DISEASES OF THE RESPIRATORY SYSTEM 2017
DR HEYAM AWAD
LECTURE 5: restrictive lung diseases, part 1: fibrosing lung diseases

Reference: Robbins, 9th : 472-478, 10th: 506-512

INTRODUCTION: RESTRICTIVE LUNG DISEASES

Restrictive lung diseases are characterized by decreased expansion of the lung with associated decreased total lung capacity. So as the name implies there is something restricting the expansion of the lung.

Restrictive lung diseases occur in two types of disorders:

1. **Chronic interstitial and infiltrative diseases**, where there is a chronic disease process involving the interstitial lung tissue (the fibrous tissue between the alveolar and epithelial lining). This disease process could be fibrosis, inflammation or granulomas.

2. **Chest wall disorders** (e.g., neuromuscular diseases such as poliomyelitis, severe obesity, pleural diseases, and kyphoscoliosis). In these disorders the lung is normal but its function is restricted by inability of the chest wall to expand.

In general, the clinical changes of restrictive lung disease include dyspnea, tachypnea, and cyanosis, without wheezing or other evidence of airway obstruction. Eventually, secondary pulmonary hypertension and right-sided heart failure associated with cor pulmonale may result.

OVERVIEW OF INTERSTITIAL LUNG DISEASES:

Interstitial lung diseases cause restrictive symptoms and they include the following categories:
A. *fibrosing diseases:* in these diseases there is interstitial fibrosis which restricts lungs' ability to expand.
1. IPF= idiopathic pulmonary fibrosis.

2. NSIP = nonspecific interstitial pneumonia

3. Cryptogenic organizing pneumonia

4. Secondary fibrosis due to collagen vascular diseases

5. Drug and radiation induced pulmonary disease

6. Smoking associated fibrosis

B. *pneumoconiosis :* these are also firosing diseases but caused by occupational exposure to certain dusts.

1. Coal workers' pneumoconiosis

2. Silicosis

3. Asbestosis

C. Granulomatous diseases: here the granulomatous inflammation expands the interstitium and restricts expansion of the lungs.

1. Tuberculosis

2. Sarcoidosis

3. Hypersensitivity pneumonitis

FIBROSING LUNG DISEASES

1. IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF)= cryptogenic fibrosing alveolitis

A difficult name, isn't it ? and as if one name isn't bad enough!!! Actually these two names tell you what the disease is. It is simply fibrosis of unknown etiology. Idiopathic and cryptogenic mean the same thing : a disease of unknown cause. The fibrosis involves mainly the sub pleural area close to the distal alveoli, hence the alveolitis in the term "cryptogenic fibrsing alveolitis."

