Rrespiratory Block

RESTRICITVE LUNG DISEASE

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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

TABLE OF CONTENTS

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)

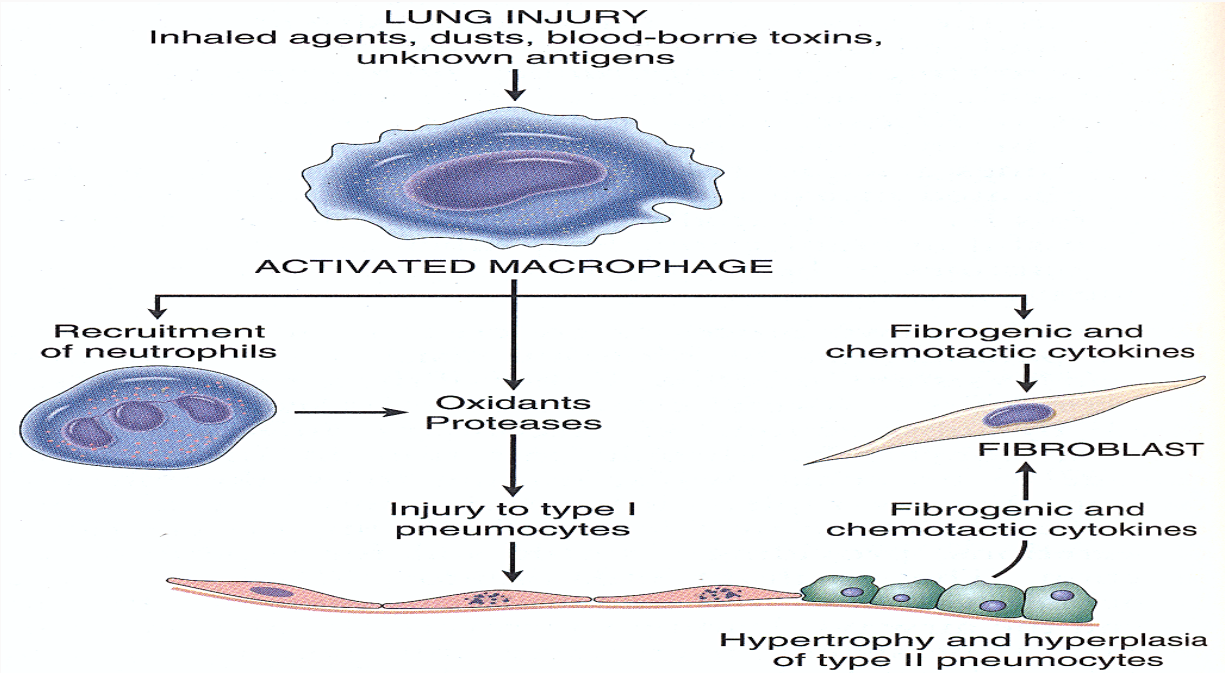


Figure 13–14

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

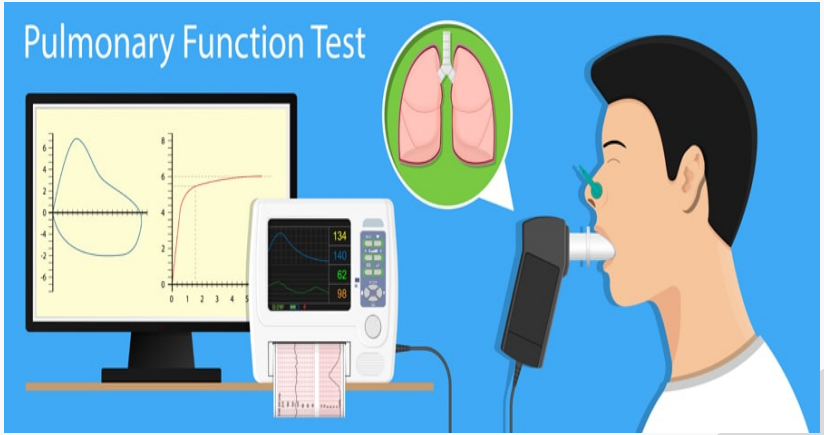
Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Collagen vascular disease-associated
Pneumoconiosis
Therapy-associated (drugs, radiation)
Granulomatous
Sarcoidosis
Hypersensitivity pneumonia
Eosinophilic
Loeffler syndrome
Drug allergy–related
Idiopathic chronic eosinophilic pneumonia
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis

Major Categories of Chronic Interstitial Lung Disease

Remember

Pulmonary function test:

1. Decrease FEV1
2. Decreased FVC
3. Normal FEV1/FVC ratio
4. Decrease in TLC



OBSTRUCTIVE VERSUS RESTRICTIVE PULMONARY DISEASES

Obstructive diseases (or *airway diseases*), characterized by limitation of air out flow due to increased air way resistance

Restrictive diseases, characterized by reduced expansion of lung parenchyma and decreased total lung capacity

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

Chronic interstitial disease

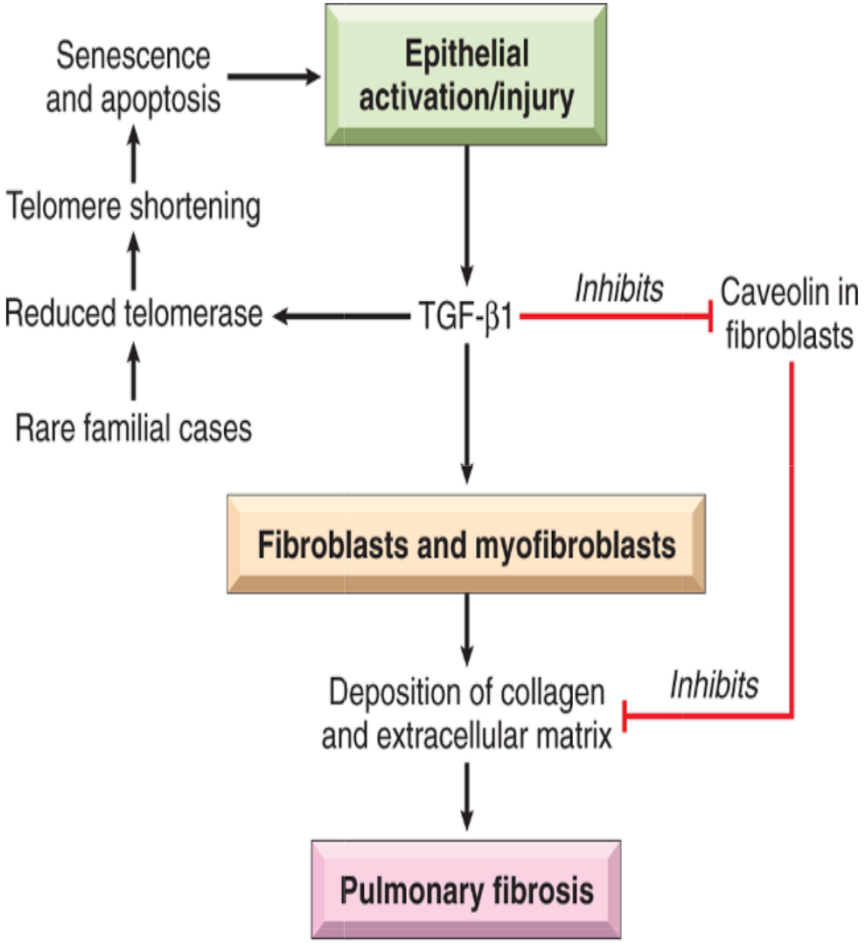
Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis

- It is a pulmonary disorder of unknown etiology characterized histologically by diffuse interstitial fibrosis
- Males are affected more often than females
- Never occurring before 50 years of age
- The radiologic and histologic pattern of fibrosis is referred to as Usual Interstitial Pneumonia (UIP)
- All the etiologic factors should be excluded before the diagnosis

Proposed pathogenic mechanisms in idiopathic pulmonary fibrosis

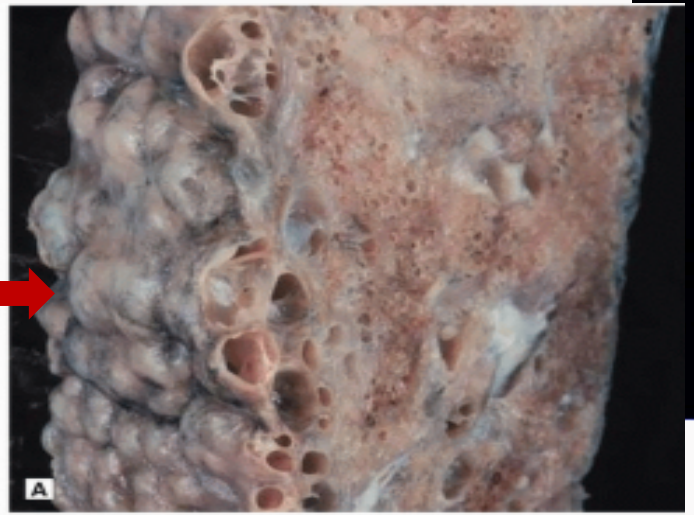
Although the mechanisms of fibrosis are incompletely understood, recent data point to excessive activation of profibrotic factors such as **TGF-β**



