Brief review of asbestos health effects and pathology of asbestos-related disease.

Bruce W. Case, M.D., Dipl. Occup. Hygiene, M.Sc., FRCP(C)

With a few things added by "the presenter":

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In the past:

- Very frequently, amphibole asbestos (amosite, crocidolite) was mixed with the chrysotile.
- There was little or no attempt to differentiate exposure to these two very different minerals.

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Chrysotile vs Amphibole asbestos

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Chrysotile

- Chrysotile is a rolled sheet material like mica.
- The sheet is about 8 angstroms (0.8 nanometers) thick and,
- because of molecular constraints, is rolled into cylindrical form.
- The cylinders are chrysotile fibrils which bunch together to form a chrysotile fiber.
- The chrysotile fiber is acid soluble (von Kobell, 1834; Pundsack, 1955).
-

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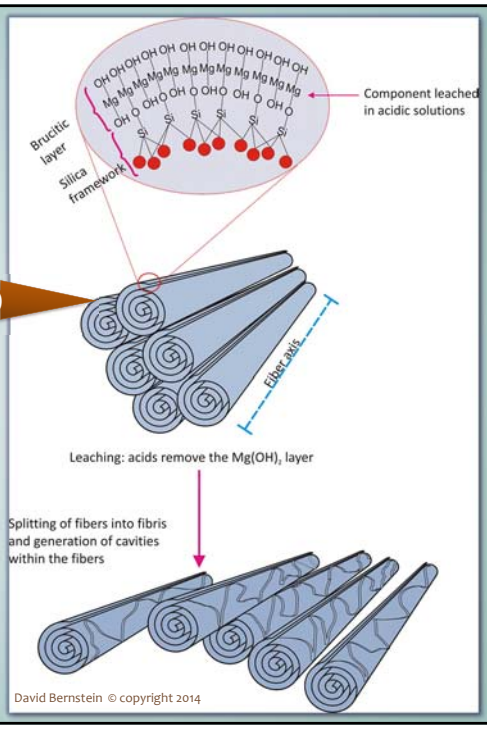
Chrysotile

8 angstroms (0.8 nanometers)

Decomposes in acid



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Chrysotile

- In acid the rolled sheet of the chrysotile fiber breaks apart into small pieces.
- This is important:
  - In the lung – the cell which clears fibers & particles from the lung – the macrophage – creates an acid environment.
  - In the gut (acid environment) .

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Amphibole asbestos

- The amphibole asbestos class of fibers are formed as solid rods/fibers (Skinner et al., 1988).
- The structure of an amphibole makes it very strong and durable.
- The external surface of the crystal structures of the amphiboles is quartz-like, and has the chemical resistance of quartz.
- Amphibole fibers, therefore, have negligible solubility at any pH that might be encountered in an organism (Speil and Leineweber, 1969).

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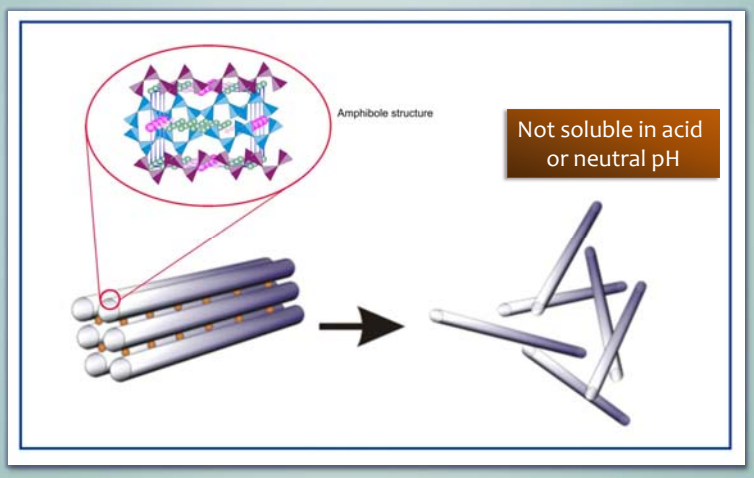
Amphibole asbestos



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In most epidemiology studies

- Either chrysotile was not differentiated from amphibole asbestos.
- Or if it was, the authors still stated that small amounts of amphibole were present.
- Differentiation between diseases caused by amphibole asbestos and chrysotile is difficult.

Occupational disease may be defined as

1. *Any loss of function or change in structure*
2. *of human tissues or organs determined in whole or in part through*
3. *exposure to agents encountered in the occupational environment.*

Role of the Pathologist

Exposure — ***Identify it*** *(in tissue)*

→ ***Mechanism, linkage***

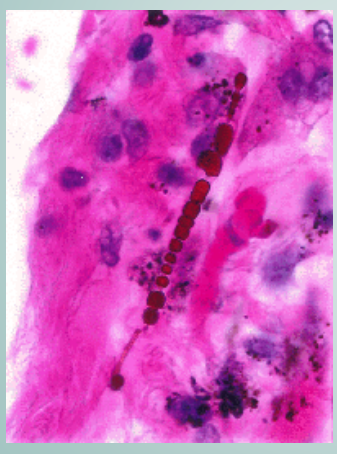
(Find out how it works)

→ **Effect**

Measure it!

Identifying an exposure by light microscopy

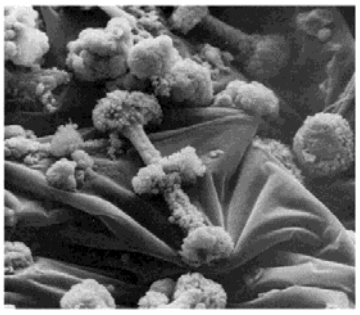
Identify it *(in tissue)*



Identifying an exposure by electron microscopy

⇐ TRANSMISSION

OR SCANNING ⇩



T = tremolite asbestos

Ch = chrysotile asbestos

Concordance (Mesothelioma only) Chest physician/radiologist – pathologist

Chest MD /radiologist	Pathologist					Total
	Definite /probable	Possible	Unlikely	Not a meso	Impossible to classify	
Definite/ probable	**46**	11	1	0	1	59
Possible	11	**8**	5	2	1	27
Unlikely	0	2	**2**	2	1	7
Not a meso	0	1	1	**2**	1	5
Impossible to classify	1	1	1	0	**1**	4
Total	58	23	10	6	5	102

Exact concordance : 57.8%

± 1 category: 84.0%

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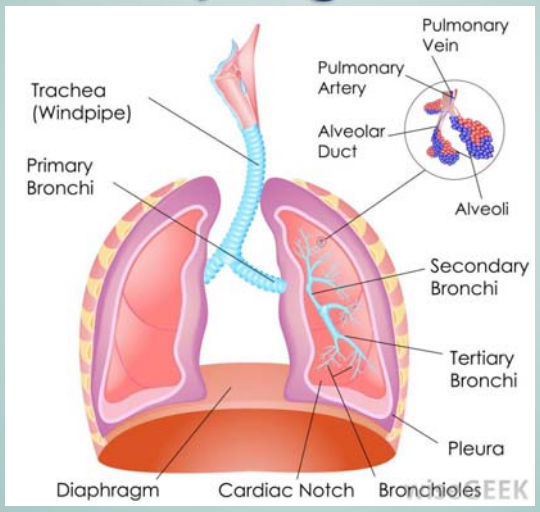
Lung, chest wall & diaphragm



Principal Asbestos Health Effects - OUTLINE

1. Malignancies – Which ones, with how much confidence?
   - all or nothing
2. Nonmalignant Effects (and ?? Noneffects)
   - may be matters of degree
3. Other potential effects

Principal Asbestos Health Effects

Malignant

All **Neoplasms? – the Doll/ Peto observations**

IARC-"certified" neoplasms:

Caveats about IARC generally

- hazard evaluation vs. risk
- who is IARC?
- problems in the IARC Process

Asbestos and all cancers

- There are 10,000 to 30,000 published papers…
- One can find case reports, "opinions", and even isolated epidemiologically oriented studies claiming to show a relationship for a large number of cancers other than mesothelioma and lung cancer – and as many in the other direction
- Meta-analyses can help, within reason

Doll R, Peto J (1987), Other asbestos-related neoplasms. In: Antman K and Aisner J. eds. *Asbestos-Related Malignancy*. Grune & Stratton.

