Pathology of Respiratory System

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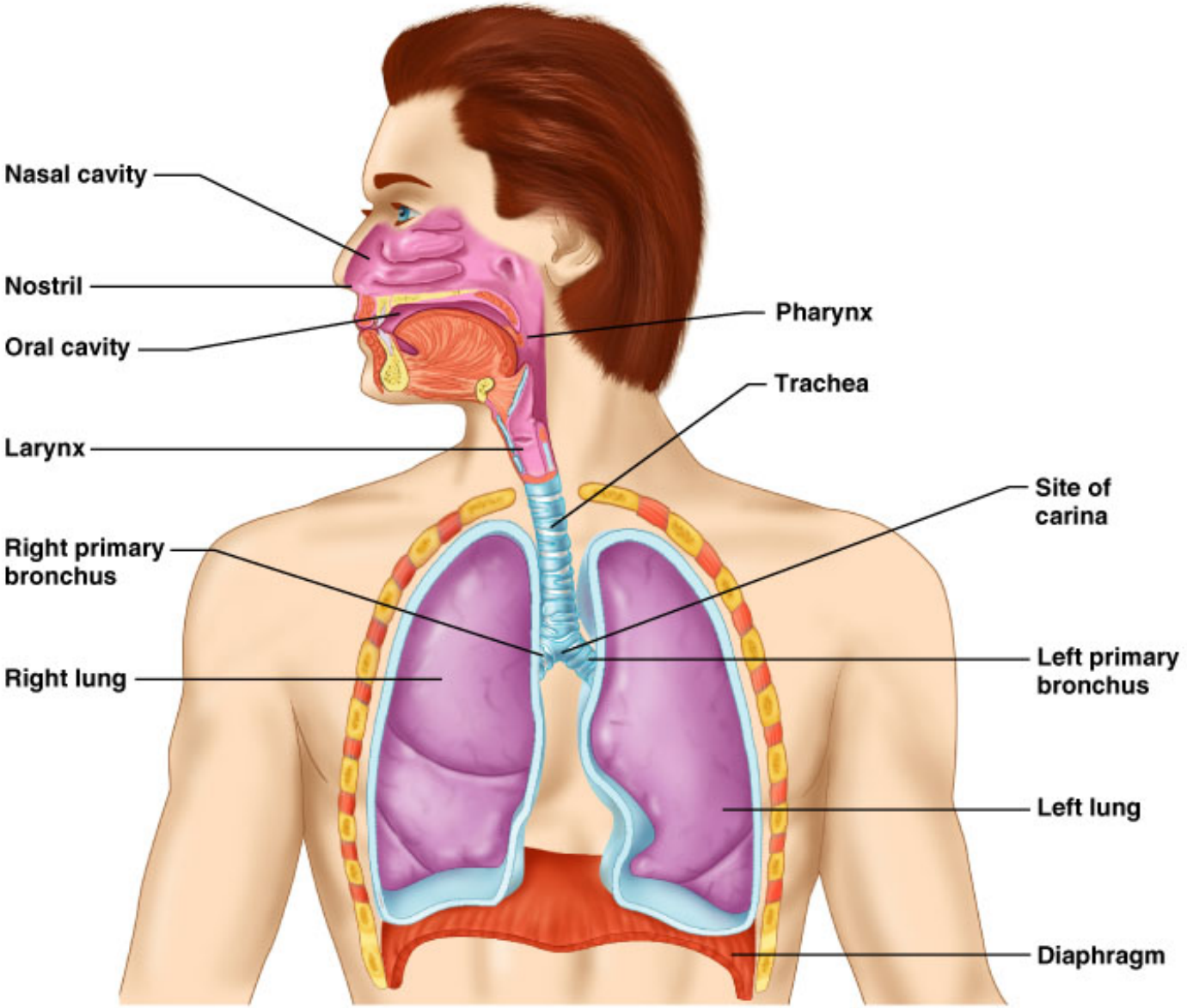
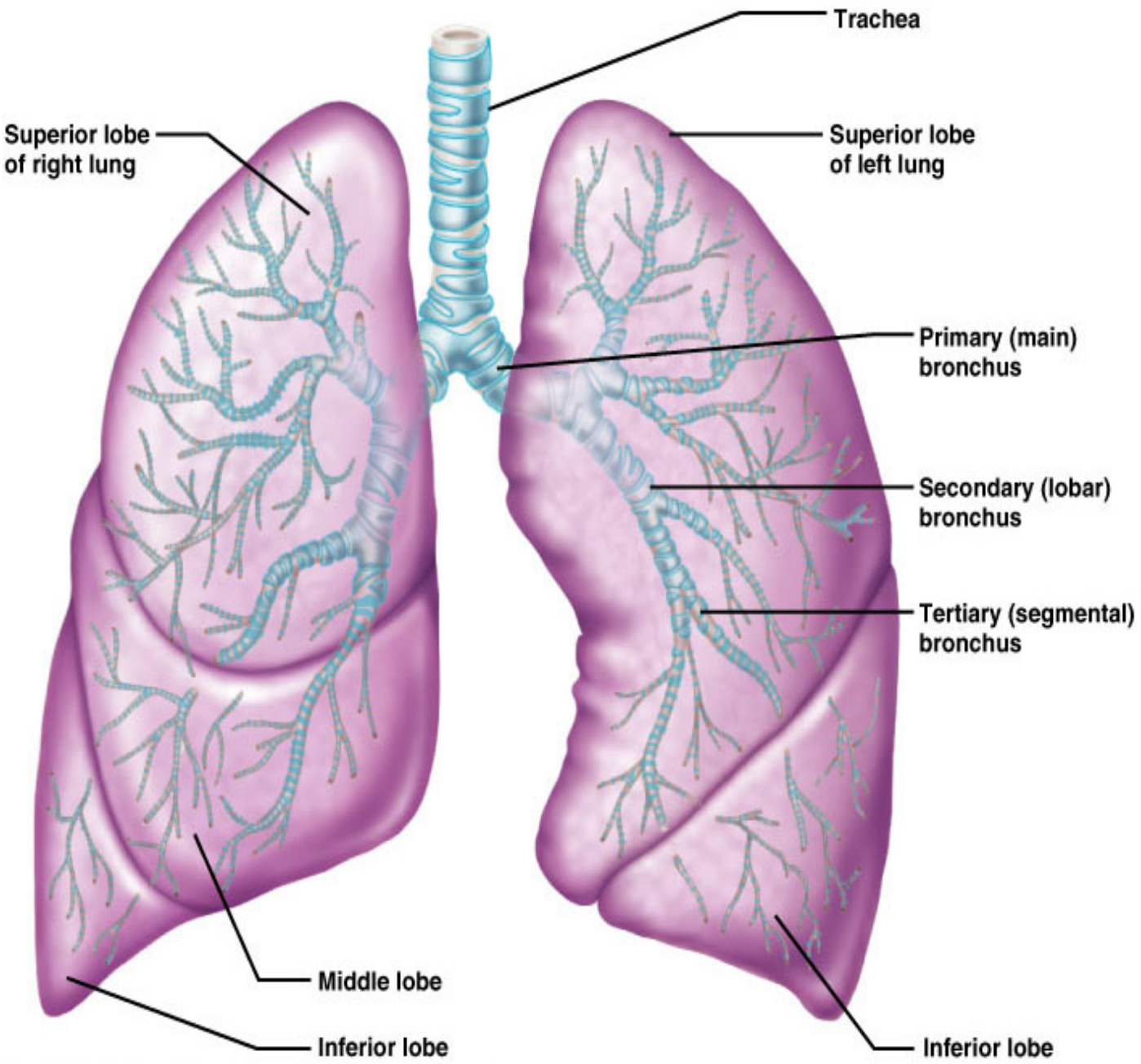
Objectives

After learning, student should be able to

- Describe anatomy and function of respiration system
- Explain pathophysiology and pathogenesis in common diseases of respiratory system

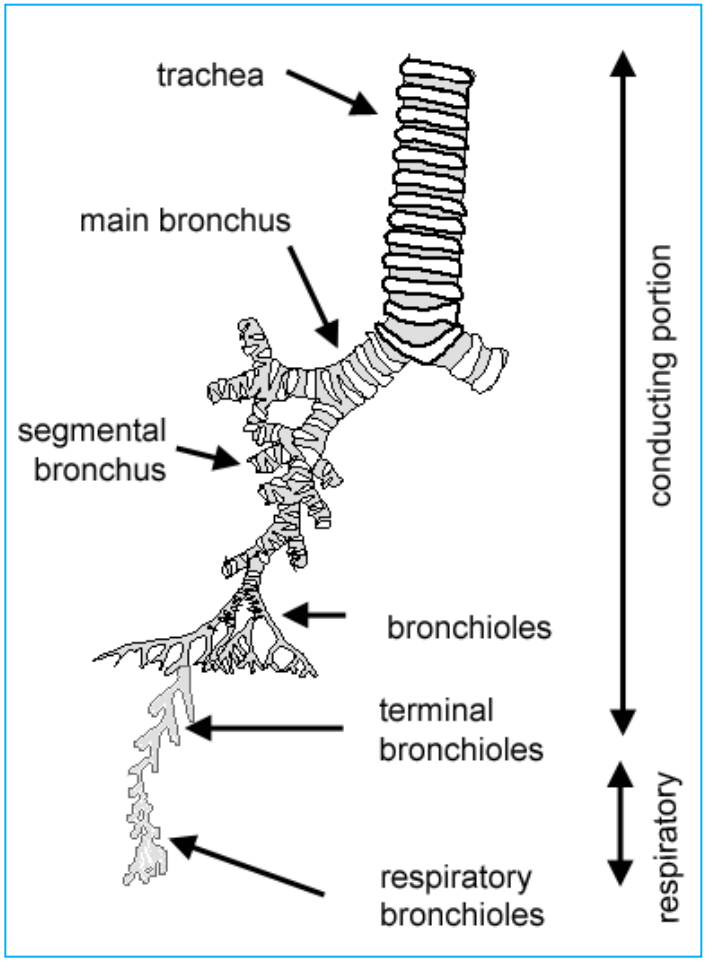
❑ The Respiratory System





1. Conducting portion:

The conduction portion is made up of nasal cavities, nasopharynx, larynx, trachea, bronchii and bronchioles



2. Respiratory portion:

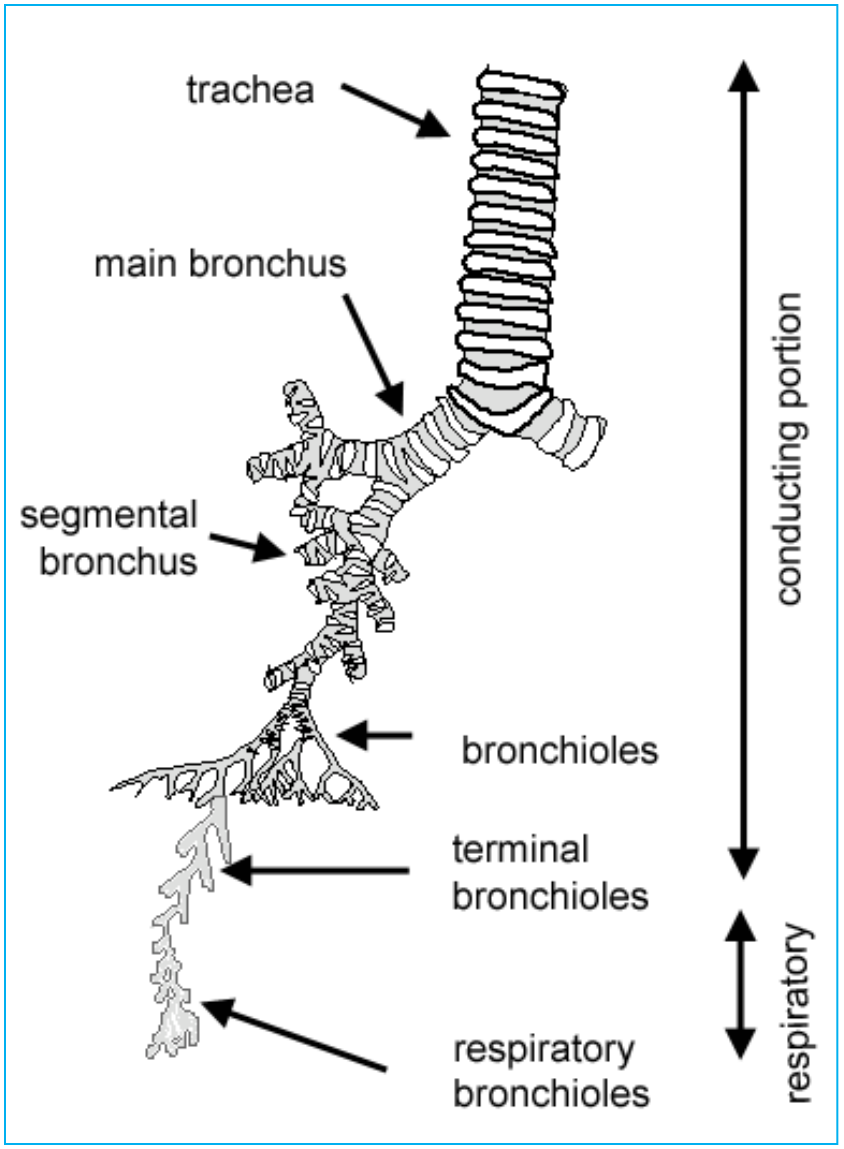
The respiratory portion is made up of respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli.

(https://www.histology.leeds.ac.uk/respiratory/conducting.php)

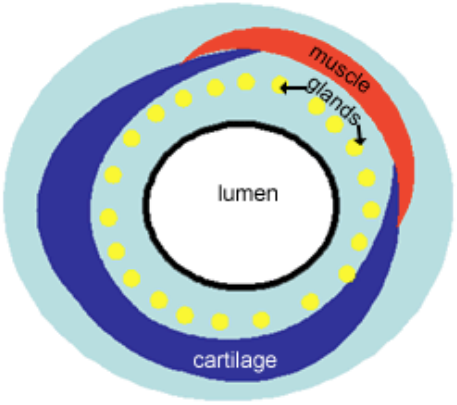
The conducting portion

- The *trachea* branches to give rise to two *primary (main) bronchii.*
- These then branch successively to give rise in turn to *secondary and tertiary bronchii.*
- These then branch to give rise to several orders of progressively *smaller airways called bronchioles,* the smallest of which are called *terminal bronchioles.*
- These are the last components of the conducting portion of the respiratory system.
- Terminal bronchioles give rise to *respiratory bronchioles,* which ultimately lead to the alveoli.

(https://www.histology.leeds.ac.uk/respiratory/conducting.php)



Trachea



The trachea is a wide flexible tube, the lumen of which is kept open by 20 tracheal cartilages, which are C-shaped rings of hyaline cartilage. The gaps between the rings of cartilage are filled by the trachealis muscle - a bundle of smooth muscle, and fibroelastic tissue. Together these hold the lumen of the trachea open, but allow flexibility during inspiration and expiration.

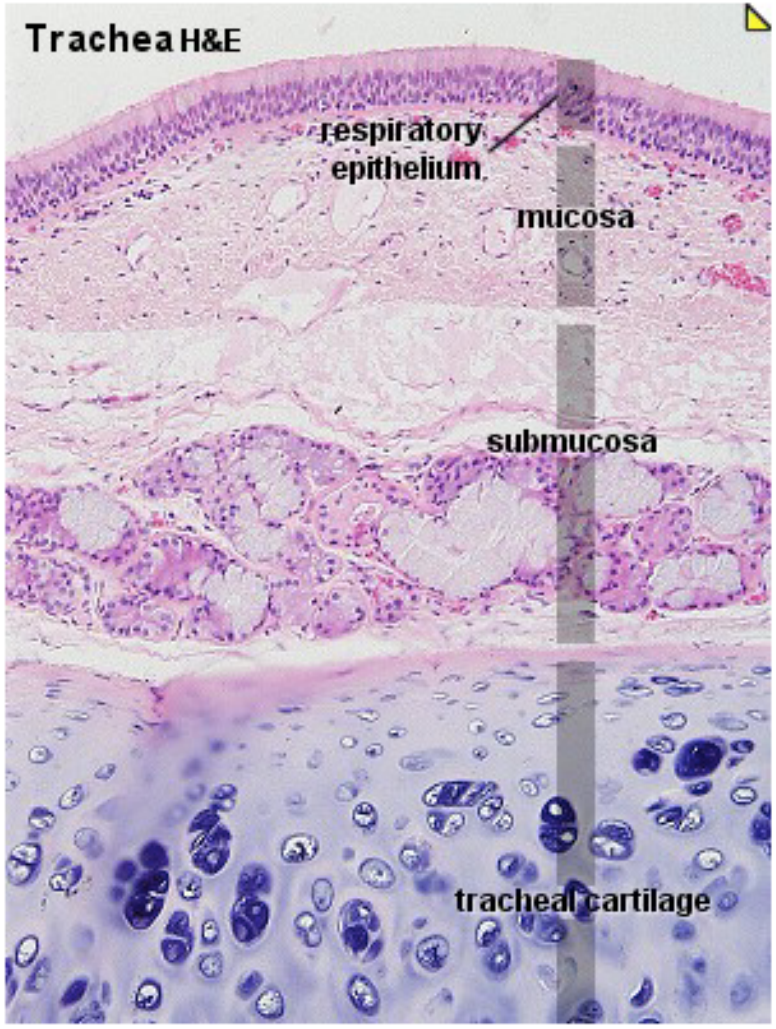
The respiratory mucosa and submucosa are adapted to warm and moisten the air, and to trap particles in mucous.

Mucosa and sub-mucosa of Trachea

The respiratory mucosa is made up of the epithelium and supporting lamina propria). The epithelium is tall columnar pseudostratified with cilia and goblet cells. The supporting lamina propria underneath the epithelium contains elastin, that plays a role in the elastic recoil of the trachea during inspiration and expiration, together with blood vessels that **warm** the air.

The sub-mucosa contains glands which are mixed sero-mucous glands. The watery secretions from the serous glands **humidify** the inspired air. The mucous, together with mucous from the goblet cells **traps particles** from the air which are transported upwards towards the pharynx by the cilia on the epithlium. This helps to keep the lungs free of particles and bacteria.

(https://www.histology.leeds.ac.uk/respiratory/conducting.php)

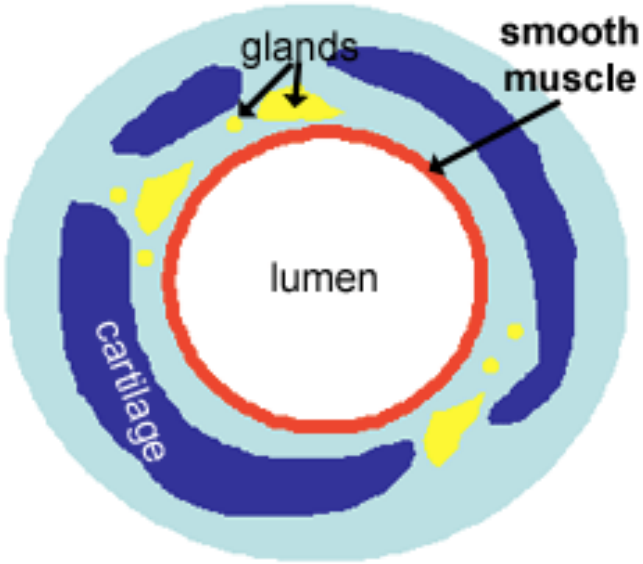


Trachea, human - H&E

In the trachea you should be able to identify the following structures: respiratory epithelium, basement membrane, *submucosal glands* (both serous and mucous parts), perichondrium, *tracheal cartilage* and trachealis muscle (smooth muscle). One can perceive different appearances of the connective tissue immediately below the epithelium and the connective tissue surrounding the submucosal glands, but the elastic lamina forming the border between the *mucosa* and submucosa is not visible in H&E stained slides. Accumulations of very dark small dots represent lymphocytes (not illustrated).

