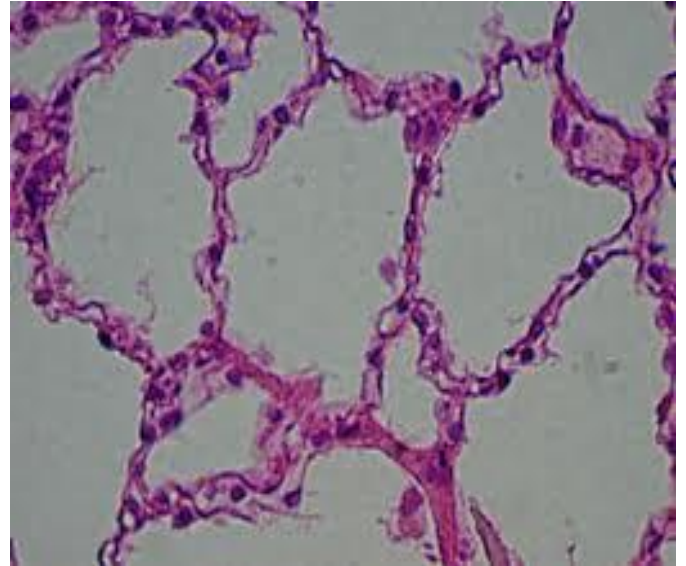


Restrictive lung diseases

Restrictive lung diseases are diseases that affect the interstitium of the lung.

Interstitium of the lung is the very thin walls surrounding the alveoli, it's formed of epithelium of the alveoli, endothelium of the capillaries, some elastic fibers, some collagen fibers, and some mononuclear cells. Interstitium is very thin and delicate, so anything affecting it would affect the thickness of the respiratory membrane so would affect the diffusion too much (affect the diffusion pathway), and as a result, would affect gas exchange. So any problem in the interstitium leads to **interstitial lung diseases**, which in turn lead to **restrictive lung diseases**.



Interstitial lung diseases could be caused by:

- 1- Fibrosis/ fibrosing diseases.
- 2- Granulomatous diseases.
- 3- Eosinophilic infiltrates.
- 4- Smoking related diseases.

From now on, the topic continues about fibrosing diseases that affect the lung:

- All share the following:

- 1- Include fibrosis which starts as patchy fibrosis then becomes diffused fibrosis.
- 2- Affect both lungs; bilateral.
- 3- Lead to restrictive lung diseases.
- 4- Idiopathic; we don't know the cause of all these diseases.

- They are:

- 1- Idiopathic pulmonary fibrosis, also called cryptogenic fibrosing alveolitis.
- 2- Nonspecific interstitial pneumonia.
(The term "pneumonia" doesn't mean the known infection of the lungs (pneumonia); it means "fibrosis" here & "interstitial" means that the problem (fibrosis) is related to the interstitium)
- 3- Cryptogenic interstitial pneumonia.
(Cryptogenic means idiopathic, also pneumonia here = fibrosis)

4- Pneumoconiosis.

This is simply a reaction to dust, it includes: coal worker's pneumoconiosis, silicosis that's due to silica inhalation, asbestosis that's due to asbestos inhalation.

We are concerned mostly about the first and the last ones.

