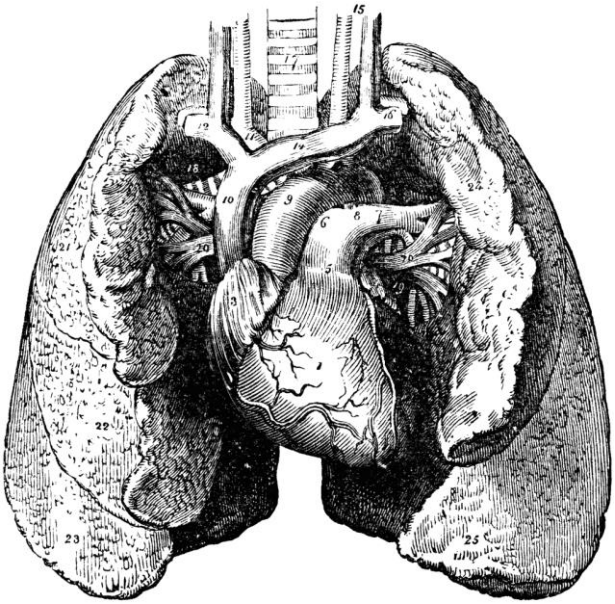
MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437



Pathology
teamwork

Lecture (3) :

pathology of restrictive lung disease including allergic alveolitis

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Revised by

Color Index :-

- **VERY IMPORTANT**
- Extra explanation
- **Examples**
- **Diseases names: Underlined**
- **Definitions**

* كيف تعلُك الدُنيا بشيء ..وأنت لعلةِ الدُنيا طبيبُ ؟..

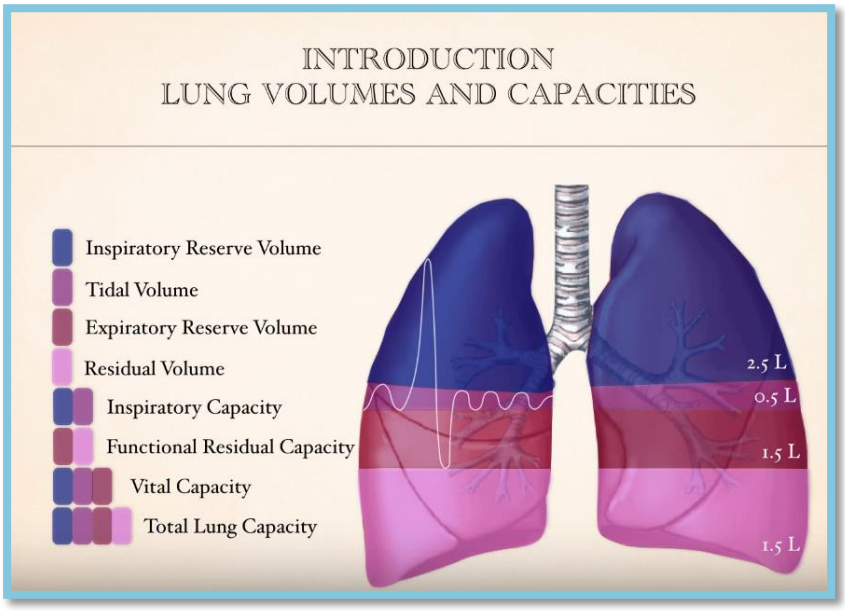
Objectives:

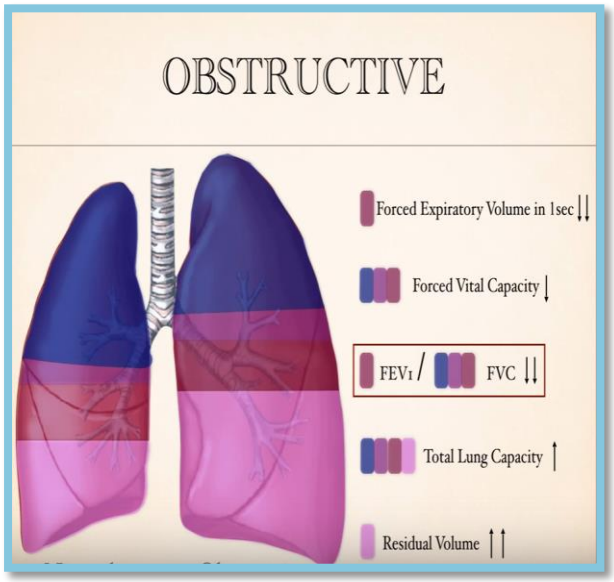
- Understand the structure and constituents of the lung interstitium as well as the restrictive changes which occur in diseases of the interstituim (ILD)
- Know the symptoms of ILD: progressive breathlessness and cough
- Know subtypes of ILD: acute and chronic
- Discuss the causes, morphology and outcome of acute ILD
- Appreciate the pathogenesis of chronic ILD regardless of their type.
- Become aware of the classification of interstitial lung diseases.
- Discuss examples of interstitial lung diseases including:
  - **idiopathic pulmonary fibrosis**
  - **Pneumoconiosis**
  - **Hypersensitibity pneumonitis**
  - **Goodpasture syndrome**
  - **Sarcoidosis**

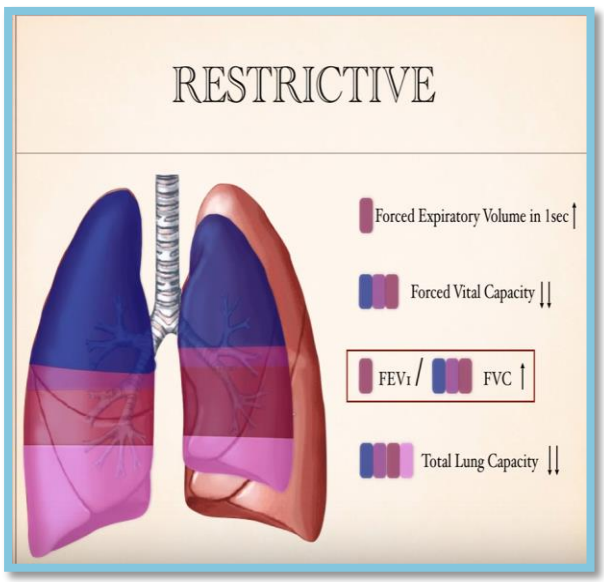
Introduction :

Restrictive lung diseases : are a category of diseases that **restrict** lung **expansion** resulting in a **decreased lung volume** so the airways are fine but the problem here is that there is something that restrict the lung such as fibrosis. But you might find a problem in the airways but in this case it's a secondary problem to the restriction.

