Medical Education Systems, Inc.

Course 302

Blood Gas and the Respiratory System

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Blood Gas Basics & The Respiratory System

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Learning Objectives

Upon completion of this course, you will be able to:

- Describe the basic elements of blood gases, how they are analyzed, and how that information is used in health care

- Identify how blood gases fit into the overall respiratory system

- Discuss blood gas analyzers and explain how they work

- List and discuss the blood gas values that are considered “normal” and “abnormal”

Introduction

In this course we will review Blood Gas Basics, all the aspects of gas exchange and Acid-Base Balance, including O2 transport, ventilation, control of respiration, and a generalized summary – animals utilize O2 and produce CO2 + heat = occurs in the mitochondria – for cellular respiration to occur, must be a steady supply of O2 and CO2 must be steadily removed. There will be some overlap since the topics are all intertwined.

Close relationship between interdependence of plants and animals e.g. plants produce O2 as a result of photosynthesis (however, can only occur during daylight) and the interconnectedness between the physical, chemical and biological aspects to life (e.g. O2 level in water, ice and atmosphere – "circle of life"

Note: balance of atmospheric gases, the needs of both animal & plants is in some way delicate & can be disturbed/disrupted via man's activities i.e. think about the environmental contaminants assignment. However, first we should review some basics of Respiration:

Blood gas terms

Arterial blood gases: measurement of the pH level and the oxygen and carbon dioxide concentrations in arterial blood; important in diagnosis of many respiratory diseases

Alternative meaning:
arterial blood gas A test which analyses arterial blood for oxygen, carbon dioxide and bicarbonate content in addition to blood pH. Used to test the effectiveness of respiration. Acronym: ABG
pH: <chemistry> The symbol relating the hydrogen ion concentration or activity of a solution to that of a given standard solution.

Numerically the pH is approximately equal to the negative logarithm of hydrogen ion concentration expressed in molarity. PH 7 is neutral, above 7 is alkaline and below is acidic.

What are Blood Gases?
There are two broad components to the blood gas panel: respiratory and metabolic. The values reported are as follows:

- pH--This is a logarithmic expression of hydrogen ion concentration--the acidity or alkalinity of the blood. The normal human arterial pH is 7.4. Any pH below this is acid, and any pH above it is alkaline.

- There is a narrow range of pH values (7.35 to 7.45) that the human body and its complicated system of enzyme-supported system operates within. pH values below 7.0 and above 7.6 are incompatible with life.

- HCO_3--This value is derived through the blood gas analyzer's manipulation of the Henderson-Hasslebach Equation. An uncompensated decrease in the HCO_3 value causes a decline in pH. An increased HCO_3 results in alkalinization of the blood. Either condition can be life threatening. Decreased HCO_3 is often the result of kidney or other major organ failure or uncontrolled diabetes. Increased HCO_3 is more rare and is usually the result of inappropriate administration of certain drugs such as some kinds of diuretics or an excess of $NaHCO_3$.

- PCO_2--This value is measured directly by the CO_2 electrode. An increased PCO_2 is often the result of acute, chronic or impending respiratory failure, whereas a decreased PCO_2 is the result of hyperventilation stimulated by a metabolic acidosis or hysteria and severe anxiety reactions. The normal arterial PCO_2 is 40 mmHg.

- PO_2--The partial pressure of oxygen in the blood is measured directly by a polarographic O_2 electrode. The normal acceptable range is roughly between 85 and 100. An increased PO_2 is usually the result of excessive oxygen administration that needs to be adjusted downwards on such results. A decreased PO_2 is often the result of any number of respiratory or cardiopulmonary problems.

Link for the technical aspects of how the equipment works:

http://www.bloodgas.org/e77b74d4-ae83-4626-ab9d-e747b1b7c492.W5Doc?track=tech

Arterial Blood Gases

How does it work?

The pH, PO_2 and pCO_2 of the sample are measured with specific electrodes. By equilibrating the sample against different CO_2, mixtures the bicarbonate concentration is calculated.

What does it tell us?

Arterial blood gas analysis is the gold standard for assessing respiratory function. The gas exchange capability of the lung can be directly measured.

The three main measurements made by the blood gas analyzer are used together to obtain a detailed picture of the state of the respiratory system.

Oxygen: the PaO_2 is the standard for measuring blood oxygenation. Decreases in PaO_2 are due to hypoventilation, inspiration of hypoxic gas mixtures or impairment of gas exchange. Further information can be gained when the inspired oxygen level is changed from 21% to 100% and the PaO_2 re-measured.

Carbon dioxide: $PaCO_2$ is set by the balance between CO_2 production and CO_2 elimination. During anesthesia, CO_2 production is fairly constant so the arterial level is determined by elimination. If the lungs are healthy the $etCO_2$ is a good substitute for $PaCO_2$ but in pulmonary dysfunction the difference between them increases which is useful diagnostically.

