Uses and Abuses of Pathology in Asbestos-exposed Populations

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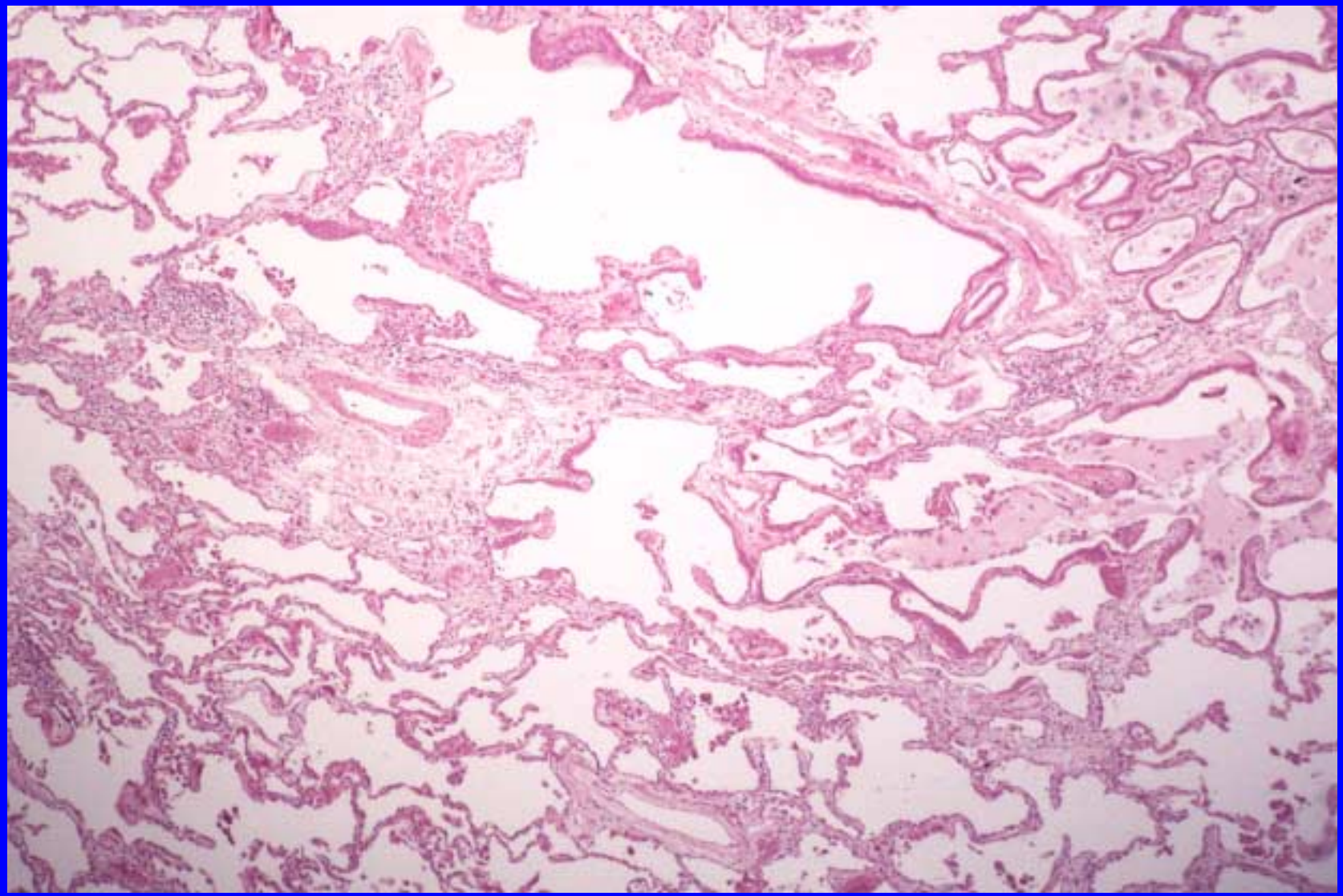
The term: Asbestosis, in usage recommended by Pathologists, refers to Lung Parenchymal Disease, not Pleural Disease

- Pulmonary Asbestosis (the Pneumoconiosis caused by asbestos inhalation)
- Not ‘Pleural Asbestosis’
- Preferred term for Pleural Fibrosis or Plaques is ‘Asbestos-Related Pleural Disease’

