# 2. Hypersensitivity Pneumonitis

- Is an immunologically mediated inflammatory lung disease that primarily affects the alveoli and is often called allergic alveolitis.
- Most often it is an occupational disease that results from heightened sensitivity to inhaled antigens such as in moldy Hay .

- The damage occurs at the level of alveolar sacs ;so manifests as a predominantly restrictive lung disease.
- The occupational exposures are diverse, but the syndromes share common clinical and pathologic findings and probably have a very similar pathophysiologic basis

Examples

Syndrome –Exposure-Antigens

a. Farmer's lung -------Moldy hay--Micropolyspora

b. Maple bark disease-Moldy maple bark -Cryptostroma

c-Pigeon breeder's lung-Pigeon droppings-Pigeon serum proteins in droppings

- Is an immunologically mediated disease

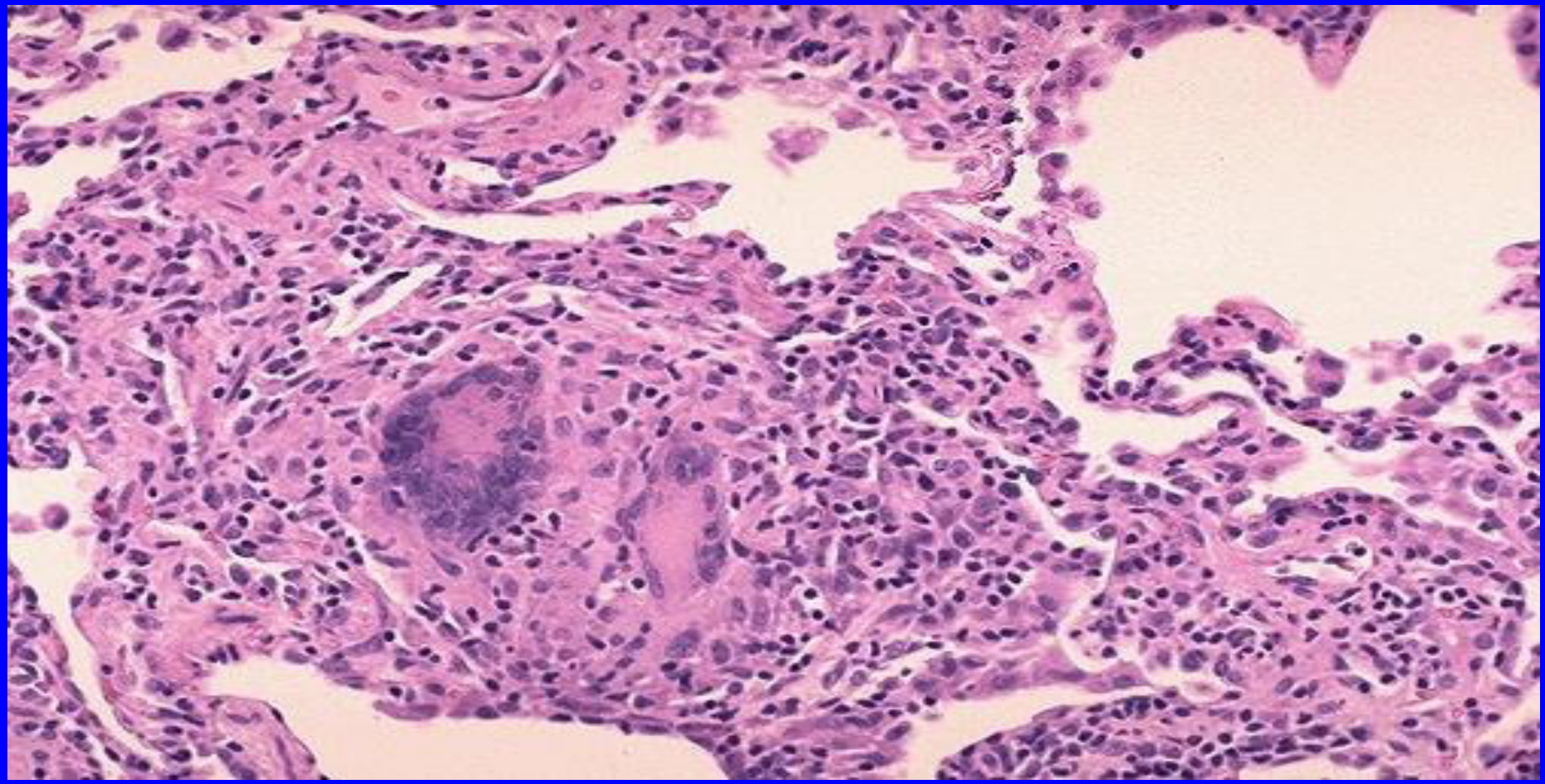
1. Bronchoalveolar lavage specimens consistently demonstrate increased numbers of T lymphocytes of both CD4+ and CD8+ phenotype.
2. Most patients have specific antibodies in their serum

