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<u>**CONCEPT:** ANATOMY AND ORGANIZATION OF THE RESPIRATORY SYSTEM</u>

● **Respiratory System** is responsible for gas exchange—handling O_2 and CO_2—in the body.

□ **Pulmonology** is the study of the respiratory system.

-**Pulmonary** is the adjective for stuff related to the respiratory system (e.g. pulmonary artery).

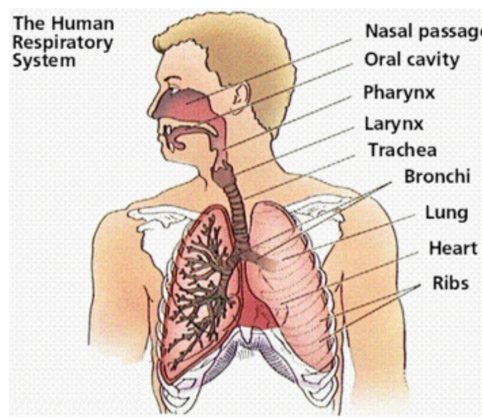
<u>The Airways:</u>

● **Lungs** are organs in the chest responsible for bringing in O_2 and getting rid of waste CO_2.

□ Two of them—right and left.

□ Right lung has _________ **lobes**, left lung has _________ (saving room for the heart).

● **Pharynx** is the back part of the mouth—shared passageway for air and food/drink.



□ Pharynx splits into **esophagus**—tube for food going to stomach—and *trachea* farther down the neck.

● **Trachea** is the "windpipe"—brings air from the pharynx into the lungs.

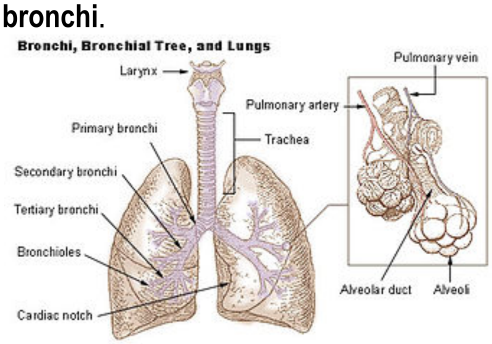
□ **Larynx** is the voicebox/vocal cords, and also the beginning of the trachea.

□ Trachea wall has many C-shaped cartilage rings, giving it extra stiffness and support (and preventing collapse).

● **Primary Bronchi** are the first airway branches off of the trachea.

□ Two of them—right and left, one per lung.

● From the primary bronchi are many, many more branches—also generally called **bronchi**.



□ These get progressively smaller and smaller.

□ Also have walls with cartilage.

● **Bronchioles** are smallest branches off of the bronchi.

□ Are collapsible—walls made largely of smooth muscle.

● **Alveoli** are the grape-like ends of the smallest bronchioles, where gas exchange between lung air and blood occurs.

Function of the Airways—Production of Mucus:

● Airways serve three major functions for the body:

1) *Warm* air up to body temperature (~37°C).

2) *Humidify* air (add water vapor).

3) *Filter* foreign material out.

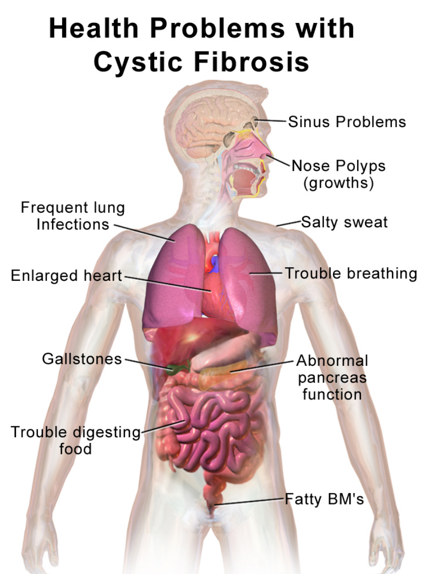
● **Ciliated Epithelial Cells** line airways of the lungs.

□ Have **cilia**—finger-like projections—that beat upward.

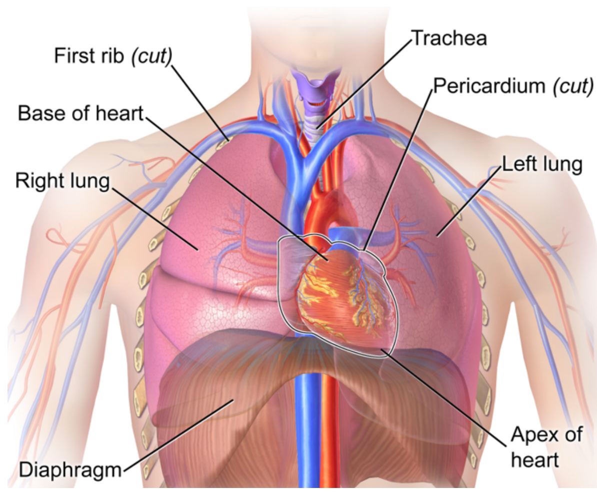
□ Also produce **mucus**—sticky water fluid—that lie on top of the cells.

-Foreign material (bacteria, dust) get trapped in the mucus. Beating cilia then push it up and out of lungs.

EXAMPLE: Cystic fibrosis patients have reduced capability to produce mucus—their mucus is thick and dry. This mucus clogs their airways and prevents them from clearing foreign material effectively.



The Thoracic Cavity:



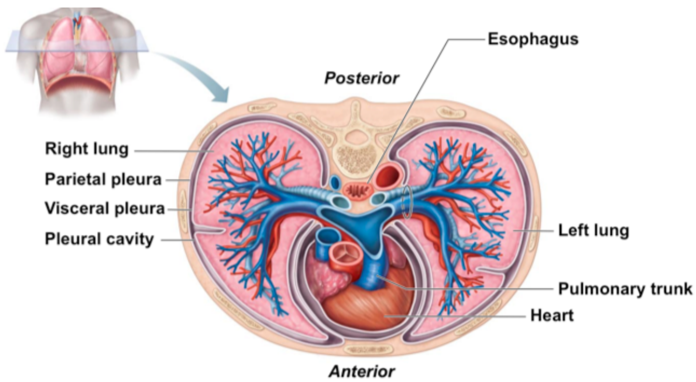
● **Thoracic Cavity** is the inside of the chest—from the neck to the diaphragm.

□ Holds lungs, heart, esophagus, etc.

□ Enclosed by the **ribs**.

□ **Diaphragm** is a sheet of skeletal muscle that separates the thoracic and abdominal cavities.

● **Pleural Cavity** is a small, thin fluid-filled space between the lungs and the ribcage.



□ **Visceral Pleura** is pleural membrane contacting lungs.

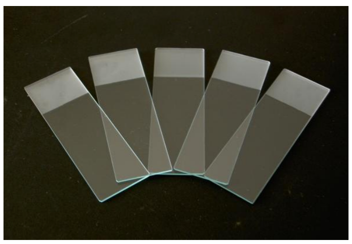
□ **Parietal Pleura** is pleural membrane contacting ribs.

● **Pleural Fluid** fills the pleural cavity. Two functions:

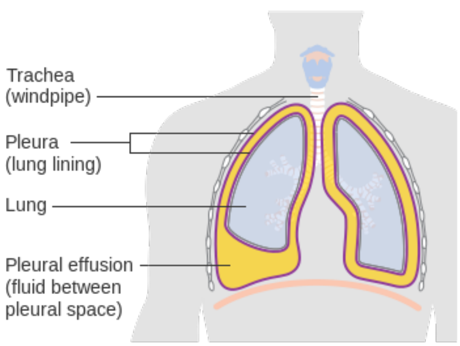
1) Acts as ______________________________, letting lungs slide smoothly across ribcage.

2) Generates surface tension, keeping lungs close to chest wall.

EXAMPLE: The pleural fluid in the pleural cavity acts like a thin layer of water between two glass microscope slides.



EXAMPLE: Pleural effusion is when extra fluid collects in pleural cavity, causing lung to collapse.



PRACTICE 1: A 16-year-old female presents to the emergency department with a 2-hour history of difficulty breathing. She is diagnosed with an asthma attack, which is caused by excessive constriction of smooth muscle in the walls of her airways. Which of the following is the part of her airways that has the most smooth muscle and is thus contributing most to her asthma attack?

a) Pharynx.
b) Larynx.
c) Trachea.
d) Primary Bronchi.
e) Bronchioles.
f) Alveoli.

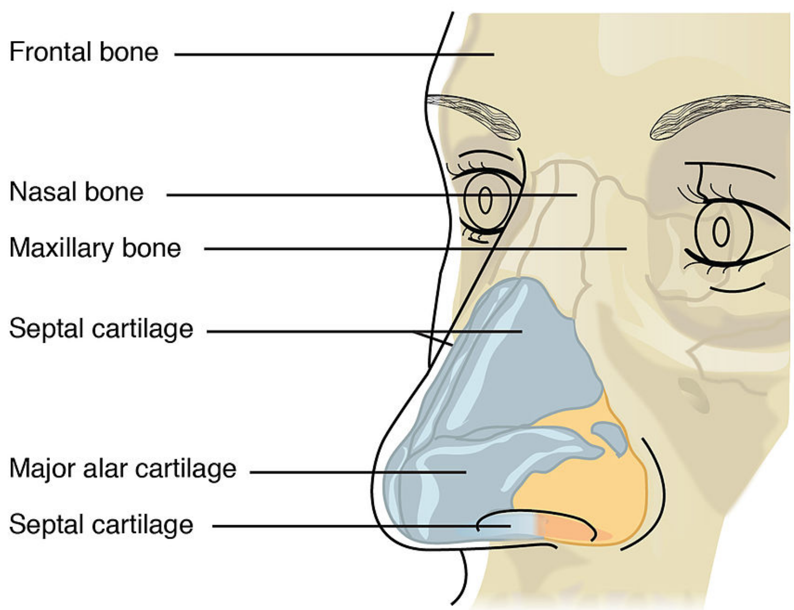
PRACTICE 2: A 57-year-old male presents to his primary care physician complaining of a chronic cough. He reports that he feels the need to cough because his lungs are full of mucus; indeed, his coughs bring up large amounts of greenish-brown mucus. He has smoked two packs of cigarettes per day for the last forty years. Which of the following parts of his respiratory tract has been damaged by his smoking, *causing mucus to accumulate in his lungs*?

a) Pharynx.
b) Larynx.
c) Trachea.
d) Alveoli.
e) Cilia.

CONCEPT: NOSE AND NASAL CAVITY

- Inhaled air first enters through the nose and nasal cavity
  - □ The **nose** is a structure made of bone, cartilage (hyaline), dense irregular connective tissue, and skin
    - The pair of **lateral cartilage** forms the __________________ of the nose
    - The pairs of **alar cartilages** form the tip of the nose
    - The **nostrils** are made of dense irregular connective tissue and lead into the nasal cavity
    - The nose is the first structure of the air conducting pathway

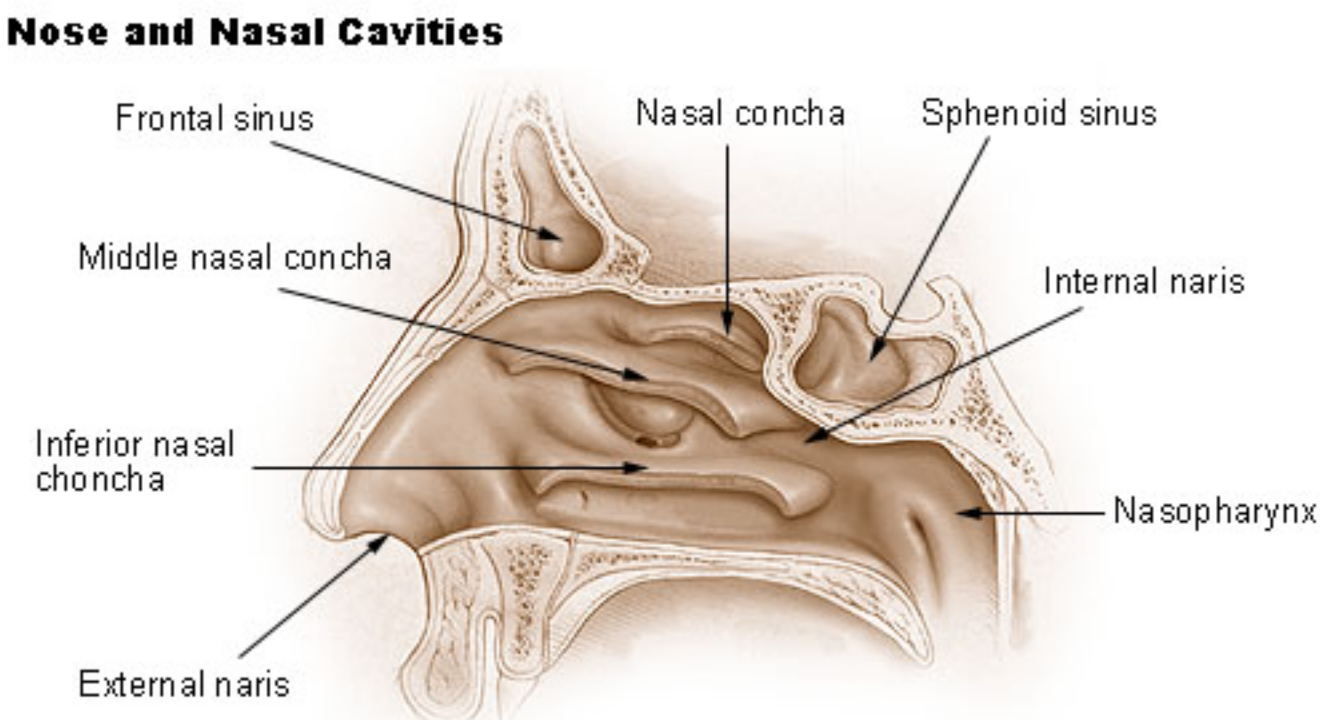
EXAMPLE:



□ The **nasal cavity** travels from the nostrils to the **choanae** (*posterior nasal aperatures)*, which leads to pharynx

- Roof: formed from nasal, frontal, sphenoid, and ____________________ bones
- Floor: formed from the hard and soft palate
- Anterior: formed by septal nasal cartilage
- Lateral: has three bony __________________: **superior, middle**, and **inferior conchae**
    - These bones produce turbulence in inhaled air and separate the cavity into *nasal meatus*
    - **Nasal meatus** is a passageway for air in the nasal cavity
- The **nasal septum** divides the cavity into left and right portions

EXAMPLE:



□ The **nasal cavity** is divided into three main subsections

1. The **nasal vestibule** traps large particulates

   - Internal to nostrils and is covered in **vibrissae** hairs

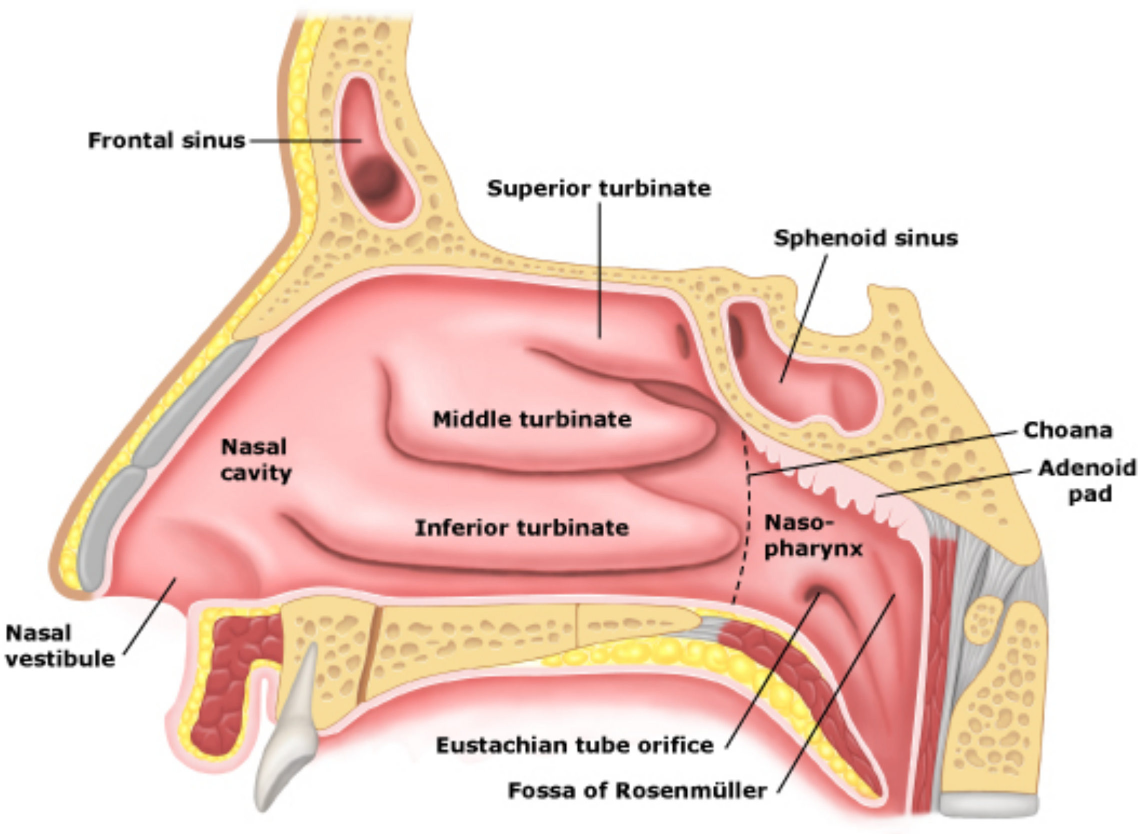
2. The **olfactory region:** superior to the nasal cavity, contain olfactory epithelium with olfactory receptors