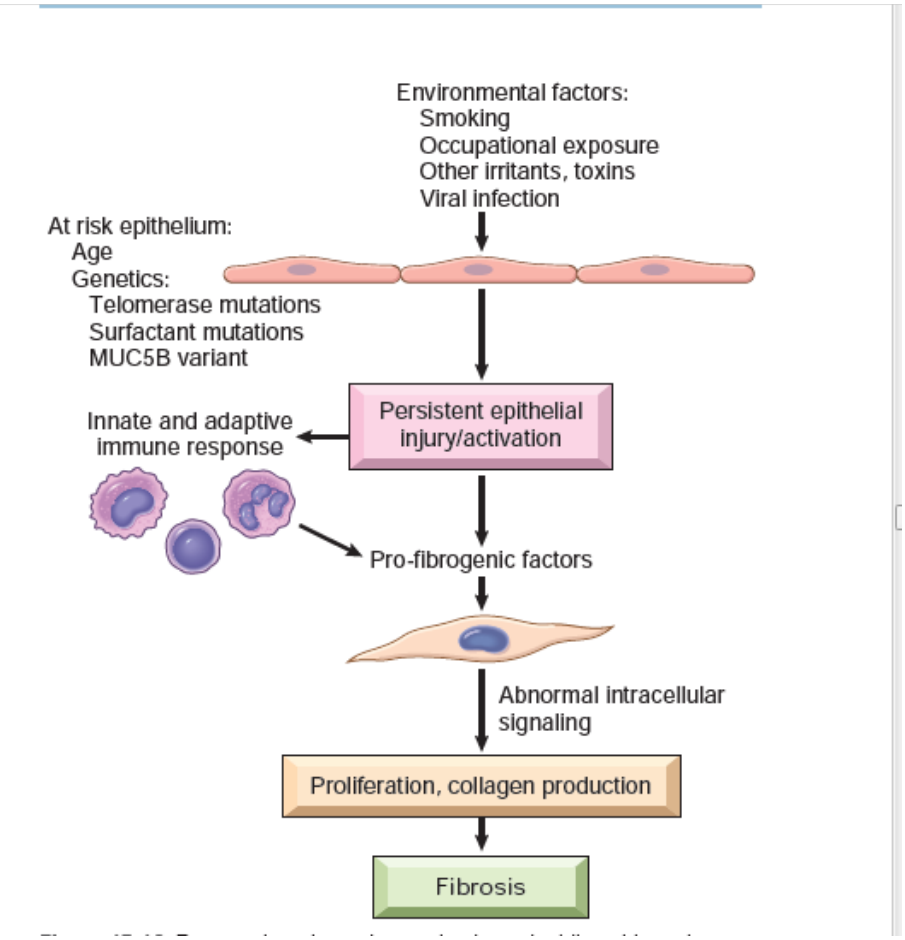
The histologic pattern of fibrosis in IPF is referred to as **usual interstitial pneumonia (UIP**). So: UIP is not a disease. It is the term used to describe the histological appearance of the fibrosis.

The UIP pattern can also be seen in other diseases, like: connective tissue diseases, chronic hypersensitivity pneumonia, and asbestosis; these must be distinguished from IPF based on other clinical, laboratory, and histological features.

Pathogenesis:

While the cause of IPF remains unknown, it appears that the fibrosis arises in genetically predisposed individuals who are prone to aberrant repair of recurrent alveolar epithelial cell injuries caused by environmental exposures .The implicated environmental factors that predispose to IPF include: cigarette smoking, metal fumes and wood dust, certain occupations, including farming, hairdressing, and stone-polishing.

It is hypothesized that exposure to environmental irritants or toxins causes recurrent alveolar epithelial cell damage. Factors secreted from injured/activated epithelium, possibly augmented by factors released from innate and adaptive immune cells responding to "danger" signals produced by damaged epithelium, **activate interstitial fibroblasts**, these proliferate and secrete collagen fibers resulting in the fibrosis.



Several theories tried to explain how injured alveolar cells cause fibrosis. One model suggests that injured epithelial cells are the source of **fibrogenic factors such as TGF-β,** whereas a second, model proposes that innate and adaptive immune cells produce such factors as part of the host response to epithelial cell damage. Other work has described abnormalities in the fibroblasts themselves that involve changes in intracellular signaling.

So the main idea is that we think there are environmental triggers that cause epithelial damage, this damage, in the genetically susceptible individual, result in increased TGF beta and other fibrogenic growth factors. The source of the TGF is postulated to be from: the injured epithelium, fibroblasts or immune cells.

The increased TGF beta decreases a fibroblast protein: caveolin which is an inhibitor of pulmonary fibrosis. So the fibrosis is the result of increased fibrogenic factor TGF beta and decreased anti-fibrogenic factor caveolin.

Genetic susceptibility:

Not every person who smokes or who is exposed to the environmental triggers we mentioned will develop IPF. There must be a certain genetic change in these individuals who will develop the disease.

It is thought that some of these patients have reduced telomerase which will result in cell senescence and apoptosis.

Clinical features:

IPF affects males more than females. Two thirds of the patients are more than 60 years of age.

The disease has an insidious onset with cough and dyspnea. Patients develop hypoxia and cyanosis. They might have pulmonary hypertension and cor pulmonale.