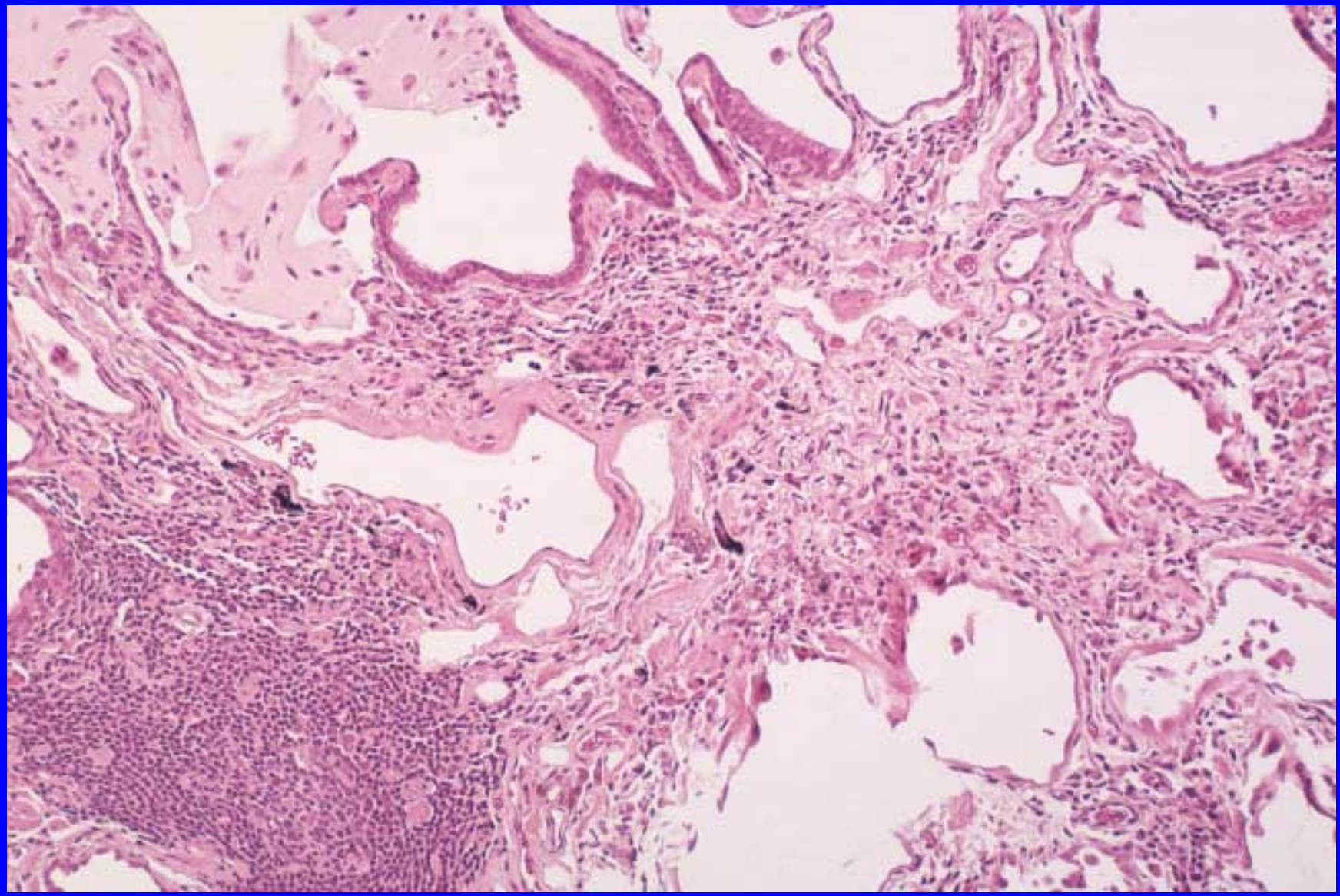
Pathologic Criteria for Diagnosis of Asbestosis

- International and USA criteria are widely used
  - ***Asbestosis is pulmonary interstitial fibrosis caused by asbestos fiber inhalation***. Four (4) Grades of severity. Earliest stage is peribronchiolar fibrosis. Severity correlates generally with exposure and with fiber burden. [See references]
- ***Asbestos Bodies*** must be found in tissue sections for a pathologic diagnosis of asbestosis
- ***Iron stained sections*** must be examined before concluding that no asbestos bodies are found
  - Many asbestos bodies will be missed by pathologists without using an Iron stain

