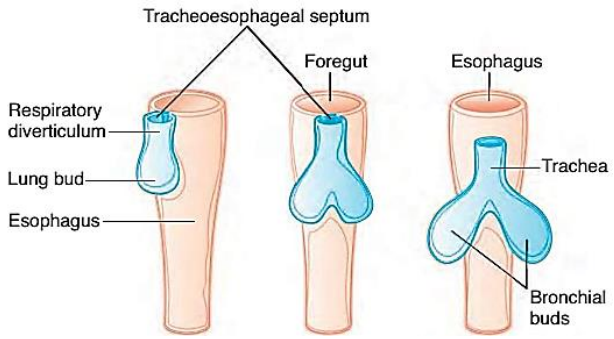
EMBRYOLOGY

LUNG DEVELOPMENT:

- The **lung bud** forms from the foregut during **week 4** of embryologic development.
- The lining of the lower respiratory tract is derived from **endoderm**, whereas the connective tissue cartilage and muscle are derived from **mesoderm**.
- Normal development causes the lung bud to completely separate from the esophagus at the level of the larynx.
- Incomplete **separation** causes a **tracheoesophageal (TE) fistula**.



STAGES OF LUNG DEVELOPMENT:

- Occurs in five stages. **E**very **P**ulmonologist **C**an **S**ee **A**lveoli.

STAGE	STRUCTURAL DEVELOPMENT	NOTES
Embryonic (weeks 4–7)	Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to tracheoesophageal fistula.
Pseudoglandular (weeks 5–17)	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.
Canalicular (weeks 16–25)	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Respiration capable at 25 weeks. Pneumocytes develop starting at 20 weeks.
Saccular (week 26–birth)	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae.	
Alveolar (week 36–8 years)	Terminal sacs → adult alveoli (due to 2° septation). In utero, "breathing" occurs via aspiration and expulsion of amniotic fluid → ↑ vascular resistance through gestation. At birth, fluid gets replaced with air → ↓ in pulmonary vascular resistance.	At birth: 20–70 million alveoli. By 8 years: 300–400 million alveoli.

CONGENITAL LUNG MALFORMATIONS

- **Pulmonary hypoplasia:**
  - Poorly developed bronchial tree with abnormal histology.
  - **Associated with 2 conditions:**
    - Congenital diaphragmatic hernia (usually left-sided).
    - Bilateral renal agenesis (Potter sequence).
      - This causes **oligohydramnios**, which increases the pressure on the fetal thorax and Potter's sequence.
      - One of the features of Potter's sequence is bilateral pulmonary hypoplasia.
- **Bronchogenic cysts:**
  - During development part of the trachea-bronchial tree gets separated.
  - Caused by **abnormal budding** of the foregut and **dilation** of terminal or large bronchi.
  - Discrete**, round, sharply defined**, fluid-filled densities on CXR (air-filled if infected).
  - Generally asymptomatic but can drain poorly, causing airway **compression** and/or recurrent respiratory **infections**.

PULMONARY ANATOMY

RESPIRATORY TREE

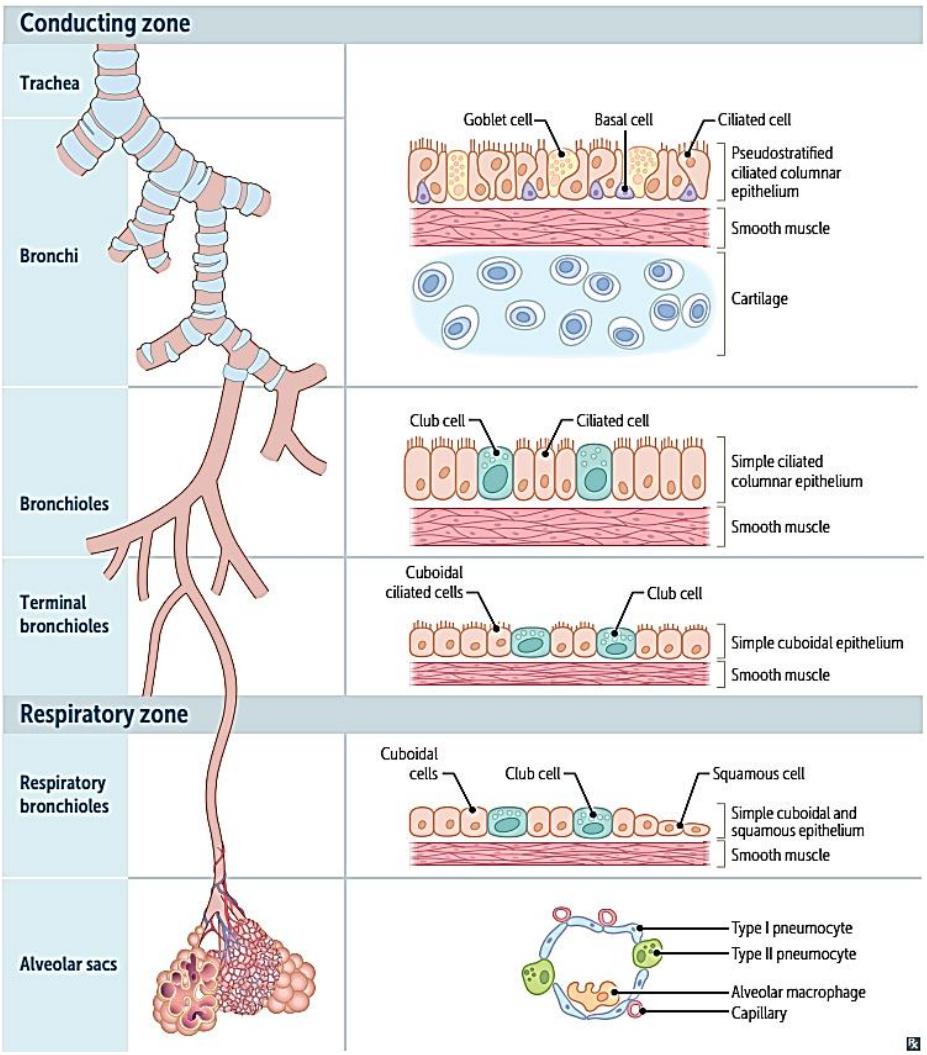
A- CONDUCTING ZONE

- **Large airways** consist of nose, pharynx, larynx, trachea, and bronchi.
- **Small airways** consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance).
- Warms, humidifies, and filters air but does not participate in gas exchange → "**anatomic dead space**."
- **Cartilage and goblet** cells extend to the end of bronchi.
- **Pseudostratifed ciliated columnar** cells primarily make up epithelium of bronchus and extend to
  beginning of terminal bronchioles, then transition to **cuboidal cells**.
- Clear mucus and debris from lungs (mucociliary escalator).
- Airway **smooth muscle** cells extend to end of *terminal bronchioles* (sparse beyond this point).

B- RESPIRATORY ZONE

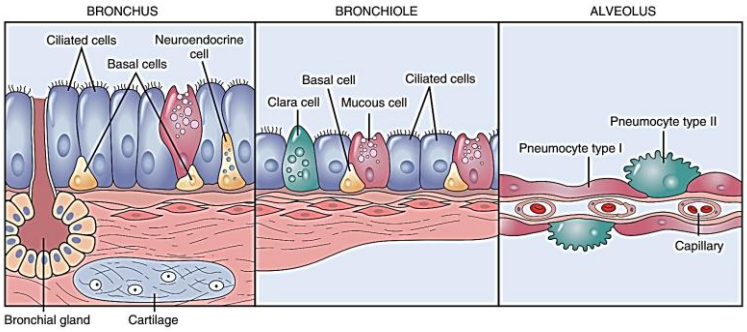
- Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli.
- Participates in **gas exchange**.
- Mostly **cuboidal cells** in respiratory bronchioles, then **simple squamous** cells up to alveoli.
- Cilia terminate in respiratory bronchioles.
- Alveolar macrophages clear debris and participate in immune response.

Conducting Zone	RESPIRATORY ZONE
❖ No gas exchange. ❖ Large airways: nose, pharynx, trachea, bronchi. ❖ Filters, warms, humidifies air.	❖ Gas exchange. ❖ Respiratory bronchioles, alveolar ducts, alveoli.



UW: In the respiratory tract, the nose, paranasal sinuses, nasopharynx, most of the larynx, and the tracheobronchial tree are lined with pseudostratified, columnar, mucus-secreting epithelium. Stratified squamous epithelium is found only in the oropharynx, laryngopharynx, and anterior epiglottis upper half of the posterior epiglottis, and vocal folds (true vocal cords).

UW: **Cilia** persist up to the end of the respiratory bronchioles **"last to disappear".**



MUCOUS

- Secretions produced by respiratory tract.
- Mostly glycoproteins and water.
- **Secreted by:**
  - **Goblet cells** in bronchi.
  - **Club cells** in bronchioles.
- Protects against particulates, infection. Beating **cilia** move mucous to epiglottis → swallowed.

CLEARANCE OF DUST PARTICLES:

- **Vary depending on the size of the particles:**
  - Particles **10-15 micro** in size are trapped in the upper respiratory tract.
  - Particles **2.5-10 micro** in size enter the trachea and bronchi and are cleared by mucociliary transport.
  - The finest particles (diameter **less than 2 micro**) reach the terminal bronchioli and alveoli and are **phagocytized by macrophages**:
    - Activate macrophages →
      - Produce cytokines → alveolar inflammation.
      - Growth factors → platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF) → stimulate fibroblasts to proliferate and produce collagen → fibrosis.
      - **Pneumoconiosis** (interstitial lung fibrosis secondary to inhalation of inorganic dust) arises by this mechanism.

ALVEOLI

❖ Small sacs for gas exchange surrounded by capillaries.

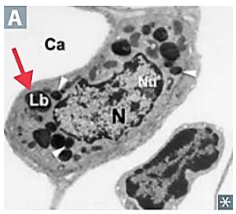
ALVEOLAR CELLS: PNEUMOCYTES

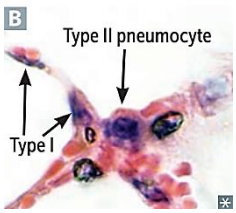
TYPE I PNEUMOCYTES

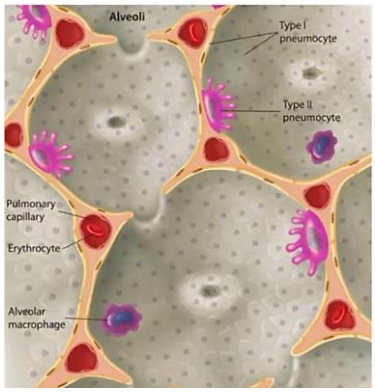
- 97% of alveolar surfaces. Line the alveoli.
- **Squamous**; **thin for optimal gas diffusion**.

TYPE II PNEUMOCYTES

- Contain foamy vesicles called **lamellar bodies** (arrow in A), which continuously produce pulmonary **surfactant:**
  - ↓ Alveolar surface tension → prevents alveolar collapse.
  - ↓ Lung recoil, and ↑ compliance.
- **Cuboidal** and **clustered** B.
- Can proliferate to other cells – key for **regeneration:**
  - Serve as precursors to type I cells and other type II cells.
  - Proliferate during lung damage.







CLARA CELLS = CLUB CELLS

- Nonciliated, low columnar/cuboidal with secretory granules.
- Located in **terminal bronchioles**.
- **Function:**
  - **Detoxify** inhaled substances (eg, Tobacco smoke) by a cytochrome P450 mechanism.
  - Secrete component of **surfactant**.
  - Act as **reserve** cells.

KULCHITSKY CELLS (ENTEROCHROMAFFIN CELLS)

- **Neuroendocrine** cells found throughout the **conducting zone** of the tracheobronchial tree.
- These cells secrete peptide **hormones** that regulate airway and vascular tone.
- They are important for the USMLE because they are the cells of origin for **small cell carcinoma** of the lung.

SURFACTANT

- During exhalation → alveoli shrink → could collapse → atelectasis → ↓ efficiency gas exchange.
- Surfactant allows alveoli to avoid collapse.
- Secreted by **type 2 pneumocytes**.
- Mix of lecithins especially dipalmitoylphosphatidylcholine.

LAPLACE LAW

- The **distending pressure** (the pressure required to keep a sphere distended) is directly proportional to the **surface tension** (T) and inversely proportional to the **radius** (r).
- P = 2T/r

FETAL LUNG MATURITY

- Lungs are "mature" when enough surfactant present. Occurs around 35 weeks.
- **Lecithin–sphingomyelin ratio (L/S ratio):**
  - Both produced equally until ~35 weeks.
  - Ratio > 2.0 in amniotic fluid suggests lungs mature.
  - Preterm delivery: betamethasone used to stimulate surfactant production in lungs.

NEONATAL RESPIRATORY DISTRESS SYNDROME

- Also called "hyaline membrane disease".
- Atelectasis.
- Severe hypoxemia/ ↑pCO2 (poor ventilation).
- Poorly responsive to O2 therapy.
  - Lungs collapsed (alveoli).
  - Intrapulmonary shunting.

Clinical Correlate

Corticosteroids induce the fetal synthesis of surfactant. High insulin levels in diabetic mothers antagonize the effects of corticosteroids.

Infants of diabetic mothers have a higher incidence of respiratory distress syndrome.

- **Risk factors for NRDS:**
  - Prematurity.
  - Maternal diabetes: high insulin levels decrease surfactant production.
  - Cesarean delivery: lack of vaginal compression stress leads to reduced fetal cortisol and reduction in surfactant.
- **Complications of NRDS:**
  - Patent ductus arteriosus (hypoxia keeps shunt open).
  - Complications of oxygen therapy → free radicals:
    1. Bronchopulmonary dysplasia.
    2. **Retinopathy of prematurity:**
       - Neovascularization in the retina.
       - Retinal detachment → blindness.

LUNG ANATOMY

❖ **Right lung:**

- Has 3 lobes; **L**eft has **L**ess **L**obes (2) and **L**ingula (homolog of right middle lobe).

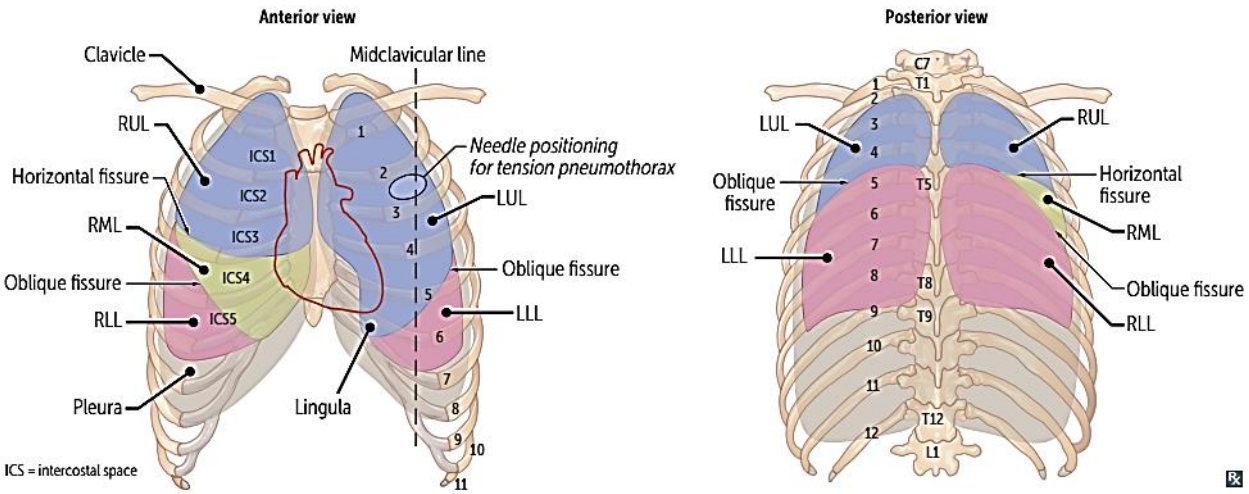
❖ **Left lung:**

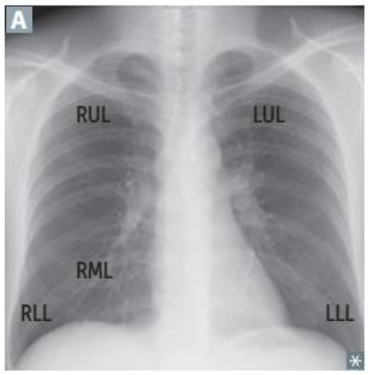
- Instead of a middle lobe, left lung has a space occupied by the heart A.

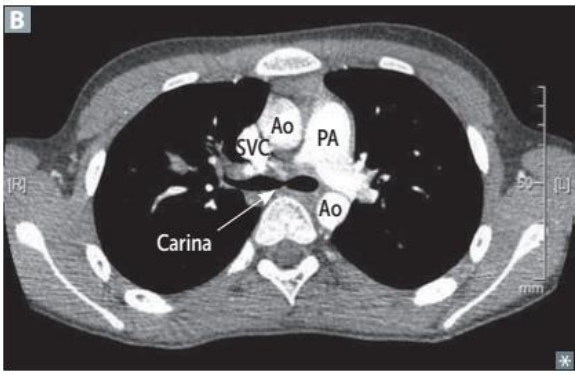
❖ **Bronchi:**

- Relation of the pulmonary artery to the bronchus at each lung hilum is described by:
  - **RALS**—**R**ight **A**nterior; **L**eft **S**uperior.

❖ **Carina** is posterior to ascending aorta and anteromedial to descending aorta.



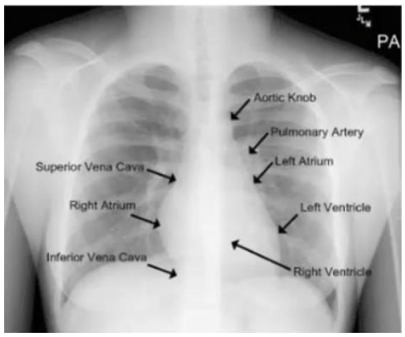




LUNG ASPIRATION

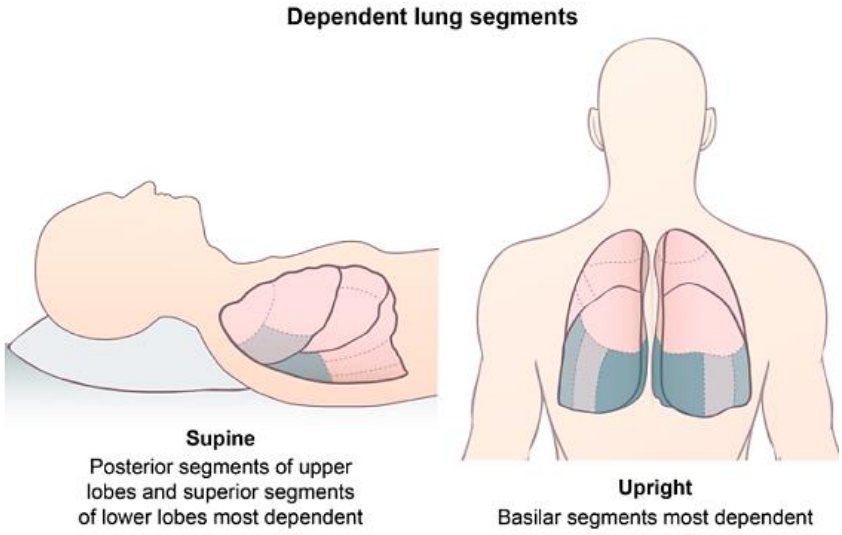
❖ ***Right lung*** is a more common site for inhaled foreign bodies:

- Because right main stem bronchus is wider, more vertical, and shorter than the left.
- "Swallow a bite, goes down the right".



❖ **Common sites for aspiration:**

- While **supine**: to the right lung:
  - Posterior segments of upper lobes.
  - Superior segments of lower lobes.
- While **upright**: usually enters right lower lobe.
- While **lying on right side:** usually enters right upper lobe.



PLEURA:

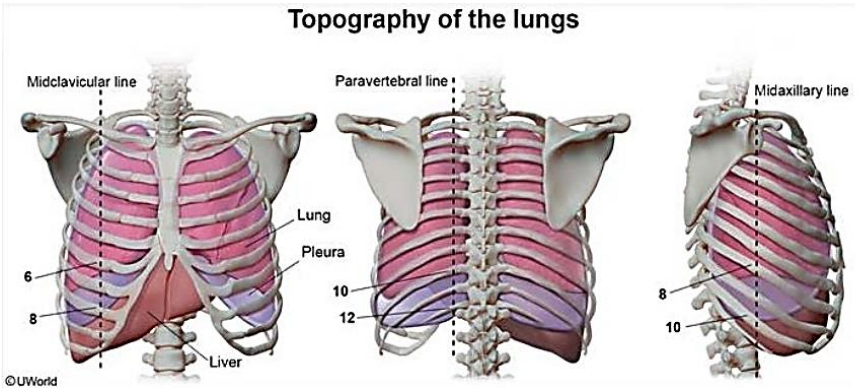
❖ **The pleura are divided into segments as follows:**

- **Visceral pleura:**
  - Covers all surfaces of the lungs.
  - Does not carry pain fibers.
- **Parietal pleura**:
  - Outer boundary of the pleural space.
  - **Subdivided as follows:**
    1. **Costal pleura:** Covers the thoracic wall, including the ribs, sternum, intercostal spaces, costal cartilages and sides of the thoracic vertebrae.
    2. **Mediastinal pleura:** Covers the mediastinum.
    3. **Diaphragmatic pleura:** Covers the surface of the diaphragm located within the thoracic cavity.
    4. **Cervical pleura:** Extends with the apices of the lung into the neck.
  - Pain arising from the **mediastinal or diaphragmatic pleura** will be carried by the **phrenic nerve** and referred to the C3-C5 distribution.

	Visceral Pleura	Parietal Pleura
Midclavicular line	6th rib	8th rib
Midaxillary line	8th rib	10th rib
Paravertebral line	10th rib	12th rib

UW: **Thoracocentesis:**

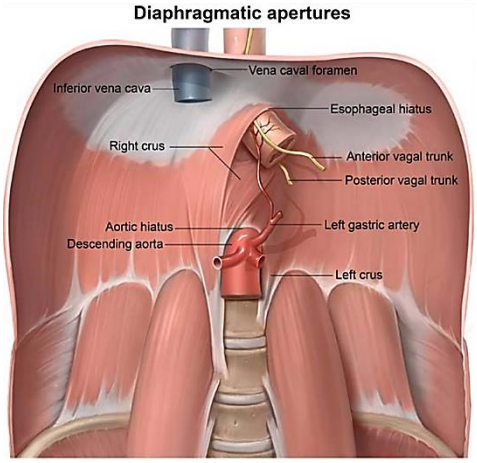
- Performed above the 7th rib in **midclavicular** line, the 8th rib along **midaxillary** line and the 11th rib along **posterior scapular line**.
- Insertion of a needle **lower** than these points increases the risk of penetrating abdominal structures.
- Insertion of the needle on the **inferior margin** of the rib risks striking the subcostal neurovascular bundle.



UW: In patients with **neck injuries**, it is important to remember that the **lung apices** and cervical pleura extend above the clavicle and first rib through the superior thoracic aperture into the neck. **Stab wounds immediately above the clavicle** and lateral to the manubrium can puncture the pleura and cause pneumothorax, tension **pneumothorax**, or **hemothorax**.

DIAPHRAGM

- **Openings:**
  - **At T8:** IVC, right phrenic nerve.
  - **At T10:** esophagus, vagus (CN **10**; 2 trunks).
  - **At T12:** aorta (red), thoracic duct (white), azygos vein (blue) ("At **T-1-2** it's the **red**, **white**, and **blue**").
  - Number of letters = T level:
    T8: vena cava
    T10: "oesophagus"
    T12: aortic hiatus



  - **I** (IVC) **ate** (8) **ten** (10) **eggs** (esophagus) **at** (aorta) **twelve** (12).
- **Innervation:**
  - By C3, C4, C5 (Phrenic nerve).
  - **Diaphragm irritation**→ "referred" shoulder pain.
    1. Classic example is gallbladder disease.
    2. Also lower lung masses.
    3. Irritation can cause dyspnea and hiccups.
  - **Cut nerve**→ diaphragm **elevation**, dyspnea.
    1. "Paradoxical movement" → Moves up with inspiration.
    2. Can see on fluoroscopy ("sniff test").

The common carotid bi**four**cates at C**4**.
The trachea bi**four**cates at T**4**.
The abdominal aorta bi**four**cates at L**4**.

- **Formation of the diaphragm:**
  - It is formed from fusion of the following structures:
    1. Septum transversum.
    2. Paired pleuroperitoneal membranes.
    3. Dorsal mesentery of the esophagus.
    4. Body wall.

- Improper formation of the **pleuroperitoneal membrane** or its failure to fuse with the other three parts of the diaphragm can lead to a **congenital diaphragmatic hernia** (CDH), a condition with serious complications.
    1. Abdominal contents are forced into the pleural cavity.
    2. Lung hypoplasia results from compression by abdominal viscera.
    3. Hernias appear most often on the left side (posterolateral).
    4. Diaphragmatic hernia is associated with polyhydramnios.
    5. Diaphragmatic hernia presents at birth as a flattened abdomen, cyanosis, and inability to breathe.

MUSCLES OF QUIET RESPIRATION:

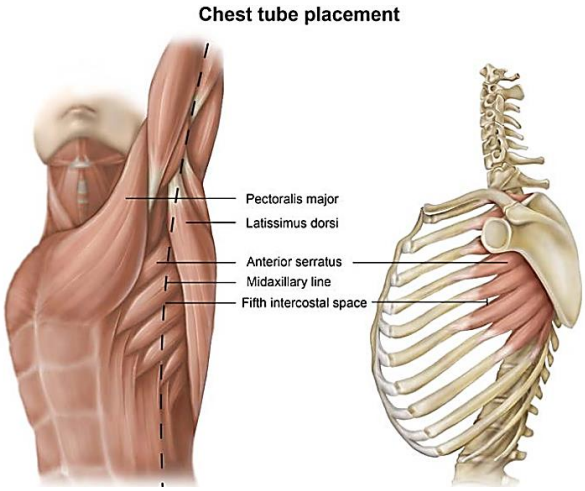
- Diaphragm → inspiration.
- Exhalation is passive with normal ("quiet") breathing.

EXERCISE BREATHING

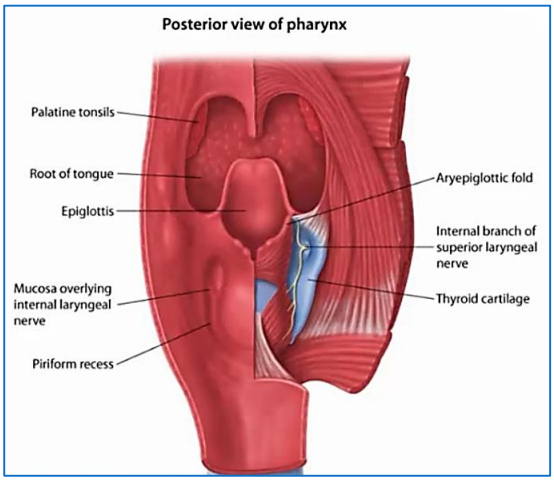
- Inspiration (neck muscles):
    1. Scalenes – raise ribs.
    2. Sternocleidomastoids – raise sternum.
- Exhalation (abdomen):
    1. Rectus muscle, internal/external obliques, transverse abdominis, internal intercostals.
- Use of accessory muscles in **respiratory distress**.

UW: **Chest tube insertion:**

- Placed into the **4th or 5th intercostal space** in the anterior axillary or **midaxillary** line.
- Traverses through the skin, subcutaneous fat, **serratus anterior muscle**, intercostal muscles, and parietal pleura.

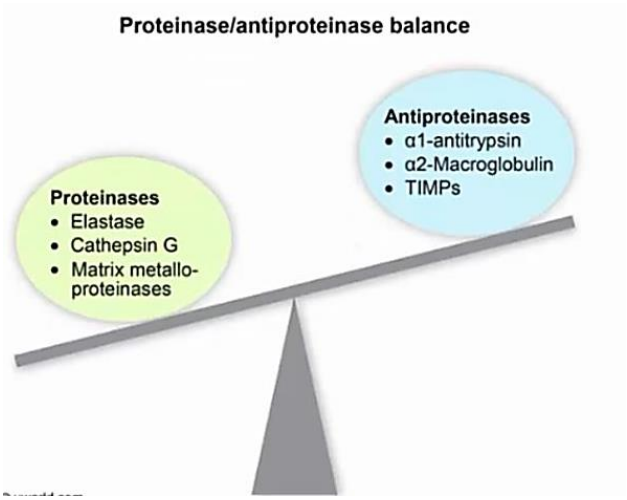


UW: Piriform recesses:



- Small cavities that lie on either side of the laryngeal orifice.
- **Boundaries:**
  - Medially → aryepiglottic folds.
  - Laterally → thyroid cartilage and thyrohyoid membrane.
- During normal swallowing, food is diverted by the epiglottis laterally through the piriform recesses into the esophagus without endangering the airway.
- A thin layer of mucosa overlying the piriform recess is all that protects the superficially coursing **internal laryngeal nerve**, a branch of the superior laryngeal nerve (CN X).
- The internal laryngeal nerve mediates the afferent limb of the **cough reflex** above the vocal cords.
- Foreign bodies (eg, chicken or fish bones) can become lodged in the piriform recess and may cause damage to the nerve, impairing the cough reflex.

