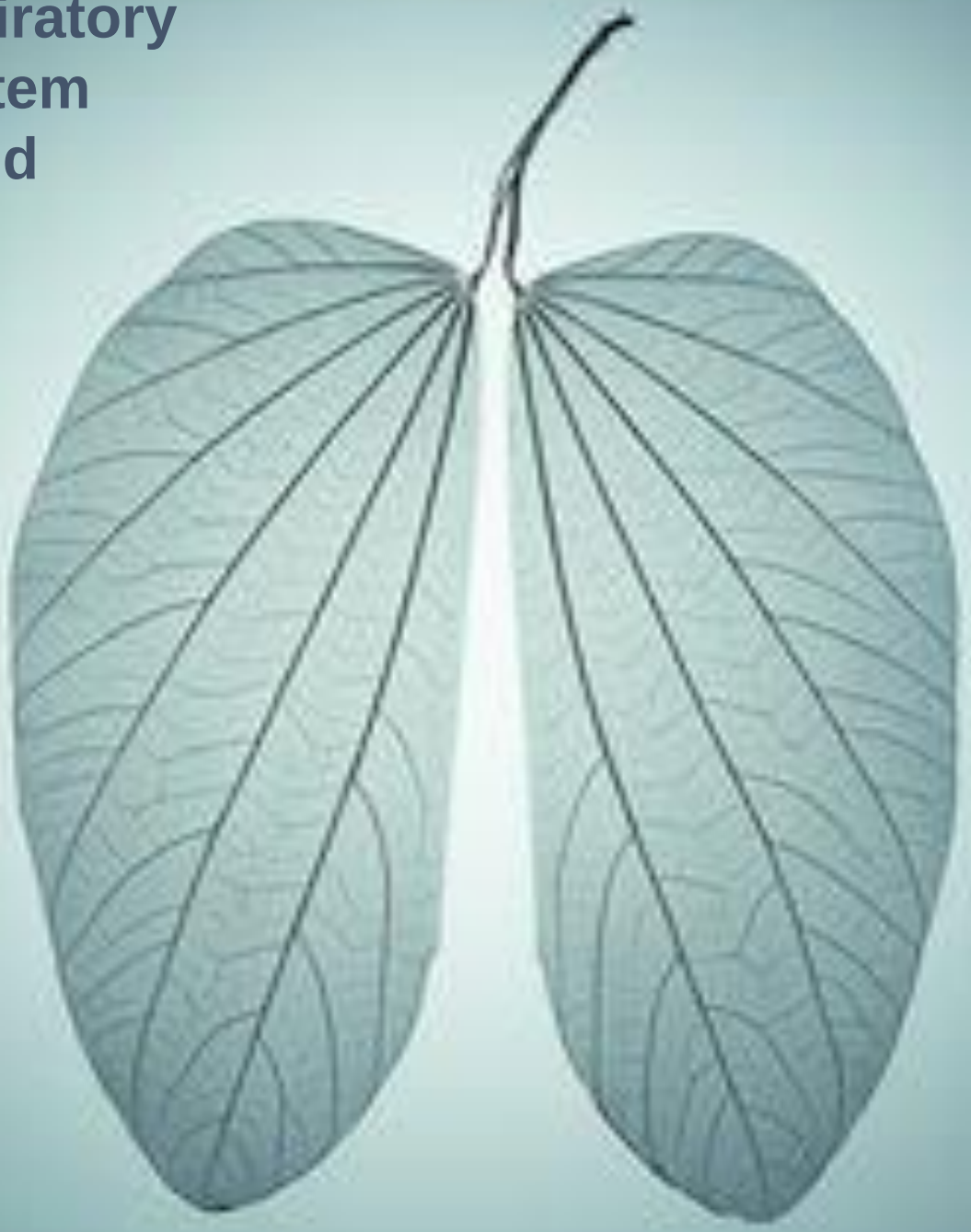
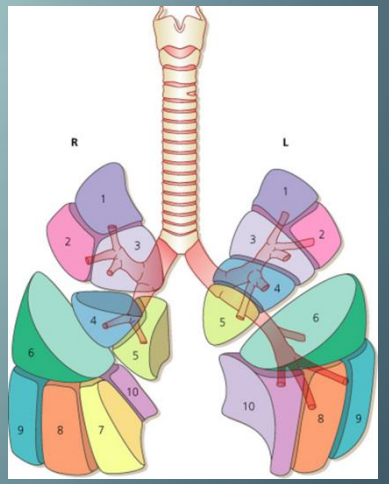
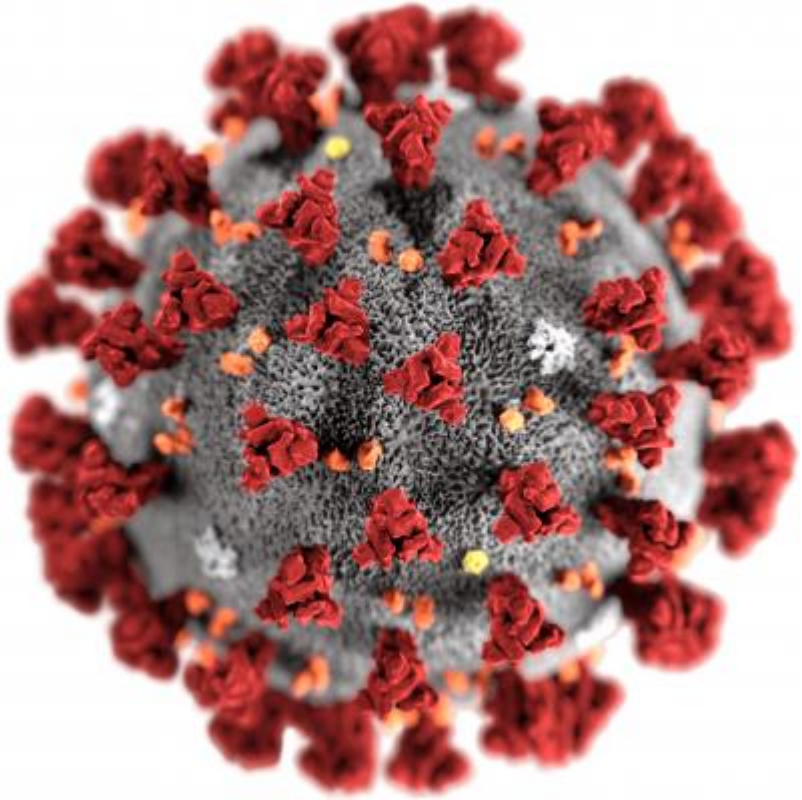
Respiratory System 2nd



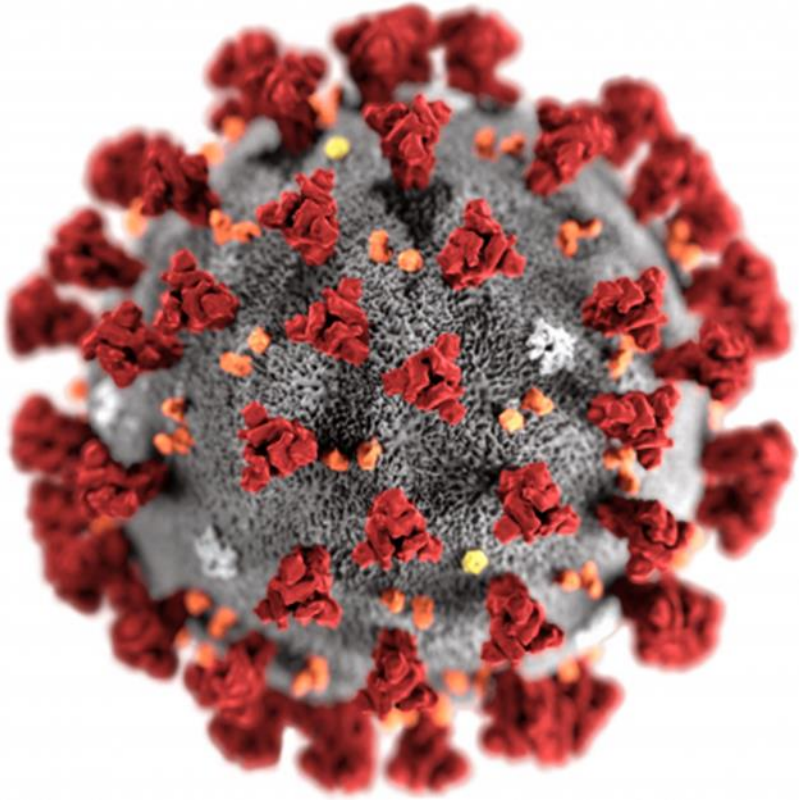


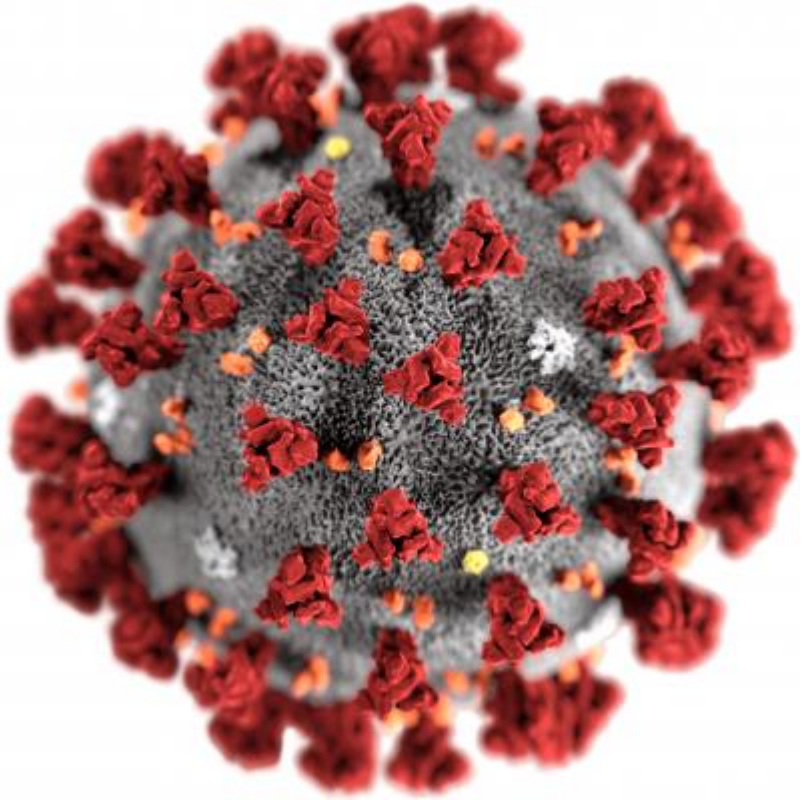
Practical Pulmonary Pathology

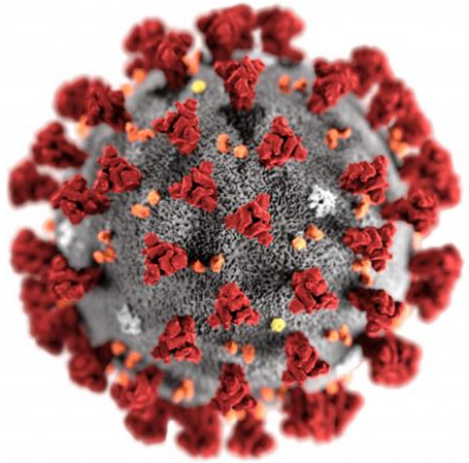


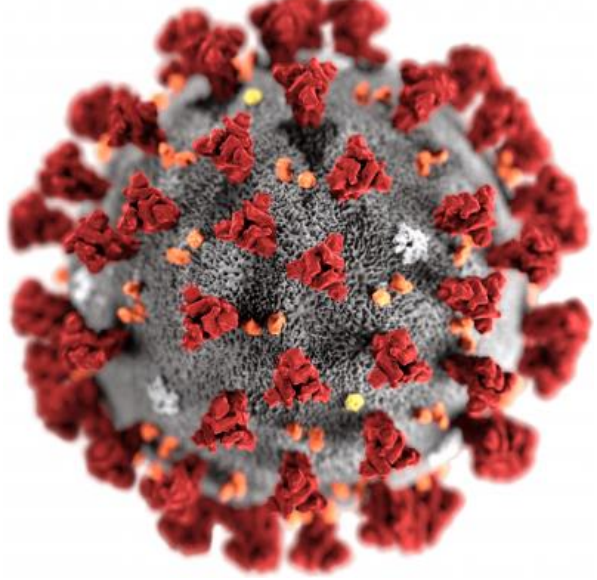
COVID-19

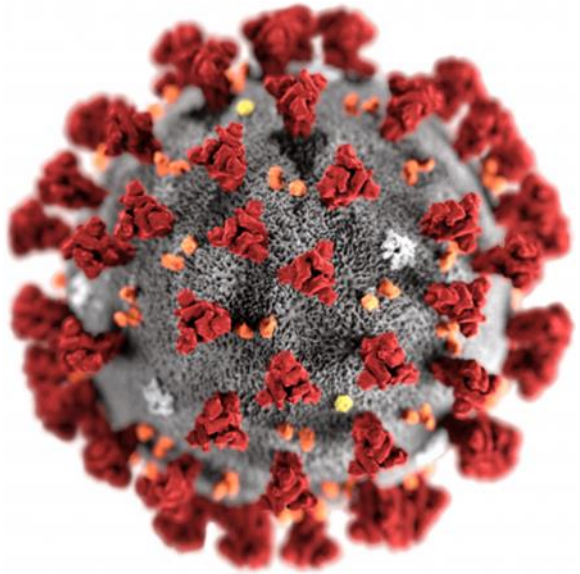
2021-03-01





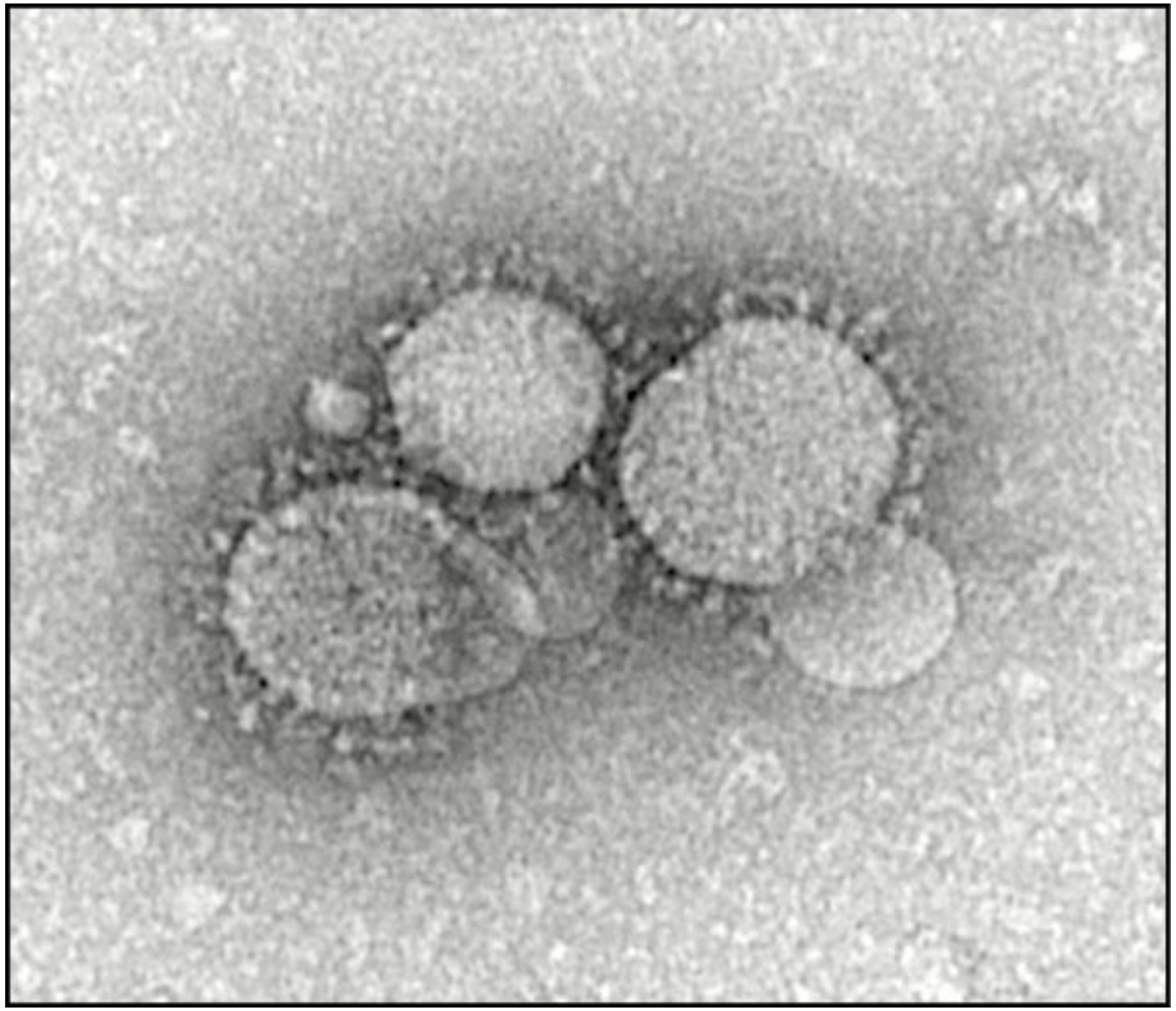






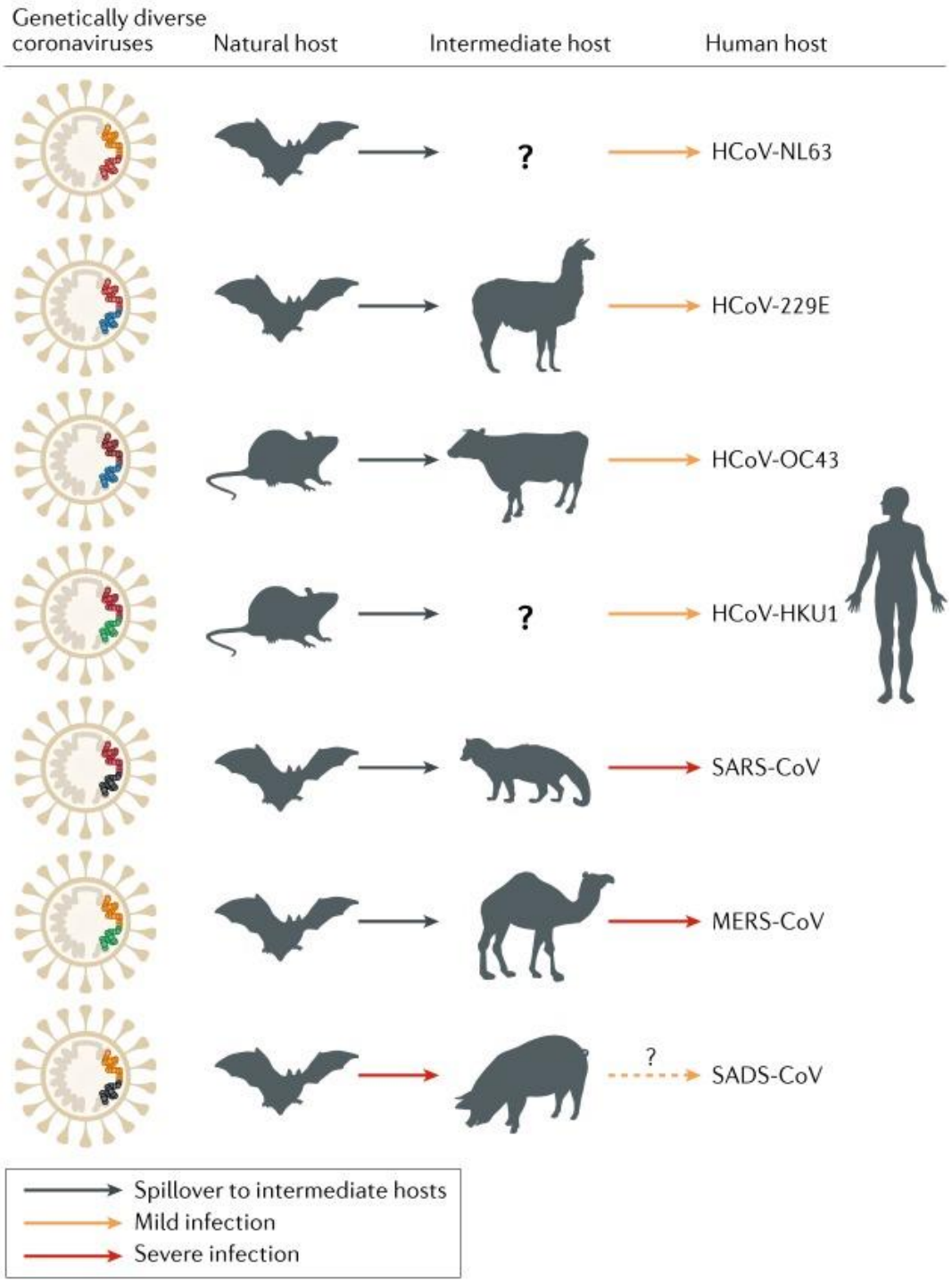
A koronavírusok lipidburokkal rendelkező, egyszálú RNS vírusok, amelyek légzőszervi és bélrendszeri infekciókat okoznak állatokban és emberekben. A humán koronavírusok közül négy folyamatosan jelen van környezetünkben, légzőszervi megbetegedéseket okoz, endemikus megjelenésük a téli hónapokra tehető.