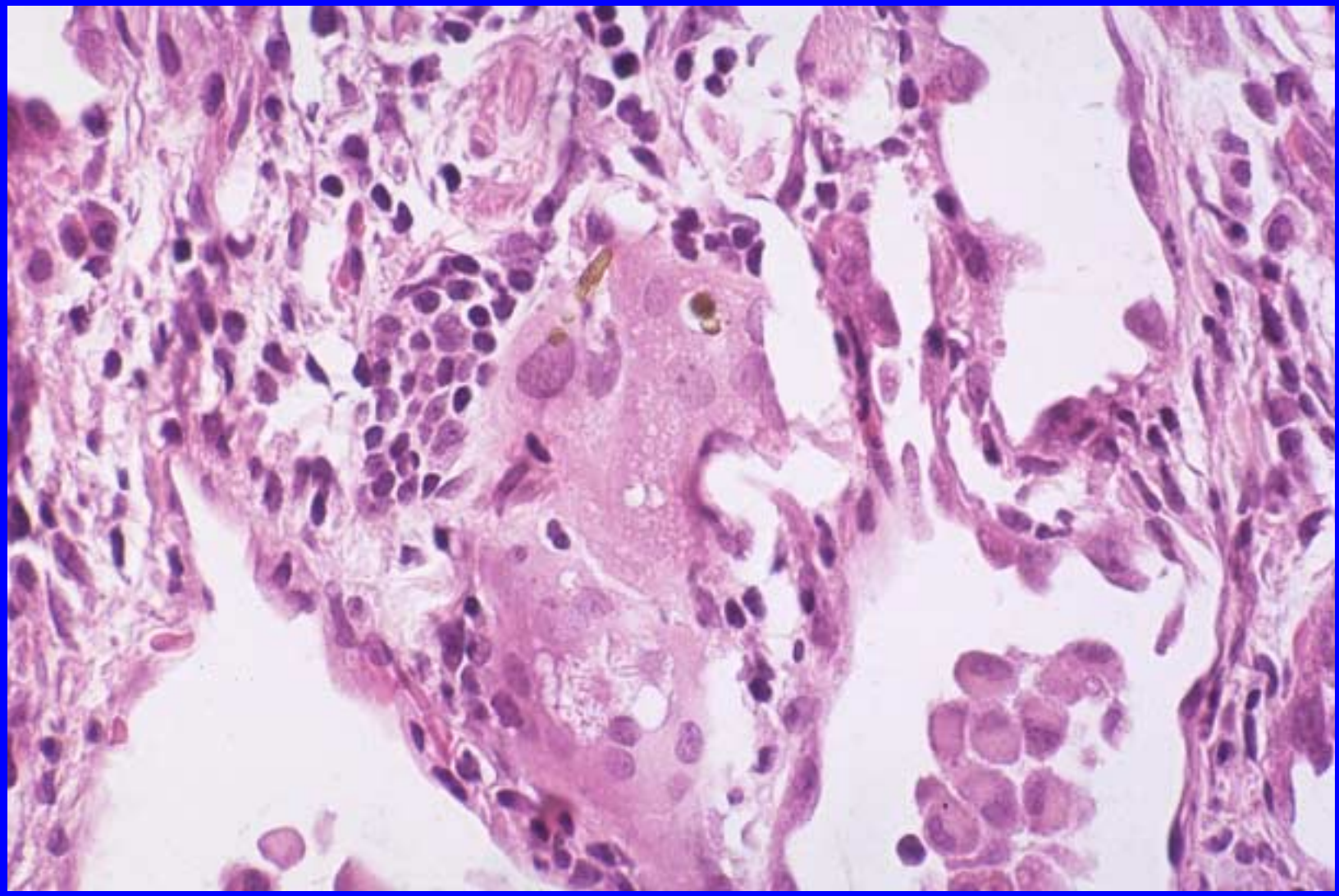
Asbestosis: Interstitial Fibrosis



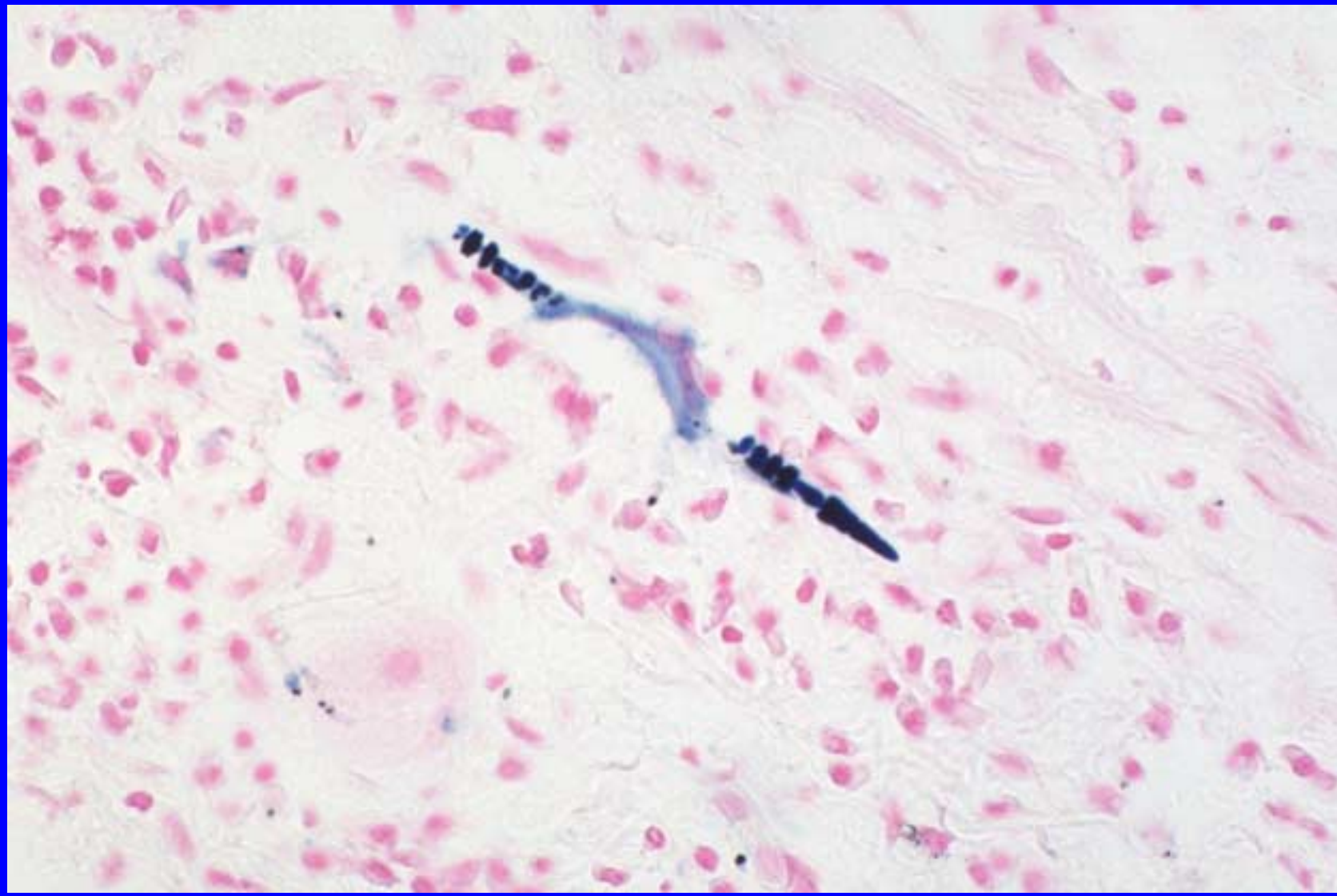