HCO_3^-, base excess, anion gap, pH: These all measure different aspects of acid-base balance. Patients with metabolic diseases may have acid-base disturbances and blood gas analysis can be used to monitor and treat them.

A blood gas analyzer is not a routine piece of monitoring equipment. Interpretation of the results requires knowledge of pulmonary and renal physiology, and because the arterial sample has to be transported to the machine for analysis there is a delay in obtaining the results. However, a blood gas analyzer is invaluable for critical care patients, pulmonary research and advanced procedures such as cardiopulmonary bypass and transplantation.

The basics of blood gases

With most lab blood work there are two types of tests that are in some way time-dependent: stat tests, which must be done as quickly as possible and routine tests. If there were such a thing as "super stat," blood gas tests would fall into that category.

The values obtained represent a mere moment in time for the patient, and although trends and stabilization of blood gas values can be obtained, more often than not the results are worthless later if changes in treatment are contemplated based on their values.

Such therapeutic changes often involve critical, life-saving and time-dependent interventions such as adjustment upwards or downwards of oxygen, carbon dioxide and pH values. There is no time to waste in a critical situation.

Most blood samples can be collected routinely, on rounds, and kept and transported at room temperature until they are analyzed. Temperature does not affect their results. This is not true for arterial blood gases. As a living tissue, blood collected for this panel degrades rapidly unless kept in an ice/water bath until analyzed if any delay at all is expected in performing the analysis. And at the moment of analysis, the sample must be re-warmed to body temperature for an accurate result as the partial pressure of oxygen and CO_2 decreases at lower temperatures and increases at higher ones. The most accurate reflection of these numbers lies in analyzing the sample at the proper temperature and correcting the values for the patient's actual body temperature if the patient is either hypothermic or febrile.

Sample Collection

Most blood labs are performed on tourniqueted venous blood drawn from a superficial vein that is easily palpated and often even visually apparent. Today, lab technologists use a special needle and a Vacutainer containing an appropriate anticoagulant, other substance or nothing at all, depending on the test. Such tubes are identified by a color-coded cap that is never removed. This makes for unparalleled safety and protection from needlesticks and accidental exposure to bloodborne pathogens.

Arterial blood gases, as their name implies, must be drawn from an artery with a free-flowing, unimpeded flow of blood coursing through it. This procedure is known as an arterial stick and is usually performed on a palpable radial artery. If this site is unavailable, the brachial artery must be used. If no upper limb artery can be used, the next most favored site is one of the femoral arteries.

In critically ill patients requiring frequent samples, physicians often insert an arterial line that simplifies the procedure immeasurably. The blood must be drawn through a needle (or directly into a syringe if an a-line is available) into a heparinized (wet or dry lithium) syringe. A milliliter or less of blood is required to perform the procedure using most modern blood gas analyzers. Any air bubble left in the hub or top of the syringe must be carefully and gently expelled and the needle capped using the safety coverlet supplied with most arterial blood gas sampling kits. The syringe is then placed in a plastic bag containing crushed ice and immediately transported for analysis.

Blood Gas Analyzers

To save time in the transport and analysis of blood samples on critically ill patients, many blood gas operations are housed in or near intensive care units as well as in or near the operating or recovery room. Because of the immediate life-threatening nature of blood gas abnormalities and the need to correct them rapidly on an objective and rational basis, blood gas labs should be equipped with a minimum of two analyzers in case one goes down due to routine maintenance or through some unforeseen malfunction or equipment failure. There can be no excuse for not being able to provide blood gas analysis rapidly and accurately on site at all times. Failure to do so can result in a potentially avoidable patient death.

Modern blood gas analyzers are electronic marvels compared to the methods used for this purpose 20 years ago. On attaching the sample syringe to the cuvette, they automatically draw the sample into a heated sampling chamber with miniaturized electrodes that quickly and accurately (if properly calibrated) measure pH, PCO_2 and PO_2 values. Based on these three measured values, these units automatically calculate HCO_3, total CO_2, percent oxygen saturation and O_2 content, which is based on entry of the patient's measured hemoglobin values.

A companion to such units, known as a co-oximeter, directly measures percent oxygen saturation and hemoglobin, and then accurately calculates oxygen content and carboxyhemoglobin, a value that reflects the degree of carbon monoxide in the blood in smoke inhalation victims.

In addition to arterial sampling, critical care specialists often order blood gas panels in blood drawn through a central venous line since PO_2 and O_2 content values of this blood, when compared against arterial PO_2 and O_2 content, enable an estimate of cardiac output, another valuable service performed by blood gas testing. Such samples are often collected and run from patients undergoing cardiac catheterization and the results must be returned while the patient is still on the table.

Types and Functions of Respiration

The primary function of the respiratory system is to supply the body with oxygen while removing carbon dioxide. Other important functions include vocalization and assisting in regulating plasma pH.

