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RS
PATHOLOGY

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CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES, PART 2

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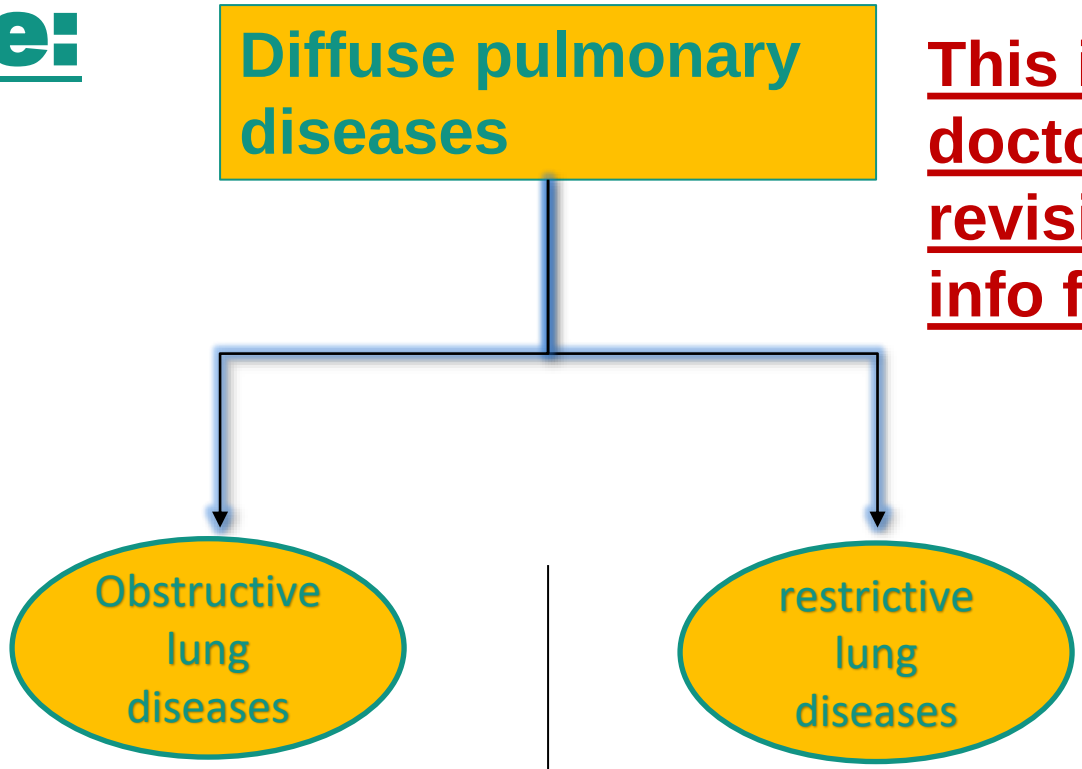
A small introduction for the lecture:



This isn't from the doctor, just some revision and extra info from the book

You cant Exhale, airways are OBSTRUCTED, FEV1 is heavily decreased, characterized by a wheezing sound when exhaling ,the total lung capacity is increased ,examples are asthma, emphysema, bronchiectasis.

You cant inhale, the problem is within the interstitium /chest wall (muscle or bone) ,the lung tissue is RESTRICTED and can't inflate, the total lung capacity is decreased, further classified into :1-granulomatous
2-Fibrosing
And other rare classifications

Fibrosing diseases

- **Idiopathic Pulmonary Fibrosis**
- **Nonspecific Interstitial Pneumonia**
- **Cryptogenic Organizing Pneumonia**
- **Pneumoconiosis**

IDIOPATHIC PULMONARY FIBROSIS(IPF)

- Pulmonary disorder of **unknown etiology** that is characterized by **patchy, progressive bilateral interstitial fibrosis**
- **Cryptogenic Fibrosing alveolitis**. *(more common term in Europe)*

The radiologic and histologic pattern of fibrosis is referred to as **Usual interstitial pneumonia (UIP)** pattern.