   - Odor particles are __________________ in the mucus and are detected by olfactory receptors

3. The **respiratory region** contains a lot of blood vessels which conditions the air for the respiratory tract

   - This helps to warm, cleanse, and humidify the air before it enters the tract

EXAMPLE:

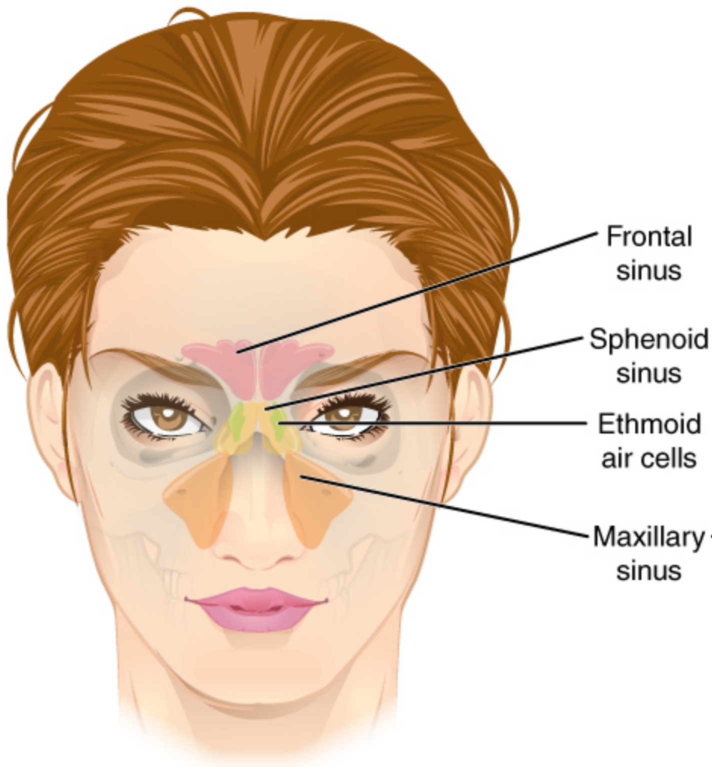


● The **paranasal sinuses** are air spaces in the skull bones and are connected with the nasal cavity

□ The paranasal sinuses include:

- **Frontal sinuses**, **ethmoidal sinuses, maxillary sinuses, sphenoidal sinuses**
- Ducts connect the sinuses to the nasal ______________________
- Continuous with the mucosa of nasal cavity, lined with pseudostratified ciliated columnar epithelium

EXAMPLE:



CONCEPT: PHARYNX

● The **pharynx** (*throat)* is a 13cm passageway posterior to the nasal cavity, oral cavity, and larynx, composed of 3 areas:

□ The **nasopharynx** is the superior-most region of the pharynx

- Extends from the inferior nasal cavity to the ___________________ palate
- Only air passes through the nasopharynx; food/drink is blocked by the soft palate
- Holds a *pharyngeal tonsil* (*adenoids* when enlarged)
- **Auditory tubes** are lateral openings that connect to the middle ear to equalize air pressure

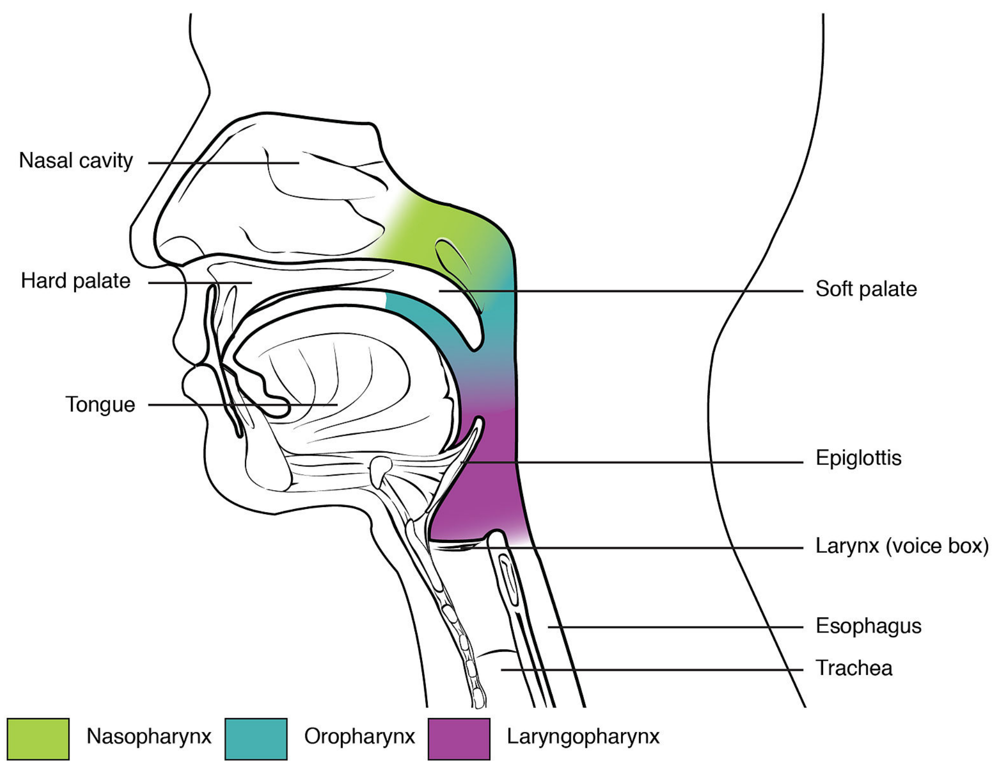
□ The **oropharynx** is the middle region of the pharynx, posterior to the oral cavity

- Extends from the soft palate to the hyoid bone
- Passageway for food and ___________
- Lateral wall holds the *palatine tonsils* while the *lingual tonsils* that are found at the anterior region

□ The **laryngopharynx** is the most inferior portion of the pharynx, and is precisely posterior to the larynx

- Extends from hyoid bone to the cricoid cartilage
- Passageway for food and air

EXAMPLE:



CONCEPT: LARYNX

● The **larynx** (*voice box*) produces sounds, is a passageway for air, and prevent materials from entering the res. tract

□ The larynx is located between the laryngopharynx (C3) and the trachea (C7)

- A **laryngeal inlet** is an opening that connects the pharynx and larynx

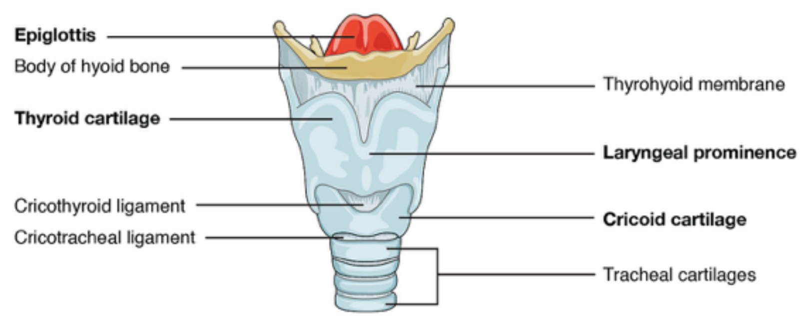
□ The larynx is made of 9 ______________________

1. **Thyroid cartilage** (1): largest; forms a shield around the anterior/lateral larynx, incomplete posteriorly
   - Has V-shaped **laryngeal prominence** (*Adam's apple*)
2. **Cricoid cartilage** (1): is inferior to thyroid cartilage and articulates with arytenoid cartilage
   - It has a complete, posteriorly-broad ring that provides the support the thyroid cartilage does not
3. **Epiglottis cartilages** (1): is attached to inner superior thyroid cartilage; shaped like a large leaf
   - During swallowing, the larynx elevates and it collapses on top of the of the laryngeal inlet

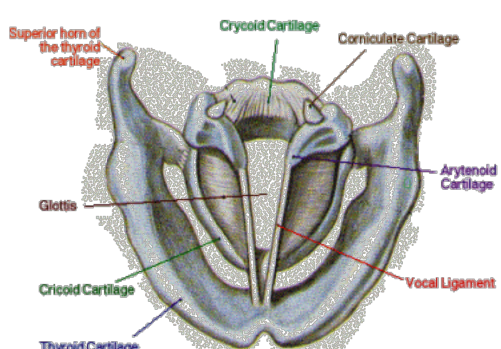
4. **Arytenoids cartilages** (2) 5. **Corniculate cartilages** (2) 6. **Cuneiform cartilages** (2)

- Are all ____________________, small, located internally to thyroid cartilage

EXAMPLE:



Anterior view



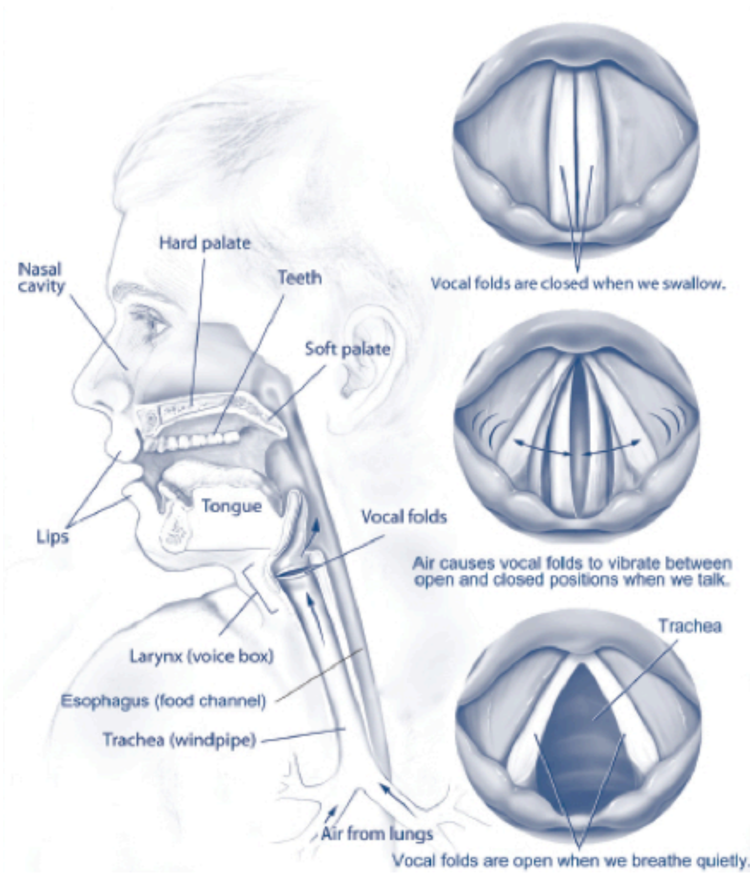
The Larynx: viewed from above

□ **Extrinsic ligaments** attach the hyoid bone to thyroid cartilage and the cricoid cartilage to trachea

□ **Intrinsic ligaments** connect all the nine cartilages together, creating the ________________; it also includes:

- **Vocal ligaments**: made of elastic connective tissue; extends from thyroid cartilage to arytenoid cartilages
    - **Vocal folds** are covered in mucosa; vibrates when air passes between them, producing sound
    - Vocal folds + **rima glottides** (the opening between the two folds) forms the **glottis**
- **Vestibular ligaments** attach the thyroid to the arytenoid and corniculate cartilages
    - VL + mucosa forms the **vestibular folds**, located superior to the vocal folds
        - Opening of vestibular fold are called **rima vestibuli**

EXAMPLE:



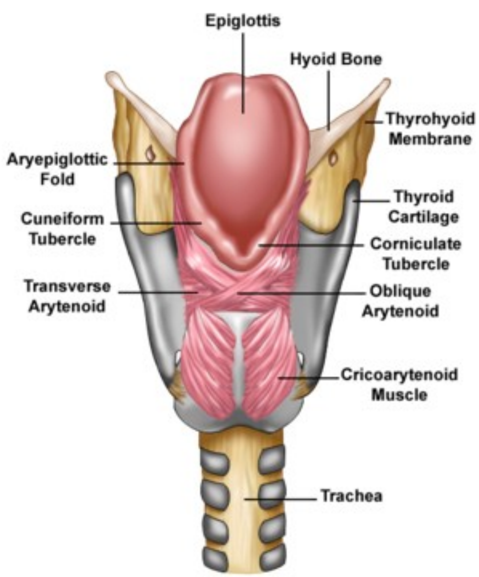
□ Sound is produced when vibrations occur in the vocal folds

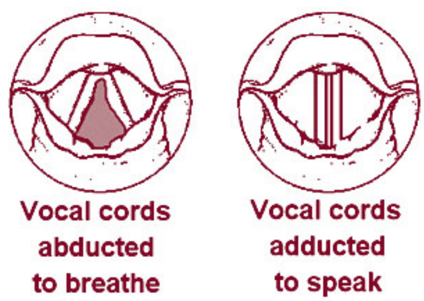
- Intrinsic muscles narrow rima glottides → air flows over vocal cords
- **Range** depends on vocal fold ______________ and thickness; lower range = thicker and longer folds
- **Pitch** depends on vocal fold tension from intrinsic muscles; More tension = higher pitch
- **Loudness** depends on force of air over vocal cords; more air = louder sound

□ Skeletal muscles also make up the larynx

- **Extrinsic muscles** extend from the hyoid or sternum bones to thyroid cartilage
    - Elevate larynx during ___________________________
- **Intrinsic muscles** are inside the larynx and extend to the arytenoid and corniculate cartilages
    - Function in voice production and closing larynx during swallowing
    - It changes the dimension of the rima glottidis
        - Adductor muscles: narrows the opening of vocal cords
        - Abductor muscles widen the the opening of vocal cords

EXAMPLE:





CONCEPT: TRACHEA

● The **trachea** (*windpipe*) is a flexible tube that extends through the neck from the larynx to the _________________

□ The tracheal wall is composed of four layers

1. Mucosa: is innermost layer with goblet cells, pseudostratified ciliated columnar epithelium, lamina propria

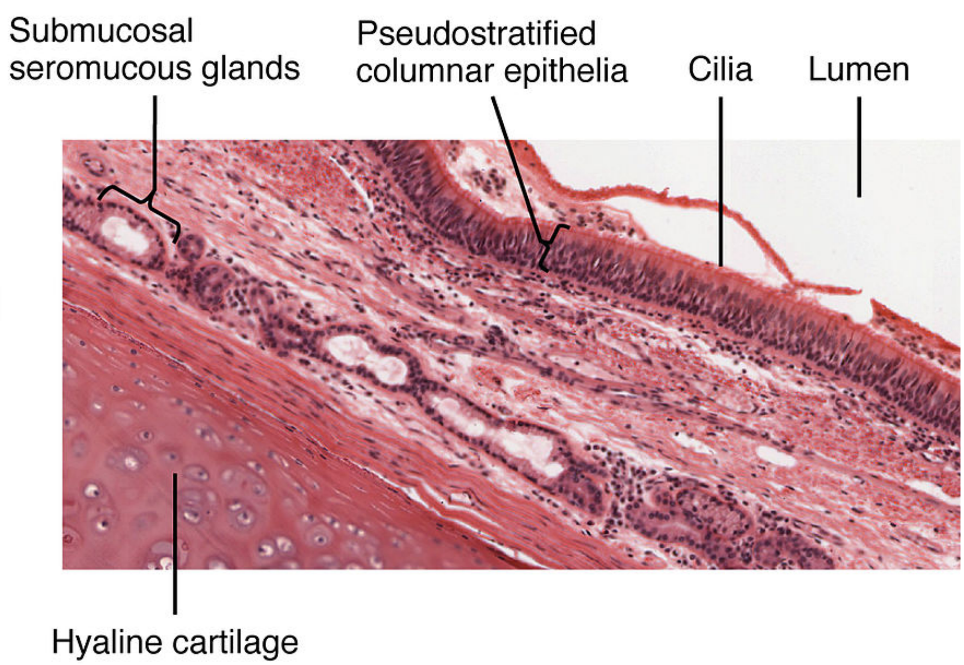
   - Contains cilia, whose movements propel microbes and dust superiorly to be swallowed