Asbestosis: Interstitial Fibrosis and Inflammation



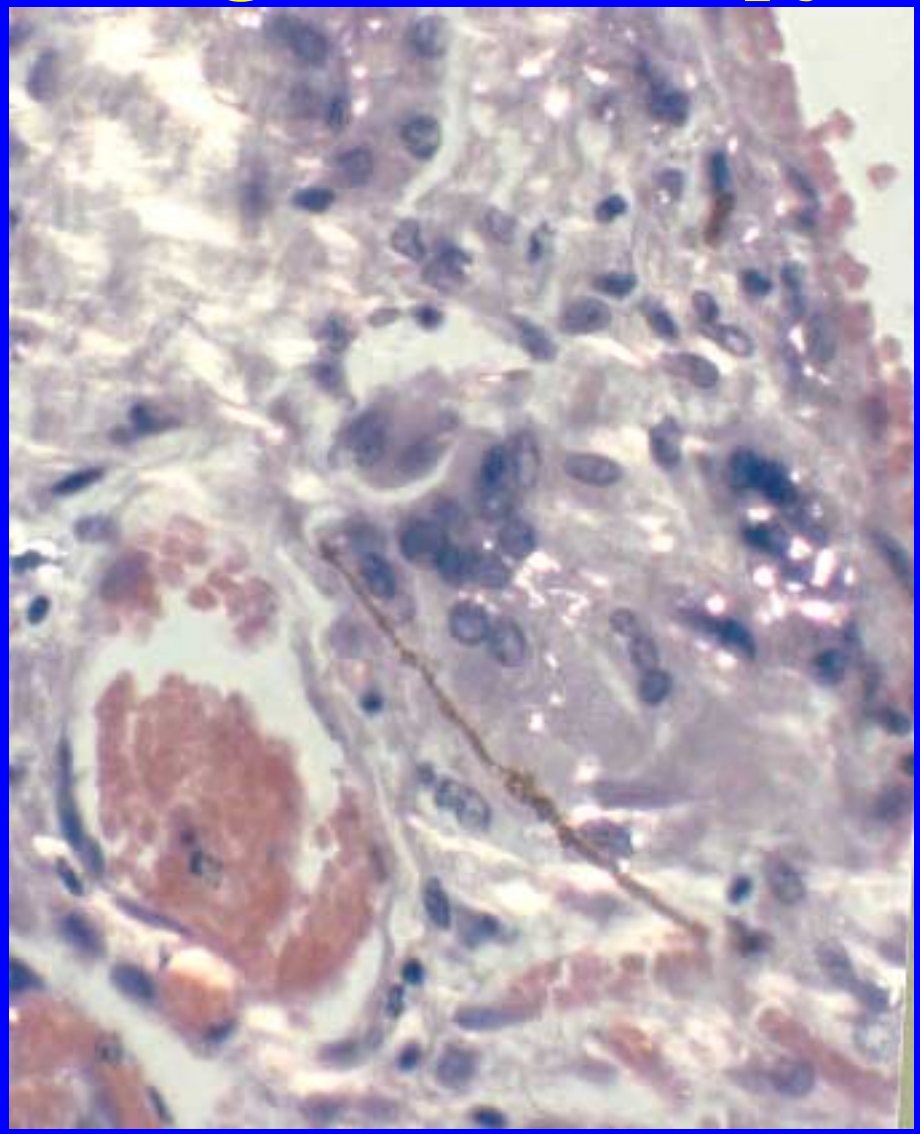
Giant Cell with Asbestos Body & Asteroid Body



