Pathology Of Restrictive Lung Disease & Allergic Alveolitis

COLOR INDEX:

MAIN TEXT (BLACK)

FEMALE SLIDES (PINK)

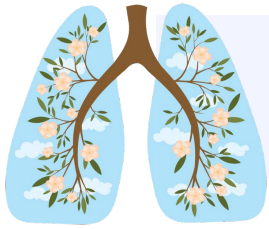
MALE SLIDES (BLUE)

IMPORTANT (RED)

DR'S NOTE (GREEN)

EXTRA INFO (GREY)

Editing file:

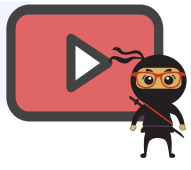


Objectives

- Understand the structure and constituents of the lung interstitium as well as the restrictive changes which occur in these diseases.
- Know the symptoms of restrictive lung disease
- Appreciate the pathogenesis of interstitial lung diseases regardless of their type
- Become aware of the classification of interstitial lung diseases.

If you want to read the lecture from Robbins click **HERE**

If you want videos of Ninja Nerd **click here**



RESTRICTIVE LUNG DISEASE

Definition

Chronic interstitial diseases are a heterogeneous group of disorders characterized by bilateral, often patchy, pulmonary fibrosis mainly affecting the walls of the alveoli

Introduction

Diffuse and usually chronic involvement of the pulmonary connective tissue, and delicate interstitium in the alveolar walls.

May be of known or unknown cause and pathogenesis

Chronic interstitial lung diseases are categorized based on clinicopathologic features and characteristic histology.

The hallmark of these disorders is reduced compliance (stiff lungs), which in turn necessitates increased effort to breathe (dyspnea).

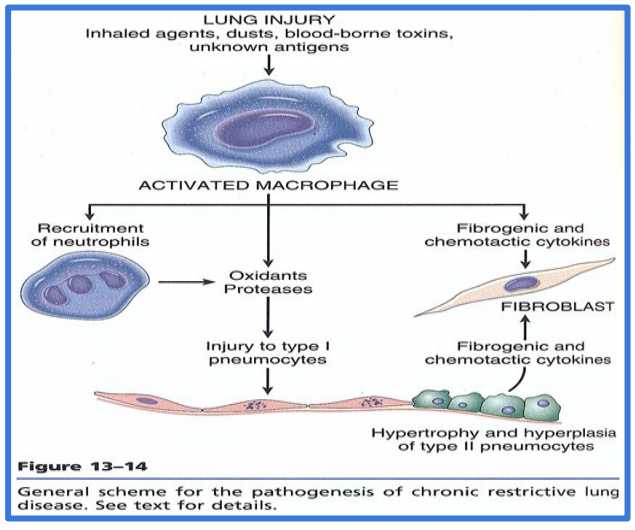


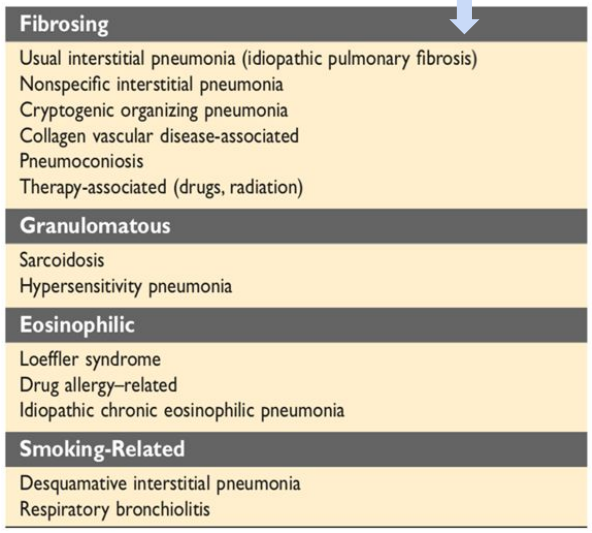
Figure 13–14

General scheme for the pathogenesis of chronic restrictive lung disease. See text for details.

RESTRICTIVE LUNG DISEASE

will be discussed in this lecture =

Major Categories of Chronic Interstitial Lung Disease	
Fibrosing	• **Usual interstitial pneumonia (idiopathic pulmonary fibrosis)** • Nonspecific interstitial pneumonia • Cryptogenic organizing pneumonia • Collagen vascular disease-associated • **Pneumoconiosis** • Therapy-associated (drugs, radiation)
Granulomatous	• **Sarcoidosis** • **Hypersensitivity pneumonia**
Eosinophilic	• Loeffler syndrome • Drug allergy-related • Idiopathic chronic eosinophilic pneumonia
Smoking-Related	• Desquamative interstitial pneumonia • Respiratory bronchiolitis



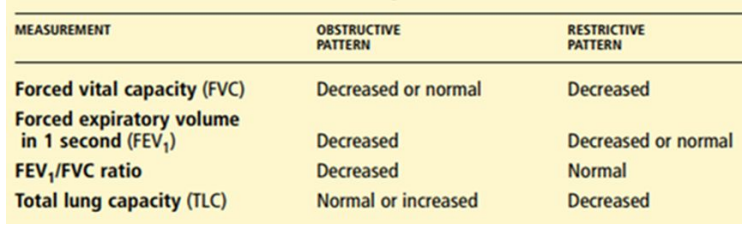
RESTRICTIVE LUNG DISEASE

Remember

Pulmonary function test:

Decrease FEV1 | Decreased FVC | Normal FEV1/FVC ratio | Decrease in TLC

	Obstructive Disease	Restrictive Disease
Definition	Limitation of air out flow due to increased airway resistance. Also called (airway diseases)	Reduced expansion of lung parenchyma & decreased total lung capacity
FVC " forced vital capacity "	Decreased or normal	Decreased
FEV1 " forced expiratory volume in 1 s"	Decreased	Decreased or normal
FEV1/FVC	Decreased	normal
TLC " total lung capacity"	increased or normal	Decreased



MEASUREMENT	OBSTRUCTIVE PATTERN	RESTRICTIVE PATTERN
Forced vital capacity (FVC)	Decreased or normal	Decreased
Forced expiratory volume in 1 second (FEV_1)	Decreased	Decreased or normal
FEV_1/FVC ratio	Decreased	Normal
Total lung capacity (TLC)	Normal or increased	Decreased