- **Males , Never before 50s**

Notes on the previous slide

Idiopathic Pulmonary Fibrosis (IPF):

- **As the name suggests, it is a pulmonary disorder from an unknown etiology(Idiopathic), it has a characteristic patchy bilateral interstitial progressive fibrotic pattern.**
- **This means that different "patches" or areas of the interstitium are fibrotic.**

(*simply, some areas have this pattern and others don't)*

- **This pattern can be also described as cryptogenic fibrosing alveolitis:-**

Cryptogenic meaning of unknown etiology, and alveolitis because the alveoli are the most common sites of fibrosis

Notes for the previous slide (Cont'd)

The histologic and radiologic pattern of IPF is called Usual interstitial Pneumonia(UIP), HOWEVER,this pattern is NOT specific for IPF, it can be found in other disorders, such as:

1. **Chronic hypersensitivity pneumonitis**
2. **Some connective tissue disorders**
3. **Asbestosis**

your usual patient is a 55-65 year old male or older.

IDIOPATHIC PULMONARY FIBROSIS

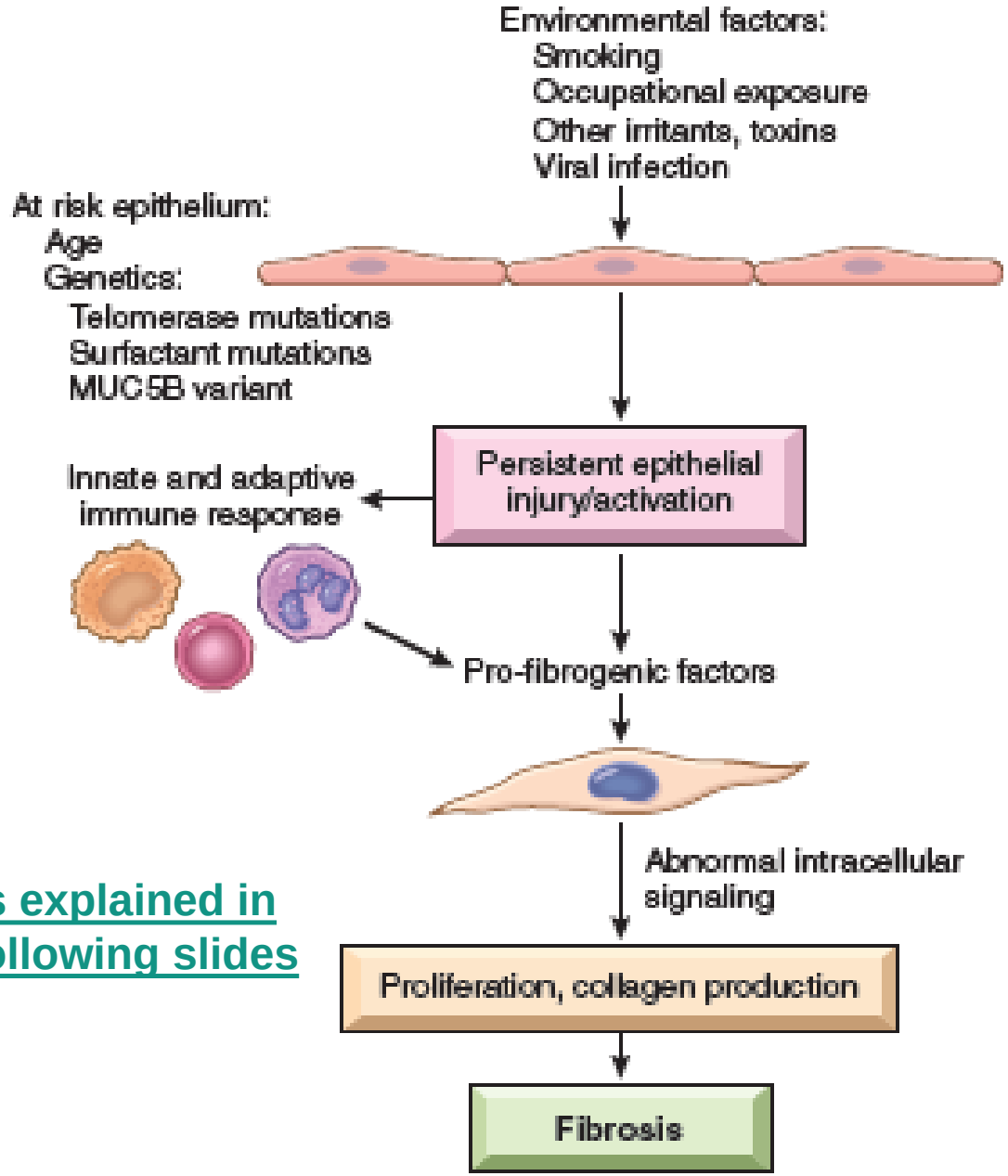
- **Diagnosis:** It is a diagnosis of exclusion(meaning you have to exclude every other disorder)via the following methods:-
  - **radiologic and histologic** pattern are needed
  - Diagnosis **of exclusion**
  - **Clinical data**

