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Pathology RS

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CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES, LEC 6

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SILICOSIS

As we said before, the most mineral dusts include coal dusts, silica and asbestos.
All of them are involved in development of pneumoconiosis.

- **The most prevalent chronic occupational disease in the world**
- Inhalation of crystalline silica mostly in **occupational** settings
- **quartz is the most common**

Silica occurs in both crystalline and amorphous forms, but the crystalline forms including quartz are more toxic and fibrogenic.
Quartz is most commonly implicated in silicosis

- Amorphus silica is less pathogenic

This diseases is mostly related to the crystalline silica and mostly the quartz

- **Workers in sandblasting and hard-rock mining are at high risk.**

The exposure is related to the workplace obviously.

PATHOGENESIS

- After **inhalation**, the particles **interact with epithelial cells and macrophages.**

- Activating the **inflammasome** and the release of **inflammatory mediators** by pulmonary macrophages

    - IL-1, TNF, fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines.

- **When mixed with other minerals, the fibrogenic effect of quartz is reduced.**

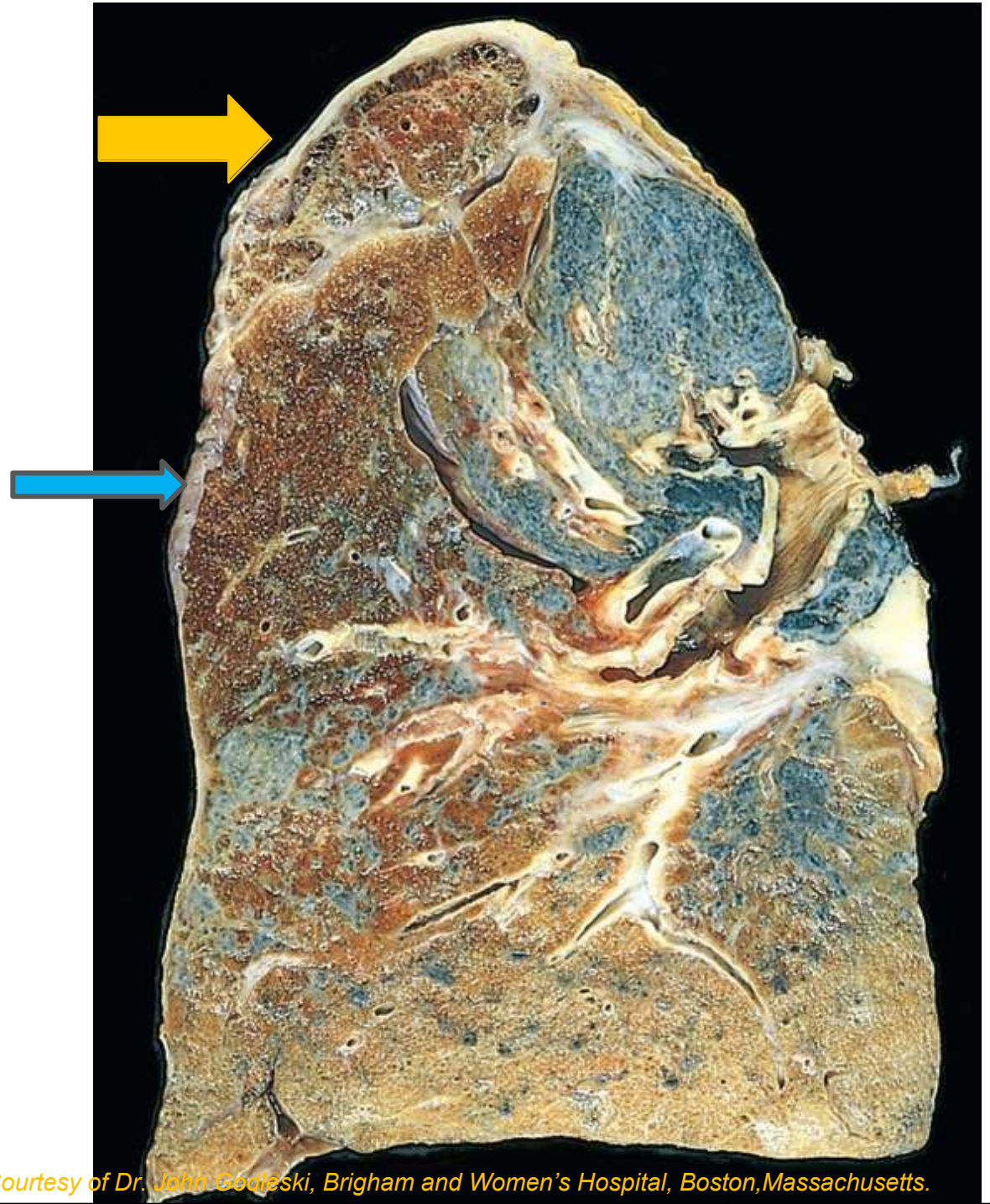
The characteristic inflammatory reaction mentioned in the previous slide with a fibrogenic effect and the release of the inflammatory mediator can be minimized.

- This fortuitous situation is commonplace, as **quartz** in the workplace is **rarely pure**.

So, the common scenario is having the quartz mixed with other minerals and thus reducing the fibrogenic effect

MORPHOLOGY, SILICOTIC NODULES:

- **Macroscopically**:
  - early stages are tiny, barely palpable, discrete, pale-to-black (if coal dust is present) nodules
  - **Upper zones** of the lungs



Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston,Massachusetts.

Gorss appearance of the lung evolved in advanced silicosis.

Scaring has contracted the upper lobe into small dark mass (yellow arrow)

the dense pleural thickening (blue arrow)

- **Microscopically:**
- **Silicotic nodules:**
  - **Concentrically arranged hyalinized collagen fibers surrounding amorphous center.**
  - With **“whorled”** collagen fibers

- **Polarized** microscopy reveals weakly birefringent silica

In the center of the nodules

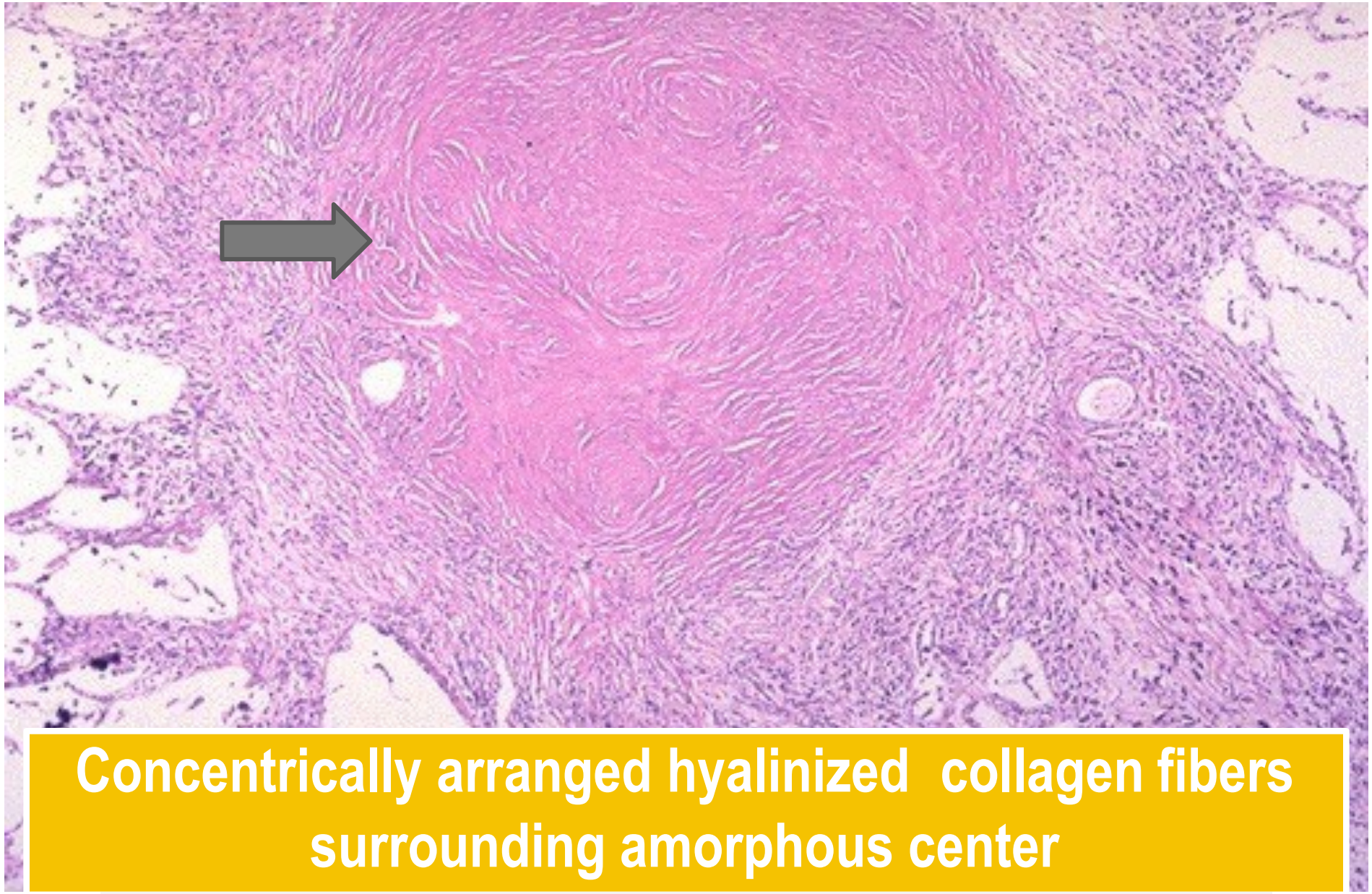
- Nodules may coalesce into **hard, collagenous scars**, with eventual **progression to PMF** (progressive massive fibrosis)