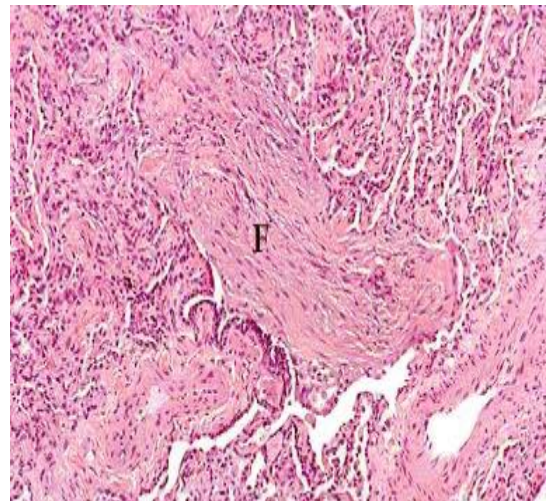
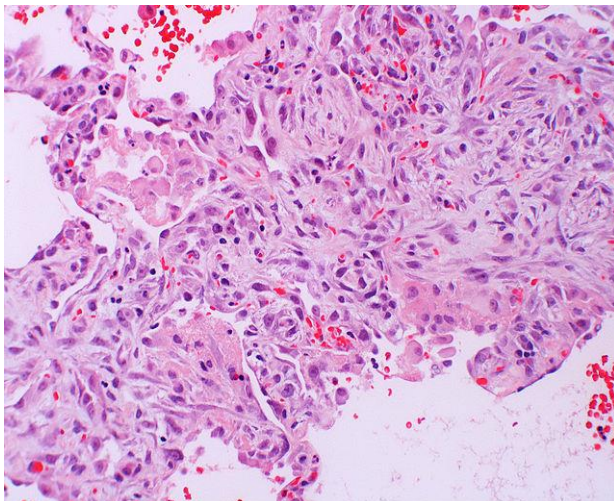
Idiopathic pulmonary fibrosis

- Another name is: cryptogenic fibrosing alveolitis.
- This is an idiopathic disease, and it affects the lungs bilaterally by fibrosis. Once started, it becomes **progressive** ending with death.
- Males are affected more than females.
- Histologic picture:

1- Usual interstitial pneumonia (UIP)

Usual Interstitial Pneumonia (UIP): This is not a disease, it's only a **histologic picture** seen in idiopathic pulmonary fibrosis and in other conditions. It's a patchy interstitial fibrosis and is formed as follows:

It starts with many cells surrounded by a little fibrosis "cellular stage, i.e. the predominant component is cellular", with time fibrous tissue and collagen increases at the expenses of the cells. So the figure on the left shows **early** lesions where we see too much cells, and the one on the right shows **late** lesions where fibrosis is the predominant.

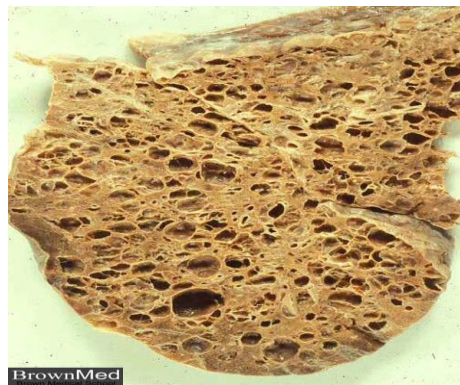


Both are called usual interstitial pneumonia.

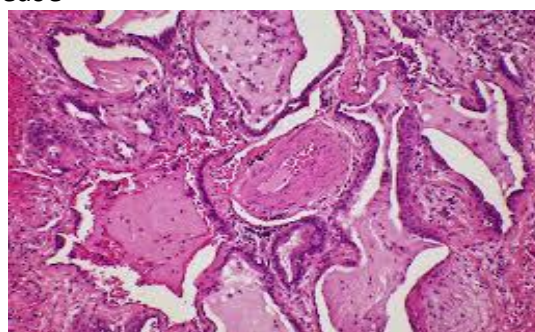
In idiopathic pulmonary fibrosis diagnosis, **both** early and late lesions coexist in the biopsy. (They don't coexist in other diseases.)

2- Honeycomb fibrosis

With time, fibrosis causes collapse of the alveolar walls and formation of cystic spaces making the lung full of cysts. This gives it the shape of honeycomb so the lung is called then honeycomb lung or honeycomb fibrosis. This is the end stage of all fibrosing diseases and isn't specific for idiopathic pulmonary fibrosis or any other disease. It's important to know that the honeycomb lung doesn't give any information about what was the initial disease that lead to it; we'll only know that the case here is an end stage interstitial disease.



It's like what you see in the pictures, grossly and under the microscope. We see the dilated alveoli (large spaces) surrounded by type two pneumocytes; the ones responsible for regeneration.