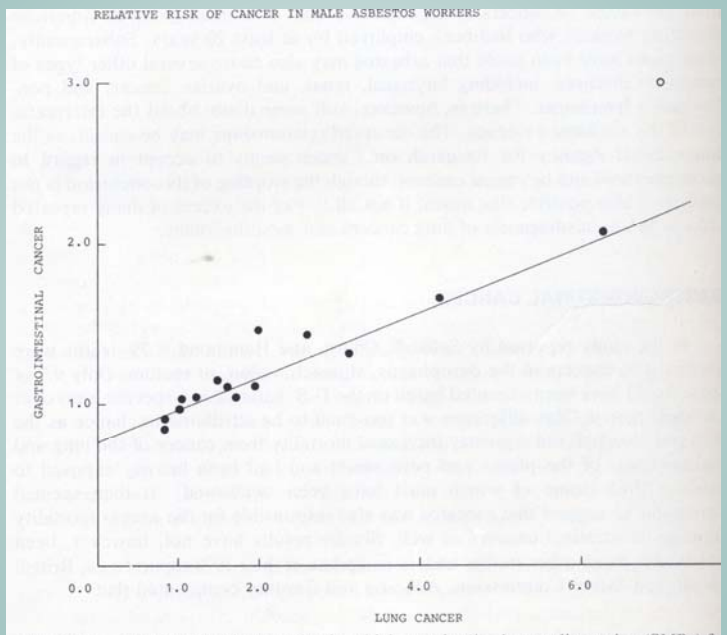


Figure 4-1. The results of 18 studies in which standardized mortality ratios (SMRs) fo

Possible interpretations:

- Asbestos as a "general carcinogen"
- Confounding effects of misdiagnosis (indeed in this particular study this was judged true: "The marked correlation across studies between the relative risk for lung cancer and for all other sites combined is entirely explicable in terms of *misdiagnosis of lung cancers and mesotheliomas*")

Principal Asbestos Health Effects

Malignant

All Neoplasms? – the Doll/ Peto observations

IARC-"certified" neoplasms:

Caveats about IARC generally

- hazard evaluation vs. risk
- who is IARC?
- problems in the IARC Process
- changes in "causation" over time

Principal Asbestos Health Effects

Malignant

IARC-"certified" neoplasms:

- mesothelioma
  - caveats
- asbestos-related lung cancer
  - caveats and the smoking interaction problem
- laryngeal cancer
  - the role of smoking and alcohol
- ovarian cancer?
  - serious problems

- IARC "rejected" neoplasms – "insufficient evidence" vs. "suspicious", e.g. colon, esophagus – not discussed here, but well discussed by National Academy of Sciences (US)/ Institute of Medicine 2006. Committee on Asbestos: Selected Health Effects.

Principal Asbestos Health Effects

Malignant

IARC-"certified" neoplasms:

- mesothelioma
  - caveats
- asbestos-related lung cancer
  - role of asbestosis if any,
- smoking interaction problem
- laryngeal cancer
  - the role of smoking and alcohol
- ovarian cancer?
  - serious problems

IARC "rejected" neoplasms

Effect of early studies of asbestos-related lung cancer

- **Doll R. 1955:**

Brit. J. industr. Med., 1955, **12**, 81.

MORTALITY FROM LUNG CANCER IN ASBESTOS WORKERS

BY

RICHARD DOLL

From the Statistical Research Unit, Medical Research Council, London

(RECEIVED FOR PUBLICATION AUGUST 10, 1954.)

TABLE 4

CAUSES OF DEATH AMONG MALE ASBESTOS WORKERS COMPARED WITH MORTALITY EXPERIENCE OF ALL MEN IN ENGLAND AND WALES

Cause of Death	No. of Deaths		Test of Significance of Difference between Observed and Expected (Value of P)
	No. Observed	Expected on England and Wales Rates	
Lung cancer* :			
with mention of asbestosis..	11	—	<0·000001
without mention of asbestosis	0	0·8	

Effect of early studies of asbestos-related lung cancer

British Journal of Industrial Medicine 1991;48:229–233

Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study

Janet M Hughes, Hans Weill

Effect of early studies of asbestos-related lung cancer

Discussion

In this study, asbestos workers without *x* ray film evidence of lung fibrosis did not experience a raised lung cancer risk whereas in workers with small opacities $\geq 1/0$ it was substantially increased even though their exposures to asbestos were similar to the long term workers without opacities. These findings are consistent with lung fibrosis (asbestosis) having been a necessary precursor for asbestos induced lung cancer in this population. Workers entered and

Asbestosis: is it "necessary"?

- substantial overlap in exposure data between lung cancer cases among asbestos workers with and without asbestosis despite the significant excesses in exposure among groups of asbestotics.
- Co-linearity of exposures = false "causal" relationship or "necessary" condition
- No > Detection limit

Asbestosis: is it "necessary"?

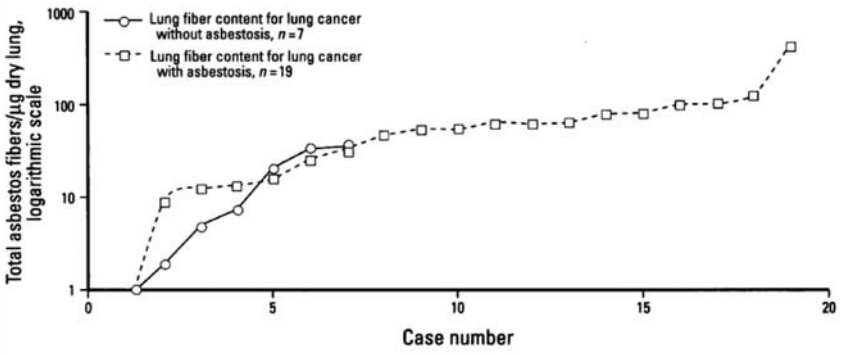


Figure 1. Total lung-retained asbestos fiber in lung cancer cases with and without asbestosis.

Asbestosis: is it "necessary"?

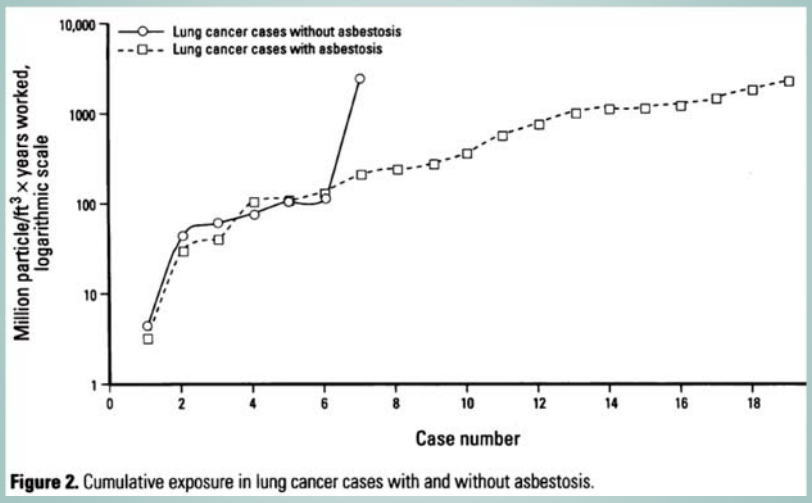


Figure 2. Cumulative exposure in lung cancer cases with and without asbestosis.