UW: Proteinase/antiproteinase balance:



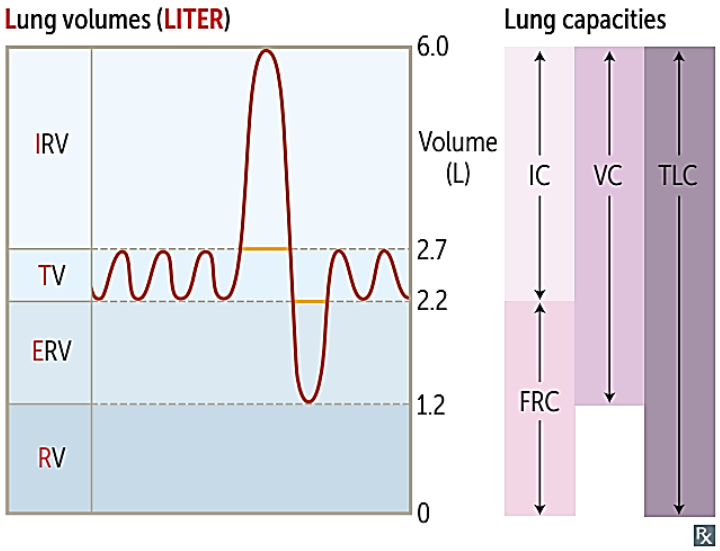
Elastase:

- Found in alveolar macrophages and neutrophils.
- Neutrophil elastase is inhibited by serum α-antitrypsin.
- Macrophage elastase is inhibited by tissue inhibitors of metalloproteinases (TIMPs).
- These proteinases can cause destruction of terminal lung parenchyma (eg, **emphysema**) when secreted in excess or if left unchecked by deficient antiprotease activity.

PULMONARY PHYSIOLOGY

LUNG VOLUMES

- **Tidal volume:**
  - In/out air with each quiet breath.
  - Typically 500 mL.
- **Expiratory reserve volume:**
  - Extra air pushed out with force beyond TV.
  - RV remains in lungs.
- **Inspiratory reserve volume:**
  - Extra air can be drawn in with force beyond TV.
  - Air that can still be breathed in after normal inspiration.
- **Residual volume:**
  - Air that can't be blown out no matter how hard you try.
  - RV and any lung capacity that includes RV cannot be measured by spirometry.
  - Increased in chronic obstructive pulmonary disease (COPD).



LUNG CAPACITIES

- Capacity = sum of two or more volumes.
- **Total lung capacity:**
  - Volume of gas present in lungs after a maximal inspiration. Sum of all volumes.
  - RV + ERV+ IRV + TV.

- **Inspiratory capacity:**
  - Air that can be inspired after normal exhalation.
  - Most air you can inspire.
  - TV + IRV.
- **Vital capacity:**
  - Maximum volume of gas that can be expired after a maximal inspiration.
  - Most you can exhale.
  - TV + IRV + ERV.
- **Functional Residual Capacity:**
  - Residual volume after quiet expiration.
  - RV + ERV.
  - Volume when system is relaxed.
  - Chest wall pulling out = lungs pulling in.

VENTILATION

- **Alveolar ventilation** = useful for gas exchange.
  - Volume of gas that reaches alveoli each minute.
  - Total ventilation minus "dead space ventilation".
  - $V_A = (V_T - V_D) \times RR$
  - Imagine 500cc in per minute:
    1. 150cc fills dead space.
    2. Only 350cc available for gas exchange.
- **Dead space ventilation (V_D)** = wasted ventilation.
  - Space filled with air but no gas exchange.
  - **Anatomic dead space:**
    1. Volume of conducting portions respiratory tract.
    2. Nose, trachea.
  - **Physiologic dead space:**
    1. Anatomic PLUS volume of alveoli that don't exchange gas.
    2. Insufficient perfusion.
    3. **Apex** is largest contributor.
    4. Physiologic dead space increases in many diseases.
    5. Physiologic dead space approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with V/Q defects.

- **Measuring physiologic dead space:**
  - **T**aco, **Pa**co, **Pe**co, **Pa**co (refers to order of variables in equation).

$$V_D = V_T \times \frac{PaCO_2 - PECO_2}{PaCO_2}$$

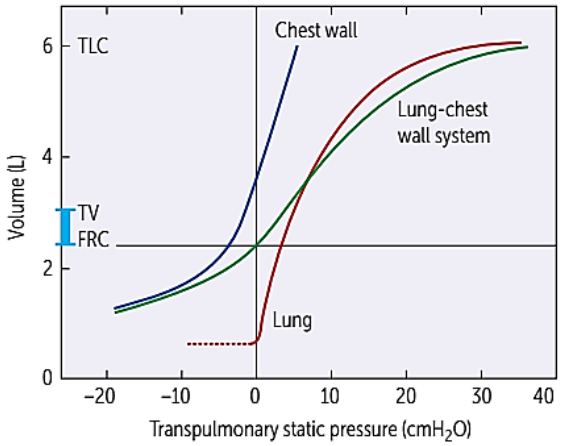
V_T = tidal volume.
$PaCO_2$ = arterial PCO_2.
$PECO_2$ = expired air PCO_2.

- **Total ventilation** = minute ventilation
  - Total volume of gas entering lungs per minute.
  - $V_E = V_T \times RR$
  - Volume in slightly > volume out due to O2 uptake.

Normal values:
Respiratory rate (RR) = 12–20 breaths/min
V_T = 500 mL/breath
V_D = 150 mL/breath

LUNG AND CHEST WALL

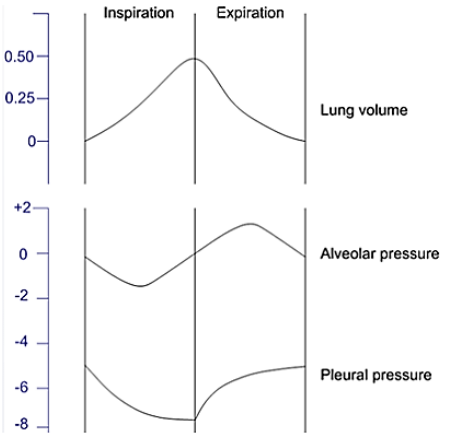
- **Elastic recoil:**
  - Tendency for lungs to collapse inward and chest wall to spring outward.



  - **At FRC:**
    1. Inward pull of lung is balanced by outward pull of chest wall. (Lung in = chest out).
    2. System pressure (airway and alveolar pressures) is atmospheric = zero.
    3. Intrapleural pressure is negative (prevents atelectasis).
    4. Pulmonary vascular resistance (PVR) is at a minimum.

ALVEOLI AND PLEURAL PRESSURES

- Quiet (tidal) breathing.
- **At the FRC**, the intrapleural pressure is negative with a value of -5 cm H2O.
- When puncture of the pleura allows intrapleural communication with the atmosphere (pressure: 0 cm H2O), the negative intrapleural pressure equilibrates with the atmospheric pressure via entry of air into the intrapleural space; thus, a **pneumothorax** will develop as the lung collapses inward and the chest wall springs outward.



TRANSPULMONARY PRESSURE

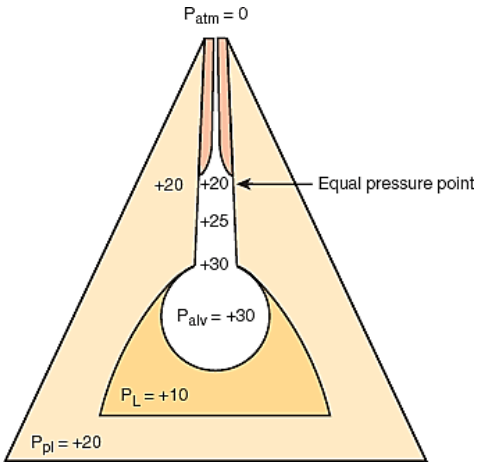
- Alveolar Pressure – Intrapleural Pressure.
- (+) Pressure: Holds airway open.
  (-) Pressure: Airway collapse.

FORCED EXHALATION

- **Pleural pressure becomes positive** → compresses airway.
- Pressure on alveoli→ positive pressure in airway.
- Pushes air out→ air flows from airways.

EQUAL PRESSURE POINT

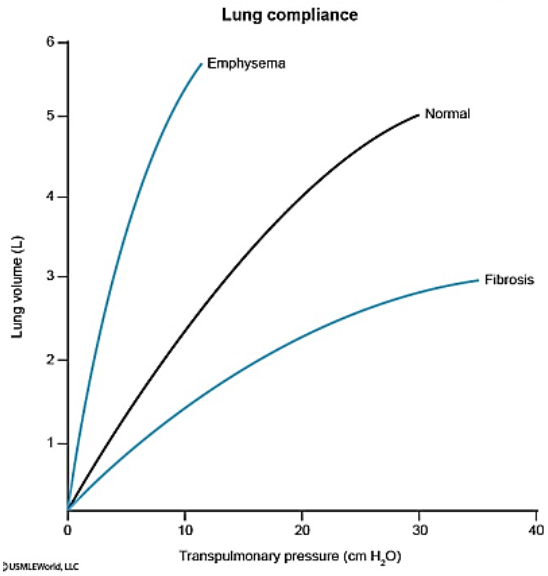
- **Pleural pressure = airway pressure**.
- **Prevents airway collapse**. Beyond this point airway collapses.
- In healthy lungs: EPP occurs in **cartilaginous** airways. Can be reached in thin-walled bronchioles.
- **Disease:** EPP moves toward alveoli.
  - Obstruction (bronchitis): more pressure drop.
  - Emphysema: loss of elastic recoil.
  - Result: Collapse, obstruction to airflow, air trapping.



LUNG COMPLIANCE

- Lung's ability to **stretch** during inhalation.
- Change in lung volume for a change in pressure (ΔV/ΔP).
- **Inversely** proportional to wall **stiffness**.

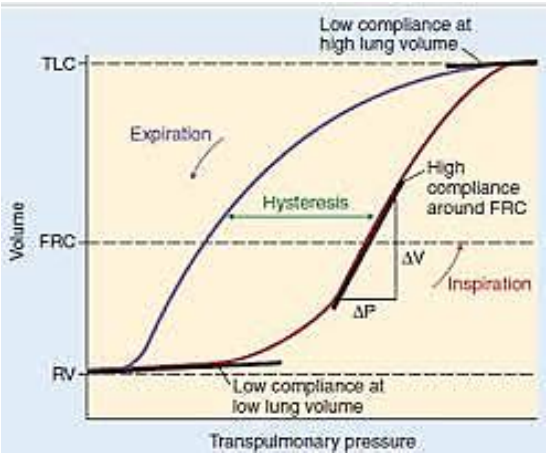
High compliance lung	Low compliance lung
▪ Lung easier to fill. ▪ Small amount diaphragm effort to distend the lung → generates small pressure change across lungs. ▪ Large volume change. ▪ Emphysema, normal aging. ▪ ***Surfactant increases compliance.***	▪ Lung harder to fill. ▪ Large amount diaphragm effort not sufficient to distend the lung → big pressure change across lung. ▪ Small volume change (lungs stiff). ▪ Pulmonary fibrosis, pneumonia, NRDS, pulmonary edema (CHF). UW: Increased hydrostatic pressure in the pulmonary circulation causes transudation of fluid from the pulmonary capillaries into the lung interstitium. The presence of fluid in the pulmonary interstitium decreases lung compliance.



1. **At functional residual capacity (FRC),** the lungs have a tendency to collapse.
2. This force is exactly balanced by the chest wall, which has a tendency to expand.
3. Because these forces are in balance at FRC, the airway pressure is 0 mm Hg. Lung volumes above FRC create a positive airway pressure, whereas volumes below FRC create a negative airway pressure.

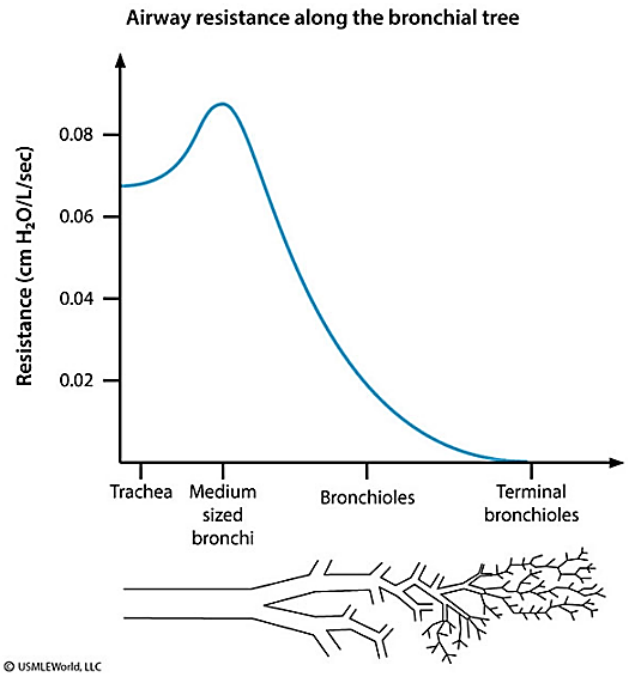
HYSTERESIS:

- Lung inflation curve follows a different curve than the lung deflation curve due to need to overcome surface tension forces in inflation.



RESISTANCE TO AIR FLOW

- **Upper respiratory tracts**:
  - "Nose, mouth, pharynx, larynx".
  - Accounts for about 50% of resistance.
- **Lower respiratory tracts:**
  - Begins at the trachea and consists of about 23 generations of airways.
  - Highest resistance in medium bronchi "2-5 generations" "segmental bronchi" due to turbulent flow.
  - Lowest resistance in terminal bronchioles - slows laminar flow.



RESPIRATORY SYSTEM CHANGES IN THE ELDERLY

- ↑ Lung compliance (loss of elastic recoil).
- ↓ Chest wall compliance (↑ chest wall stiffness).
- ↑ RV.
- ↓ FVC and FEV1.
- Normal TLC.
- ↑ ventilation/perfusion mismatch.
- ↑ A-a gradient.
- ↓ Respiratory muscle strength.

HEMOGLOBIN

- **Globin chains:**
  - 4 Polypeptides chains in 2 pairs.
  - Globin Protein Types "Alpha (α), Beta (β), Gamma (γ), Delta (δ)."
- **Heme:**
  - Non-peptide molecule with iron (Fe) in the middle.
  - Ring around Fe called a **porphyrin**.
  - Oxygen binds **iron**.

HEMOGLOBIN TYPES

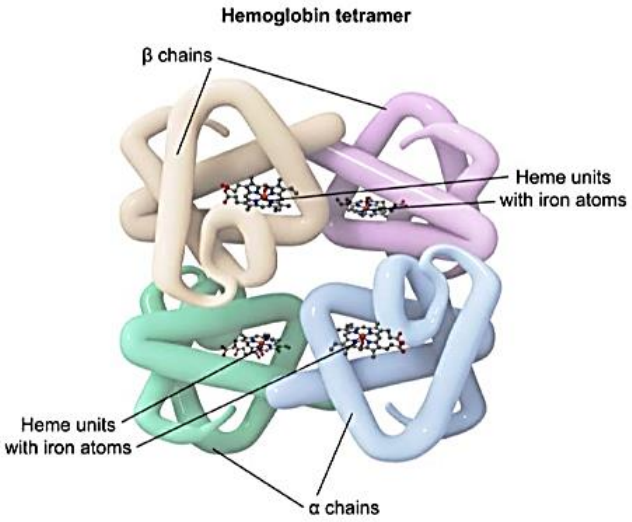
- **Hemoglobin A:**
  - Adult type. Most common type found (95%).
  - α2 β2.
- **Hemoglobin A2:**
  - Adult type. Less common type (2-3%).
  - α2 δ2.
- **Hemoglobin F:**
  - Fetal type.
  - α2 γ2.
  - Higher O2 affinity than HbA. Due to ↓ affinity of HbF for 2,3-BPG.
  - Helps transport oxygen from maternal circulation.

GLOBIN CHAIN DISEASES:

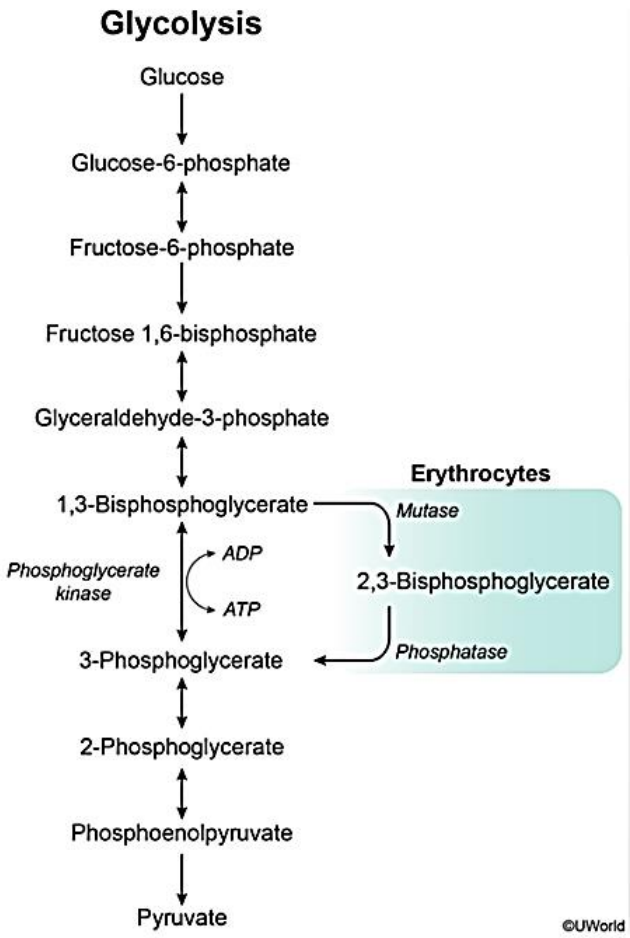
- α-thalassemia → Underproduction alpha chain.
- β-thalassemia minor/major → Underproduction beta chain.
- Sickle Cell Anemia → HbS production.

2,3-BISPHOSPHOGLYCERATE (2,3 BPG)

- Found in RBCs.
- Promotes O2 **release** from hemoglobin.
- Increasing levels:
  - **Decrease oxygen affinity** of hemoglobin.
  - Increase delivery oxygen to tissues.
- More BPG at <u>high altitude.</u>



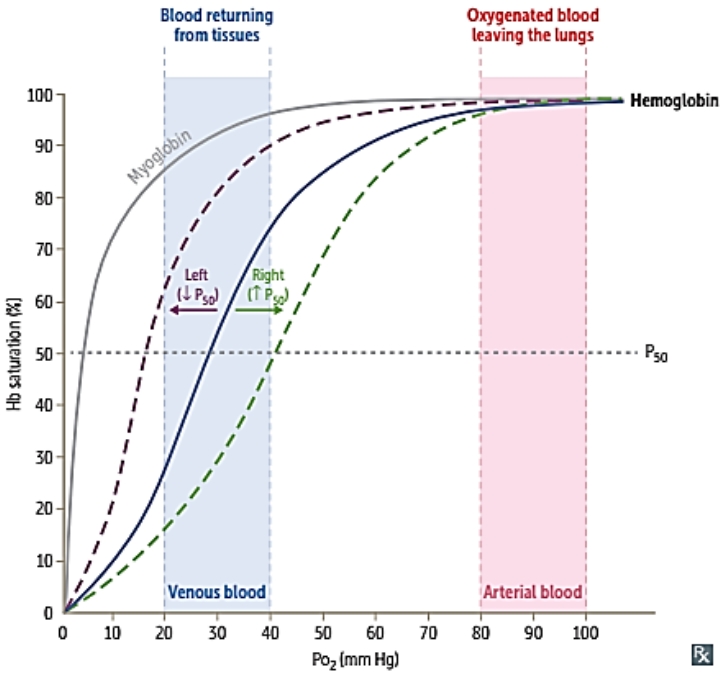
Hemoglobin		
Type	**Name**	**Components**
Embryonic	Gower 1	ζ2ε2
	Portland	ζ2γ2
	Gower 2	α2ε2
Fetal	F*	α2γ2
Adult	A	α2β2
	A2*	α2δ2
α-thalassemia intermedia	H	β4
α-thalassemia major	Barts	γ4



HEMOGLOBIN FORMS

Taut form (T)	Relaxed form (R)
• **Deoxygenated**. • Low O2 affinity. • Tends to release O2. • Favored form in **tissues**. • ↑ Cl-, H+, CO2, 2,3-BPG, and temperature favor deoxygenated form over oxygenated form (shifts dissociation curve right → ↑ O2 unloading).	• **Oxygenated**. • High O2 affinity. • Holds on to O2. • Favored form in **lungs**.

DISSOCIATION CURVES



Left shift (↓ O_2 unloading to tissue) Left = Lower	Right shift (↑ O_2 unloading to tissues) Right shift – ACE Bats right handed
↓ H^+ (↑ pH, base) ↓ Pco_2 ↓ 2,3–BPG ↓ Temperature	↑ H^+ (↓ pH, Acid) ↑ Pco_2 Exercise ↑ 2,3–BPG High Altitude ↑ Temperature

COOPERATIVITY:

- Hb exhibits **positive cooperativity** and **negative allostery**.
- Four heme groups "tetrameric" do not undergo simultaneous oxygenation.
- First O2 molecule that binds INCREASES affinity of hemoglobin for 2nd molecule.
- Makes curve **S shaped "sigmoid"**.
- Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

ALLOSTERIC EFFECTS:

- Allosteric proteins **change affinity** for binding when influenced by other (smaller) molecules. Usually multi-subunit proteins.
- Hemoglobin is an allosteric structure.
- Cooperativity is a positive allosteric effect.
- **Hb Allosteric Effectors:** • PH, • Temperature, • 2,3 BPG, • CO2.

HEMOGLOBIN AS A BUFFER FOR H+

- **Hemoglobin acts as buffer for H+ ions. Why???**
  - Haemoglobin can accept H+ as it has **histidine**, which is a basic amino acid. Moreover, deoxygenated haemoglobin has higher tendency to accept H+ (it's a better base as compared to oxygenated haemoglobin).
  - At the level of tissues, where CO2 is more, haemoglobin accepts H+. This is due to the fact that most of the CO2 is present as H2CO3 (bicarbonate) in the body, and H2CO3 remains in an ionized state as H+ and bicarbonate ion. Thus haemoglobin accepts H+ **(Haldane effect).**
  - At the level of the lungs, where O2 is more haemoglobin releases H+ and combines with O2 (oxyhaemoglobin is a stronger acid). The released H+ can combine with bicarbonate ion to form H2CO3 again which can break down into H2O and CO2 (catalyzed by carbonic anhydrase enzyme). This CO2 formed is removed by lungs.

HEMOGLOBIN MODIFICATIONS

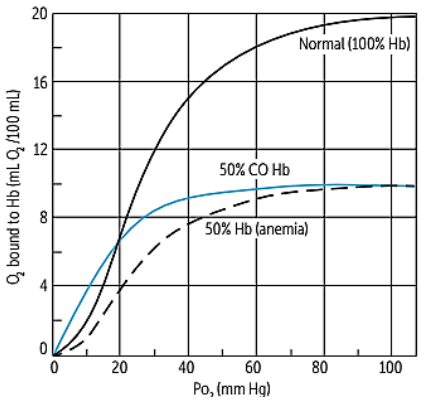
- Lead to tissue hypoxia from ↓ **O2 saturation** and ↓ **O2 content**.

METHEMOGLOBIN

- Iron in Hb is normally in a reduced state (ferro**us**, Fe^{2+}; "just the **2** of **us**"). Fe^{2+} binds O_2.
- Oxidized form of Hb (ferric, Fe^{3+}), does not bind O_2 as readily as Fe^{2+}, but has ↑ affinity for cyanide.
- Methemoglobinemia may present with **cyanosis** and **chocolate-colored blood**.
- **Meth**emoglobinemia can be treated with **meth**ylene blue and vitamin C.
- **Nitrites** (eg, from dietary intake or polluted/high altitude water sources) and **benzocaine** cause poisoning by oxidizing Fe^{2+} to Fe^{3+}.

CARBOXYHEMOGLOBIN

- Form of Hb bound to **CO** in place of O_2.
- Causes ↓ **oxygen-binding capacity** with left shift in oxygen-hemoglobin dissociation curve.
- ↑ O_2 unloading in tissues.
- CO binds competitively to Hb and with 200× greater affinity than O_2.
- CO poisoning can present with **headaches**, dizziness, and **cherry red skin**.
- May be caused by fires, car exhaust, or gas heaters.
- Treat with 100% O_2 and hyperbaric O_2.

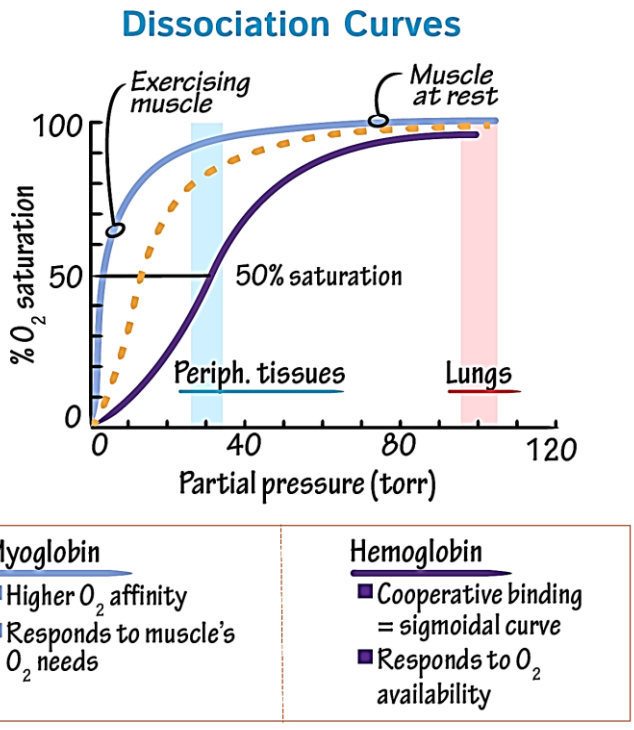


CYANIDE POISONING

- Usually due to **inhalation injury** (eg, fires).
- Inhibits aerobic metabolism via complex IV inhibition → hypoxia unresponsive to supplemental O2 and ↑ anaerobic metabolism.
- **Findings:**
  - **Almond breathe odor**, pink skin, and cyanosis.
  - Rapidly fatal if untreated.
- **Treat with induced methemoglobinemia:**
  - First give **nitrites** (oxidize hemoglobin to methemoglobin, which can trap cyanide as cyanmethemoglobin).
  - Then **thiosulfates** (convert cyanide to thiocyanate, which is renally excreted).

MYOGLOBIN

- Composed of a single polypeptide chain associated with one heme moiety.
- **Higher affinity** for oxygen than Hb.



Fetal Hemoglobin
Greater O_2 affinity: facilitates O_2 transfer from mother to fetus.

OXYGEN CONTENT OF BLOOD

- **O_2 content = (1.34 × Hb × Sa_{O2}) + (0.003 × Pa_{O2})**
  - Hb = hemoglobin level, SaO_2 = arterial O_2 saturation, PaO_2 = partial pressure of O_2 in arterial blood.
  - Normally 1 g Hb can bind 1.34 mL O_2; normal Hb amount in blood is 15 g/dL.
  - O_2 binding capacity ≈ 20.1 mL O2/dL of blood.
- With ↓ Hb there is ↓ O_2 content of arterial blood, but no change in O_2 saturation and Pa_{O2}.
- **O_2 delivery to tissues = cardiac output × O_2 content of blood.**

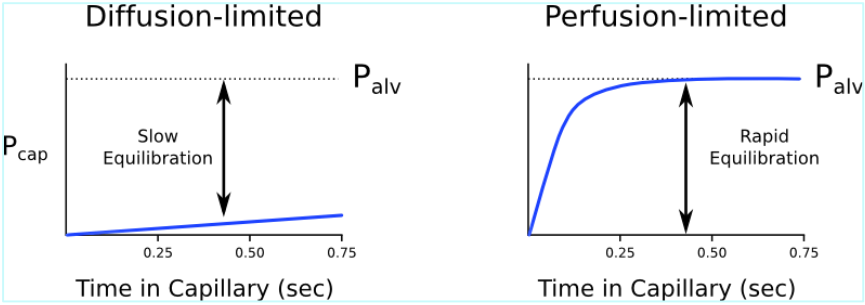
	PaO_2	SaO_2	Oxygen content
CO poisoning	Normal	Decreased*	↓
Cyanide poisoning	Normal	Normal	Normal
Anemia (↓ Hgb)	Normal	Normal	↓
Polycythemia (↑ Hgb)	Normal	Normal	↑
High altitude	↓	↓	↓

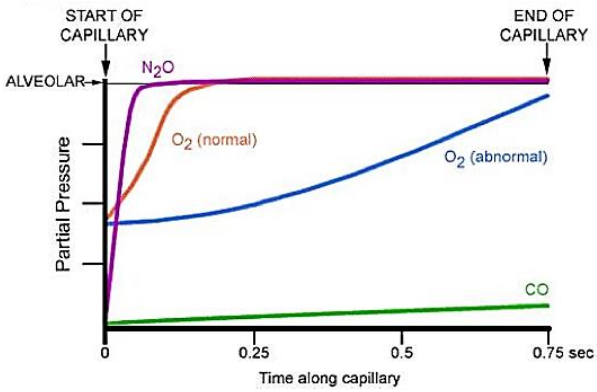
*Detected as normal using standard probes.

CO = carbon monoxide; **Hgb** = hemoglobin; **PaO_2** = arterial oxygen tension; **SaO_2** = arterial oxygen saturation.

PULMONARY CIRCULATION

- Normally a **low-resistance**, **high-compliance** system.
- **P_{O2} and P_{CO2} exert opposite effects on pulmonary and systemic circulation:**
  - A ↓ in PaO_2 causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.
- **Perfusion limited:**
  - O_2 (normal health), CO_2, N_2O.
  - Gas equilibrates early along the length of the capillary.
  - Diffusion can be ↑ only if blood flow ↑.
- **Diffusion limited:**
  - O_2 (emphysema, fibrosis, exercise), CO.
  - Gas does not equilibrate by the time blood reaches the end of the capillary.