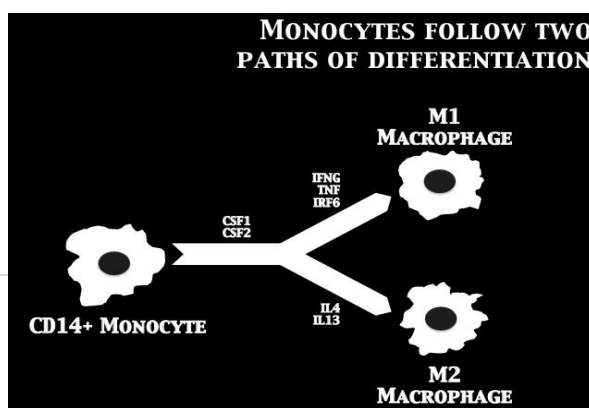
Remember: honeycomb fibrosis is different from emphysema where no fibrosis occurs with alveolar dilatation, but in honeycomb fibrosis, there's dilatation of alveoli along with fibrosis.

So, whenever we see honeycomb fibrosis, that is the end stage of that interstitial disease and no treatment would be taken since it's a progressive disease that ends with death.

- Pathogenesis:
Again, we don't know the exact initial causative insult; epidemiologic studies found no specific common triggering factor shared by the patients, yet we know the mechanism or the pathogenesis by which this disease happens. The sequence of events goes like this:
The unknown cause makes repeated cycles of epithelial injuries and once injured, inflammation takes place, and fibrosis follows. Then another injury happens, and the whole story is repeated again and again ending with patchy fibrosis which converts into diffuse progressive fibrosis and finally the lung gets honeycomb-like.

Now, what inflammatory cell mediates fibrosis?

Macrophages, which can be stimulated by either of two pathways:



1- Classical pathway: certain mediators stimulate macrophages to become type one macrophages (M1), which in turn produce phagocytosis and inflammation (M1 releases all cytokines & inflammatory mediators)

2- Alternative pathway: other mediators stimulate macrophages to become type two macrophages (M2), which in turn are anti-inflammatory and produce fibrosis and scarring.

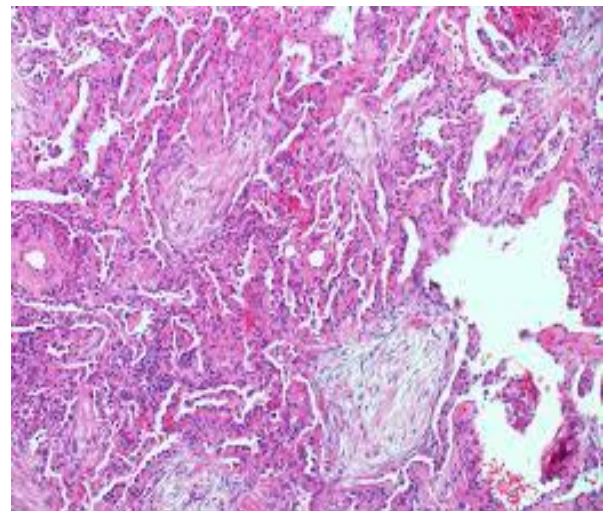
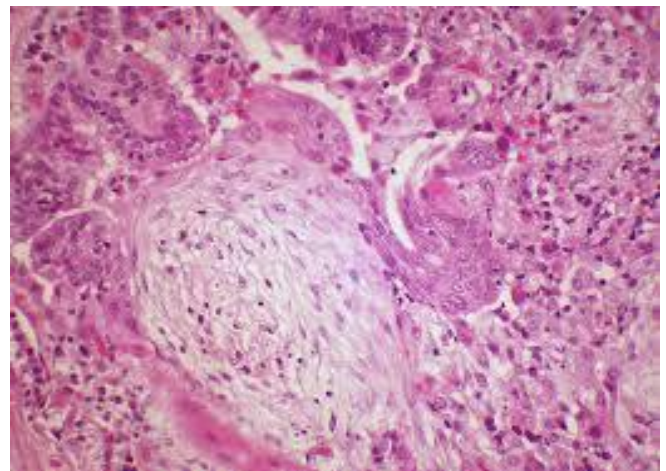
Note: Fibroblasts are stimulated by M2.

So the most important inflammatory cell responsible for fibrosis and pathogenesis of idiopathic pulmonary fibrosis is: type two macrophages (M2).

