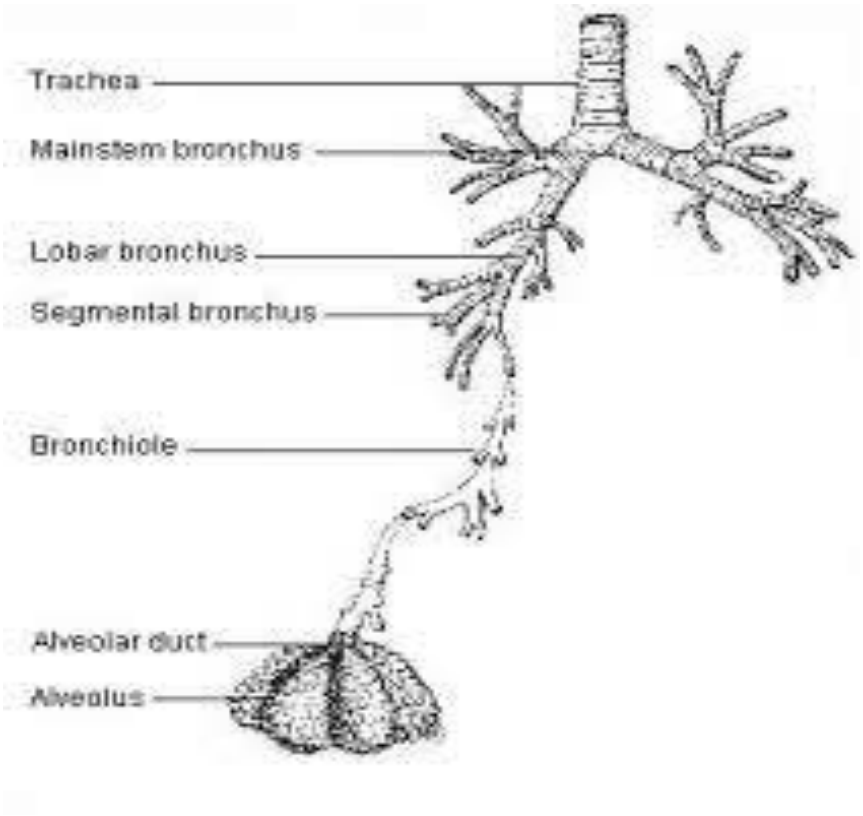
Diseases of the respiratory system

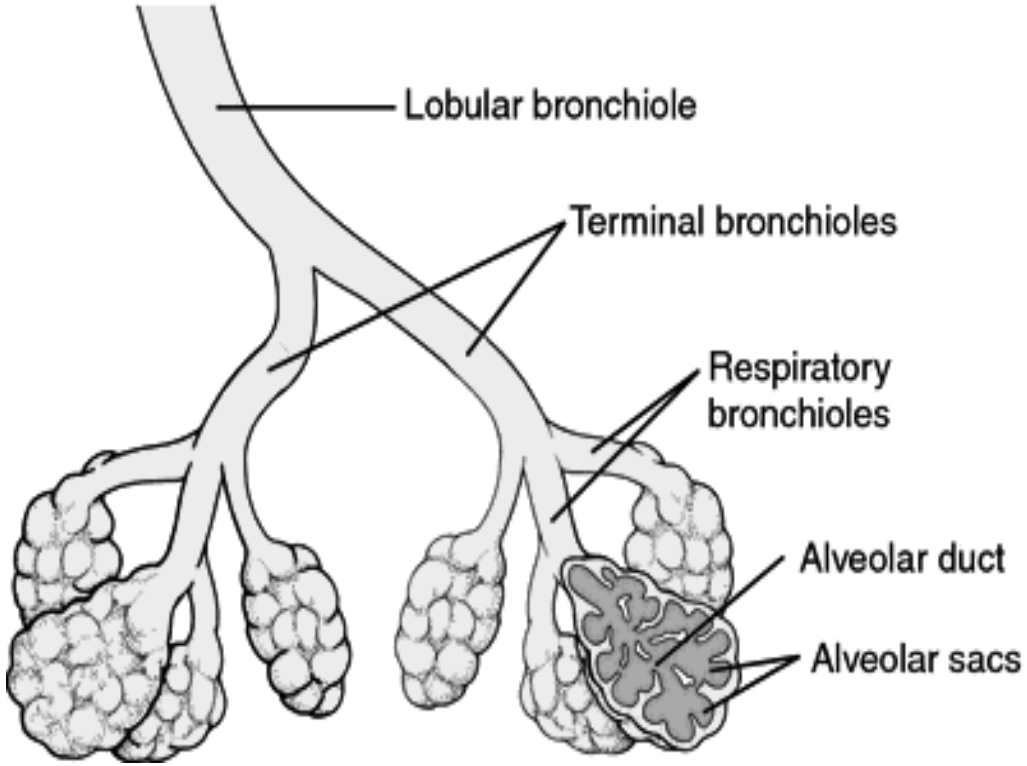
Dr Heyam Awad

FRCPath

STRUCTURE OF THE RESPIRATORY SYSTEM



The part of the lung distal to terminal bronchioles= acinus
note: every 3-5 acini form a lobule.



alveoli

- Alveoli are the site of gas exchange
- Alveoli are lined by flat pneumocytes (type I pneumocytes that occupy 95% of the alveolar surface) and type II pneumocytes .
- type II pneumocytes secrete **surfactant** and are the main cells involved in **repair** after injury of type I pneumocytes.

- **Surfactant lowers the surface tension inside the alveolar membrane to prevent them from collapsing during exhalation..**
- Surfactant in the lung is important so the alveoli do not collapse after expiration.

Diffusion of gases

- Oxygen and CO2 exchange happens through diffusion
- Diffusion depends on: surface area, thickness of the diffusion membrane and concentration gradient.. All criteria favoring maximum diffusion are seen in the alveoli.

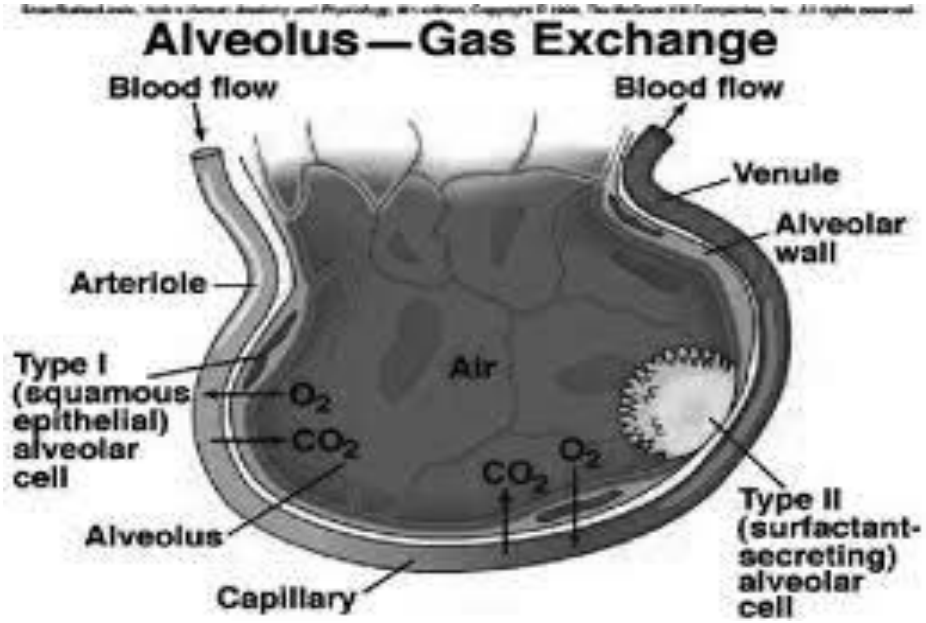
Alveoli are designed to achieve maximum gas exchange :

1.They have a huge surface area

2.Thin diffusion membrane

3.Concentration gradient kept to maximum because of the rich blood supply

ALVEOLI


Alveolus—Gas Exchange
Blood flow
Blood flow
Venule
Alveolar wall
Arteriole
Type I (squamous epithelial) alveolar cell
Air
O_2
CO_2
CO_2
O_2
Alveolus
Capillary
Type II (surfactant-secreting) alveolar cell

ALVEOLI: LARGE SURFACE AREA

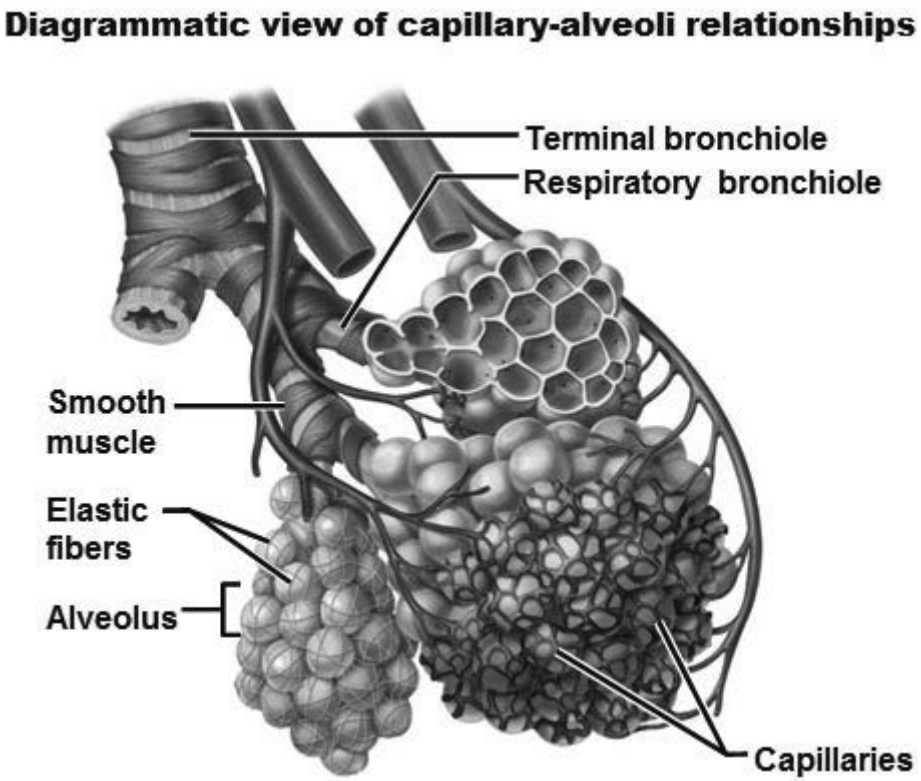
Lungs

A pair of lungs contains about *300 million alveoli*.

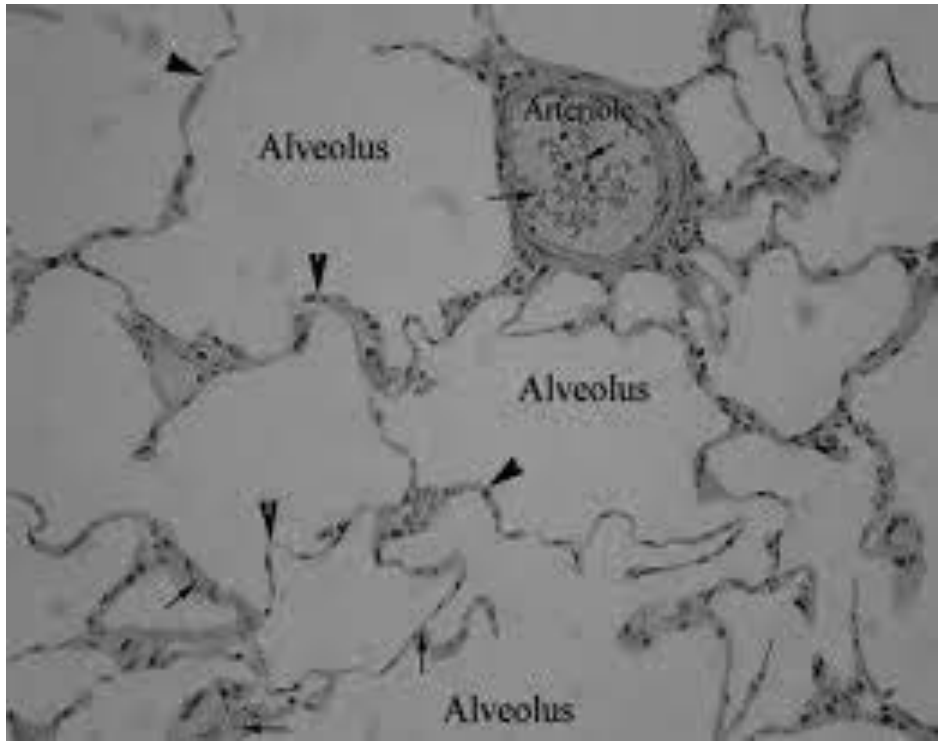
This subdivides the volume of the lungs and creates a total alveolar surface area of about 1000 ft.^{2} (like a room 33 ft. x 30 ft.).

The advantage to having this is that it allows for a very ***large surface area for gas exchange***.

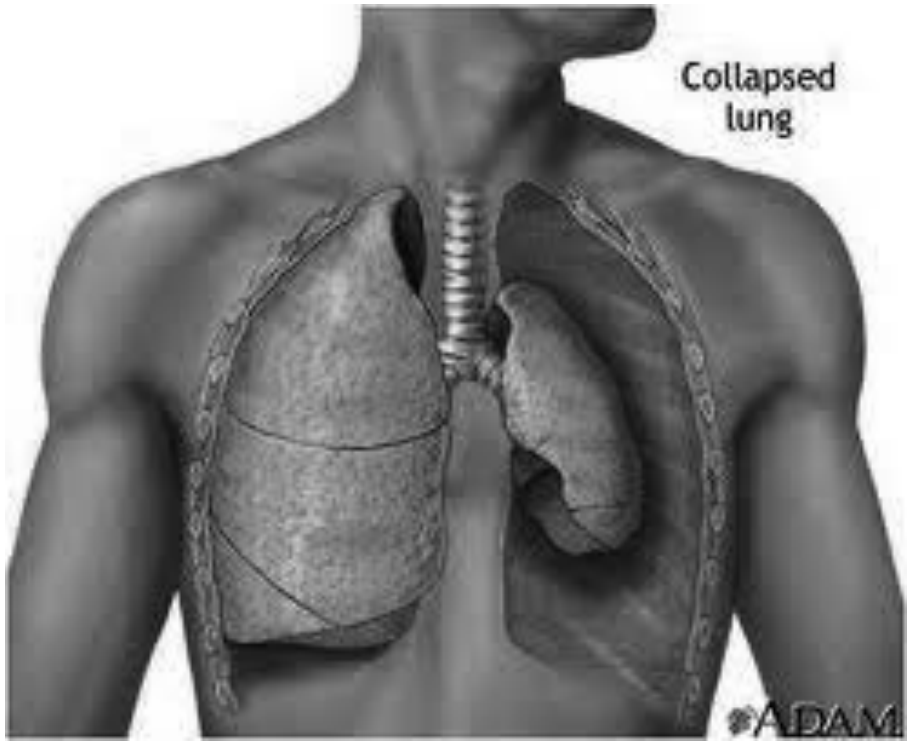
ALVEOLI: RICH BLOOD SUPPLY which keeps a high concentration gradient



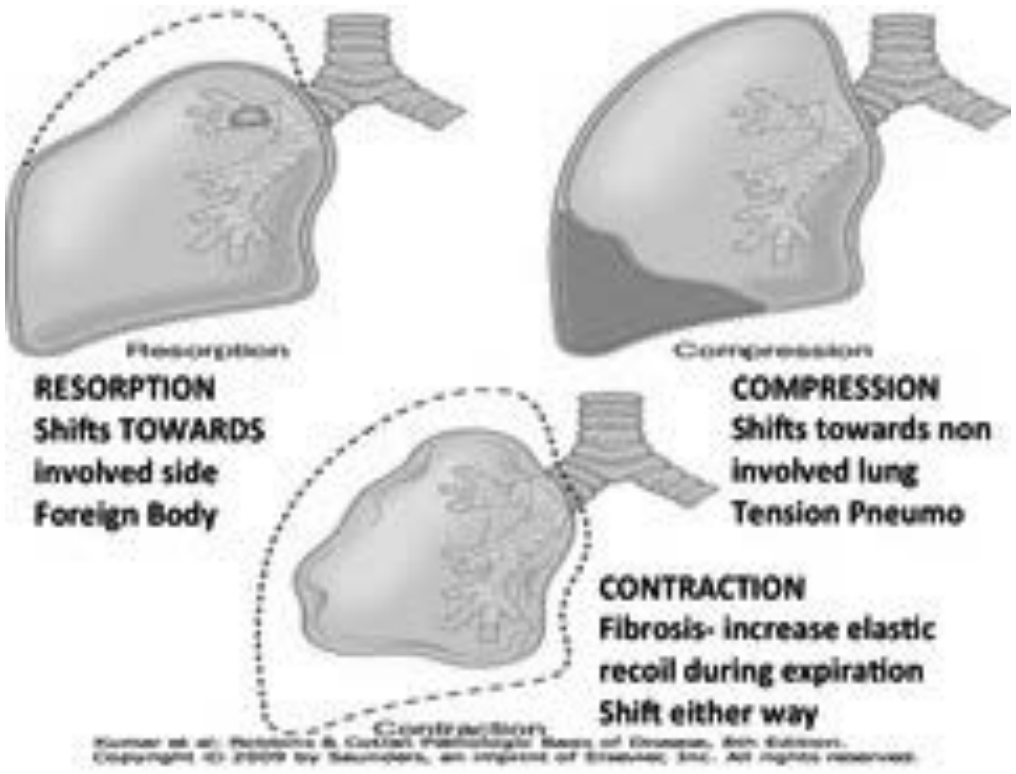
ALVEOLI: THIN MEMBRANES



ATELECTASIS = LUNG COLLAPSE =انْخِماص



TYPES OF ATELECTASIS



RESORPTION ATELECTASIS

- ***OBSTRUCTION BY:***

  *MUCOUS OR MUCOPURULENT PLUG (POST-OP, ASTHMA, BRONCHIECTASIS OR CHRONIC BRONCHITIS)

  *TUMOUR.

  *FOEIGN BODY .

COMPRESSION ATELECTASIS

ACCUMOLATION OF :

- *FLUID* (PLEURAL EFFUSION)
- BLOOD (HAEMOTHORAX)
- AIR (PNEUMOTHORAX)

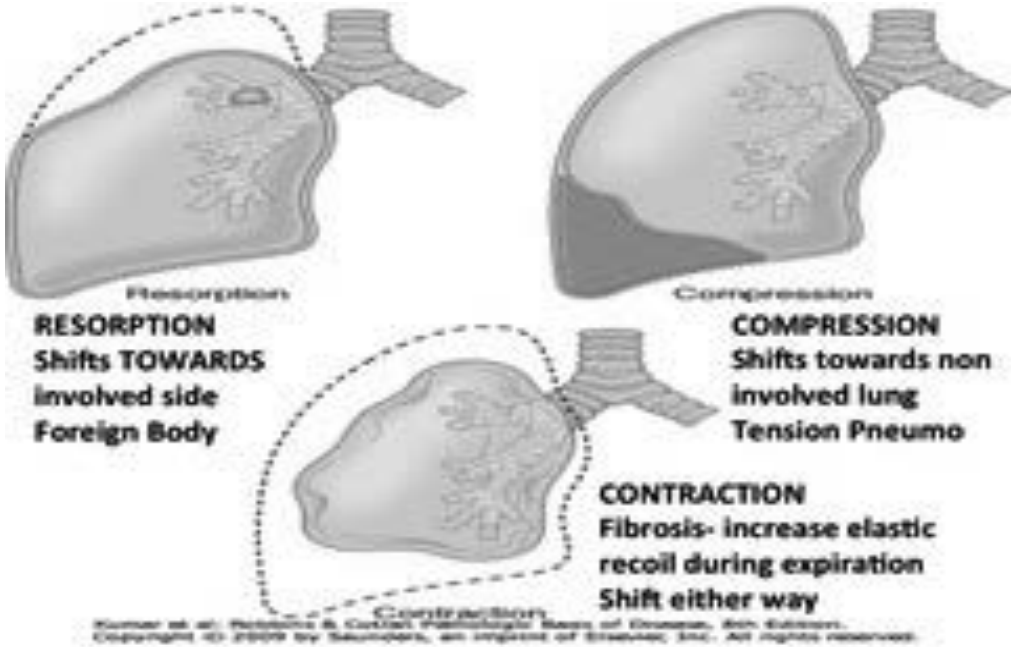
ALL WITHIN THE PLEURAL CAVITY.

- Compression can also be due to elevated diaphragm
- This occurs post-op and due to ascitis

CONTRACTION ATELECTASIS

- LOCAL OR GENERALISED FIBROSIS.

- ATELECTASIS…….IS IT REVERSIBLE???????



Atelectasis (except when caused by contraction) is potentially reversible and should be treated promptly to prevent hypoxemia and superimposed infection of the collapsed lung.

Question: what are the complications of atelectasis? ……. Answer: Read above

Acute lung injury and ARDS (adult respiratory distress syndrome)

- **متلازمة الضائقة التنفسية الحادة = ARDS**

- Acute lung injury includes a spectrum of bilateral pulmonary damage (endothelial and epithelial), which can be initiated by numerous conditions.

Acute lung injury manifests as:

1. Acute onset of dyspnea,
2. Decreased arterial oxygen pressure (hypoxemia),refractory to oxygen
3. Development of bilateral pulmonary infiltrates on the chest radiograph (due to pulmonary edema)
4. Absence of clinical evidence of primary left-sided heart failure

NOTE:

The pulmonary infiltrates in acute lung injury are caused by damage to the alveolar capillary membrane, rather than by left-sided heart failure , such accumulations constitute an example of *noncardiogenic pulmonary edema*.

- **<u>Note</u>**-
- Acute lung injury can progress to the more severe *acute respiratory distress syndrome*

ARDS

- clinical syndrome caused by diffuse, bilateral alveolar capillary and epithelial damage.

The usual course is characterized by:

A. Rapid onset of life-threatening respiratory insufficiency

B. severe arterial hypoxemia that is refractory to oxygen therapy and may progress to multisystem organ failure

ARDS

- Occurs in a multitude of clinical settings
- And is associated with either

a. Direct injury to the lung or

b. Indirect injury in the setting of a systemic process

Direct Lung Injury

I. Common Causes

1.Pneumonia

2. Aspiration of gastric contents

II. Uncommon Causes

1. Pulmonary contusion

- Indirect causes

I. common causes

1. Sepsis

2. Severe trauma with shock

II. Uncommon causes

Acute pancreatitis

Causes of ARDS

Direct lung injury	Indirect lung injury
Common causes: - Pneumonia - Aspiration of gastric contents	Common causes: - Sepsis - Severe trauma with shock and multiple transfusions
Less common causes: - Pulmonary contusion - Fat emboli - Near-drowning - Inhalational injury - Reperfusion pulmonary oedema	Less common causes: - Cardiopulmonary by-pass - Drug overdoes - Acute pancreatitis - Transfusion of blood products

Note:

- Respiratory distress syndrome of the newborn is pathogenetically distinct; it is caused by a primary deficiency of surfactant

PATHOGENESIS

- The alveolar-capillary membrane is formed by two separate barriers: the microvascular endothelium and the alveolar epithelium.
- In ARDS, the integrity of this barrier is compromised by either endothelial or epithelial injury, or, more commonly, both.

The acute consequences of damage to the alveolar capillary membrane include:

1. Increased vascular permeability and alveolar flooding
2. Loss of diffusion capacity,
3. Widespread surfactant abnormalities caused by damage to type II pneumocytes

Suggested mechanism:

- *In ARDS,* ***lung injury is caused by an imbalance of pro-inflammatory and anti-inflammatory mediators.***

ARDS: pathogenesis

A. Increased synthesis of interleukin 8 (IL-8), a potent neutrophil chemotactic and activating agent, by pulmonary macrophages. This is seen as early as the first 30 minutes of lung injury.

- B. Release of IL-1 and tumor necrosis factor (TNF), leading to endothelial activation

C. Activated neutrophils release a variety of oxidants, proteases, leukotrienes that cause damage to the alveolar epithelium and endothelium.

D- Combined assault on the endothelium and epithelium increases vascular leakiness and loss of surfactant that render the alveolar unit unable to expand.

- The destructive forces by neutrophils can be counteracted by
- 1. antiproteases
- 2.antioxidants
- 3. anti-inflammatory cytokines (**e.g., IL-10)**

- In the end, it is the balance between the destructive and protective factors that determines the degree of tissue injury and clinical severity of ARDS

Note:

- Neutrophils are thought to have an important role in the pathogenesis of ARDS

MORPHOLOGY

In the **acute phase of ARDS**

Gross,

1. The lungs are red, firm
2. Airless, and heavy.

Histopathological features of ARDS

1. Capillary congestion,
2. Necrosis of alveolar epithelial cells,
3. Interstitial and intra-alveolar edema and hemorrhage,
4. Increased numbers of neutrophils within the vascular space, the interstitium, and the alveoli
5. The most characteristic finding is the presence of **hyaline membranes** lining the alveolar ducts

Hyaline membrane

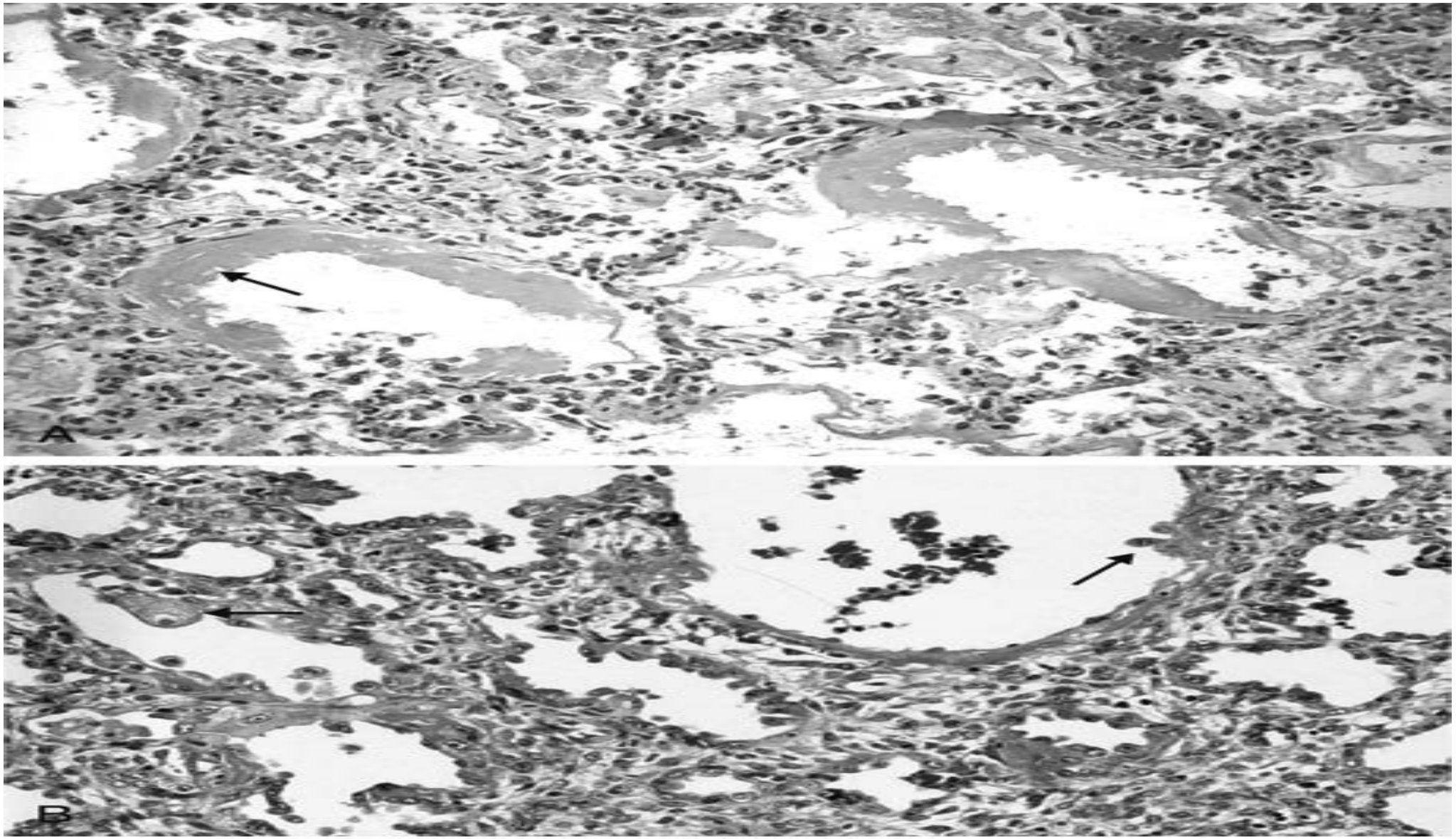
Composed of :

a. fibrin-rich edema fluid

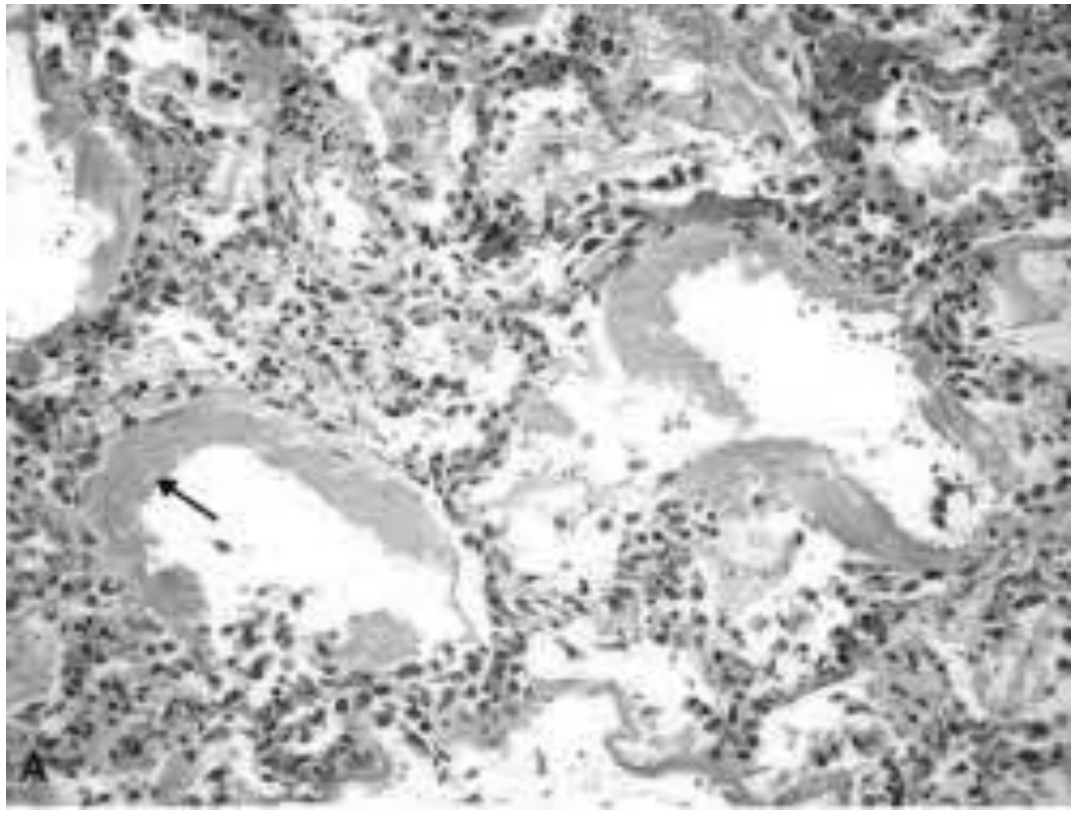
b. Remnants of necrotic epithelial cells.

NOTE: Overall, the picture is similar to that seen in respiratory distress syndrome in the newborn

ARDS



ARDS



Histological changes of ARDS

In the organizing stage,

- Vigorous proliferation of *type II pneumocytes* occurs in an attempt to regenerate the alveolar lining.

Histological changes after recovery

Resolution is unusual-

a. More commonly, there is *organization of the fibrin* exudates, with resultant *intra-alveolar fibrosis.*

b. Marked thickening of the alveolar septa occurs, caused by proliferation of interstitial cells and deposition of collagen..

ARDS: outcome

-With improvements in supportive therapy, the mortality rate ARDS cases occurring yearly has decreased from 60% to 40% in the last decade.

- If the patient survives the acute stage, diffuse interstitial fibrosis may occur, with continued compromise of respiratory function.
- in most patients who survive the acute insult and are spared the chronic fibrosis, normal respiratory function returns within 6 to 12 months

Predictors of poor prognosis include

- Advanced age
- Underlying bacteremia (sepsis)
- The development of multisystem (especially cardiac, renal, or hepatic) failure.

ARDS treatment (this is extra, just FYI)

- Supportive
- Teat in the ICU
- Intubation
- Give oxygen but avoid barotrauma!
- ECMO **(Extracorporeal membrane oxygenation**)

Diseases of the respiratory system lecture 2

Dr Heyam Awad

FRCPath

Obstructive versus restrictive lung diseases

Obstructive lung diseases: limitation of airflow due to partial or complete obstruction. Expiration affected more than inspiration.

Expiratory obstruction may result either from

A. **Anatomic** airway narrowing, such as in asthma and chronic bronchitis

B. **Loss of elastic recoil** (functional obstruction)characteristic of emphysema

- Restrictive lung diseases: reduced expansion of the lungs and decreased total lung capacity.
- Caused by:

1. Chest wall disorders that decrease lung expansion like in obesity or pleural diseases
2. Interstitial lung diseases: these are divided to acute (ARDS) and chronic (fibrosis, sarcoidosis.. Etc)

Obstructive versus restrictive lung diseases

Obstructive vs restrictive lung diseases

Obstructive	restrictive
characterized by limitation of airflow due to partial or complete obstruction	characterized by reduced expansion of lung parenchyma accompanied by decreased total lung capacity.
Eg are emphysema, chronic bronchitis, bronchiectasis, and asthma	Eg are ILD like Fibrosing alveolitis, idiopathic pulmonary fibrosis, interstitial pneumonia, Pneumoconiosis,Sarcoidosis; and chest wall neuromuscular diseases
total lung capacity normal	decreased
forced vital capacity (FVC) normal	reduced
decreased expiratory flow rate, measuerd as forced expiratory volume at 1 second (FEV_1)	Normal or reduced
FEV1/FVC ratio < 0.80	normal

OBSTRUCTIVE VS. RESTRICTIVE

Obstructive disorders	Restrictive disorders
• **Characterized by:** reduction in airflow. • So, shortness of breath → in exhaling air. **(the air will remain inside the lung after full expiration)** 1. COPD 2. Asthma 3. Bronchiectasis	• **Characterized by** a reduction in lung volume. • So, Difficulty in taking air inside the lung. **(DUE TO stiffness inside the lung tissue or chest wall cavity)** 1. Interstitial lung disease. 2. Scoliosis 3. Neuromuscular cause 4. Marked obesity

Obstructive pulmonary diseases

1. Emphysema,
2. Chronic bronchitis,
3. Bronchiectasis,
4. Asthma.

COPD= chronic obstructive pulmonary disease

- = Chronic bronchitis and emphysema
- These two are distinct diseases but they overlap and coexist in the same patient because both are caused by smoking.

