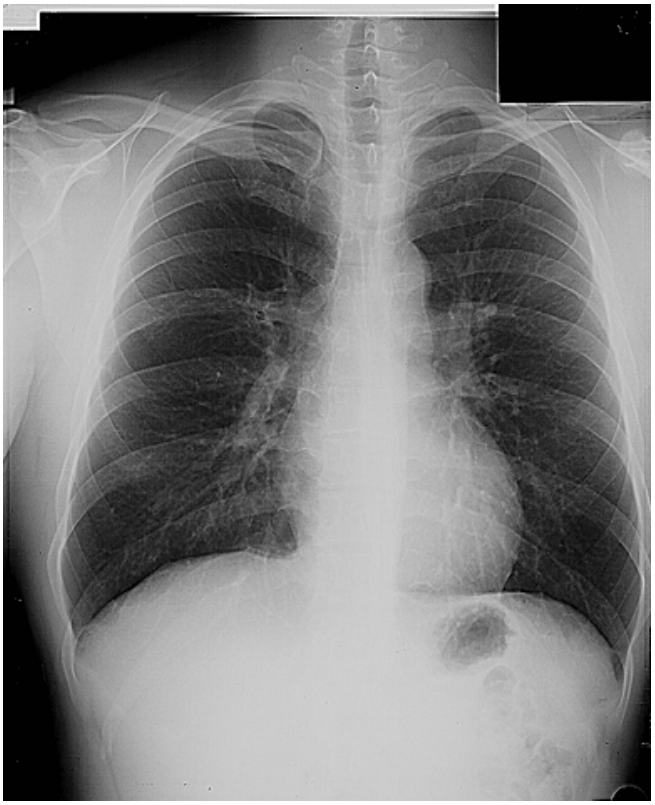
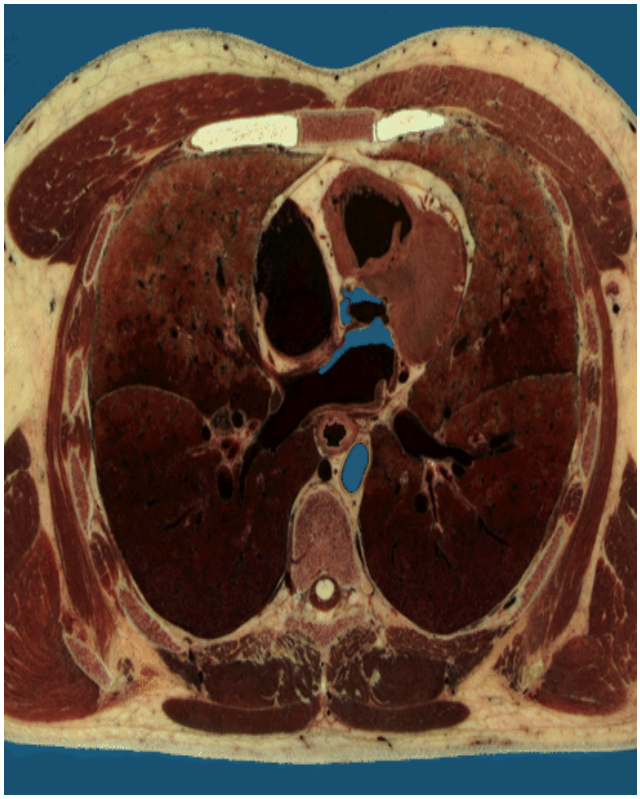
The Respiratory System
Danil Hammoudi.MD





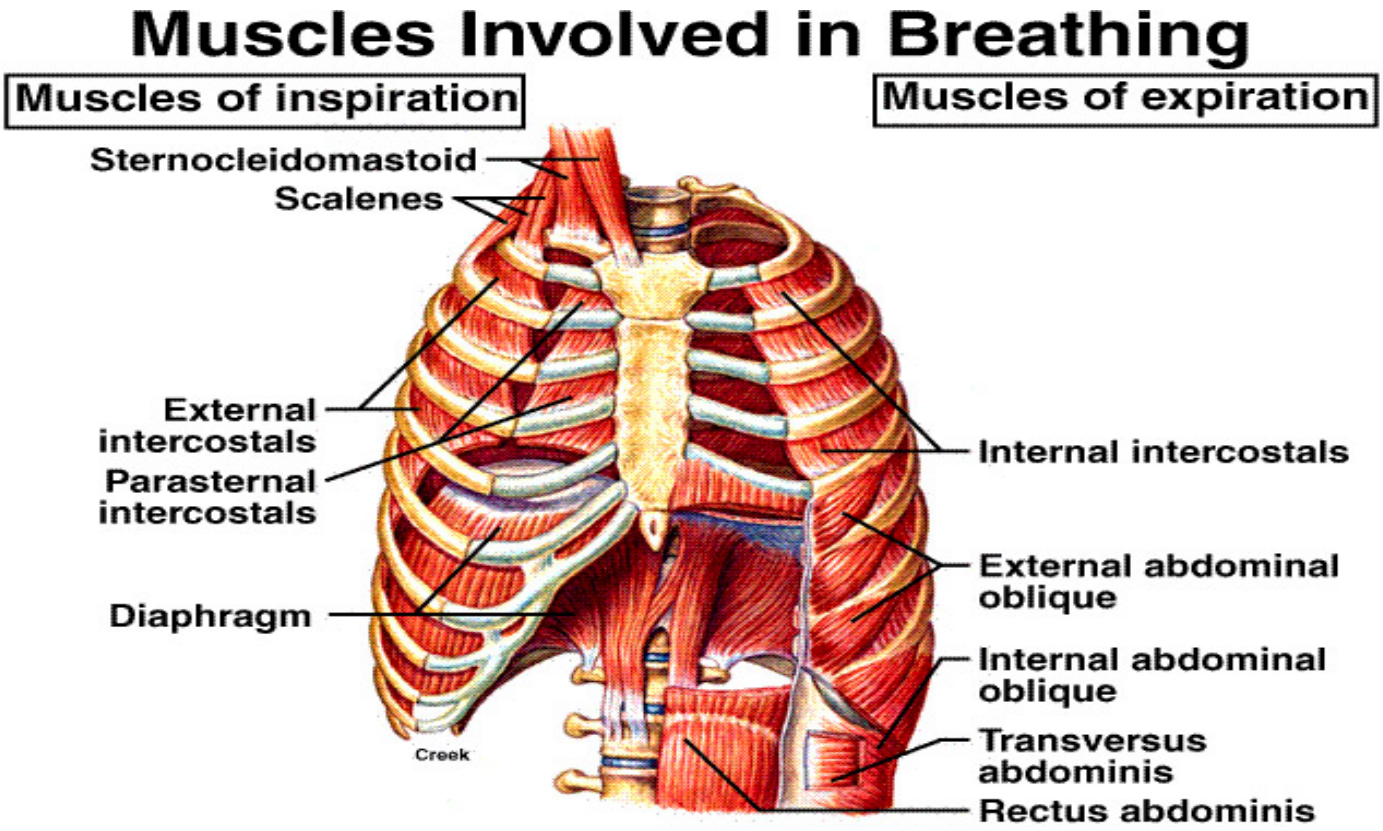
Respiratory System
- Consists of the respiratory and conducting zones
- Respiratory zone:
  - Site of gas exchange
  - Consists of bronchioles, alveolar ducts, and alveoli
- Conducting zone:
  - Conduits for air to reach the sites of gas exchange
  - Includes all other respiratory structures (e.g., nose, nasal cavity, pharynx, trachea)
- Respiratory muscles – diaphragm and other muscles that promote ventilation

Major Functions of the Respiratory System
The main function of the lungs is to provide continuous gas exchange between inspired air and the blood in the pulmonary circulation, supplying oxygen and removing carbon dioxide, which is then cleared from the lungs by subsequent expiration.

Survival is dependent upon this process being reliable, sustained and efficient, even when challenged by disease or an unfavourable environment.

Evolutionary development has produced many complex mechanisms to achieve this, several of which are compromised by anaesthesia.

- To supply the body with oxygen and dispose of carbon dioxide
- Respiration – four distinct processes must happen
  - Pulmonary ventilation – moving air into and out of the lungs
  - External respiration – gas exchange between the lungs and the blood
  - Transport – transport of oxygen and carbon dioxide between the lungs and tissues
  - Internal respiration – gas exchange between systemic blood vessels and tissues



- A) Upper Respiratory Tract (URT)
    - 1) paranasal structures
        - a) external nares
        - b) nasal cavity and septum
        - c) nasal conchae
        - d) nasal meatuses
        - e) olfactory epithelium
        - f) paranasal sinuses
        - g) ciliated pseudostratified epithelium
    - 2) pharynx
        - a) internal nares
        - b) auditory tubes
        - c) oropharynx
        - d) laryngopharynx
- B) Lower Respiratory Tract (LRT)
    - 1) layrnx
        - a) thyroid & cricoid cartilage
        - b) vocal box
        - c) hyoid
    - 2) trachea
        - a) "C" rings of cartilage
        - b) carina
            - i) receptors sensitive to irritants
            - ii) initiates cough reflex
        - c) bronchi

- 3) lungs (right lung = three lobes; left lung = two lobes)
    - a) pleural membranes
    - b) bronchi
    - c) bronchioles
    - d) terminal bronchioles
    - e) smooth muscles within bronchiole walls
        - i) parasympathetic NS activates (using histamine) bronchiole smooth muscle (constriction)
        - ii) sympathetic NS inhibits (using epinephrine) bronchiole smooth muscle (dilation)
    - f) alveolar ducts
    - g) alveolar sacs
    - h) alveoli
        - i) simple squamous lining
        - ii) septal cells - produce surfactant
        - iii) macrophage (Kuppfer cells) - remove alveolar irritants, debris
        - iv) entire alveolar surface area = 750 sqft
        - v) alveolar surface area site of external respiration

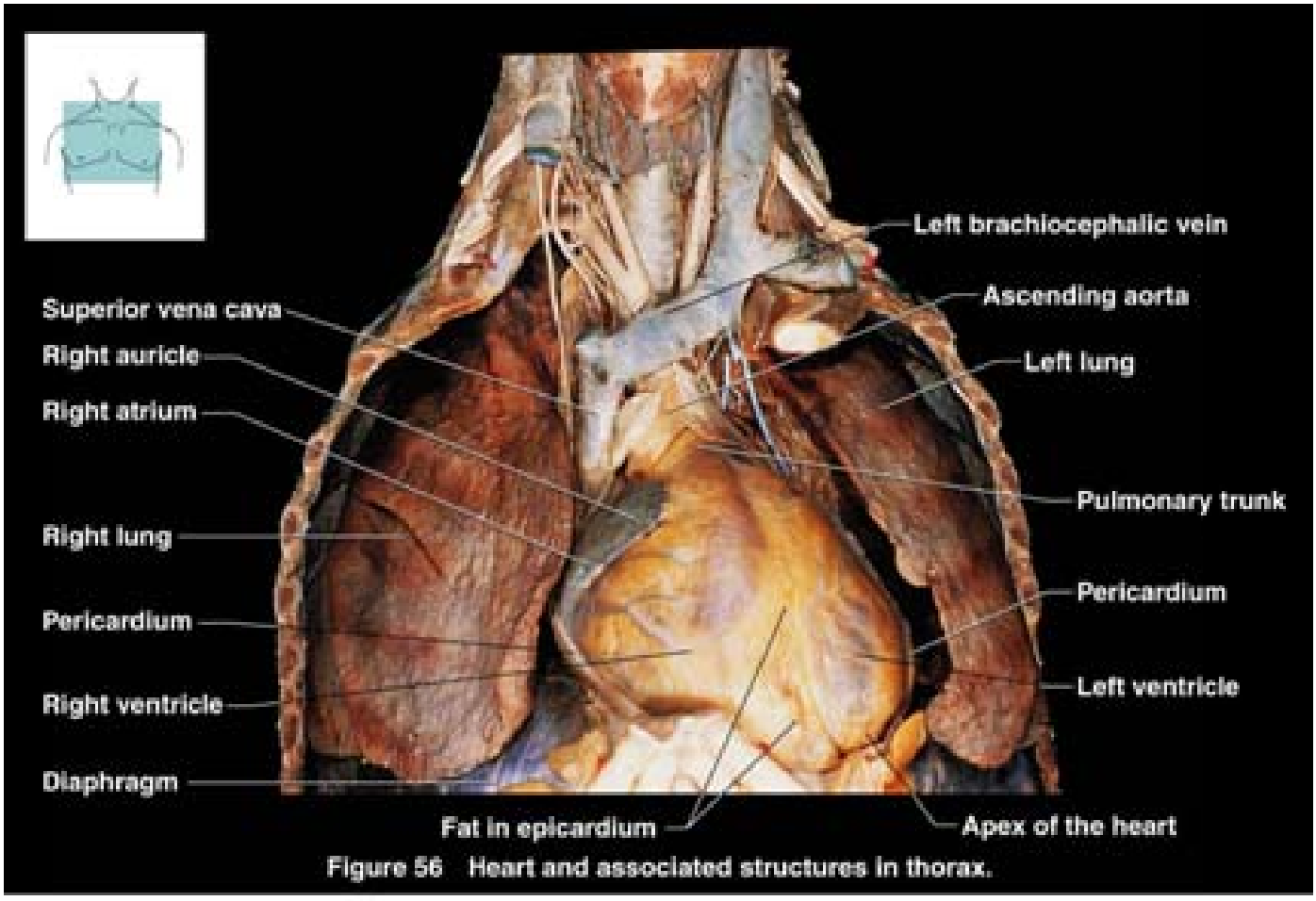
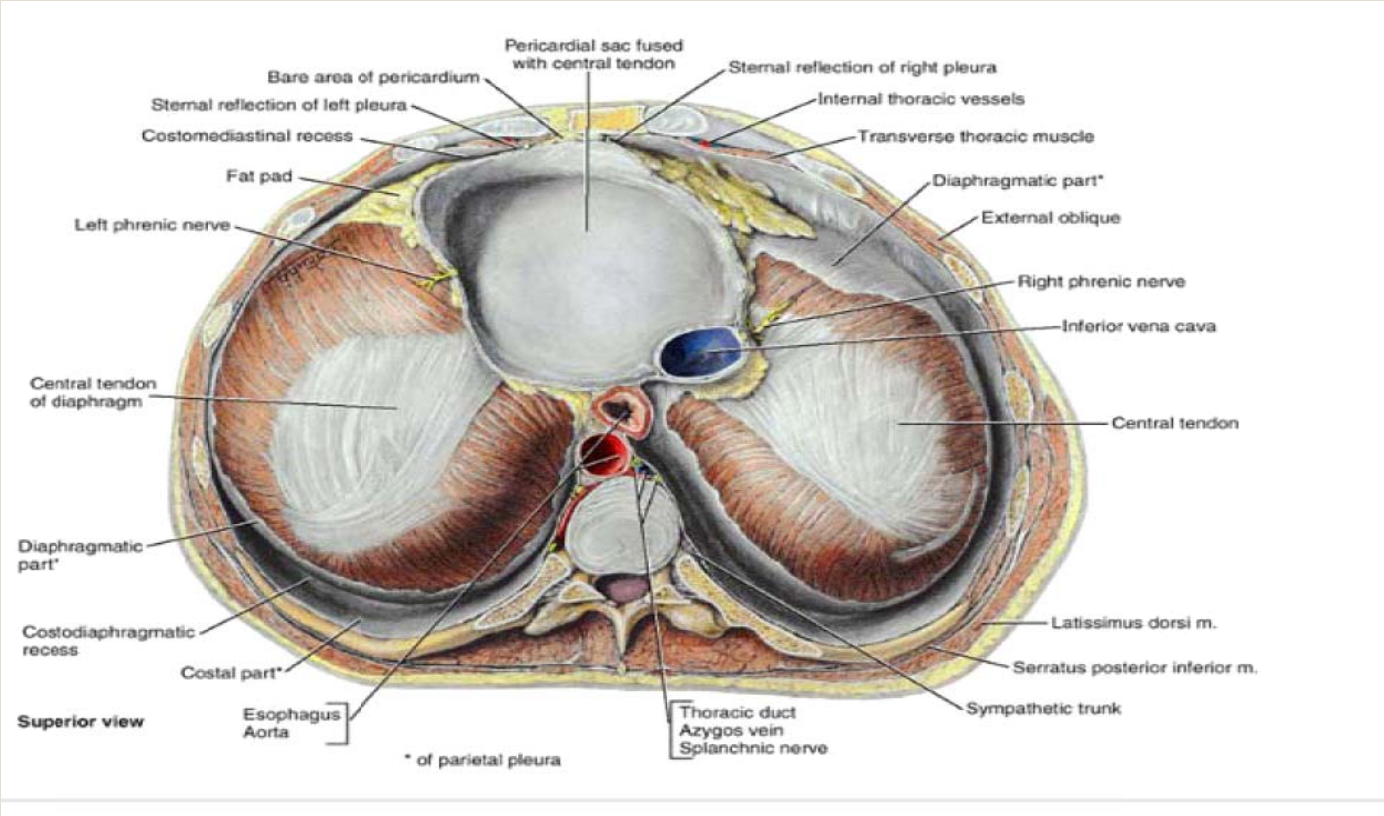


Figure 56 Heart and associated structures in thorax.



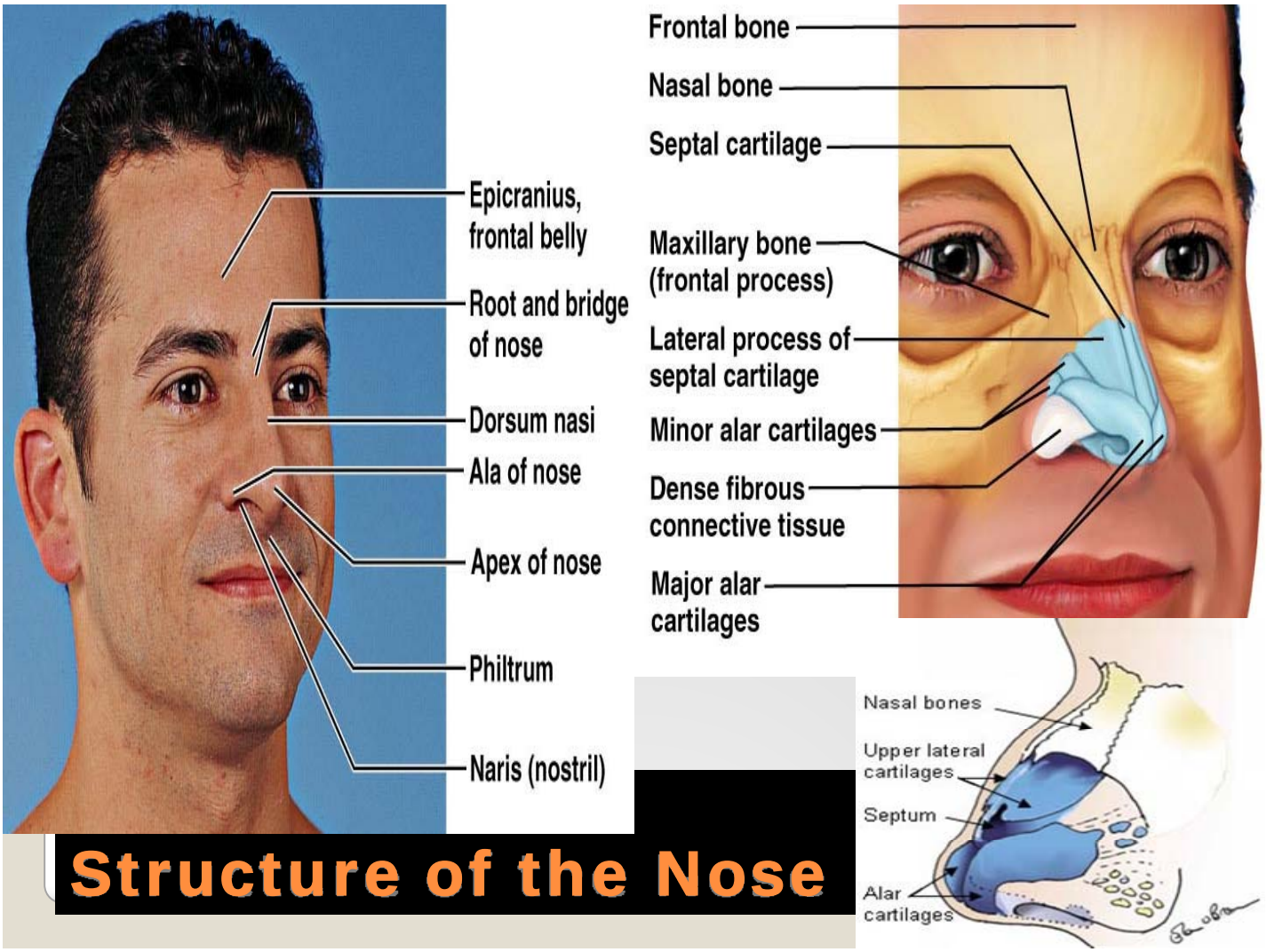
Anatomy

The respiratory tract extends from the mouth and nose to the alveoli.