3. Complement and immunoglobulins have been demonstrated within vessel walls by immunofluorescence, indicating **type III hypersensitivity.**
4. The presence of noncaseating granulomas in two thirds of patients with this disorder suggests a role for type **IV hypersensitivity as well**.

# Morphology

- Patchy mononuclear cell infiltrates in the pulmonary interstitium mainly lymphocytes
- Interstitial non-caseating granulomas are present in about 2 thirds of th cases
- In advanced cases, diffuse interstitial fibrosis

# Hypersensitivity Pneumonitis



## Clinical Manifestations

- May manifest either as:

A. An acute reaction:

- Characterized by fever, cough, dyspnea, and constitutional signs and symptoms arising 4 to 8 hours after exposure.

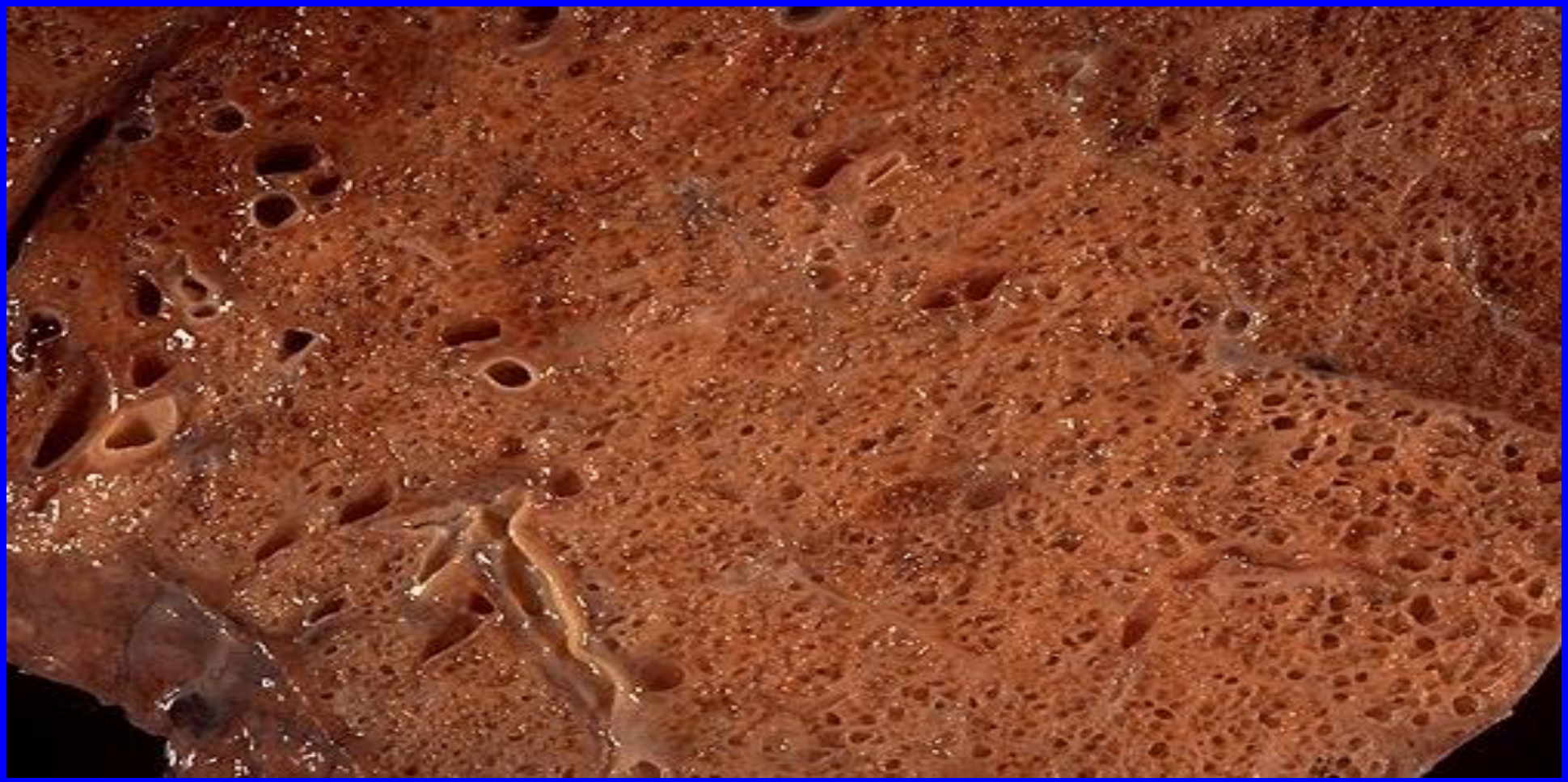
- With the acute form of this disease, the diagnosis is usually obvious because of the temporal relationship of symptom onset to exposure to the incriminating antigen.

