |
| 20 | 1906 | 53 | W | F | + | Spent whole life in village on wagon route to Kimberley | + | − | − | |
| 21 | 1912 | 44 | W | M | + | Lived in the vicinity of mines until the age of 16: | | | | |

# Epidemiology of Asbestosis

Insulation Workers Findings (n=1117):

- 10% asbestosis if 0-9 years employment
- 44% asbestosis if 10-19 “ “
- 73% asbestosis if 20-29 “ “
- 87% asbestosis if 30-39 “ “

# Epidemiology of Mesothelioma

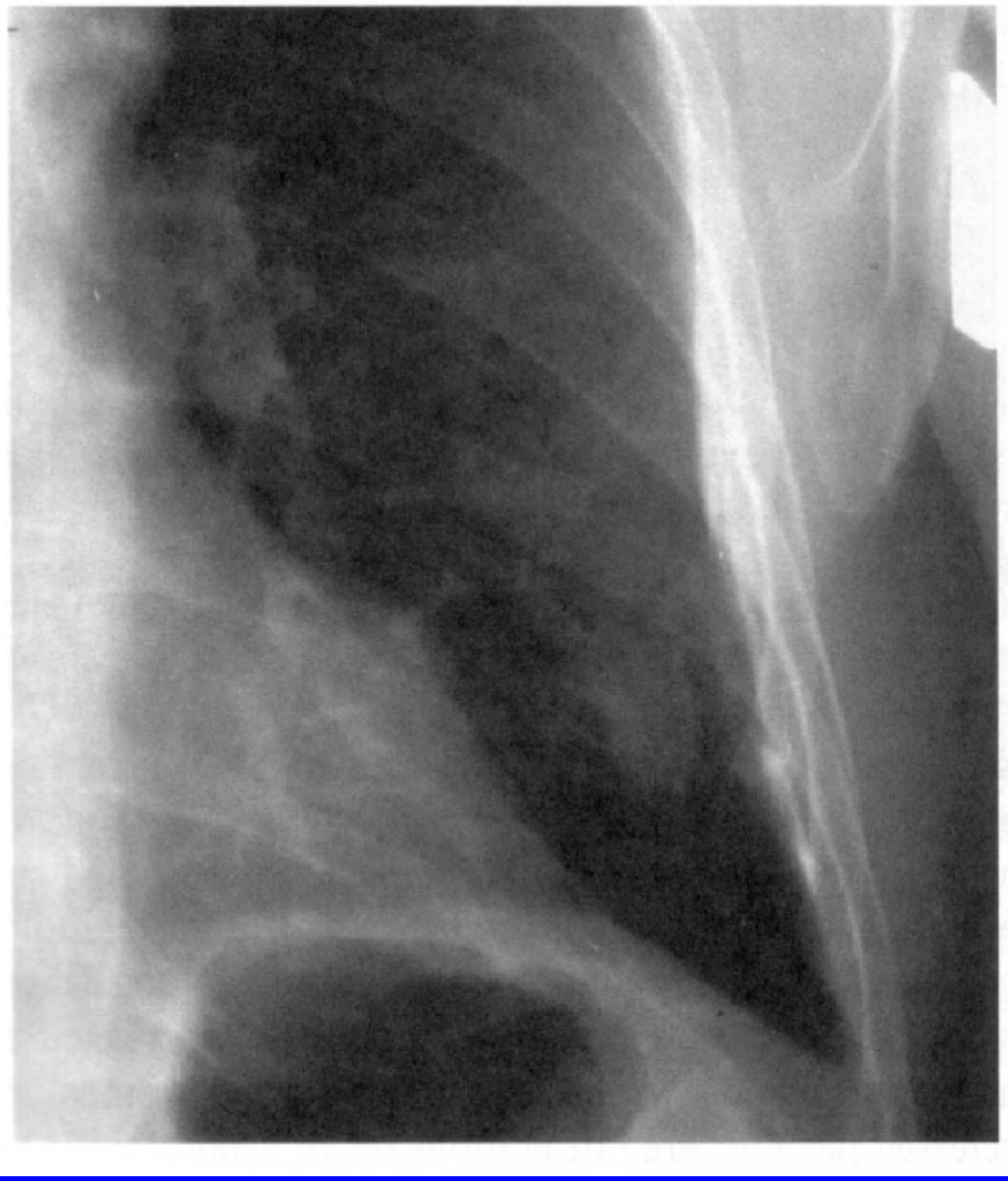
- First described by Wagner, 1960
- Majority with occupational exposure
- Most common in ages 50-70
- Indirect exposure also presents risk
- Fiber type plays a role

# Symptoms and Signs of Mesothelioma

- Most common complaint is chest pain
- Pleural effusion usually present (exudate)
- Local invasion
- Cough, phlegm, wheezing inversely proportional to pulmonary function
- Restrictive defect on PFTs with reduction in lung volumes

# Natural History

- Survival better with epithelial type, with pleural vs. peritoneal, if under 65 years
- Mean survival 8-12 months