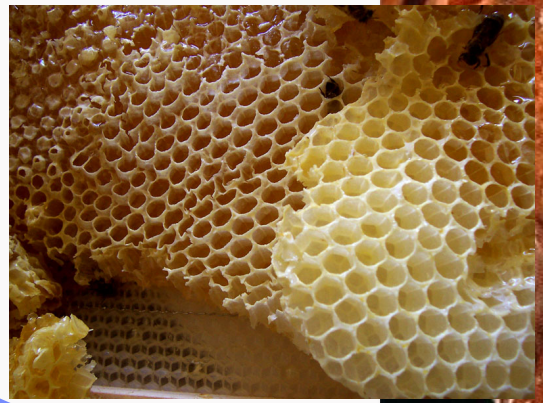
MORPHOLOGY

Gross morphology

- 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

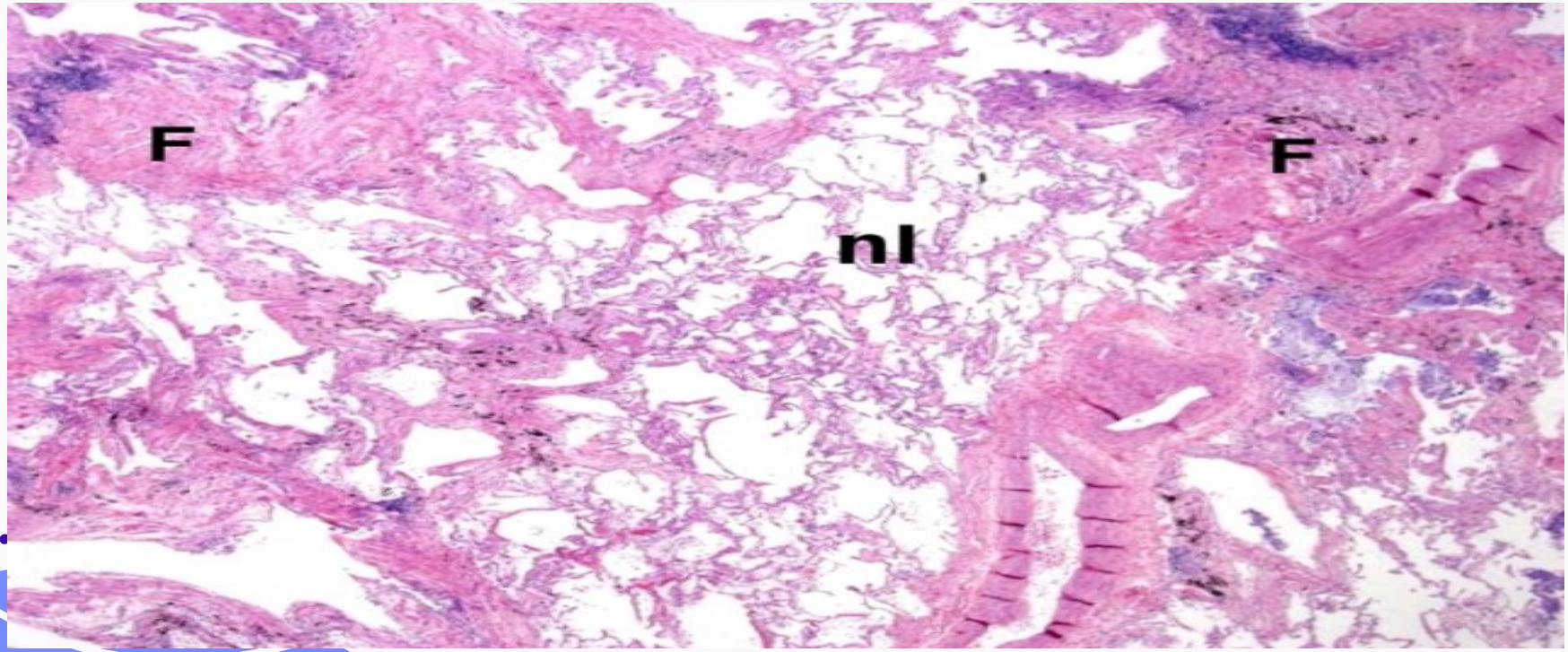


Area of honeycombing



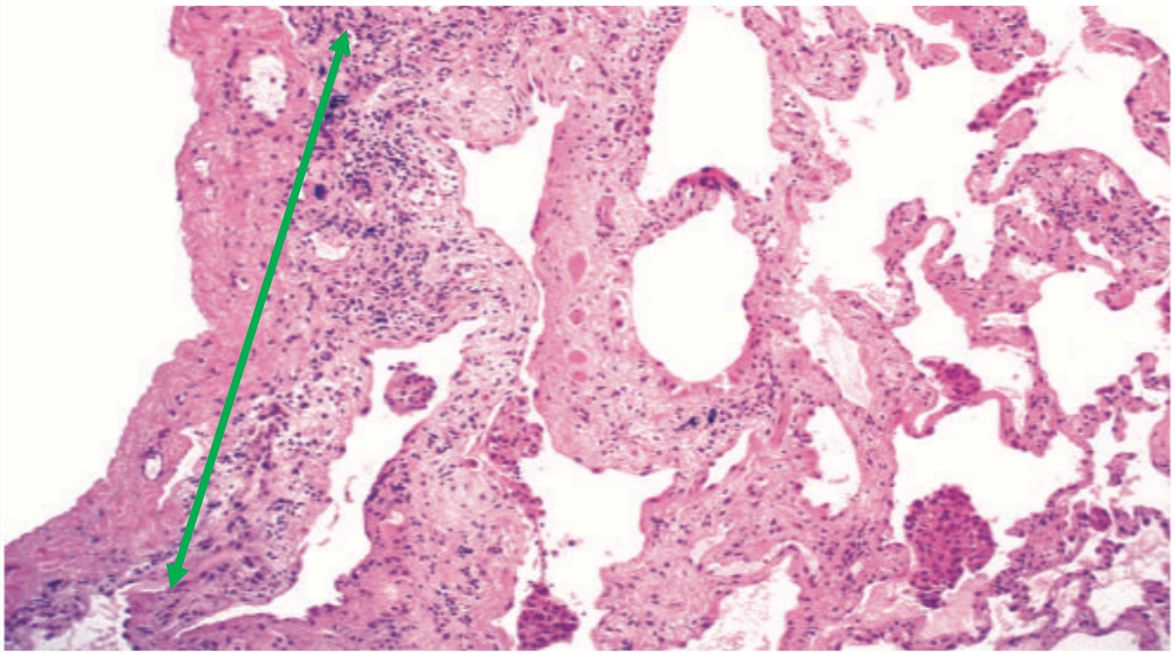
Microscopic morphology

Patchy interstitial fibrosis (geographic heterogenicity)