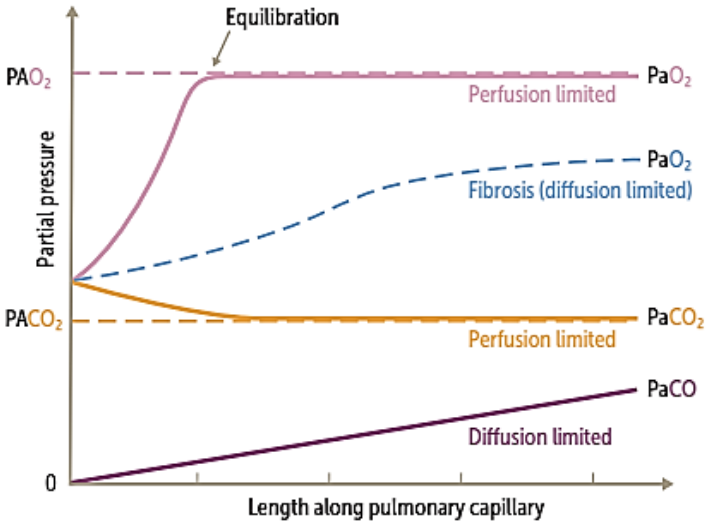


Diffusion: $\dot{V}_{gas} = A \times D_k \times \frac{P_1 - P_2}{T}$ where

A = area, T = alveolar wall thickness, D_k = diffusion coefficient of gas, $P_1 - P_2$ = difference in partial pressures.

- A ↓ in emphysema.
- T ↑ in pulmonary fibrosis.

D_{LCO} is the extent to which CO, a surrogate for O_2, passes from air sacs of lungs into blood.



Pa = partial pressure of gas in pulmonary capillary blood
PA = partial pressure of gas in alveolar air

- A consequence of pulmonary hypertension is **cor pulmonale** and subsequent right ventricular failure.

PULMONARY VASCULAR RESISTANCE

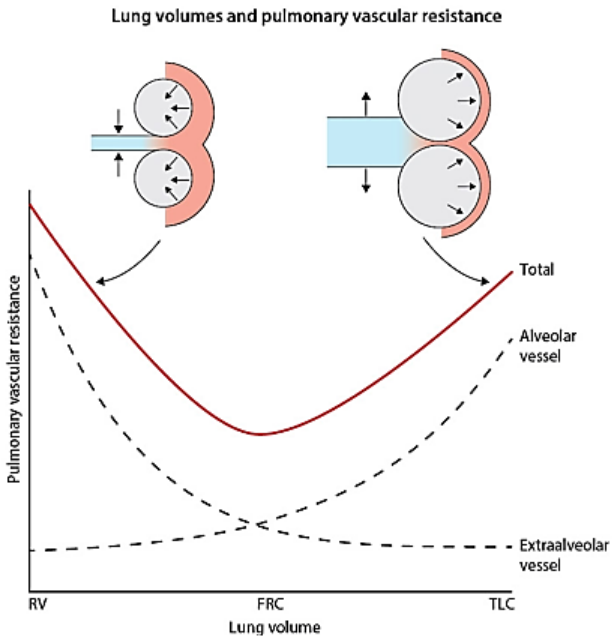
$$PVR = \frac{P_{pulm\ artery} - P_{L\ atrium}}{cardiac\ output}$$

$P_{pulm\ artery}$ = pressure in pulmonary artery
$P_{L\ atrium}$ ≈ pulmonary capillary wedge pressure
Q = cardiac output (flow)
R = resistance
η = viscosity of blood
l = vessel length
r = vessel radius

Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$

$R = 8\eta l / \pi r^4$

- **UW: Pulmonary vascular resistance (PVR) is lowest at the functional residual capacity.**
  1. **Increased lung volumes** increase PVR due to the longitudinal stretching of **alveolar capillaries** by the expanding alveoli.
  2. **Decreased lung volumes** also increase PVR due to decreased radial traction from adjacent tissues on the **large extra-alveolar vessels**.



- UW: In order to provide continuous blood flow to the body**, the blood flow per minute (mL/min) in the pulmonary circulation must be identical to the blood flow in the systemic circulation.**
- This is true for conditions of both exercise and rest.
- If the flow of blood through the pulmonary circulation were slower than the flow of blood in the systemic circulation, the left ventricle would soon empty completely.
- Alternatively, if the flow of blood were faster in the pulmonary circulation than in the systemic circulation, the left ventricle would soon be overloaded.
- Because the circulatory system is a continuous circuit, the volume output of the left ventricle must equal the output of the right ventricle at all times.

ALVEOLAR GAS EQUATION

$$P_{A}O_2 = PIO_2 - \frac{PaCO_2}{R}$$

$$\approx 150 \text{ mm Hg}^a - \frac{PaCO_2}{0.8}$$

[a]At sea level breathing room air

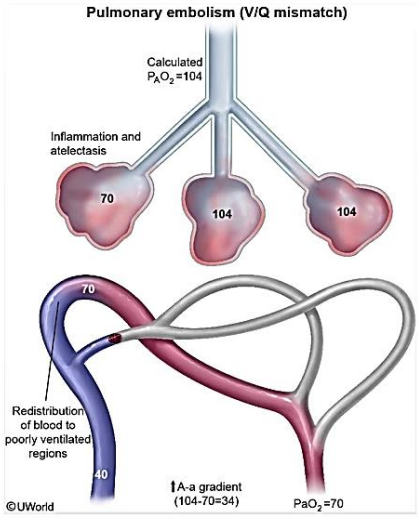
$P_{A}O_2$ = alveolar P_{O_2} (mm Hg)
PIO_2 = P_{O_2} in inspired air (mm Hg)
$PaCO_2$ = arterial P_{CO_2} (mm Hg)
R = respiratory quotient = CO_2 produced/O_2 consumed
A-a gradient = $P_{A}O_2 - PaO_2$. Normal range = 10–15 mm Hg
↑ A-a gradient may occur in hypoxemia; causes include shunting, V̇/Q̇ mismatch, fibrosis (impairs diffusion)

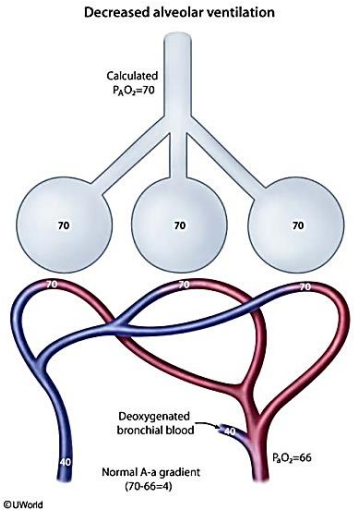
OXYGEN DEPRIVATION

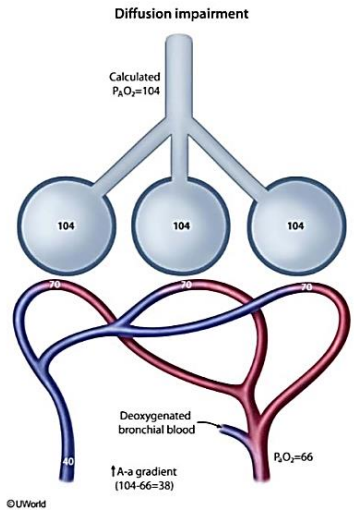
Hypoxia (↓ O2 delivery to tissue)	Hypoxemia (↓ PaO2 < 80)	Ischemia (loss of blood flow)
• ↓ Cardiac output • Hypoxemia • Anemia • CO poisoning	**Normal A-a gradient** (10-15 mm Hg): 1. High altitude 2. Hypoventilation: a. Central: as opioid use. b. Peripheral: as myasthenia gravis, obesity. **↑ A-a gradient:** 1. V/Q mismatch. 2. Diffusion limitation (eg, fibrosis, emphysema). 3. Right-to-left shunt (eg, cyanotic heart disease).	• Impeded **arterial** flow. • ↓ **Venous** drainage.

Etiologies of hypoxemia	
Normal alveolar to arterial gradient	**Elevated alveolar to arterial gradient**

• **Hypoventilation**
  ○ Obesity hypoventilation syndrome, neuromuscular disorders
• **Low inspired fraction of oxygen**
  ○ High altitude
	• **Right-to-left shunt**
	  ○ Cardiac septal defects, pulmonary edema
	• **Ventilation/perfusion mismatch**
	  ○ Pulmonary embolism, chronic obstructive lung disease
	• **Impaired diffusion**
	  ○ Interstitial lung disease

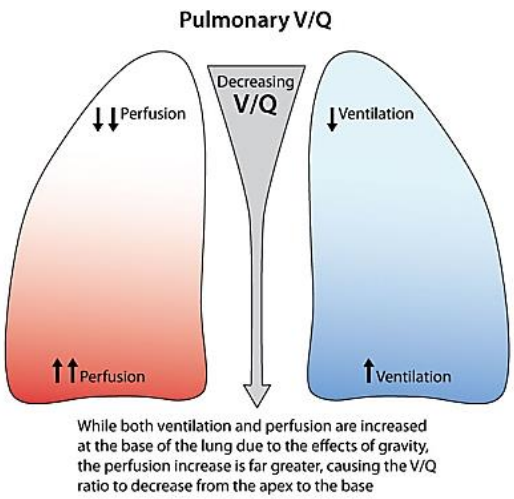




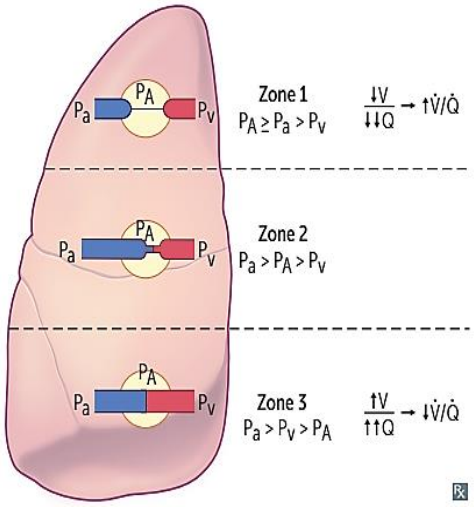


VENTILATION/PERFUSION MISMATCH

- Ideally, ventilation is matched to perfusion (i.e., V/Q = 1) for adequate gas exchange.
- **Lung zones:**
  - V/Q at **apex** of lung = 3 (wasted ventilation).
  - V/Q at **base** of lung = 0.6 (wasted perfusion).
- Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.



- **With exercise** (↑ cardiac output), there is vasodilation of apical capillaries → **V/Q ratio approaches 1**.
- Certain organisms that thrive in high O_2 (eg, TB) flourish in the apex.
- **V/Q = 0 = "oirway" obstruction (shunt).**
  - In shunt, 100% O_2 does not improve Pao_2 (eg, foreign body aspiration).
- **V/Q = ∞ = blood flow obstruction (physiologic dead space).**
  - Assuming < 100% dead space, 100% O_2 improves Pao_2 (eg, pulmonary embolus).



During exercise, pulmonary vascular resistance decreases as a result of dilation of the lung arterioles by metabolic products. The **V/Q ratio becomes uniform** over the entire lung.

Zone 1 (apex): $P_A > P_a > P_V$

- The **arterial pressure** is low in this region as the heart must pump blood "uphill" against the force of gravity.
- Because arterial pressure is lower than alveolar pressure, the pulmonary capillaries are collapsed and there is no blood flow (i.e., zone 1 represents **alveolar dead space**).
- These regions can form when there is low pulmonary arterial pressure (eg hemorrhage) or high alveolar pressure (eg. positive-pressure ventilation).

Zone 2: $P_a > P_A > P_V$

- Because alveolar pressure is greater than venous pressure, the pulmonary capillaries are initially obstructed near the
  venous end of the capillary bed.
- However, as arterial pressure rises during systole, capillary pressure becomes high enough to overcome alveolar pressure. For this reason, blood flows through zone 2 in a **pulsatile fashion**.

Zone 3: $P_a > P_V > P_A$

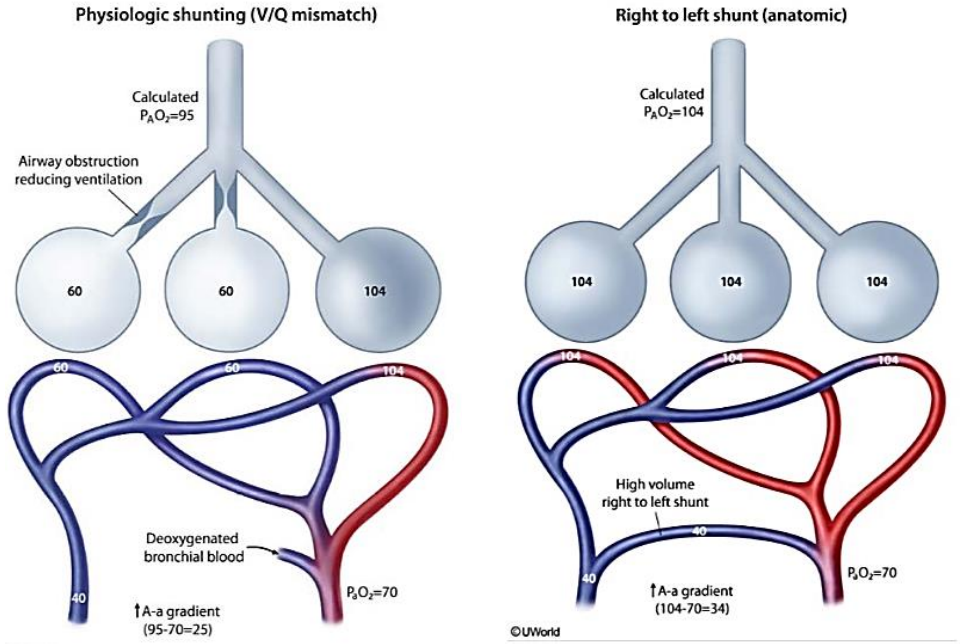
- Arterial and venous pressures are both greater than alveolar pressure, and therefore blood flows continuously through the pulmonary capillaries.

When a person lies supine, the differences in lung perfusion are negated as gravity then affects the lung equally from apex to base.

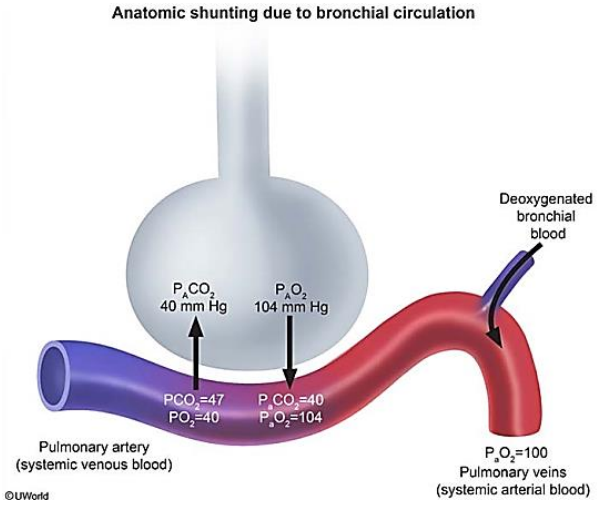
What is the difference between an anatomic shunt and a physiologic shunt?

Most **anatomic shunts** occur within the heart when deoxygenated blood from the right side of the heart crosses the septum and mixes with oxygenated blood from the left side of the heart. This mixture results in varying degrees of hypoxemia that **cannot be improved with the administration of 100% O_2.**

In a **physiologic shunt**, deoxygenated blood bypasses the gas-exchanging unit. Atelectasis can occur in many lung diseases including pneumonia. In atelectasis, ventilatory obstruction to the gas-exchanging unit leads to a subsequent loss of volume and a **V/ Q ratio of 0**.



UW: ANATOMIC SHUNTING DUE TO BRONCHIAL CIRCULATION

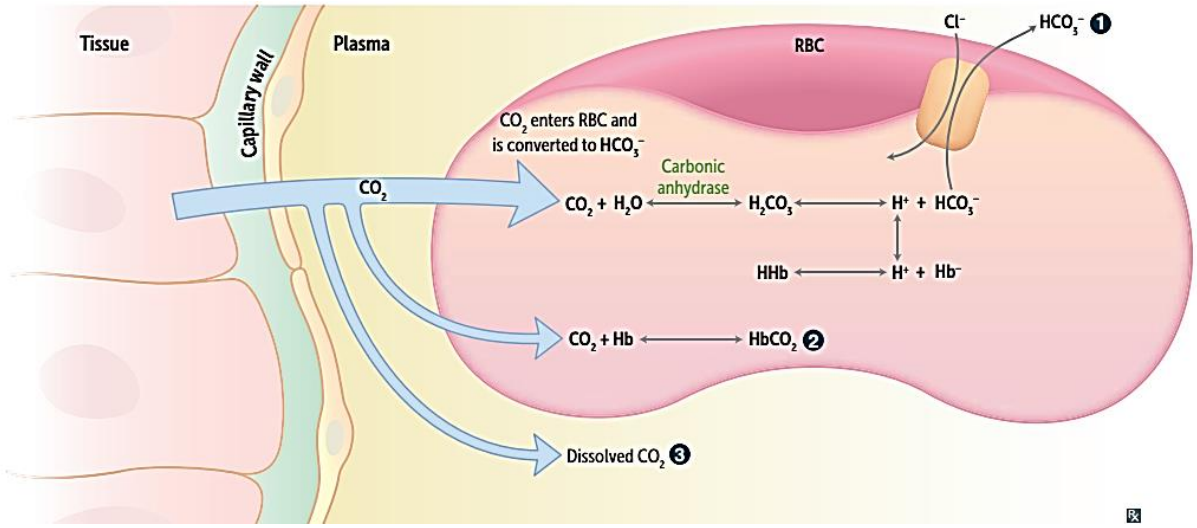


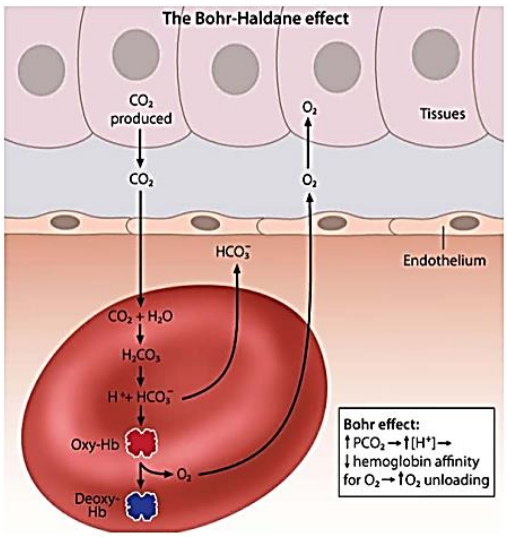
- **PAO2** normally is 104 mm Hg.
- Incoming systemic venous blood typically has PaO2 of 40 mm Hg.
- Blood PO2 normally reaches the PAO2 by the time it passes through the first third of the alveolar capillaries due to a high rate of O2 **diffusion** through the respiratory membrane.
- When this oxygenated blood then enters the left atrium its PO2 drops to 100 mm Hg due to the addition of deoxygenated bronchial blood that drains directly into the pulmonary veins (bypassing the right side of the heart).
- As a result, the partial pressure of oxygen in arterial blood (PaO2) is normally around 100 mm Hg.

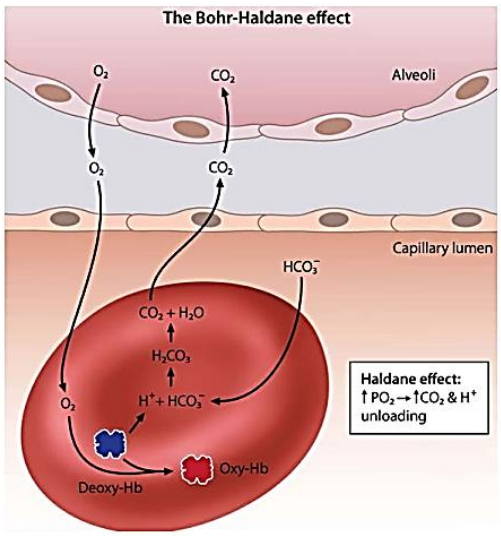
- UW: Normal **tracheal** PO2 is 150 mm Hg and normal **alveolar** PO2 is 104 mm Hg, which lies between the tracheal (150 mm Hg) and **venous** blood (40 mm Hg) PO2 concentrations.
    - In cases where perfusion is poor (**pulmonary embolus**), equilibrium will occur slowly or may not occur at all.
    - The result is complete failure of atmospheric and venous blood gas equilibration.
    - In this situation, the **tracheal air and the alveolar air would have approximately the same composition.**

CARBON DIOXIDE TRANSPORT

- **CO2 is transported from tissues to lungs in 3 forms:**
    1. **HCO3 -** (70%). Majority of blood CO2 is carried as HCO3- in the plasma.
    2. **Carbaminohemoglobin** or HbCO2 (21–25%).
        a. CO2 bound to Hb at N-terminus of globin (not heme).
        b. CO2 favors deoxygenated form (O2 unloaded).
    3. **Dissolved CO2** (5–9%).
- In lungs, oxygenation of Hb promotes dissociation of H+ from Hb.
- This shifts equilibrium toward CO2 formation; therefore, CO2 is released from RBCs **(Haldane effect)**.
- In peripheral tissue, ↑ H+ from tissue metabolism shifts curve to right, unloading O2 **(Bohr Effect)**.







- UW: Many of the bicarbonate ions diffuse out of the RBC into the plasma to maintain the electrical neutrality chloride ions diffuse into the RBC to take their place.
  This process is called **"chloride shift."** and it is the principal cause **of high RBC chloride content in venous blood.**

RESPONSE TO HIGH ALTITUDE

- ↓ Atmospheric oxygen (PO_2) → ↓ Pao_2 → ↑ ventilation → ↓ $PaCO_2$ → respiratory alkalosis → altitude sickness.
- Chronic ↑ in ventilation.
- **↑ Erythropoietin** → ↑ Hct and Hb (due to chronic hypoxia).
- ↑ 2,3-BPG (binds to Hb causing right shift so that Hb releases more O_2).
- Cellular changes (↑ mitochondria).
- ↑ Renal excretion of HCO^{3-} to compensate for respiratory alkalosis (can augment with acetazolamide).
- Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

RESPONSE TO EXERCISE

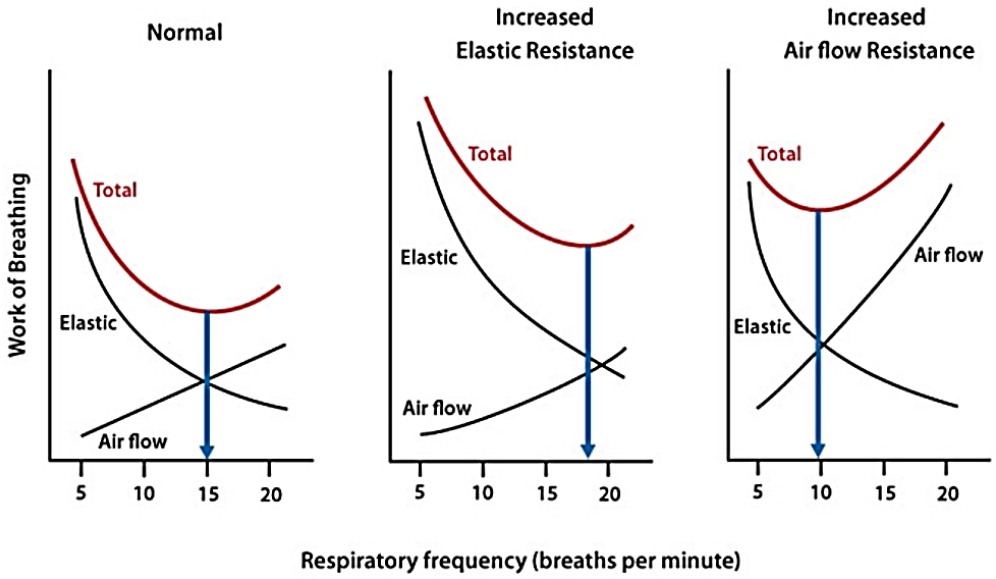
- ↑ CO_2 production.
- ↑ O_2 consumption.
- ↑ Ventilation rate to meet O_2 demand.
- V/Q ratio from apex to base becomes more uniform.
- ↑ Pulmonary blood flow due to ↑ cardiac output.
- ↓ PH during strenuous exercise (2° to lactic acidosis).
- No change in Pao_2 and $Paco_2$, but ↑ in venous CO_2 content and ↓ in venous O_2 content.

RESPONSE TO VAGAL STIMULATION

- Bronchoconstriction and increased bronchial mucus secretion.
- These effects **increase airway resistance** and the **work of breathing**.
- Anticholinergic agents such as tiotropium and ipratropium work to counteract these effects.

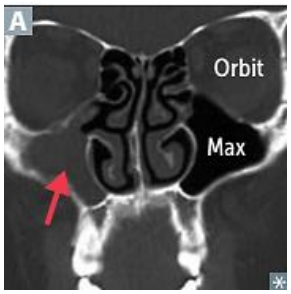
WORK OF BREATHING

- The work is done against:
  1) **Elastic resistance of the lung:**
     - Increased when the **tidal volume** is increased.
     - **For patients with stiff lungs** (increased elastic resistance):
       - The work of breathing is minimized when the respiratory rate is high and the tidal volume is low.
       - Therefore, **rapid and shallow breaths** are favored in diseases that increase elastic resistance (e.g., pulmonary fibrosis, pulmonary edema, acute respiratory distress syndrome).
  2) **Airflow resistance:**
     - Increased when the **breathing frequency** is increased.
     - **For patients with high airflow resistance** (e.g., asthma, COPD):
       - Patients breathe at a lower rate **(slow, deep breaths)** in order to minimize the work of breathing.
- If the two components are summated and the total work is plotted against respiratory frequency there will be an **optimal breathing rate** at which the total work of breathing is minimized.
  1) For the normal adult, this rate is on average 15 breaths per minute.



PATHOLOGY

RHINOSINUSITIS



- **Etiology:**
  - **Adenovirus** is the most common cause.
  - May lead to superimposed **bacterial** infection, most commonly *S pneumoniae, H influenzae, M catarrhalis.*
- **Presentation:**
  - Presents with sneezing, congestion, and runny nose (**common cold**).
  - Obstruction of sinus drainage into nasal cavity → inflammation and **pain over affected area**.
- **Site:**
  - Typically affects **maxillary sinuses**, which drain against gravity due to ostia located superomedially (red arrow points to fluid-filled right maxillary sinus in **A**).
- **Complications:**
  - Infections in **sphenoid** or **ethmoid** sinuses may extend to cavernous sinus and cause complications (eg, **cavernous sinus syndrome**).

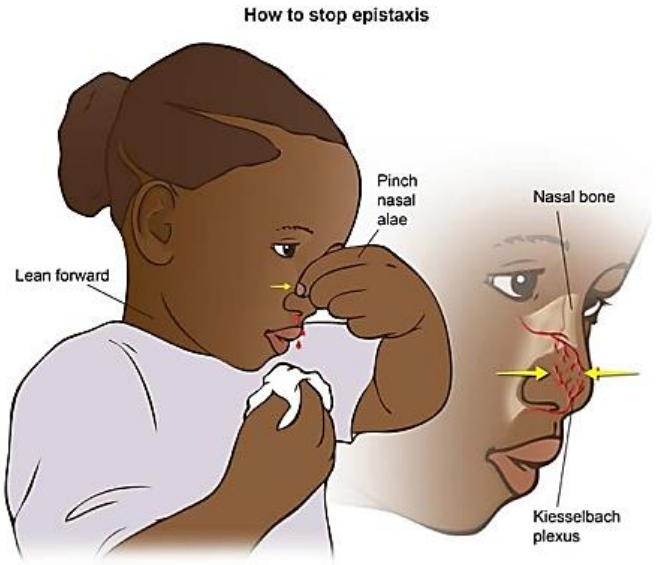
NASAL POLYP

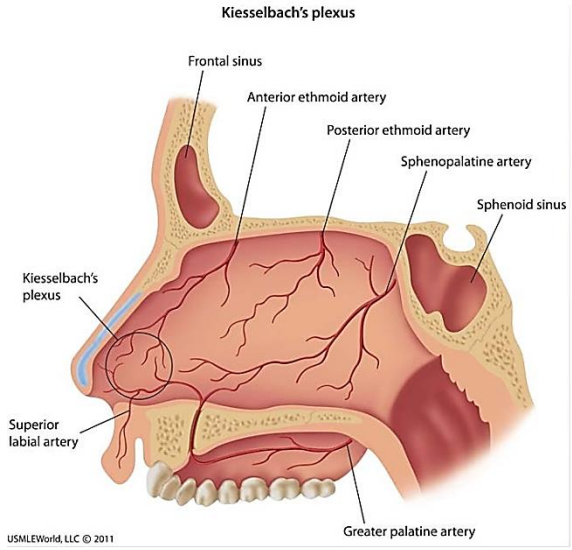
- Protrusion of edematous, inflamed nasal mucosa.
- Usually secondary to **repeated bouts of rhinitis**.
- Also occurs in **cystic fibrosis** and **aspirin-intolerant asthma**:
  - **Aspirin-intolerant asthma** is characterized by the triad of asthma, aspirin induced bronchospasms, and nasal polyps; seen in 10% of asthmatic adults.

EPISTAXIS

- Nose bleed.
- **Types:**
  1. **Anterior nosebleeds:**
     - **Kiesselbach's plexus:**
       - **Kiesselbach** drives his **Lexus** with his **LEGS**: superior **L**abial artery, anterior and posterior **E**thmoidal arteries, **G**reater palatine artery, **S**phenopalatine artery.
     - Common in children/adolescents (most common overall).
     - Most commonly caused by trauma (nose picking).
  2. **Posterior nosebleeds:**
     - **Woodruff's plexus** (sphenopalatine artery, branch of maxillary artery).
     - Life threatening.
     - Common in older adults with **hypertension**, not caused by trauma.
  3. **Other causes:**
     - **Nasopharyngeal angiofibroma** (recurrent obstructions or nosebleeds without history
       of trauma or blood dyscrasia, common in adolescent males).
     - Leukemia, blood dyscrasias (e.g. vWD, Hemophilia, Osler-Weber-Rendu Syndrome), cocaine/intranasal drug use, any cause of thrombocytopenia (e.g. ITP).