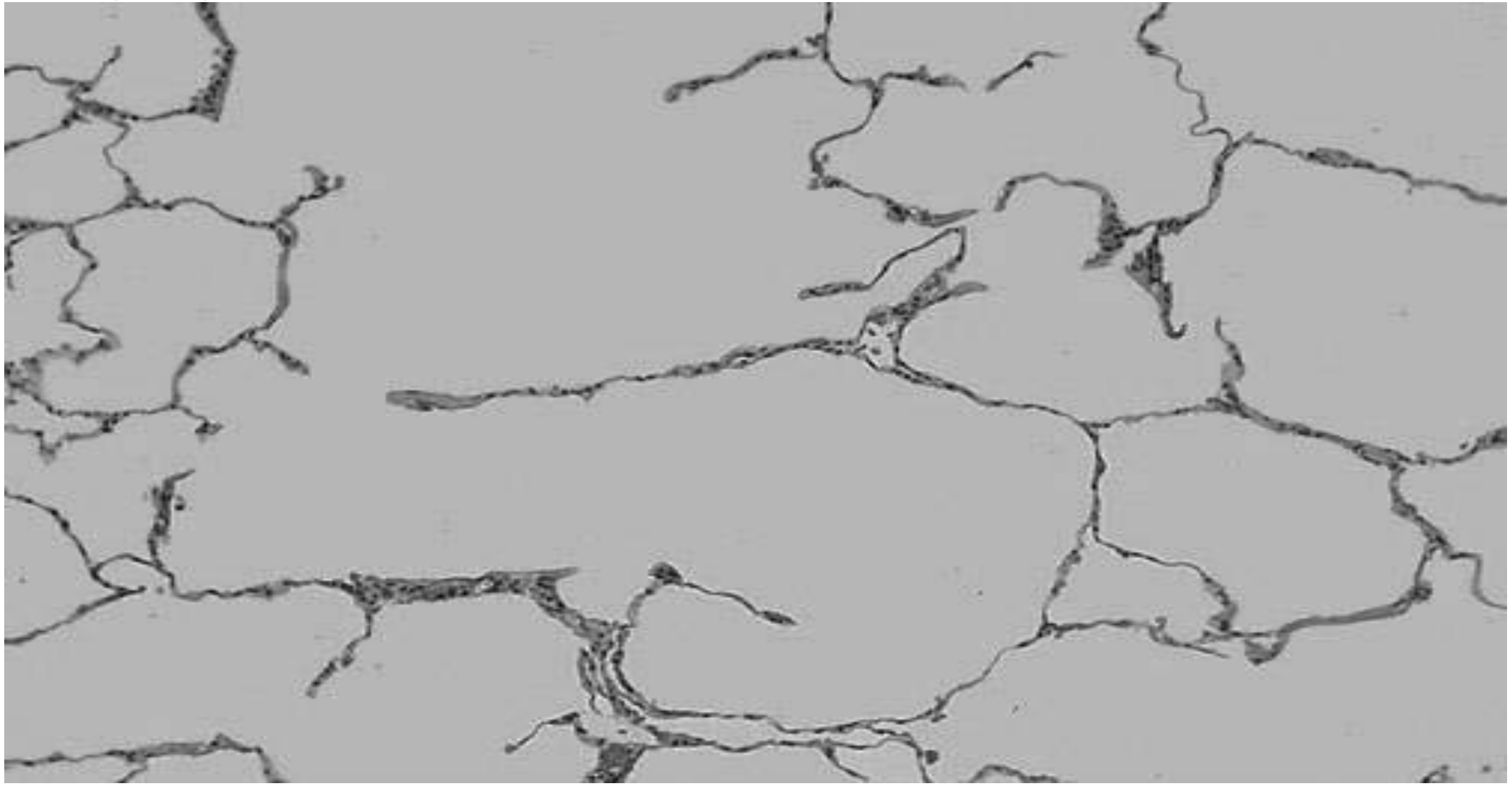
Differences between chronic bronchitis and emphysema

- The definition of emphysema is morphologic, whereas chronic bronchitis is defined on the basis of clinical features
- The anatomic distribution is different; chronic bronchitis initially involves the large airways, whereas emphysema affects the acini.
- Clinical presentation differs (details later)

Emphysema: definition

- Abnormal **permanent enlargement** of the air spaces **distal to the terminal bronchioles** accompanied by **destruction of their walls without fibrosis**

Emphysema



Types of emphysema

- Emphysema is classified according to its anatomic distribution within the lobule, the acinus is the structure distal to terminal bronchioles, and a cluster of three to five acini is called a lobule

-There are four major types of emphysema:

(1) Centriacinar,

(2) Panacinar

(3) Distal acinar,

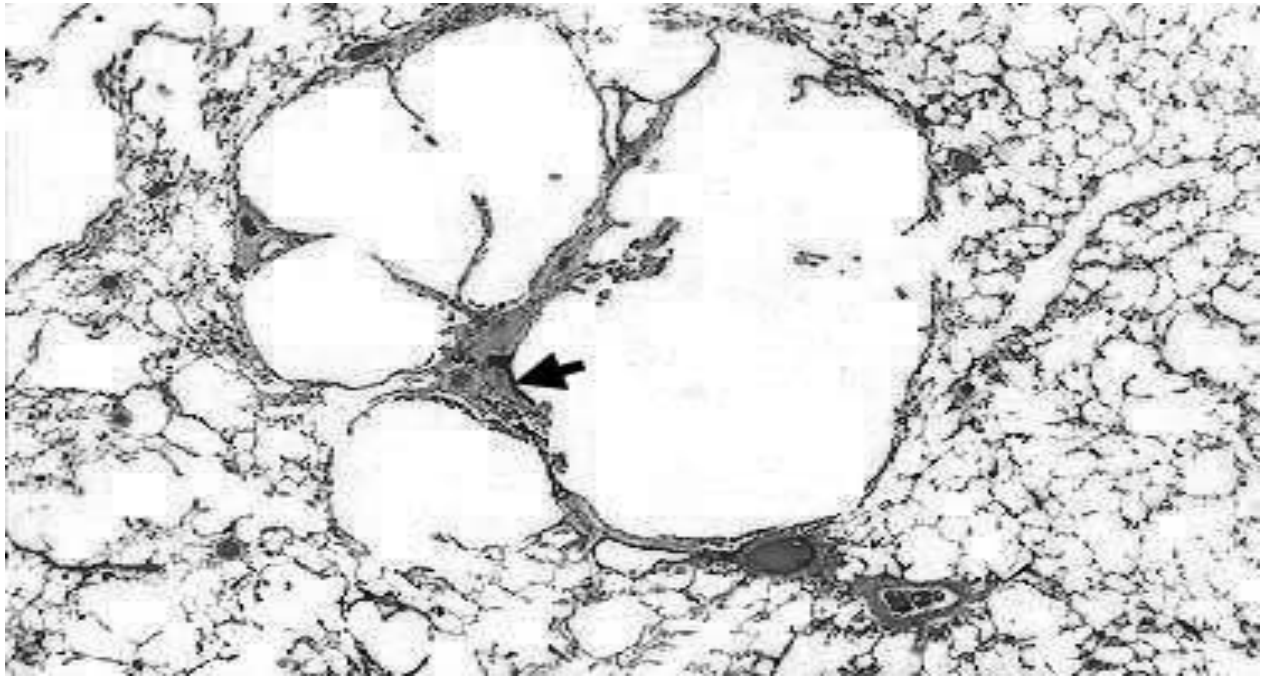
(4) Irregular.

Types of emphysema

1. Centriacinar (Centrilobular) Emphysema

- The central or proximal parts of the acini, formed by respiratory bronchioles, are affected, while distal alveoli are spared
- Both emphysematous and normal air spaces exist within the same acinus and lobule

Centriacinar emphysema



CENTRIACINAR EMPHYSEMA

-The lesions are more common and severe in the upper lobes.

- This type of emphysema is most commonly caused by smoking

2. Panacinar (Panlobular) Emphysema

- *The acini are uniformly enlarged,* from the level of the respiratory bronchiole to the terminal blind alveoli
- Tends to occur more commonly in the lower lung zones
- It occurs in α_1-antitrypsin deficiency.

3. Distal Acinar (Paraseptal)

- It involves the distal part of the acinus.
- The proximal portion of the acinus is normal
- Is more striking adjacent to the pleura, along the lobular connective tissue septa

PARASEPTAL EMPHYSEMA

- It occurs adjacent to areas of fibrosis
- The characteristic finding is the presence of multiple, enlarged air spaces ranging in diameter from less than 0.5 mm to more than2.0 cm, sometimes forming cystic structures that, with progressive enlargement, are referred to as *bullae*
- Ruptured bullae cause spontaneous pneumothorax especially in young adults.

4. Irregular Emphysema

- The acinus is irregularly involved,
- Is almost invariably associated with scarring, such as that resulting from healed inflammatory diseases.
- Although clinically asymptomatic, this may be the **most common** form of emphysema.

PATHOGENESIS/ 1

- Exposure to toxic substances such as tobacco smoke and inhaled pollutants induces ongoing inflammation with accumulation of neutrophils, macrophages and lymphocytes in the lung.
- Neutrophils release elastases, cytokines (including IL-8) and oxidants causing epithelial injury and proteolysis of the extracellular matrix (ECM).

PATHOGENESIS/ 2

-Unless checked by antielastases (e.g., α_1-antitrypsin) and antioxidants, the cycle of inflammation and ECM proteolysis continues.

- More than 80% of patients with congenital α_1-antitrypsin deficiency develop symptomatic panacinar emphysema, which occurs at an earlier age and with greater severity if the affected person smokes .

PATHOGENESIS/ 3

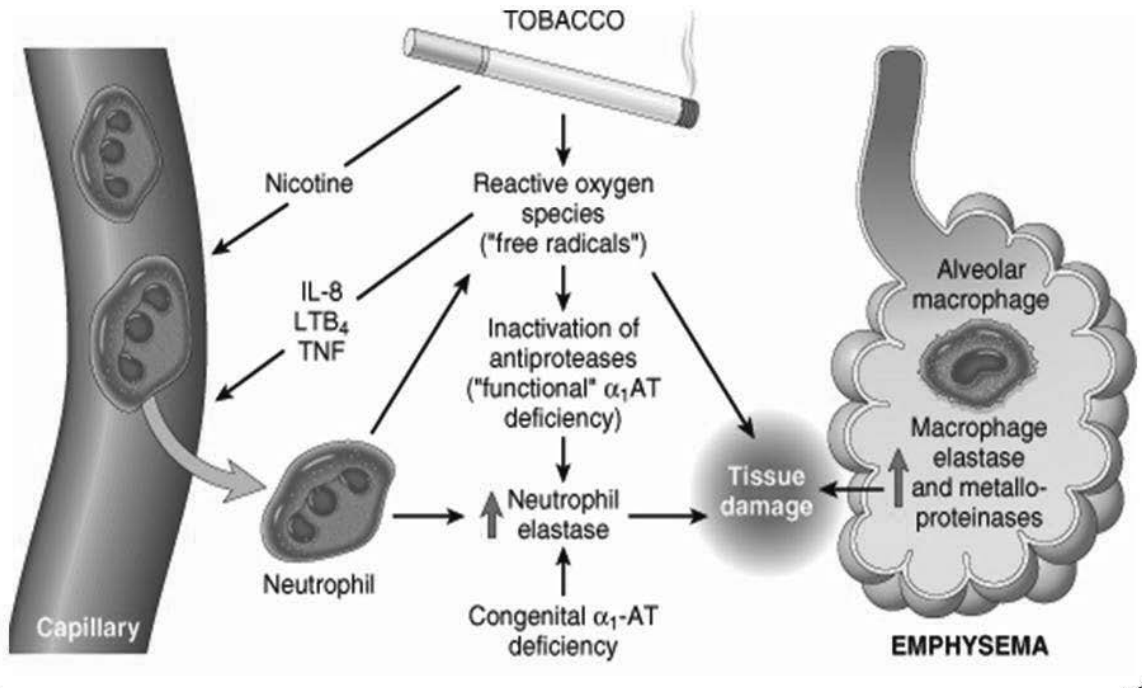
In emphysema there is loss of not only epithelial and endothelial cells but also **mesenchymal cells**, leading to **lack of extracellular matrix**, the scaffolding upon which epithelial cells would have grown.

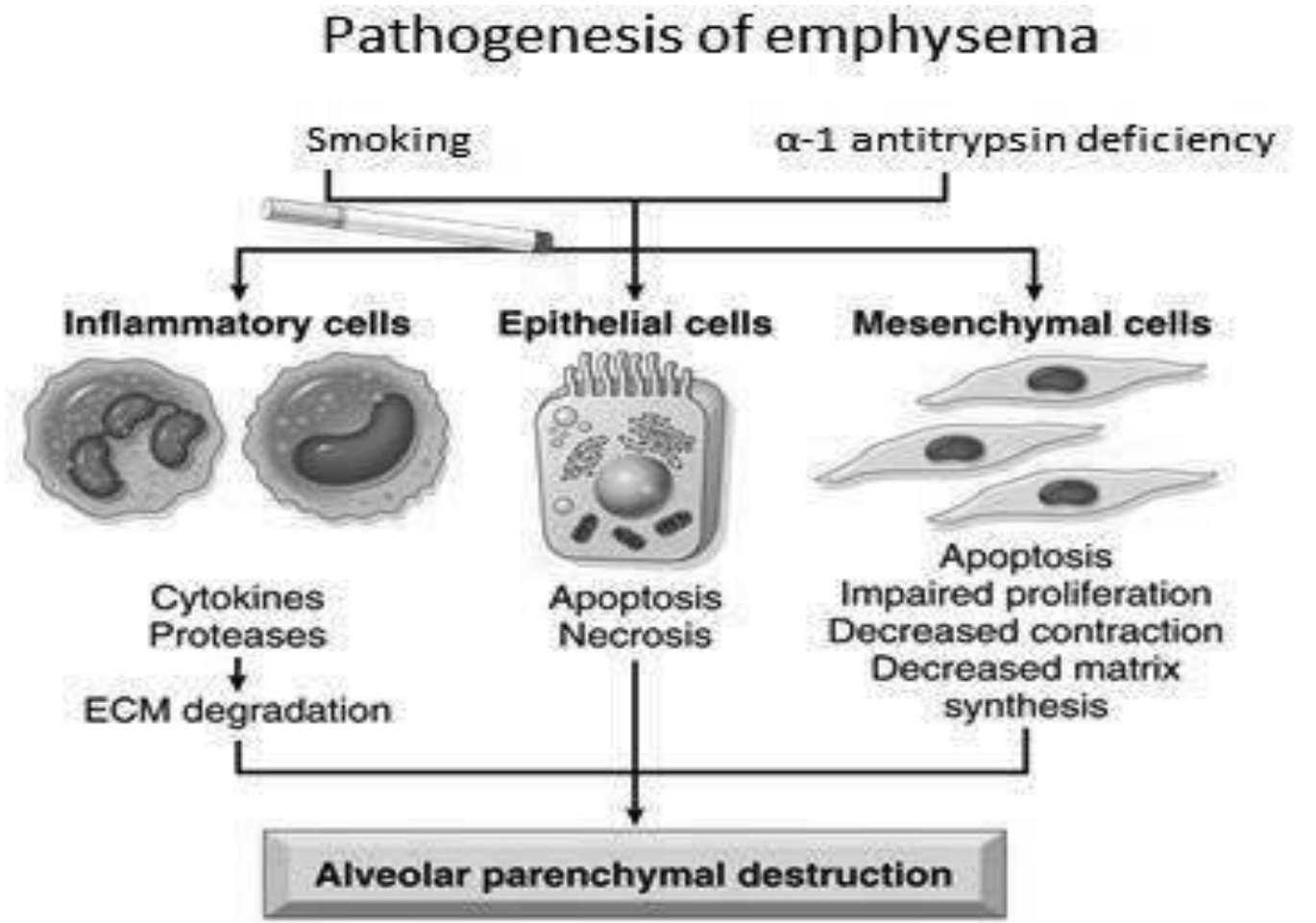
- *Thus,* ***emphysema can be thought of as resulting from insufficient wound repair*****.**

- With the **loss of elastic tissue** in the surrounding alveolar septa, radial traction on the small airways is reduced.
- As a result, they tend to collapse during expiration-an important cause of chronic airflow obstruction in severe emphysema.

Pathogenesis of Emphysema

- The protease-antiprotease hypothesis explains the effect of cigarette smoking in the production of centriacinar emphysema.




Pathogenesis of emphysema
Smoking
α-1 antitrypsin deficiency
Inflammatory cells
Epithelial cells
Mesenchymal cells
Cytokines
Proteases
ECM degradation
Apoptosis
Necrosis
Apoptosis
Impaired proliferation
Decreased contraction
Decreased matrix synthesis
Alveolar parenchymal destruction

GENETIC FACTORS

-Multiple genetic factors control the response to injury after smoking.

-The ***TGFB* gene** exhibits **polymorphisms** that influence susceptibility to the development of COPD by **regulating the response of mesenchymal cells to injury.**

with certain polymorphisms, mesenchymal cell response to TGF-β signaling is reduced, which results in inadequate repair of elastin injury caused by inhaled toxins

Genetic factors

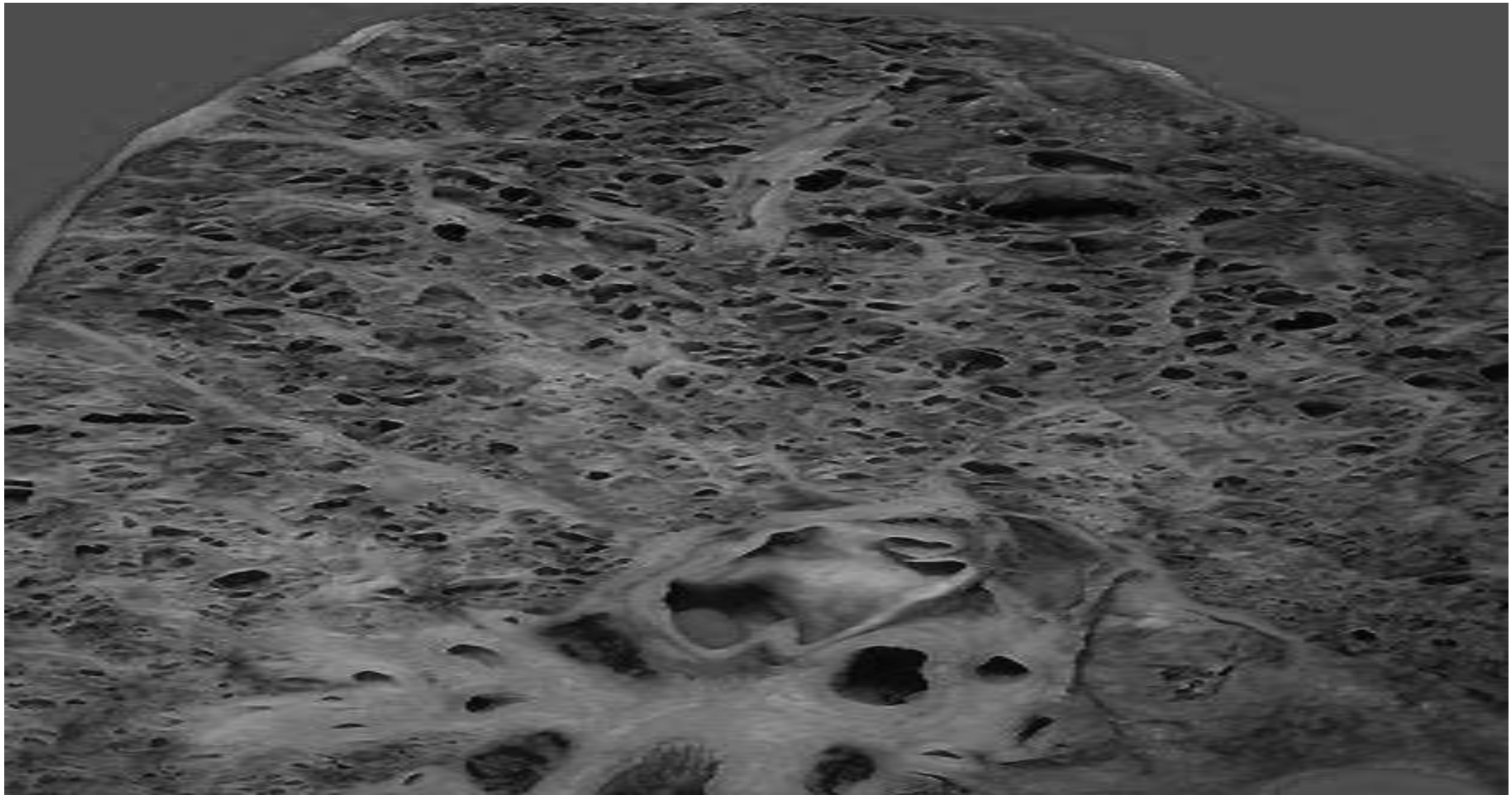
- metalloproteinases play a role: MMP-9 gene polymorphisms and higher levels of both MMP-9 and MMP-12 have been found in some emphysema patients.
- Moreover, MMP-12-deficient mice are protected from cigarette smoke-induced emphysema.

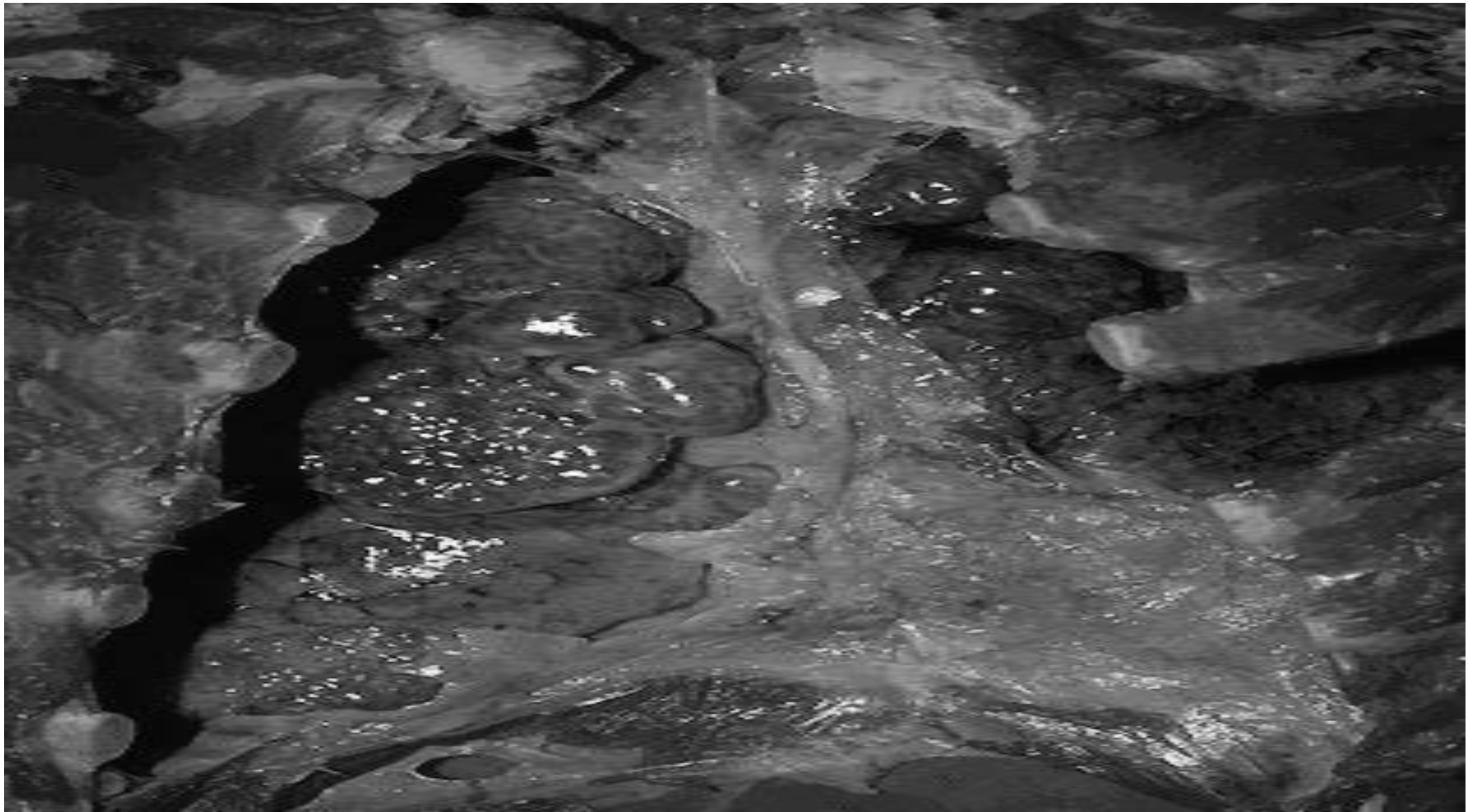
Histologic examination reveals :

a. Destruction of alveolar walls without fibrosis, leading to enlarged air spaces

b. The number of alveolar capillaries is diminished.

Emphysema





Clinical Features

- Dyspnea usually is the first symptom which begins insidiously but is steadily progressive.

-Weight loss is common and may be so severe as to suggest a hidden malignant tumor.

- The classic presentation in emphysema with no "bronchitic" component is one in which the patient is

a. Barrel-chested and dyspneic,

b. with obviously prolonged expiration,

c. Sitting forward in a hunched-over position, attempting to squeeze the air out of the lungs with each expiratory effort.

Clinical features:

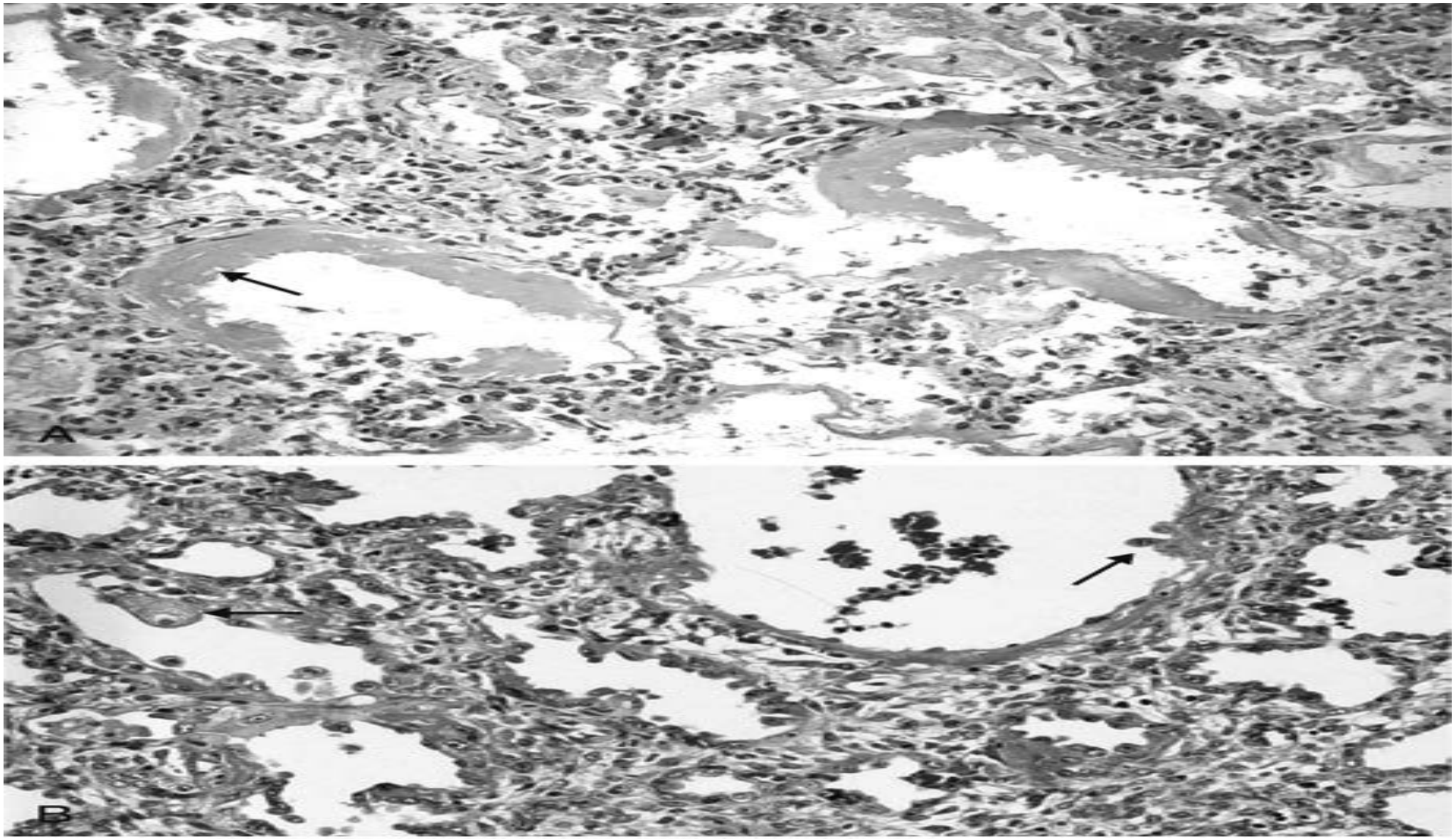
-Dyspnea and hyperventilation are prominent, so that until very late in the disease, gas exchange is adequate and blood gas values are relatively normal.

- Because of prominent dyspnea and adequate oxygenation of hemoglobin, these patients sometimes are called **"pink puffers**."