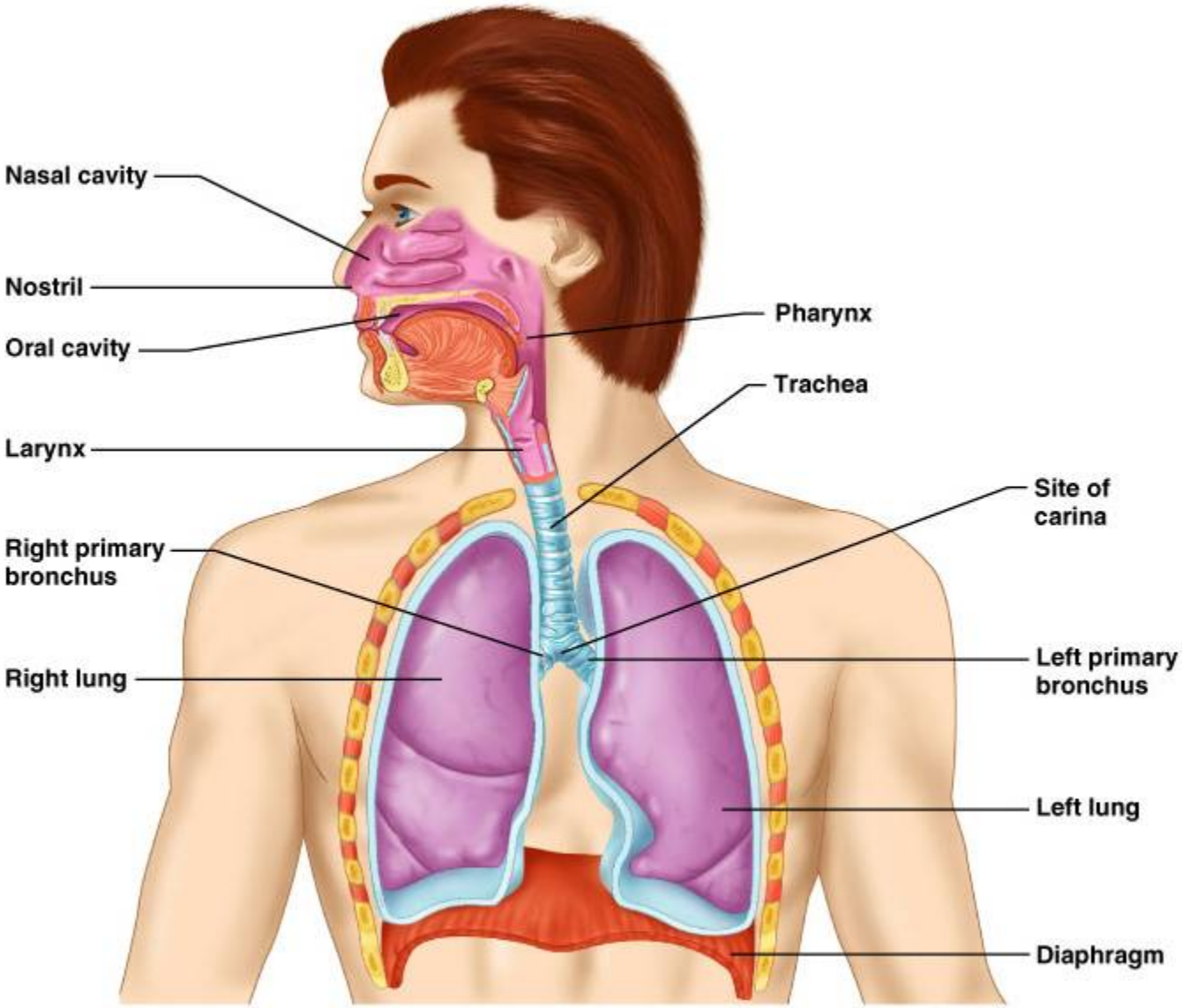
"Respiration" is actually several distinct processes:

1. Ventilation - movement of air into/out of the lungs
2. External Respiration - gas exchange between blood and the air-filled chambers of the lungs
3. Transport of gases between the lungs and the rest of the body tissues
4. Internal Respiration - gas exchange between systemic blood and the tissue cells.
5. Cellular Respiration - the mitochondrial process in which oxygen is utilized during ATP synthesis. (Note that this type of cellular respiration is often referred to as "aerobic respiration" as opposed to "anaerobic respiration," where ATP synthesis occurs without oxygen.)

Functions of the respiratory system include:

1. Oxygen intake
2. Expulsion of carbon dioxide
3. Sound/voice production
4. Regulation of plasma pH
5. Removal/destruction of airborne pathogens and toxins.