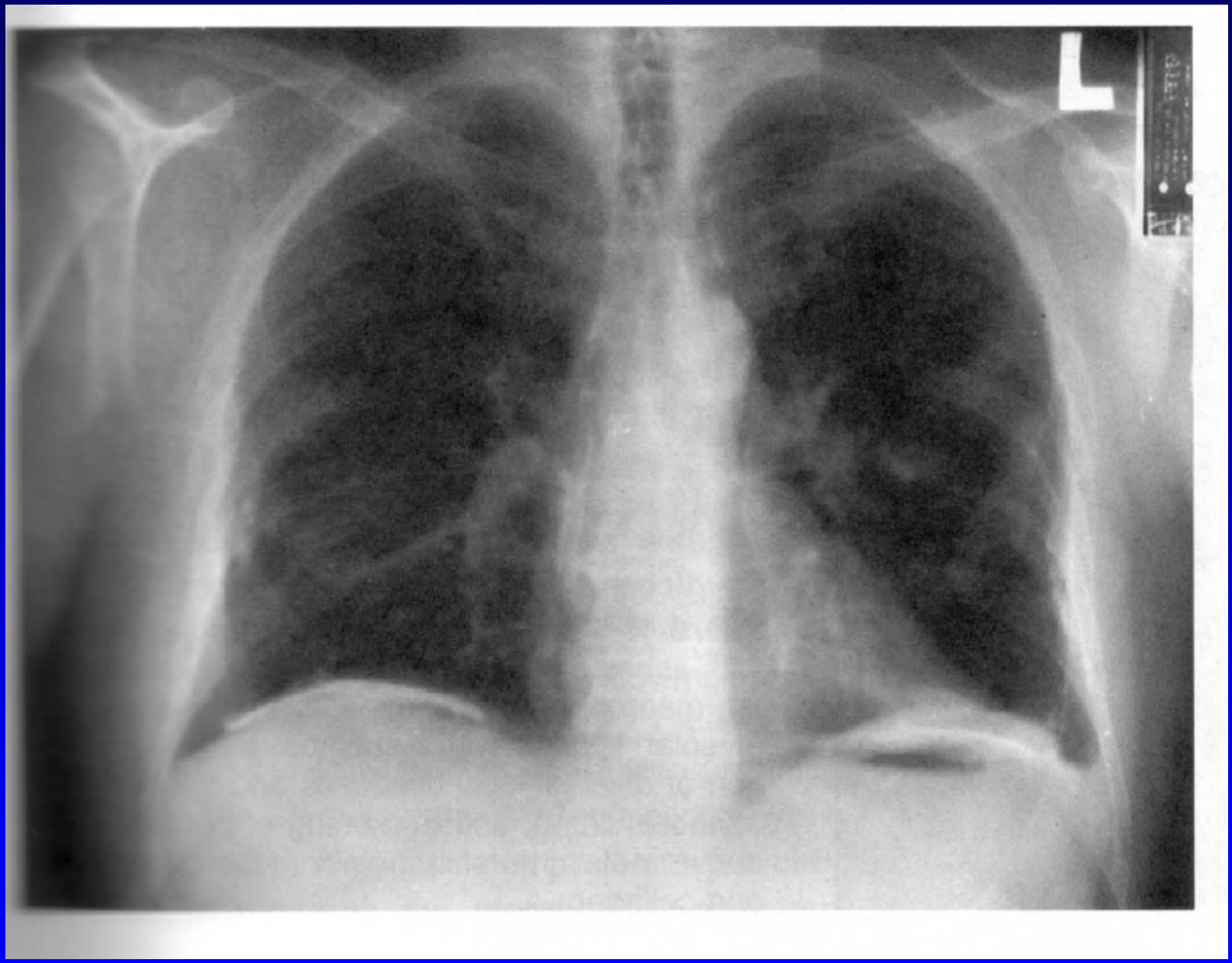


# Pleural Plaques

- 1596 men followed from 1963 to 1985[1]
- 89% with occupational exposure
- Bilateral circumscribed plaques that did not involve the costophrenic angle
- Risk for bronchogenic cancer without asbestosis=1.4*
- Risk for bronchogenic cancer with asbestosis=2.3*
- 9 mesotheliomas; 0.8 expected

[1]Hillerdal, Chest 1994

*$p<0.05$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# Empirical Evidence

- Fiber content in asbestos-related lung diseases
  - Asbestosis
  - Pleural mesothelioma
  - Pleural plaques