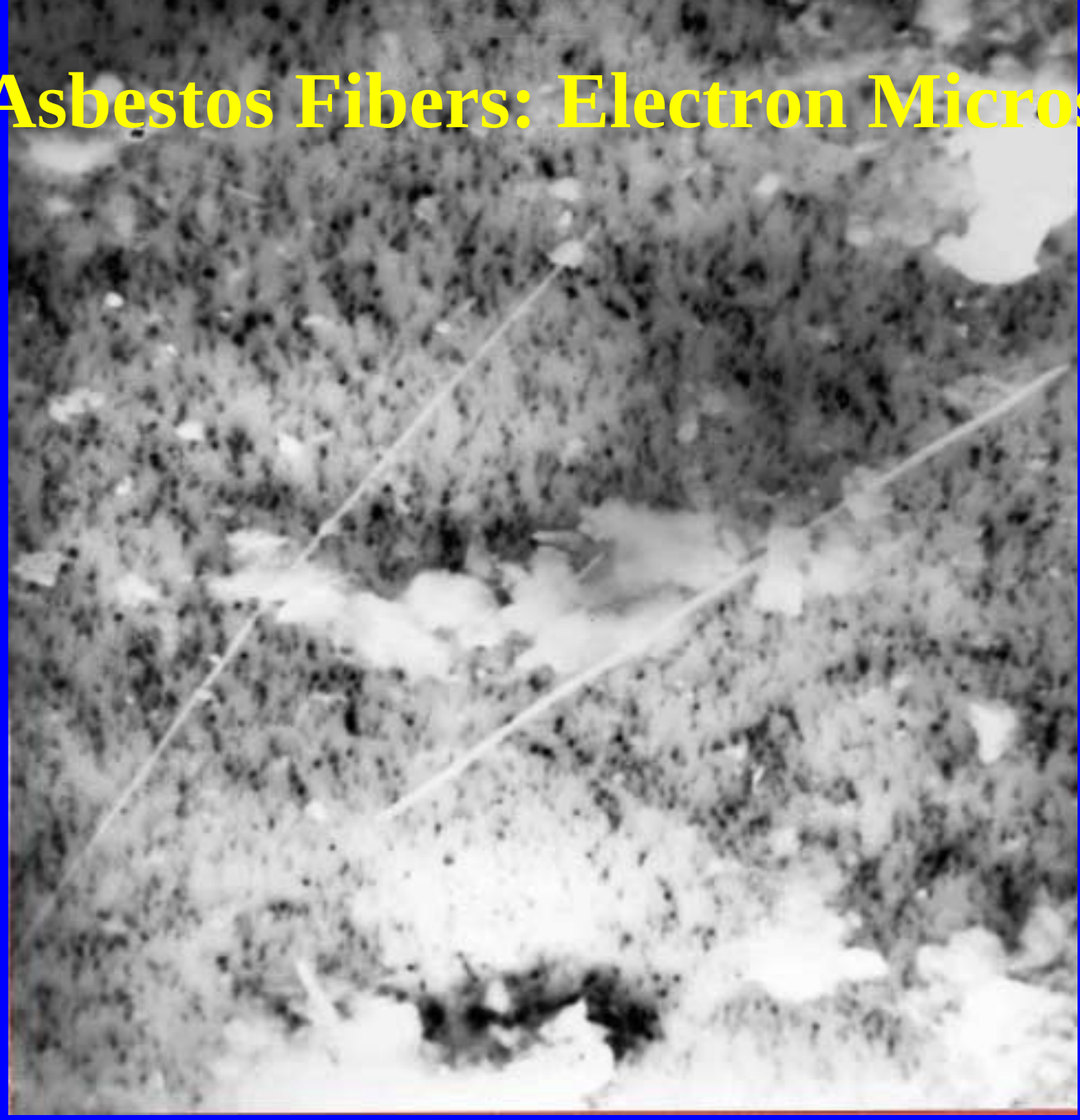
Asbestos Body: Iron Stain



Asbestos Body:
Light microscopy and Electron Microscopy



Asbestos Fibers: Electron Microscopy



Asbestosis is widely underdiagnosed by pathologists in routine practice

- Pathologists must be 'sensitized' to be vigilant for asbestosis (and other occupational diseases).
- Pathologists must be trained to examine more lung parenchyma in surgical resections (need to examine lung not involved by cancer as well as the cancer).
- Pathologists will not improve the accuracy and frequency of correct diagnosis of asbestosis and other occupational disease unless they become interested in and aware of public health issues

Etiologic Diagnosis by Pathologists

- Part of diagnosis is identification of **etiology**. For example:
  - pathologist would not want to miss the diagnosis of tuberculosis in a case of granulomatous disease
  - likewise pathologist should not want to miss the diagnosis of asbestosis in case of pulmonary fibrosis

Diagnosis of Malignant Mesothelioma (1)

- **Correct Diagnosis** is essential to good patient care and to epidemiology and legal issues
- **Adequate biopsy** is essential
  - Cytology and Fine Needle Aspiration (FNA) are usually inadequate for definitive diagnosis
- **Immunohistochemistry** is currently the ‘gold standard’ for diagnosis; Electron microscopy is useful but less efficient and less available
  - Usually a ‘battery’ or ‘panel’ of stains is useful. (The most useful stains are always improving, so keeping up with the literature on this is helpful.)

Diagnosis of Malignant Mesothelioma (2)

- Epithelial Mesothelioma Vs Adenocarcinoma is the most frequent diagnostic problem.
- Sarcomatous mesothelioma vs. sarcoma is sometimes a problem
- Reactive (benign) mesothelium vs. Mesothelioma is a growing diagnostic problem.

Asbestos Etiology of Mesothelioma

- Nearly all mesotheliomas are attributable to asbestos exposure.