Anatomy of the Respiratory Tract



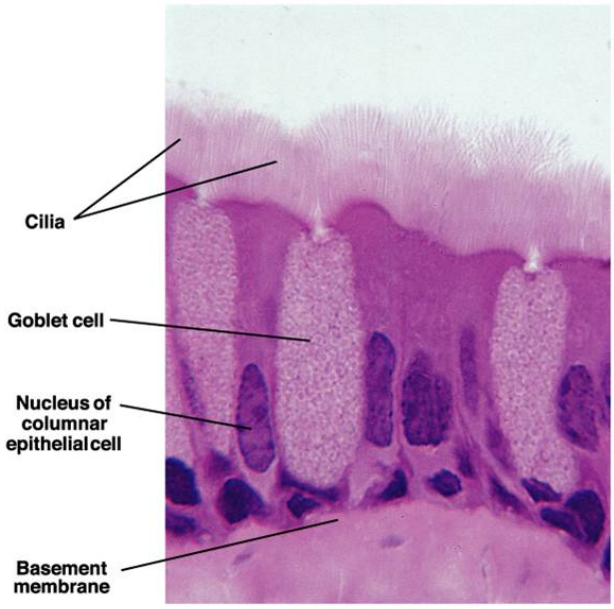
Anatomical structures of the respiratory system include: nose, nasal cavity, pharynx, larynx, trachea, bronchi, bronchioles, and alveoli. We can divide these structures into conducting zones and respiratory zones.

Conducting zones transport, cleanse, warm and humidify incoming air. They are not involved in gas exchange. The conducting portions include the nose, nasal cavity, pharynx, larynx, trachea, all bronchi, and all bronchioles except for the respiratory bronchioles.

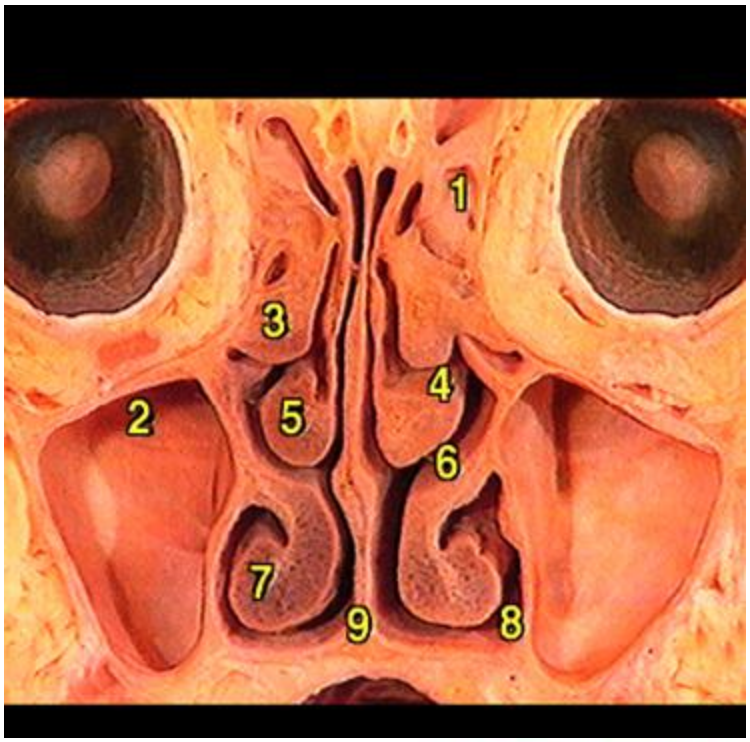
The respiratory zones function in gas exchange. They include respiratory bronchioles and alveoli.