PATHOGENESIS

- **The cause is unknown**
- **This interstitial fibrosis is believed to result from:**
  - Repeated cycles of epithelial activation/injury by some unidentified agents
  - Genetic predisposition **(This is believed to be the main factor)**
  - Defective repair of alveolar epithelium

The thing you need to understand from this is that, not every individual exposed to those different environmental factors will have this disease , it's a complex combination of prolonged damage to alveolar tissue along with defective repair caused by the genetic predisposition.

This is the PROPOSED pathogenises



This picture is explained in detail in the following slides

Fig. 13.13 Proposed pathogenic mechanisms in idiopathic pulmonary fibrosis. See text for details.

Robbin's basic pathology, 10th edition

Notes on the previous slide:

The Proposed pathogenesis and different factors leading to IPF, described in the previous picture as the following:

- **Individuals at risk for IPF have epithelial cells with certain genetic mutations such as:**

➢ **Mutations in genes that are part of the Telomerase complex(the complex responsible for maintaining the repeated protective sequences at the end of the chromosome, a problem in it means reduced telomere length maintenance leading in an unknown way to defective healing and repair)**

➢ **Surfactant mutations, abnormal Type II alveolar cells with a defect in their surfactant , meaning the epithelial cells are more prone to injury and activation.**

➢ **A genetic polymorphism in the MUC5B gene , which increases the production of mucin, and produces a “special” type of mucin that could make the cells more prone to damage**

Notes for the previous slide(Cont'd):

- Another factor that could be a predisposing factor for IPF is aging, as we said before usually patients are 65 years of age or older, it is also associated with increased probabity of having mutations. (older patients could have telomerase or other mutations predisposing to IPF)
- Environmental factors, in addition to having the genetic predisposition, there are certain environmental factors that could trigger cell injury and IPF, such as:-

1-smoking 2-Occupational exposure(sprays,dyes,metals,mine workers)
3-other irritants,toxins 4-Viral infections 5-Acid reflux

- This could create a cycle of trauma and activation of inflammatory cells(neutrophils and macrophages) and injury ,followed by activation of fibroblasts and fibrogenic factors(by the inflammatory cells) in an attempt to repair and heal the damage, and the prolongation of this cycle will eventually cause IPF.

MORPHOLOGY, MACROSCOPIC:

- **Cobblestones appearance** of the pleural surface, due to retraction of scars along the interlobular septa.

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

This characteristic appearance of IPF is caused by the depression and elevation of different areas ; the fibrotic areas or "patches" are depressed and seem "backwards", and the normal areas are "elevated" or seem like they are bulging forward

A clearer picture is shown in the next slide showing the pleura.

Cobblestones appearance of the pleural surface

- The cut surface shows fibrosis (**firm**(because of collagen deposition), **rubbery white areas**)

- **Lower lobe and subpleural regions** and along the **interlobular septa** are mostly affected.

- **Usual interstitial pneumonia (UIP) pattern of fibrosis**

MORPHOLOGY, MICROSCOPIC:

Fibrosis:

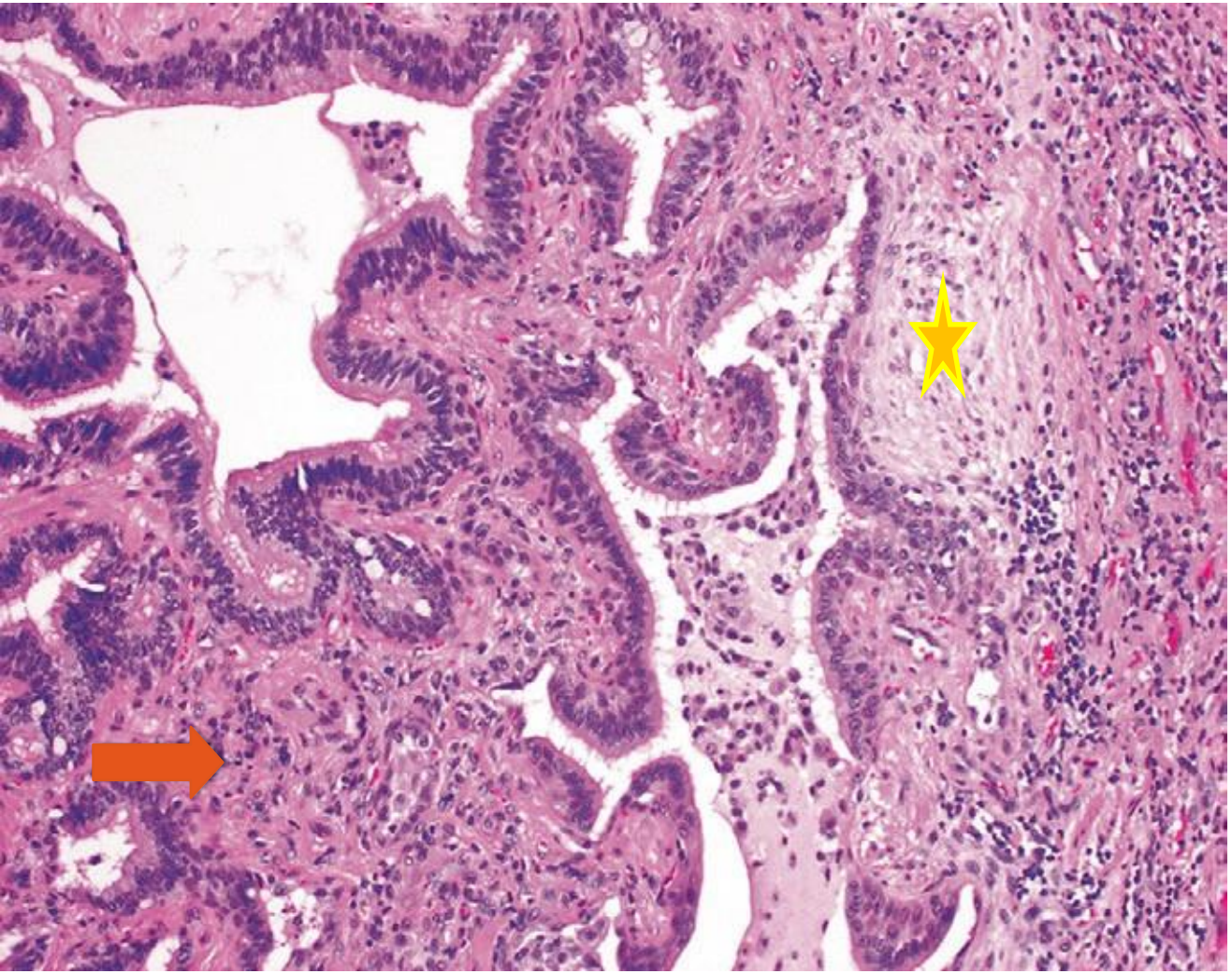
- Hallmark is **patchy** interstitial fibrosis, **which varies in intensity and worsens with time**.

- **Temporal heterogeneity is typical** (**early and late lesions coexist**): **lesions of different age**
  - earliest lesions: Fibroblastic foci made of exuberant fibroblastic proliferations. (a center of fibroblast proliferation)
  - Late **advanced** lesions are more collagenous and less cellular and may show honeycomb fibrosis **(honeycomb lung is the end stage fibrotic lung)**

mild to moderate **inflammation** within the fibrotic areas (lymphocytes, few plasma cells, neutrophils, eosinophils, and mast cells).

+/- Foci of squamous metaplasia and smooth muscle hyperplasia

pulmonary arterial hypertensive changes (intimal fibrosis and medial thickening).



The area marked by the yellow star is myxoidish (pale bluish and less dense) and cellular, it represents a fibroblastic focus and it's the earliest fibrotic lesion, that is marked by proliferation of fibroblasts.

The area marked by the orange arrow has extensive fibrosis, with dense collagen deposition, the alveolar spaces are destroyed, and the only residual alveolar space is lined by bronchiolar epithelium, this is the end stage honeycomb lung but on histology.