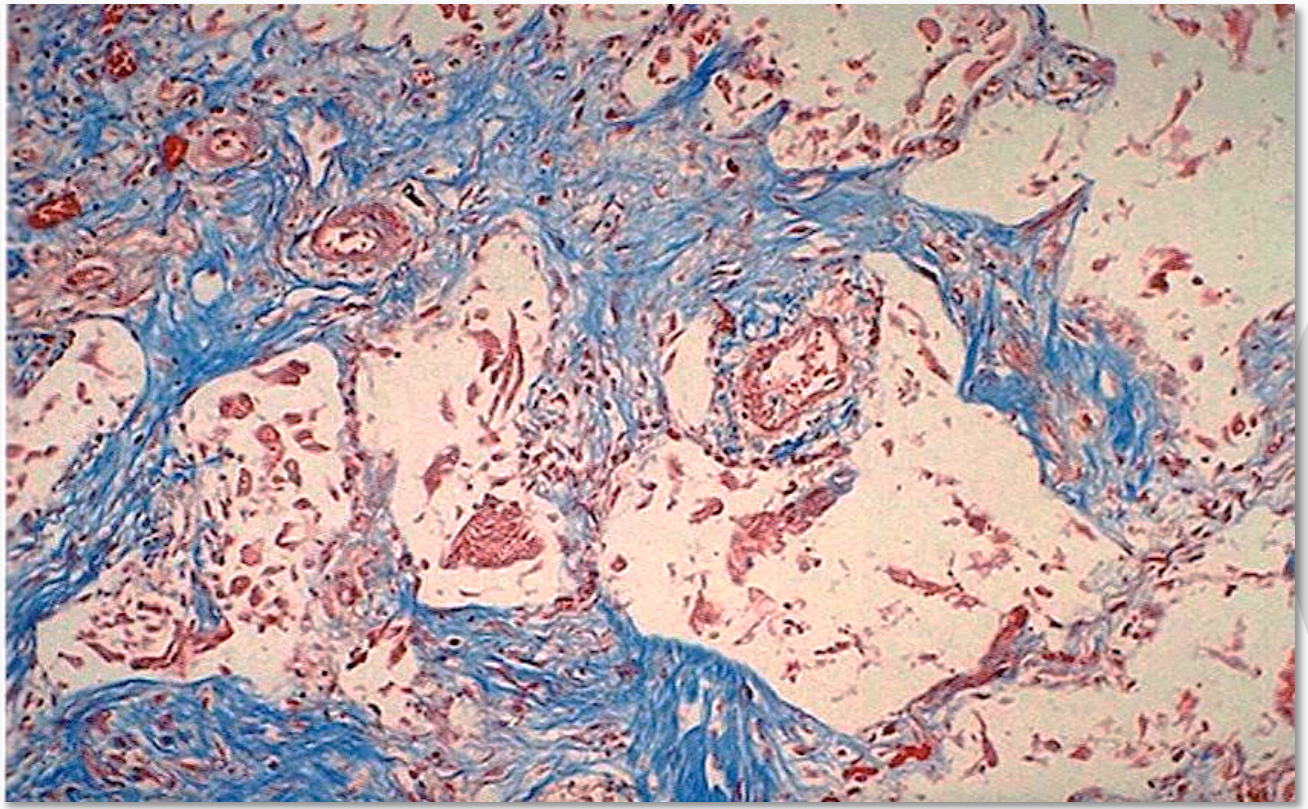
Microscopic morphology

More pronounced in the subpleural region



Microscopic morphology

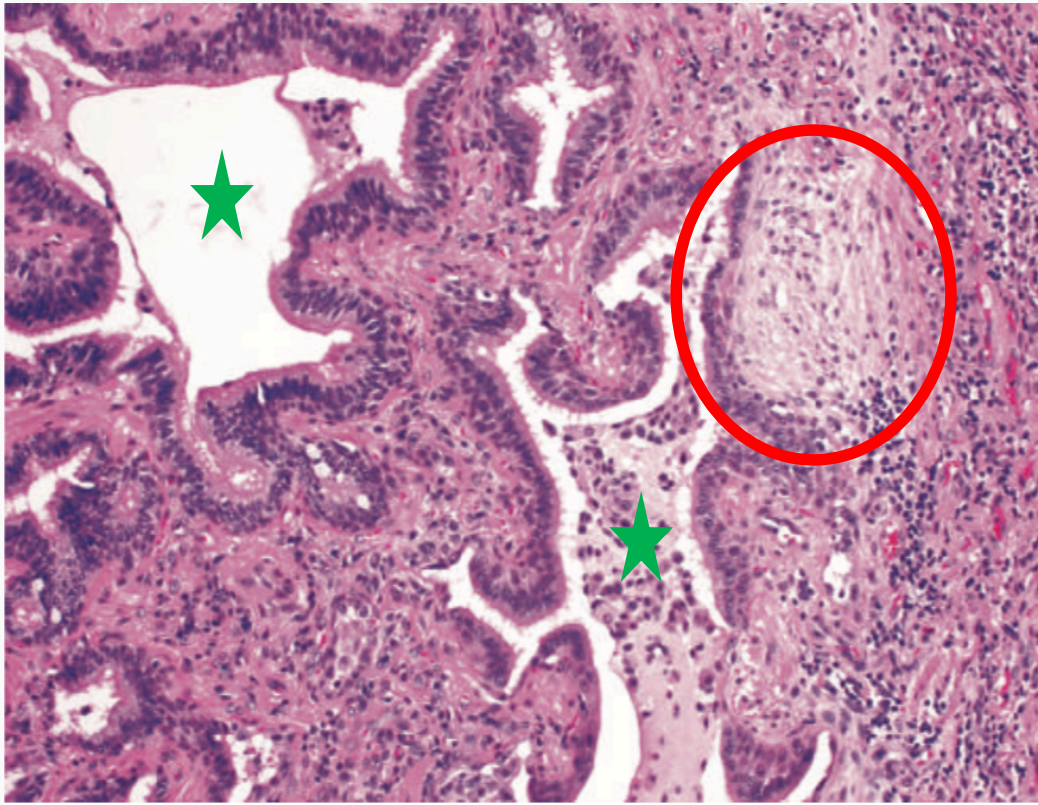
Diffuse interstitial fibrosis
(Masson's trichrome stain)



Microscopic morphology

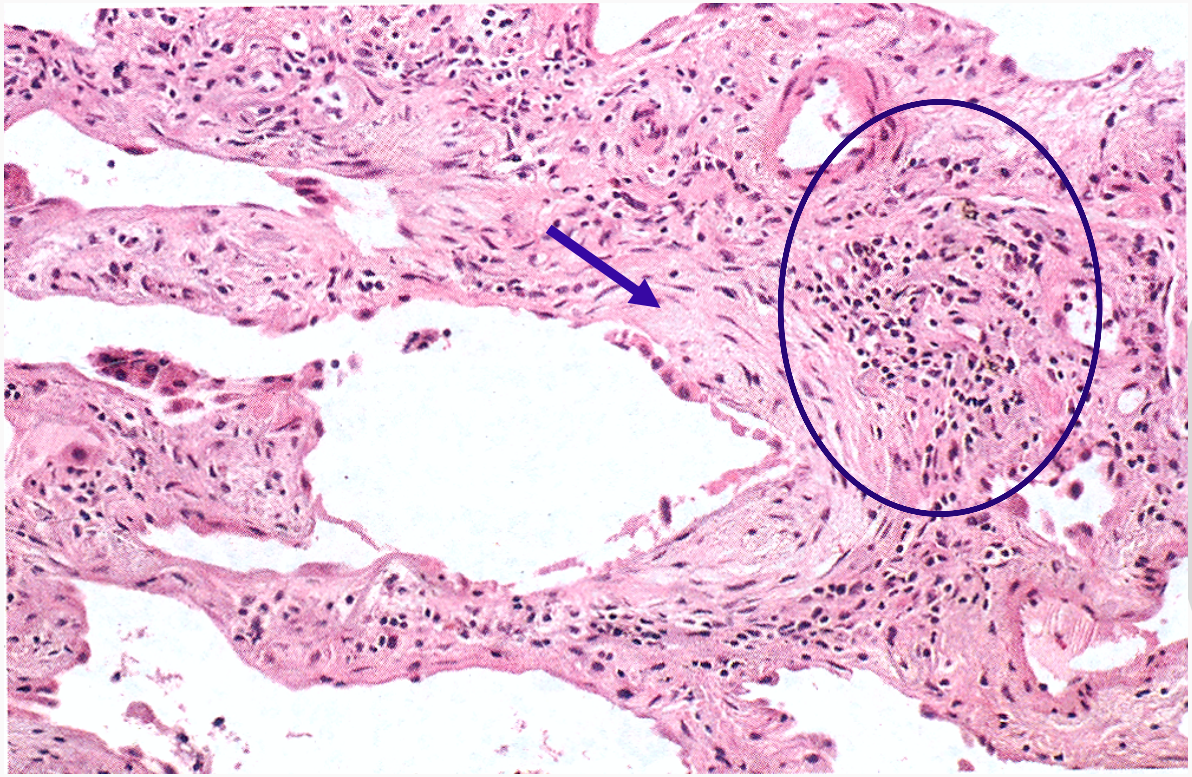
- **Honeycomb fibrosis: t**he dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium

- Temporal heterogenicity with formation of Fibroblastic proliferation (**fibroblastic foci**)



Microscopic morphology

- Fibroblastic foci
- Minimal inflammation

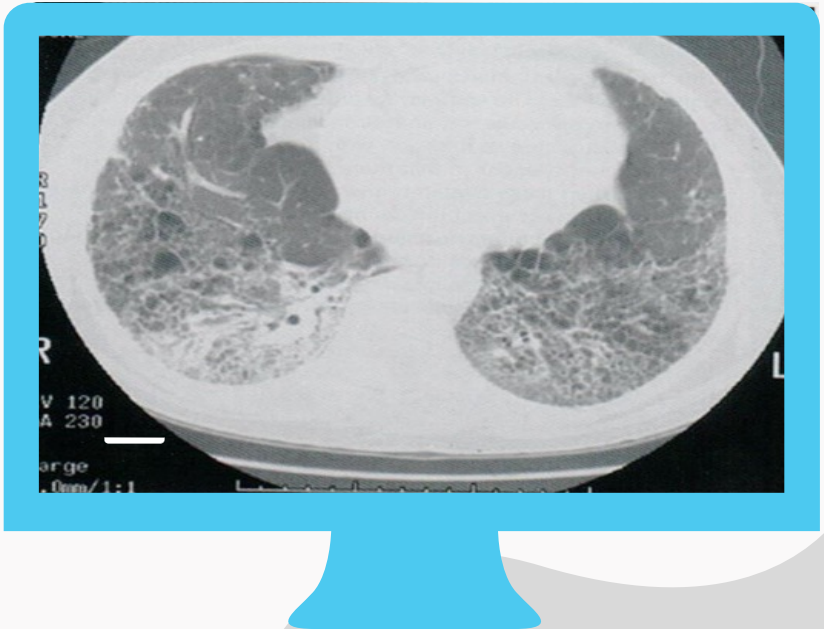


Clinical picture

- Gradual onset of a non-productive cough and progressive dyspnea

- **Velcrolike" crackles** during inspiration
- Radiologic finding:
  1. subpleural and basilar involvement (apico-basal gradient)
  2. reticular abnormalities, and
  3. honeycombing

- Later stage: sever hypoxia, pulmonary hypertension and corpulmonale



Summery

•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).

Pneumoconioses

Pneumoconioses

- 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 airways
  2. Size, shape of the particles
  3. Particle solubility and physiochemical reactivity
  4. Possible additional effects of other irritants (e.g., concomitant tobacco smoking)

- The most common mineral dust pneumoconiosis
  - Coal dust
  - Silica
  - Asbestos

- With asbestos exposure lead to increased risk for cancer

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

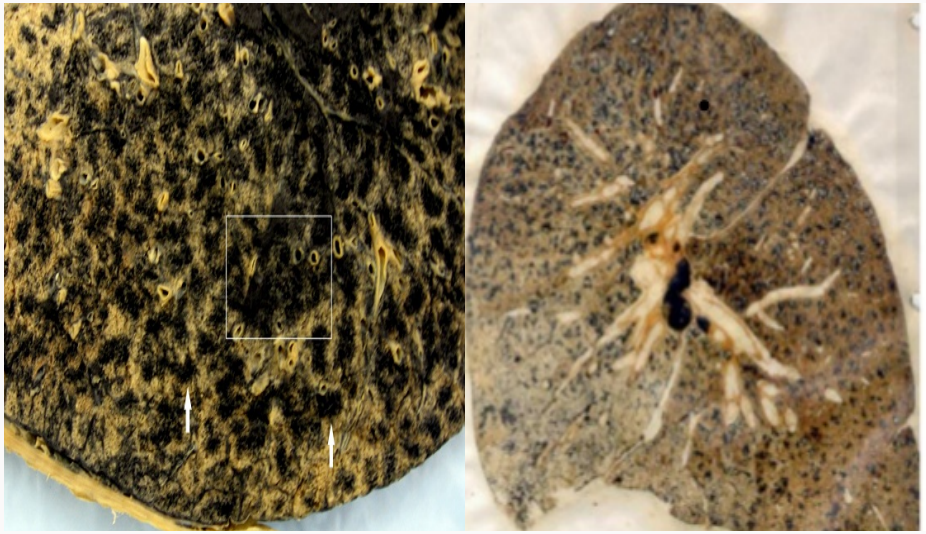
- Coal is mainly carbon, coal mine dust contains a variety of trace metals, inorganic minerals, and crystal- line silica
- Commonly seen in urban dwellers and tobacco smokers
- **Pulmonary anthracosis** is the most innocuous coal-induced pulmonary lesion in coal miners
- Inhaled carbon pigment is engulfed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

