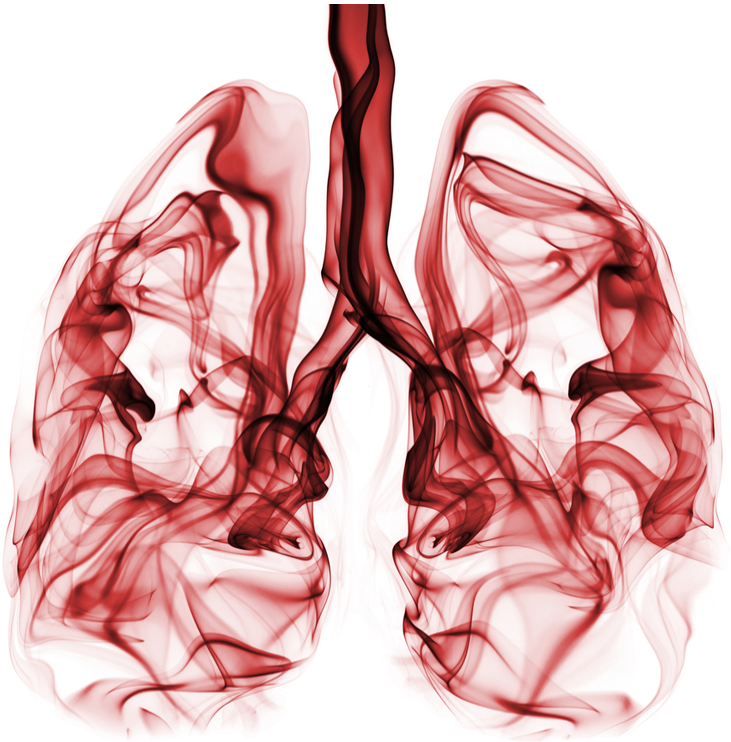
Restrictive Lung Diseases & ARDS



@pathology434

Objectives:

- Understand the structure and constituents of the lung interstitium as well as the restrictive changes which occur in these diseases and lead to the development of symptoms of progressive breathlessness and cough in affected patients.
- Appreciate the pathogenesis of interstitial lung diseases regardless of their type. This pathogenesis include the influx of inflammatory cells into the alveoli and alveolar walls, distortion of the normal structure of alveoli, release of chemical mediators and promotion of fibrosis (honey-comb lung).
- Become aware of the classification of interstitial lung diseases.

Important note: During the previous blocks, we noticed some mistakes just before the exam and we didn't have the time to edit the files. To make sure that all students are aware of any changes, please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: **Pathology Edit**

At the beginning of the lecture, we would like to differentiate (As Robbins does) between restrictive lung diseases & acute lung injury. Acute lung injury includes Acute Respiratory Distress Syndrome (ARDS) & Neonatal Respiratory Distress Syndrome (NRDS). Restrictive lung diseases should be distinguished, & these include: fibrosis of the alveolar walls & pneumoconiosis.

Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome (ARDS) & Neonatal Respiratory Distress Syndrome (NRDS) have different pathogeneses. In ARDS there is diffuse alveolar damage which injures the alveolar walls. In NRDS, however, the primary cause is decreased surfactant, which causes collapse of alveoli. In this section we will talk about these diseases & their pathogeneses.

Acute Lung Injury.

The term acute lung injury encompasses a spectrum of bilateral pulmonary damage (endothelial and epithelial), which can be initiated by numerous conditions.

Clinically, acute lung injury manifests as:

1. Acute onset of dyspnea.
2. Decreased arterial oxygen pressure (hypoxemia).
3. Development of bilateral pulmonary infiltrates on the chest radiograph (caused by damage to the alveolar capillary membrane).

Acute lung injury can progress to the **more severe** acute respiratory distress syndrome, described next.

Adult Respiratory Distress Syndrome (ARDS):

ARDS is a clinical syndrome caused by diffuse alveolar capillary and epithelial damage. **How do patients get ARDS?**

Direct Lung Injury	Indirect Lung Injury
Common Causes	
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock
Uncommon Causes	
Pulmonary contusion	Cardiopulmonary bypass
Fat embolism	Acute pancreatitis
Near-drowning	Drug overdose
Inhalational injury	Transfusion of blood products
Reperfusion injury after lung transplantation	Uremia

Oxygen toxicity: is a condition resulting from the harmful effects O2 at elevated partial pressures, free radicals will elevate and these free radicals will cause damage to the pneumocystis.