Idiopathic Pulmonary Fibrosis

1. It is a pulmonary disorder of unknown etiology characterized histologically by diffuse interstitial fibrosis

2. Males are affected more often than females.

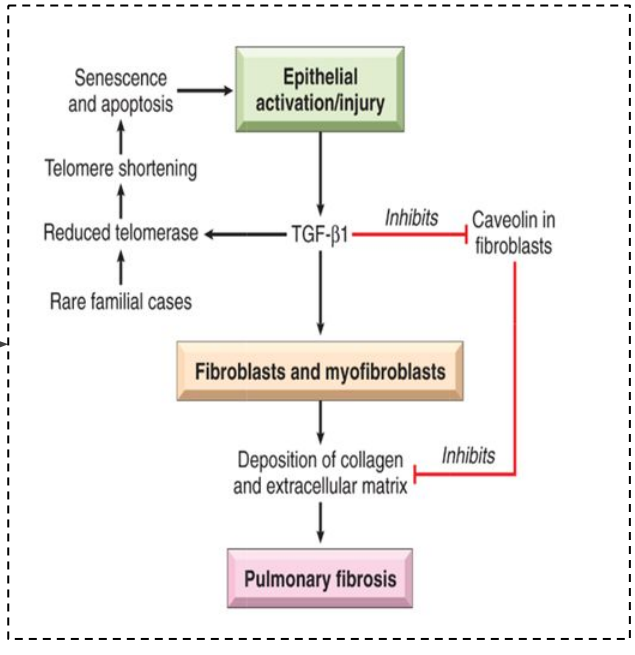
3. Never occurring before 50 years of age.

4. The radiologic and histologic pattern of fibrosis is referred to as Usual Interstitial Pneumonia (UIP)

5. All the etiologic factors should be excluded before the diagnosis.

Proposed pathogenic mechanisms in idiopathic pulmonary fibrosis

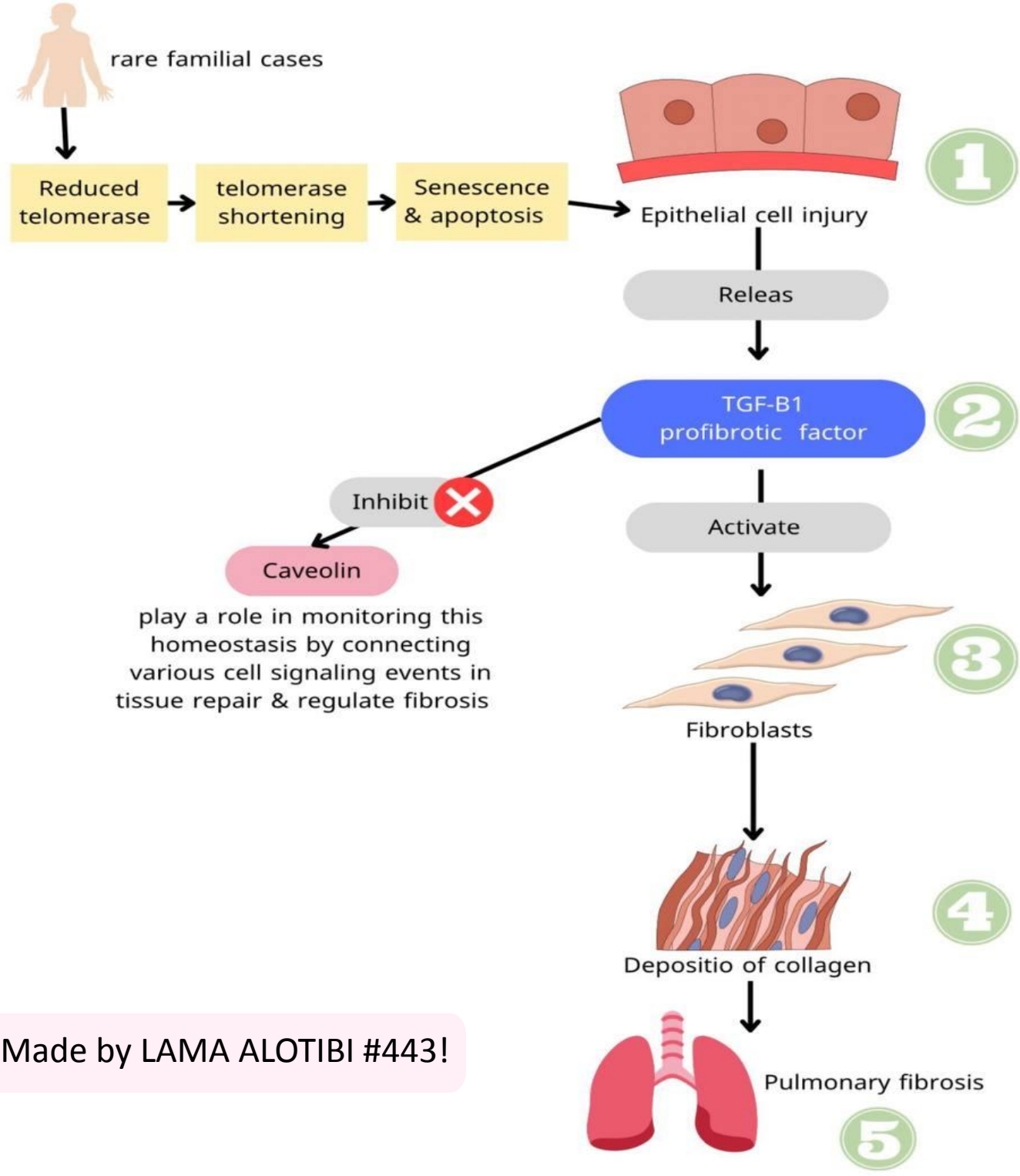
Although the mechanisms of fibrosis are incompletely understood, recent data point to excessive activation of profibrotic factors such as **TGF-β**



Idiopathic Pulmonary Fibrosis

EXTRA SLIDE

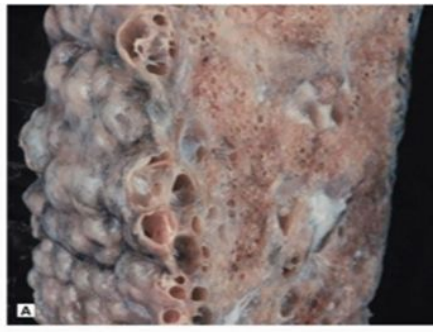
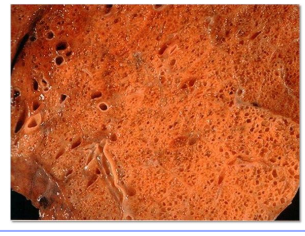
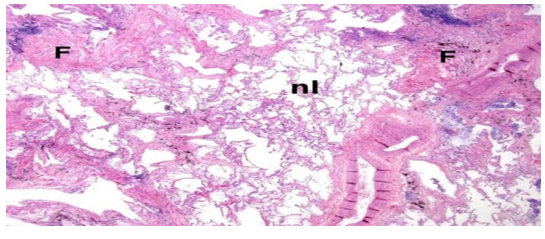
Pathogenesis



Made by LAMA ALOTIBI #443!