PMF is associated with extensive fibrosis and deterioration in the lung function. So, it's a generic term that applies to a confluent fibrosing reaction in the lung that can be a complication of any of the pneumoconiosis.

- **Fibrotic lesions** also may occur in **hilar lymph nodes and pleura.**

Due to the expansion of the nodules and the progression to extensive fibrosis in some cases, the intervening lung parenchyma is compressed or over expanded and this will result in what we call a honeycomb or end stage lung.

SILICOTIC NODULE

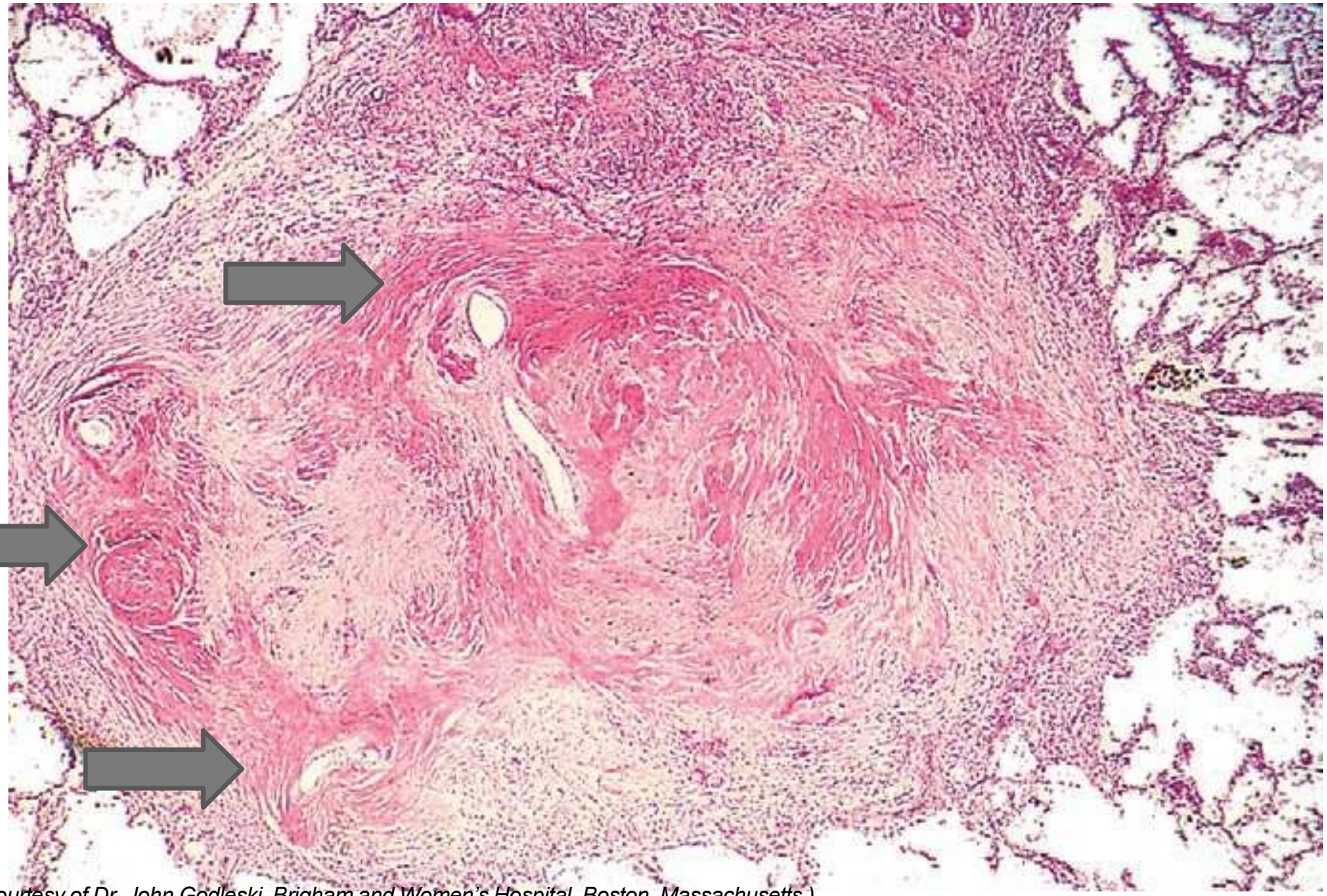


Concentrically arranged hyalinized collagen fibers surrounding amorphous center

Webpath

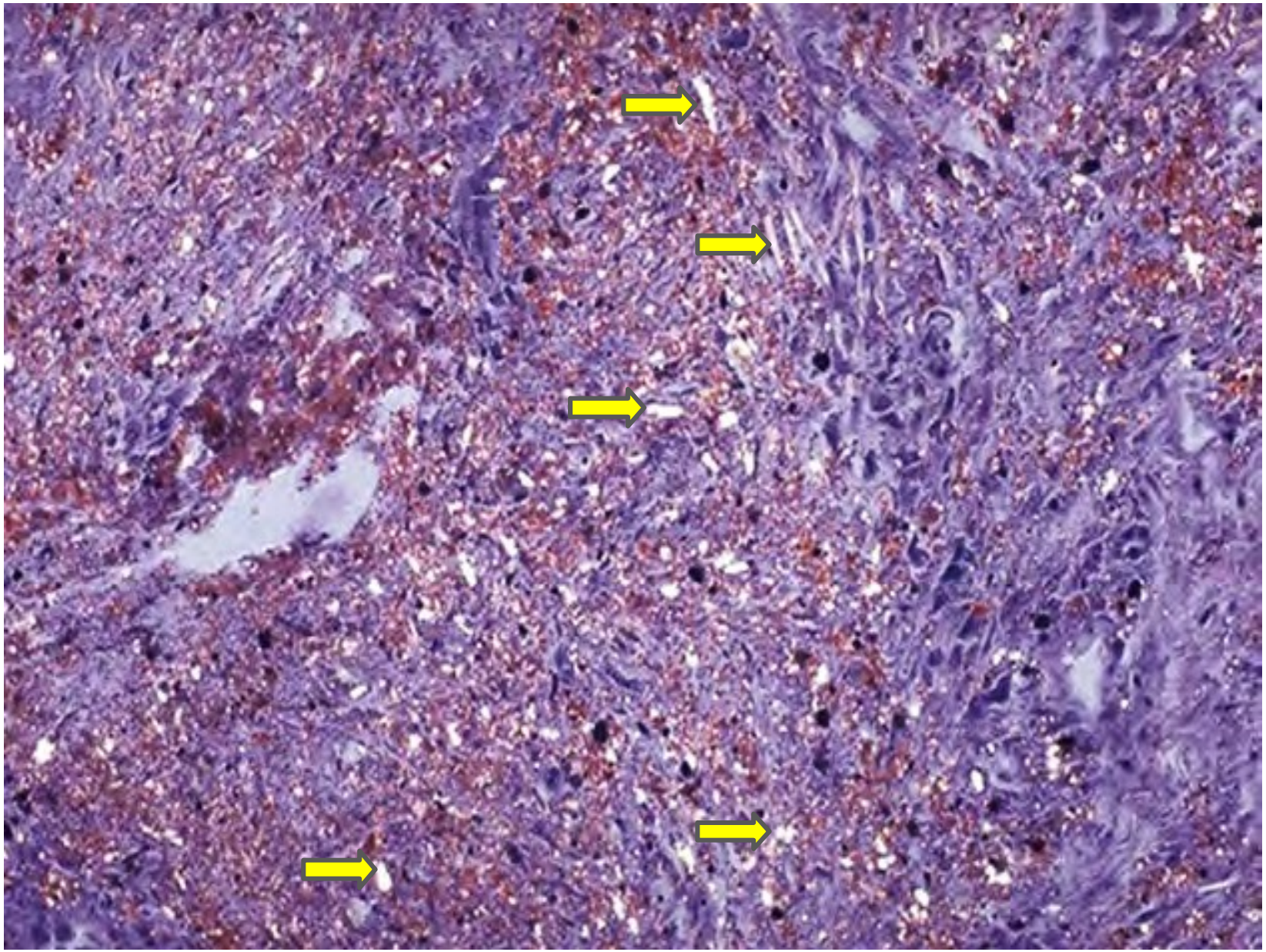
At the periphery, you can see the alveolar spaces are still patent

SEVERAL COALESCENT COLLAGENOUS SILICOTIC NODULES



Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston, Massachusetts.)

Silicotic nodules, each is composed of bundles of interlacing pale pink collagen. Notice the surrounding inflammatory reaction. a greater degree of exposure to silica and increasing length of exposure determine the amount of silicotic nodule formation and the degree of the restrictive lung disease which is a progressive and irreversible one.



Silica cystals

this figure shows silica crystals under the polarized light microscope. The crystals are bright white with variable sizes (yellow arrow).
So the silica crystals that are inhaled reach the alveoli and get ingested by the macrophages, which secrete cytokines to induce a predominantly fibrogenic response. Now because the inorganic matrix of the crystals is never completely digested, this process continues indefinitely and is made worse by repeated exposures to the dusts that contain silica. The result is the production of many scattered nodular fossa of collagen deposition in the lung which we call the silicotic nodules and eventually restrictive lung disease progressing into cor pulmonale.

CLINICAL FEATURES:

- **Asymptomatic**: detected as fine nodularity in the upper zones of the lung on routine chest radiographs

most patients do not develop shortness of breath until late in the course of the disease

- after **PMF**: Shortness of breath, pulmonary hypertension and cor pulmonale

Shortness of breath (dyspnea)

- **slowly progressive**, impairing pulmonary function to a degree that limits physical activity.

- **Increased susceptibility to tuberculosis**