Pathogenesis:

- The damage is usually on the epithelium (alveolar side) & endothelium (capillary side)

Cellular injury → increased vascular permeability (Hemorrhage) → infiltration of fluid into the alveoli (Exudate edema) → loss of diffusion capacity

- This cellular injury affects type II pneumocytes → surfactant abnormalities

Neutrophils come to the alveoli (Inflammation) → neutrophils release products (such as proteases) → damage to the alveolar epithelium & endothelium

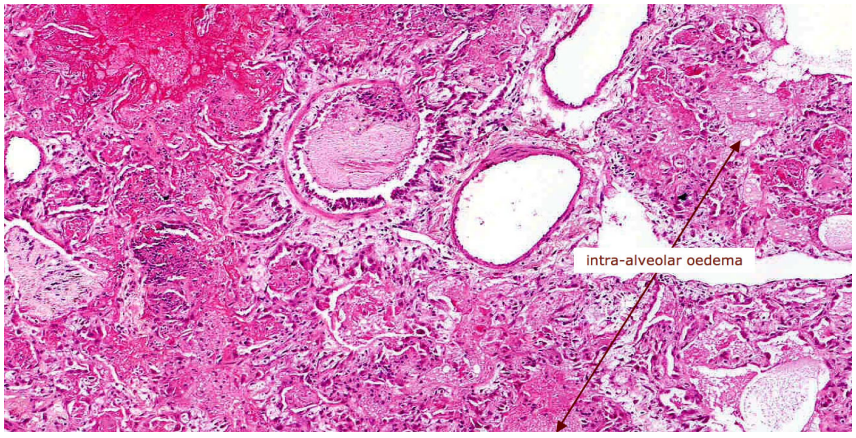
This inflammation resolves as fibrin rich edema fluid with necrotic epithelial cells. This explains the hyaline membrane appearance under the microscope coming up next.

Microscopic finding of a patient with ARDS:

1-Acute phase: Inflammatory cells infiltrate the alveolar wall (Edema)

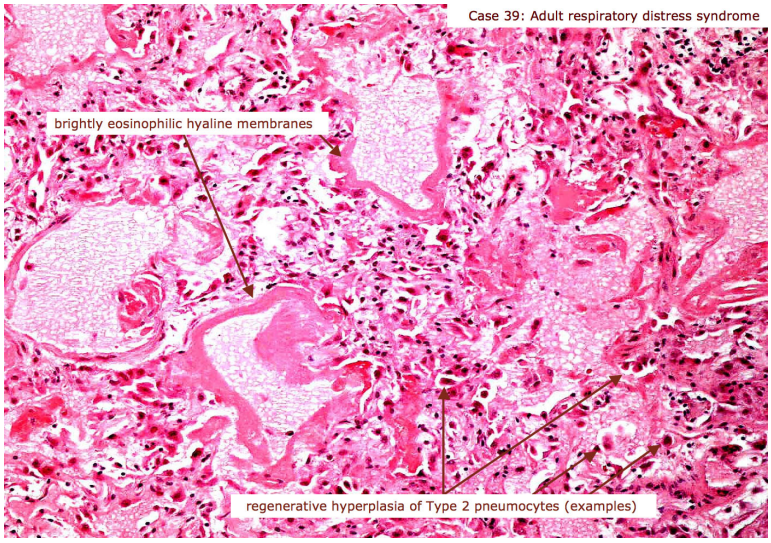
We find fibrin and necrotic cells instead of type II pneumocytes lining. Exudate coming from the vascular permeability and vascular dilation caused by the inflammatory reaction caused by the initial injury . (Any one of the types mentioned above)