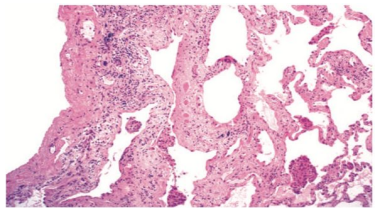
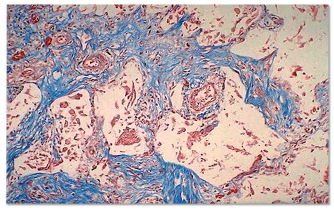
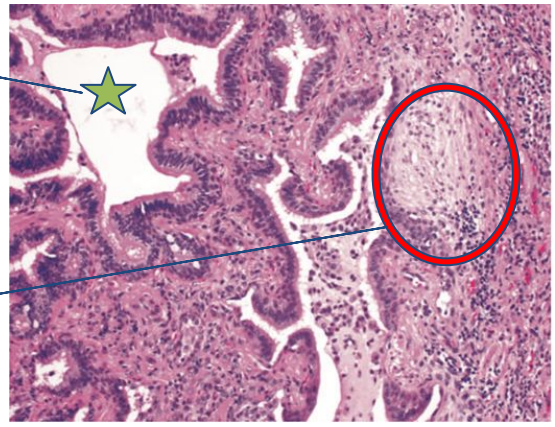
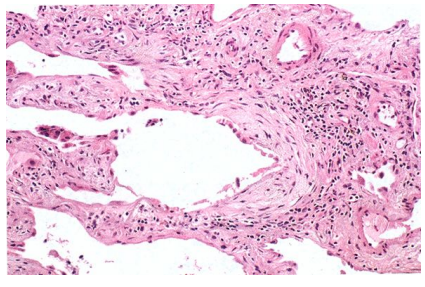
Idiopathic Pulmonary Fibrosis

Morphology

	Description	Pictures
Gross	• Pleural surfaces of the lung are cobblestoned due to retraction of scars along the interlobular septa • Firm, rubbery white areas of fibrosis preferentially within the lower lobe, the subpleural regions, and along the interlobular septa	  
	Area of honeycombing(cystic dilated areas)	 
Microscopic	Patchy interstitial fibrosis (geographic heterogenicity)	

Idiopathic Pulmonary Fibrosis

Morphology

	Description	Pictures
Microscopic	More pronounced in the subpleural region	
	Diffuse interstitial fibrosis (Masson's trichrome stain)	
	•Honeycomb fibrosis: the dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium •Temporal heterogenicity with formation of Fibroblastic proliferation (fibroblastic foci)	
	• Fibroblastic foci. • Minimal inflammation	

Idiopathic Pulmonary Fibrosis

Clinical presentation of IPF

gradual onset of a non-productive cough and progressive

Velcro like" crackles during inspiration

(produce a velcro like sound in inspiration)

velcro

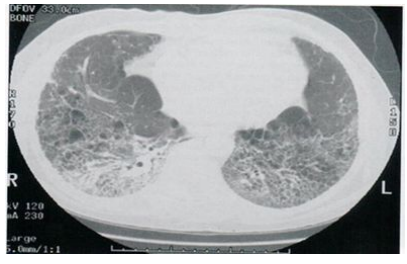
Radiologic finding:

1.subpleural and basilar involvement (apico-basal gradient)

2.reticular abnormalities

3.honeycombing

• Later stage: severe hypoxia, pulmonary hypertension and cor pulmonale.



Summary

• Diffuse interstitial fibrosis of the lung gives rise to restrictive lung diseases characterized by reduced lung compliance and reduced forced vital capacity (FVC). The ratio of FEV to FVC is normal.

• Diseases that cause diffuse interstitial fibrosis are heterogeneous. The unifying pathogenic factor is injury to the alveoli leading to activation of macrophages and release of fibrogenic cytokines such as TGF-β.

• Idiopathic pulmonary fibrosis is prototypic of restrictive lung diseases. It is characterized by patchy interstitial fibrosis, fibroblastic foci, and formation of cystic spaces (honeycomb lung). This histologic pattern is known as usual interstitial pneumonia (UIP).

Pneumoconiosis

Definition

Lung disorders caused by inhalation of mineral dusts include diseases induced by organic and inorganic particulates.

❖ The development of a pneumoconiosis depends on:

1. Amount of dust retained in the lung and airway
2. Size , shape of particles
3. particle solubility and physico chemical reactivity
4. Possible additional effects of other irritants (e.g., concomitant tobacco smoking)

most common mineral dust pneumoconiosis

- Coal dust
- Silica
- Asbestos

With **asbestos** exposure lead to increased risk for **cancer**

Pneumoconiosis

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
abestoases	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

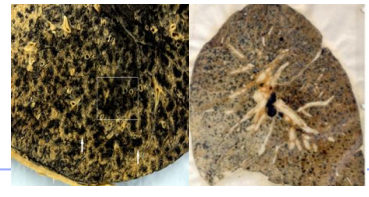
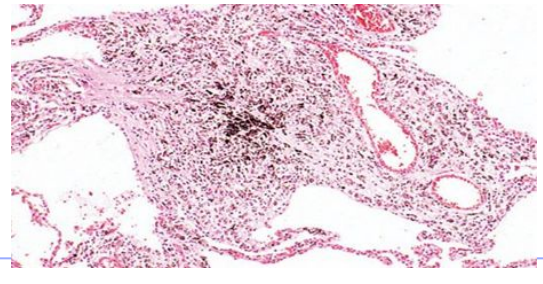
Table 13.3 Mineral Dust–Induced Lung Disease