Coronaviruses are enveloped, nonsegmented, single-stranded, positive-sense RNA viruses that have a characteristic appearance on electron microscopy negative staining



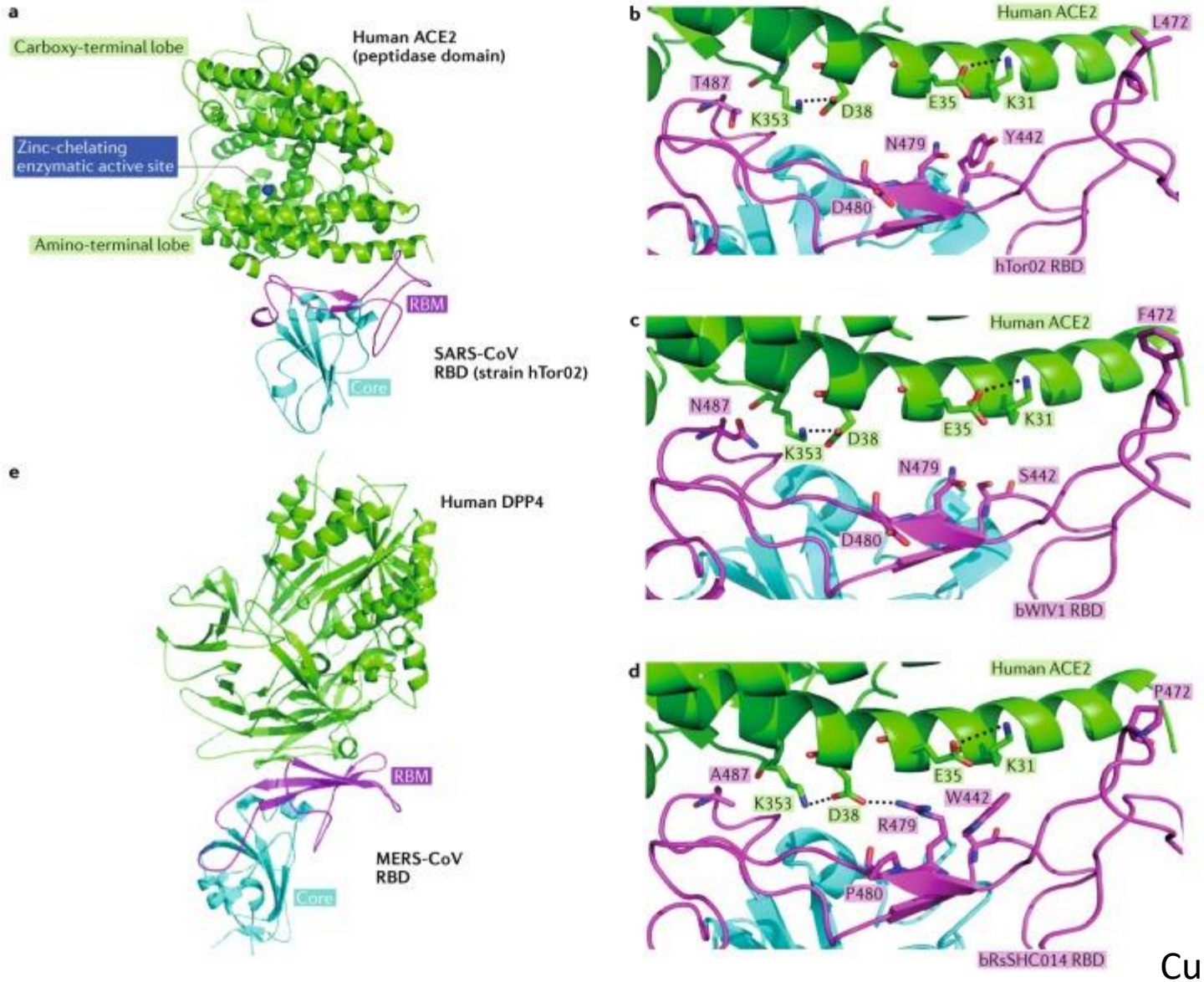
SARS-CoV and MERS-CoV have had different behaviors, SARS-CoV-2 will likely have unique features of its own

Guarner J. **Three Emerging Coronaviruses in Two Decades**. Am J Clin Pathol. 2020 Mar 9;153(4):420-421. doi: 10.1093/ajcp/aqaa029. PMID: 32053148; PMCID: PMC7109697.



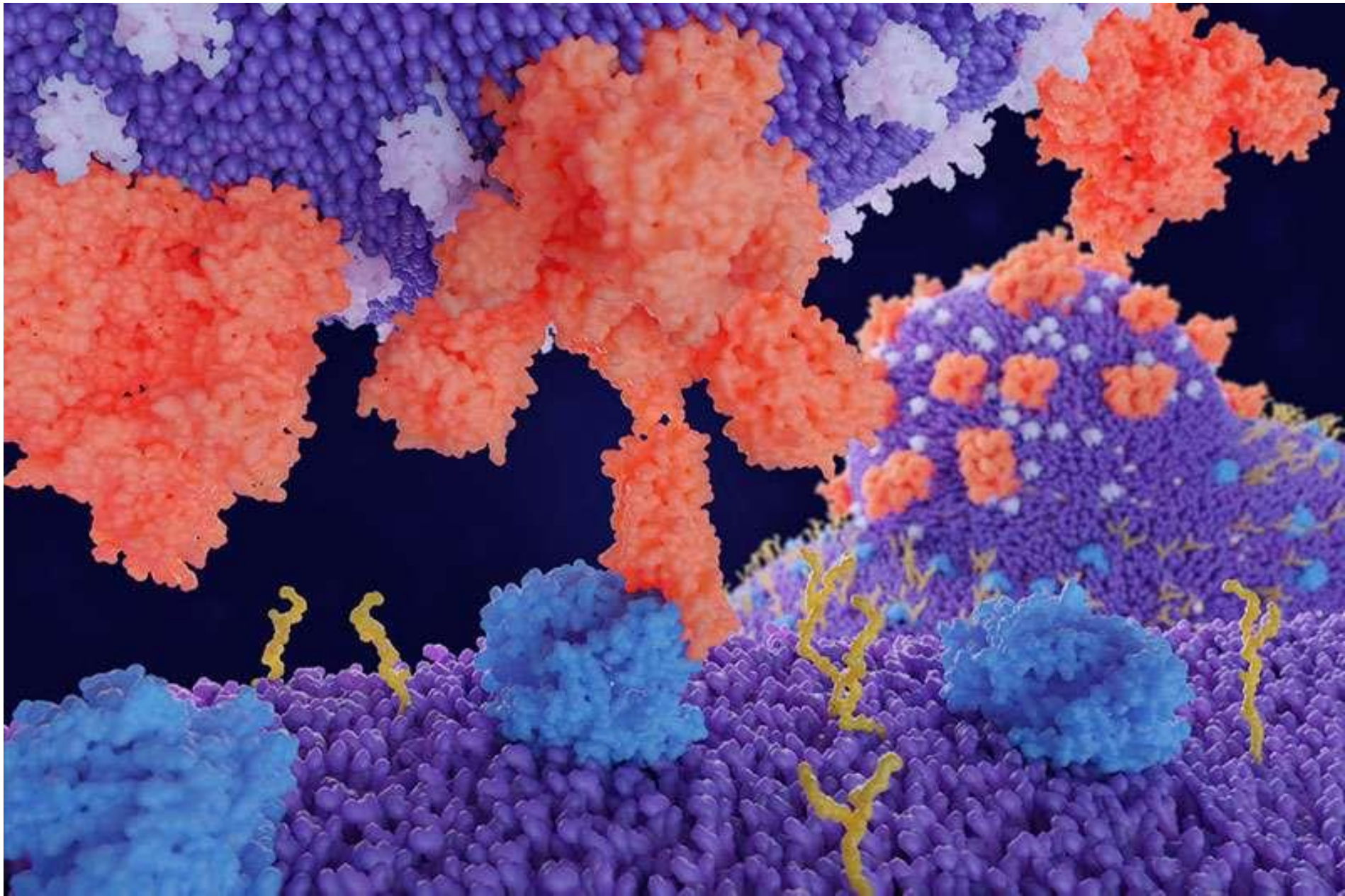
Animal origins of human coronaviruses.

Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019 Mar;17(3):181-192.

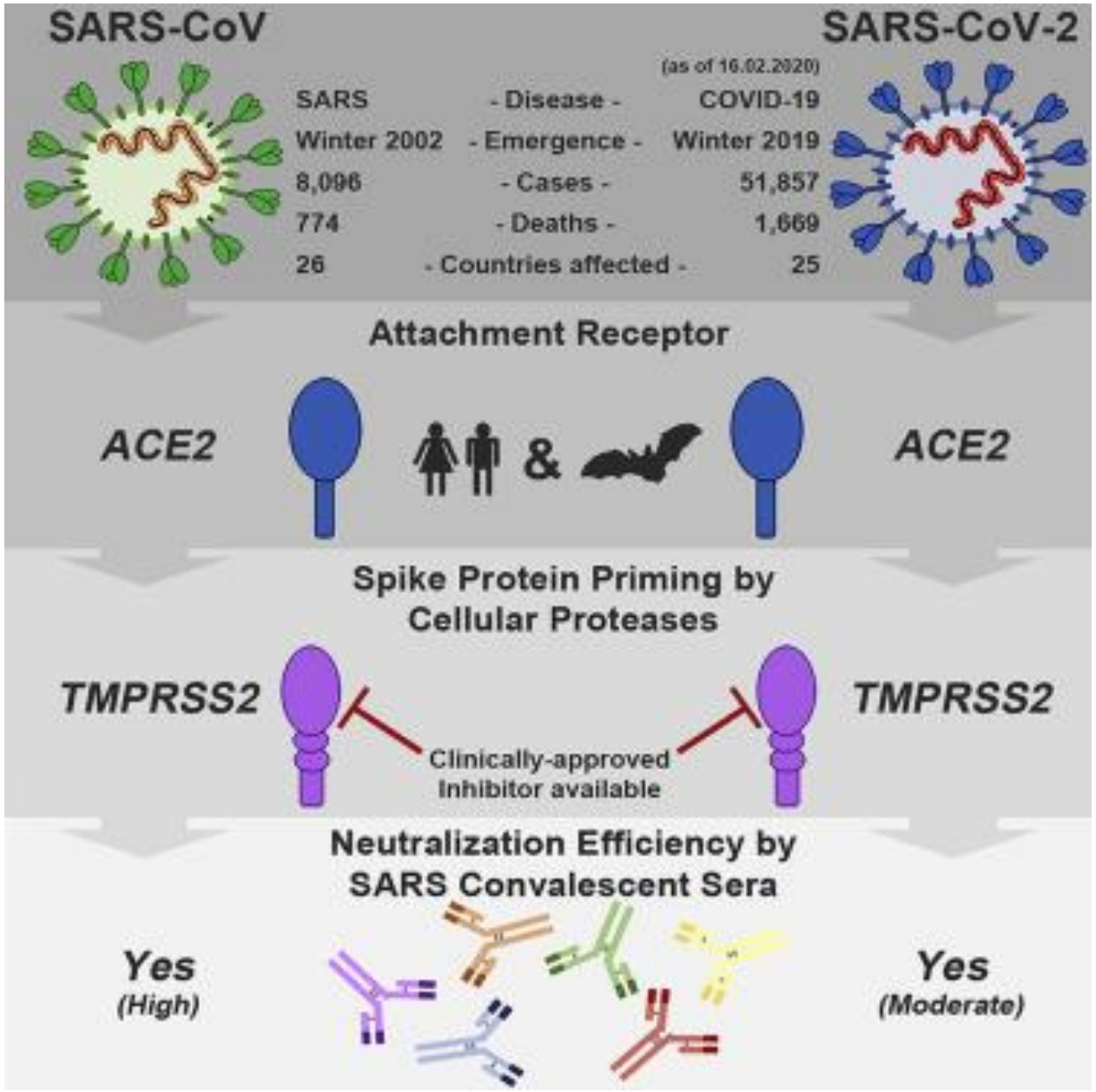


Receptor recognition by SARS-CoV and MERS-CoV.

Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019 Mar;17(3):181-192.



https://www.cas.org/blog/ace2-covid-19-target



Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052. Epub 2020 Mar 5. PMID: 32142651; PMCID: PMC7102627.

Vírus	Átmeneti gazda Intermediate host	Rezervoár	Receptor	Első felbukkanás
SARS-COV-2 **2019……..**	? 	Denevér Bat	ACE2	Vuhan, Kína
SARS-COV **2002-2003**	Cibetmacska Cat	Denevér Bat	ACE2	Guangzhou, Kína
MERS-COV **2012----**	Teve Camel	Denevér Bat	CD26/DPP4	Szaúd-Arábia

Wang H, Wei R, Rao G, Zhu J, Song B. Characteristic CT findings distinguishing 2019 novel coronavirus disease (COVID-19) from influenza pneumonia. Eur Radiol. 2020 Apr 22.

COVID-19

HOW DOES IT AFFECT YOU?

Designed by Avesta Rastan
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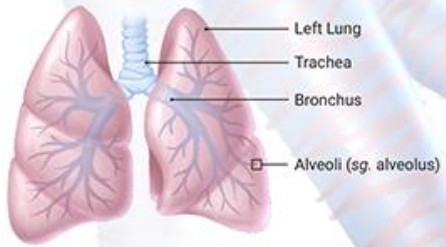
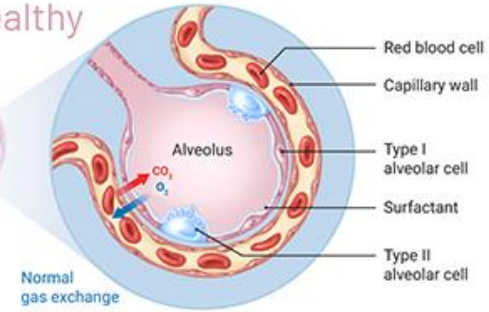
@azuravesta
@azuraviz

Coronavirus Disease 2019 (COVID-19) is a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2, also called SARS-CoV-2. Despite the widespread awareness regarding COVID-19, many are still unaware about how it affects the human body.



SARS-CoV-2 starts its journey in the nose, mouth, or eyes and travels down to the alveoli in the lungs. Alveoli are tiny sacs of air where gas exchange occurs.

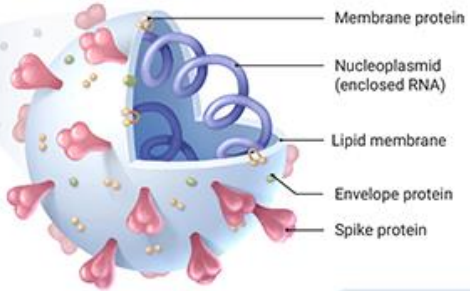
Healthy



Gas Exchange

Each sac of air, or alveolus, is wrapped with capillaries where red blood cells release **carbon dioxide** (CO_2) and pick up **oxygen** (O_2). Two alveolar cells facilitate gas exchange; **Type I** cells are thin enough that the oxygen passes right through, and **Type II** cells secrete **surfactant** – a substance that lines the alveolus and prevents it from collapsing.

Infected

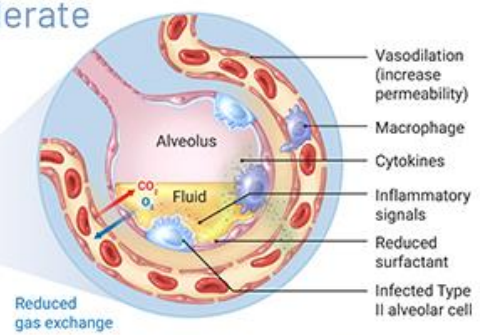


SARS-CoV-2 Structure

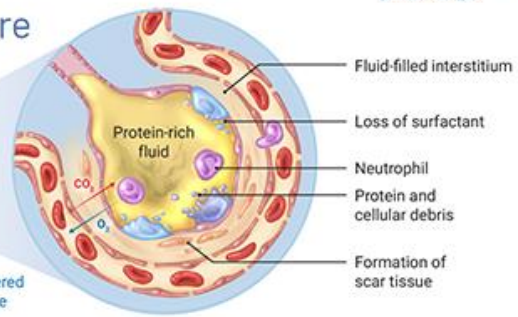
Viral Infection

The spike proteins covering the coronavirus bind ACE2 receptors primarily on type II alveolar cells, allowing the virus to inject its RNA. The RNA "hijacks" the cell, telling it to assemble many more copies of the virus and release them into the alveolus. The host cell is destroyed in this process and the new coronaviruses infect neighbouring cells.

Moderate



Severe



Impaired Gas Exchange

When the immune system attacks the area of infection it also kills healthy alveolar cells. This results in three things that hinder gas exchange:

1) Alveolar collapse due to loss of surfactant from Type II cells
2) Less oxygen enters the blood-stream due to lack of Type I cells
3) More fluid enters the alveolus

Stay Home

Symptoms may start to show (e.g. dry cough, fever, etc.)

Pneumonia develops

Shortness of breath

Hospitalization

Dangerous for high-risk individuals; secondary infections may occur

Intensive Care (ICU)

Patients may require ventilators and life-support

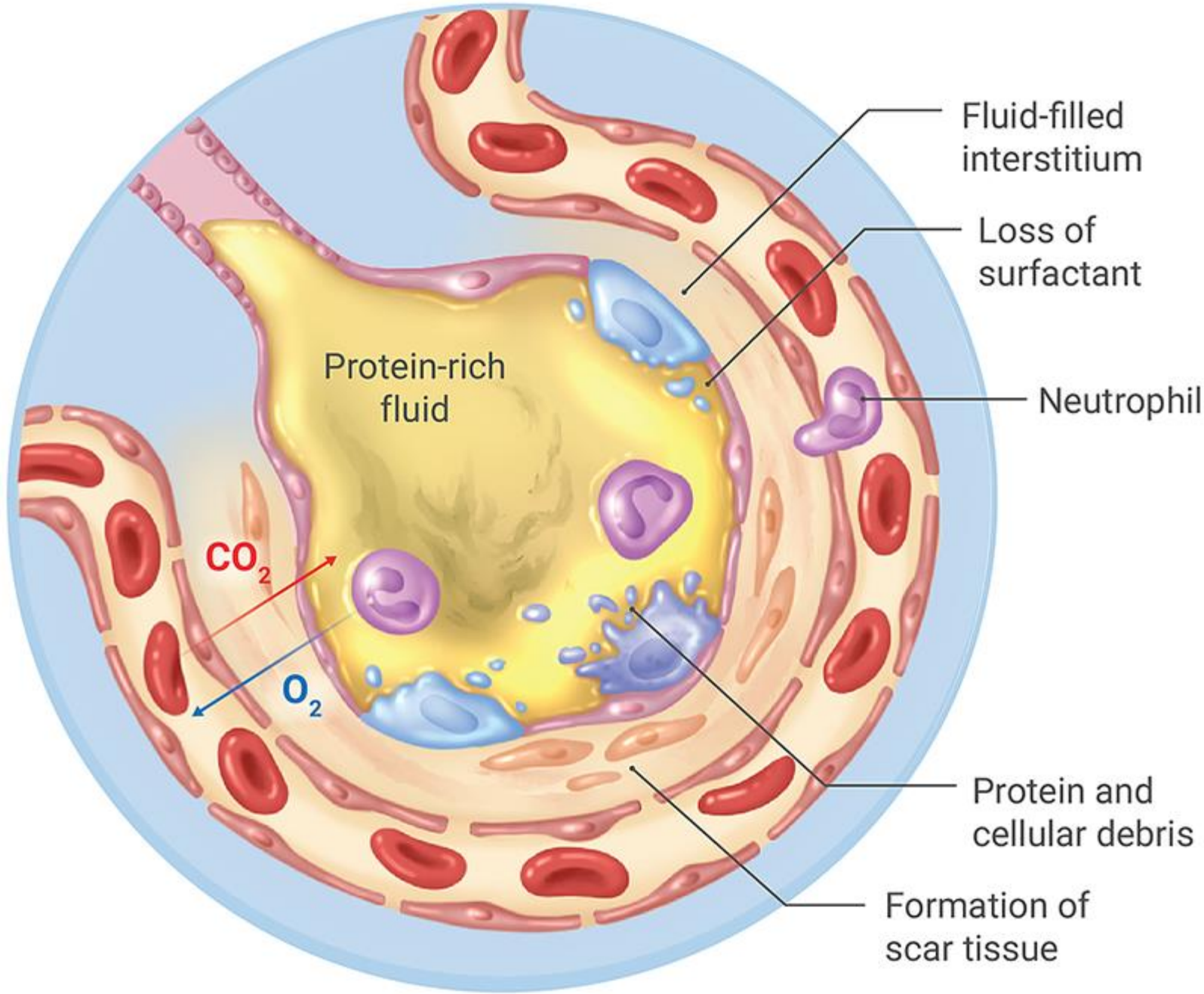
Complications unrelated to COVID-19 may occur

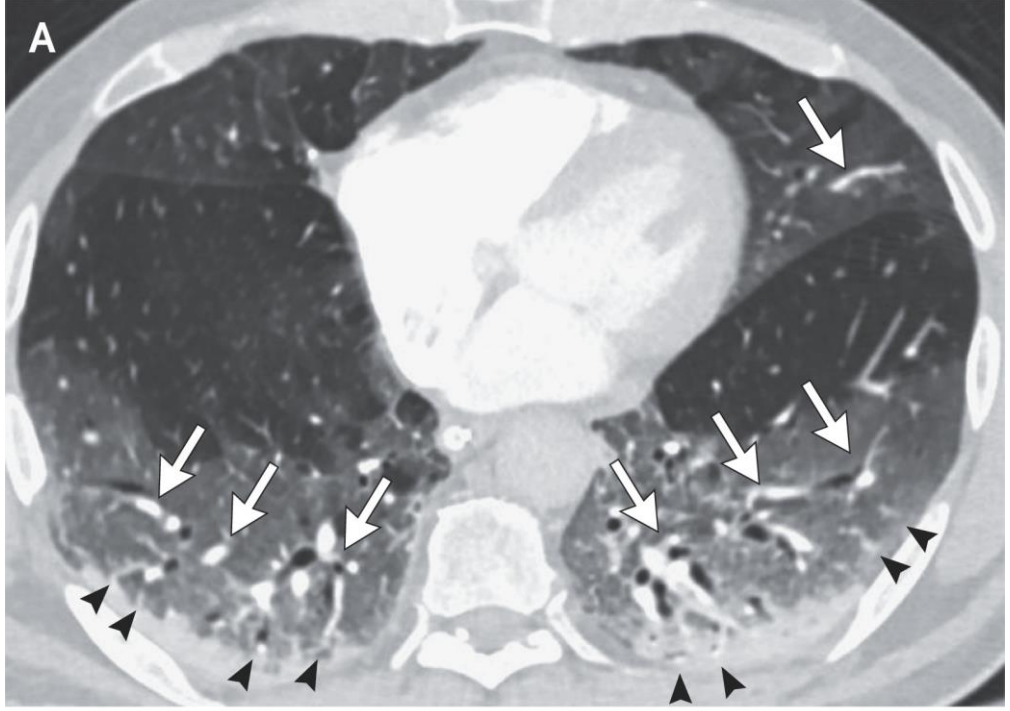
With proper care, patients may recover at any point during this process