Type 1 pneumocytes are incapable of regeneration. Which one regenerate ? Type II



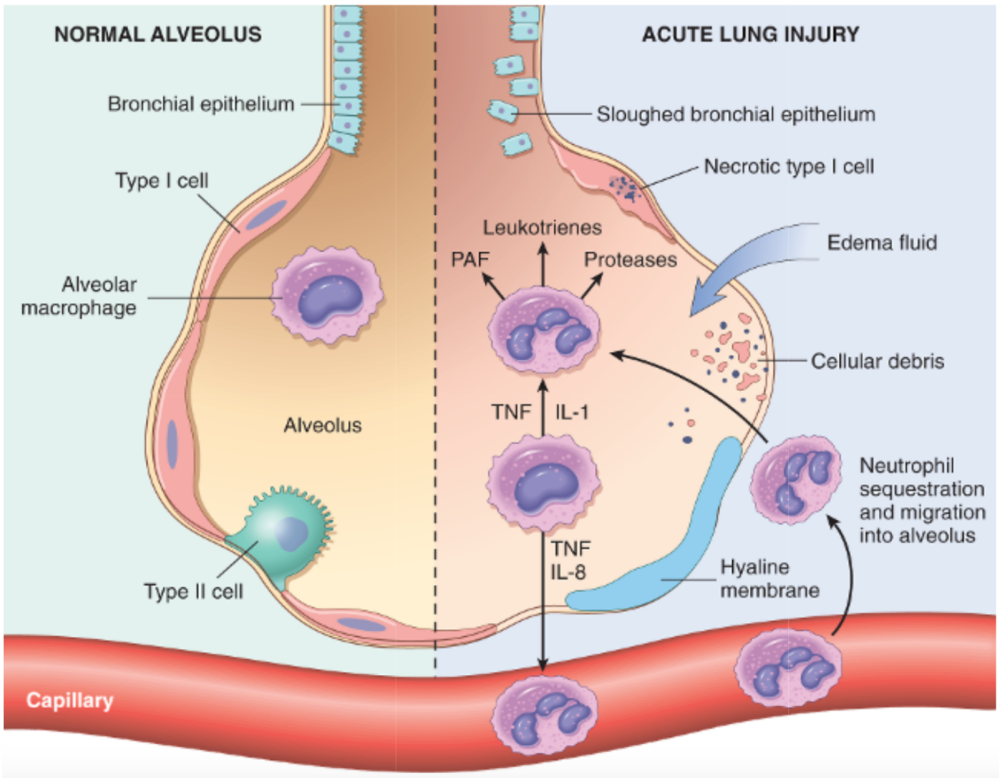
2- regenerating phase if we could help this man we will have:

Hyperplasia of type II pneumocytes and the hyaline membrane will disappear and get replaced by type II pneumocytes And he may regain his function but a lot dies .



After this stage the patient either recover or die (at least 20-25 % will die), if he recovers (with treatment) he'll go to the next stage.

Regenerating phase:
regeneration of type II pneumocyte " type I can't regenerate" → Type II will line the alveolar again → Removal of hyaline membrane " we'll still have fibrosis and inflammation".



Acute Respiratory Distress Syndrome

- ARDS is a clinical syndrome of progressive respiratory insufficiency caused by diffuse alveolar damage in the setting of sepsis, severe trauma, or diffuse pulmonary infection.
- Neutrophils and their products have a crucial role in the pathogenesis of ARDS by causing endothelial and epithelial injury.
- The characteristic histologic picture is that of alveolar edema, epithelial necrosis, accumulation of neutrophils, and presence of hyaline membranes lining the alveolar ducts.

Neonatal Respiratory Distress Syndrome.

The main pathology in NRDS is lack of surfactant. Of note, Amniotic fluids aspiration may be a cause.if the baby aspirate the amniotic fluid (maybe because prolonged labor) so this will cause damage to type I pneumocyte and will develop RDS).