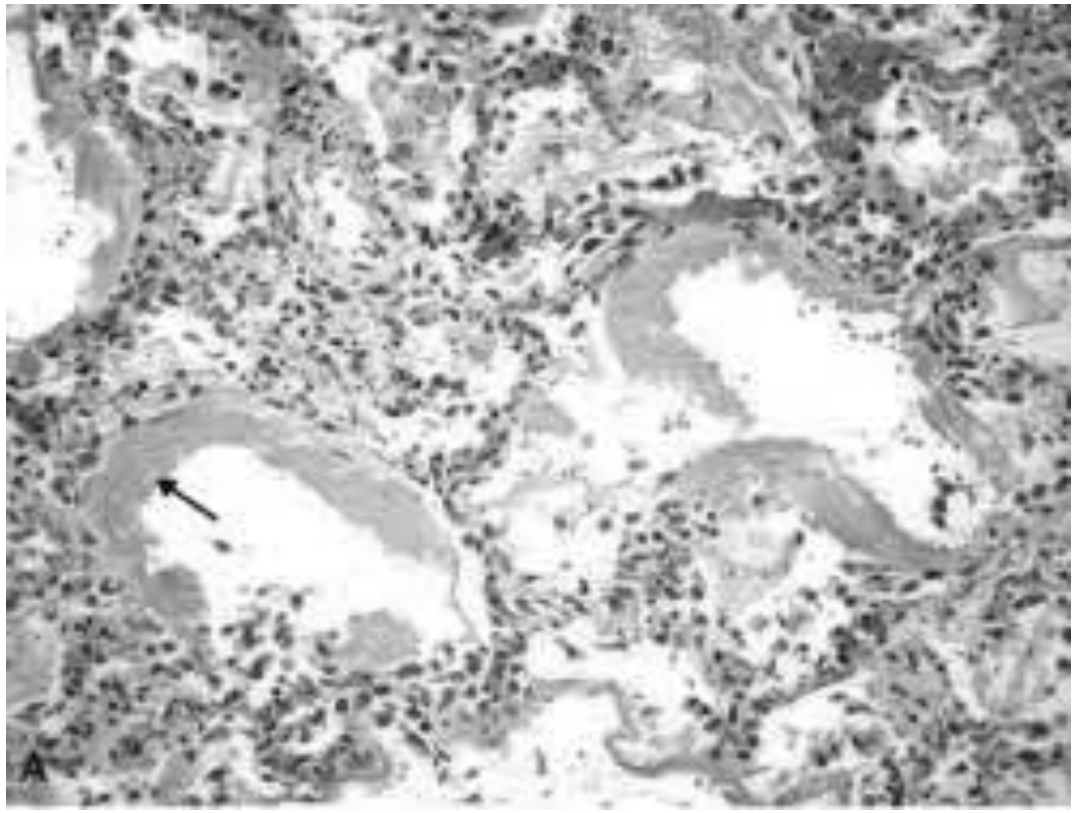
Pink puffers

Diseases of the respiratory system pictures

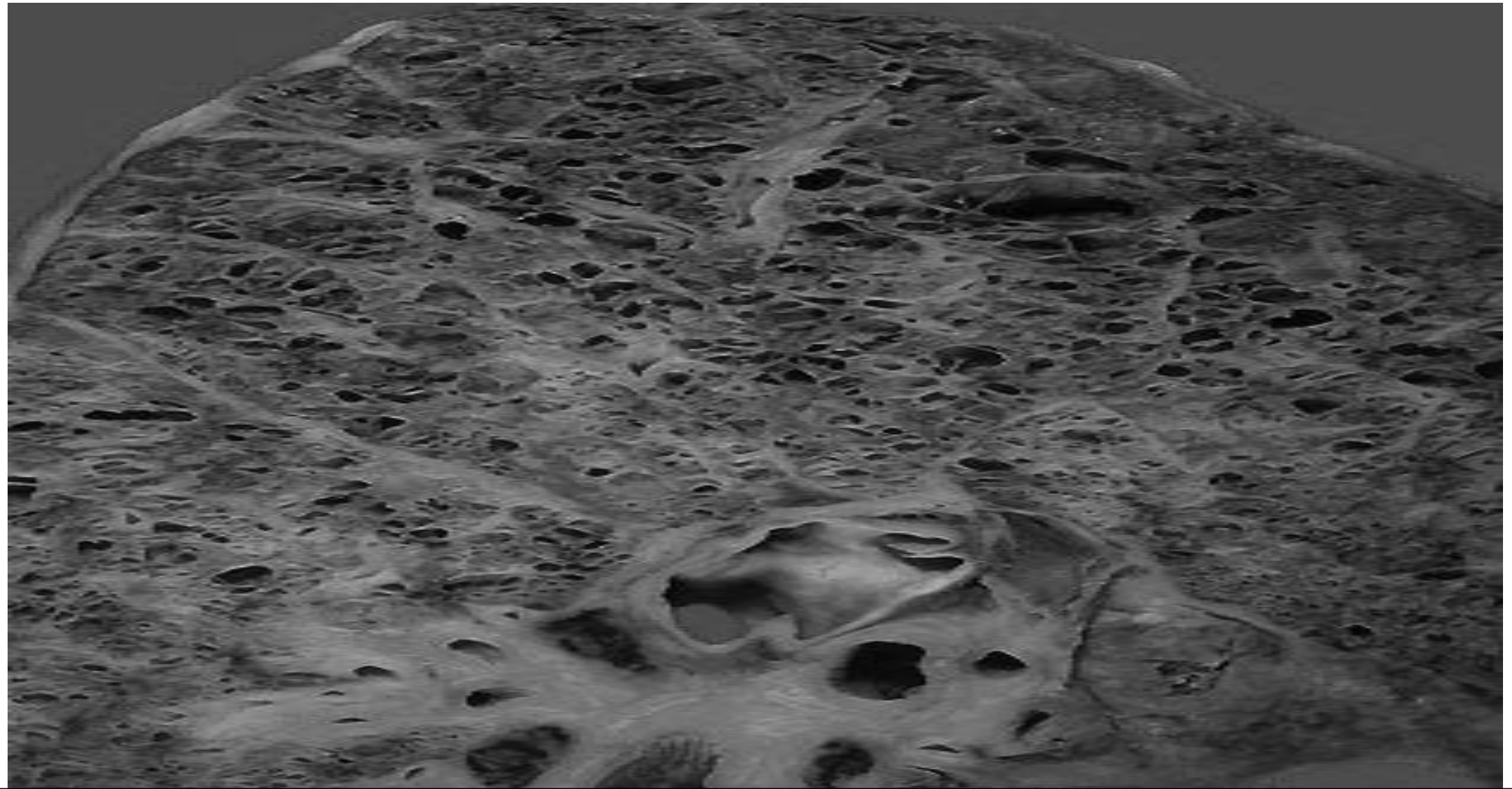
ARDS

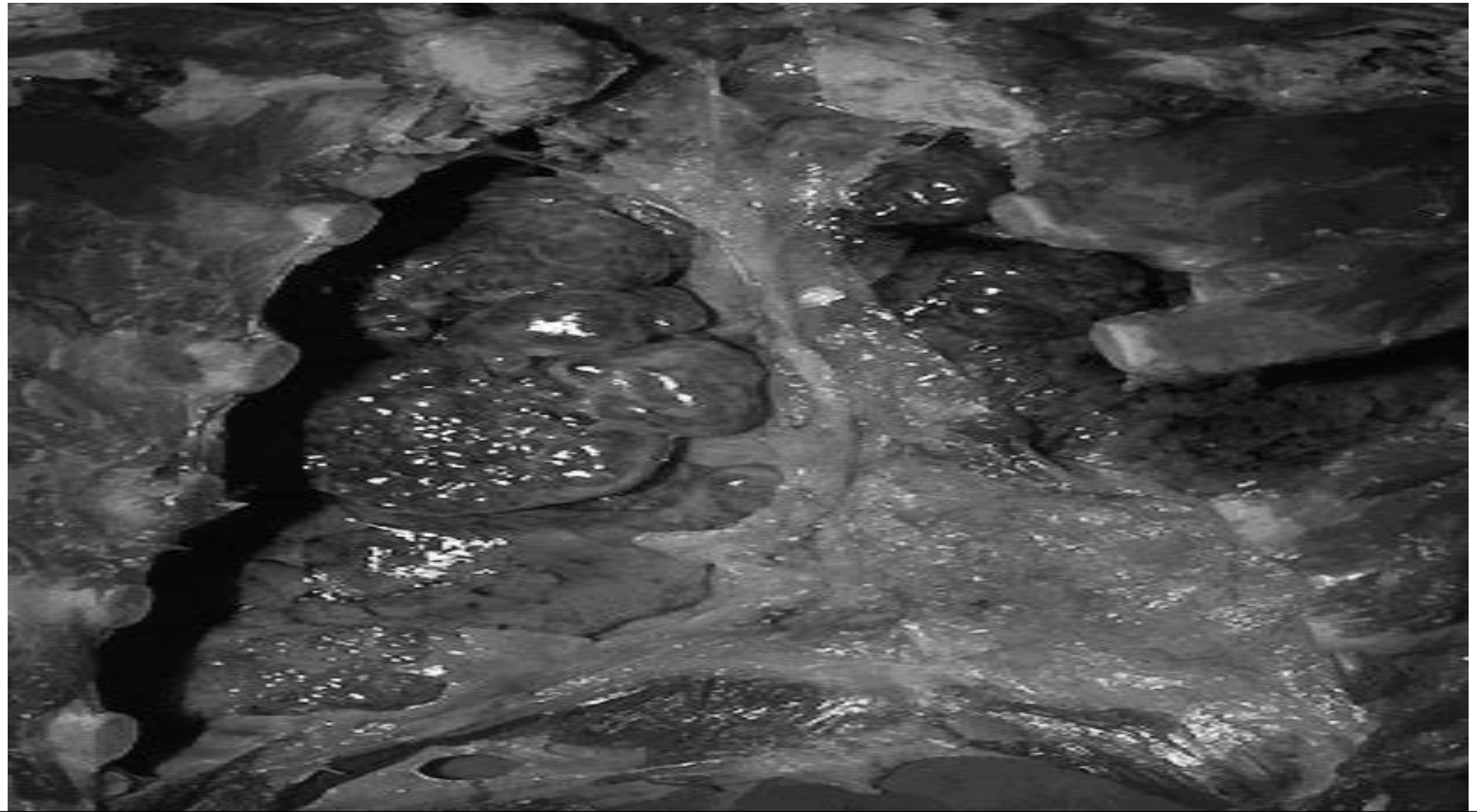


ARDS

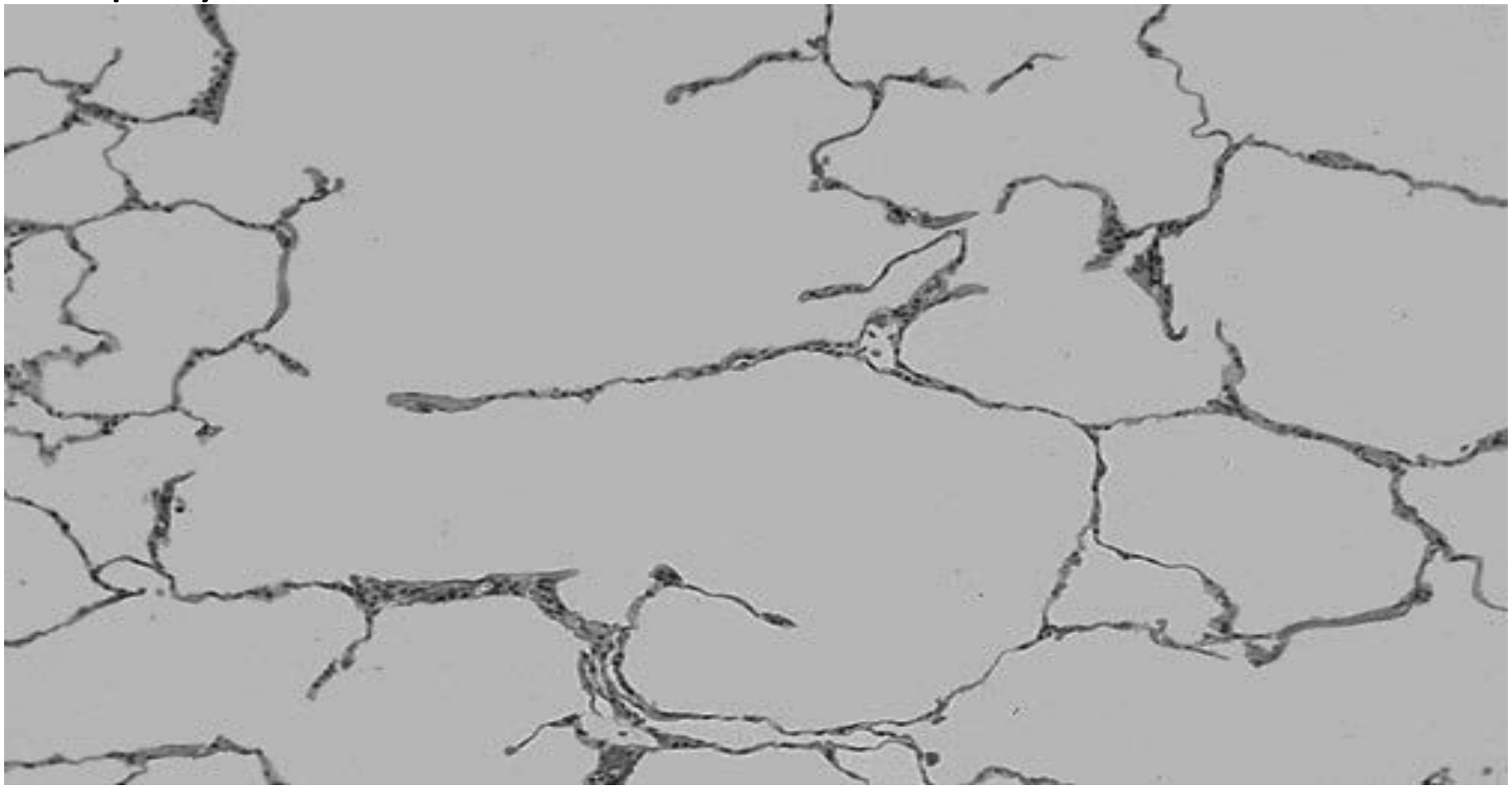


Emphysema





Emphysema



Pink puffers

Diseases of the respiratory system lecture 3

Dr Heyam Awad

FRCPath

CHRONIC BRONCHITIS/ definition

- The presence of a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.
- so: diagnosis is based on clinical criteria (remember that emphysema diagnosis is based on morphological features)

etiology

- Smoking.
- Air pollution

pathogenesis

- Smoking causes:
- 1. inflammation and fibrosis of trachea and bronchi. This inflammation is mediated by neutrophils, macrophages and lymphocytes.
- 2. hypertrophy of sub mucosal mucous secreting glands as well as goblet cell hyperplasia of smaller bronchi and bronchioles

- Changes in Point 2 in the previous slide result in increased mucous secretion…. Manifests clinically as productive cough

Note

- In the early stages of the disease, the productive cough raises mucoid sputum, but airflow is not obstructed (because ***large*** airways are affected and even narrowed, they are large enough for the inhalation and exhalation to remain within normal limits)

Obstructive features in chronic bronchitis are the result of:

1. ***Small airway disease –(chronic bronchiolitis)*** which is induced by:

a. Goblet cell metaplasia with mucous plugging of the bronchiolar lumen,

b. Inflammation,

c. Bronchiolar wall fibrosis,

2. ***Coexistent emphysema***

Note

- Small airway disease (chronic bronchiolitis) is an important component of early and relatively mild airflow obstruction,
- Significant airflow obstruction is almost always caused by coexistent emphysema

MORPHOLOGY

Gross:

- Hyperemia and swelling of the mucosal lining of the large airways.
- The mucosa of bronchi is covered by a layer of mucinous or mucopurulent secretions

Morphology/ microscopic features

- Enlargement of the mucus-secreting glands in trachea and large bronchi.
- The magnitude of the increase in size is assessed by the ratio of the thickness of the submucosal gland layer to that of the bronchial wall (the Reid index-normally 0.4).

Clinical Features

- In patients with chronic bronchitis, a **prominent cough and the production of sputum** may persist indefinitely without ventilatory dysfunction
- Some patients develop significant COPD with **outflow obstruction**.

- Patients have :hypercapnia, hypoxemia, and (in severe cases) cyanosis (hence the term "blue bloaters").
- Hypercapnea: due to expiratory obstruction causing CO_2 retention
- Hypoxemia: due to ventilation/perfusion mismatch that happens due to increased cardiac output.

Complications of COPD (emphysema and chronic bronchitis)

- Pneumonia and recurrent respiratory infections
- Respiratory fiailure
- Right sided cardiac failure: cor pulmonale = cardiac failure secondary to lung disease
- Bronchiectasis.

Bronchiectasis

- permanent dilation of bronchi and bronchioles caused by destruction of the muscle and the elastic tissue, resulting from or associated with chronic necrotizing infections.
- It is not a primary disease but secondary to persisting infection or obstruction caused by a variety of conditions.

The Predisposing conditions include:

1. Bronchial obstruction and common causes are :

a- Tumors, foreign bodies, and impaction of mucus.

- With these conditions, the bronchiectasis is localized to the obstructed lung segment.

b- Bronchiectasis can also complicate atopic asthma and chronic bronchitis.

3. *Necrotizing,* or *suppurative, pneumonia,* particularly with *Staphylococcus aureus* or *Klebsiella* spp., may predispose affected patients to development of bronchiectasis.

Note: Posttuberculosis bronchiectasis continues to be a significant cause of morbidity in endemic areas.

PATHOGENESIS of bronchiectasis:

- Two processes are crucial in pathogenesis : obstruction and chronic infection and **either of these may come first.**
- Normal clearance mechanisms are hampered by obstruction, so secondary infection soon follows conversely, chronic infection over time causes damage to ; bronchial walls, leading to weakening and dilation.

1- For example, obstruction caused by a primary lung cancer or a foreign body impairs clearance of secretions, providing substrate for superimposed infection and the resultant inflammatory damage to the bronchial wall and the accumulating exudate further distend the airways, leading to irreversible dilation.

2- Conversely, a persistent necrotizing inflammation in the bronchi or bronchioles may cause obstructive secretions, inflammation in the wall (with peribronchial fibrosis and traction on the walls), and eventually the train of events .

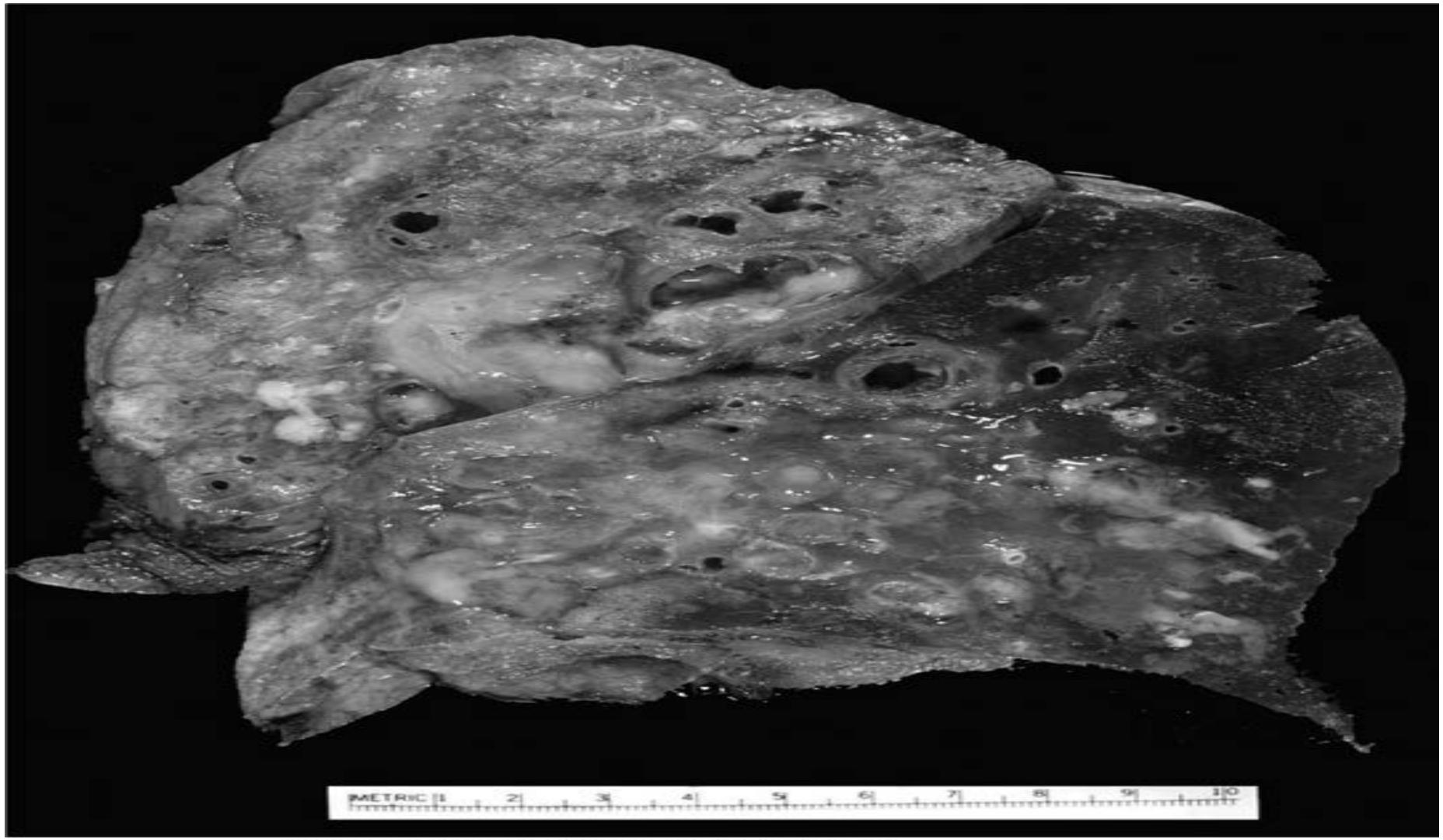
MORPHOLOGY

- Bronchiectasis usually affects the **lower lobes bilaterally,**
- When caused by tumors or foreign bodies the involvement may be localized to a single segment and the most severe involvement is in the more distal bronchi and bronchioles.

Gross:

- The airways may be **dilated** to as much as four times their usual diameter and on gross examination of the lung can be followed almost to the pleural surfaces
- By contrast, in normal lungs, the bronchioles cannot be followed by ordinary gross examination beyond a point 2 to 3 cm from the pleural surfaces

Bronchiectasis



Clinical Features

- severe, persistent cough with expectoration of mucopurulent sputum.
- The sputum may contain flecks of blood; frank hemoptysis can occur.

.

- Symptoms often are episodic and are precipitated by upper respiratory tract infections or the introduction of new pathogenic agents.
- **Clubbing of the fingers** may develop

Diseases of the respiratory system lecture 4

Dr Heyam Awad

FRCPath

Bronchial asthma

- Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or early in the morning.

Asthma is characterized by:

1. Intermittent and reversible airway obstruction,
2. Chronic bronchial inflammation with eosinophils
3. Bronchial smooth muscle cell hypertrophy and hyperreactivity,
4. Increased mucus secretion.

Types of asthma

1. Atopic Asthma

- This is the most common type of asthma,
- Usually beginning in childhood,
- Is a classic example of type I IgE-mediated hypersensitivity reaction
- A positive family history of atopy and/or asthma is common,
- Asthmatic attacks are often preceded by allergic rhinitis, urticaria, or eczema.
- The disease is triggered by environmental antigens, such as dusts, pollen, and foods

-A skin test with the offending antigen results in an immediate wheal-and-flare reaction.

- Atopic asthma also can be diagnosed based on serum radioallergosorbent tests (RASTs) that identify the presence of IgE specific for a panel of allergens

Types of asthma

2. Non-Atopic Asthma

- No evidence of allergen sensitization,
- Skin test results usually are negative.
-A positive family history of asthma is less common than in atopic sthma.
- Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus) and inhaled air pollutants (e.g., sulfur dioxide,) are common triggers.
- It is thought that virus-induced inflammation of the respiratory mucosa lowers the threshold of the subepithelial vagal receptors to irritants.

Note:

-Although the connections are not well understood, the ultimate humoral and cellular mediators of airway obstruction (e.g., eosinophils) are common to both atopic and nonatopic variants of asthma, so they are treated in a similar way.

Types of asthma

3. Drug-Induced Asthma

- Several pharmacologic agents provoke asthma--***aspirin*** being the most striking example

-Patients with aspirin sensitivity present with recurrent rhinitis and nasal polyps, urticaria, and bronchospasm

-The precise mechanism remains unknown, but it is presumed that aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thereby shifting the balance of production toward leukotrienes that cause bronchial spasm.

PATHOGENESIS

- The major etiologic factors of asthma are:

1. Genetic predisposition to type I hypersensitivity (atopy)
2. Acute and chronic airway inflammation,
3. and bronchial hyperresponsiveness to a variety of stimuli.

pathogenesis

Role of type 2 helper T (T_H2) cells may be critical to the pathogenesis of asthma.

- The classic atopic form of asthma is associated with an excessive T_H2 reaction against environmental antigens.

T helper 2 ells

Cytokines produced by T_H2 cells account for most of the features of asthma

a.IL-4 stimulates IgE production,

b. IL-5 activates eosinophils,

c. IL-13 stimulates mucus production

IgE role

- IgE coats submucosal mast cells, which, on exposure to **allergen, release granule contents.**

- **This induces two waves of reaction**: an early (immediate) phase and a late phase

- **- Early reaction is dominated by**

a. Bronchoconstriction, triggered by direct stimulation of subepithelial vagal receptors

b. Increased mucus production and

c. Vasodilation.

ALL THESE EFFECTS ARE CAUSED BY MEDIATORS MAINLY HISTAMINE

The late-phase reaction consists of inflammation, with

a. Activation of eosinophils, neutrophils, and T cells.

b. Epithelial cells are activated to produce chemokines that promote recruitment of more T_H2 cells and eosinophils (including eotaxin, a potent chemoattractant and activator of eosinophils),

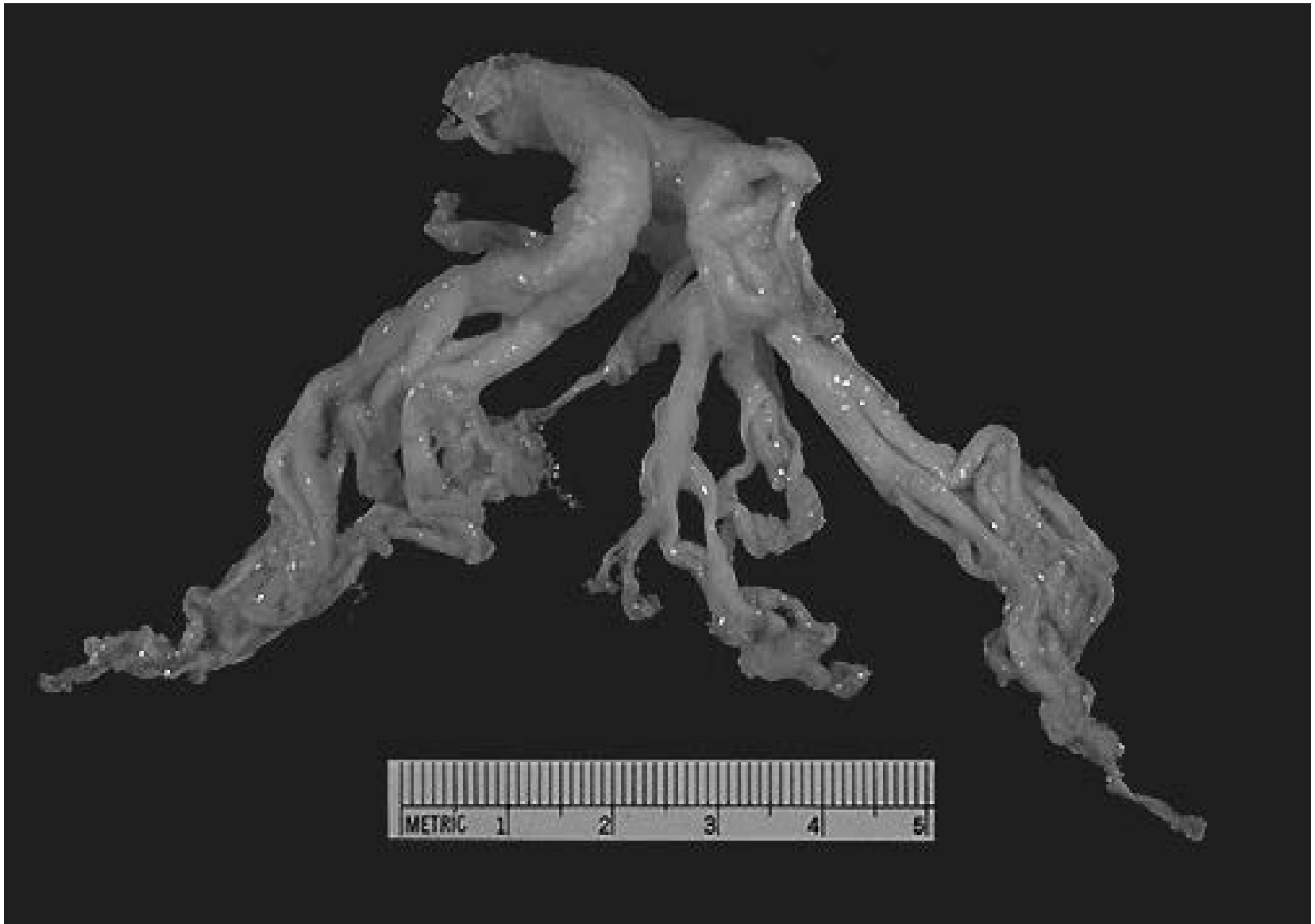
- Repeated bouts of inflammation lead to structural changes in the bronchial wall, referred to as ***airway remodeling*****:**

1. Hypertrophy of bronchial smooth muscle and mucus glands,
2. Deposition of subepithelial collagen.

Gross:

- The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick, mucous plugs.

Mucus plug of Asthma



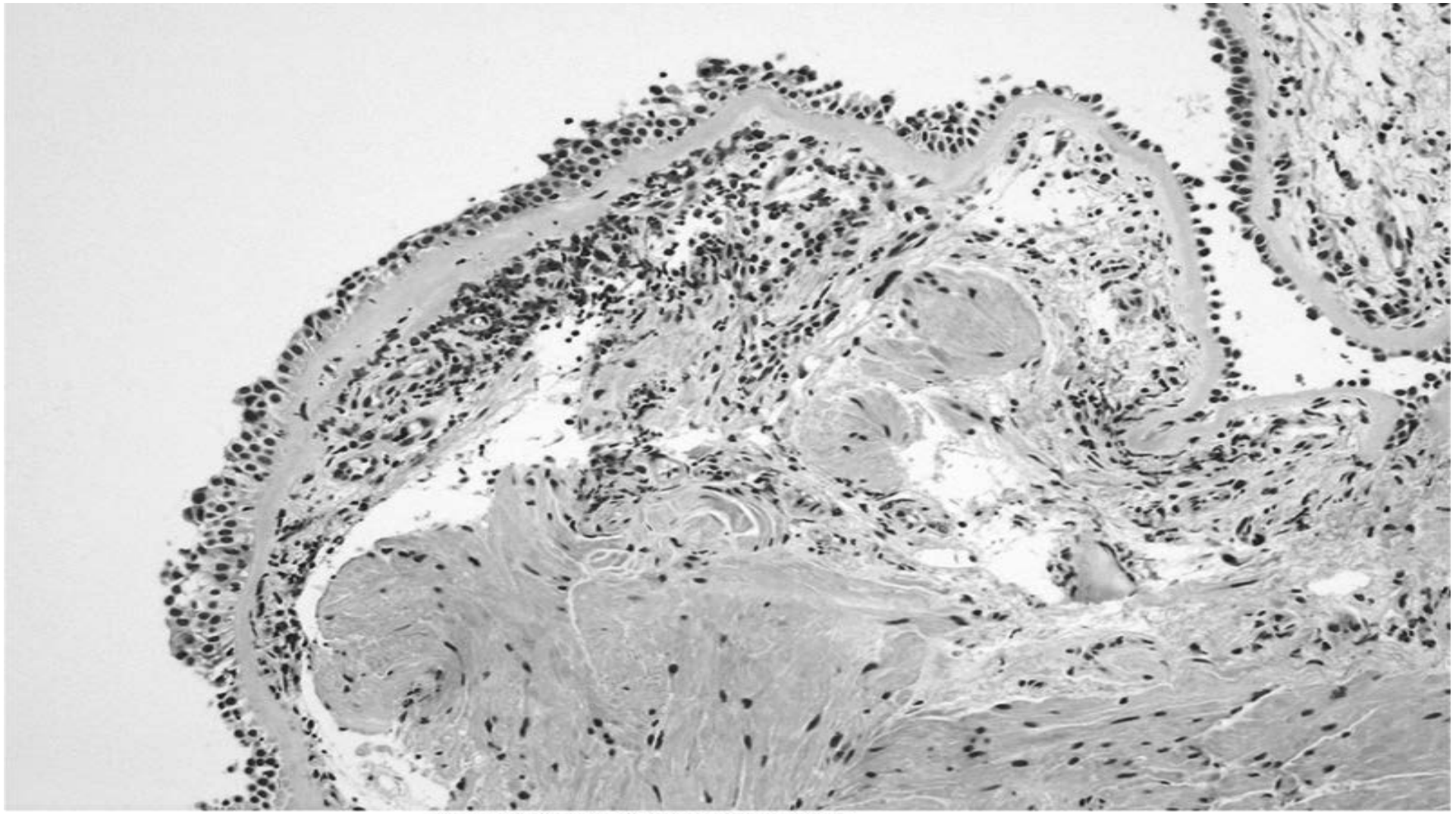
Histologically,

a. The mucous plugs contain whorls of shed epithelium (Curschmann spirals).

b. Numerous eosinophils

c. Charcot-Leyden crystals (collections of crystalloids made up of eosinophil proteins) in the mucus.

Asthma



Airway remodeling," include

a. Thickening of airway wall Sub-basement membrane fibrosis

b. Increased vascularity in submucosa

c. An increase in size of the submucosal glands and goblet cell metaplasia of the airway Epithelium

d.Hypertrophy and/or hyperplasia of the bronchial muscles

- Asthma is a complex genetic disorder in which multiple susceptibility genes interact with environmental factors to initiate the pathologic reaction.
- There is significant variation in the expression of these genes and in the combinations of polymorphisms that effect the immune response or tissue remodeling.

Clinical Features

- An attack of asthma is characterized by severe dyspnea with wheezing; the chief difficulty lies in expiration.

.

- Occasionally a severe paroxysm occurs that does not respond to therapy and persists for days and even weeks (*status asthmaticus*).

Diseases of the respiratory system lecture 5

Dr Heyam Awad

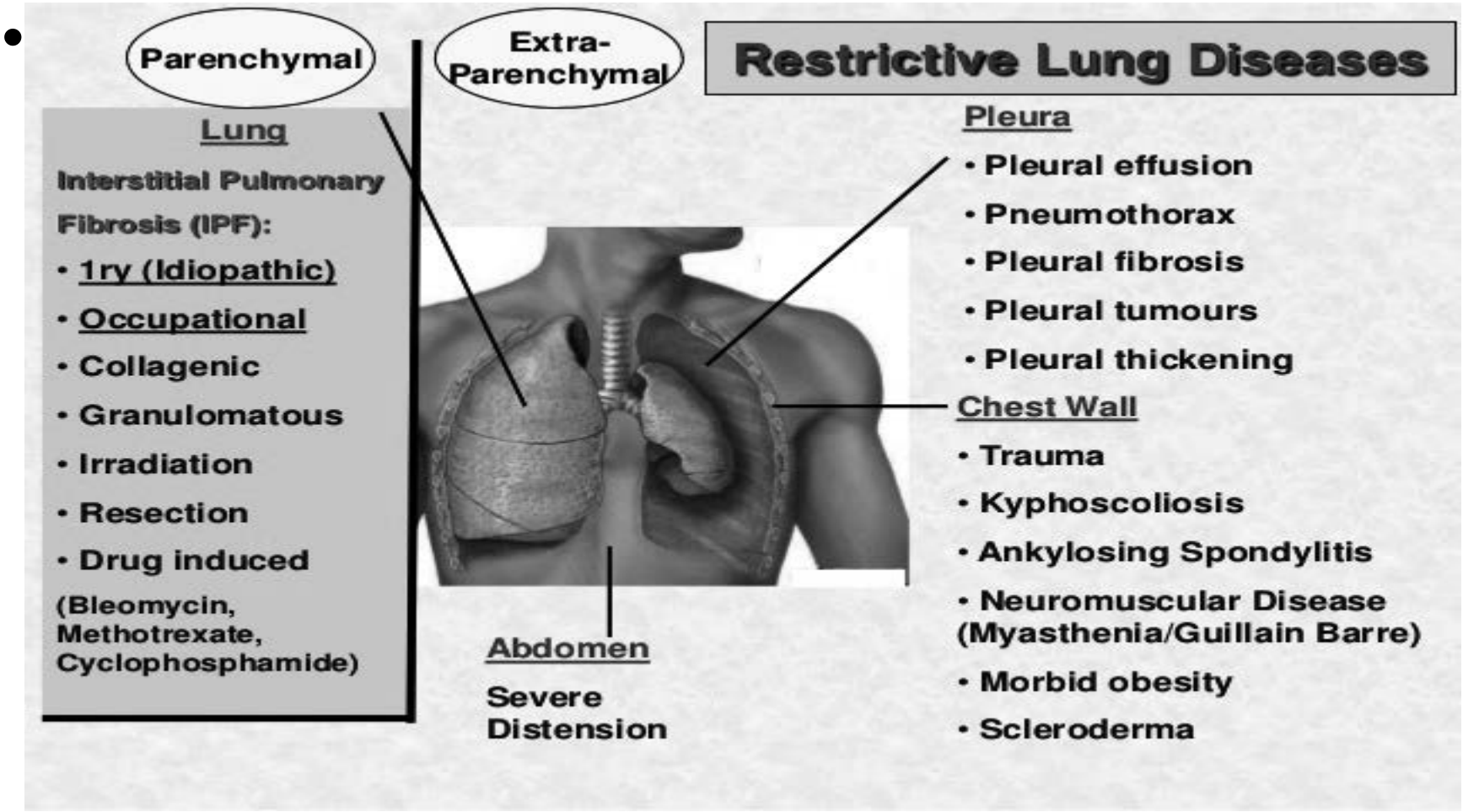
FRCPath

Restrictive lung diseases

- Are a group of disorders characterized by bilateral, patchy, chronic involvement of the lung connective tissue, mainly the interstitium in the alveolar walls.
- The hallmark feature of these disorders is reduced compliance (i.e., more pressure is required to expand the lungs because they are stiff), which in turn necessitates increased effort of breathing (dyspnea).
- Chest radiographs show diffuse infiltration by small nodules, irregular lines, or "ground-glass shadows

- With progression, patients can develop respiratory failure, and pulmonary hypertension and cor pulmonale
- Advanced forms of these diseases may be difficult to differentiate because they result in scarring and gross destruction of the lung, referred to as "honeycomb" lung.