This happens because silicosis is associated with depressed cell mediated immunity. Furthermore, the crystalline silica inhibits the ability of the pulmonary macrophages to kill the phagocytosed mycobacteria

- **lung cancer ?**

The relationship between silica and lung cancer is still unsettled because most studies suggest that silica exposure is associated with some increased risk however this topic is still controversial

ASBESTOSIS AND ASBESTOS-RELATED DISEASES

It’s the third mineral dust associated with Pneumoconiosis.

https://en.wikipedia.org/wiki/Asbestos

ASBESTOS

- **Family of crystalline hydrated silicates with a fibrous geometry.**

Asbestos is one of the mineral dust that can cause pneumoconiosis, other common mineral dusts as we discussed before are the cold dust and silica. Usually the exposure happens in workplace, this is true except for the asbestos as with this mineral, the increased risk for cancer extends to the family members of the asbestos workers and also to the individuals exposed to the asbestos outside their workplace. So, the risk of asbestos is increased in any patient who is exposed to the asbestos in workplace or outside the workplace and also to the family members of the asbestos workers. Furthermore, studies showed an increased incidence of asbestos-related cancers in family members of asbestos workers.

ASSOCIATED WITH:

on the basis of epidemiologic studies occupational exposure to asbestos is linked to

(1)parenchymal interstitial fibrosis (asbestosis);

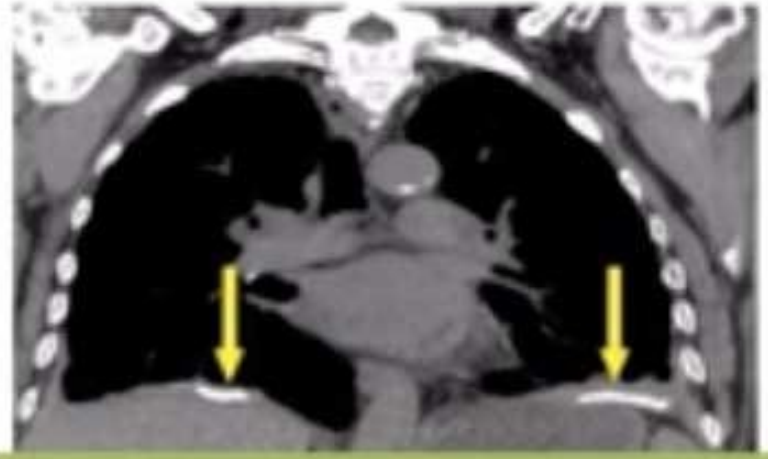
(2)localized fibrous plaques or, rarely, diffuse pleural fibrosis.

(3) pleural effusions

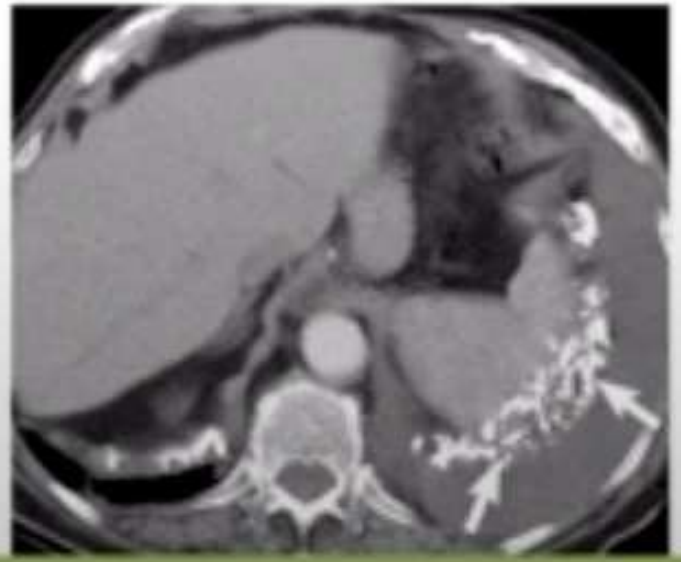
(4) Lung carcinomas

(5)malignant pleural and peritoneal mesotheliomas

(6) laryngeal carcinoma



Pleural Plaques suggest asbestos exposure and do not cause symptoms



Malignant Pleural Mesothelioma: Rare cancer of the lung lining

ASBESTOSIS:
IS SCARRING OF THE LUNG CAUSED BY ASBESTOS EXPOSURE

PATHOGENESIS:

As with the silica crystals, the pulmonary macrophage is the key cellular element in inflammation, lung injury and fibrosis

- once phagocytosed by macrophages→ asbestos fibers activate the inflammasome and damage phagolysosomal membranes → release of proinflammatory factors and fibrogenic mediators→

1. cellular and fibrotic lung reactions this will initiate an inflammatory response that leads to fibroblast proliferation and collagen deposition
2. tumor initiator and a promoter
    - mediated by the oncogenic effects of reactive free radicals generated by asbestos fibers on the mesothelium.