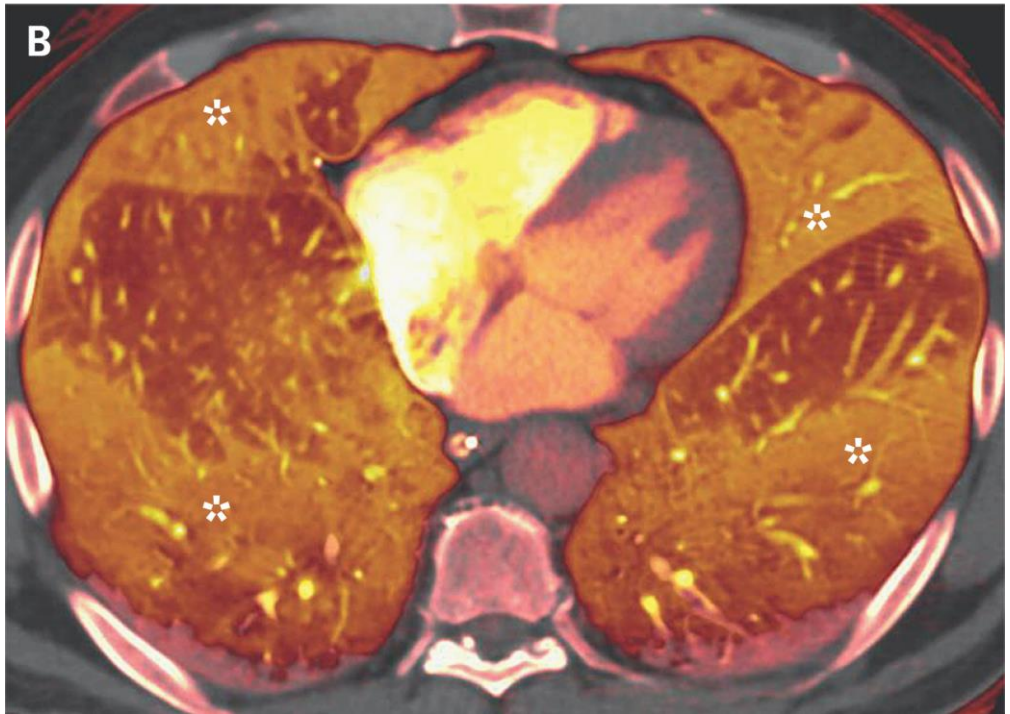
Immune Response

1. After infection, Type II cells release **inflammatory signals** that recruit **macrophages** (immune cells).
2. Macrophages release **cytokines** that cause vasodilation, which allows more immune cells to come to the site of injury and exit the capillary.
3. Fluid accumulates inside the alveolus.
4. The fluid dilutes the surfactant which triggers the onset of alveolar collapse, decreasing gas exchange and increasing the work of breathing.
5. **Neutrophils** are recruited to the site of infection and release Reactive Oxygen Species (ROS) to destroy infected cells.
6. Type I and II cells are destroyed, leading to the collapse of the alveolus and causing **Acute Respiratory Distress Syndrome** (ARDS).
7. If inflammation becomes severe, the protein-rich fluid can enter the bloodstream and travel elsewhere in the body, causing **Systemic Inflammatory Response Syndrome** (SIRS).
8. SIRS may lead to **septic shock** and **multi-organ failure**, which can have fatal consequences.

Published 11 months ago on April 10, 2020By Nick Routley

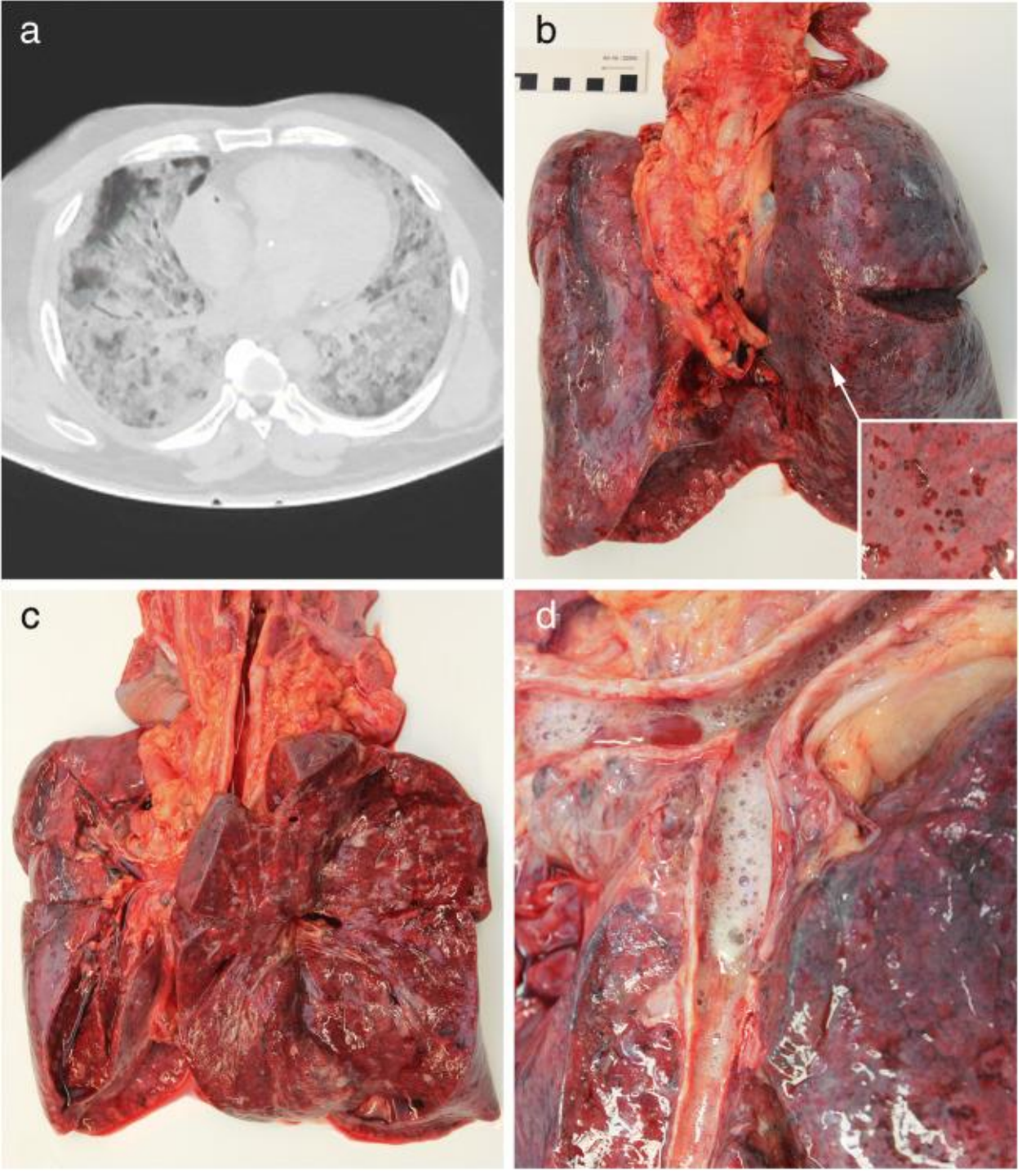

Fluid-filled interstitium
Loss of surfactant
Protein-rich fluid
Neutrophil
CO_2
O_2
Protein and cellular debris
Formation of scar tissue





Decreased perfusion in the posterior lungs (B) corresponds to a small amount of consolidation seen in Panel A.

August 27, 2020
N Engl J Med 2020; 383:886-889
DOI: 10.1056/NEJMc2022068



a Representative image of post-mortem chest CT scan revealing bilaterally diffuse ground-glass opacities and consolidations. b Lung, gross (inset: hemorrhage on the pleural surface). c Gross cross section of the right lung. d Gross cross section of the right lower lobe with fluid-filled bronchi

Suess C, Hausmann R. Gross and histopathological pulmonary findings in a COVID-19 associated death during self-isolation. Int J Legal Med. 2020 Jul;134(4):1285-1290. doi: 10.1007/s00414-020-02319-8. Epub 2020 Jun 5. PMID: 32504146; PMCID: PMC7273129.

Pulmonary pathology of COVID-19: a review of autopsy studies

Alain C. Borczuk

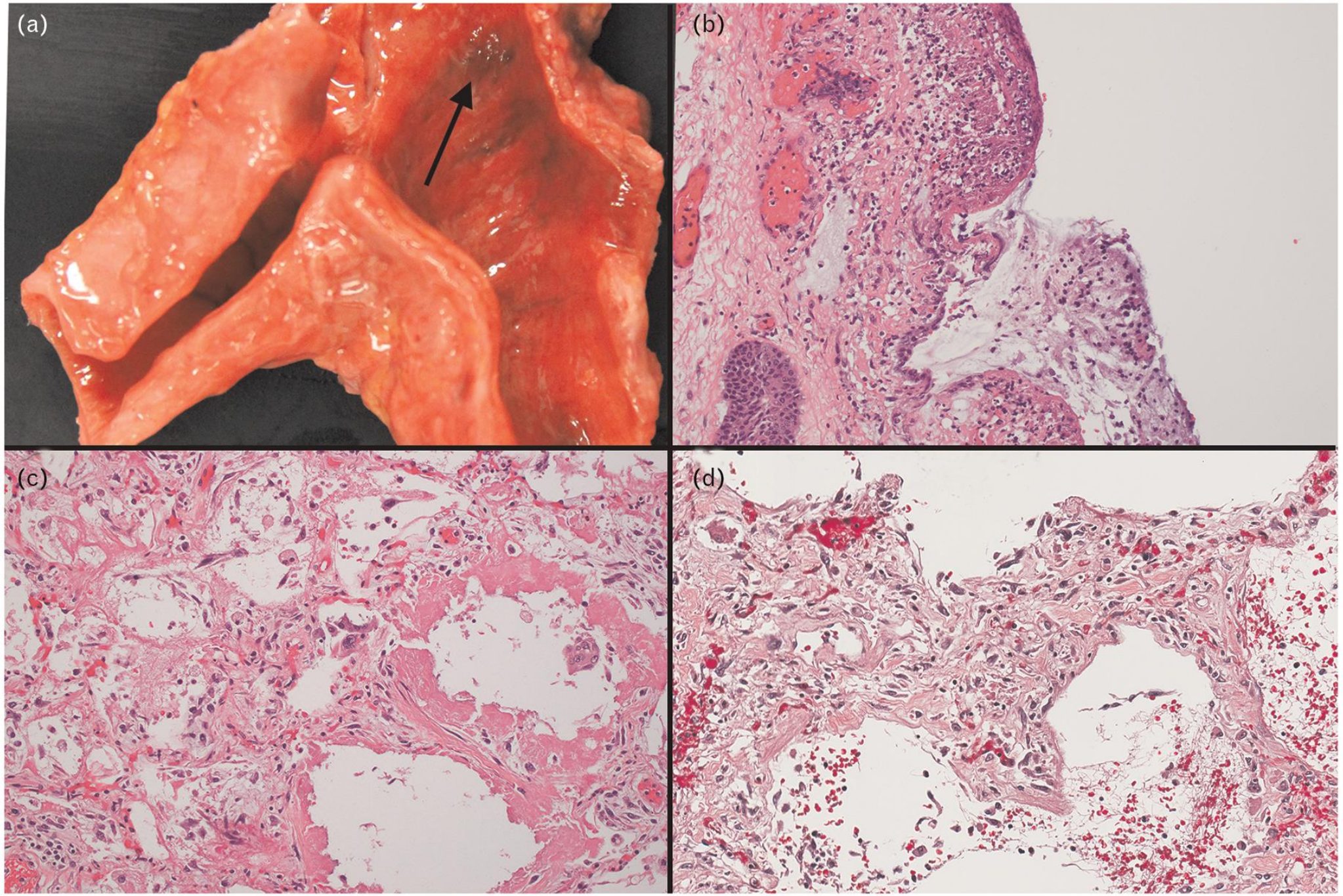
KEY POINTS

The histology of COVID-19 lung injury is diffuse alveolar damage, often temporally heterogeneous.

Thrombosis, especially microthrombi, are common in lung and extra-pulmonary sites.

Lung injury can lead to lung fibrosis.

A less common neutrophil-rich COVID-19 pneumonia may provide insight into disease pathogenesis, perhaps in a subset of severe cases.


(a)
(b)
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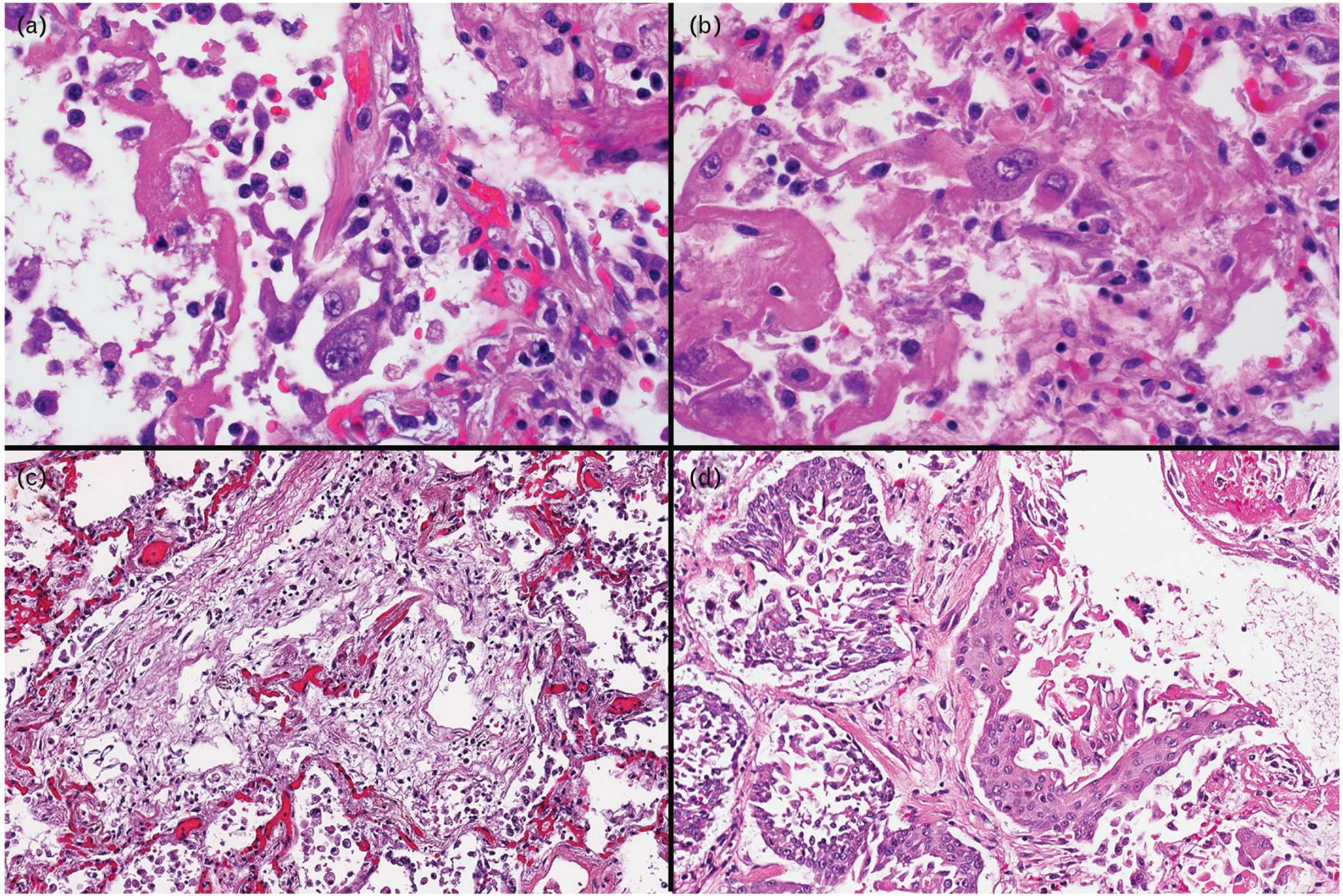
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(a)
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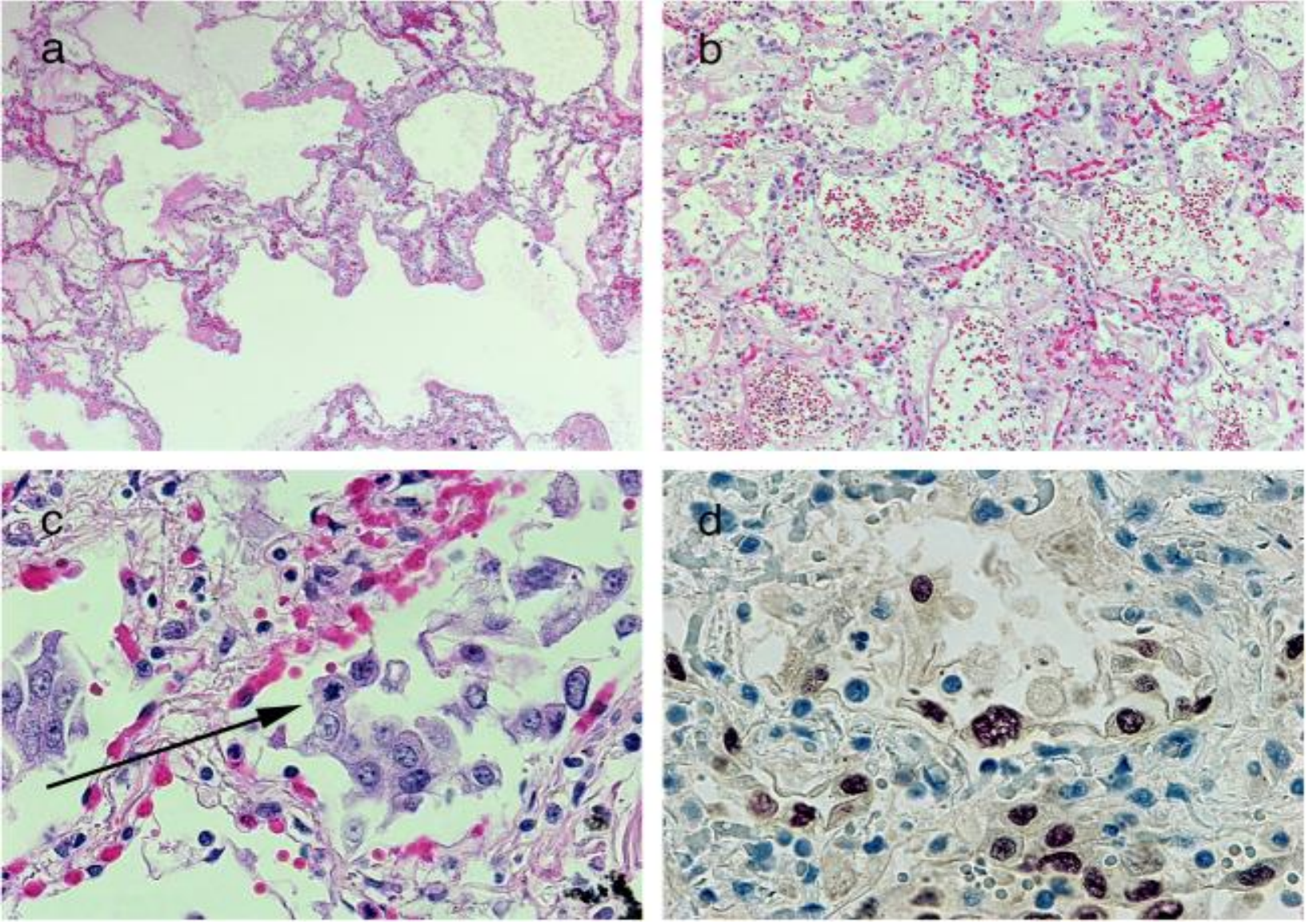
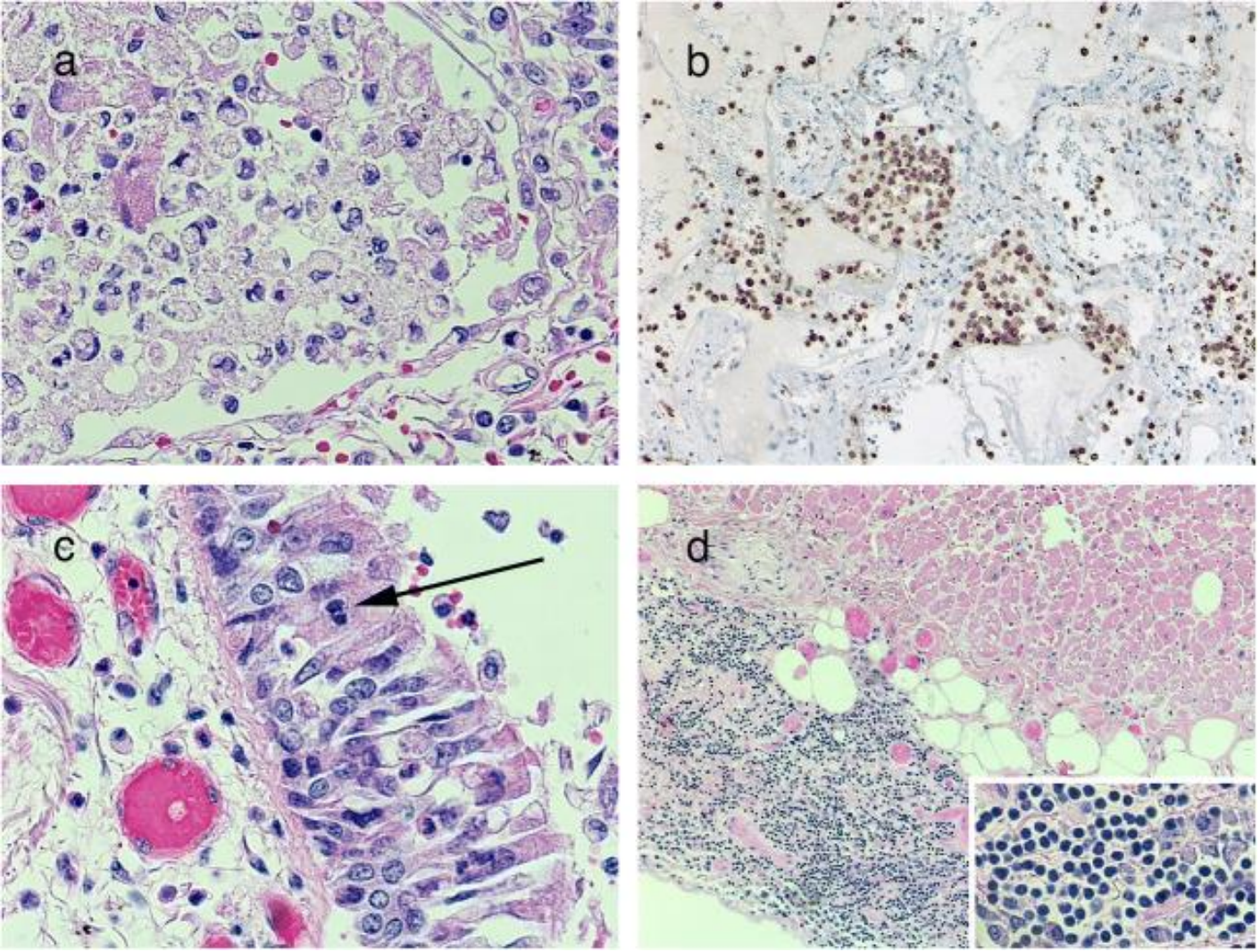
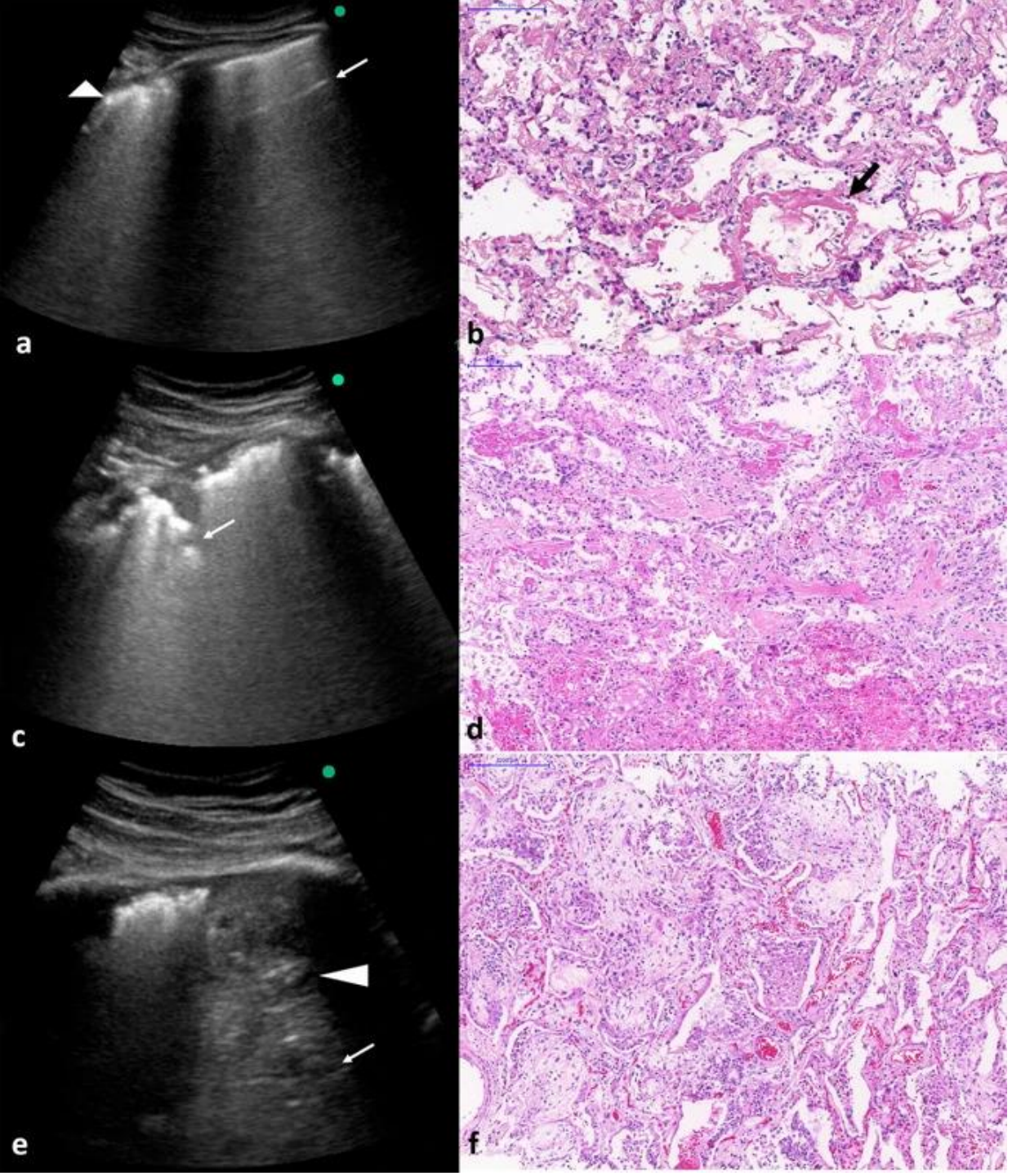