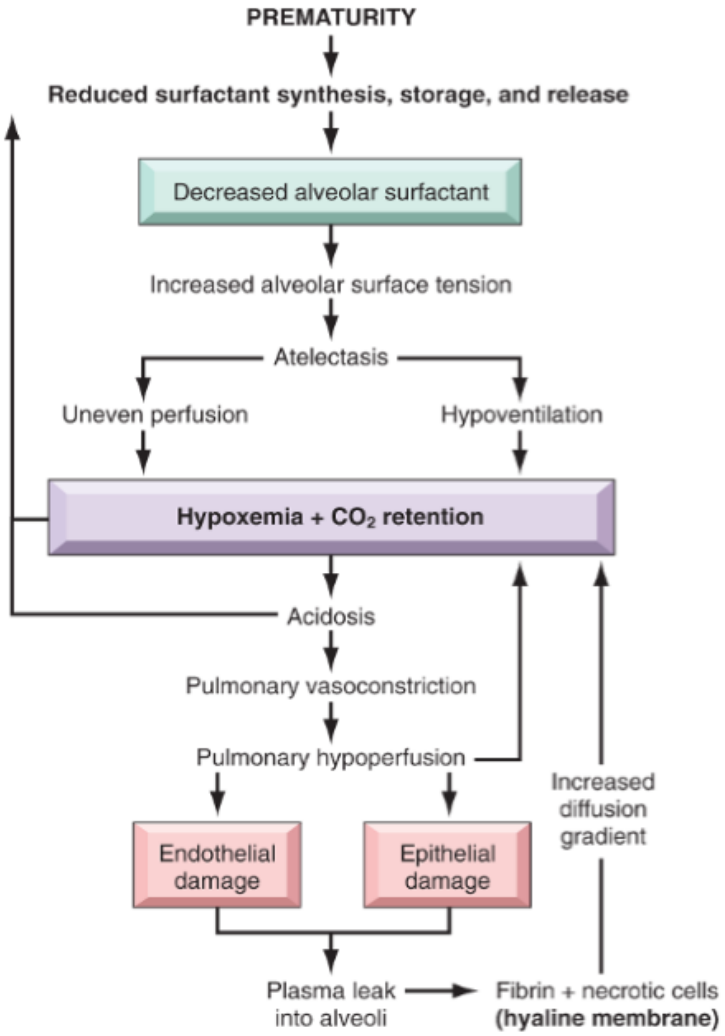
Let us talk about surfactant: to make this make sense, we should point out a couple of things about surfactant.

- It is not fully developed in premature babies because it needs time to develop. If you like to see the numbers, they are quite interesting: P.250 Robbins Pathogenesis green box.
- It's synthesis depends on glucocorticoids (stress hormones)

There are many causes of neonatal RDS and this may include:

1. **Those who were born prematurely " less than 36 weeks".**

   Premature deliveries have a higher risk because surfactant is less likely developed.



2. **Delivery by caesarean section (some not all).**

This is related to glucocorticoids. What do you think is more stressful for the neonate & mother: squeezing his whole body out of the vigina or getting out by a C- section? Obviously the first is more stressful. Therefore, normally, lots of stress hormones are released from the mother & neonate. This explains why C - section delivery increases the risk of NRDS.

Neonatal distress syndrome sometimes called **hyaline membrane disease**.

All of these are associated with type II pneumocytes damage or immature type II pneumocytes " if it was immature baby " and that means that they will not produce SURFACTANT .

Surfactant decrease the tension inside the alveoli and therefore keep them open, also the surfactant prevent the lung from collapsing.

pathogenesis:

Alveolar collapse → hypoxia → alveolar lining damage → he'll go through the same sequences as in adult → formation hyaline membrane

- some may recover and others may die.