Mean survival is three years

The only curative treatment is lung transplant.

2. NON SPECIFIC INTERSTITIAL PNEUMONIA

This is a disease characterized by bilateral fibrosis of unknown etiology.

The disease is similar to IPF in this definition! And also in the clinical presentation.

HOWEVER, the disease has certain histological features different from IPF. And IT IS VERY IMPORTANT TO TAKE A BIOPSY TO DIFFERENTIATE THESE TWO DISEASES BECAUSE NON SPECIFIC INTERSTITIAL PNEUMONIA HAS A MUCH BETTER PROGNOSIS.

3. CRYPTOGENIC ORGANIZING PNEUMONIA = BRONCHIOLITIS OBLITERANCE ORGANIZING PNEUMONIA = BOOP

This is another fibrosing disease of the lung. It is of unknown etiology but can be triggered by infections or other lung inflammations.

It has a characteristic histologic appearance: polypoid plug of loose connective tissue within alveolar ducts, alveoli, and bronchioles.

The prognosis is good and patients are treated with steroids for at least 6 months.

NOTE ABOUT THE ABOVE THREE DISEASE:

I know these are confusing! What you need to know is the following concepts:

1. There are several primary lung diseases that cause interstitial fibrosis.

2. All of these diseases cause restrictive lung disease with decreased total lung capacity.

3. All of them present with cough (usually dry), and dyspnea.

4. The patients have hypoxia and high CO2

5. In all of them there is increase in fibrogenic cytokines, mainly TGF beta.

6. the most common of these diseases is IPF

7. The diagnosis of these diseases depends on certain histologic and radiologic criteria.

8. IPF patients have a bad prognosis, with around 3 years survival after diagnosis, whereas the other entities can be treated with steroids and they have a much better prognosis.

Please note that steroids are known to decrease fibrosis, that's why they are used for treatment. I hope you remember from year 2 lectures that patients who take steroids have impaired wound healing, and that's because of their antifibrogenic effect.

PULMONARY INVOVEMENT IN COLLAGEN VASCULAR DISEASES

In the diseases we studied so far, patients had primary fibrosis of the lungs. But there are also diseases that are systemic and cause fibrosis in several organs of the body including the lungs. These are called collagen vascular diseases and include: SLE, rheumatoid arthritis, systemic sclerosis.

So if you have a patient suffering from one of these diseases, his lungs might be affected and they might have restrictive lung disease due to fibrosis.

DRUG AND RADIATION INDUCED PULMONARY DISEASE AND SMOKING RELATED INTERSITIAL DISEASE

Several drugs can cause fibrosis including bleomycin and amiodarone

Radiation: can cause fibrosis.

Smoking as you know causes obstructive lung disease. But it can also cause restrictive lung disease and fibrosis.

PNEUMOCONIOSIS

Pneumoconiosis is a non-neoplastic lung reaction to inhalation of mineral dust. Mineral dust pneumoconioses are usually related to *occupational exposure*. The main dusts implicated are: coal dust, silica and asbestos.

Not all dust causes disease. Most inhaled dust is entrapped in the mucus and rapidly removed from the lung by ciliary movement. However, some of the particles become impacted at alveolar duct bifurcations, where macrophages accumulate and engulf the trapped particulates. These engulfed particles can evoke an inflammatory response leading to fibrosis.

The reaction of the lung to mineral dusts depends on their **size**, **shape**, **solubility**, and **reactivity** as well **as purity, concentration and duration of exposure**

Regarding size: large particles (5 to 10 µm Particles) are unlikely to reach distal airways so they are cleared by mucus. Particles smaller than 0.5 µm move into and out of alveoli, often without substantial deposition and injury. *The most dangerous particles are the ones of 1 to 5 µm in size because they get lodged at bifurcation of the distal airways*.