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

Coal Worker's Pneumoconiosis(CWP)

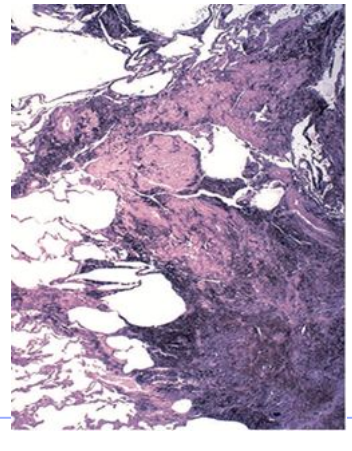
- Coal is mainly carbon, coal mine dust contains a variety of trace metals,inorganic minerals, and crystal- line silica.
- Commonly seen in urban dwellers and tobacco smokers.
- **Pulmonary anthracosis** is the most innocuous coal-induced pulmonary lesion in coal miners.
- Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages.

The spectrum

4 Types	description	morphology	
Asymptomatic	—		
Simple CWP	•Pigment deposits (coal macules) without a perceptible cellular reaction. •Macrophages accumulate with little to no pulmonary dysfunction. •Slight cough and blackish sputum.	Gross	o Upper lobes are more heavily involved o Nodules small is size (1-2 mm) 
		Micro	Aggregation of dust-laden macrophages and small amounts of collagen fibers arrayed in a delicate network 

Coal Worker's Pneumoconiosis

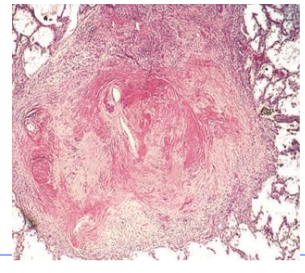
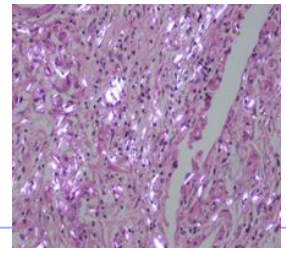
The spectrum

type	description	morphology	
Centrilobular emphysema	—		
Complicated CWP (PMF)	•Occur after many years of underground mine work. •Fibrosis is extensive and lung function is compromised. •10% of cases of simple CWP progress to progressive massive fibrosis PMF.	Gross	oMultiple, dark black scars larger than 2 cm and sometimes up to 10 cm. 
		Micro	oDense collagen and pigmen with fibrous scarring appear. 

Silicosis

it is caused by inhalation of crystalline silica (e.g.: quartz), mostly in occupational settings

- Stony-hard large fibrous scars.
- Fibrotic nodules in upper lobes of lung.
- Silicotic nodules contain concentrically arranged collagen

	Description	Pictures
Gross	**Silicotic nodules** in their early stages are tiny, barely palpable, discrete, pale-to-black (if coal dust is present) nodules in the upper zones of the lungs	
Microscopic	Concentrically arranged hyalinized collagen fibers surrounding an amorphous center	
	Examination of the nodules by polarized: weakly birefringent silica particles in the center of the nodules.	

Asbestosis and Asbestos -Related Diseases

click here

Definition

- Asbestos is a family of crystalline hydrated silicates that form fibers.
- Use of asbestos is seriously restricted in many developed countries.

Exposure to asbestos is linked to

- Parenchymal interstitial fibrosis (asbestosis)
- Fibrous pleural plaques.
- Pleural effusions
- Lung carcinoma
- Malignant pleural and peritoneal mesothelioma
- Laryngeal carcinoma

Asbestosis

Pathogenesis

1. There are two distinct geometric forms of asbestos: serpentine and amphibole.

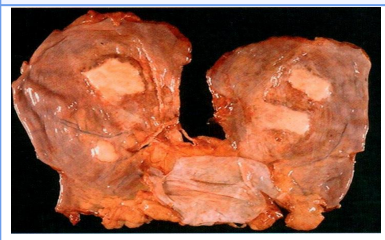
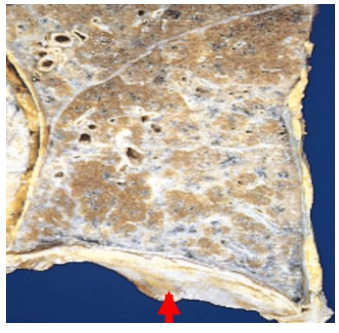
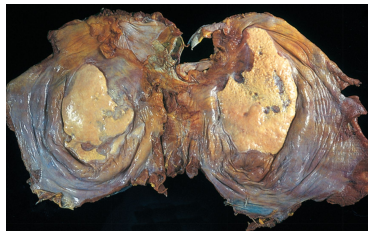
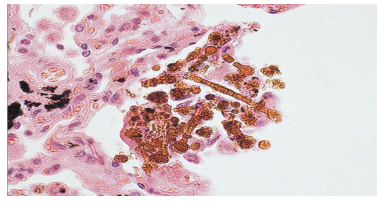
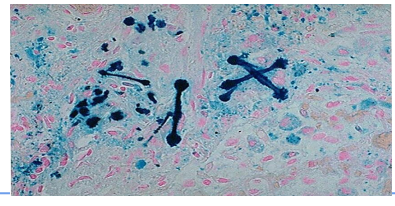
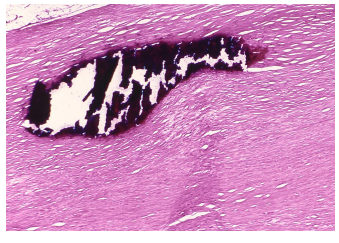
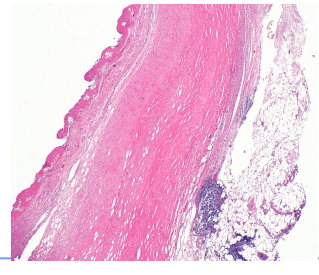
2. Both of them are fibrogenic, and increasing doses are associated with a higher incidence of all asbestos-related diseases except mesothelioma, which is only associated with amphibole exposure.

3. Some of the oncogenic effects of asbestos on the mesothelium are mediated by reactive free radicals generated by asbestos fibers, which preferentially localize in the distal lung close to the mesothelial layer.