# Asbestos Content in Lung Tissue of Asbestos-Associated Disease

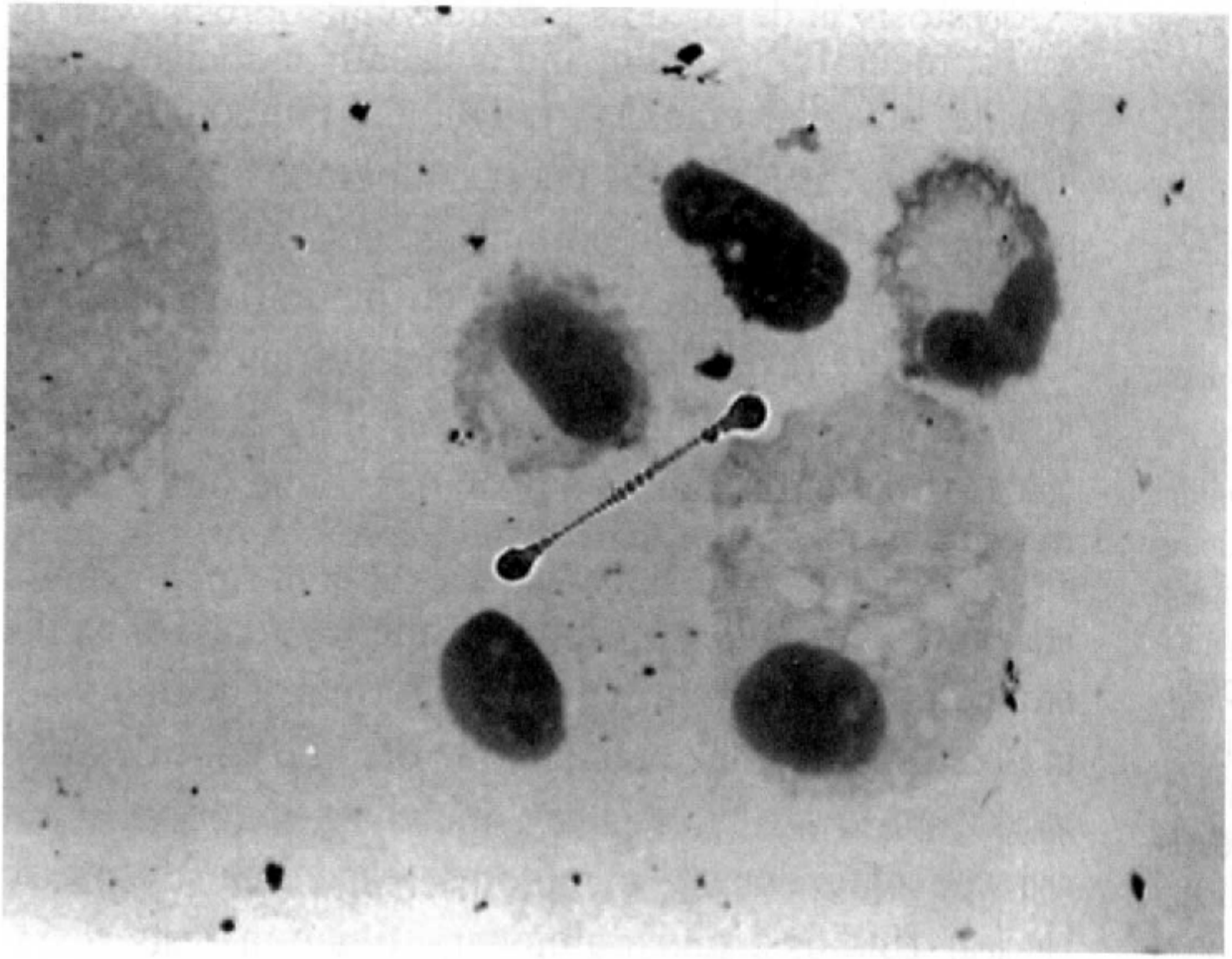
| Disease | N | Asbestos Bodies[a] | Fiber Count[b] |
|---|---|---|---|
| Mesothelioma (pl) | | | |
| +asbestos | 30 | 15,900 | 121,000 |
| +pl plaques | 63 | 900 | 23,200 |
| Reference | 19 | 2.9 | <600 |

[a]number / gm wet tissue

[a]fibers >5 microns / gm wet tissue

# Fiber Type in Asbestos Disease

| Disease | N | Amos/croc | Trem | Chrysotile |
|---|---|---|---|---|
| Mesothelioma (pl) | | | | |
| +asbestosis | 30 | 94,500 | 10,500 | <5500 |
| +pl plaque | 63 | 17,500 | 2,800 | <1500 |
| Reference | 19 | <600 | <600 | <600 |



# Results from Animal Toxicology Studies on Short Fibers

Berman and Crump, 2003:

- Short structures (less than between5-10 microns) do not appear to contribute to risk
- Most potent cancer causing fibers are those longer than 10-20 microns that are also thin in diameter (less than 5 microns)
- Controversy