Regarding type of particles: Coal dust is relatively inert, and large amounts must be deposited before lung disease is clinically detectable. Silica, asbestos, and beryllium are more reactive than coal dust, resulting in fibrotic reactions at lower concentrations

PATHOGENESIS

The alveolar macrophage is a key cellular element in the initiation of lung injury and fibrosis. The engulfed particles activate the inflammasome and induce IL-1 . The more reactive particles trigger the macrophages to release a number of products that mediate inflammation and initiate fibroblast proliferation and collagen deposition. Some of the inhaled particles may reach the lymphatics either by direct drainage or within migrating macrophages and thereby initiate an immune response to components of the particulates and/or to self-proteins that are modified by the particles and this then leads to an amplification and extension of the local reaction.

Tobacco smoking worsens the effects of all inhaled mineral dusts, more with asbestos than other particles

NOW LET'S DISCUSS THESE PARTICLES AND THE TYPES OF PNEUMOCONIOSIS THEY PRODUCE:

1. **Coal dust pneumoconiosis:**

Coal is mainly carbon but coal mine dust contains also: trace metals, inorganic minerals and silica

Coal miners can develop three types of reactions:

1. Asymptomatic anthracosis: pigment accumulates without any reaction

2. Simple coal workers pneumoconiosis (CWP) : accumulation of macrophages with little or no pulmonary dysfunction. There is minimal fibrosis.

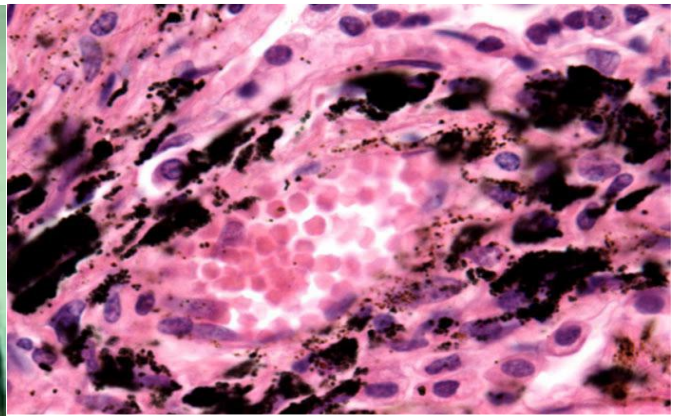
3. Complicated CWP = progressive massive fibrosis (PMF)= extensive fibrosis with compromised lung function

Note: PMF is a generic term that applies to a confluent fibrosing reaction in the lung; this can be a complication of any one of the pneumoconiosis

Each of the above types can progress to the more severe form. Less than 10% of simple CWP progress to PMF

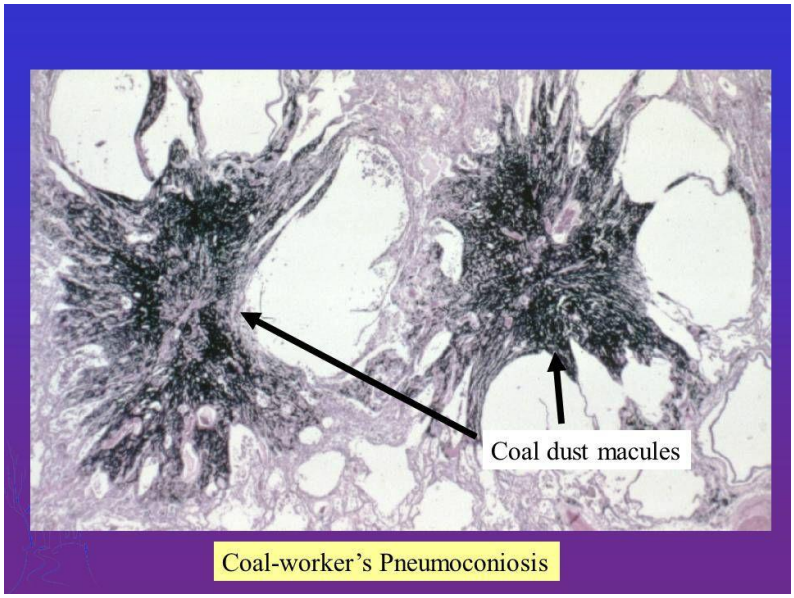
Once smoking-related risk has been taken into account, there is no increased frequency of lung carcinoma in coal miners, a feature that distinguishes CWP from both silica and asbestos exposure.