Remember that : **total lung volume** and **forced expiratory volume in one second (FEV1)** and **forced vital capacity (FVC)** are reduced with **normal to high FEV1/FVC** قسمة عدد صغير على صغير يساوي عدد كبير



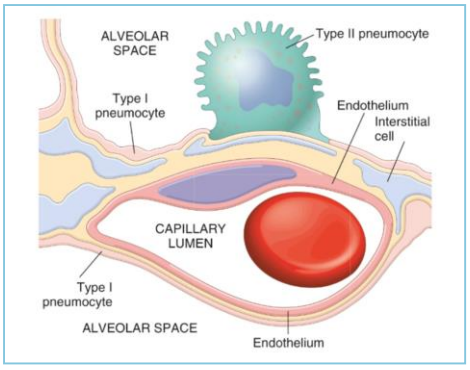




RESTRICTIVE LUNG DISEASE

The restrictive lung diseases are divided into:

Intrinsic lung disease / disease of the lung parenchyma / primary ILD	Extrinsic disorders or extraparenchymal diseases
The disease cause : -inflammation -scarring of the lung tissue (ILD) -Result in filling of the air spaces with exudate and debris (pneumonitis)	The chest wall, pleura, and respiratory muscles are the components of the respiratory pump, and they need to function normally for effective ventilation. Abnormalities of the chest wall include: -bony abnormalities (kyphosis or kypho-scoliosis) -massive pleural effusion -morbid obesity -neuromuscular disease of respiratory muscles results in respiratory muscle
They are characterized by: -Inflammatory infiltrates in the interstitial space - The interstitium becomes thickened and fibrotic (stiff lung)	
There is decreased oxygen-diffusing capacity. (they are acute or chronic)	weakness and respiratory failure e.g. myopathy or myositis, quadriplegia, or phrenic neuropathy from infectious or metabolic causes



Constituents of the lung interstitium

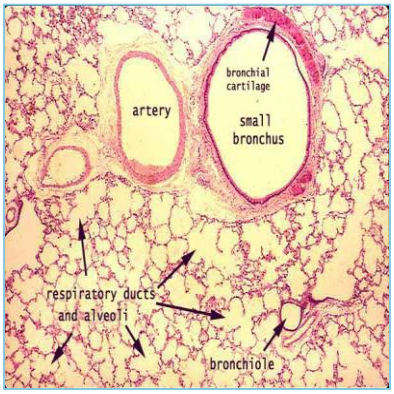
Guillain-Barré Syndrome:
is a neurological disease , can manifest with paralysis with limbs , upper limbs or lower , sometimes effect the respiratory muscles , intercostal or diaphragm , could lead to Restrictive lung disease
مجموعة امراض أدت ل مرض الرئة العاصرة

INTRINSIC TYPE OF RESTRICTIVE LUNG DISEASES

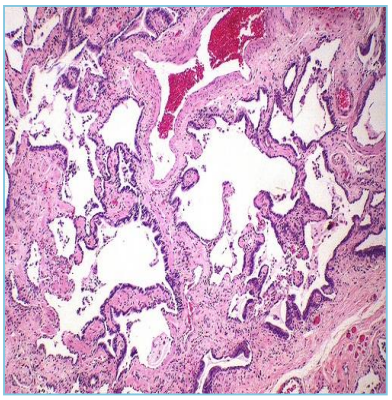
- Intrinsic type of restrictive lung diseases
  - Characterized By :
    - reduced compliance of the lung. It can be : **Acute** or **Chronic**.
  - Important sign and symptoms
    - Dyspnea
    - Hypoxia
    - In advanced cases of restrictive lung disease there is
      - severe hypoxia
      - hypercapnia
      - Cyanosis
      - respiratory failure
      - cor pulmonale.

The final stage of all restrictive lung disease is extensive fibrosis with honeycomb lung. The lung becomes more stiff and solid.

End stage lung disease: **Honeycomb lung** (both alveoli and bronchioles coalescence to form cysts lined with cuboidal or columnar epithelium and seperated by inflammatory fibrous tissue).



Normal



Honeycomb lung

To differentiate between all types we have to see:

- Clinically features
- X-ray
- Grossly
- Microscopic
- Other laboratory tests

Extra explanation:

-**why is there "dyspnea" ?** because the hallmark of this disease is reduce compliance (more pressure is required to expand the lung because they are stiff) which in turn necessitate increased of breathing leading to dyspnea

-**why it causes hypoxia?** Because there is damage to the alveolar epithelium and interstitial vasculature produces abnormalities in the ventilation-perfusion ratio leading to hypoxia.

Acute restrictive lung diseases (INTRINSIC TYPE)

- Adult respiratory distress syndromes — ARDS overview
- Neonatal respiratory distress syndromes — NRDS overview

Adult Respiratory Distress Syndrome (ARDS)

Very useful video

- **What is AEDS?**

ARDS is a **severe acute** lung **injury** with diffuse alveolar injury. * هو عباره عند اي انجري تحدث فجأه للرئتان وتأثر على .. مثل احتراق المنزل واستنشاق الدخان أو حادث مرور وأثر على الرئه

- **What is the other names for ARDS?**

shock lung / diffuse alveolar damage / adult respiratory failure/acute alveolar injury/ traumatic wet lung

- **What are the clinical Features of ARDS?**

1. rapid acute onset progressive severe **life threatening** respiratory insufficiency, **cyanosis**, **severe arterial hypoxia**
2. refractory to oxygen therapy and that may progress to multi- organ failure **
3. bilateral (both lungs) pulmonary infiltrates (edema) in the **absence** of evidence of left sided heart failure (because the left sided heart failure also can cause a bilateral pulmonary edema so we should make sure of absence of evidence of left sided heart failure)