b. or as a chronic disease

- characterized by insidious onset of cough, dyspnea, malaise, and weight loss.

- If antigenic exposure is terminated after the acute attacks, complete resolution of pulmonary symptoms occurs within days
- Failure to remove the inciting agent eventually results in an irreversible chronic interstitial pulmonary disease

# Honeycomb lung



# II. Fibrosing diseases

1. Idiopathic pulmonary fibrosis (IPF),

- Also known as ***cryptogenic fibrosing alveolitis***, refers to a pulmonary disorder of unknown etiology.
- It is characterized by patchy but progressive bilateral interstitial fibrosis, which in advanced cases results in severe hypoxemia and cyanosis.

- Males are affected more often than females,
- Two thirds of patients are older than 60 years of age at presentation.
- The radiologic and histologic pattern of fibrosis is referred to as *usual interstitial pneumonia* (UIP), which is required for the diagnosis of IPF.

- However, similar pathologic changes in the lung may be present in well-defined entities such as asbestosis and the collagen vascular diseases.
- Therefore, known causes must be ruled out before the term of *idiopathic* is used

# PATHOGENESIS

- IPF is caused by "repeated cycles" of epithelial activation/injury by unidentified agent
- Histopathologic features include inflammation and induction of $T_H2$ type T cell response with eosinophils, mast cells, IL-4, and IL-13 in the lesions.

- Abnormal epithelial repair at the sites of damage and inflammation gives rise to exuberant fibroblastic or myofibroblastic proliferation leading to the characteristic fibroblastic foci.

a.- TGF-β1, which is released from injured type I pneumocytes induces transformation of fibroblasts into myofibroblasts leading to excessive and continuing deposition of collagen and ECM .

b.- TGF-β1 also downregulates fibroblast caveolin-1, which acts as an endogenous inhibitor of pulmonary fibrosis

# MORPHOLOGY

- The pattern of fibrosis in IPF is referred to as usual interstitial pneumonia (UIP)