Anthracosis: carbon pigment accumulation without any reaction.



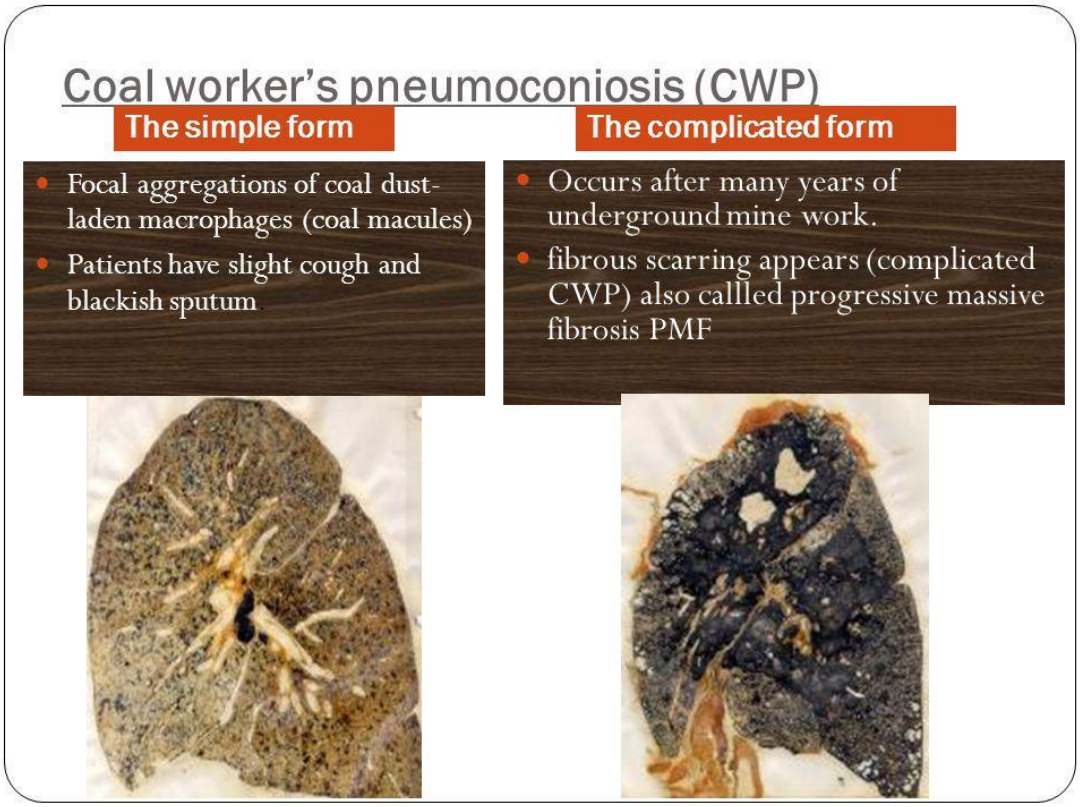
Simple CWP: Characterized by coal macules and coal nodules

Coal macules: carbon laden macrophages and small amount of collagen fibers arranged in a delicate network. If the macules are large they are called coal nodules.



Complicated CWP= PMF: There is coalescence of coal nodules forming multiple black scars

Histologically: dense collagen and pigment



Clinical features

•Simple CWP is usually a benign disease that produces little effect on lung function

•PMF : pulmonary dysfunction, pulmonary hypertension and cor pulmonale

•Once PMF developed: it progresses even without additional exposure

•there is NO increased risk of lung cancer in relation to coal exposure.

2. SILICOSIS

Silica crystals:

Silicosis is the most prevalent chronic occupational disease in the world. Caused by inhalation of crystalline silica (pics above) mostly in occupational settings

Silica (Silicon dioxide)is a chemical compound that is an oxide of silicon with the chemical formula SiO_2.