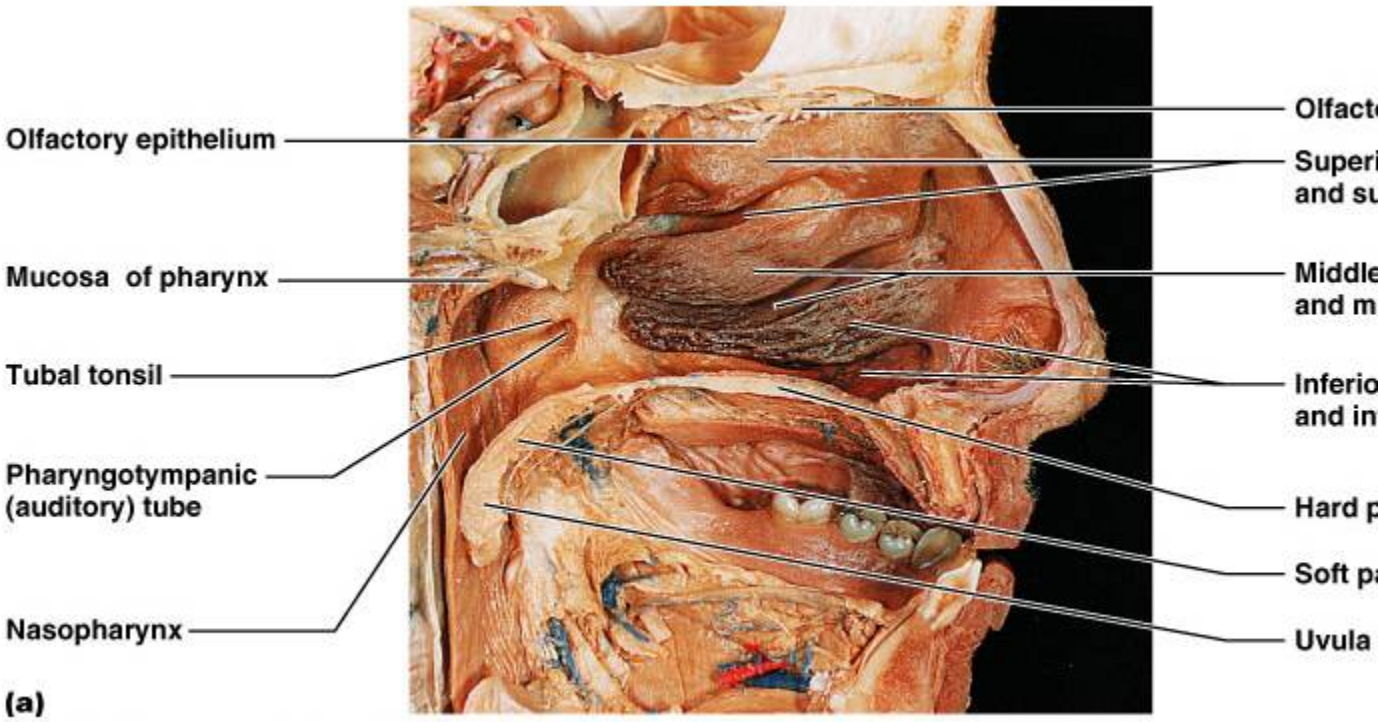
Nasal Cavity

The nasal cavity contains olfactory epithelium (*which is involved in?*) as well as pseudo-stratified columnar ciliated epithelium with goblet cells, a.k.a. respiratory epithelium.



The connective tissue that underlies the respiratory epithelium is quite vascular. This helps warm the inspired air. There are also a good number of mucous glands, Together with the goblet cells; they secrete the mucus that will help trap any pathogens or particulate matter within the air. The mucus also contains lysozyme and IgA antibodies. In the nasal cavity, there are 3 bony projections on each lateral wall. These are the nasal conchae (#'s 3,5,and 7 in the frontal section below).





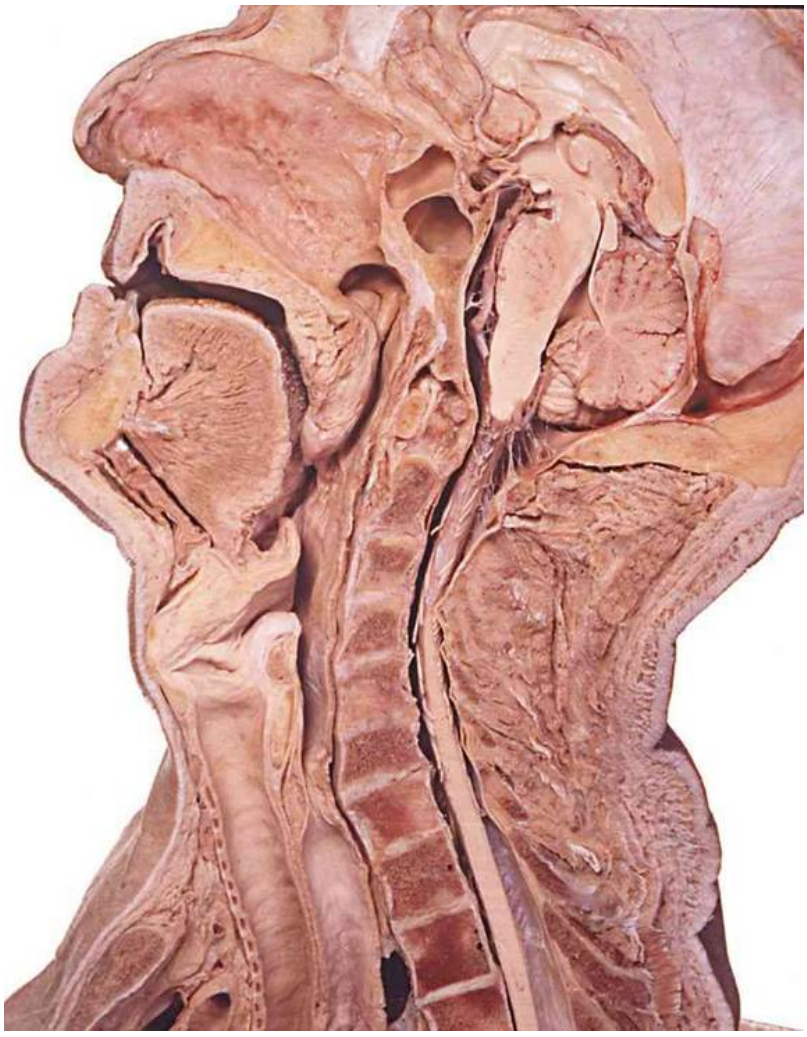
The nasal conchae act to increase the surface area exposed to the air. They also make the air flow turbulent, which makes it slow down. These factors increase our ability to filter the inspired air.