- **Treatment:**
  1. Have patient lean forward so that blood passed through nares instead of down pharynx.
  2. **Treat anterior epistaxis with:**
     - Compression, topical vasoconstriction (Phenylephrine), nasal packing, chemical/electrocautery, arterial ligation or embolization.
  3. **Treat posterior epistaxis with:**
     - Blood pressure reduction, posterior nasal packing, arterial ligation or embolization.





HEAD AND NECK CANCER

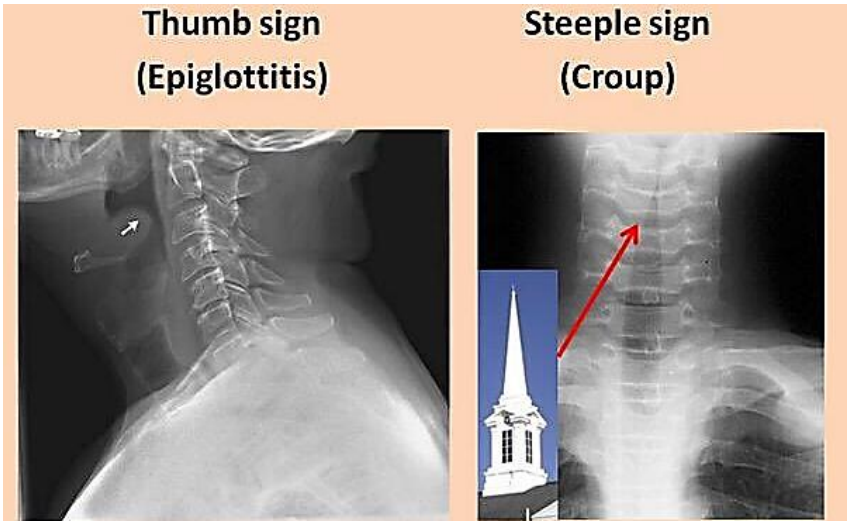
- Mostly **squamous cell carcinoma**.
- Risk factors include tobacco, alcohol, **HPV-16** (oropharyngeal), **EBV** (nasopharyngeal).
- **Field cancerization:** carcinogen damages wide mucosal area → multiple tumors that develop independently after exposure.

NASOPHARYNGEAL CARCINOMA

- Associated with EBV; classically seen in **African children** and **Chinese** adults.
- Biopsy usually reveals pleomorphic **keratin-positive epithelial cells** (poorly differentiated squamous cell carcinoma) in a **background of lymphocytes**.
- Often presents with involvement of **cervical lymph nodes**.

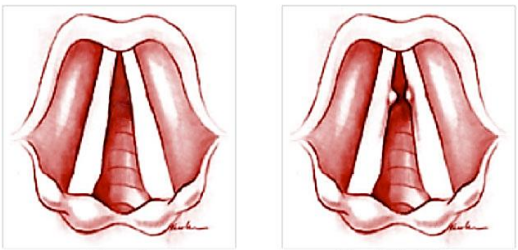
Major upper body lymph node groups	
Location	**Lymphatic drainage**
Posterior cervical	Scalp & neck, skin of arms & pectorals, thorax, cervical & axillary nodes
Postauricular	External auditory meatus, pinna, scalp
Preauricular	Eyelids & conjunctivae, temporal region, pinna
Right supraclavicular node	Mediastinum, lungs, esophagus
Left supraclavicular node	Thorax, abdomen via thoracic duct

ACUTE EPIGLOTTITIS	LARYNGOTRACHEOBRONCHITIS (CROUP)
• ***H influenzae* type b** (especially in non-immunized children)	• ***parainfluenza virus***
• Muffled voice, sore throat. • **Drooling with dysphagia**, and inspiratory **stridor.** • Risk of airway obstruction (medical emergency).	• Hoarse, **"barking" cough** and inspiratory **stridor**.
• Lateral X-ray → "**thumb print sign**".	• AP X-ray → "**steeple sign**" • Lateral X-ray → subglottic narrowing.



VOCAL CORD NODULE (SINGER'S NODULE)

- Nodule that arises on the **true vocal cord**.
- Due to excessive use of vocal cords; usually **bilateral**.
- Composed of **degenerative (myxoid) connective tissue**.
- Presents with hoarseness; resolves with resting of voice.

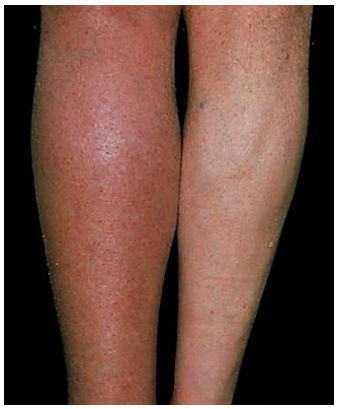

Normal

Vocal Nodules

LARYNGEAL PAPILLOMA

- Benign papillary tumor of the vocal cord.
- Due to **HPV 6** and **11**.
- Usually **single** in adults and **multiple** in children.
- Presents with hoarseness.

DEEP VENOUS THROMBOSIS

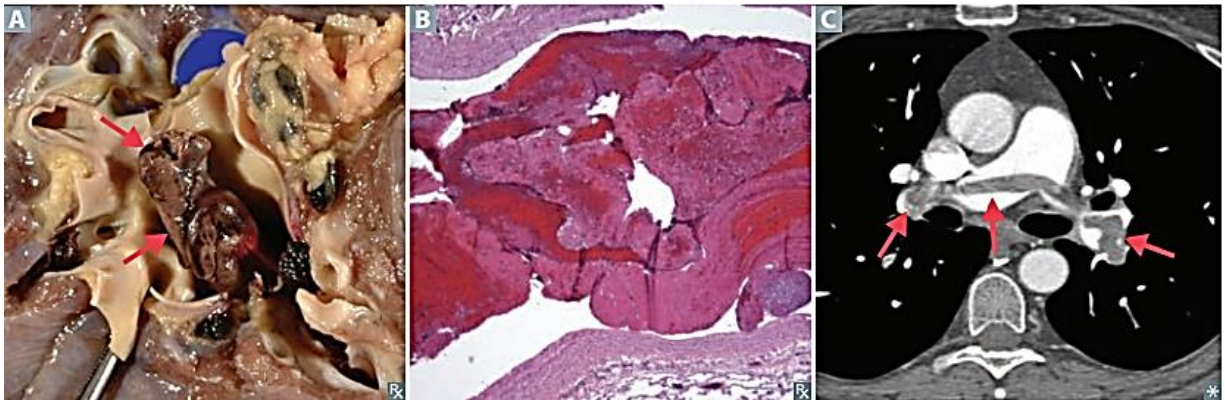


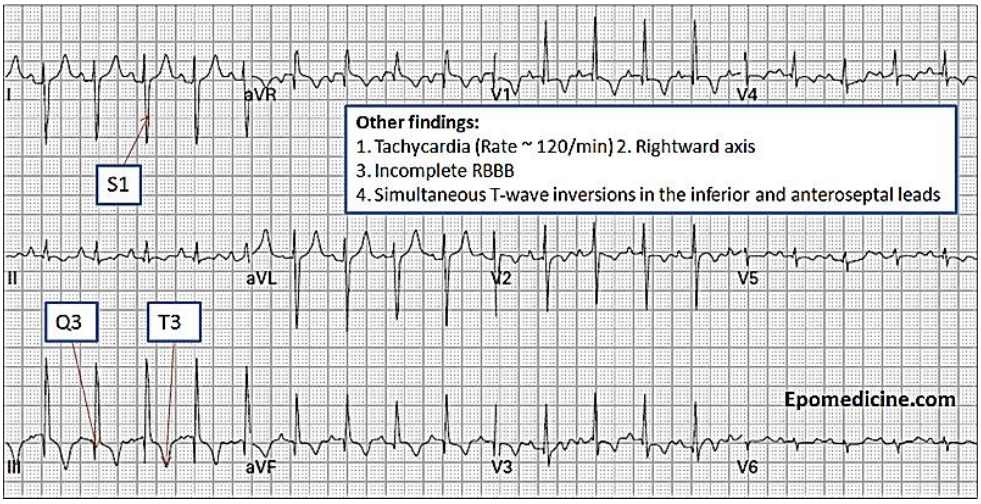
- Blood clot within a deep vein → swelling, redness, warmth, pain.
- Predisposed by Virchow triad (**SHE**):
    1. **S**tasis (eg, post-op, long drive/flight).
    2. **H**ypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden; oral contraceptive use).
    3. **E**ndothelial damage (exposed collagen triggers clotting cascade).
- Most pulmonary emboli arise from proximal deep veins of lower extremity.
- **Diagnosis:**
    1. **D-dimer** lab test used clinically to rule out DVT (high sensitivity, low specificity).
    2. Imaging test of choice is compression ultrasound with **Doppler**.
- **Management:**
    1. Use unfractionated **heparin** or low-molecularweight heparins (eg, enoxaparin) for prophylaxis and acute management.
    2. Use oral **anticoagulants** (eg, warfarin, rivaroxaban) for treatment (long-term prevention).

PULMONARY EMBOLI

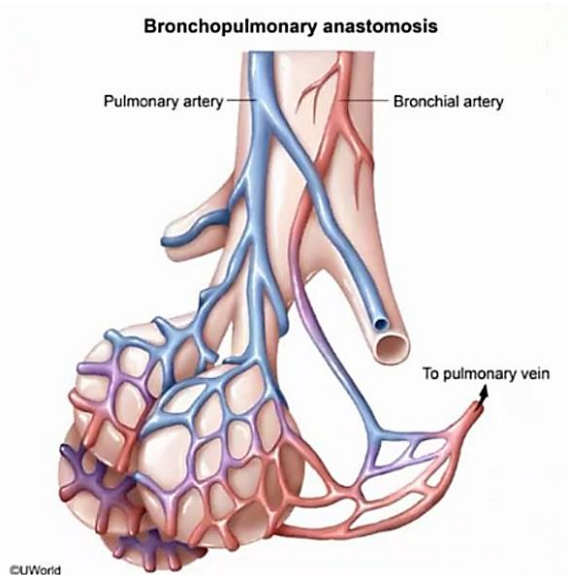
- V/Q mismatch, hypoxemia, respiratory alkalosis.
- Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia.
- Large emboli or saddle embolus A may cause sudden death due to electromechanical dissociation.
- **Lines of Zahn** are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi B.
- Types: **F**at, **A**ir, **T**hrombus, **B**acteria, **A**mniotic fluid, **T**umor.
    - An embolus moves like a **FAT BAT.**

- **Fat emboli:**
  - Associated with long bone fractures and liposuction.
  - **Classic triad** of hypoxemia, neurologic abnormalities, upper body petechial rash.
  - Fat globules stain black with osmium tetroxide.
- **Air emboli**:
  - **Nitrogen bubbles** precipitate in ascending divers (caisson disease/ decompression sickness). Treat with hyperbaric O_2,
  - Can be **iatrogenic** 2° to invasive procedures (eg, central line placement).
- **Amniotic fluid emboli:**
  - Can lead to **DIC**, especially postpartum.
- **Diagnosis:**
  - CT pulmonary angiography is imaging test of choice for PE (look for filling defects) C.
  - May have S1Q3T3 abnormality on ECG.





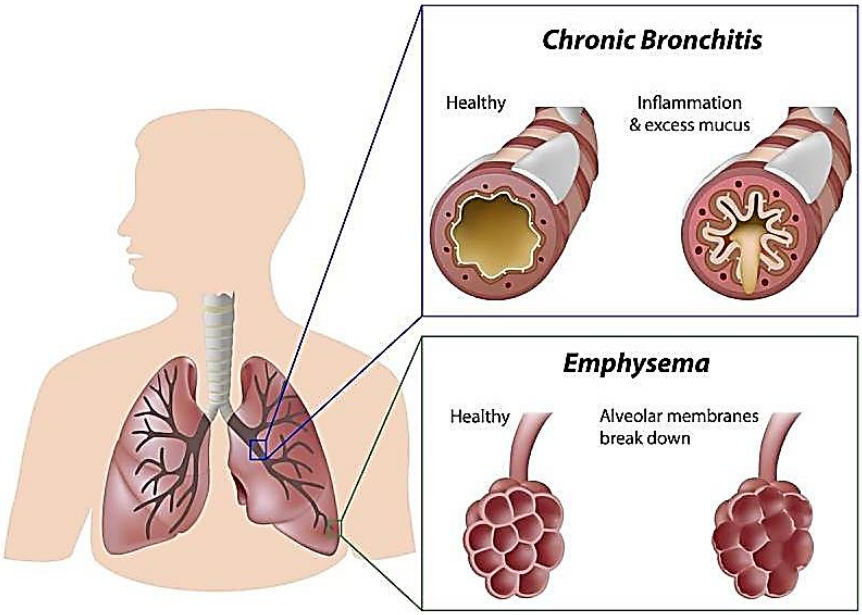
UW: The lung is supplied by **dual circulation** from the pulmonary and bronchial systems (**collateral circulation**). As a result, lung **infarction only rarely develops** as a complication of pulmonary embolism.



CHRONIC OBSTRUCTIVE PULMONARY DISEASE

BASIC PRINCIPLES

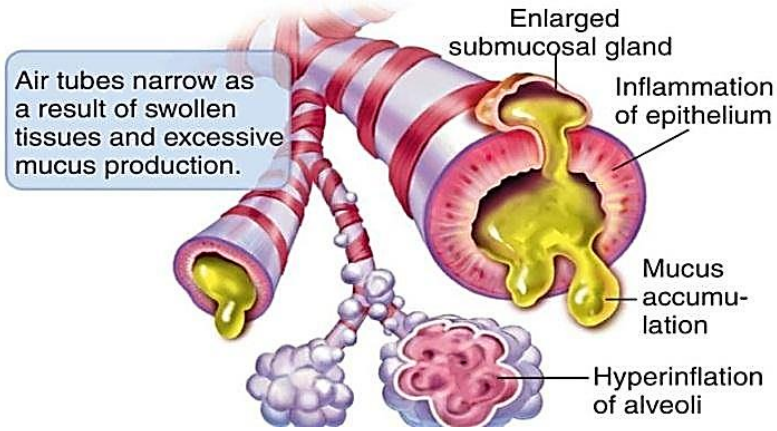
- Group of diseases characterized by **airway obstruction**; lung does not empty, and air is trapped.
    1. Volume of air that can be forcefully expired is decreased **(↓ FVC)**, especially during the first second of expiration **(↓↓ FEV1)**; results in **↓ FEV1: FVC** ratio.
    2. Total lung capacity (TLC) is usually increased due to air trapping.



CHRONIC BRONCHITIS ("BLUE BLOATER")

- Chronic productive cough lasting at least 3 months over a minimum of 2 years; highly associated with smoking.
- Characterized by **hypertrophy of bronchial mucinous glands**:
    - Leads to increased thickness of mucus glands relative to overall bronchial wall thickness (Reid index increases to > 50%; normal is < 40%).
    - The degree of elevation of the Reid index correlates with the duration and severity of the chronic bronchitis.
    - DLCO usually normal:
        - Diffusing capacity or transfer factor of the lung for carbon monoxide CO.
        - The extent to which **oxygen passes from the air sacs** of the lungs into the blood. Commonly, it refers to the test used to determine this parameter.
- **Clinical features:**
    - Wheezing, crackles, dyspnea.
    - **Productive cough** due to excessive mucus production.

- **Cyanosis** ('blue bloaters'): Mucus plugs trap carbon dioxide; ↑ $PaCO_2$, and ↓PaO_2
- Increased risk of infection, 2° polycythemia, and cor pulmonale.

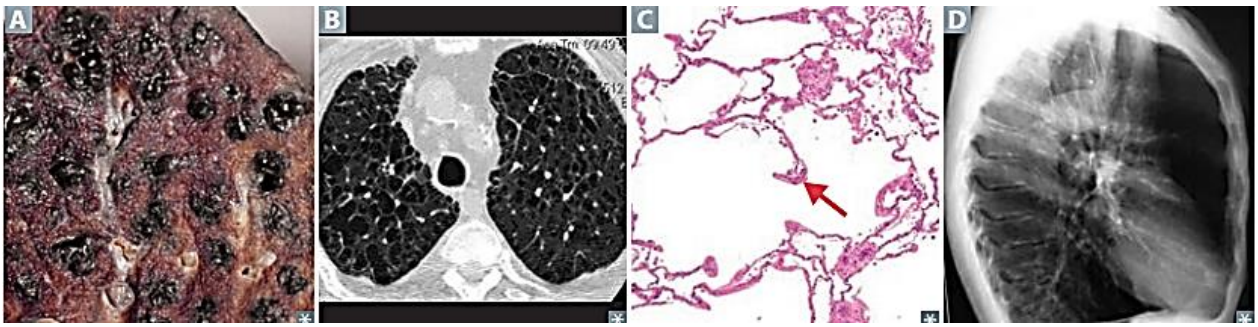


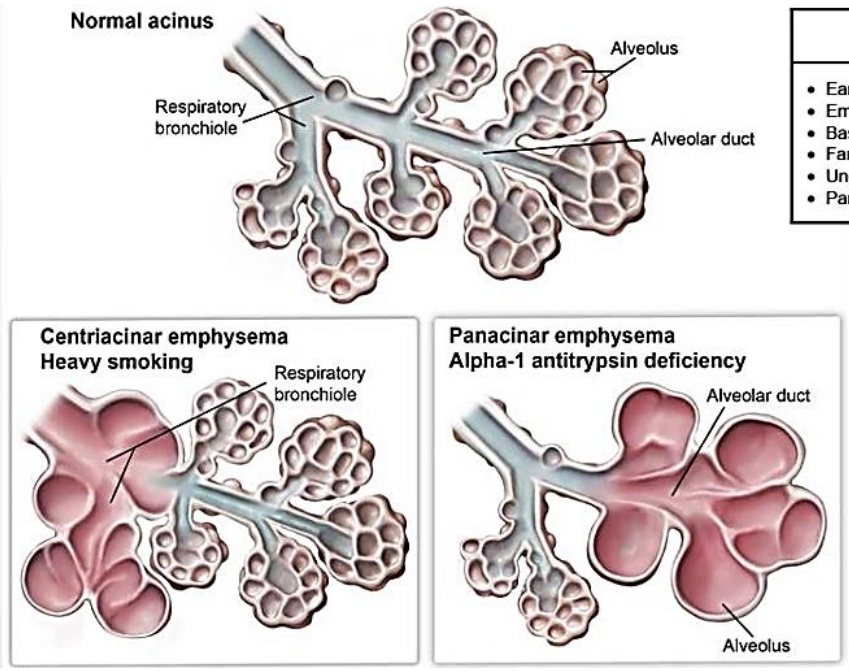
EMPHYSEMA ("PINK PUFFER")

- **Destruction of alveolar air sacs:**
  1. Loss of elastic recoil → collapse of airways *during exhalation* results in obstruction and air trapping.
- **Due to imbalance of proteases and antiproteases**
  1. Inflammation in the lung normally leads to release of proteases by neutrophils and macrophages.
  2. A1-antitrypsin (AlAT) neutralizes proteases.
  3. Excessive inflammation or lack of AlAT leads to destruction of the alveolar air sacs.
- **Smoking** is the most common cause of emphysema.
  1. Pollutants in smoke lead to excessive inflammation and protease-mediated damage.
  2. Results in **centriacinar** emphysema that is most severe in the upper lobes.
- **AlAT deficiency** is a rare cause of emphysema.
  1. Lack of antiprotease leaves the air sacs vulnerable to protease-mediated damage.
  2. Results in **panacinar** emphysema that is most severe in the lower lobes.
  3. **Liver cirrhosis** may also be present.
     - AlAT deficiency is due to misfolding of the mutated protein.
     - Mutant AlAT accumulates in the endoplasmic reticulum of hepatocytes, resulting in liver damage.
     - Biopsy reveals pink, PAS-positive globules in hepatocytes.

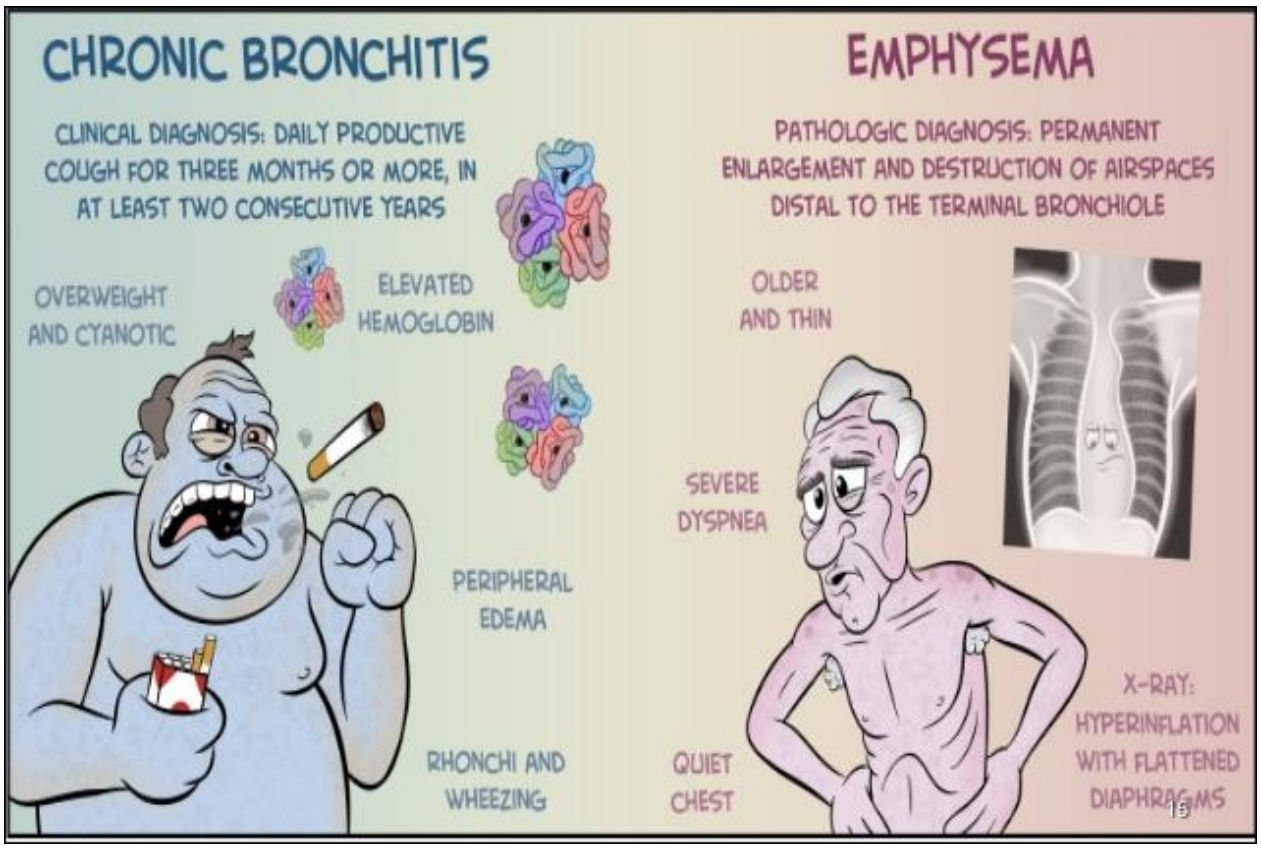
4. Disease severity is based on the degree of A1AT deficiency.
    - PiM is the normal allele; two copies are usually expressed (PiMM).
    - PiZ is the most common clinically relevant mutation; results in significantly low levels of circulating AIAT.
    - PiMZ heterozygotes are usually asymptomatic with decreased circulating levels of AlAT; however, significant risk for emphysema with smoking exists.
    - PiZZ homozygotes areal significant risk for panacinar emphysema and cirrhosis.

- **Clinical features** of emphysema include:
    1. Dyspnea and cough with **minimal sputum**.
    2. **Prolonged expiration with pursed lips** (increases airway pressure and prevents airway collapse).
    3. **"Pink puffer":**
        - Pink refers to the lack of cyanosis from the nearly normal arterial oxygen pressures.
        - Puffer refers to the severe dyspnea seen in these patients.
    4. Weight loss.
    5. Increased anterior-posterior diameter of chest ('barrel-chest' D).
    6. Hypoxemia (due to destruction of capillaries in the alveolar sac) and cor pulmonale are late complications.
- **Pathology:**
    1. **Centriacinar**—associated with **smoking** A B. Frequently in **up**per lobes (**smoke** rises **up**).
    2. **Panacinar**—associated with α1-antitrypsin deficiency. Frequently in lower lobes.
    3. Enlargement of air spaces ↓ recoil, ↑ compliance.
    4. ↓ DLCO from destruction of alveolar walls (arrow in C).
    5. Imbalance of proteases and antiproteases → ↑ elastase activity → ↑ loss of elastic fibers → ↑ lung compliance.
- **CXR:**
    1. ↑ AP diameter, flattened diaphragm, ↑ lung field lucency.





Testing for A1AT deficiency
• Early-onset emphysema (<age 45) • Emphysema in nonsmokers or light smokers • Basilar emphysema on chest x-ray • Family history of emphysema and/or liver disease • Unexplained chronic liver disease • Panniculitis

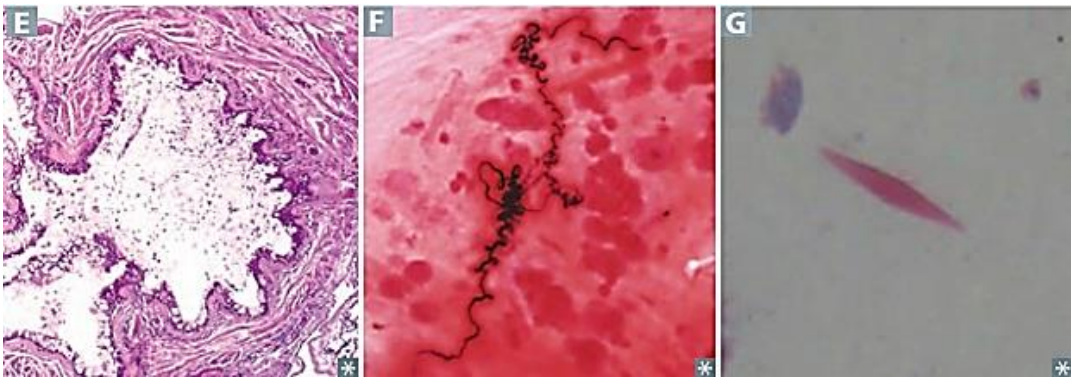


Pulmonary function tests in chronic obstructive lung disease		
	Chronic bronchitis	**Emphysema**
Forced vital capacity	Normal or ↓	Normal or ↓
Forced expiratory volume in 1 second	↓	↓
FEV_1/FVC	↓	↓
Total lung capacity	Normal	↑↑
Functional residual capacity	↑	↑↑
Pulmonary compliance	Normal	↑
Bronchodilator response	Partial response	Nonreversible
D_LCO	Normal	↓

ASTHMA

- **Reversible** airway bronchoconstriction.
- Most often due to allergic stimuli (type I hypersensitivity).
    1. Presents in childhood; often associated with allergic rhinitis, eczema, and a family history of atopy.
- **Pathogenesis:**
    1. Allergens induce **TH2** phenotype in CD4+T cells of genetically susceptible individuals.
    2. TH2 cells secrete IL-4 (mediates class switch to IgE), IL-5 (attracts eosinophils), and IL-10 (stimulates TH2 cells and inhibits TH1).
    3. Reexposure to allergen leads to IgE-mediated activation of mast cells
        - Release of preformed histamine granules and generation of leukotrienes C4, D4, and E4 lead to bronchoconstriction, inflammation, and edema (early phase reaction).
        - Inflammation, especially major basic protein derived from eosinophils, damages cells and perpetuates bronchoconstriction (late-phase reaction).

- **Clinical features of asthma:**
    1. **Episodic**; triggers: viral URIs, allergens, stress.
        - Animal dander is the most common type.
    2. Dyspnea and wheezing.
    3. Productive cough, classically with spiral-shaped mucus plugs (**Curschmann spirals**) and eosinophil-derived crystals (**Charcot-Leyden crystals**).
    4. **Pulsus paradoxus**: exaggerated fall in a patient's blood pressure during inspiration by > 10 mm Hg
    5. Severe, unrelenting attack can result in status asthmaticus and death.
- Asthma may also arise from nonallergic causes such as exercise, viral infection, aspirin (e.g., aspirin intolerant asthma), and occupational exposures.
- **Pathology:**
    1. Hyperresponsive bronchi → reversible bronchoconstriction.
    2. **Curschmann spirals F** (shed epithelium forms whorled mucous plugs).
    3. **Charcot-Leyden crystals G** (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum).
    4. DLCO normal or ↑.
- **Histology:**
    1. Tracheobronchial tree exists in a state of **chronic subacute inflammation**.
    2. Bronchial biopsy typically demonstrates a thickened mucosa with eosinophilic infiltrates.
    3. Smooth muscle hypertrophy and hyperplasia.
- **Diagnosis:**
    1. Spirometry.
    2. **Methacholine challenge test:**
        - Nonselective muscarinic receptor (M3) agonist.
        - A negative methacholine challenge test can help to exclude (rule out) the diagnosis (**highly sensitive)**.



UW: Intermittent respiratory symptoms in a patient with a normal CXR, occasional sputum, eosinophils, and reduced FEV1 suggest a diagnosis of asthma.