  - Most studies claiming 50-80% of mesotheliomas are caused by asbestos (especially in women) are not based on tissue fiber analyses.
    - Histories of exposure may be inaccurate. Diagnosis of mesothelioma may be inaccurate.
  - Cases without autopsy or lung fiber burden analysis may be misclassified.
- "Familial" mesotheliomas may indicate common exposure to asbestos in a family: occupational or secondary household-childhood exposures

Attribution of Death to Asbestos Exposure

- It is often argued that a person died of causes other than asbestos-related disease
  - None of the other exposures (e.g., smoking) or diseases (e.g., heart disease or pneumonia caused the asbestosis or mesothelioma or asbestos-related lung cancer
  - The asbestos-related disease itself reduced the person's ability to maintain vital functions -- thus contributing to earlier death than without the asbestosis, etc.

Lung Cancer, Asbestos Exposure and Asbestosis (1)

- Several articles in recent medical literature deal with this issue
- Basically, my understanding of this relies on ‘common sense’ approach:
  - **Asbestos Exposure** has been shown in epidemiological studies to be *related in a dose-response manner* to the development of **asbestosis**, and also to the development of lung cancer
  - Asbestosis is an *inflammatory/fibrotic* disease of the lung parenchyma
  - Lung cancer is a *neoplastic* disease, most commonly of the large airway (bronchial) epithelium

Lung Cancer, Asbestos Exposure and Asbestosis (2)

- There is no more logic in ‘requiring’ a diagnosis of pulmonary asbestosis to attribute a lung cancer to asbestos exposure than there would be in requiring a diagnosis of pulmonary emphysema to attribute a lung cancer to cigarette smoking [emphysema and lung cancer are distinct diseases which happen to both be related to cigarette smoking in a dose-response manner]
  - *This controversy is more legal than medical or scientific*.