The upper airway serves to filter airborne particles, humidify and warm the inspired gases.

The patency of the airway in the nose and oral cavity is largely maintained by the bony skeleton, but in the pharynx is dependent upon the tone in the muscles of the tongue, soft palate and pharyngeal walls.

Nasal Cavity



Function of the Nose

- The only externally visible part of the respiratory system that functions by:
  - Providing an airway for respiration
  - Moistening and warming the entering air
  - Filtering inspired air and cleaning it of foreign matter
  - Serving as a resonating chamber for speech
  - Housing the olfactory receptors

Structure of the Nose

- Nose is divided into two regions:
  - External nose, including the root, bridge, dorsum nasi, and apex
  - Internal nasal cavity
- Philtrum – a shallow vertical groove inferior to the apex

- The external nares (nostrils) are bounded laterally by the alae

Nasal Cavity

- Lies in and posterior to the external nose
- Is divided by a midline nasal septum
- Opens posteriorly into the nasal pharynx via internal nares
- The ethmoid and sphenoid bones form the roof
- The floor is formed by the hard and soft palates
- Vestibule – nasal cavity superior to the nares
  - Vibrissae – hairs that filter coarse particles from inspired air
- Olfactory mucosa
  - Lines the superior nasal cavity
  - Contains smell receptors
- Respiratory mucosa
  - Lines the balance of the nasal cavity
  - Glands secrete mucus containing lysozyme and defensins to help destroy bacteria
- Inspired air is:
  - Humidified by the high water content in the nasal cavity
  - Warmed by rich plexuses of capillaries
- Ciliated mucosal cells remove contaminated mucus
- Superior, medial, and inferior conchae:
  - Protrude medially from the lateral walls
  - Increase mucosal area
  - Enhance air turbulence and help filter air
- Sensitive mucosa triggers sneezing when stimulated by irritating particles

Functions of the Nasal Mucosa and Conchae

- During inhalation the conchae and nasal mucosa:
  - Filter, heat, and moisten air
- During exhalation these structures:
  - Reclaim heat and moisture
  - Minimize heat and moisture loss

Paranasal Sinuses

- Sinuses in bones that surround the nasal cavity
- Sinuses lighten the skull and help to warm and moisten the air

Pharynx

- Funnel-shaped tube of skeletal muscle that connects to the:
  - Nasal cavity and mouth superiorly
  - Larynx and esophagus inferiorly
- Extends from the base of the skull to the level of the sixth cervical vertebra
- It is divided into three regions
  - Nasopharynx
  - Oropharynx
  - Laryngopharynx

a/Nasopharynx

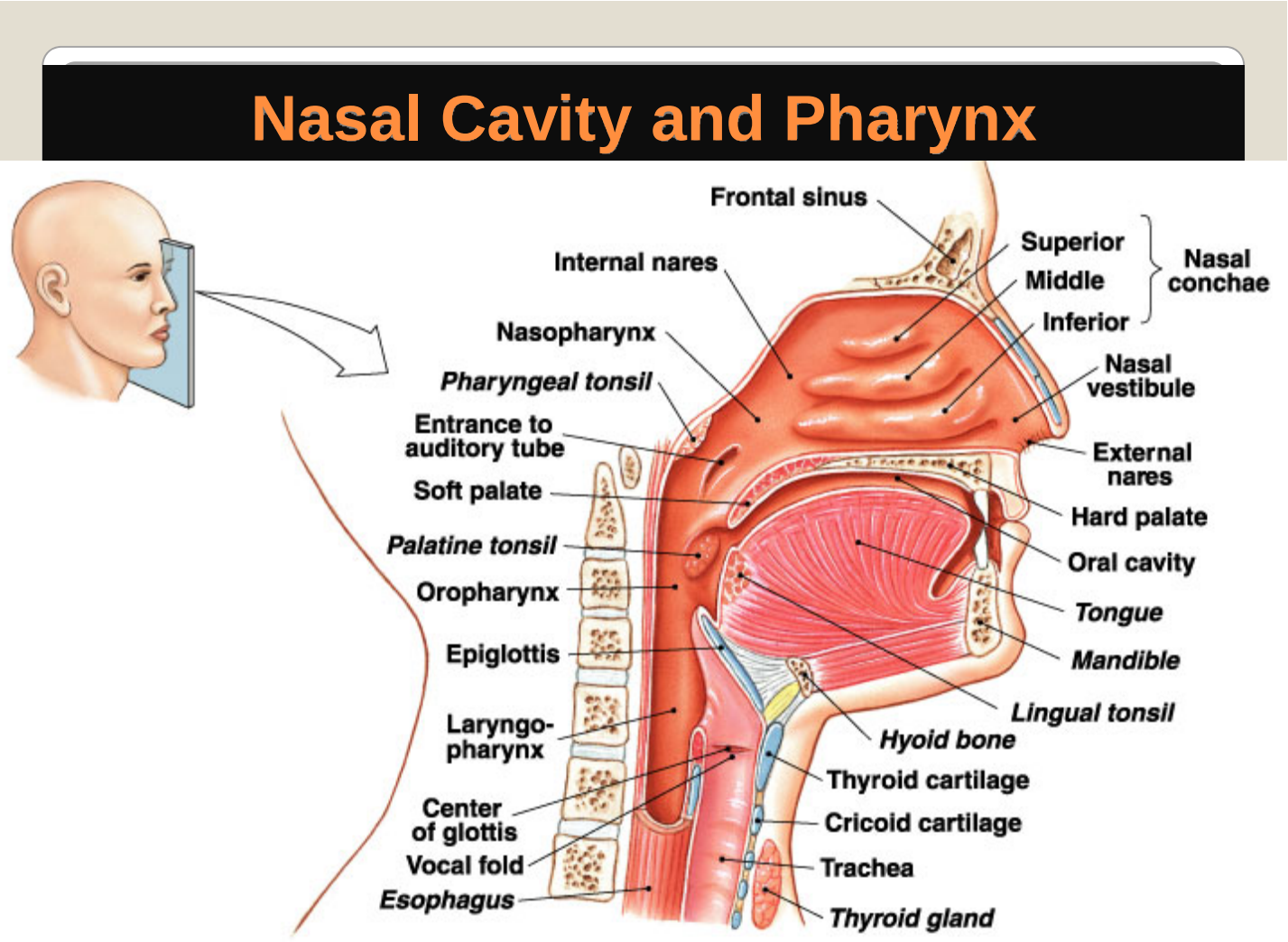
- Lies posterior to the nasal cavity, inferior to the sphenoid, and superior to the level of the soft palate
- Strictly an air passageway
- Lined with pseudostratified columnar epithelium
- Closes during swallowing to prevent food from entering the nasal cavity
- The pharyngeal tonsil lies high on the posterior wall
- Pharyngotympanic (auditory) tubes open into the lateral walls

b/Oropharynx

- Extends inferiorly from the level of the soft palate to the epiglottis
- Opens to the oral cavity via an archway called the fauces
- Serves as a common passageway for food and air
- The epithelial lining is protective stratified squamous epithelium
- Palatine tonsils lie in the lateral walls of the fauces
- Lingual tonsil covers the base of the tongue

c/Laryngopharynx

- Serves as a common passageway for food and air
- Lies posterior to the upright epiglottis
- Extends to the larynx, where the respiratory and digestive pathways diverge



The Nasal cavity is divided into three structurally and functionally different parts.

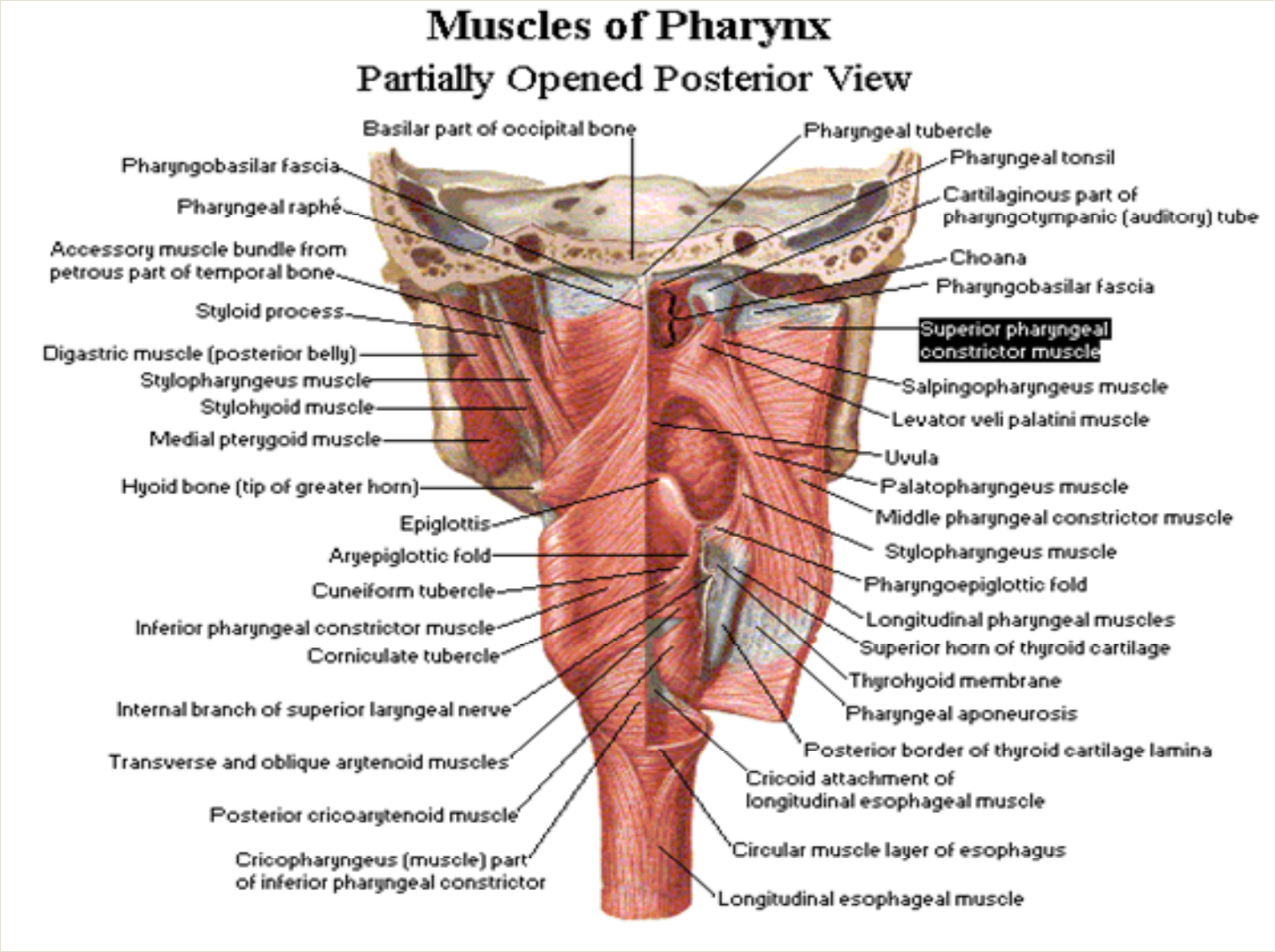
- The vestibules (the first ~1.5 cm of the conductive portion following the nostrils) are lined with a keratinised stratified squamous epithelium.

Hairs, which filter large particulate matter out of the airstream, and sebaceous glands are also present.

- At the transition from the vestibule to the respiratory region of the nasal cavity the epithelium becomes first stratified squamous and then pseudostratified columnar and ciliated.
- This type of epithelium is characteristic for all conductive passages dedicated to the respiratory system and therefore also called respiratory epithelium. Mucus producing goblet cells are present in the epithelium.
- The surface of the lateral parts of the nasal cavity is thrown into folds by bony projections called conchae.
- These folds increase the surface area of the nasal cavity and create turbulence in the stream of passing air, both of which facilitate the conditioning (warming, cooling and filtration) of the air. Mucous and serous glands in the connective tissue underlying the epithelium, the lamina propria, supplement the secretion of the goblet cells.
- Veins in the lamina propria form thin-walled, cavernous sinusoids, also called cavernous bodies.

- Tissues on the superior concha and the nasal septum form the olfactory region of the nasal cavity. Cilia in the epithelium of the olfactory region arise from olfactory cells.
- Although their internal structure resembles largely that of normal cilia they do not move, because they lack dynein arms which are necessary for cilial motility.
- The cell membrane covering the surface of the cilia contains olfactory receptors which respond to odour-producing substances, odorants, dissolved in the serous covering the epithelium.
- The axons of the olfactory cells collect into bundles in the lamina propria. The olfactory cells and their processes receive mechanical and metabolic support from supporting cells (or sustentacular cells).
- Basal cells can divide and differentiate into either olfactory or supporting cells.
  The supporting cells and the secretion of the serous glands contain lipofuscin granules, which give a yellow-brown colour to the surface of the olfactory region.

Larynx



The larynx lies at the level of upper cervical vertebrae, C4-6, and its main structural components are the thyroid and cricoid cartilages, along with the smaller arytenoid cartilages and the epiglottis, which sit over the laryngeal inlet.

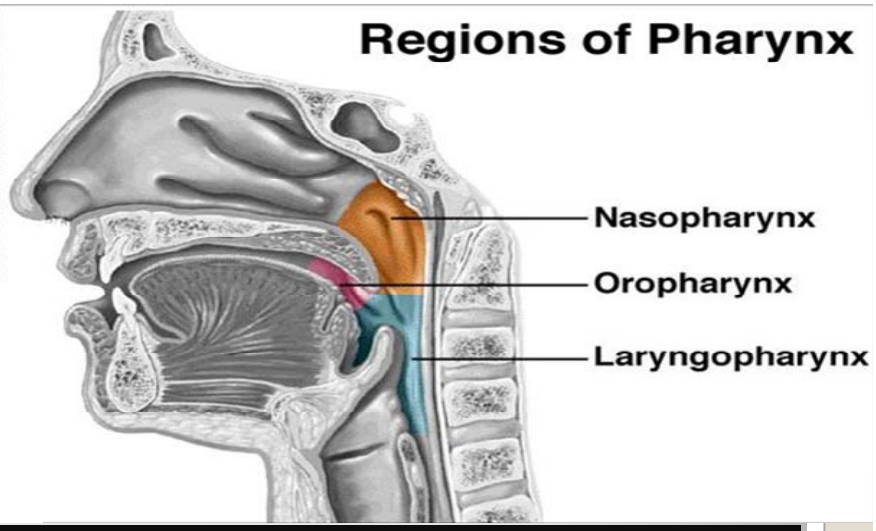
A series of ligaments and muscles link these structures, which, by a co-ordinated sequence of actions, protect the larynx from solid or liquid material during swallowing as well as regulating vocal cord tension for phonation (speaking).

The technique of cricoid pressure is based on the fact that the cricoid cartilage is a complete ring, which is used to compress the oesophagus behind it against the vertebral bodies of C5-6 to prevent regurgitation of gastric contents into the pharynx.

The thyroid and cricoid cartilages are linked anteriorly by the cricothyroid membrane, through which access to the airway can be gained in an emergency.

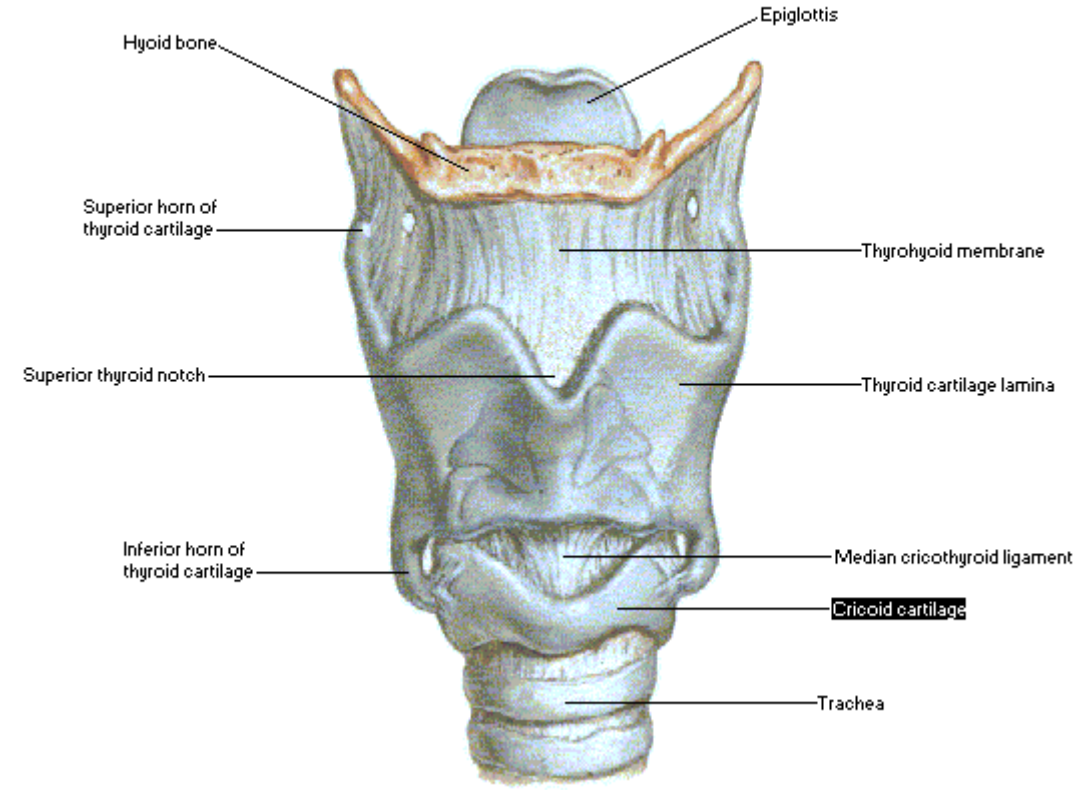
Pharynx

- It is divided into three regions
  - **Nasopharynx**
  - **Oropharynx**
  - **Laryngopharynx**