- **What does it cause?**

It is the most common cause of **non-cardiogenic pulmonary edema**

- **What cause ARDS?**

It can be caused by many conditions such as

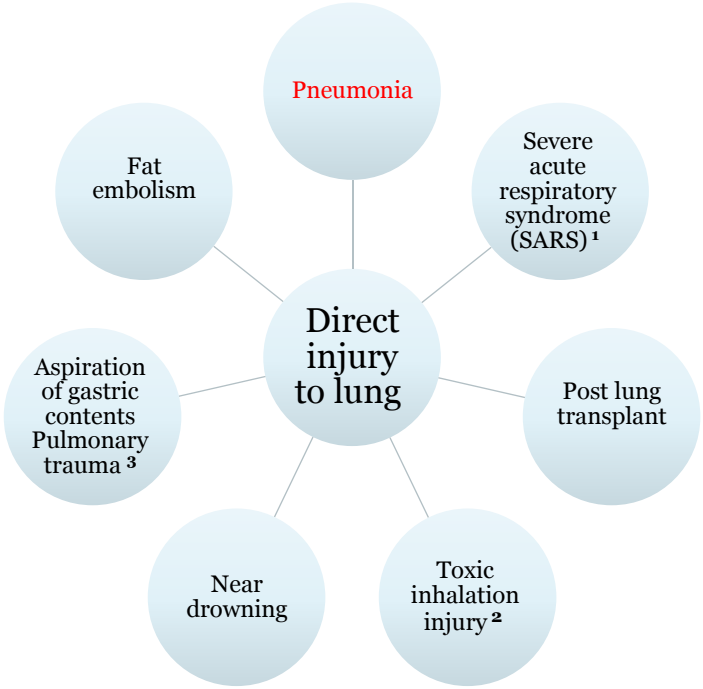
1. Direct lung injury (look in the next slide for more information)
2. Indirect lung injury (look in the next slide for more information)

- **What is the most common cause of ARDS?**

Pneumonia and sepsis are the **most common** cause

*ARDS is an accumulation of fluid in the alveoli due to increase permeability of alviolar blood capillary

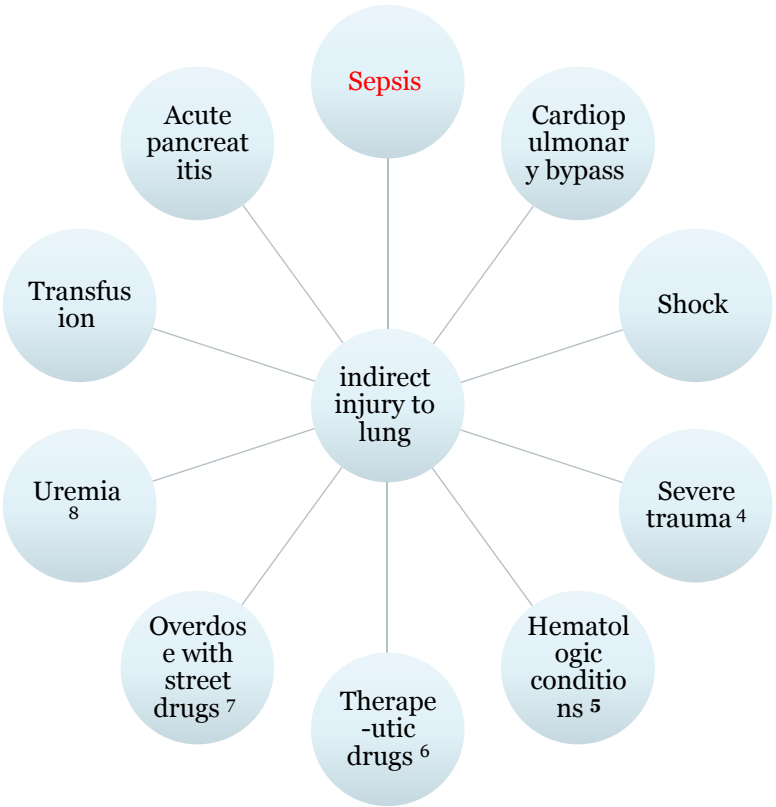
** wont able to exchange the oxygen since the alveoli is full of fluid and will lead to decrease Po2 in the blood and may lead to multi- organ failure if the oxygen multi- organ failure is not enough



[1] The virus is a coronavirus that destroys the type II pneumocytes and causes diffuse alveolar damage

[2] Irritants such as chlorine, O2 toxicity

[3] Aspiration of oropharyngeal or gastric contents into the lower respiratory tract



[4] e.g. bone fractures, head injury, burns, radiation

[5] e.g multiple transfusion, coagulation disorders

[6] such as bleomycin

[7] such as heroin

[8] blood in the urine

Pathophysiology of ARDS Important

- ARDS is associated with diffuse alveolar damage.

- **It is initiated by injury to:**
  1. alveolar capillary endothelium with a resultant increase in alveolar capillary permeability
  2. alveolar epithelium

- **The injury is induced by :**
  A. Neutrophils releasing substances toxic to alveolar wall.
  B. Activation of the coagulation cascade.
  C. O2 toxicity (due to formation of free radicals).

- This causes leakage of protein-rich fluid **into alveoli**, form alveolar hyaline membranes, line the inner surface of alveoli (the membrane is composed of fibrin and cellular debris)

- The lungs become **remarkably heavy and stiff** due to
  1. inflammation
  2. edema
  3. later interstitial fibrosis.

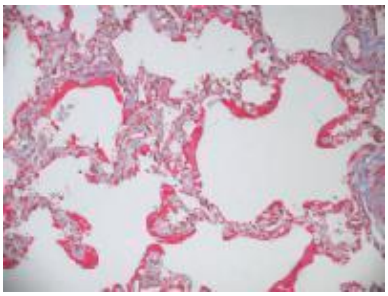
- **What you can see in chest x-ray?**

bilateral and diffuse pulmonary infiltrates (look at pic3)

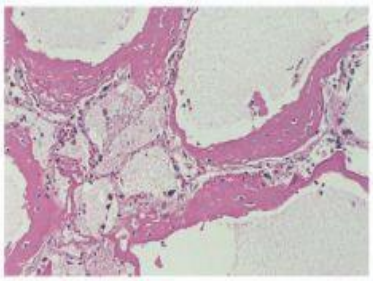
- **What is the outcome of ARDS?**

Mortality was 100% but Now 30 -40% with good ICU support

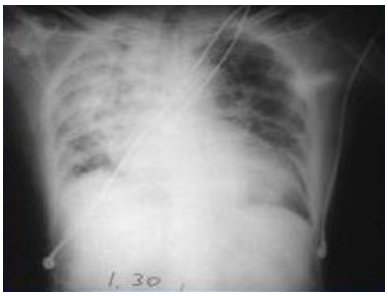
- Poor prognosis in case of:
  1. old age
  2. multisystem failure
  3. high level of **IL-1**