2. Submucosa: made up of areolar connective tissue, blood vessels, nerve endings, glands

3. **Tracheal cartilage:** rings of hyaline cartilage

4. **Adventita** is the outermost layer; composed of elastic connective tissue

EXAMPLE:

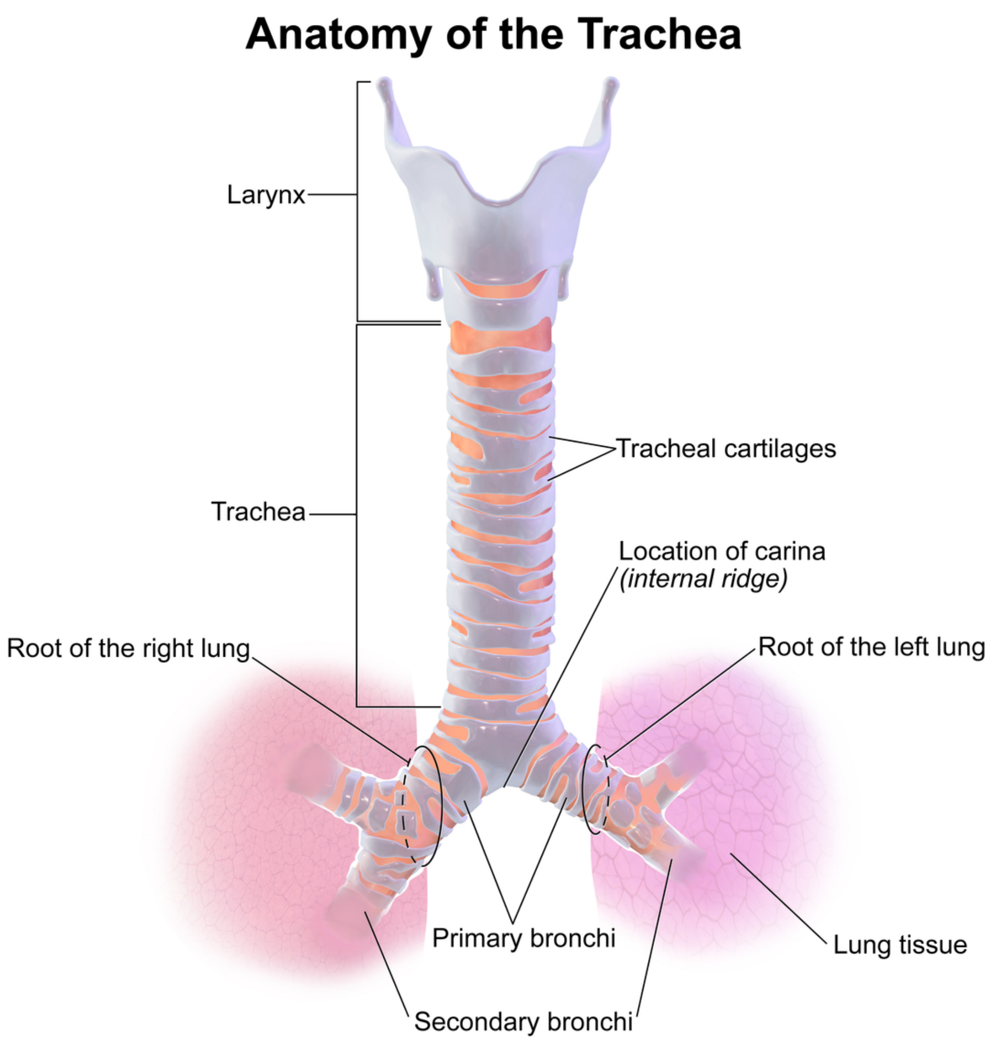


□ It is 13 cm long and is characterized by **tracheal cartilages,** 15-20 C-shaped rings of hyaline cartilage

- These cartilages are connected via **anular ligaments** which are elastic connective tissue
- Are attached to the **trachealis muscle** to provide support and keep the trachea open

□ Where the trachea splits into bronchi, there is an internal mucosal-covered ridge of cartilage called **carina**

EXAMPLE:



CONCEPT: BRONCHIAL TREE

● The **bronchial tree** is a set of branched passageways that conduct air from the main bronchi to smallest bronchiole

□ Trachea splits → right and left **main bronchi** (*primary bronchi*) that travel inferiorly and laterally into a lung

- The right bronchus is ______________________, shorter, and more vertical than the left
- Bronchi are made of cartilage, following the same organization as the trachea
- **Carina**: an internal ridge that is the last tracheal cartilage before it bifurcates

□ Main bronchi → **lobar bronchi** (*secondary bronchi*)

- Right branch has three lobar bronchi, as the right lung has three lobes
- Left branch has two lobar bronchi, as the left lung has two lobes

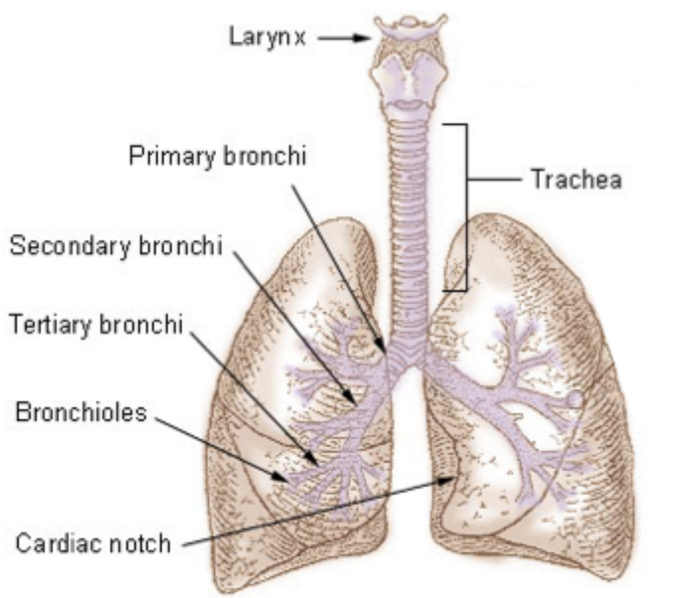
□ Lobar bronchi → **segmental bronchi** (*tertiary bronchi*)

- Right lung has 10 segmental bronchi
- Left lung has 8-10 segmental bronchi

□ There is a total of 9-12 bronchi branches before branching into *bronchioles*

- **Bronchioles** are tubes <1mm in diameter and do not have cartilage, but more _______________ muscle
    - The muscle causes *bronchoconstriction* and *bronchodilation*
- **Terminal bronchioles** are last portion of the conducting pathway, these lead into the respiratory

EXAMPLE:



CONCEPT: RESPIRATORY ZONE

● The **respiratory zone** is an area of microscopic structures that function in O_2 and CO_2 exchange in the lungs

□ The **respiratory bronchioles** begin the respiratory zone

- The respiratory bronchioles ____________________ into **alveolar ducts** that lead into **alveolar sacs**

□ **Alveoli** are small sac-like pockets inside the alveolar ducts and respiratory bronchioles

- 300-400 million alveoli in each lung

- **Alevolar pores** are openings that sit in between alveoli

□ Epithelium of the respiratory zone is much thinner then that of conducting, since it facilitates gas exchange

□ Two cells form an alveolar __________________

- **Alveolar type I cell** (*pneumocyte type 1*) is the major (95%) cell of the wall

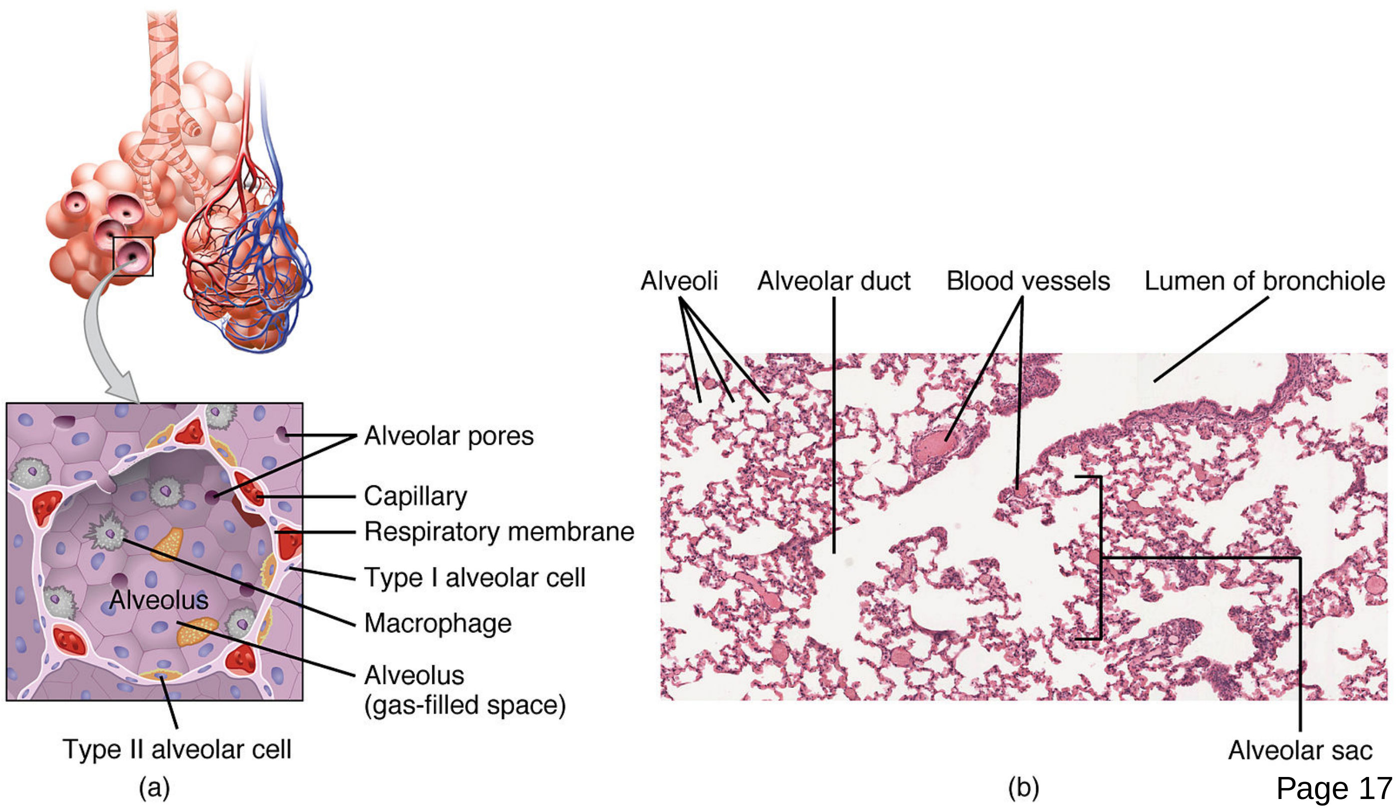
  - Forms a thin barrier to separate alveolar air from blood in pulmonary capillaries

- **Alveolar type II cell** (*pneumocyte type 2*) secretes the oily **pulmonary surfactant** to coat the surface

  - This keeps the surface moist and prevents alveolar collapse during expiration

□ **Alveolar macrophage** (*dust cell*) is a leukocyte that attack microorganisms or foreign materials

EXAMPLE:



CONCEPT: LUNGS

● The **lungs** are paired organs in the thoracic cavity where oxygen exchange takes place

□ Each lung has an inferior **base** and an **apex** that sits superior and posterior to the clavicle

- The **costal surface** faces the ___________________

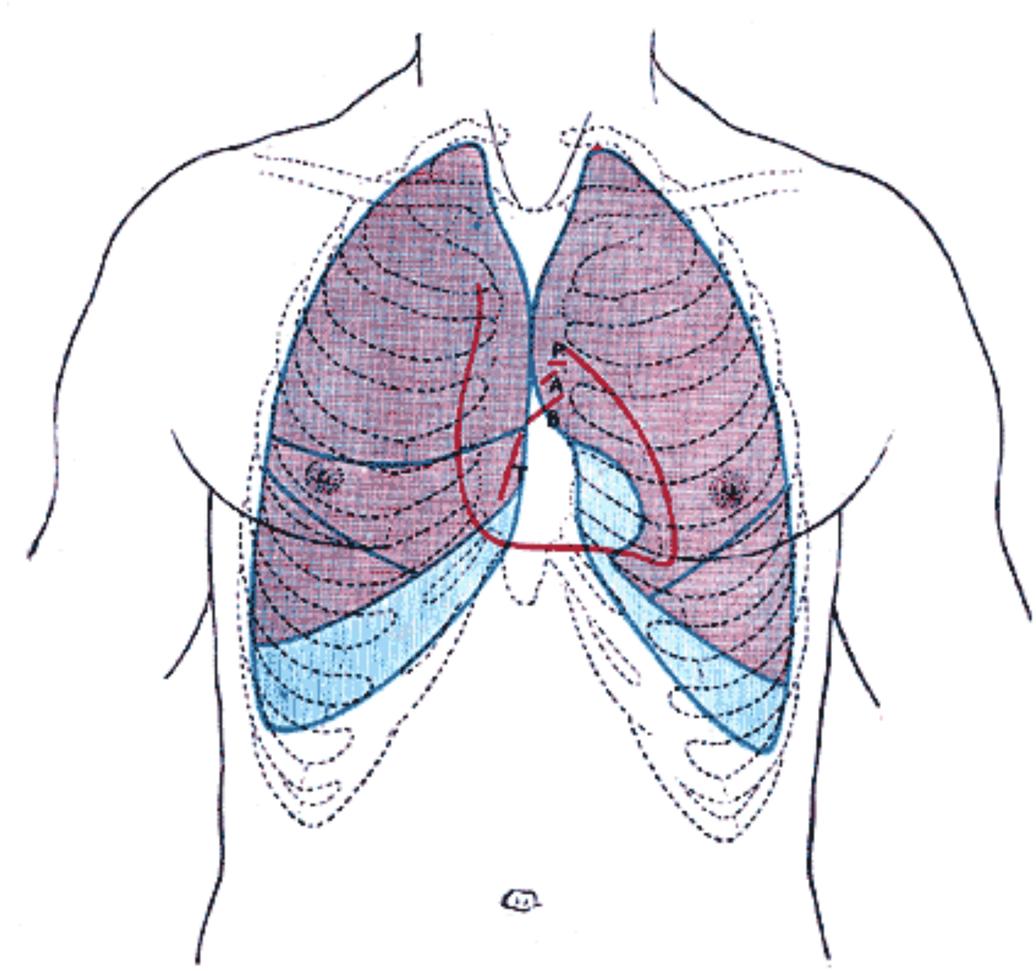
- The **mediastinal surface** faces the mediastinum

- The **diaphragmatic surface** faces the diaphragm

□ The **hilum** is an indented region on the mediastinal surface where bronchi, vessels, and nerve pass