Restrictive lung diseases

- 

- NOTE: ARDS is an acute restrictive lung disease

Restrictive lung diseases of primary lung etiology

I. Granulomatous diseases : mainly sarcoidosis

2. Fibrosing diseases

2a. IPF

2b. Nonspecific interstitial pneumonia

2c. Cryptognic organizing pneumonia

2d. Pneumoconioses

2e. Drug and radiation induced fibrosis

- IPF

= Idiopathic pulmonary fibrosis, 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.

IPF

- 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 are 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

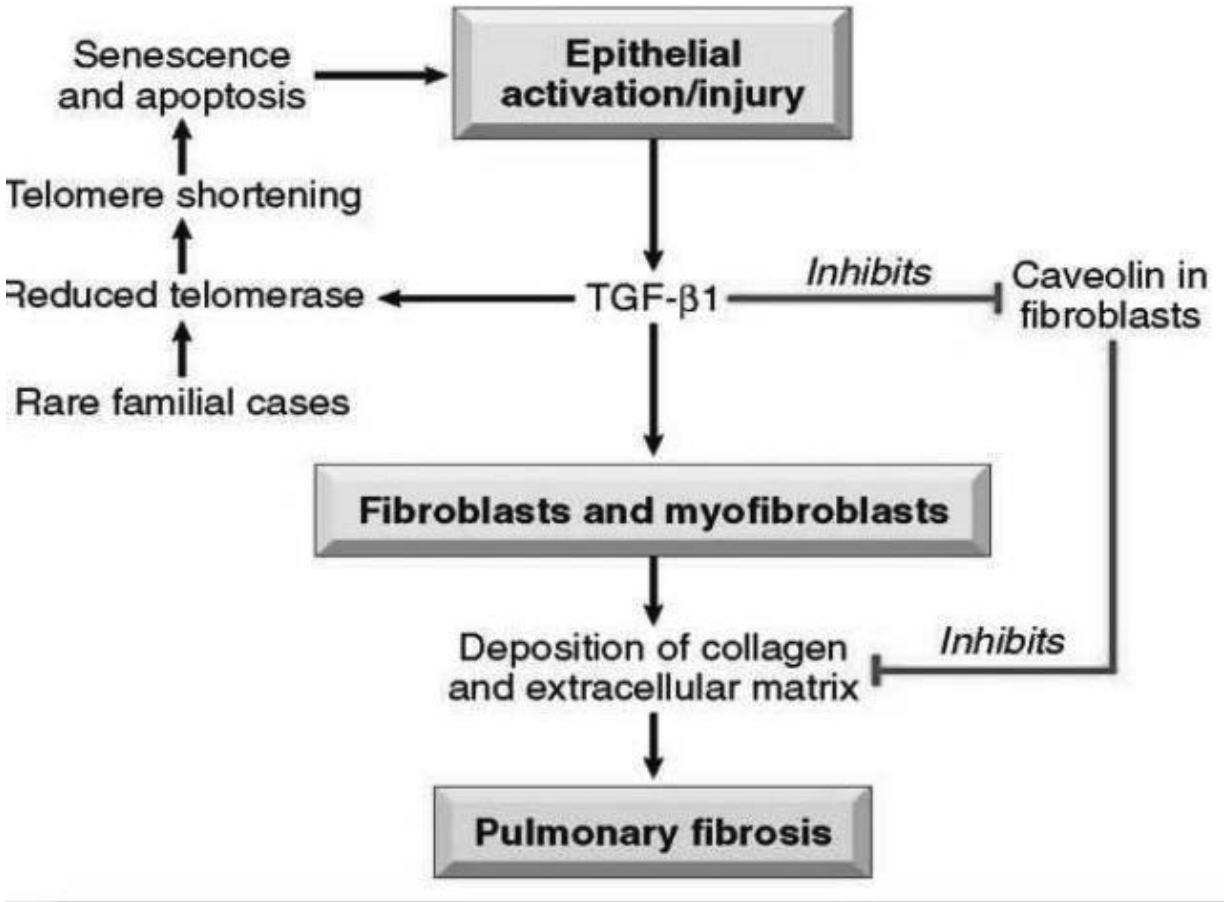
- IPF is caused by "repeated cycles" of epithelial activation/injury by unidentified agent
- inflammation and induction of T_H2 type T cell response with eosinophils, mast cells, IL-4, and IL-13 in the lesions.
- Alternatively activated macrophages (M2) are important in its pathogenesis
- Abnormal epithelial repair at the sites of damage and inflammation gives rise to exuberant fibroblastic or myofibroblastic proliferation leading to the characteristic fibroblastic foci.

Pathogenesis/ continued

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 .

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

IPF


Senescence and apoptosis
Epithelial activation/injury
Telomere shortening
Reduced telomerase
TGF-β1
Inhibits
Caveolin in fibroblasts
Rare familial cases
Fibroblasts and myofibroblasts
Deposition of collagen and extracellular matrix
Inhibits
Pulmonary fibrosis

MORPHOLOGY

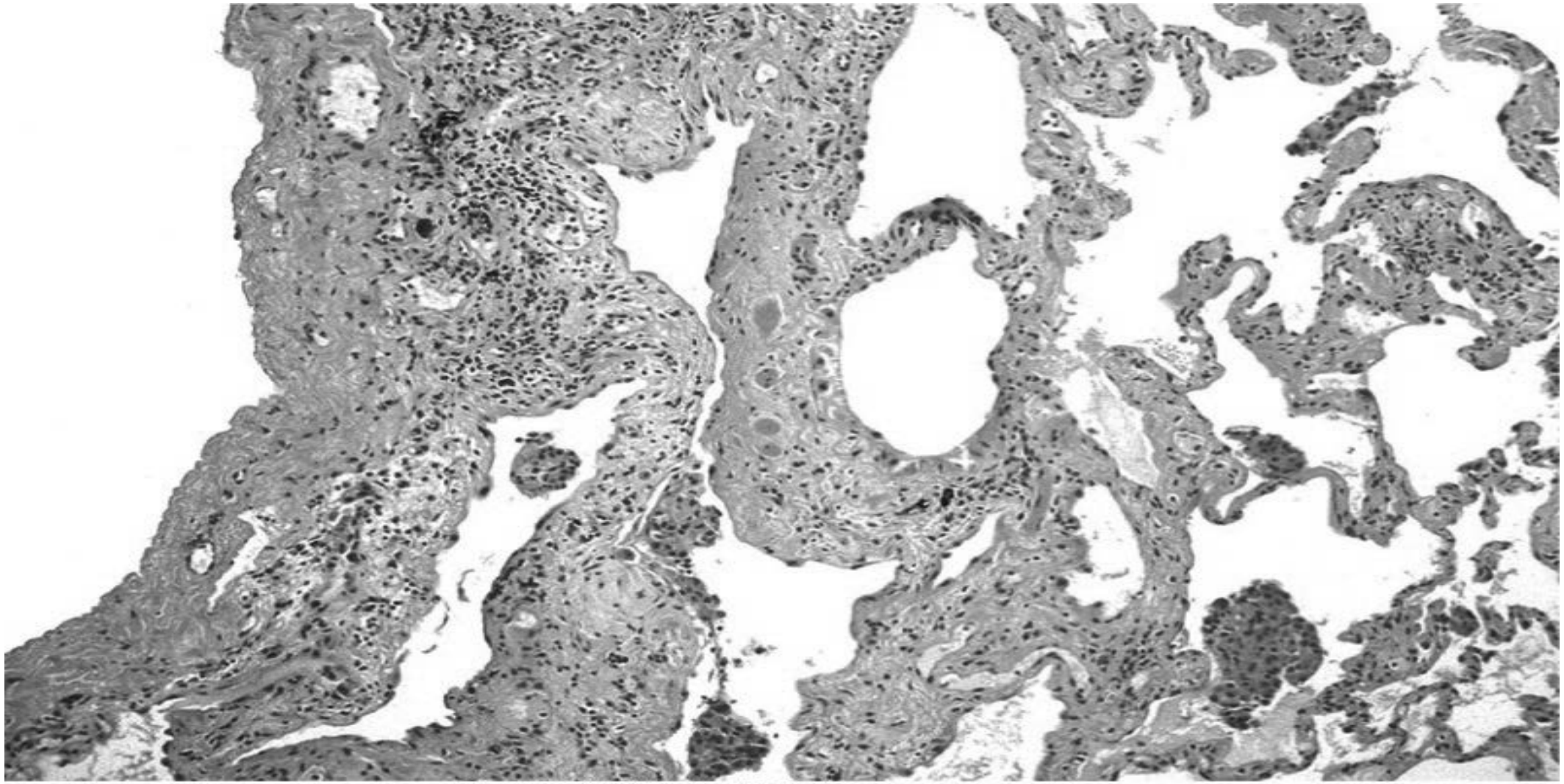
- The pattern of fibrosis in IPF is referred to as usual interstitial pneumonia (UIP)

-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



Clinical fatures

- Insidious onset
- Nonproductive cough and progressive dyspnea
- Cyanosis and cor pulmonale can develop
- Poor outcome, patients survive 3 years only
- Only hope: lung transplantation

Nonspecific interstitial pneumonia

- Chronic, bilateral interstitial disease of unknown etiology
- Has a better prognosis than IPF
- Cellular OR fibrosing pattern on microscopy.. The 2 patterns do not coexist

Cryptogenic organizing pneumonia

- = BOOP = bronchiolitis obliterans organizing pneumonia
- Unknown etiology
- Histologically: polypoid plugs of loose organizing connective tissue within alveoli, alveolar ducts and bronchioles
- The fibrosis present is all of the same age
- Some patients recover spontaneously, others need 6 months of steroid treatment
- Good prognosis

Pulmonary involvement by collagen vascular diseases

- Collagen vascular diseases: systemic diseases that include scleroderma and SLE
- Lung fibrosis can be present in such diseases
- Outcome depends on the underlying disease

Drug and radiation induced fibrosis

- Bleomycin is a chemotherapeutic drug that can cause pulmonary fibrosis
- Amiodarone is an antiarrhythmic drug also can cause fibrosis
- Chronic radiation pneumonitis after radiotherapy is characterized by fibrosis

Respiratory 6 pneumoconioses

Dr H AWAD

FRCPath

Mineral dust pneumoconiosis

- Pneumoconiosis = non- neoplastic lung reactions to inhalation of mineral dust

- Mineral dust pneumoconioses are usually related to occupational exposure

- Mineral dust pneumoconioses : related to coal dust, silica and asbestos

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

PATHOGENESIS :

The reaction of the lung to mineral dusts depends on their size ,shape, solubility, and reactivity as well as purity, concentration and duration of exposure.

Effects 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

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

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

pathogenesis

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

a. 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.

Pathogenesis/ continued

Some of the inhaled particles may reach the lymphatics either by direct drainage or within migrating macrophages and thereby initiate an immune response to components of the particulates and/or to self-proteins that are modified by the particles and this then leads to an amplification and extension of the local reaction.

Note:

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

Coal workers pneumoconiosis

- Coal is mainly carbon
- Coal mine dust contains also: trace metals, inorganic minerals and silica

Coal workers pneumoconiosis: three types

- Asymptomatic anthracosis : pigment accumulates without any reaction
- Simple coal workers pneumoconiosis (CWP) : accumulation of macrophages with little or no pulmonary dysfunction. There is minimal fibrosis.
- Complicated CWP = progressive massive fibrosis (PMF)= extensive fibrosis with compromised lung function

- Each can progress to the more severe form

NOTE

- Less than 10% of simple CWP progress to PMF

- Carbon is relatively inert… so lung damage is less than that of silicosis or asbestosis.

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 .

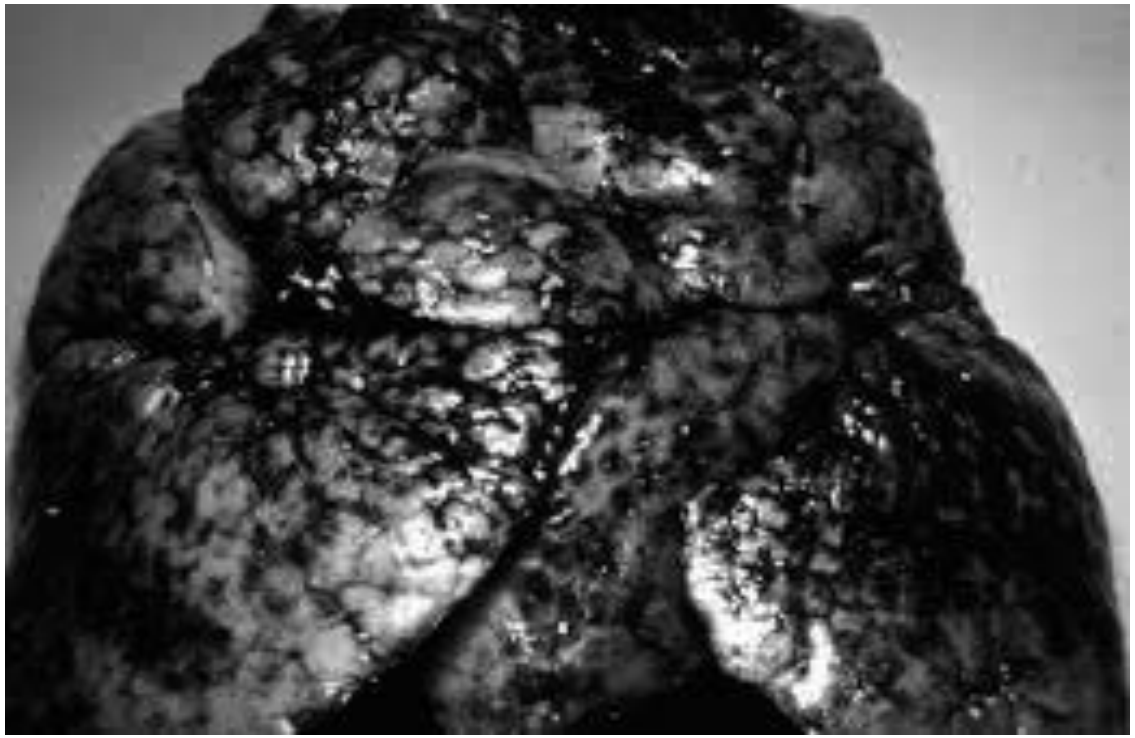
Morphology/Pulmonary anthracosis

- Carbon pigments engulfed by alveolar or interstitial macrophages
- These macrophages accumulate along the lymphatic vessels or in the lymph nodes
- Also seen in smokers and urban dwellers

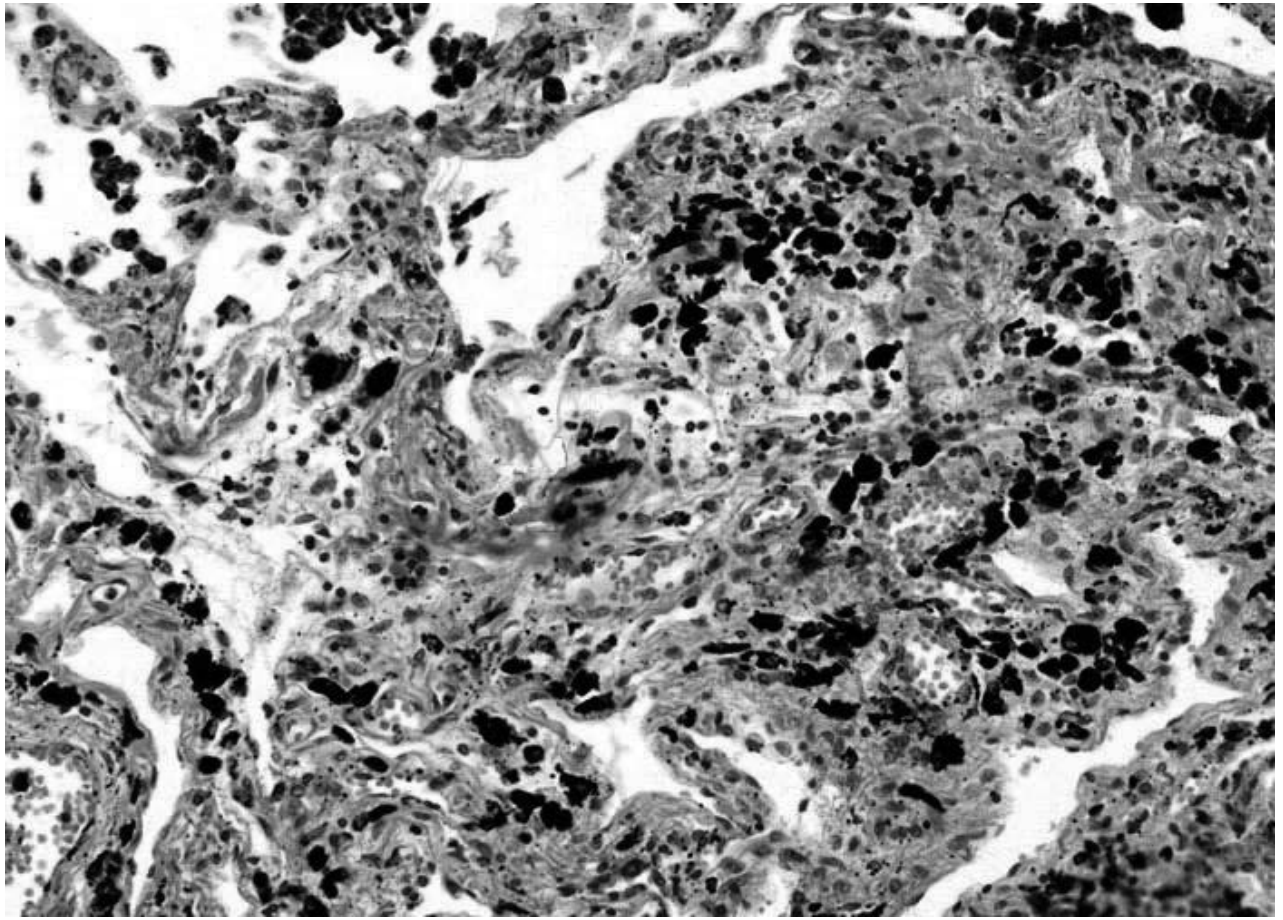
Note:

- 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

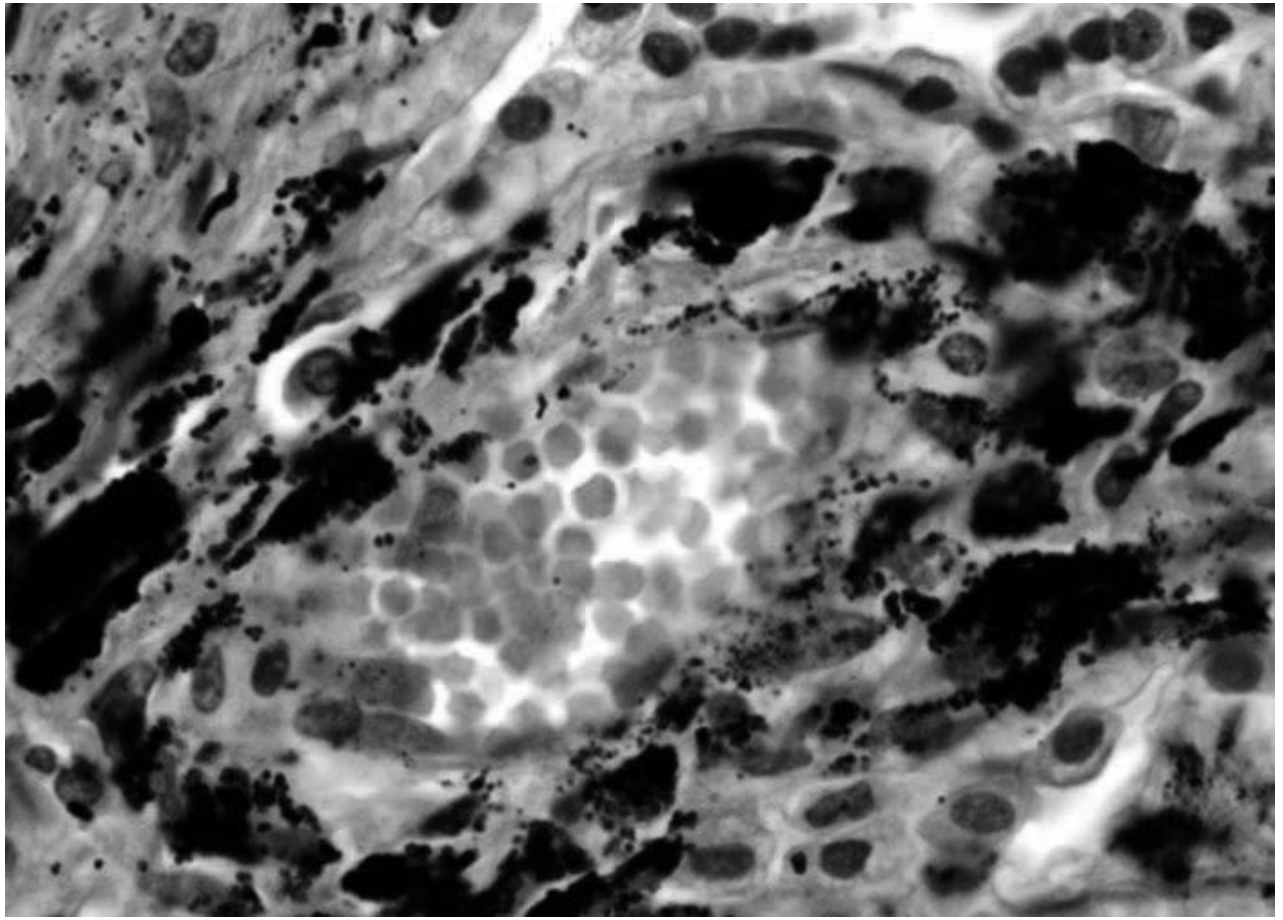
Anthracosis: accumulation of carbon pigment



anthracosis

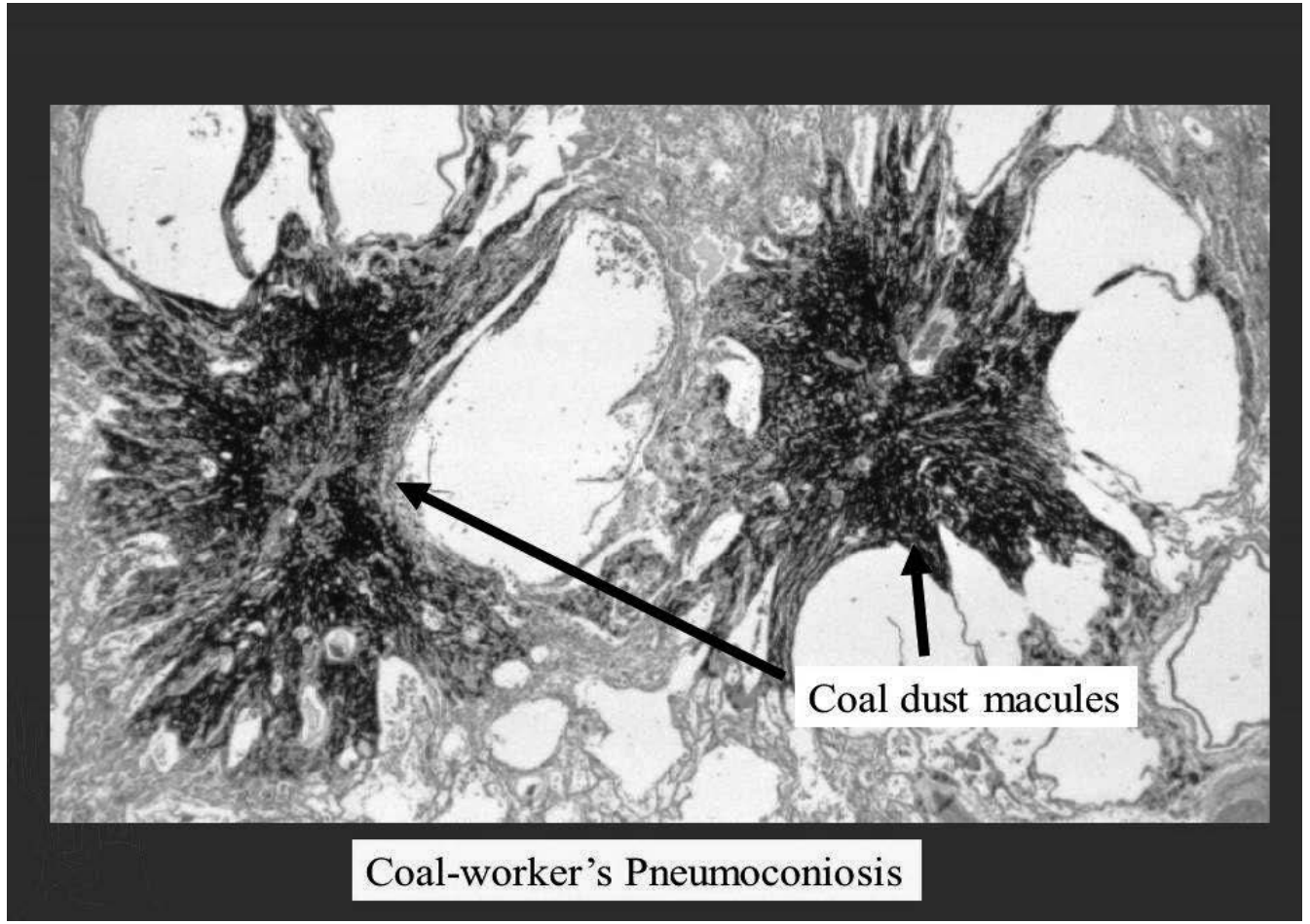


anthracosis



Simple CWP

- Characterized by coal macules and coal nodules
- Coal macules: carbon laden macrophages and small amount of collagen fibers arranged in a delicate network
- These are found mainly in the upper lung lobes
- Centrilobular emphysema can complicate these macules
- If the macules are large they are called coal nodules


Coal dust macules
Coal-worker's Pneumoconiosis

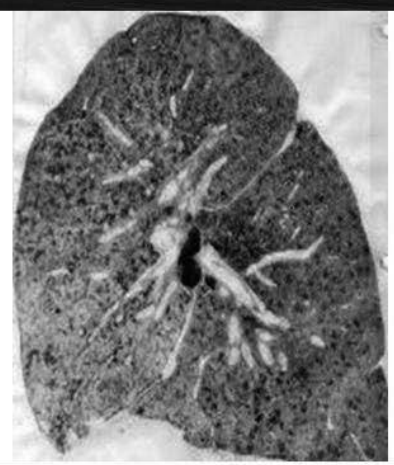
Complicated CWP= PMF

- There is coalescence of coal nodules .
- Multiple black scars
- Histologically: dense collagen and pigment
- This needs several years of exposure to develop

Coal worker's pneumoconiosis (CWP)

The simple form

- Focal aggregations of coal dust-laden macrophages (coal macules)
- Patients have slight cough and blackish sputum



The complicated form

- Occurs after many years of underground mine work.
- fibrous scarring appears (complicated CWP) also callled progressive massive fibrosis PMF

Clinical features

- Simple CWP is usually a benign disease that produces little effect on lung function
- PMF : pulmonary dysfunction, pulmonary hypertension and cor pulmonale
- Once PMF developed: it progresses even without additional exposure
- No increased risk of lung cancer in relation to coal exposure.

silicosis

silicosis

- The most prevalent chronic occupational disease in the world. Caused by inhalation of crystalline silica mostly in occupational settings
- Silica (Silicon dioxide)is a chemical compound that is an oxide of silicon with the chemical formula SiO_2.
- Silica is most commonly found in nature as quartz and is a major constituent of sand.

Uses of silica

- Glass industry
- Sandblasting : the process used to clean a surface by means of an abrasive such as sand
- Hard rock mining


THROW AWAY
"DO NOT EAT"
DESICCANT
SILICA
GEL
THROW AWAY
"DO NOT EAT"

sandblasting

Silica Forms

a. Crystalline (such as quartz) are the most toxic and fibrogenic .

NOTE: quartz is most commonly implicated in silicosis and when mixed with other minerals, it has a reduced fibrogenic effect (this is an example of importance of purity of the dust!!)

b. Amorphous forms : less fibrogenic

MORPHOLOGY

Silicotic nodules :- Characterized grossly in early stages by barely palpable pale-to-blackened (if coal dust is present) nodules in the upper zones of the lungs.

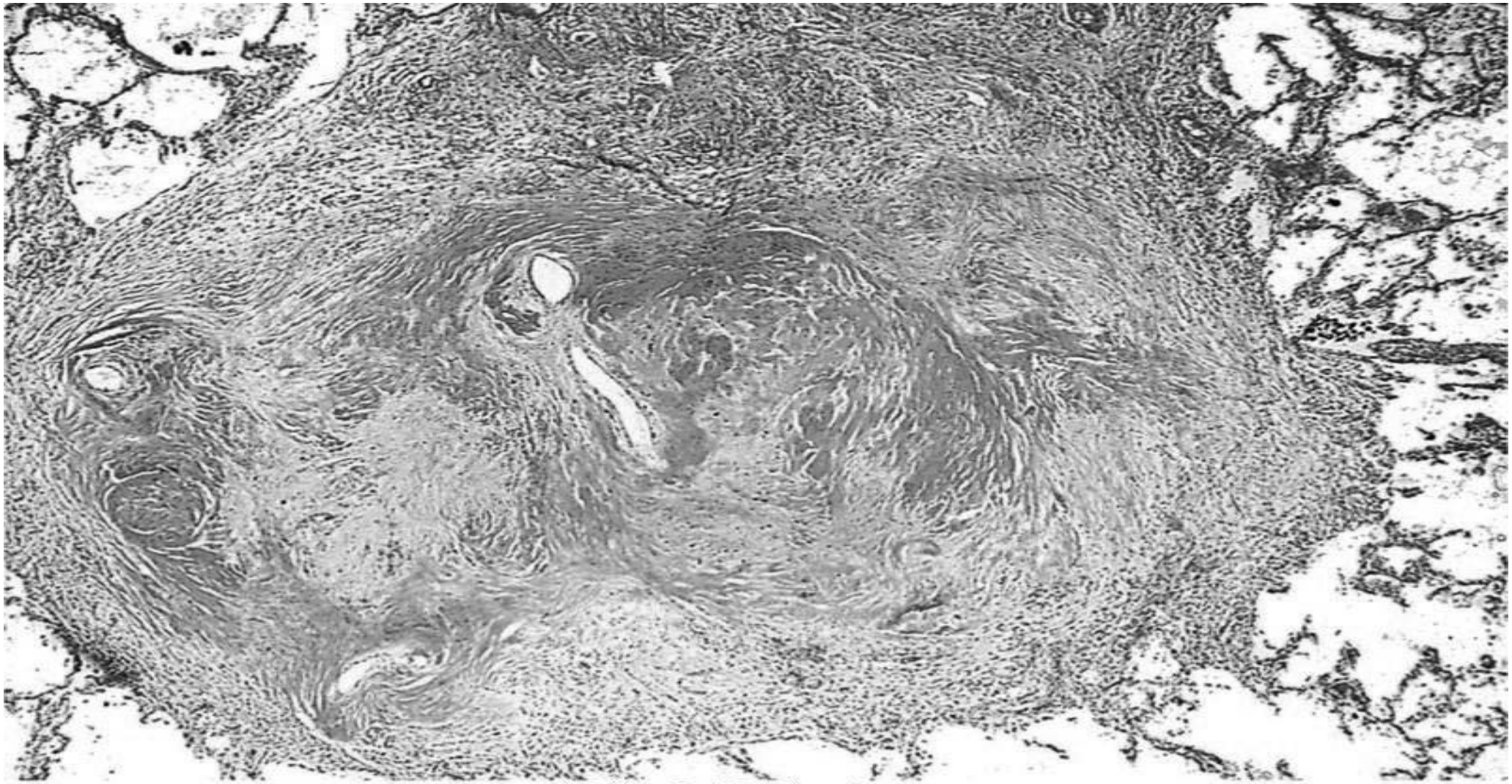
Microscopically,

- concentrically arranged hyalinized collagen fibers surrounding amorphous center
- this “whorled" appearance of the collagen fibers is distinctive for silicosis

Morphology:

- As the disease progresses, the individual nodules may coalesce into hard, collagenous scars, with eventual progression to PMF
- Fibrotic lesions may also occur in the hilar lymph nodes and pleura.

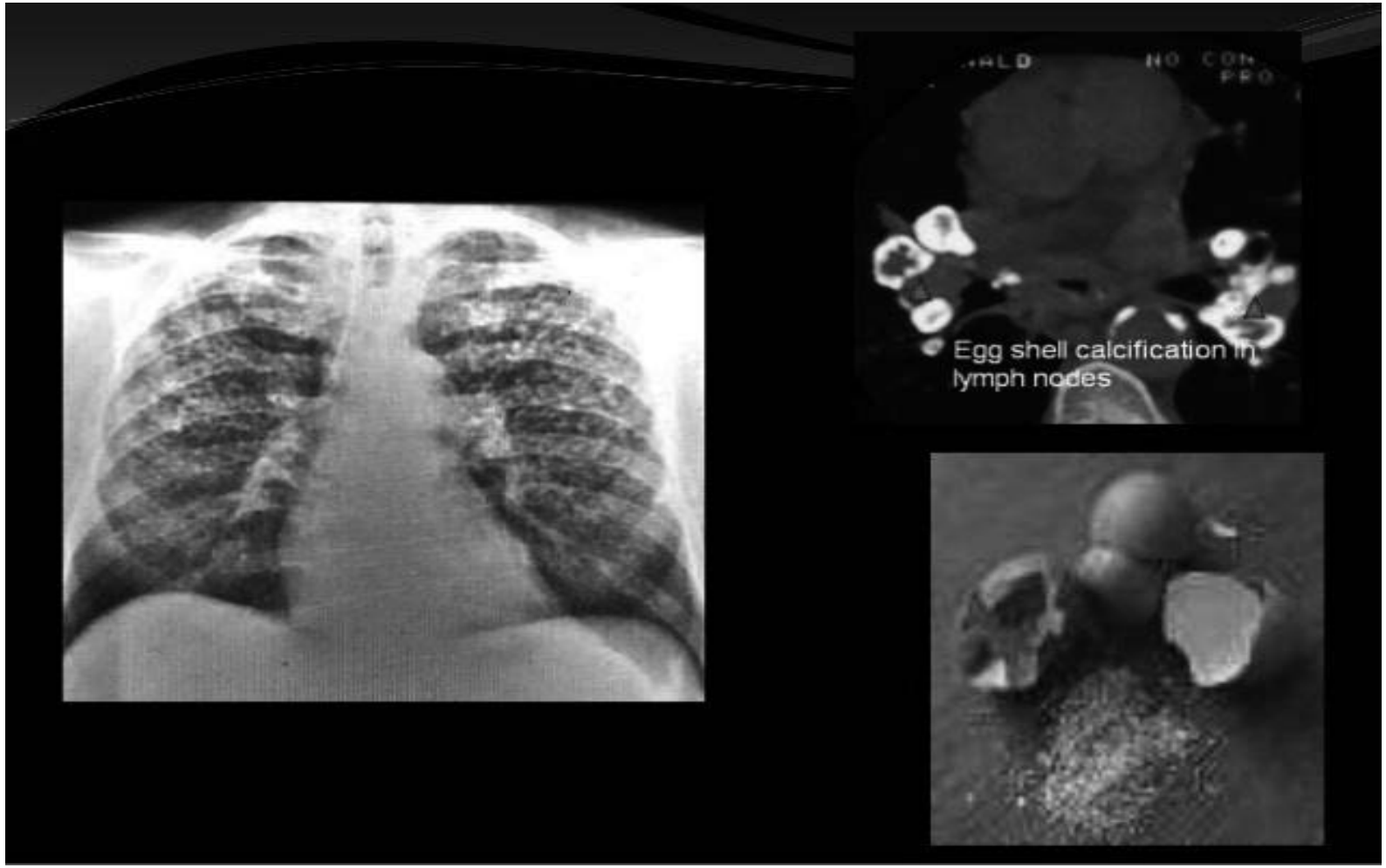
silicosis



Silicosis... radiology

- Sometimes, thin sheets of calcification occur in the lymph nodes and are appreciated radiographically as "eggshell" calcification (e.g., calcium surrounding a zone lacking calcification).