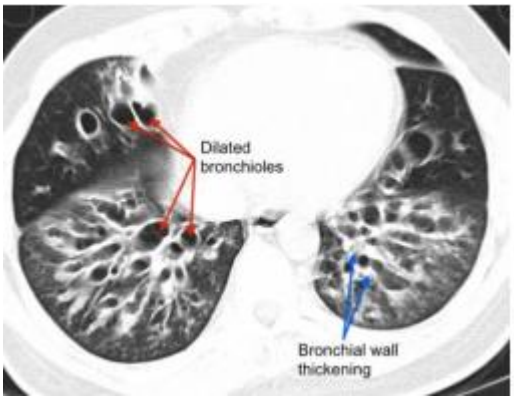
UW: Asthma develops due to the interaction of **genetic** and **environmental** factors. Increased quantities of **Th2 cells** predispose the child to developing asthma under certain environmental conditions. Children exposed to second-hand **smoke** are at increased risk for developing asthma over the long-term. Similarly, infants of mothers who smoked during pregnancy have heightened airway responsiveness compared to the infants of non-smoking mothers. Environmental irritants, such as ***smoking*** trigger bronchospasm in predisposed individuals.

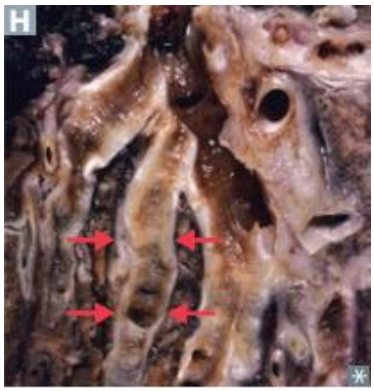
UW: **Major basic protein** released by **eosinophils** normally functions to kill helminthes. It is also thought to contribute to the **bronchial epithelial damage** sustained by patients with atopic (extrinsic allergic) asthma.

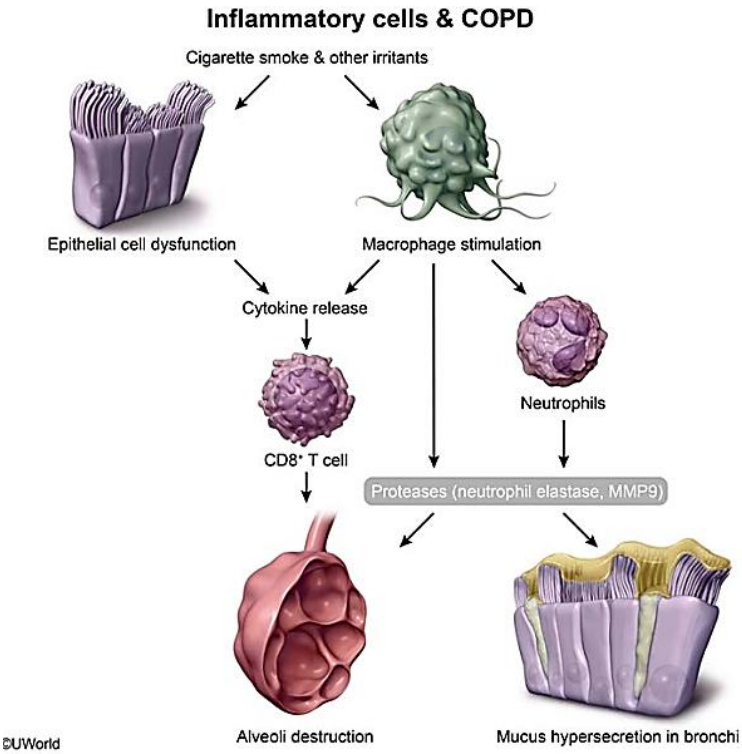
BRONCHIECTASIS

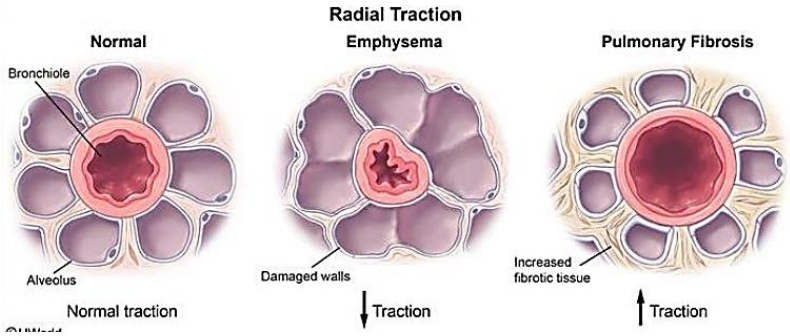
- Permanent (irreversible) **dilatation** of bronchioles and bronchi.
- Loss of airway tone results in **air trapping**.
- Due to necrotizing **inflammation** with damage to airway walls.
- **Causes include:**
    1. **Cystic fibrosis**.
    2. Kartagener syndrome: inherited defect of the dynein arm, which is necessary for ciliary movement. Associated with sinusitis, infertility (poor motility of sperm), and situs inversus (position of major organs is reversed, e.g., heart is on right side of thorax).
    3. Tumor or foreign body.
    4. Necrotizing infection.
    5. Allergic bronchopulmonary aspergillosis: Hypersensitivity reaction to Aspergillus leads to chronic inflammatory damage; usually seen in individuals with asthma or cystic fibrosis.
- **Clinical features:**
    1. Cough, dyspnea, and foul-smelling sputum.
    2. Recurrent infections, hemoptysis, digital clubbing.
    3. Complications include hypoxemia with cor pulmonale and secondary (AA) amyloidosis.

- **Pathology:**
  - Chronic necrotizing infection of bronchi or obstruction → **permanently dilated airways**.









RESTRICTIVE DISEASES

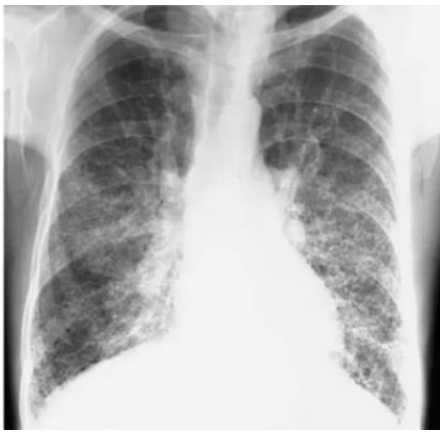
Obstructive disorders	Restrictive disorders
• **Characterized by:** reduction in airflow. • So, shortness of breath → in exhaling air. (the air will remain inside the lung after full expiration) 1. COPD 2. Asthma 3. Bronchiectasis	• **Characterized by** a reduction in lung volume. • So, Difficulty in taking air inside the lung. (DUE TO stiffness inside the lung tissue or chest wall cavity) 1. Interstitial lung disease. 2. Scoliosis 3. Neuromuscular cause 4. Marked obesity

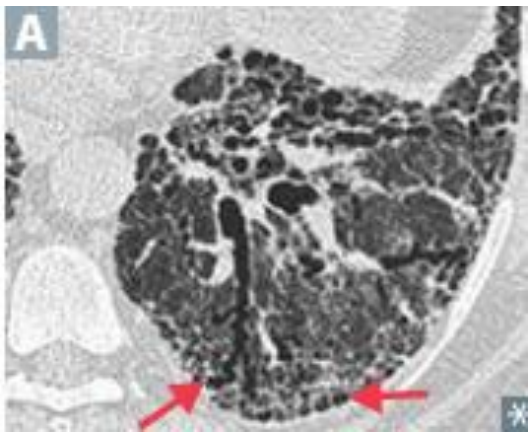
BASIC PRINCIPLES

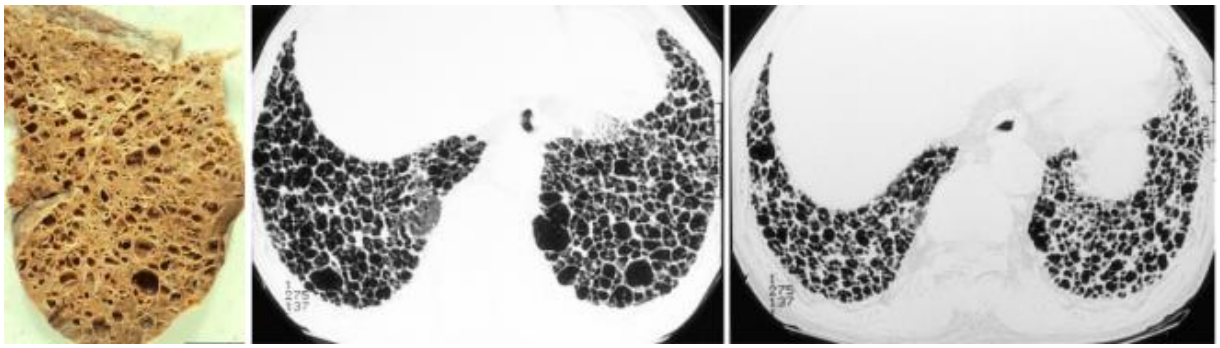
A. Restricted lung **expansion** causes ↓ lung volumes (↓TLC, ↓↓ FVC, ↓ FEV1).
B. PFTs: ↑ **FEV1/FVC ratio** (>80%).
C. Patient presents with short, shallow breaths.
D. Most commonly due to interstitial diseases of the lung; may also arise with chest wall abnormalities (e.g., massive obesity).
E. **Types:**
    a. **Poor breathing mechanics** (extrapulmonary, peripheral hypoventilation, normal A-a gradient):
        i. Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome.
        ii. Poor structural apparatus—scoliosis, morbid obesity.
    b. **Interstitial lung diseases** (pulmonary ↓ diffusing capacity, ↑ A-a gradient):
        i. Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, and asbestosis).
        ii. Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca^{2+}
        iii. **Pulmonary fibrosis.**
        iv. Goodpasture syndrome.
        v. Granulomatosis with polyangiitis (Wegener).
        vi. Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma).
        vii. Hypersensitivity pneumonitis.
        viii. Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate).

IDIOPATHIC PULMONARY FIBROSIS

- Fibrosis of lung interstitium.
- **Pathogenesis:**
  - Etiology is unknown.
  - Likely related to repeated cycles of lung injury and wound healing with ↑ collagen deposition.
  - **TGF-β** from injured pneumocytes induces fibrosis.
  - Secondary causes of interstitial fibrosis must be excluded such as:
    - Drugs (e.g., bleomycin and amiodarone) and radiation therapy.
    - Sarcoidosis.
    - Collagen vascular diseases.
- **Clinical features:**
  - **Gradually progressive dyspnea** first with exertion and then progressing to symptoms at rest.
  - Chronic cough.
  - **End-inspiratory crackles** at the lung bases.
  - Digital **clubbing**.
- **Imaging:**
  - CXR → Bilateral **reticulonodular** opacities.
  - CT →
    - Initially seen in subpleural patches.
    - Eventually results in diffuse fibrosis with end-stage "honeycomb" lung.
      - **Honeycomb** lung appearance "paraseptal and subpleural cystic airspace enlargement" → pulmonary interstitial fibrosis causes alveolar wall collapse and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium.
- **Treatment:**
  - Lung transplantation.





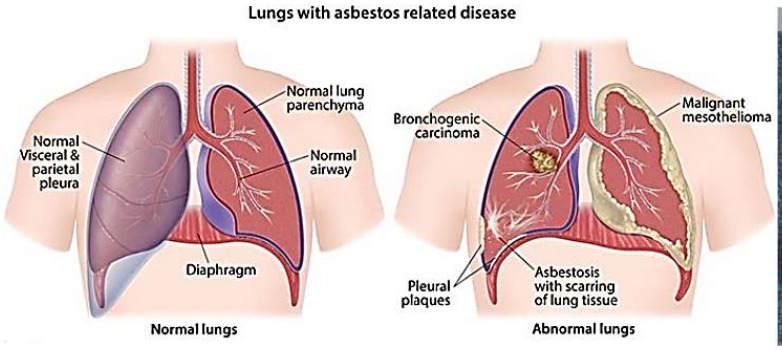


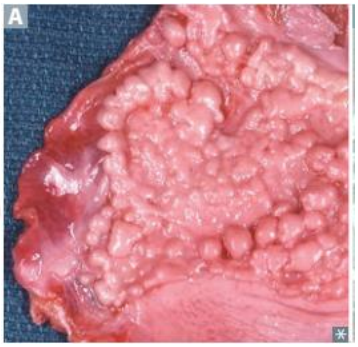
PNEUMOCONIOSES

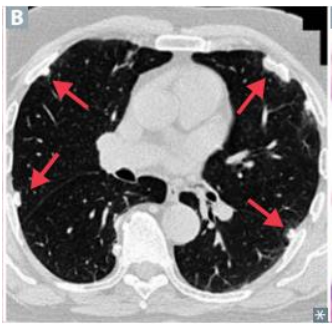
- Interstitial fibrosis due to ***occupational*** exposure.
- Requires chronic exposure to **small particles** that are fibrogenic.
    1. Alveolar **macrophages** engulf foreign particles and induce fibrosis.
- **Asbestos** is from the **roof** (was common in insulation), but affects the **base** (lower lobes).
- **Silica and coal** are from the **base** (earth), but affect the **roof** (upper lobes).

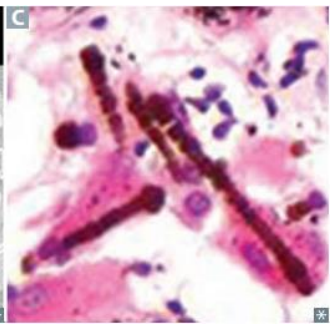
ASBESTOSIS

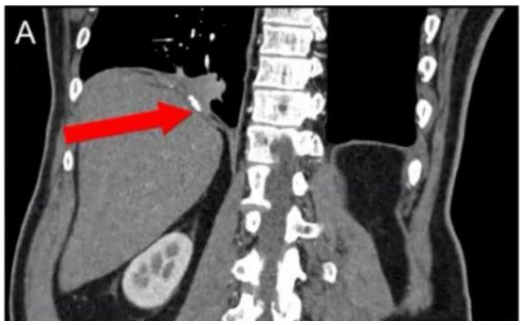
Epidemiology	• Associated with shipbuilding, roofing, plumbing, construction workers, and textile industries.
Findings	• **Pleura:** ▪ **Pleural thickening**, plaques and **calcifications** "Ivory white pleura". ▪ Supradiaphragmatic **parietal pleura**. ▪ ↑ Risk of pleural effusions. ▪ ↑ Risk of mesothelioma. • **Lung:** ▪ Diffuse pulmonary fibrosis. Affects **lower lobes**. ▪ **Asbestos (ferruginous) bodies**: ○ Golden-brown beaded rods with translucent centers resembling dumbbells **C**. ○ Obtained by bronchoalveolar lavage. ○ Visualized using Prussian blue stain. ▪ **Risk of bronchogenic carcinoma > risk of mesothelioma**. ○ Bronchogenic carcinoma is the most common malignancy associated with asbestos exposure. ○ Smoking and asbestos exposure have a synergistic effect on the development of bronchogenic carcinoma.





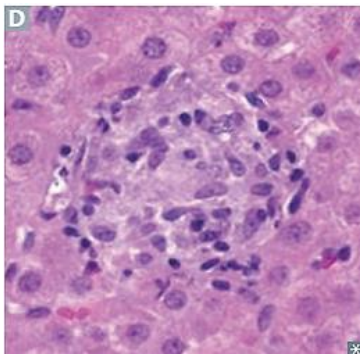






BERYLLIOSIS

- Associated with exposure to beryllium in **aerospace** and manufacturing industries.
- **Noncaseating granulomas** **D** in the lung, hilar lymph nodes, and systemic organs → therefore occasionally **responsive to steroids**.
- ↑ Risk of cancer and cor pulmonale.
- Affects **upper lobes**.



COAL WORKERS' PNEUMOCONIOSIS

- Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis.
- Also known as **black lung disease**.
- ↑ Risk for **Caplan syndrome** (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).
- Affects **upper lobes**.
- Small, rounded nodular opacities seen on imaging.

ANTHRACOSIS (ANTHRAC- MEANING COAL, CARBON + -OSIS MEANING CONDITION)

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

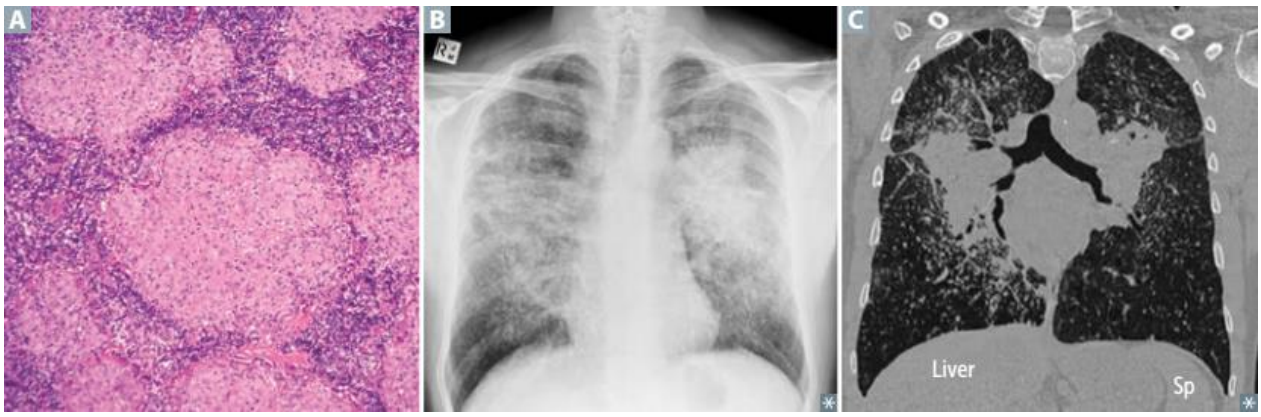
SILICOSIS

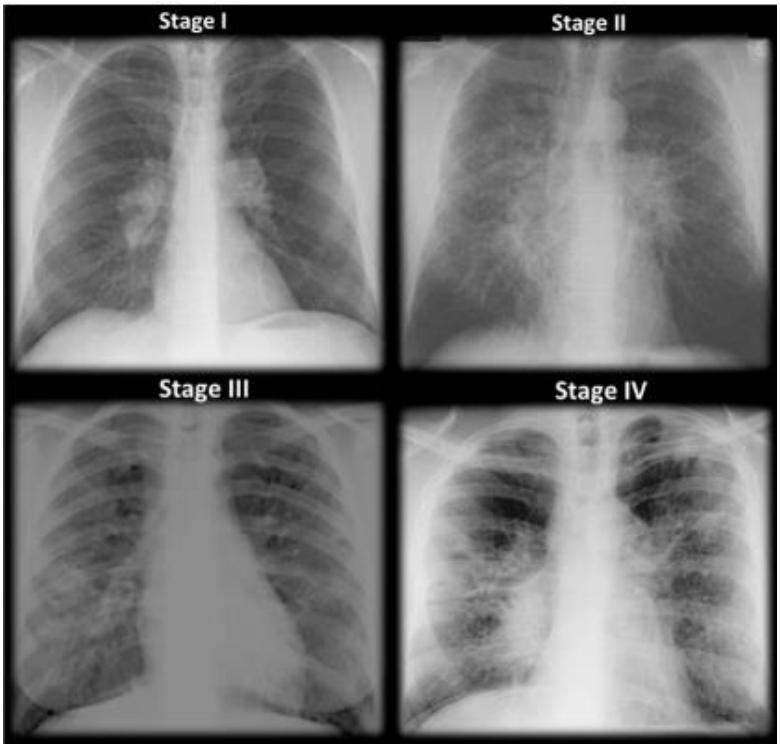
- Associated with **sand**blasting, **found**ries, **mine**s.
- Macrophages respond to silica and release fibrogenic factors, leading to **fibrosis**.
- It is thought that silica may **disrupt phagolysosomes** and impair macrophages, increasing susceptibility to TB.
- ↑ Risk of cancer, cor pulmonale, and Caplan syndrome.
- Affects upper lobes. **"Egg**shell" **calcification** of hilar lymph nodes on CXR.
- The **silly egg sand**wich I **found** is **mine**!

SARCOIDOSIS

Epidemiology	• More common in African-American females.
Pathology	• Immune-mediated, widespread **noncaseating granulomas** **A** that stain negative for fungi & acid-fast bacilli. ○ Granulomas most commonly involve the hilar lymph nodes and lung, leading to restrictive lung disease. ○ Characteristic stellate inclusions ('asteroid bodies') are often seen within giant cells of the granulomas.
Clinical	• Often asymptomatic except for enlarged hilar lymph nodes. • Constitutional symptoms. • Cough, dyspnea (most common presenting symptom), chest pain. • Extrapulmonary findings: ➢ Associated with **Bell palsy**, **U**veitis, **G**ranulomas (epithelioid, containing microscopic Schaumann and asteroid bodies), **L**upus pernio (skin lesions on face resembling lupus), **I**nterstitial fibrosis (restrictive lung disease), **E**rythema nodosum, **R**heumatoid arthritis-like arthropathy. A **facial droop** is **UGLIER**. ➢ Salivary and lacrimal glands can be affected (mimics Sjogren syndrome).
Laboratory	• Elevated serum **ACE levels.** • Elevated **CD4+/CD8+ ratio** in bronchoalveolar lavage fluid. • **Hypercalcemia** (due to ↑ 1α-hydroxylase–mediated vitamin D activation in macrophages)/ hypercalciuria.

Imaging	• **Stage I** → bilateral hilar lymphadenopathy. • **Stage II** → bilateral hilar lymphadenopathy + pulmonary infiltrates in the upper lobes (coarse reticular opacities **B)**. • **Stage III** → disappearance of hilar lymphadenopathy + lung infiltrates only.
Differential diagnosis	• **UW:** Dry cough, pulmonary infiltrates, and hilar adenopathy can be found in a number of lung diseases including tuberculosis, sarcoidosis, endemic mycoses (histoplasmosis, coccidioidomycosis), silicosis, berylliosis, lymphoma, and bronchogenic carcinoma. • Transbronchial biopsy may be required to establish and/or confirm the diagnosis.
Treatment	• Often resolves spontaneously without treatment. • Steroids (if symptomatic).





HYPERSENSITIVITY PNEUMONITIS

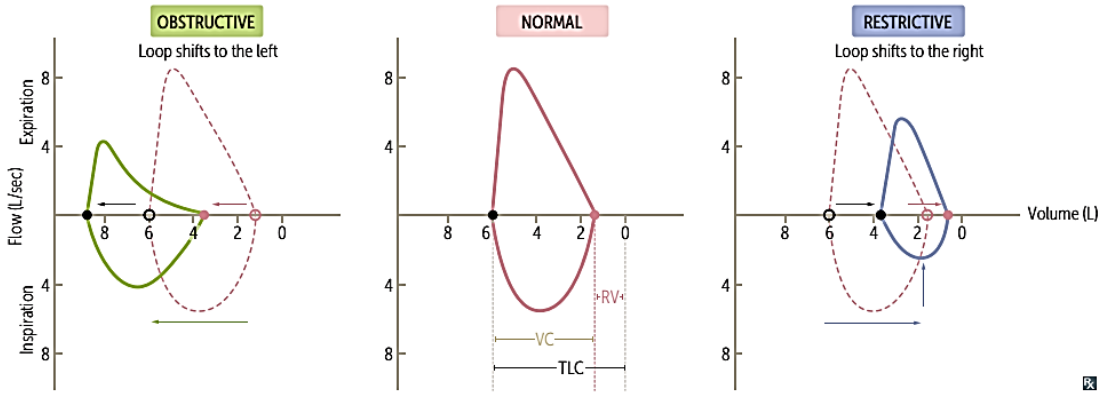
- **Granulomatous reaction** to inhaled organic antigens (e.g., pigeon breeder's lung).
    1. Mixed type III/IV hypersensitivity reaction to environmental antigen.
    2. Often seen in farmers and those exposed to birds.
    3. Chronic exposure leads to interstitial fibrosis.
    4. Reversible in early stages if stimulus is avoided.
- Presents with fever, cough, and dyspnea hours after exposure; resolves with removal of the exposure.

FLOW-VOLUME LOOPS "OBSTRUCTIVE VS. RESTRICTIVE LUNG DISEASES"

A. In **restrictive disorders** such as interstitial fibrosis, **radial traction of the airway increases** → increasing airway diameter → decreasing airway resistance → **increasing expiratory airflow**. Despite the increased expiratory airflow, the reduced lung compliance will decrease both forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1). Therefore, the **FEV_1/FVC ratio is normal or increased**.

B. In **obstructive disorders** such as emphysema, destruction of elastic fibers → **decreases radial traction** → decreasing airway diameter → increasing resistance → **decreasing expiratory airflow and FEV_1/FVC ratios**.

FLOW-VOLUME PARAMETER	Obstructive lung disease	Restrictive lung disease
RV	↑	↓
FRC	↑	↓
TLC	↑	↓
FEV_1	↓↓	↓
FVC	↓	↓
FEV_1/FVC	↓ FEV_1 decreased more than FVC	Normal or ↑ FEV_1 decreased proportionately to FVC



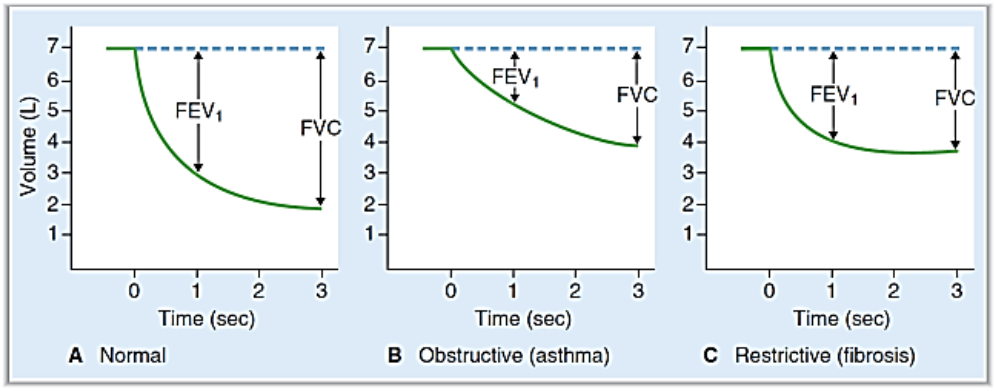
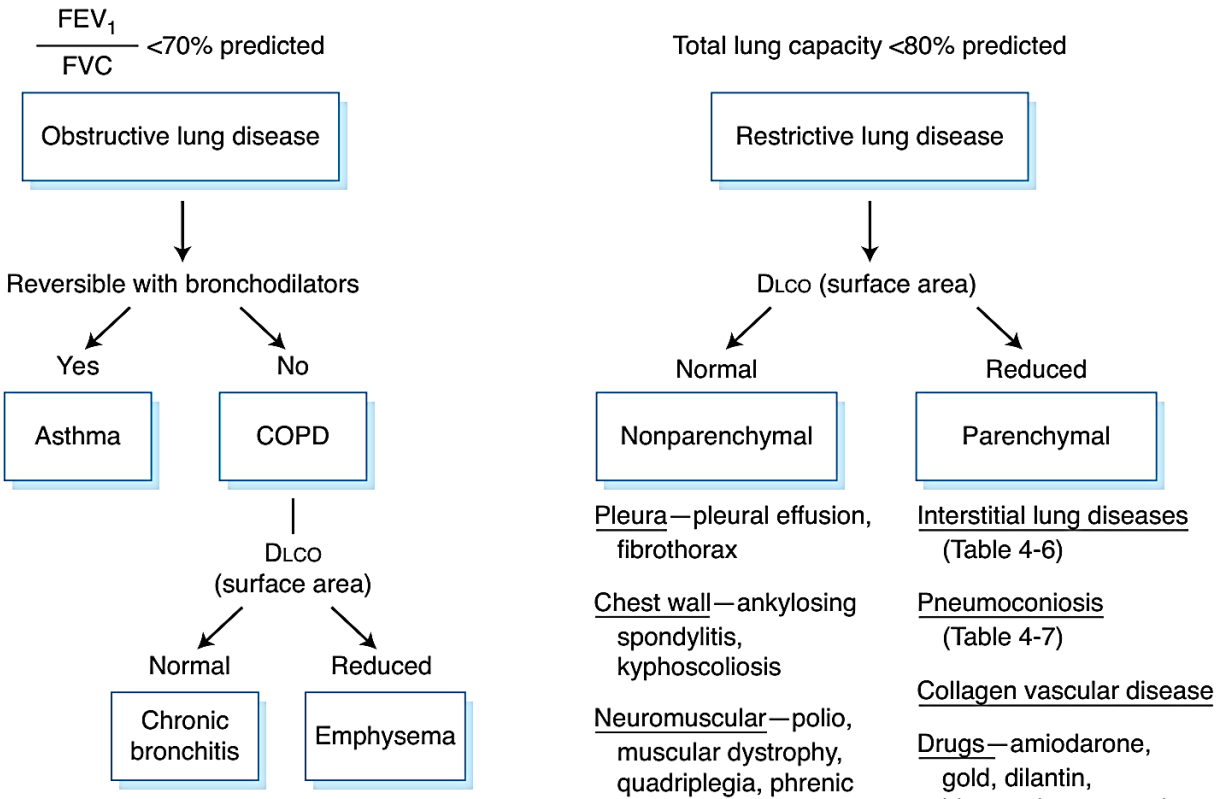


FIGURE 4.2 Forced vital capacity (FVC) and FEV_1 in normal subjects and in patients with lung disease. FEV_1 = volume expired in first second of forced maximal expiration.

OBSTRUCTIVE LUNG DISEASES

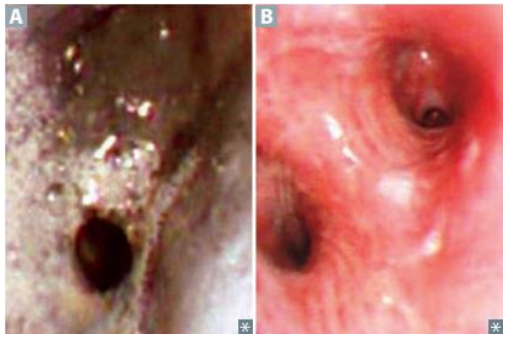
- Obstruction of air flow → air trapping in lungs.
- Airways close prematurely at high lung volumes → ↑ **FRC**, ↑ **RV**, ↑ **TLC**.
- **PFTs**: ↓↓ FEV1, ↓ FVC → ↓ FEV1/FVC ratio (hallmark).
- V/Q mismatch.
- Chronic, hypoxic pulmonary vasoconstriction can lead to cor pulmonale.
- Chronic obstructive pulmonary disease (**COPD**) includes chronic bronchitis and emphysema.
- "**FR**i**C**kin' **RV** needs some increased **TLC**, but it's hard with **COPD**!