Silica is most commonly found in nature as quartz and is a major constituent of sand. Uses of silica include:

•Glass industry

•Sandblasting : the process used to clean a surface by means of an abrasive such as sand

•Hard rock mining

Sand blasting

Silica Forms:

a. **Crystalline(such as quartz)** are the most toxic and fibrogenic.

NOTE: quartz is most commonly implicated in silicosis but when mixed with other minerals it has a reduced fibrogenic effect (this is an example of importance of purity of the dust!!)

b. **Amorphous** forms: less fibrogenic

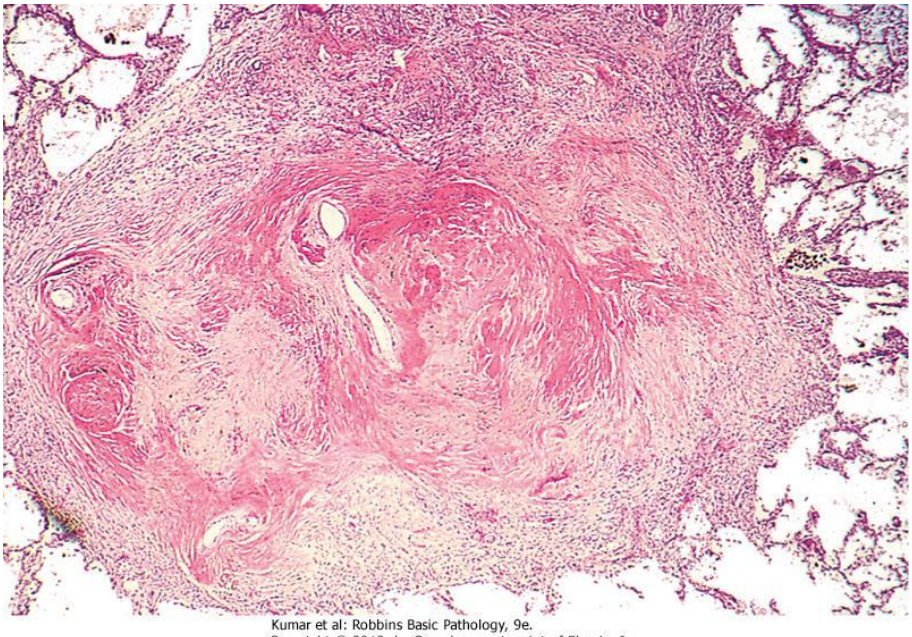
MORPHOLOGY

Silicotic nodules :-Characterized grossly in early stages by barely palpable pale-to-blackened (if coal dust is present) nodules in the upper zones of the lungs.

Microscopically there are concentrically arranged hyalinized collagen fibers surrounding amorphous center, this “whorled" appearance of the collagen fibers is distinctive for silicosis

As the disease progresses, the individual nodules may coalesce into hard, collagenous scars, with eventual progression to PMF

Silicotic nodules:



Kumar et al: Robbins Basic Pathology, 9e.

Clinical Features:

-Silicosis usually is detected on routine chest radiographs obtained in asymptomatic workers.

-The radiograph shows a fine nodularity in the upper zones of the lung, but pulmonary function is either normal or only moderately affected.

-Most patients do not develop shortness of breath until late in the course, after PMF is present

-Once PMF develops , the disease may be progressive, even if the person is no longer exposed.

-Many patients with PMF develop pulmonary hypertension and cor pulmonale.