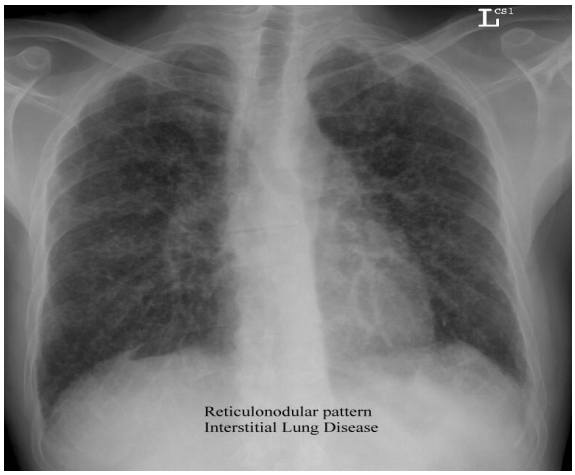
SUMMARY

Neonatal Respiratory Distress Syndrome

- Neonatal RDS (hyaline membrane disease) is a disease of prematurity; most cases occur in neonates born before 28 weeks of gestational age.
- The fundamental abnormality in RDS is insufficient pulmonary surfactant, which results in failure of lungs to inflate after birth.
- The characteristic morphologic pattern in RDS is the presence of hyaline membranes (consisting of necrotic epithelial cells and plasma proteins) lining the airways.
- RDS can be ameliorated by prophylactic administration of steroids, surfactant therapy, and by improved ventilation techniques.

Introduction to Restrictive Lung Diseases.

They are chronic interstitial diseases, heterogeneous group characterized by **reduced compliance** which leads to dyspnea. Damage in alveolar epithelium and interstitial vasculature lead to hypoxia. Patients have difficulties in inspiration and x-ray will show you small nodules or irregular lines.



Symptoms.

- severe dyspnea
- hypoxia or hypoxemia
- cyanosis
- dry cough
- exertion [1]on breathing

N.B remember the cough in COPD is productive

- reduce in the lung volume and elasticity, therefore the lung is less compliant
- finally may lead to fibrosis of lung

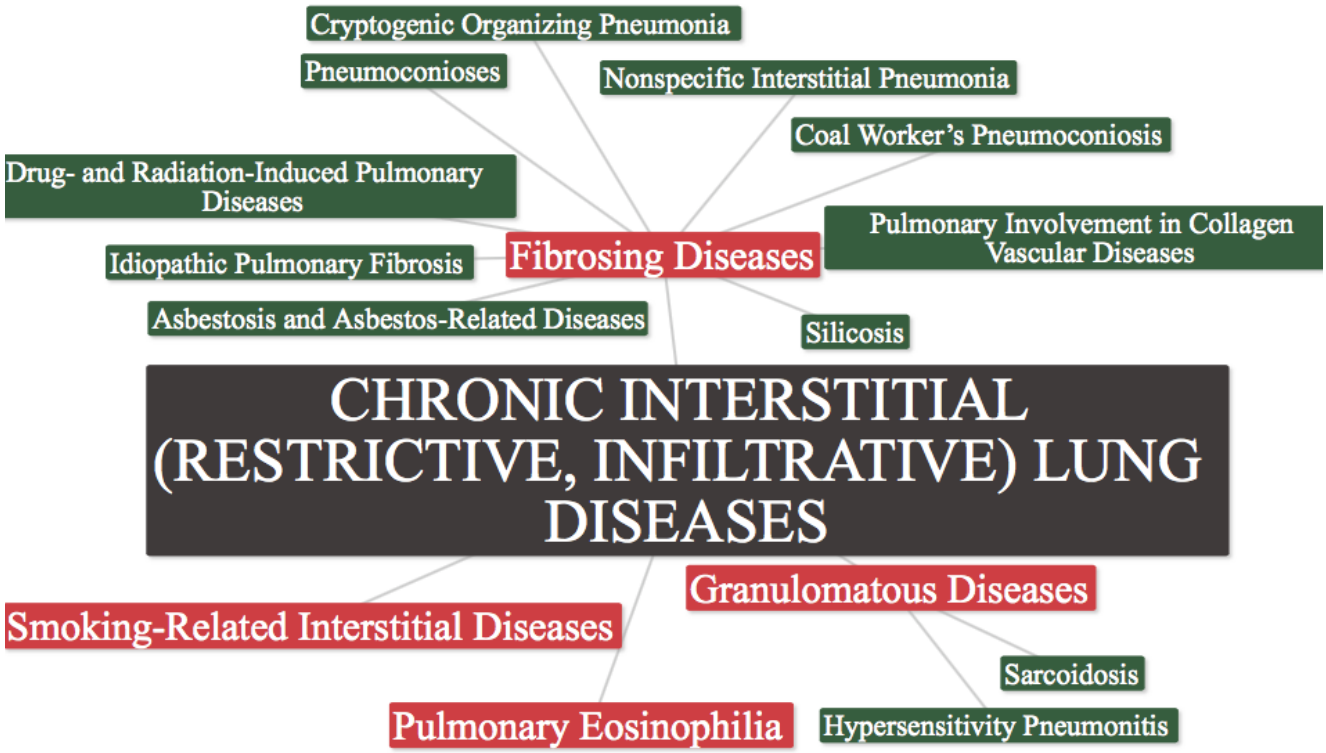
Obstructive Vs. Restrictive pulmonary diseases.