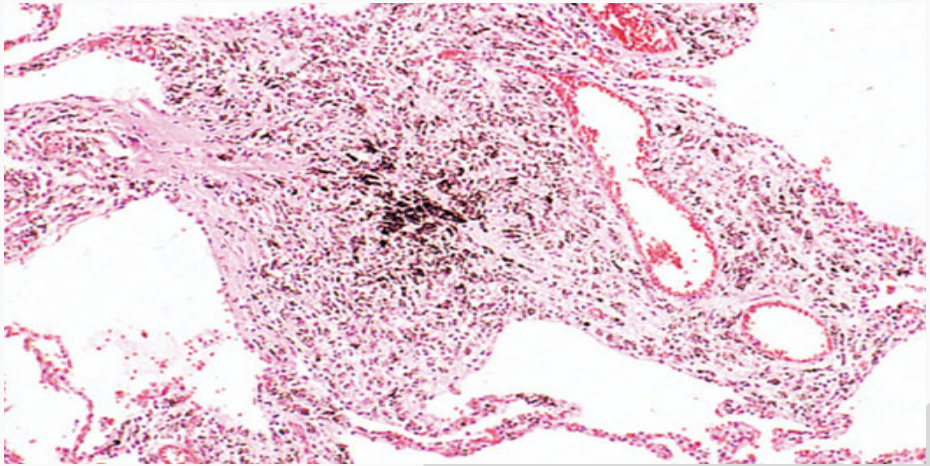
The spectrum

1. **Asymptomatic**
2. **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:
  - Upper lobes are more heavily involved
  - Nodules small is size (1-2 mm)
- Micro:
  - Aggregation of dust-laden macrophages and small amounts of collagen fibers arrayed in a delicate network

3. Centrilobular emphysema

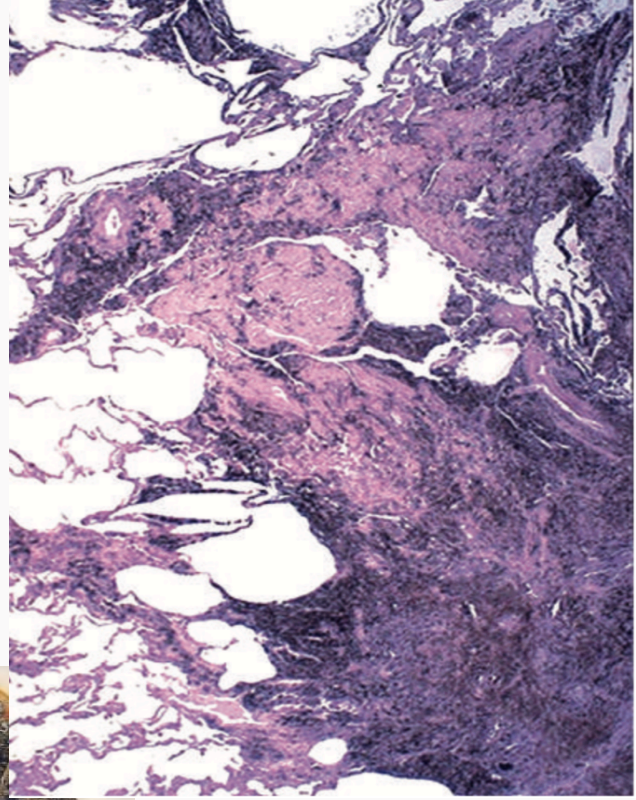


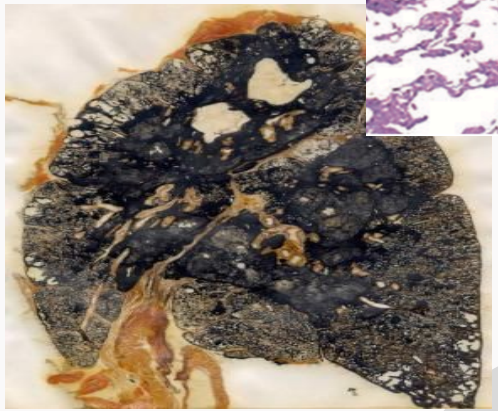


The spectrum

4. Complicated PWF:

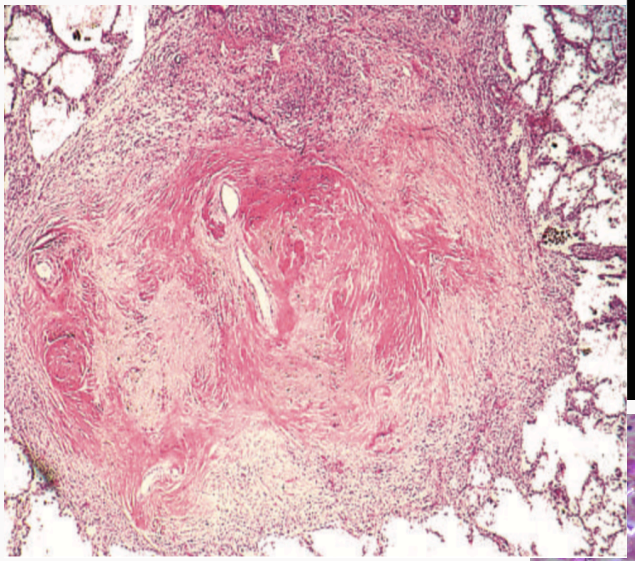
- Occur after many years of underground mine work
- Fibrosis is extensive and lung function is compromised
- 10% of cases of simple CWP progress to progressive massive fibrosis PMF
- **Gross:**
  - Multiple, dark black scars larger than 2 cm and sometimes up to 10 cm
- **Micro:**
  - Dense collagen and pigmen with fibrous scarring appear

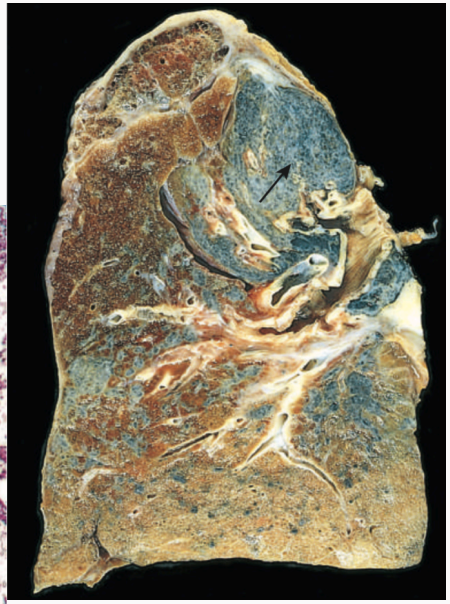


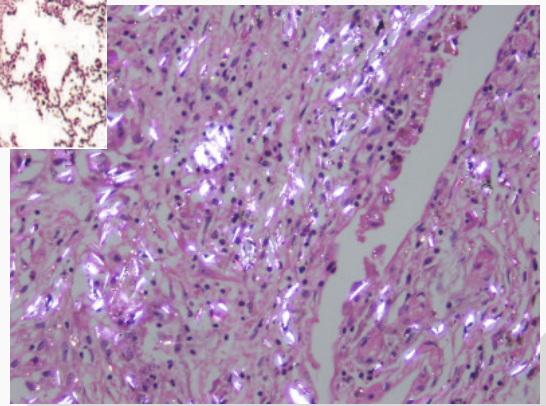


Silicosis

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

- 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
  1. **Parenchymal interstitial fibrosis (asbestosis)**
  2. **Fibrous pleural plaques**
  3. **Pleural effusions;**
  4. **Lung carcinoma**
  5. **Malignant pleural and peritoneal mesothelioma**
  6. **Laryngeal carcinoma**

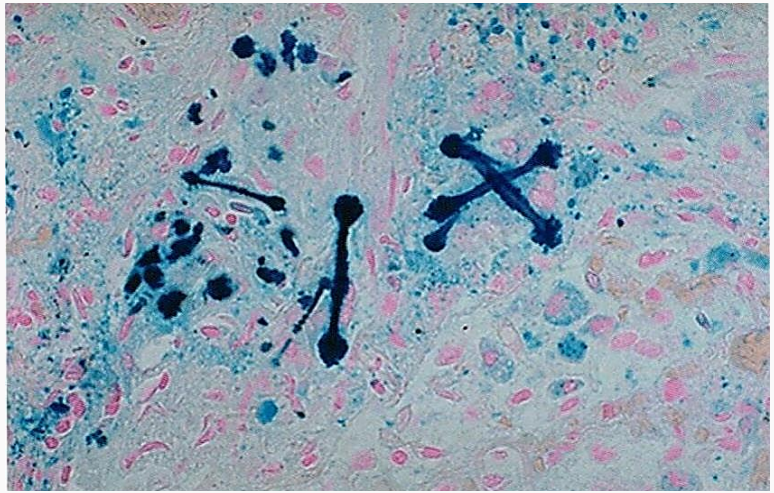
Pathogenesis

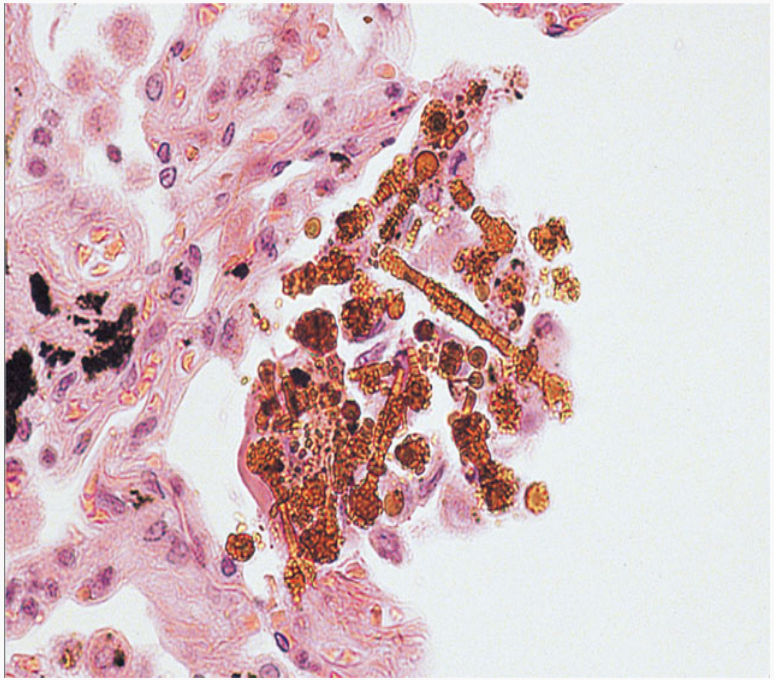
- There are two distinct geometric forms of asbestos: serpentine and amphibole
- Both of them are fibrogenic, and increasing doses are associated with a higher incidence of all asbestos-related diseases except mesothelioma, which is only associated with amphibole exposure
- Some of the oncogenic effects 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
- Macrophages, both alveolar and interstitial, attempt to ingest the fibers and are activated to release chemotactic factors and fibrogenic mediators that amplify the response
- Chronic deposition of fibers and persistent release of mediators eventually lead to generalized interstitial pulmonary inflammation and interstitial fibrosis