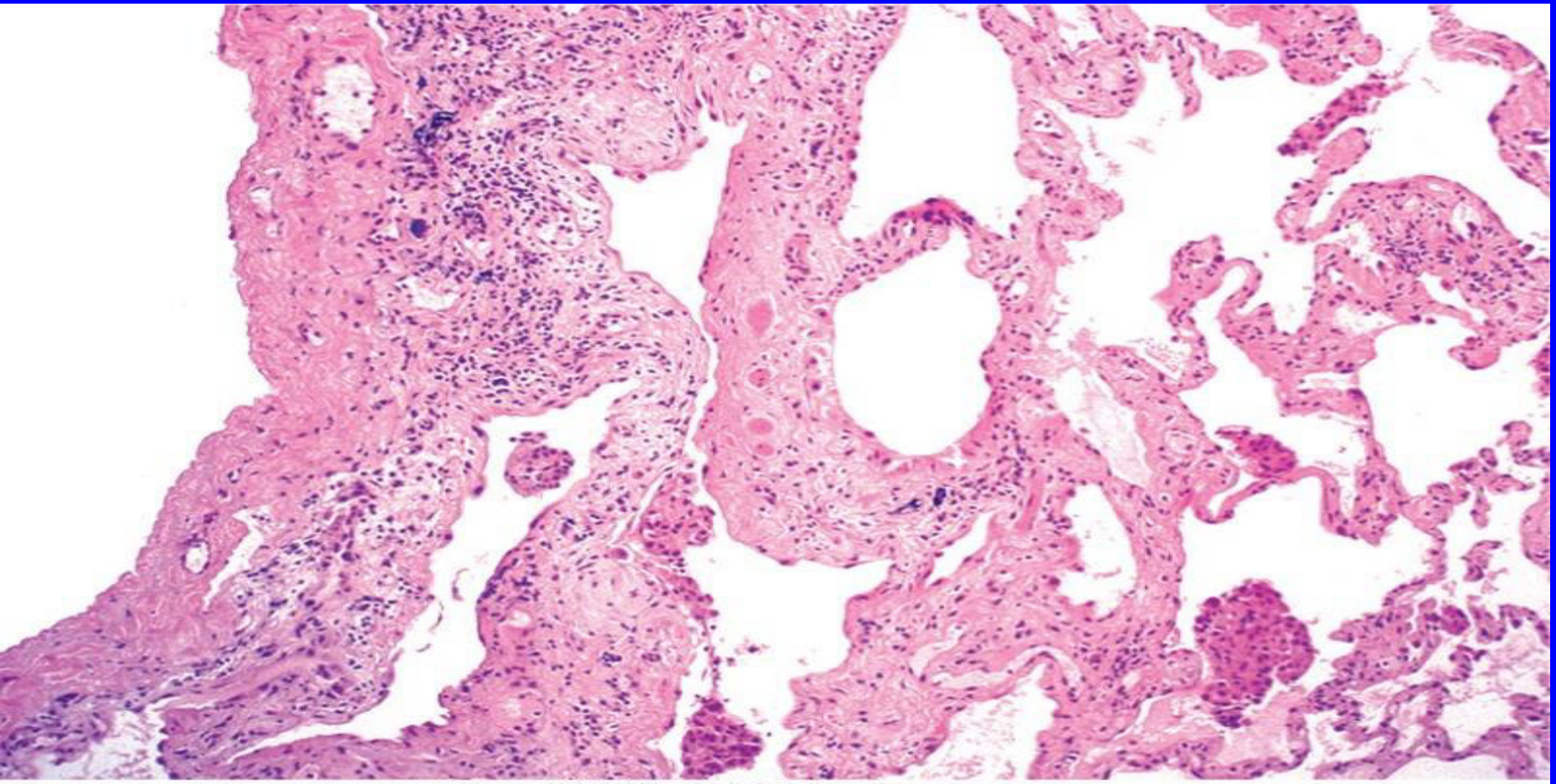
-The histologic hallmark of UIP is patchy interstitial fibrosis, which varies in intensity and worsens with time.