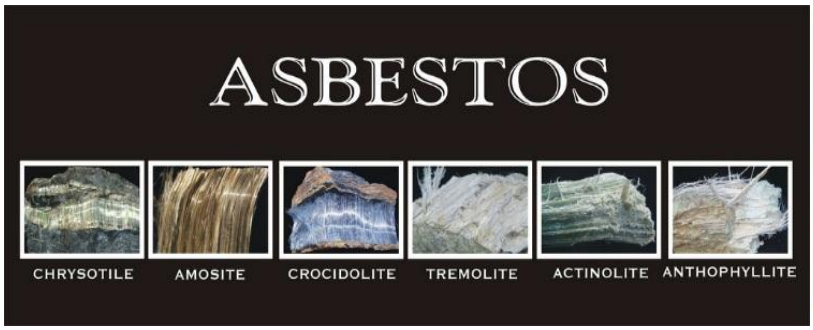
-The disease is slow to kill, but impaired pulmonary function may severely limit activity

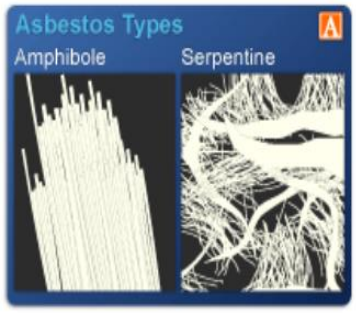
NOTE: Silicosis is associated with an increased susceptibility to tuberculosis. It is postulated that crystalline silica may inhibit the ability of pulmonary macrophages to kill phagocytosed mycobacteria.

NOTE: The relationship between silica and lung cancer has been a contentious issue. In 1997, based on evidence from several epidemiologic studies, the International Agency for Research on Cancer concluded that crystalline silicais carcinogenic-However, this subject continues to be controversial

3. Asbestosis

Asbestos is a heat-resistant fibrous silicate mineral that can be woven into fabrics, and is used in fire-resistant and insulating materials such as brake linings.





There are two types of asbestos fibres:

A. *Serpentine fibers* :

These fibers are curly and flexible, so they are likely to become impacted in the upper respiratory passages and removed by the mucociliary elevator

If some serpentine fibers are trapped in the lungs, they are gradually leached from the tissues, because they are more soluble than amphiboles.

Chrysotile (a serpentine fiber) accounts for most of the asbestos used in industry

b. *Amphibole fibers*: The fiber is straight and stiff.

Amphiboles, are less prevalent but more pathogenic than the serpentine and align themselves in the airstream and are delivered deeper into the lungs where they may penetrate epithelial cells to reach the interstitium

Occupational exposure to asbestos is linked to

1. Parenchymal interstitial fibrosis (asbestosis);

2. localized fibrous plaques and rarely, diffuse fibrosis in the pleura;