Morphology

Morphology

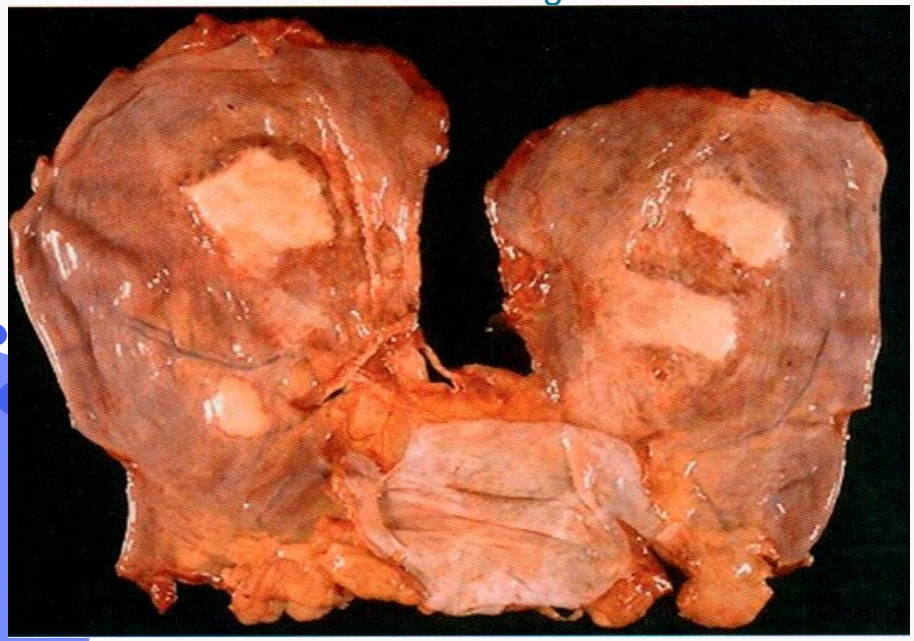
Asbestos bodies; long golden brown, fusiform or beaded rods (drumstick pattern) with a translucent center. They consist of asbestos fibers coated with an iron-containing proteinaceous material (Ferruginous bodies)

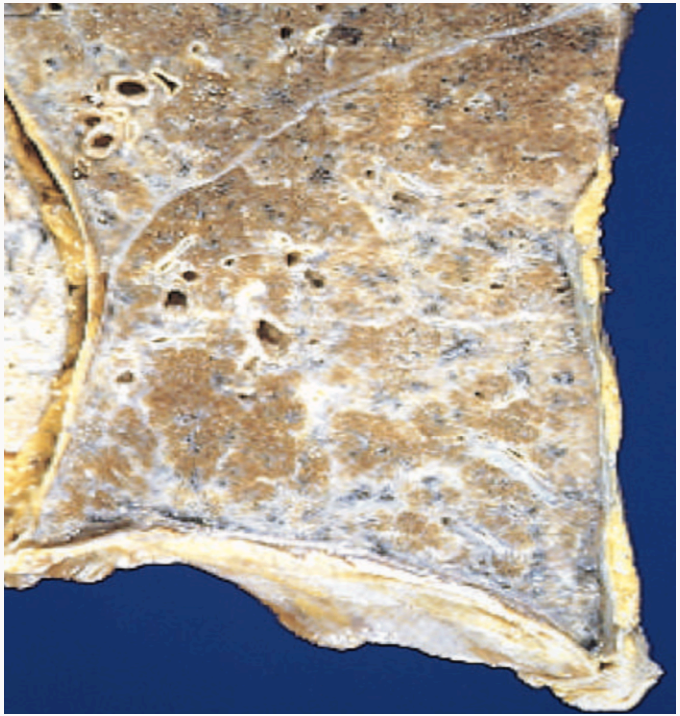




Morphology

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

Morphology

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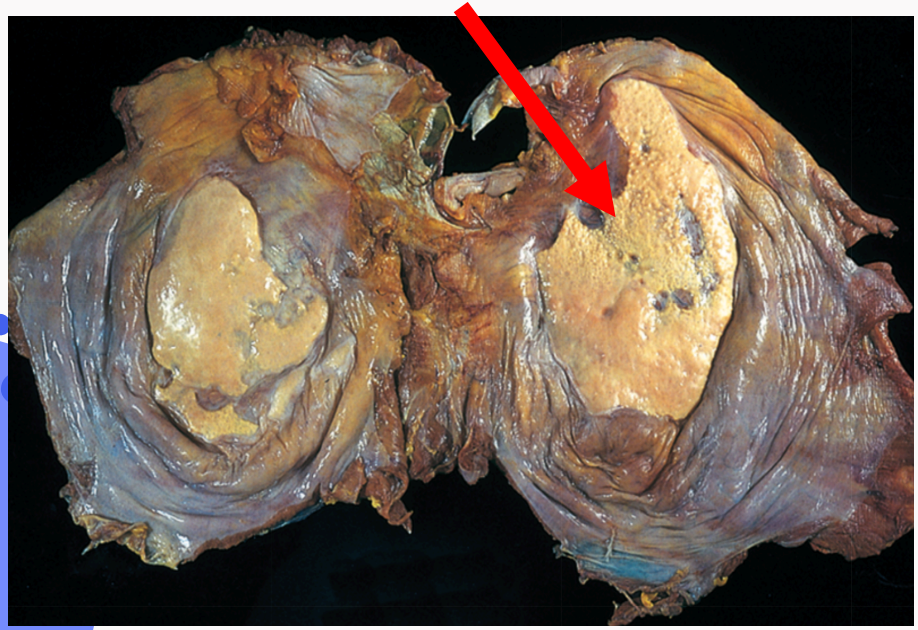
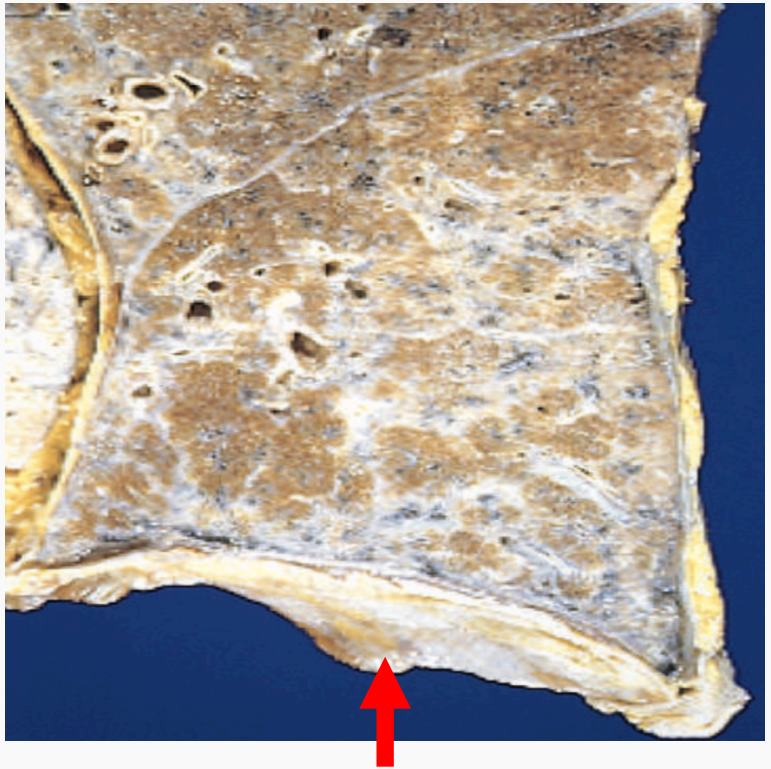
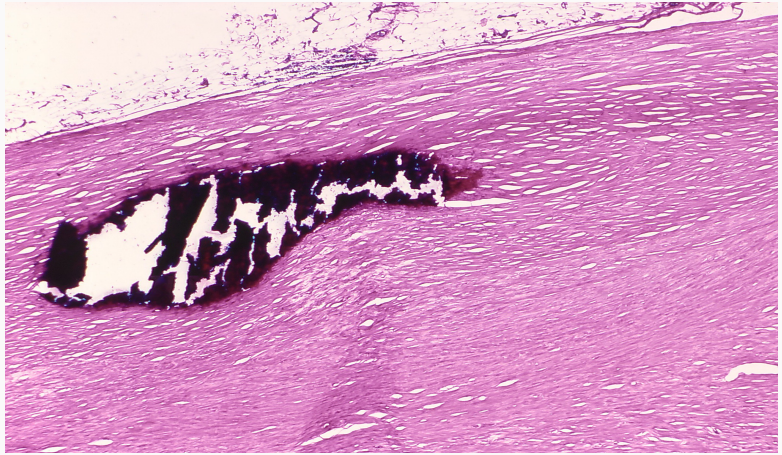