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Pathology of Asbestosis—An Update of the Diagnostic Criteria

Report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society

Victor L. Roggli, MD; Allen R. Gibbs, MD; Richard Attanoos, MD; Andrew Churg, MD; Helmut Popper, MD; Philip Cagle, MD; Bryan Corrin, MD; Teri J. Franks, MD; Francoise Galateau-Salle, MD; Jeff Galvin, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Koichi Honma, MD

Arch Pathol Lab Med—Vol 134, March 2010

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- Asbestosis is defined as diffuse pulmonary fibrosis caused by the inhalation of excessive amounts of asbestos fibers. Pathologically, both pulmonary fibrosis of a particular pattern and evidence of excess asbestos in the lungs must be present. Clinically, the disease usually progresses slowly, with a typical latent period of more than 20 years from first exposure to onset of symptoms.

- **Differential Diagnosis: Idiopathic Pulmonary Fibrosis.—**
- The pulmonary fibrosis of asbestosis is interstitial and has a basal subpleural distribution, similar to that seen in idiopathic pulmonary fibrosis, which is the principal differential diagnosis.
- However, there are differences between the 2 diseases apart from the presence or absence of asbestos.
- First, the interstitial fibrosis of asbestosis is accompanied by very little inflammation, which, although not marked, is better developed in idiopathic pulmonary fibrosis.
- Second, in keeping with the slow tempo of the disease, the fibroblastic foci that characterize idiopathic pulmonary fibrosis are infrequent in asbestosis.
- Third, asbestosis is almost always accompanied by mild fibrosis of the visceral pleura, a feature that is rare in idiopathic pulmonary fibrosis.
-

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- **Differential Diagnosis: Respiratory Bronchiolitis.—**
- Asbestosis is believed to start in the region of the respiratory bronchiole and gradually extends outward to involve more and more of the lung acinus, until the separate foci of fibrosis link, resulting in the characteristically diffuse pattern of the disease.
- These early stages of the disease are diagnostically problematic because similar centriacinar fibrosis is often seen in cigarette smokers and is characteristic of mixed-dust pneumoconiosis.
- Fibrosis limited to the walls of the bronchioles does not represent asbestosis.

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- **Role of Asbestos Bodies.—**
- Histologic evidence of asbestos inhalation is provided by the identification of asbestos bodies either lying freely in the air spaces or embedded in the interstitial fibrosis.
- Asbestos bodies are distinguished from other ferruginous bodies by their thin, transparent core.
- Two or more asbestos bodies per square centimeter of a 5-mm thick lung section, in combination with interstitial fibrosis of the appropriate pattern, are indicative of asbestosis.
- Fewer asbestos bodies do not necessarily exclude a diagnosis of asbestosis, but evidence of excess asbestos would then require quantitative studies performed on lung digests.

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- **Role of Fiber Analysis.—**
- Quantification of asbestos load may be performed on lung digests or bronchoalveolar lavage material, employing either light microscopy, scanning electron microscopy, or transmission electron microscopy.
- Whichever technique is employed, the results are only dependable if the laboratory is well practiced in the method chosen, frequently performs such analyses, and the results are compared with those obtained by the same laboratory applying the same technique to a control population.

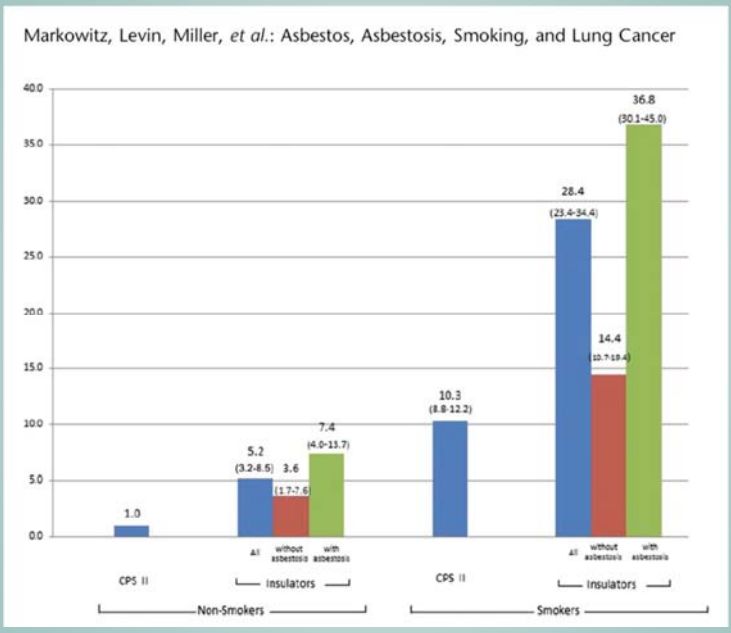
Original (and largely discredited) model based on insulators

	SMOKING	
	NO	YES
ASBESTOS EXPOSURE		
NO	1	10
YES	5	?

Original (and largely discredited) model based on insulators

SMOKING		
	NO	YES
ASBESTOS EXPOSURE		
NO	1	10
YES	5	50

Lung cancer and smoking: interaction (more than additive)



Am J Respir Crit Care Med Vol 188, Iss. 1, pp 90–96, Jul 1, 2013

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What does smoking do?

- It increases effective dose to the lung of asbestos.
  - Decreases cilia efficiency for clearing fibers
  - May decrease ability of the macrophages to clear fibers
  - May act synergistically with the fibers.

Lung cancer and smoking: interaction (more than additive)

- Unanswered (unanswerable?) question: how does one know "which cases" in those with smoking AND asbestos exposure are "due to" the latter?
- What does "due to" mean?
- Implications for litigation / compensation
- Role of exposure assessment/ lung-retained fibre analysis

For lung cancer candidate "pathology types" include

1. ***Site (Lobe, central / peripheral)***
2. ***Histological type***
3. ***Molecular pathology (huge number of possible markers)***

Increasingly another part of "what a lung cancer is" pathologically has to do with the cancer's *molecular pathology*

- **This can be related to histological type (or not);**
- **Two examples are EGFR and *ALK* mutations* in adenocarcinoma; mutations which if present may change treatment.**
- **Attempts have been made to relate this aspect of "what a lung cancer is" to exposure**

*Epidermal growth factor receptor (EGFR) mutations and anaplastic large-cell lymphoma kinase (ALK) rearrangements (Cureus. 2016 Feb 26;8(2): Concurrent EGFR Mutation and ALK Translocation in Non-Small Cell Lung Cancer. Sweis RF, Thomas S, Bank B, Fishkin P, Mooney C, Salgia R)

Tuononen K ET AL. ALK fusion and its association with other driver gene mutations in Finnish non-small cell lung cancer patients. Genes Chromosomes Cancer. 2014 Nov;53(11):895-901.