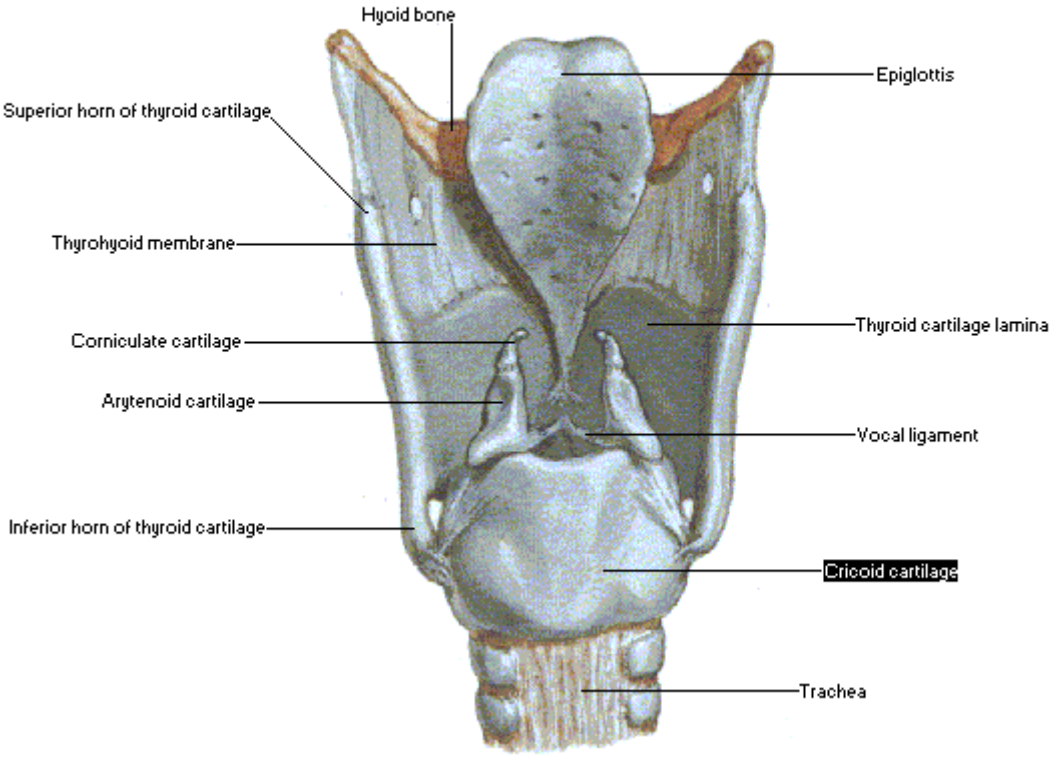
Cartilages of Larynx

Anterior View



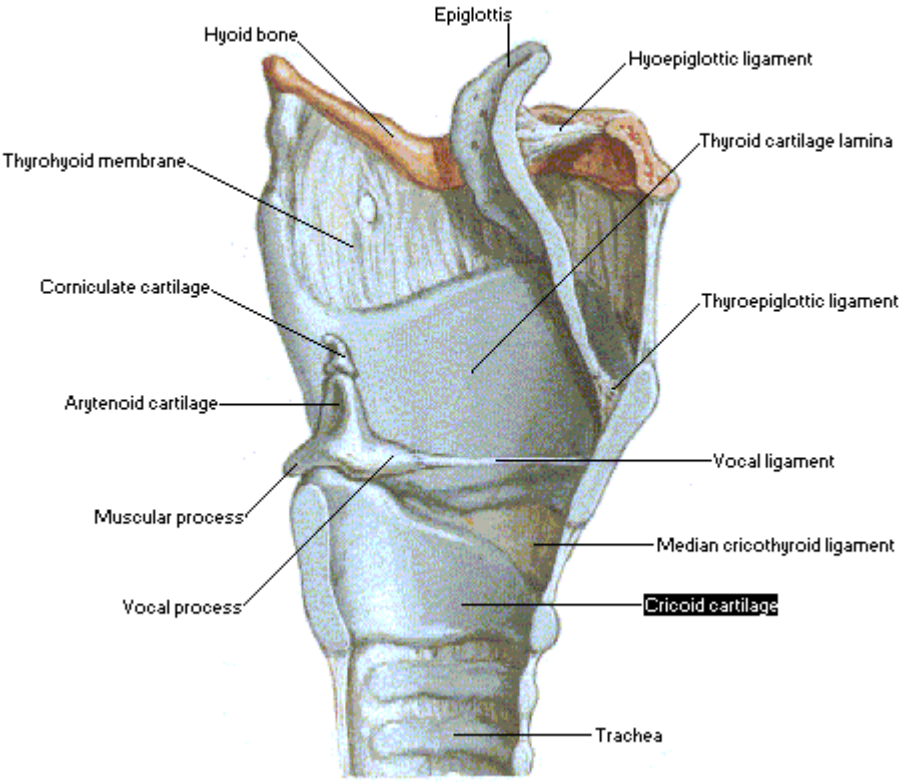
Cartilages of Larynx

Posterior View



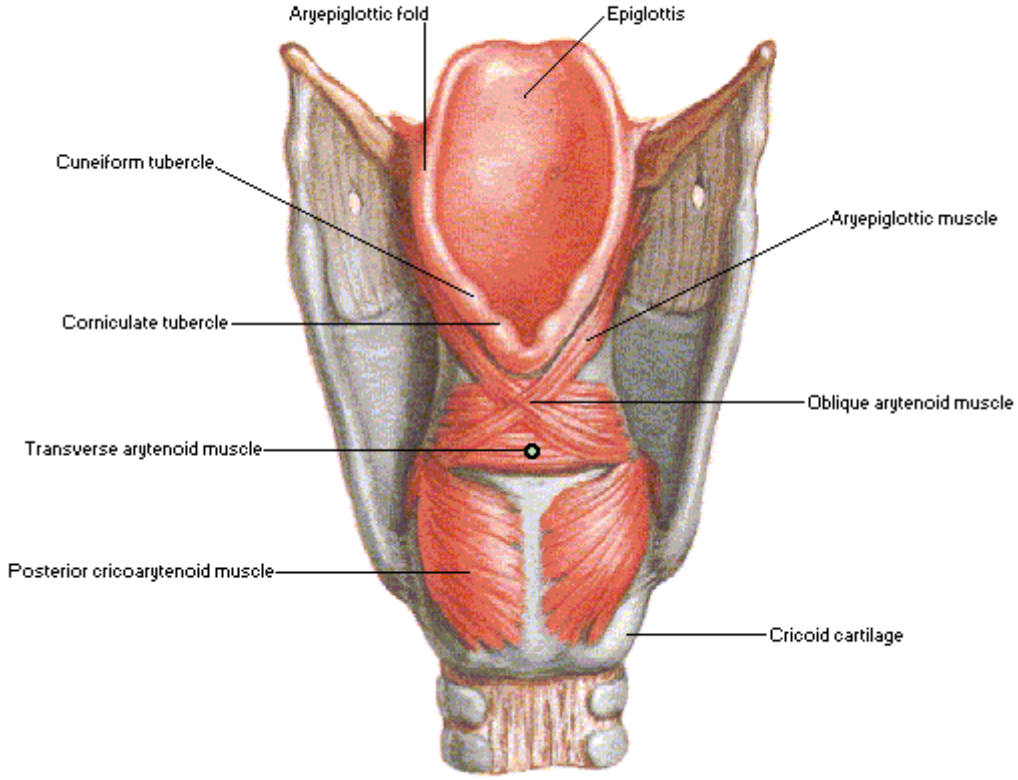
Cartilages of Larynx

Sagittal Section



Intrinsic Muscles of Larynx

Posterior View



Muscles of the larynx

Muscles of the larynx can be categorized into extrinsic and intrinsic Extrinsic muscles are infrahyoid and suprahyoid muscles that move larynx as a whole, stylopharyngeus muscle is also involved.

Intrinsic larynx musclea are concerned with the movement of the laryngeal parts. All intrinsic muscles are innervated by recurrent laryngeal nerve except the cricothyroid muscle which is innervated by the external laryngeal nerve (both from CN 10).

Muscles of the vocal cord

Adductors of the vocal cord:

lateral cricoarytenoid muscle

Abductors of the vocal cord

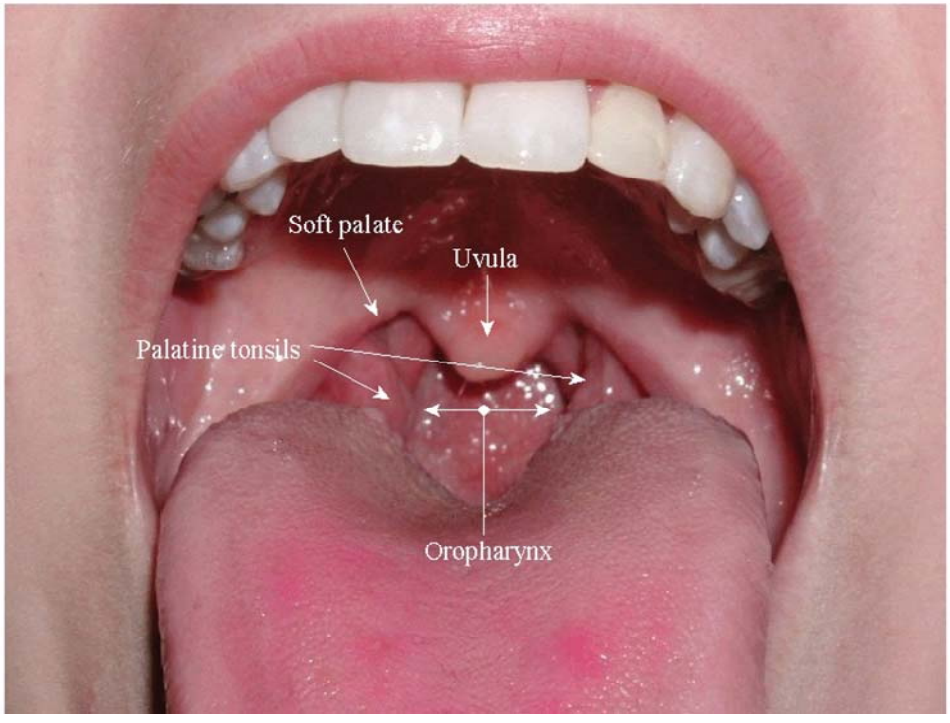
posterior cricoarytenoid muscle

Tensor of the vocal cord

cricothyroid muscle, increases the tension of the vocal cord

Relaxer of the vocal cord

thyroarytenoid muscle



Larynx (Voice Box)

- Attaches to the hyoid bone and opens into the laryngopharynx superiorly
- Continuous with the trachea posteriorly
- The three functions of the larynx are:
  - To provide a patent airway
  - To act as a switching mechanism to route air and food into the proper channels
  - To function in voice production

Framework of the Larynx

- Cartilages (hyaline) of the larynx
  - Shield-shaped anterosuperior thyroid cartilage with a midline laryngeal prominence (Adam's apple)
  - Signet ring–shaped anteroinferior cricoid cartilage
  - Three pairs of small arytenoid, cuneiform, and corniculate cartilages
- Epiglottis – elastic cartilage that covers the laryngeal inlet during swallowing

Vocal Ligaments

- Attach the arytenoid cartilages to the thyroid cartilage
- Composed of elastic fibers that form mucosal folds called true vocal cords
  - The medial opening between them is the glottis
  - They vibrate to produce sound as air rushes up from the lungs

Vocal Ligaments

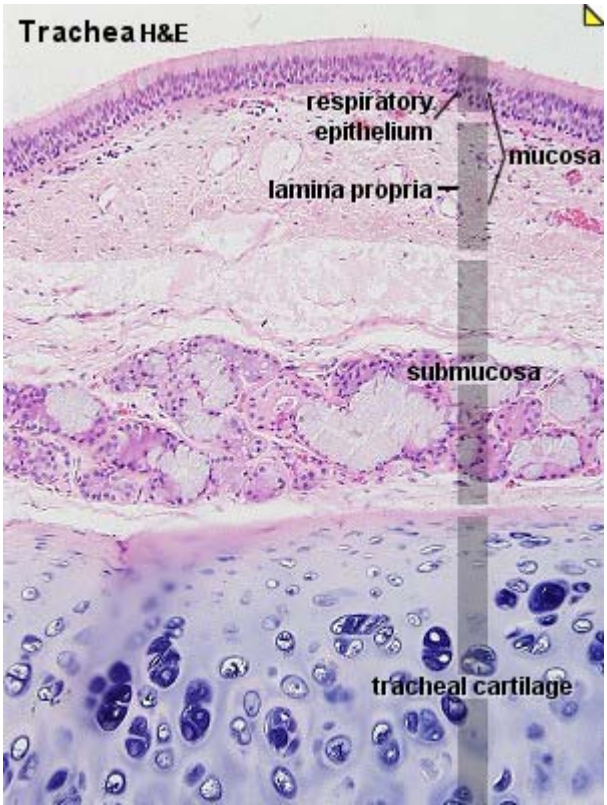
- False vocal cords
  - Mucosal folds superior to the true vocal cords
  - Have no part in sound production

Vocal Production

- Speech – intermittent release of expired air while opening and closing the glottis
- Pitch – determined by the length and tension of the vocal cords
- Loudness – depends upon the force at which the air rushes across the vocal cords
- The pharynx resonates, amplifies, and enhances sound quality
- Sound is "shaped" into language by action of the pharynx, tongue, soft palate, and lips

Sphincter Functions of the Larynx

- The larynx is closed during coughing, sneezing, and Valsalva's maneuver
- **Valsalva's maneuver**
  - Air is temporarily held in the lower respiratory tract by closing the glottis
  - Causes intra-abdominal pressure to rise when abdominal muscles contract
  - Helps to empty the rectum
  - Acts as a splint to stabilize the trunk when lifting heavy loads



Trachea and bronchi

The trachea extends from below the cricoid cartilage to the carina, the point where the trachea divides into the left and right main bronchus, with a length of 12-15cm in an adult and an internal diameter of 1.5-2.0cm.

The carina lies at the level of T5 (5^{th} thoracic vertebra) at expiration and T6 in inspiration.

Most of its circumference is made up of a series of C-shaped cartilages, but the trachealis muscle, which runs vertically, forms the posterior aspect.

When the trachea bifurcates, the right main bronchus is less sharply angled from the trachea than the left, making aspirated material more likely to enter the right lung.

In addition, the right upper lobe bronchus arises only about 2.5cm from the carina and must be accommodated when designing right-sided endobronchial tubes.

Trachea

- Flexible and mobile tube extending from the larynx into the mediastinum
- Composed of three layers
  - Mucosa – made up of goblet cells and ciliated epithelium
  - Submucosa – connective tissue deep to the mucosa
  - Adventitia – outermost layer made of C-shaped rings of hyaline cartilage

Conducting Zone: Bronchi

- Carina of the last tracheal cartilage marks the end of the trachea and the beginning of the bronchi
- Air reaching the bronchi is:
  - Warm and cleansed of impurities
  - Saturated with water vapor
- Bronchi subdivide into secondary bronchi, each supplying a lobe of the lungs
- Air passages undergo 23 orders of branching

Conducting Zone: Bronchial Tree

- Tissue walls of bronchi mimic that of the trachea
- As conducting tubes become smaller, structural changes occur
  - Cartilage support structures change
  - Epithelium types change
  - Amount of smooth muscle increases
- Bronchioles
  - Consist of cuboidal epithelium
  - Have a complete layer of circular smooth muscle
  - Lack cartilage support and mucus-producing cells

Respiratory Zone

- Defined by the presence of alveoli; begins as terminal bronchioles feed into respiratory bronchioles
- Respiratory bronchioles lead to alveolar ducts, then to terminal clusters of alveolar sacs composed of alveoli
- Approximately 300 million alveoli:
  - Account for most of the lungs' volume
  - Provide tremendous surface area for gas exchange

Respiratory Membrane

- This air-blood barrier is composed of:
  - Alveolar and capillary walls
  - Their fused basal laminas
- Alveolar walls:
  - Are a single layer of type I epithelial cells
  - Permit gas exchange by simple diffusion
  - Secrete angiotensin converting enzyme (ACE)
- Type II cells secrete surfactant

Alveoli

- Surrounded by fine elastic fibers
- Contain open pores that:
  - Connect adjacent alveoli
  - Allow air pressure throughout the lung to be equalized
- House macrophages that keep alveolar surfaces sterile

Gross Anatomy of the Lungs

- Lungs occupy all of the thoracic cavity except the mediastinum
  - Root – site of vascular and bronchial attachments
  - Costal surface – anterior, lateral, and posterior surfaces in contact with the ribs
  - Apex – narrow superior tip
  - Base – inferior surface that rests on the diaphragm
  - Hilus – indentation that contains pulmonary and systemic blood vessels

Lungs

- Cardiac notch (impression) – cavity that accommodates the heart

- Left lung – separated into upper and lower lobes by the oblique fissure
- Right lung – separated into three lobes by the oblique and horizontal fissures
- There are 10 bronchopulmonary segments in each lung

▪Lungs and pleura

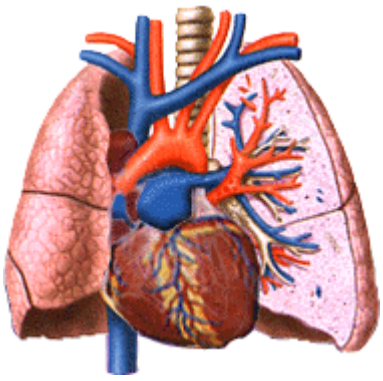
▪The right lung is divided into 3 lobes (upper, middle and lower) whereas the left has only 2 (upper and lower), with further division into the broncho-pulmonary segments (10 right, 9 left).
▪In total there are up to 23 airway divisions between trachea and alveoli. The bronchial walls contain smooth muscle and elastic tissue as well as cartilage in the larger airways. Gas movement occurs by tidal flow in the large airways. In the small airways, by contrast, (division 17 and smaller) it results from diffusion only.
▪The pleura is a double layer surrounding the lungs, the visceral pleura enveloping the lung itself and the parietal pleura lining the thoracic cavity. Under normal circumstances the interpleural space between these layers contains only a tiny amount of lubricating fluid. The pleura and lungs extend from just above the clavicle down to the 8th rib anteriorly, the 10th rib laterally and the level of T12 posteriorly.

Blood Supply to Lungs

- Lungs are perfused by two circulations: pulmonary and bronchial
- Pulmonary arteries – supply systemic venous blood to be oxygenated
  - Branch profusely, along with bronchi
  - Ultimately feed into the pulmonary capillary network surrounding the alveoli
- Pulmonary veins – carry oxygenated blood from respiratory zones to the heart
- Bronchial arteries – provide systemic blood to the lung tissue
  - Arise from aorta and enter the lungs at the hilus
  - Supply all lung tissue except the alveoli
- Bronchial veins anastomose with pulmonary veins
- Pulmonary veins carry most venous blood back to the heart

Blood supply

The lungs have a double blood supply, the *pulmonary circulation* for gas exchange with the alveoli and the *bronchial circulation* to supply the parenchyma (tissue) of the lung itself. Most of the blood from the bronchial circulation drains into the left side of the heart via the pulmonary veins and this deoxygenated blood makes up part of the normal physiological shunt present in the body. In the pulmonary circulation, deoxygenated blood exits the heart through the pulmonary arteries, enters the lungs and oxygenated blood comes back through pulmonary veins. The blood moves from right ventricle of the heart to the lungs back to the left atrium.



Right heart

Oxygen-depleted blood from the body leaves the systemic circulation when it enters the right heart, more specifically the right atrium through the superior vena cava and inferior vena cava. The blood is then pumped through the tricuspid valve (or right atrioventricular valve), into the right ventricle.

Arteries

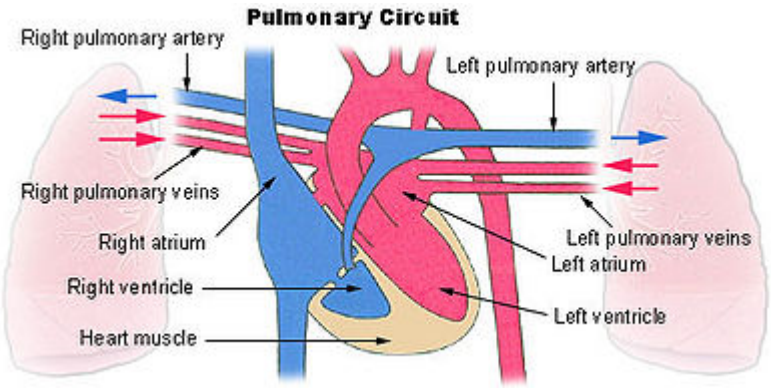
From the right ventricle, blood is pumped through the pulmonary semilunar valve into the pulmonary artery. This blood enters the two pulmonary arteries (one for each lung) and travels through the lungs.

Lungs

The pulmonary arteries carry blood to the lungs, where red blood cells release carbon dioxide and pick up oxygen during respiration.

Veins

The oxygenated blood then leaves the lungs through pulmonary veins, which return it to the left heart, completing the pulmonary cycle. This blood then enters the left atrium, which pumps it through the bicuspid valve, also called the mitral or left atrioventricular valve, into the left ventricle. The blood is then distributed to the body through the systemic circulation before returning again to the pulmonary circulation.



The other component of physiological shunt is from the thebesian veins, which drain some coronary blood directly into the chambers of the heart.

The pulmonary circulation is a low-pressure (25/10mmHg), low-resistance system with a capacity to accommodate a substantial increase in blood flowing through it without a major increase in pressure.