(http://lecannabiculteur.free.fr)

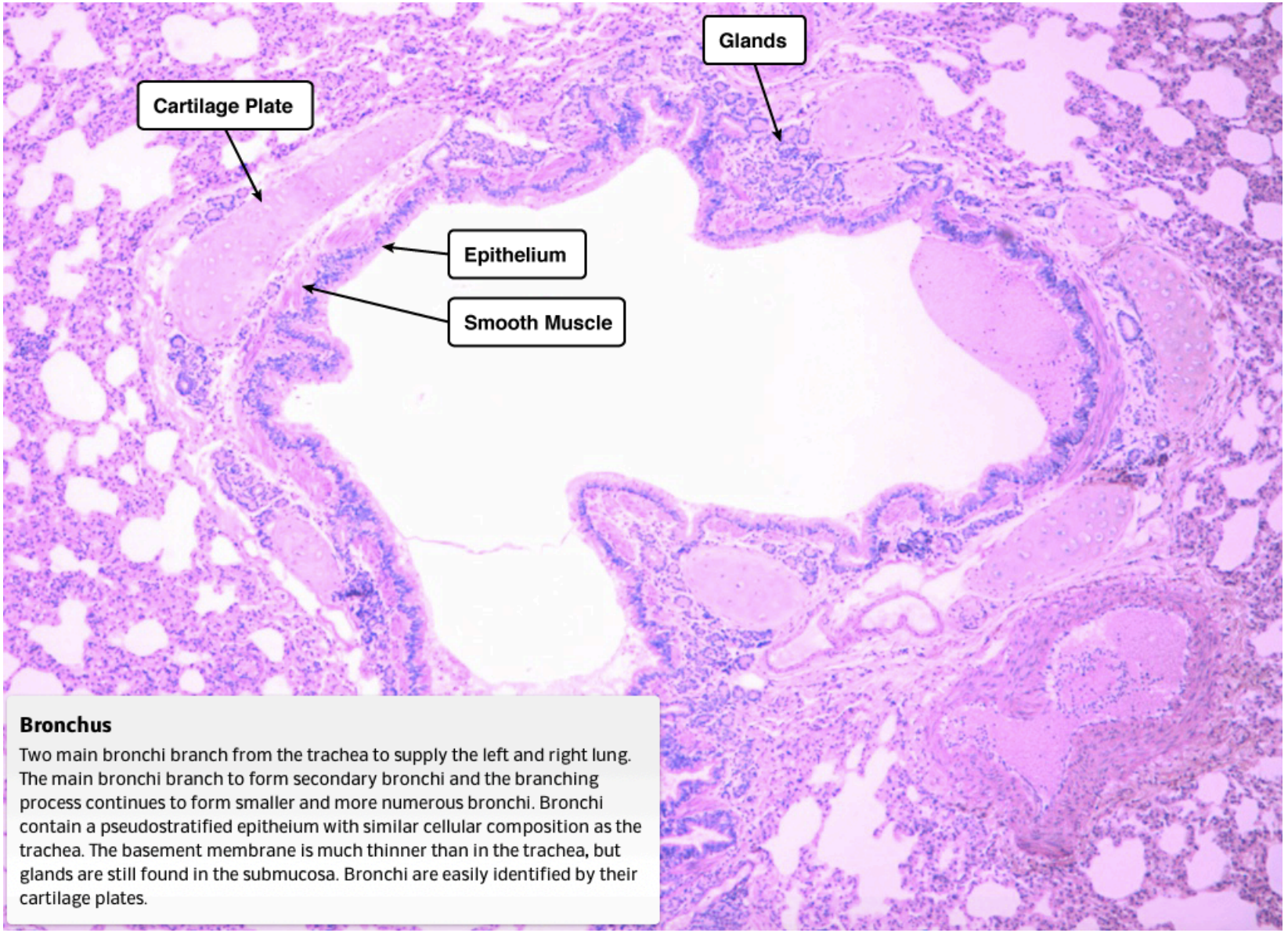
Bronchii



The trachea branches into two primary bronchii, which branch into secondary and then tertiary bronchii. In the tertiary bronchii, there is less cartilage, and it does not completely encircle the lumen, as shown diagramatically above.

Notice also how the mucosa is folded, and think about how this might change as you breathe in and out.

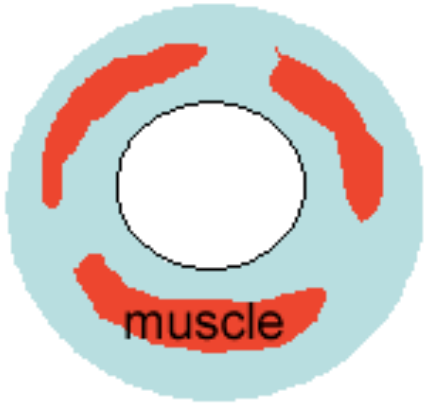
(https://www.histology.leeds.ac.uk/respiratory/conducting.php)



(http://medcell.med.yale.edu/histology/respiratory_system_lab/bronchus.php)

Bronchioles

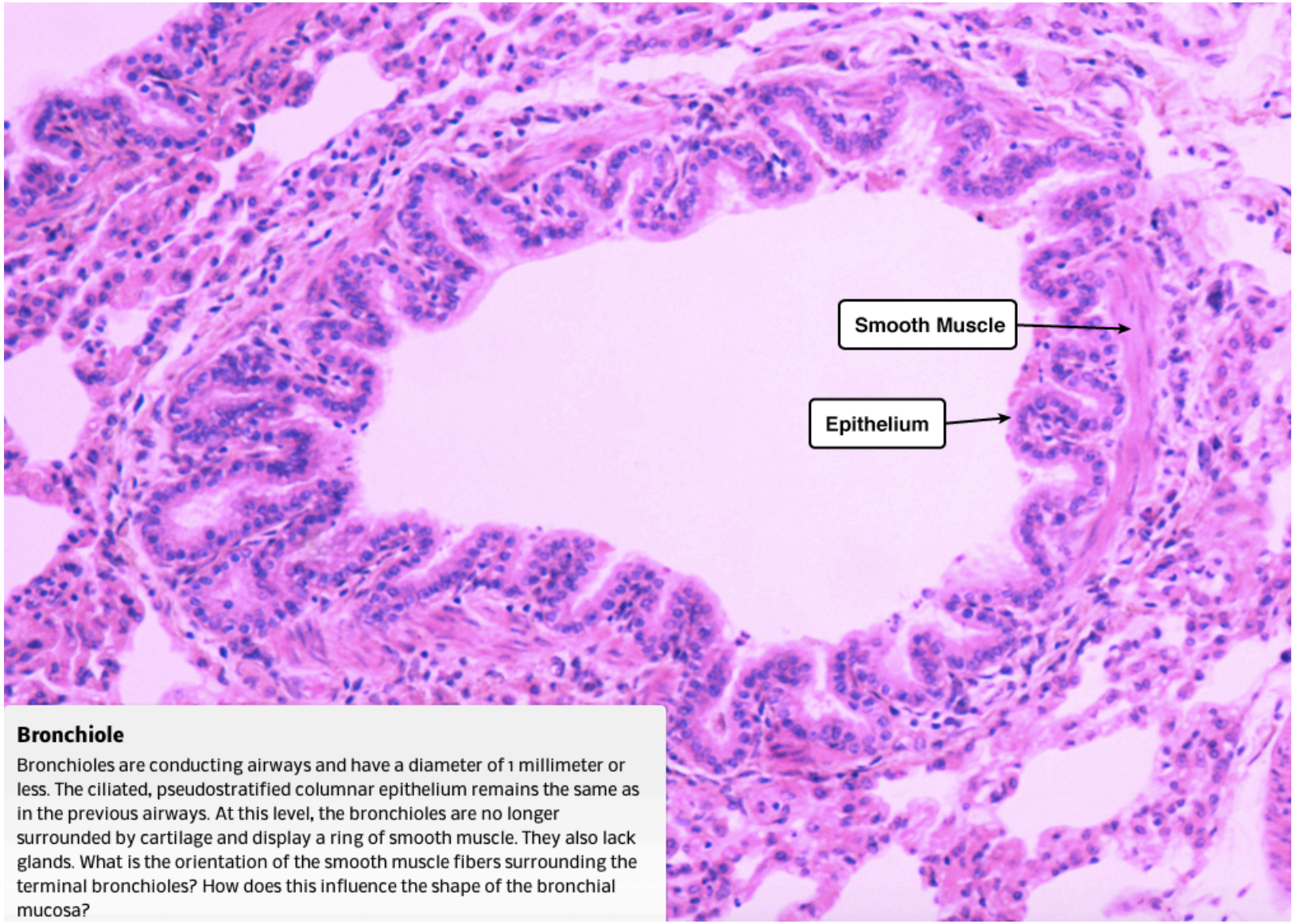
The tertiary bronchii branch into bronchioles, which have a diameter of 1mm or less, and the wall structure changes.



The epithelium is made up of ciliated columnar cells in larger bronchioles, or non-ciliated in smaller bronchioles (difficult to see at this magnification). There are no goblet cells, but there are cells called **Clara cells.** These cells are secretory - they secrete one of the components of surfactant.

Asthma: because the diameter of the bronchioles is reliant on smooth muscle tone, these airways can almost completely shut if the smooth muscles contract strongly, which can happen in an asthmatic attack.

(https://www.histology.leeds.ac.uk/respiratory/conducting.php)



Bronchiole

Bronchioles are conducting airways and have a diameter of 1 millimeter or less. The ciliated, pseudostratified columnar epithelium remains the same as in the previous airways. At this level, the bronchioles are no longer surrounded by cartilage and display a ring of smooth muscle. They also lack glands. What is the orientation of the smooth muscle fibers surrounding the terminal bronchioles? How does this influence the shape of the bronchial mucosa?

(http://medcell.med.yale.edu/histology/respiratory_system_lab/bronchus.php)

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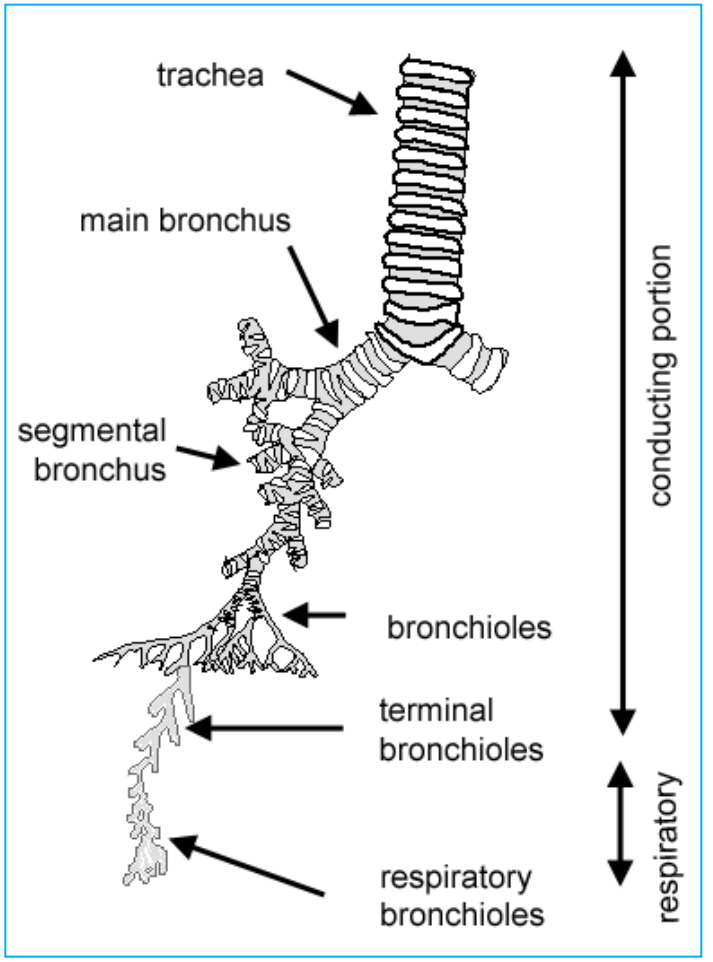
2. Respiratory portion:

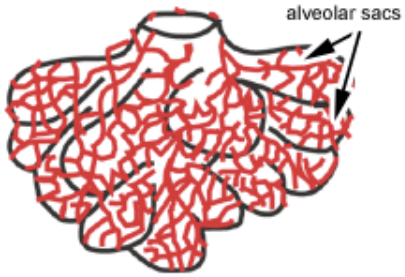
The respiratory portion is made up of respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli.



(https://www.histology.leeds.ac.uk/respiratory/conducting.php)

Functions of the Respiratory Portion

The respiratory portion consists of respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli. It is hard to investigate the organisation of these structures in sections, because when the lungs are removed, they collapse. Basically the respiratory system consists of a branching set of air spaces, which are in close proximity to pulmonary capillaries. The air space is exchanged around 10 to 15 times a minute. The air spaces are within 0.2µm of the blood, which is a very thin barrier to diffusion. This arrangement means there is a fast efficient transfer of oxygen and carbon dioxide between the blood and the air, the major function of the respiratory portion.



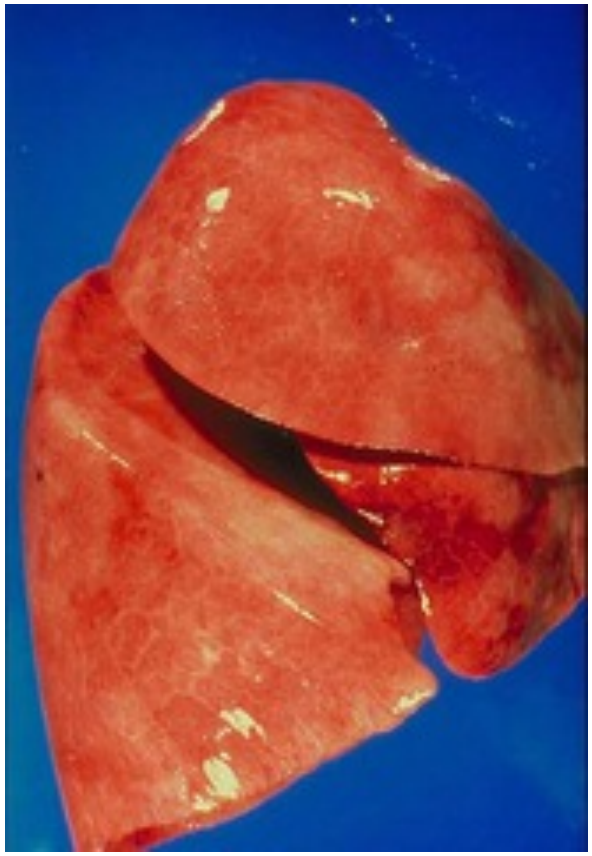
The terminal bronchioles branch to give rise to respiratory bronchioles, which lead to alveolar ducts, alveolar sacs and alveoli.

This diagram shows a diagram of an alveolar sac, showing how the organisation of the alveoli, and the network of blood capillaries that surround the alveoli (in red). These capillaries are derived from the pulmonary arterioles.

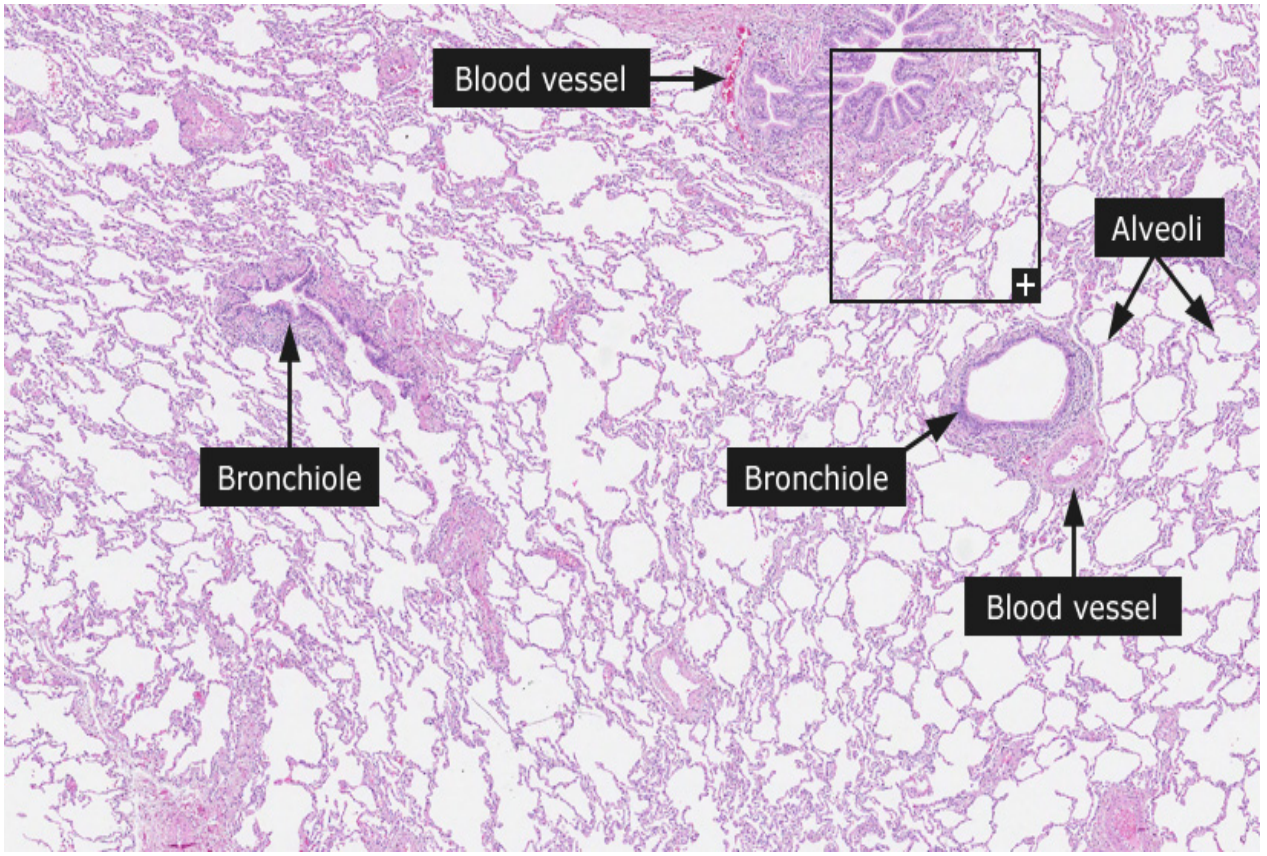
Gaseous exchange between the blood and air takes place in the alveoli, but the detailed structure of the alveolar walls cannot be resolved with the light microscope.

(https://www.histology.leeds.ac.uk/respiratory/conducting.php)

❑ Alveoli--- the ultimate site of gas exchange



(http://quizlet.com)



(http://www.proteinatlas.org)

Alveoli

The epithelium of the alveoli, contains two main types of cells:

1. type I pneumocytes: large flattened cells - (95% of the total alveolar area) which present a very thin diffusion barrier for gases. They are connected to each other by tight junctions.