INTERPRETING PULMONARY FUNCTION TESTS: OBSTRUCTIVE VERSUS RESTRICTIVE



COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of lung for carbon monoxide; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity.

INHALATION INJURY AND SEQUELAE

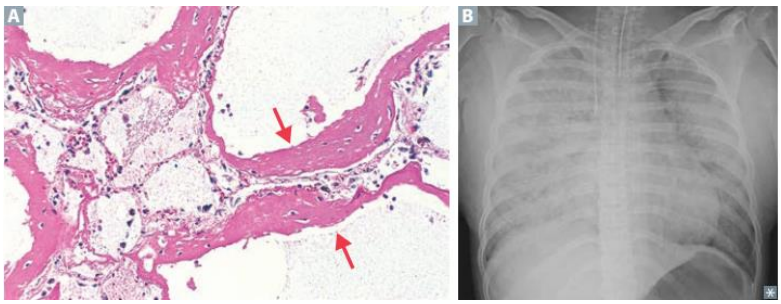


- Complication of **smoke inhalation** from fires or other noxious substances.
- Caused by heat, particulates (< 1 µm diameter), or irritants (eg, NH_3) → chemical tracheobronchitis, edema, pneumonia, **ARDS**.
- Many patients present 2° to burns, **CO inhalation**, **cyanide** poisoning, or **arsenic** poisoning.
- **Singed nasal hairs** common on exam.
- **Bronchoscopy** shows severe edema, congestion of bronchus, and **soot deposition** (**A**, 18 hours after inhalation injury;**B**, resolution at 11 days after injury).

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

- **Pathophysiology**
  - Alveolar insult → release of pro-inflammatory cytokines → neutrophil recruitment, activation, and release of toxic mediators (eg, reactive oxygen species, proteases, etc) → capillary endothelial damage and ↑ vessel permeability → leakage of protein-rich fluid into alveoli → formation of intra-alveolar **hyaline membranes** (arrows in **A**) and noncardiogenic pulmonary edema (normal PCWP).
  - Loss of surfactant also contributes to **alveolar collapse**.
- **Causes**
  - Sepsis (most common), aspiration, pneumonia, trauma, pancreatitis.
- **Diagnosis**
  - Diagnosis of exclusion with the following criteria (**ARDS**):
    - **A**bnormal chest X-ray (bilateral lung opacities).
    - **R**espiratory failure within 1 week of alveolar insult.
    - **D**ecreased PaO_2/FiO_2 (ratio < 300, hypoxemia due to ↑ intrapulmonary shunting and diffusion abnormalities).
    - **S**ymptoms of respiratory failure are not due to HF/fluid overload "exclude cardiogenic pulmonary edema".
- **Consequences**
  - Impaired gas exchange → V/Q mismatch → **physiological shunting** "Blood is getting to the lung without being oxygenated" → hypoxemia.
  - ↓ Lung compliance due to atelectasis & fibrosis.
  - Pulmonary hypertension.

- **Management**
  - Treat the underlying cause.
  - **Mechanical ventilation:**
    - ↓ **Tidal volumes** "prevent ventilator induced lung injury: overdistention & collapse".
    - ↑ **PEEP**.



PATHOLOGIC BREATHING PATTERNS

Table 2-2 Breathing Patterns

	Condition	Description	Causes
	Eupnea	Normal breathing rate and pattern	
	Tachypnea	Increased respiratory rate	Fever, anxiety, exercise, shock
	Bradypnea	Decreased respiratory rate	Sleep, drugs, metabolic disorder, head injury, stroke
	Apnea	Absence of breathing	Deceased patient, head injury, stroke
	Hyperpnea	Normal rate, but deep respirations	Emotional stress, diabetic ketoacidosis
	Cheyne-Stokes	Gradual increases and decreases in respirations with periods of apnea	Increasing intracranial pressure, brain stem injury, CHF
	Biot's	Rapid, deep respirations (gasps) with short pauses between sets	Spinal meningitis, many CNS causes, head injury
	Kussmaul's	Tachypnea and hyperpnea	Renal failure, metabolic acidosis, diabetic ketoacidosis
	Apneustic	Prolonged inspiratory phase with shortened expiratory phase	Lesion in brain stem

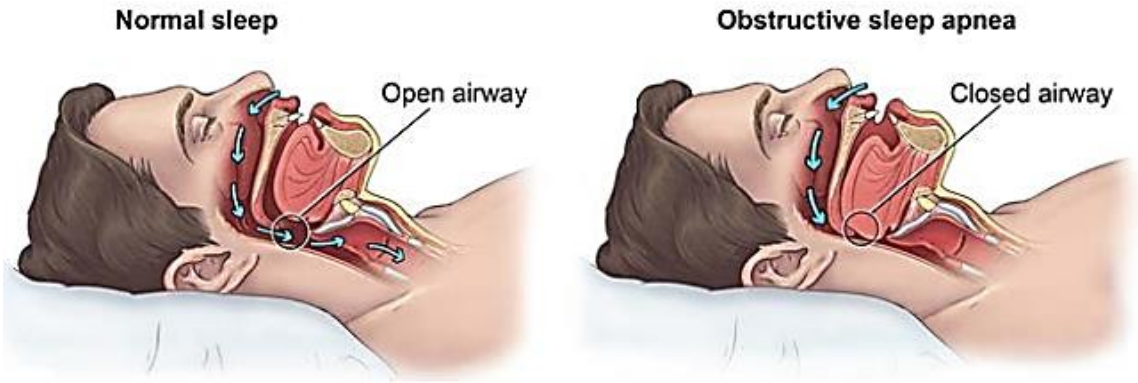
CHEYNE-STOKES BREATHING (CSB)

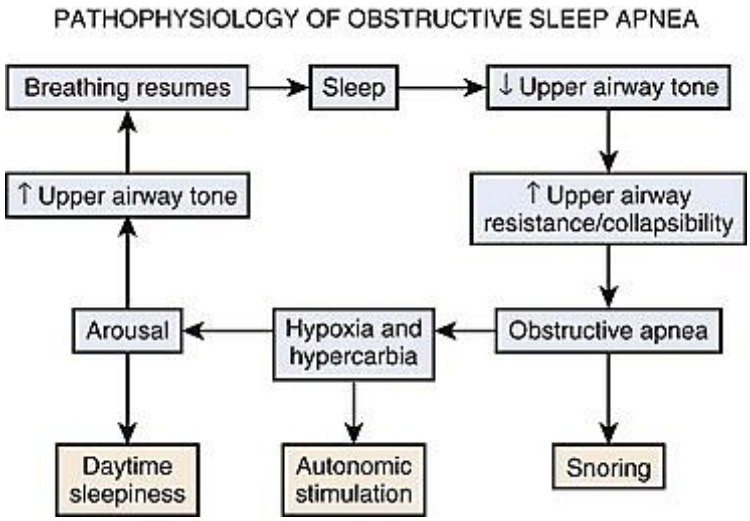
- Cyclic breathing pattern in which apnea is followed by gradually increasing then decreasing tidal volumes until the next apneic period.
- **Commonly seen in patients with advanced congestive heart failure** (CHF).
  - Patients with CHF have chronic hyperventilation with hypocapnia, which induces apnea during sleep when PaCO2 falls below a certain level ("apneic threshold").
  - Apnea causes excessive buildup of CO2 (hypercapnia): this stimulates a ventilator response that overshoots (hyperpnea); causing the PaCO2 to again fall below the apneic threshold.
  - This cycle of apnea and hyperventilation is further perpetuated by prolonged circulation time between the lungs and brain, which results in a discrepancy between PaCO2 levels sensed by central chemoreceptors and PaCO2 concentration in alveoli.
- CSB is also seen in **neurologic disease** (eg, stroke, brain tumors, traumatic brain injury) and is frequently a **poor prognostic sign**.

SLEEP APNEA

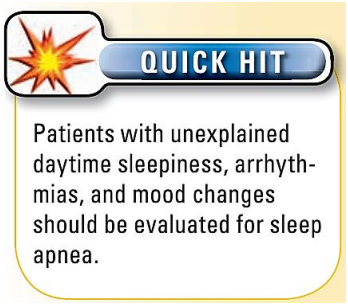
- Repeated **cessation of breathing > 10 seconds** during sleep → disrupted sleep → daytime somnolence.
- Diagnosis confirmed by sleep study.
- Normal PaO_2 during the day.
- Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death.
- Hypoxia → ↑ EPO release → ↑ erythropoiesis.

OBSTRUCTIVE SLEEP APNEA (OSA)

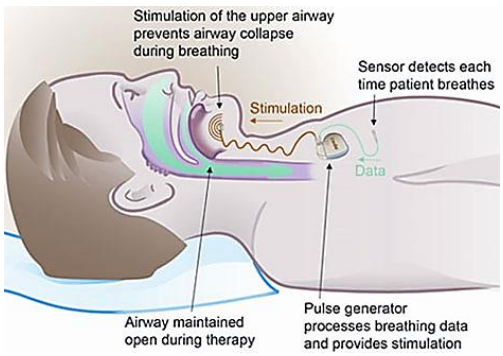




- **Pathophysiology:**
  - **Neuromuscular weakness** of the oropharynx → respiratory effort against airway obstruction → loud snoring with periods of apnea.
  - Caused by excess parapharyngeal tissue in adults, adenotonsillar hypertrophy in children.
  - Associated with obesity, loud snoring, and daytime sleepiness.
- **Symptoms:**
  - Daytime somnolence.
  - Non-restorative sleep with frequent awakenings with snoring.
  - Morning headaches.
  - Affective & cognitive symptoms.



- **Complications:**
  - Systemic hypertension.
  - Pulmonary hypertension & right heart failure.
- **Treatment:**
  - Weight loss, CPAP, surgery.
  - ***Electrical stimulation of the hypoglossal nerve*** increases the diameter of the oropharyngeal airway and decreases the frequency of apneic events.



CENTRAL SLEEP APNEA

- Your brain doesn't send proper signals to the muscles that control your breathing.
- Due to **CNS** injury/toxicity, HF, opioids.
- May be associated with **Cheyne-Stokes respirations** (oscillations between apnea and hyperpnea).
- Treat with **positive airway pressure**.

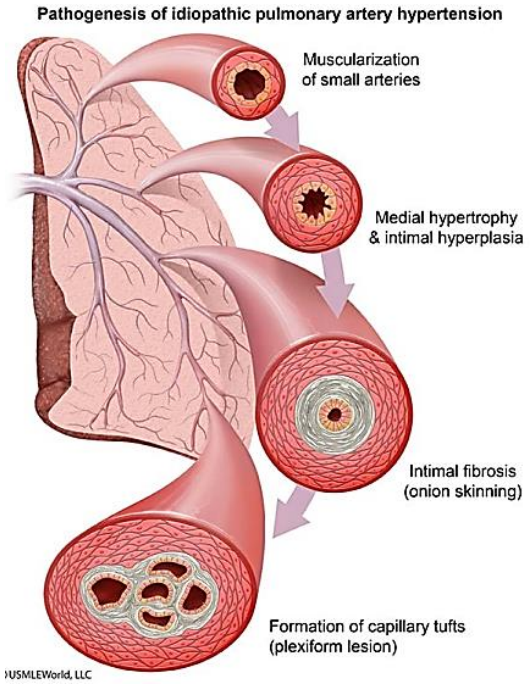
OBESITY HYPOVENTILATION SYNDROME (PICKWICKIAN SYNDROME)

- Restricted **expansion** of the chest wall due to severe obesity (BMI ≥ 30 kg/m2).
- This leads to **hypoventilation** with a **chronically elevated PCO2 and reduced PO2** "abnormal blood gases during daytime Vs. OSA in which there is normal ABG during daytime".

PULMONARY HYPERTENSION

- Normal mean pulmonary artery pressure = 10 –14 mm Hg; **pulmonary hypertension ≥ 25 mm** Hg at rest.

Classification of pulmonary hypertension
Pulmonary arterial hypertension (primary) • Idiopathic (sporadic) • Hereditary
Pulmonary hypertension (secondary) • Left heart failure • Chronic lung disease &/or hypoxia • Chronic pulmonary thromboembolism



- **Characterized by:**
  - Atherosclerosis of the pulmonary trunk.
  - Smooth muscle hypertrophy of pulmonary arteries.
  - Intimal fibrosis; plexiform lesions.
- **Course:**
  - Severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.

PRIMARY PULMONARY HYPERTENSION

- Classically seen in **young adult females**.
- Etiology is unknown:
  - Some familial forms are related to inactivating mutations of **BMPR2** (normally inhibits vascular smooth muscle proliferation); leading to proliferation of vascular smooth muscle, poor prognosis.
  - Pulmonary vasculature endothelial dysfunction results in ↑ **vasoconstrictors** (eg, endothelin) and ↓ **vasodilators** (eg, NO and prostacyclins).

SECONDARY PULMONARY HYPERTENSION

LEFT HEART DISEASE

- Causes include systolic/diastolic dysfunction and valvular disease.

LUNG DISEASES OR HYPOXIA

- Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).

CHRONIC THROMBOEMBOLIC

- Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.

MULTIFACTORIAL

- Causes include hematologic, systemic (eg, connective tissue disease), and metabolic disorders, along with compression of the pulmonary vasculature by a tumor.
- Other causes include drugs (eg, amphetamines, cocaine), HIV infection, portal hypertension, congenital heart disease, schistosomiasis.
- UW: Pulmonary hypertension develops in patients with **scleroderma** as a result of damage to the pulmonary arterioles. It manifests with an accentuated pulmonary component of the second heart sound and signs of right-sided heart failure.

TREATMENT OF PULMONARY HYPERTENSION

Drug	Mechanism	Clinical use
Endothelin receptor antagonists	Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance.	Hepatotoxic (monitor LFTs). Example: bosentan.
PDE-5 inhibitors	Inhibits PDE-5 → ↑ cGMP → prolonged vasodilatory effect of NO.	Also used to treat erectile dysfunction. Contraindicated when taking nitroglycerin or other nitrates. Example: sildenafil.
Prostacyclin analogs	PGI_2 (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.	Side effects: flushing, jaw pain. Examples: epoprostenol, iloprost.

PLEURAL EFFUSIONS

- Excess accumulation of fluid **A** between pleural layers → restricted lung expansion during inspiration.
- Can be treated with thoracentesis to remove/reduce fluid **B**.

TRANSUDATE

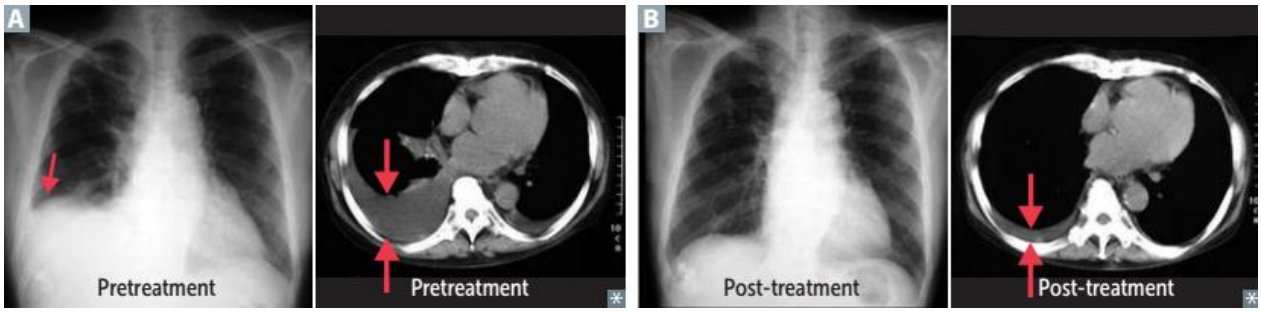
- ↓ Protein content.
- Due to ↑ **hydrostatic** pressure (eg, HF) or ↓ **oncotic** pressure (eg, nephrotic syndrome, cirrhosis).

EXUDATE

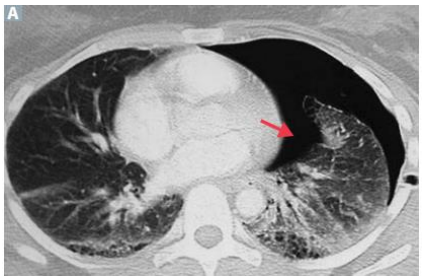
- ↑ Protein content, cloudy.
- Due to malignancy, pneumonia, collagen vascular disease, trauma (occurs in states of ↑ vascular permeability).
- Must be drained due to risk of infection.

LYMPHATIC

- Also known as chylothorax.
- Due to **thoracic duct** injury from trauma or malignancy.
- Milky appearing fluid; ↑ triglycerides.



PNEUMOTHORAX



- Accumulation of air in pleural space **A**.
- Dyspnea, uneven chest expansion.
- Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.

PRIMARY SPONTANEOUS PNEUMOTHORAX

- Due to rupture of **apical subpleural bleb** or cysts.
  - These blebs may arise due to distal acinar (paraseptal) emphysema.
- Occurs most frequently in **tall, thin, young males and smokers**.

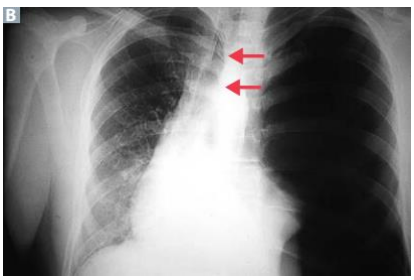
SECONDARY SPONTANEOUS PNEUMOTHORAX

- Due to **diseased lung** (eg, bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.

TRAUMATIC PNEUMOTHORAX

- Caused by **blunt** (eg, rib fracture), **penetrating** (eg, gunshot), or **iatrogenic** (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.

TENSION PNEUMOTHORAX



- Can be from any of the above.
- Air enters pleural space but cannot exit.
- Increasing trapped air → tension pneumothorax.
- Trachea deviates away from affected lung **B**.
- Needs immediate needle decompression and chest tube placement.

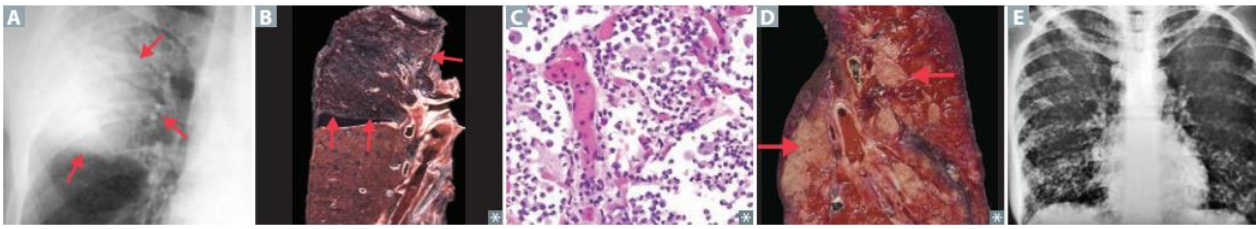
  May lead to ↑ intrathoracic pressure → ↓ venous return → ↓ cardiac function.

PNEUMONIA

- Infection of the lung **parenchyma**.
- Occurs when normal defenses are impaired (e.g., impaired cough reflex, damage to mucociliary escalator, or mucus plugging).
- **Clinical features include:**
  - Fever and chills, **productive cough** with yellow-green (pus) or rusty (bloody) sputum, tachypnea with pleuritic chest pain, decreased breath sounds, dullness to percussion, and elevated WBC count.
- Diagnosis is made by chest x-ray, sputum gram stain and culture, and blood cultures.
- Three patterns are classically seen on chest x-ray: lobar pneumonia, bronchopneumonia, and interstitial pneumonia.

Type	Typical organisms	Characteristics
Lobar pneumonia	• ***S pneumoniae*** most frequently. • *Klebsiella.* • *Legionella.*	• Intra-alveolar exudate → consolidation **A**. • May involve entire lobe **B** or the whole lung.
Bronchopneumonia	• Variety of bacterial organisms → ***S pneumoniae***, *S aureus, H influenzae, Klebsiella.*	• Characterized by scattered patchy consolidation centered around bronchioles; often multifocal and bilateral. • Acute inflammatory infiltrates **C** from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe **D**.
Interstitial (atypical) pneumonia	• *Mycoplasma, Chlamydophila pneumoniae, Chlamydophila psittaci, Legionella*, viruses (RSV, CMV, influenza, adenovirus)	• Diffuse patchy inflammation localized to interstitial areas at alveolar walls. • Diffuse distribution involving ≥ 1 lobe **E**. • Presents with relatively mild upper respiratory symptoms (minimal sputum and low fever); **"atypical" presentation**. • Generally follows a more **indolent course** ("**walking" pneumonia**).

Cryptogenic organizing pneumonia	• Etiology unknown. • Secondary organizing pneumonia caused by **chronic inflammatory diseases** (eg, rheumatoid arthritis) or medication side effects (eg, amiodarone). • ⊖ sputum and blood cultures, no response to antibiotics.	• Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). • **Noninfectious pneumonia** characterized by inflammation of bronchioles and surrounding structure.



LOBAR PNEUMONIA

CAUSES OF LOBAR PNEUMONIA

ORGANISM	HIGH-YIELD ASSOCIATIONS
Streptococcus pneumoniae	• Most common cause of community-acquired pneumonia. • Usually seen in middle aged adults and elderly.
Klebsiella pneumoniae	• Affects malnourished and debilitated individuals, especially elderly in nursing homes, alcoholics, and diabetics (enteric flora that is aspirated). • Thick mucoid capsule results in gelatinous sputum (currant jelly); often complicated by abscess.

NATURAL HISTORY OF LOBAR PNEUMONIA

Stage	Macroscopic appearance	Microscopic appearance
Congestion (first 24 hours)	The affected lobe is red, heavy and boggy	Vascular dilatation Alveolar exudate contains mostly bacteria
Red hepatization (days 2-3)	Red, firm lobe (liver-like consistency)	Alveolar exudate contains erythrocytes, neutrophils, and fibrin
Gray hepatization (days 4-6)	Gray-brown firm lobe	RBCs disintegrate Alveolar exudate contains neutrophils and fibrin
Resolution	Restoration of normal architecture	Enzymatic digestion of the exudate

BRONCHOPNEUMONIA (CAUSES):

ORGANISM	HIGH-YIELD ASSOCIATIONS
Staphylococcus aureus	• Most common cause of **secondary pneumonia** (bacterial pneumonia superimposed on a viral upper respiratory tract infection). • Often complicated by abscess or empyema.
Haemophilus influenza	• Common cause of secondary pneumonia and pneumonia superimposed on COPD (leads to **exacerbation of COPD**).
Pseudomonas aeruginosa	• Pneumonia **in cystic fibrosis** patients
Moraxella cattarhalis	• Community-acquired pneumonia and pneumonia superimposed on COPD (leads to **exacerbation of COPD**)
Legionella pneumophila	• Community-acquired pneumonia, pneumonia superimposed on **COPD**, or pneumonia in **immunocompromiscd** states; transmitted from **water source.** • Intracellular organism that is best visualized by silver stain

INTERSTITIAL (ATYPICAL) PNEUMONIA (CAUSES)

ORGANISM	HIGH-YIELD ASSOCIATIONS
Mycoplasma pueumouiae	• Most common cause of atypical pneumonia. • Usually affects young adults (classically, military recruits or college students living in a dormitory). • Complications include **autoimmune hemolytic anemia** (IgM against antigen on RBCs causes cold hemolytic anemia) and erythema multiforme. • Not visible on gram stain due to lack of cell wall.
Chlamydia pneumoniae	• Second most common cause of atypical pneumonia in young adults.
Respiratory syncytial virus (RSV)	• Most common cause of atypical pneumonia in **infants**.
Cytomegalovirus (CMV)	• Atypical pneumonia with **post-transplant immunosuppressive therapy**.
Influenza virus	• Atypical pneumonia in the elderly, immunocompromised, and those with preexisting lung disease. • Also increases the risk for superimposed S aureus or H influenza bacterial pneumonia.

Coxiella burnetii	• Atypical pneumonia with high fever (Q fever); seen in **farmers and veterinarians** (Coxiella spores are deposited on cattle by ticks or are present in cattle placentas). • Coxiella is a rickettsial organism, but it is distinct from most rickettsiae because it (1) causes pneumonia, (2) does not require arthropod vector for transmission (survives as highly heal-resistant endospores), and (3) does not produce a skin rash.

LUNG—PHYSICAL FINDINGS

ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
Pleural effusion	↓	Dull	↓	None if small Away from side of lesion if large
Atelectasis (bronchial obstruction)	↓	Dull	↓	Toward side of lesion
Simple pneumothorax	↓	Hyperresonant	↓	None
Tension pneumothorax	↓	Hyperresonant	↓	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy	Dull	↑	None

LUNG CANCER

BASIC PRINCIPLES

A. Most common cause of cancer mortality in the US; average age at presentation is 60 years.

B. **Key risk factors** are cigarette smoke, secondhand smoke, radon, and asbestos:

1. **Cigarette** smoke, secondhand smoke:
   i. Contain over 60 carcinogens; 85% of lung cancer occurs in smokers.
   ii. Polycyclic aromatic hydrocarbons and arsenic are particularly mutagenic.
   iii. Cancer risk is directly related to the duration and amount of smoking ('packyears').
2. **Radon** is formed by radioactive decay of uranium, which is present in soil.
   i. Accumulates in closed spaces such as basements.
   ii. Responsible for most of the public exposure to ionizing radiation; 2nd most frequent cause of lung carcinoma in US.
   iii. Increased risk of lung cancer is also seen in uranium miners.

C. **Presenting symptoms** are nonspecific (e.g., cough, weight loss, hemoptysis, and post obstructive pneumonia).

D. Imaging often reveals a **solitary nodule** ('coin-lesion'); biopsy is necessary for a diagnosis of cancer.
   1. Benign lesions, which often occur in younger patients, can also produce a **"coin lesion"**.
      Examples include:
      i. **Granuloma**: often due to TB or fungus especially Histoplasma in the Midwest.
      ii. **Bronchial hamartoma**: benign tumor composed of lung tissue and cartilage; often calcified on imaging.

E. Lung carcinoma is classically divided into 2 categories:
   1. **Small cell carcinoma** (15%): usually not amenable to surgical resection (treated with chemotherapy).
   2. **Non-small cell carcinoma** (85%): treated upfront with surgical resection (does not respond well to chemotherapy); subtypes include adenocarcinoma (40%), squamous cell carcinoma (30%), large cell carcinoma (10%), and carcinoid tumor (5%).

F. TNM staging:
   1. **T- T**umor size and local extension:
      i. **Pleural** involvement is classically seen with adenocarcinoma.
      ii. Obstruction of **SVC** leads to distended head and neck veins with edema and
      blue discoloration of arms and face (superior vena cava syndrome).
      iii. Involvement of **recurrent laryngeal** (hoarseness) or **phrenic** (diaphragmatic
      paralysis) nerve.
      iv. Compression of **sympathetic chain** leads to Horner syndrome characterized
      by ptosis (drooping eyelid), miosis (pinpoint pupil), and anhidrosis (no sweating); usually due to an apical (Pancoast) tumor.
   2. **N-** Spread to regional lymph **n**odes (hilar and mediastinal).
   3. **M-** Unique site of distant **m**etastasis is the **adrenal gland**.
   4. Overall, 15% 5-year survival; often presents late due to the absence of an effective screening method.

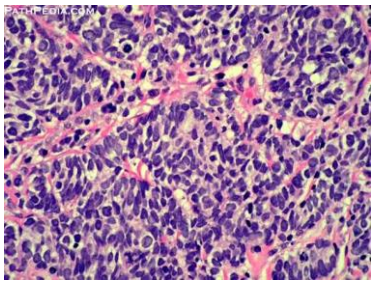
G. Lung metastasis:
   1. Usually multiple lesion.
   2. More common than 1° neoplasms.
   3. Most often from breast, colon, prostate, and bladder cancer.

H. **SPHERE of complications:**
   1. **S**uperior vena cava/thoracic outlet syndromes.
   2. **P**ancoast tumor.
   3. **H**orner syndrome.
   4. **E**ndocrine (paraneoplastic).
   5. **R**ecurrent laryngeal nerve compression (hoarseness).
   6. **E**ffusions (pleural or pericardial)

I. **S**quamous and **S**mall cell carcinomas are **S**entral (central) and often caused by **S**moking.

SMALL CELL CARCINOMA

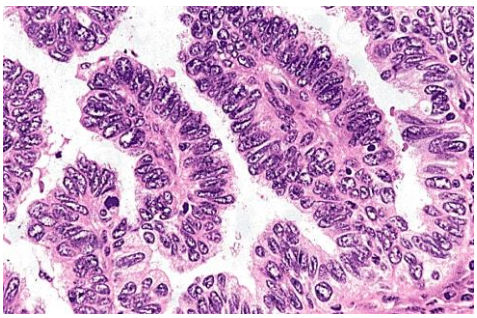
- Poorly differentiated small cells; arises from **neuroendocrine** "Kulchitsky" cells.
- **Most aggressive** type of lung cancer. Most patients have distant metastases at the time of diagnosis.
- Location: Central.
- **Characteristics:**
  - Undifferentiated → very aggressive.
  - May produce **A**CTH (Cushing syndrome), SI**A**DH, or **A**ntibodies against presynaptic Ca^{2+} channels (LambertEaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration).
  - **A**mplifcation of *myc* oncogenes common.
  - Managed with chemotherapy +/– radiation.
- **Pathology:**
  - Neoplasm of neuroendocrine **Kulchitsky cells** → **small dark blue cells** **A** → round or oval cells with scant cytoplasm and large hyperchromatic nuclei (resemble lymphocytes but are typically larger).
  - Tumor cells can form **sheets** or clusters. **Abundant mitoses** are usually seen.
  - **Neuroendocrine markers:** neural cell adhesion molecule (NCAM, also known as CD56), Chromogranin **A** ⊕, neuron-specific enolase ⊕, synaptophysin ⊕.