pic1

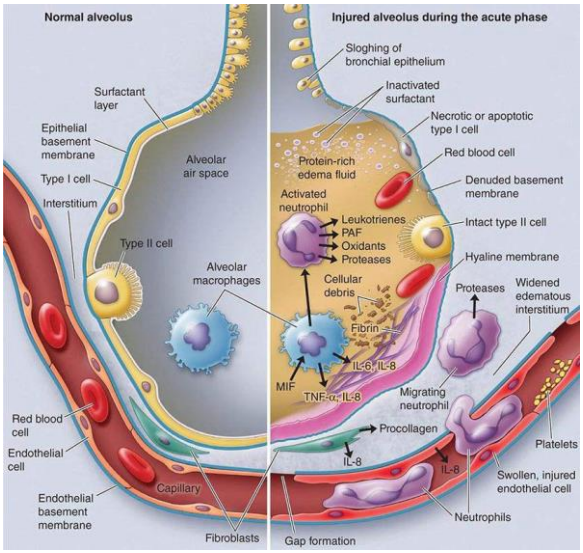


pic2



pic3

Extra picture



In normal situation there is a little amount of fluid in the interstitial space between the alveoli and capillaries due to the hydrostatic pressure but it will drain in the lymphatic vessels and nothing will make it to the alveoli but in some cases it will due to injury in the alveolar blood capillary which will increase the blood permeability to the interstitial space or due to injury in the alveolar epithelium itself the so the fluid will get inside the alveoli and prevent gas exchange
So what cause the injury of the capillaries or alveolar epithelium?

- Neutrophils releasing substances toxic to alveolar wall
- Activation of the coagulation cascade
- O2 toxicity (due to formation of free radicals)

Neonatal Respiratory Distress Syndrome

- **What is the other name for NRDS?**

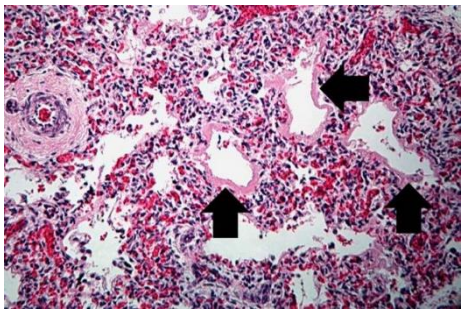
Hyaline membrane disease

- **What does it cause?**

It is the most common cause of respiratory failure in the newborn and is **the most common cause of death in premature infants.**

- **What cause it?**

It is the same as ARDS **except** that it is caused by a deficiency of pulmonary surfactants in new borns, most often as a result of immaturity.



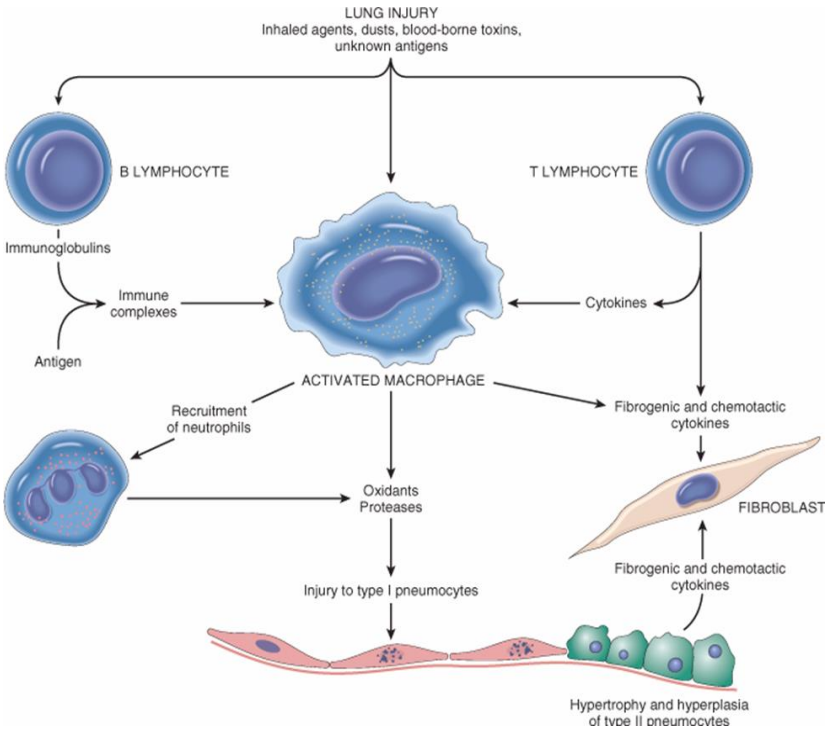
CHRONIC RESTRICTIVE LUNG DISEASE (INTRINSIC TYPE)

Definition:

- Are a **heterogenous group** of diseases.
- **Many** entities "existence" are of **unknown cause and pathogenesis**.
- They have **similar** clinical signs, symptoms, radiographic alterations and pathophysiologic changes.
- Account for about **15% of non-infectious lung diseases**.
- **End-stage**: diffuse interstitial pulmonary fibrosis.

Pathogenesis:

- **Lung injury**
- **Influx** of inflammatory cells **into** the alveoli and alveolar walls
- **Release** of chemical mediators and promotion of fibrosis
- **Distortion** of the normal structure of alveoli



Categories:

Idiopathic fibrosing:

Usual interstitial pneumonia (idiopathic pulmonary fibrosis)

Occupational: Pneumoconiosis

Anthracosis and coal worker's pneumoconiosis,

- Silicosis
- Berylliosis
- Asbestosis

Immune diseases:

- Sarcoidosis
- Goodpasture syndrome
- Hypersensitibity pneumonitis (extrinsic allergic alveolitis)
- Systemic lupus erythematosus
- Systemic sclerosis (scleroderma)
- Wegener granulomatosis

Drug:

Chemotherapy, methotrexate, bleomyxin toxicity

Smoking related:

- Eosinophilic granuloma
- Desquamative interstitial pneumonia
- Respiratory bronchiolitis-associated interstitial lung disease

Radiation Reactions:

Occur after radiation with diffuse alveolar damage, severe atypia of **hyperplastic type II cells** and **fibroblasts**

Extra notes on Restrictive Lung Disease :
امراض الرئة الحاصرة
Heterogeneous group of disease
Characterized by:
Reduction of lung volume
Pure lung complains
Inability of the lung to expand
Vital capacity is induced
FEV1 normal or reduce so the ratio may not change
Dry cough , progressive dyspnea
When a patient has a disease, interstitial lung is effect the lung parenchyma .
The pathological change usually have fibrosis
Usually effect the basement membrane, the wall of alveoli , the connective tissue of the lung , the wall of blood vessel
It doesn't effect the airways and that is the difference between it and the chronic air way