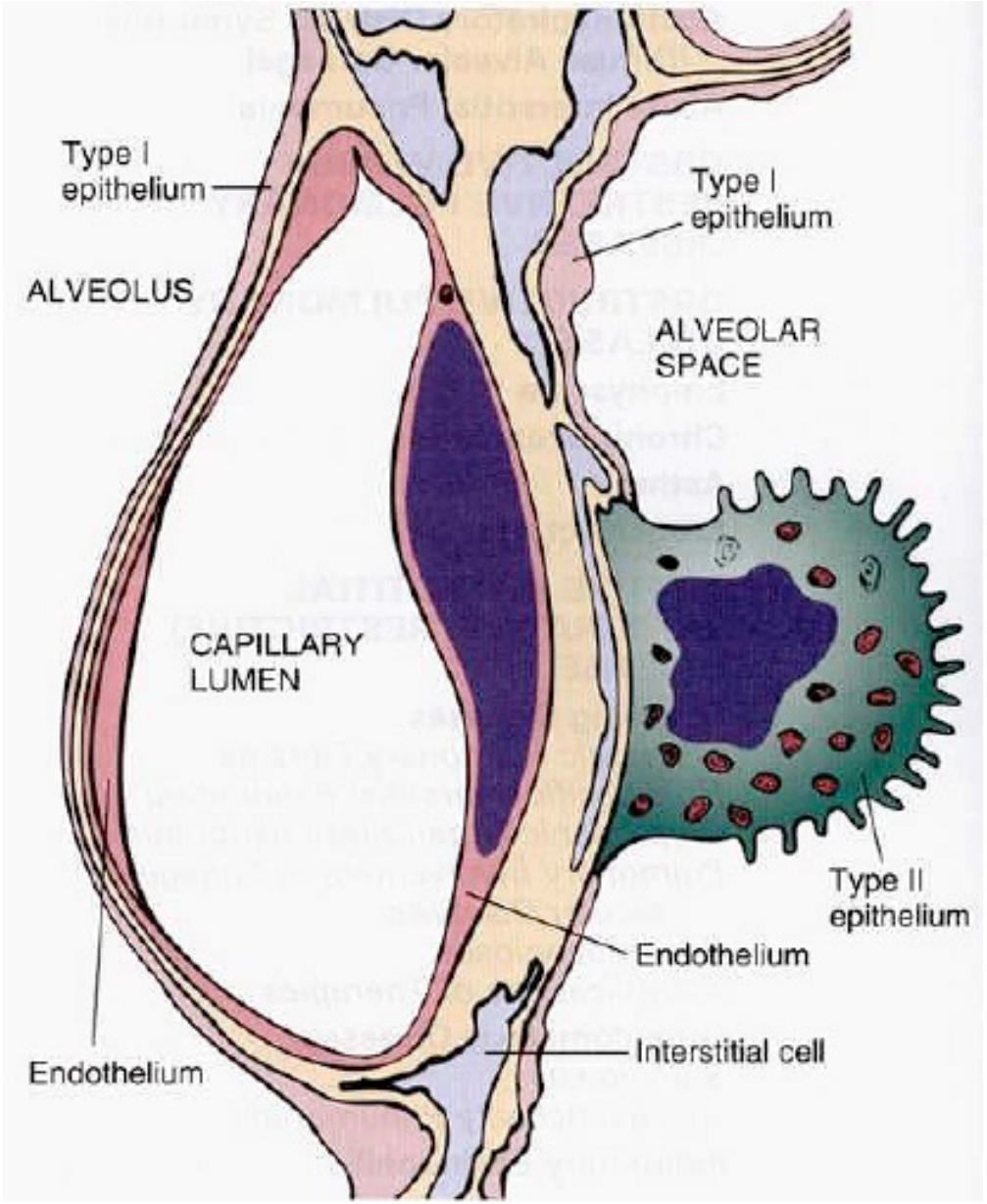
2. **type II pneumocytes** (making up 5% of the total alveolar area, but 60% of total number of cells). These cells secrete 'surfactant' which decreases the surface tension between the thin alveolar walls, and stops alveoli collapsing when you breathe out. these cells are connected to the epithelium and other constituent cells by tight junctions.

The surfactant is made up of phospholipids, combined with carbohydrate and protein, which are released by exocytosis, and form a tubular lattice of lipoprotein. The surfactant overcomes surface tension, where the two alveolar surfaces come together. Otherwise the two thin alveolar walls might stick together, rather like a balloon that is deflated, after being inflated.

Macrophages are important for ingesting bacteria and particles, and arise from monocytes, which have escaped from the blood capillaries.

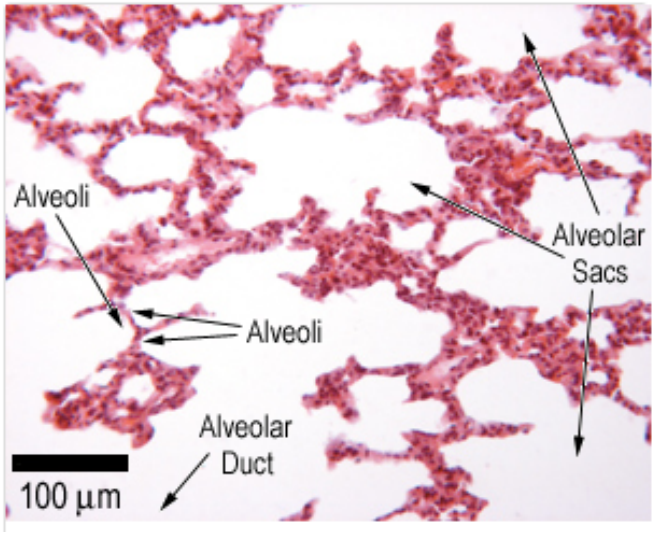
(https://www.histology.leeds.ac.uk/respiratory/conducting.php)

❑ Structure of the alveolar wall

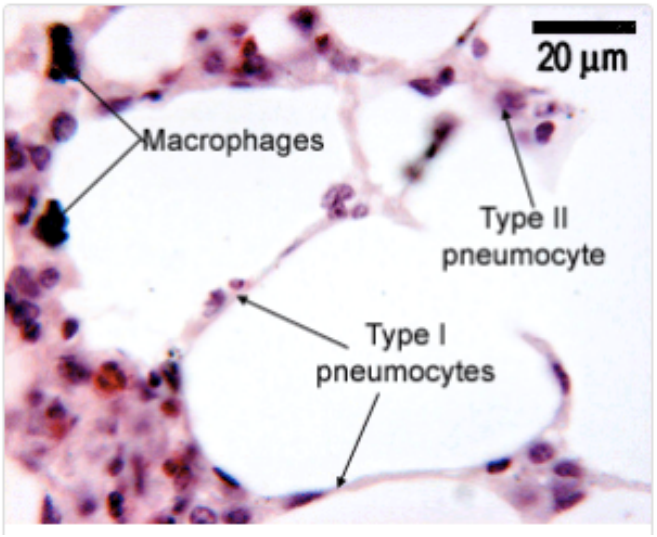


- ❖ Type I pneumocytes---flattened type, 95% of the alveolar surface
- ❖ Type II pneumocytes---rounded type, pulmonary surfactant
- ❖ Alveolar MØ

(Kumar 2015)



- This is a cross section through the lung, showing alveolar sacs, and alveoli



- This is a section through the lung at higher magnification, showing the thin type I pneumocytes, and the type II pneumocytes. Notice how the type II pneumocytes look shorter and fatter, and have paler staining nuclei. Macrophages are also present.

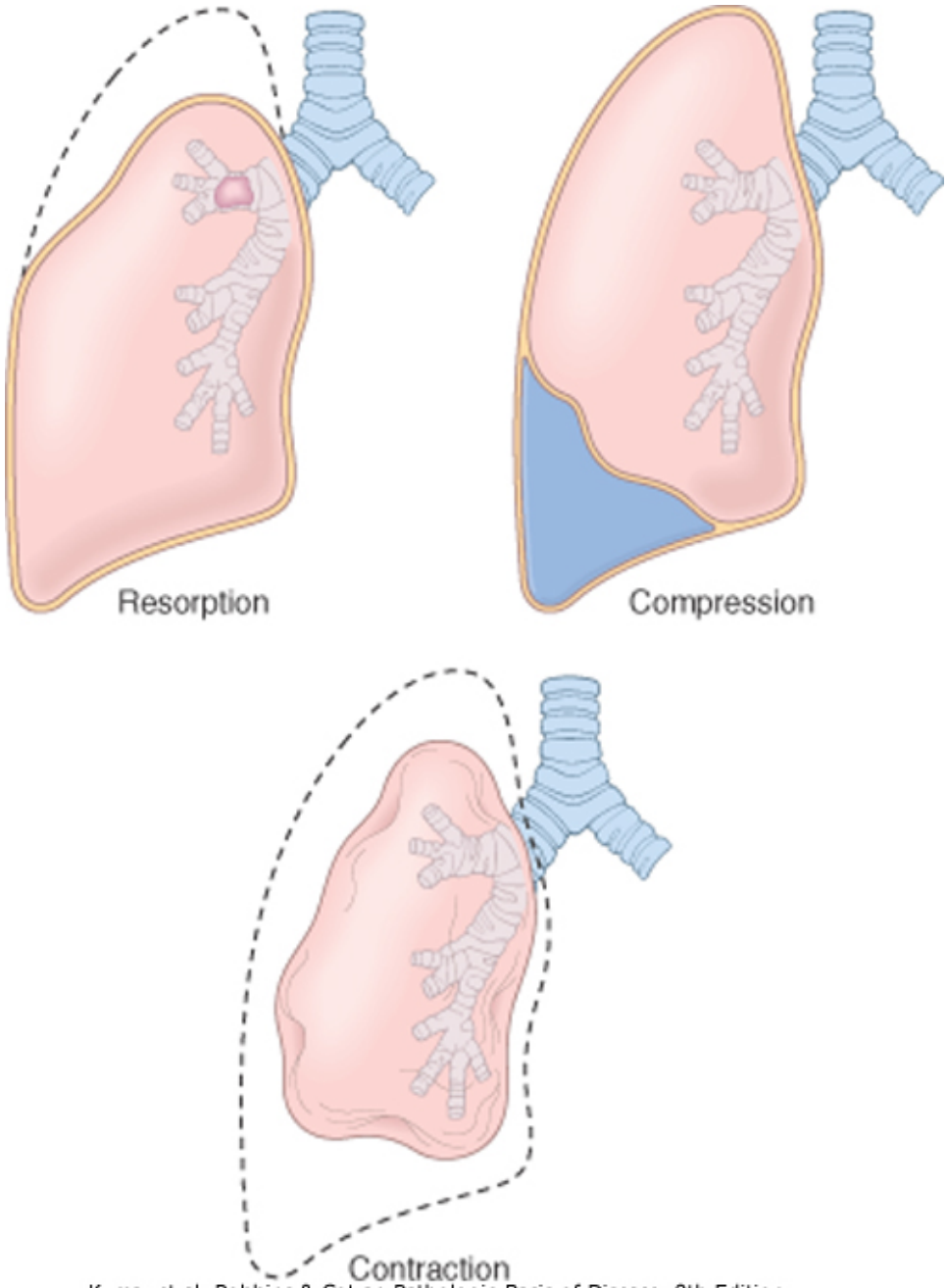
(https://www.histology.leeds.ac.uk/respiratory/conducting.php)

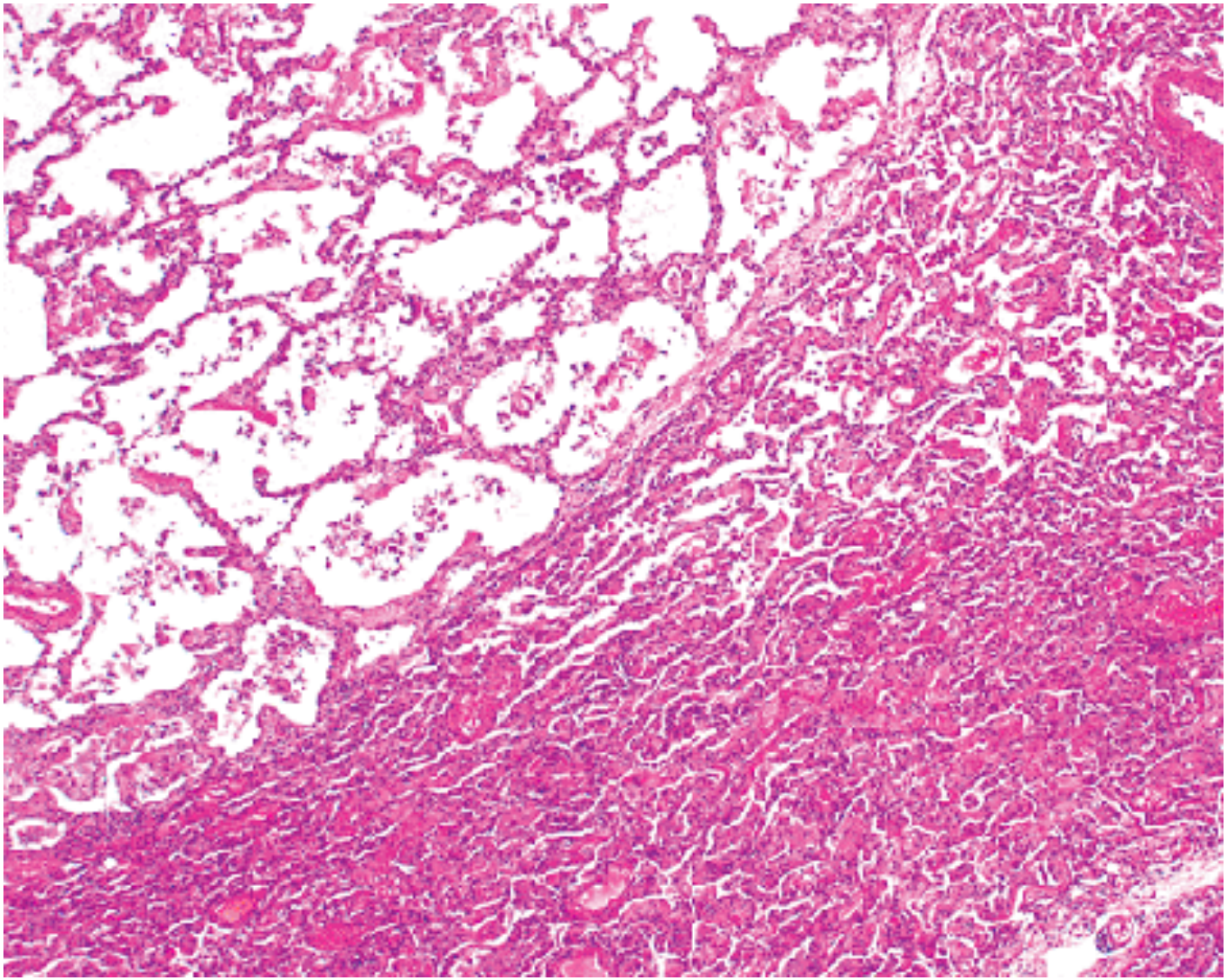
Respiratory function

- Gas exchange--- to replenish *oxygen* and excrete *carbon dioxide* from blood
- Oxygen from the air is transferred to the blood.
- Carbon dioxide from the blood is eliminated into the atmosphere.

Atelectasis (Collapse)

- The loss of lung volume caused by inadequate expansion of air spaces
- Atelectasis is classified into 3 forms:
  - *Resorption atelectasis*
  - *Compression atelectasis*--- passive or relaxation atelectasis
  - *Contraction atelectasis*

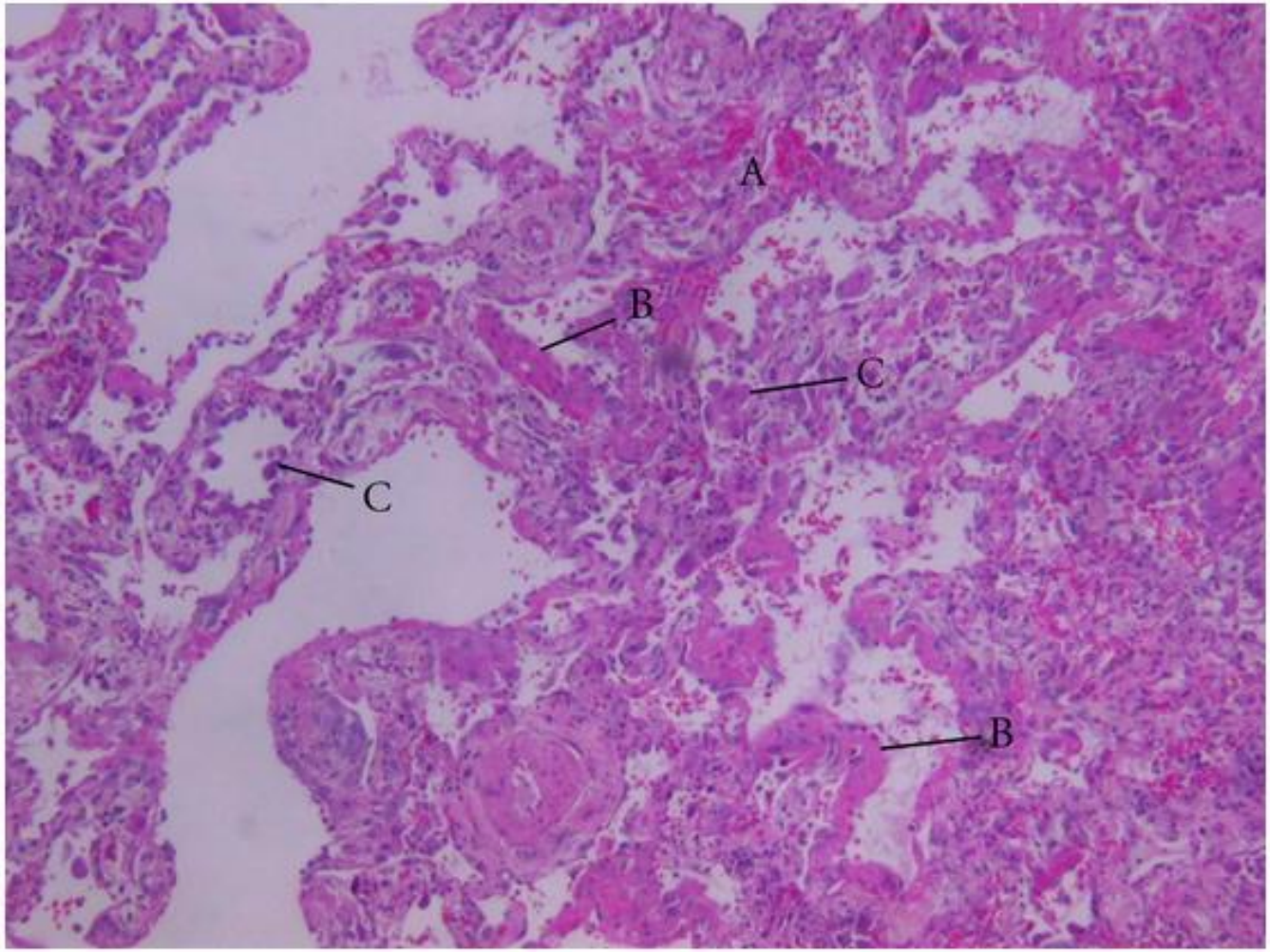




(http://flylib.com/books/en/)

Acute lung injury & Acute respiratory distress syndrome (ARDS)

- Acute lung injury--- acute onset of dyspnea, decreased arterial oxygen pressure *(hypoxemia)*, and development of bilateral pulmonary infiltrates on the chest radiograph
- ARDS is a clinical syndrome caused by diffuse alveolar capillary and epithelial damage.