- Non small-cell LC with ALK gene rearrangements.
- Assessed 469 lung cancers in FINLAND
- Only 11 (2.3%) were ALK+; 9 adenocarcinoma; median age 15 years younger; 100% *Nonsmokers or ex-light smokers; NONE had history of asbestos exposure. (But devil in details…)*

Principal Asbestos Health Effects

Malignant

IARC-"certified" neoplasms:

- mesothelioma

- asbestos-related lung cancer

- caveats and the smoking interaction problem

- laryngeal cancer

- the role of smoking and alcohol

- ovarian cancer?

- serious problems

IARC "rejected" neoplasms

- **Pathology of mesothelioma**

  Subtypes – History

  The importance and history of immunohistochemistry

  Are pleural and peritoneal mesothelioma the same disease?

Are pleural and peritoneal mesothelioma the same disease?

- Historically peritoneal mesothelioma was particularly associated with **high commercial amphibole dose** such as that experienced by American insulators (Selikoff, Churg et al. 1964, Ribak, Lilis et al. 1988).
- In the 1988 study, more insulation workers (N = 222; amosite and chrysotile) died of peritoneal mesothelioma; vs 134 of pleural mesothelioma (deaths 1967-1984).
- Was this "real"?

Are pleural and peritoneal mesothelioma the same disease?

- Conversely for chrysotile mining and milling, among 8009 deaths all of 33 cases before 1993 were pleural (McDonald, Case et al. 1997).
- Recently that pattern seems to have changed, particularly for younger cases, with peritoneal cases in fact *less likely to be associated with asbestos exposure than pleural cases* in some studies ((Ribak, Lilis et al. 1988, Moolgavkar, Meza et al. 2009)).
- Outlier: ?? Chinese "chrysotile" textile workers??

Are pleural and peritoneal mesothelioma the same disease?

- Histological and immunohistochemical profiles: more epithelioid cases for peritoneal*
- More possible genetic "events" potentially leading to pleural mesothelioma, which could also explain the greater rate of disease at that site and greater asbestos susceptibility (Dragon, Thompson et al. 2015).
- Different (and changing) response to treatment
- A "biologically different disease"?

*There are three major types—epithelioidtype (Papillo-tubular structure is prominent), sarcomatoid type (Proliferation of spindle cells mimies true sarcoma) and biphasic type—and the pro-portion of each is approximately 60, 20 and 20%,respectively (Inai, 2008).

Pathology of mesothelioma

How accurate is the diagnosis?

How many false negatives and false positives are there, and

Is there any way to avoid them?

How accurate is the diagnosis? How many false negatives and false positives

ORIGINAL ARTICLE

Pleural mesothelioma surveillance: Validity of cases from a tumour registry

France Labrèche PhD[1,2], Bruce W Case MD MSc Dipl Occup Hygiene FRCPC[3], Gaston Ostiguy MD MSc FRCPC[4,5], Jean Chalaoui MD FRCPC FACR[6,7], Michel Camus PhD[2,8], Jack Siemiatycki PhD[7,9]

How accurate is the diagnosis? How many false negatives and false positives?

- 187 pleural mesothelioma cases registered in the QTR in 2001 and 2002
- higher proportion of men, average age of 67 years at diagnosis, Mostly epithelioid histological type

clinical and pathological review of chart summaries of Quebec mesothelioma cases

- 143 (81 %) definite/probable or possible
- 14 (8%) improbable
- 19 (11 %) not mesothelioma

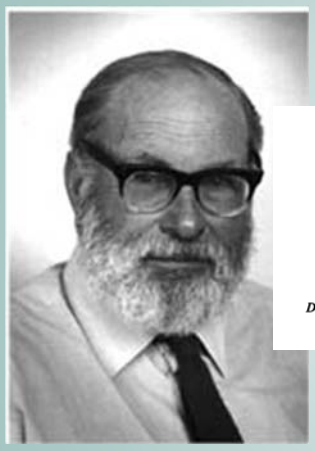
Vs. five studies 1974 – 1995 in USA, Australia, Europe: only 33% to 68% of cases classified as definite mesotheliomas (HOPEFULLY in part because old cases, which raises another problem…)

So…
There ARE false positives.

But…
Not possible to accurately measure false NEGATIVES

… but they are very likely, e.g. because of use of death certificate diagnoses

diagnosis and how the diagnosis developed



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)

But Dr. Sleggs, this doesn't look like TB under the microscope!

John Christopher Wagner, MD 1923 - 2000

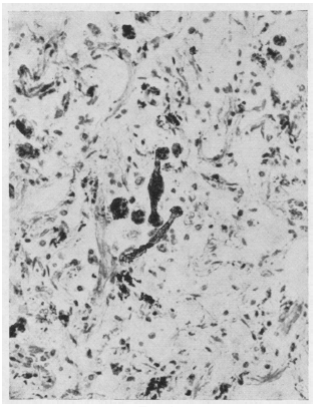


FIG. 4

Wagner used Elliot McCaughey (Irish/ Canadian pathologist 1927-2003) classification developed in 1958 and Is still the basis of our classification:

1. EPITHELIAL
2. MESENCHYMAL (OR "SARCOMATOUS")
3. MIXED (OR "BIPHASIC")
4. ANAPLASTIC (OR "POORLY DIFFERENTIATED")

ABSENCE OF CARCINOEMBRYONIC ANTIGEN-LIKE MATERIAL IN MESOTHELIOMA

An Immunohistochemical Differentiation from Other Lung Cancers

NAI-SAN WANG, MD, PHD, FRCP(C),* SHAO-NAN HUANG, MD, FRCP(C),† AND PHIL GOLD, MD, PHD, FRCP(C), FRSC‡

This study is to examine the potential usefulness of immunohistochemical staining for carcinoembryonic antigen (CEA)-like material in the differential diagnosis of mesotheliomas (12 cases) from other lung cancers (14 cases) that had been previously diagnosed by transmission and scanning electron microscopy and conventional light microscopy. Indirect immunofluorescent staining for CEA was carried out on formalin-fixed paraffin-embedded sections, and the slides were examined under code. All 9 cases of diffuse mesothelioma were negative, and all 12 cases of adenocarcinoma and bronchioloalveolar carcinoma were positive for CEA-like material. Three localized mesotheliomas and a carcinoid tumor were also negative. A squamous cell carcinoma was positive. A positive immunohistochemical result for CEA-like material in lung cancers will raise the possibility of its being of bronchial epithelial origin.

***Cancer* 44:937–943, 1979.**

19 YEARS LATER…

17 YEARS LATER...

Path. Res. Pract. 192, 137–147 (1996)

The Calcium Binding Protein Calretinin is a Selective Marker for Malignant Pleural Mesotheliomas of the Epithelial Type

V. Gotzos, P. Vogt[1] and M. R. Celio
Institute of Histology and General Embryology, University of Fribourg, Fribourg and [1]Institute of Clinical Pathology, University of Zürich, Zürich, Switzerland

18 YEARS LATER...

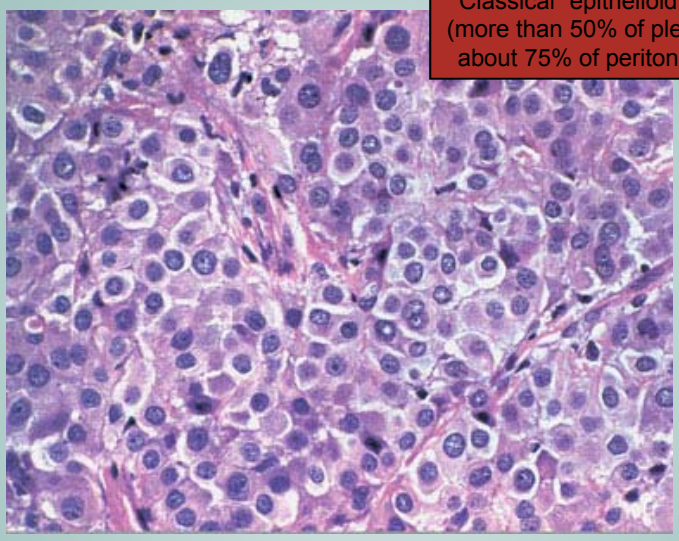
Beginning with
CEA (positive mostly NOT mesothelioma)
and
Calretinin (positive mostly ARE mesothelioma)

Pathologists have developed a huge number of immunohistochemical tests...