# Short Fiber Clearance Mechanisms

A. Muco-ciliary
B. Alveolar macrophage
C. Dissolution (narrow fibers)

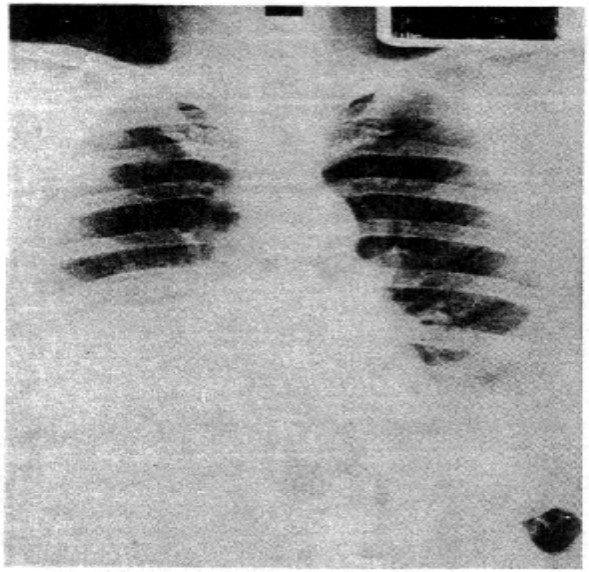


FIG. 5.—On July 21, 1954.

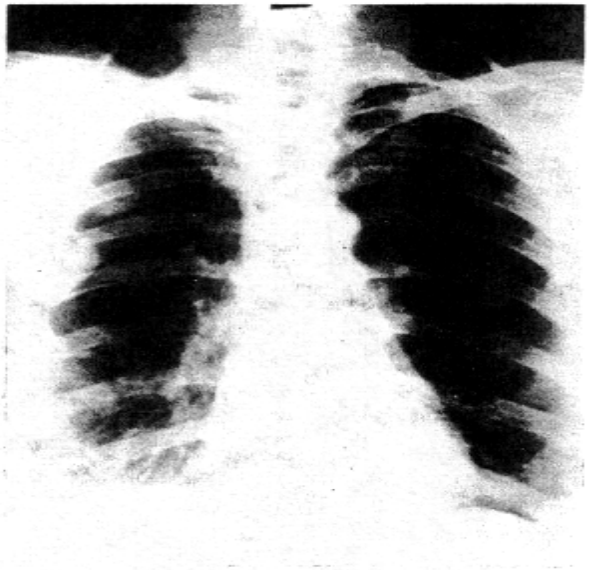


FIG. 6.—On July 7, 1955.

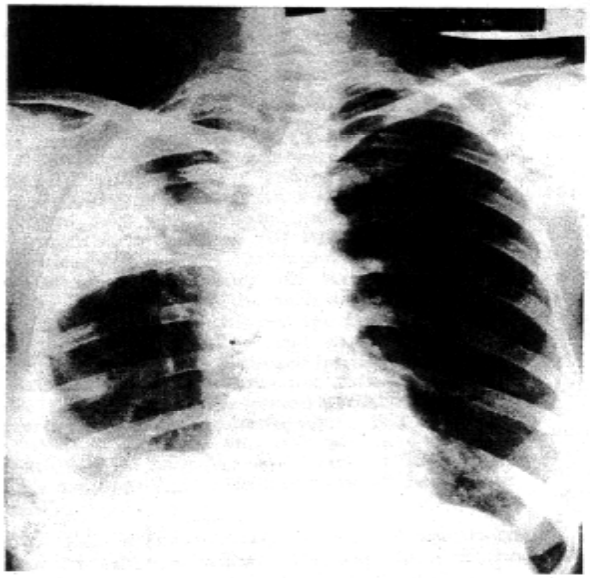


FIG. 7.—On March 3, 1956.

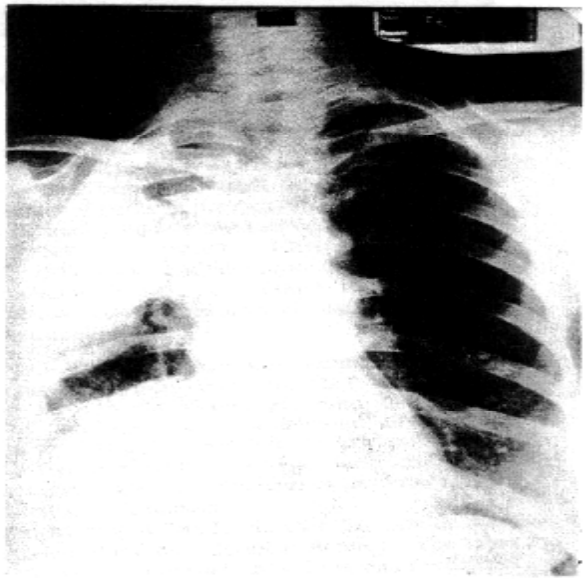


FIG. 8.—On July 3, 1956

FIGS. 5, 6, 7, and 8.—Radiographs showing development of tumour in Case 4.