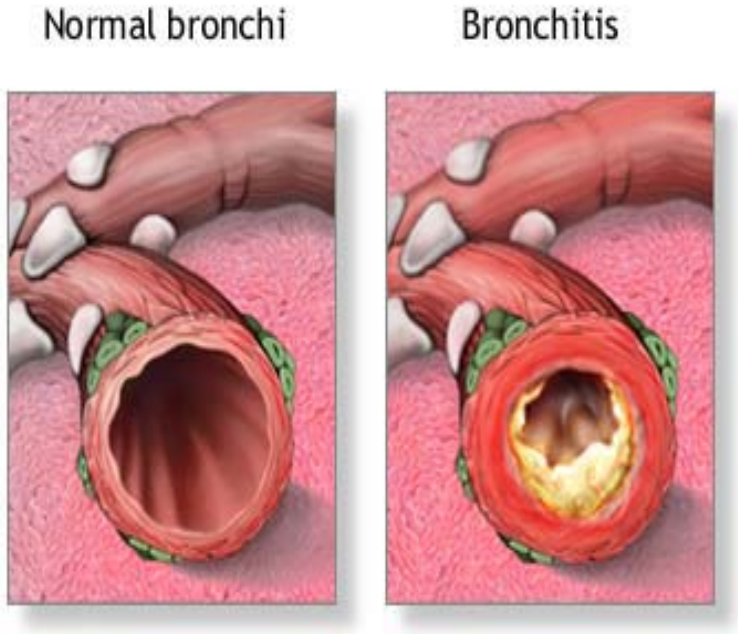
ARDS-- interstitial edema & hemorrhage (A), diffuse alveolar wall thickening by formation of hyaline membranes, (B) and type II pneumocyte hyperplasia (C)

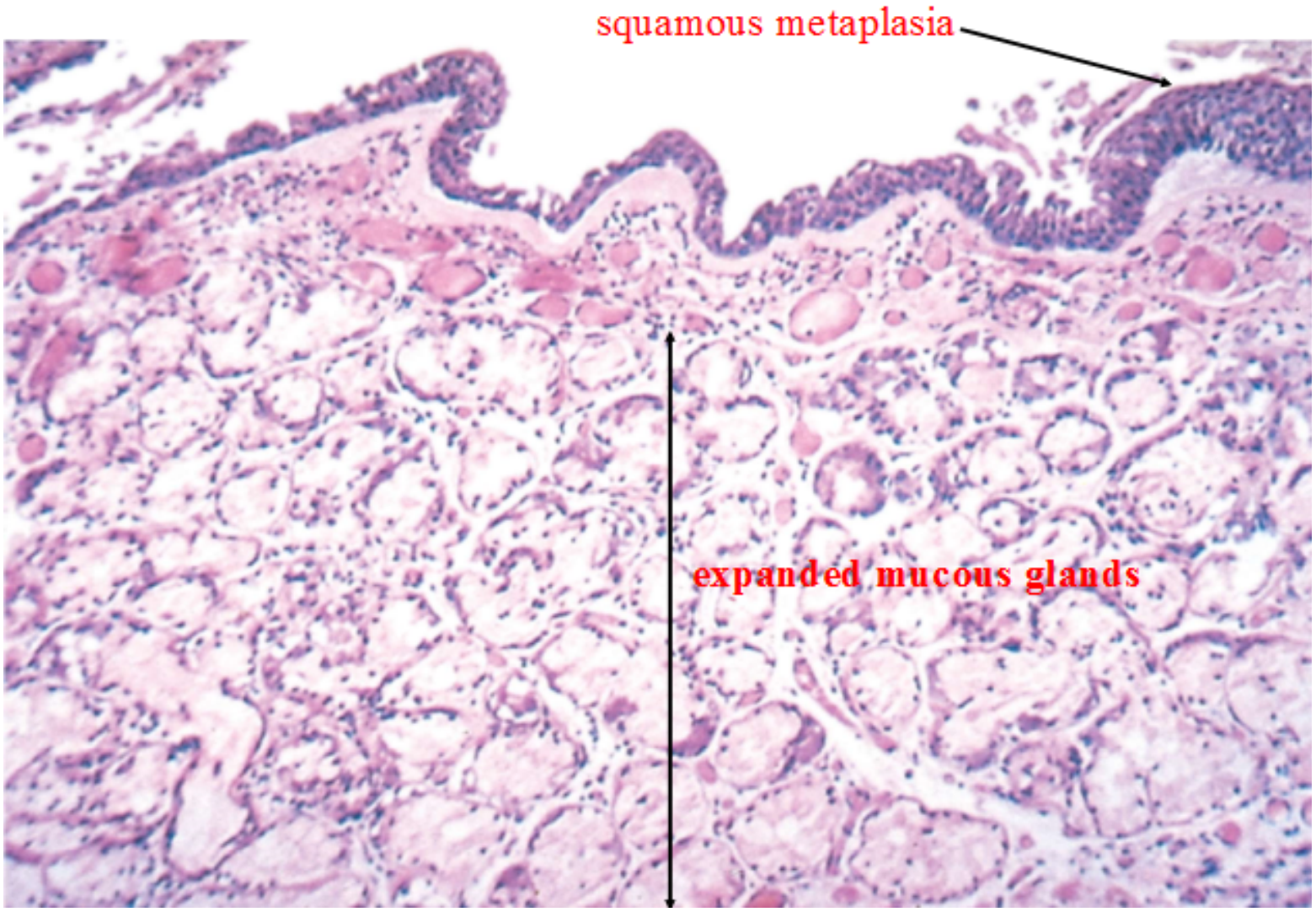
(http://www.studyblue.com)

Bronchitis

- Inflammation of the large airways or bronchi
- Increased production of mucus

- Narrowing of airway
- ↑ airflow resistance
- ↑ work of breathing
- Hypoventilation & CO_2 retention (hypercapnea)--- hypoxemia



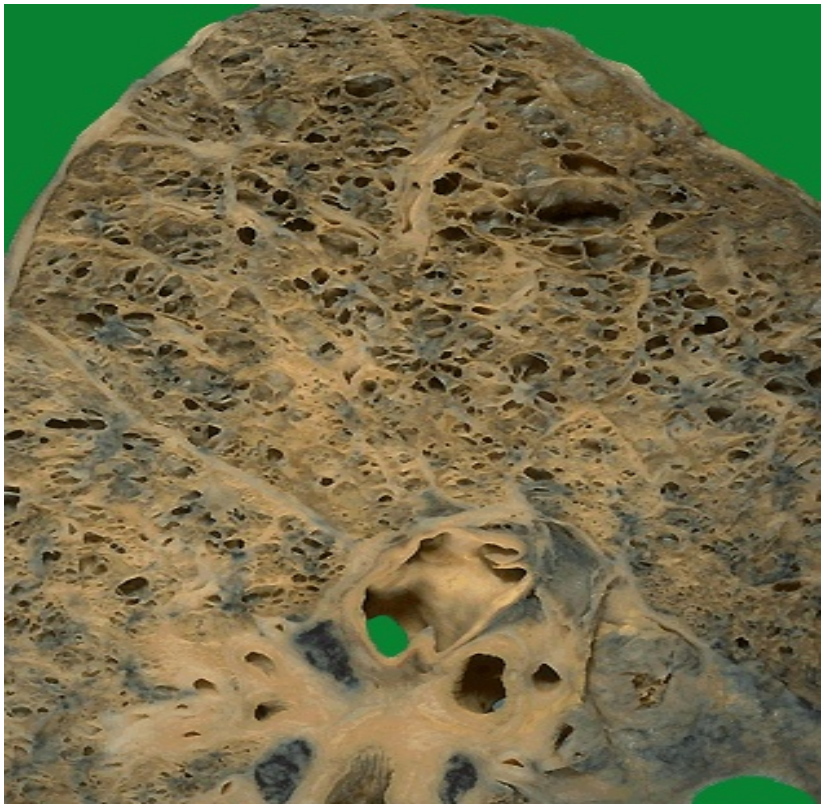


(www.vwmin.org)

- Chronic bronchitis is common among *cigarette smokers* and urban dwellers in smog-ridden cities.
- The diagnosis--- presence of a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years
- Some patients may demonstrate hyper responsive airways with intermittent bronchospasm and wheezing.
- A subset of bronchitis patients develops chronic outflow obstruction, usually with associated *emphysema*.

Emphysema

Is characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchioles--- destruction of their walls *without significant fibrosis.*



(http://en.wikipedia.org)

❖ Major pattern of emphysema

- Centriacinar
- Panacinar
- Distal acinar
- Irregular

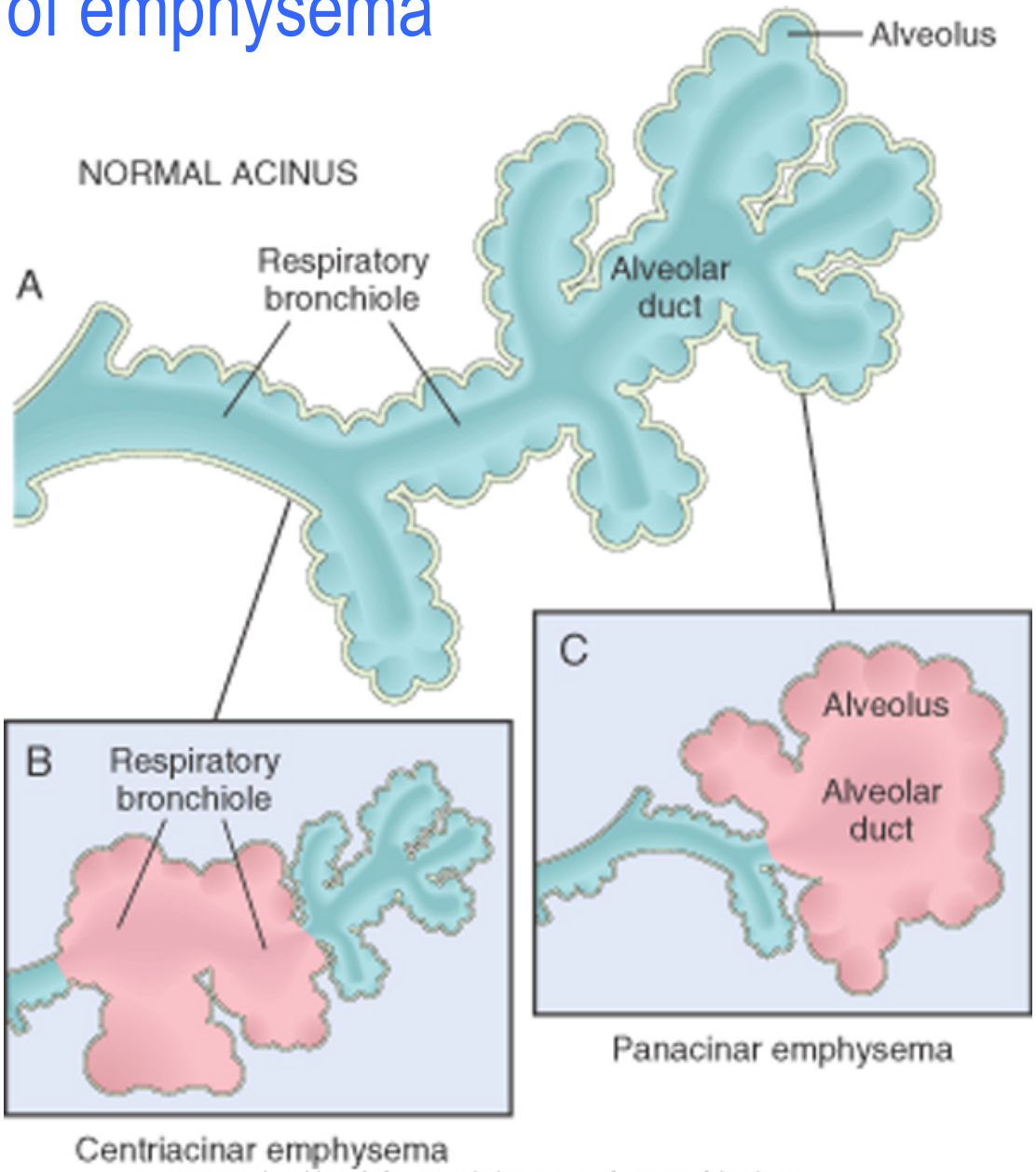


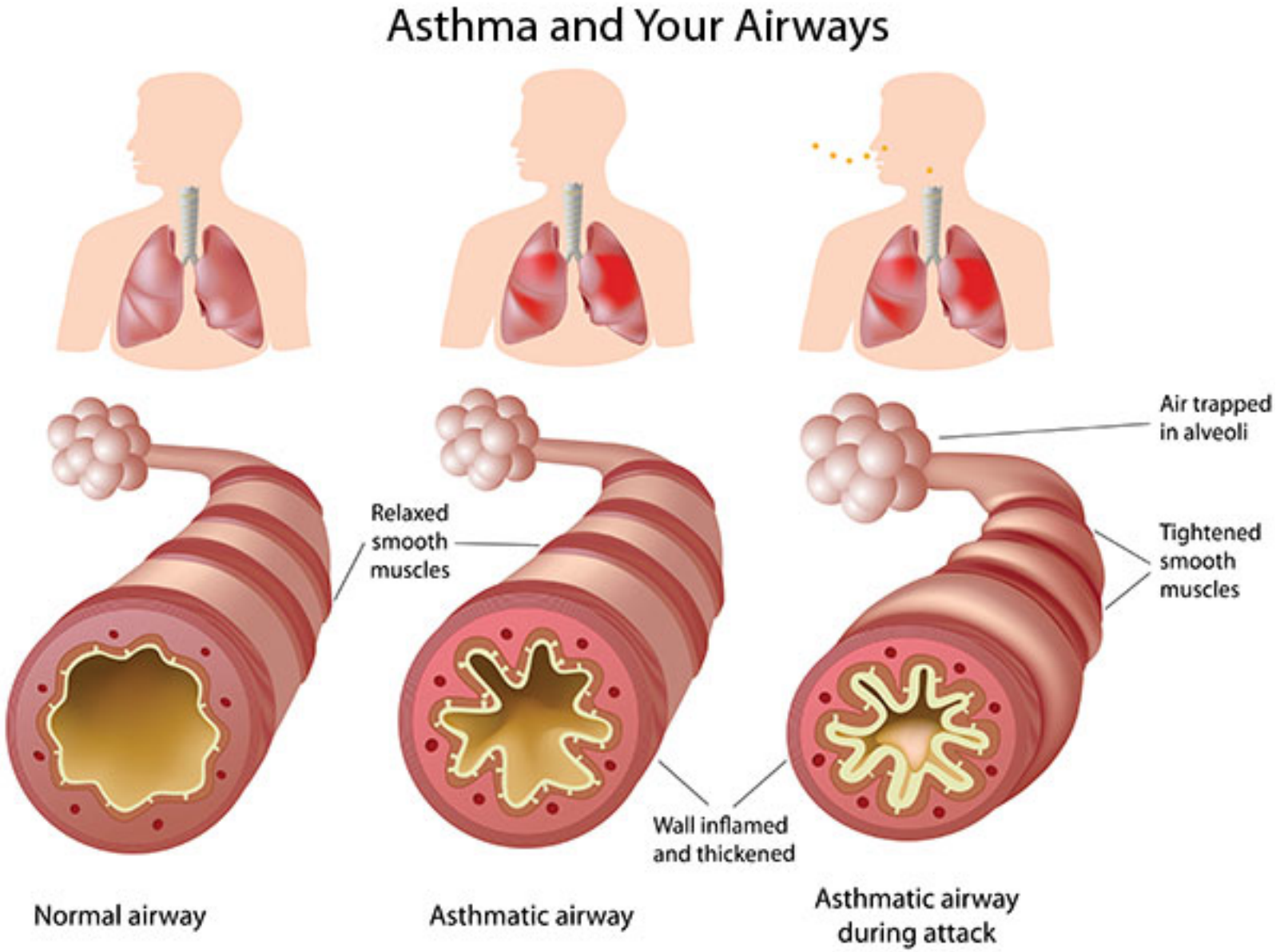
TABLE 15–4 Emphysema and Chronic Bronchitis

	Predominant Bronchitis	Predominant Emphysema
Age (yr)	40–45	50–75
Dyspnea	Mild; late	Severe; early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Occasional
Respiratory insufficiency	Repeated	Terminal
Cor pulmonale	Common	Rare; terminal
Airway resistance	Increased	Normal or slightly increased
Elastic recoil	Normal	Low
Chest radiograph	Prominent vessels; large heart	Hyperinflation; small heart
Appearance	*Blue bloater*	*Pink puffer*

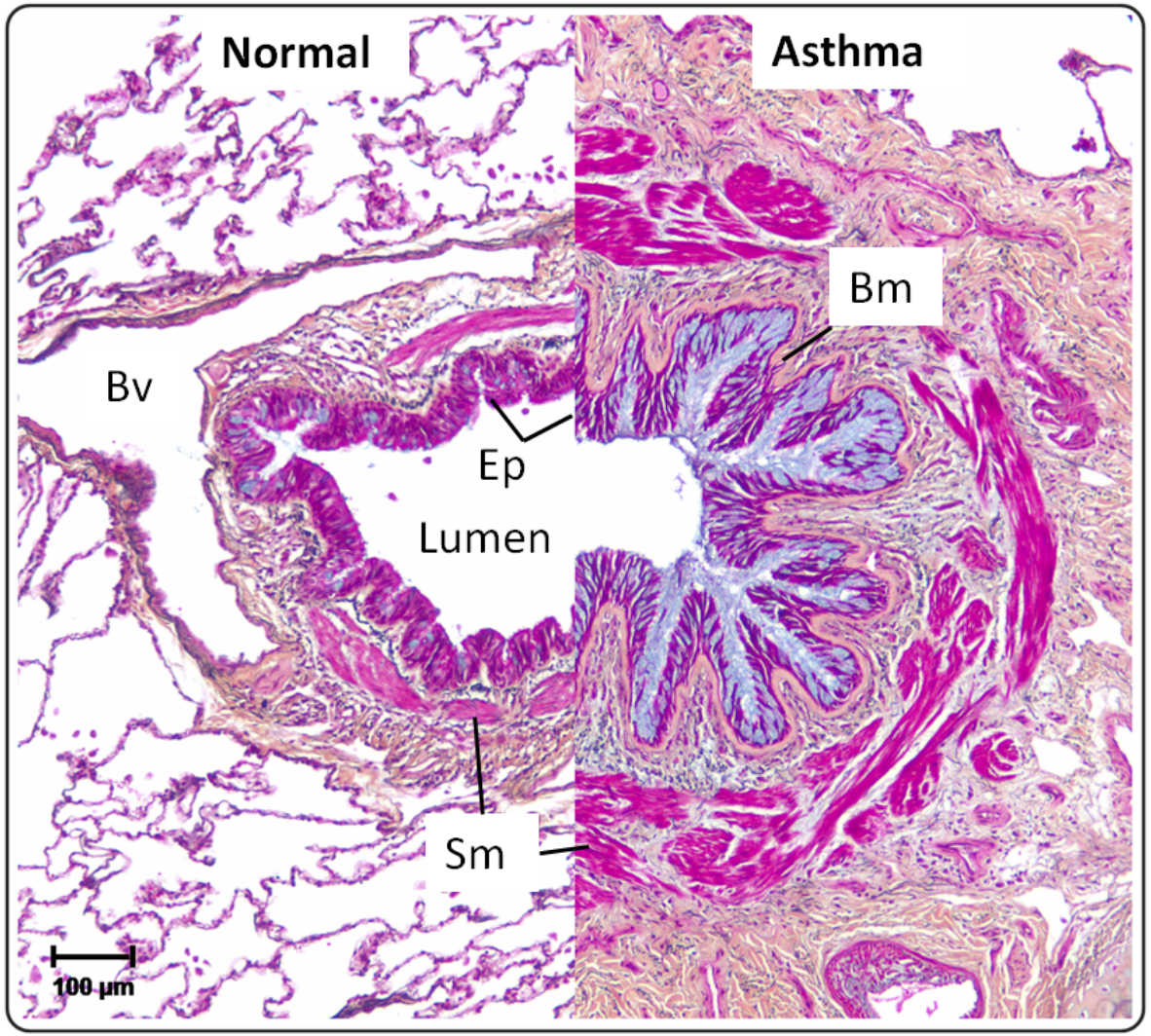
(Kumar 2015)

Asthma

- Chronic lung disease that obstructs airflow.
- It involves difficulty in breathing due to inflammation (swelling).
- Mucus in the airways
- Tightening of muscles around the airways