a Low power demonstrating the predominance of acute diffuse alveolar damage. b Intermediate power demonstrating edema, hemorrhage, and fibrin deposition. c High power demonstrates atypical enlarged intra-alveolar cells characterised by large nuclei with increased mitotic figures (arrow). d Immunhistochemical staining with TTF-1 confirmed the atypical enlarged cells with type II pneumocytes



a High power demonstrating collections of intra-aveolar foamy macrophages. b Immunhistochemical staining with CD68 highlighted the abundance of macrophages in lung tissue. c High power demonstrating reactive changes of the bronchial epithelium with enlarged nuclei and increased mitotic figures (arrow). d Low power demonstrating patchy nonspecific pericardial infiltration with aggregates of inflammatory cells (inset: high power demonstrating the predominance of lymphocytes mixed with plasma cells without neutrophils or granulomas)



Three distinct histological patterns were identified in severe COVID-19 affected lungs:
A. Acute pulmonary injury: defined as exudative inflammatory changes that include exudative diffuse alveolar damage (DAD), alveolar edema, neutrophilic pneumonia and hemorrhage;

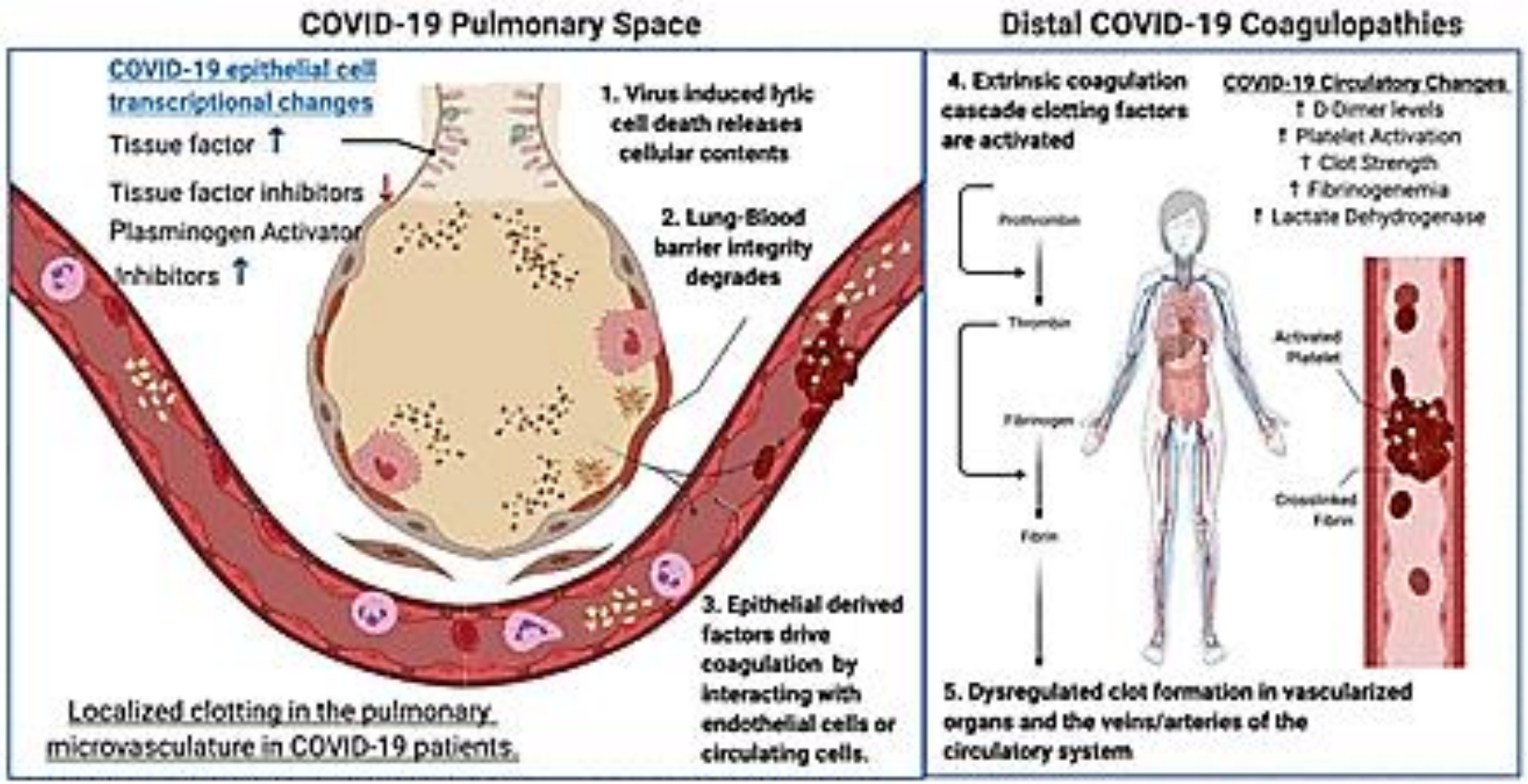
B. Early fibroproliferative changes: defined as a mixed pattern of acute and fibroproliferative changes, with organization of the exudative process and deposition of loose extracellular matrix;

C. Predominant pattern of fibroproliferation (fibroproliferative DAD).

We tested the agreement between US image patterns and histological alterations in 10 COVID-19 fatal cases by blindly comparing the diagnosis made by ultrasound and those obtained by histopathological analysis.

Histological–ultrasonographical correlation of pulmonary involvement in severe COVID-19
Renata Aparecida Almeida Monteiro, Ellen Pierre de Oliveira, Paulo Hilário Nascimento Saldiva, Marisa Dolhnikoff & Amaro Nunes Duarte-Neto & BIAS – Brazilian Image Autopsy Study Group

Original Source: Intensive Care Medicine (2020)



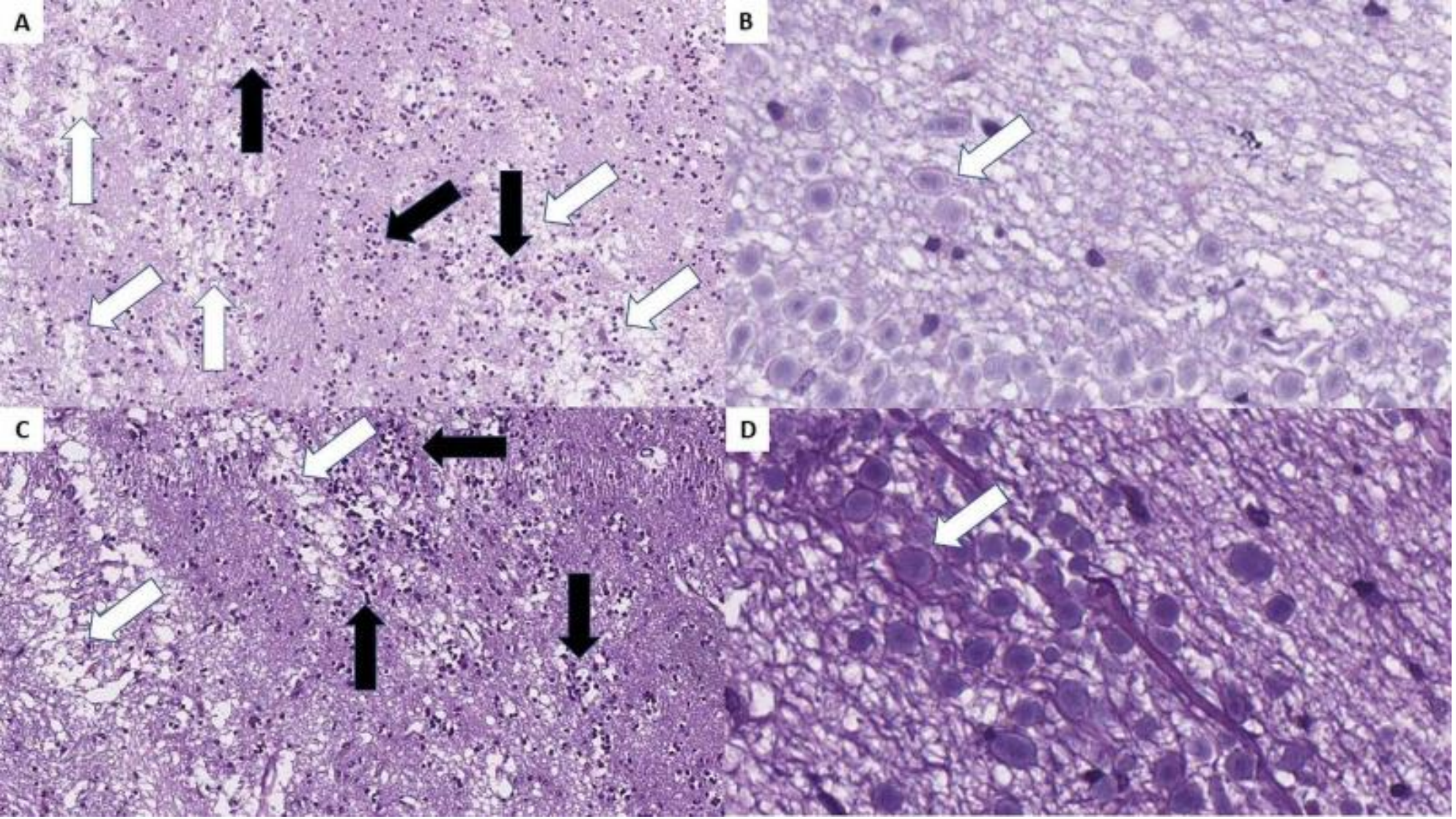
Unique transcriptional changes in coagulation cascade genes in SARS-CoV-2-infected lung epithelial cells: A potential factor in COVID-19 coagulopathies
Ethan S. FitzGerald, View ORCID ProfileAmanda M. Jamieson
doi: https://doi.org/10.1101/2020.07.06.182972

The hyper-activation of the extrinsic blood coagulation cascade and the suppression of the plasminogen activation system in SARS-CoV-2 infected epithelial cells may drive diverse coagulopathies in the lung and distal organ systems.

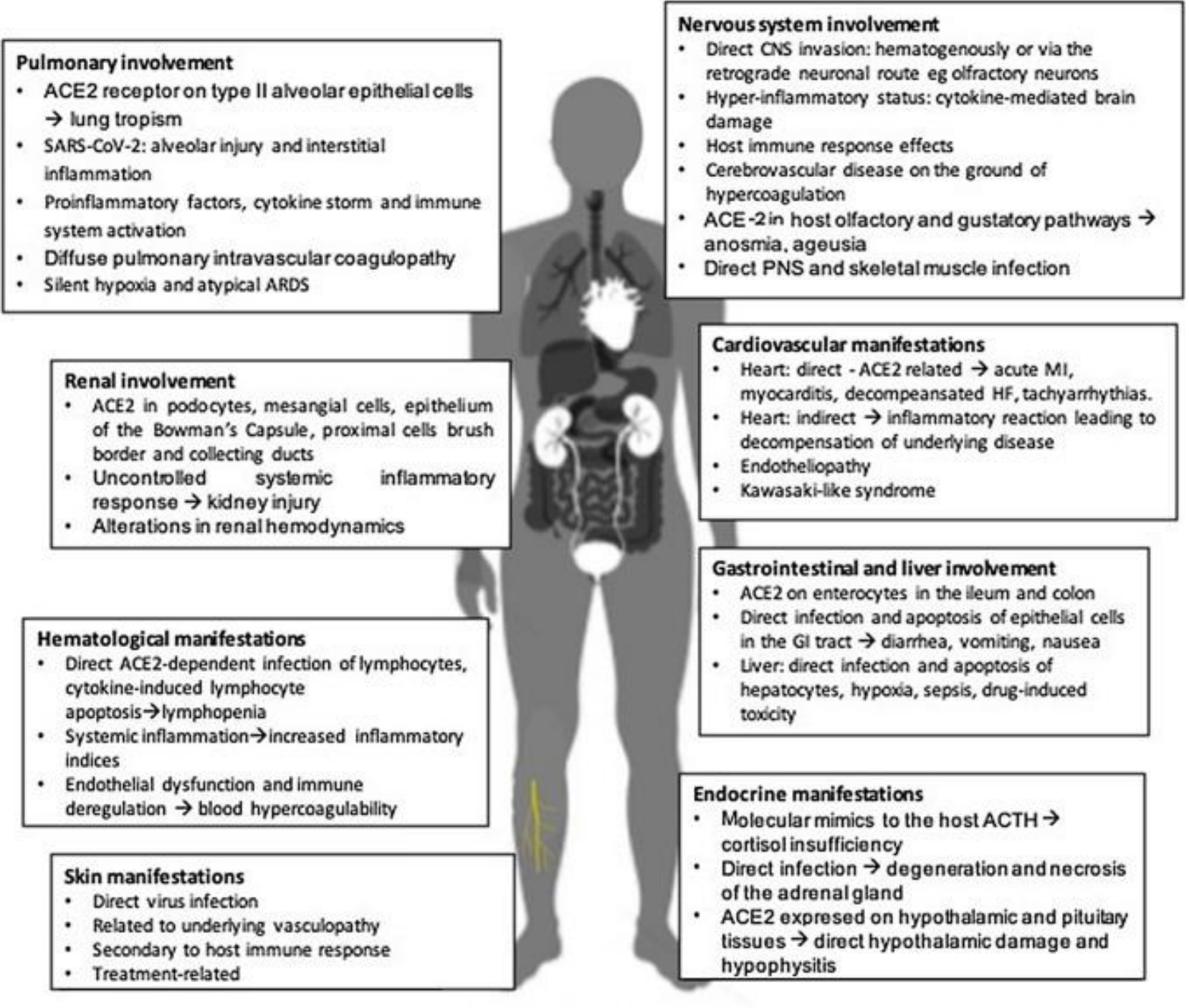
The gene transcription pattern in SARS-CoV-2 infected epithelial cells is distinct from IAV infected epithelial cells with regards to the regulation of blood coagulation.

Gross and Histopathology of COVID-19 With First Histology Report of Olfactory Bulb Changes

George S. Stoyanov, Lilyana Petkova, Deyan L. Dzhenkov, Nikolay R. Sapundzhiev, Iliyan Todorov



Necrotizing olfactory bulbitis as observed in both cases.
A and C: severe edema (white arrows) and diffuse inflammatory cell infiltration (black arrows), H&E stain, original magnification 100x; B and D: diffuse degenerative changes, H&E stain, original magnification 400x.



Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, Terpos E, Dimopoulos MA. Organ-specific manifestations of COVID-19 infection. Clin Exp Med. 2020 Nov;20(4):493-506. doi: 10.1007/s10238-020-00648-x. Epub 2020 Jul 27. PMID: 32720223; PMCID: PMC7383117.

Lung diseases

- Acute lung injury (ARDS)
- Inflammation: pneumonia

nota bene: pneumonitis – non-organic hypersensitive reaction

- **COPD (chronic obstructive lung disease)**
- **Restrictive lung diseases**
- Neoplasma- primary & secondary

Chronic Obstructive Pulmonary Disease (COPD)

Major symptom - dyspnea

- **cigarette** smoking!!!