# Mesothelioma in Spouses

- Italian cement factory (1907-1985)*
- Cohort of 1780 spouses of factory workers
- SMR for malig. meso= 25.0 (95%CI=12.6-45.1)
- SMR for lung cancer= 1.2 (95% CI=0.6-2.0)

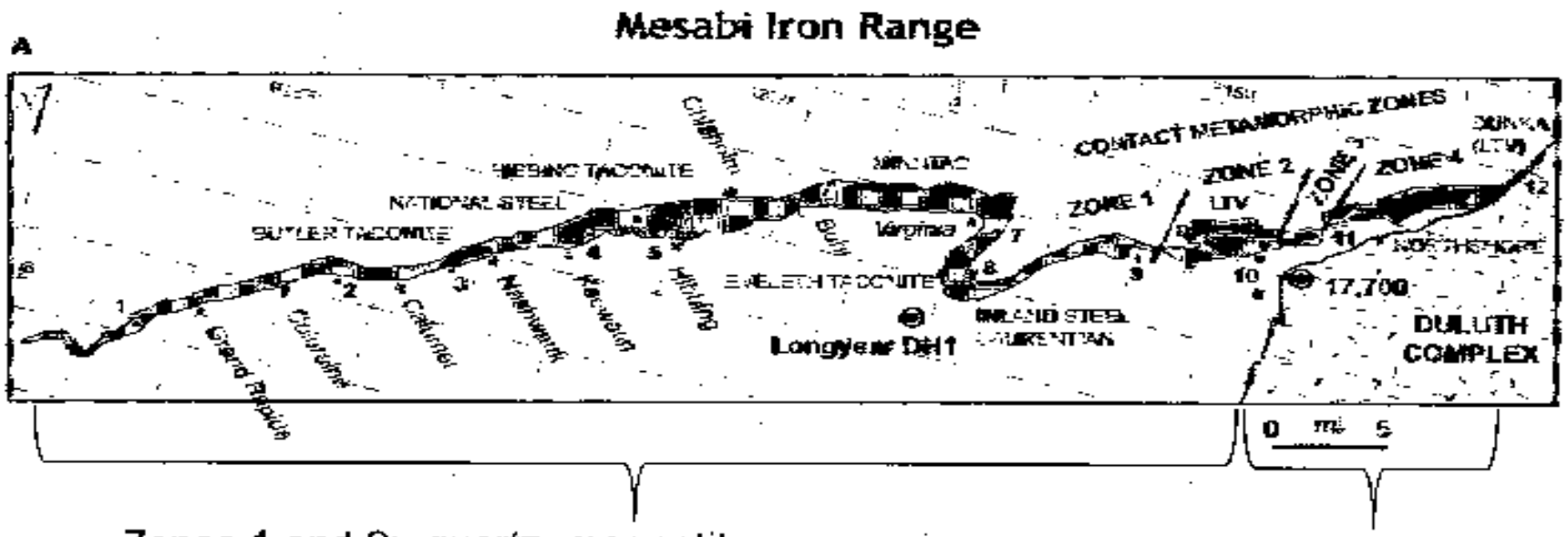
*Ferrante ***et al.,*** EHP, Oct., 2007

# SIRs for Spouses of Cement Workers

| Latency | Duration 0-19 | Duration >20 |
|---|---|---|
| <30 | 12 | --- |
| 30-39 | 37 | 14 |
| >40 | --- | 51 (14-129) |