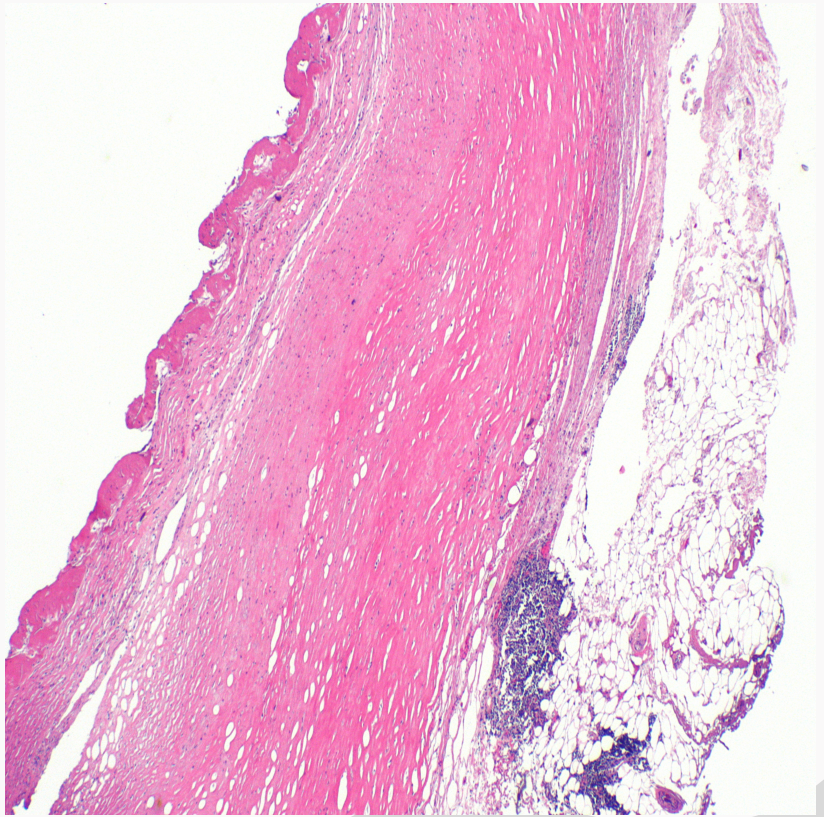


Markedly thickened visceral pleura covers the lateral and diaphragmatic surface of the lung. Note also severe interstitial fibrosis diffusely affecting the lower lobe of the lung

Morphology

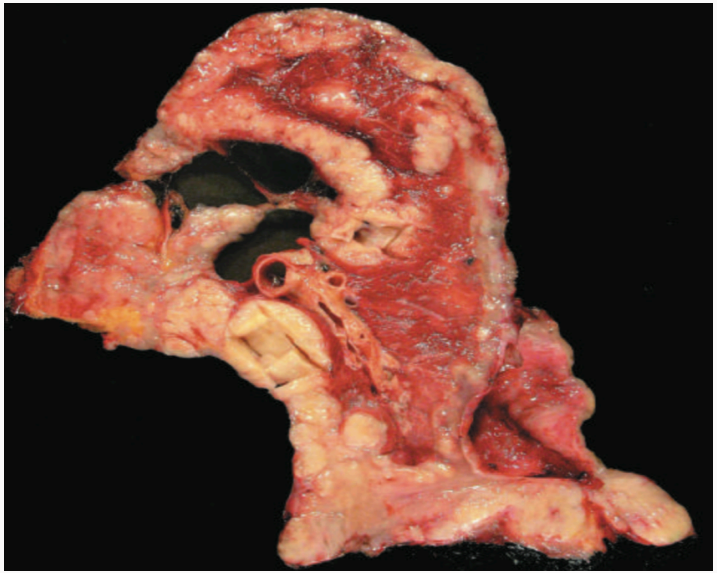
Fibrous pleural plaque : dense collagen, often containing calcium. They develop most frequently on the anterior and posterolateral aspects of the parietal pleura and over the domes of the diaphragm.

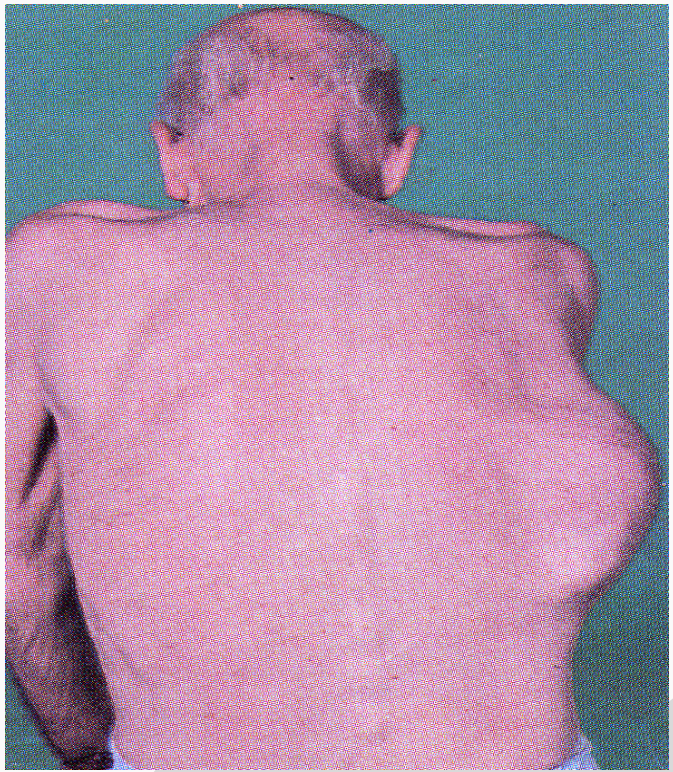




Mesothelioma

- 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





SUMMERY

- 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.

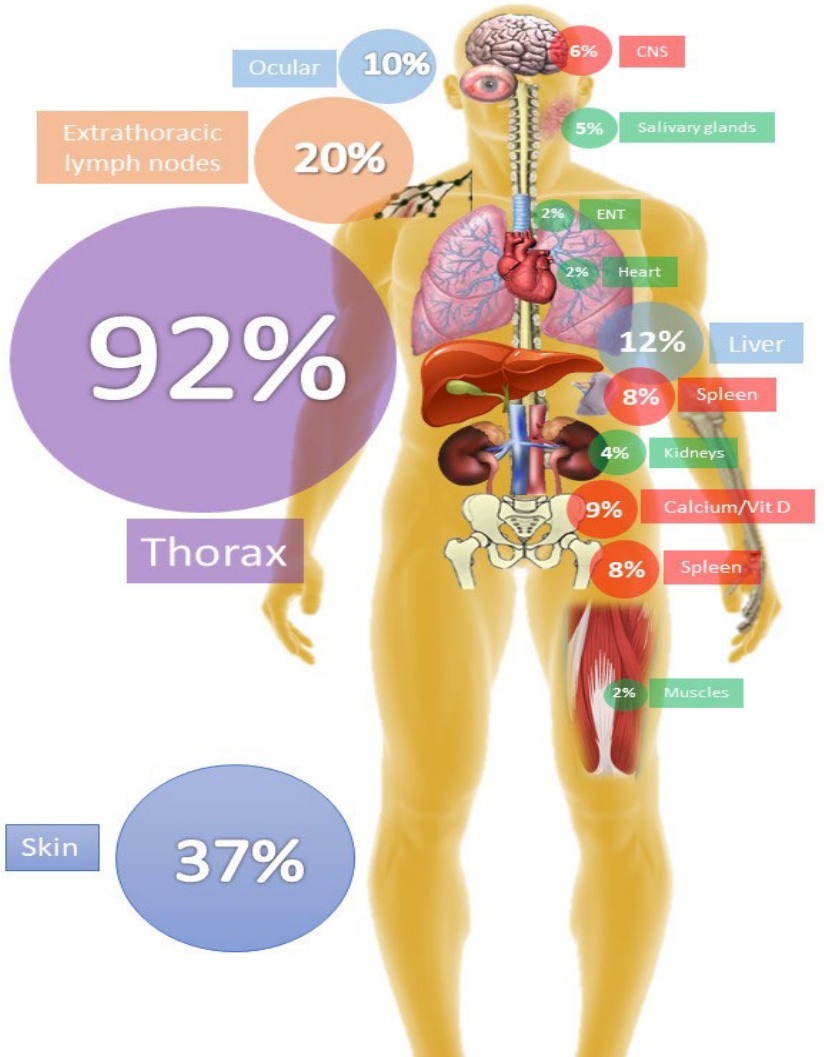
Granulomatous Diseases

Sarcoidosis

Sarcoidosis

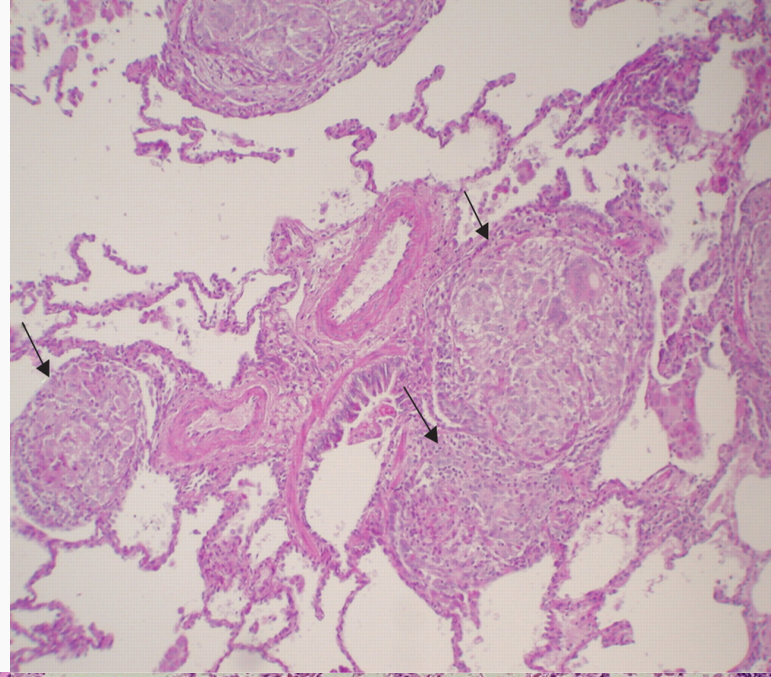
- Multisystem disease of unknown etiology characterized by noncaseating granulomatous inflammation in many tissues and organs
- Etiology remains unknown
- Epidemiologic trends:
  - Adults younger than 40 years of age
  - high incidence in Danish, Swedish populations and in the United States among African Americans
  - Non-smokers