IDIOPATHIC PULMONARY FIBROSIS
FIBROSING ALVEOLITIS
HAMMAN-RICH SYNDROME
USUAL INTERSTITIAL PNEUMONIA (UIP)

Definition:

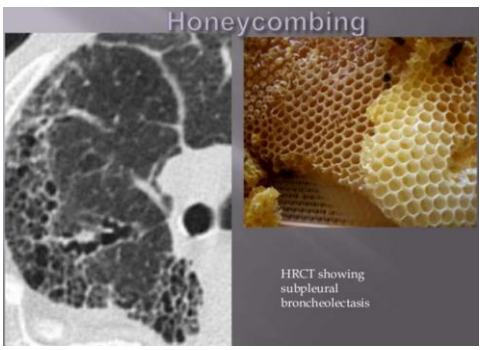
- UIP is **progressive fibrosing disorder** of unknown cause.
- It is an **idiopathic interstitial pneumonia** with **diffuse interstitial fibrosis** and **inflammation** (**Scars formation along the interlobular septa**)
- Age: **Adults 30 to 50 years** they will improve respiratory failure from 6 months – 2 years then die so these treatment will prolong life
- Usually affects lower lobe
- **Prognosis: poor.**
  - **Respiratory** and **heart failure** may develop within few years.
  - **No effective therapy is available** for the **treatment** of **idiopathic pulmonary fibrosis.**
  - **Lung transplant** is the **only solution**

Pathogenesis:

- Smoke. environmental pollutants ,dust ,viral infections & gastroesophageal reflux disease.

Clinical features:

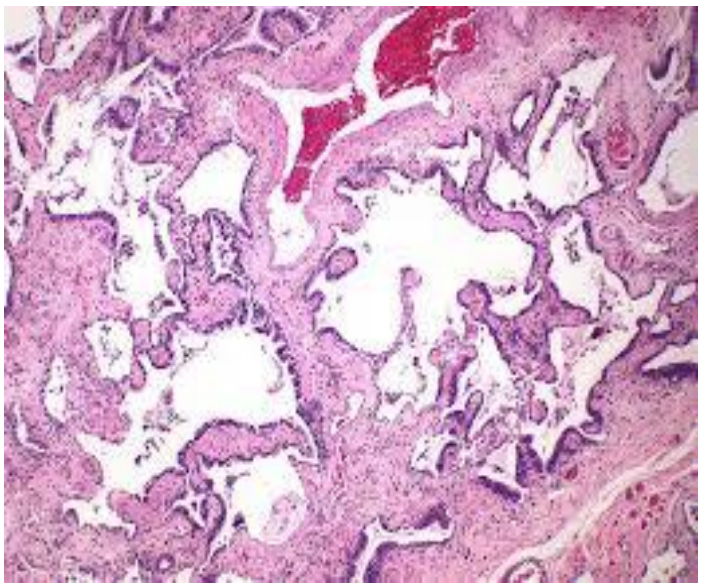
- Most patients present with **exertional dyspnea** and a **nonproductive cough**
- A **chest radiograph** and **high-resolution computed tomography** typically **reveals diffuse reticular opacities.**
- **Honeycombing**



Morphology:

- The morphologic **changes vary according to the stage of the disease.**
- **Early cases:**
  - **Intra-alveolar** and **interstial inflammation.**
  - **Hyperplasia of type II pneumocytes**

- **Advancing disease:**
  - **Prominent interstitial fibrosis.**
  - Alternating areas of fibrosis and normal tissue will be **seen**.
  - In the end, the lung consists of **peripheral cystic spaces lined** by cuboidal or columnar epithelium **separated** by inflammatory fibrous tissue **(honeycomb lung).**
  - Foci of normal lung tissue were also **seen**, It is the end stage of lung disease.



Scars formation along the interlobular septa

Dr. Rikabi's Notes:
We need' biopsy to see it by transbronchial biopsy or open lung biopsy and stain it by connective tissue stain وهذه الصبغة تصبغ الفايبر باللون الأزرق ونلاحظ أنه الفايبر تحيط بواحدة وتترك اللي بعدها بشكل غير منتظم

PNEUMOCONIOSIS

Pneumoconiosis is a group of pulmonary diseases caused by chronic exposure to inorganic mineral dust inhalation and this leads to lung damage.

- More than 40 inhaled minerals can cause lung problems.
- They include **carbon dust, silica, asbestos, beryllium** etc.

Pathophysiology:

Alveolar macrophages ingest the particles, become activated, and release cytokines and chemotactic factors that recruit other inflammatory cells.

Inflammation damages lung cells and damages the interstitium of the lung by degrading the extracellular matrix glycoproteins.

Fibroblasts are stimulated and proliferated to produce collagen; fibrosis results.

As the disease progresses the blood vessels become compromised, and ischemic necrosis may occur.

The development of pneumoconiosis is dependent on:

- The amount of dust retained in the lung and airways.
    a. Concentration of the dust in the ambient air.
    b. Duration of the exposure.
    c. Effectiveness of the clearance mechanisms.
- The **size** (1-5μ) shape.
- Their **solubility** and physiochemical activity.
- The possible additional effects of **other irritants**, tobacco smoking.

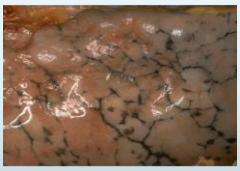
COAL WORKERS PNEUMOCONIOSIS

Coal worker's pneumoconiosis (CWP) can be defined as the accumulation of coal dust in the lungs and the tissue's reaction to its presence.

The disease is divided into 2 categories:

1. Simple coal worker's pneumoconiosis
2. Complicated coal worker's pneumoconiosis (CCWP), or pulmonary massive fibrosis (PMF), depending on the extent of the disease.

❖ Pulmonary massive fibrosis in association with rheumatoid arthritis is known as **Caplan syndrome**.



Anthracosis

The asymptomatic, milder type of pneumoconiosis, caused by the accumulation of carbon in the lungs due to repeated exposure to air pollution or inhalation of smoke or coal dust particles.

Simple coal worker pneumoconiosis

Black macules (1 to 5 mm) are scattered through the lung.