Variable	Obstructive Pattern, e.g., Emphysema	Restrictive Pattern, e.g., Fibrosis
Total lung capacity	↑	↓
FEV_1	↓	↓
Forced vital capacity	↓	↓
FEV_1/FVC	↓	↑ or normal
Peak flow	↓	↓
Functional residual capacity	↑	↓
Residual volume	↑	↓

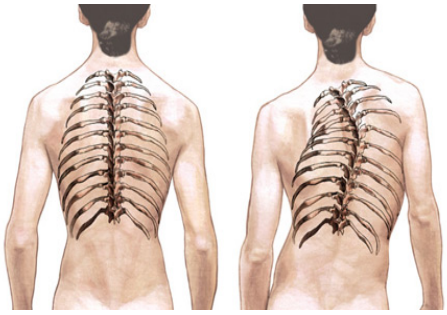
[1] extra effort

Types of Interstitial Pulmonary Diseases.

This graph gives you a general overview of the diseases in this category. For the purposes of our lectures, we are only going to talk about some diseases. Don't worry about others.



Causes of Interstitial Lung Diseases.



1. Deformity in the thoracic cage. (Chest wall /ribs)

When does it happen? Congenital abnormalities in the vertebral column or in the shape of the chest such as kyphosis, scoliosis, or kyphoscoliosis.[2]
So the lung can't expand its full capacity therefore it will be restricted.

2. Neuromuscular diseases interfering with the function of the muscles of chest wall or diaphragm.
Which we'll lead to the inability to breathe freely,the breathing becomes restricted due to muscular dystrophy; therefore those muscles can't contract or expand as they should. Think about severe forms of Myasthenia Gravis or Guillain Barre syndrome.[3]

3. Lung affected by idiopathic pulmonary fibrosis.

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[2] abnormal curvature of the vertebral column الحدب والجنف

[3] In this disease there is loss of myelination of peripheral nerves & may lead to the paralysis of the diaphragm

Idiopathic Pulmonary Fibrosis. (Robbins p 472)

- There is bilateral [4]interstitial fibrosis of the lungs
- Unknown etiology: however, the current concept is that there are repeated injuries to the lungs that cause IPS.

Morphology:

- **Honeycomb fibrosis**: collapsed alveoli with fibrosis & hyperplastic [5] type II alveolar cells.

Clinical findings:

- Faver
- Dyspnea
- Chronic nonproductive cough
- Poor prognosis (median survival 6 months to 5 years after diagnosis).

Pneumoconiosis

- Non-neoplastic lung reaction to inhalation of mineral dusts
- We are going to talk about three important substances: coal dust, silica, & asbestos.
- Particles that are 1-5 micrometers are dangerous
- Alveolar macrophage grabs these substances and causes lung injury & fibrosis
- All of these minerals **may** progress to **progressive massive fibrosis** which is very bad.

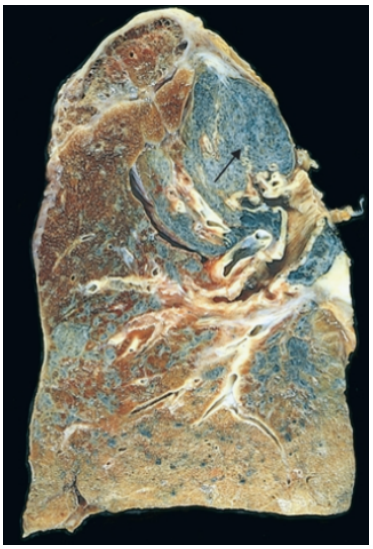
1- Coal worker pneumoconiosis

It ranges from asymptomatic to progressive massive fibrosis, in which fibrosis is extensive and lung function is compromised Although coal is mainly carbon, coal mine dust contains a variety of trace metals, inorganic minerals, and crystalline silica.