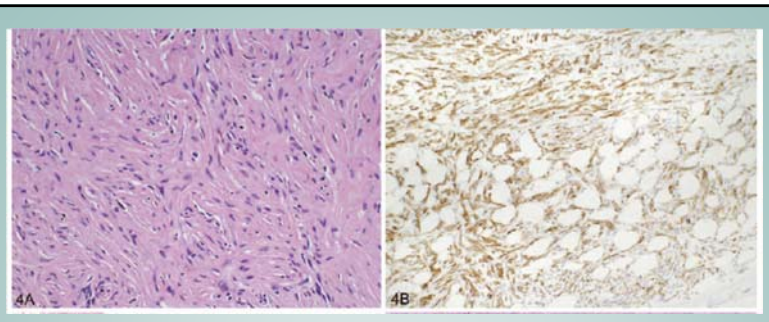
But the ordinary microscope appearance and two to five of the most specific immunstains are most helpful...

Diagnosis of *DMM*

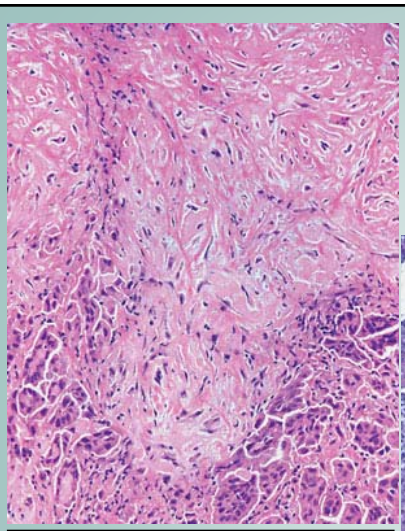
- ***Gross Appearances:*** ***These are important if "classical" (growth around the lung surface; pleural-based masses) but they are NOT always classical.***
- ***This is an autopsy section. Usually we do not have that luxury so we must depend on imaging (CT, PET especially useful) – but these can mislead as well.***



Classical "epithelioid" histology (more than 50% of pleural cases; about 75% of peritoneal cases)

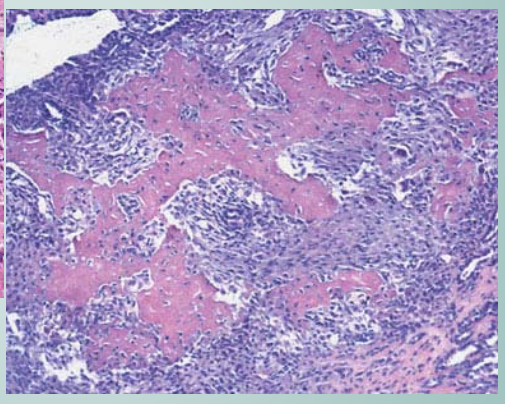


- **Sarcomatous / Sarcomatoid variant; keratin staining (may have to try various keratins; in desmoplastic variant staining may be rare)**



Any combination is possible, but "mixed" or "biphasic" generally means at least 10% of each.

The third pattern – and second most common – is a combination of the two; "biphasic" or "mixed" mesothelioma; about 30% of pleural tumors and 20%+ of peritoneal cases



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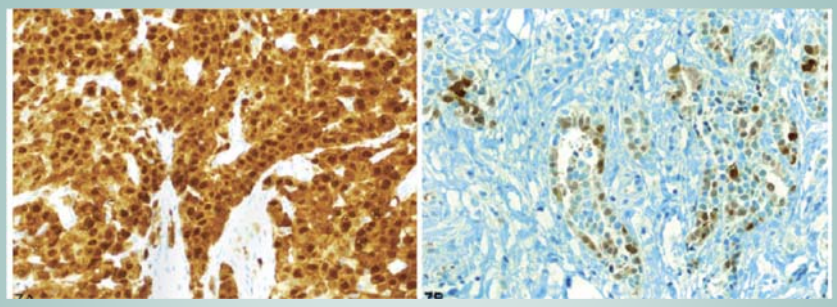

Immuno: Calretinin

Adenoca lung
(what's the difference?)

FEATURES NOT USEFUL IN MAKING THE DIAGNOSIS OF MM

History of Asbestos Exposure

Because there is an association of asbestos exposure and the development of MM, many pathologists may adopt the position that a history of asbestos exposure makes a tumor more likely to be a mesothelioma, and, conversely, in the absence of such a history, they are reluctant to diagnose mesothelioma. However, the history of exposure to asbestos or the absence of such a history is not useful to the pathologist in making a diagnosis of mesothelioma. The situation is analogous to that of lung cancer: Although most lung cancers occur in cigarette smokers, no one would hesitate to diagnose a lung cancer if told that the patient was a nonsmoker. For mesothelioma a similar scenario applies: The diagnosis is based on clinical, radiologic, and, ultimately, pathologic features, and the issue of asbestos exposure is irrelevant.

Principal Asbestos Health Effects

Malignant

IARC-"certified" neoplasms:

- mesothelioma
  - caveats
- asbestos-related lung cancer
  - caveats and the smoking interaction problem
- laryngeal cancer
  - the role of smoking and alcohol
- ovarian cancer?
  - serious problems

IARC "rejected" neoplasms

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IARC "rejected" neoplasms

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Grazie molto

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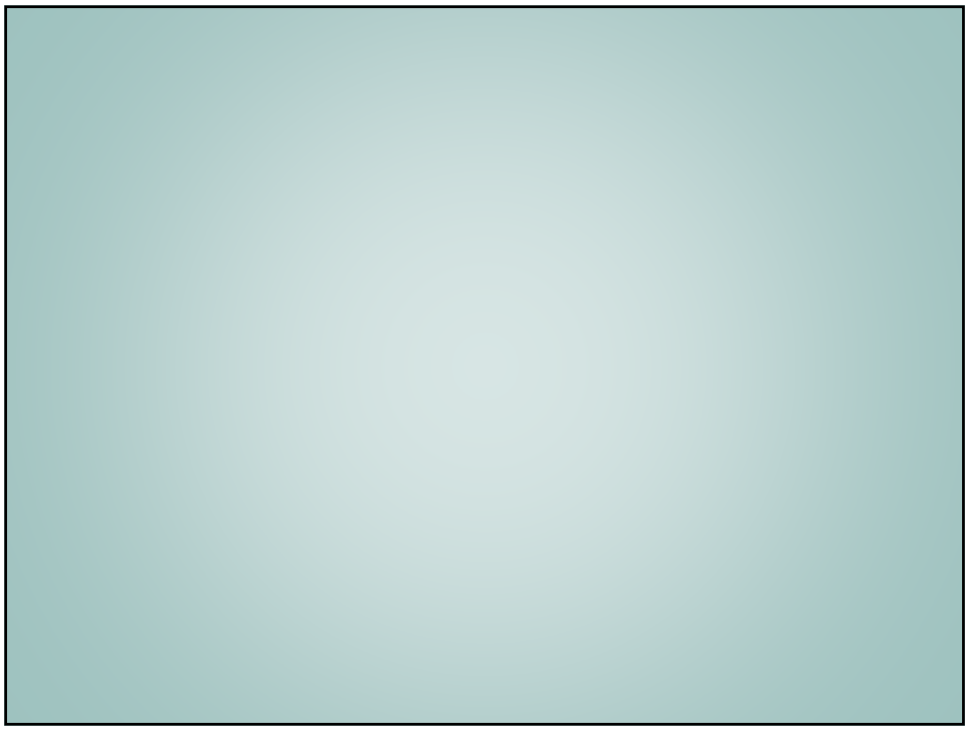