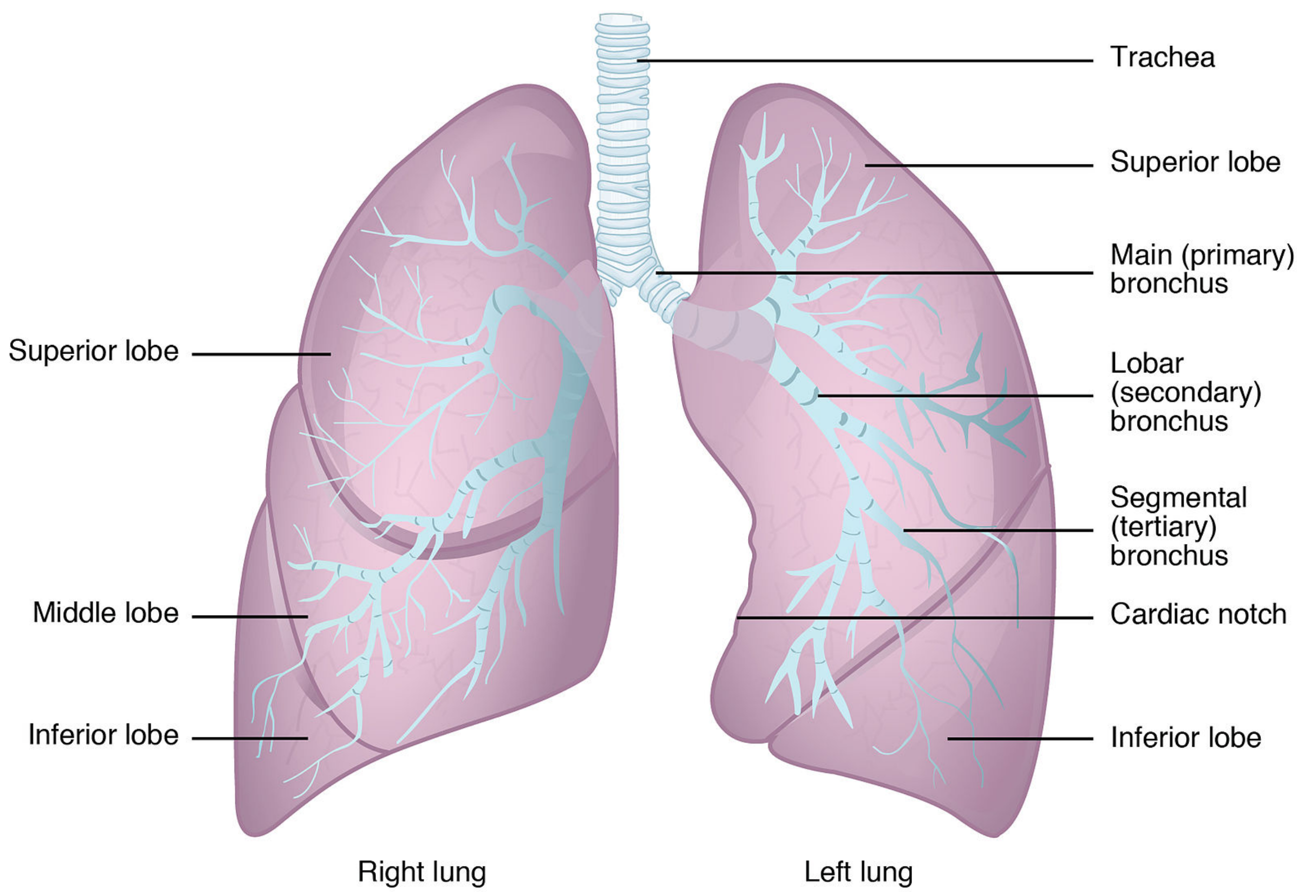
- Called the **root** of the lung

EXAMPLE:



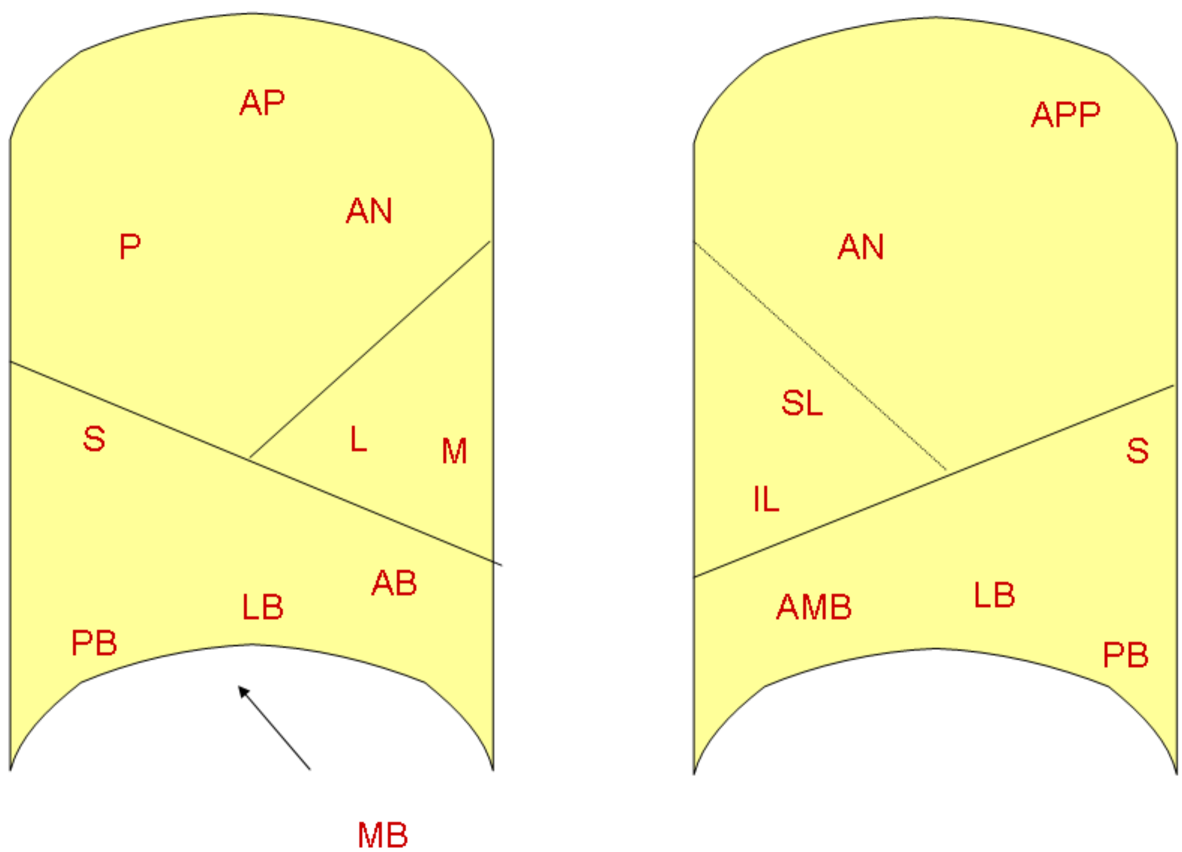
- The right and left lung have slightly different structures
  - □ The **right lung** is wider, has two fissures, and _________________ lobes
    - The **horizontal fissure** separates the **superior lobe** and **middle lobe**
    - The **oblique fissure** separates the middle lobe and the **inferior lobe**
  - □ The **left lung** is smaller, one fissure, two lobes and two indentions
    - The **oblique fissure** separates a **superior lobe** and **inferior lobe**
      - The **lingual** projections from the superior lobe, and is similar to the right middle lobe
    - The **cardiac impression** is an indention on the medial surface to accommodate the heart
    - The **cardiac notch** is an anterior indention that accommodates the heart

EXAMPLE:



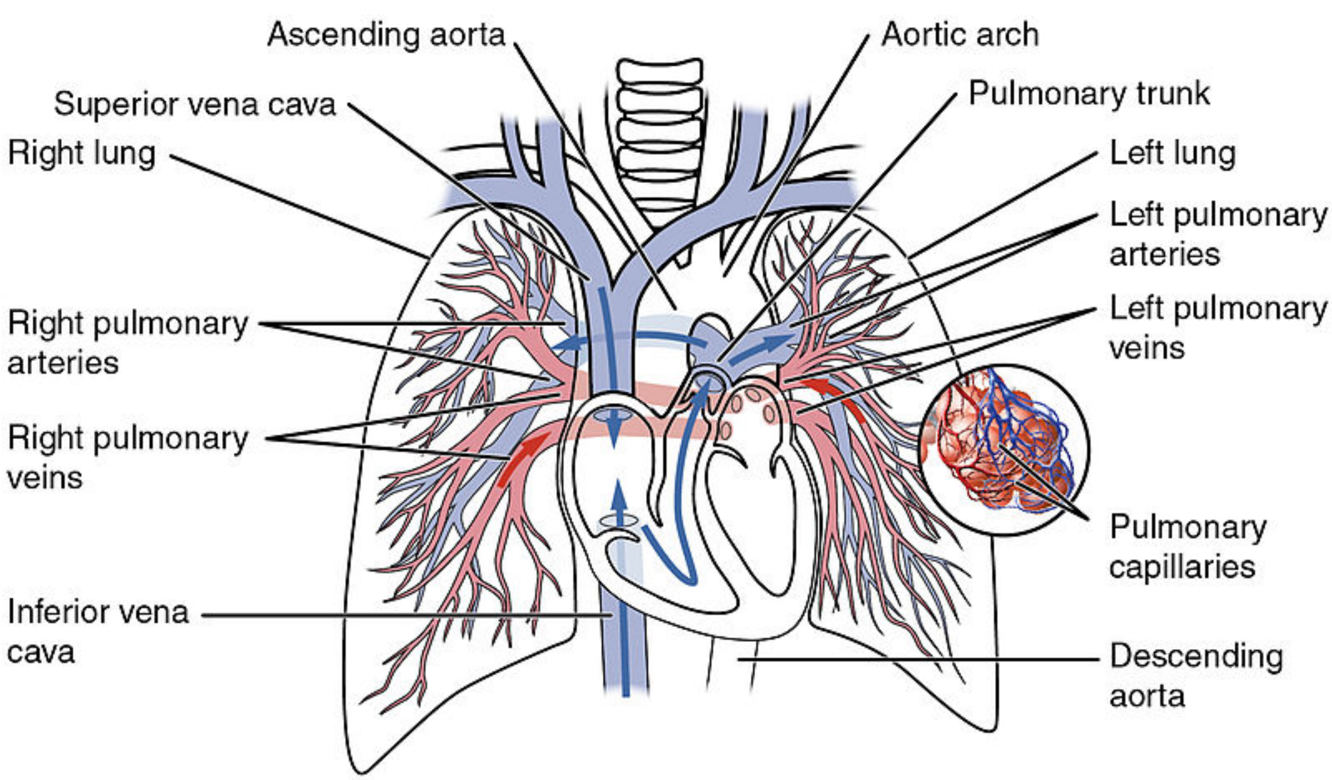
- Each lung is divided into **bronchopulmonary segments**
    - □ The right lung has 10 and the left lung has 8-10
        - \- Inside each section the lung is also organized into **lobules**
    - □ Each segment has its own tissue, bronchus, a branch of pulmonary artery and vein, and lymph vessels
    - □ Each segment functions ______________________________ of other sections

EXAMPLE:



- There are two ______________________________ that are associated with the lungs
  - □ *Pulmonary circulation* is when deoxygenated blood is circulated through the lungs to gain oxygen
  - □ **Bronchial circulation** is *systemic circulation* that transports oxygenated blood to the lungs
    - **Bronchial arteries** branch from the descending thoracic aorta to supply the *bronchial tree*
    - **Bronchial veins** carry deoxygenated blood to the heart and pulmonary veins
- Each lung also has lymph drainage and innervation
  - □ Lymph drainage occurs from lymph vessels and lymph nodes around the bronchi and in the pleura;
    - Lymph drainage helps to remove excess fluid from the lungs and helps clean our particulates
  - □ The lungs are innervated by the _____________________
    - Sympathetic innervation comes from T1-T5 segments of spinal cord – causes bronchodilation
    - Parasympathetic innervation comes from Vagus nerve (CN X) – causes bronchoconstriction

EXAMPLE:



CONCEPT: PROPERTIES OF THE LUNGS—COMPLIANCE, ELASTICITY, RESISTANCE AND SURFACE TENSION

Compliance and Elasticity of the Lungs:

● **Compliance** refers to the lungs' ability to ________________ (like Silly Putty).

□ ↑Compliance→less force required to change shape.

● **Elasticity** refers to the lungs' ability to return to their original shape *after* stretching (like a rubber band).

□ ↑Elasticity→↓Compliance (resists change in shape—tries to recoil back to normal shape).

● Loss of elasticity or compliance compromise lung function.

□ **Restrictive** lung diseases increase "stiffness" of tissue→↓Compliance.

-Lots of force/energy required to breathe.

□ **Emphysema** causes ↓Elasticity.

-Lungs don't recoil—very hard to breathe out.

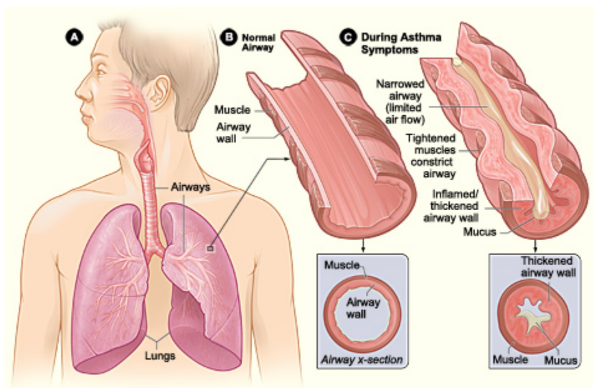
EXAMPLE: Emphysema damages elastic tissue, requiring increased effort to breathe out.

Resistance to Airflow in the Lungs:

- Air moving through airways in the lungs is a fluid moving through a tube—subject to Poiseuille's Law.
- **Poiseuille's Law** lets you determine the resistance to flow for a specific tube and fluid.
  - $R = \frac{8\eta\ell}{\pi r^4}$

    R= resistance η=viscosity (thickness) of fluid ℓ=length of tube r=radius of tube
- Radius is the major determinant of resistance in the lungs—bronchioles have smooth muscle in their walls.
  - **Bronchoconstriction** is when bronchiolar smooth muscle contracts→↓radius→↑resistance.
  - **Bronchodilation** is when bronchiolar smooth muscle relaxes→↑radius→↓resistance.

EXAMPLE: Asthma attacks are caused by sudden bronchoconstriction→↑resistance, making breathing much harder.



Surface Tension, Surfactant, and the Law of LaPlace:

● Two “forces” in the lungs *resist* breathing/expansion of lung tissue: *elasticity* of the lung tissue and *surface tension*.

● **Surface Tension** is attractive force across a thin layer of liquid.

□ Inside of lungs—notably the alveoli—are coated in a thin layer of fluid.

□ Surface tension of this layer pulls inward, tending to cause lung collapse/prevent lung expansion.

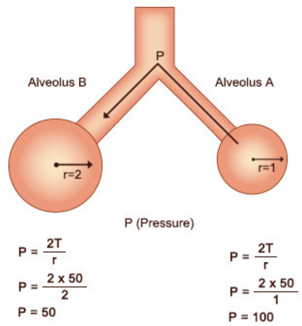
● **Law of LaPlace** lets you calculate pressure within an alveolus as a result of surface tension.

□ P=2T/r

P=Pressure in alveolus T=Surface Tension r=radius of alveolus

□ ↓Radius→↑Pressure in alveolus.

-Especially small alveoli would tend to push out air and collapse.



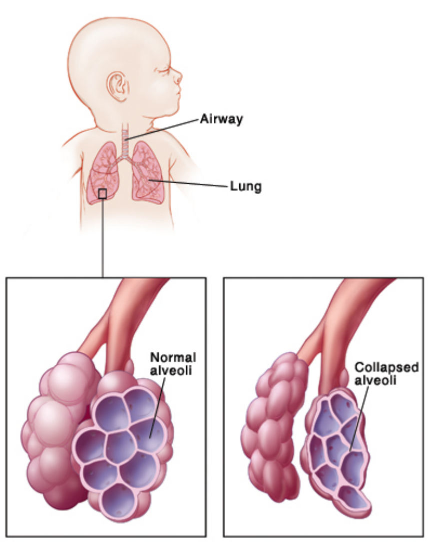
● **Surfactant** is a substance secreted by some alveolar cells.

□ Reduces surface tension, helping to prevent lung collapse from surface tension.

● Surfactant disrupts surface tension, stabilizing smaller alveoli.

□ ↓T→↓P→↓outward airflow→no collapse.

EXAMPLE: Neonatal Respiratory Distress Syndrome is when premature babies have trouble breathing. Caused by the inability of immature lungs to produce surfactant. ↓Surfactant→↑Surface Tension→↑Lung Collapse→↑Effort to Breathe.