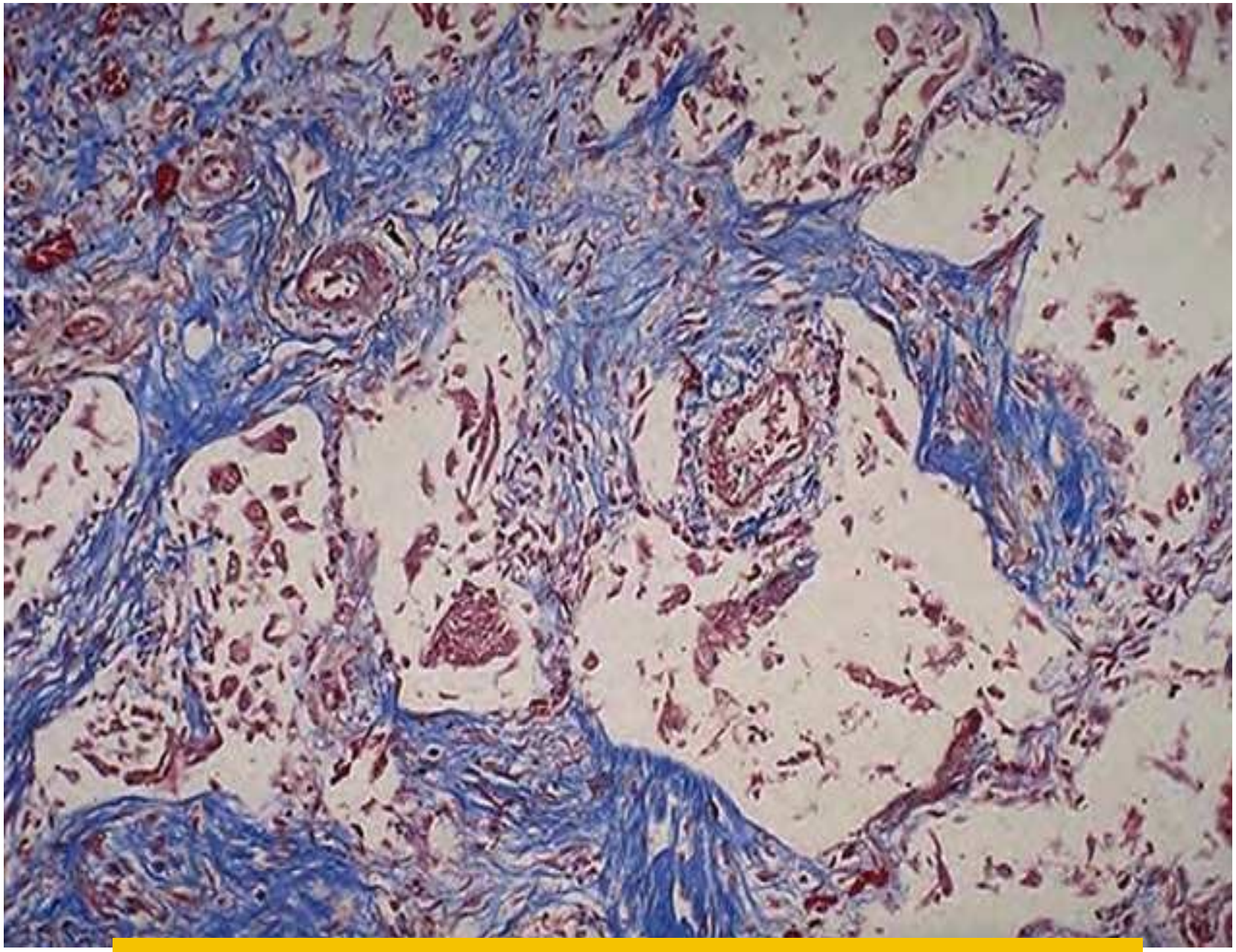
Why the mesothelium ?
Because asbestos fibers are usually localized in the distal lung close to the mesothelial layer

- **Asbestos and tobacco:**
  - The adsorption of carcinogens in tobacco smoke onto asbestos fibers results in remarkable **synergy** between tobacco smoking and the development of lung carcinoma in asbestos workers.

https://health.clevelandclinic.org/even-smoking-just-one-or-two-cigarettes-a-day-increases-your-risk-of-lung-disease/

In general, the adsorption of potentially toxic chemicals into the asbestos fibers increases its pathogenicity, and as we all know tobacco smoking is considered number one risk factor for the development of lung cancer on one hand and on the other hand and as we mentioned in the previous slides, asbestos occupational exposure is linked to the development of lung cancer too, but what will happen when the patient have both ?
When the patient is a tobacco smoker and has an occupational exposure to asbestos, the risk exceeds the sum of each factor alone so the absorption of carcinogens in the tobacco smoke into the asbestos fibers is the basis for the remarkable synergy between tobacco smoking and the development of lung carcinoma in asbestos workers, and in general tobacco smoking worsens the effect of all inhaled mineral dusts especially the asbestos.