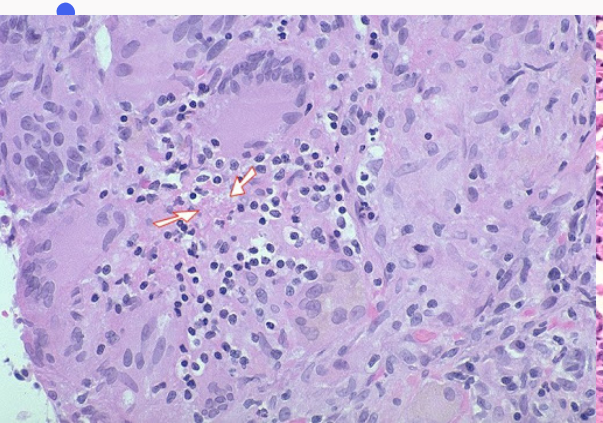
Sarcoidosis organ involvement

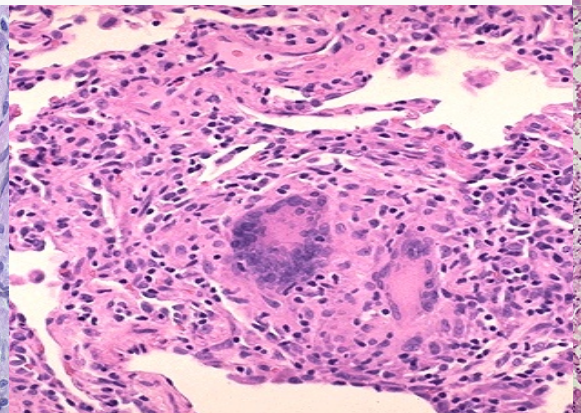


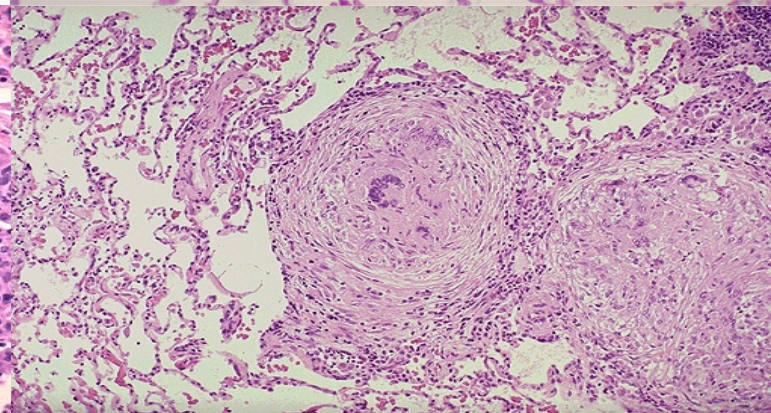
Morphology

1. **Nonnecrotizing 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



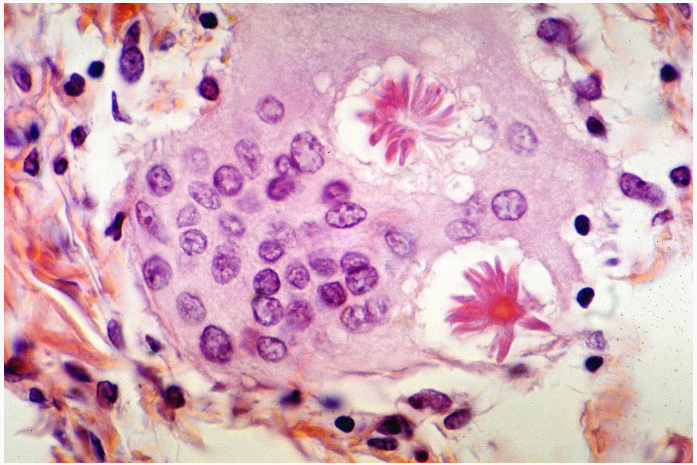


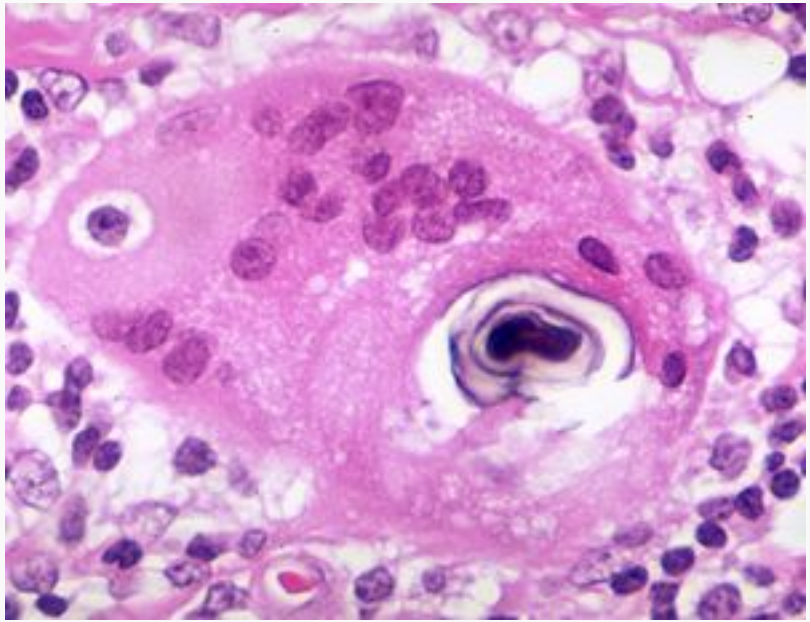




Morphology

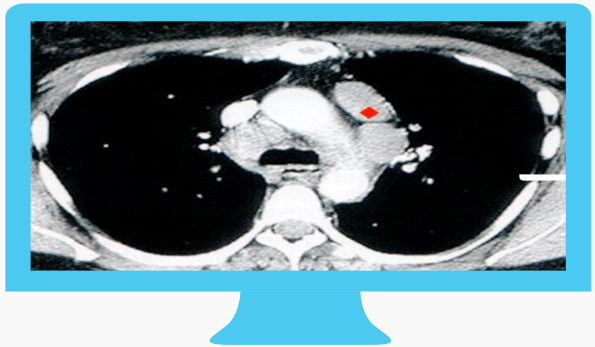
1. **Schaumann bodies:** aminated concretions composed of calcium and proteins
2. **asteroid bodies:** stellate inclusions enclosed within giant cells

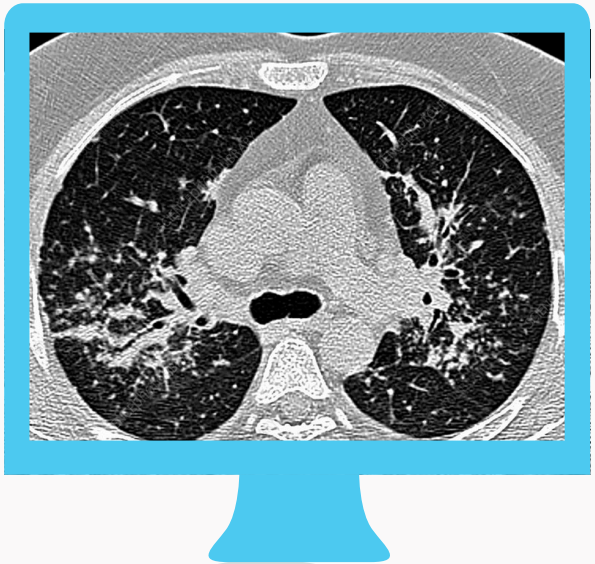




Clinical pictures

- Asymptomatic, or
- Respiratory symptoms: SOB, dry cough, or vague sub-sternal discomfort
- Constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats)
- 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 corpulmonale

Summery

- 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

Hypersensitivity Pneumonitis

Aimmunologically mediated inflammatory lung disease

Results from heightened sensitivity to inhaled antigens

Primarily affects the alveoli

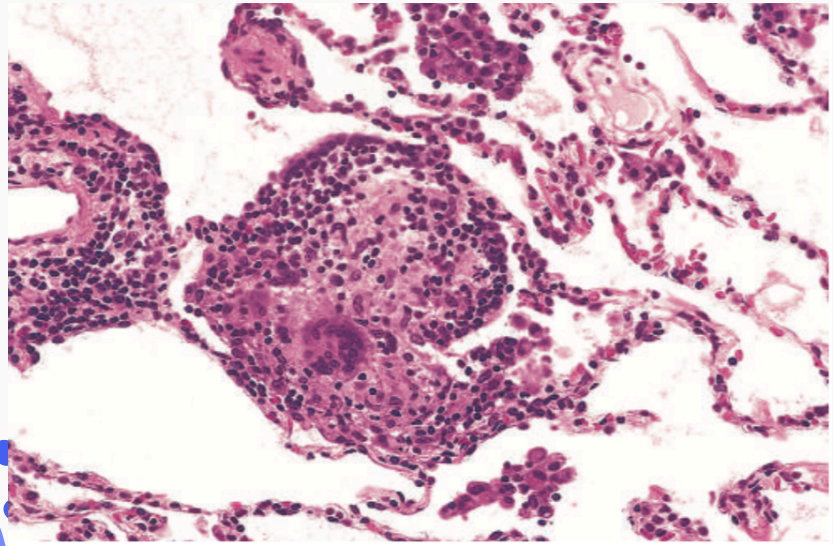
Loose, poorly formed granulomas

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.