Asbestos Bodies and Fibers in Lungs

- **Asbestos bodies** are asbestos fibers which have been coated with iron and proteins by pulmonary macrophages
  - Most asbestos fibers do NOT get coated to become asbestos bodies.
  - Studies have shown that the ratio of asbestos fibers to asbestos bodies is usually between several hundred and several thousand to one.
- So, there can be a significant lung burden of asbestos fibers despite low numbers of asbestos bodies [this is especially so for chrysotile fibers, which are less likely to form asbestos bodies than amphibole fibers]

Lung Fiber Burden Analyses (1)

- Have been performed for many years by several labs internationally
- Requires specialized facility (Electron microscopy) as well as specialized expertise and experience (for meaningful, reproducible results)
- Important to note that techniques and reference values vary from one laboratory to another (examination of technical details essential)

Lung Fiber Burden Analyses (2)

- In Legal cases, it is often recommended to *control chain of custody of tissues carefully* from biopsy/autopsy to analysis, making sure adequate tissue is available for more than one analysis
- **Never allow any one lab to use up all the tissue -- analyses can be done using very little tissue**

Abuses of asbestos body analyses

- The argument that “everybody has asbestos fibers in his/her lungs” is not a valid argument against **quantitative** results showing more asbestos bodies or fibers in a person’s lungs than in background populations
- **Finding asbestos bodies in lung tissue sections is evidence of more than background exposure**
  - if ‘background’ concentration of asbestos bodies is ≤ 100 asbestos bodies/gram wet lung (≅ per ml lung) then one would expect to have to search 50 to 100 sections of lung to find ONE asbestos body.
    - the rationale for the NIOSH/CAP requirement for finding “more than one” asbestos body in a single section -- to exclude the chance finding of a single asbestos body in someone without asbestos exposure

Additional abuses of fiber burden analysis

- lung parenchyma is the only site for which lung fiber burden data has background data for comparison
  - analysis of pleura and lymph node tissue is of interest for research, but not for comparative purposes at present (year 2000). Analysis of cancer tissue itself is misleading.
  - The argument in mesothelioma cases that analyses should be of the pleura (or of airway wall in lung cancer cases) deserves consideration: however, in the absence of relevant background data (a very difficult task to analyze normal pleura or airway wall), the fiber burden of lung parenchyma must remain as the standard for evaluation of retained asbestos as it relates to evidence of past asbestos exposure

Chrysotile vs. Amphiboles (1)

- Differences in Clearance
  - Chrysotile cleared very rapidly from lungs, especially short fibers
    - Long Chrysotile fibers are retained for long periods
  - Amphiboles are retained very efficiently in lungs
  - Therefore, as has been shown in experimental animal studies by Wagner et al,
    - Tremolite fibers (so rare as to be undetectable in original nearly ‘pure’ chrysotile exposures) are found to be the main component of the lung burden many months after exposure (due to selective retention of the amphiboles and very efficient clearance of the chrysotile)

Chrysotile vs. Amphiboles (2)

- Implications for estimation of exposures and disease causation
- Important to note that lung fiber burden only reveals the ***retained*** fiber burden; this is not the same as the ***exposure***.
  - Just because chrysotile is not found in a lung fiber burden analysis, it does not mean there was no exposure (or that chrysotile did not contribute to the person's asbestos-related disease).
  - At least with most chrysotile exposures, the chrysotile is rarely 'pure' chrysotile, and the trace or larger amount of associated tremolite, etc. will often be revealed in the lung fiber analysis

Chrysotile vs. Amphiboles (3)

- Chrysotile and Mesothelioma
  - A complex problem
    - **All types of asbestos can cause mesothelioma**
  - Epidemiology linking chrysotile to mesothelioma in humans indicates less potency than for amphiboles (crocidolite, amosite, tremolite), but very few if any chrysotile exposures are ‘pure’ in the real world

Biopsy vs. Autopsy

- Autopsy, while providing more thorough study than biopsy, is NOT absolutely necessary for diagnosis of any of the asbestos related diseases.

Diagnosis of Asbestosis: Radiologic and Clinical vs. Pathologic (1)

- Examination of lung tissue is more sensitive than radiologic or clinical exam in detecting/diagnosing asbestosis.
  - Therefore, it is much more likely to have a positive diagnosis by biopsy or autopsy associated with a false-negative radiologic or clinical diagnosis
  - Insisting on radiologic or clinical diagnosis of asbestosis even when the pathology is positive is not reasonable, any more than saying that someone with a lung cancer diagnosed by biopsy does not have it if it was not seen on chest x-ray or diagnosed clinically!

Diagnosis of Asbestosis: Radiologic and Clinical vs. Pathologic (2)

- Likewise, denying a claim or diagnosis because x-rays were not taken, or were lost, or because a biopsy or autopsy was not performed is open to serious ethical and rational questioning
  - However, radiologic and clinical examinations can study the entire lungs, and sometimes lung biopsies are limited and may give a false-negative result
    - The argument that the patient had no asbestosis or no asbestos-related disease cannot be supported by a biopsy or autopsy which was inadequate to allow full evaluation of the lung parenchymal tissues.