Site of disease:

bronchi- **chronic bronchitis**,

bronchioles-bronchiolitis,

acini- **emphysema**

„Non-smoking" etiology –
Asthma

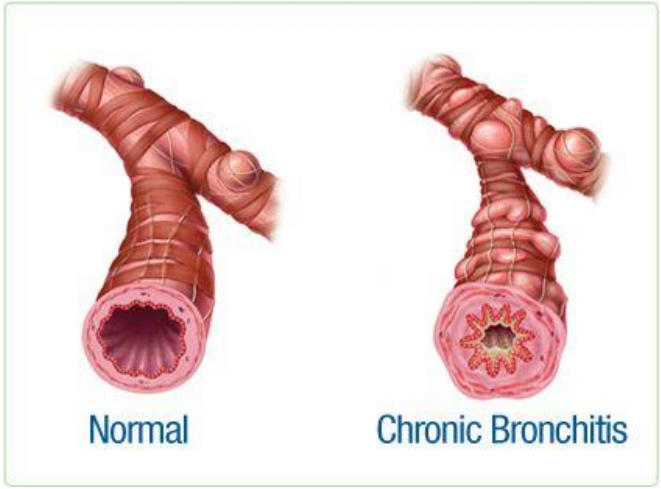
Bronchiectasis

- **Obstructive airway disease**
- increase in resistance to airflow due to obstruction at any level of aiways;
- **reduced** maximal airflow rates (**FEV1**)

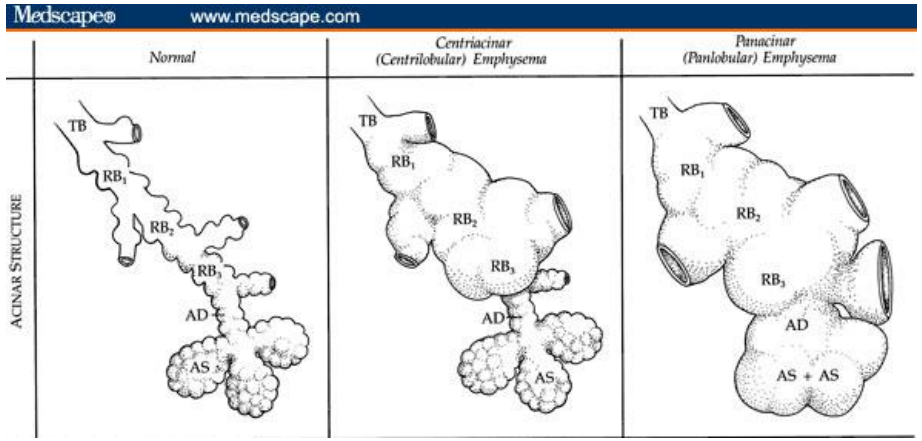
(forced expiratory volume in 1 second, FEV1%VC)

Chronic Obstructive Pulmonary Disease (COPD)

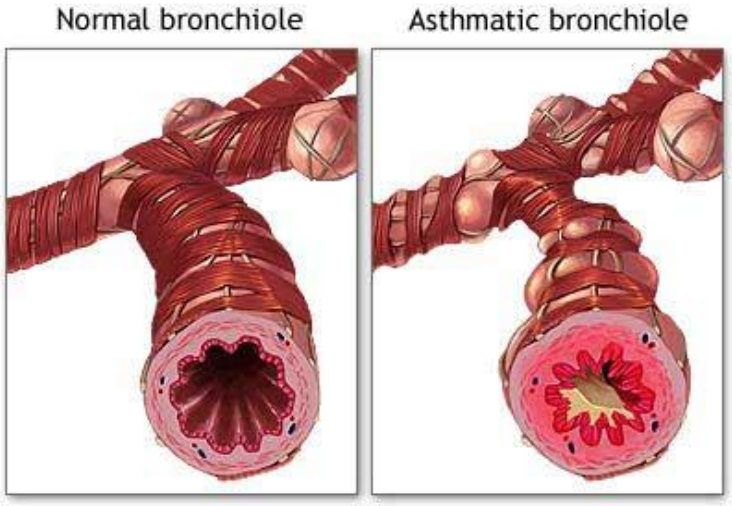
- **Chronic bronchitis**



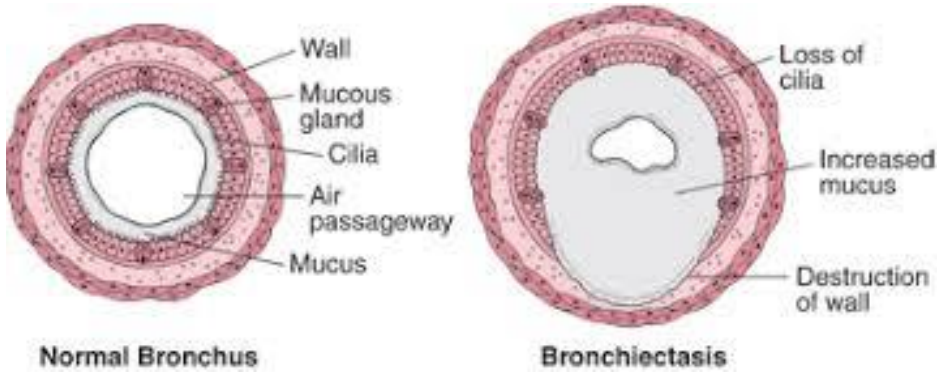
- **Emphysema**



- **Bronchial asthma**

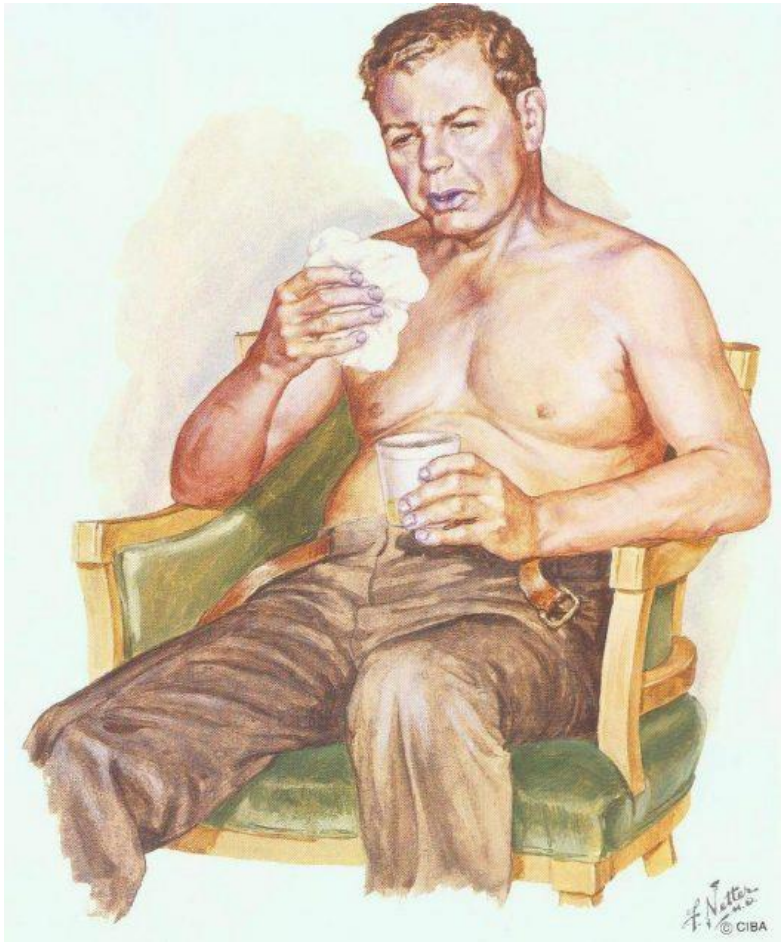


- **Bronchiectasis**



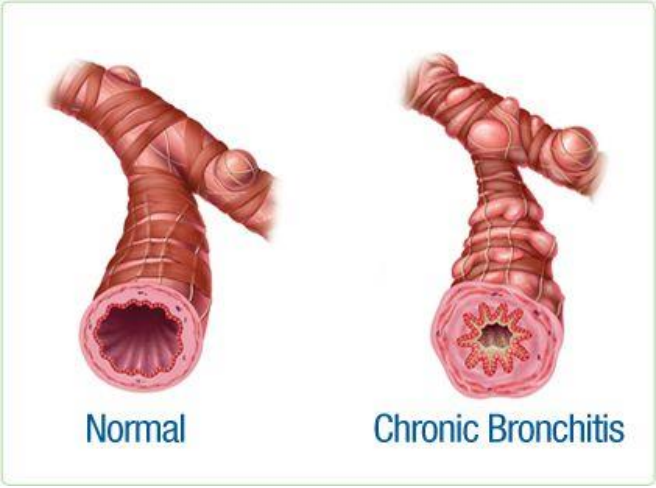
Chronic Bronchitis

- **Diagnosis:** persistent cough with sputum for 3 months in 2 consecutive years
- More infections, purulent sputum, hypercapnia, hypoxia than emphysema; clinically called "**blue bloaters**"
- **Causes:** 4-10x more common in smokers, also chronic irritation, infections

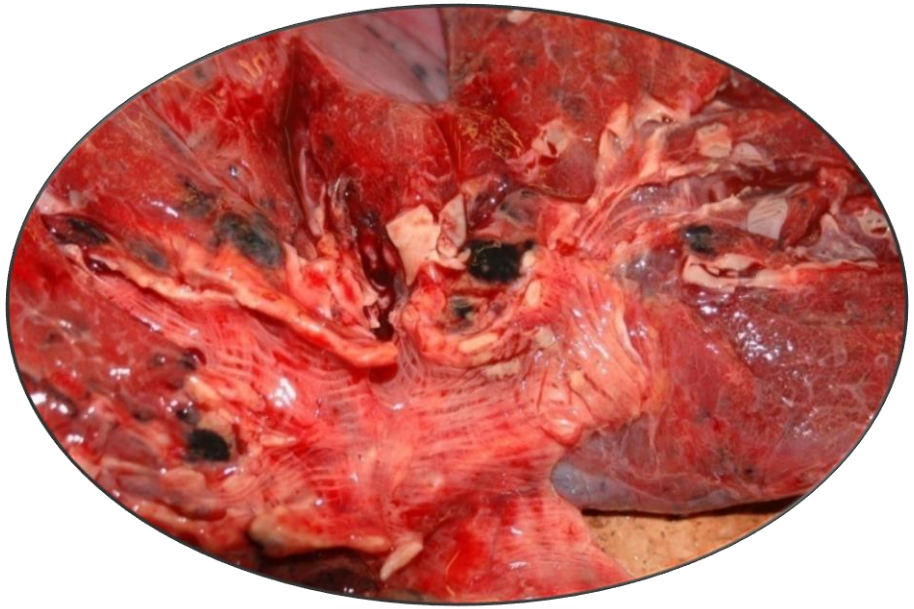


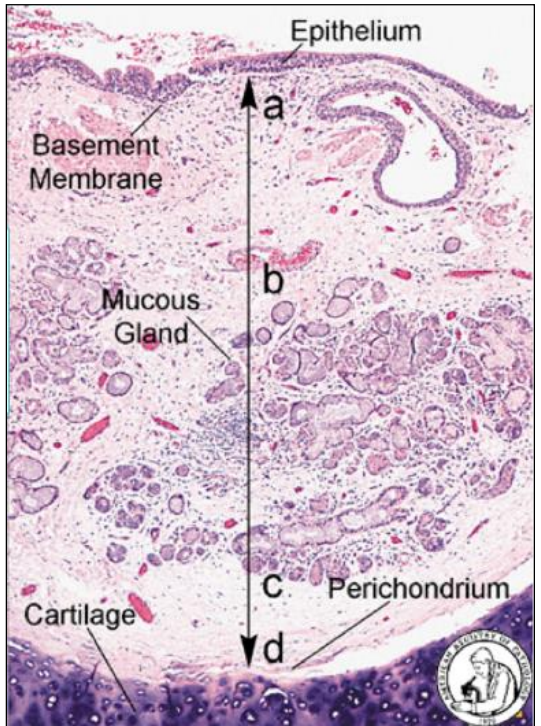
A person with chronic bronchitis who demonstrates evidence of cyanosis and pedal edema.

Chronic Bronchitis



- **Simple** bronchitis: mucoid sputum wo obstruction
- Intermittant bronchial spasmus
- **Chronic obstructive** bronchitis w emphysema (heavy smokers)





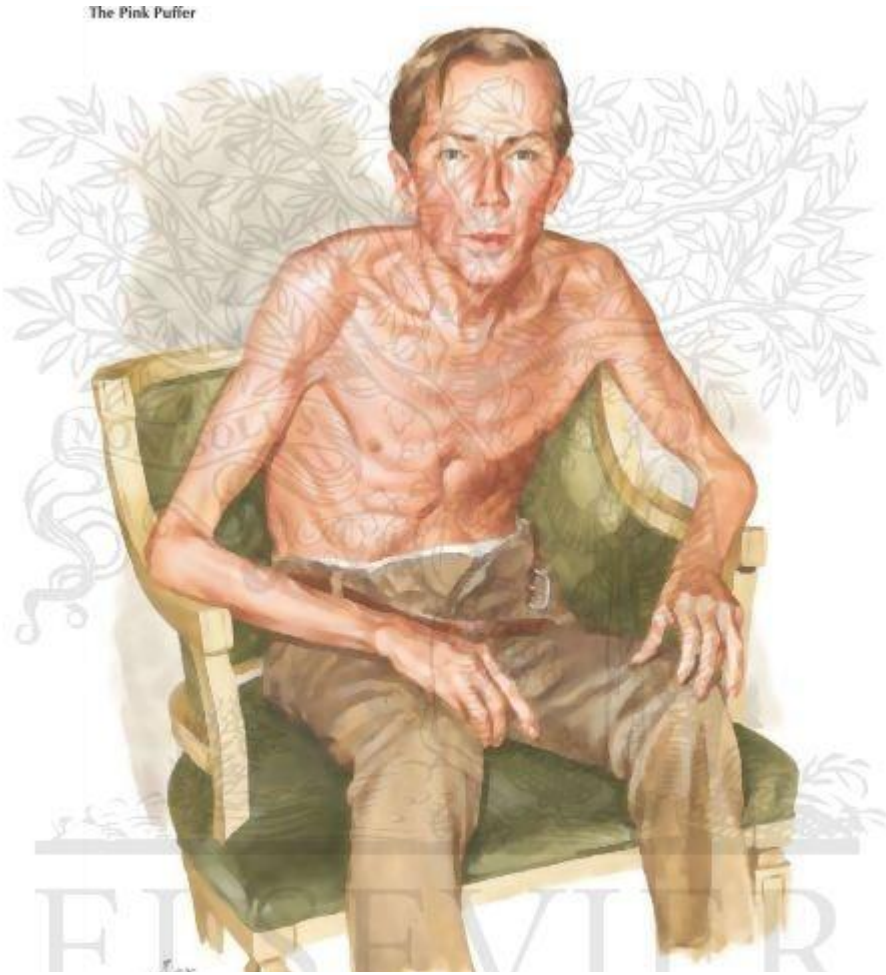
Reid index:

ratio of thickness of mucus gland layer to thickness of wall between epithelium and cartilage;

normal is 0.4, increased in chronic bronchitis

Emphysema

- Permanent enlargement of air spaces distal to terminal bronchiole **with** wall destruction but **without** fibrosis
- Acinar and airspace enlargement is usually **due to tobacco** related wall destruction



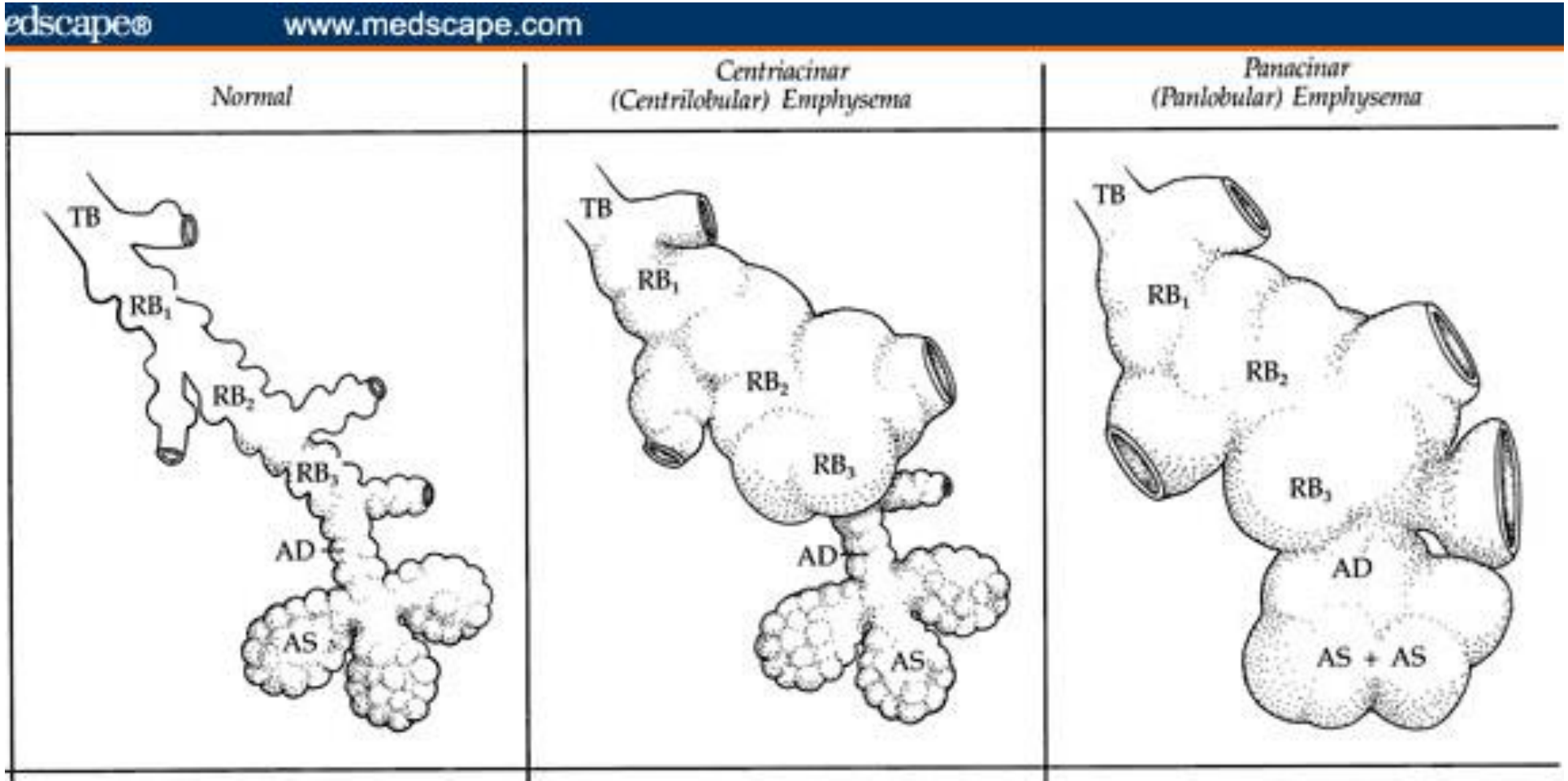
Patients breathless from **CHRONIC** lungdisease but still able to maintain sufficient oxygenation of the blood to avoid **CYANOSIS**.

Emphysema

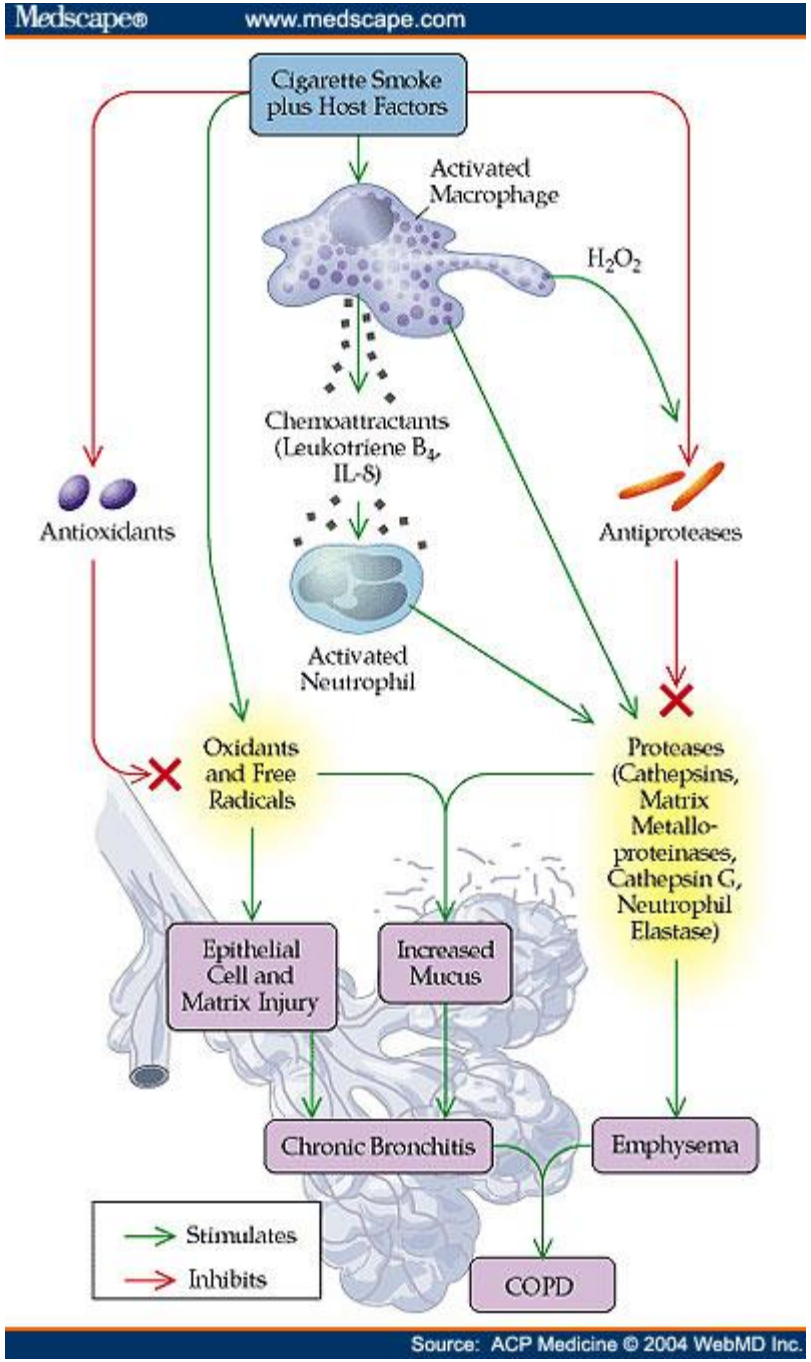
Emphysema

Subtypes

- Centriacinar/lobular - smoking
- Panacinar/lobular - (α-AT def)
- Distal acinar
- Irregular