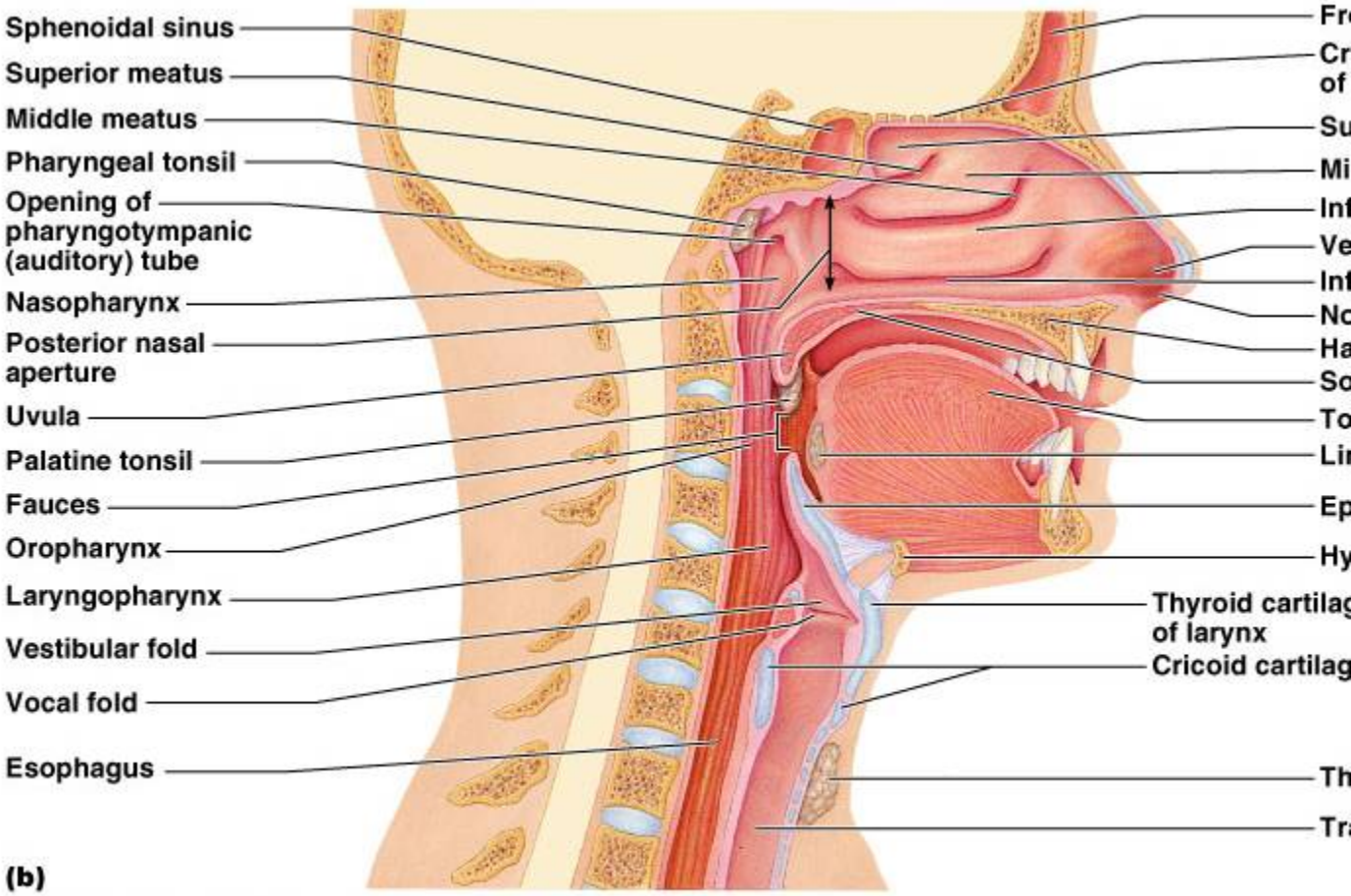
The nasal cavity is surrounded by a ring of paranasal sinuses located in the frontal, sphenoid, ethmoid, and maxillary bones. These sinuses assist in the warming and humidification of inspired air.

Pharynx

From the nasal cavity, we travel into the pharynx. There are 3 regions of the pharynx: nasopharynx, oropharynx, and laryngopharynx. The nasopharynx is lined by respiratory epithelium and contains the pharyngeal tonsils. The oropharynx is lined by stratified squamous epithelium (because it is also a passageway for food/drink) and contains the palatine tonsils. The laryngopharynx is also lined by stratified squamous epithelium (it is also a common pathway) and extends to the larynx - where the respiratory and digestive paths diverge.