- Pathogenesis is same as we have talked about in the previous paragraph

[4] Affecting both sides
[5] Rapidly dividing

2- Silicosis.

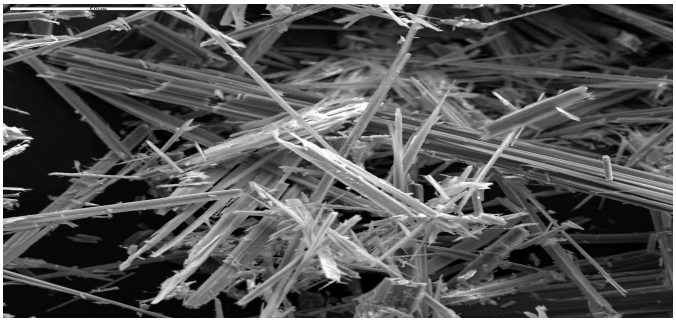


Silicosis *is currently the most prevalent chronic occupational disease in the world*. It is caused by inhalation of crystalline silica mostly in occupational settings. Workers in several occupations but especially those involved in (stone cutters, ceramic cutter and builders).

Pathogenesis: The silica is engulfed by macrophages and enters the cycle we explained earlier. As a result of this you'll get fibrosis and restrictive lung disease.. **Take a look at the arrow in the picture. Why is this part black ?** Because of carbon accumulation.

- *Silicosis is associated with an increased susceptibility to tuberculosis caused by the decrease in the immunity*.

3-Asbestosis and asbestos-related diseases.

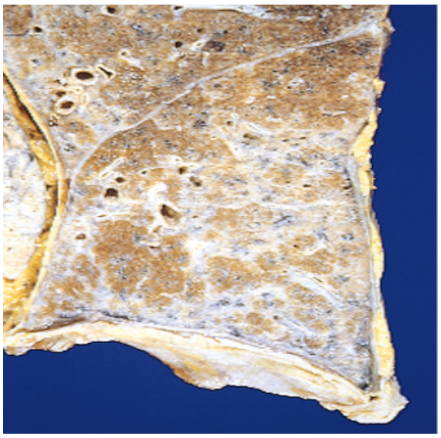


Asbestos is a chemical substance and it is fibres and these fibres are components of isolating substances (isolates).

Now this is caused by needles formed from asbestosis and these needles have **different types**:

1-amphibole: the worst one is amphibole because it is **straight and stiff**.

2-Serpentine: the fibers are flexibility, more solubility and less severity.
When asbestos enters the lungs it irritates the lung, it cause small bleeding and because of that small bleeding the color will be brownish, look at the picture:



Types of cancer related to asbestos:

They cause two types of cancer or more: **Asbestosis** an interstitial disease, **bronchogenic carcinoma**, **lung carcinoma** and **mesothelioma** which is a **malignant** tumour affecting the mesothelial cells in the pleura , so it can cause also **fibrosis** and cancer of the pleura.
The pleura is very thick and it is diminished by this tumour.

Pneumoconioses

- Pneumoconioses encompass a group of chronic fibrosing diseases of the lung resulting from exposure to organic and inorganic particulates, most commonly mineral dust.
- Pulmonary alveolar macrophages play a central role in the pathogenesis of lung injury by promoting inflammation and producing reactive oxygen species and fibrogenic cytokines.
- Coal dust–induced disease varies from *asymptomatic anthracosis,* to *simple coal worker's pneumoconiosis* (coal macules or nodules, and centrilobular emphysema), to progressive massive fibrosis (PMF), manifested by increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.
- Silicosis is the most common pneumoconiosis in the world, and crystalline silica (e.g., quartz) is the usual culprit.
- The manifestations of silicosis can range from asymptomatic silicotic nodules to PMF; persons with silicosis also have an increased susceptibility to tuberculosis. The relationship between silica exposure and subsequent lung cancer is controversial.
- Asbestos fibers come in two forms; the stiff *amphiboles* have a greater fibrogenic and carcinogenic potential than the serpentine *chrysotiles*.
- Asbestos exposure is linked with six disease processes: (1) parenchymal interstitial fibrosis (*asbestosis*); (2) localized fibrous plaques or, rarely, diffuse pleural fibrosis; (3) pleural effusions; (4) lung cancer; (5) malignant pleural and peritoneal mesotheliomas; and (6) laryngeal cancer.
- Cigarette smoking increases the risk of lung cancer in the setting of asbestos exposure; moreover, even family members of workers exposed to asbestos are at increased risk for cancer.