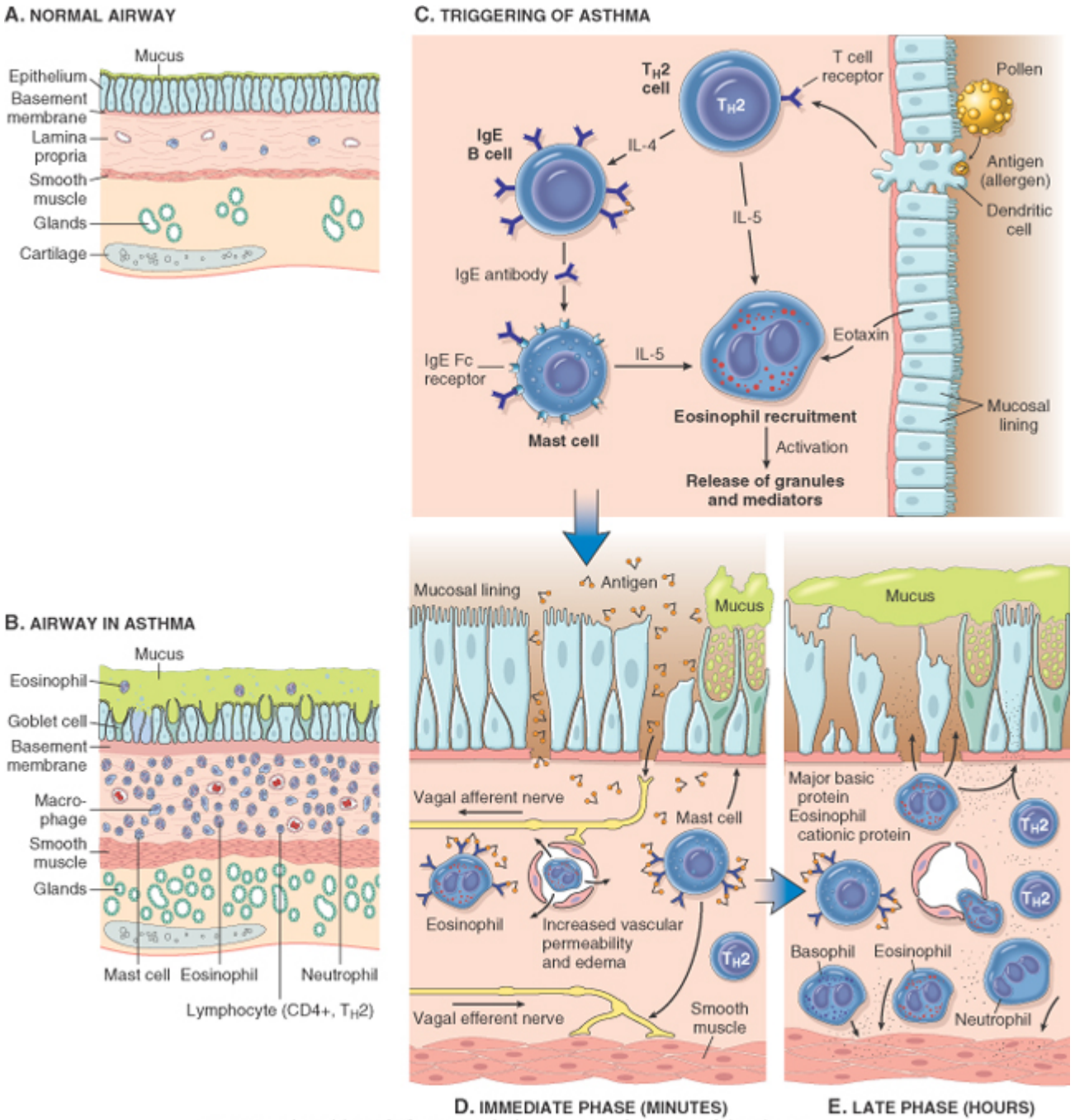


(http://www.nlm.nih.gov/)

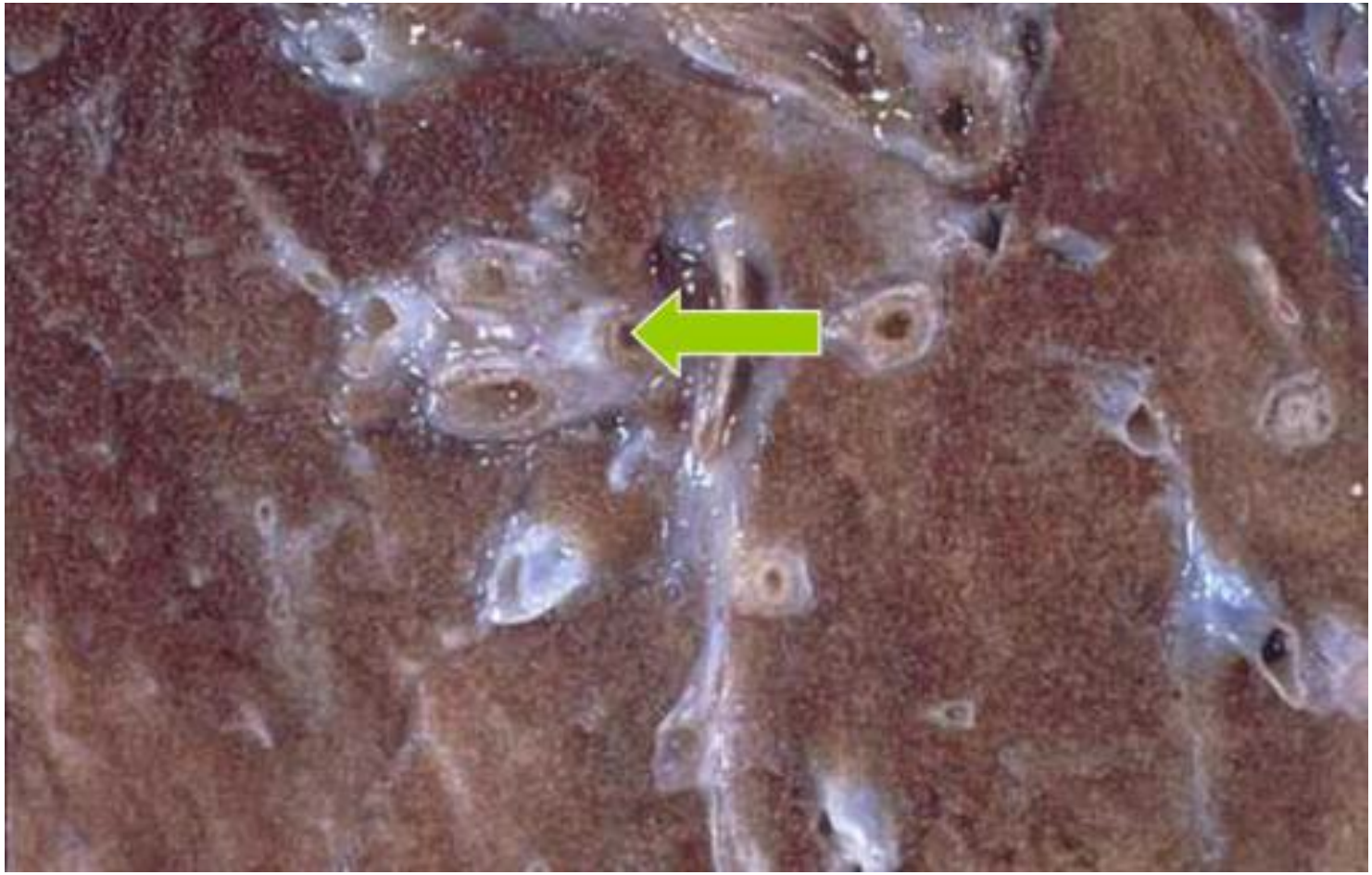


The epithelium (Ep) in asthma shows mucous hyperplasia and hyper secretion (blue), and significant basement membrane (Bm) thickening

(http://www.intechopen.com)



❑ Thick bronchi with mucous plugs

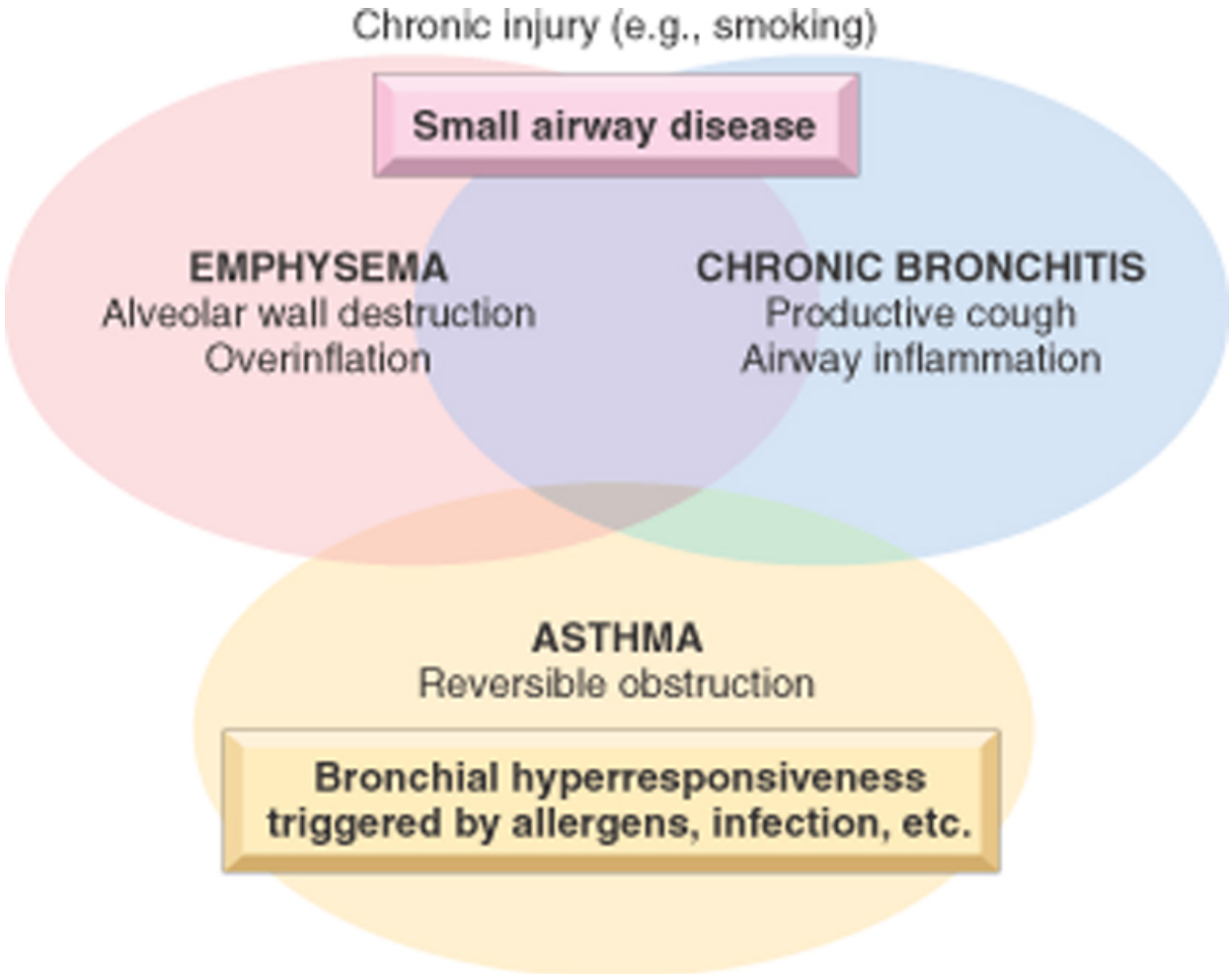


(https://ak47boyz90.wordpress.com)

(http://library.med.utah.edu/WebPath/LUNGHTML/LUNG051.html)

This cast of the bronchial tree is formed of inspissated mucus and was coughed up by a patient during an asthmatic attack. The outpouring of mucus from hypertrophied bronchial submucosal glands, the bronchoconstriction, and dehydration all contribute to the formation of mucus plugs that can block airways in asthmatic patients.

❖ Schematic representation of chronic obstructive lung diseases

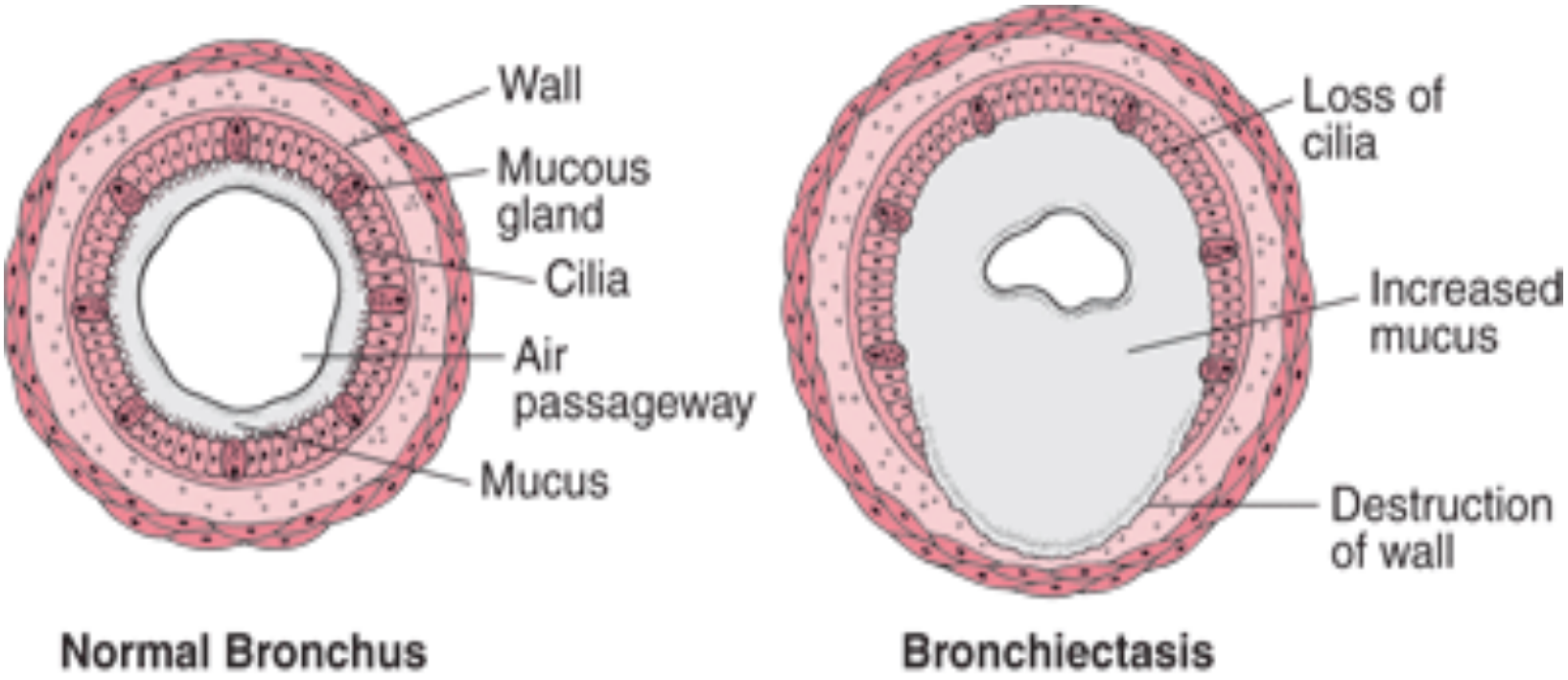


Chronic obstructive pulmonary disease (COPD)

- COPD is an umbrella term used to describe progressive lung diseases including *emphysema, chronic bronchitis,* asthma, and some forms of bronchiectasis.
- COPD is a progressive disease that makes it hard to breathe, it can cause coughing, large amount of mucus, wheezing, shortness of breath, and chest tightness.

Bronchiectasis

Dilatation of the medium and smaller airways--- *bronchi and bronchioles*



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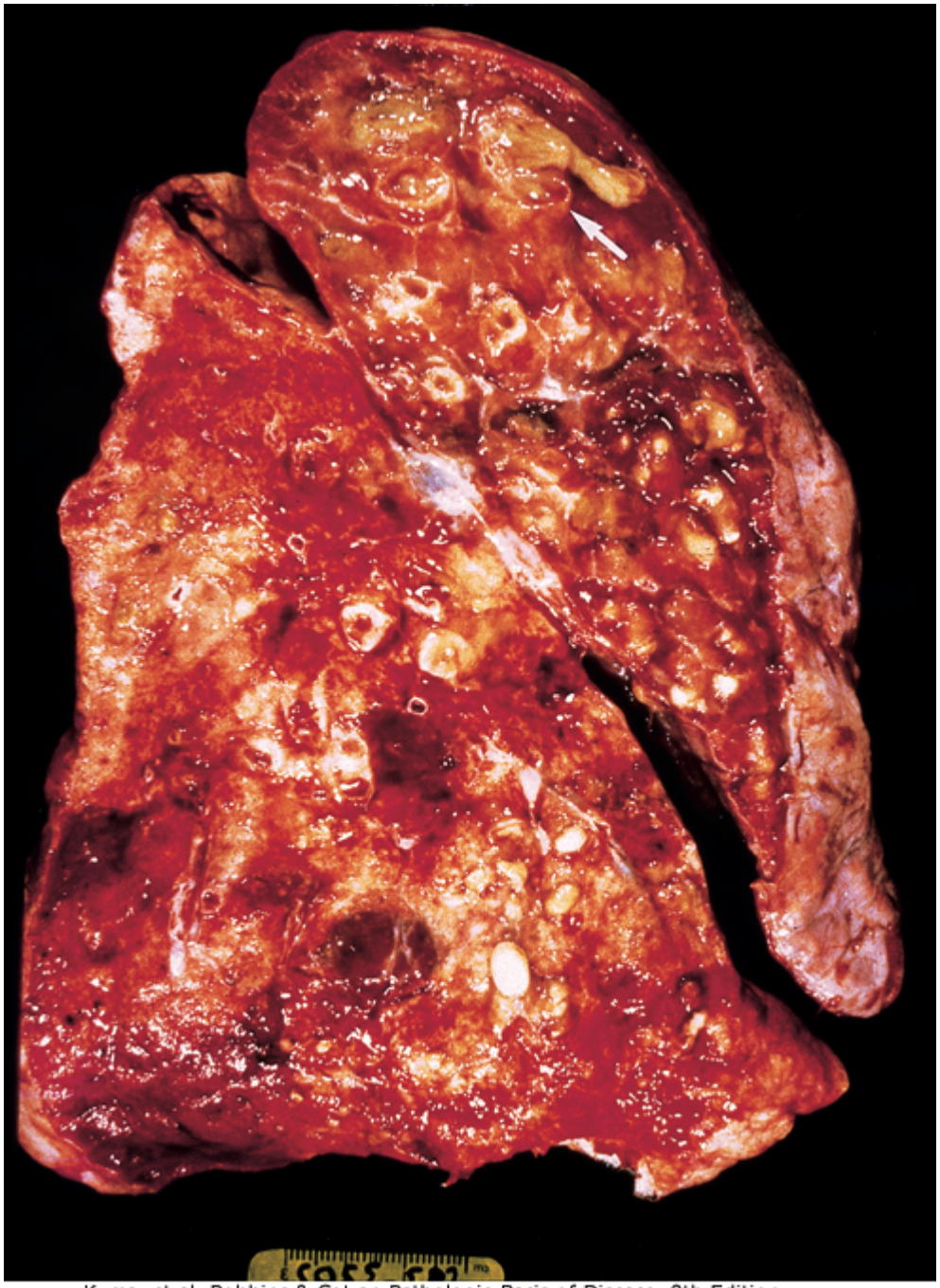
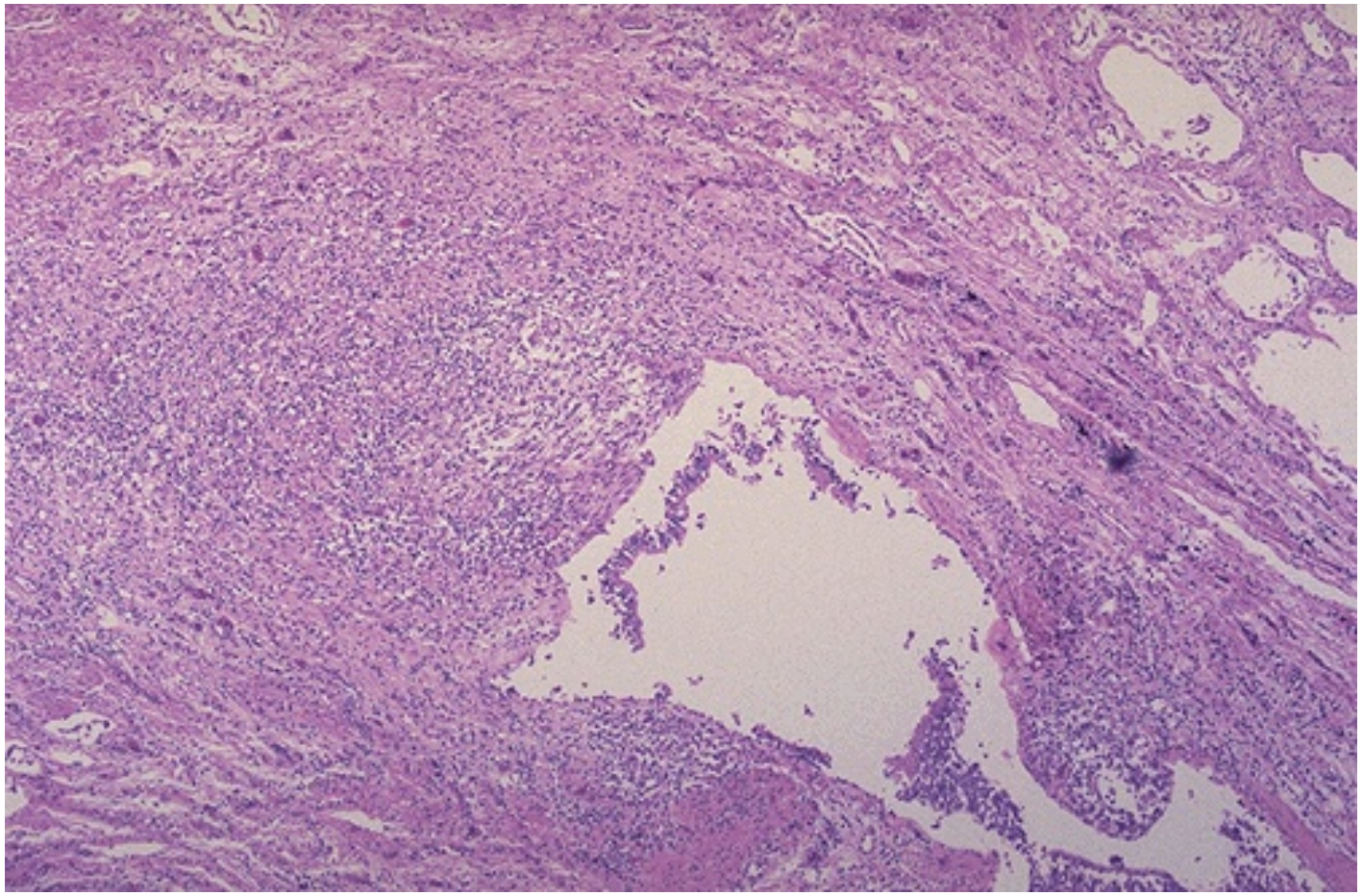