Principal Asbestos Health Effects

- **Nonmalignant**
  - **Pleural**
    - **Benign asbestos effusion**
    - **Localized Pleural Thickening ("pleural plaques")**
      - **Health effect or marker?**

Benign asbestos effusion

- Most common effect during first ten years after first exposure
- Up to 2000 ml. fluid in pleural space
  - MUST
    - Rule out other cause (TB, etc.)
    - Rule out malignancy especially
    - Have a history of (occupational) exposure
    - Follow for two years to ensure no malignancy

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Nonmalignant

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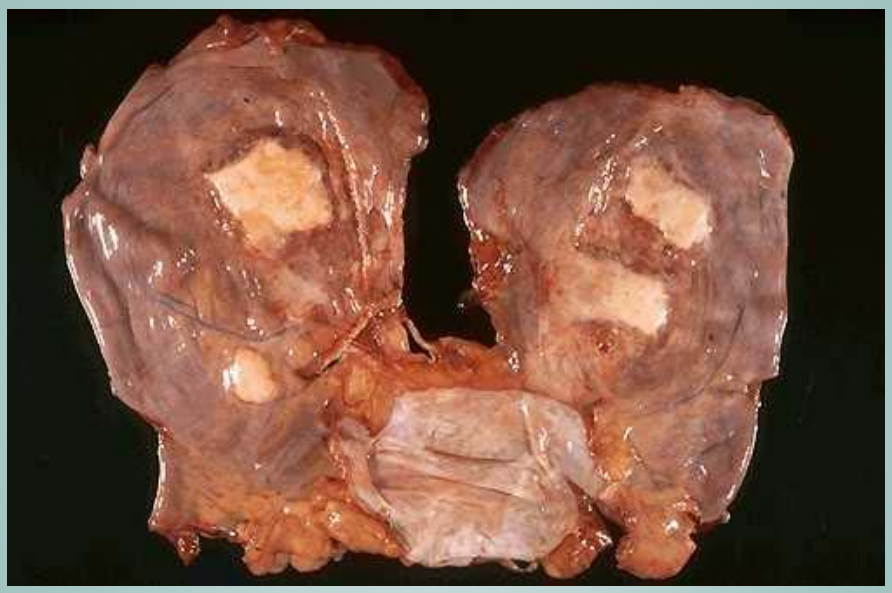
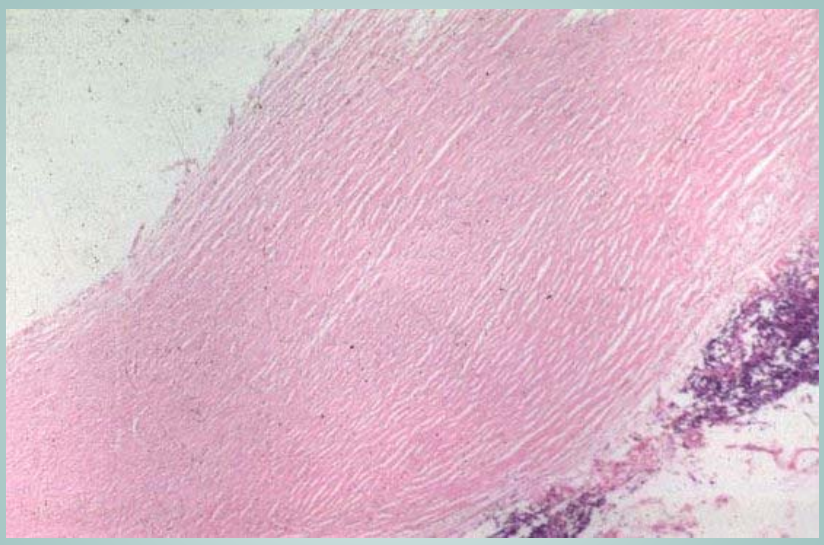
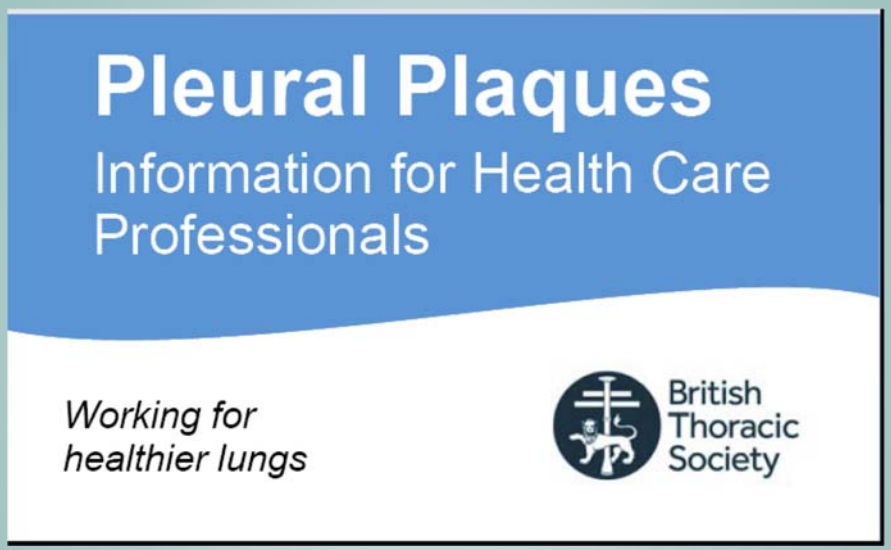
- Health effect or marker?





How common?

- 1 – 2% males general population
- < 1% females
- Much higher in autopsy series
- Often missed (even when clearly present) on Chest x-ray; often said to be present when it is not.
- Can occur at (very) low dose; most commonly with amphibole asbestos exposures
- Since they denote exposure, they are also associated with increased risk of other asbestos-related diseases, but do not *confer* this risk.



https://www.brit-thoracic.org.uk/document-library/clinical-information/mesothelioma/pleural-plaques-information-for-health-care-professionals/

From: British Thoracic Society (2011)