- Clinical feature:
Gradual onset of respiratory symptoms, like dyspnea and cough. Then end stage lung disease comes about.
- Mean survival rate is only 3 years because of developing respiratory failure.
- Therapy: We said no drugs or treatment would help, nevertheless, lung transplant could be the patient's only hope. (Humans who donate one lung can live with their remaining one lung.)
- Genetics play no role here.
- Like all other fibrosing diseases, it's not common.

Cryptogenic organizing pneumonia

- Another fibrosing disease.
- Bilateral and of unknown etiology, too.
- Clinical features: causes respiratory symptoms. (cough and dyspnea)
- Histologic features: "NO UIP" are **distinctive** here for that the collagen and fibrosis are organized (whorling pattern of the collagen); hence the name of this disease. As you see in the picture, whorling pattern of the collagen makes circles of fibrosis that are called: **Masson bodies**
It's not UIP, yet it's like the late stage of UIP except for the fibrosis here is organized (whorling pattern).
The lung doesn't reach the stage of honeycomb because this is a treatable disease meaning that it doesn't reach the end stage because once treated, everything goes back to normal. But if it's not treated, there might be honeycomb fibrosis.
- Prognosis or mean survival rate is **better** here. The problem in the lungs resolves either spontaneously or by treatment



with steroids for at least six months (the majority of cases need steroids). So the patient will have a good chance to survive.

- Question asked in class: What do the steroids do?
Since they are anti-inflammatory (by inhibiting phospholipase A2 and all the reactions after), they stop inflammation & progression of the disease, which gives the lungs the chance to resolve the initial fibrosis and recover.
- Note regarding Masson body: it's a polypoid plug –like a ball- of loose organizing connective tissue within the lumen of small airways that extends into the alveolar duct & alveoli. These bodies form intraluminal polyps within bronchioles & air spaces... this definition is from the internet.

Pneumoconiosis

- Most pneumoconiosis diseases are **occupational lung diseases** that are produced by inhaling dust. They are defined as inhaled dust causing changes in the lungs ending with fibrosis.
- Pneumoconiosis includes a spectrum of diseases which have the following in common: there's an inhaled dust which accumulates in macrophages –it's a foreign body after all- & this causes an inflammatory response.
- The dust or occupational things that mainly can be inhaled are: coal, asbestos, and silica.
- Question asked in class: What is the difference between pneumoconiosis and asthma?
Asthma is an obstructive lung disease where an allergen triggers an allergic response as in atopic asthma.
In pneumoconiosis, the inhaled dust doesn't trigger an allergic response; it's engulfed by the macrophages causing an inflammatory response ending in fibrosis... totally different mechanism.
- The lungs react to mineral dust depending on several things:
1- Size. 2- Shape. 3- Solubility. 4- Reactivity.

Size:

If the dust is big (more than 5 microns), cilia would drive it out and it won't reach the alveoli... no problem developed here.

If the dust is small (less than 0.5 microns), it can go within the alveoli without causing a problem.

The problem starts when the size of the dust is between **1-5** microns, because this enables the dust to go down, get entrapped/ lodged inside the alveoli and become engulfed by macrophages & that causes the problem.

So don't forget: **1-5 micrometers** is the most dangerous size due to which the dust lodges in the alveoli.

Reactivity:

If the dust is inert and not reactive nor toxic, it will stay there for a long time without causing any harm. **Coal** dusts are inert –not reactive-, this makes them need a very long time inside macrophages in order to cause fibrosis. Whereas **silica and asbestos** are very reactive and toxic so they trigger an inflammatory response at an early stage.

- Pathogenesis:

When dust is inhaled, it's engulfed by the macrophages, which stimulates an inflammatory response. Again if the dust is inert, it will stay as such & inflammatory response is elicited after reaching a certain stage after a long time. If the dust is reactive and toxic, inflammation is elicited at an early stage.

Inflammation then stimulates the M2 macrophages and other inflammatory cells and this causes fibrosis until reaching the end stage which is diffuse fibrosis.

Sorry for any mistake!

All the best ☺