PRACTICE 1: Albuterol is β_2 adrenergic receptor agonist used to treat asthma attacks; when it binds to β_2 receptors on smooth muscle cells in the walls of airways it causes the smooth muscle cells to relax, leading to bronchodilation. Which of the following variables in Poiseuille's Law is directly affected by the activity of albuterol and what is the resulting effect on resistance to flow (R) through the airways?

a) η | ↑R
b) η | ↓R
c) ℓ | ↑R
d) ℓ | ↓R
e) r | ↑R
f) r | ↓R

PRACTICE 2: Two alveoli are next to each other in the lungs, connected by a bronchiole. Alveolus X has radius of 5; alveolus Y has a radius of 10. In which direction is air likely to flow?

a) From alveolus X to alveolus Y.
b) From alveolus Y to alveolus X.
c) There is unlikely to be any net flow in any direction.

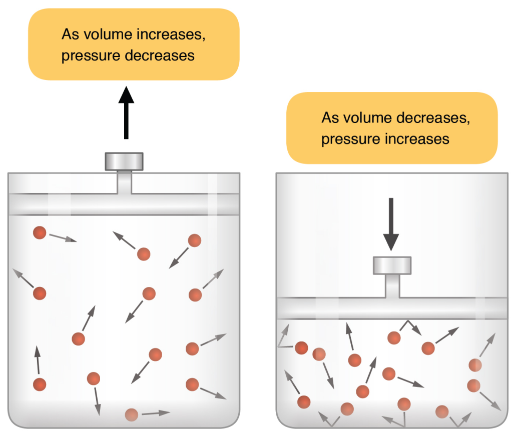
CONCEPT: VENTILATION I: BOYLE'S LAW

Boyle's Law:

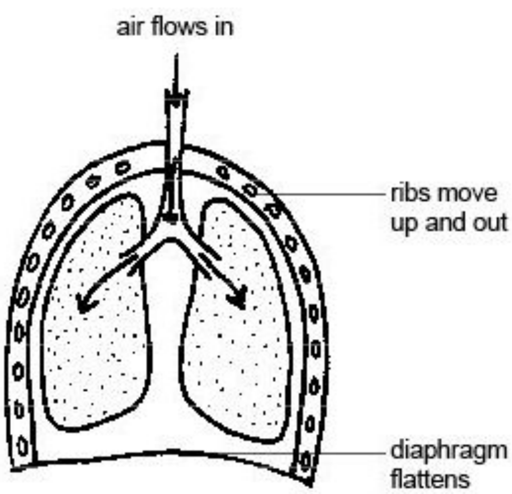
- **Boyle's Law** describes the relationship between pressure and volume in a container of gas.
  - □ $P_1V_1=P_2V_2$

    P=Pressure V=Volume 1 or 2=Before or After.
  - □ ↑Volume→↓Pressure, and vice-versa.
- The lungs (and the thoracic cavity they're in) behave like a container of gas, and so follow Boyle's Law.
  - □ ↑Volume in thoracic cavity→↓Pressure in thoracic cavity→Air moves in, and vice-versa.

EXAMPLE: Boyle's Law.



EXAMPLE: Breathing in results from an increase in thoracic cavity volume.



PRACTICE 1: Harry Potter, during the second task of the Triwizard Tournament, is at a depth of 40 meters beneath the surface of the Black Lake where the ambient pressure is about 4 atm. He takes a full breath of air (thanks, Gillyweed!) and fills his lungs to a volume of 6 L. Then, *without exhaling any air*, he ascends to the surface. What is the volume of the air in his lungs once he gets to the surface? (Hint: This was a breathtakingly—pun intended—stupid thing to do.)

a) 3 L.
b) 6 L.
c) 12 L.
d) 24 L.
e) 30 L.

CONCEPT: VENTILATION II: MECHANICS OF INSPIRATION AND EXPIRATION

Inspiration

● **Inspiration**=Inhaling—moving air from outside→lungs.

● Inspiration happens when ↑Volume of thoracic cavity→↓Pressure in thoracic cavity/lungs (Boyle's Law).

□ Air moves down pressure gradients. When ↓Pressure in lungs, air moves in to lungs.

● Inspiration is an *active* process—requires the use of ___________________________.

□ **Diaphragm** is a sheet of muscle between thoracic and abdominal cavities.

-When *relaxed*, diaphragm is dome shaped, pressing up into thoracic cavity.

-When it *contracts,* diaphragm flattens→↑Volume of the thoracic cavity.

-**Phrenic Nerve** holds the motor neurons that control the diaphragm.

□ **External Intercostals** are muscles between the ribs.

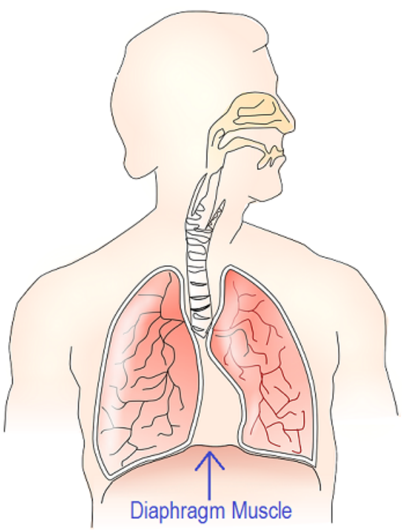
-When they *contract*, help to lift ribcage upward and outward→↑Volume of the thoracic cavity.

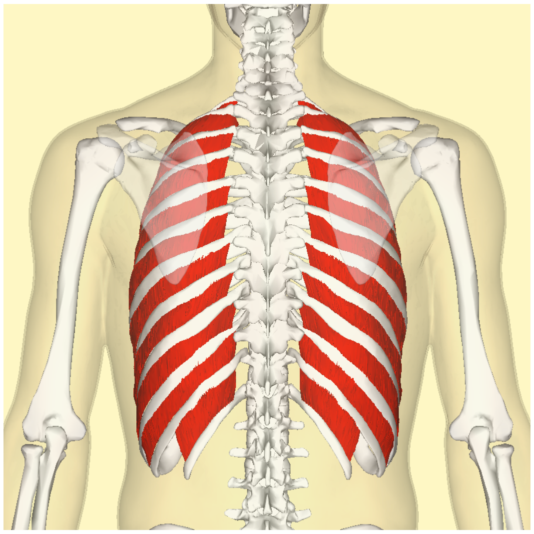
□ **Sternocleidomastoids** are big bands of muscle in the neck that connect to the clavicles and sternum.

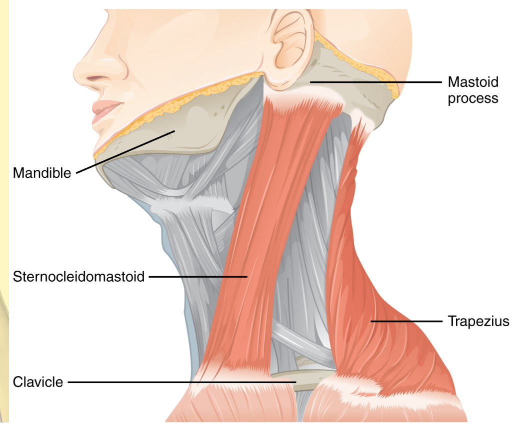
-When they *contract*, also help to lift ribs and chest wall→↑Volume of the thoracic cavity.

● Overall: Muscle contraction→↑Volume→↓Pressure→Air moving in to lungs

EXAMPLE: The diaphragm, intercostals, and sternocleidomastoids are the muscles of inspiration.







Expiration:

● **Expiration**=Exhaling—moving air from lungs→outside.

● Expiration happens when ↓Volume of thoracic cavity→↑Pressure in thoracic cavity/lungs.

□ Air moves down pressure gradients. When ↑Pressure in lungs, air moves out of lungs.

● *Resting* expiration is a *passive* process—no active muscle contraction required.

□ Lungs are elastic. When diaphragm and other inspiratory muscles relax, lungs naturally recoil to smaller shape.

● Two sets of muscles can *assist* expiration to make it more forceful or to expire larger volumes.

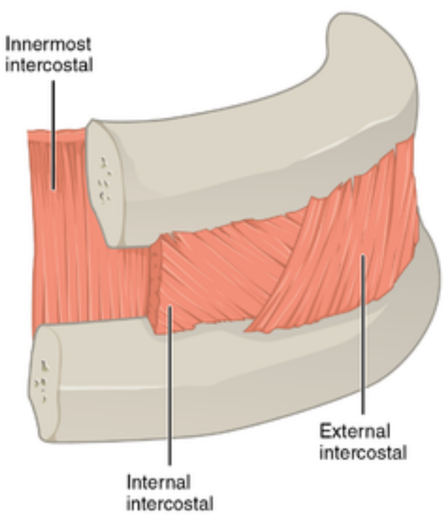
□ ***Internal*** **Intercostals** are also muscles between the ribs.

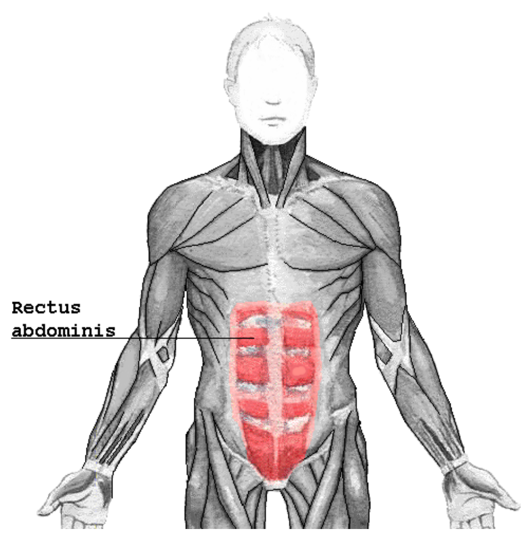
-But, oriented such that contraction causes them to pull ribcage down and in→↓Volume in thoracic cavity.

□ **Abdominals** are muscles at front of the abdominal cavity.

-When contract, they push abdominal contents (your guts) against diaphragm up into thoracic cavity.

EXAMPLE: The internal intercostals and abdominals are the muscles of active/forceful expiration.





PRACTICE 1: The diaphragm, external intercostal, and sternocleidomastoid muscles contract. Which of the following describes the effect of this muscle activity on the volume of the thoracic cavity?

a) Increased volume.
b) Decreased volume.
c) No change in volume.

PRACTICE 2: A (very good) father is blowing up 100 pink balloons while decorating the house for his daughter's birthday party. Which of the following muscles is/are likely to be *actively contracting* while he is blowing air into a balloon? (Choose all that apply.)

a) Diaphragm.
b) External intercostals.
c) Sternocleidomastoids.
d) Internal intercostals.
e) Abdominals.

CONCEPT: LUNG SPIROMETRY: LUNG VOLUMES AND CAPACITIES

Lung Spirometry: Lung Volumes and Capacities:

● **Lung Spirometry** is a type of lung testing where the patient does a series of breathing exercises—breathe normally, expire as much as possible, inspire as much as possible, etc.—to assess lung function.

□ **Volumes** are amounts of air moved (inspired or expired) during different segments/types of breathing.

□ **Capacities** are combinations of 2+ volumes.

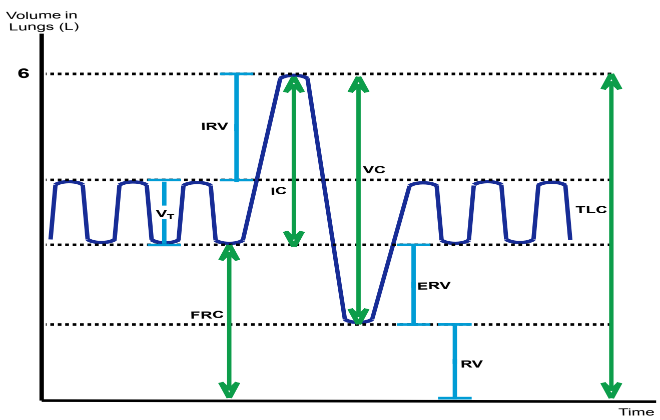
● The four lung volumes are:

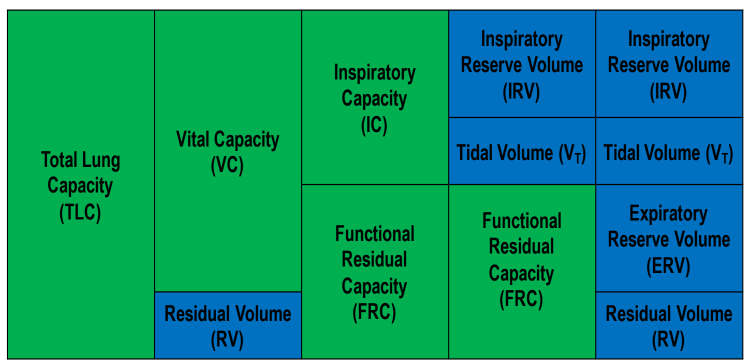
□ **Tidal Volume (V_T)**= Volume moved during *normal/resting* inspiration or expiration.

□ **Inspiratory Reserve Volume (IRV)**= Extra volume that can be inspired after *normal inspiration*.

□ **Expiratory Reserve Volume (ERV)**= Extra volume that can be expired after *normal expiration*.

□ **Residual Volume (RV)**= Volume that's still left in lungs after forceful, maximal expiration.





● The four lung capacities are:

□ **Total Lung Capacity (TLC)**= Maximum volume lungs can hold.

$TLC=RV+ERV+V_T+IRV$

□ **Vital Capacity (VC)**= Maximum volume that can actually be moved with one breath.

$VC=TLC-RV$ $VC=ERV+V_T+IRV$

□ **Functional Residual Capacity (FRC)**= Volume left in lungs after *normal* expiration.

$FRC=RV+ERV$ $FRC=TLC-IC$

□ **Inspiratory Capacity (IC)**= Maximum volume that can be inspired following normal expiration.

$IC=V_T+IRV$ $IC=VC-ERV$

PRACTICE 1: A 19-year-old female with a three-year history of asthma presents to her allergist for pulmonary function testing. She is connected to a spirometer asked to *breathe normally*. Which of the following is being measured?

a) Tidal Volume.
b) Inspiratory Reserve Volume.
c) Expiratory Reserve Volume.
d) Residual Volume.
e) Vital Capacity.

PRACTICE 2: A 19-year-old female with a three-year history of asthma presents to her allergist for pulmonary function testing. She is connected to a spirometer asked to *exhale as much as she can, then inhale as much as she can*. Which of the following is being measured?

a) Tidal Volume.
b) Inspiratory Reserve Volume.
c) Expiratory Reserve Volume.
d) Residual Volume.
e) Vital Capacity.

PRACTICE 3: A 19-year-old female with a three-year history of asthma presents to her allergist for pulmonary function testing. She is connected to a spirometer asked to *inhale normally, then additionally inhale as much as she can*. Which of the following is being measured?

a) Tidal Volume.
b) Inspiratory Reserve Volume.
c) Expiratory Reserve Volume.
d) Residual Volume.
e) Vital Capacity.

CONCEPT: MEASURING PRESSURE OF A MIXTURE OF GASES—PARTIAL PRESSURES AND DALTON'S LAW

Measuring "Amount" of Gas as Pressures:

● **Pressure** is the force of a fluid (liquid or gas) pushing against the walls of its container.

● **Dalton's Law** says that the total pressure of a mixture of gases is the _________ of the pressures of each individual gas.

$P_{Total}=P_1+P_2+P_3+\ldots$

● **Partial Pressure** of a gas is the pressure that individual gas contributes to the whole mixture.

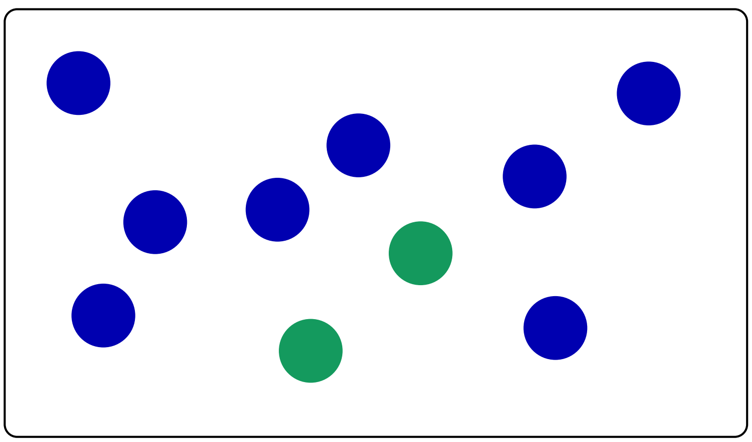
□ i.e. P_1 or P_2 in Dalton's Law.

● Partial pressures are a convenient way to measure the "concentration" (that is, compare amounts) of 2+ gases.

□ More of one gas in a mixture→higher partial pressure for that gas.