1. The cause of pleural plaques is exposure to asbestos fibres, most commonly in an occupational setting.

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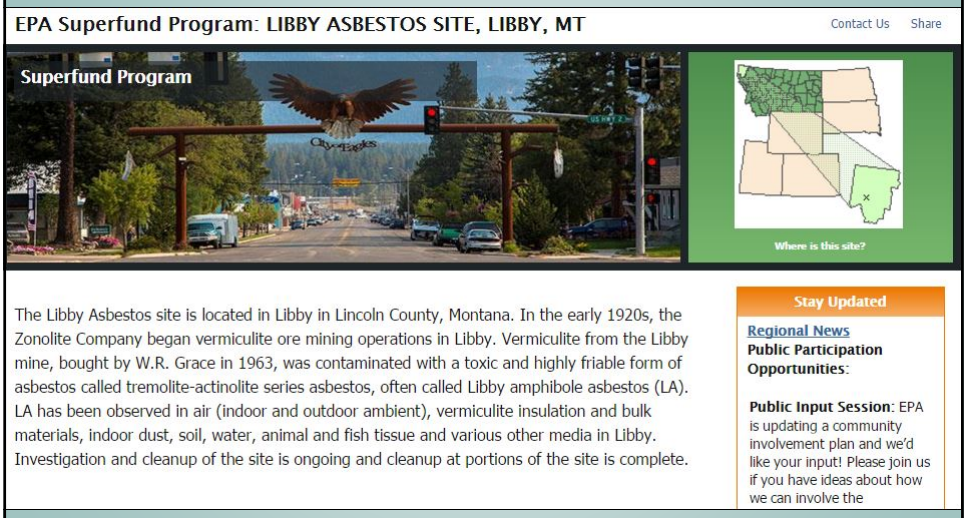
1. The cause of pleural plaques is exposure to asbestos fibres, most commonly in an occupational setting.
2. Pleural plaques are benign and are the commonest manifestation of past exposure to asbestos.
3. Plaques only indicate that there has been exposure to asbestos.
4. **Pleural plaques are nearly always asymptomatic.**

US EPA – A different perspective



Until "Libby Amphibole", US EPA had never published a risk assessment for NONCANCER health outcomes…

"Libby Amphibole Asbestos" (LAA, aka 'tremolite' or 'tremolite-actinolite' in the historical literature, but more accurately a combination of the *three* amphiboles tremolite, winchite and richterite in association with vermiculite

1. Carcinogenicity (duh…)
2. A risk value specified for "nonmalignant respiratory disease" – this was a first for the EPA RA (IRIS) system
3. Where pathology came in: What could be used as a marker of such risk, *and what exposure is needed ("RfC")?*

- RfC was derived from studies (1984-2008) of O.M. Scott, Marysville, OHIO 280 vermiculite exfoliation plant workers
- Libby Amphibole asbestos (LAA) exposure was estimated
- OUTCOME included pleural plaques (localized pleural thickening), corrected for smoking, age, etc.

- exposure reconstruction: cumulative exposure estimate for each individual. 1963 – 1980 for each, assuming 8-hours / 365 days

- Estimated cumulative exposure 0.01 to 19.03 fibers/cc-year (mean = 2.48).

Outcome: Marysville cohort

- **small opacities (interstitial changes in the lung) increased from 0.2% in the original study* to 2.9% in the follow-up study****
- **Prevalence of pleural thickening increased from 2%* to 28.6%**.**

* Lockey JE et al.. Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. Am Rev Respir Dis. 1984. 129:952-958.
** Rohs AM et al. Low-level fiber-induced radiographic changes caused by Libby vermiculite: a 25-year follow-up study. Am J Respir Crit Care Med. 2008. 177:630-637.

BUT Rationale: LPT (plaques) NOT JUST CHANGE IN STRUCTURE BUT associated with "respiratory dysfunction"

- Nontraditional view
- Based entirely on statistical differences (in SOME studies) in numerical values
- ?? Clinical significance?? – hard to estimate either way.
- To the degree that dysfunction is associated, it may well be due to "missed" other disease such as subclinical lung disease, etc.

Principal Asbestos Health Effects

Nonmalignant

Pleural

Localized Pleural Thickening ("pleural plaques")

- Health effect or marker?

Diffuse Pleural Thickening

Rounded Atelectasis

Parenchymal (Lung)

Pulmonary fibrosis ("asbestosis")

- Definitions

Immune System?

Diffuse pleural thickening (DPT)

Thickness from less than 1 mm up to 1 cm or more. (Exact thickness can be important for definitions for compensation; some > 5 mm)

Adhesions to the parietal pleura are common.

May extend for a few millimeters into the lung parenchyma (but NOT "asbestosis" if only finding)

Source: ATS 2004

Diffuse pleural thickening (DPT)

Diffuse pleural thickening may have a significantly greater impact on pulmonary function than circumscribed plaques.

This effect is unrelated to the radiographic *extent* of pleural thickening (more WHERE it is than HOW MUCH)

Deficits associated with diffuse pleural thickening reflect pulmonary restriction as a result of adhesions of the parietal with the visceral pleura.

Source: ATS 2004

Diffuse pleural thickening (DPT) – how much is definitional? How much results in compensation?

Definition (UK 2009):

"unilateral or bilateral diffuse pleural thickening ***w. obliteration of costophrenic angle"***

In other jurisdictions DPT usually requires pleural ***thickening*** (e.g. of 5mm or more on a standard chest radiograph), sometimes:

to cover 25% or more of the combined area of the chest wall of both lungs if bilateral, or 50% or more if unilateral.

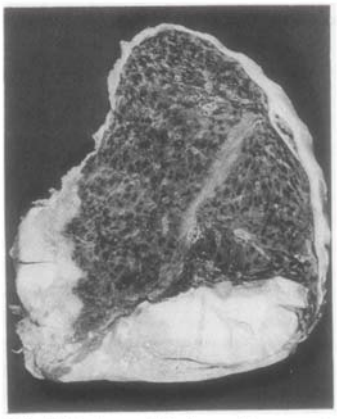


Fig 1 *The lung from case 2, showing complete encasement by diffuse pleural thickening. The under surface is shown in the lower part of the figure.*

Stephens M et al. Asbestos induced diffuse pleural fibrosis: pathology and mineralogy. Thorax 1987;42:583

Principal Asbestos Health Effects

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Benign asbestos effusion

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Parenchymal (lung)

Asbestosis

Asbestosis

- Definition can be pathologic (which has changed slightly), but most of the time it is – and should be –
- CLINICAL
- American Thoracic Society – Clinical Definition
- College of American Pathologists – Pathologic Definition (BIOPSIES NOT DONE for asbestosis!)

Definition of Asbestosis

- interstitial pneumonitis and fibrosis caused by
- inhalation of asbestos fibers.

Clinical Asbestosis

- History of exposure (cannot "see" asbestos)
- Presence of fibrosis
- "moderate to heavy asbestos exposure, typically, but not always, occupational and often protracted for many years". (NOT inevitable)
- "A profusion of irregular opacities at the level of 1/0 is used as the boundary between normal and abnormal in the evaluation of the film, although the measure of profusion is continuous and there is no clear demarcation between 0/1 and 1/0"
- Pulmonary function abnormalities (restriction);
- Bibasilar rales on auscultation

Clinical Asbestosis

- History of exposure (cannot "see" asbestos)
- Presence of fibrosis
  - Generally by radiological criterion
- reticular-linear diffuse opacities in the
- lower zones of the lung fields
  - E.g., grading scheme for parenchymal changes *such as* ILO (per ATS 2004):
- "A profusion of irregular opacities at the level of 1/0 is used as the boundary between normal and abnormal in the evaluation of the film, although the measure of profusion is continuous and there is no clear demarcation between 0/1 and 1/0"
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Thus it becomes easier CLINICALLY (at 0/1) to state clinically that a person "has asbestosis"

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Pathologic asbestosis

- Definition has changed – become more restrictive – between 1982 and 2010 (CAP)
- What was once considered low grade asbestosis no longer "makes the grade"
- "Asbestos bodies" must be seen, but how many are "enough"?