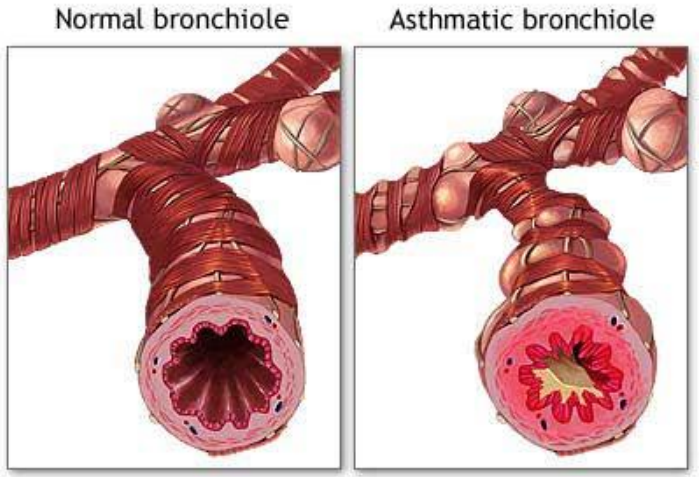
COPD Pathogenesis



Oxidants and Free Radicals

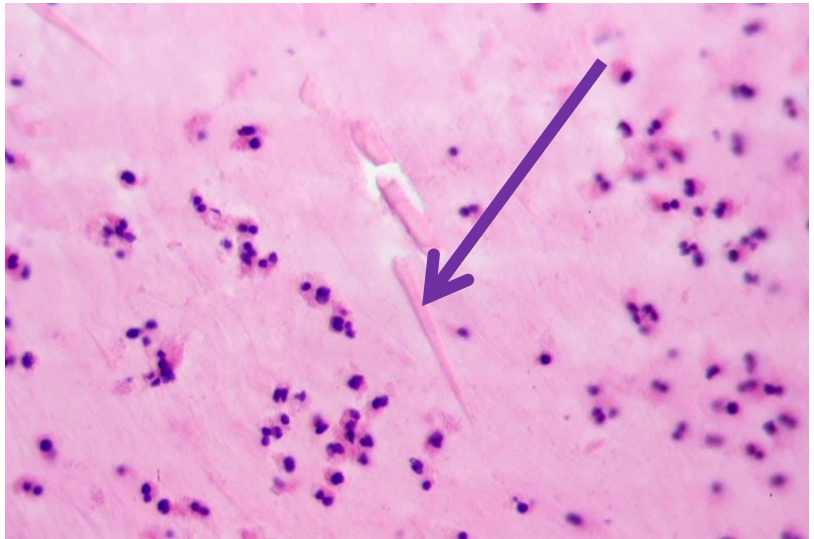
Proteases (elastase)

Asthma



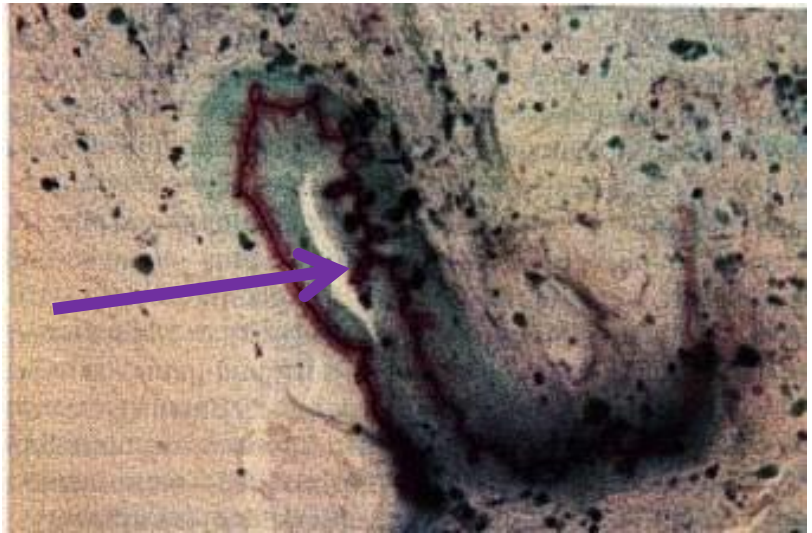
- reversible **bronchoconstriction**
- atopic: T_H2 and IgE mediated immunologic reaction to allergens characterized by acute and late-phase reactions
- non-atopic: viral infections and air pollutants
- eosinophils are key inflammatory cells
- basement membrane thickening and hypertrophy of smooth muscle of bronchi

CHARCOT-LEYDEN CRYSTALS

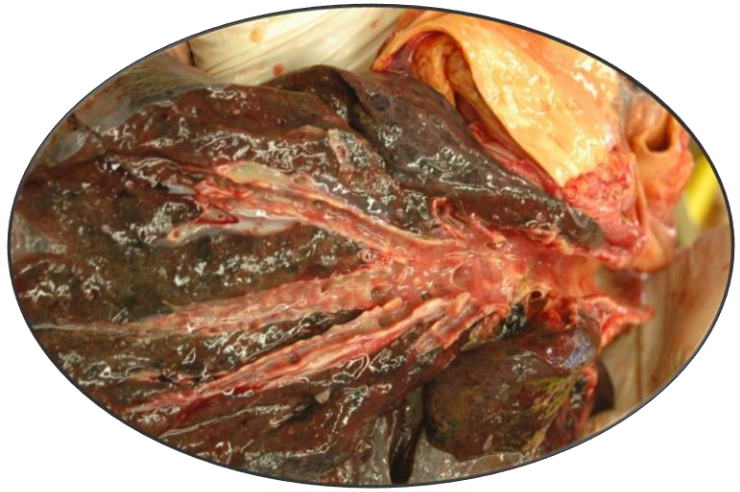


CURSCHMANN'S SPIRAL

Spiral shaped mucous plug in asthma patients



Bronchiectasis



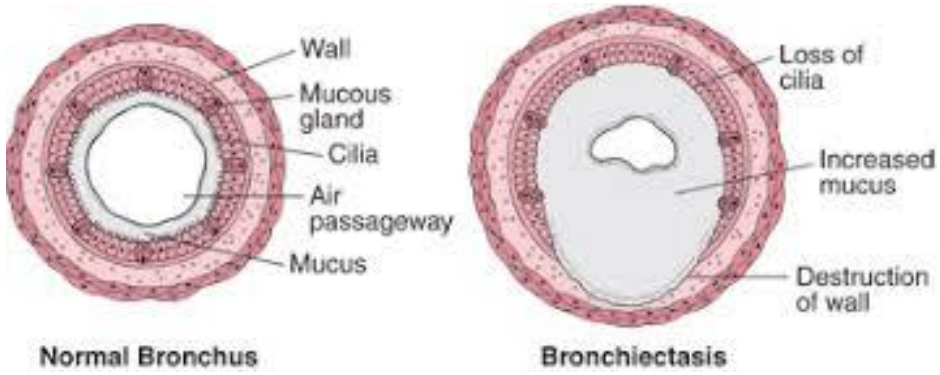
Etiology

- **Bronchial obstruction**
- **Cystic fibrosis**
- **Chronic (necrotizing) infection of bronchi and bronchioles associated with permanent dilatation of these airways**
- **Symptoms:** cough, fever, purulent sputum

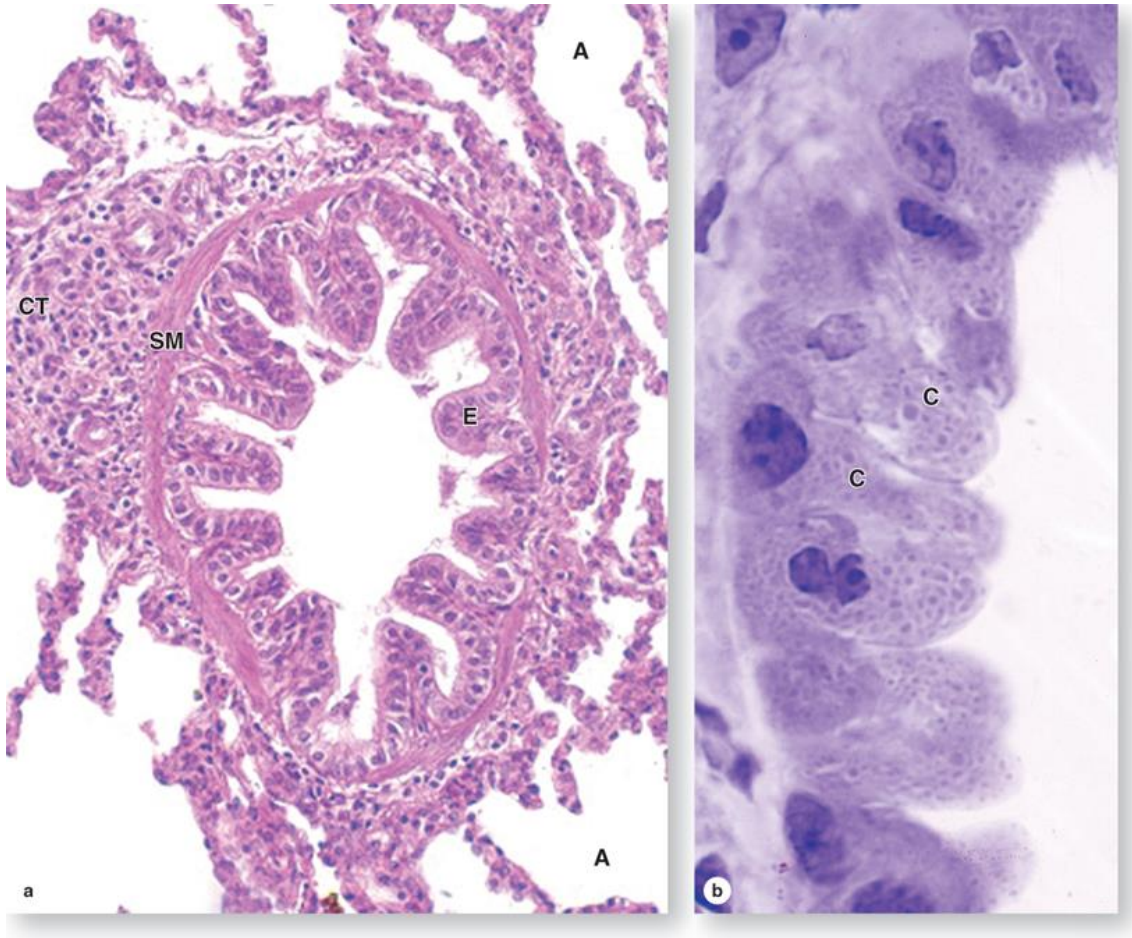
Sec amyloidosis!!!!

- **Gross:**

  markedly distended peripheral bronchi, **usually in lower lobes**, can **trace to pleural** surface;



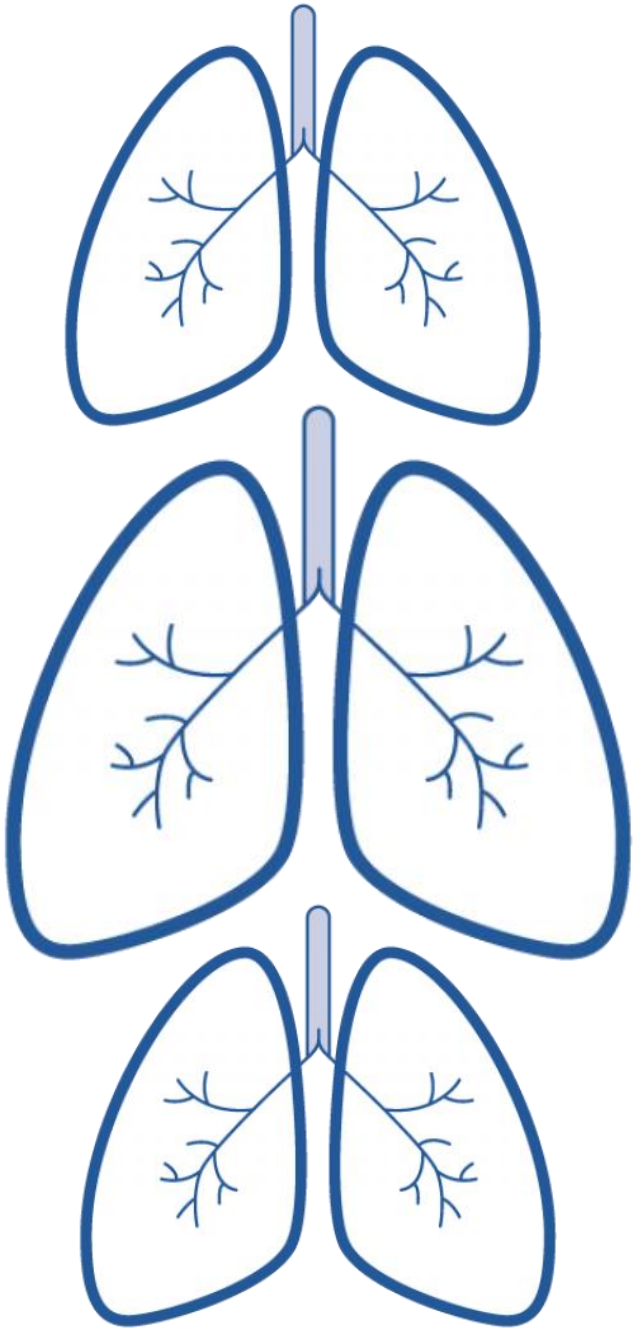
Kartagener Syndrome/Primary Ciliary Dyskinesia (PCD)



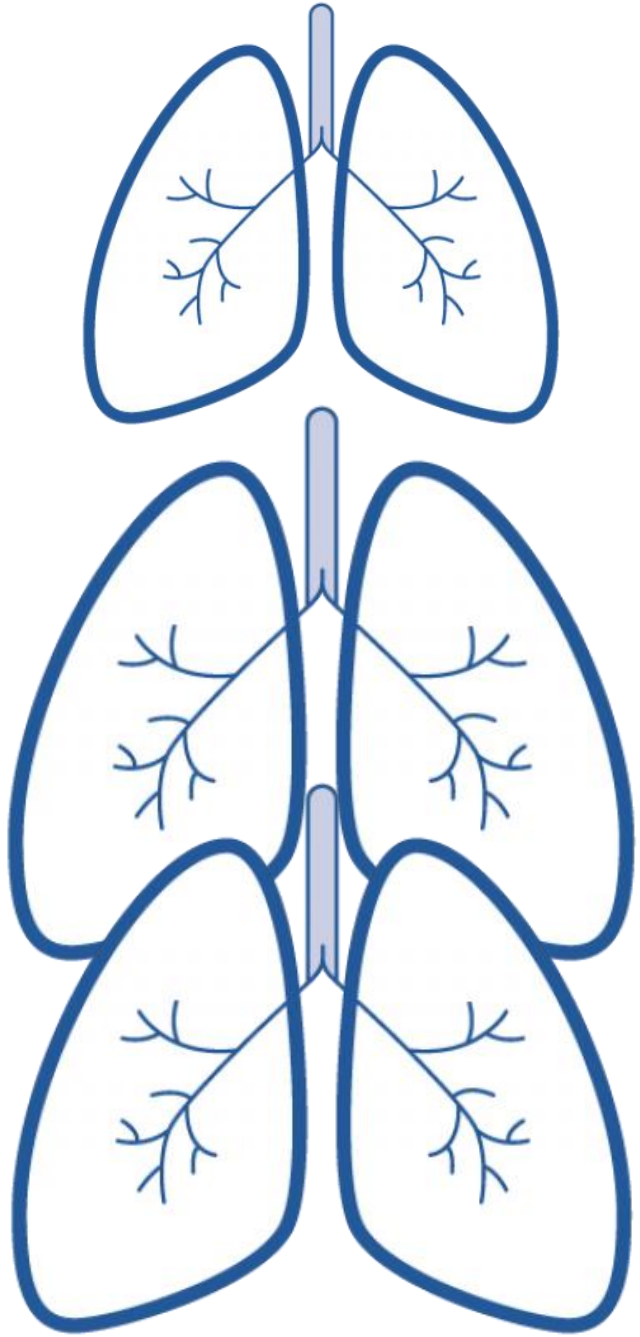
Source: Anthony L. Mescher: Junqueira's Basic Histology, 14th Edition.
www.accessmedicine.com

- Situs inversus, *bronchiectasis* and sinusitis, due to defective ciliary action
- PCD is a genetically heterogeneous disor der affecting motile of cilia which are made up of approximately 250 proteins.

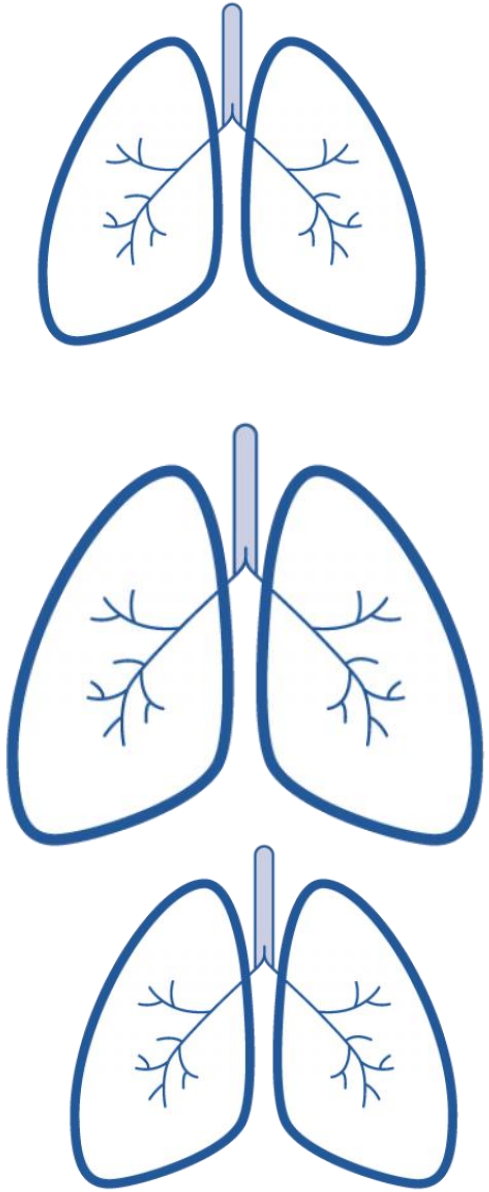
NORMAL



COPD



RESTRICTIVE



Restrictive Lung Disease

reduced expansion (compliance) of lung parenchyma with decrease in total lung capacity;

NORMAL FEV1

1. **Fibrosing** diseases
   - Interstitial / infiltrative lung diseases - **ILD** interstitial fibrosis
   - Pneumoconioses
   - Autoimmune disease
2. **Granulomatous** diseases **(i.e. sarcoidosis)**
3. **Eosinophilic**
4. **Smoking-related**

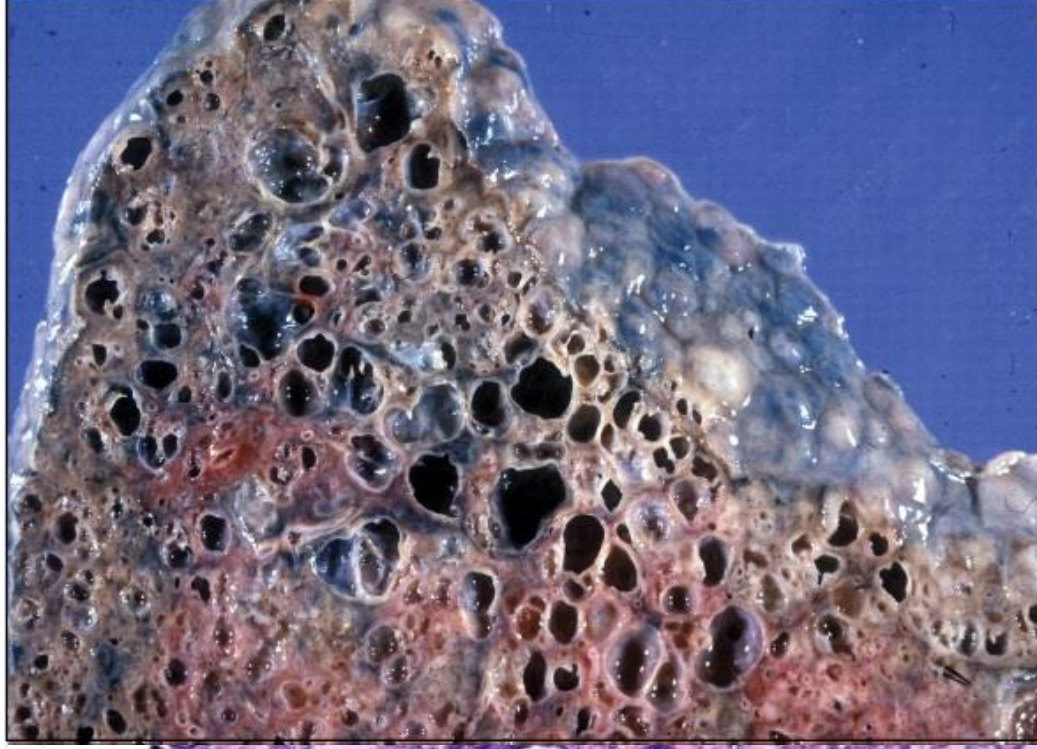
Fibrosing diseases

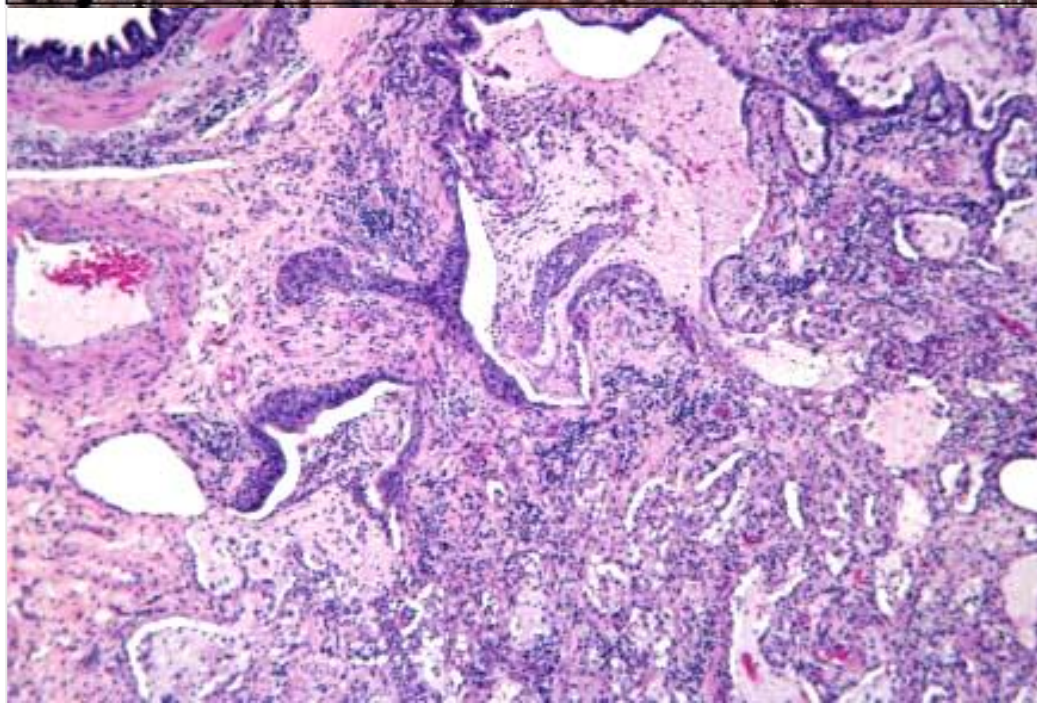
Idiopathic pulmonary fibrosis (IPF)
(usual interstitial pneumonia - **UIP**)