It's a dense thick fibrotic tissue, with dilated alveolar spaces that are lined by metaplastic bronchiolar epithelium, instead of type I and type II alveolar epithelium

Robbin's basic pathology, 10th edition

CLINICAL FEATURES

- **55 to 75 years old at presentation**
- **Gradual onset of Nonproductive cough** and **progressive dyspnea on exertion.**
- **On physical exam**, **“dry” or "Velcro"**(a tape like material that when removed produces this kind of crackle sound,like the ones found in the blood pressure cuff)-like crackles during inspiration.due to the opening of closed distal airways
- Cyanosis, cor pulmonale, and peripheral edema may develop later.
- Radiologic findings include subpleural and basilar fibrosis(in the lower lobes near the pleura), reticular abnormalities, and “honeycombing”(honeycombing is found in radiology and histology)

OUTCOME:

- The overall prognosis remains **poor**

Worst prognosis out of the fibrosing diseases

- Median survival after diagnosis **3 years**

- **lung transplantation is the only definitive treatment**.

MANAGEMENT:

- Anti-inflammatory therapies

- Anti-fibrotic therapies

Anti-fibrotic and Anti-inflammatory treatment is given , but its only job is to slow down the progression of the disease, until a lung transplantation could be done

Fibrosing diseases

- Idiopathic Pulmonary Fibrosis
- **Nonspecific Interstitial Pneumonia**
- Cryptogenic Organizing Pneumonia
- Pneumoconiosis

NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

- despite its name it has **Distinct clinical, radiologic, and histologic features.**

- **Chronic bilateral interstitial lung disease of Unknown etiology**

- **Better prognosis** than IPF**.**

- Clinically: female nonsmokers in their 6th decade of life with Dyspnea and cough of several months

Notes on the previous slide:

a group of disorders that have a type of fibrosis that is non specific and not enough to diagnose them as IPF or cryptogenic organizing fibrosis , or pneumoconiosis
that doesn't mean that they don't have their own specific features, it just means that their features don't fit any of the other three.
Its very important to diagnose it because its prognosis is better than IPF

Again , remember that the name doesn't mean it doesn't have any specific features ,it has its own radiologic and histologic features, the demographic associated with it are usually Nonsmoker females , unlike IPF which was more common in males.

NONSPECIFIC INTERSTITIAL PNEUMONIA

- **Idiopathic or associated** with collagen vascular disorders such as rheumatoid arthritis.

- characterized by **patchy but uniform** mild to moderate **interstitial chronic inflammation and/or fibrosis**.**(no fibroblastic foci and no honeycomb lung,(no early or late lesions,the lesions are mild to moderate))**

- Key features on radiology: bilateral, symmetric, predominantly lower lobe reticular opacities.

A strong factor to differentiate between it and IPF is the fact that the patchy fibrotic lesions are all of the same age and progress.

Histology:

NSIP is divided into cellular and fibrosing patterns.

- **The cellular pattern**: mild to moderate **chronic** interstitial **inflammation** (lymphocytes and a few plasma cells), in a uniform or patchy distribution.
- **The fibrosing pattern**: diffuse or patchy interstitial **fibrotic lesions of the same stage of development** (an important distinction from UIP).
- The cellular pattern usually carries a better prognosis than the relatively later fibrosing pattern.

Fibrosing diseases

- Idiopathic Pulmonary Fibrosis
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CRYPTOGENIC ORGANIZING PNEUMONIA

Remember, cryptogenic means unknown, organizing because it is associated with or seen as a response to the exposure to different factors mentioned below

- Uncommon

- Unknown etiology (BUT seen as a response viral and bacterial pneumonia, inhaled toxins, drugs, connective tissue disease, and graft-versus-host disease in BM transplant recipients).

- **progressive** Cough and dyspnea

- CXR: subpleural or peribronchial patchy airspace consolidation**(opacity)**(radiopaque or white areas).

- Microscopically:
  - **Masson bodies:** Intraalveolar plugs of loose organizing connective tissue (of the same age) within alveolar ducts, alveoli, and often bronchioles**(this is characteristic)**
  - the underlying lung architecture is normal.**(no infiltration)**
  - no interstitial fibrosis or honeycomb lung.

- Some patients recover spontaneously while most require treatment, usually with oral steroids.

- The prognosis for these patients is dependent on the underlying disorder.

https://baytowncrimestoppers.com/baytowns-most-wanted/unsolved-crimes/

A **59 year old lady** works as **electrical engineer** and **nonsmoker**, has a 4-month history of increasing **(progressive)**dyspnea. On examination she is afebrile**(clue for no infection)** and normotensive. Chest CT shows **lower lobe reticular(meaning its restrictive) opacities**. A transbronchial biopsy is performed and microscopically shows **patchy interstitial inflammation with lymphocytes and plasma cells (no granuloma and little fibrosis). No organisms are identified**. Her condition slowly worsens over the next **10 years(chronic disease with no bad prognosis)**. Which of the following is the most likely diagnosis?