4. Macrophages, both alveolar and interstitial, attempt to ingest the fibers and are activated to release chemotactic factors and fibrogenic mediators that amplify the response.

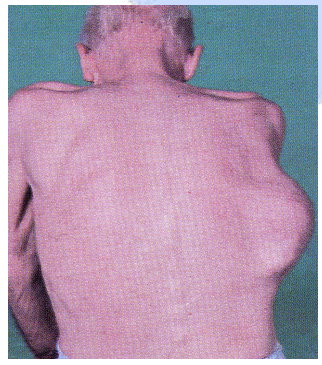
5. Chronic deposition of fibers and persistent release of mediators eventually lead to generalized interstitial pulmonary inflammation and interstitial fibrosis.

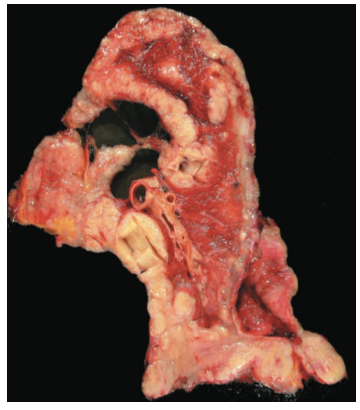
Asbestosis

	Description	Pictures
Gross	• **Pleural plaques** are the most common manifestation of asbestos exposure and are well-circumscribed plaques of dense collagen • Markedly thickened visceral pleura covers the lateral and diaphragmatic surface of the lung. Note also severe interstitial fibrosis diffusely affecting the lower lobe of the lung	  
Microscopic	• **Asbestos bodies:** long golden brown, fusiform or beaded rods (drumstick pattern) with a translucent center. They consist of asbestos fibers coated with an iron-containing proteinaceous material (Ferruginous bodies)	 
	• Fibrous pleural plaque (thickening): dense collagen, often containing calcium. They develop • most frequently on the anterior and posterolateral aspects of the parietal pleura and over the domes of the diaphragm.	 

Asbestosis

Mesothelioma





- Malignant is a rare cancer of mesothelial cells.
- Highly related to exposure to asbestos.
- Arising in the parietal or visceral pleura; it also occurs. much less commonly in the peritoneum and pericardium.

Summary

- a group of chronic fibrosing diseases of the lung resulting from exposure to organic and inorganic particulates, most commonly mineral dust.
- Pulmonary alveolar macrophages play a central role in the pathogenesis of lung injury by promoting inflammation and producing reactive oxygen species and fibrogenic cytokines.
- Coal dust–induced disease varies from asymptomatic anthracosis, to simple coal worker's pneumoconiosis to progressive massive fibrosis (PMF), manifested by increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.
- Silicosis is the most common pneumoconiosis in the world.
- The manifestations of silicosis range from asymptomatic silicotic nodules to PMF; individuals with silicosis also have an increased susceptibility to tuberculosis. The relationship between silica exposure and subsequent lung cancer is controversial.
- Asbestos exposure is linked with six disease processes.
- Cigarette smoking increases the risk for lung cancer in the setting of asbestos exposure; moreover, even family members of workers exposed to asbestos are at increased risk for cancer.

Sarcoidosis

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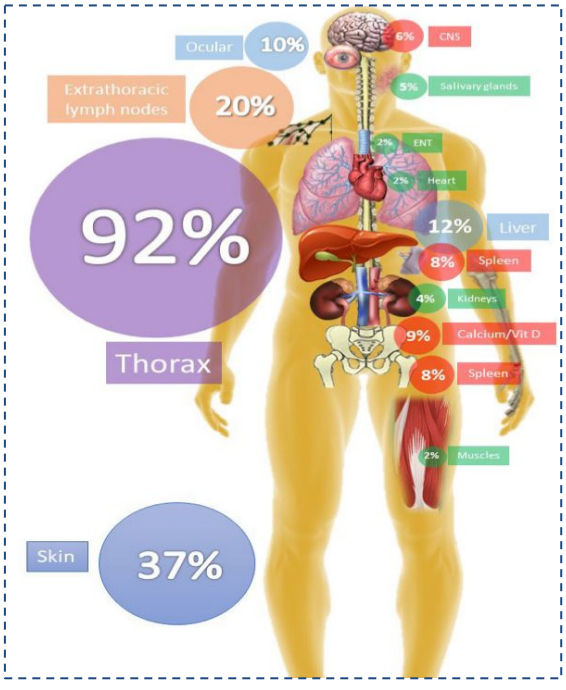
Definition

Multisystem disease of unknown etiology characterized by noncaseating granulomatous inflammation in many tissues and organs.

Sarcoidosis



Etiology remains unknown

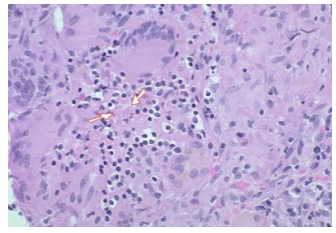
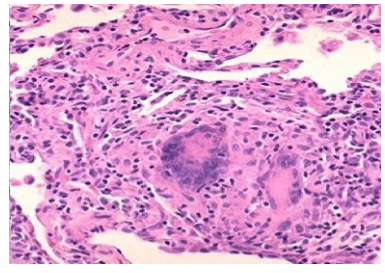
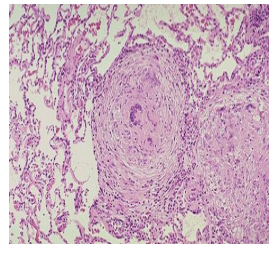
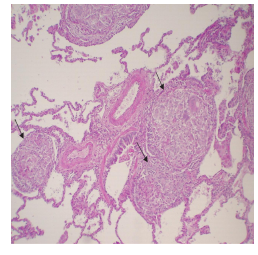
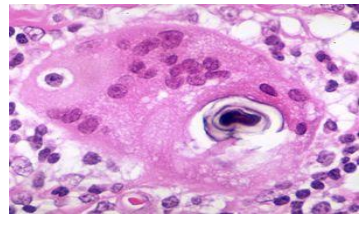
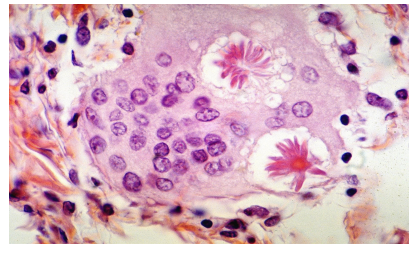
- Epidemiologic trends:
  - Adults younger than 40 years of age.
  - High incidence in Danish, Swedish populations and in the United States among African Americans.
  - Non-smokers
  - Females more than males