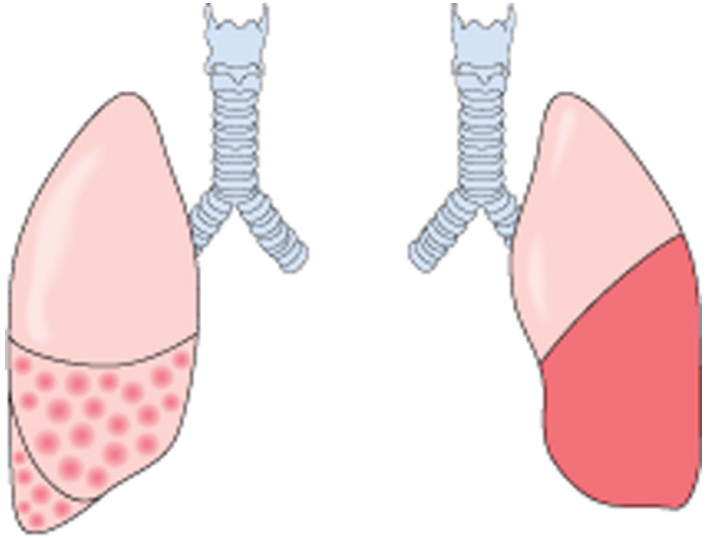


(ibrary.med.utah.edu)

- A dilated bronchus in which the mucosa and wall is not clearly seen because of the necrotizing inflammation with destruction.

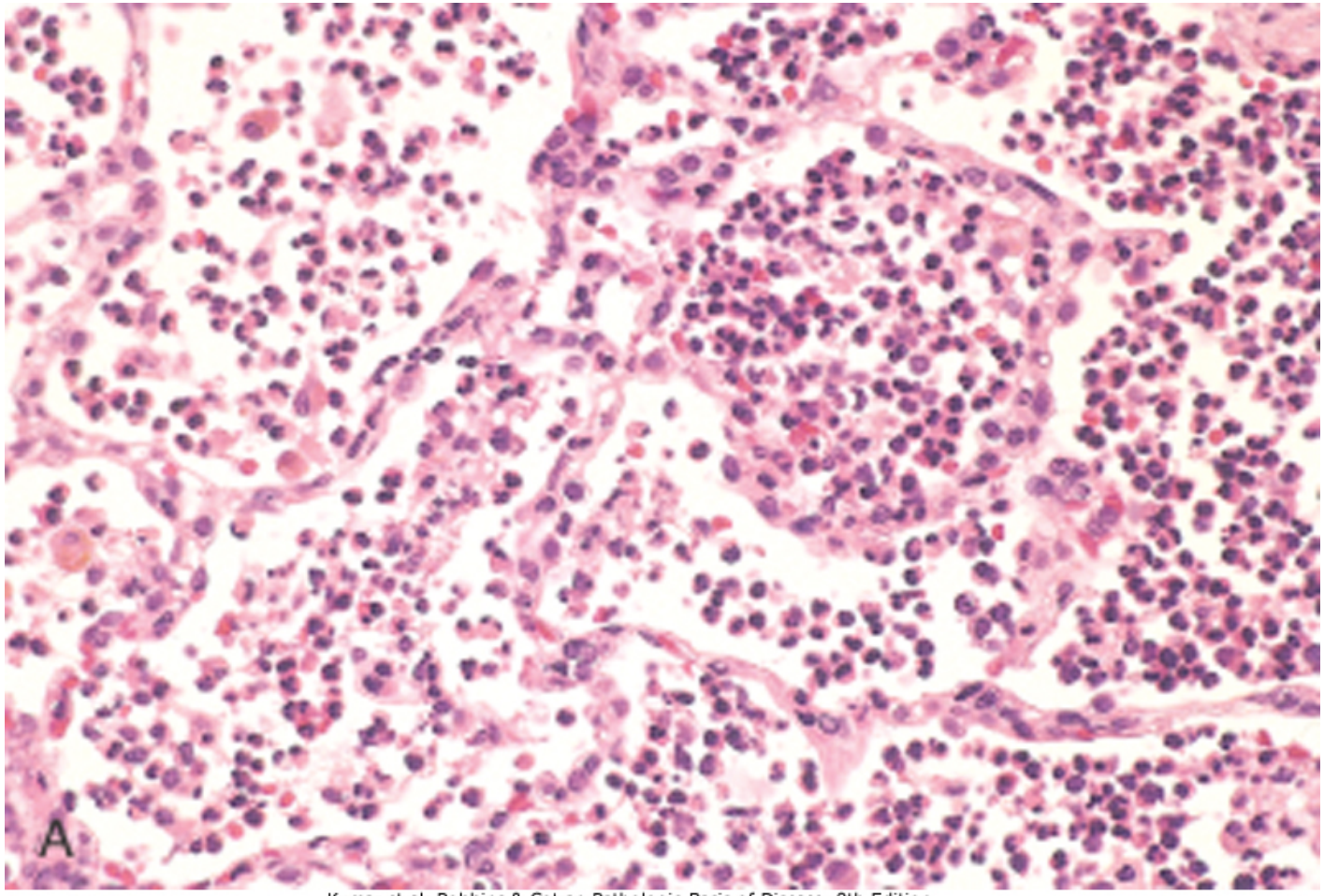
Pneumonia

- Sudden onset of fever, cough productive of purulent sputum or dry cough, dyspnea.
- Pneumonia basically is a problem where alveoli (air sacs at the end of breathing tubes) get contaminated and is filled with fluid.
- The distribution--- *Bronchopneumonia & Lobar pneumonia*



❑ Community-acquired acute pneumonias

- ❖ Most community-acquired acute pneumonias are bacterial in origin.
- ❖ *S. pneumoniae*--- most common cause of community-acquired acute pneumonias
- ❖ Other pathogens--- H. influenzae, M. catarrhalis, S aureus, K. pneumoniae, P. aeruginosa, L. pneumophila



- Acute pneumonia--- neutrophil, exudation

❑ Community-acquired atypical pneumonias

- ❖ Is caused by a variety of organisms--- Mycoplasma pneumoniae, Viruses
- ❖ Pathologic mechanism is attachment of the organisms to the respiratory epithelium followed by necrosis of cells and inflammatory response.

❑ Hospital-acquired pneumonias

- ❖ Pseudomonas spp. and Acinetobacter baumannii are the most common isolates.

❑ Aspiration pneumonias

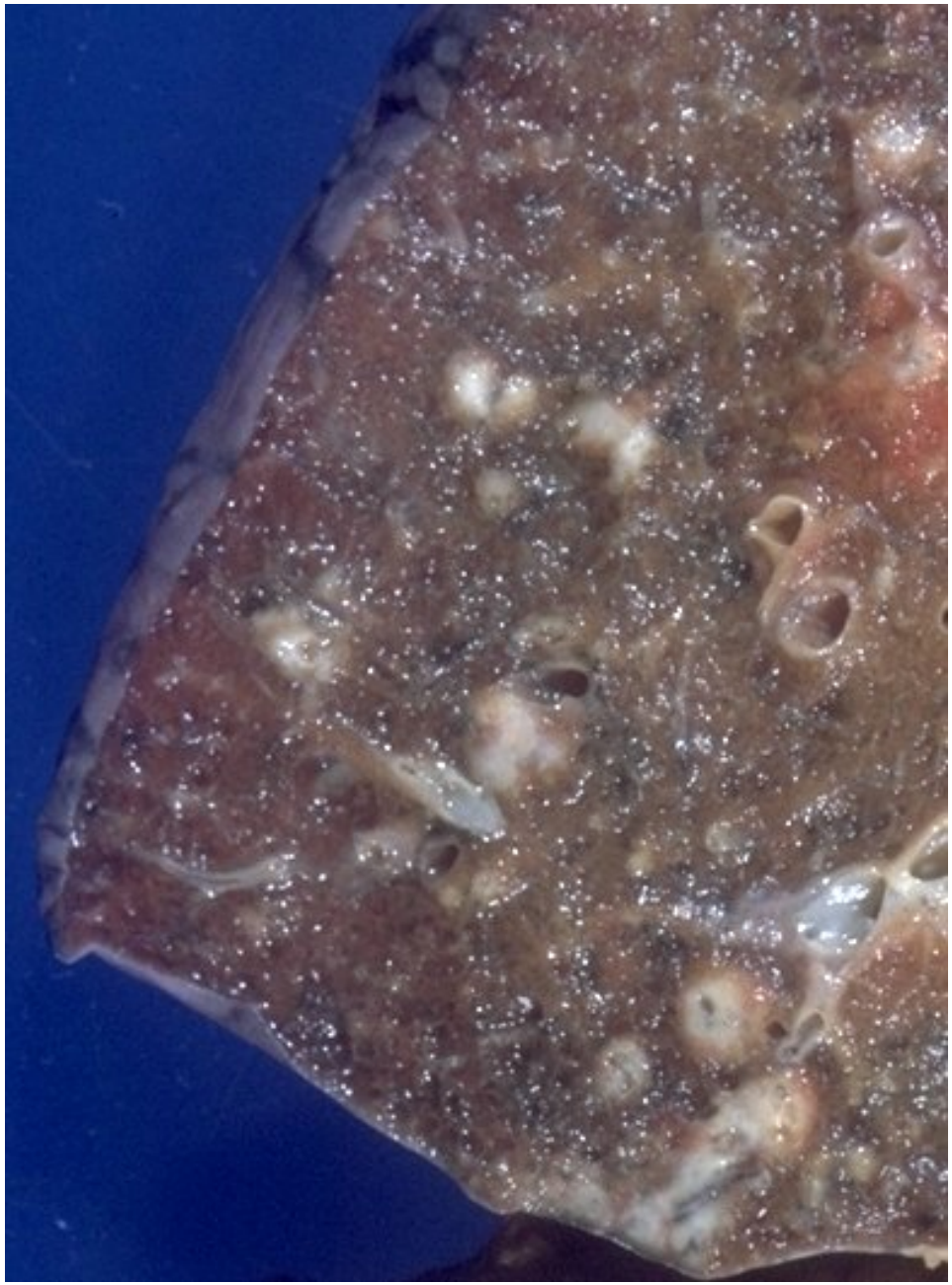
- ❖ Aspiration is defined as the inhalation of either oropharyngeal or gastric contents into the lower airways, that is, the act of taking foreign material into the lungs.

❑ Chronic pneumonias

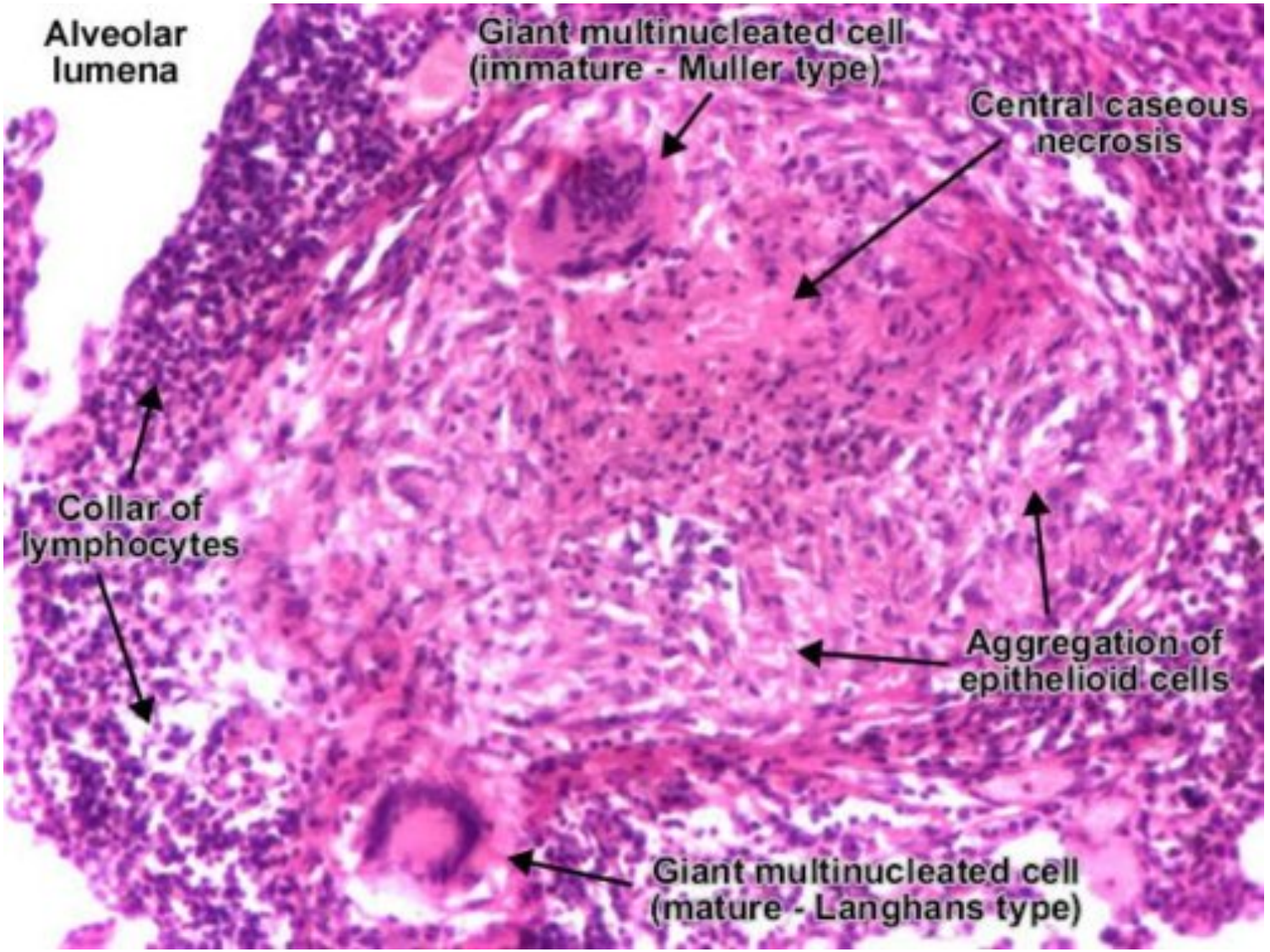
- ❖ Most often in *an immunocompetent person*, with and without regional lymph node involvement

Tuberculosis

- Mycobacterium tuberculosis
- 90% of those infected have asymptomatic, latent TB infection, only 10% will progress to TB disease.
- Tuberculosis is classified as one of the *granulomatous inflammation*.



(http://granuloma.homestead.com/TB_cavitary_gross.html)



(http://fyeahmedlab.tumblr.com)

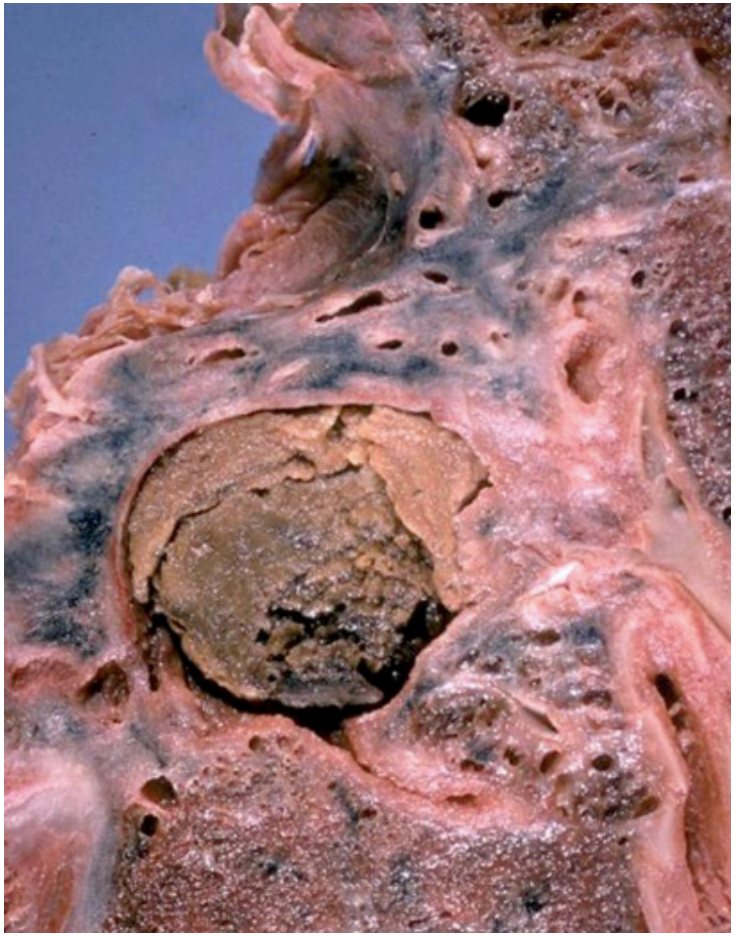
Fungal Lung Infections

- A fungus is a tiny type of germ that usually doesn't cause any problems
- In some situations, particularly if you have other serious illnesses, fungi (the plural of fungus) can infect your lungs.
- People with *a weakened immune system* from other illnesses like HIV, tuberculosis, or cystic fibrosis are those who are most affected by fungal lung infections.
- People who take *medications that suppress their immune system,* like steroids or immunosuppressants.