Egg-shell calcification



Clinical Features:

- Silicosis usually is detected on routine chest radiographs obtained in asymptomatic workers.
- The radiographs shows a fine nodularity in the upper zones of the lung, but pulmonary function is either normal or only moderately affected.
- Most patients do not develop shortness of breath until late in the course, after PMF is present.

Clinical features

- Once PMF develops , the disease may be progressive, even if the person is no longer exposed.
- Many patients with PMF develop pulmonary hypertension and cor pulmonale.
- The disease is slow to kill, but impaired pulmonary function may severely limit activity

NOTE: Silicosis is associated with an increased susceptibility to tuberculosis.

- It is postulated that crystaline silica may inhibit the ability of pulmonary macrophages to kill phagocytosed mycobacteria.
- Nodules of silicotuberculosis often contain a central zone of caseation

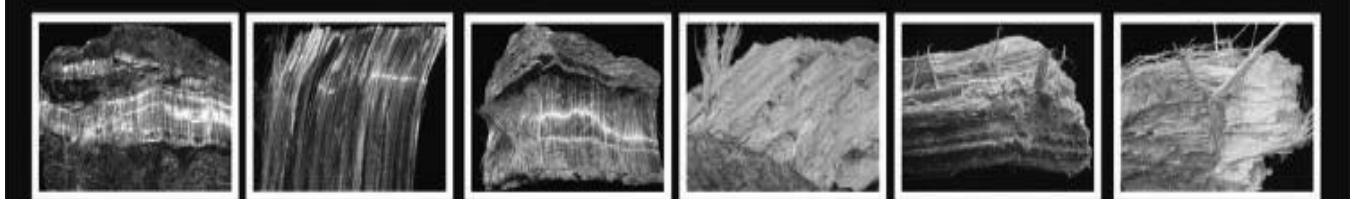
The relationship between silica and *lung cancer* has been a contentious issue.

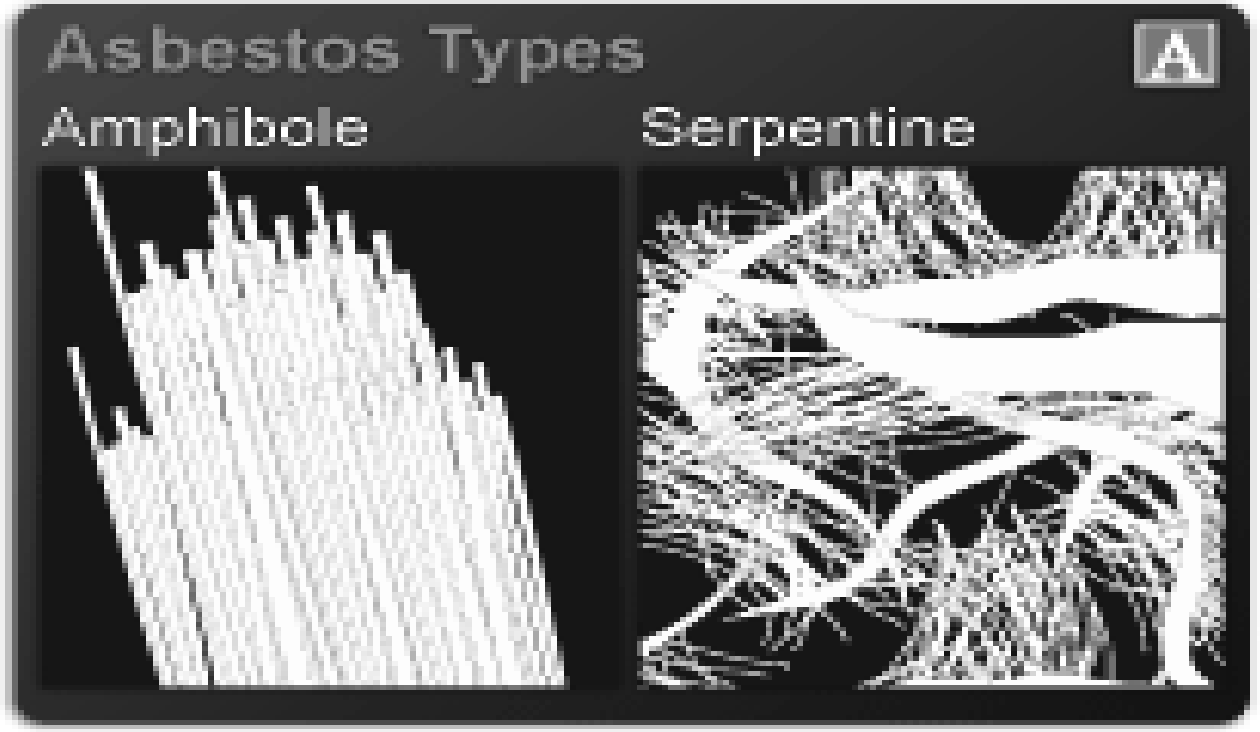
- In 1997, based on evidence from several epidemiologic studies, the International Agency for Research on Cancer concluded that *crystalline silica* is carcinogenic in humans.
- However, this subject continues to be controversial

asbestosis

- a heat-resistant fibrous silicate mineral that can be woven into fabrics, and is used in fire-resistant and insulating materials such as brake linings.

ASBESTOS


CHRYSOTILE
AMOSITE
CROCIDOLITE
TREMOLITE
ACTINOLITE
ANTHOPHYLLITE


Asbestos Types
A
Amphibole
Serpentine

AMPHIBOLES

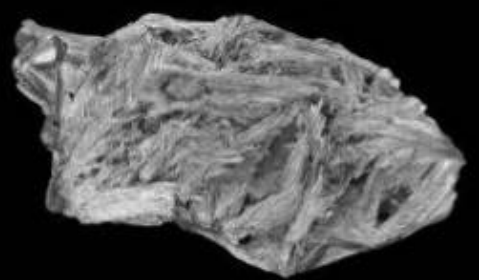
The Big Three made up about 5% of all asbestos commercially used

Anthophylite

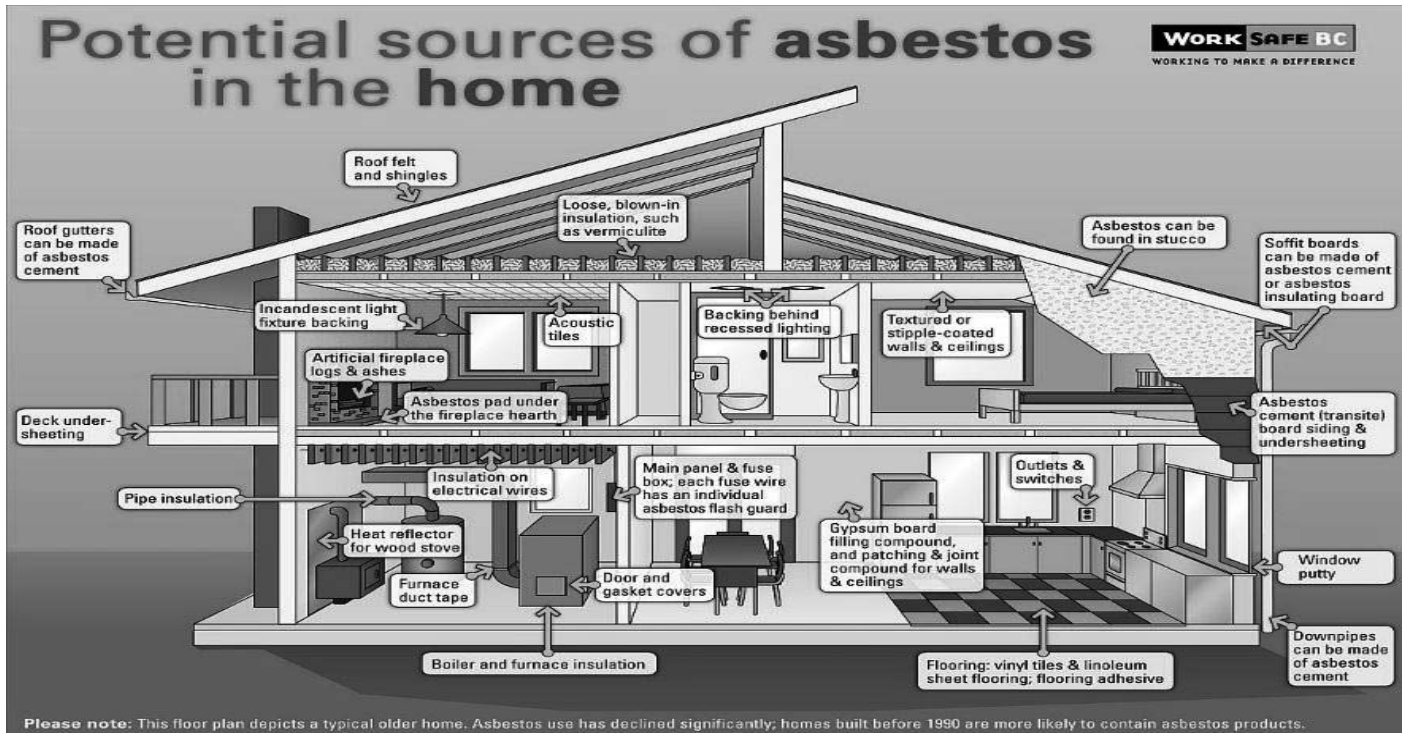
Amosite

crocidolite

While its evil cousin Tremolite is blamed as the toxic contaminate of chrysotile and thus makes chrysotile toxic.



Tremolite


Potential sources of asbestos in the home
WORK SAFE BC
WORKING TO MAKE A DIFFERENCE
Roof felt and shingles
Loose, blown-in insulation, such as vermiculite
Roof gutters can be made of asbestos cement
Asbestos can be found in stucco
Soffit boards can be made of asbestos cement or asbestos insulating board
Incandescent light fixture backing
Acoustic tiles
Backing behind recessed lighting
Textured or stipple-coated walls & ceilings
Artificial fireplace logs & ashes
Asbestos pad under the fireplace hearth
Deck under-sheeting
Asbestos cement (transite) board siding & undersheeting
Main panel & fuse box; each fuse wire has an individual asbestos flash guard
Outlets & switches
Insulation on electrical wires
Pipe insulation
Heat reflector for wood stove
Gypsum board filling compound, and patching & joint compound for walls & ceilings
Window putty
Furnace duct tape
Door and gasket covers
Downpipes can be made of asbestos cement
Boiler and furnace insulation
Flooring: vinyl tiles & linoleum sheet flooring; flooring adhesive
Please note: This floor plan depicts a typical older home. Asbestos use has declined significantly; homes built before 1990 are more likely to contain asbestos products.

- Occupational exposure to asbestos is linked to

1. Parenchymal interstitial fibrosis (*asbestosis*);
2. Localized fibrous plaques and rarely, diffuse fibrosis in the pleura;
3. Pleural effusions;
4. Lung carcinomas;
5. Malignant pleural and peritoneal mesotheliomas;
6. Laryngeal carcinoma.

Important note

- There is an increased incidence of asbestos-related cancers in family members of asbestos workers
- Asbestos can affect people in non-occupational settings

PATHOGENESIS: Forms of asbestos:

A. Serpentine :

- the fiber is curly and flexible, so they are likely to become impacted in the upper respiratory passages and removed by the mucociliary elevator
- Those that are trapped in the lungs are gradually leached from the tissues, because they are more soluble than amphiboles.

- chrysotile (a serpentine fiber) accounts for most of the asbestos used in industry

Second form of asbestos:

b. Amphibole, in which the fiber is straight, stiff

- Amphiboles, are less prevalent but more pathogenic than the serpentine and align themselves in the airstream and are delivered deeper into the lungs where they may penetrate epithelial cells to reach the interstitium

-- Asbestos also functions as both a tumor initiator and a promoter

- Some of the oncogenic effects of asbestos on the mesothelium are mediated by reactive free radicals generated by asbestos fibers

.

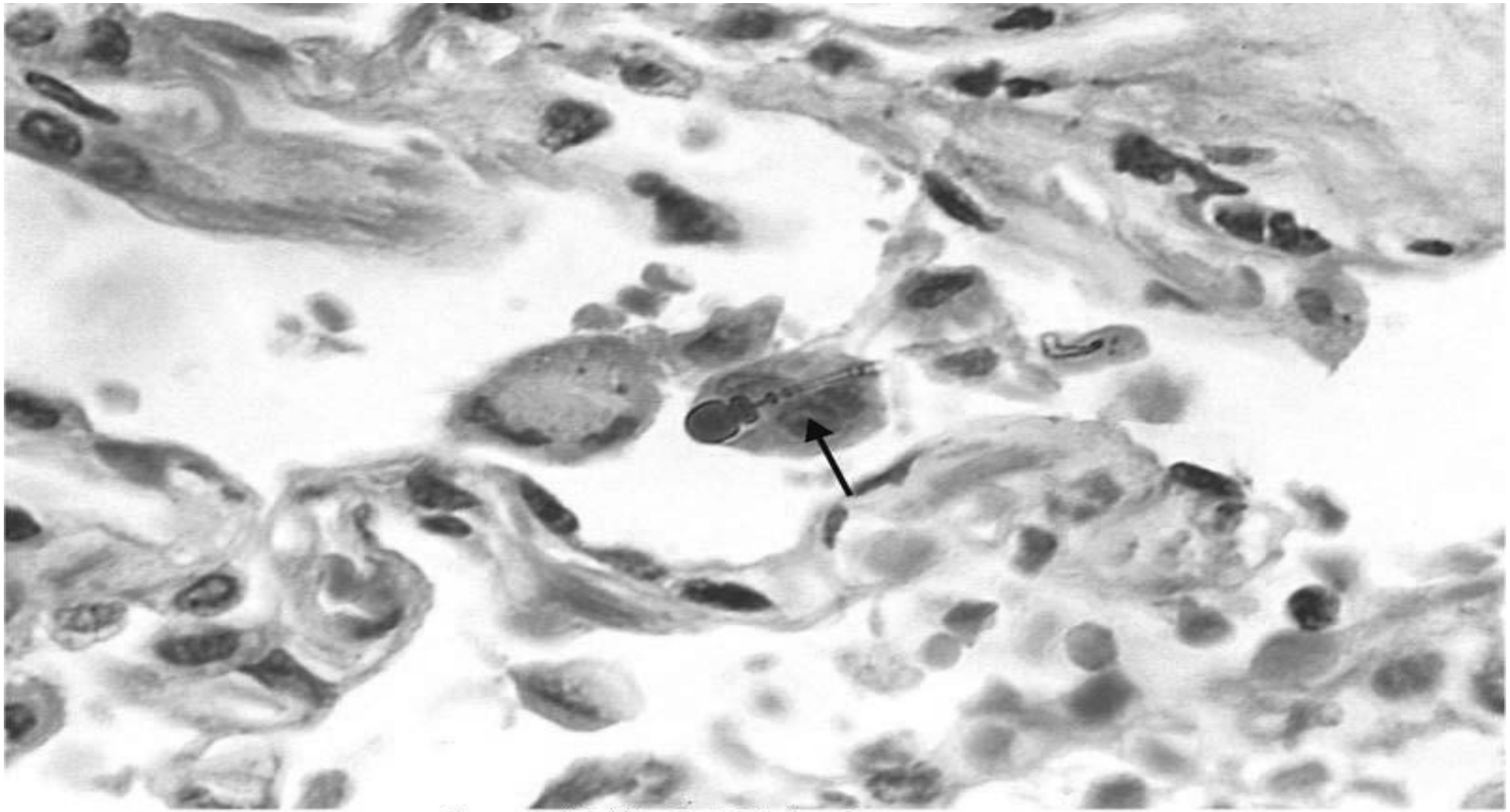
MORPHOLOGY

1. **Asbestosis** is marked by diffuse pulmonary interstitial fibrosis which is indistinguishable from UIP, except for the presence of asbestos bodies,

Asbestos bodies

- = golden brown, fusiform or beaded rods with a translucent center and consists of asbestos fibers coated with an iron-containing material are formed when macrophages attempt to phagocytose asbestos fibers; the iron is derived from phagocyte ferritin.

Asbestos body

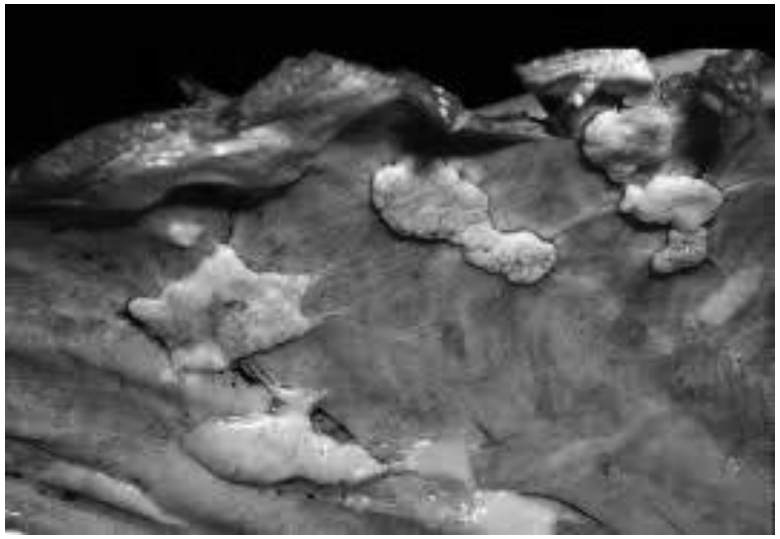


- Asbestos bodies sometimes can be found in the lungs of normal persons, but usually in much lower concentrations and without an accompanying interstitial fibrosis.

- Note
- - In contrast with CWP and silicosis, asbestosis begins in the lower lobes and subpleurally

Morphology 2. Pleural plaques :

- Are the most common manifestation of asbestos exposure
- Are well-circumscribed plaques of dense collagen , often containing calcium.



- Pleural plaques develop most frequently on the anterior and posterolateral aspects of the parietal pleura and do not contain asbestos bodies, and rarely do they occur in persons with no history or evidence of asbestos exposure.

NOTE:Uncommonly, asbestos exposure induces pleural effusion or diffuse pleural fibrosis

Note

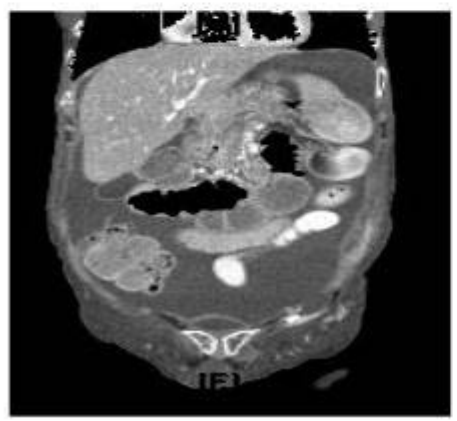
- Both lung carcinoma and malignant mesothelioma (pleural and peritoneal) develop in workers exposed to asbestos.
- The risk of lung carcinoma is increased about five-fold for asbestos workers; and the relative risk for mesothelioma, normally a very rare tumor (2 to 17 cases per 1 million persons), is more than 1000 times greater.

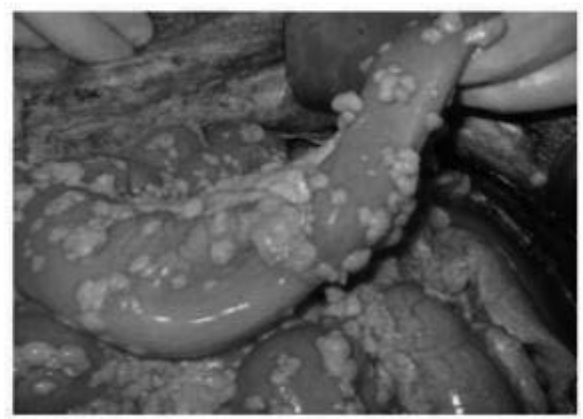
Important note

- Concomitant cigarette smoking greatly increases the risk of lung carcinoma but not that of mesothelioma .

Peritoneal Mesothelioma

- 2nd most common site of mesothelioma is the peritoneum
  - 10-30% of cases of mesothelioma
  - 300-400/cases in U.S. year





Respiratory system lecture 7-9 part 1

Dr Heyam Awad

FRCPath

sarcoidosis

- Granulomatous disease that affects many organs.
- In the lungs, sarcoidosis causes restrictive lung disease.

- Although sarcoidosis is an example of a restrictive lung disease, **it is important to note that sarcoidosis is a multisystem disease of unknown etiology characterized by noncaseating granulomas in many tissues and organs**.

- Other diseases, including mycobacterial or fungal infections may also produce noncaseating granulomas; so the histologic ***diagnosis of sarcoidosis is one of exclusion***.

Epidemiology

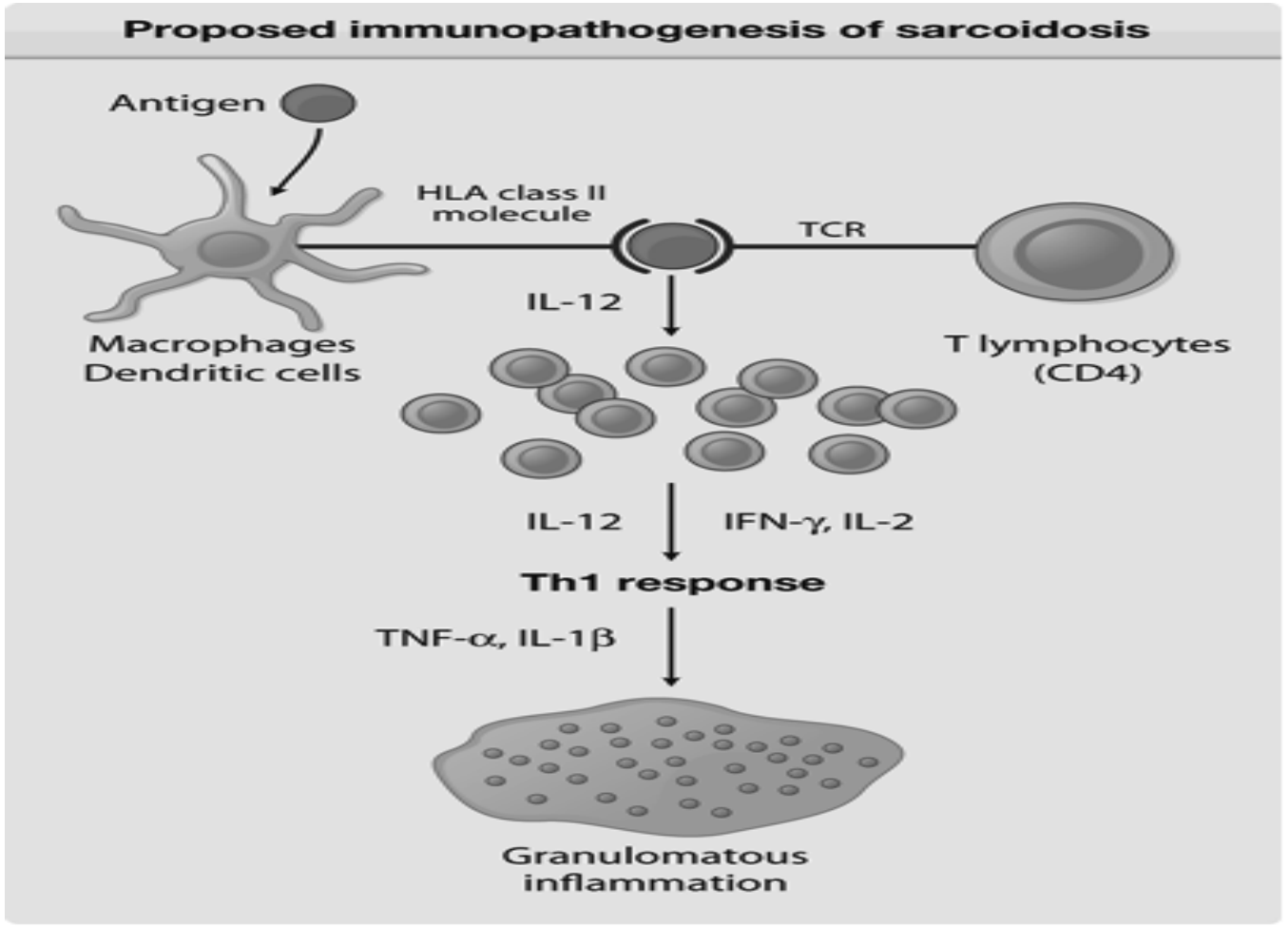
- It occurs throughout the world, affecting both genders and all races and age groups.
- There is a consistent predilection for adults younger than 40 years of age
- A high incidence has been noted among African Americans
- Sarcoidosis is one of the few pulmonary diseases with a higher prevalence among nonsmokers.

ETIOLOGY AND PATHOGENESIS

- etiology of sarcoidosis is unknown, but several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed persons exposed to certain environmental agents

- Immunologic abnormalities in sarcoidosis suggest the development of a cell-mediated response to an unidentified antigen and the process is driven by CD4+ helper T cells. These abnormalities include:

1. Intra-alveolar and interstitial accumulation of CD4+ T_H1 cells
2. Increases in T cell-derived T_H1 cytokines such as IL-2 and IFN-γ, resulting in T cell expansion and macrophage activation, respectively
3. Anergy to common skin test antigens such as purified protein derivative (PPD), that may result from pulmonary recruitment of CD4+ T cells and consequent peripheral depletion



Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

- The role of genetic factors is suggested by

a. Familial clustering of cases and

b. Association with certain human leukocyte antigens (HLA) (class I HLA-A1 and HLA-B8)

- After lung transplantation, sarcoidosis recurs in the new lungs in 75% of patients.

- **MORPHOLOGY**

- The diagnostic histopathologic feature of sarcoidosis is the **noncaseating epithelioid granuloma**, irrespective of the organ involved

Two other microscopic features are sometimes seen:

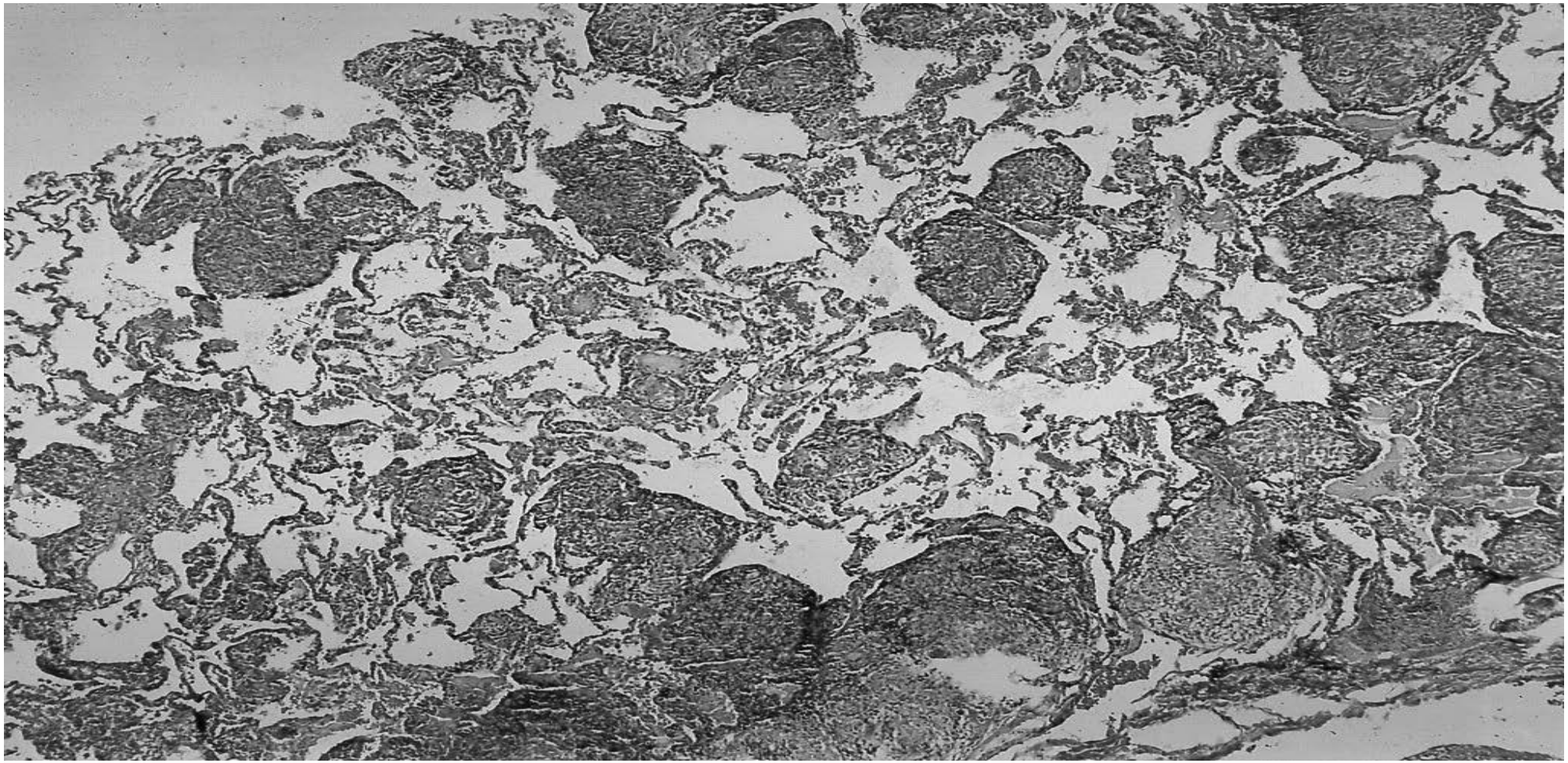
1. **Schaumann bodies**, laminated concretions composed of calcium and proteins

- 2. **Asteroid bodies**, stellate inclusions enclosed within giant cells. .

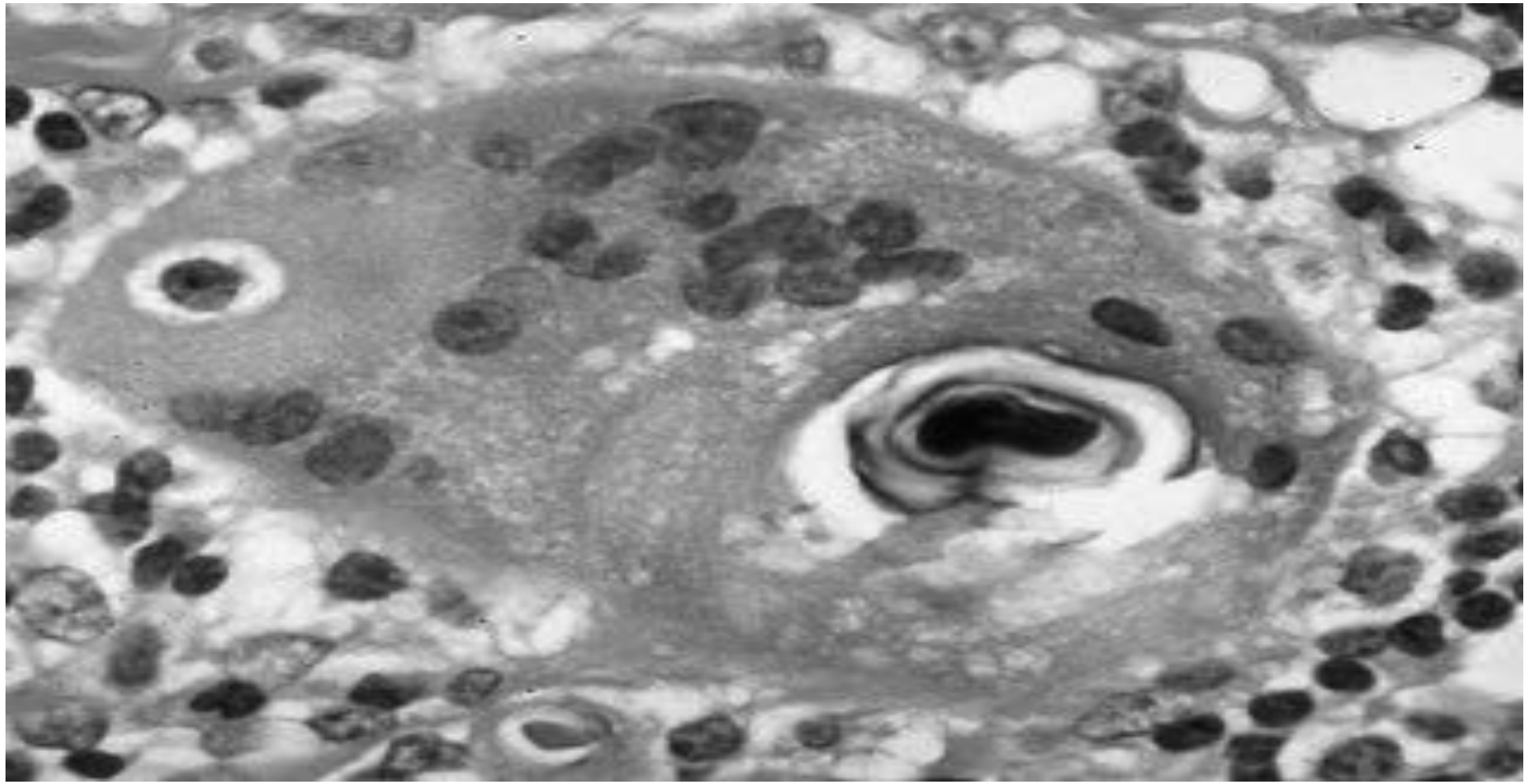
- (1&2) above are not required for diagnosis of sarcoidosis-they also may occur in granulomas of other origins.