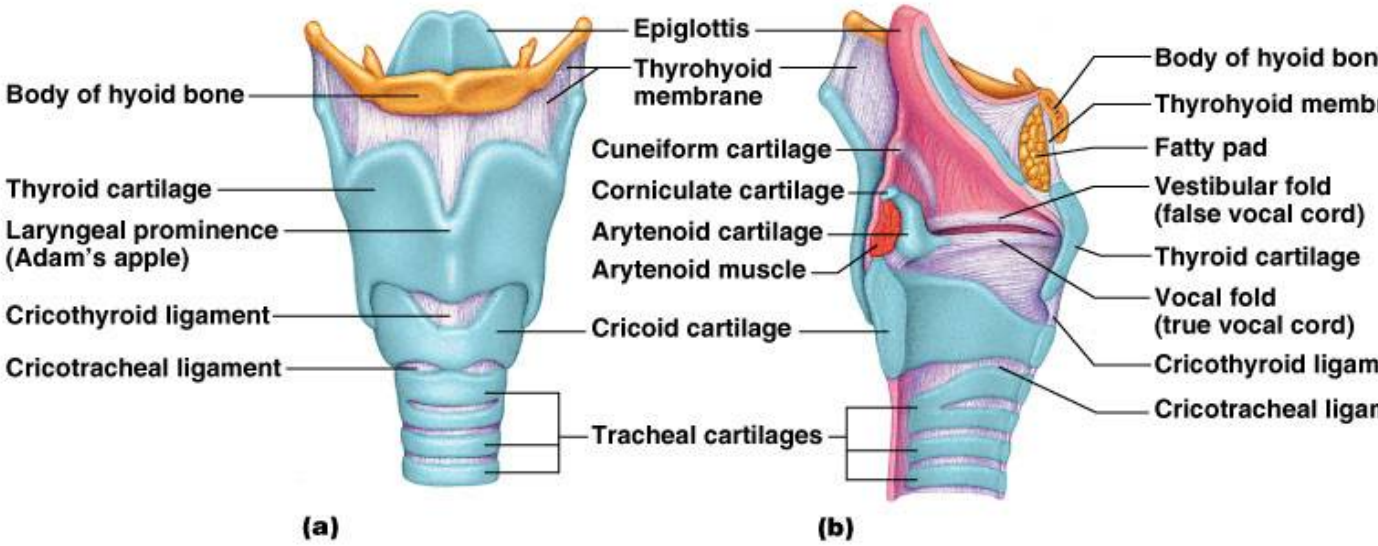
Take a look at these sagittal sections and see what respiratory structures you can identify.