□ Partial pressure is determined by straight proportion—molecular weight doesn't matter.

EXAMPLE: In a mixture of gases with P_{total}= 100 mmHg that is 80% O_2 and 20% CO_2: P_{O2}= 80 mmHg and P_{CO2}= 20 mmHg.

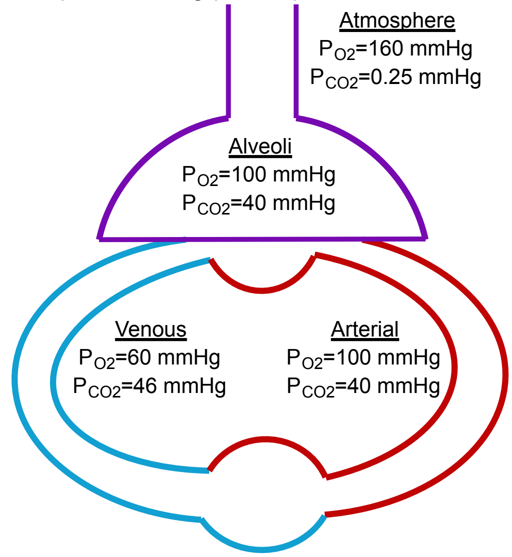


P_{O2}= 80 mmHg
P_{CO2}= 20 mmHg

P_{total}= 100 mmHg

Partial Pressures of O_2 and CO_2 in the Atmosphere, Alveoli, Arterial Blood, and Venous Blood:

● Can measure the relative amounts of gases in different physiologically-relevant places using partial pressures:



□ In *atmosphere* (at ~sea level): P_{O2}=160 mmHg, P_{CO2}=0.25 mmHg.

□ In *alveoli*: P_{O2}=100 mmHg, P_{CO2}=40 mmHg.

□ In *arterial blood*: P_{O2}=100 mmHg, P_{CO2}=40 mmHg.

-Equilbrates with air in alveoli.

□ In *venous blood*: P_{O2}=40 mmHg, P_{CO2}=46 mmHg.

-Tissues pick-up $O_2 \longrightarrow \downarrow P_{O2}$. Tissues dump $CO_2 \longrightarrow \uparrow P_{CO2}$.

CONCEPT: TOTAL VS. ALVEOLAR VENTILATION AND THE ANATOMIC DEAD SPACE

Total vs. Alveolar Ventilation and the Anatomic Dead Space:

- **Total Pulmonary Ventilation** (aka **Minute Ventilation**)= Volume of air moved into and out of lungs every minute.

  Total Pulmonary Ventilation (mL/min)= Respiratory Rate (breaths/min) × Tidal Volume (mL/breath)

  □ Typical Numbers: V_T= 500 mL, Respiratory Rate= 12 br/min ⇒ Total Pulmonary Ventilation= 6000 mL/min.

- **Anatomic Dead Space** is the portion of lung volume that doesn't allow for *exchange* of gases between lungs and blood.

  □ *Only* the *alveoli* allow for exchange.

  -Anatomic Dead Space is total volume of all the conducting airways—trachea, bronchi, bronchioles.

  □ Typical Anatomic Dead Space= 150 mL.

- Every resting inspiration brings about V_T= 500 mL of fresh air into lungs.

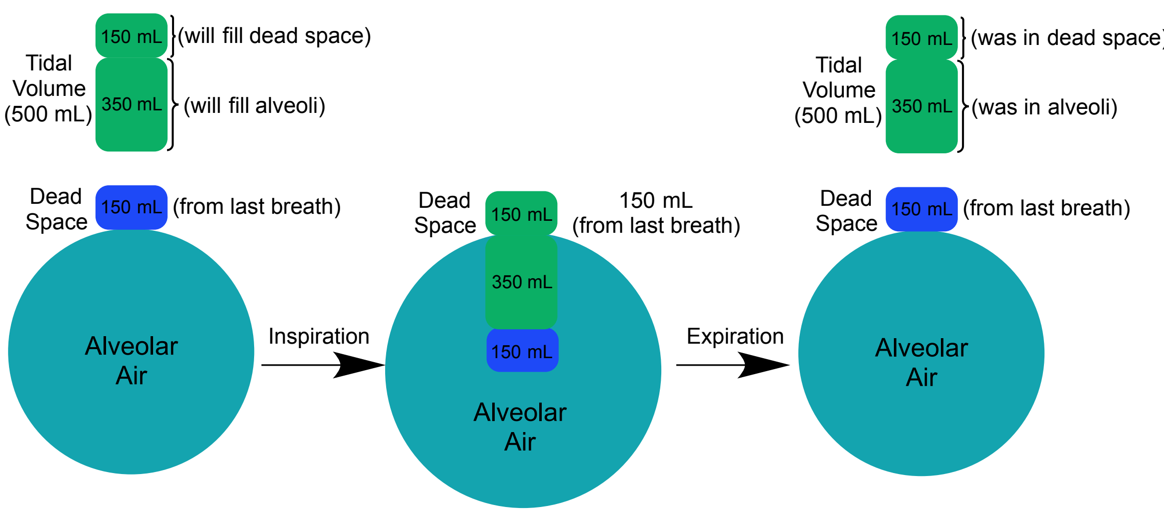
  □ But, only 350 mL of that fresh air reaches alveoli, since 150 mL has to be used to fill the dead space.

  □ Also, the first 150 mL to reach the alveoli is "stale" air from the dead space.

- **Alveolar Ventilation**= Volume of *fresh* air that reaches the alveoli every minute (accounting for anatomic dead space).

  Alveolar Ventilation (mL/min)= Respiratory Rate (breaths/min) × (V_T-Anatomic Dead Space)

EXAMPLE: During inspiration, the first 150 mL of air to hit the alveoli is stale air from the dead space.



Effect of Respiration Changes on Alveolar Ventilation and P_{O2}, P_{CO2}:

● Changing respiration can cause changes in CO_2 levels.

□ **Hypoventilation** is breathing less than normal so that CO_2 accumulates.

-i.e. Alveolar ventilation doesn't "keep up" with CO_2 production by body.

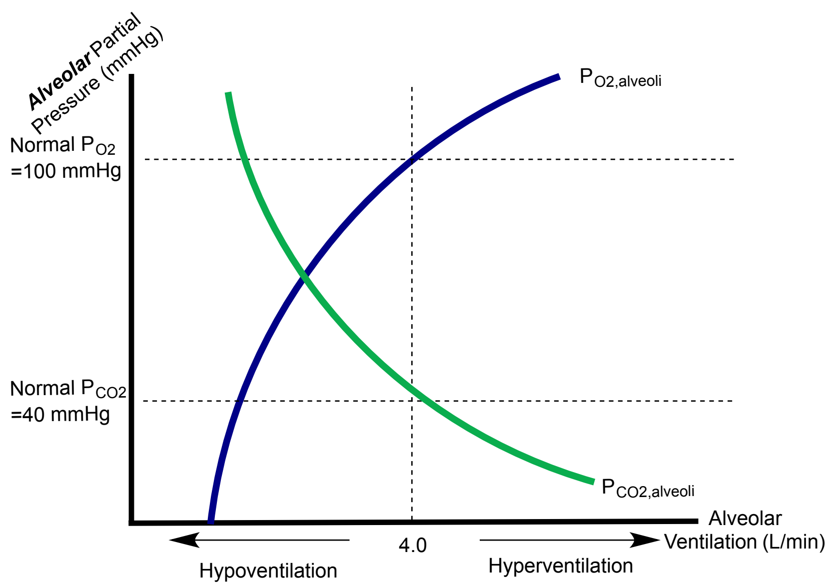
□ **Hyperventilation** is breathing more than normal so that more CO_2 than usual is cleared from the body.

-i.e. Alveolar ventilation surpasses CO_2 production.

● Hypoventilation causes CO_2 to build up in the alveoli and alveolar O_2 levels to drop (eventually to 0 mmHg).

● Hyperventilation causes CO_2 in the alveoli to drop and alveolar O_2 levels to build up.

EXAMPLE: Effects of changes in alveolar ventilation on P_{O2} and P_{CO2}.



PRACTICE 1: You and your significant-other go on a romantic snorkeling trip while on a vacation in Miami, FL. While *snorkeling*, you notice that you have to breathe more rapidly than you normally would while swimming. Which of the following variables in the alveolar ventilation equation ($AV=[V_T\text{-Dead Space}]\times RR$) has *been changed by using a snorkel*, and what is the effect on that change on alveolar ventilation (AV)?

a) V_T | ↑AV
b) V_T | ↓AV
c) Dead Space | ↑AV
d) Dead Space | ↓AV

CONCEPT: GAS EXCHANGE I: DIFFUSION IN THE ALVEOLI

Diffusion in the Lungs:

● **Diffusion** is the *passive* movement of substance from high concentration→low concentration.

□ This is how O_2 and CO_2 move between the blood and lungs.

● **Diffusion Rate**—how quickly diffusion happens—is affected by a handful of variables.

□ Diffusion Rate ∝ Surface Area×Concentration Gradient×Permeability.

□ Diffusion Rate ∝ $1/(\text{Distance})^2$

□ In healthy people, all of these are optimized for ~maximal diffusion.

-i.e. Lots of surface area (alveoli), large concentration gradient, good permeability, short distance.

● Some lung diseases cause changes in diffusion rates and thereby compromise lung function.

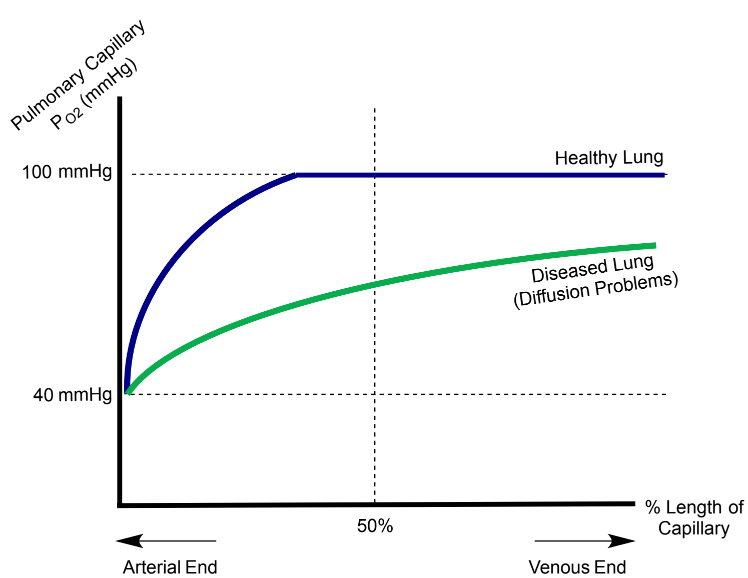
□ *Emphysema* causes destruction of alveoli→↓Surface Area→↓Diffusion Rate.

□ *Pulmonary Edema* is accumulation of fluid between alveoli and blood. ↑Diffusion Distance→↓Diffusion Rate.

● In healthy lungs, diffusion is so fast that $P_{O2,alveoli}$=$P_{O2,capillary}$ by the time blood is ~20-30% through the capillary.

□ Diseases compromise this, so that $P_{O2,capillary}$ never quite equilibrates with the alveoli.

EXAMPLE: Diseased lungs often have compromises in diffusion so that P_{O2} in pulmonary capillaries rises more slowly.



PRACTICE 1: In which of the following patients is $P_{O2,alveoli}$ *least likely* to equilibrate with $P_{O2,capillary}$ along the length of a pulmonary capillary?

a) Healthy 24-year-old man at rest.
b) Healthy 36-year-old woman doing tempo runs on a high school track with a current heart rate of 175 BPM.
c) 65-year-old man with congestive heart failure causing pulmonary edema.
d) 30-year-old woman smoking her first cigarette.

CONCEPT: GAS EXCHANGE II: VENTILATION AND PERFUSION AND V/Q RATIOS

Matching Ventilation (V) and Perfusion (Q):

● Two important variables determine how much gas exchange can happen in the lungs.

□ **Ventilation (V)** is the amount of air arriving to a given region of lung (i.e. the *alveolar ventilation* at a region).

□ **Perfusion (Q)** is the amount of blood being delivered to those specific alveoli.

□ **V/Q Ratio** is the ratio of ventilation to perfusion.

-Measures how "balanced" V and Q are in a region of lung (ideally $V/Q \cong 1.0$).

● **Ventilation-Perfusion Mismatches** are when a change in V or Q cause a change in V/Q ratio.

□ **Dead Space** is a region with ventilation but no alveolar blood flow ($V/Q \rightarrow \infty$).

-"Wasted" ventilation—that air doesn't do anything.

□ **Shunt** is a region with blood flow but no ventilation ($V/Q=0$).

-"Wasted" blood flow—that blood doesn't get oxygenated.

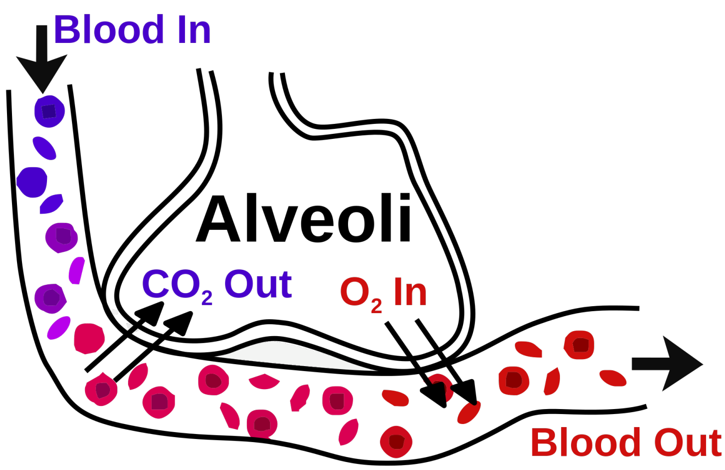
● Lungs and pulmonary arteries have mechanisms to keep V and Q reasonably matched.

● If ↓V in some lung region→↑P_{CO2} and ↓P_{O2} in those alveoli.

□ ↓$P_{O2,alveoli}$→*Vaso<u>constriction</u>*→↓Q in that region.

-Less blood flow to poorly-ventilated areas—don't "waste" blood flow on areas without O_2.

EXAMPLE: A decrease in ventilation leads to vasoconstriction, reducing perfusion as well.



Ventilation-Perfusion Changes in Lung Regions:

● In a person standing upright, gravity has an effect on both V and Q in the lungs. From *top to bottom*:

□ Ventilation *increases* slowly.

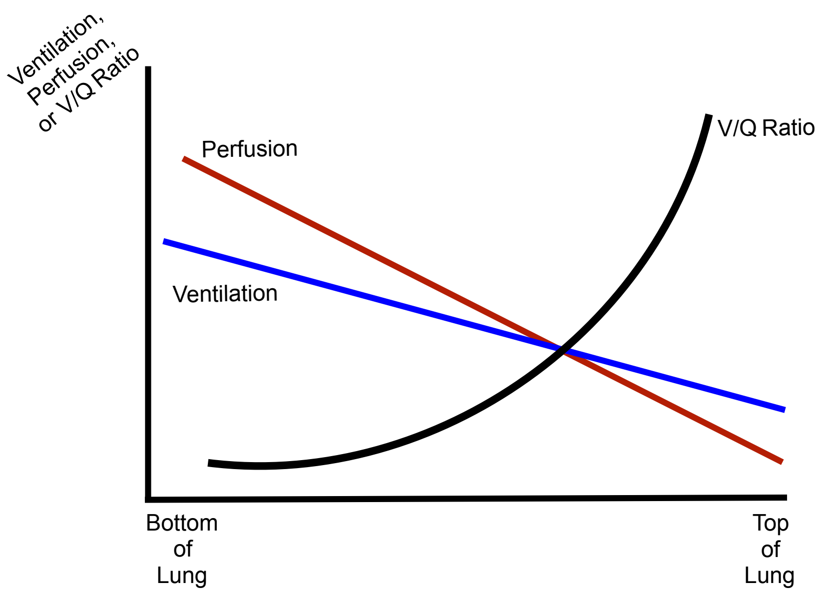
-Alveoli at base of lungs are *less* inflated *at rest*, so more capacity to inflate with each breath→↑V.

□ Perfusion *increases* more dramatically.

-Blood is pulled by gravity into pulmonary blood vessels in lower lung regions→↑Q.

● Both V and Q increase from top to bottom, but Q increases more dramatically→↓V/Q from top to bottom.