# Taconite Mineralogy

## West to East

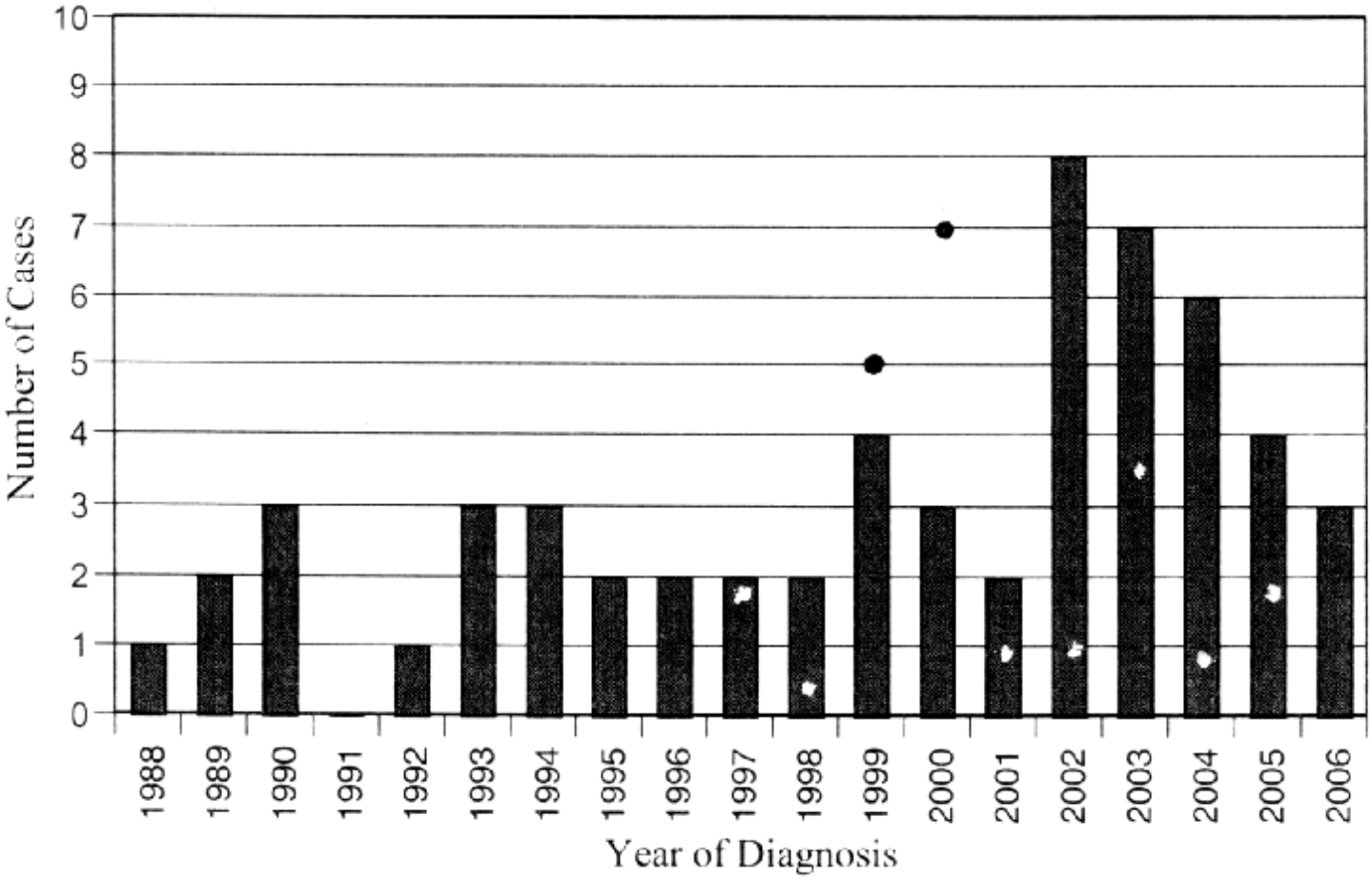



Zones 1 and 2: quartz, magnetite, hematite, carbonates, talc, chamosite, greenalite, minnesotaite and stilpnomelane

Zones 3 and 4: grunerite, hornblende, hedenbergite, ferrohypersthene (ferrosilite), and fayalite

From: OVERVIEW OF THE MINERALOGY OF THE BIWABIK IRON FORMATION, MESABI IRON RANGE, NORTHERN MINNESOTA Peter L. McSwiggen and G.B. Morey (in press).

**Mesothelioma Cases (N=58) Identified by MCSS Record Linkage Among 71,648 Minnesota Iron Miners by Year of Diagnosis, 1988-2006***




*Record linkage with MCSS performed on 06/18/07; 2006 data not yet complete; no cases identified for 2007 as of linkage date.

# 58 Mesothelioma Cases

- Represent cases from 1988 via MCSS
- Occur throughout the Iron Range based on where miners worked
- Rates elevated across age groupings
- Likely under-represents actual number
- Role of mining??

# Estimated Risk Comparisons

- Libby cohort (tremolite)

  15 cases / 1871 workers followed over 34 years ⟶

  23 / 100,000 p-y's

- Taconite cohort (cummingonite, grunerite)

  58 cases / 72,000 workers followed over 18 years ⟶

  4.5 / 100,000 p-y's

Cooper *et al.*, JOM, 1988

**TABLE 2**

Observed and Expected Deaths by Major Causes, 1948–1983 in Taconite Miners and Mill Workers Employed in Taconite-exposed Jobs for 3 Months or More Prior to Jan 1, 1959, Compared with US White Men

| Cause of Death (ICD 7th Rev, 1955) | Deaths | | SMR* | Confidence limits | |
|---|---|---|---|---|---|
| | Observed | Expected | | 95% | 99% |
| All causes (001–998) | 801 | 914.0 | 88† | 82–94 | 80–96 |
| All malignant neoplasms (140–205) | 158 | 188.2 | 84‡ | 71–98 | 68–103 |
| Digestive organs and peritoneum (150–159) | 48 | 49.6 | 97 | 71–128 | 64–139 |
| Stomach (151) | 5 | 8.7 | 58 | 19–135 | 13–164 |
| Large intestine (153) | 21 | 16.4 | 128 | 79–196 | 68–220 |
| Respiratory system (160–164) | 41 | 67.7 | 61† | 43–82 | 39–89 |
| Bronchus, trachea, lung (162–163) | 38 | 64.3 | 59† | 42–81 | 37–89 |
| Kidney (180) | 9 | 4.9 | 185 | 85–351 | 64–411 |
| Lymphopoietic system (200–205) | 22 | 18.9 | 117 | 73–177 | 62–197 |
| All diseases circulatory system (400–468) | 360 | 406.4 | 89‡ | 80–98 | 77–101 |
| Arteriosclerotic heart disease (420) | 289 | 339.6 | 85† | 76–96 | 73–99 |
| Non-malignant respiratory disease (470–527) | 34 | 51.7 | 66‡ | 45–92 | 40–101 |
| Cirrhosis of liver (581) | 22 | 27.5 | 80 | 50–121 | 43–135 |
| All external causes of death (800–998) | 105 | 94.3 | 111 | 91–135 | 86–143 |
| All accidents (800–962) | 73 | 62.9 | 116 | 91–146 | 84–156 |
| Motor vehicle accidents (810–835) | 30 | 29.3 | 102 | 69–146 | 61–161 |
| Suicides (963, 970–979) | 29 | 22.6 | 128 | 86–184 | 75–203 |
| Cause unknown | 23 | — | — | — | — |
| Number of workers | | | 3,444 | | |
| Number of person-years | | | 86,341 | | |
| Deaths per 1,000 person-years | | | 9.3 | | |
| Adjustment of cause-specific SMRs for missing certificates | | | +3.0% | | |