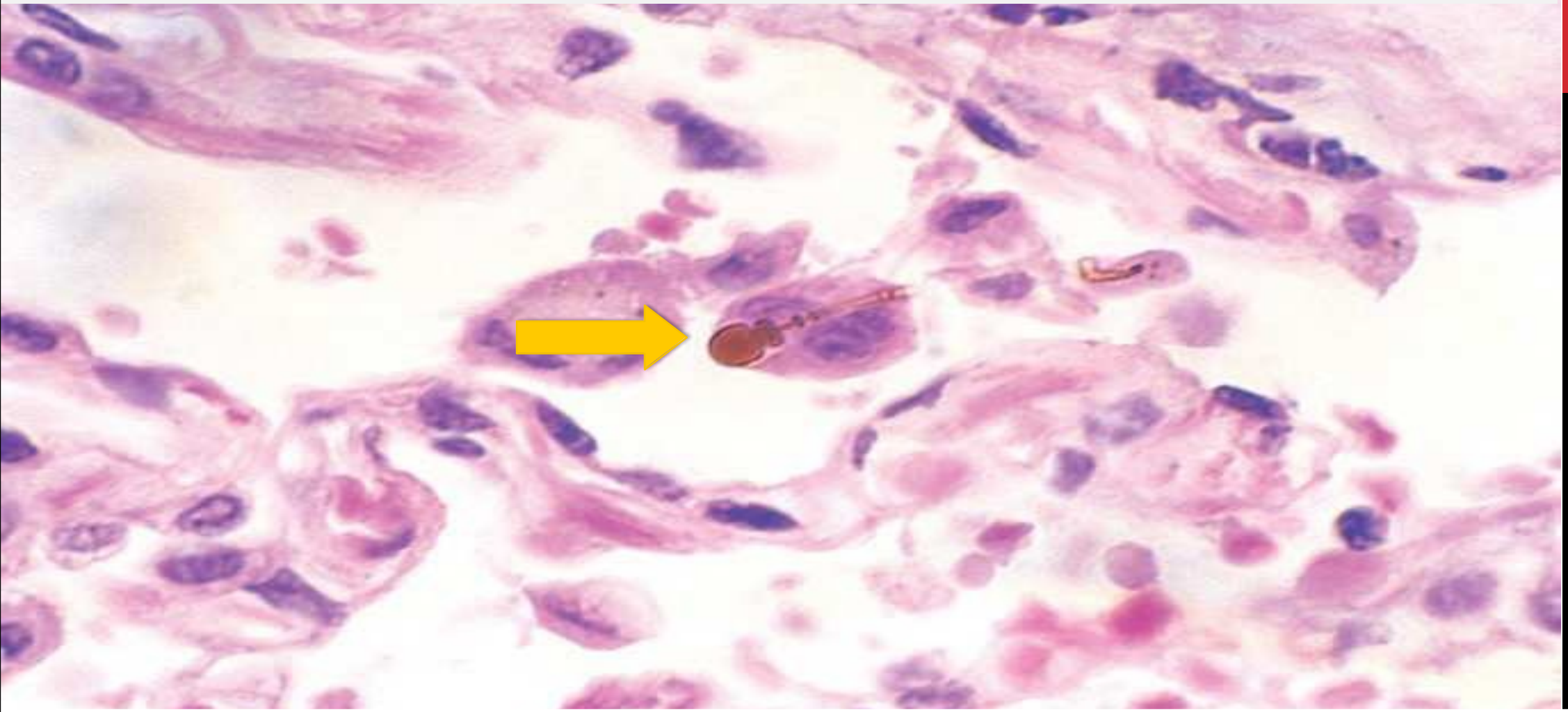
MORPHOLOGY



diffuse pulmonary interstitial fibrosis

The tissue section here is stained using trichrome stain which highlights collagen in blue. Notice how all the blue areas of the interstitium are expanded and distorted by fibroblastic proliferation and deposition. The extent of fibrosis determines the severity of the disease which is marked by a progressively worsened dyspnea clinically. So the first characteristic feature is the presence of diffuse pulmonary interstitial fibrosis.

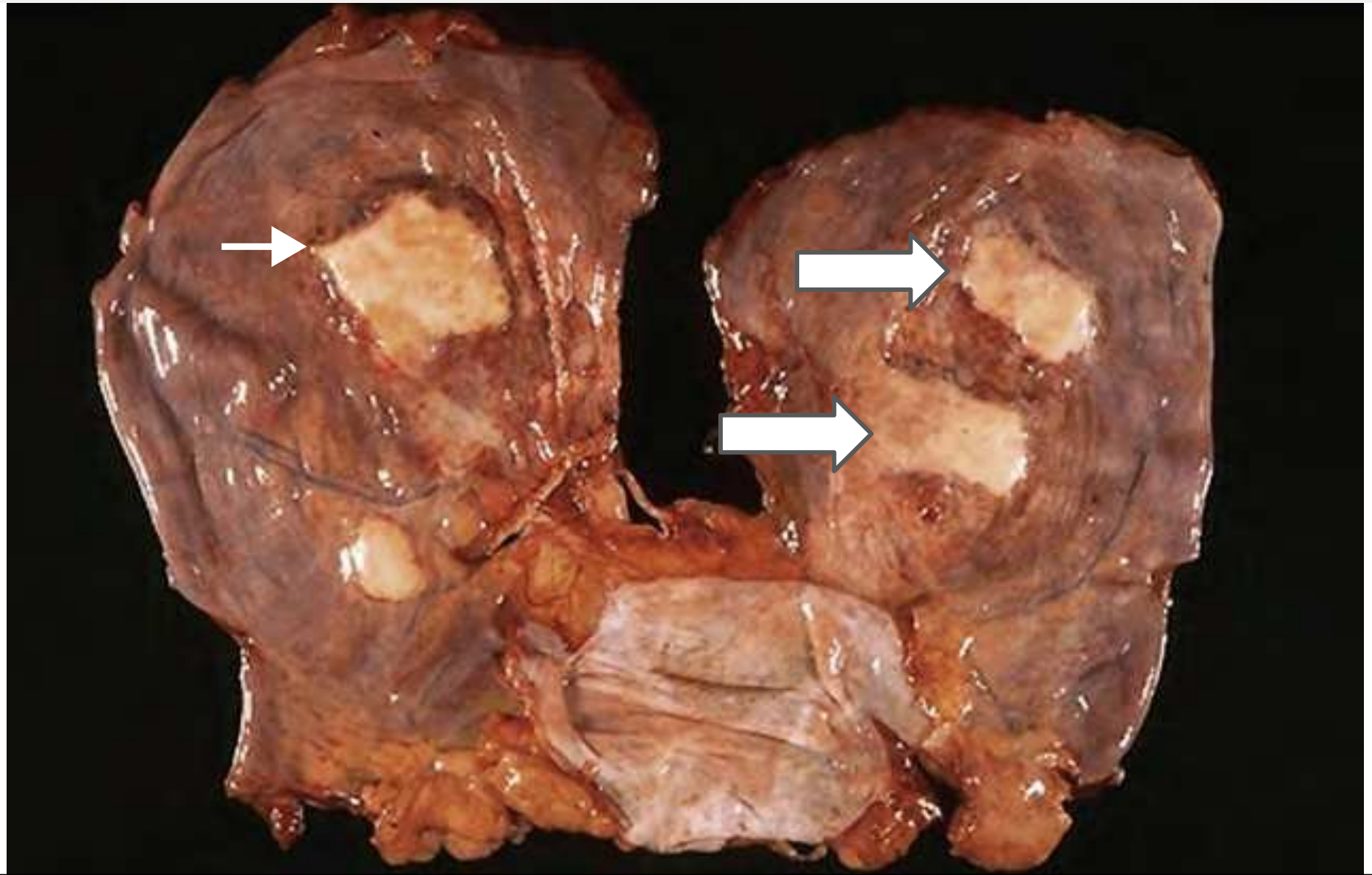
Another characteristic feature is the presence of asbestos bodies which are golden brown fusiform or beaded rods with a translucent centre (yellow arrow)



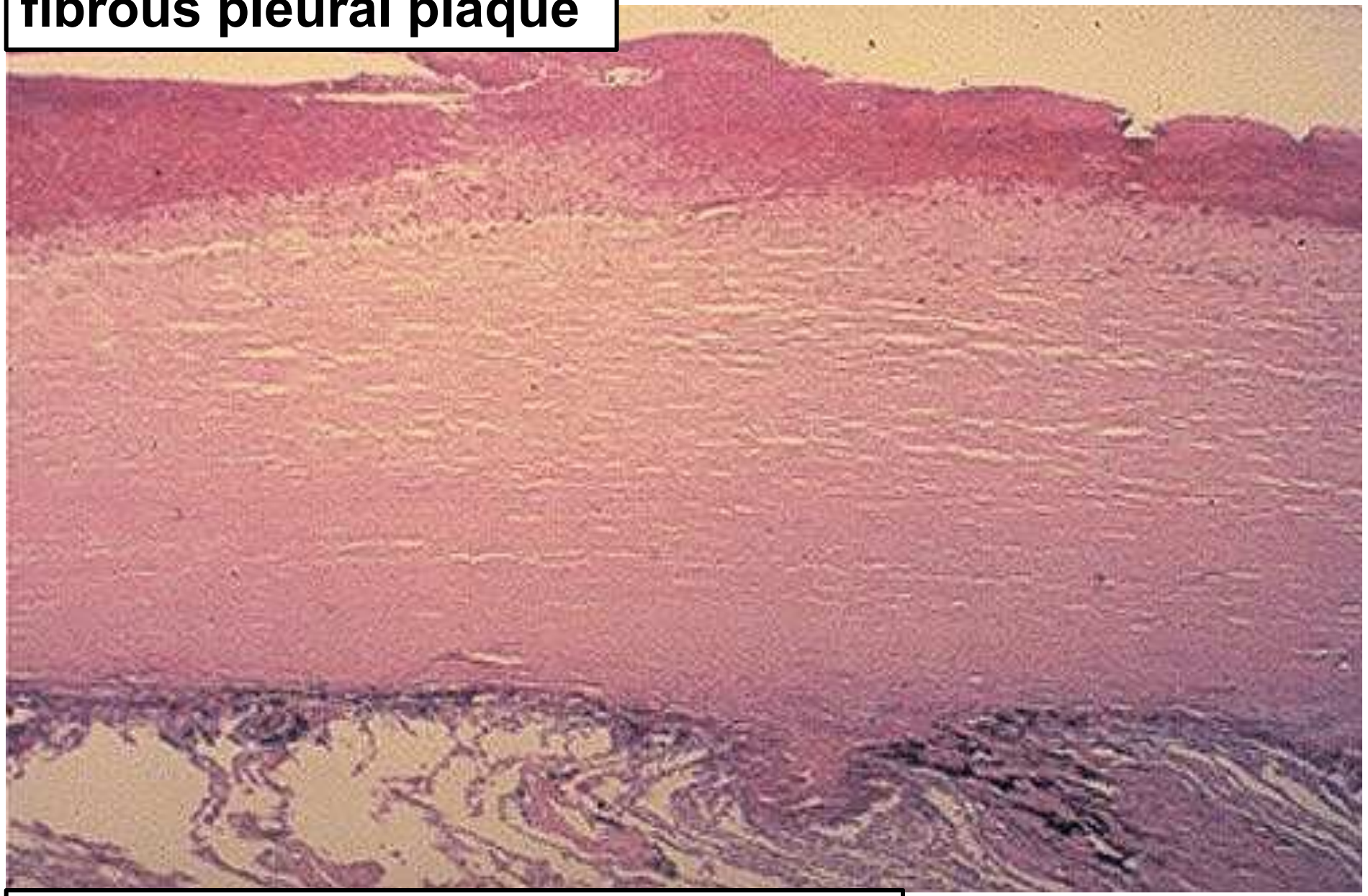
Asbestos body with beading and knobbed ends