Complicated coal worker's pneumoconiosis

- Black scars exceed **2 -10 cm**
- Fibrous scarring appears (**progressive massive fibrosis**)
- Produces cough, dyspnea, and lung function impairment.
- Cor pulmonale
- **No convincing evidence** that coal dust increases susceptibility to tuberculosis or cancer (non-smoker)

(it does not increase the susceptibility to cancer and TB in nonsmokers.)

2.SILICOSIS

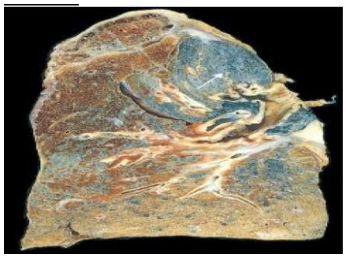
- Silicosis is a fibro-nodular lung disease caused by long term exposure to inhalation of crystalline silica particles (alpha-quartz or silicon dioxide).
- Industrial exposure: mining of gold, tin, copper and coal ,sandblasting, metal grinding, ceramic manufacturing.
- Chronic forms manifest after several years of exposure
- The symptoms may be indolent or progressive: complicated progressive massive fibrosis.
- Silicosis predispose to lung cancer and tuberculosis.

Pathogenesis:

• Crystalline silica is highly fibrogenic.

• Scattered lymphocytes and macrophages are drawn rapidly with fibrosis.

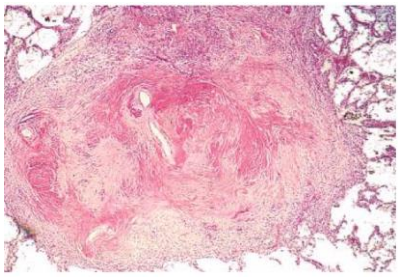
• Some particles are transported to lymph nodes.



Morphology

• Tiny collagenous nodules that enlarge forming stony-hard large fibrous scars usually in the upper lobes.
• Calcifications may appear(eggshell calcification)
• Similar collagenous nodules within the lymph nodes.
• Fibrous pleural plaques may develop.

- Hyalinized collagen fiber surround an amorphous center (fibrous nodules).
- Scarring progress to progressive massive fibrosis.



Prognosis:

- Scarring extending and encroching the pulmonary arteries leading to Cor pulmonale.
- Increased susceptibility to tuberculosis (crystalline silica inhibits the ability of pulmonary macrophages to kill phagocytosed mycobacteria)
- Patients with silicosis have double the risk for developing lung cancer

3.ASBESTOSIS

- Caused by asbestos inhalation.
- Asbestos fibers are long and thin. They can curved or straight.
- All types of asbestos (crocidolite and amosite) are fibrogenic to lungs. • Asbestosis occurs decades after exposure has ended.
- Characterized by scars containing asbestos bodies “ferruginous bodies” (long, thin asbestos fibers coated with hemosiderin and protein to form brown filaments with a beaded or drumstick pattern.).
- They can cause:

➢ pleural effusion.

➢ pleural adhesions.

➢ parietal pleural fibrocalcific plaques.

➢ Some types of asbestos are carcinogenic(especially crocidolite) and prolong asbestos exposure can predisposes to bronchogenic carcinoma and malignant mesothelioma.

- Both bronchogeniccarcinoma andmesothelioma develop in workersexposed to asbestos. The risk of bronchogenic carcinoma is fivefold and for mesothelioma is 1000 fold greater

4.BERYLLIOSIS

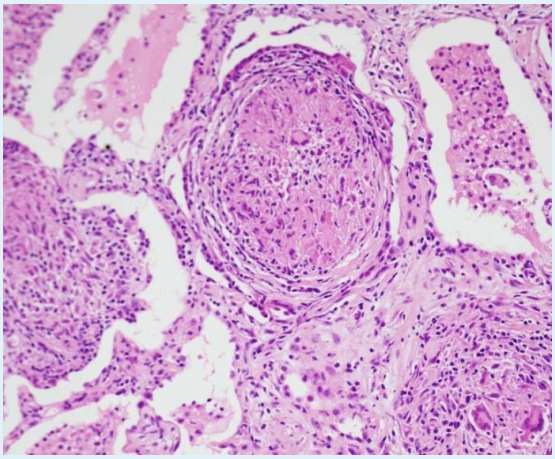
- Beryllium Mining, Aerospace manufacturing.
- -non-necrotizing granulomata distributed in the parenchyma, LN and other organs.
- Pedispose to lung cancer.

PNEUMOCONIOSIS
BERYLLIOSIS

- Beryllium Mining, Aerospace manufacturing

-non-necrotizing granulomata distributed in the parenchyma, LN and other organs

-Pedispose to lung cancer



SUMMARY

Entity	Example	Pathological features	Comment
coal worker's pneumoconi-osis	coal dust in coal miners	-Simple coal worker's -Complicated coal worker's pneumoconiosis (with rheumatoid arthritis is called Caplan syndrome)	**Anthracosis** is the accumulation of coal without consequent cellular reaction in air polution /smoker
Silicosis	**silicon dioxide**	industries: mining of gold, tin, copper and coal, sandblasting, metal grinding, ceramic manufacturing	-Complicated progressive massive fibrosis -Predispose to lung cancer and TB
Berylliosis	Beryllium Mining, Aerospace manufacturing	non-necrotizing granulomata distributed in the parenchyma, LN and other organs	Pedispose to lung cancer
Asbestosis	Pipes, sheets, vinyl-asbestos floor tiles, asbestos paper in filtering and insulating products	Pulmonary fibrosis Pleural fibrosis	Bronchogenic Carcinoma and Malignant Mesothelioma

HYPERSENSITIVITY PNEUMONITIS

- Prolonged exposure to inhaled organic antigens

- **Hypersensitivity pneumonitis an immunologically mediated (type III or IV)**
- **Caused by intense and often prolonged exposure to inhaled organic dust**
- **It primarily affects the alveoli and is therefore often called allergic alveolitis**