NON–SMALL CELL CARCINOMAS

ADENOCARCINOMA

- Location: Peripheral.
- **Characteristics:**
  - **Most common 1° lung cancer**.
  - More common in **women** than men, most likely to arise in ***nonsmokers***.
  - Activating mutations include ***KRAS***, *EGFR*, and *ALK*.
  - Associated with **hypertrophic osteoarthropathy** (**clubbing**).
  - **Bronchioloalveolar subtype** (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis.
  - Bronchial carcinoid and bronchioloalveolar cell carcinoma have lesser association with smoking.
- **Histology:**
  - **Glandular pattern** on histology, often stains **mucin** ⊕.
  - Bronchioloalveolar subtype: grows along alveolar septa → apparent "thickening" of alveolar walls.
  - Tall, **columnar** cells containing mucus.

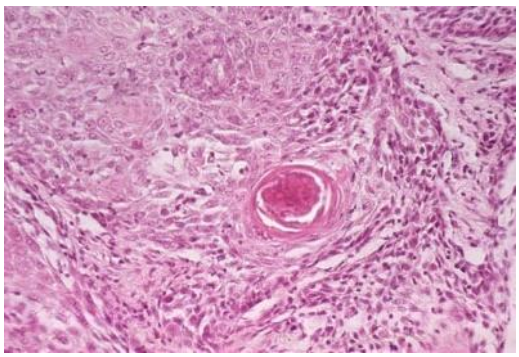


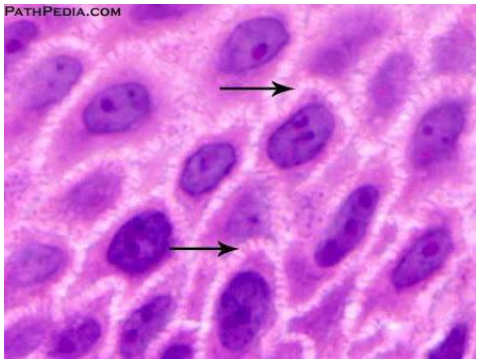
UW: **Adenocarcinoma in situ (formerly known as bronchioloalveolar carcinoma)**

- One of the major subtypes of lung adenocarcinoma.
- Not related to smoking.
- The tumor arises from the **alveolar epithelium** and is of the major subtypes of lung adenocarcinoma.
- It is considered a **preinvasive** lesion characterized by growth a**long intact alveolar septa** without vascular or stromal invasion (adenocarcinoma in situ).
- Microscopic examination reveals **well-differentiated, dysplastic columnar cells** that grow along preexisting bronchioles and alveoli (compare to normal lung).
- The tumor has a tendency to undergo aerogenous spread (along the airways) and can progress to **invasive disease if not resected**.
- Clinical manifestations are similar to other types of lung cancer and include cough, shortness of breath, and hemoptysis.
- Mucinous forms can also result in the production of copious amounts of watery sputum (**bronchorrhea**).
- Imaging shows a discrete mass or **pneumonia-like consolidation**.

SQUAMOUS CELL CARCINOMA

- **Location: C**entral
- **Characteristics:**
  - **Hilar mass** arising from bronchus; **C**avitation; **C**igarettes; hyper**C**alcemia (produces PTHrP).
- **Histology:**
  - **Keratin pearls** and **intercellular bridges**.





UW: **Smoking** induces **squamous bronchial metaplasia** while long-standing reflux results in columnar metaplasia of the distal esophagus (Barrett's esophagus). Both these conditions increase the risk of malignancy and are therefore referred to as premalignant

UW: **Vitamin A** maintains orderly differentiation of specialized epithelia, including the mucus-secreting columnar epithelia of the ocular conjunctiva, respiratory and urinary tracts, and pancreatic and other exocrine ducts. Avitaminosis A can cause **squamous metaplasia** of such epithelia to a keratinizing epithelium.

LARGE CELL CARCINOMA

- Location: Peripheral.
- **Characteristics:**
  - Highly anaplastic undifferentiated tumor; poor prognosis.
  - Less responsive to chemotherapy; removed surgically.
  - Strong association with **smoking**.
- **Histology:**
  - Poorly differentiated **"Pleomorphic" giant cells**.
  - No keratin pearls, intercellular bridges, glands, or mucin.

BRONCHIAL CARCINOID TUMOR

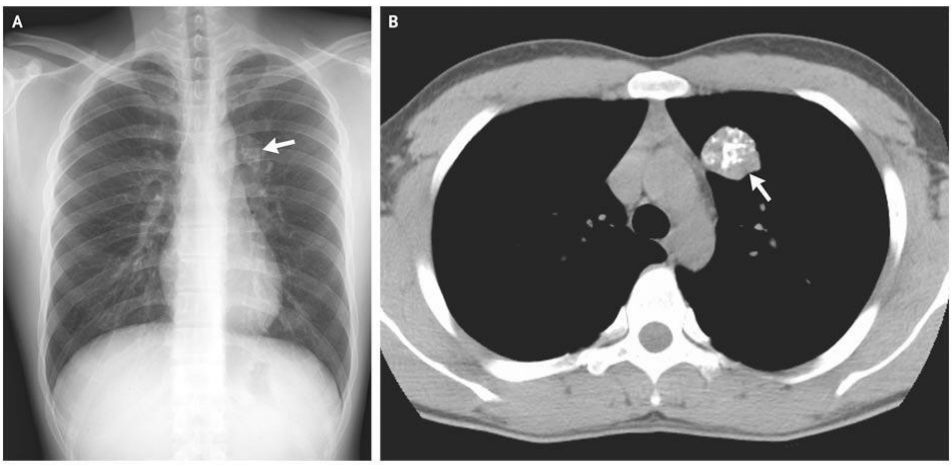
- Location: Central or peripheral
- **Characteristics:**
  - Excellent prognosis; metastasis rare.
  - Symptoms due to mass effect or **carcinoid syndrome** (flushing, diarrhea, wheezing).
- **Histology:**
  - Nests of **neuroendocrine cells**; chromogranin A ⊕.

Lung malignancies & associated paraneoplastic syndromes	
Small cell	• SIADH (ectopic ADH) • Cushing syndrome (ectopic ACTH) • Lambert-Eaton myasthenic syndrome • Cerebellar ataxia
Squamous cell	• Hypercalcemia (secretion of PTHrP)
Adenocarcinoma	• Hypertrophic osteoarthropathy • Dermatomyositis or polymyositis • Migratory thrombophlebitis (Trousseau syndrome)

Type of tumor	Incidence	Location	Clinical associations
Adenocarcinoma	40%-50%	• Peripheral	• Clubbing • Hypertrophic osteoarthropathy
Squamous cell carcinoma	20%-25%	• Central • Necrosis & cavitation	• Hypercalcemia
Small cell carcinoma	10%-15%	• Central	• Cushing syndrome • SIADH • Lambert-Eaton syndrome
Large cell carcinoma	5%-10%	• Peripheral	• Gynecomastia • Galactorrhea

LUNG HAMARTOMAS

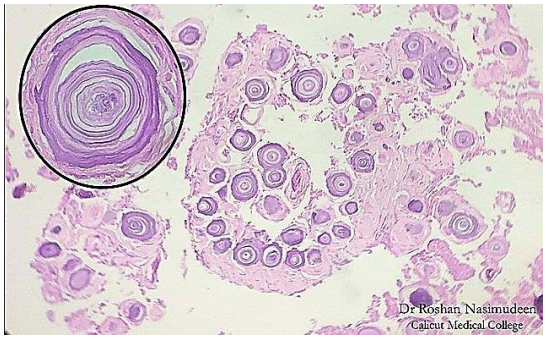
- A hamartomas is an excessive growth of a tissue type native to the organ of involvement.
- The lung is the most common location.
- Also called pulmonary **chondroma**.
- Usually present as incidental findings on chest x-ray, with the appearance of a **well-defined coin lesion** with "**popcorn calcifications**".
- Pathology: often contain islands of mature hyaline **cartilage**, fat, smooth muscle and clefts lined by respiratory epithelium.
- This incidentally discovered solitary lung nodule (or "coin lesion") is probably benign, but malignant and metastatic disease must be ruled out via tissue **biopsy**.



MESOTHELIOMA

- Malignancy of the pleura.
- **Risk factors:**
  - Associated with **asbestosis**.
  - Smoking not a risk factor.
- **Findings:**
  - **Hemorrhagic pleural effusion** (exudative).
  - **Pleural thickening**.
- **Histology:**
  - **Psammoma bodies** seen on histology.
  - Tumor cells with numerous, long slender **microvilli** and abundant **tonofilaments**.

- **Markers of mesothelioma:**
  - Immunohistochemical markers (eg, **pancytokeratin**) are useful in diagnosis.
  - **Calretinin** ⊕ in almost all mesotheliomas, ⊖ in most carcinomas.

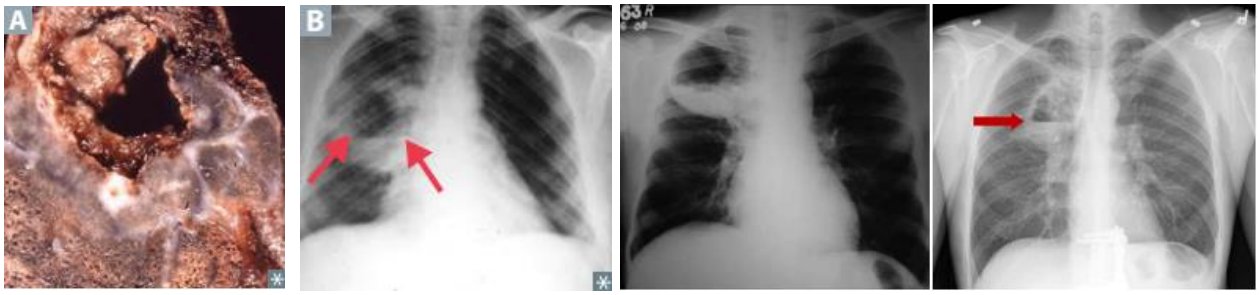


LUNG ABSCESS

- Localized collection of pus within parenchyma **A**.
- **Caused by the following mechanisms:**
  1. **Aspiration of oropharyngeal contents:**
     - Most common cause of lung abscess.
     - Often contain mixed aerobic and **anaerobic oral flora**; particularly Peptostreptococcus, Prevotella, Bacteroides, and Fusobactenum species.
     - Risk factors include conditions associated with **loss of consciousness** or **dysphagia**, such as alcoholism, drug overdose, seizure disorders, prolonged anesthesia, and severe neurologic diseases.
     - Most often found in **right lung**.
     - Location depends on patient's position during aspiration.
  2. **Complication of bacterial pneumonia:**
     - Predisposing factors include immunosuppression, old age, and underlying chronic lung disease.
     - Necrotizing pneumonias are usually **nosocomial** and caused by **Staphylococcus aureus**, Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa.
  3. **Hematogenous spread:**
     - In patients with septicemia or **infectious endocarditis**.
     - Often **multiple** and **monomicrobial**.
     - The most common causative agents are Staphylococcus and Streptococcus species.
  4. **Bronchial obstruction** (eg, cancer).
- **Symptoms:**
  1. Fever, night sweats, weight loss.
  2. Cough **productive of foul-smelling sputum** (indicative of anaerobes).
- **Dx:**
  1. Air-fluid levels **B** often seen on CXR.
  2. Fluid levels common in cavities; presence suggests cavitation.
- Treatment: antibiotics.

- UW: Tissue damage and resultant abscess formation is primarily caused by **lysosomal enzyme release** from neutrophils and macrophages.

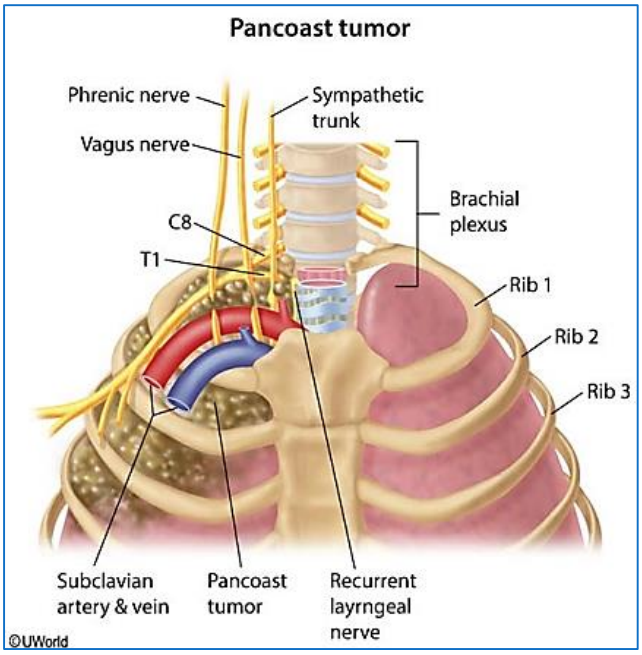
UW: **Mycobacterium tuberculosis** infection characteristically demonstrates granulomatous inflammation with caseous necrosis. Granuloma formation assists in disease containment and occurs mainly through an interaction among macrophages, multinucleated giant cells and CD4 T lymphocytes. Extensive **macrophage activation** can also result in collateral **tissue damage**, resulting in caseous necrosis with formation of cavitary lung lesions.

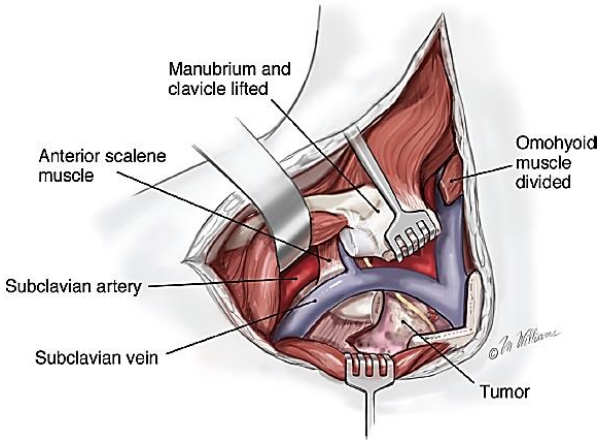


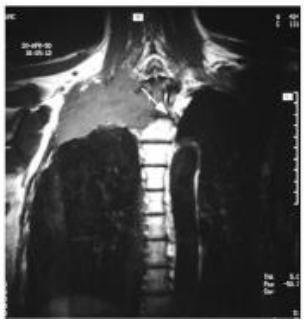
PANCOAST TUMOR

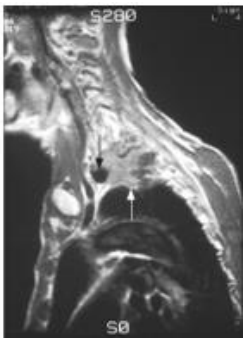
- Also known as **superior sulcus tumor** (groove formed by the subclavian vessels in the 1st rib).
- Carcinoma that occurs in the apex of lung **A** may cause Pancoast syndrome by invading **cervical sympathetic chain**.
- **Symptoms:** from compression of the surrounding structures:

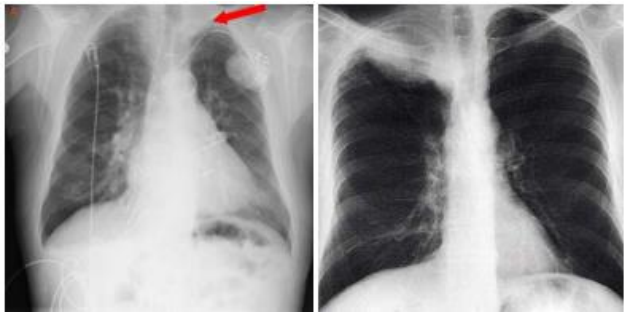
Compressed structure	Associated symptoms
Lower brachial plexus	• **Shoulder pain:** ▪ Radiating toward the axilla and scapula (most common presenting symptom). ▪ Other associated symptoms include arm paresthesia, weakness, and muscle atrophy.
Cervical sympathetic ganglia "stellate ganglion"	• **Horner syndrome:** ▪ Symptoms include ipsilateral ptosis, miosis, and anhydrosis.
Subclavian vessels	• **SVC syndrome** → Upper extremity edema.
Brachiocephalic vein	• Brachiocephalic syndrome (unilateral symptoms).
Recurrent laryngeal nerve	• **Hoarseness.**







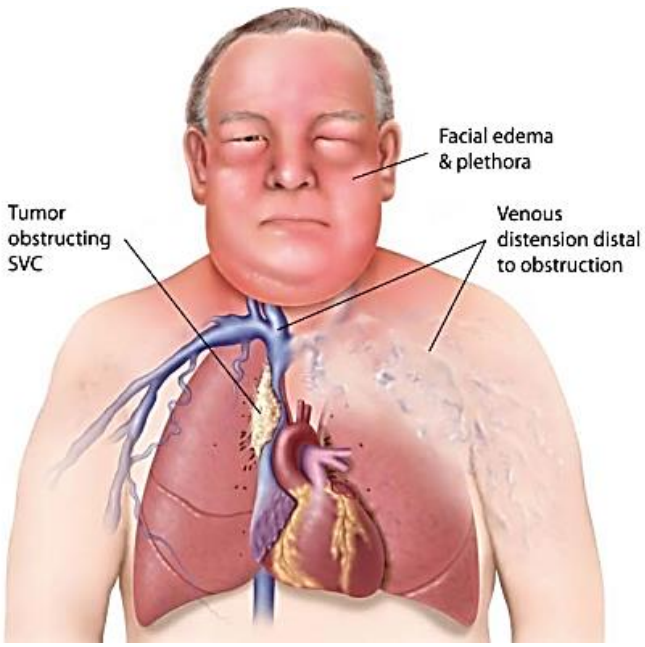


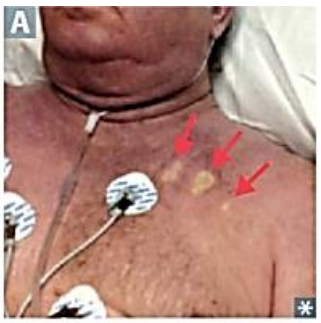


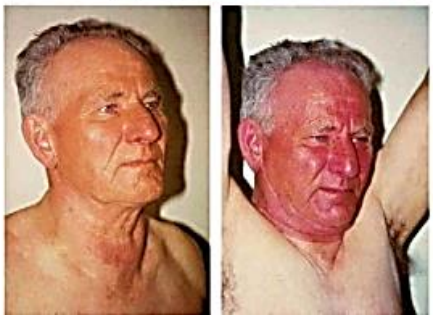
SUPERIOR VENA CAVA SYNDROME

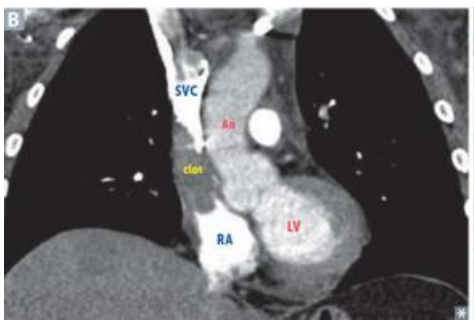
- **Presentations:**
  - An obstruction of the SVC that impairs blood drainage from the following:
    - **Head** → "facial plethora"; note blanching after fingertip pressure in **A**. Headaches, dizziness, confusion, ↑ risk of aneurysm/ rupture of intracranial arteries may occur due to cerebral edema and elevated intracranial pressure.
    - **Neck** → jugular venous distention.
    - **Upper extremities** → edema.
- **Causes:**
  - **Malignancy** (eg, mediastinal mass, Pancoast tumor).
  - **Thrombosis** from indwelling catheters **B**. Medical emergency.

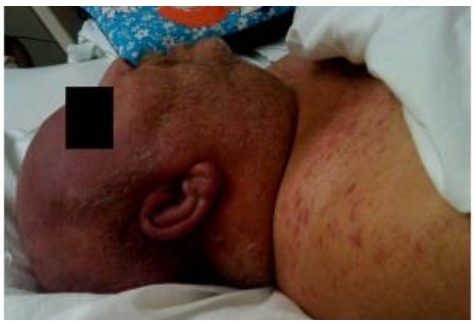
UW: Superior vena cava syndrome can sometimes occur with **Pancoast tumors**, but **shoulder pain** and **Horner's syndrome** are more frequent manifestations

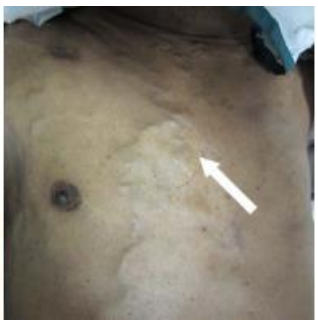




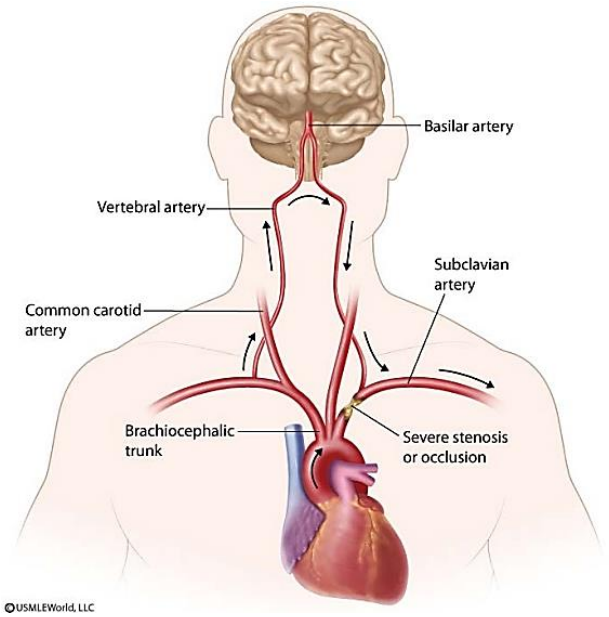






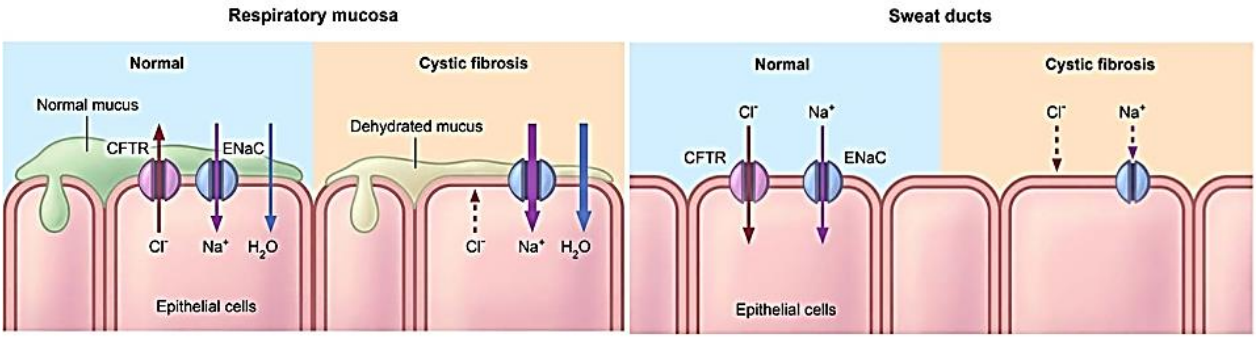


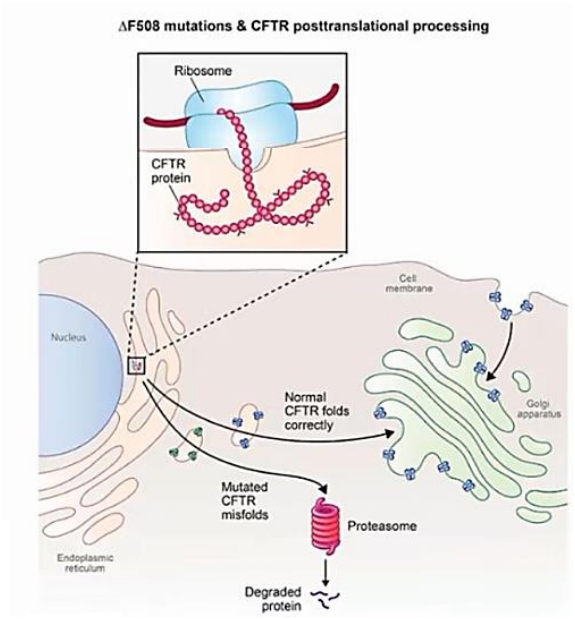
SUBCLAVIAN STEAL PHENOMENON

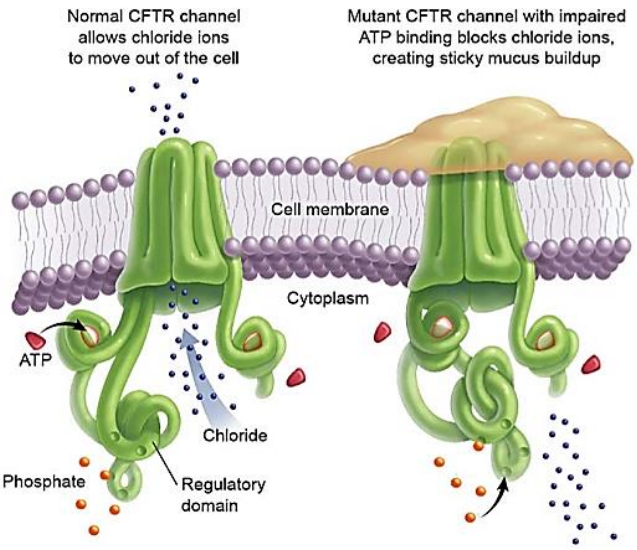


- **Definition:**
  - **Retrograde** blood flow in the **vertebral artery** associated with proximal ipsilateral **subclavian artery** stenosis or occlusion, usually in the setting of subclavian artery occlusion or stenosis proximal to the origin of the vertebral artery.
- **Symptoms & signs:**
  - Usually asymptomatic and discovered accidentaly.
  - **Arm muscle cramping** due to arm ischemia typically occurs in laborers performing vigorous work, often with *arms elevated above the head*.
  - **posterior-circulation cerebral ischemia:**
    - If the increased oxygen demand from arm exercise exceeds the ability of collateral vessels to provide sufficient blood flow to the brain as more blood is siphoned from the brain via the vertebrobasilar system.
    - Symptoms of dizziness, vertigo, syncope and dysarthria.
  - **Difference in blood pressure between both arms (high sensitivity)**.
  - The internal mammary artery (IMA) arises from the inferior aspect of the proximal subclavian artery, opposing the origin of the vertebral artery. **Recurrent symptoms of angina pectoris after otherwise successful coronary revascularization with a left IMA** (LIMA) graft may also indicate a hemodynamically significant proximal left subclavian stenosis.

CYSTIC FIBROSIS:







Genetics	• **Autosomal recessive**; defect in CFTR gene on chromosome 7; commonly a **deletion** of 3 base pairs of Phe508. • Most common lethal genetic disease in Caucasian population.
Pathophysiology	• *CFTR* encodes an **ATP-gated Cl^- channel** that secretes Cl- in lungs and GI tract, and reabsorbs Cl- in sweat glands. • Most common mutation → **misfolded protein** → protein retained in RER and not transported to cell membrane, causing ↓ Cl- (and H2O) secretion; ↑ intracellular Cl- results in compensatory ↑ Na+ reabsorption via epithelial Na+ channels → ↑ H2O reabsorption → abnormally **thick mucus** secreted into lungs and GIT. • ↑ Na+ reabsorption also causes more **negative transepithelial potential difference.**

Labs	• **↑ Cl- concentration** (> 60 mEq/L) in sweat is diagnostic. • If the sweat chloride test is equivocal, measurement of **nasal transepithelial potential difference** and **genetic testing** for CFTR mutations should be performed to confirm the diagnosis. • Can present with **contraction alkalosis** and **hypokalemia** (ECF effects analogous to a patient taking a loop diuretic) because of ECF H2O/Na+ losses and concomitant renal K+/H+ wasting. • **↑ Immunoreactive trypsinogen** (newborn screening).
Symptoms & complications	• **Pulmonary:** ▪ Recurrent **pulmonary** infections (eg, *S aureus* [early infancy], *P aeruginosa* [adolescence]). ▪ Obstructive lung disease & chronic bronchitis → bronchiectasis → reticulonodular pattern on CXR, opacification of sinuses. ▪ Nasal polyps, clubbing of nails. • **GIT:** ▪ **Meconium ileus** in newborns (MCCO meconium ileus). ▪ **Pancreatic** insufficiency, malabsorption with steatorrhea, fat-soluble vitamin deficiencies (A, D, E, K), ▪ **Biliary** cirrhosis, liver disease. • **Infertility** in men: ▪ Although spermatogenesis is usually normal, almost all males with CF are unable to secrete semen "**azoospermia"** due to **congenital bilateral absence of the vas deferens)** and • **Subfertility** in women: ▪ Amenorrhea, abnormally **thick cervical mucus**. ▪ CFTR mutations are likely responsible for **abnormal development of Wolffian structures** → vasal agenesis and defective sperm transport. • UW: Patients with CF produce eccrine sweat that contains high concentrations of sodium and chloride compared to normal individuals → **easy to collapse with exercise**.
Treatment	• Multifactorial: chest physiotherapy, albuterol, **aerosolized dornase alfa** (DNAse), and hypertonic saline facilitate mucus clearance. • **N-acetylcysteine** to loosen mucus plugs (cleaves disulfde bonds within mucus glycoproteins) • **Azithromycin** used as anti-inflammatory agent. • **Ibuprofen** slows disease progression. • Pancreatic enzymes for insufficiency.

	• FA 2018: In patients with Phe508 deletion: combination of **lumacaftor** (corrects misfolded proteins and improves their transport to cell surface) and **ivacaftor** (opens Cl^- channels → improved chloride transport).