Sarcoidosis organ involvement Mainly in the mediastinal lymph nodes

Sarcoidosis

click here

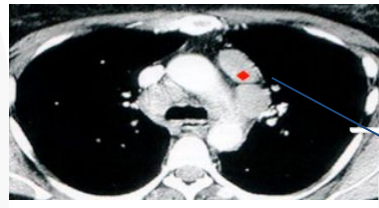
Morphology

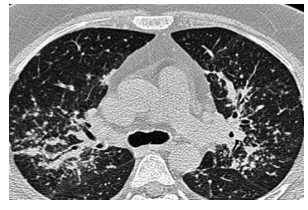
	Description	Pictures
Microscopic	**Non Necrotizing epithelioid granuloma:** • Predominantly involve the interstitium rather than air spaces. • tendency to localize in the connective tissue around bronchioles and pulmonary venules and in the pleura (“lymphangitic” distribution). • Discrete, compact collection of epithelioid cells rimmed by lymphocytes (CD4+ T cells). • Multinucleate giant cells.	   
	Schaumann bodies: aminated concretions composed of calcium and proteins.	
	Asteroid bodies: stellate inclusions enclosed within giant cells.	

Sarcoidosis

Clinical Pictures for Sarcoidosis

1. Asymptomatic.
2. Respiratory symptoms: SOB, dry cough, or vague sub-sternal discomfort.
3. Constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats).
4. Radiologic finding:
   1.Bilateral hilar lymphadenopathy.
   2.Multiple micronodules with peribronchovascular distribution in both lungs.





Prognosis

The remissions may be spontaneous or initiated by steroid therapy and often are permanent.
Overall, 65% to 70% of affected individuals recover with minimal or no residual manifestations.
Another 20% develop permanent lung dysfunction or visual impairment. Remaining 10% to 15%, most succumb to progressive pulmonary fibrosis and cor pulmonale.

Sarcoidosis

Summary

● Sarcoidosis is a multisystem disease of unknown etiology; the diagnostic histopathologic feature is the presence of noncaseating granulomas in various tissues.
● Immunologic abnormalities include high levels of CD4+ TH1 cells in the lung that secrete cytokines such as IFN-γ.
● Clinical manifestations include lymph node enlargement, eye involvement (sicca syndrome [dry eyes], iritis, or iridocyclitis), skin lesions (erythema nodosum, painless subcutaneous nodules), and visceral involvement (liver, skin, bone marrow). Lung involvement occurs in 90% of cases, with formation of granulomas and interstitial fibrosis.

Hypersensitivity Pneumonitis

click here

• HP is an immunologically mediated inflammatory lung disease that primarily affects the alveoli.

• Most often it is an occupational disease that results from heightened sensitivity to inhaled antigens such as those found in moldy hay.

• it manifests predominantly as restrictive lung disease with the typical decreases in diffusion capacity, lung compliance, and total lung volume.

Table 13.4 Sources of Antigens Causing Hypersensitivity Pneumonitis

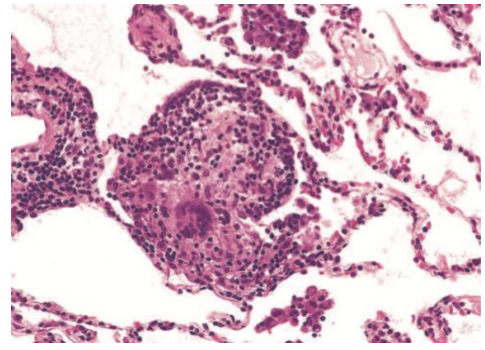
Source of Antigen	Types of Exposures
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Birds	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

From Lacasse Y, Girard M, Cormier Y: Recent advances in hypersensitivity pneumonitis, *Chest* 142:208, 2012.

click here

Hypersensitivity pneumonitis vs sarcoidosis

Hypersensitivity Pneumonitis

	Description	Pictures
Microscopic	• Patchy mononuclear cell infiltrates in the pulmonary interstitium, peribronchiolar accentuation. • Epithelioid macrophages. • **"Loose," poorly formed granulomas:** - **Without necrosis** - **Present in more than two-thirds of cases.** • In advanced chronic cases, bilateral, upper- lobe–dominant interstitial fibrosis (UIP pattern) occurs.	

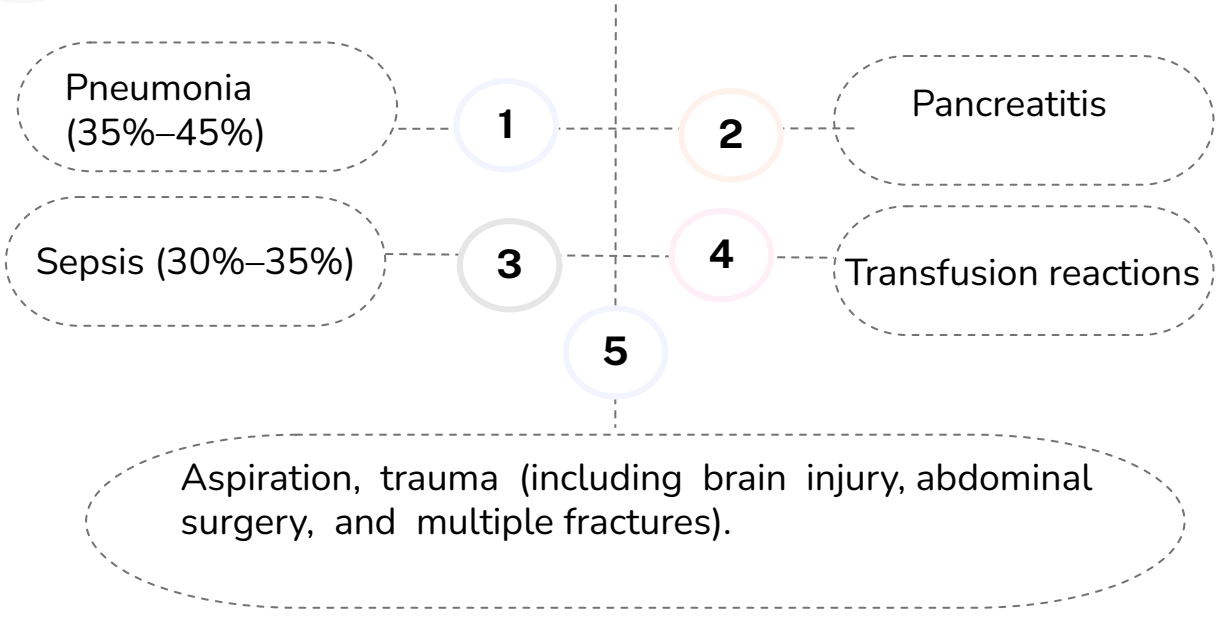
Clinical Pictures for Hypersensitivity Pneumonitis