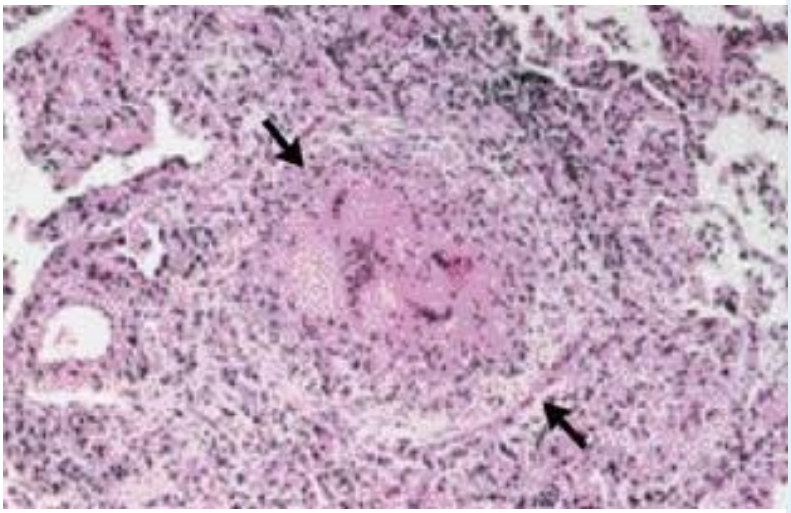
- **These dusts come from:**
  1. **Evaporative coolers (Desert coolers/ wet air cooler) type AC**
  2. **Dairy and grain products**
  3. **Animal droppings and animal proteins**
  4. **Poultry and other bird handlers are commonly exposed to droppings, feathers, and serum proteins of pigeons etc.**

- **The most common antigens are thermophilic *Actinomycetes* and avian proteins**
- **The most common diseases are farmer's lung and bird fancier's/handler's lung.**

HYPERSENSITIVITY PNEUMONITIS

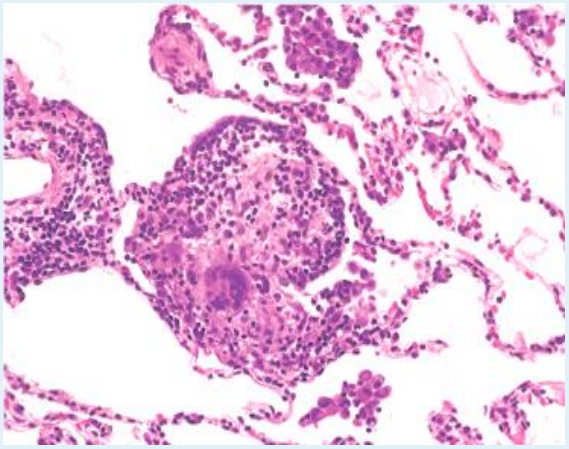
		
Farmer's lung Thermophilic actinomycetes in hay	Pigeon breeder's	Air-cooler lung Thermophilic bacteria

Sugarcane bagasse
(Bagassosis)



HYPERSENSITIVITY PNEUMONITIS

Morphology:
noncaseating interstitial granulomas
(IV hypersensitivity reaction), bronchiolitis, interstitial pneumonitis, and diffuse interstitial fibrosis.
Clinical course is variable

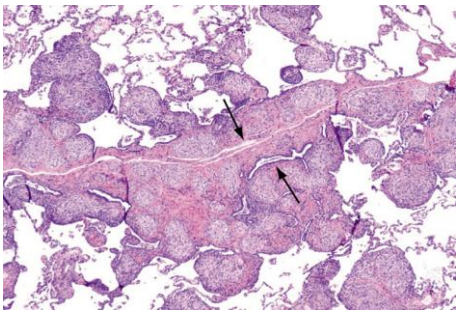


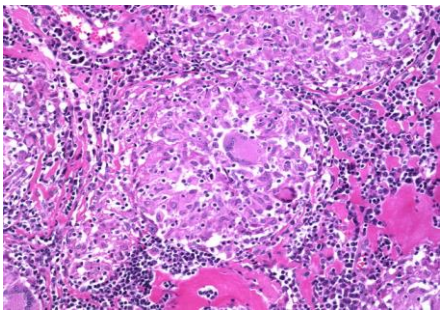
- **Hypersensitivity pneumonitis can present as:**
  1. **Acute:** fever, cough, dyspnea
  2. **Subacute (intermittent)**
  3. **Chronic progressive:** cough, dyspnea, malaise, and weight loss

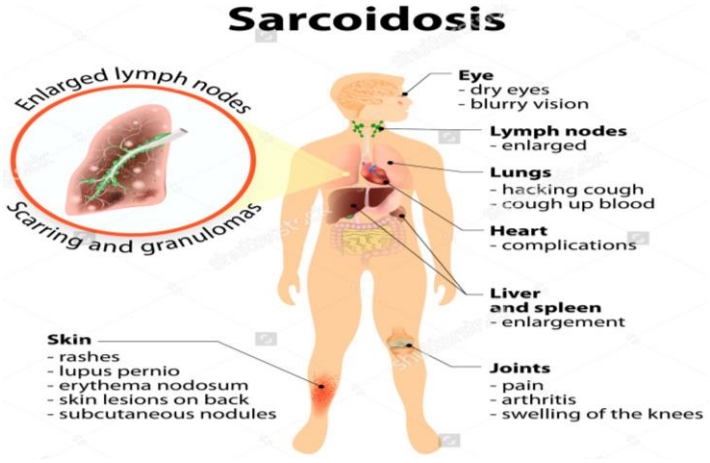
SARCOIDOSIS
IMMUNE DISEASE

- **Sarcoidosis is an inflammatory disease**
  - **Epidemiology:** affecting all races and both sexes equally
  - **Cause:** unknown
  - **Sites:** predominantly affects the lungs and intrathoracic lymph nodes
    - Other organs that may be involved include eyes, skin, liver, spleen and bone marrow.
    - Occasionally kidney, heart, CNS and endocrine organs may be involved.
  - **Morphology:** non-caseating/ non-necrotizing granulomas in affected organ tissues.

Sarcoidosis granulomas in the lung







The **prognosis** of sarcoidosis is unpredictable. It can progressive and chronic. It may present as episodes of activity.

Majority of the patients respond well to treatment.