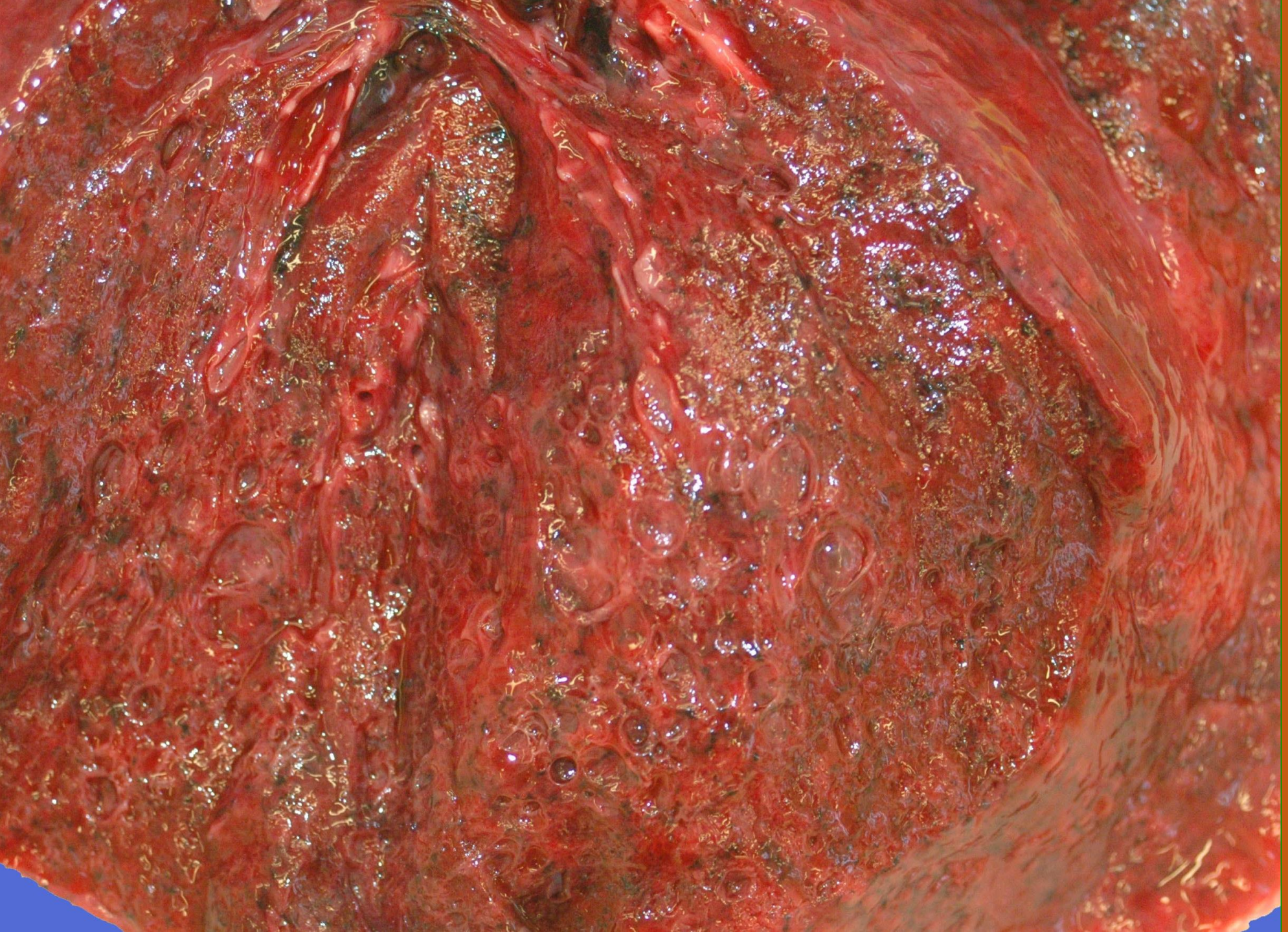
- 60+ (male>female)
- recurrent alveolitis
- Diagnosis of exclusion
  (no asbest, no vascular disease etc)

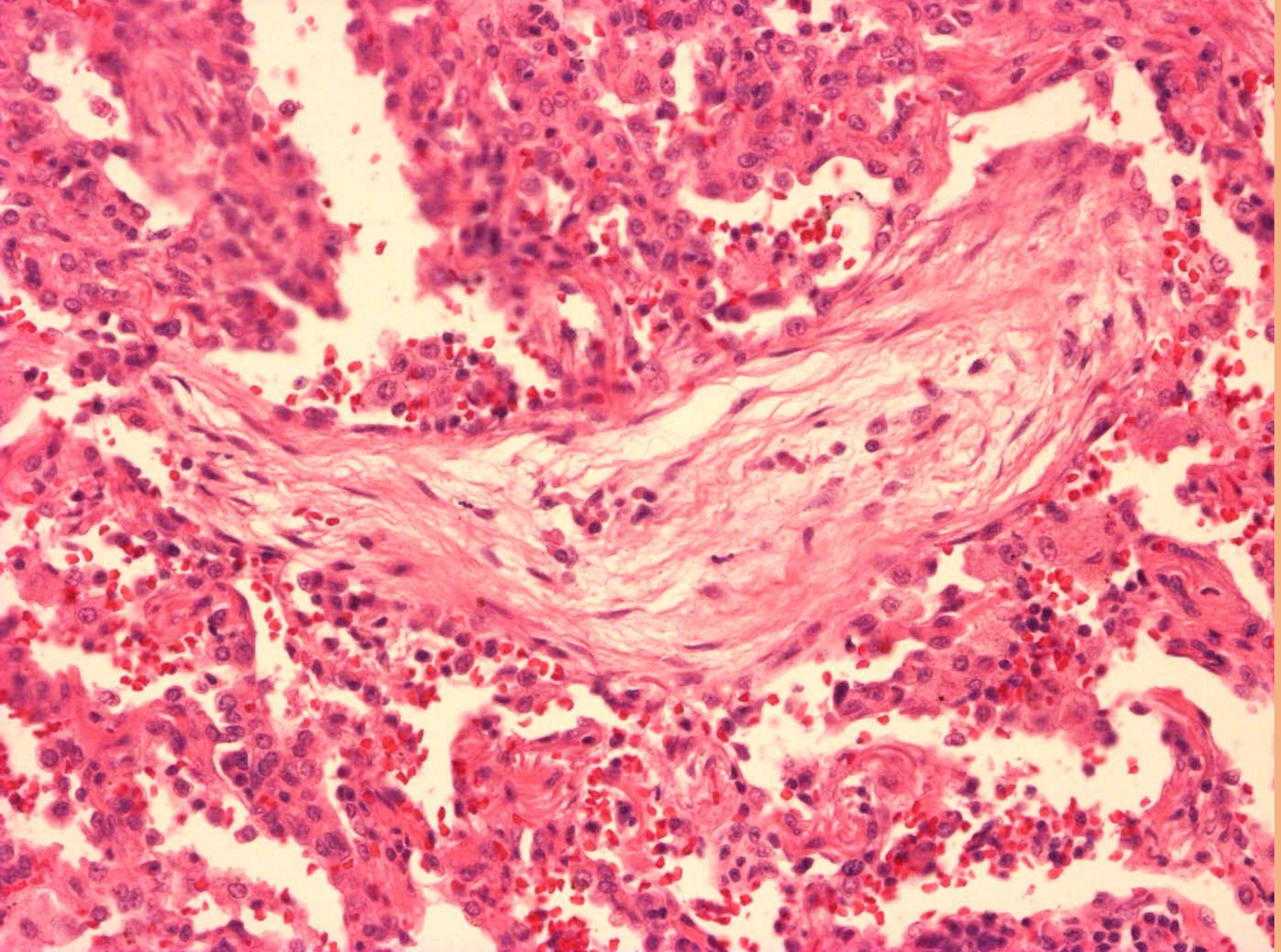
TGF-beta 1!!

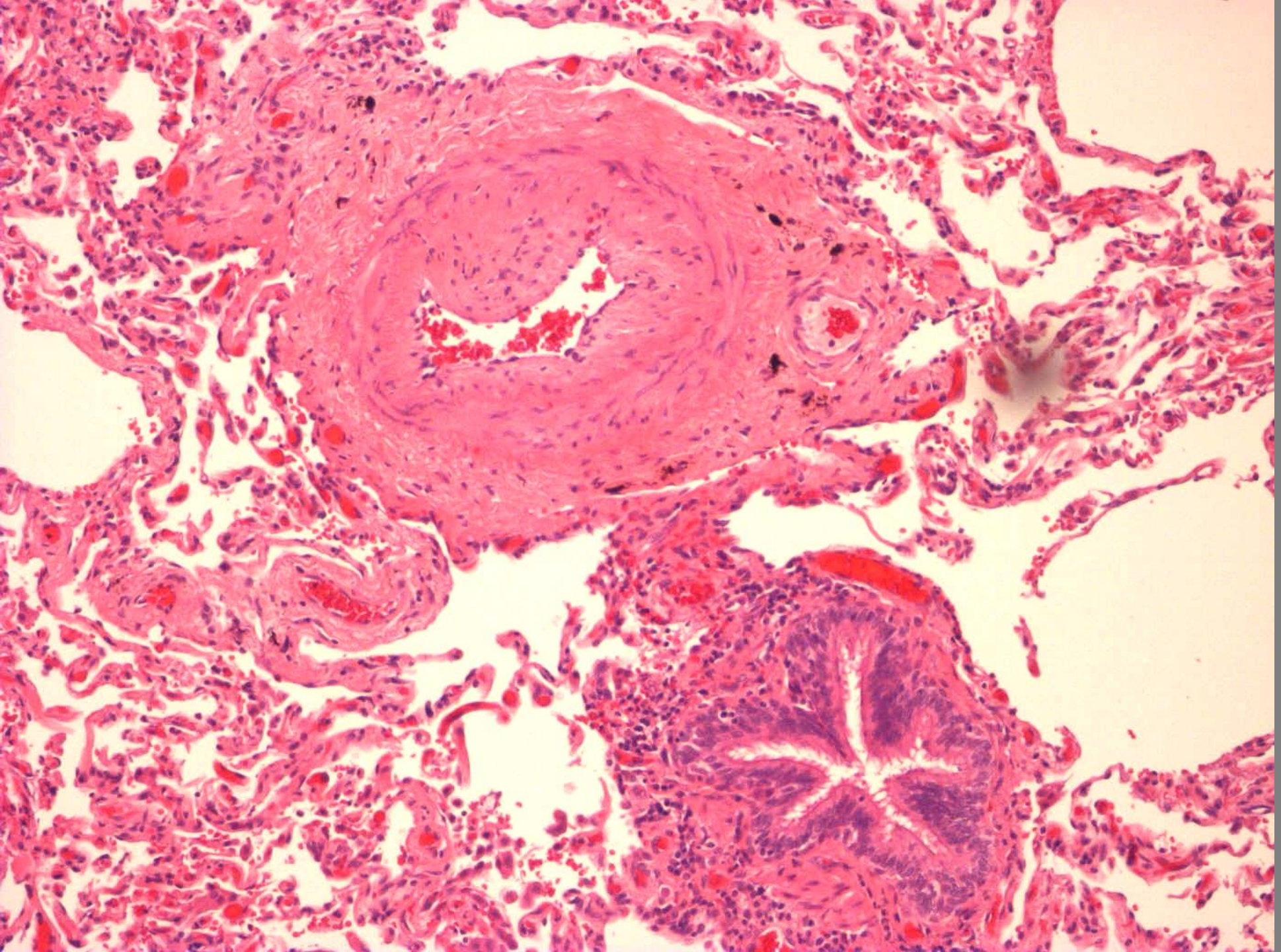
Non-specific interstitial pneumonia











Pneumoconioses

Diseases

Silicosis

Coal-worker’s pneumoconiosis

Asbestosis

(talcosis, siderosis, aluminosis,berylliosis)

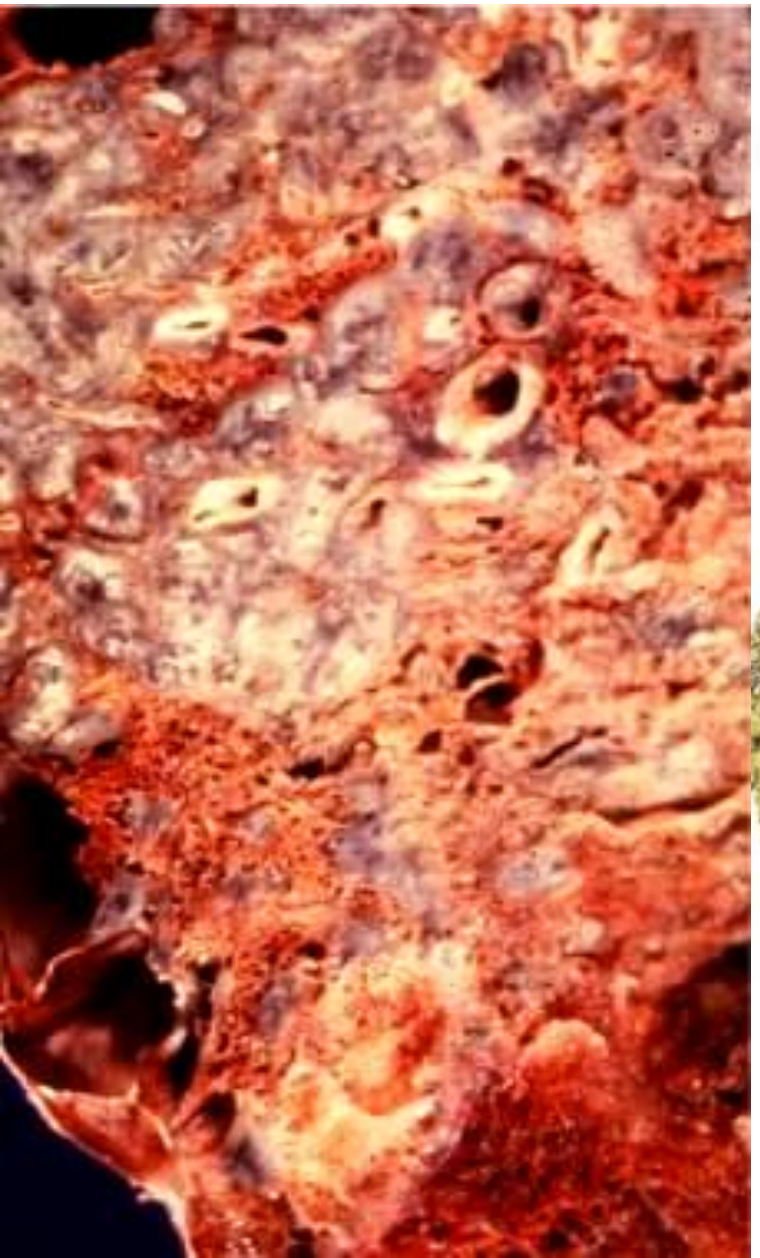
Definition

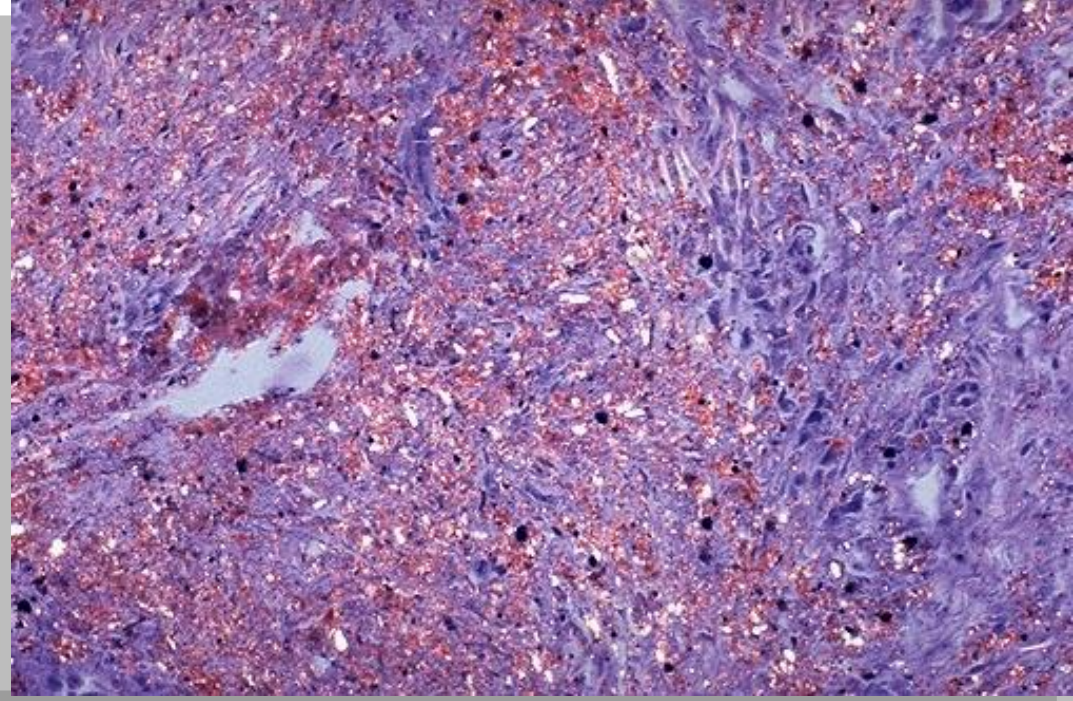
dust in the lung

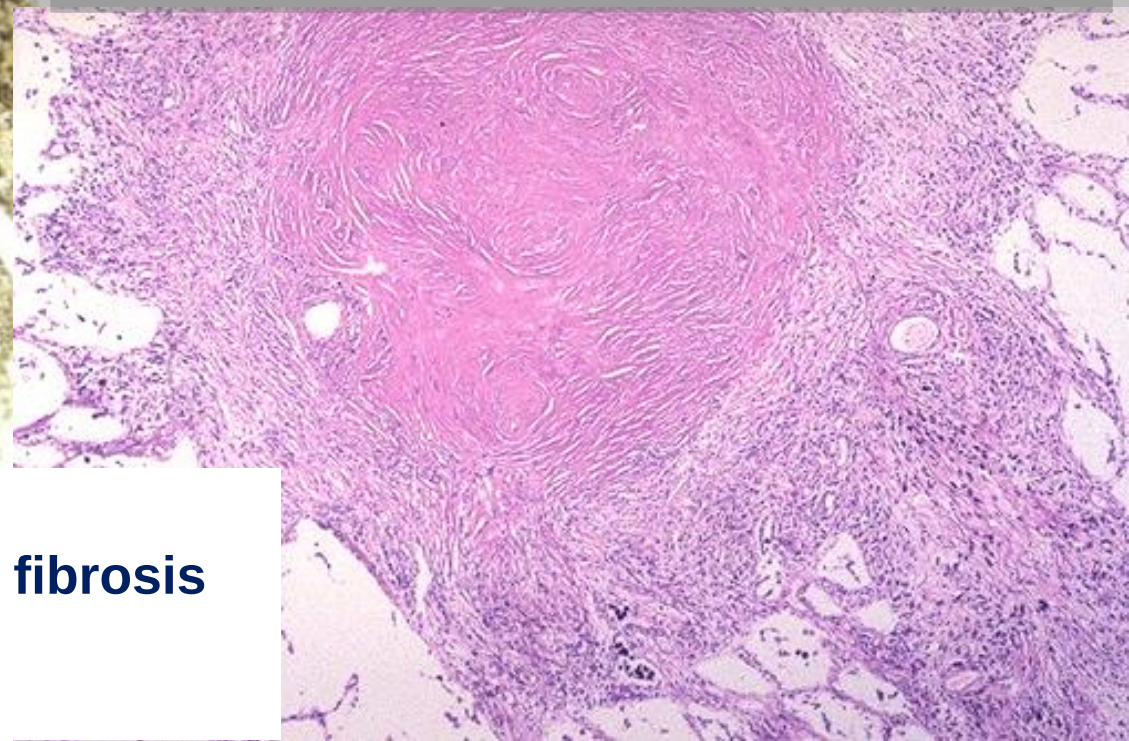
diseases of the lung

related to the inhaled dust

Silicotic lung







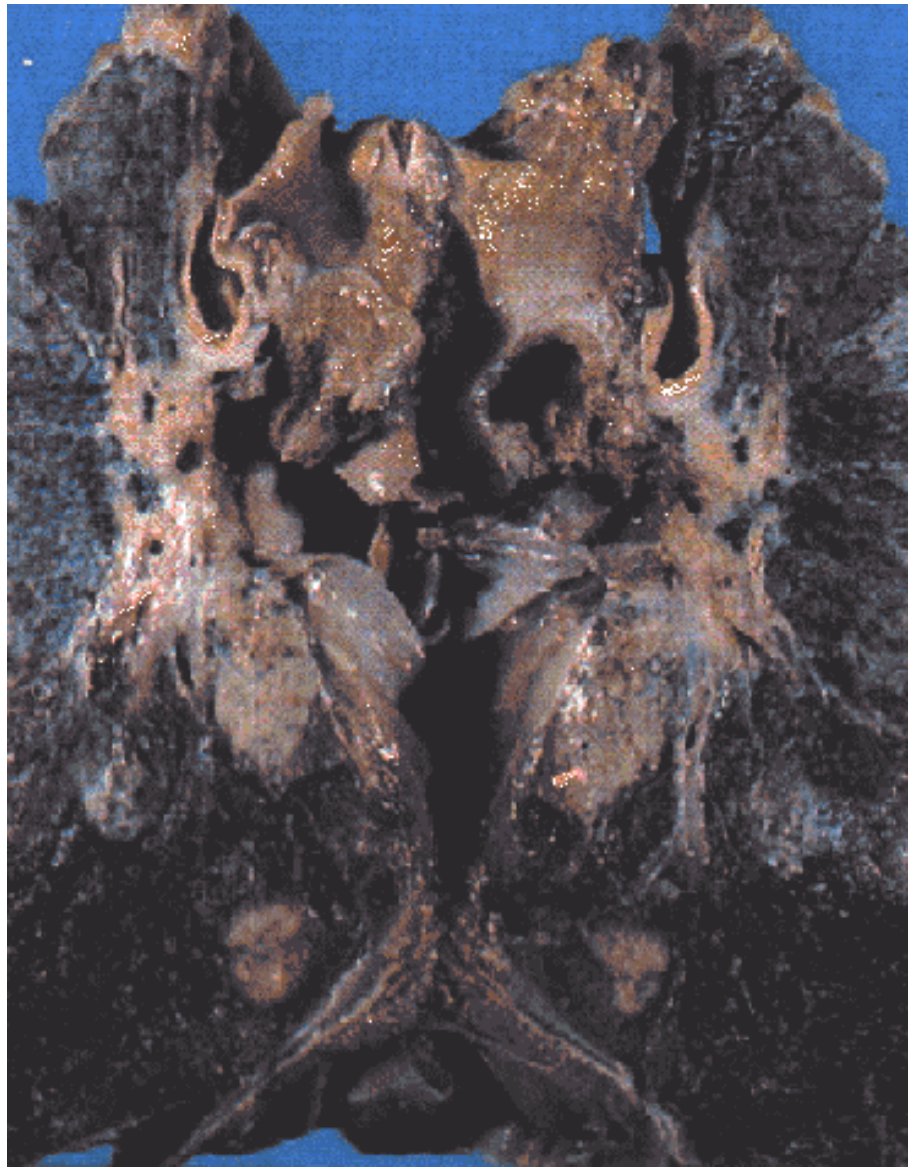
a. Fibrotic nodules
b. Progressive massive fibrosis
c. Alveolar proteinosis