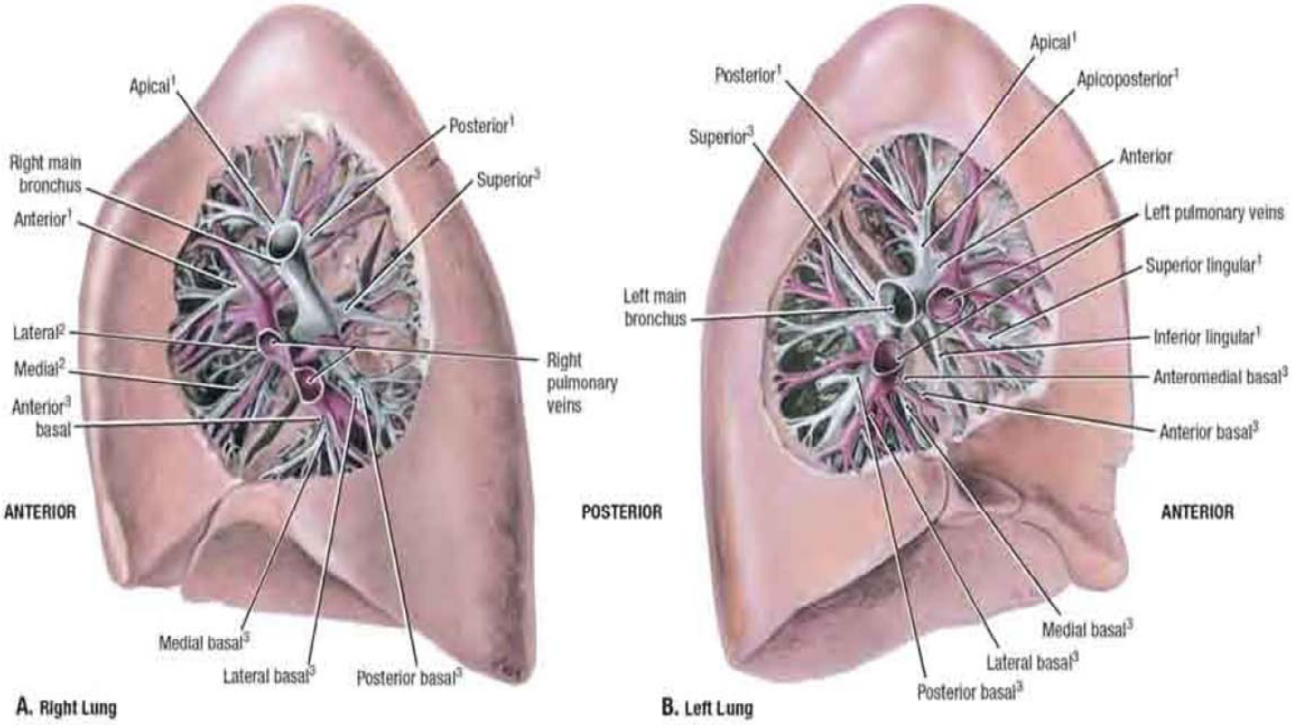
Vascular distension and recruitment of unperfused capillaries achieve this.

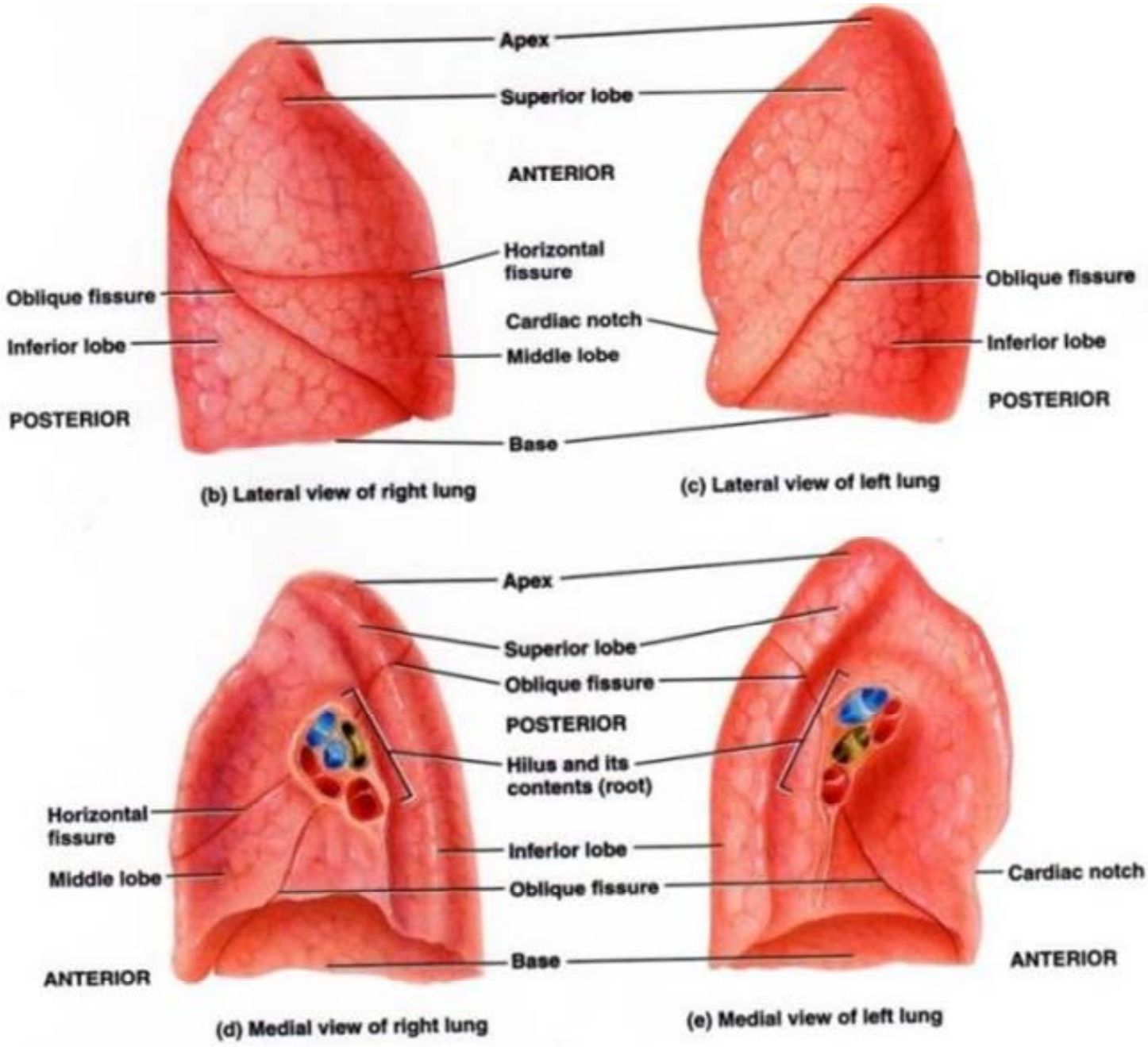
The main stimulus which produces a marked increase in pulmonary vascular resistance is hypoxia

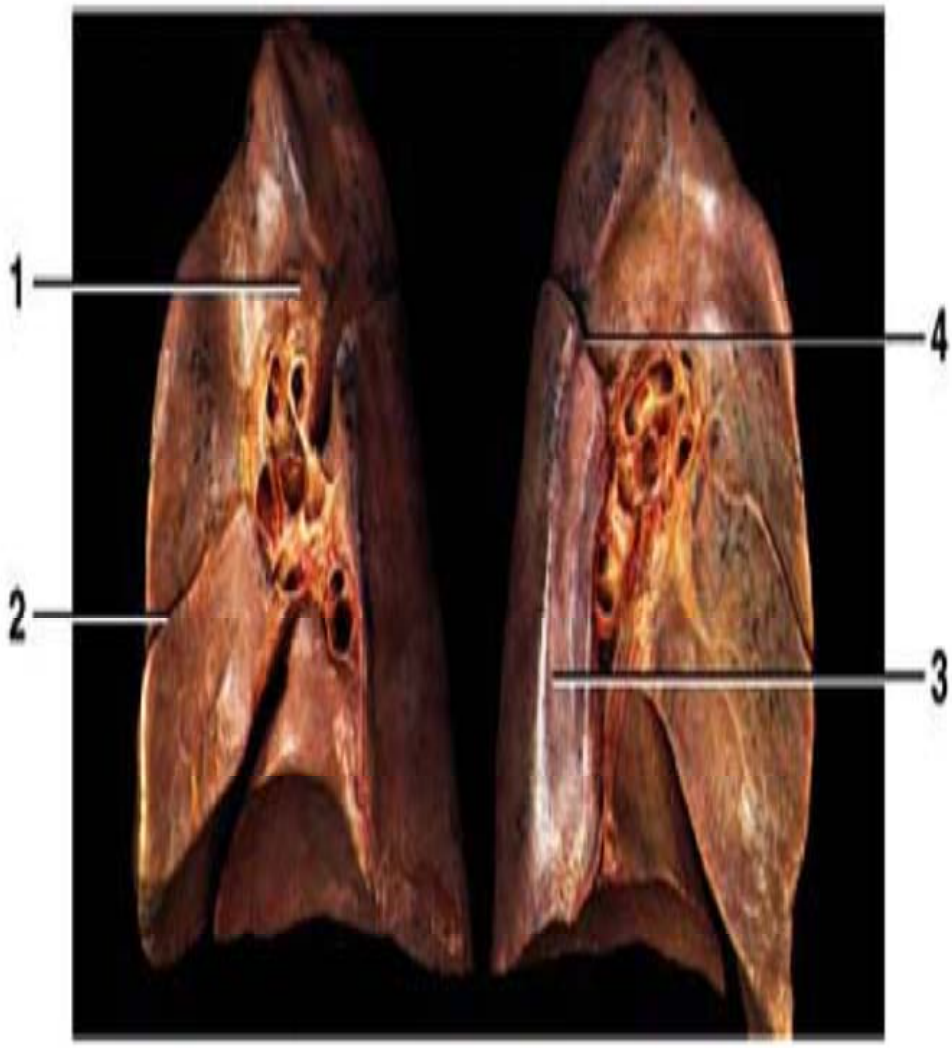
Pleurae

- Thin, double-layered serosa
- Parietal pleura
  - Covers the thoracic wall and superior face of the diaphragm
  - Continues around heart and between lungs
- Visceral, or pulmonary, pleura
  - Covers the external lung surface
  - Divides the thoracic cavity into three chambers

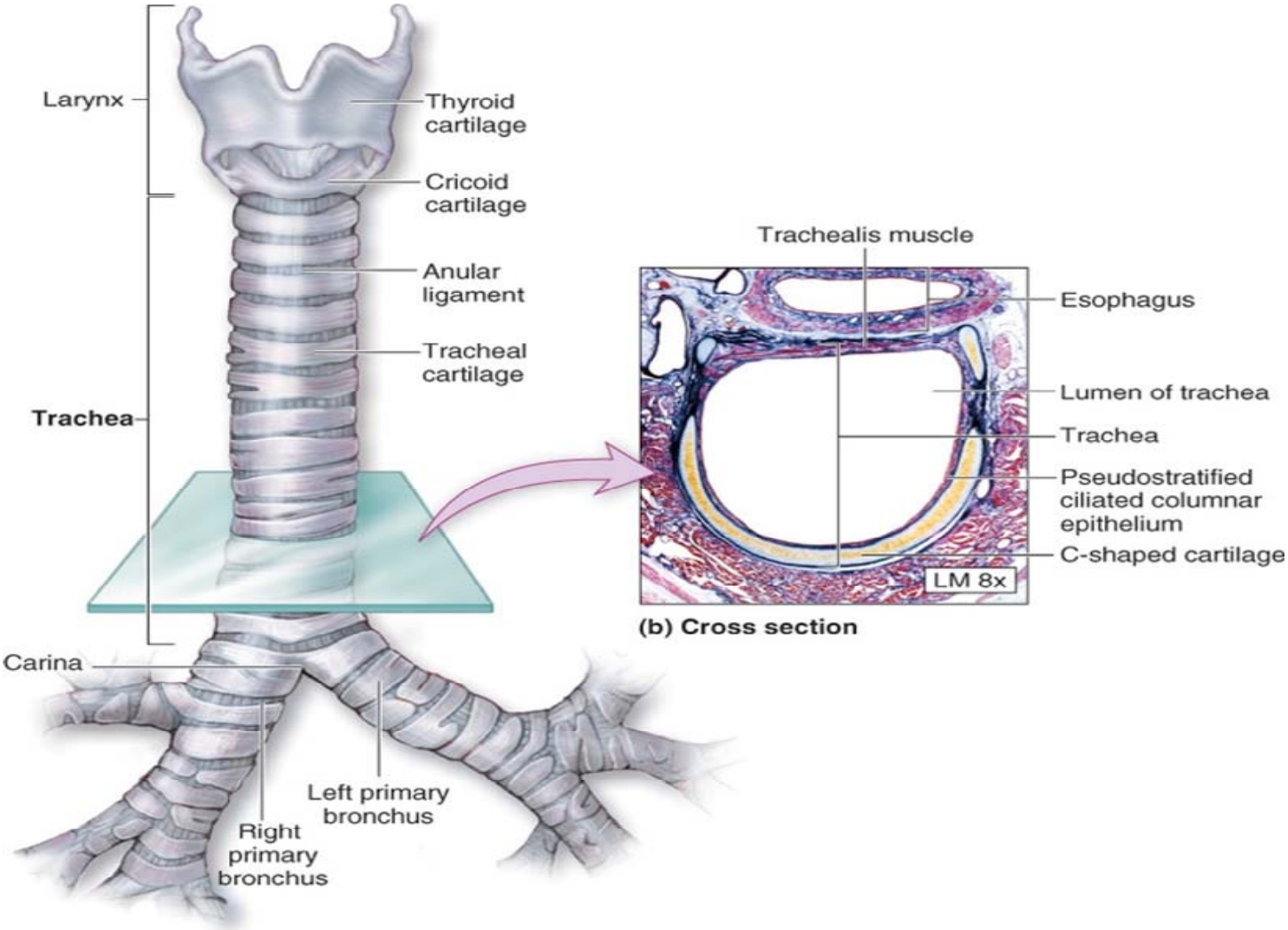
- The central mediastinum
- Two lateral compartments, each containing a lung

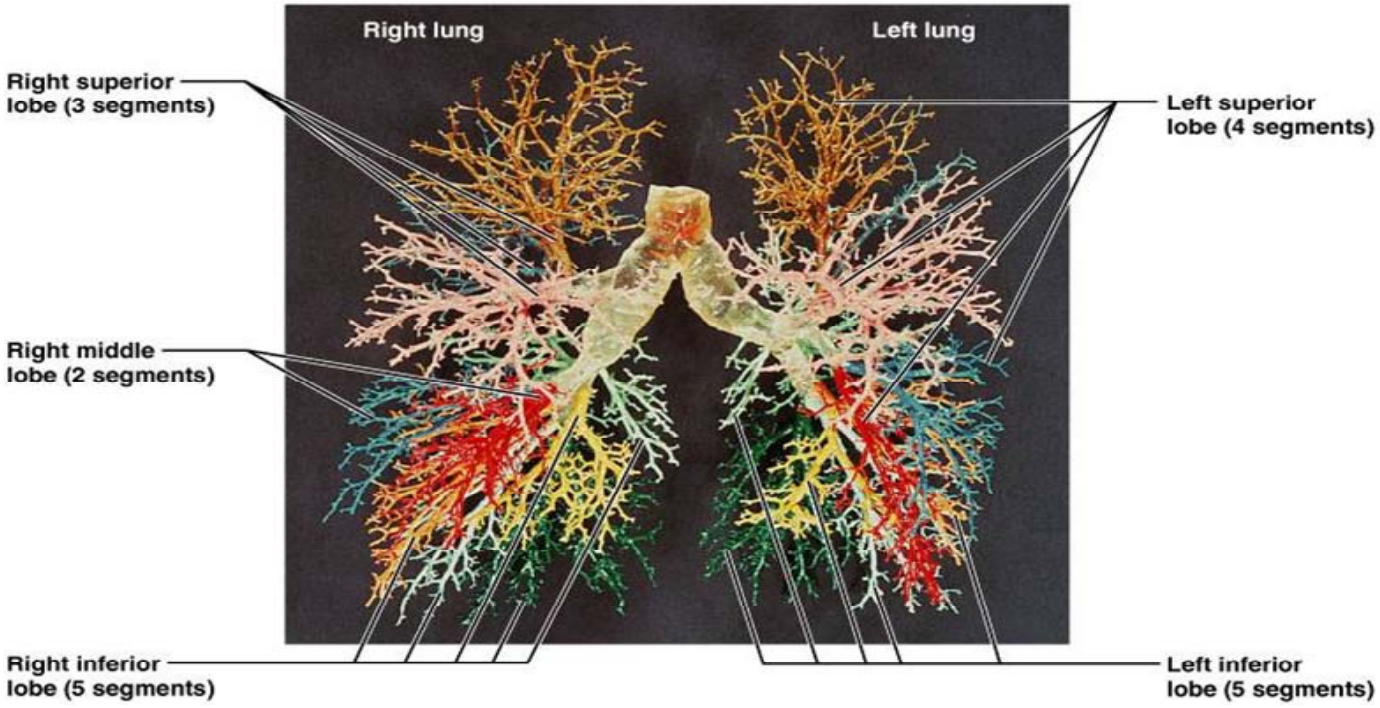


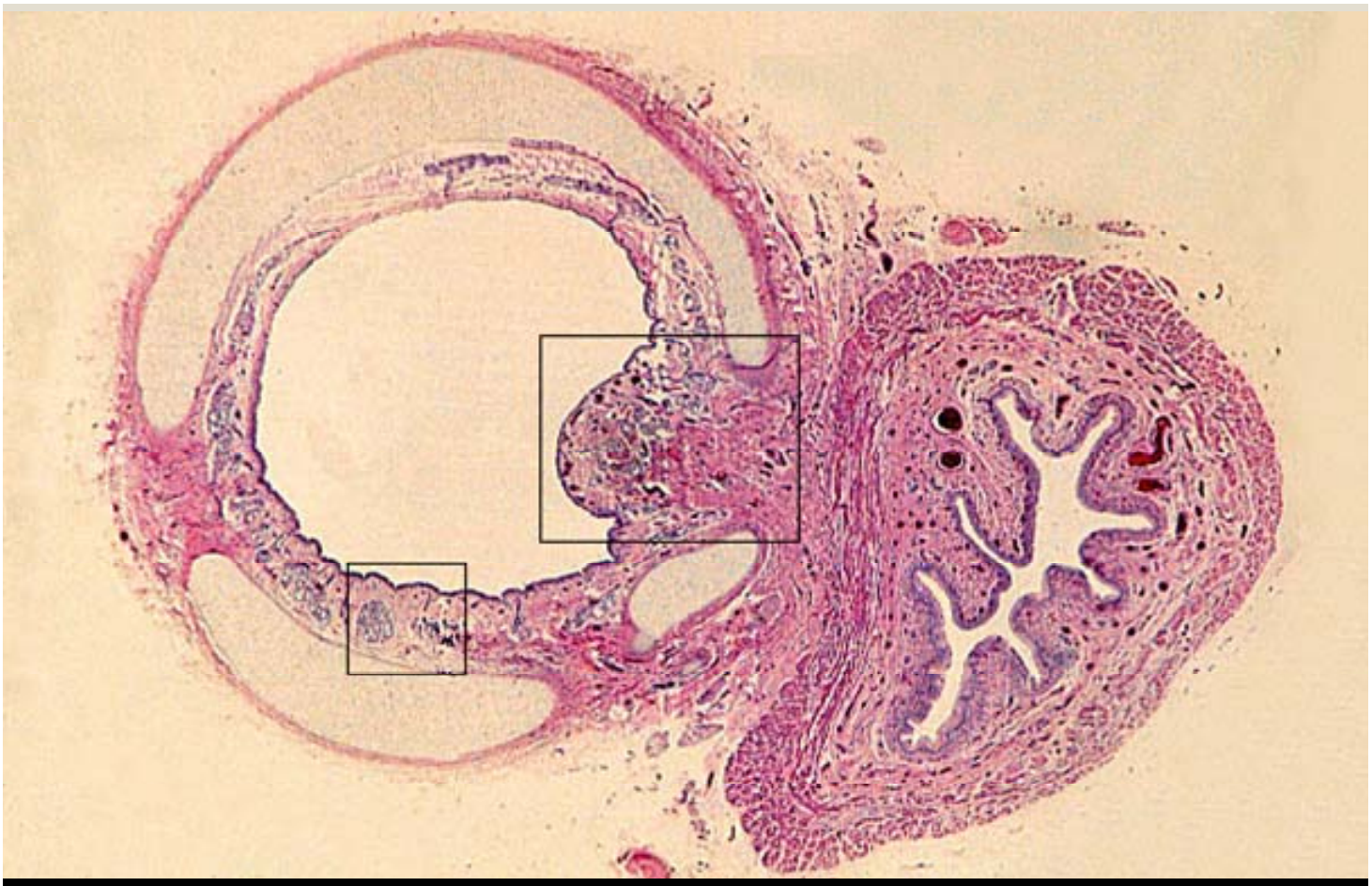

Apex
Superior lobe
ANTERIOR
Horizontal fissure
Oblique fissure
Cardiac notch
Inferior lobe
Middle lobe
POSTERIOR
Base
(b) Lateral view of right lung
(c) Lateral view of left lung
Apex
Superior lobe
Oblique fissure
POSTERIOR
Hilus and its contents (root)
Horizontal fissure
Inferior lobe
Middle lobe
Oblique fissure
Cardiac notch
Base
ANTERIOR
(d) Medial view of right lung
(e) Medial view of left lung



1. **groove for azygos vein; vein arches over root of right lung to enter superior vena cava**
2. **horizontal fissure of right lung; right lung has two fissures, left has one**
3. **groove for thoracic aorta**
4. **oblique fissure of left lung**


Larynx
Thyroid cartilage
Cricoid cartilage
Anular ligament
Tracheal cartilage
Trachea
Carina
Left primary bronchus
Right primary bronchus
(a) Anterior view
Trachealis muscle
Esophagus
Lumen of trachea
Trachea
Pseudostratified ciliated columnar epithelium
C-shaped cartilage
LM 8x
(b) Cross section


Right lung
Left lung
Right superior lobe (3 segments)
Left superior lobe (4 segments)
Right middle lobe (2 segments)
Right inferior lobe (5 segments)
Left inferior lobe (5 segments)



TRACHEA / ESOPHAGUS

HistologY

The histologic features of the trachea and bronchi are practically the same.