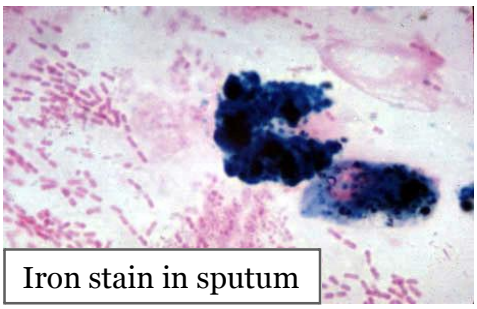
GOODPASTURE SYNDROME/ ANTI-GBM DISEASE

IMMUNE DISEASE

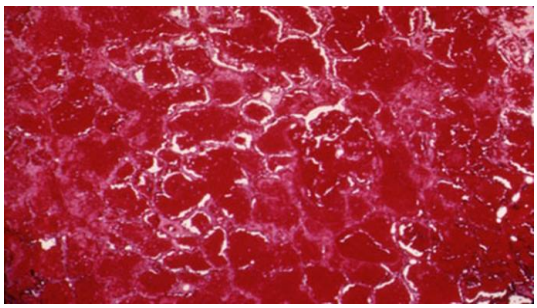
- Rare **autoimmune disorder**
- Is a **triad of**
  - diffuse pulmonary hemorrhage,
  - glomerulonephritis,
  - circulating (anti-GBM) antibodies against alveolar and glomerular basement membranes
- The antibody can **usually** be found in **serum**.
- **Morphology**:
  - The lung: acute necrotizing alveolitis with hemorrhage
  - Kidney: rapidly progressive glomerulonephritis, may lead to renal failure

* only the kidney and the lungs are affected

- **Clinical features:**
  - Pulmonary symptoms (hemoptysis and dyspnea)
  - Renal symptoms (hematuria, proteinuria, RBC casts and renal failure)
  - Arthralgias

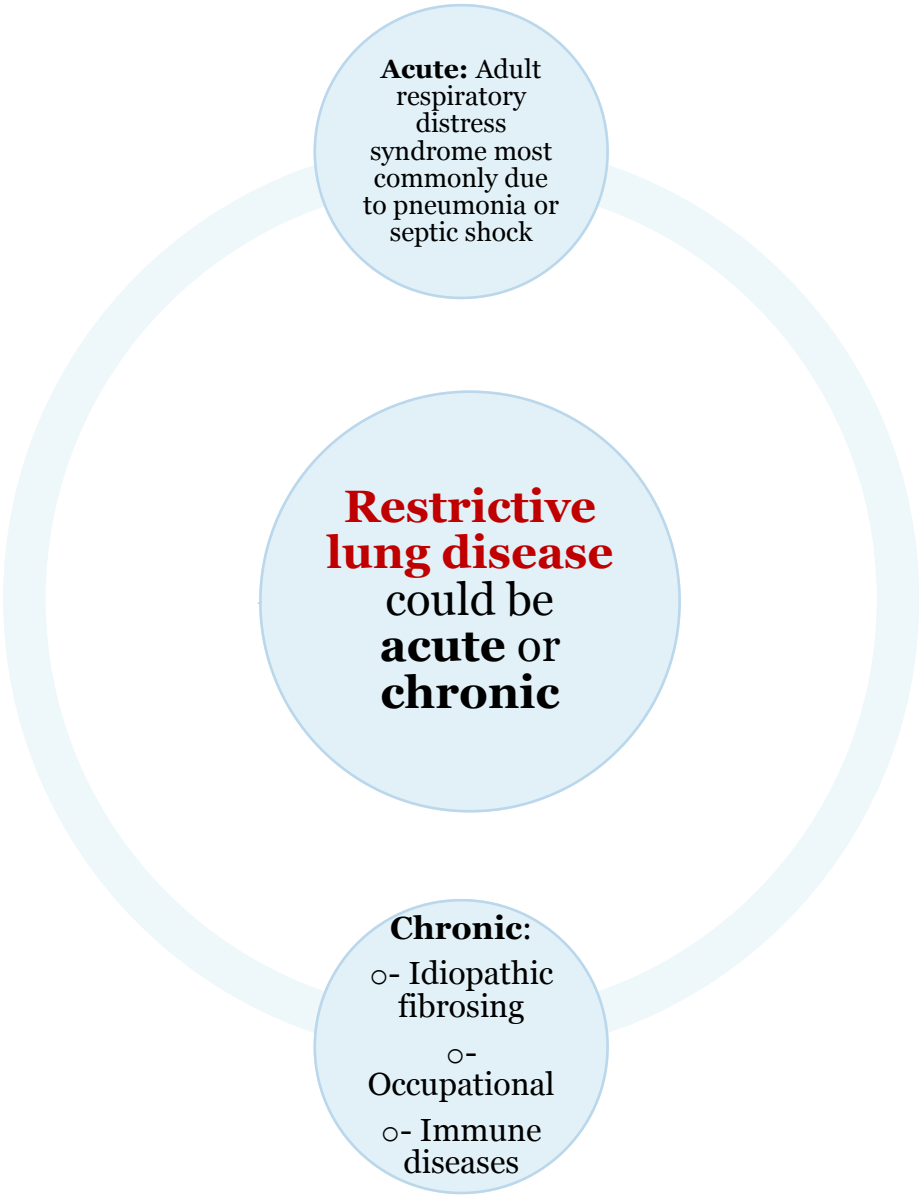


Iron stain in sputum



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

SUMMARY:


Acute: Adult respiratory distress syndrome most commonly due to pneumonia or septic shock
Restrictive lung disease could be **acute** or **chronic**
Chronic:
○- Idiopathic fibrosing
○- Occupational
○- Immune diseases

Females:

-Leader : بثينة آل ماجد

-فاطمة بالشرف

-روان الحربي

-رهف الشمري

-رناد الفرم

-هديل عورتاني

-منيرة المسعد

-الجوهرة الشنيفي

-رزان الزهراني

-روان مشعل

-نوف العتيبي

-ابتسام المطيري

-غرام جليدان

-بلقيس الراجحي

-نورة القاضي

-آلاء الصويخ

-ريم القحطاني

-شوق القحطاني

Males:

-Leader : محمد باحاذق

فهد عبدالله الفايز

سيف المشاري

محمد الأصقه

خالد المطيري

داود اسماعيل

خالد محمد العقيلي

احمد وليد الراشد

فهد النحابي

عبدالله السرحاني

رشيد سليمان البلاع

معاذ ابراهيم الحمود

فايز غياث الدرسوني

عبد الحكيم إبراهيم العنيق

خالد محمد العقيلي

عبدالله سليمان احمد بالعبيد

أنس عبدالله السيف

سعد محمد الفوزان

عبدالعزيز بن خالد السرحاني

عبد الإله الحسين

PATHOLOGY
TEAM 437

Kindly contact us if you have any questions/comments and suggestions:

* EMAIL: pathology437@gmail.com
* TWITTER : @pathology437

GOOD LUCK ! ☺

Pathology
teamwork

*references:

-Robbins Basic Pathology
- doctor's slides