- The earliest lesions demonstrate exuberant fibroblastic proliferation and appear as **fibroblastic Foci**

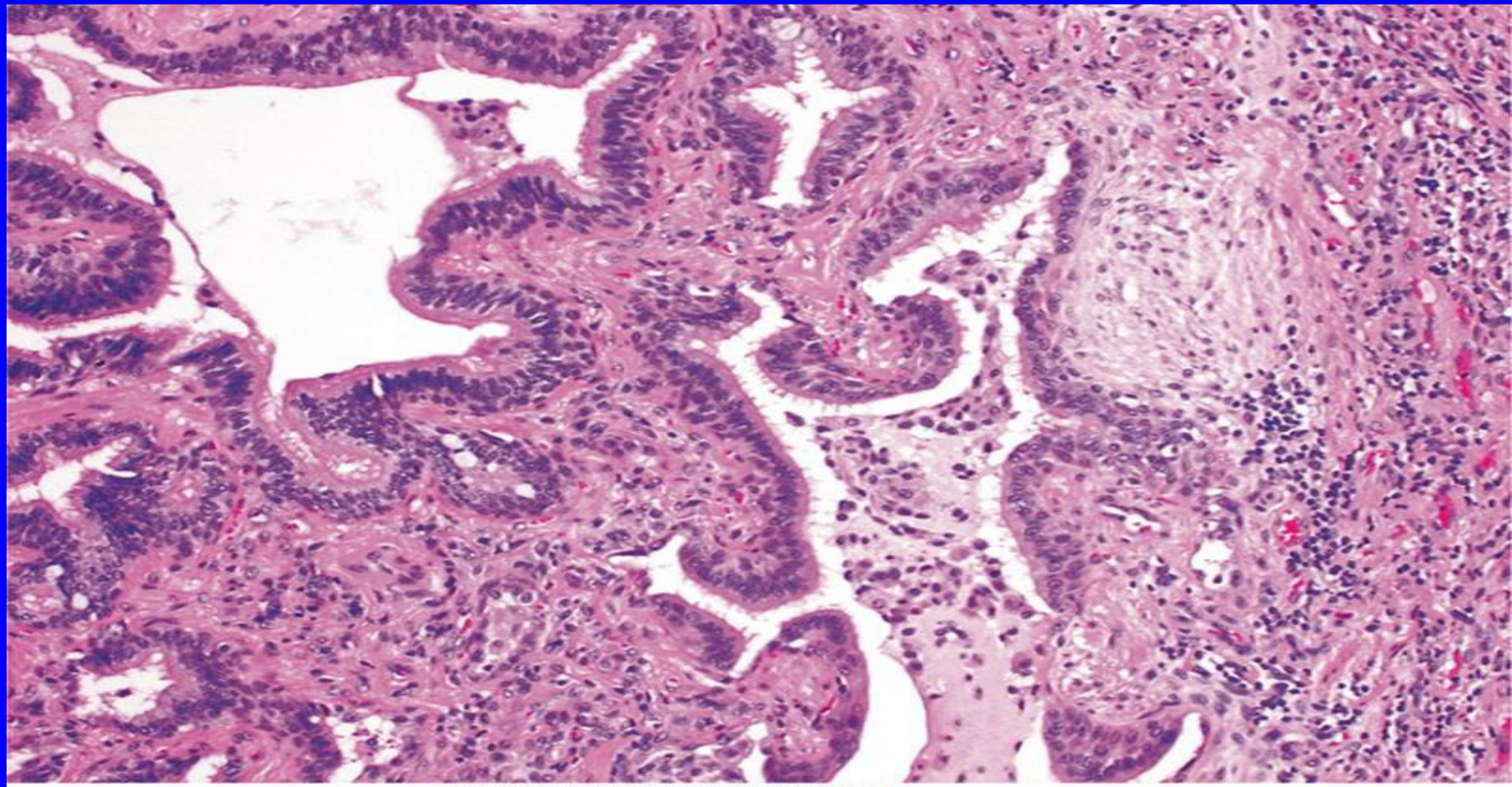
Over time these areas become more collagenous and less cellular.

- Quite typical is the existence of both early and late lesions (temporal heterogeneity)

# Usual interstitial pneumonia



# Usual interstitial pneumonia



- The dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium (honeycomb fibrosis).

- The interstitial inflammation usually is patchy and consists of an alveolar septal infiltrate of mostly lymphocytes and occasional plasma cells, mast cells, and eosinophils.