* Standardized mortality ratio.
† Significant at the 1% level, $P = \leq .01$.
‡ Significant at the 5% level, $P = \leq .05$.

Cooper *et al.*, JOM, 1988

## Slide 33

**jhm1** jmandel, 11/10/2007

Cooper *et al.*, JOM, 1988

**TABLE 5**

Observed and Expected Deaths 1948–1983 for Selected Causes in Subcohorts of Taconite Miners and Mill Workers Who Ever or Never Worked in Indicated Areas (US Rates)

| Subcohort (Work Area Code) | All Deaths | | | Respiratory Cancer | | | Kidney Cancer | | |
|---|---|---|---|---|---|---|---|---|---|
| | Observed | Expected | SMR* | Observed | Expected | SMR | Observed | Expected | SMR |
| Mining (01) | | | | | | | | | |
| Ever 398 | 398 | 462 | 86† | 24 | 34 | 70 | 5 | 2.4 | 205 |
| Never 403 | 403 | 452 | 89† | 17 | 33 | 51† | 4 | 2.3 | 172 |
| Grinding and Conc (02–04) | | | | | | | | | |
| Ever 243 | 243 | 297 | 82† | 12 | 23 | 52‡ | 4 | 1.7 | 241 |
| Never 558 | 558 | 617 | 91‡ | 29 | 45 | 65‡ | 5 | 2.2 | 156 |
| Pelletizing (05) | | | | | | | | | |
| Ever 245 | 245 | 281 | 87‡ | 12 | 21 | 56‡ | 3 | 1.5 | 198 |
| Never 556 | 556 | 633 | 88† | 29 | 46 | 62‡ | 6 | 3.4 | 179 |
| In any of above | | | | | | | | | |
| Ever 589 | 589 | 695 | 85† | 30 | 52 | 58† | 8 | 3.7 | 217 |
| Never 212 | 212 | 219 | 97 | 11 | 16 | 69 | 1 | 1.2 | 84 |
| In high or medium dust area | | | | | | | | | |
| Ever 539 | 539 | 571 | 94 | 27 | 43 | 63‡ | 6 | 3.1 | 195 |
| Never 262 | 262 | 343 | 77 | 14 | 25 | 56 | 3 | 1.8 | 170 |
| In high dust area | | | | | | | | | |
| Ever 270 | 270 | 282 | 96 | 12 | 21 | 57‡ | 0 | 1.5 | — |
| Never 531 | 531 | 632 | 84 | 29 | 47 | 62‡ | 9 | 3.4 | 265 |
| **Total population** | **801** | **914** | **88†** | **41** | **68** | **61†** | **9** | **4.9** | **185** |

* Standardized mortality ratio.
† Significant at the 1% level, $P = \leq .01$.
‡ Significant at the 5% level, $P = \leq .05$.