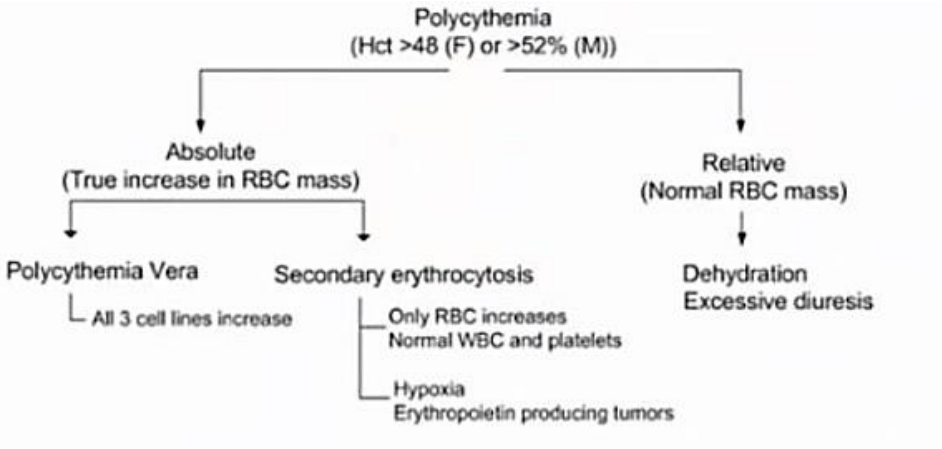
Primary ciliary dyskinesia versus cystic fibrosis

	Primary ciliary dyskinesia	Cystic fibrosis
Pathogenesis	• **Dynein arm defect** → abnormal ciliary motion & impaired mucociliary clearance	• Mutation in the ***CFTR* gene** → impaired ion transport
Respiratory tract features	• Chronic sinopulmonary infections • Nasal polyps • Bronchiectasis • Digital clubbing	• Chronic sinopulmonary infections • Nasal polyps • Bronchiectasis • Digital clubbing
Extrapulmonary features	• Situs inversus (50% of cases) • Infertility due to immotile spermatozoa • Normal growth	• Pancreatic insufficiency • Infertility due to absent vas deferens (azoospermia) • Failure to thrive
Diagnosis	• Low nasal nitric oxide levels • Bronchoscopy & electron microscopic visualization of ciliary abnormalities • Genetic testing	• Elevated sweat chloride levels • Abnormal nasal transepithelial potential difference • Genetic testing

UW TOPICS

POLYCYTHEMIA (ERYTHROCYTOSIS)

- Defined as a hematocrit level > **52%** in men and > **48%** in women.
- It may be the result of a true increase in the red blood cell (RBC) mass (absolute erythrocytosis) or decrease in the plasma volume (relative erythrocytosis).



- **Absolute vs. relative polycythemia** → measurement of RBCs mass.
- **Primary vs. secondary erythrocytosis** → measurement of EPO level.
- **Hypoxic vs. other causes of secondary erythrocytosis** → measurement of the SaO2 (<92% → hypoxic).

LUNG TRANSPLANT REJECTION

- **Hyperacute rejection:**
  1. Occurs within **minutes** of transplantation.
  2. **Preformed antibodies** against ABO or human leukocyte antigens (HLA) are the cause.
  3. There is graft **blood vessel spasm** and **diffuse intravascular coagulation**, with resultant ischemia.
  4. For this reason, hyperacute rejection is sometimes called **"white graft" reaction**.
  5. It is rare and often irreversible.
- **Acute rejection:**
  1. Occurs **1-2 weeks** after receiving a transplant.
  2. It represents the recipient's reaction to the HLA of the graft.
  3. This is a **cell-mediated** immune response and CD8 T cells play a central role.
  4. Acute rejection causes **vascular** damage.

5. Light microscopy shows perivascular and peribronchial **lymphocytic infiltrates**.
6. In lung transplantation, acute rejection manifests with dyspnea, dry cough, and low-grade fever.
7. Chest x-rays can show **perihilar and lower lobe opacities**.
8. Immunosuppressants can successfully treat acute rejection.

- **Chronic rejection**
  1. Occurs months or years following transplantation.
  2. It is the major cause of mortality in lung transplantation.
  3. Chronic rejection causes inflammation of the **small bronchioles** (i.e., **bronchiolitis obliterans**).
  4. Inflammation and fibrosis of the bronchiolar walls lead to narrowing and obstruction of the affected bronchioli.
  5. Clinically, bronchiolitis obliterans presents with dyspnea, nonproductive cough, and wheezing.
  6. This mechanism contrasts to the chronic rejection often seen in renal transplantation (primarily vascular obliteration).

PULMONARY EDEMA CELLS

- **Acute pulmonary edema (cardiogenic)** → transudate of plasma into the lung interstitium and alveoli.
- **Chronic pulmonary edema (CHF)** → Hemosiderin-containing macrophages in the alveoli (ie, siderophages, or “heart failure cells").

CAUSE OF GREENISH SPUTUM

- The green discoloration of pus or sputum noted during bacterial infections is associated with the release of **myeloperoxidase** (MPO) from neutrophil azurophilic granules.
- MPO is a heme-containing pigmented molecule.

Pharmacology

HISTAMINE-1 BLOCKERS

- Reversible inhibitors of H1 histamine receptors.

FIRST GENERATION:

- Diph**en**hydram**ine**, dim**en**hydrin**ate**, chlorph**en**iram**ine**. Names contain "-en/-ine" or "-en/-ate."
- **Clinical use:** Allergy, motion sickness, sleep aid.
- **Adverse effects:** Sedation, antimuscarinic, anti-α-adrenergic.

SECOND GENERATION

- Lorat**adine**, fexofen**adine**, deslorat**adine**, cetirizine. Names usually end in "-adine."
- **Clinical use:** Allergy.
- **Adverse effects:** Far less sedating than 1st generation because of ↓ entry into CNS.

GUAIFENESIN

- **Expectorant**—thins respiratory secretions; does not suppress cough reflex.

N-ACETYLCYSTEINE

- **Mucolytic**—liquefies mucus in chronic bronchopulmonary diseases (eg, COPD, CF) by disrupting **disulfide bonds**.
- Also used as an **antidote for acetaminophen** overdose.

DEXTROMETHORPHAN

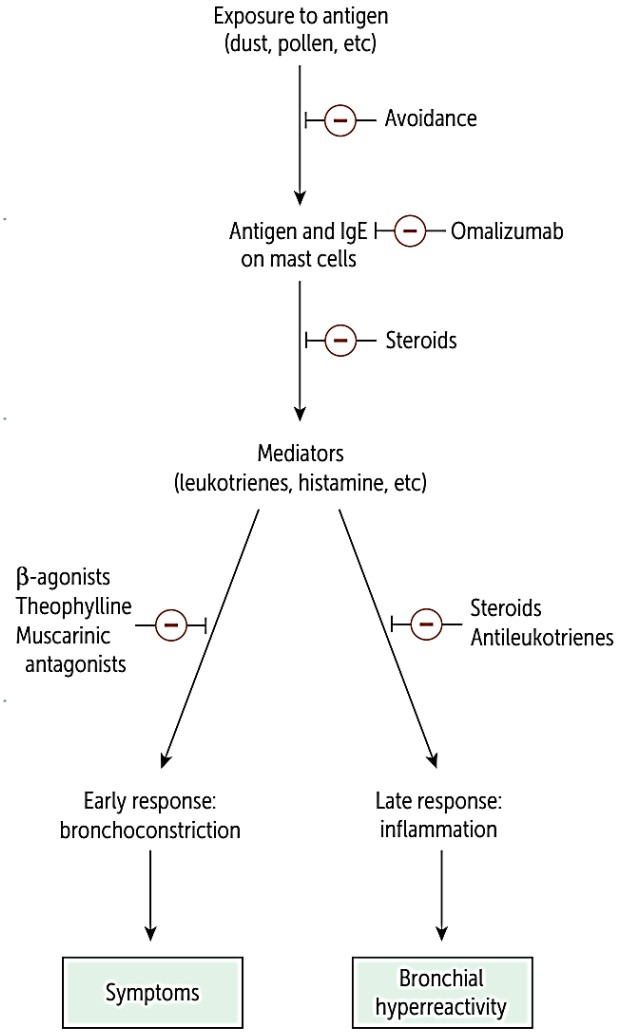
- **Antitussive** (antagonizes NMDA glutamate receptors). Synthetic **codeine analog**.
- Has mild opioid effect when used in excess.
- Naloxone can be given for overdose.
- Mild abuse potential.
- May cause serotonin syndrome if combined with other serotonergic agents.

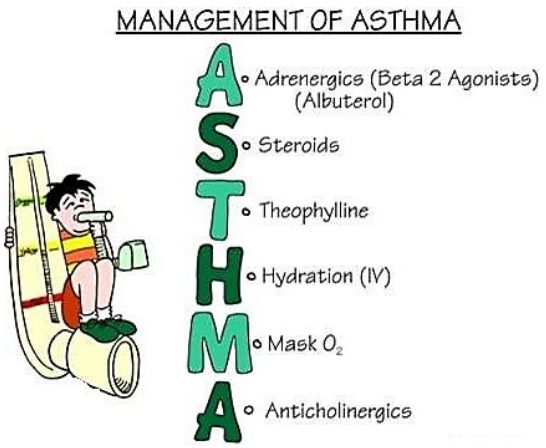
PSEUDOEPHEDRINE, PHENYLEPHRINE

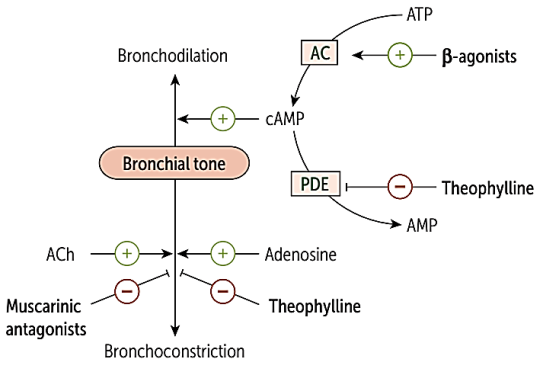
- **Mechanism:** α-adrenergic agonists, used as nasal decongestants.
- **Clinical use:** Reduce hyperemia, edema, nasal congestion; open obstructed eustachian tubes.
- **Adverse effects:** Hypertension. **Rebound congestion** if used more than 4–6 days. Can also cause CNS stimulation/ anxiety (pseudoephedrine).

ASTHMA DRUGS

- **Bronchoconstriction** is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.







B2-AGONISTS

- **Albuterol:**
  - Relaxes bronchial smooth muscle (**short acting** β2-agonist).
  - Used during acute exacerbation.
- **Salmeterol, formoterol:**
  - **Long-acting** agents for prophylaxis.
  - Adverse effects are tremor and arrhythmia.

INHALED CORTICOSTEROIDS

- **Fluticasone, budesonide:**
  - Inhibit the synthesis of virtually all cytokines.
  - Inactivate NF-κB, the transcription factor that induces production of TNF-α and other inflammatory agents.
  - **1st-line therapy for chronic asthma**.
  - Use a spacer or **rinse mouth after use to prevent oral thrush (oropharyngeal candidiasis)**.

MUSCARINIC ANTAGONISTS

- **Tiotropium, ipratropium**
  - Competitively block muscarinic receptors, preventing bronchoconstriction.
  - Also used for COPD.
  - Tiotropium is long acting.

ANTILEUKOTRIENES

- **Montelukast, zafrlukast:**
  - Block leukotriene receptors (CysLT1).
  - Especially good for **aspirin-induced and exercise-induced asthma**.
- **Zileuton:**
  - 5-lipoxygenase pathway inhibitor.
  - Blocks conversion of arachidonic acid to leukotrienes.
  - Hepatotoxic.

ANTI-IGE MONOCLONAL THERAPY

- **Omalizumab:**
  - Binds mostly unbound serum IgE and blocks binding to FcεRI.
  - Used in allergic asthma with ↑ IgE levels resistant to inhaled steroids and long-acting β2-agonists.

METHYLXANTHINES (THEOPHYLLINE)

- Likely causes **bronchodilation** by inhibiting phosphodiesterase → ↑ cAMP levels due to ↓ cAMP hydrolysis.
- **Adverse effects:**
  - Usage is limited because of **narrow therapeutic index**.
  - **Cardiotoxicity**:
    - ✓ Tachyarrhythmias are the other major concern but usually do not cause QT prolongation.
  - **Neurotoxicity**:
    - ✓ Mild cortical arousal and **insomnia**, much like caffeine.
    - ✓ **Seizures** are the major cause of morbidity and mortality in theophylline intoxication.
  - **Metabolized by cytochrome P-450**.
  - Blocks actions of adenosine.
- **Treatment of theophylline intoxication:**
  - Administration of **activated charcoal** to reduce gastrointestinal absorption.
  - **Beta blockers** are the drugs of choice for theophylline-induced cardiac tachyarrhythmias.
  - Theophylline-induced seizures are difficult to treat but benzodiazepines and barbiturates are the most effective agents.

MAST CELL STABILIZERS: CROMOLYN, NEDOCROMIL

- Prevent **release** of inflammatory mediators from mast cells.
- Used for **prevention** of bronchospasm, not for acute bronchodilation.

Respiratory first aid 2021 updates

- Oxygen content of blood P. 25

Methemoglobinemia	Normal	↓ (Fe^{3+} poor at binding O_2)	Normal	↓
Cyanide toxicity	Normal	Normal	Normal	Normal

- Head and neck cancer P. 37

Nasopharyngeal carcinoma may present with unilateral nasal obstruction, discharge, epistaxis. Eustachian tube obstruction may lead to otitis media +/– effusion, hearing loss.

- Pulmonary emboli P. 41

Obstruction of the pulmonary artery or its branches by foreign material (usually thrombus) that originated elsewhere. Affected alveoli are ventilated but not perfused ($\dot{V}/\dot{Q}$ mismatch).
May present with sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia, hypoxemia, respiratory alkalosis.
Treatment: anticoagulation (eg, heparin, direct thrombin/factor Xa inhibitors), IVC filter (if anticoagulation is contraindicated).

- Asthma presentation P. 48

Asymptomatic baseline with intermittent episodes of coughing, wheezing, tachypnea, dyspnea, hypoxemia, inspiratory/expiratory ratio, mucus plugging. Severe attacks may lead to pulsus paradoxus.
Triggers: viral URIs, allergens, stress.

- Restrictive lung diseases P. 51

Radiation-induced lung injury—Associated with proinflammatory cytokine release (eg,TNF-α, IL-1, IL-6). May be asymptomatic but most common symptoms are dry cough and dyspnea ± low-grade fever. Acute radiation pneumonitis develops within 3–12 weeks (exudative phase); radiation fibrosis may develop after 6–12 months.

- Idiopathic pulmonary fibrosis P. 51

Progressive fibrotic lung disease of unknown etiology. May involve multiple cycles of lung injury, inflammation, and fibrosis. Associated with cigarette smoking, environmental pollutants, genetic defects.
Findings: progressive dyspnea, fatigue, nonproductive cough, crackles, clubbing. Imaging shows peripheral reticular opacities with traction bronchiectasis
+/– "honeycomb" appearance of lung (advanced disease).
Histologic pattern: usual interstitial pneumonia.
Complications: pulmonary hypertension, respiratory failure, lung cancer, arrhythmias.

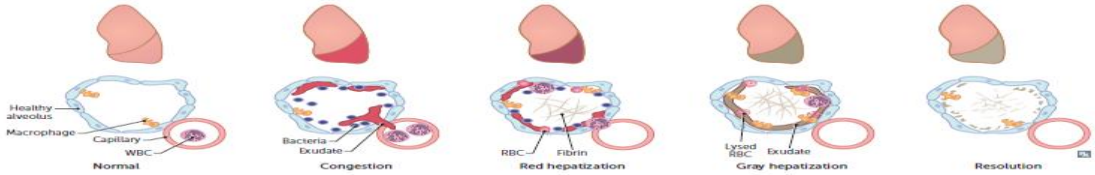
- Hypersensitivity pneumonitis P. 57

Mixed type III/IV hypersensitivity reaction to environmental antigens. Often seen in farmers and bird-fanciers. Acutely, causes dyspnea, cough, chest tightness, fever, headache. Often self-limiting if stimulus is removed. Chronically, leads to irreversible fibrosis with noncaseating granuloma, alveolar septal thickening, traction bronchiectasis.

➢ Digital clubbing P. 49

Increased angle between nail bed and nail plate (> 180°) A . Pathophysiology not well understood; in patients with intrapulmonary shunt, platelets and megakaryocytes become lodged in digital vasculature local release of PDGF and VEGF. Can be hereditary or acquired. Causes include respiratory diseases (eg, idiopathic pulmonary fibrosis, cystic fibrosis, bronchiectasis, lung cancer), cardiovascular diseases (eg, cyanotic congenital heart disease), infections (eg, lung abscess, TB), and others (eg, IBD). Not typically associated with COPD or asthma.

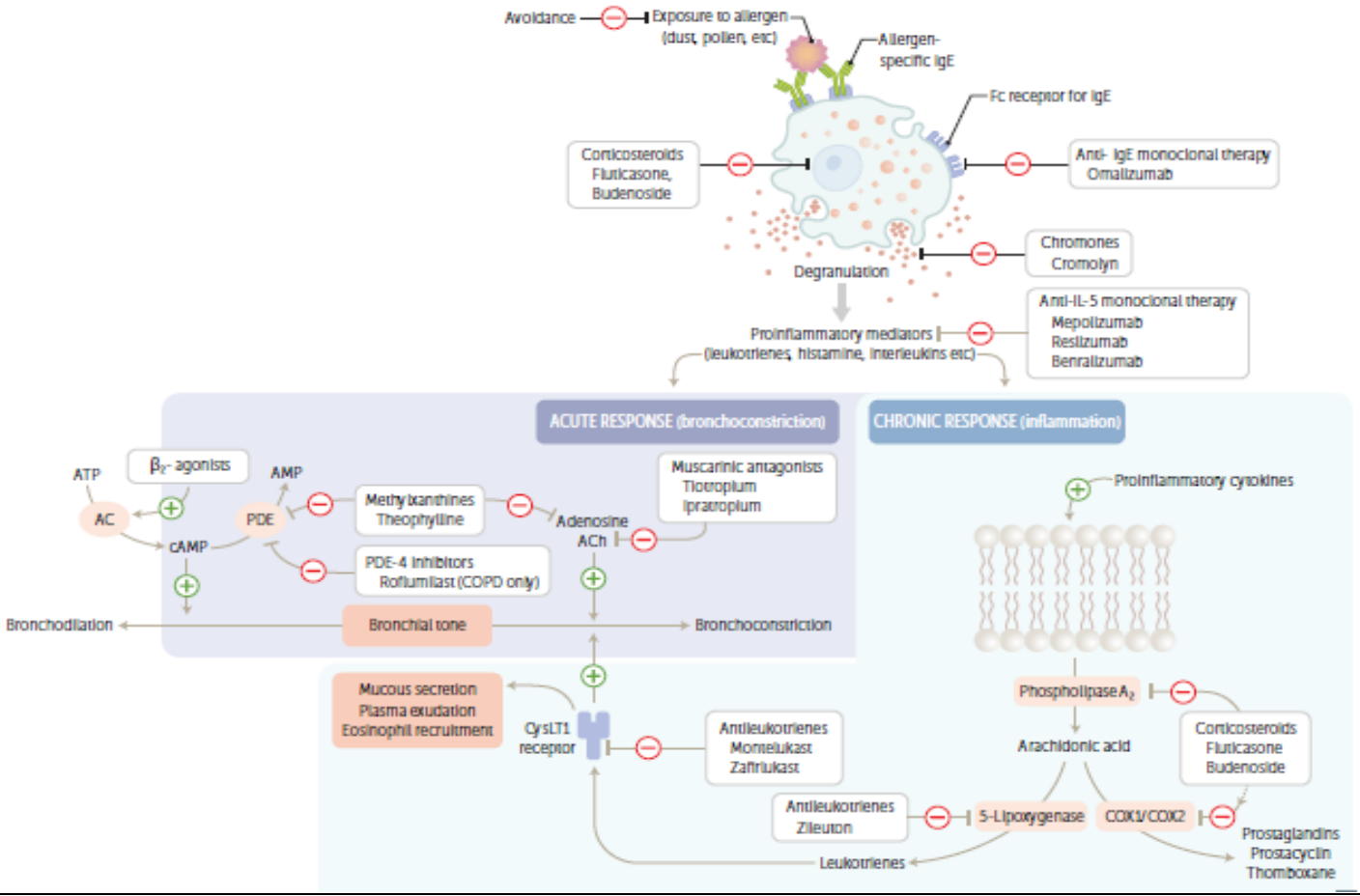
➢ Natural history of lobar pneumonia P. 69



➢ Pseudoephedrine, phenylephrine adverse effects P. 89

Rebound congestion (rhinitis medicamentosa) if used more than 4–6 days.

➢ Asthma drugs P. 89



Respiratory UW updates

- Amniotic fluid total protein & albumin ↓↓ by 50% from early gestation till term

- Amniocentesis:

1. assess lung maturity → L/S ratio.
2. neural tube colure defect → elevated AFP.
3. suspected eryhroblastosis fetalis → elevated bilirubin.
4. suspected chromosomal anomalies and metabolic disorders → karyotypingfor obtained cells in the AF.
5. suspected cystic fibrosis → fetal cells → genetic mutation analysis.
6. suspected fetal CAH → 17-hydroxyprogesterone levels or detection of abnormal genes via molecular probes or gene linkage analysis involving the HLA region of chromosome 6.

- Panic attacks → hyperventilation → excess CO2 wash → hypocapnia & respiratory alkalosis (↓↓ PCO2, ↓↓ H+) → vasoconstriction of the cerebral vessels → ↓ cerebral blood flow → neurological symptoms including dizziness, blurred vision, and lightheadedness.

- Pulmonary HTN not affect lung compliance … it is a vascular disease not parenchymal.

- Cyanide metabolized in tissues by rhodanese → enzyme that transfer a sulfur molecule to cyanide → to form thiosulfate → *excreted in urine*.

- Pathological features of cryptogenic organizing pneumonia (COP): present acutely with fever & weight loss. It shows intra-luminal plugs of granulation tissue & inflammatory debris in distal airways.

- Causes of digital clubbing :
  - ⇨ It is due t ↑↑ PG E → ↑↑ platelets activation & production of PDGFs → cytokines.

1. Lung diseases: large cell lung carcinoma, TB, CF, P. hypertension, bronchiectasis.
2. CV diseases: cyanotic heart diseases, endocarditis.
3. IBD, hyperthyroidism, malabsoprtion.

- V/Q scans are 2-part studies that compare regional ventilation and perfusion. The initial phase uses a radiolabeled aerosol that is inhaled and delivered throughout the tracheobronchial tree. The second phase uses an intravenous tracer that is distributed throughout the pulmonary vasculature. The images are then overlaid for comparison.

- Normal results show even distribution of both radionucleotide tracers throughout the lung (ie,V/Q match).

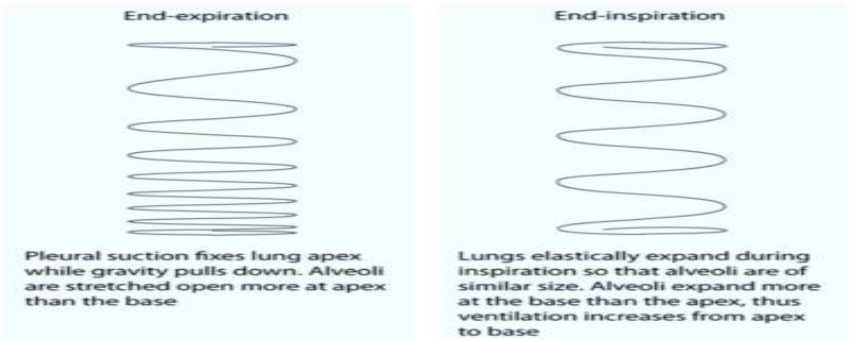
- Paraseptal: most common in young, otherwise healthy males, does not obstruct airway, associated with bullae, occurs near pleura, increased risk for spontaneous pneumothorax.

- Lofgren syndrome: *acute form of sarcoid with bilateral hilar lymph nodes, erythema nodosum, polyarthritis*.

- Define dynamic hyperinflation:
  In COPD patients (*especially during exercise)* more time is needed for expiration but, expiration time is reduced in exercise due to rapid breathing → more air trapping in the lung → main mechanism of dyspnea & exercise limitless in COPD patients.

- PAS stain features of AAT deficiency ➔ intra-cellular granules of unsecreted AAT seen in the periportal hepatocytes with pinkish color on PAS, resist digestion by diastase.

- The "slinky effect" of lung ventilation



- Diagnostic studies for PE:

1. Initially, CTPA is the preferred diagnostic modality.
2. In patient with CKD → contrast cannot be injected → *the preferred choice then is V/Q scan.*

- PAS stain features of AAT deficiency ➔ intra-cellular granules of unsecreted AAT seen in the periportal hepatocytes with pinkish color on PAS, resist digestion by diastase.

- Smoking induced emphysema :
  1. Smoke → activation of resident alveolar macrophages → neutrophils recruitment lead to activation and release of proteases eg elastase that degrade lung parenchyma.
  2. Also generate oxygen free radicles → oxidation of methionine resideus on the anti-trypsin enzyme → permanent deactivation → impair protease inhibitors.

❖ A) **Centriacinar**	❖ B) **Panacinar**
❖ Smoking (>30 pack-year)	❖ ATT deficiency
❖ Proximal portion of acini is exposed first to smoke → centri	❖ Elastases present everywhere throughout acini → panacinar
❖ Relative higher ventilation in upper lobes → more in upper lobes	❖ Relative higher perfusion in lower lobes → more neutrophil infiltration → more release of elastases → more in lower lobes
❖ Older age	❖ Younger age (around age 30)

- Risks of secondhand smoke (SHS) exposure:
  - Prematurity, low birth weight
  - Sudden infant death syndrome
  - Middle ear disease (otitis media)
  - Asthma
  - Respiratory tract infections (bronchitis, pneumonia)

- Somehow difficult to DD with hypersensitivity pneumonitis → BAL
  CD8 cells → more ↑↑↑ in cases of hypersensitivity pneumonitis.
  CD4 cells → more ↑↑↑ in cases of Sarcoidosis (*CD4/CD8 ratio is usually > 2:1)*

- Collagen Vascular Pneumonitis :

  restrictive lung disease resulting from a variety of autoimmune disorders, causes:
  A) SLE: pleuritis + pleural effusions.
  B) RA (Rheumatoid Lung Disease):

1. pleuritis + pleural effusions.
2. presents with gradual-onset dyspnea, end-inspiratory rales at lung base.
3. CXR shows bilateral, diffuse appearance.
4. lung biopsy shows patchy interstitial lymphoid infiltrate into walls of alveolar units.
5. not associated with rheumatoid lung nodules seen in Caplan syndrome.
6. severe forms may progress to honeycomb lung disease.

C) Systemic Sclerosis (Scleroderma): may also manifest as CREST Syndrome (variant of Scleroderma with less systemic involvement).

- ✓ presents with interstitial fibrosis due to collagen deposition triggered by accumulation of TGF-β-secreting T-cells in lungs.
- ✓ primarily involves capillaries and small arterioles.
- ✓ may lead to pulmonary hypertension and cor pulmonale.

- Iatrogenic Pneumonitis **:**

1. Drugs: anti-cancer agents (Bleomycin, Busulfan, Methotrexate, Nitrosourea, Cyclophosphamide), antiarrhythmics (Amiodarone).
2. Radiation: post-treatment pneumonitis (1-6 months after treatment), presents with fever, dyspnea, pleural effusions.

- Hypersensitivity Pneumonitis granulomatous reaction to inhaled organic antigens. types:
  1.) Silo Filler's Disease: caused by NO gases released by plant matter.
  2.) Byssinosis: caused by textile dusts (cotton, hemp, linen).
  3.) Farmer's Lung: caused by *Saccharopolyspora rectivirgula* (thermophilic *Actinomyces*).

- Define Ranke complex in TB
  - Ghon's focus is the primary pathology is TB, when macrophages are activated by the cytokines, it lead to fibrosis, calcification of the primary TB in > 95% of patients, the fibrosed & calcified Ghon's focus can be easily seen radiologically … this is Ranke complex.
  - The wall is fibrosed not but the organism still not eliminated from the body → if the walls of the granuloma weakens, the organism can escape and cause reactivation.

- Undine's curse (congenital central hypoventilation $): abnormalities in involuntary respiration with ↓ ↓ frequency / amplitude of respiration.

- Cutaneous manifestations range from macules / papules to erythema nodosum (*painful nodules on shin).*

- Causes of Cryptogenic Organizing Pneumonia (Bronchiolitis Obliterans):

  1) Transplant Rejection: chronic rejection in lung or allogenic bone marrow transplant, serious problem in lung transplant patients, vasculature relatively unaffected unlike rejection of other organs (e.g. kidney).
  2) Viral Infections.
  3) Collagen Vascular Diseases.
  4) Toxic Fumes.
  5) Drugs: Amiodarone.
  6) RA.

- Significance of ALK gene, and its role in malignancy, treatment :
  - On the short arm of chromosome 2 → inversion occur lead to fusion gene between EML4 (*microtubule …),* ALK (*anaplastic lymphoma kinase).*
  - This change occur in 4% of patient with non small cell lung adenocarcinoma.
  - This fusion protein act through *active tyrosine kinase lead to malignancy*.
  - *It occur in adenocarcinoma who lack the mutation in EGFR and Kras activity (intact tyrosine kinase pathway).*
  - Treatment is through crizotinib.

- Pulmonary Alveolar Proteinosis :

1. pneumonitis characterized by filing of alveoli with proteinaceous material.
2. may be primary (idiopathic) or secondary (due to infection or malignancy).
3. caused by increased surfactant production, defective macrophage clearance, or atypical infection.
4. histology: alveoli filled with focally dense pink, PAS⊕ proteinaceous material (hyaline globs) called “chatter” or “dense bodies”.