Granulomatous Diseases. (Robbins Page 478)

1. Sarcoidosis.

Sarcoidosis is a multisystem disease of unknown etiology characterized by **noncaseating** [6] granulomas in many tissues and organs.

2. Hypersensitivity pneumonitis "It is recommended to read this in Robbins as it is more organized p.480"

It is an immunologically mediated inflammatory lung diseases that primarily affects the alveoli therefore often called **allergic alveolitis**. Most often it is an occupational disease: related to the workplace (allergy from my boss for example).

What is the difference between this & asthma?
In asthma the pathology is related to the bronchi, where they become constricted and increased mucus secretion causes all the trouble. Here, however, the alveoli -& not the bronchi- is involved in the pathology.
Pathogenesis: the response to the antigen involves immune complexes (type three hypersensitivity) & delayed type hypersensitivity (type four hypersensitivity).

Examples of Hypersensitivity pneumonitis:

1-Fumes: Some people have hypersensitivity to fumes.

2-Farmers Lung.

3-Pigeon Breeder.
The most common hobby causing hypersensitivity pneumonitis specially here in saudi arabia are **pigeon** (being exposed to pigeon wastes). The birds feathers might cause to a lot of people some type of hypersensitivity pneumonitis like granulomas and fibrosis and they manifest as interstitial lung disease either this person is a pigeon breeder, or he is exposed to cleaning after them. We call this **pigeon breeders disease**. which is an interstitial lung disease characterised by **fibrosis**, **dyspnea**, **dry cough** and these factors might develop small granuloma.

Chronic Interstitial Lung Diseases

- Diffuse interstitial fibrosis of the lung gives rise to restrictive lung diseases characterized by reduced lung compliance and reduced forced vital capacity (FVC). The ratio of FEV to FVC is normal.
- The diseases that cause diffuse interstitial fibrosis are heterogeneous. The unifying pathogenetic factor is injury to the alveoli with activation of macrophages and release of fibrogenic cytokines such as TGF-β.
- Idiopathic pulmonary fibrosis is prototypic of restrictive lung diseases. It is characterized by patchy interstitial fibrosis, fibroblastic foci, and formation of cystic spaces (honeycomb lung). This histologic pattern is known as *usual interstitial pneumonia* (UIP).

[6] A major difference between sarcoidosis & TB is that TB usually has caseating necrosis in the middle of the granuloma

MCQ's.

1.Most common symptoms of RESTRICTIVE PULMONARY DISEASE:
a)Dyspnea
b)Productive cough
c)Dry cough
d)Both A+B
e)Both A+C

2. Honeycomb is the best describe of :
a)COPD.
b)Restrictive pulmonary disease
c)Both A+B
d)None of them

3. The size of dust that can cause disease:
a)<1µm
b)Between 1 to 5 µm
c)>5 µm
d)None of them

4. Which one of these restrictive diseases has unknown etiology:
a)Silicosis
b)Asbestosis
c)Sarcoidosis

5. Which one of these diseases is an acute restrictive lung disease:
a)Adult respiratory distress syndrome
b)Farmers lung
c)Coal worker's pneumoconiosis

6. Which one of these diseases is found in the insulation workers:
a)Asbestosis
b)Anthracosis
c)Silicosis

7. Which one of the following could be found in a normal person:
a)Anthracosis
b)Farmers lung

1- e
2- b
3-b
4-c
5- a
6-a
7-a

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Good Luck!

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أنس الزهراني
أحمد الصالح

مها الربيعة
ريما الناصر
مشاعل حسين
الجوهرة الدهيش