The four layers from the inside to the outside are:
1a. Mucous membrane with ciliated pseudostratified columnar epithelium
1b. Lamina propria
The physiology of the respiratory system concerns the transport and exchange of oxygen and carbon dioxide.
2. Submucosa with mixed seromucous glands
3. Cartilaginous smooth layer. Characteristically, this layer is formed by hyaline cartilage of incomplete rings, united by smooth muscle and some fibrous elements.
4. Adventitia

The formation of air flow depends upon the synergistic action of atmospheric, alveolar, and intrapleural pressures.

The following anatomic entities are related to the pressures
– Atmospheric (nose and mouth)
– Alveolar (alveolar ducts and alveoli)
When atmospheric pressure is higher than the alveolar pressure, air (containing oxygen) enters the lungs.
When atmospheric pressure is lower than the alveolar pressure, air (containing carbon dioxide) exits the lungs.
– Intrapleural (thoracic cavity)

By its own intrapleural pressure, the thoracic cavity negotiates both atmospheric and alveolar pressure.

The inspiratory muscles are the
– Diaphragm (the most effective muscle of inspiration)
– External intercostals
– Sternocleidomastoid muscles
– Scalenes
– Serratus posterior muscles (superior and inferior)

The diaphragm and external intercostal muscles are innervated by the phrenic and intercostal nerves, respectively. The sternocleidomastoid muscles and scalenes (the
upper airway muscles) are innervated by the cervical nerves.
The expiratory muscles are the
The entire right ventricular output enters the lungs. The low-pressure, low-resistance pulmonary circulation causes the gas exchange.

The respiratory centers of the pontomedullary area of the brain are responsible for breathing.
– Three flat muscles (external oblique, internal oblique, transversus abdominis)
– Rectus abdominis
– Internal intercostals

Pharynx

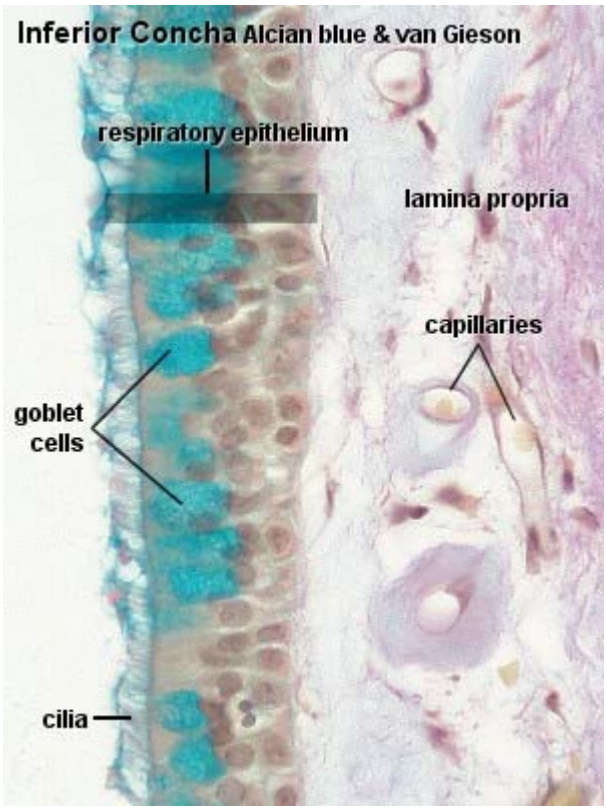
The pharynx connects the nasal cavity with the larynx.

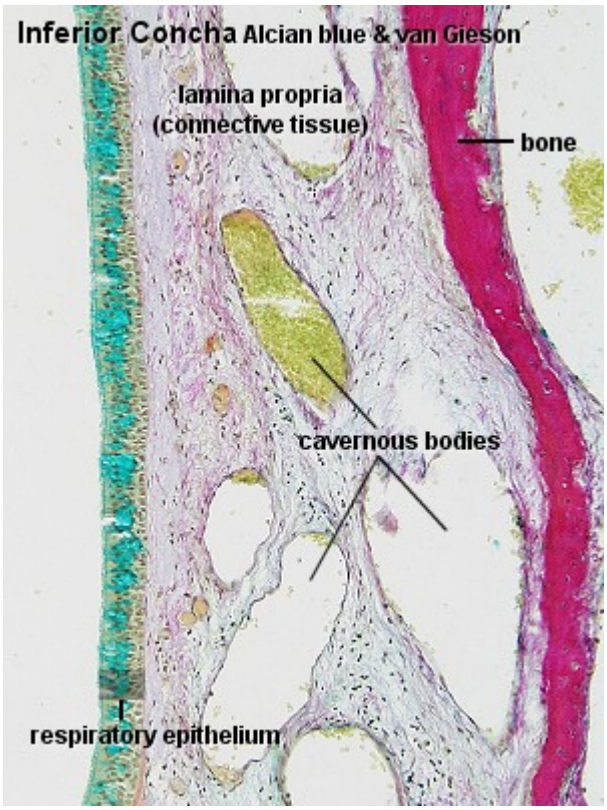
Depending on the extent of abrasive forces on the epithelium, the pharynx is either lined with respiratory epithelium (nasopharynx or epipharynx) or with a stratified squamous epithelium (oropharynx or meso- and hypopharynx), which also covers the surfaces of the oral cavity and the oesophagus.

Lymphocytes frequently accumulate beneath the epithelium of the pharynx.

Accumulations of lymphoid tissues surrounding the openings of the digestive and respiratory passages form the tonsils.

The nasal cavity and pharynx form the upper respiratory passages.





Respiratory (conditioning) epithelia:

a) ciliated cells:

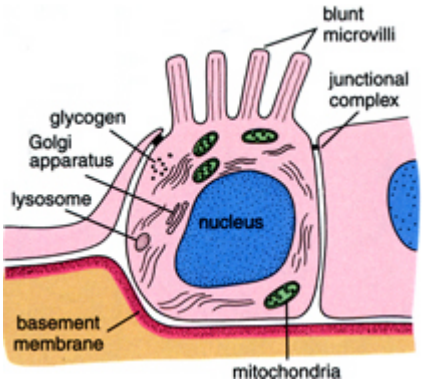
i) columnar cells with ca 300 cilia/cell, 14 cycles/s, propel mucus at 2 cm/min
ii) cilia beat in one direction (towards oropharynx) propelling mucus and particulates to be removed (spit it out or swallow it)
iii) loss of cilia activity results in respiratory infections
iv) microvilli also at apex of cell

b) mucous goblet cells:

i) secrete mucus that traps particulate matter
ii) have sparse microvilli

c) brush cells:

i) columnar cell with short, blunt microvilli on apical surface
ii) sensory receptor cell ?

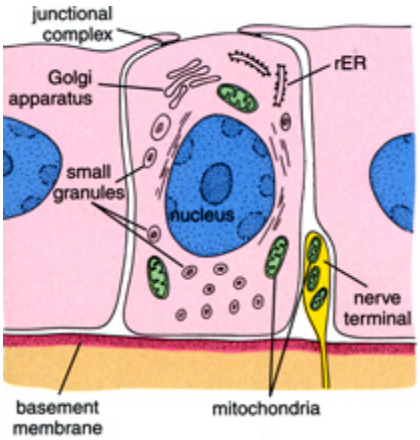


d) basal (short) cells:

i) located at the base of epith. and do not reach lumen
ii) stem cell function

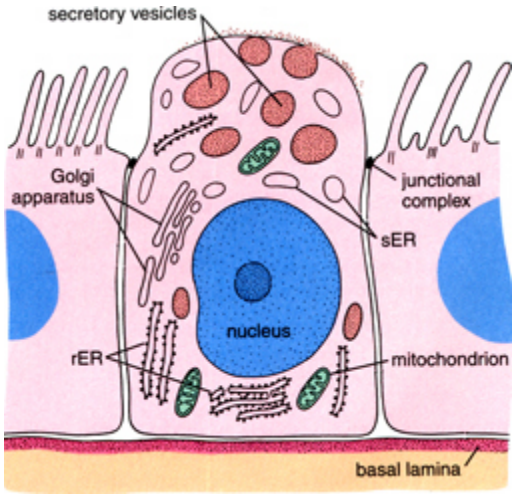
e) small granule cells (bronchial Kulchitsky cells):

i) contain granules at base of cell
ii) thought to have neuroendocrine function (similar to enteroendocrine cell of gut)



f) **<u>Clara cells</u>** [(distal elements of conducting portion (bronchioles and terminal bronchioles)]

i) secrete lipoprotein that is a surface active agent



IV. Gas exchange epithelia:

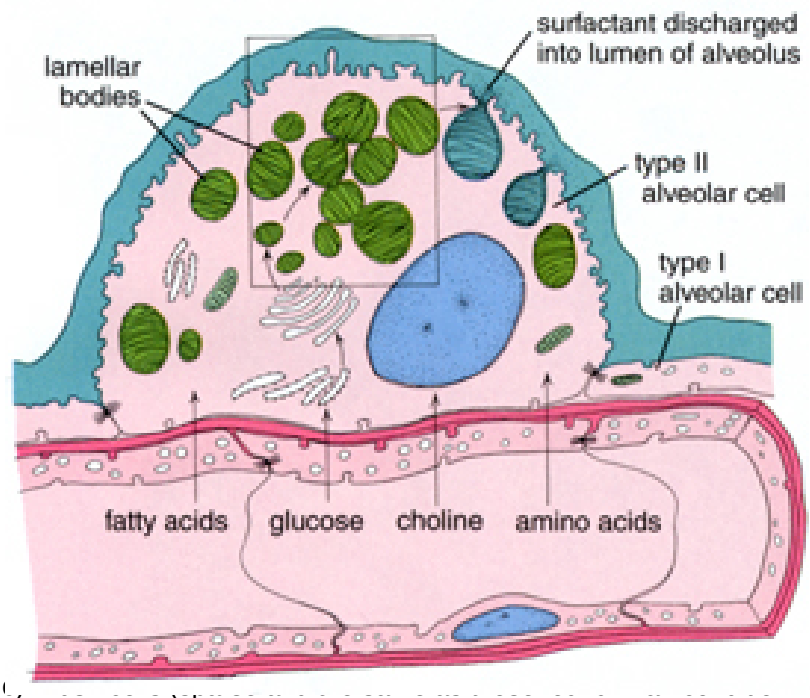
a) type I cells (pneumocytes):

i) very squamous (25 nm) epithelia
ii) organelles are very near nucleus so that the extranuclear regions can be very thin
iii) have occluding junctions and intercellular linkages via desmosomes
iv) cover 95% of the gas exchange surface

b) type II cells (septal cells, great alveolar cells):

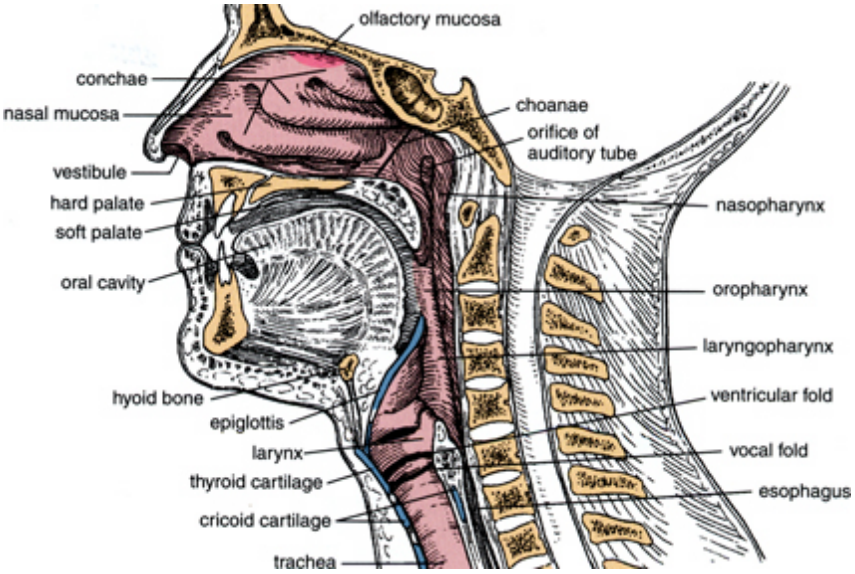
i) simple cuboidal cells typically found at alveolar wall junctions (septa)
ii) junctions like and with type I cells
iii) cover 5% of the gas exchange surface
iv) has lamellar bodies containing phospholipid, GAGs, and proteins that constitute pulmonary surfactant

-reduces surface tension between alveolar wall and air



g epithelia)

V. Conducting portion:



a) 3 to 5 layers: mucosa (epithelia, basal lamina, and lamina propria), muscularis (some) submucosa (some), bone or cartilage (some), then adventicia
b) nasal cavity: bone cavity lined with respiratory epith. that propels mucus toward oropharynx

i) nares (vestibule or nostril): initial portion lined with strat. sq. epith. with hairs (vibrissae, filter function)
ii) nasal fossae: lined with respiratory epithelia and abundant seromucous glands in lamina propria

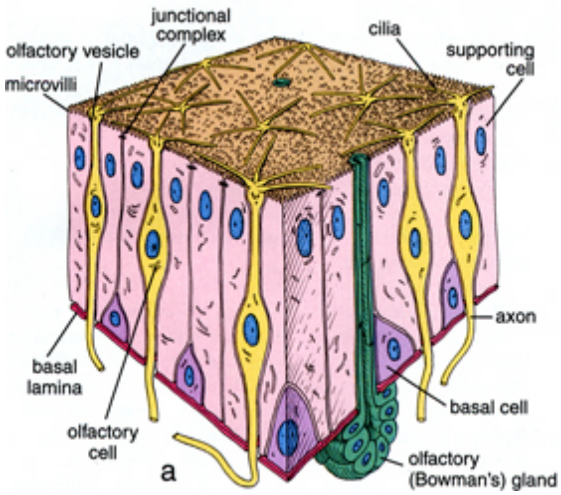
- shelf-like (3) projections protrude into the cavity and are called conchae (turbinates) that increase surface area and cause turbulent flow of the air that facilitates cleansing and moistening of the inspired air

- upper chonchae contains olfactory epithelia responsible for the sense of smell:

- 3 cell types present:

- basal cell: stem cell function
- sustentacular or supporting cells: microvilli on apex
- olfactory receptor cells: sensory neurons
- unique cilia project from apex
- initial portion of cilia has standard 9/2 arrangement of microtubule
- distal portion becomes narrower and microtubules are not arranged in doublets
- specific odorant receptors are located on the cilia

- surface continually washed with protein-containing mucus from olfactory glands (Bowman's glands) to trap odorants and "clean" receptors



- within the lamina propria of the epithelia covering the conchae are swell bodies:
- swell bodies are venous plexi that engorge with blood causing occlusion of air flow between the chonchae shelves
-occlusion occurs one side at a time about every 30 min.
-allows for "resting" on respiratory epith.

iii) para nasal sinuses: blind cavities lined by respiratory epithelia that drain into nasal cavity through small openings

c) pharynx (naso/oro regions): junction between oral cavity and respiratory tract
i) stratified sq. nk epithelia in oro regions, resp. epithelia in naso regions
ii) abundant mucous glands in submucosa

d) larynx: junction between pharynx and trachea

i) cartilage rings in tube prevent closing
ii) epiglottis: flap that closes off larynx when swallowing
iii) false vocal cords (upper folds or ventricular folds in larynx)
iv) true vocal cords (lower or vocal folds in larynx):

-covered with strat. sq. epith
-controlled indirectly by skeletal muscle (vocalis muscle)

v) abundant mucous glands in submucosa

e) trachea: tube linking larynx to primary bronchi

i) C-shaped hyaline cartilage rings maintain a patent tube
ii) smooth muscle (trachealis muscle) bridges open ends of C, constriction decreases diameter of lumen
iii) elastic fibers and sero-mucous glands present in submucosa, glands predominate between cartilage rings
iv) fibriocartilage also bridges ends of C preventing over distention

f) primary bronchi: tubes which penetrate lung at hilum

i) left and right bronchi from trachea supplying respective lungs
ii) intrapulmonary bronchi branch (2 in left, 3 in right) into intralobar bronchi
iii) further branching into small bronchi
iv) typical transitional epithelium, fewer goblet cells and glands
v) irregular rings of hyaline cartilage
vi) crisscrossing spiral bundles of smooth muscle
vii) abundant elastic fibers

g) small bronchi: bifurcations from primary bronchi to bronchioles

i) typical respiratory epithelia, few goblet cells and mucous glands
ii) plates of cartilage
iii) crisscrossing bundles of smooth muscle
iv) abundant elastic fibers

h) bronchioles: (regular and terminal)

i) transition from ps. ciliated columnar to ciliated simple columnar
ii) few to no goblet cells, no mucous glands
iii) no cartilage
iv) crisscrossing bundles of smooth muscle
v) abundant elastic fibers
vi) terminal bronchioles contain Clara cells in the epithelia

VI. Respiratory (gas exchange) portion:

a) respiratory bronchiole:

i) conduit between conducting and gas exchange portions (alveoli)
ii) ciliated simple cuboidal epithelia and Clara cells predominate the closer to the alveolar duct
iii) no goblet cells, glands or cartilage
iv) cross crossing bundles of smooth muscle
v) abundant elastic fibers
vi) alveolar ducts branch from respiratory bronchioles

b) alveolar ducts:

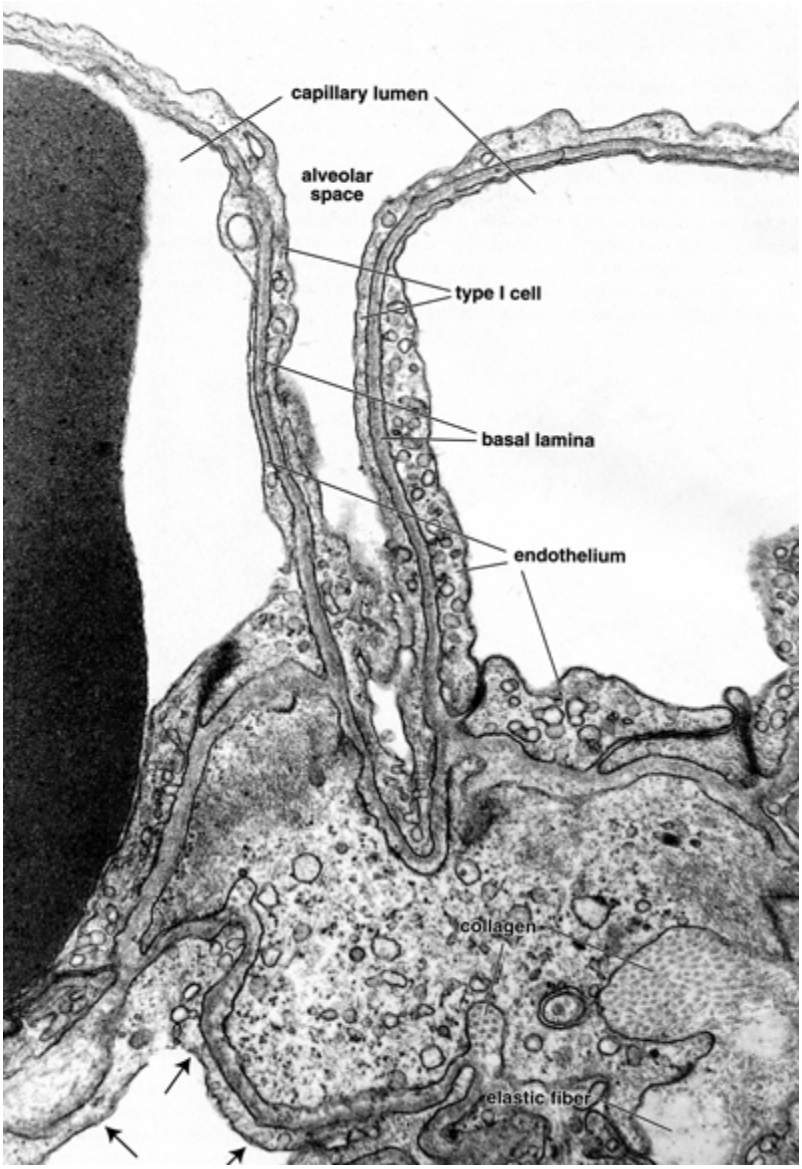
i) passage to alveolar sacs (cluster or sac of alveoli)
ii) entry into sacs are lined with a smooth muscle sphincter
iii) epithelia lined by mostly simple squamous epithelia

c) alveoli:

i) primary site of gas exchange between air and blood
ii) blood air barrier consists of:

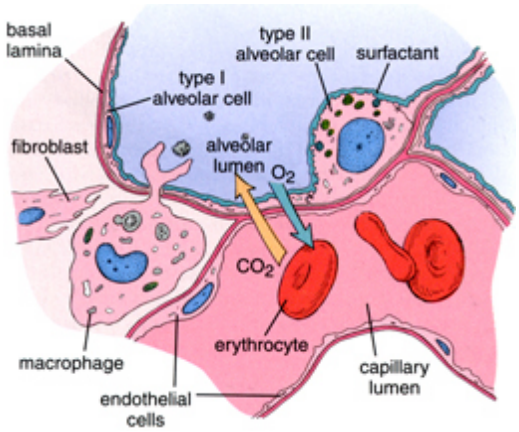
- endothelial cell of capillary (continuous type)
- basement membrane between endothelial and epithelial cells
- epithelial cell (simple sq.) of alveolar lining
- surfactant layer

iii) very thin layer 0.1 - 1.5 microns allowing for rapid and efficient gas exchange
iv) rich capillary network that anastomose through the wall of the alveoli, total endothelial surface area of about 125 square meters for gas exchange



vi) alveolar septum (two epithelial walls with capillary in between)

- material between epithelial walls called interstitium
- includes capillaries, connective tissue, fibroblasts, macrophages, mast cells, and contractile cells
- elastic and reticular fibers found in this region
- collagen type I and type III (reticular fibers) in the interstitium
- lung macrophages are called dust cells and are found both in the interstitium and on the alveolar wall surface (air side)

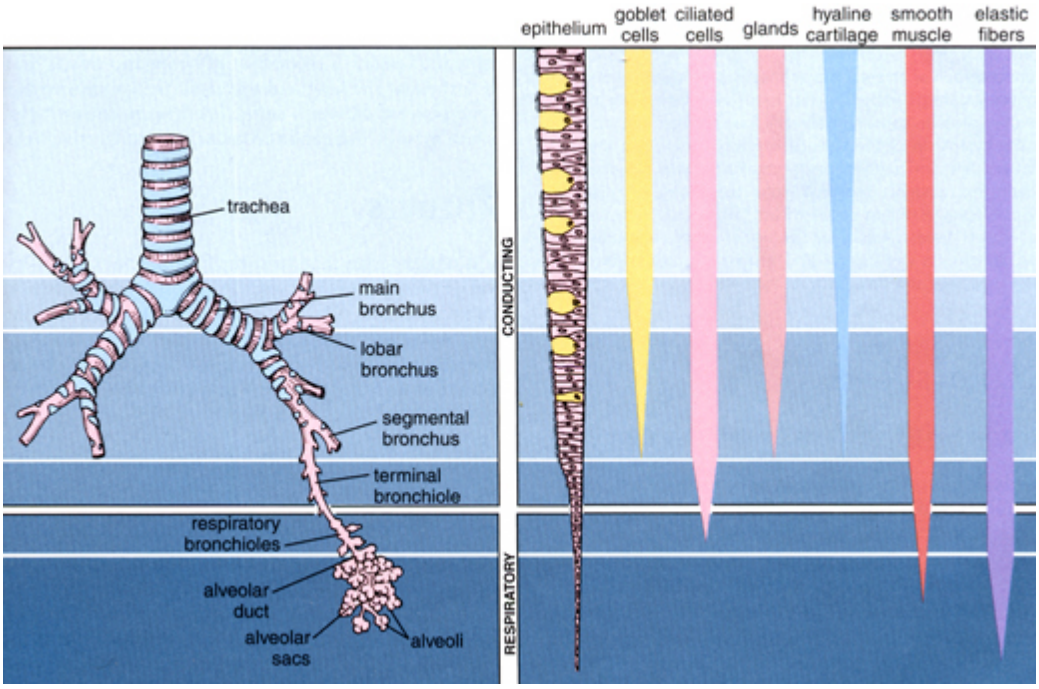


d) alveoli structure/function:

i) surface tension of alveolar wall decreased by presence of pulmonary surfactant
ii) elastic fibers in alveolar interstitium allows for elastic recoil of alveolar sac during expiration
iii) contractile cells in interstitium can contract and reduce sac volume
iv) alveolar pores between sacs equalizes pressure gradient between sacs
v) pathology:

- premature infants lack surfactant resulting in respiratory distress syndrome
- emphysema: loss of elastic fibers caused by over activity of macrophages (protease activity) dealing with particulates, result is a loss of functional respiratory capacity-- difficulty in breathing

VII. Features of the wall of the respiratory tube through the system:



VIII. Lung lobulation/respiratory unit

a) 2 lungs (right and left) supplied by right and left extra pulmonary bronchi
b) lung enclosed within thoracic cavity by the pleura that has two layers

i) visceral layer = mesothelium with a thin lamina propria rich in elastin fibers between it and the lung parenchyma
ii) parietal layer = mesothelium with a thin lamina propria rich in elastin fibers between it and the thoracic cavity
iii) visceral and parietal mesothelium separated by thin, lubricating film, space can be filled with plasma or air (collapsed lung) altering lung function

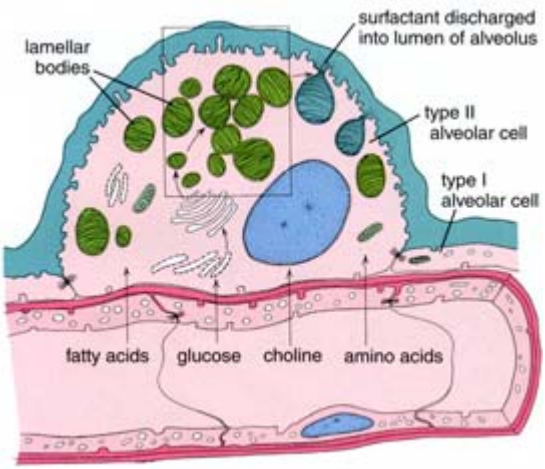
c) vessels (blood, lymph), nerves, and bronchi enter and exit at hilum
d) lung parenchyma divided into lobe and lobules by connective tissue septa
e) lung parenchyma divided into lobes (3 in the right, 2 in the left) supplied by lobar bronchi (secondary bronchi)
f) lobes subdivided into lobules (10 in the right, 8 in the left) supplied by the segmental bronchi (tertiary bronchi)
g) lobules subdivided into pulmonary acinus that is supplied by the terminal bronchiole
h) terminal bronchiole supplies respiratory bronchioles
i) respiratory bronchiole supplies alveolar duct then alveolar sac then alveolus
j) respiratory bronchiolar unit = the respiratory bronchiole and the alveoli that is supplies

IX. Blood plumbing:

a) primarily two arterial branches and one venous branch

b) pulmonary (functional) branch:
i) right ventricle > pulmonary artery > distributing arteries > pulmonary arteriole > alveolar capillary bed > venules > collecting veins >pulmonary vein > left atrium > left ventricle
ii) much lower pressure than systemic circulation (6 - 10 fold lower)
iii) pulmonary arteries have much thinner media and are in association with adventicia of and branch with the bronchial tree
iv) arterioles empty into a rich capillary bed at the level of the respiratory bronchiolar unit
v) venules collect oxygenated blood and empty into small veins at the level interlobular connective tissue septa, then into pulmonary veins that follow the course of the bronchial tree to the hilum, the venous system is not in close association with the bronchiolar trees
vi) close association of pulmonary arterial system with “functional unit” important for regulation of ventilation of functional units (hypoxic vasoconstriction)

c) systemic (feeding or bronchial) branch:
i) left ventricle > aorta > bronchial arteries > bronchiole arterioles > terminal bronchiole arterioles > respiratory bronchiole arterioles > pulmonary arteriole (pulmonary loop)
ii) primarily feeds (oxygenates) the wall of the bronchi and bronchioles
iii) bronchiolar arteries are within the submucosa of the bronchi and bronchioles and appear as the systemic vasculature (thicker media than pulmonary arteries)



Breathing

- Breathing, or pulmonary ventilation, consists of two phases
  - Inspiration – air flows into the lungs
  - Expiration – gases exit the lungs

Pressure Relationships in the Thoracic Cavity

- Respiratory pressure is always described relative to atmospheric pressure
- Atmospheric pressure (P_{atm})
  - Pressure exerted by the air surrounding the body
  - Negative respiratory pressure is less than P_{atm}
  - Positive respiratory pressure is greater than P_{atm}
- Intrapulmonary pressure (P_{pul}) – pressure within the alveoli
- Intrapleural pressure (P_{ip}) – pressure within the pleural cavity

Pressure Relationships

- Intrapulmonary pressure and intrapleural pressure fluctuate with the phases of breathing
- Intrapulmonary pressure always eventually equalizes itself with atmospheric pressure
- Intrapleural pressure is always less than intrapulmonary pressure and atmospheric pressure
- Two forces act to pull the lungs away from the thoracic wall, promoting lung collapse
  - Elasticity of lungs causes them to assume smallest possible size
  - Surface tension of alveolar fluid draws alveoli to their smallest possible size
- Opposing force – elasticity of the chest wall pulls the thorax outward to enlarge the lungs

Lung Collapse

- Caused by equalization of the intrapleural pressure with the intrapulmonary pressure
- Transpulmonary pressure keeps the airways open
  - Transpulmonary pressure – difference between the intrapulmonary and intrapleural pressures ($P_{pul} – P_{ip}$)

Pulmonary Ventilation

- A mechanical process that depends on volume changes in the thoracic cavity
- Volume changes lead to pressure changes, which lead to the flow of gases to equalize pressure

Boyle's Law

- Boyle's law – the relationship between the pressure and volume of gases
  $P_1V_1 = P_2V_2$
  - P = pressure of a gas in mm Hg
  - V = volume of a gas in cubic millimeters
  - Subscripts 1 and 2 represent the initial and resulting conditions, respectively

Inspiration

- The diaphragm and external intercostal muscles (inspiratory muscles) contract and the rib cage rises
- The lungs are stretched and intrapulmonary volume increases
- Intrapulmonary pressure drops below atmospheric pressure (–1 mm Hg)
- Air flows into the lungs, down its pressure gradient, until intrapleural pressure = atmospheric pressure

Expiration

- Inspiratory muscles relax and the rib cage descends due to gravity
- Thoracic cavity volume decreases
- Elastic lungs recoil passively and intrapulmonary volume decreases
- Intrapulmonary pressure rises above atmospheric pressure (+1 mm Hg)
- Gases flow out of the lungs down the pressure gradient until intrapulmonary pressure is 0

Physical Factors Influencing Ventilation:

Airway Resistance

- Friction is the major nonelastic source of resistance to airflow
- The relationship between flow (F), pressure (P), and resistance (R) is:
- The amount of gas flowing into and out of the alveoli is directly proportional to ΔP, the pressure gradient between the atmosphere and the alveoli
- Gas flow is inversely proportional to resistance with the greatest resistance being in the medium-sized bronchi
- As airway resistance rises, breathing movements become more strenuous
- Severely constricted or obstructed bronchioles:
  - Can prevent life-sustaining ventilation
  - Can occur during acute asthma attacks which stops ventilation

- Epinephrine release via the sympathetic nervous system dilates bronchioles and reduces air resistance

Resistance in Repiratory Passageways

Alveolar Surface Tension

- Surface tension – the attraction of liquid molecules to one another at a liquid-gas interface
- The liquid coating the alveolar surface is always acting to reduce the alveoli to the smallest possible size
- Surfactant, a detergent-like complex, reduces surface tension and helps keep the alveoli from collapsing

Lung Compliance

- The ease with which lungs can be expanded
- Specifically, the measure of the change in lung volume that occurs with a given change in transpulmonary pressure
- Determined by two main factors
  - Distensibility of the lung tissue and surrounding thoracic cage
  - Surface tension of the alveoli

Factors That Diminish Lung Compliance

- Scar tissue or fibrosis that reduces the natural resilience of the lungs
- Blockage of the smaller respiratory passages with mucus or fluid
- Reduced production of surfactant
- Decreased flexibility of the thoracic cage or its decreased ability to expand

Examples include:

- Deformities of thorax
- Ossification of the costal cartilage
- Paralysis of intercostal muscles

Mechanism of Breathing

A pressure gradient is required to generate flow.

In spontaneous respiration inspiratory flow is achieved by creating a sub-atmospheric pressure in the alveoli (of the order of -5cmH2O during quiet breathing) by increasing the volume of the thoracic cavity under the action of the inspiratory muscles.

During expiration the intra-alveolar pressure becomes slightly higher than atmospheric pressure and gas flow to the mouth results.

Motor pathways

The main muscle generating the negative intrathoracic pressure that produces inspiration is the *diaphragm*, a sheet separating the thorax from the abdomen. Its muscular part is peripheral, attached to the ribs and lumbar vertebrae, with a central tendon. Innervation is from the *phrenic nerves* (C3-5) with contraction moving the diaphragm downwards forcing the abdominal contents down and out. Additional inspiratory efforts are produced by the *external intercostal muscles* (innervated by their intercostal nerves T1-12) and the *accessory muscles of respiration* (sternomastoids and scalenes), although the latter only become important during exercise or respiratory distress.

During quiet breathing expiration is a passive process, relying on the elastic recoil of the lung and chest wall. When ventilation is increased, such as during exercise, expiration becomes active with contraction of the muscles of the abdominal wall and the internal intercostals. The same muscles are also used when producing a Valsalva manoeuvre (BACK Cardiovascular Physiology - Part 1, *Update in Anaesthesia* 1999;**10:**2).

Central control

The mechanism by which respiration is controlled is complex. There is a group of *respiratory centres* located in the brainstem producing automatic breathing activity. This is then regulated mainly by input from *chemoreceptors* (see below). This control can be overridden by *voluntary control* from the cortex. Breath-holding, panting or sighing at will are examples of

this voluntary control. The main respiratory centre is in the floor of the 4th ventricle, with inspiratory (dorsal) and expiratory (ventral) neurone groups. The inspiratory neurones fire automatically, but the expiratory ones are used only during forced expiration. The 2 other main centres are the apneustic centre, which enhances inspiration, and the pneumotaxic centre, which terminates inspiration by inhibition of the dorsal neurone group above.

The *chemoreceptors* that regulate respiration are located both centrally and peripherally. Normally control is exercised by the central receptors located in the medulla, which respond to the CSF hydrogen ion concentration, in turn determined by CO2, which diffuses freely across the blood-brain barrier from the arterial blood. The response is both quick and sensitive to small changes in arterial CO2 (PaCO2). In addition, there are peripheral chemoreceptors located in the carotid and aortic bodies most of which respond to a fall in O2, but some also to a rise in arterial CO2. The degree of hypoxia required to produce significant activation of the O2 receptors is such that they are not influential under normal circumstances, but will do so if profound hypoxia (<8kPa or 60mmHg) occurs, for example at high altitude when breathing air (see later - Special circumstances). It also happens when the response to CO2 is impaired, which can occur if the PaCO2 is chronically elevated, leading to a blunting of the central receptor sensitivity. In this event the plasma bicarbonate ($HCO3^-$) concentration will also be elevated.