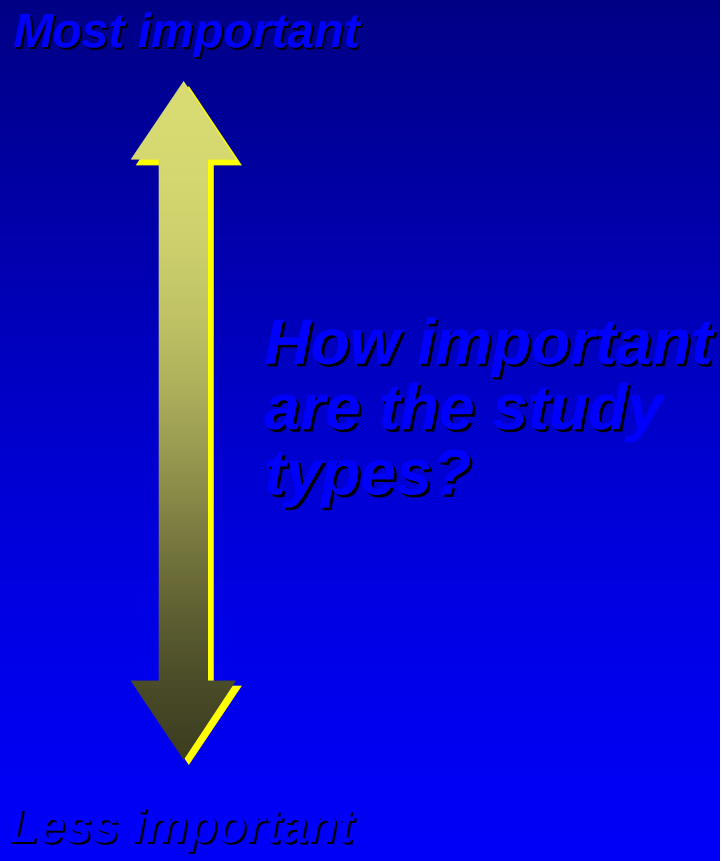
Cooper *et al.*, JOM, 1988

# Study Types:
# (Different types have different importance ):

1. Hypothesis testing studies
   - Randomized trial

   (normally used for studying drugs)
   - Cohort
   - Case-control

2. Hypothesis generating studies
   - Case series
   - Case reports



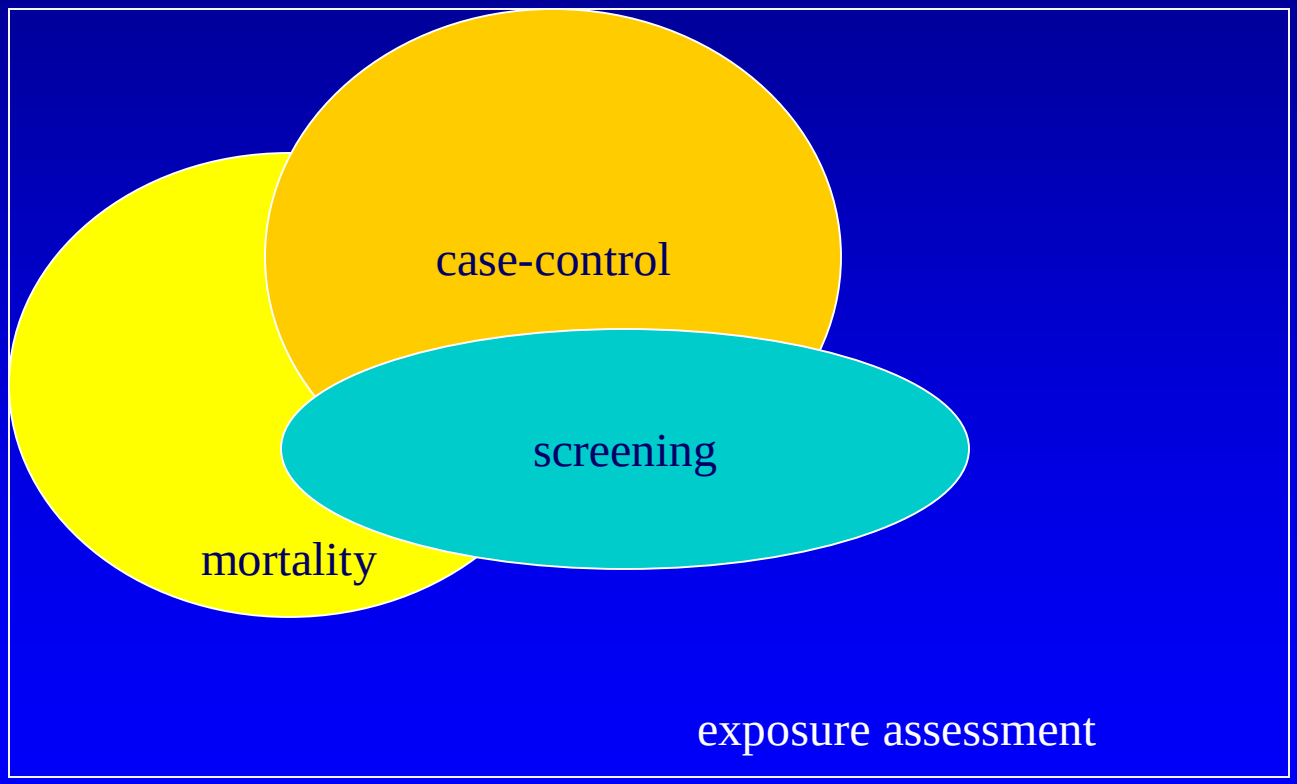
# Consistency

Best evidence when…

- Multiple studies with same findings
- Different investigators with same findings
- Various times with similar results
- Alternative methodologies with similar results
- Variety of geographic or cultural settings with similar results
- Various comparable populations with similar results

# Health Assessment Approach

Combined study types:



# Summary

- Mesothelioma presents with chest pain and typical x-ray appearance
- Risk related to amount and type of exposure
- Risk varies by occupation
- Asbestos type and size plays a role in determining risk
- Pleural plaques indicate exposure but may have risk associated
- Case series in northeastern MN needs further investigation to determine factors associated