EXAMPLE: Ventilation and perfusion both increase toward the bottom of the lung, but perfusion increases more.



PRACTICE 1: A tumor growing in a bronchus grows so large that it completely obstructs the passage and blocks air flow. Which of the following describes the space downstream of the blocked bronchus and the resulting V/Q ratio in that area?

a) Dead Space | V/Q=0
b) Dead Space | V/Q=∞
c) Shunt | V/Q=0
d) Shunt | V/Q=∞

PRACTICE 2: In a normal person standing upright, which of the following *increase* from the top to the bottom of the lung? (Choose all that apply.)

a) Ventilation (V).
b) Perfusion (Q).
c) Ventilation/Perfusion Ratio (V/Q).

CONCEPT: GAS TRANSPORT IN THE BLOOD I: OXYGEN AND HEMOGLOBIN BINDING

● O_2 is a nonpolar gas—not very soluble in aqueous blood plasma.

- □ To get enough in blood and around body, must be bound to an O_2-carrier—*hemoglobin*.

Oxygen Binding to Hemoglobin:

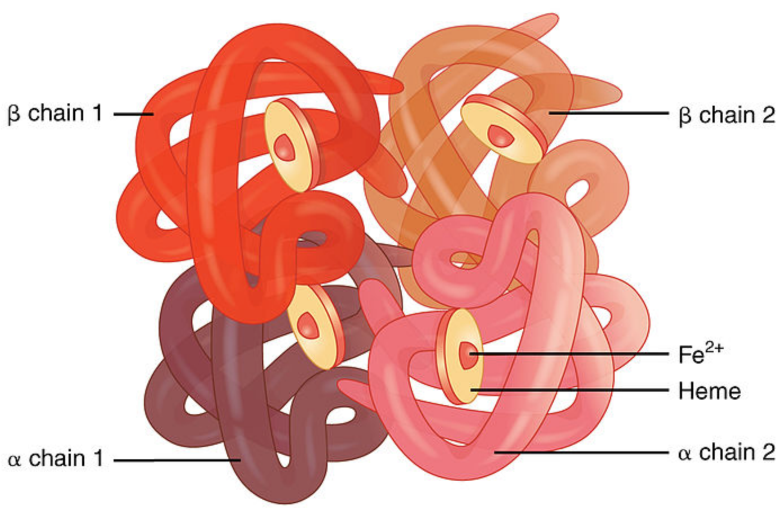
● **Hemoglobin (Hb)** is the protein contained within red blood cells (RBCs) that bind and carry O_2.

- □ Has four subunits, each with an Fe-based center called **heme.**

● This is a reversible binding reaction: $Hb+O_2 \rightleftharpoons HbO_2$

- □ HbO_2="**Oxyhemoglobin**"
- □ Because each Hb has four subunits, each can bind up to *four* O_2 molecules.

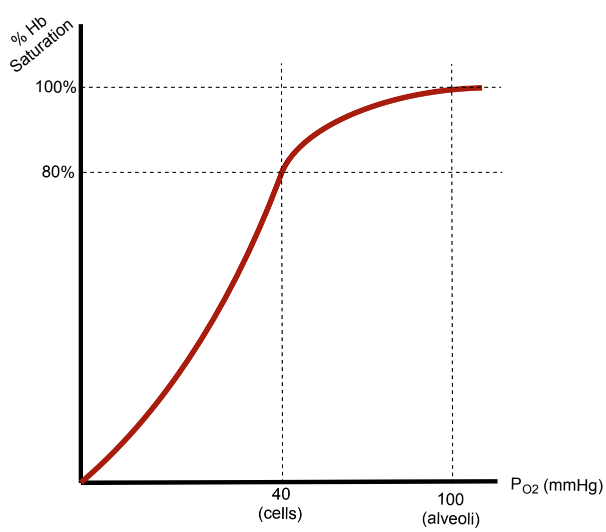
EXAMPLE: The structure of hemoglobin, with its four subunits.



Oxyhemoglobin Saturation Curves and Cooperative Binding:

- **Oxyhemoglobin Saturation Curves** show percent saturation of Hb in blood at different P_{O2} in the blood.
    - □ Saturation increases *dramatically* at intermediate P_{O2} values.
        - -Hb has **cooperative binding**—binding of one O_2 makes binding of next three "easier."
- Cooperative binding of Hb helps it do its job: pick up O_2 in the lungs and release in the tissues.
    - □ In high P_{O2} of lungs, Hb picks up O_2 and binds it tightly.
    - □ In lower P_{O2} of tissues, Hb unbinds O_2, releasing O_2 to cells that need it.

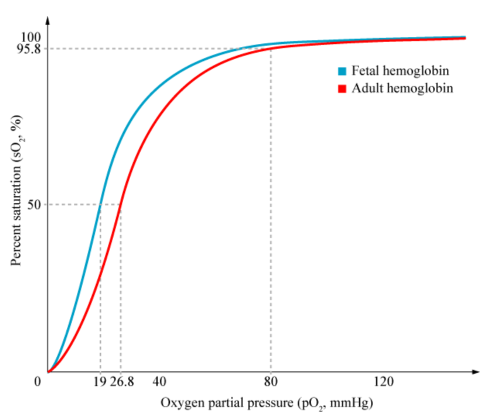
EXAMPLE: A normal oxyhemoglobin saturation curve.



Maternal (Adult) vs. Fetal Hemoglobin:

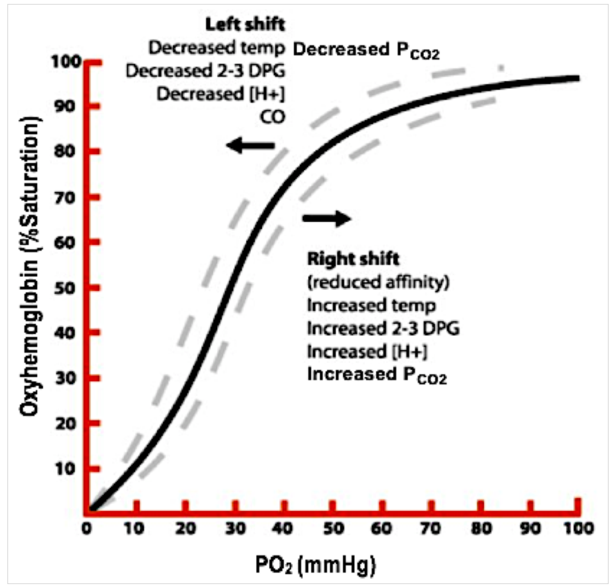
- Hb in fetuses binds to O_2 more tightly than Hb in adults (i.e. pregnant mothers).
    - □ Shows up as a *leftward/upward* shift in the saturation curve for fetal Hb.
        - -At any given P_{O2}, fetal Hb is bound to more O_2 than maternal Hb.
    - □ Lets mother's Hb give up O_2 to the fetus, thereby oxygenating fetus's blood.

EXAMPLE: Oxyhemoglobin saturation curves for maternal and fetal Hb.



Factors That Affect O_2-Binding—The Bohr Effect and Others:

- Several variables affect Hb's affinity for O_2. These are all typical of "working" (e.g. exercising) tissue that needs O_2.
  - □ ↑Temperature→↓Hb Affinity
    - -Exercising tissue is warmer.
  - □ ↑**2,3-diphosphoglycerate (2,3-DPG)**→↓Hb Affinity
    - -2,3-DPG is a byproduct of glycolysis. Produced more when exercising and at high altitude (where low O_2).
  - □ ↑[H^+] (↓pH)→↓Hb Affinity
    - -Exercising tissues make lactate acid & CO_2→↓pH.
  - □ ↑P_{CO2}→↓Hb Affinity
    - -Exercising tissues use more O_2 and make more CO_2.
  - □ **Bohr Effect** is combination of ↑P_{CO2} and ↓pH→↓Hb Affinity
  - □ All the opposite changes—↓Temp, ↓2,3-DPG, etc.—cause ↑Hb Affinity.



PRACTICE 1: In which of the following locations will hemoglobin be most saturated with oxygen? (Choose all that apply.)

a) Pulmonary artery.

b) Pulmonary vein.

c) Systemic artery.

d) Systemic vein

PRACTICE 2: In which of the following locations will hemoglobin bind oxygen least avidly (i.e. least “tightly”—be most likely to let oxygen unbind)?

a) Resting muscle capillary, PO2= 80 mmHg.

b) Exercising muscle capillary, PO2= 60 mmHg.

c) Systemic artery, PO2= 100 mmHg.

PRACTICE 3: A 16-year-old cross country athlete is running up a hill. As a result, his quadriceps muscles (in his legs) generate excess lactic acid, causing a decrease in the pH around those muscles. Which of the following describes the direction of the resulting shift in the hemoglobin saturation curves for the hemoglobin in the blood around his quadriceps muscles?

a) Rightward shift.

b) Leftward shift.

c) Upward shift.

d) Downward shift

CONCEPT: GAS TRANSPORT II: CARBON DIOXIDE

Mechanisms of Carbon Dioxide Transport in the Blood:

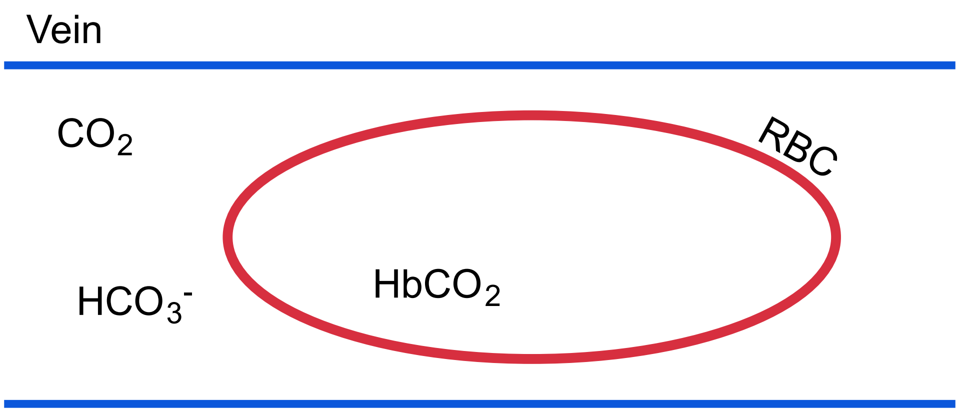
- CO_2 is carried in the blood in three different ways:

    1) Dissolved CO_2 in the plasma (~7%).

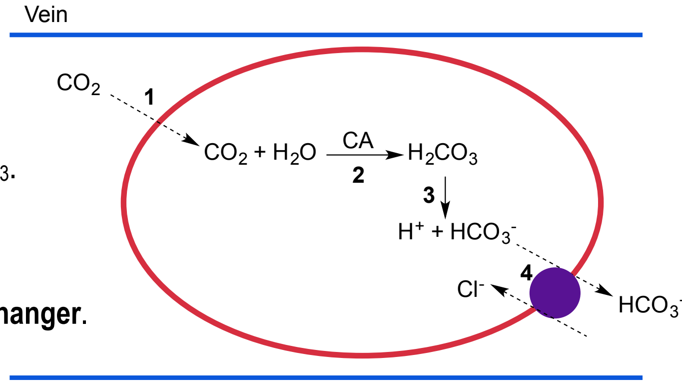
    2) As **carbaminohemoglobin ($HbCO_2$)** bound to hemoglobin (~23%).

    3) As **Bicarbonate (HCO_3^-)** dissolved in the blood plasma (~70%).

EXAMPLE: The three mechanisms of CO_2 transport in blood.



Formation of Bicarbonate in Plasma and RBCs:



- To generate HCO_3^- from CO_2 in venous blood:
  - 1) CO_2 diffuses into red blood cell.
  - 2) In RBC, **carbonic anhydrase** catalyzes $H_2O+CO_2 \rightleftharpoons H_2CO_3$.
  - 3) H_2CO_3 deprotonates: $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$.
  - 4) HCO_3^- pumped *out* of RBC into plasma by **HCO_3^-/Cl^- Exchanger**.
    - -Cl^- is brought into RBC.
- In the lungs, the reverse process happens.
  - □ HCO_3^- brought into RBC in exchange for Cl^-, protonated, H_2CO_3 decomposes to H_2O+CO_2, CO_2 diffuses out.

The Chloride Shift:

● **The Chloride Shift** refers to changes in $[Cl^-]_{plasma}$ (or $[Cl^-]_{RBC\ cytosol}$) because of HCO_3^-/Cl^- Exchanger activity.

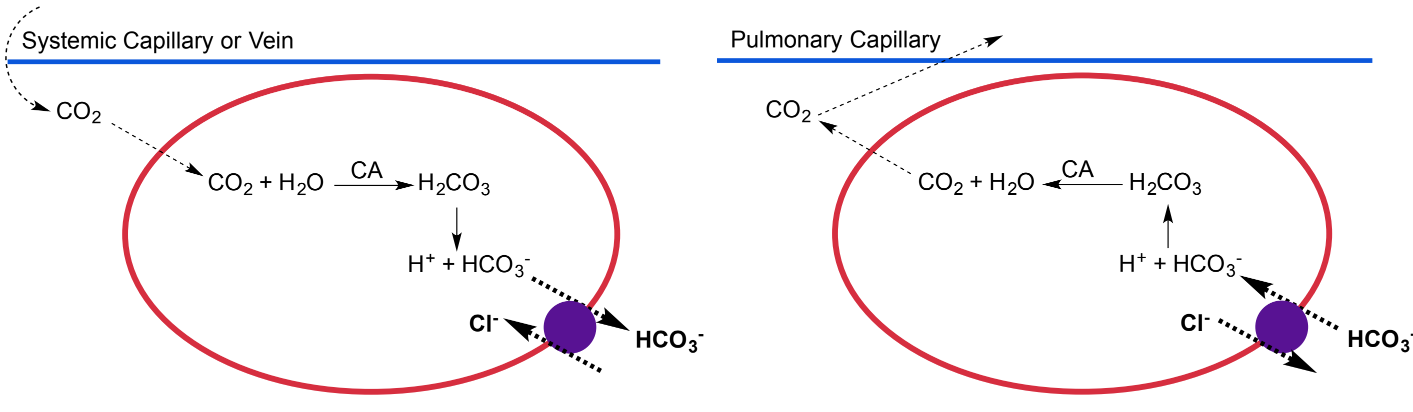
□ In systemic capillaries, blood picks up lots of $CO_2 \rightarrow \uparrow P_{CO2}$. From systemic capillaries→pulmonary capillaries:

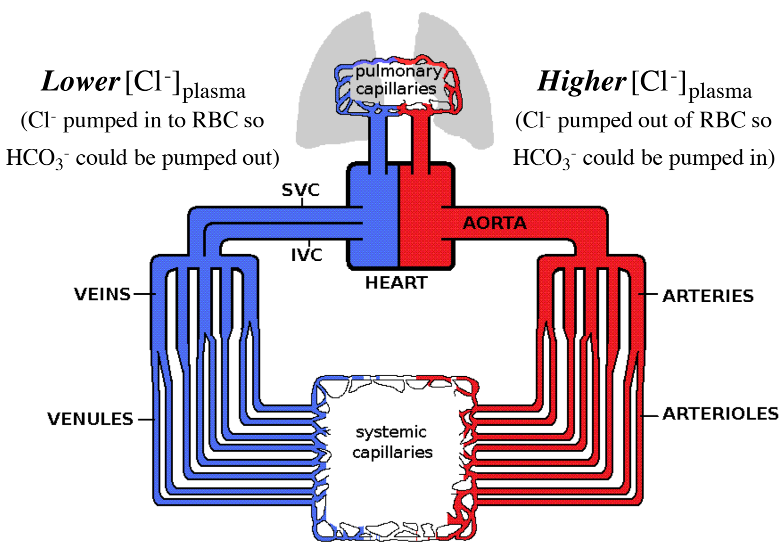
-$\uparrow P_{CO2} \rightarrow \uparrow HCO_3^-$ made in RBCs→$\uparrow HCO_3^-$ pumped out of RBCs→$\uparrow Cl^-$ brought in to RBCs→$\downarrow [Cl^-]_{plasma}$.

□ In pulmonary capillaries, RBCs bring HCO_3^- back in to remake CO_2 so it can be exhaled. From pulmonary capillaries→systemic capillaries:

-$\uparrow HCO_3^-$ brought into RBC→$\uparrow Cl^-$ pumped back *out* of RBC→$\uparrow [Cl^-]_{plasma}$.

EXAMPLE: Chloride shift causes $\uparrow [Cl^-]_{plasma}$ when $\downarrow P_{CO2}$ (from pulmonary capillaries→systemic capillaries).