A) Desquamative interstitial pneumonitis

B) Hypersensitivity pneumonitis

C) Idiopathic interstitial fibrosis

D) Nonatopic bronchial asthma

E) Nonspecific interstitial pneumonia

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organisms are identified. Her condition slowly worsens over the next 10 years. Which of the following is the most likely diagnosis?

A) Desquamative interstitial pneumonitis

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https://www.pennlive.com/news/2019/03/cold-case-findings-generating-news-throughout-pa.html

Fibrosing diseases

- Idiopathic Pulmonary Fibrosis
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- **Pneumoconiosis**

PNEUMOCONIOSES

Group of diseases that are related to inhaled dust usually , at first it was said to only be related to mineral dust , but later on the definition expanded to other causes.

- **lung reaction to inhalation of mineral dusts, organic and inorganic particulates, chemical fume and vapor.** The dusts are able to reach the distal airways at the bifurcation of the alveolar ducts to induce a reaction in the epithelium there , and also through the pulmonary macrophages .this is where the name came from.

- (so they are a group of chronic interstitial diseases caused by inhalation of mineral dusts that can cause a reaction in the alveolar epithelium, most commonly in workers exposed in a prolonged way to those dust)
- The most common mineral dust are induced by inhalation of **Coal dust, silica, and asbestos**.

- usually related to **workplace exposure**, because the workers are at a higher risk for prolonged exposure to those dusts and other causes.

(all that has been said in concern of workplace exposure is true to coal dust and silica, but Asbestos is a bit different)

- However, In **Asbestos** the **risk of cancer is increased in family members of asbestos workers and to individuals exposed outside of the workplace.**(such as old building)

Asbestos is found in insulating materials , in paints ,and materials that were used to build the older buildings.

PMF is progressive massive fibrosis

Table 13.3 Mineral Dust–Induced Lung Disease

Agent	Disease	Exposure
Coal dust	Simple coal worker's pneumoconiosis: macules and nodules Complicated coal worker's pneumoconiosis: PMF	Coal mining
Silica	Silicosis	Sandblasting, quarrying, mining, stone cutting, foundry work, ceramics
Asbestos	Asbestosis, pleural effusions, pleural plaques, or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx	Mining, milling, and fabrication of ores and materials; installation and removal of insulation

PMF, Progressive massive fibrosis.

Silicosis is the most common

Robbin's basic pathology, 10th edition

PATHOGENESIS:

- **The development of a pneumoconiosis depends on:**

(1) the **amount** of dust retained in the lung and airways (concentration in air, duration) and the effectiveness of clearance mechanisms)

(2) the **size and shape** of the particles:

Particles that are 1 to 5 μm in diameter are the most dangerous

(3) particle **solubility and reactivity**.

(4) other irritants: **concomitant tobacco smoking** worsens the effects of a inhaled mineral dusts, more so with asbestos.

The pulmonary alveolar macrophage is a key cellular element of lung injury and fibrosis.

Notes on the previous slide:

the pathogenesis of Pneumoconiosis depends on many different factors:

1-concentration of the inhaled dust, which is affected by the duration(it could take many years (10-15)) , and the effectiveness of clearance, an example for this is smoking, which causes a defective function of clearance , which will cause increased concentration of the dust

2-The size and shape of the particles:

smaller particles(<1μm) will go in and out of the airway without causing damage, and larger particles (5-10μm) will not reach the airways

the dangerous ones are those between 1 and 5 μm , which will reach the airways and cause an inflammatory reaction there.

3-The solubility and reactivity:the more soluble the particles are the more acute the reaction will be , and they wont cause a chronic disease, the ones causing a chronic instersitial disease are those with with lower solubility

Notes on the previous slide:(Cont'd)

3-(Continuing the 3rd point): coal dust for example is not very reactive and takes a long time and a needs a higher concentration to cause a reaction, but silica and asbestos are more reactive and need less time and concentration to cause a reaction

4-other irritants: like the smoking example we mentioned)

The key player of Pneumoconiosis are the pulmonary macrophages, when they recognize the particles and try to phagocytose them , and by doing so they cause an inflammatory reaction mediated by the different mediators released from the phagosome of those macrophages, and they are also responsible for the fibrosing reaction

THANK YOU!