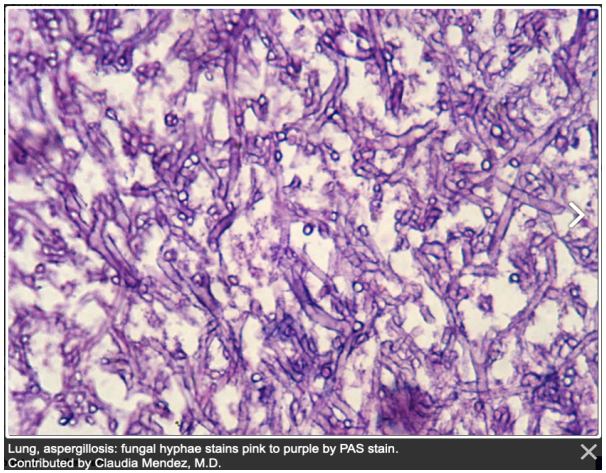
Fungal lung infection symptoms: the symptoms are quite similar to any other type of chest infection:

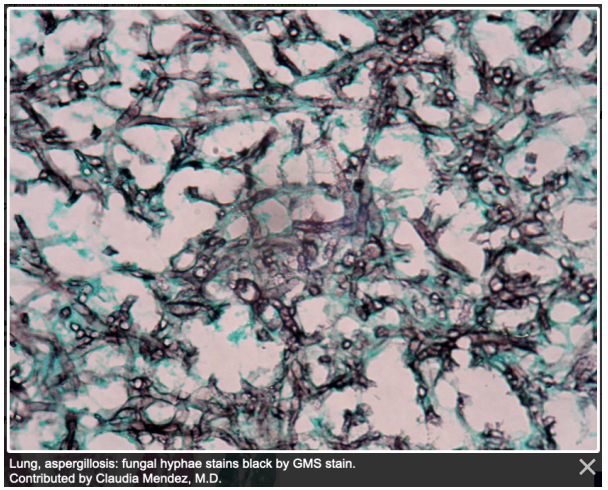
- A high temperature (fever)
- A cough
- A feeling of breathlessness
- Coughing up sputum or blood (in severe case)
- A general feeling of weakness

Pulmonary aspergilloma is a mass caused by a fungal infection. It usually grows in lung cavities.



https://radiopaedia.org/cases/aspergilloma-gross-pathology-2



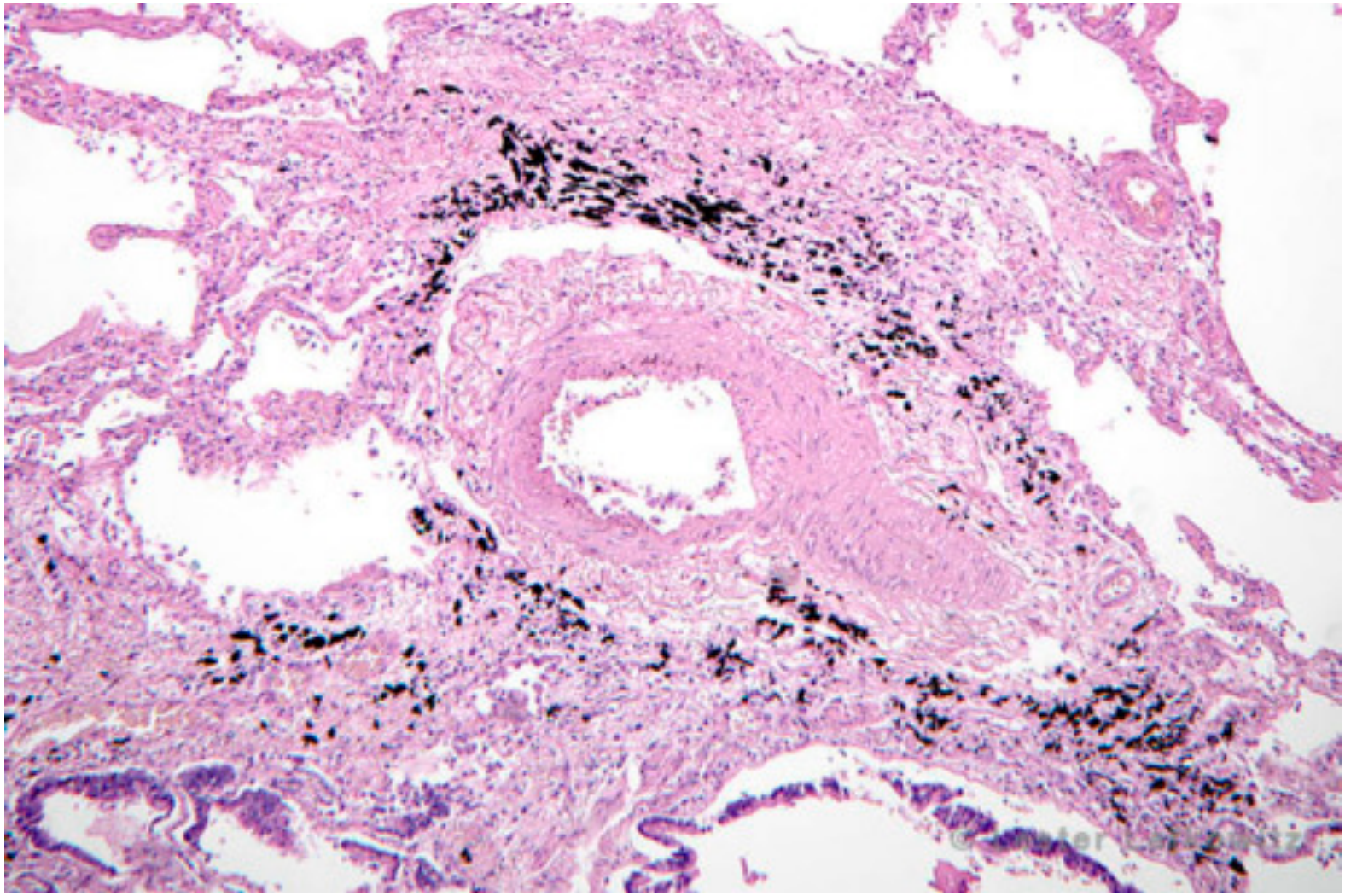


https://www.pathologyoutlines.com/topic/lungnontumoraspergillosis.html

Pneumoconioses

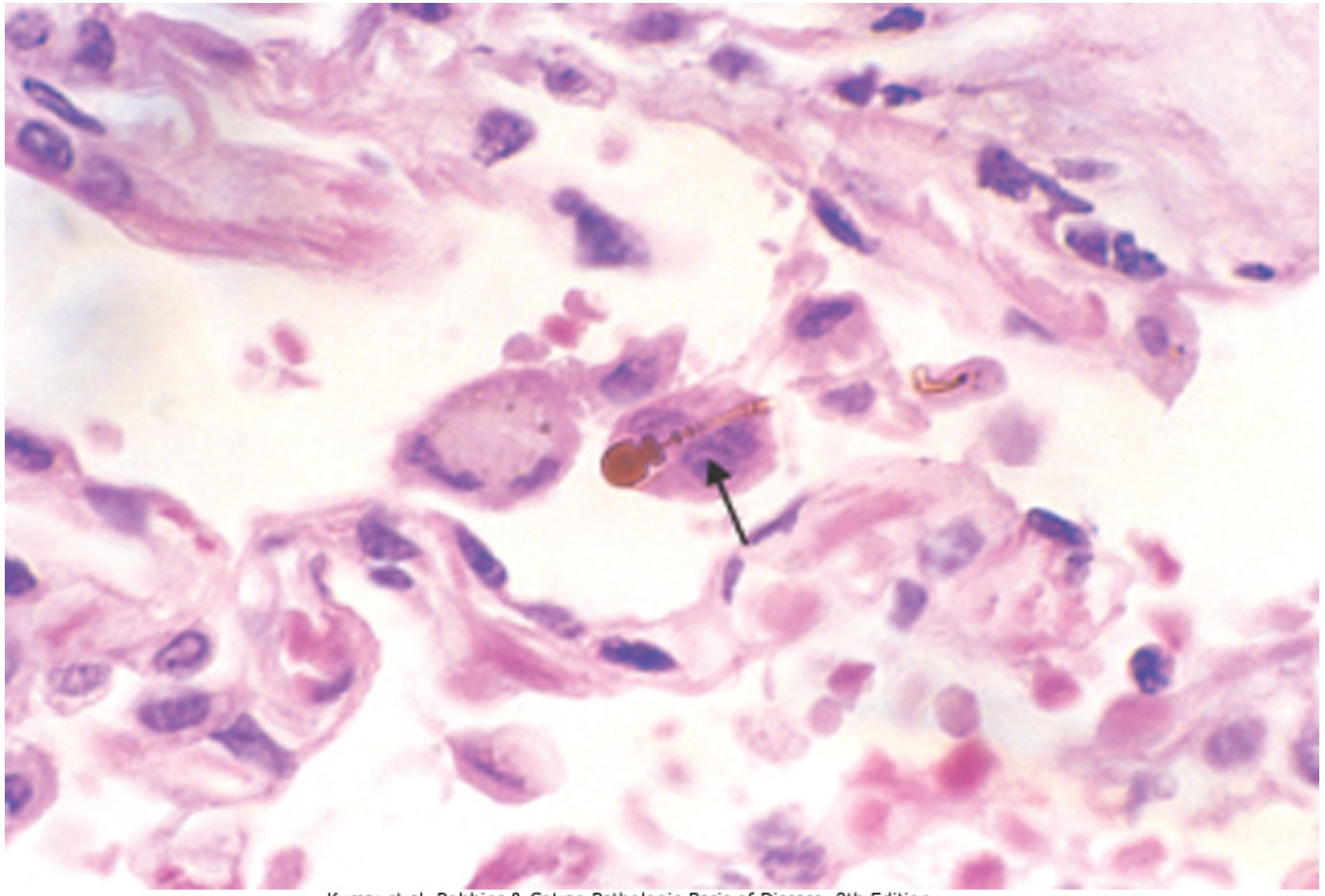
- Occupational lung
- A restrictive lung disease caused by the inhalation of dust
- Depending upon the type of dust

❑ Anthracosis



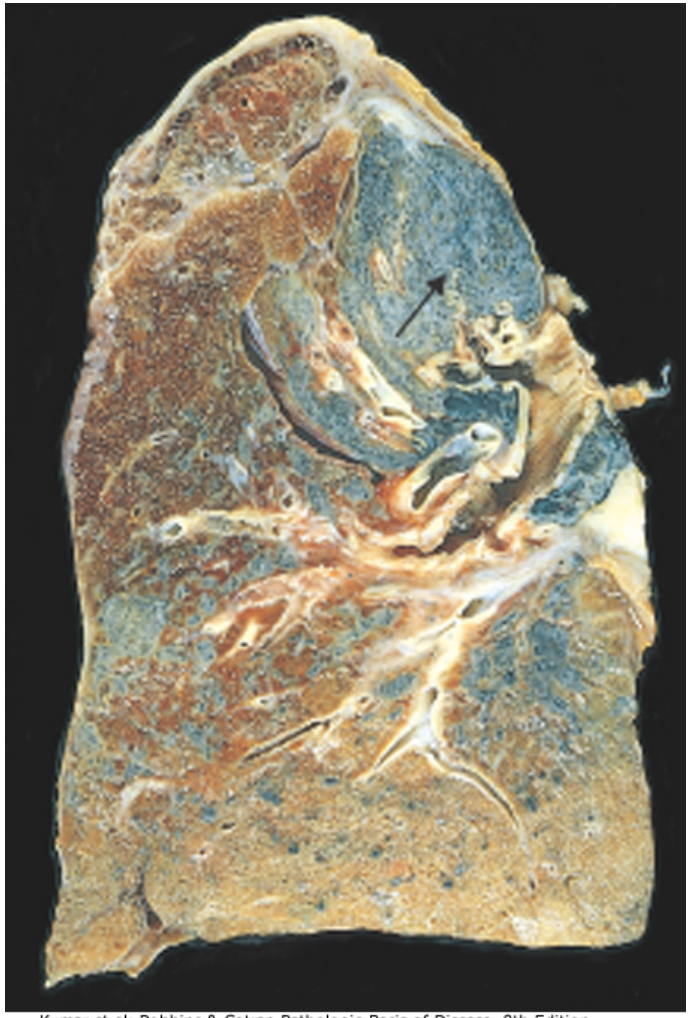
(http://genieknowledge.ning.com)

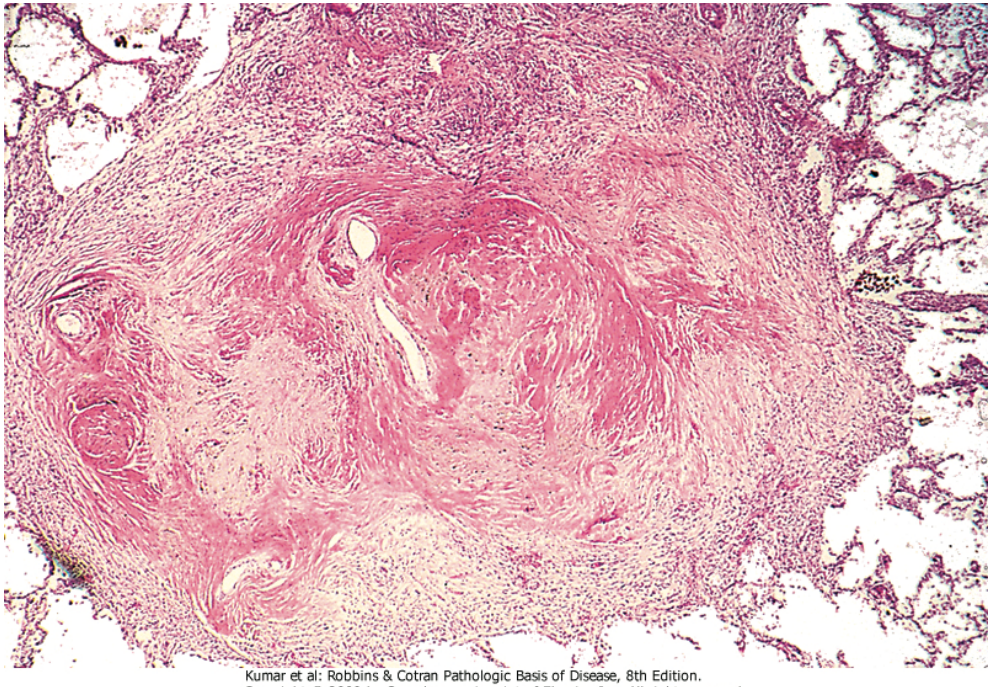
❑ Asbestosis



❖ an asbestos body

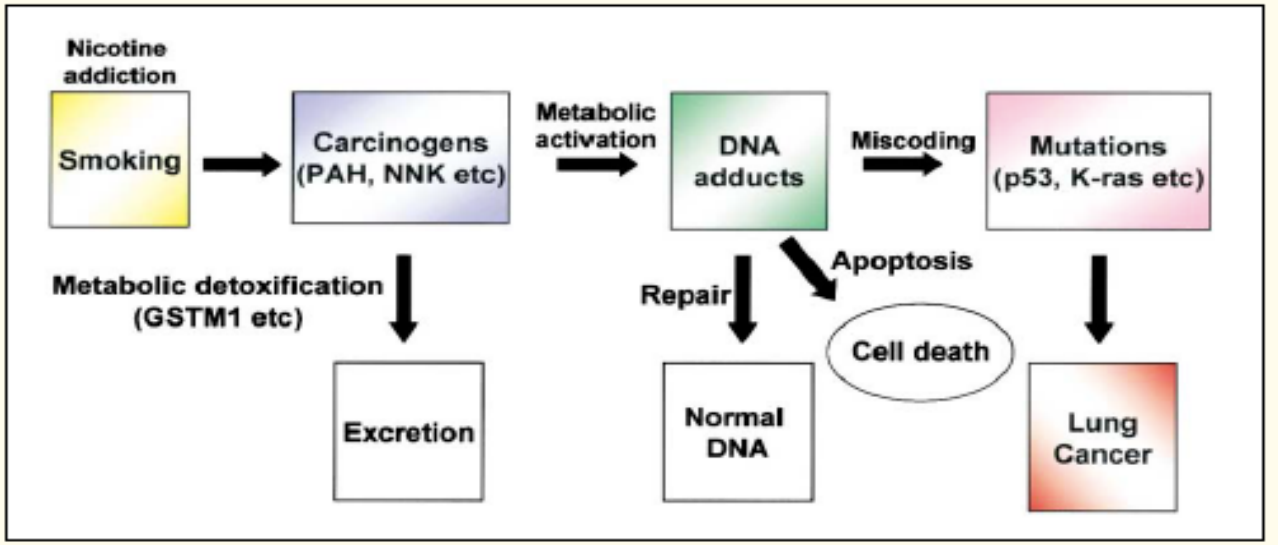
❑ Silicosis



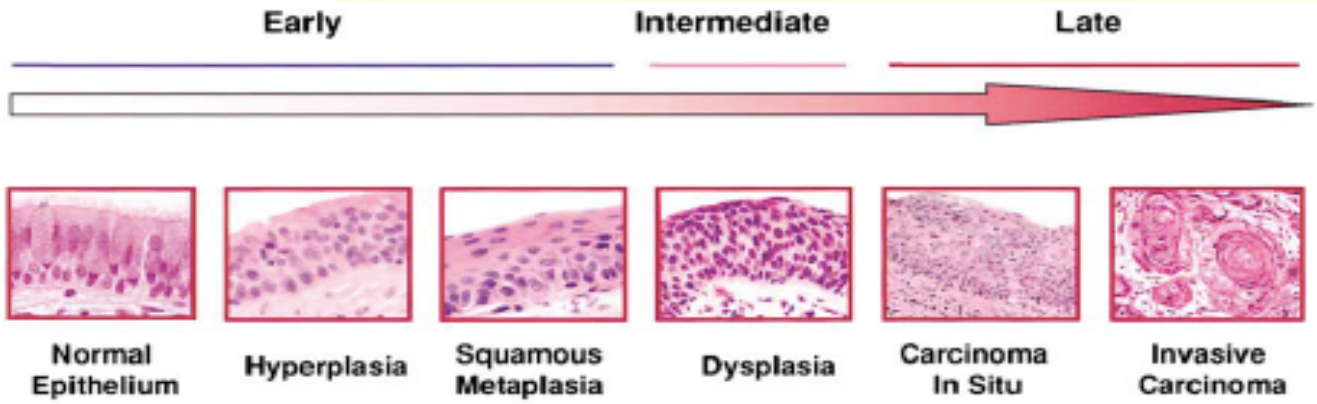


- ❖ Several coalescent collagenous silicotic nodules

Lung Cancer



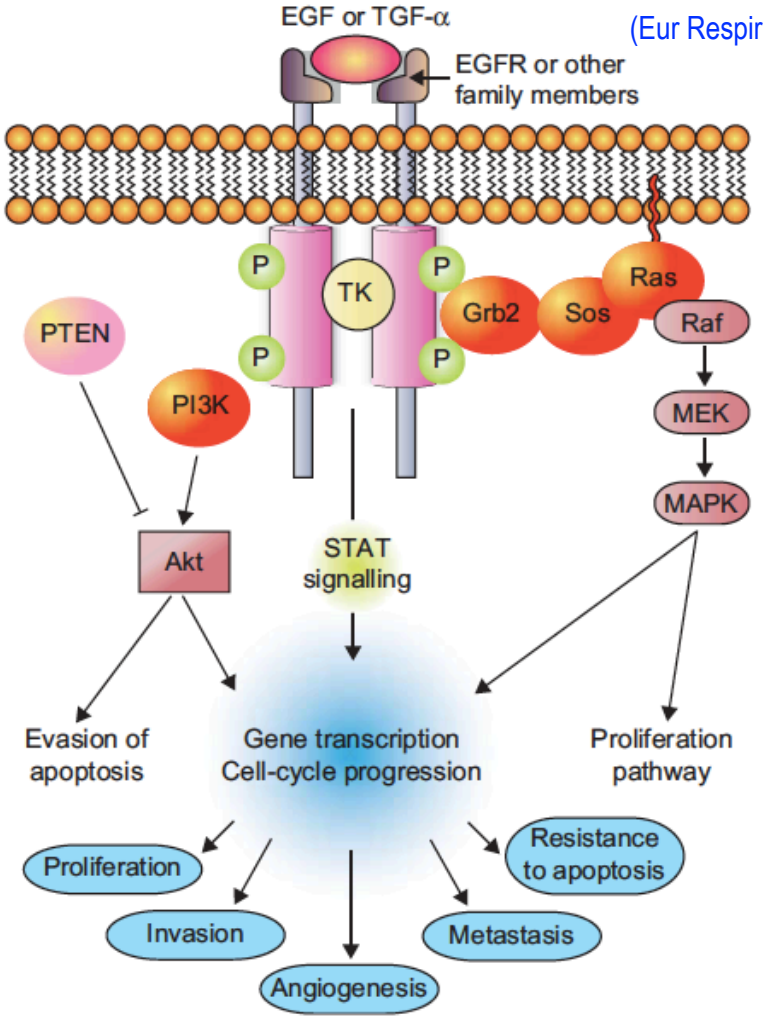
CANCER CELL : FEBRUARY 2002 · VOL. 1 · COPYRIGHT © 2002 CELL PRESS



The many lung cancer-specific carcinogens (including polycyclic aromatic hydrocarbons and nitrosamines) in the particulate matter of tobacco smoke have to be metabolized before they are either secreted or can bind to DNA with the formation of adducts. DNA adducts may be *repaired* or lead to *apoptosis*. If they persist, miscoding mutations in key genes such *as P53 or RAS* may cause genetic instability, leading to further mutational damage and eventually to cancer.