PRACTICE 1: A 6-year-old boy gets very angry at his parents because he is only allowed to have four Reese's Peanut Butter Cups after dinner (he wants six—one for each year of his life). In protest, he threatens to hold his breath until he passes out. He starts to hold his breath, causing CO_2 to accumulate in his bloodstream. Which of the following forms of CO_2 will accumulate *to the highest levels* in his blood?

a) Carbon Dioxide (CO_2).
b) Carbaminohemoglobin ($HbCO_2$).
c) Bicarbonate (HCO_3^-).
d) Oxygen (O_2).

PRACTICE 2: In which type of blood vessel is $[Cl^-]_{plasma}$ lowest?

a) Systemic artery.
b) Systemic vein.

CONCEPT: REGULATION OF VENTILATION I: NEURAL CONTROL OF RESPIRATORY MUSCLES

Neural Control of Respiratory Muscles:

● Inspiration is an active process controlled by *skeletal* muscles, primarily the diaphragm and external intercostals.

□ *Skeletal* muscles—require activation by a ___________ neuron to contract.

-**Phrenic Nerve** holds axons of motor neurons that control the diaphragm.

● Rhythmic breathing is caused by bursts of APs in these motor neurons that then stop.

□ Burst of APs→Contraction→Inspiration □ No APs→Relaxation→Chest/Lung Recoil→Expiration

● Most control comes from two **respiratory groups** in the *medulla* (part of the brain stem).

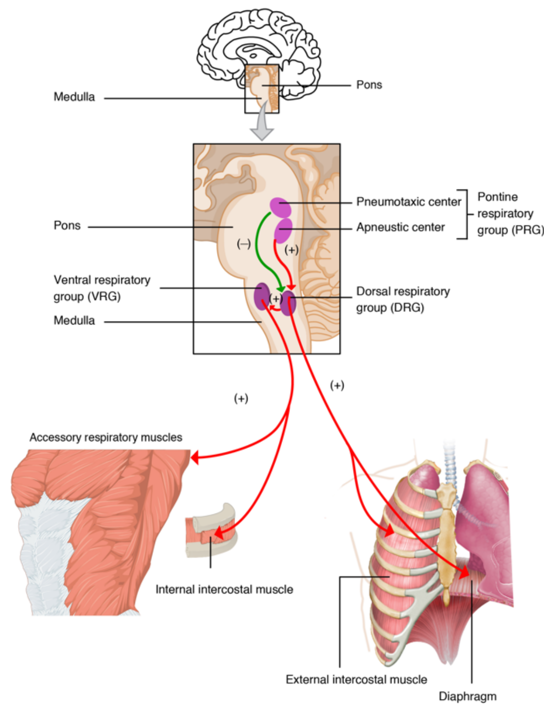
□ **Dorsal Respiratory Group (DRG)** directly controls inspiration.

-Causes inspiratory muscles' motor neurons to fire APs.

□ **Ventral Respiratory Group (VRG)** contains the *pre-Botzinger Complex* and some other stuff.

-**Pre-Botzinger Complex** probably has the pacemaker neurons that set basic respiratory rhythm.

-Other parts control accessory muscles—i.e. those for active expiration or very large inspiration.



● Two other centers in the *pons* give input to the respiratory groups in medulla.

□ **Apneustic Center** *promotes* inspiration.

-Stimulation causes **apneusis**—deep inspiratory gasps with little expirations in between.

□ **Pneumotaxic Center** *inhibits* inspiration and promotes *expiration.*

-i.e. Helps in the transition from breathing in to breathing out.

● All this *involuntary* brain stem control can be overridden (to an extent) by voluntary control from the frontal lobe.

□ You can choose to breathe in, hold your breath, breathe out, etc.

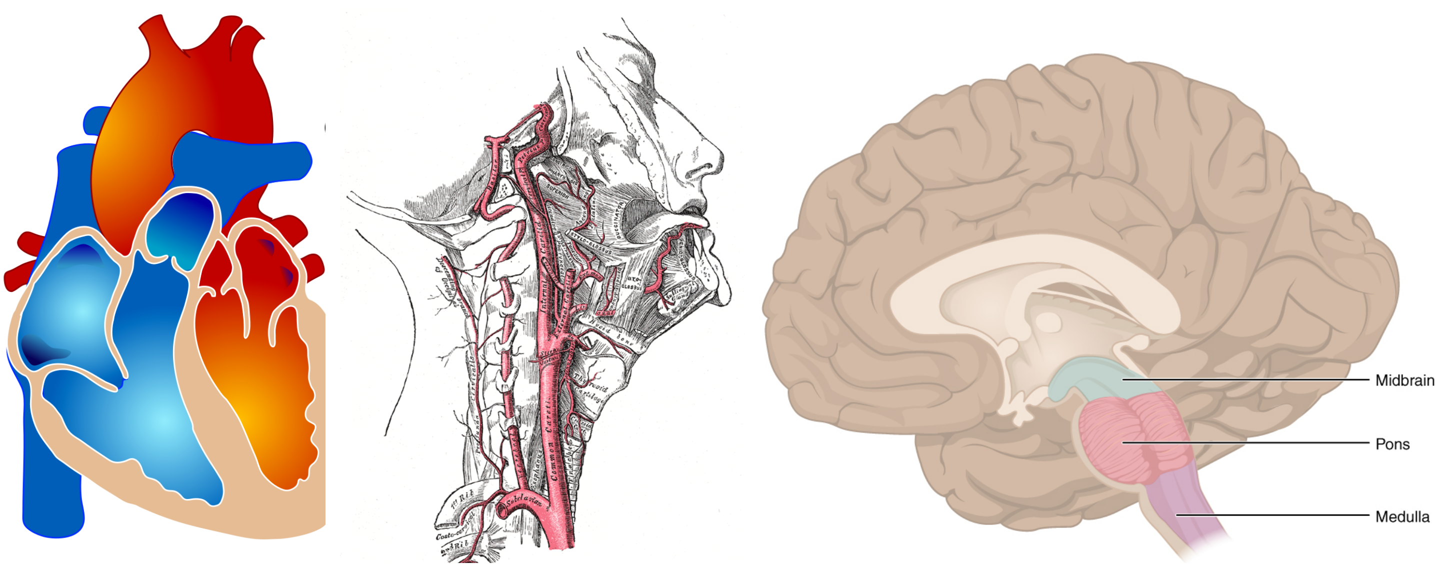
-Unless you hold your breath until you pass out—then involuntary control takes over again.

CONCEPT: REGULATION OF VENTILATION II: CHEMORECEPTORS AND EFFECTS OF CO_2, pH, O_2

Peripheral and Central Chemoreceptors:

- **Chemoreceptors** are sensory neurons specialized to sense levels of ________________________ in the blood.
  - □ Sense three important variables: CO_2 (P_{CO2}), H^+ (pH), and O_2 (P_{O2}).
- All three of these variables can signal a "need" to breathe more.
  - □ ↓Ventilation⟶↑P_{CO2}.
    - ↑P_{CO2}⟶↓pH (because $H_2O+CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$)
    - (↓pH may also come from cells making lactic acid during anaerobic metabolism.)
  - □ ↓Ventilation⟶↓P_{O2}.
- Three types of chemoreceptors in two locations throughout the body.
  - □ **Peripheral Chemoreceptors** in the *aortic arch* and *carotid sinus* monitor CO_2, pH, O_2 in the *blood*.
    - -Same locations as peripheral *baro*receptors (which monitor blood pressure).
  - □ **Central Chemoreceptors** in the _______________________ monitor mostly CO_2 in the *cerebrospinal fluid.*

EXAMPLE: Locations of the peripheral and central chemoreceptors.



Activation and Effects of Peripheral Chemoreceptors:

● Peripheral chemoreceptors in the aortic arch and carotid sinus monitor P_{CO2}, pH, P_{O2}.

● ↑P_{CO2}, ↓pH, and/or ↓P_{O2} all activate these chemoreceptors.

□ But, P_{O2} has to change *dramatically* to cause much change in chemoreceptor activity.

● **Hypercapnic Drive**- Most people's respirations are driven by ↑P_{CO2} (and ↓pH).

□ Hypercapnic=High CO_2.

□ P_{O2} doesn't change dramatically enough in day-to-day life to change chemoreceptor activity.

● Sensory neurons from peripheral chemoreceptors project into medulla.

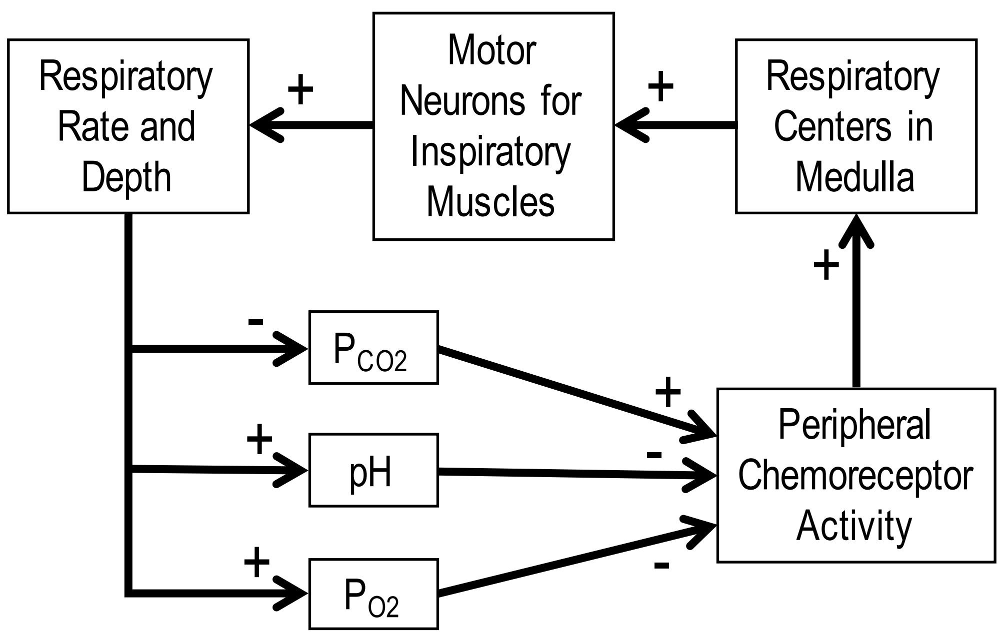
□ ↑P_{CO2} or ↓pH→↑Chemoreceptor Activity→↑Ventilation

● Two related effects of ↑Chemoreceptor Activity on ventilation rhythm: ↑*Rate* and ↑*Depth*.

□ **Rate**=How often a breath is taken (breaths/min).

□ **Depth**=How much air is inspired or expired (tidal volume)(mL/breath).

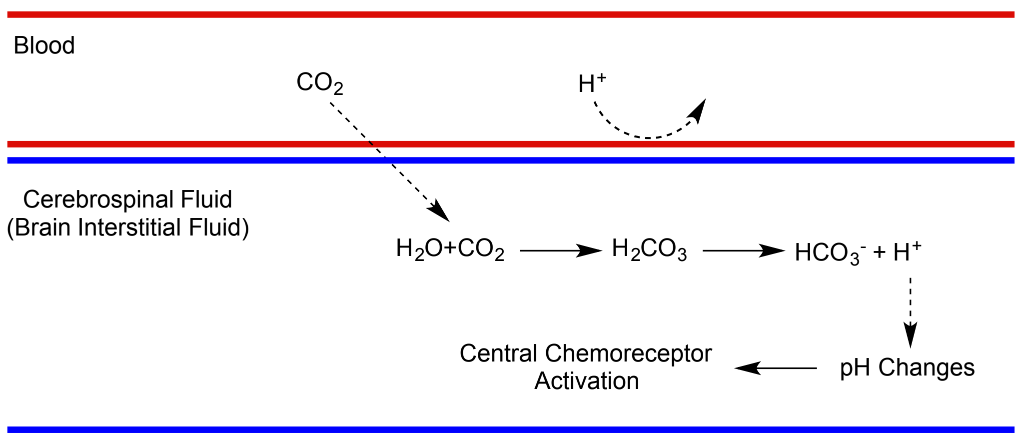
EXAMPLE: Feedback loop of peripheral chemoreceptor activation and effects.



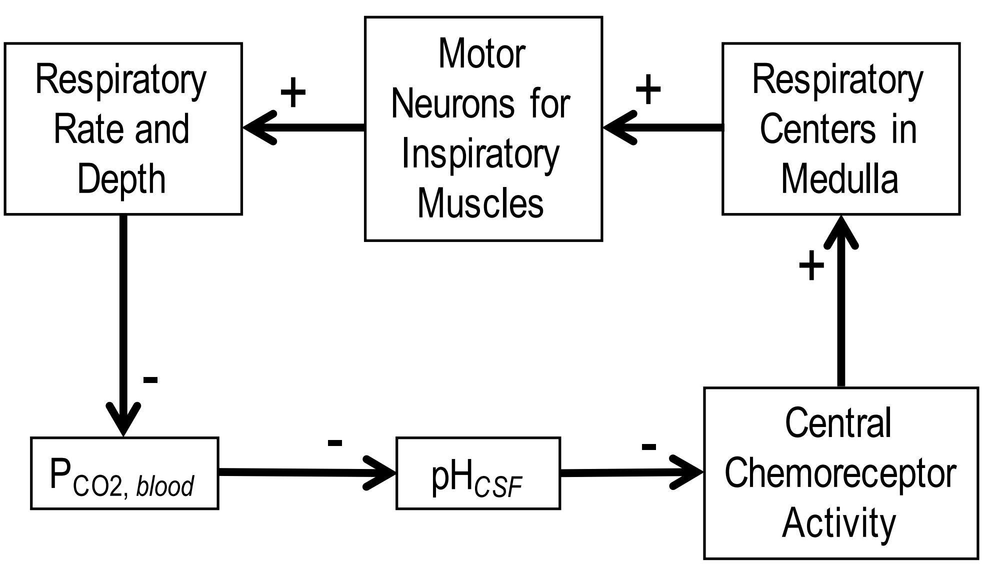
Activation and Effects of Central Chemoreceptors:

- Central chemoreceptors monitor variables in the cerebrospinal fluid (CSF; interstitial fluid in the brain), not the blood.
  - □ H^+ is charged, so can't cross from blood to CSF→central chemoreceptors do *not* directly monitor blood pH.
  - □ P_{O2} has to change a lot for chemoreceptors to "notice"→central chemoreceptors don't really monitor blood P_{O2}.
- Central chemoreceptors monitor and respond to changes in *blood* P_{CO2}.
  - □ CO_2 is small and nonpolar (lipophilic)→able to cross blood-brain barrier from blood into CSF.
- Central chemoreceptors monitor blood P_{CO2} *by sensing changes in pH in the CSF.*
  - □ $\uparrow P_{CO2,\ blood} \rightarrow \uparrow P_{CO2,\ CSF} \rightarrow \uparrow [H_2CO_3]_{CSF} \rightarrow \uparrow [H^+]_{CSF} \rightarrow \downarrow pH_{CSF} \rightarrow \uparrow$Central Chemoreceptor Activity.
- Central chemoreceptor activation has similar effects to peripheral chemoreceptors: ↑ventilation rate and depth.

EXAMPLE: Central chemoreceptors monitor blood P_{CO2} indirectly by directly responding to changes in CSF pH.



EXAMPLE: Feedback loop of central chemoreceptor activation and effects. (Look at all the sign inversions!)



PRACTICE 1: A 7-year-old boy throws a tantrum because his mom won't buy him a Nintendo Switch. As part of the tantrum he holds his breath. He is unable to hold his breath until he passes out; the urge to breathe becomes overpowering and he starts breathing again. Which substance(s) accumulated in his bloodstream and activated his *peripheral* chemoreceptors to create this overpowering urge to breathe? (Choose all that apply.)

a) Oxygen.
b) Carbon Dioxide.
c) Hydrogen Ions (protons; H^+).
d) Gorons.

PRACTICE 2: A 7-year-old boy throws a tantrum because his mom won't buy him a Nintendo Switch. As part of the tantrum he holds his breath. He is unable to hold his breath until he passes out; the urge to breathe becomes overpowering and he starts breathing again. Which substance(s) accumulated in his bloodstream and activated his *central* chemoreceptors to create this overpowering urge to breathe? (Choose all that apply.)

a) Oxygen.
b) Carbon Dioxide.
c) Hydrogen Ions (protons; H^+).
d) Zoras.