Physiology to know

Respiratory Volumes
- Tidal volume (TV) – air that moves into and out of the lungs with each breath (approximately 500 ml)
- Inspiratory reserve volume (IRV) – air that can be inspired forcibly beyond the tidal volume (2100–3200 ml)
- Expiratory reserve volume (ERV) – air that can be evacuated from the lungs after a tidal expiration (1000–1200 ml)
- Residual volume (RV) – air left in the lungs after strenuous expiration (1200 ml)

Respiratory Capacities
- Inspiratory capacity (IC) – total amount of air that can be inspired after a tidal expiration (IRV + TV)
- Functional residual capacity (FRC) – amount of air remaining in the lungs after a tidal expiration (RV + ERV)
- Vital capacity (VC) – the total amount of exchangeable air (TV + IRV + ERV)
- Total lung capacity (TLC) – sum of all lung volumes (approximately 6000 ml in males)

Dead Space
- Anatomical dead space – volume of the conducting respiratory passages (150 ml)
- Alveolar dead space – alveoli that cease to act in gas exchange due to collapse or obstruction
- Total dead space – sum of alveolar and anatomical dead spaces

Pulmonary Function Tests
- Spirometer – an instrument consisting of a hollow bell inverted over water, used to evaluate respiratory function
- Spirometry can distinguish between:
  - Obstructive pulmonary disease – increased airway resistance
  - Restrictive disorders – reduction in total lung capacity from structural or functional lung changes

Pulmonary Function Tests
- Total ventilation – total amount of gas flow into or out of the respiratory tract in one minute
- Forced vital capacity (FVC) – gas forcibly expelled after taking a deep breath
- Forced expiratory volume (FEV) – the amount of gas expelled during specific time intervals of the FVC

Pulmonary Function Tests
- Increases in TLC, FRC, and RV may occur as a result of obstructive disease
- Reduction in VC, TLC, FRC, and RV result from restrictive disease

Alveolar Ventilation
- Alveolar ventilation rate (AVR) – measures the flow of fresh gases into and out of the alveoli during a particular time
- Slow, deep breathing increases AVR and rapid, shallow breathing decreases AVR

Nonrespiratory Air Movements
- Most result from reflex action
- Examples include: coughing, sneezing, crying, laughing, hiccupping, and yawning

Basic Properties of Gases:

Dalton's Law of Partial Pressures
- Total pressure exerted by a mixture of gases is the sum of the pressures exerted independently by each gas in the mixture
- The partial pressure of each gas is directly proportional to its percentage in the mixture

Basic Properties of Gases: Henry's Law
- When a mixture of gases is in contact with a liquid, each gas will dissolve in the liquid in proportion to its partial pressure
- The amount of gas that will dissolve in a liquid also depends upon its solubility:
  - Carbon dioxide is the most soluble
  - Oxygen is $1/20^{th}$ as soluble as carbon dioxide
  - Nitrogen is practically insoluble in plasma

Composition of Alveolar Gas
- The atmosphere is mostly oxygen and nitrogen, while alveoli contain more carbon dioxide and water vapor
- These differences result from:
  - Gas exchanges in the lungs – oxygen diffuses from the alveoli and carbon dioxide diffuses into the alveoli
  - Humidification of air by conducting passages
  - The mixing of alveolar gas that occurs with each breath

External Respiration: Pulmonary Gas Exchange
- Factors influencing the movement of oxygen and carbon dioxide across the respiratory membrane
  - Partial pressure gradients and gas solubilities
  - Matching of alveolar ventilation and pulmonary blood perfusion
  - Structural characteristics of the respiratory membrane

Partial Pressure Gradients and Gas Solubilities
- The partial pressure oxygen (PO_2) of venous blood is 40 mm Hg; the partial pressure in the alveoli is 104 mm Hg
  - This steep gradient allows oxygen partial pressures to rapidly reach equilibrium (in 0.25 seconds), and thus blood can move three times as quickly (0.75 seconds) through the pulmonary capillary and still be adequately oxygenated

Partial Pressure Gradients and Gas Solubilities
- Although carbon dioxide has a lower partial pressure gradient:
  - It is 20 times more soluble in plasma than oxygen
  - It diffuses in equal amounts with oxygen

Oxygenation of Blood

Ventilation-Perfusion Coupling
- Ventilation – the amount of gas reaching the alveoli
- Perfusion – the blood flow reaching the alveoli
- Ventilation and perfusion must be tightly regulated for efficient gas exchange
- Changes in P_{CO2} in the alveoli cause changes in the diameters of the bronchioles
  - Passageways servicing areas where alveolar carbon dioxide is high dilate
  - Those serving areas where alveolar carbon dioxide is low constrict

Surface Area and Thickness of the Respiratory Membrane
- Respiratory membranes:
  - Are only 0.5 to 1 μm thick, allowing for efficient gas exchange
  - Have a total surface area (in males) of about 60 m^2 (40 times that of one's skin)
  - Thicken if lungs become waterlogged and edematous, whereby gas exchange is inadequate and oxygen deprivation results
  - Decrease in surface area with emphysema, when walls of adjacent alveoli break through

Internal Respiration
- The factors promoting gas exchange between systemic capillaries and tissue cells are the same as those acting in the lungs
  - The partial pressures and diffusion gradients are reversed
  - P_{O2} in tissue is always lower than in systemic arterial blood
  - P_{O2} of venous blood draining tissues is 40 mm Hg and P_{CO2} is 45 mm Hg

Oxygen Transport

- Molecular oxygen is carried in the blood:
  - Bound to hemoglobin (Hb) within red blood cells
  - Dissolved in plasma

Oxygen Transport: Role of Hemoglobin
- Each Hb molecule binds four oxygen atoms in a rapid and reversible process
- The hemoglobin-oxygen combination is called oxyhemoglobin (HbO_2)
- Hemoglobin that has released oxygen is called reduced hemoglobin (HHb)

Hemoglobin (Hb)
- Saturated hemoglobin – when all four hemes of the molecule are bound to oxygen
- Partially saturated hemoglobin – when one to three hemes are bound to oxygen
- The rate that hemoglobin binds and releases oxygen is regulated by:
  - P_{O2}, temperature, blood pH, P_{CO2}, and the concentration of BPG (an organic chemical)
    - These factors ensure adequate delivery of oxygen to tissue cells

Influence of P_{O2} on Hemoglobin Saturation
- Hemoglobin saturation plotted against P_{O2} produces a oxygen-hemoglobin dissociation curve
- 98% saturated arterial blood contains 20 ml oxygen per 100 ml blood (20 vol %)
- As arterial blood flows through capillaries, 5 ml oxygen are released
- The saturation of hemoglobin in arterial blood explains why breathing deeply increases the P_{O2} but has little effect on oxygen saturation in hemoglobin

Hemoglobin Saturation Curve
- Hemoglobin is almost completely saturated at a P_{O2} of 70 mm Hg
- Further increases in P_{O2} produce only small increases in oxygen binding
- Oxygen loading and delivery to tissue is adequate when P_{O2} is below normal levels
- Only 20–25% of bound oxygen is unloaded during one systemic circulation
- If oxygen levels in tissues drop:
  - More oxygen dissociates from hemoglobin and is used by cells
  - Respiratory rate or cardiac output need not increase

Other Factors Influencing Hemoglobin Saturation
- Temperature, H^+, P_{CO2}, and BPG
  - Modify the structure of hemoglobin and alter its affinity for oxygen
  - Increases of these factors:
    - Decrease hemoglobin's affinity for oxygen
    - Enhance oxygen unloading from the blood
  - Decreases act in the opposite manner
- These parameters are all high in systemic capillaries where oxygen unloading is the goal

Factors That Increase Release of Oxygen by Hemoglobin
- As cells metabolize glucose, carbon dioxide is released into the blood causing:
  - Increases in P_{CO2} and H^+ concentration in capillary blood
  - Declining pH (acidosis), which weakens the hemoglobin-oxygen bond (Bohr effect)
- Metabolizing cells have heat as a byproduct and the rise in temperature increases BPG synthesis
- All these factors ensure oxygen unloading in the vicinity of working tissue cells

Hemoglobin-Nitric Oxide Partnership
- Nitric oxide (NO) is a vasodilator that plays a role in blood pressure regulation
- Hemoglobin is a vasoconstrictor and a nitric oxide scavenger (heme destroys NO)
- However, as oxygen binds to hemoglobin:
  - Nitric oxide binds to a cysteine amino acid on hemoglobin
  - Bound nitric oxide is protected from degradation by hemoglobin's iron

Hemoglobin-Nitric Oxide Partnership

- The hemoglobin is released as oxygen is unloaded, causing vasodilation
- As deoxygenated hemoglobin picks up carbon dioxide, it also binds nitric oxide and carries these gases to the lungs for unloading

Carbon Dioxide Transport

- Carbon dioxide is transported in the blood in three forms
  - Dissolved in plasma – 7 to 10%
  - Chemically bound to hemoglobin – 20% is carried in RBCs as carbaminohemoglobin
  - Bicarbonate ion in plasma – 70% is transported as bicarbonate (HCO_3^-)

Transport and Exchange of Carbon Dioxide

- Carbon dioxide diffuses into RBCs and combines with water to form carbonic acid (H_2CO_3), which quickly dissociates into hydrogen ions and bicarbonate ions
- In RBCs, carbonic anhydrase reversibly catalyzes the conversion of carbon dioxide and water to carbonic acid
- At the tissues:
  - Bicarbonate quickly diffuses from RBCs into the plasma
  - The chloride shift – to counterbalance the outrush of negative bicarbonate ions from the RBCs, chloride ions (Cl^-) move from the plasma into the erythrocytes
- At the lungs, these processes are reversed
  - Bicarbonate ions move into the RBCs and bind with hydrogen ions to form carbonic acid
  - Carbonic acid is then split by carbonic anhydrase to release carbon dioxide and water
  - Carbon dioxide then diffuses from the blood into the alveoli

Haldane Effect

- The amount of carbon dioxide transported is markedly affected by the P_{O2}
- Haldane effect – the lower the P_{O2} and hemoglobin saturation with oxygen, the more carbon dioxide can be carried in the blood
- At the tissues, as more carbon dioxide enters the blood:
  - More oxygen dissociates from hemoglobin (Bohr effect)
  - More carbon dioxide combines with hemoglobin, and more bicarbonate ions are formed
- This situation is reversed in pulmonary circulation

Influence of Carbon Dioxide on Blood pH

- The carbonic acid–bicarbonate buffer system resists blood pH changes
- If hydrogen ion concentrations in blood begin to rise, excess H^+ is removed by combining with HCO_3^-
- If hydrogen ion concentrations begin to drop, carbonic acid dissociates, releasing H^+
- Changes in respiratory rate can also:
  - Alter blood pH
  - Provide a fast-acting system to adjust pH when it is disturbed by metabolic factors

Control of Respiration:

Medullary Respiratory Centers

- The dorsal respiratory group (DRG), or inspiratory center:
  - Is located near the root of nerve IX
  - Appears to be the pacesetting respiratory center
  - Excites the inspiratory muscles and sets eupnea (12-15 breaths/minute)
  - Becomes dormant during expiration
- The ventral respiratory group (VRG) is involved in forced inspiration and expiration

Pons Respiratory Centers

- Pons centers:
  - Influence and modify activity of the medullary centers
  - Smooth out inspiration and expiration transitions and vice versa
- The pontine respiratory group (PRG) – continuously inhibits the inspiration center

Respiratory Rhythm

- A result of reciprocal inhibition of the interconnected neuronal networks in the medulla
- Other theories include
  - Inspiratory neurons are pacemakers and have intrinsic automaticity and rhythmicity
  - Stretch receptors in the lungs establish respiratory rhythm

Depth and Rate of Breathing

- Inspiratory depth is determined by how actively the respiratory center stimulates the respiratory muscles

- Rate of respiration is determined by how long the inspiratory center is active
- Respiratory centers in the pons and medulla are sensitive to both excitatory and inhibitory stimuli

Medullary Respiratory Centers
Depth and Rate of Breathing: Reflexes
- Pulmonary irritant reflexes – irritants promote reflexive constriction of air passages
- Inflation reflex (Hering-Breuer) – stretch receptors in the lungs are stimulated by lung inflation
- Upon inflation, inhibitory signals are sent to the medullary inspiration center to end inhalation and allow expiration

Depth and Rate of Breathing: Higher Brain Centers
- Hypothalamic controls act through the limbic system to modify rate and depth of respiration
  - Example: breath holding that occurs in anger
- A rise in body temperature acts to increase respiratory rate
- Cortical controls are direct signals from the cerebral motor cortex that bypass medullary controls
  - Examples: voluntary breath holding, taking a deep breath

Depth and Rate of Breathing: P_{CO2}
- Changing P_{CO2} levels are monitored by chemoreceptors of the brain stem
- Carbon dioxide in the blood diffuses into the cerebrospinal fluid where it is hydrated
- Resulting carbonic acid dissociates, releasing hydrogen ions
- P_{CO2} levels rise (hypercapnia) resulting in increased depth and rate of breathing

Depth and Rate of Breathing: P_{CO2}
- Hyperventilation – increased depth and rate of breathing that:
  - Quickly flushes carbon dioxide from the blood
  - Occurs in response to hypercapnia
- Though a rise CO_2 acts as the original stimulus, control of breathing at rest is regulated by the hydrogen ion concentration in the brain
- Hypoventilation – slow and shallow breathing due to abnormally low P_{CO2} levels
  - Apnea (breathing cessation) may occur until P_{CO2} levels rise
- Arterial oxygen levels are monitored by the aortic and carotid bodies
- Substantial drops in arterial P_{O2} (to 60 mm Hg) are needed before oxygen levels become a major stimulus for increased ventilation
- If carbon dioxide is not removed (e.g., as in emphysema and chronic bronchitis), chemoreceptors become unresponsive to P_{CO2} chemical stimuli
- In such cases, P_{O2} levels become the principal respiratory stimulus (hypoxic drive)

Depth and Rate of Breathing: Arterial pH
- Changes in arterial pH can modify respiratory rate even if carbon dioxide and oxygen levels are normal
- Increased ventilation in response to falling pH is mediated by peripheral chemoreceptors

Peripheral Chemoreceptors
Depth and Rate of Breathing: Arterial pH
- Acidosis may reflect:
  - Carbon dioxide retention
  - Accumulation of lactic acid
  - Excess fatty acids in patients with diabetes mellitus
- Respiratory system controls will attempt to raise the pH by increasing respiratory rate and depth

Respiratory Adjustments: Exercise
- Respiratory adjustments are geared to both the intensity and duration of exercise
- During vigorous exercise:
  - Ventilation can increase 20 fold
  - Breathing becomes deeper and more vigorous, but respiratory rate may not be significantly changed (hyperpnea)
- Exercise-enhanced breathing is not prompted by an increase in P_{CO2} or a decrease in P_{O2} or pH
  - These levels remain surprisingly constant during exercise

- As exercise begins:
  - Ventilation increases abruptly, rises slowly, and reaches a steady state
- When exercise stops:
  - Ventilation declines suddenly, then gradually decreases to normal
- Neural factors bring about the above changes, including:
  - Psychic stimuli
  - Cortical motor activation
  - Excitatory impulses from proprioceptors in muscles

Respiratory Adjustments: High Altitude

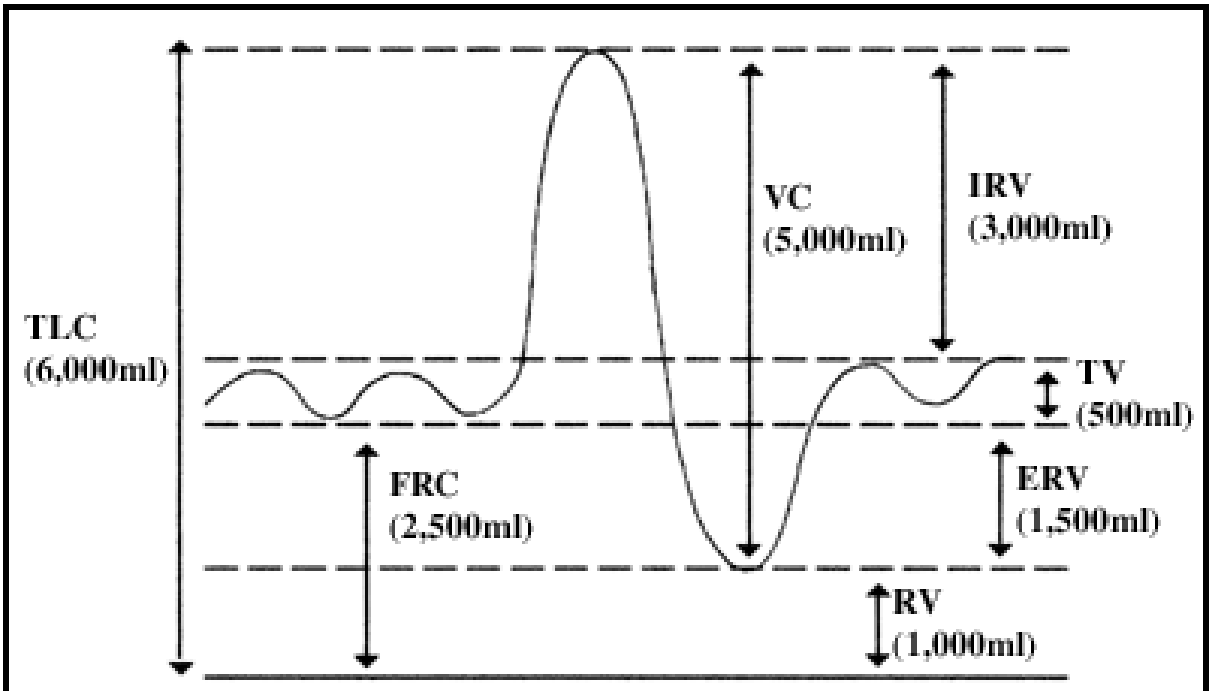
- The body responds to quick movement to high altitude (above 8000 ft) with symptoms of acute mountain sickness – headache, shortness of breath, nausea, and dizziness
- Acclimatization – respiratory and hematopoietic adjustments to altitude include:
  - Increased ventilation – 2-3 L/min higher than at sea level
  - Chemoreceptors become more responsive to P_{CO2}
  - Substantial decline in P_{O2} stimulates peripheral chemoreceptors

Respiratory Process

Respiratory values

The various terms used to describe lung excursion (movement) during quiet and maximal respiration are shown in figure 1:

The tidal volume (500ml) multiplied by the respiratory rate (14 breaths/min) is the *minute volume* (7,000ml/min). Not all of the tidal volume takes part in respiratory exchange, as this process does not start until the air or gas reaches the respiratory bronchioles (division 17 of the respiratory tree). Above this level the airways are solely for conducting, their volume being known as the *anatomical dead-space.* The volume of the anatomical dead-space is approximately 2ml/kg or 150ml in an adult, roughly a third of the tidal volume. The part of the tidal volume which does take part in respiratory exchange multiplied by the respiratory rate is known as the *alveolar ventilation* (approximately 5,000ml/min).



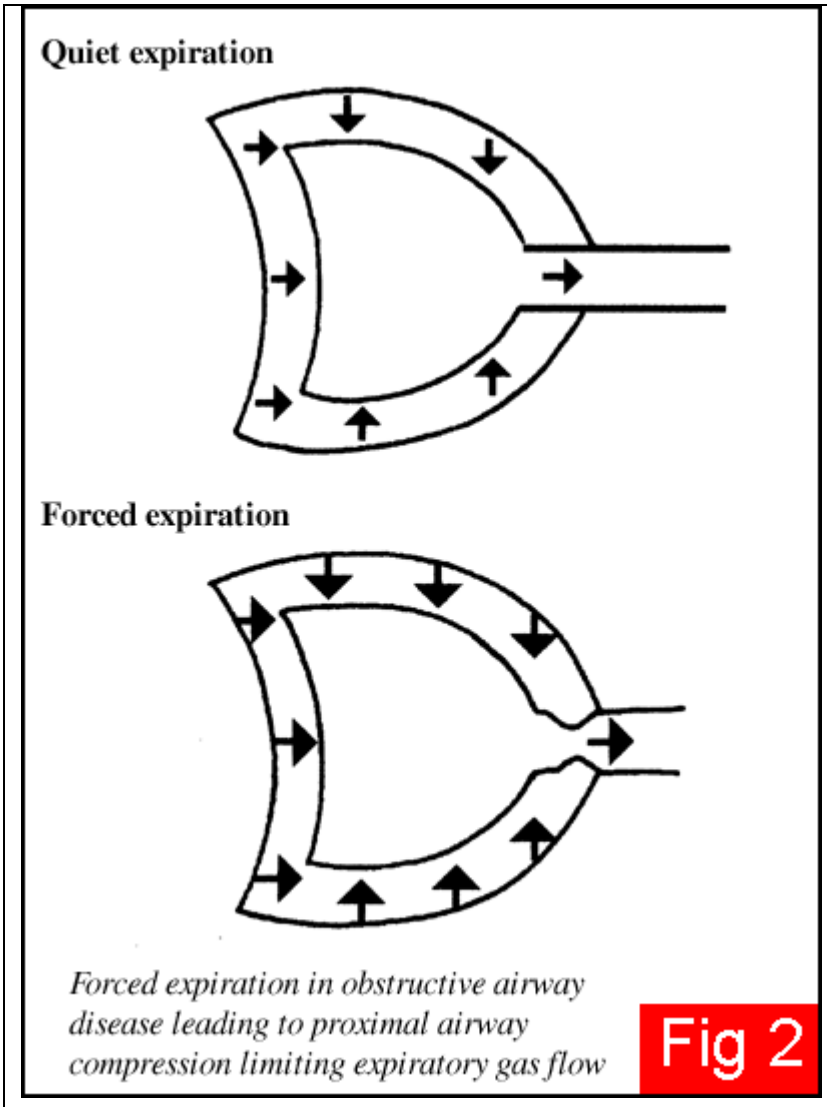
Lung Volumes measured with a spirometer during quiet breathing with one maximum breath. Values shown are for an average-sized healthy young male.