1. May manifest either as an acute reaction, with fever, cough, dyspnea.
2. Constitutional signs and symptoms arising 4 to 8 hours after exposure.
3. chronic disease characterized by insidious onset of cough, dyspnea, malaise, and weight loss.
4. With the acute form, the diagnosis is usually obvious because of the temporal relationship of symptom onset and exposure to the incriminating antigen.
5. Failure to remove the inciting agent from the environment eventually results in an irreversible chronic interstitial pulmonary disease.

Diffuse Alveolar Damage (DAD)

Acute interstitial disease

1. Is the histologic manifestation of ARDS.
2. ARDS: as respiratory failure occurring within 1 week of a known clinical insult with bilateral opacities on chest imaging.
3. Severe ARDS is characterized by rapid onset of life-threatening respiratory insufficiency.
4. May occur in a multitude of clinical settings and is associated with primary pulmonary diseases and severe systemic inflammatory disorders such as sepsis.
5. **The most frequent triggers of ARDS are:**



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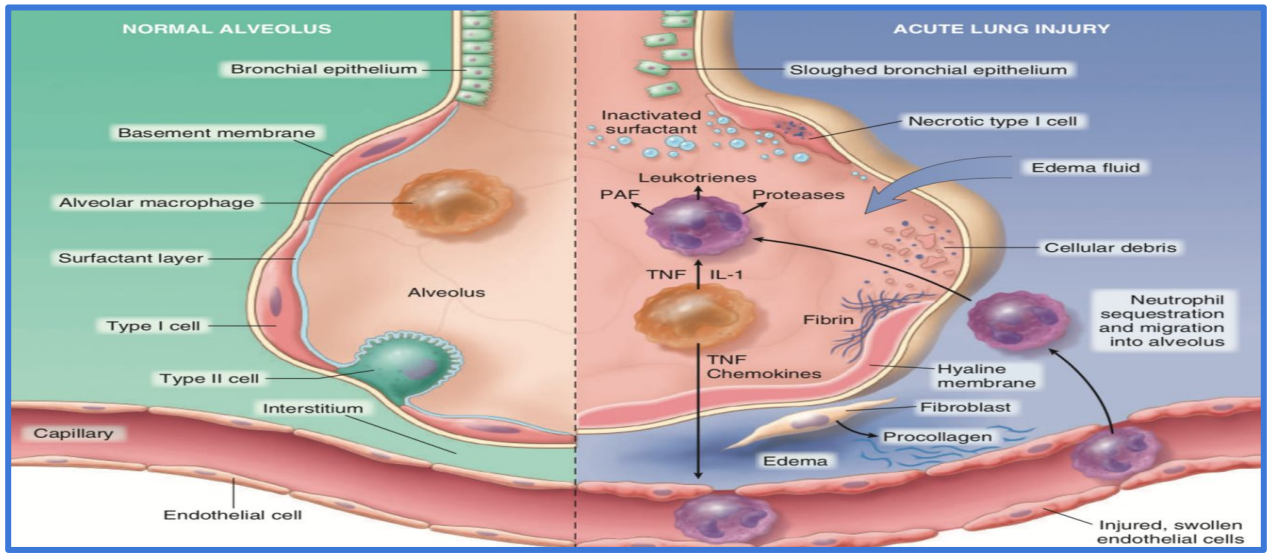
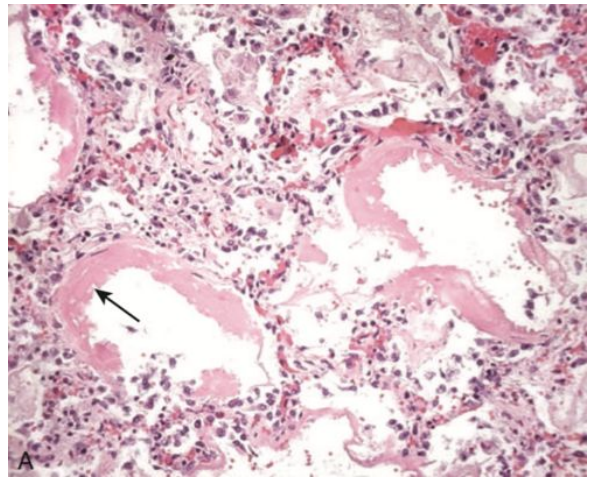
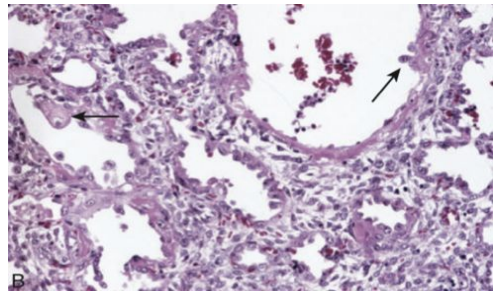
Acute interstitial disease

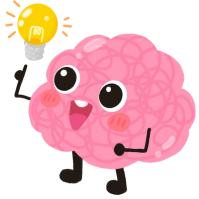


	Description	Pictures
Microscopic	Acute phase: • Hyaline membranes: fibrin-rich edema fluid admixed with remnants of necrotic epithelial cells and lining the alveolar wall. • Capillary congestion. • Necrosis of alveolar epithelial cells, interstitial and intra- alveolar edema • Hemorrhage. • Particularly with sepsis: collections of neutrophils in capillaries.	
	Organizing phase: • Resorption of hyaline membranes. • Thickening of alveolar septa by inflammatory cells, fibroblasts, and collagen. • Numerous reactive type II pneumocytes.	