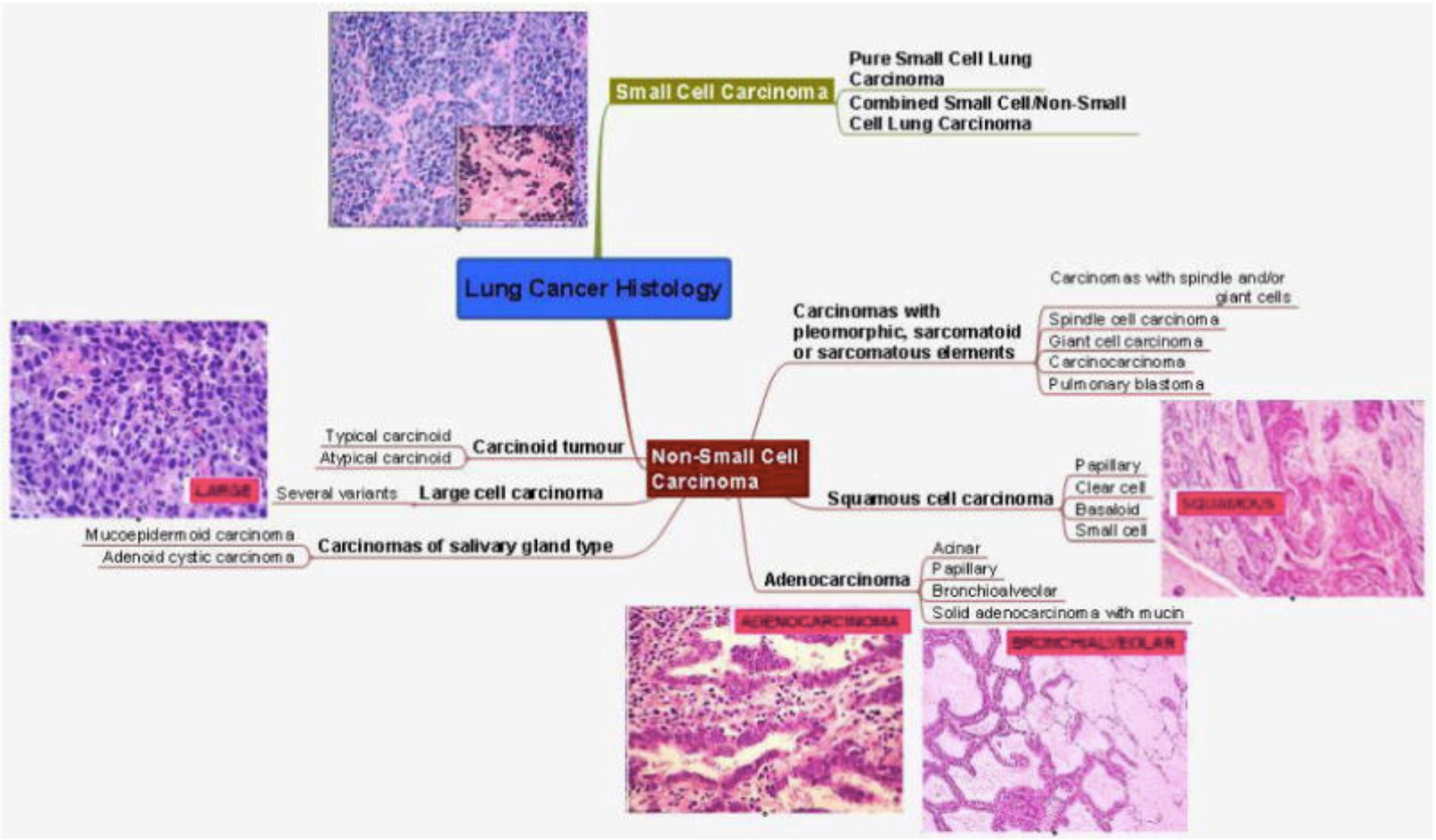
- Lung cancer consists of several histologic types, including *small-cell lung carcinoma (SCLC)* and *non–small cell lung carcinoma (NSCLC)*, with the latter comprising the majority of diagnosed (85%) lung tumors.
- NSCLC is composed of the following three major histologic subtypes: lung *adenocarcinomas* (LUAD), *lung squamous cell carcinomas* (LUSC), and *large-cell lung carcinomas* (LCLC).

(Eur Respir J 2009; 33: 1485–1497)



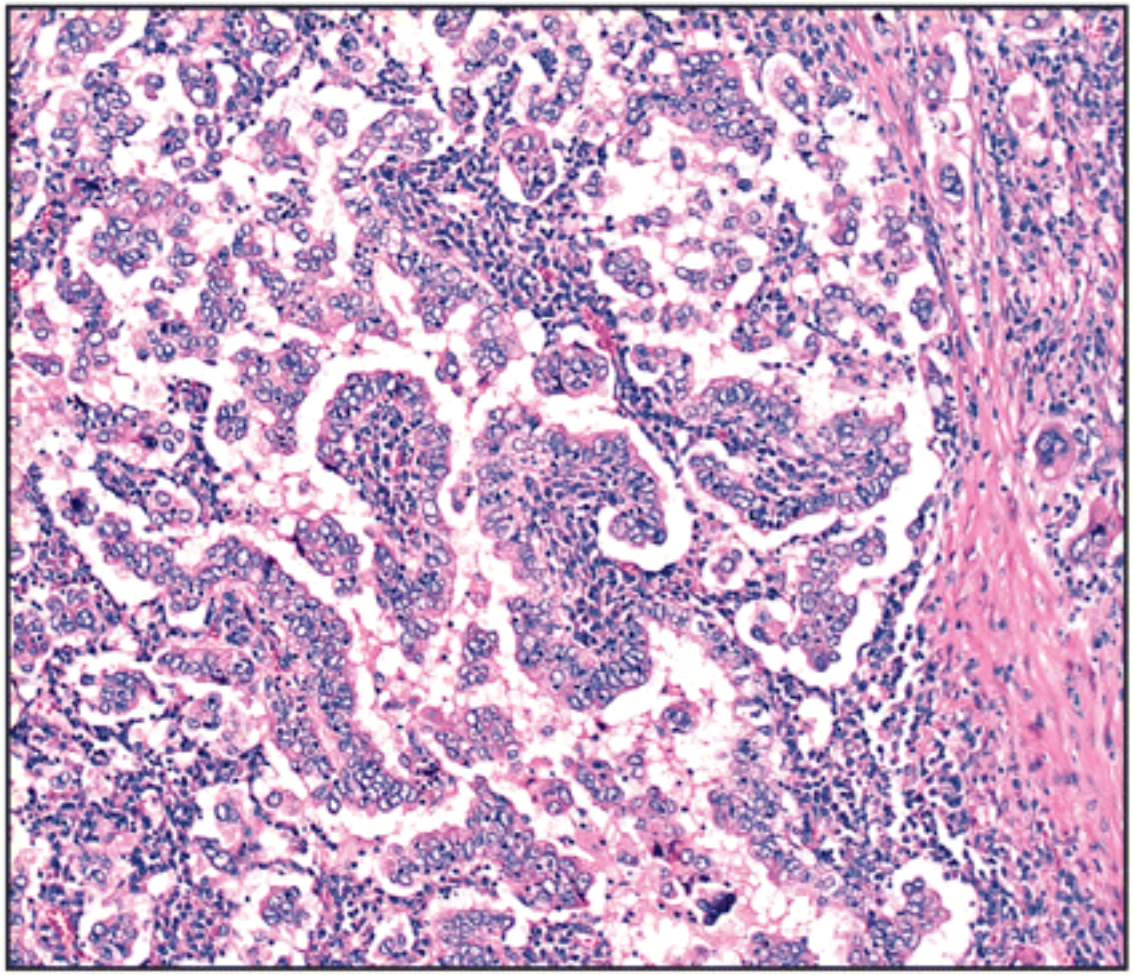
Mutations or deregulated expression might cause them to function as potentoncogenes.

Epidermal growth factor receptor (EGFR) pathway. Ligands, such as epidermal growth factor (EGF), transforming growth factor (TGF)-a, or others, bind to the homo- and heterodimer kinase domain (TK), resulting in activation and receptor transphosphorylation. This creates docking sites for the adaptor proteins, Grb2 and Sos, which recruit Ras and phosphatidylinositol 3-kinase (PI3K), leading to the formation of two major signalling pathway branches, Ras/MAPK and PI3K/Akt. These networks result in, amongst others, proliferation, evasion of apoptosis and angiogenesis. MAPK: mitogen-activated kinase-like protein.



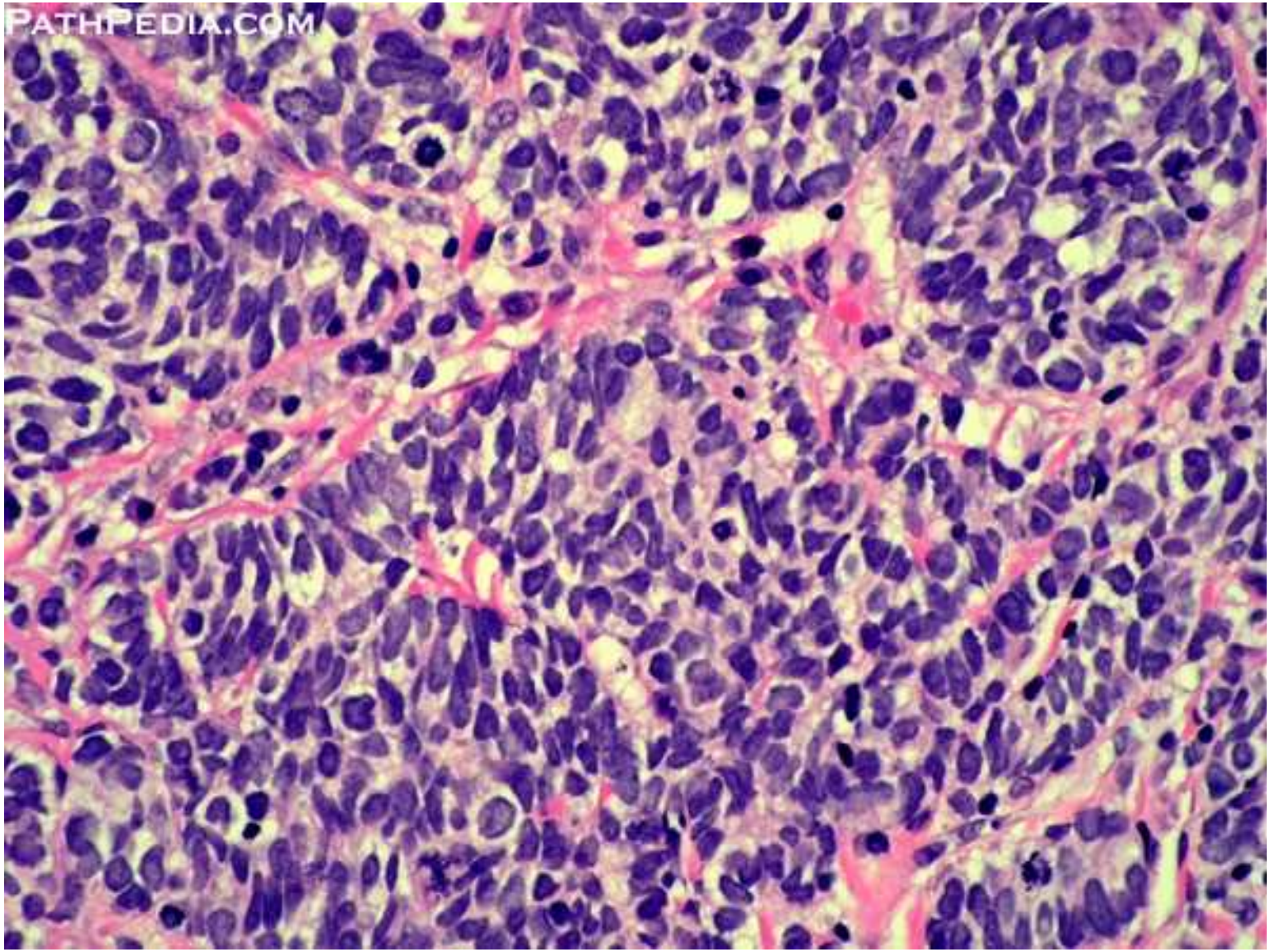
(https://europepmc.org/article/PMC/3077059)

❑ Lung: Adenocarcinoma



(http://ajcp.ascpjournals.org)

❑ Small cell carcinoma



(http://www.pathpedia.com/)

EDITORIAL
INFECTIOUS DISEASE

Pathogenesis of COVID-19 from a cell biology perspective

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@ERSpublications
COVID-19 can be understood by the region of the lung that is infected. Mild disease will be confined to the conducting airways and severe disease will involve the gas exchange portion of the lung. https://bit.ly/2vGndRQ

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Stage 1: Asymptomatic state (initial 1–2 days of infection)

The inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV2 and SARS-CoV [2, 3]. *In vitro* data with SARS-CoV indicate that the ciliated cells are primary cells infected in the conducting airways [4]. However, this concept might need some revision, since single-cell RNA indicates low level of ACE2 expression in conducting airway cells and no obvious cell type preference [5]. There is local propagation of the virus but a limited innate immune response. At this stage the virus can be detected by nasal swabs. Although the viral burden may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to predict the viral load and the subsequent infectivity and clinical course. Perhaps super spreaders could be detected by these studies. For the RT-PCR cycle number to be useful, the sample collection procedure would have to be standardised. Nasal swabs might be more sensitive than throat swabs.

Stage 2: Upper airway and conducting airway response (next few days)

The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response. At this time, the disease COVID-19 is clinically manifest. The level of CXCL10 (or some other innate response cytokine) may be predictive of the subsequent clinical course [6]. Viral infected epithelial cells are a major source of beta and lambda interferons [7]. CXCL10 is an interferon responsive gene that has an excellent signal to noise ratio in the alveolar type II cell response to both SARS-CoV and influenza [8, 9]. CXCL10 has also been reported to be useful as disease marker in SARS [6, 10]. Determining the host innate immune response might improve predictions on the subsequent course of the disease and need for more aggressive monitoring.

For about 80% of the infected patients, the disease will be mild and mostly restricted to the upper and conducting airways [1]. These individuals may be monitored at home with conservative symptomatic therapy.

Stage 3: Hypoxia, ground glass infiltrates, and progression to ARDS

Unfortunately, about 20% of the infected patients will progress to stage 3 disease and will develop pulmonary infiltrates and some of these will develop very severe disease. Initial estimates of the fatality rate are around 2%, but this varies markedly with age [1]. The fatality and morbidity rates may be revised once the prevalence of mild and asymptomatic cases is better defined. The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells [11, 12]. The infected alveolar units tend to be peripheral and subpleural [13, 14]. SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die (figure 1) [8]. The end result is likely a self-replicating pulmonary toxin as the released viral partides infect type II cells in adjacent units. I suspect areas of the lung will likely lose most of their type II cells, and secondary pathway for epithelial regeneration will be triggered. Normally, type II cells are the precursor cells for type I cells. This postulated sequence of events has been shown in the murine model of influenza pneumonia [15, 16]. The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells [17, 18]. The aberrant wound healing may lead to more severe scarring and fibrosis than other forms of ARDS. Recovery will require a vigorous innate and acquired immune response and epithelial regeneration. From my perspective, similar to influenza, administrating epithelial growth factors such as KGF might be detrimental and might increase the viral load by producing more ACE2 expressing cells [19]. Elderly individuals are particularly at risk because of their diminished immune response and reduced ability to repair the damaged epithelium. The elderly also have reduced mucociliary clearance, and this may allow the virus to spread to the gas exchange units of the lung more readily [20].

There are significant knowledge gaps in the pathogenesis of COVID-19 that will be filled in over the next few months. I based my comments on the assumption that viral entry by SARS-CoV-2 will be the same as SARS-CoV. We do not know if there are alternate receptors for viral entry. CD209L is an alternative receptor for SARS-CoV [21]. We await detailed studies on infection and the innate immune response of differentiated primary human lung cells. The apical cilia on airway cells and microvilli on type II cells may be important for facilitating viral entry.

DEFINITION

Post-COVID Conditions

Some people who have been infected with the virus that causes COVID-19 can experience long-term effects from their infection, known as post-COVID conditions (PCC) or long COVID.

People call post-COVID conditions by many names, including: long COVID, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), long-term effects of COVID, and chronic COVID.

What You Need to Know

- Post-COVID conditions can include a wide range of ongoing health problems; these conditions can last weeks, months, or years.
- Post-COVID conditions are found more often in people who had severe COVID-19 illness, but anyone who has been infected with the virus that causes COVID-19 can experience post-COVID conditions, even people who had mild illness or no symptoms from COVID-19.
- People who are not vaccinated against COVID-19 and become infected may also be at higher risk of developing post-COVID conditions compared to people who were vaccinated and had breakthrough infections.
- While most people with post-COVID conditions have evidence of infection or COVID-19 illness, in some cases, a person with post-COVID conditions may not have tested positive for the virus or known they were infected.
- CDC and partners are working to understand more about who experiences post-COVID conditions and why, including whether groups disproportionately impacted by COVID-19 are at higher risk.

(https://www.cdc.gov, 2021)

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