RV	*Residual volume*	*FRC*	*Functional residual capacity*
ERV	*Expiratory reserve volume*	*TV*	*Tidal vlume*
IRV	*Inspiratory reserve volume*	*VC*	*Vital capacity*
TLC	*Total lung capacity*		

Fig 1

Functional residual capacity (FRC) is the volume of air in the lungs at the end of a normal expiration. The point at which this occurs (and hence the FRC value) is determined by a balance between the inward elastic forces of the lung and the outward forces of the respiratory cage (mostly due to muscle tone). FRC falls with lying supine, obesity, pregnancy and anaesthesia, though not with age. The FRC is of particularly importance to anaesthetists because:

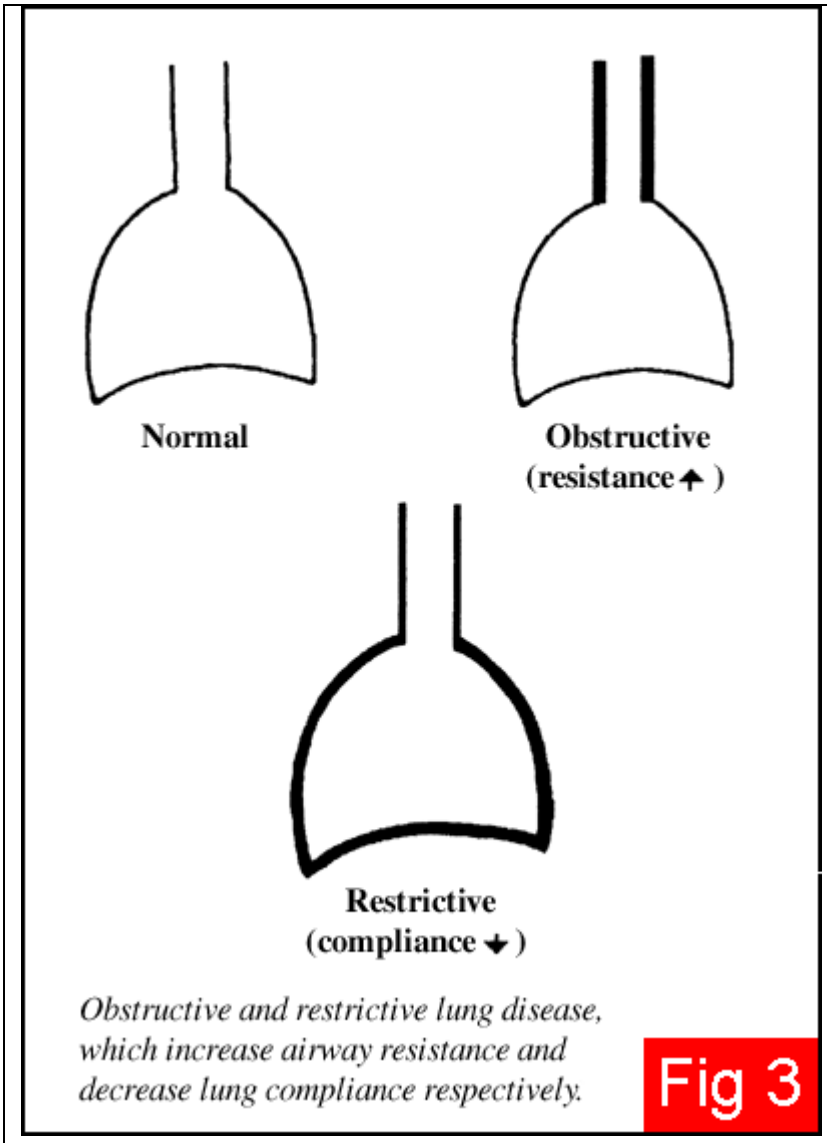
- During apnoea it is the reservoir to supply oxygen to the blood
- As it falls the distribution of ventilation within the lungs changes leading to mismatching with pulmonary blood flow
- If it falls below a certain volume (the closing capacity), airway closure occurs leading to shunt (see later - Ventilation/perfusion/shunt)



Resistance / compliance

In the absence of respiratory effort, the lung will come to lie at the point of the FRC. To move from this position and generate respiratory movement, two aspects need to be considered which oppose lung expansion and airflow and therefore need to be overcome by respiratory muscle activity. These are the airway resistance and the compliance of the lung and chest wall.

Resistance of the airways describes the obstruction to airflow provided by the conducting airways, resulting largely from the larger airways (down to division 6-7), plus a contribution from tissue resistance resulting produced by friction as tissues of the lung slide over each other during respiration. An increase in resistance resulting from airway narrowing such as bronchospasm leads to obstructive airways disease.

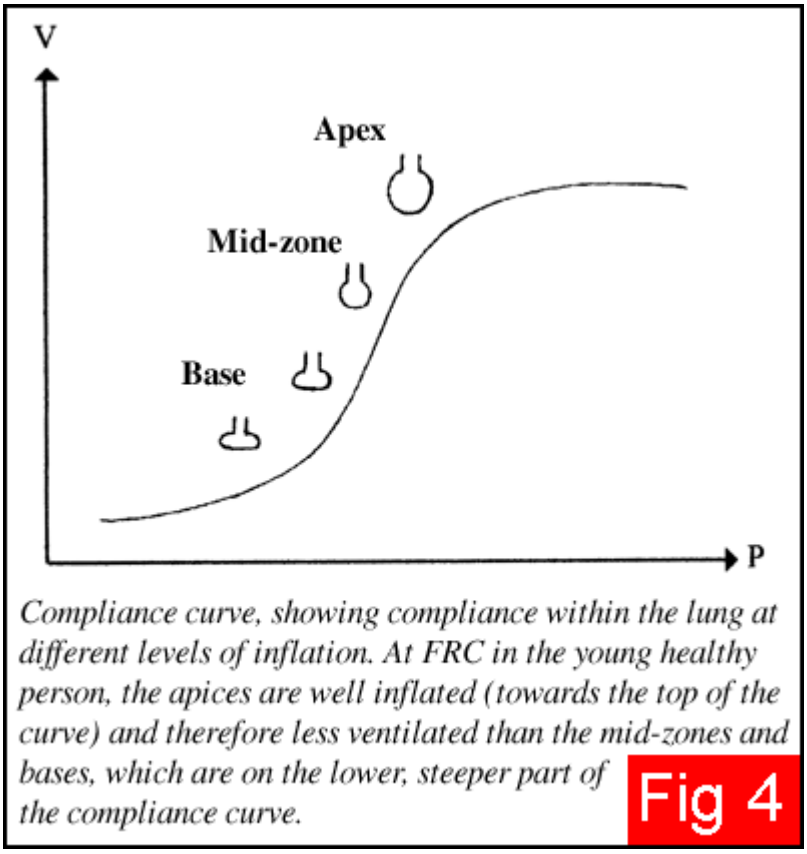


Obstructive and restrictive lung disease, which increase airway resistance and decrease lung compliance respectively.

Fig 3

Teaching Point

In obstructive airways disease, it might be expected that airflow could be improved by greater respiratory effort (increasing the pressure gradient) to overcome the increase in airways resistance. Whilst this is normally true for inspiration, it is not necessarily the case during expiration, as the increase in intrapleural pressure may act to compress airways proximal to the alveoli, leading to further obstruction with no increase in expiratory flow and air-trapping distally. This is shown in figure 2 and demonstrates why expiration is usually the major problem during an asthmatic attack.



Compliance curve, showing compliance within the lung at different levels of inflation. At FRC in the young healthy person, the apices are well inflated (towards the top of the curve) and therefore less ventilated than the mid-zones and bases, which are on the lower, steeper part of the compliance curve.

Fig 4

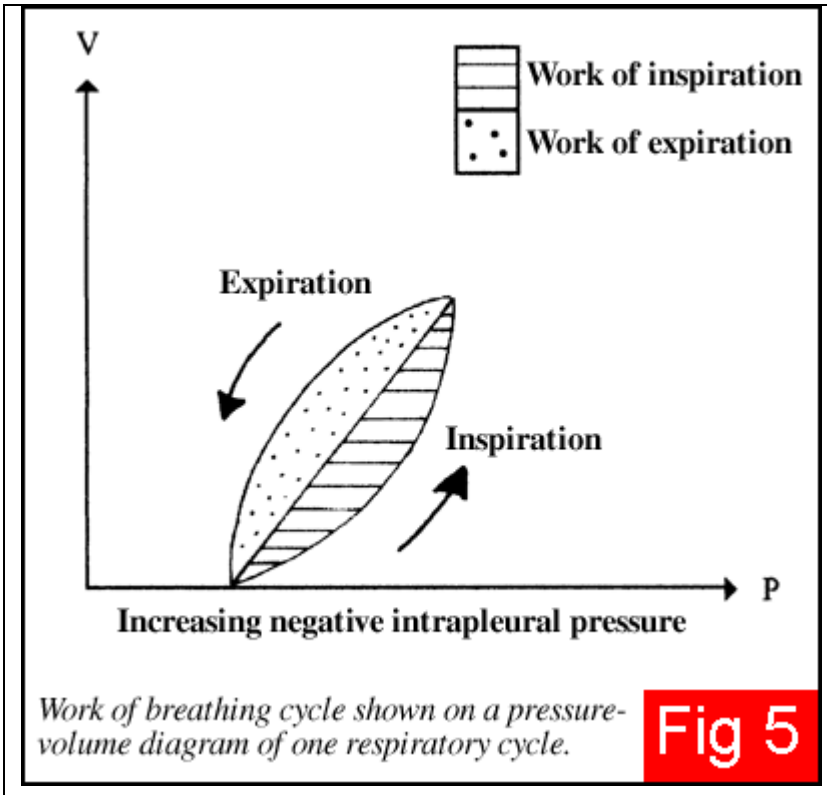
Compliance denotes distensibility (stretchiness), and in a clinical setting refers to the lung and chest wall combined, being defined as the volume change per unit pressure change. When compliance is low, the lungs are stiffer and more effort is required to inflate the alveoli. Conditions that worsen compliance, such as pulmonary fibrosis, produce *restrictive lung disease*.

Compliance also varies within the lung according to the degree of inflation, as shown in figure 4. Poor compliance is seen at low volumes (because of difficulty with initial lung inflation) and at high volumes (because of the limit of chest wall expansion), with best compliance in the mid-expansion range.

Work of breathing

Of the two barriers to respiration, airway resistance and lung compliance, it is only the first of these, which requires actual work to be done to overcome it. Airway resistance to flow is present during both inspiration and expiration and the energy required to overcome it, which represents the actual *work of breathing*, is dissipated as heat.

Although energy is required to overcome compliance in expanding the lung, it does not contribute to the actual work of breathing as it is not dissipated but converted to potential energy in the distended elastic tissues. Some of this stored energy is used to do the work of breathing produced by airways resistance during expiration.



Work of breathing cycle shown on a pressure-volume diagram of one respiratory cycle. Fig 5

The work of breathing is best displayed on a pressure-volume curve of one respiratory cycle (figure 5) which shows the different pathways for inspiration and expiration, known as *hysteresis*. The total work of breathing of the cycle is the area contained in the loop.

Teaching Point

With high respiratory rates, faster airflow rates are required, increasing the frictional forces. This is more marked in obstructive airways disease - such patients therefore generally minimise the work of breathing by using a slow respiratory rate and large tidal volumes. In contrast, patients with restrictive lung disease (poor compliance) reach the unfavourable upper part of the compliance curve soon as the tidal volume increases. The pattern of breathing seen in such patients usually involves small tidal volumes and a fast respiratory rate.

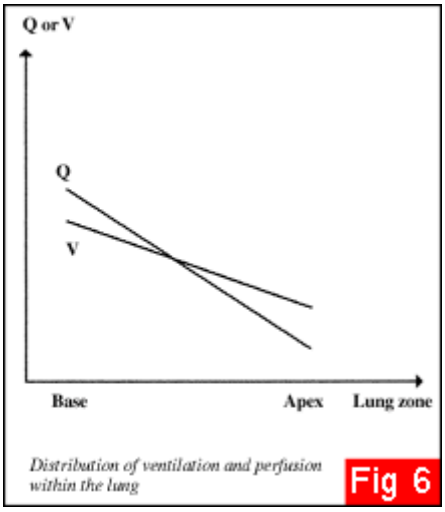
Diffusion

The alveoli provide an enormous surface area for gas exchange with pulmonary blood (between 50-100m^2) with a thin membrane across which gases must diffuse. The solubility of oxygen is such that its diffusion across the normal alveolar-capillary membrane is an efficient and rapid process. Under resting conditions pulmonary capillary blood is in contact with the alveolus for about 0.75 second in total and is fully equilibrated with alveolar oxygen after only about a third of the way along this course. If lung disease is present which impairs diffusion there is therefore still usually sufficient time for full equilibration of oxygen when at rest. During exercise, however, the pulmonary blood flow is quicker, shortening the time available for gas exchange, and so those with lung disease are unable to oxygenate the pulmonary blood fully and thus have a limited ability to exercise.

For carbon dioxide, which diffuses across the alveolar-capillary membrane 20 times faster than oxygen, the above factors are less liable to compromise transfer from blood to alveoli.

Ventilation / perfusion / shunt

In an ideal situation the ventilation delivered to an area of lung would be just sufficient to provide full exchange of oxygen and carbon dioxide with the blood perfusing that area. In the normal setting, whilst neither ventilation (V) nor perfusion (Q) is distributed evenly throughout the lung, their matching is fairly good, with the bases receiving substantially more of both than the apices (figure 6).

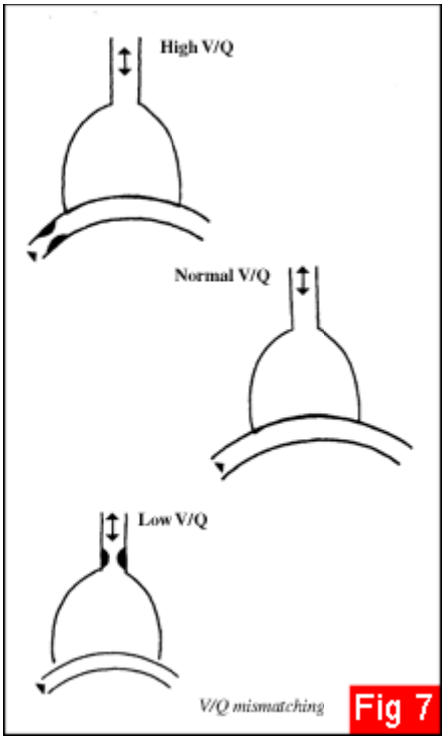


Distribution of ventilation and perfusion within the lung **Fig 6**

For *perfusion*, the distribution throughout the lung is largely due to the effects of gravity. Therefore in the upright position this means that the perfusion pressure at the base of the lung is equal to the mean pulmonary artery pressure (15mmHg or 20cmH2O) plus the hydrostatic pressure between the main pulmonary artery and lung base (approximately 15cmH2O). At the apices the hydrostatic pressure difference is subtracted from the pulmonary artery pressure with the result that the perfusion pressure is very low, and may at times even fall below the pressure in the alveoli leading to vessel compression and intermittent cessation of blood flow.

The distribution of *ventilation* across the lung is related to the position of each area on the compliance curve at the start of a normal tidal inspiration (the point of the FRC). Because the bases are on a more favourable part of the compliance curve than the apices, they gain more volume change from the pressure change applied and thus receive a greater degree of ventilation. Although the inequality between bases and apices is less marked for ventilation than for perfusion, overall there is still good V/Q matching and efficient oxygenation of blood passing through the lungs.

Disturbance of this distribution can lead to V/Q *mismatching* (figure 7). For an area of low V/Q ratio the blood flowing through it will be incompletely oxygenated, leading to a reduction in the oxygen level in arterial blood (hypoxaemia). Providing some ventilation is occurring in an area of low V/Q, the hypoxaemia can normally be corrected by increasing the FiO2, which restores the alveolar oxygen delivery to a level sufficient to oxygenate the blood fully.



V/Q mismatching **Fig 7**

V/Q mismatch occurs very commonly during anaesthesia because the FRC falls leading to a change in the position of the lung on the compliance curve. The apices, therefore, move to the most favourable part of the curve whilst the bases are located on a less favourable part at the bottom of the curve.

At the extremes of V/Q mismatch, an area of lung receiving no perfusion will have a V/Q ratio of (infinity) and is referred to as *alveolar dead-space*, which together with the anatomical dead-space makes up the *physiological dead-space*. Ventilating the dead space is, in effect, wasted ventilation, but unavoidable.

In contrast an area of lung receiving no ventilation, owing to airway closure or blockage, its V/Q ratio will be zero and the area is designated as shunt. Blood will emerge from an area of shunt with a PO2 unchanged from the venous level (5.3kPa or 40mmHg) and produce marked arterial hypoxaemia. This hypoxaemia cannot be corrected by increasing the FiO2, even to 1.0, as the area of shunt receives no ventilation at all. The well-ventilated parts of the lung cannot compensate for the area of shunt because Hb is fully saturated at a normal PO2 . Increasing the PO2 of this blood will not increase the oxygen content substantially (*see Oxygen Carriage later*).

In the case of shunt, therefore, adequate oxygenation can only be re-established by restoring ventilation to these areas using measures such as physiotherapy, PEEP or CPAP, which clear blocked airways and reinflate areas of collapsed lung. Because closing capacity (CC) increases progressively with age, and is also higher in neonates, these patients are at particular risk during anaesthesia as the FRC may fall below CC and airway closure result.

Teaching Point

A physiological mechanism exists which reduces the hypoxaemia resulting from areas of low V/Q ratio, by producing local vasoconstriction in these areas and diverting blood to other, better-ventilated parts of the lung. This effect, known as hypoxic pulmonary vasoconstriction (HPV), is mediated by unknown local factors. The protective action of HPV is, however, inhibited by various drugs, including inhalational anaesthetic agents.

Surfactant

Any liquid surface exhibits surface tension, a tendency for the molecules on the surface to pull together. This why, when water lies on a surface, it forms rounded droplets. If the surface tension is reduced, such as by adding a small amount of soap, the droplets collapse and the water becomes a thin film.

When a liquid surface is spherical, it acts to generate a pressure within the sphere according to Laplace's law:

$$P = \frac{4T}{R}$$ if there are 2 liquid surfaces *(such as a bubble)*

$$P = \frac{2T}{R}$$ if there is 1 liquid surface *(such as lining an alveolus)*

P Pressure in sphere

R Radius of sphere

T Surface tension of liquid

The film of liquid lining the alveoli exhibits surface tension in such a manner to increase the pressure in the alveoli, with a greater rise in small alveoli than in large ones. Surfactant is a substance secreted by type II alveolar epithelial cells, which lowers the surface tension of this respiratory surface liquid markedly. Mainly consisting of a phospholipid (dipalmitoyl lecithin), its physiological benefits are:

- an increase (improvement) in overall lung compliance
- a reduction in the tendency for small alveoli to empty into large ones, leading to collapse
- a reduction in the fluid leak from pulmonary capillaries into the alveoli, as the surface tension forces act to increase the hydrostatic pressure gradient from capillary to alveolus

DISEASE AND CONDITION

Chronic Obstructive Pulmonary Disease (COPD)
- Exemplified by chronic bronchitis and obstructive emphysema
- Patients have a history of:
  - Smoking
  - Dyspnea, where labored breathing occurs and gets progressively worse
  - Coughing and frequent pulmonary infections
- COPD victims develop respiratory failure accompanied by hypoxemia, carbon dioxide retention, and respiratory acidosis

Pathogenesis of COPD

Asthma
- Characterized by dyspnea, wheezing, and chest tightness
- Active inflammation of the airways precedes bronchospasms
- Airway inflammation is an immune response caused by release of IL-4 and IL-5, which stimulate IgE and recruit inflammatory cells
- Airways thickened with inflammatory exudates magnify the effect of bronchospasms

Tuberculosis
- Infectious disease caused by the bacterium *Mycobacterium tuberculosis*
- Symptoms include fever, night sweats, weight loss, a racking cough, and splitting headache
- Treatment entails a 12-month course of antibiotics

Lung Cancer
- Accounts for 1/3 of all cancer deaths in the U.S.
- 90% of all patients with lung cancer were smokers
- The three most common types are:
  - Squamous cell carcinoma (20-40% of cases) arises in bronchial epithelium
  - Adenocarcinoma (25-35% of cases) originates in peripheral lung area
  - Small cell carcinoma (20-25% of cases) contains lymphocyte-like cells that originate in the primary bronchi and subsequently metastasize

Developmental Aspects
- Olfactory placodes invaginate into olfactory pits by the 4^{th} week
- Laryngotracheal buds are present by the 5^{th} week
- Mucosae of the bronchi and lung alveoli are present by the 8^{th} week

Developmental Aspects
- By the 28^{th} week, a baby born prematurely can breathe on its own
- During fetal life, the lungs are filled with fluid and blood bypasses the lungs
- Gas exchange takes place via the placenta

Respiratory System Development

Developmental Aspects
- At birth, respiratory centers are activated, alveoli inflate, and lungs begin to function
- Respiratory rate is highest in newborns and slows until adulthood
- Lungs continue to mature and more alveoli are formed until young adulthood
- Respiratory efficiency decreases in old age