- Caseation necrosis typical of tuberculosis is absent

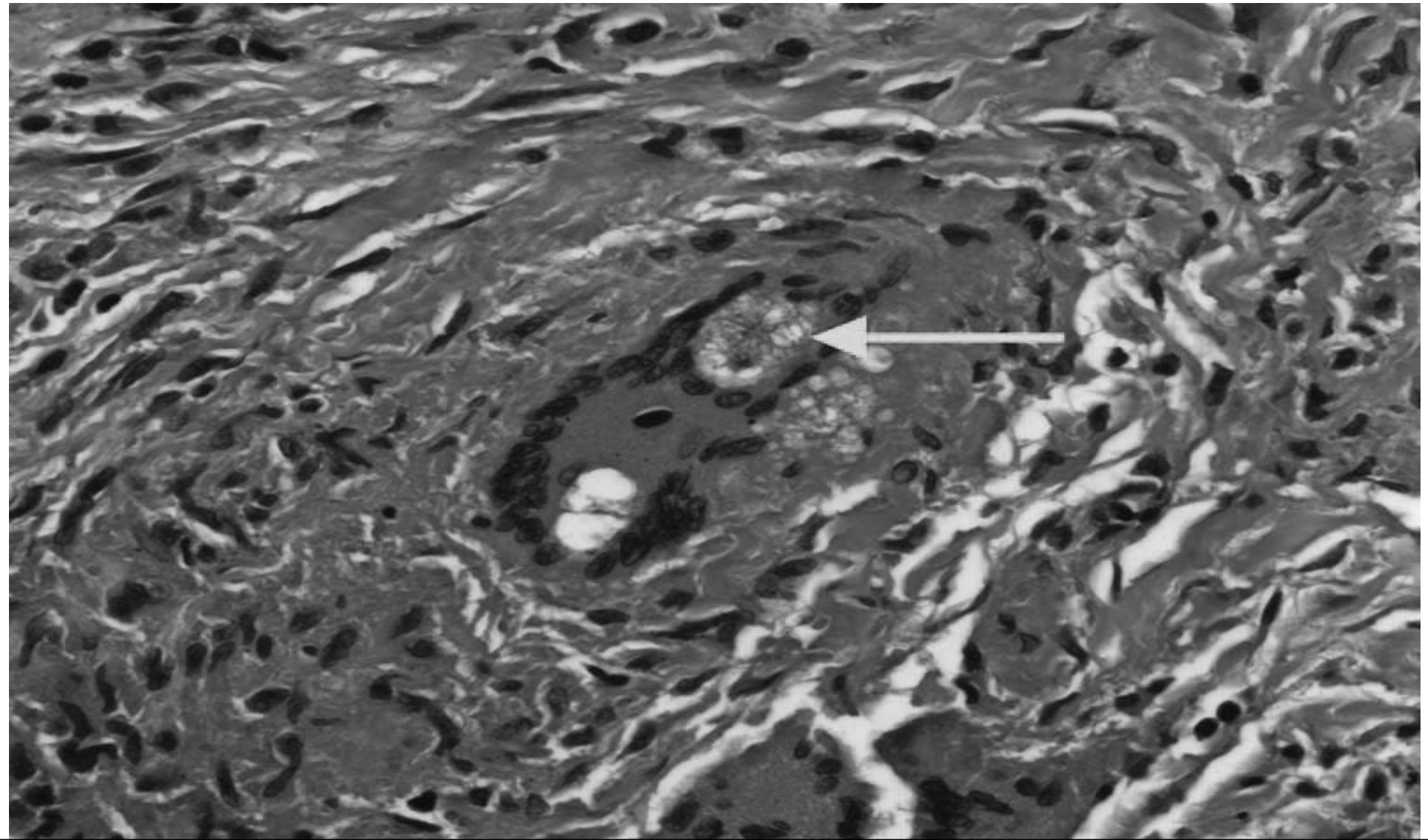
sarcoidosis



Shaumann bodies: laminated concretions composed of calcium and proteins



Asteroid bodies: stellate inclusion within giant cells



Involved organs:

1. The **lungs** are involved at some stage of the disease in 90% of patients:

- The granulomas predominantly involve the interstitium rather than air spaces, with some tendency to localize in the connective tissue around bronchioles and venules and in the pleura

2. Intrathoracic hilar and paratracheal lymph nodes are enlarged in 75% to 90% of patients, while a third present with peripheral lymphadenopathy.

3. Skin lesions are encountered in approximately 25% of patients:

a.Erythema nodosum,

- The hallmark of acute sarcoidosis, consists of raised, red, tender nodules on the anterior aspects of the legs.
- Sarcoidal granulomas are uncommon in these lesions.

b. Subcutaneous nodules

- Are discrete and painless
- These usually reveal abundant noncaseating granulomas.

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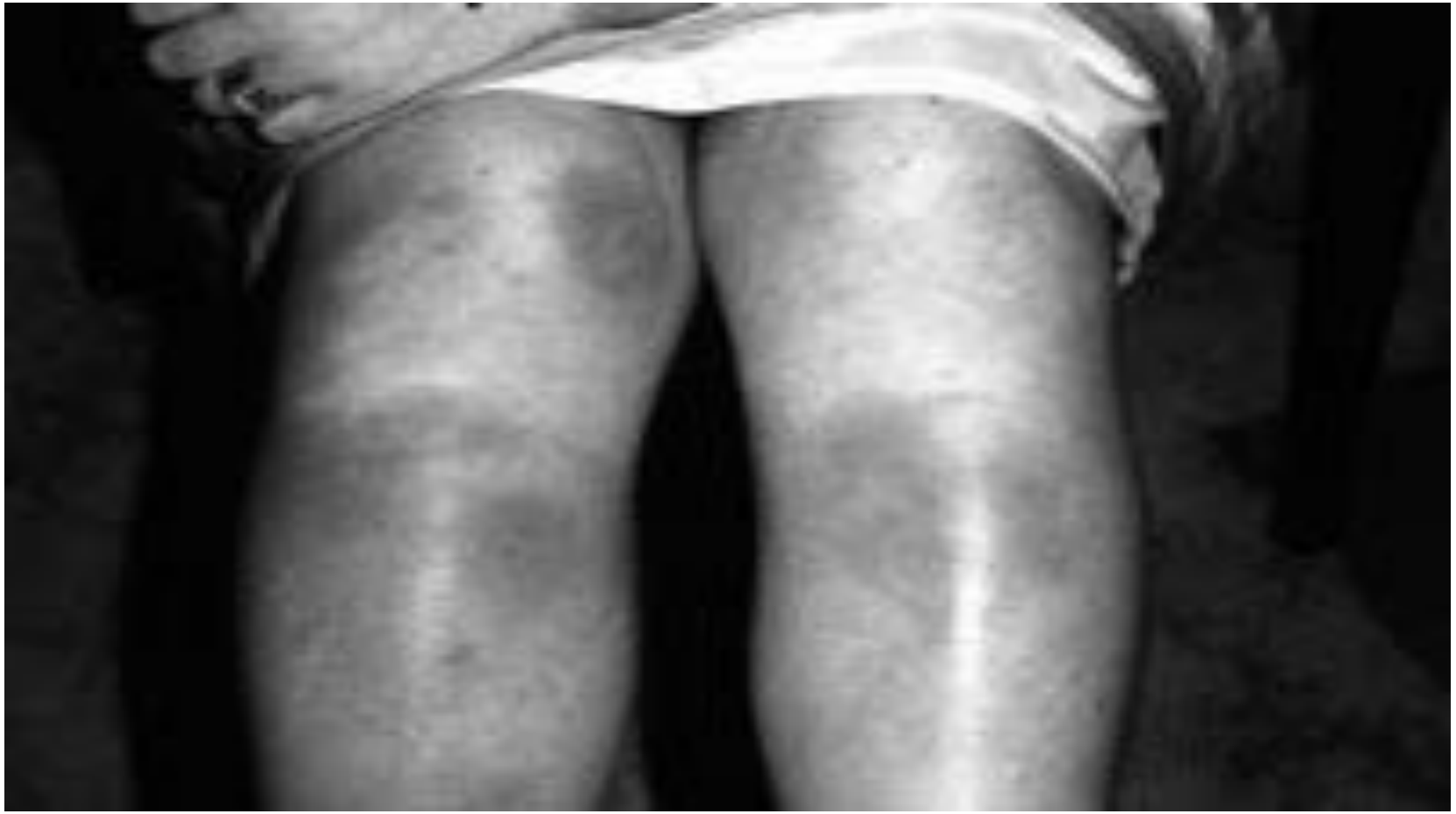
Erythema Nodosum



4. Involvement of the eye and lacrimal glands occurs in about one fifth to one half of patients and the ocular involvement takes the form of iritis or iridocyclitis and may be unilateral or bilateral-

-As a consequence, corneal opacities, glaucoma, and (less commonly) total loss of vision may develop.

- These ocular lesions are frequently accompanied by inflammation in the lacrimal glands, with suppression of lacrimation (sicca syndrome).

5. Unilateral or bilateral parotitis with painful enlargement of the parotid glands

- Some patients develop xerostomia (dry mouth).

Note:

- Combined uveoparotid involvement is designated **Mikulicz syndrome**.

Clinical Features

-In many persons the disease is asymptomatic and discovered on routine chest films as bilateral hilar adenopathy or as an incidental finding at autopsy.

- In others, peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly may be presenting manifestations.

- In about two thirds of symptomatic cases, there is gradual appearance of respiratory symptoms (shortness of breath, dry cough, or vague substernal discomfort) or constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats

***Note*:**

- Other findings include hypercalcemia and is not related to bone destruction but rather are caused by increased calcium absorption secondary to production of **active vitamin D by the mononuclear phagocytes in the granulomas.**

Clinical course:

- Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periods of activity interspersed with remissions.

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

Hypersensitivity pneumonitis

- A granulomatous disease that can cause restrictive lung disease

Hypersensitivity pneumonitis = allergic alveolitis

- A granulomatous disease that can cause restrictive lung disease
- Immunologically mediated
- Causative agent: known!!.. Usually occupational

- 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 sensitivity to inhaled antigens such as in moldy Hay .

- The occupational exposures are diverse, but the syndromes share common clinical and pathologic findings and probably have a very similar pathophysiologic basis

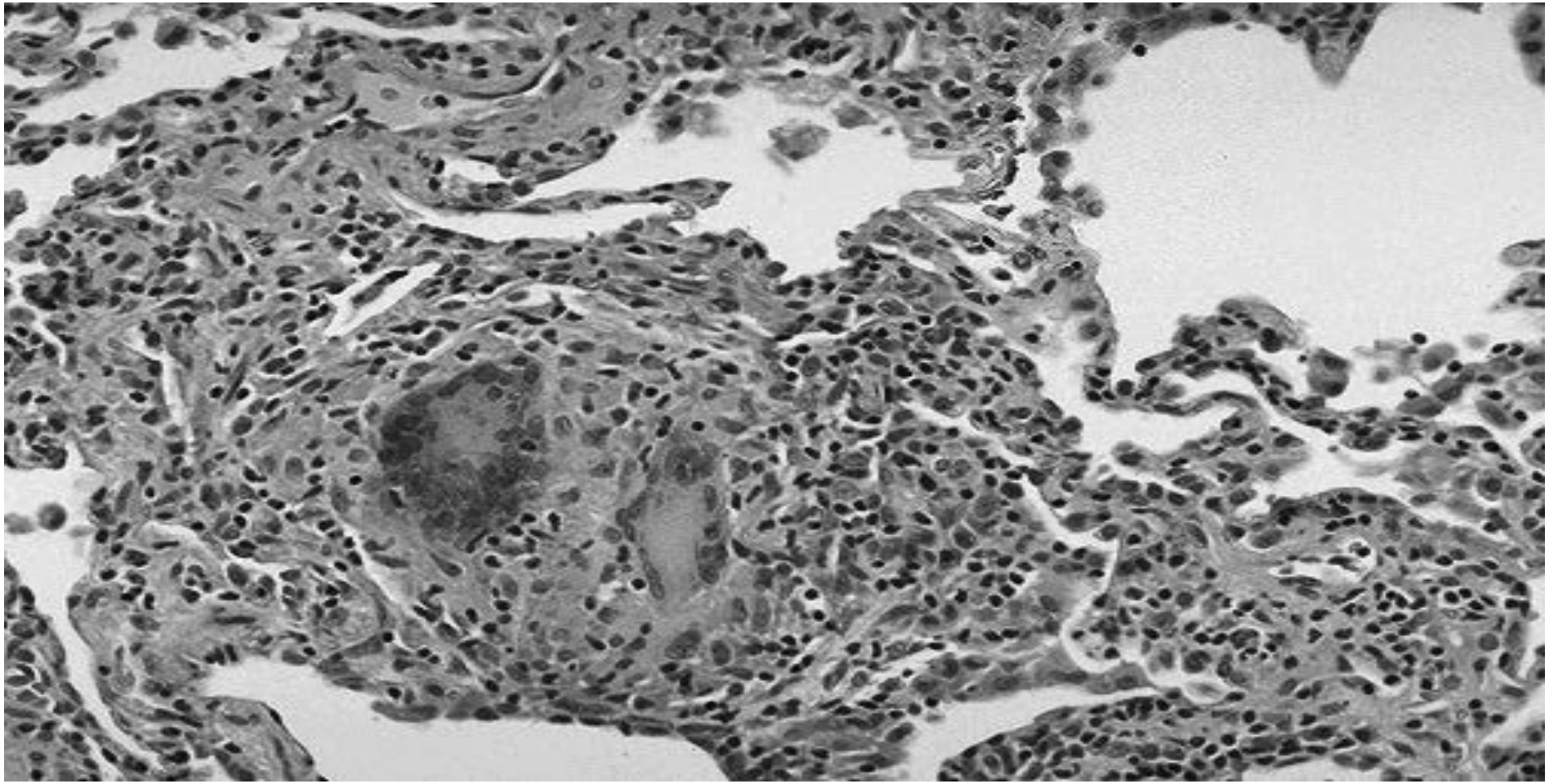
syndrome	exposure	antigen	
Farmer's lung	Moldy hay	micropolyspora	
Maple bark disease	Moldy maple bark	cryptostroma	
Pigeon breeder's lung	Pigeon droppings	Pigeon serum protein	

diagnosis

- 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.
- Can present 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

Hypersensitivity Pneumonitis



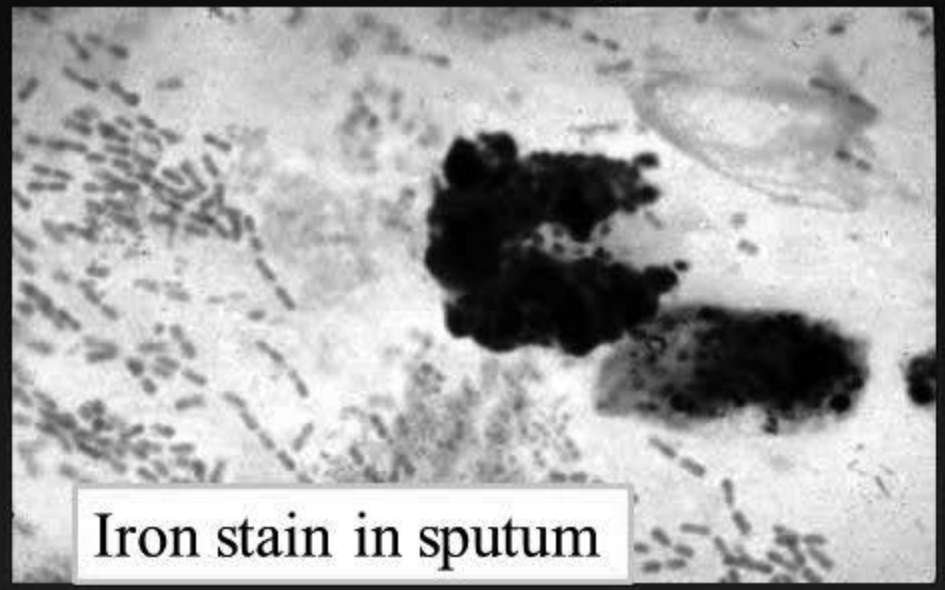
Diffuse alveolar hemorrhagic syndromes

- 1. Goodpasture syndrome

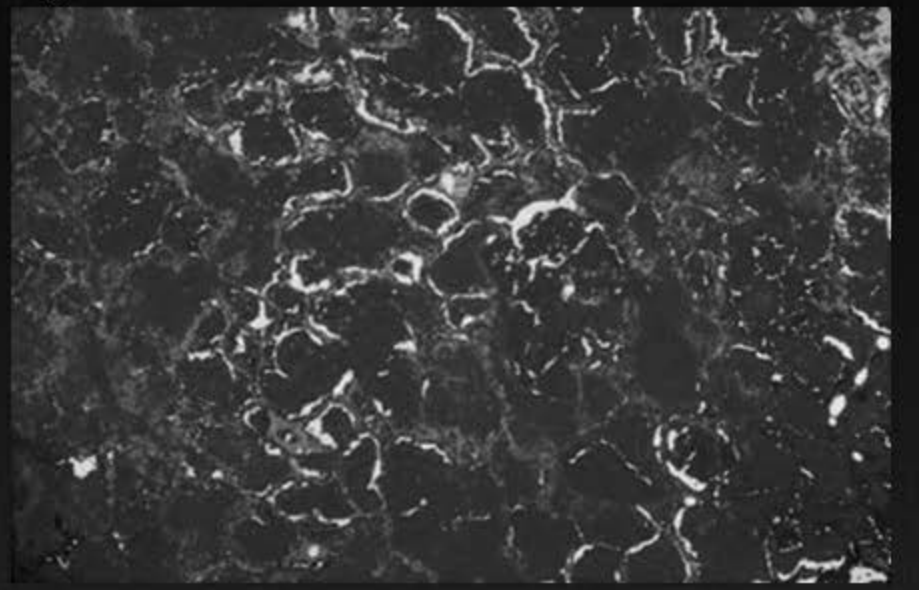
uncommon , rapidly progressive, glomerulonephritis and hemorrhagic interstitial pneumonitis.

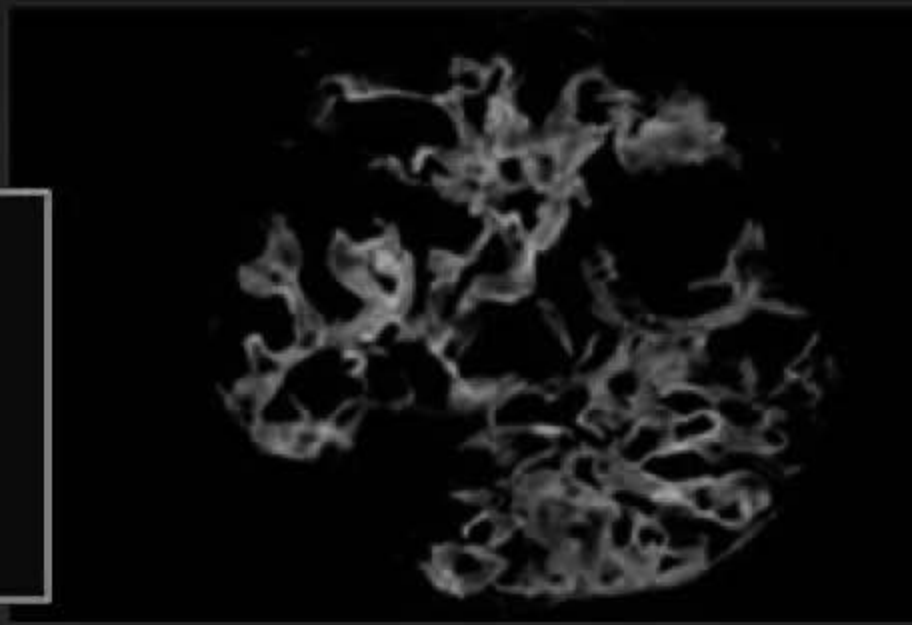
- Both the renal and the pulmonary lesions are caused by **antibodies targeted against the noncollagenous domain of the α3 chain of collagen IV which can be detected in the serum of more than 90% of patients**

Goodpasture syndrome

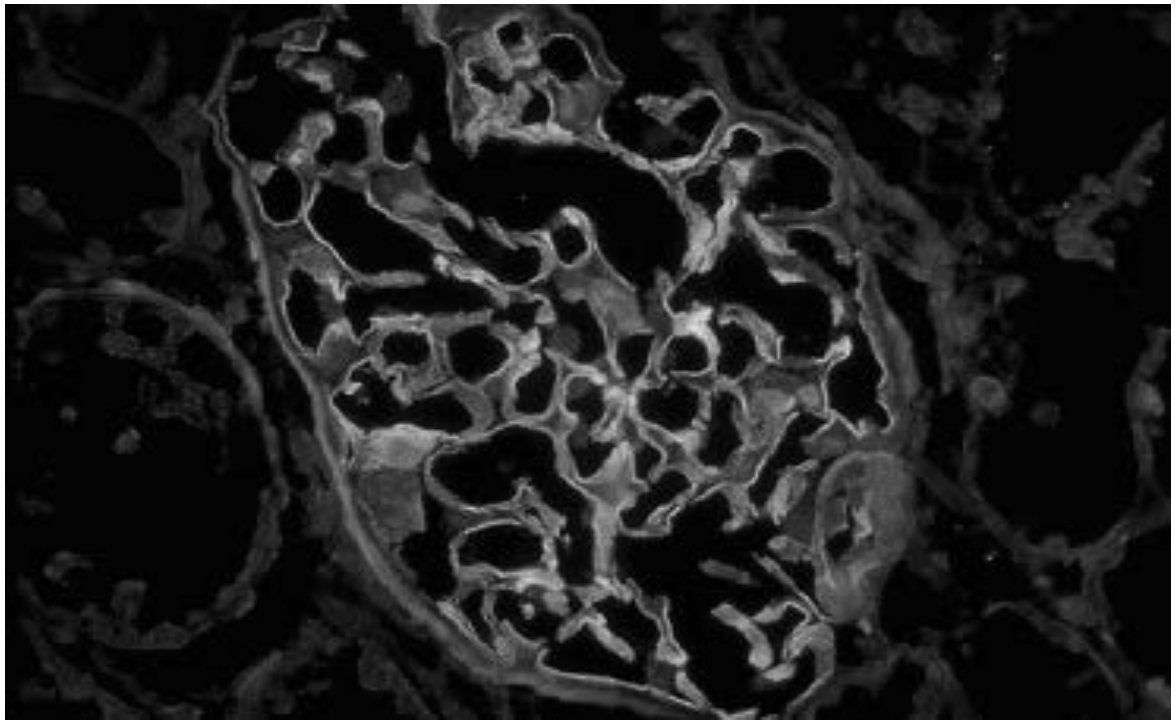


Iron stain in sputum





Immunofluorescence of renal biopsy staining for IgG in a linear pattern in patient with anti-glomerular basement membrane (anti-GBM) disease



- The characteristic linear pattern of immunoglobulin deposition (usually IgG, that is the hallmark diagnostic finding in renal biopsy specimens may be seen along the alveolar septa by immunoflurescence studies.
- - Plasmapheresis which removes the offending agent and immunosuppressive therapy that inhibits antibody formation have markedly improved the prognosis
- With severe renal disease, renal transplantation is eventually required

2.Idiopathic Pulmonary Hemosiderosis

- similar to those of Goodpasture syndrome but

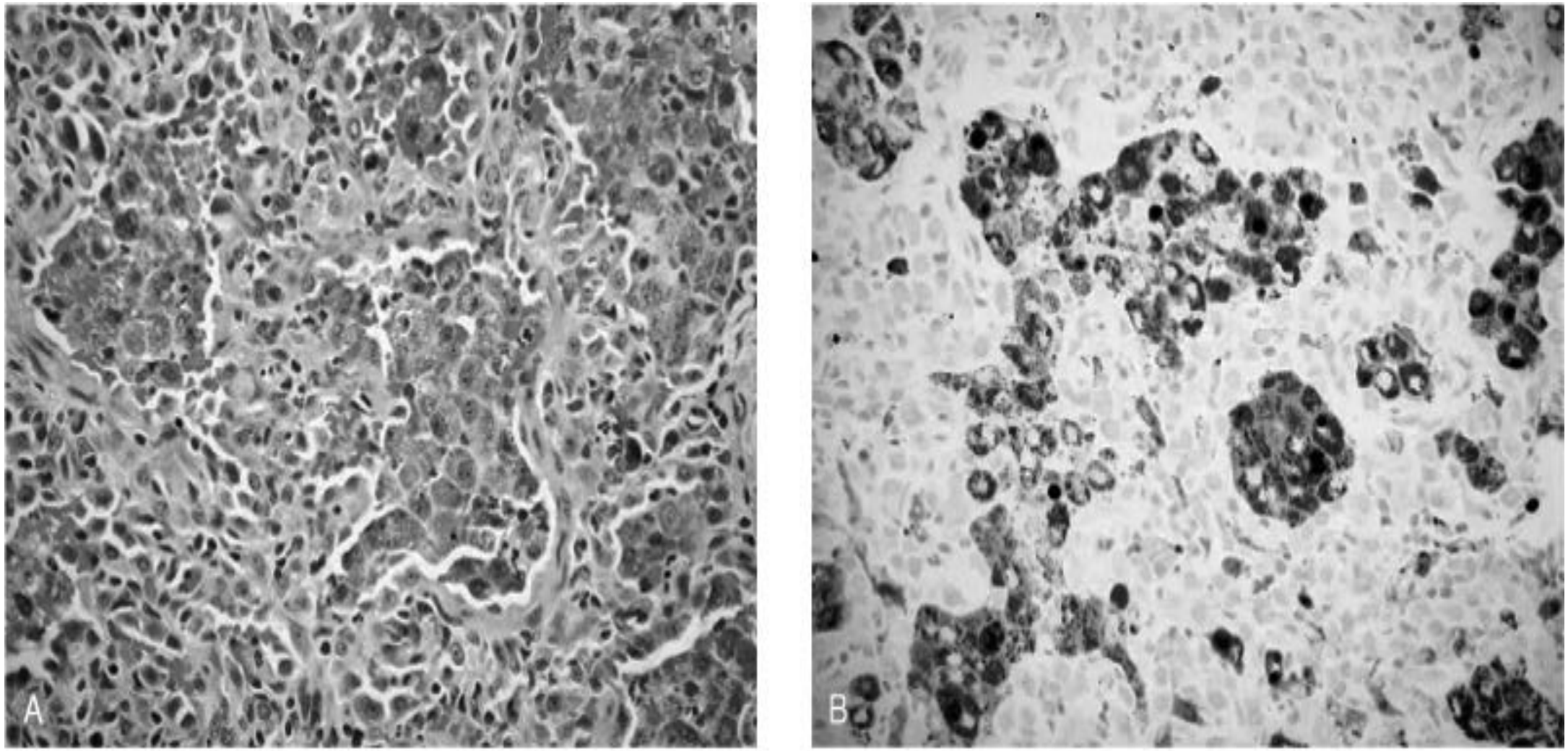
a. No associated renal disease

b. No circulating anti-basement membrane antibody.

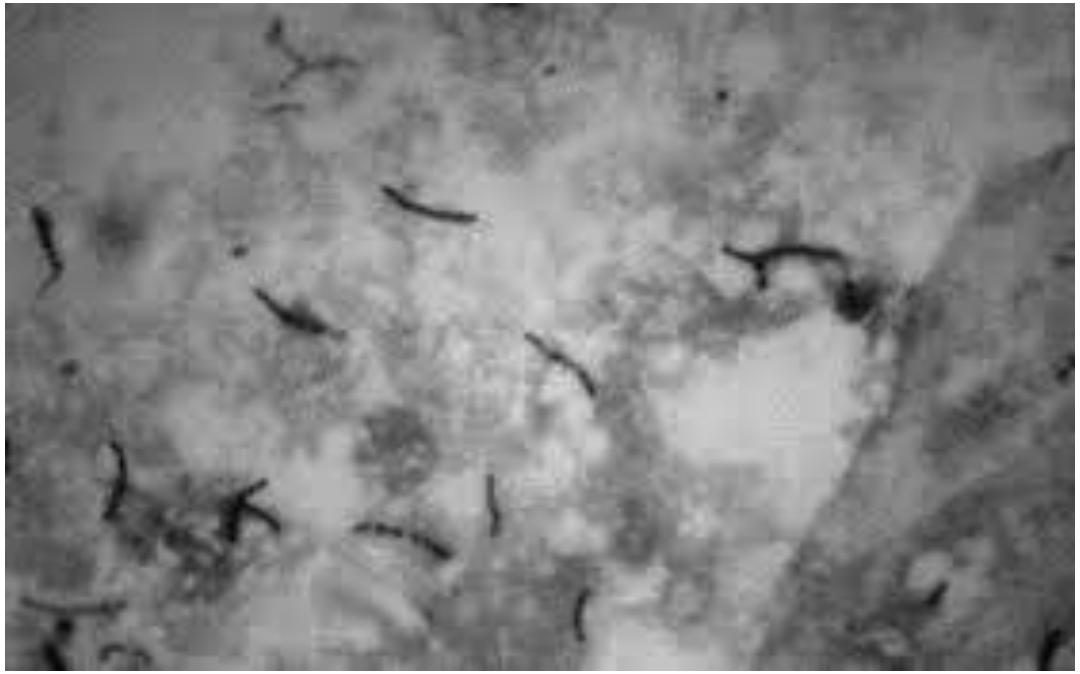
.

- Most cases occur in children, although the disease is reported in adults as well, who have a better prognosis
- With steroid and immunosuppressive therapy, survival has markedly improved from the historical 2.5 years;
- thus, an immune-mediated etiology is postulated

Diffuse alveolar hemorrhage syndrome –perl'sstain



Tuberculosis



- Tuberculosis is a communicable chronic disease

Epidemiology

- It flourishes under conditions of poverty, crowding, in old people and disease states such as

a. Diabetes mellitus,

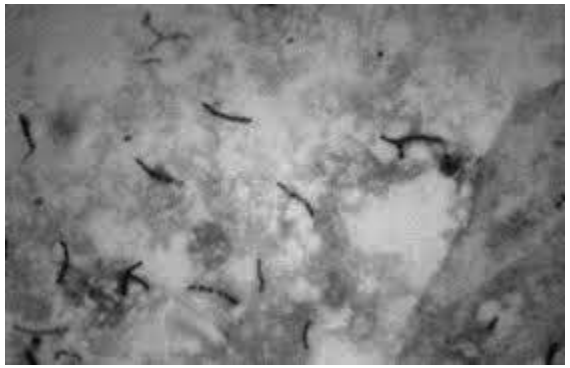
b. Hodgkin lymphoma,

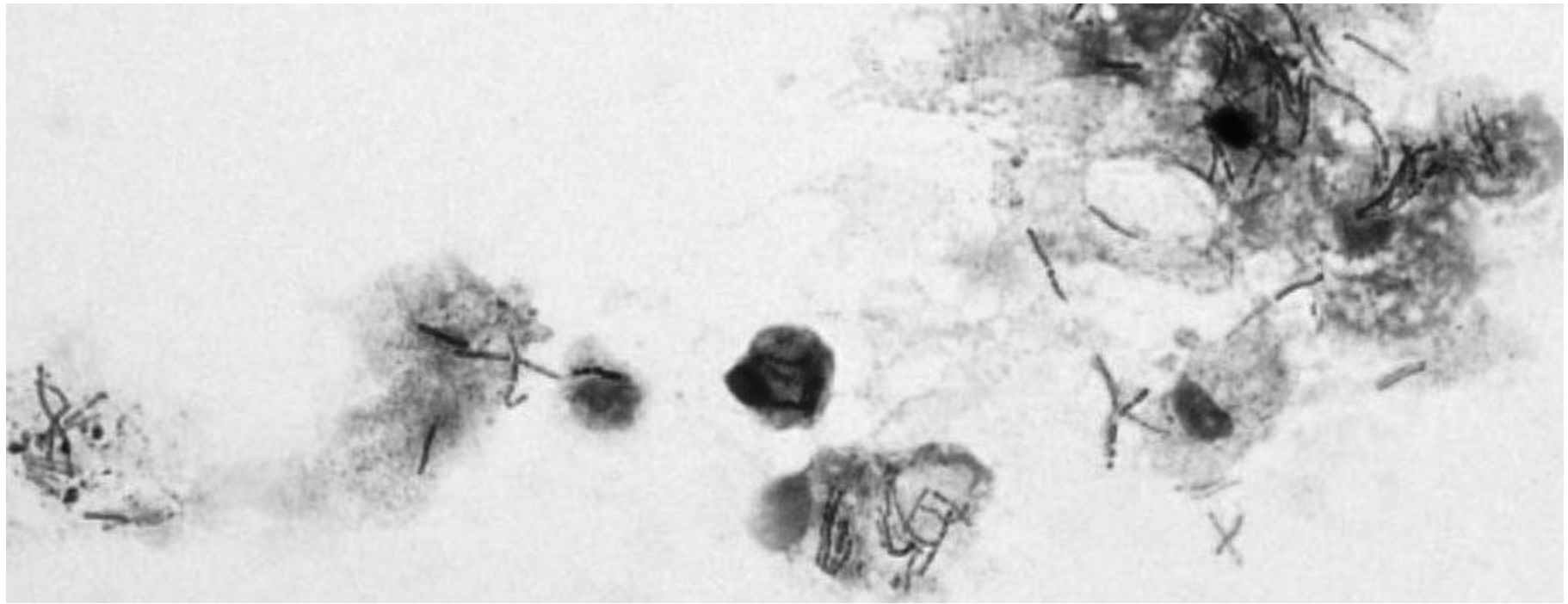
c. Silicosis

d. Immunosuppression.. Including AIDS..