Robbin's Basic pathology, 10 th edition

The most common manifestation of asbestos exposure is the pleural plaques. The white arrows points to the 10 white multiple pleural plaques on the pleural aspects of the diaphragm. These flags develop most frequently on the anterior and posterior lateral aspects of the parietal pleura and over the dome of the diaphragm.



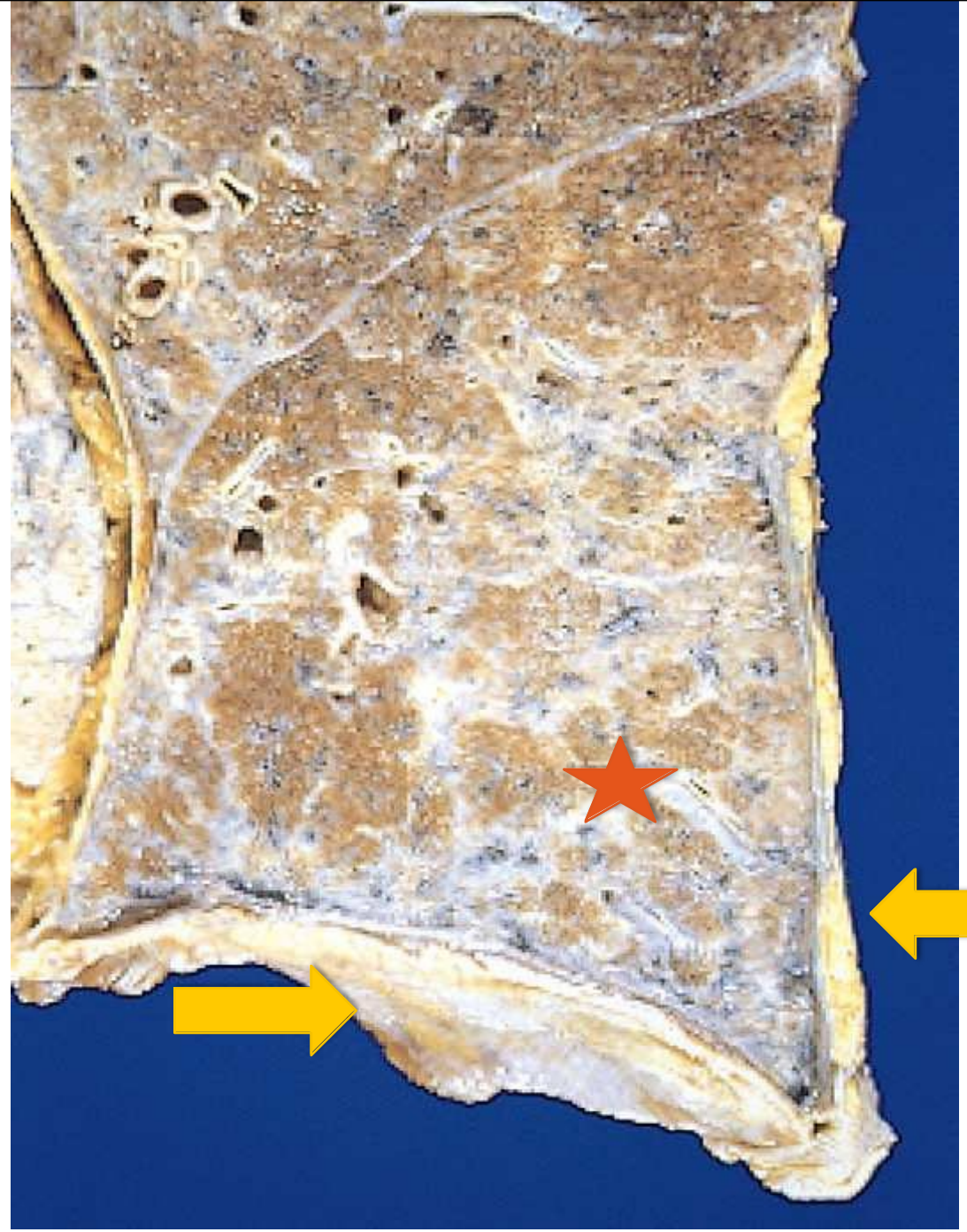
fibrous pleural plaque



dense laminated layers of collagen (pink)

This figure shows the histologic appearance of the pleural plaques which are made of dense laminated layers of collagen.

Robbin's and Cotran Atlas of pathology, 3rd edition



This figure shows the gross appearance of two important findings. The yellow arrows point to a markedly thickened area of the visceral pleura covering the lateral and the diaphragmatic surface of the lung. The area under the red star shows severe interstitial fibrosis affecting the lower lobe

Robbin's Basic pathology, 10 th edition

MORPHOLOGY

- **Diffuse pulmonary interstitial fibrosis** indistinguishable from UIP.

Diffuse pulmonary interstitial fibrosis is usually patchy in distribution associated with fibroblastic foci and the formation of cystic species (a pattern that is known histologically as usual interstitial pneumonia). So, diffuse pulmonary interstitial fibrosis related to asbestosis is similar to the one seen in the usual interstitial pneumonia.

- **Asbestos bodies:**
  - golden brown, fusiform or beaded rods with a translucent center.
  - Formed of asbestos fibers coated with an iron-containing proteinaceous material

Asbestos bodies are formed from when the macrophages try to phagocytose asbestos fibers. The iron coat or the outer crust is derived from the phagocyte ferritin.

- Begins in the **lower lobes and subpleurally**

Spreading to the middle and the upper lobes of the lungs as the fibrosis progresses. This is the opposite of what happens in the silicosis and coal worker pneumoconiosis.

Robbin's Basic pathology, 10 th edition

- **Pleural plaques:**
  - the most common manifestation of asbestos exposure
  - well-circumscribed plaques of dense collagen containing calcium
  - anterior and posterolateral aspects of the parietal pleura and over the domes of the diaphragm

CLINICAL FEATURES:

The clinical findings in asbestosis are similar to those related to other chronic interstitial lung diseases

- Progressively worsening dyspnea **10 to 20 years after exposure**.
- cough and production of sputum.
- **static or progress** to congestive heart failure, cor pulmonale, and death.
- Pleural plaques are usually asymptomatic. Detected on radiographs as circumscribed densities

OUTCOMES:

- The risk for developing **lung carcinoma** is increased **5-fold** for asbestos workers

- the relative risk for **mesothelioma** is more than **1000 times** greater than the risk for lung cancer. Mesothelioma is a very rare tumor
- Concomitant **cigarette smoking** increases the risk for lung carcinoma **but not for mesothelioma**. Mesothelioma development is highly related to the asbestos exposure not to the tobacco smoking however and as it does with all other respiratory diseases, tobacco smoking worsens the symptoms of mesothelioma and reduces the body ability to heal.