Morphology



- 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 picture

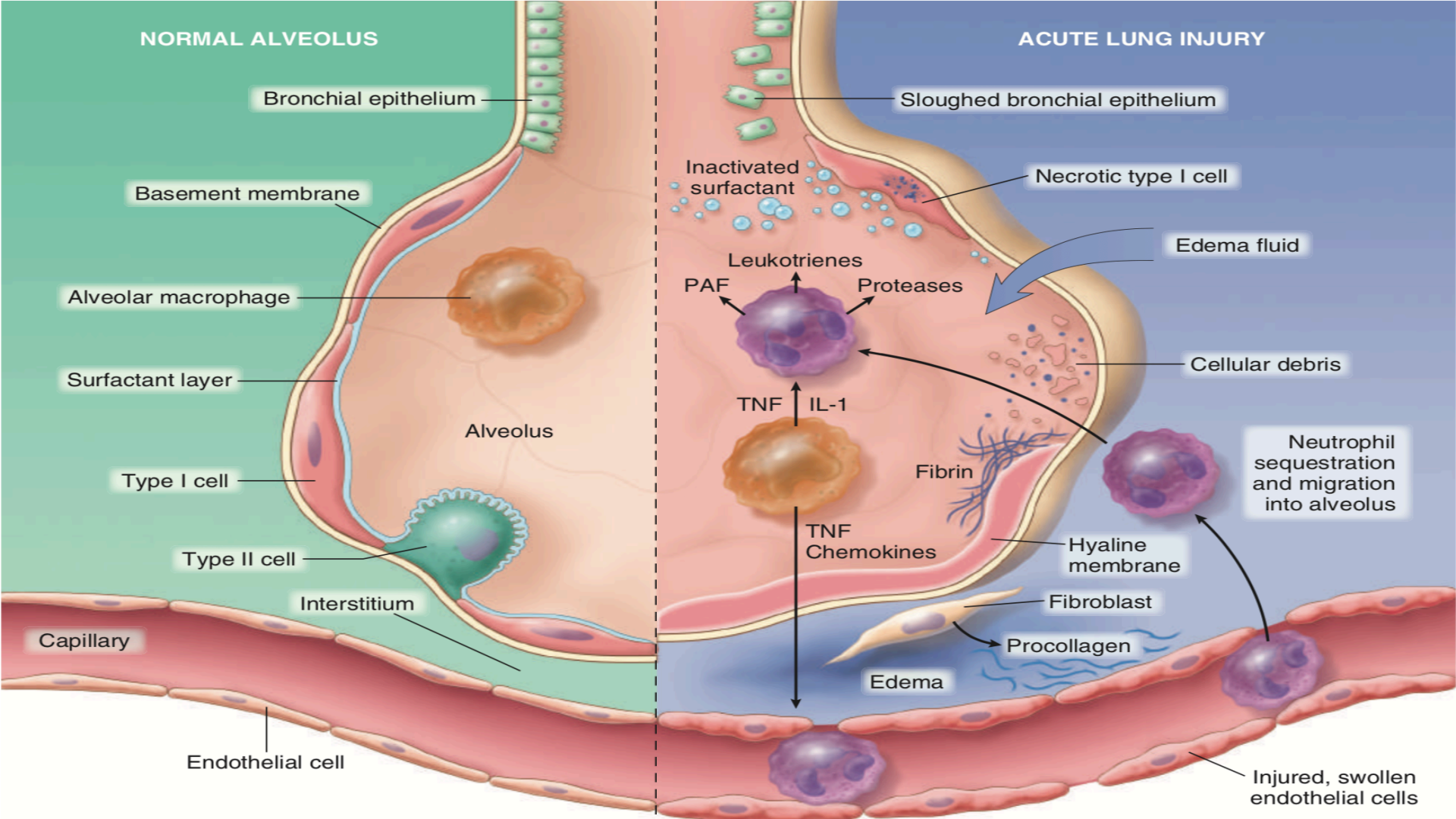
- May manifest either as an acute reaction, with fever, cough, dyspnea
- Constitutional signs and symptoms arising 4 to 8 hours after exposure
- Or as a chronic disease characterized by insidious onset of cough, dyspnea, malaise, and weight loss
- With the acute form, the diagnosis is usually obvious because of the temporal relationship of symptom onset and exposure to the incriminating antigen
- If antigenic exposure is terminated after acute attacks of the disease, complete resolution of pulmonary symptoms occurs within days
- Failure to remove the inciting agent from the environment eventually results in an irreversible chronic interstitial pulmonary disease

Acute interstitial disease

Diffuse alveolar damage (DAD)

Diffuse alveolar damage

- Is the histologic manifestation of ARDS
- ARDS : as respiratory failure occurring within 1 week of a known clinical insult with bilateral opacities on chest imaging
- Severe ARDS is characterized by rapid onset of life- threatening respiratory insufficiency, cyanosis, and severe arterial hypoxemia that is refractory to oxygen therapy
- may occur in a multitude of clinical settings and is associated with primary pulmonary diseases and severe systemic inflammatory disorders such as sepsis
- The most frequent triggers of ARDS are:
  1. pneumonia (35%–45%)
  2. sepsis (30%–35%)
  3. aspiration, trauma (including brain injury, abdominal surgery, and multiple fractures)
  4. Pancreatitis
  5. transfusion reactions


NORMAL ALVEOLUS
Bronchial epithelium
Basement membrane
Alveolar macrophage
Surfactant layer
Alveolus
Type I cell
Type II cell
Interstitium
Capillary
Endothelial cell
ACUTE LUNG INJURY
Sloughed bronchial epithelium
Inactivated surfactant
Necrotic type I cell
Edema fluid
Leukotrienes
PAF
Proteases
Cellular debris
TNF
IL-1
Fibrin
Neutrophil sequestration and migration into alveolus
TNF
Chemokines
Hyaline membrane
Fibroblast
Procollagen
Edema
Injured, swollen endothelial cells

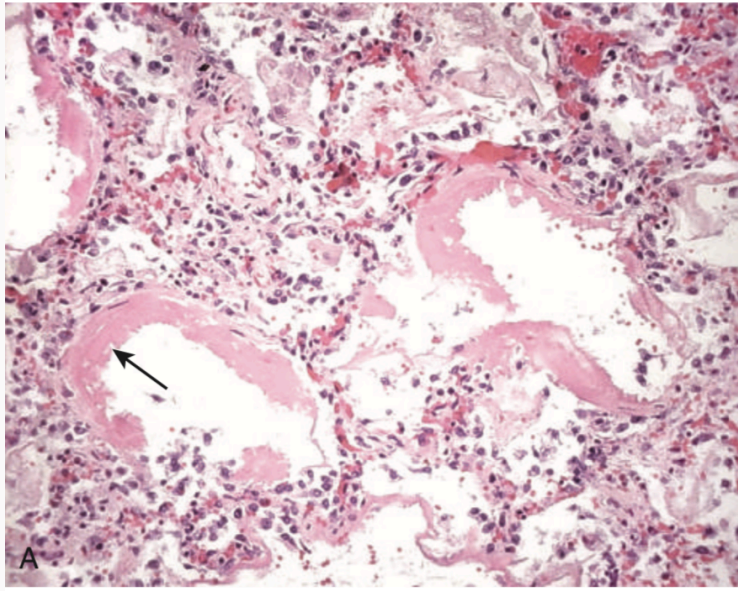
Morphology

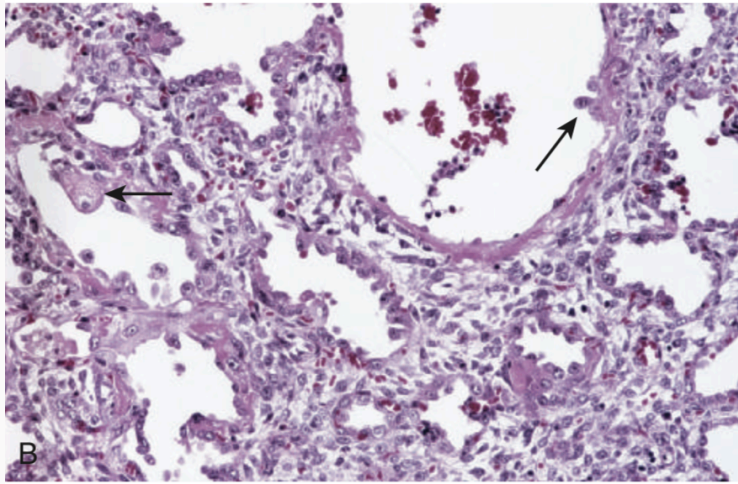
Acute phase:

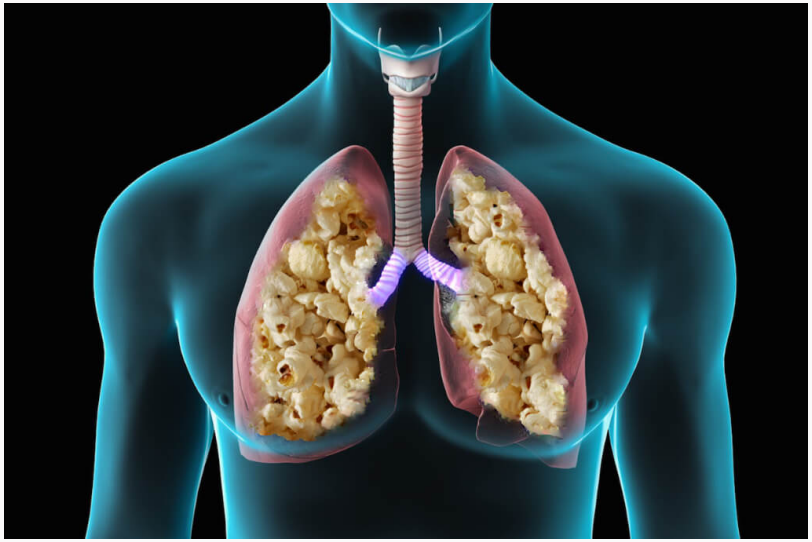
- **Hyaline membranes: fi**brin-rich edema fluid admixed with remnants of necrotic epithelial cells and lining the alveolar wall.
- Capillary congestion
- Necrosis of alveolar epithelial cells, interstitial and intra- alveolar edema
- Hemorrhage
- particularly with sepsis: collections of neutrophils in capillaries

Organizing stage,

- Resorption of hyaline membranes and
- Thickening of alveolar septa by inflammatory cells, fibroblasts, and collagen
- Numerous reactive type II pneumocytes







Vaping-associated pulmonary injury (VAPI

- The CDC says that the THC agent and vitamin E is very strongly implicated in VAPI
- Can give many form of lung injury in particularly bronchiolitis obliterans.

Thanks for your attention