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Pathologic asbestosis

- 1982 minimum criteria necessary for a diagnosis of asbestosis:
- "discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of asbestos bodies" in histologic sections.

Pathologic asbestosis

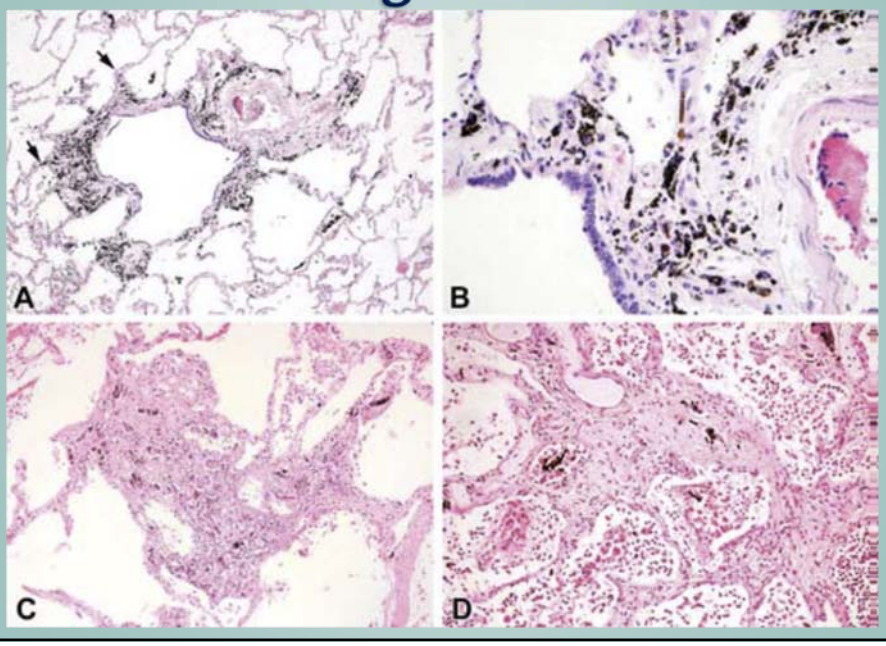
- 2010 CAP criteria recognize that similar minimum criteria for *fibrosis* can be seen with any dust, and indeed in smokers

Pathologic asbestosis

- 2010 CAP criteria recognize that similar minimum criteria for *fibrosis* can be seen with any dust, and indeed in smokers
- Must now be "fibrosis of the walls of the respiratory bronchioles and alveolar ducts" (that is, more extensive; a more restrictive definition – CONTROVERSIAL), since

Thus it becomes HARDER PATHOLOGICALLY to state that a person "has asbestosis"

Pathologic asbestosis



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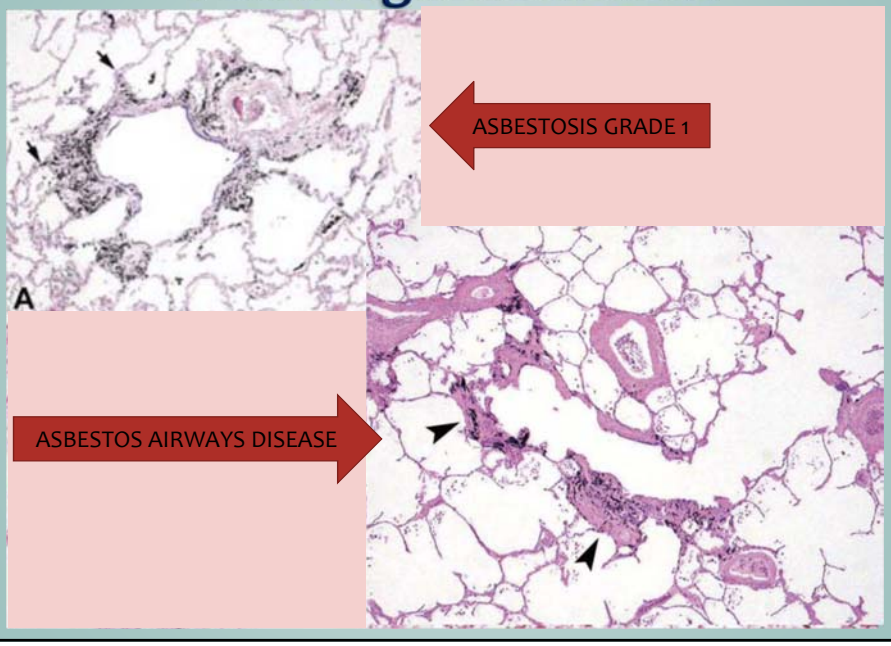

requirement

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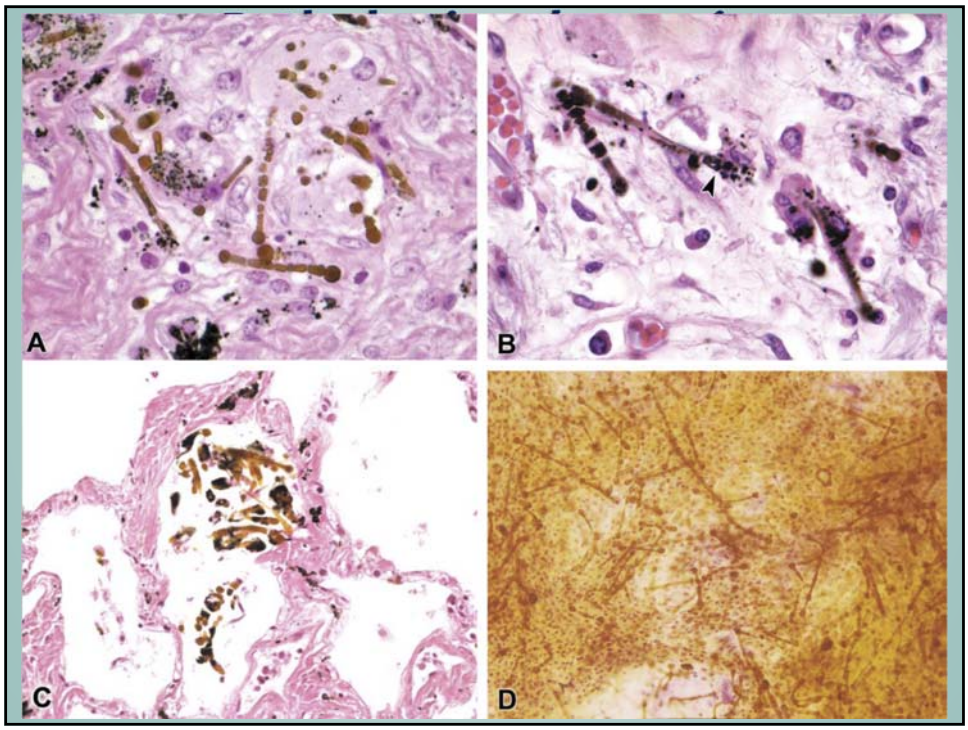

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  - Parenchymal (lung)
    - Asbestosis
- **Immunological Effects**

- "asbestos immune disease" – PubMed search – 304 articles
- Autoantibodies; Systemic AI Diseases (RA, SLE)
- Pfau J. - articles centering on Libby Amphibole effects – but deficiencies make it difficult to conclude Chicken vs. Egg problems, in particular the small numbers of epidemiological studies
- Fiber type differences?

Pfau JC, Serve KM, Noonan CW. Autoimmunity and asbestos exposure. Autoimmune Dis. 2014;2014:782045.