- **Lung or pleural cancer** associated with asbestos exposure carries a particularly **poor prognosis**.

Summary

Coal worker pneumoconiosis, silicosis and asbestos are all occupational diseases related to workplace exposure.

Coal worker pneumoconiosis is caused by long term exposure to coal dust and this may happen in coal miners, urban dwellers and tobacco smokers.

Silicosis is caused by inhalation of a crystalline silica dust. Risky occupations include hard rock mining and sand blasting (cleaning the surface of rocks with a jet of sand that is driven by compressed air or steam).

Asbestosis-related interstitial lung disease is related to asbestos fiber inhalation. Risky occupations include construction painter, railroad workers and miners. The reaction of the lung to mineral dust depend on the size of the particles, so particles greater than 5-10 micrometres are unlikely to reach the distal airways and are usually cleared out by the cilia in the large airways, whereas particles smaller than 0.5 micrometre may move into and out of the alveoli with gas exchange without causing any injury. So, the most dangerous particles are the ones between 1-5 micrometre in diameter because these can be launched at the bifurcation of the distal airways and they are considered small to be detected by the cilia of the large airways and also large to be moving through the alveoli during the gas exchange.

The main player in the reaction to the mineral dust's exposure are the macrophages.

Summary

Anthracosis develops gradually over many years of exposure and is characterized by black spotting of the lungs grossly. Histologically the alveolar macrophages are seen engulfing the coal dust.

Over many years of exposure and with more accumulation in the macrophages, those macrophages release inflammatory mediators that result in fibrosis
and may eventually result in a progressive massive fibrosis.
The spectrum of changes range from asymptomatic anthracosis to progressive massive fibrosis. After inhalation of silica particles, they are engulfed by the pulmonary macrophages and this results in the release of inflammatory mediators that will stimulate the cell mediated immune reaction. However, silica particles affect the macrophages and decrease their phagolysosomal capacity with time, that's why patients with silicosis are more prone or at higher risk of the tuberculosis infection.

Spectrum of changes:

- Asymptomatic anthracosis
- Simple CWP: coal macules and nodules +/- centrilobular emphysema
- Complicated CWP or PMF: coalescence of coal nodules

Microscopically. silicotic nodules show amorphous centres containing silica particles and macrophages which are surrounded by multiple concentric layers of arranged hyalinized collagen fibers.

In asbestos, once the fibers are phagocytosed by the macrophages, they activate the inflammasomes causing a damage for the phagolysosomal membranes resulting in cellular and fibrotic lung reaction and this reaction acts also as a tumor initiator and promoter.

Summary

Lung involvement in coal worker pneumoconiosis and silicosis affect the upper zones in the Lung while asbestos is centred in the lower zones.

PULMONARY EOSINOPHILIA

PULMONARY EOSINOPHILIA

- number of disorders of immunologic origin, characterized by pulmonary infiltrates rich in eosinophils. The etiology is still not understood

DIVIDED INTO:

- Acute eosinophilic pneumonia with respiratory failure
- Simple pulmonary eosinophilia (Loeffler syndrome)
- Tropical eosinophilia
- Secondary eosinophilia
- Idiopathic chronic eosinophilic pneumonia

Dr. Maram: Just know that these diseases are under the umbrella of eosinophilic diseases. We won't talk about each one separately so skip the next 3 slides.

- **Acute eosinophilic pneumonia with respiratory failure:**
  - rapid onset of fever, dyspnea, hypoxia
  - respond to corticosteroids.
  - The bronchoalveolar lavage fluid typically contains more than 25% eosinophils.

- **Simple pulmonary eosinophilia (Loeffler syndrome):**
  - transient pulmonary lesions
  - eosinophilia in the blood
  - benign clinical course
  - Histologically, the alveolar septa are thickened, and we this happens due to an infiltration by eosinophils within the alveolar septa. Sometimes, this eosinophilic infiltrate is mixed with occasional giant cells.

- **Tropical eosinophilia*:***
  - caused by infection with microfilariae and helminthic parasites. This figure shows 2 types of microfilaria that can tropical eosinophilia.

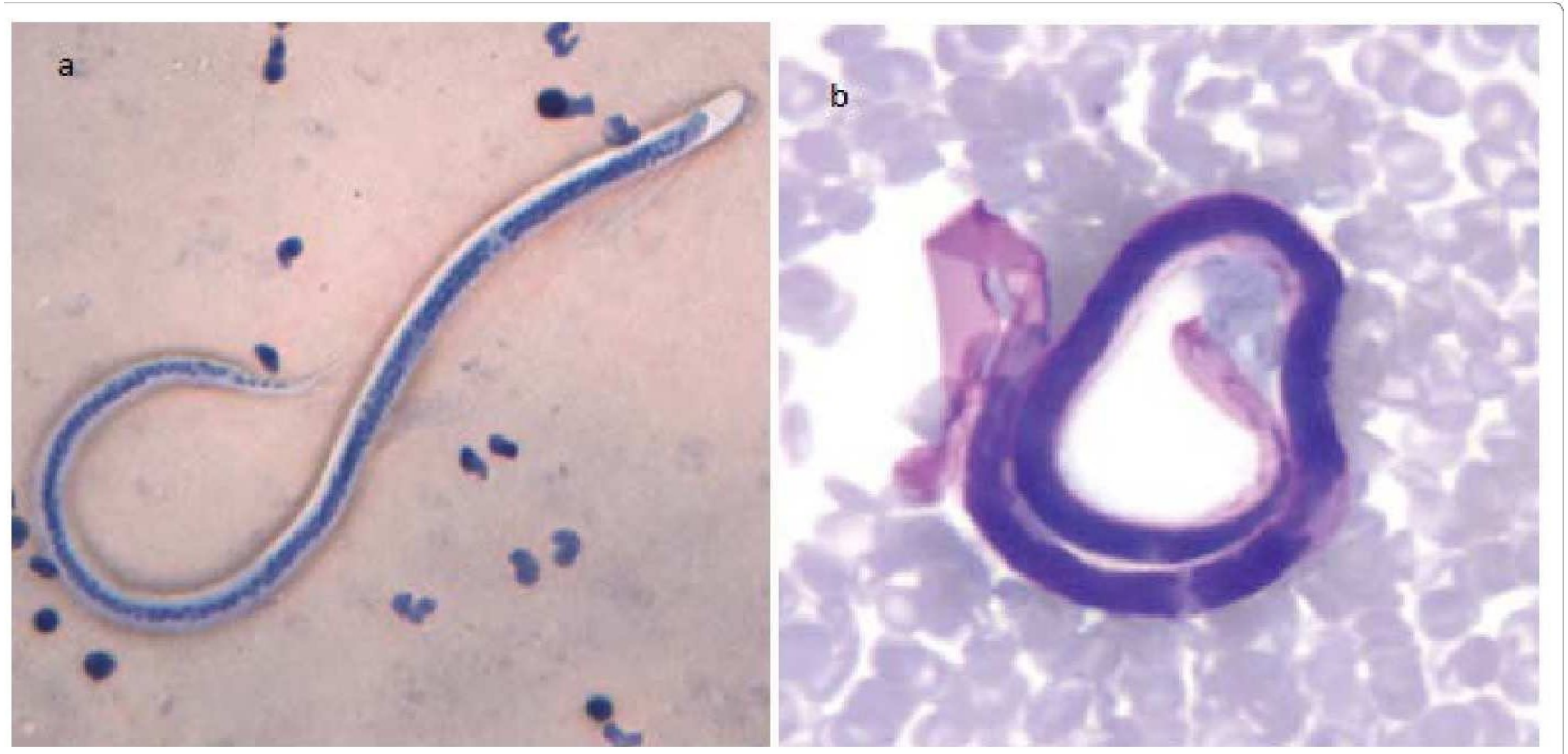


Figure 1: a) Microfilaria of *W. bancrofti* in a thick blood smear stained with Giemsa; b) Microfilaria of *B. malayi* in a thin blood

Tropical Pulmonary Eosinophilia: An Epidemiological and Clinical Review, Medicine Published 2019 DOI:10.23937/2378-3516/1410102

- **Secondary eosinophilia:**
  - in association with asthma, drug allergies, and certain forms of vasculitis.