Relationship of HIV and Tuberculosis

Etiology: mycobacterium tuberculosis which are acid fast bacilli





I. In the first 3 weeks of infection

- Once the mycobacteria gains entry into the macrophage endosomes , the organisms are able to inhibit normal microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole and this allows unchecked mycobacterial proliferation

- It is characterized by bacillary proliferation within the alveolar macrophages with resulting bacteremia

II. 3 weeks after exposure

- Development of cell-mediated immunity

a. Processed mycobacterial antigens reach the draining lymph nodes and are presented to CD4 T cells by macrophages which secret IL-12, which stimulates TH1 subtype of CD4+ T cells that secret Gamma- IFN which activates macrophages

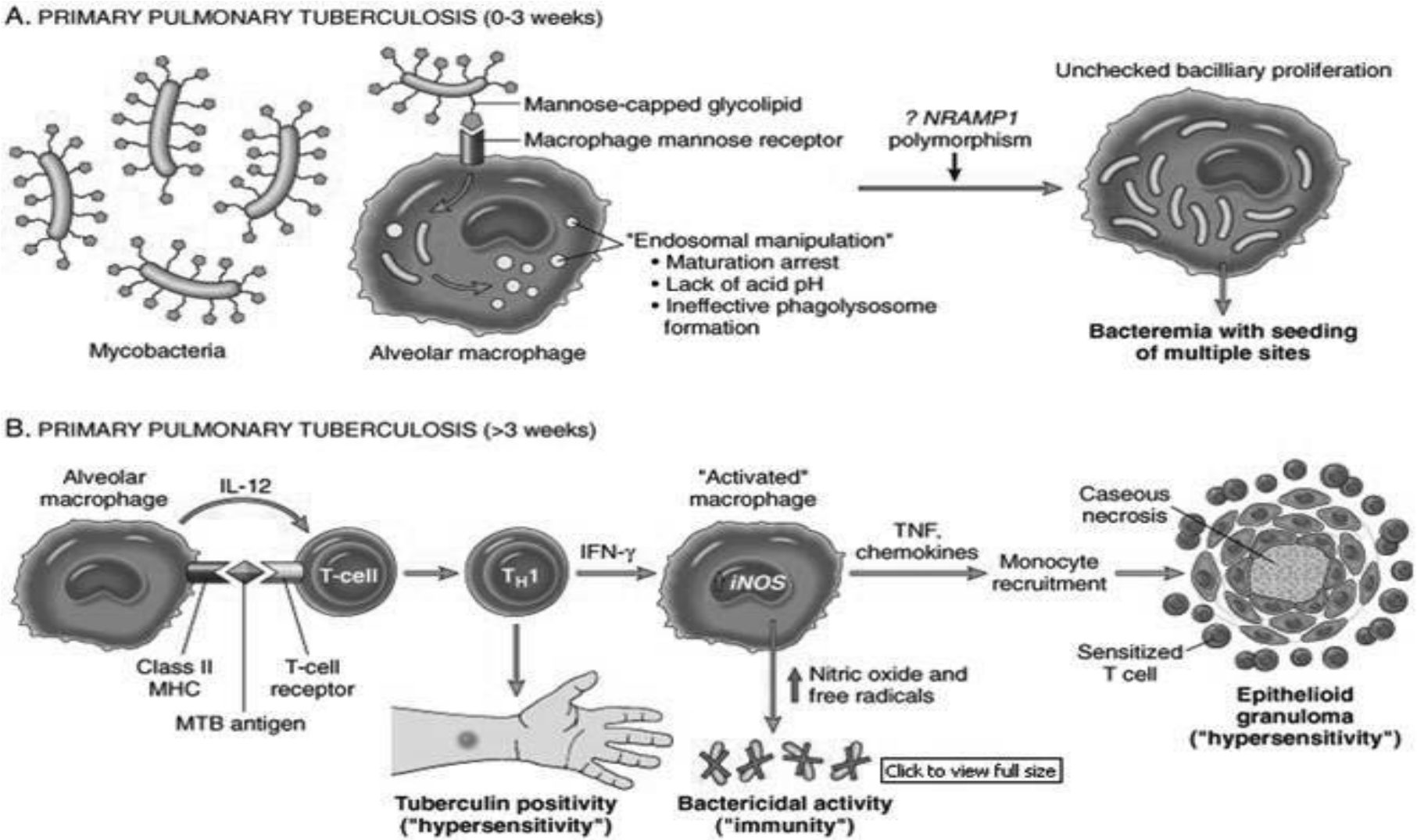
b. Activated macrophages release a variety of mediators

1) TNF, which is responsible for recruitment of monocytes, which in turn undergo activation and differentiation into the "epithelioid histiocytes

(2) Expression of the inducible nitric oxide synthase (iNOS) gene, which results in elevated nitric oxide levels with antibacterial activity;

(3) Generation of reactive oxygen species, which can have antibacterial activity

pathogenesis



Note:

- It is important that infection be differentiated from disease

- Infection implies seeding of a focus with organisms, which may or may not cause clinically significant tissue damage (i.e., disease).

- Infection with M. tuberculosis typically leads to the development of delayed hypersensitivity, which can be detected by the tuberculin (Mantoux) test

Tuberculin test test

About 2 to 4 weeks after the infection has begun, intracutaneous injection of 0.1 mL of PPD induces a visible and palpable induration (at least 5 mm in diameter) that peaks in 48 to 72 hours.

- A positive tuberculin skin test Signifies cell-mediated hypersensitivity to tubercular antigens but it doesn’t differentiate infection from disease

- False-negative tuberculin reactions (or skin test anergy)

a. Certain viral infections,

b. Sarcoidosis

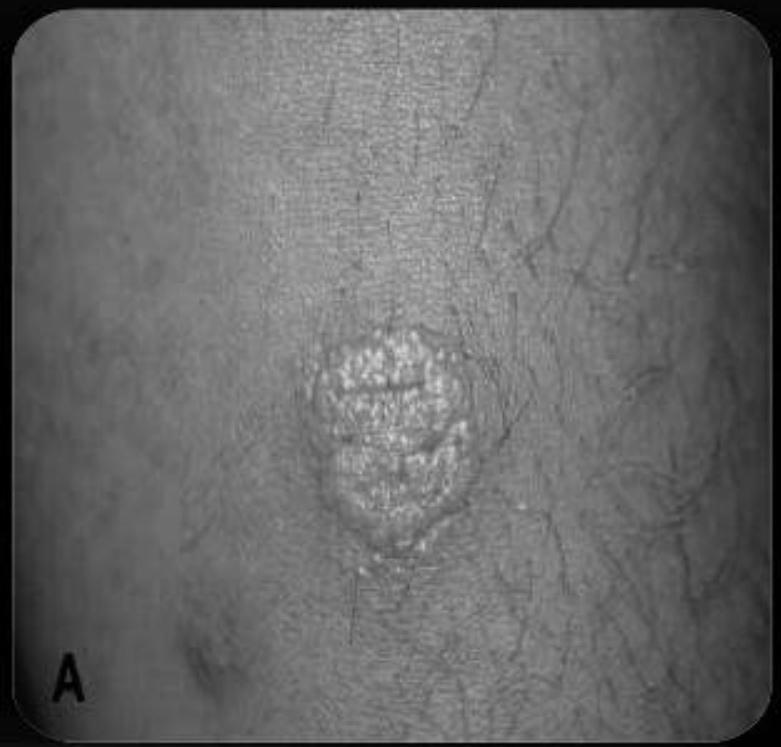
c. Immunosuppression

False-positive reactions

- May result from infection by atypical mycobacteria

READING THE TUBERCULIN SKIN TEST

- Read 2-3 days after placing the test
- Feel for induration
- Color change without induration is ***not*** included in the measurement
- Use a ruler or calipers
- Have someone else check if unsure
- Always document the exact size (mm) – not just “positive” or “negative”



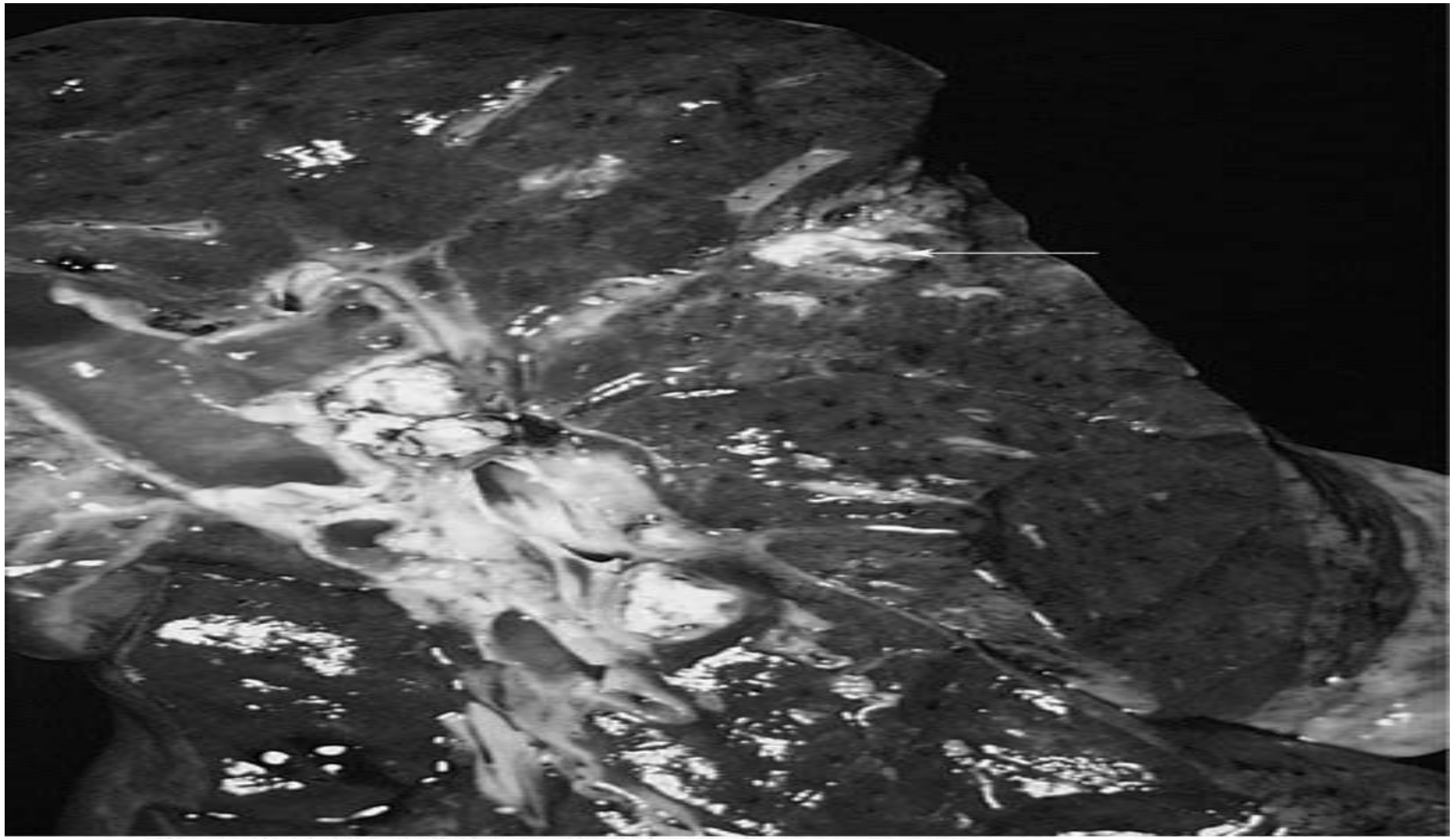
- About 80% of the population in certain Asian and African countries is tuberculin positive.
- About 3% to 4% of previously unexposed persons acquire active tuberculosis during the first year after "tuberculin conversion," and no more than 15% do so thereafter.
- **Thus, only a small fraction of those who contract an infection develop active disease**

- Primary TB: Is the form of disease that develops in previously unexposed and unsensitized patient.
- The inhaled bacilli implant in the alveoli of the of the lower part of the upper lobe or the upper part of the lower lobe,usually close to the pleura.
- 2-3 weeks after exposure , a 1-to 1.5- cm lesion develops (Ghon focus) composed of granulomas

Primary TB

- Granulomas in the primary lung site: Ghon focus
- Ghon focus and granulomas in draining lymph nodes = Ghon complexaes

Primary Tuberculosis



- The Ghon complex undergoes progressive fibrosis, followed by radiologically detectable calcification (Ranke complex)

The major consequences of primary tuberculosis are that

(1) It induces hypersensitivity and increased resistance;

(2) The foci of scarring may harbor viable bacilli for years, perhaps for life, and thus be the nidus for reactivation at a later time when host defenses are compromised.

3) uncommonly, it may lead to progressive primary tuberculosis and this complication occurs in patients who are immunocompromised or in

- Secondary TB: Is the pattern of disease that arises in a previously sensitized host.

a. It may follow shortly after primary tuberculosis,

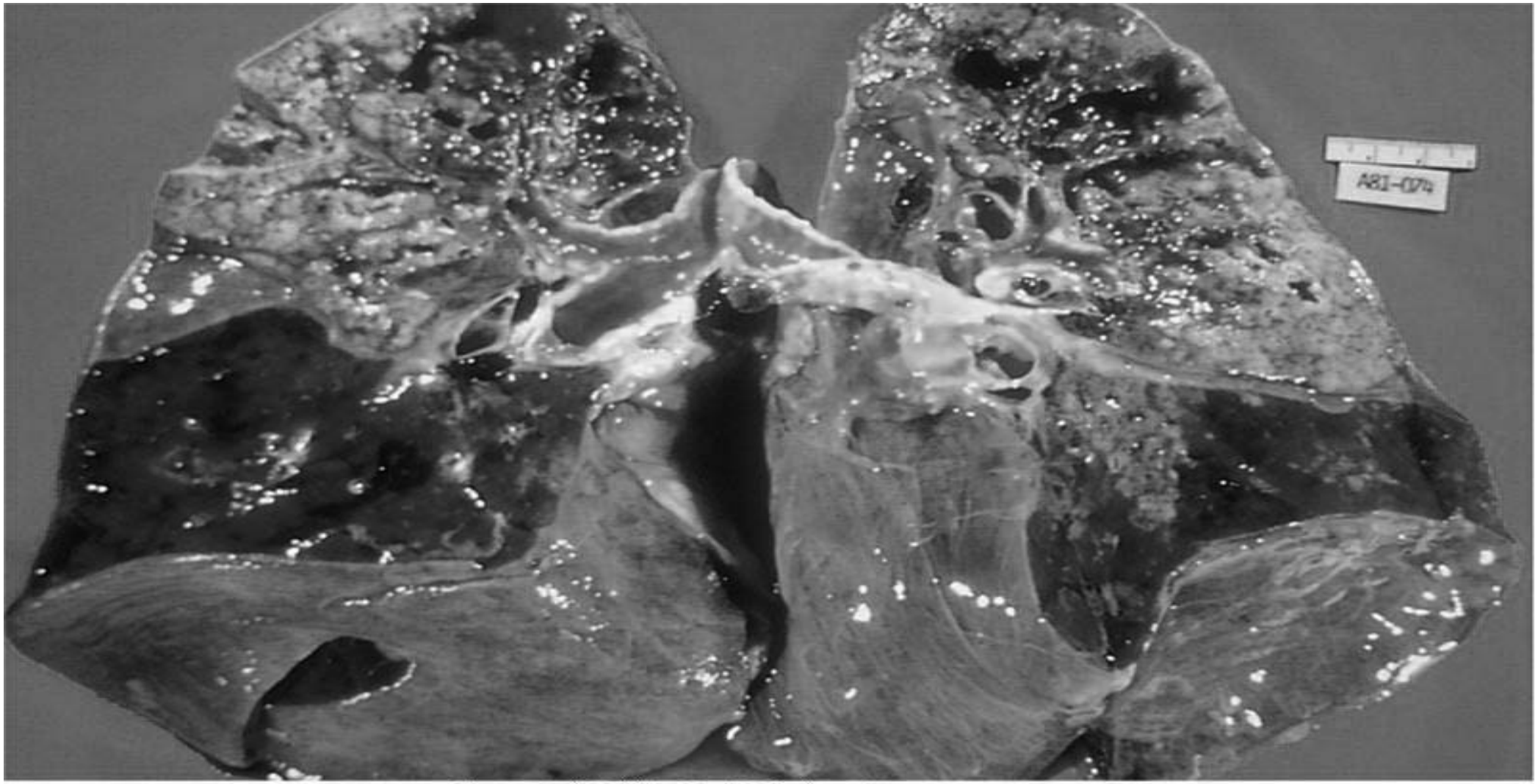
b. More commonly arises from reactivation of dormant primary TB decades after initial infection, particularly when host resistance is weakened.

c. It also may result from exogenous reinfection because of waning of the protection afforded by the primary disease

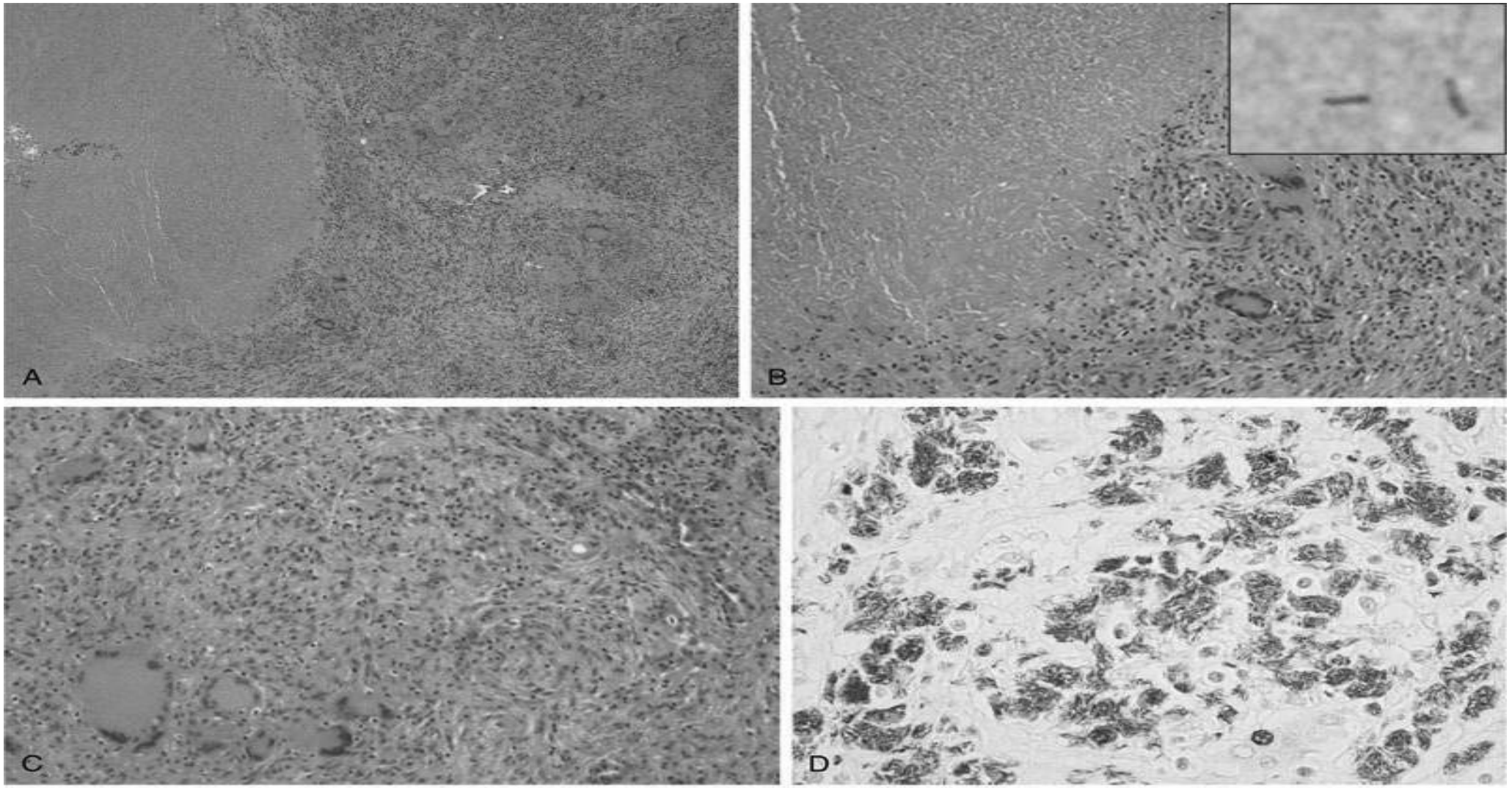
- Only a few patients with primary disease subsequently (5%) develop secondary tuberculosis.
- Secondary tuberculosis is classically localized to the apices of upper lobes related to high oxygen tension in the apices.

- Because of the preexistence of hypersensitivity, the bacilli excite marked tissue response to wall off the focus .
- As a result of this localization, the regional lymph nodes are less prominently involved early in the disease than they are in primary tuberculosis
- Cavitation occurs in the secondary form, leading to erosion into and dissemination along airways.

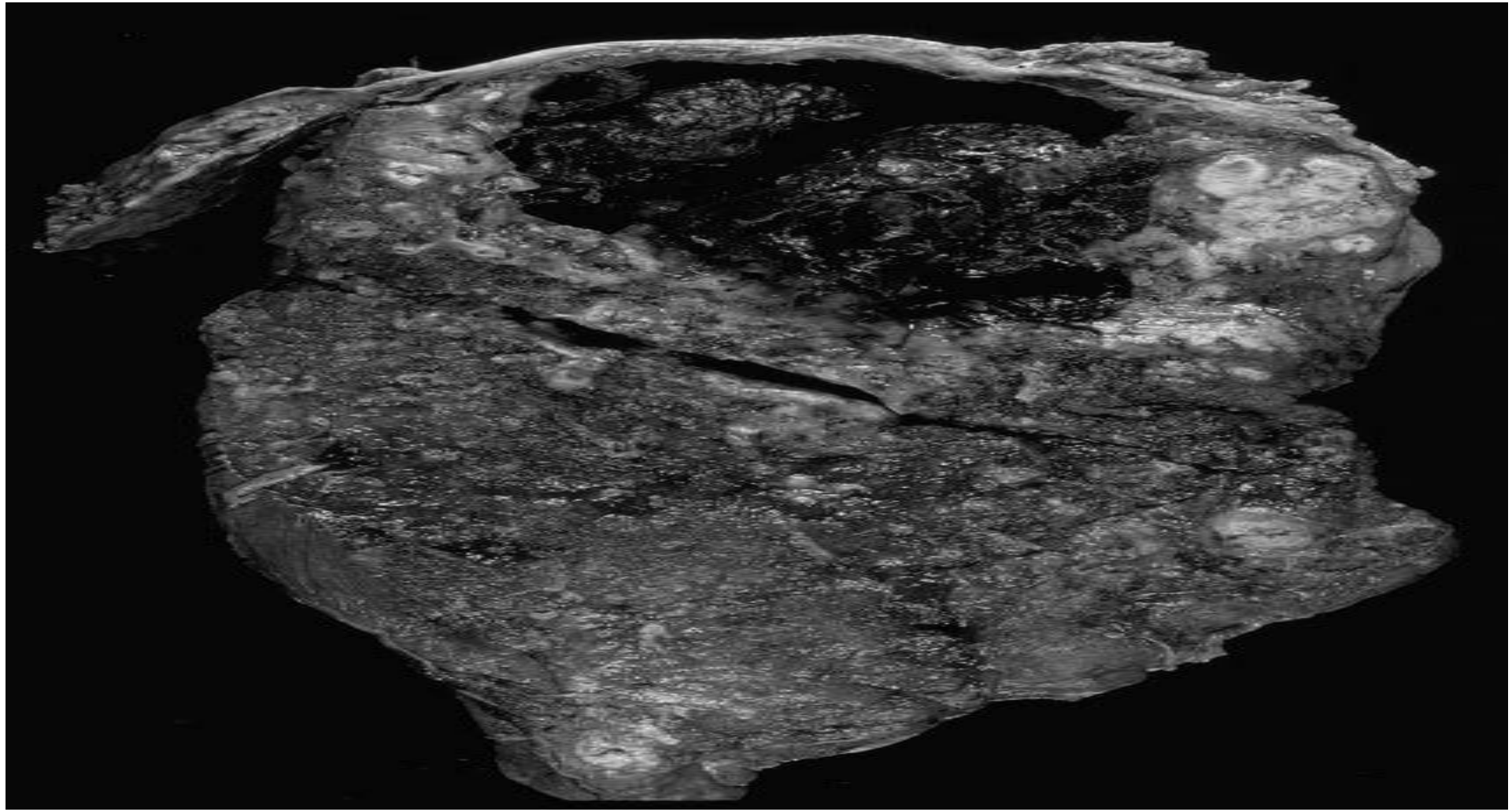
Secondary tuberculosis

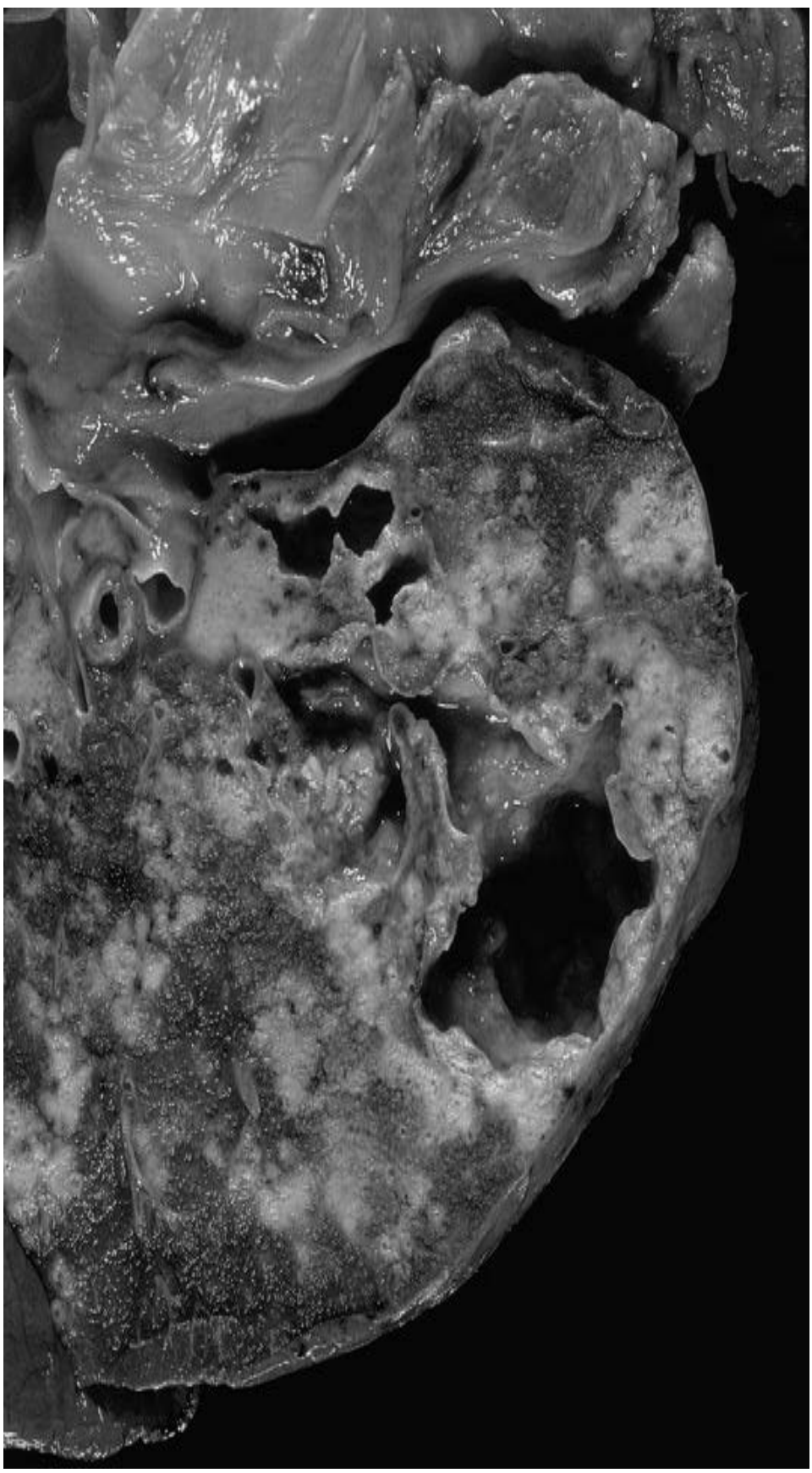


Tuberculosis



CAVITATION





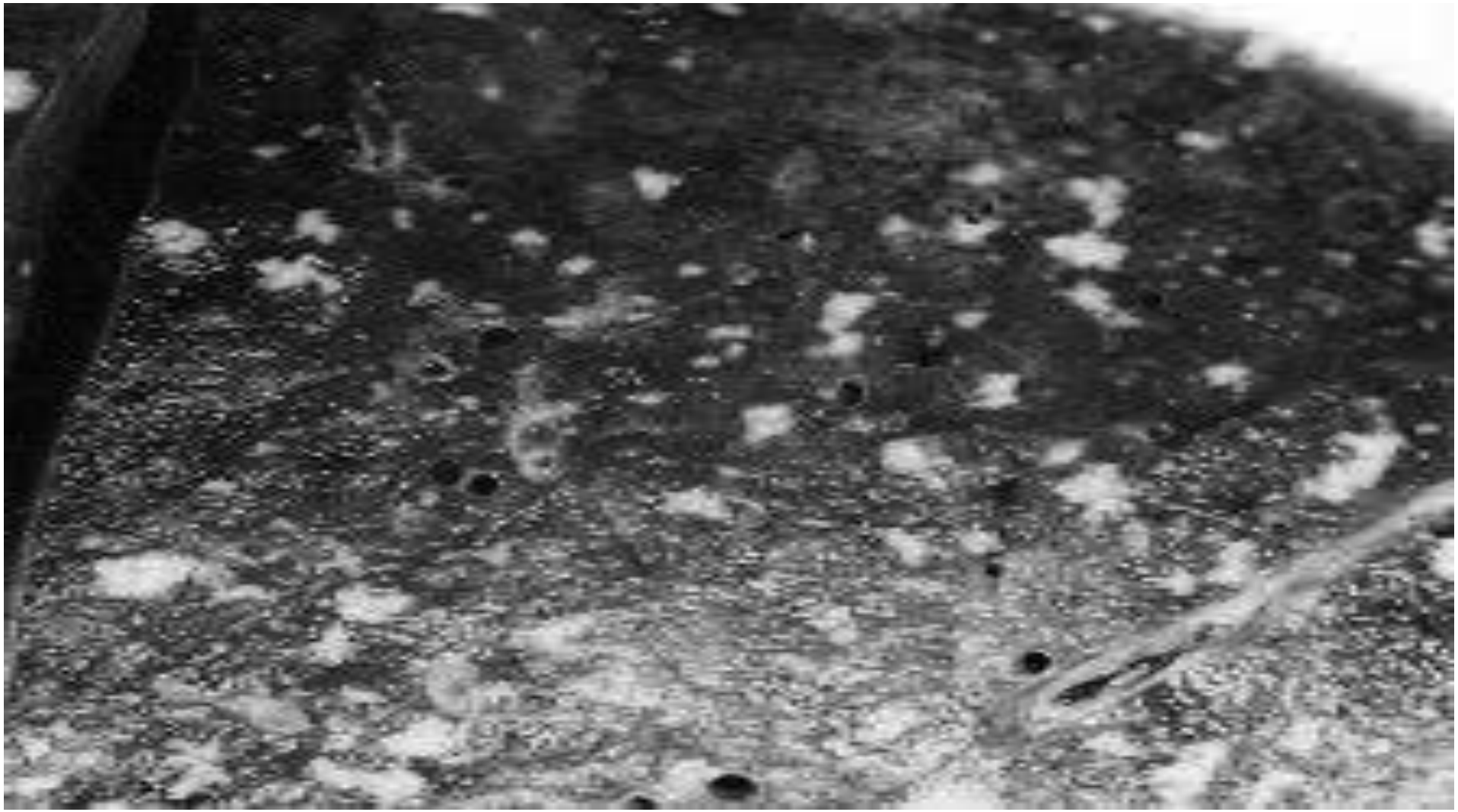
Morphology of secondary TB

- The initial lesion usually is a small focus less than 2 cm within 2 cm of the apical pleura.
- Erosion of blood vessels results in hemoptysis
- With adequate treatment, the process may be arrested, although healing distorts the pulmonary architecture

1. Miliary pulmonary disease

- Occurs when organisms drain through lymphatics into the lymphatic ducts, then empty into the venous return to the heart and then into the pulmonary arteries
- Individual lesions are small, (2 mm) foci scattered through the lung parenchyma

Pulmonary MILIARY TB



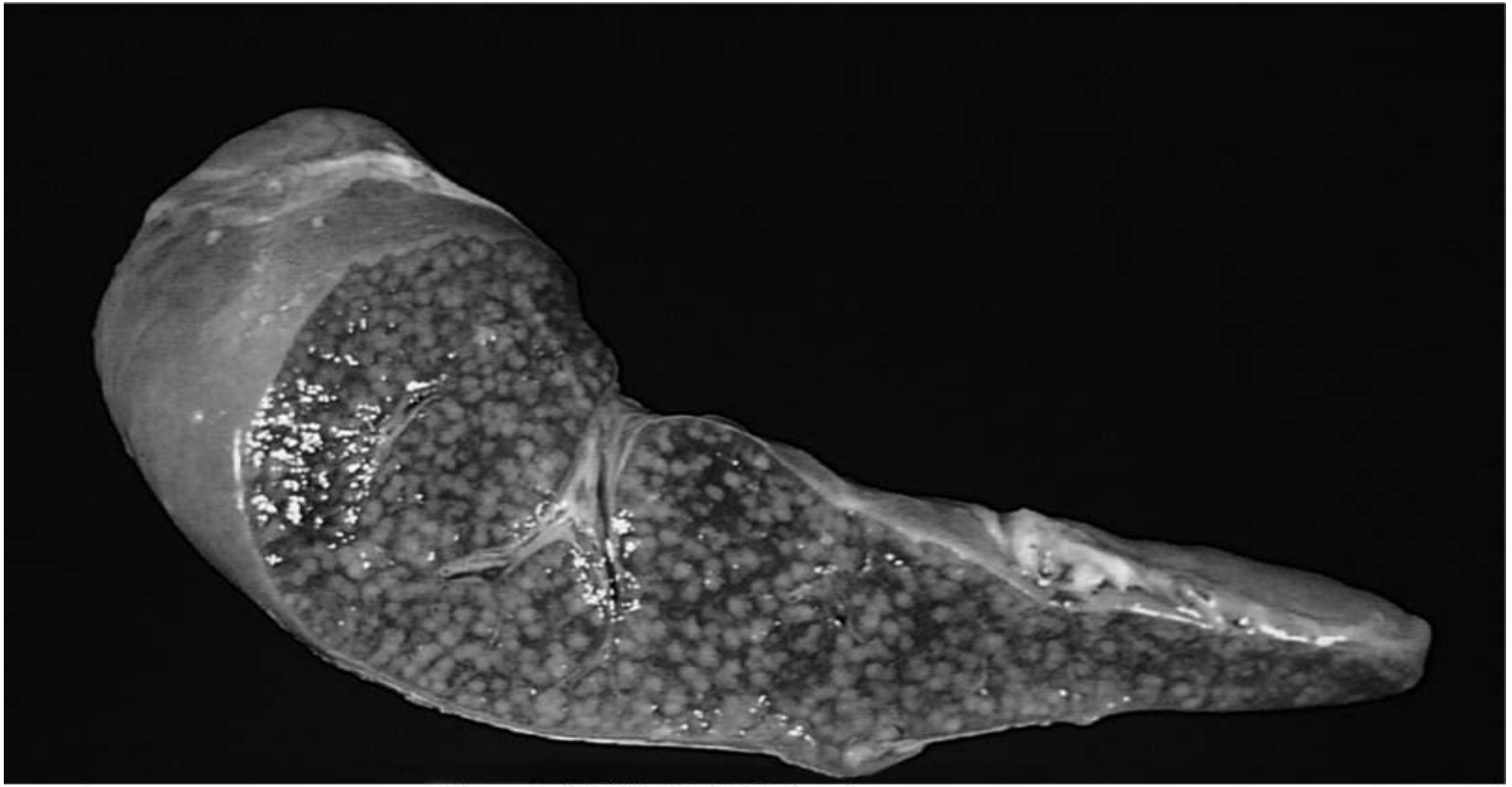
2. Systemic miliary tuberculosis

- Occurs when the organisms disseminate through the systemic arterial system to almost every organ in the body and Is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis

3. Isolated-organ tuberculosis

- Tuberculous involvement of Vertebrae is called (Pott disease).