Vaping-associated pulmonary injury (VAPI)

1. The CDC assures that the THC and vitamin E are very strongly implicated in VAPI

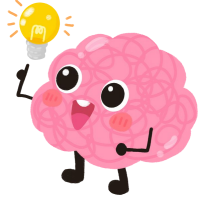
2. Can give many form of lung injury in particularly bronchiolitis obliterans



KEYWORDS

Extra slide

Acute respiratory distress syndrome	• Leads to oxygen toxicity
Idiopathic Pulmonary Fibrosis	• TGF-β • fingers clubbing and fine inspiration "Velcro" like crackling in both bases of lungs • Honey -comp lung
Coal workers pneumoconiosis	• Dense collagen & pigmen with fibrous scarring appear Thickning of pleura Compressing the lung
Silicosis	• occupations : Stone cutting , Sandblasting • Fibrotic nodule in upper zones of the lung • Peripheral calcification • Associated with TB
Asbestosis	• ferrogenous bodies • fibrous calcified pleural plaques • Pleural effusion • Mesothelioma
Sarcoidosis	• Noncaseating granulomatous • Inflammation in many tissues • Bilateral hilar lymphadenopathy (lymph node enlargement) • Dyspnea , Dry cough (not specific)
Hypersensitivity pneumonitis	• Noncaseating granulomatous • Interstitial pneumonitis with goblet cell in alveoli • Fungi , Piogens • Fever Cough dyspnea (not specific) • Non-necrotizing granuloma on the alveolar septa Antigens loose poorly , formed granuloma



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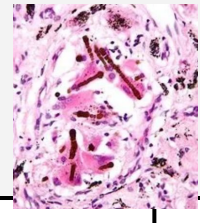
Answers:
1- D 2- B 3- B 4- C

MCQ

1- Most common symptoms of RESTRICTIVE PULMONARY DISEASE:			
A)Dyspnea	B)Dry Cough	C)Productive Cough	D)Both A&B
2- Honeycomb is the best describe of:			
A)COPD	B)Restrictive Pulmonary Disease	C)Both A&B	D)None of them
3- The size of dust that can cause disease:			
A) <1µm	B)Between 1-5 µm	C)Between 1-5m	D)None of them
4- Which one of these restrictive diseases has unknown etiology?			
A)Silicosis	B)Asbestosis	C)Sarcoidosis	D)None of them

Answers:
1- B 2- C 3- A 4- D

Cases

1- A 72-year-old man comes to the ER with difficulty in breathing. His pulmonary function tests show an increase in the FEV1/FVC ratio, a decrease in DLCO, and an increase in the A-a gradient. Digital clubbing is noted on physical examination. Which of the following is the most likely the diagnosis.			
A) COPD	B)Restrictive Lung Disease	C) Asthma	D) None
2- A patient presents with new-onset dyspnea. The patient was in the building especially in ceiling decoration industry for 30 years. Which of the following diseases must the patient be worked up for?			
A) Coal worker	B) Sarcoidosis	C) Asbestosis	D) IPF
3- A 56-year-old man presents to his primary care physician with a non-productive cough and associated shortness of breath with exertion. He reports his symptoms started after he began working as a manager in a textile factory. He reports he is otherwise healthy and does not take any medications daily. His temperature is 37° C (98.6°F), pulse is 61/min, respirations are 18/min, blood pressure is 131/74 mmHg, and oxygen saturation is 96% on room air. Physical examination is otherwise unremarkable. As part of his work-up, he undergoes a transbronchial biopsy, which demonstrates the following histologic findings:  This patient likely has occupational exposure to which of the following inorganic compounds?			
A) Asbestosis Industry	B) Coal Industry	C) Silicone Industry	D) None
4- A 58-year-old man presents to his primary care physician with progressive shortness of breath over the past year. He reports he is otherwise healthy and does not take any medications daily. He works as an accountant and smokes two to three cigarettes on the weekend. The patient is lost to follow-up, and several years later, the patient requires a bilateral lung transplantation. Pathologic evaluation of the patient's lungs reveals a honeycomb pattern with fibrotic walls most prominent in the subpleural and perilobular regions. Which of the following best describes the underlying pathophysiology of this patient's condition?			
A) Multisystem Granulomatous disorder.	B) Recurrent episodes of lung injury and disordered healing.	C) Proliferation of undifferentiated neuroendocrine cells.	D) a1 antitrypsin deficiency

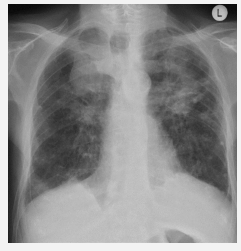
Answers:
1- B
2- D

Cases

External cases, require some extra info

1- A 54-year-old man presents to his primary care physician for a routine visit. He reports that he is otherwise feeling well aside from a chronic cough. He reports that he continues to smoke 10-15 cigarettes per day despite attempting to quit earlier this year. His past medical history is notable for hypertension diabetes, and hyperlipidemia He has been working in an underground coal mine for the past twenty years. The patient has a screening chest x-ray performed which is demonstrated below.

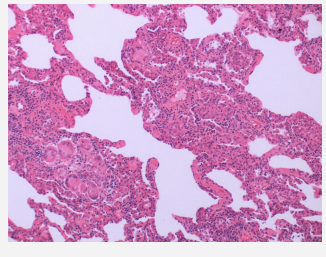
Which of the following best describes the underlying pathophysiology resulting in this patient's clinical condition?



A) Type IV hypersensitivity reaction and granuloma formation	B) Aggregation of carbon laden macrophages	C) Imbalance in protease-antiprotease activity and enlargement of alveolar space	D) Calcification and fibrosis of the pleura

2-A 39-year-old man comes to the office for follow up regarding pulmonary function testing for ongoing shortness of breath . The pulmonary function testing was notable for decreased total lung capacity , an increased FEV1/FVC, and decreased residual volume .He subsequently undergoes a lung biopsy that demonstrates the following histologic image:

Which of the following diseases is implicated in the above microscopic lesion?



A) COPD	B) Asthma	C) Idiopathic pulmonary fibrosis	D) Hypersensitivity pneumonitis

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