- **Idiopathic chronic eosinophilic pneumonia*:***
  - disease of exclusion, once other causes of pulmonary eosinophilia have been ruled out. It's characterized by aggregates of lymphocytes and eosinophils within the septal walls and the alveolar spaces, typically seen at the periphery of the lung. Clinically, this condition is associated with high fever, night sweats and dyspnea.

SMOKING-RELATED INTERSTITIAL DISEASES

In addition to the obstructive lung Diseases, smoking is also associated with restrictive or interstitial lung diseases.

https://health.clevelandclinic.org/even-smoking-just-one-or-two-cigarettes-a-day-increases-your-risk-of-lung-disease/

SMOKING-RELATED INTERSTITIAL DISEASES

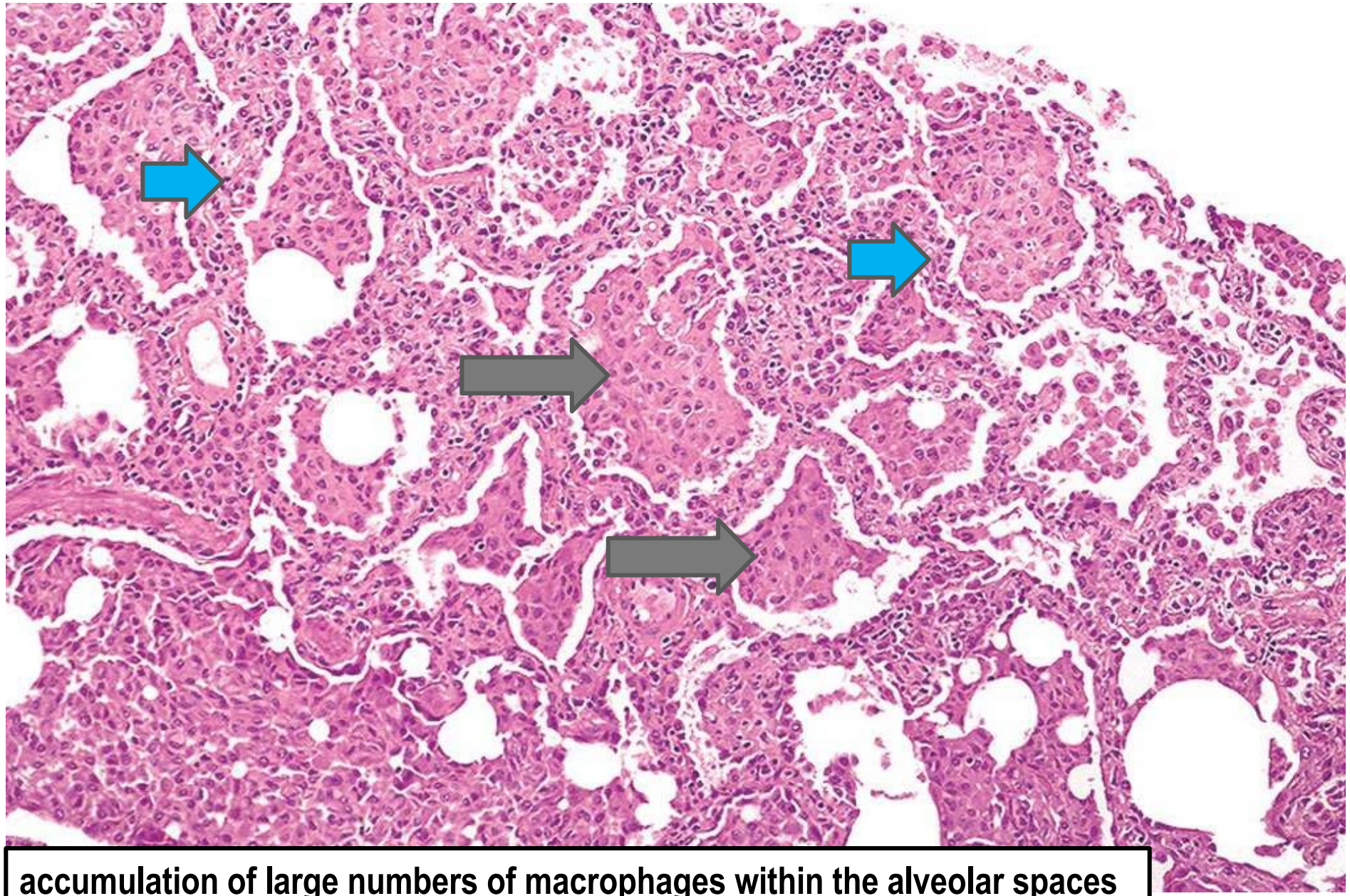
- Desquamative interstitial pneumonia (DIP)
- respiratory bronchiolitis

DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

- The most striking histologic feature of DIP is the accumulation of large numbers of macrophages containing dusty-brown pigment *(smoker's macrophages)* in the air spaces

- Lymphocytes in alveolar septa

- +/- mild Interstitial fibrosis



The grey arrows in this figure point to the collections of smokers macrophages or pigmented macrophages within the alveolar spaces.

The blue arrows point to mildly expanded alveolar septa by lymphocytes and mild fibrosis

accumulation of large numbers of macrophages within the alveolar spaces

only slight fibrous thickening of the alveolar walls.

Robbin's Basic pathology, 10 th edition

Outcome:

- good prognosis

- excellent response to steroids and smoking cessation, however, some patients progress despite therapy.

RESPIRATORY BRONCHIOLITIS

- common lesion in smokers

presence of pigmented intraluminal macrophages akin to those in DIP, **but** in a "bronchiolocentric" distribution (first- and second-order respiratory bronchioles). pigmented macrophages are present within the lumens of first and second order respiratory bronchioles instead of being within the alveolar spaces like what we see in DIP.

- Mild peribronchiolar fibrosis.

- As with DIP, presents with gradual onset of dyspnea and dry cough

- symptoms recede with smoking cessation.

A 60 year old gentleman had progressively worsening dyspnea over the past 12 years. He has noticed a 7-kg weight loss in the past 2 years. He has a chronic cough with minimal sputum production and no chest pain. On physical examination, he is afebrile and normotensive. A chest radiograph shows extensive interstitial disease. Pulmonary function tests show diminished lung volumes and capacities. Increased exposure to which of the following pollutants is most likely to produce these findings?

A Carbon monoxide

B Silica

C Tobacco smoke

D Wood dust

A 60 year old gentleman had progressively worsening dyspnea over the past 12 years (chronic exposure). He has noticed a 7-kg weight loss in the past 2 years. He has a chronic cough with minimal sputum production and no chest pain. On physical examination, he is afebrile and normotensive. A chest radiograph shows extensive interstitial disease. Pulmonary function tests show diminished lung volumes and capacities (this is a restrictive lung disease). Increased exposure to which of the following pollutants is most likely to produce these findings?

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ANOTHER CASE?!

A 42 year old lady had a low-grade fever and worsening non productive cough and dyspnea for the past 2 years. On examination, she has breath sounds in all lung fields. A chest CT scan shows reticulonodular pattern of infiltrate. An arterial blood gas show mild hypoxemia and normal CO2. Pulmonary function tests show decreased lung capacities and volumes. Her pulmonary compliance is reduced. What is the most likely diagnosis?

A α1-Antitrypsin deficiency

B Diffuse alveolar damage

C Nonatopic asthma

D Sarcoidosis

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A α1-Antitrypsin deficiency → obstructive lung capacity with increases lung capacity.

B Diffuse alveolar damage → acute

restrictive, underlying severe injury, sepsis

C Nonatopic asthma → acute obstructive,

dyspnea

D Sarcoidosis

FOR YOUR QUESTIONS:

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Or E-learning

THANK YOU!