Miliary TB in spleen



Clinical Features

- Localized secondary tuberculosis may be asymptomatic.
- If symptomatic, symptoms are insidious in onset.
- Systemic manifestations, include malaise, anorexia,

  weight loss, low grade fever, and night sweat

- With progressive pulmonary involvement, increasing amounts mucopurulent sputum
- Some degree of hemoptysis is present some cases of pulmonary tuberculosis.
- pleuritic pain

.

Extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved for example,:

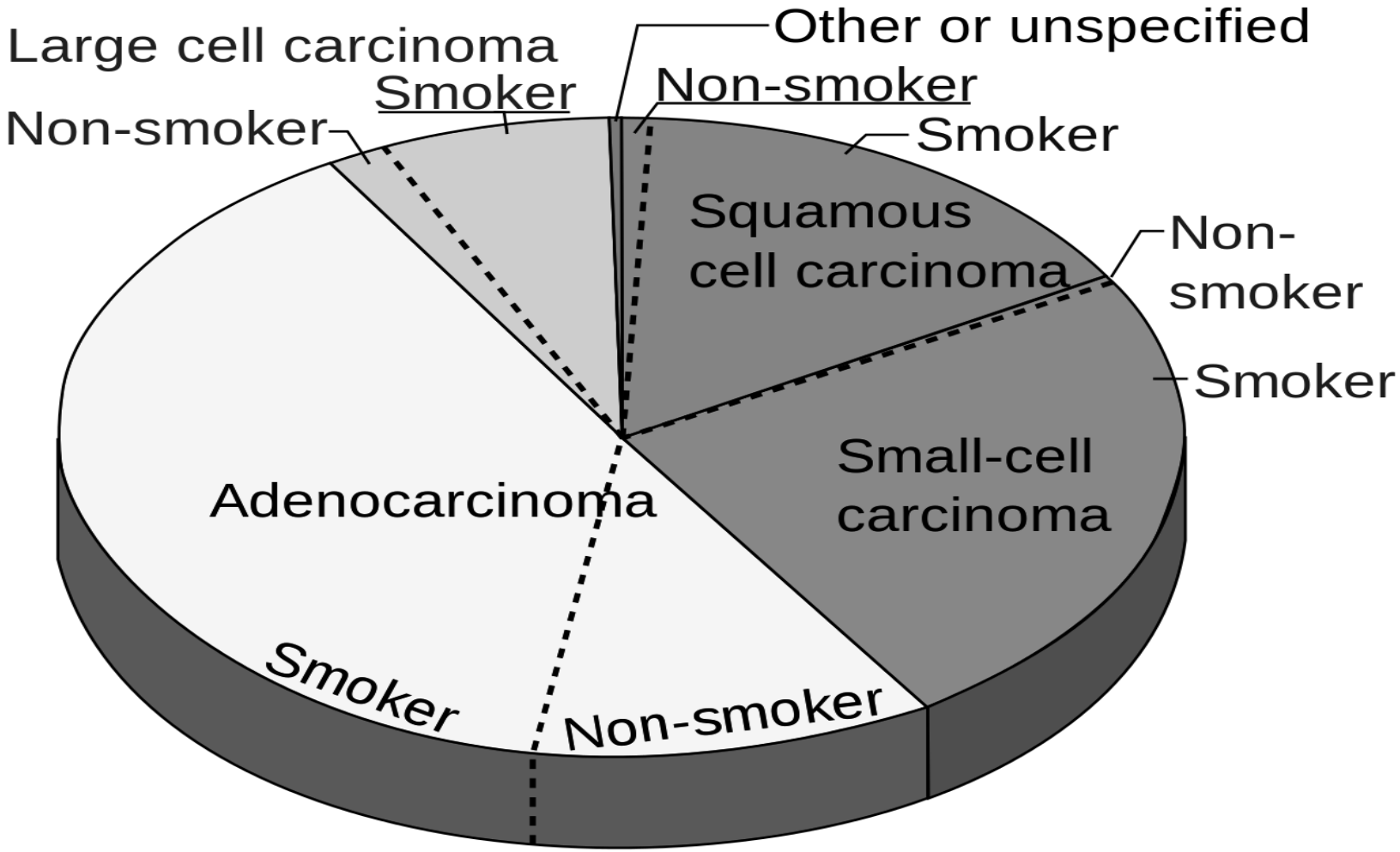
a. Tuberculous salpingitis may present as infertility,

b.Tuberculous meningitis with headache and neurologic deficits,

c. Pott disease with back pain and paraplegia

Lung carcinoma

Lung tumors


Large cell carcinoma
Smoker
Non-smoker
Other or unspecified
Non-smoker
Smoker
Squamous cell carcinoma
Non-smoker
Smoker
Small-cell carcinoma
Adenocarcinoma
Smoker
Non-smoker

- Primary lung cancer is a common disease accounting for 95% of primary lung tumors
- Carcinoma: Is the single most important cause of cancer-related deaths in industrialized countries accounts for about one third of cancer deaths in men, and has become the leading cause of cancer deaths in women

- The peak incidence of lung cancer is in persons in their 50s and 60s.
- The prognosis with lung cancer is dismal:

1.The 5- year survival rate for all stages of lung cancer combined is about 16%,

2. Disease localized to the lung, the 5-year survival rate is 45%

- The four major histologic types of carcinomas of the lung

a. Adenocarcinoma

b. Squamouscell carcinoma,

c. Small cell carcinoma,

d. Large cell carcinoma

- Because of changes in smoking patterns in the U.S., adenocarcinoma has replaced squamous cell carcinoma as the most common primary lung tumor in recent years
- Carcinomas of the lung were classified into two groups:

a. Small cell lung cancer (SCLC) and

b. Non-small cell lung cancer (NSCLC), including adenocarcinomas and squamous cell carcinomas.

- The reason for this historical distinction was that virtually all SCLCs have metastasized by the time of diagnosis and are not curable by surgery and are treated by chemotherapy, with or without radiation therapy

- By contrast, NSCLCs were more likely to be resectable and usually responded poorly to chemotherapy

; however, now therapies are available that target specific mutated gene products present in the various subtypes of NSCLC, mainly in adenocarcinomas.

- NSCLC must be classified into histologic and molecular subtypes

- There is strong evidence that cigarette smoking and, to a much lesser extent, other environmental insults are responsible for the genetic changes in lung cancers.
- About 90% of lung cancers occur in active smokers or those who stopped recently.
- The increased risk becomes 60 times greater among habitual heavy smokers (two packs a day for 20 years) than among nonsmokers

- Since only 11% of heavy smokers develop lung cancer, however, other predisposing factors must play a role.
- The mutagenic effect of carcinogens is conditioned by (genetic) factors.
- Many chemicals (procarcinogens) require metabolic activation via the P- 450 monooxygenase enzyme system for conversion into ultimate carcinogens

- Persons with specific genetic polymorphisms involving the P-450 genes have an increased capacity to metabolize procarcinogens derived from cigarette smoke, and thus have the greatest risk for development of lung cancer
- For reasons not clear, women have a higher susceptibility to carcinogens in tobacco than men.

- Although cessation of smoking decreases the risk of developing lung cancer over time, it may never return to baseline levels
- Passive smoking increases the risk of developing lung cancer to approximately twice that of nonsmoker
- The smoking of pipes and cigars also increases the risk, but only modestly

- There is increased incidence of lung carcinoma in asbestos workers; and workers exposed to dusts containing arsenic, chromium, uranium

Note

- Exposure to asbestos increases the risk of lung cancer fivefold in nonsmokers.

- Heavy smokers exposed to asbestos have an approximately 55 times greater risk for development of lung cancer than that for

  nonsmokers not exposed to asbestos

- Smoking-related carcinomas of the lung arise by a stepwise accumulation of a multitude of genetic abnormalities that result in transformation of benign progenitor cells in the lung into neoplastic cells.
- The sequence of molecular changes is not random but follows a predictable sequence that parallels the histologic progression toward cancer.

1. Inactivation of tumor suppressor genes located on the short arm of chromosome 3 (3p) is a very early event, whereas TP53 mutations or activation of the KRAS

2. In Adenocarcinomas

a. Activating mutations of the epidermal growth factor receptor (EGFR) and these tumors are

sensitive to agents that inhibit EGFR signaling, but the response often is short-lived.

b. MET tyrosine kinase gene amplifications

c. In 4% of adenocarcinomas are EML4-ALK tyrosine kinase fusion genes and

4. ALK tyrosine kinase fusion genes and c-

- These abnormalities, while rare, are important because of their therapeutic implications, as they can be targeted with tyrosine kinase inhibitors.

- The identification of genetic alterations producing overactive EGFR, ALK, and MET has opened up a new era of "personalized" lung cancer therapy

- Among the major histologic subtypes of lung cancer, squamous and small-cell carcinomas show the strongest association with tobacco exposure.

- MORPHOLOGY

1. Squamous cell carcinomas :

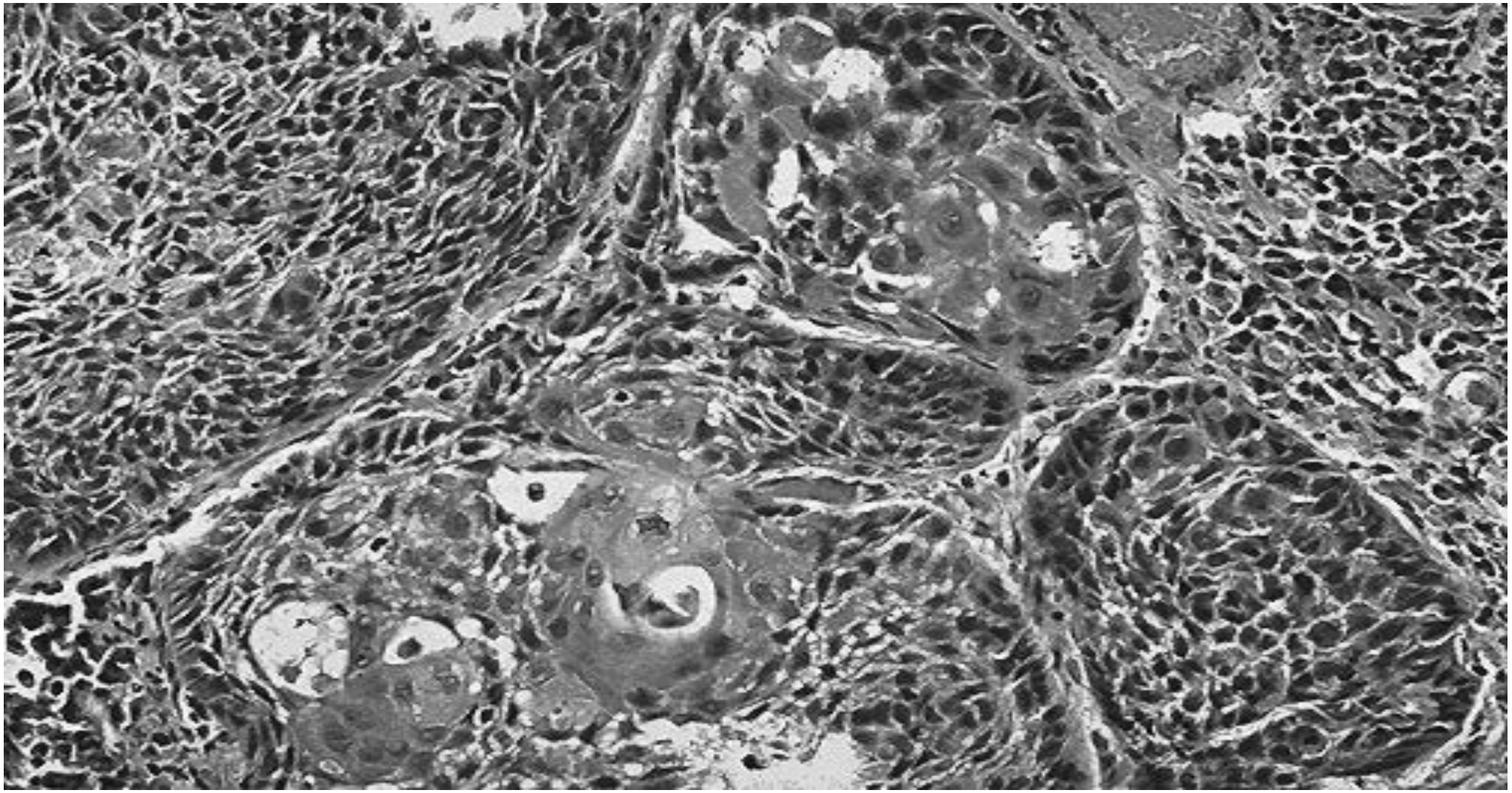
a. Are more common in men than in women

b. Are closely correlated with a smoking history;

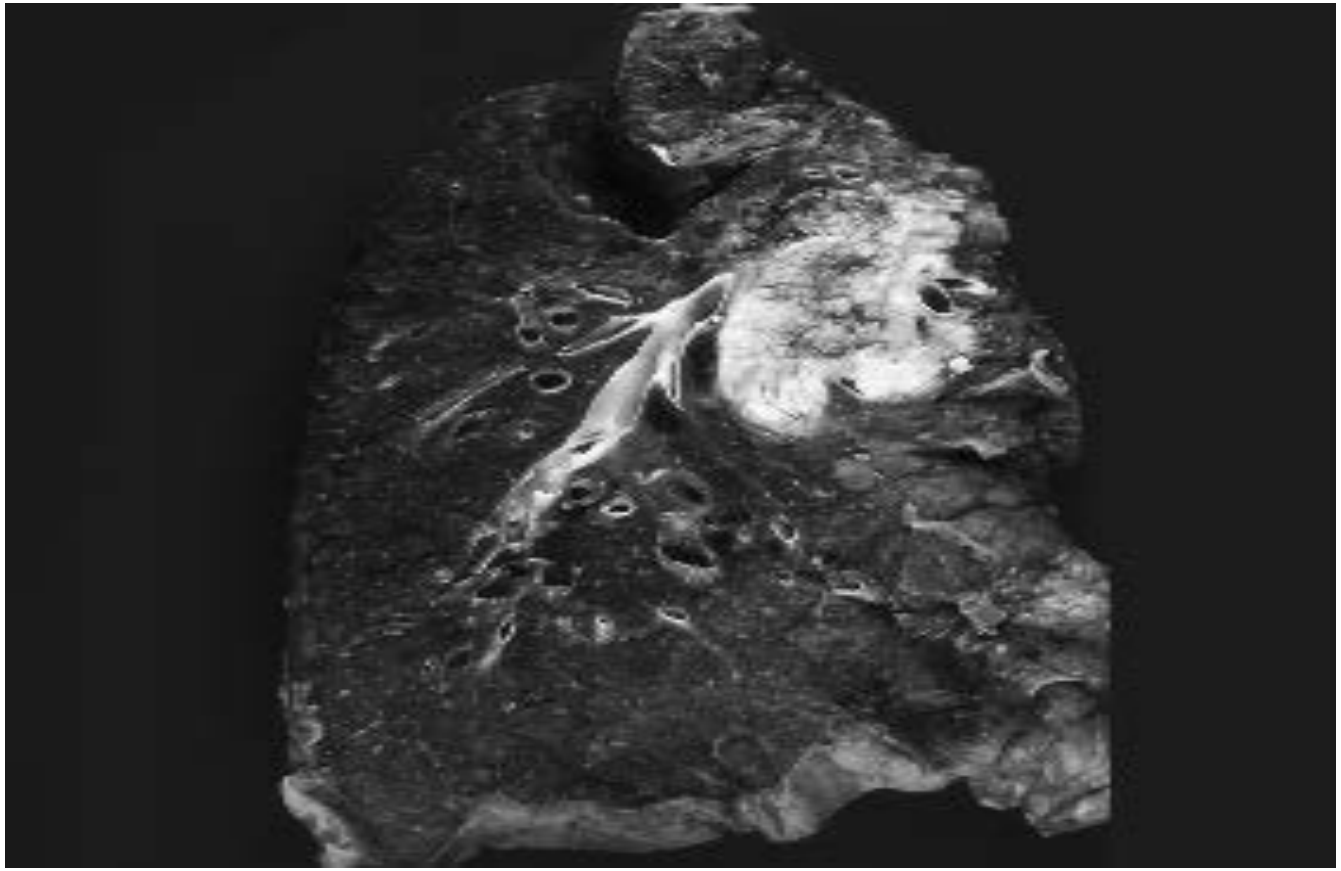
c. They tend to arise centrally in major bronchi and eventually spread to local hilar nodes,

d. Disseminate outside the thorax later than do other histologic types

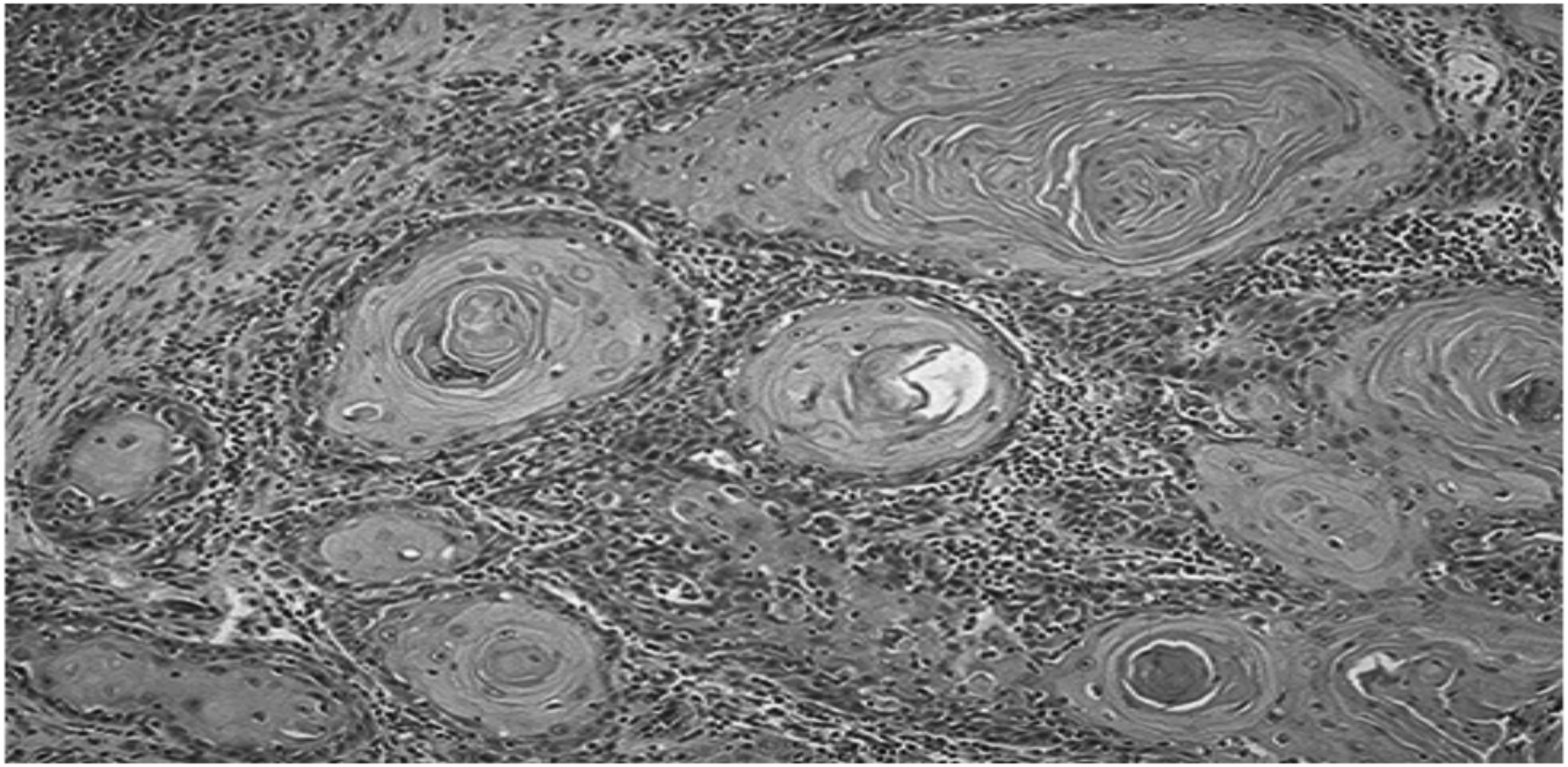
Squamous cell carcinoma of lung



SCC.. Centrally located



SCC.. Keratin production



2. Adenocarcinomas:

a. May occur as central lesions but usually are more

peripherally located, many with a central scar.

b. Are the most common type of lung cancer in women and nonsmokers

c. In general, adenocarcinomas grow slowly and form smaller masses than do the other subtypes

d. They tend to metastasize widely at an early stage

- The precursor of peripheral adenocarcinomas is atypical adenomatous hyperplasia which progresses to

a. Adenocarcinoma in situ

b. Minimally invasive adenocarcinoma (tumor less than 3 cm and invasive component measuring 5 mm or less),

c. Invasive adenocarcinoma (tumor of any size that has invaded to depths greater than 5 mm).

3. Small cell lung carcinomas (SCLCs) are:

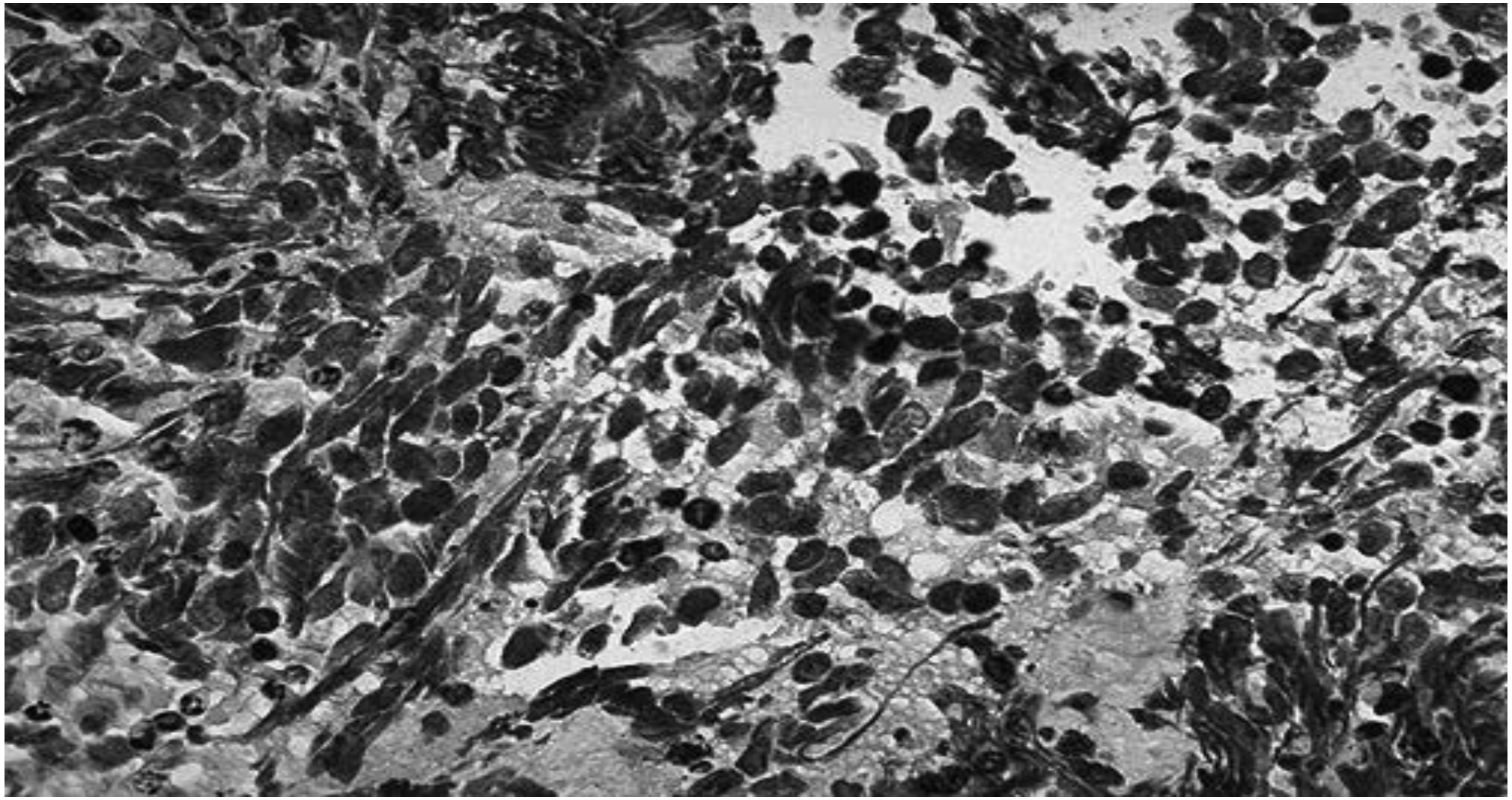
a. Centrally located with extension into the lung parenchyma

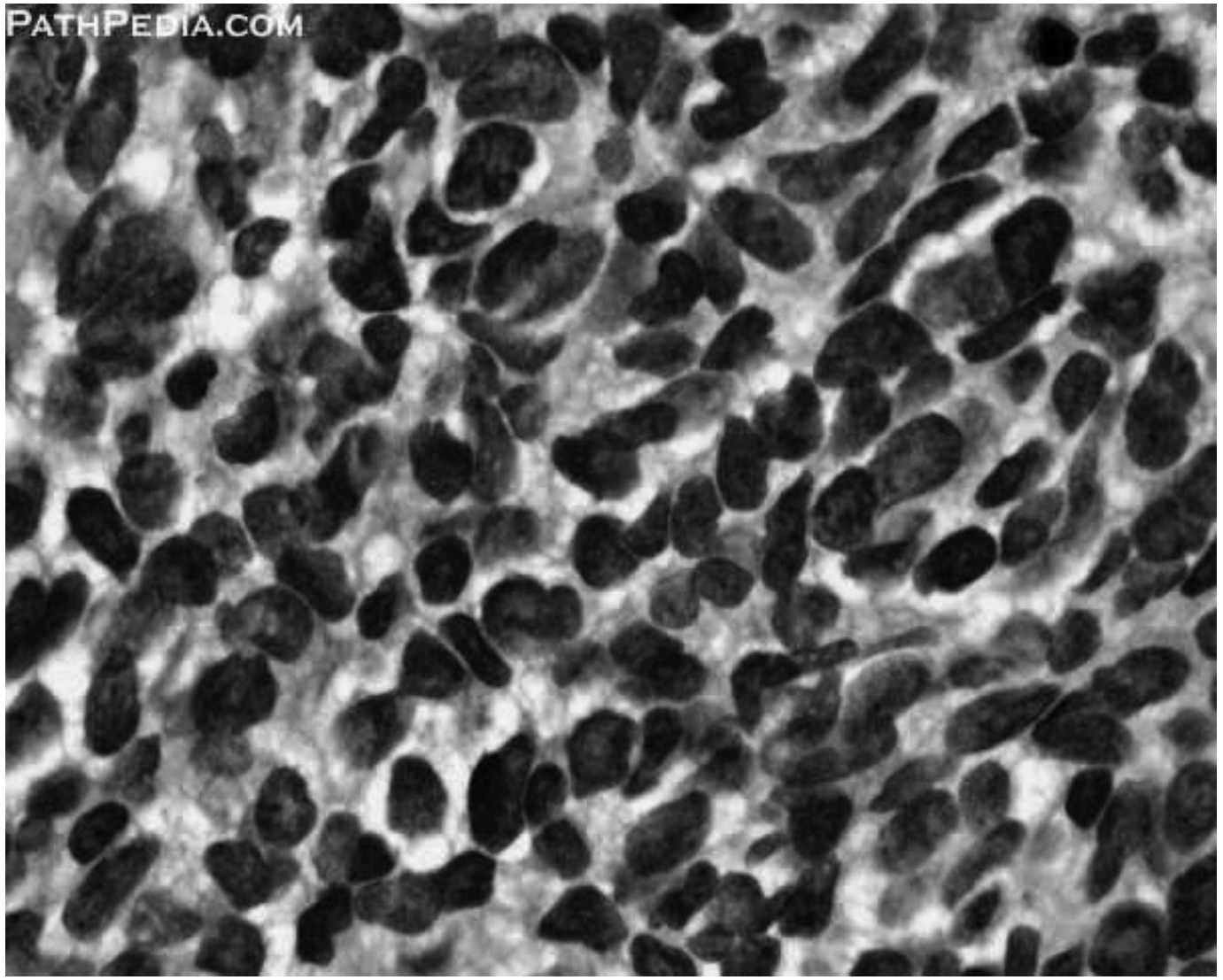
b. Early involvement of the hilar and mediastinal nodes.

c. Are composed of tumor cells with a round shape, scant cytoplasm, and finely granular chromatin with many mitotic figures .

- Necrosis is invariably present and may be extensive
- Fragile cells that show fragmentation and "crush artifact".
- Nuclear molding resulting from close apposition of tumor cells that have scant cytoplasm.

Small cell carcinoma of the lung

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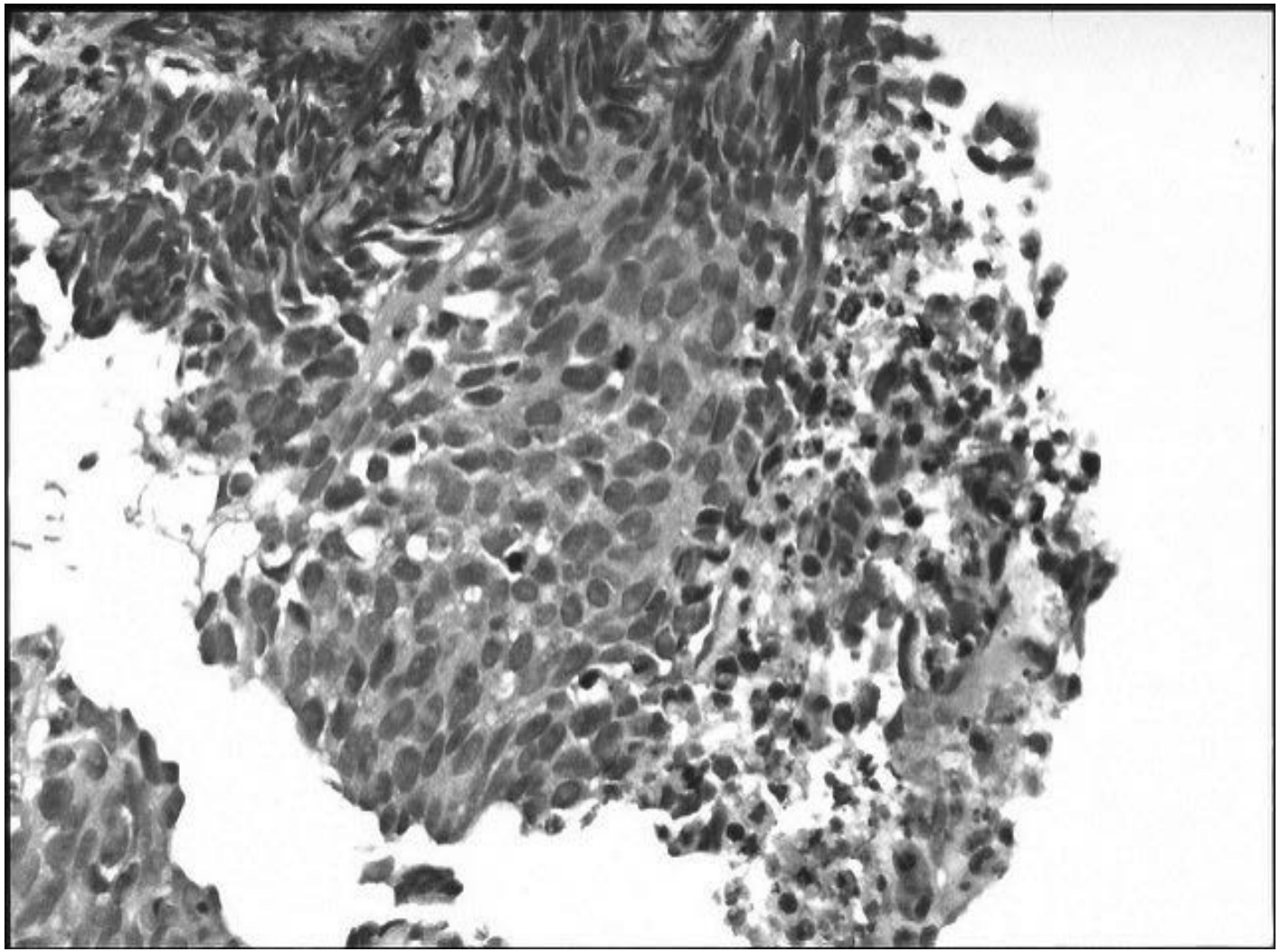
Crushing artefacts in small cell carcinoma



Clinical Course

- Are silent, cancers that in many cases have spread so as to be unresectable before they produce symptoms.
- In some instances, chronic cough call attention to still localized, resectable disease.
- By the time hoarseness, chest pain, superior vena cava syndrome, pleural effusion, makes its appearance, the prognosis is grim

- Too often, the tumor presents with symptoms resulting from metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain).
- Although the adrenals may be nearly obliterated by metastatic disease, adrenal insufficiency (Addison disease) is uncommon,

- About 3% to 10% of all patients with lung cancer develop clinically overt paraneoplasticsyndromes.

1. Hypercalcemia: caused by secretion of a parathyroid hormone-related peptide by squamous cell carcinoma
2. Cushing syndrome (production of

Adrenocorticotropic hormone);by small cell carcinoma

3. Syndrome of inappropriate secretion of antidiuretic hormone; by small cell carcinoma

4. neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis

5) clubbing of the fingers and hypertrophic pulmonary osteoarthropathy by any type of carcinoma


THANK YOU!