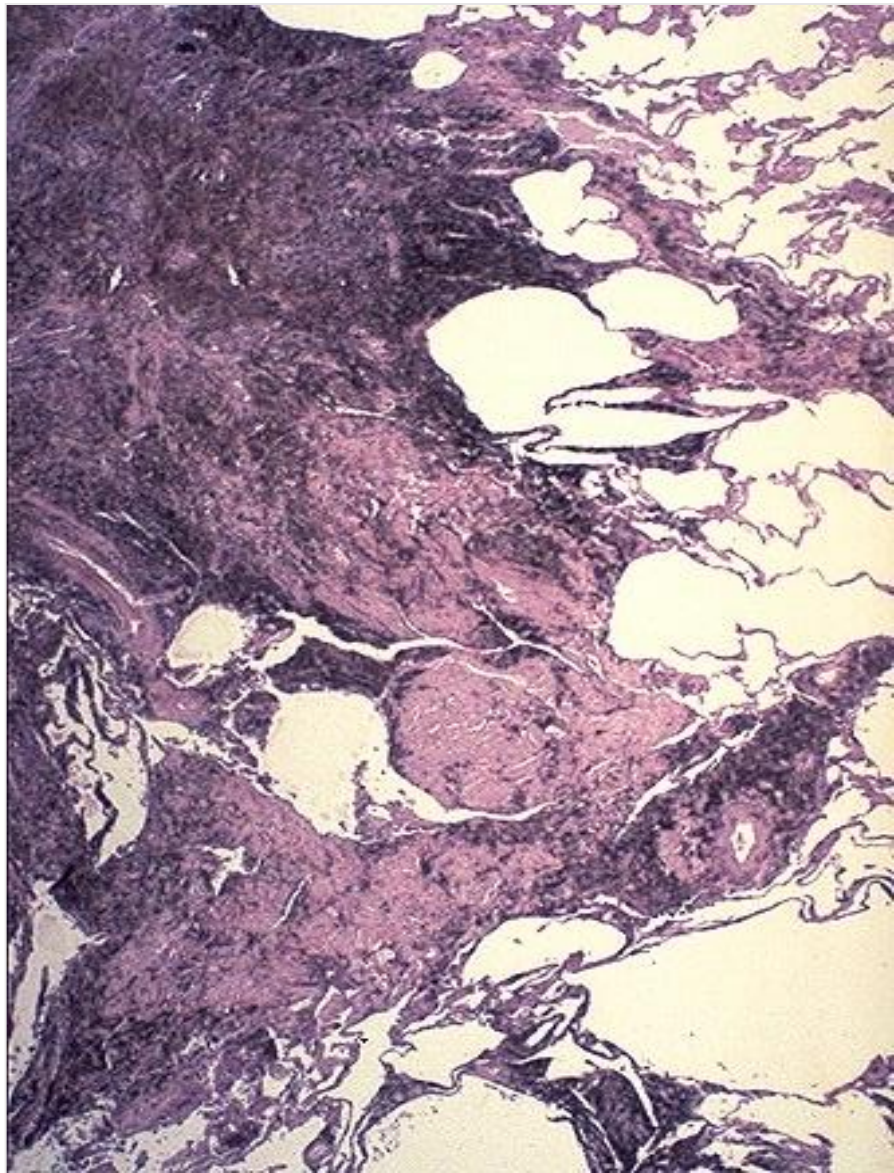
Coal worker's pneumoconiosis (CWP)

Primary macules
< 7 mm

Nodular lesions
_> 2.0 cm

Progressive massive fibrosis

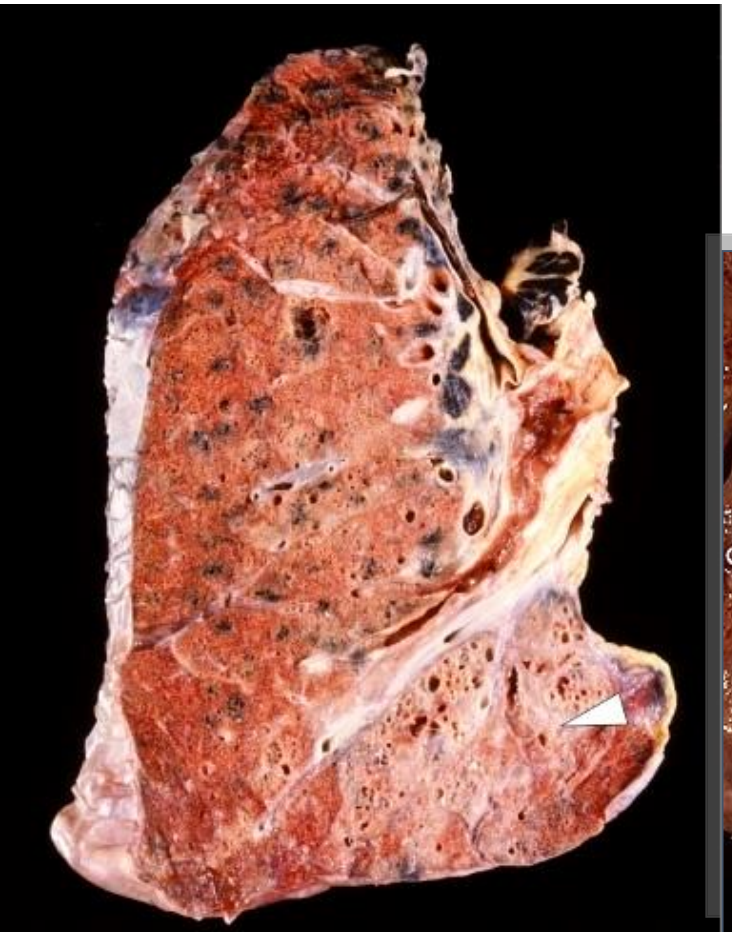


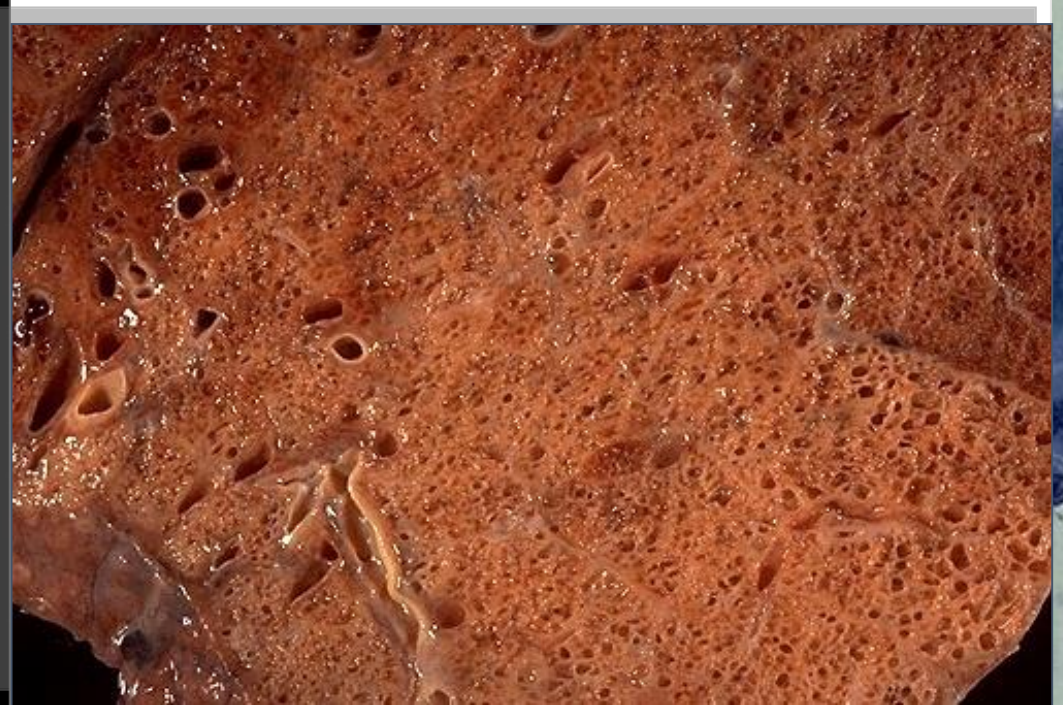


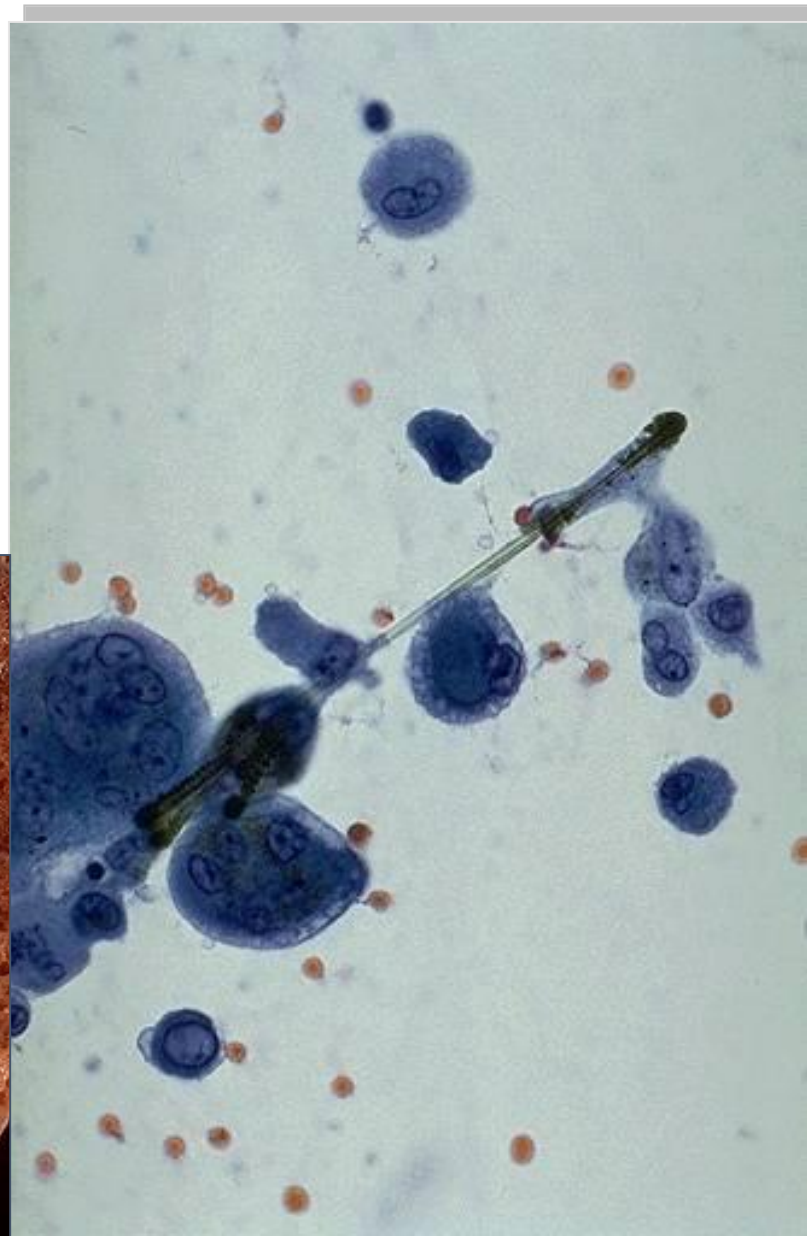
Asbestosis

The histologic changes vary from bronchiolocentric fibrosis to honeycomb lung.

An asbestos body consists of a central core fiber of asbestos that is coated with an **iron-protein-mucopolysaccharide laye. Iron stains e.g. Prussian blue**, can make detection easy.



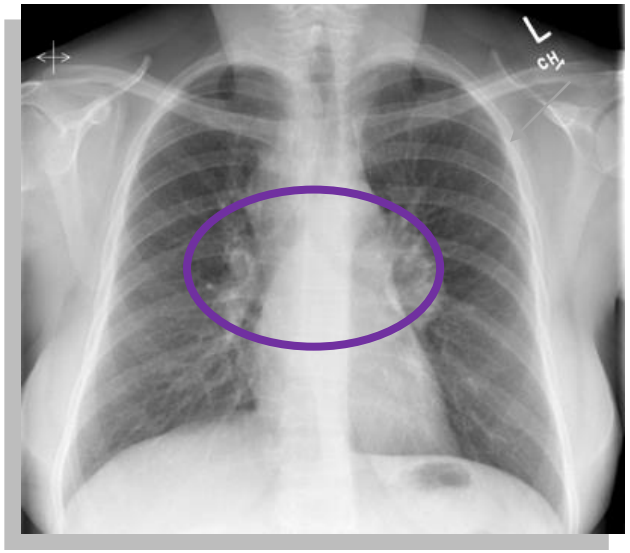




Granulomatous inflammation (non-infectious)

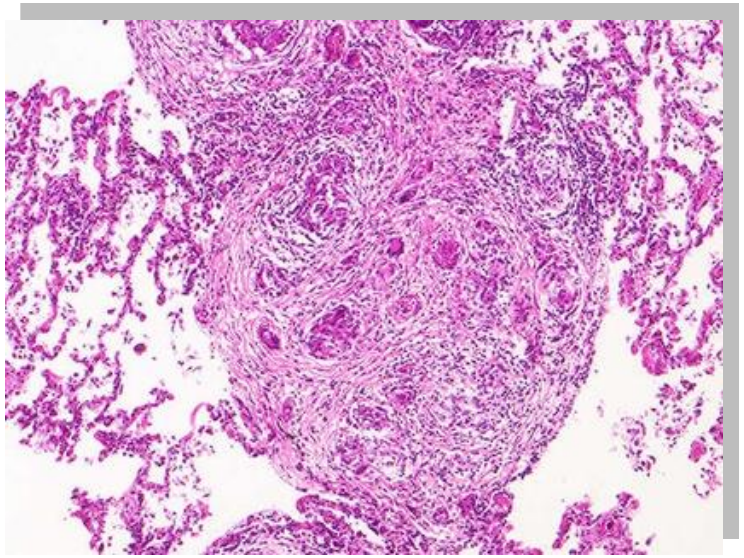
Boeck's sarcoidosis

- **Multisystemic disease of unknown origin that involves lung in 90% of cases**



- **Presents as bilateral hilar lymphadenopathy (BHL)**

- **65%** recover without further problems; **20%** have permanent pulmonary loss;
- **Skin: erythema nodosum**



- **Diagnosis of exclusion**, culture and special stains – Ziehl-Neelsen
- **Treatment:** steroids for severe symptoms, advanced disease

Diff dg!!!!!!!

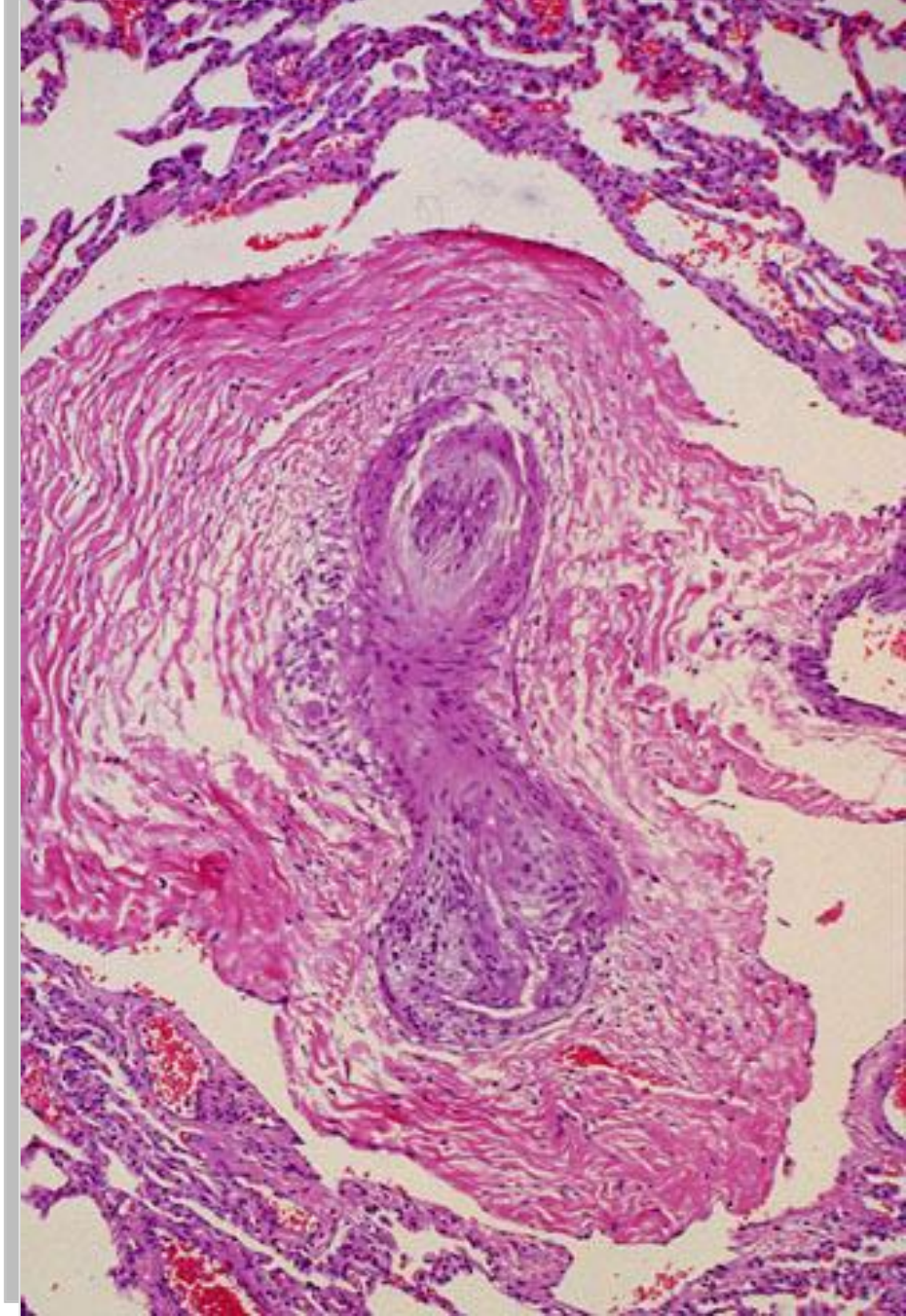
Complications

Regardless of the etiology for restrictive lung diseases, many eventually **lead to extensive fibrosis**

Complications

Both restrictive and obstructive lung diseases
can affect the pulmonary arterial circulation.

The loss of normal lung parenchyma leads to **pulmonary hypertension**
that leads to thickening of the small arteries



Lung transplantation

27% chronic obstructive pulmonary disease (COPD), including emphysema;
16% idiopathic pulmonary fibrosis;
14% cystic fibrosis;
12% idiopathic (formerly known as "primary") pulmonary hypertension;
5% alpha 1-antitrypsin deficiency;
2% replacing previously transplanted lungs that have since failed;
24% other causes,
including bronchiectasis and sarcoidosis.