Examples of Abuses of Pathology (1)

- Biopsy not adequate to evaluate
  - too small; no lung parenchyma
  - Only tumor sampled/preserved
  - Only upper lobe sampled
  - No tissue saved for further analysis
- No biopsy done
- No autopsy done
- It is outrageous to state “There is no evidence of asbestosis” when there is inadequate tissue sampling!

Examples of Abuses of Pathology (2)

- Pathologist omits comment on asbestosis or presence of asbestos bodies *to avoid involvement in litigation*
- Pathologist (or other specialist) is *ostracized* by colleagues or loses job because of company influence in community [see www.seattle-pi.com]
- Pathologists' reports are *taken out of context* to attempt to influence compensation or other litigation
- Pathologists may *lose intellectual/scientific independence and credibility* when retained or funded exclusively by plaintiffs or defendants in asbestos claims
  - points out need for *neutral* medical/scientific experts, if possible

Additional abuses of pathology

- Lung cancer caused by asbestos is grossly and microscopically the same as lung cancer caused by cigarettes
  - The **location of the primary cancer** (upper vs. lower lobe; central vs. peripheral) does not distinguish between asbestos-related and cigarette-related cancers
  - All the **major histologic types** of lung cancer are more frequent with asbestos exposure
- Synergistic effect with asbestos and cigarette smoking does not permit precise **numerical** attribution of proportionate risk to one or the other causal factor in any individual case
- the fact that 90% of lung cancer occurs in smokers does not mean asbestos is not a substantial causative factor in any given case

What happens to patients' tissues??

- Who controls this in different countries?
- Who decides on autopsy performance?
- **Who controls access and use of tissues?**
- Who has right to the information being gathered?
  - For example: if a worker dies and the company has a fiber analysis performed, does the family have to give permission? Does the family have to be notified that such a study is being done? Does the family get the results?

Asbestos Fiber size and numbers

- Asbestos fibers are very small.
- Individual asbestos fibers are mostly too small to visualize by light microscopy (LM): electron microscopy is needed [therefore: not finding fibers by LM does not mean fibers are not present]
- Assume a fiber 0.5 microns (μm) diameter and 10 μm length
- One such fiber would have a mass of **10^{-12} -10^{-13} grams**

Useful Calculations re Asbestos Fibers (1)

- Assume a fiber 0.5 microns (μm) diameter and 10 μm length
  - a conservative assumption, as most fibers retained in lungs are less than 0.3 μm diameter
- One such fiber would have a mass of **10^{-12} -10^{-13} grams**
- Therefore, in Pure (100%) asbestos, there would be 10^{12} -10^{13} fibers/gram
- If a product were 'only' 1% asbestos there would be 10^{10}-10^{11} fibers/gram
- If a product were 'only' 0.01% asbestos there would be 10^{8}-10^{9} fibers/gram
- If a product contained only 1 **ppm** (0.0001%) asbestos, there would be **10^{6}-10^{7} fibers/gram**

Useful Calculations re Asbestos Fibers (2)

- **Note**: in USA routine analytical reporting, the term *'trace' asbestos* means: "less than 1%" asbestos by weight!
  - [Sometimes as a result of analytical techniques used, this is reported as "No Asbestos"! -- or worse, "No asbestos present"]
  - This problem in terminology has led to USA products containing asbestos fibers being allowed for consumer use, such as:
    - Children's play sand containing asbestos
    - Children's crayons containing asbestos
    - Asbestos-containing Products for gardening, insulation and construction
- I have suggested that more informative, correct and honest labeling of such products would be *"Less than 10 Billion asbestos fibers per gram"* instead of "Trace Asbestos" or "Less than 1% Asbestos"!

Beware the coming arrival of the 'non-asbestos' Asbestos!!

- Believe it or not, some forms of asbestos are not legally 'defined' as a type of asbestos to be regulated
- Therefore, such fibers, although asbestos morphologically, mineralogically and toxicologically, are not controlled as asbestos fibers
- See many relevant articles in Seattle Post-Intelligencer series (www.seattle-pi.com)

Regulatory reform is needed for better prevention of asbestos exposure

References

- 1982 NIOSH/CAP report: Asbestos-Associated Diseases of the Lungs and Pleural Cavities: Diagnostic Criteria and Proposed Grading Schema. Archives of Pathology and Laboratory Medicine.vol. 106 (no. 11): 541-597.
- Textbooks: Churg, A. and Green, F. Pathology of Occupational Lung Disease. Igaku-Shoin, New York., etc.
- Journals. Am J Industrial Med. Commentaries, December,1994.vol. 26 (no. 6): 835-838; 839-842.
- Seattle Post-Intelligencer series on Asbestos (www.seattle-pi.com)

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