3. Pleural effusions;

4. Lung carcinomas;

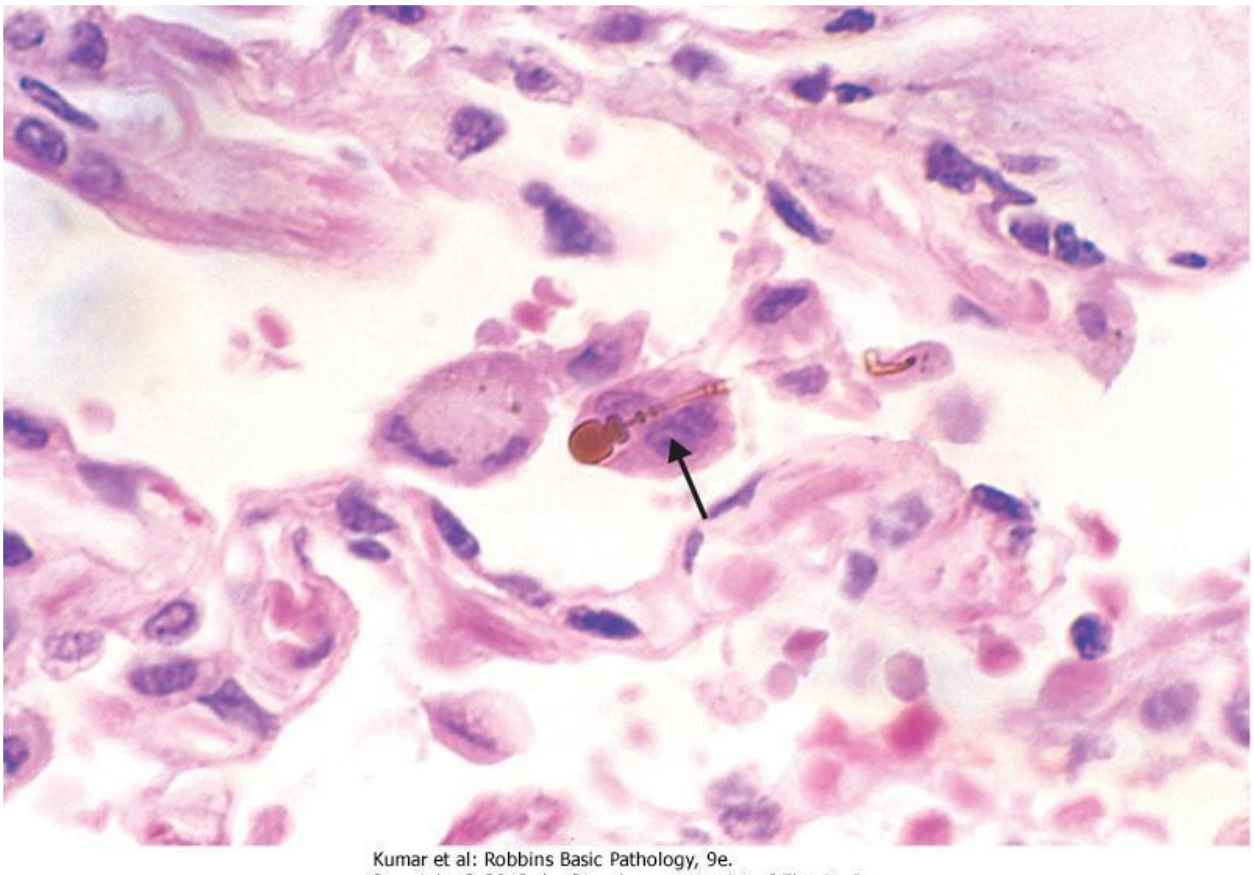
5. Malignant pleural and peritoneal mesotheliomas;

6. Laryngeal carcinoma

MORPHOLOGY

1. Asbestosis is marked by diffuse pulmonary interstitial fibrosis with asbestos bodies,

Asbestos bodies are golden brown, fusiform or beaded rods with a translucent center and consists of asbestos fibers coated with an iron-containing material. They are formed when macrophages attempt to phagocytosed asbestos fibers; the iron is derived from phagocyte ferritin.



Kumar et al: Robbins Basic Pathology, 9e.

Asbestos bodies sometimes can be found in the lungs of normal persons, but usually in much lower concentrations and without an accompanying interstitial fibrosis.

2. Pleural plaques:

Are the most common manifestation of asbestos exposure. These are well-circumscribed plaques of dense collagen , often containing calcium.

Pleural plaques:

Pleural plaques develop most frequently on the anterior and posterolateral aspects of the parietal pleura and **do not** contain asbestos bodies, **and rarely do they occur in persons with no history or evidence of asbestos exposure.**

NOTE: Uncommonly, asbestos exposure induces pleural effusion or diffuse pleural fibrosis

ASBESTOS AND CANCER

Both lung carcinoma and malignant mesothelioma (pleural and peritoneal) develop in workers exposed to asbestos.

The risk of lung carcinoma is increased about five-fold for asbestos workers; and the relative risk for mesothelioma, normally a very rare tumor (2 to 17 cases per 1 million persons), is more than 1000 times greater.

NOTE: Concomitant cigarette smoking greatly increases the risk of lung carcinoma but not that of mesothelioma

Important notes:

-There is an increased incidence of asbestos-related cancers in family members of asbestos workers

-Asbestos functions as both a tumor initiator and a promoter

-Some of the oncogenic effects of asbestos on the mesothelium are mediated by reactive free radicals generated by asbestos fibers

THANK YOU