- Secondary pulmonary hypertensive changes (intimal fibrosis and medial thickening of pulmonary arteries) are often present.

Clinical Features

- IPF usually manifests insidiously, with the gradual onset of a nonproductive cough and progressive dyspnea.
- On physical examination, most patients with IPF have characteristic “dry” crackles during inspiration.
- Cyanosis, cor pulmonale, and peripheral edema may develop in later stages of the disease.

- The clinical and radiologic findings are diagnostic;
- Surgical lung biopsy is needed for diagnosis in selected cases.
- Unfortunately, progression of IPF is relentless despite medical therapy, and the mean survival is 3 years or less.
- Lung transplantation is the only definitive therapy available

# 2.Pneumoconioses

- Is a term originally coined to describe the non-neoplastic lung reaction to inhalation of mineral dusts.
- The term has been broadened to include diseases induced by organic as well as inorganic particulates

- The mineral dust pneumoconioses-the three most common of which result from exposure to :

a. Coal dust
b. Silica,
c. Asbestos

## PATHOGENESIS :

- The reaction of the lung to mineral dusts depends on their size shape, solubility, and reactivity

-Effect of size

a. 5 to 10 µm Particles are unlikely to reach distal airways,

b. Particles smaller than 0.5 µm move into and out of alveoli, often without substantial deposition and injury.

c. 1 to 5 μm particles are the most dangerous, because they get lodged at bifurcation of the distal airways.

Reactivity

1- Coal dust is relatively inert, and large amounts must be deposited before lung disease is clinically detectable.

2. Silica, asbestos, and beryllium are more reactive than coal dust, resulting in fibrotic reactions at lower concentrations.

Note:

- Most inhaled dust is entrapped in the mucus blanket and rapidly removed from the lung by ciliary movement,- However, some of the particles become impacted at alveolar duct bifurcations, where macrophages accumulate and engulf the trapped particulates

- The alveolar macrophage is a key cellular element in the initiation and perpetuation of lung injury and fibrosis.

a. Many particles activate the inflammasome and induce IL-1

b. The more reactive particles trigger the macrophages to release a number

of products that mediate inflammation and initiate fibroblast proliferation and collagen deposition.

c. Some of the inhaled particles may reach the lymphatics either by direct drainage or within migrating macrophages and thereby initiate an immune response.

Note:

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

# A. Coal Worker's Pneumoconiosis

-The spectrum of lung findings in coal workers :

**1. Pulmonary anthracosis**

- Is the most benign coal-induced pulmonary lesion in coal miners and also is commonly seen in all urban dwellers and tobacco smokers.

- Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages, which then accumulate in the connective tissue along the lymphatics, including the pleural lymphatics, or in lymph nodes
- **The pigment accumulates without cellular reaction**

**2. Simple coal worker's pneumoconiosis (CWP),**

- In which accumulations of macrophages occur with little to no pulmonary dysfunction,

**a. Coal macules** :- Consists of dust-laden macrophages;

**b. Coal Nodules**:- In addition, it contains small amounts of collagen fibers arrayed in a delicate network

Note:

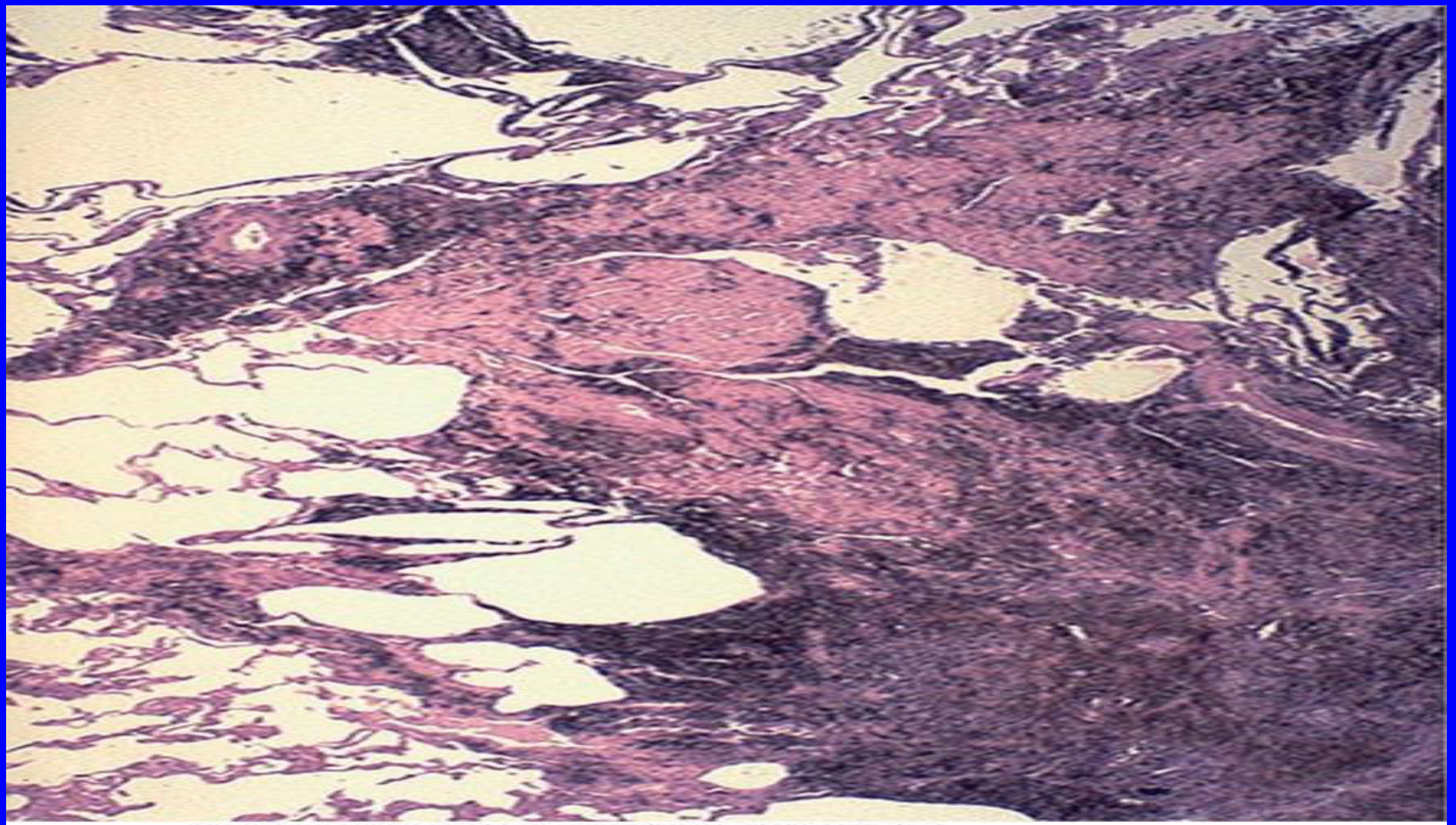
- Although these lesions are scattered throughout the lung, the upper lobes and upper zones of the lower lobes are more heavily involved.

# 3. **Complicated CWP or (PMF) :**

- *Progressive massive fibrosis* (PMF), in which fibrosis is extensive and lung function is compromised and occurs on a background of simple CWP by coalescence of coal nodules and generally requires many years to develop.

- Characterized by usually multiple, blackened scars larger than 2 cm, sometimes up to 10 cm in diameter.
- On microscopic examination the lesions are seen to consist of dense collagen and pigment
- Less than 10% of cases of simple CWP progress to PMF.

# CWP



Note:

- PMF is a generic term that applies to a confluent fibrosing reaction in the lung;
- This can be a complication of any one of the pneumoconioses

## Clinical Features

- CWP is usually a benign disease that produces little decrement in lung function.
- In those in whom PMF develops, there is increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.

- Progression from CWP to PMF has been linked to a variety of conditions including coal dust exposure level and total dust burden.
- Unfortunately, PMF has a tendency to progress even in the absence of further exposure.

***Note:***

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