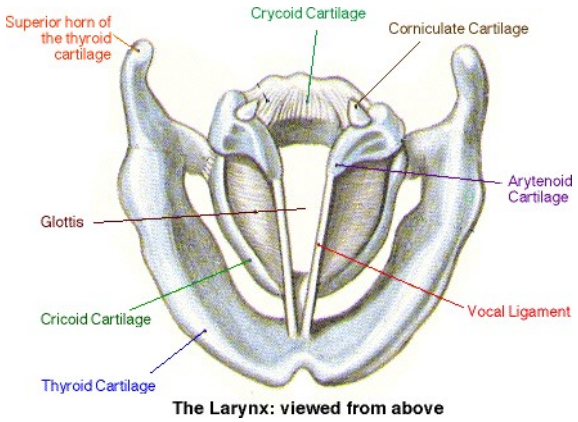


Larynx

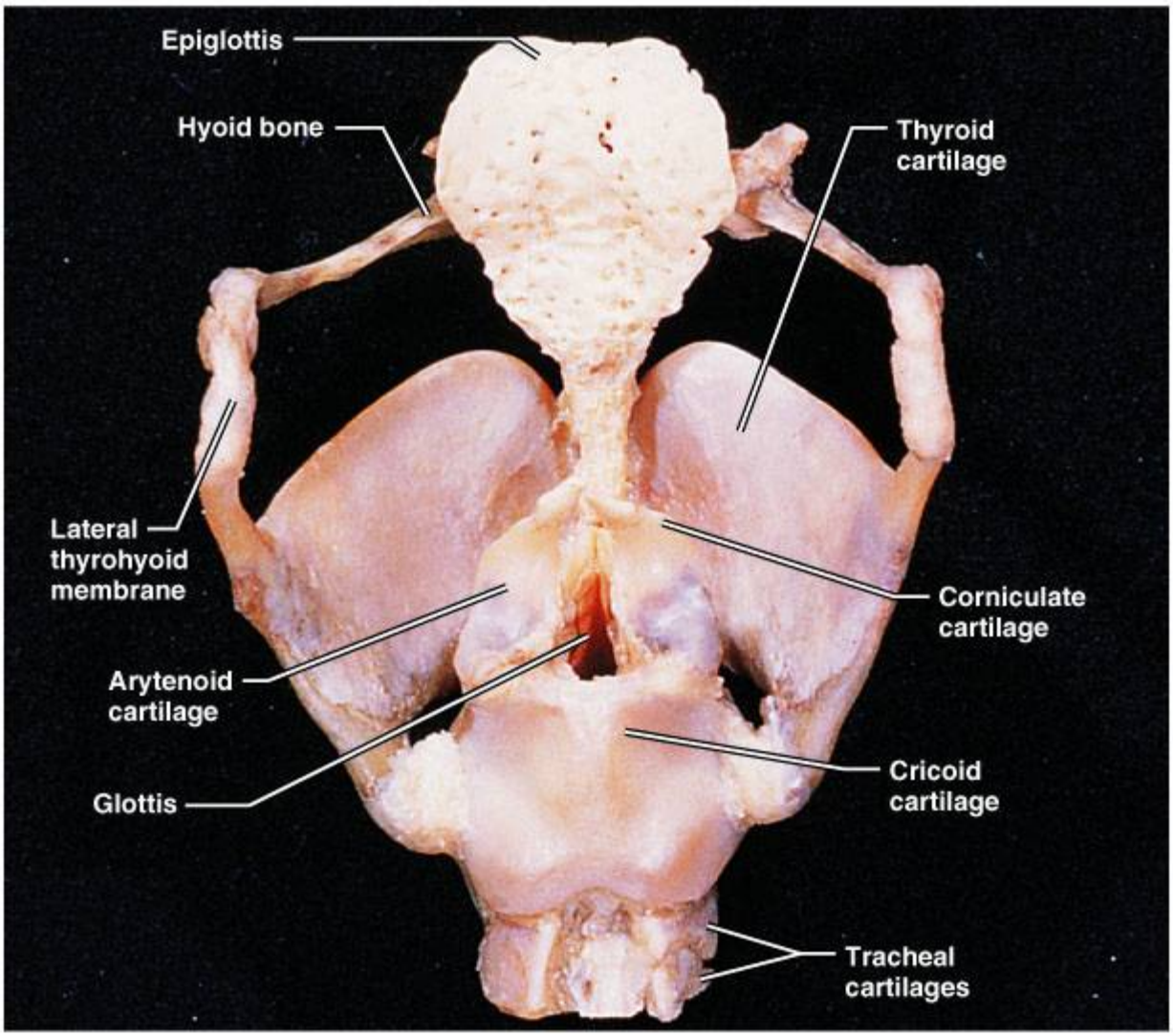
The larynx connects the laryngopharynx superiorly and the trachea inferiorly.



The larynx has a base framework of 9 cartilages connected by membranes and ligaments. There are 8 pieces of hyaline cartilage: the thyroid, cricoid, and the 3 sets of small paired cartilages. The 9th piece of cartilage, the epiglottis, is composed of elastic cartilage. The lumen of the larynx is lined by both stratified squamous epithelium (above the vocal cords) and respiratory epithelium (below the vocal cords). Lying underneath the laryngeal mucosa are the vocal ligaments which function in voice production. Air expelled through the larynx causes vibration of the vocal cords and results in sound production. The length and tension of the vocal cords are regulated by the state of contraction of the intrinsic laryngeal muscles. The vocal ligaments and overlying mucosa are referred to as the vocal folds or true vocal cords. Lying just superior to them is a similar pair of mucosal folds called the vestibular folds, or false vocal cords, which play no role in voice production.

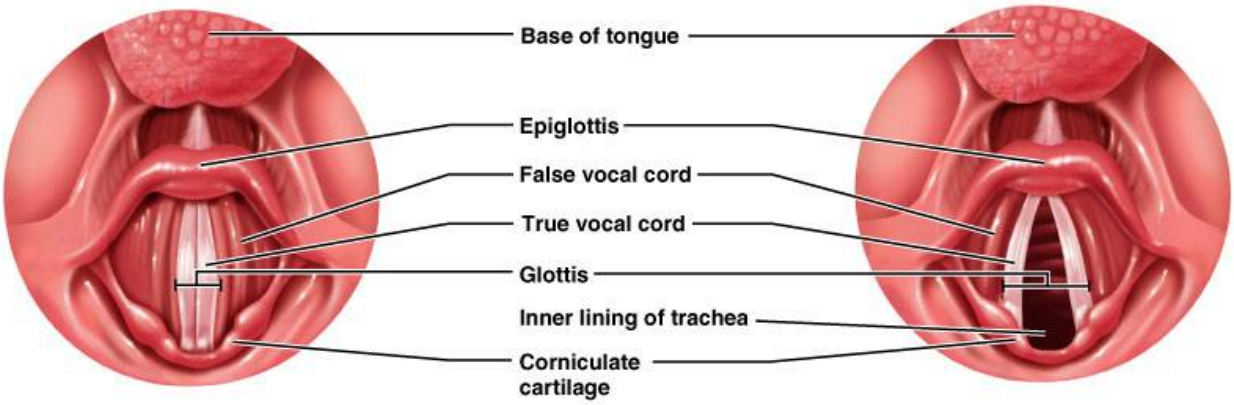


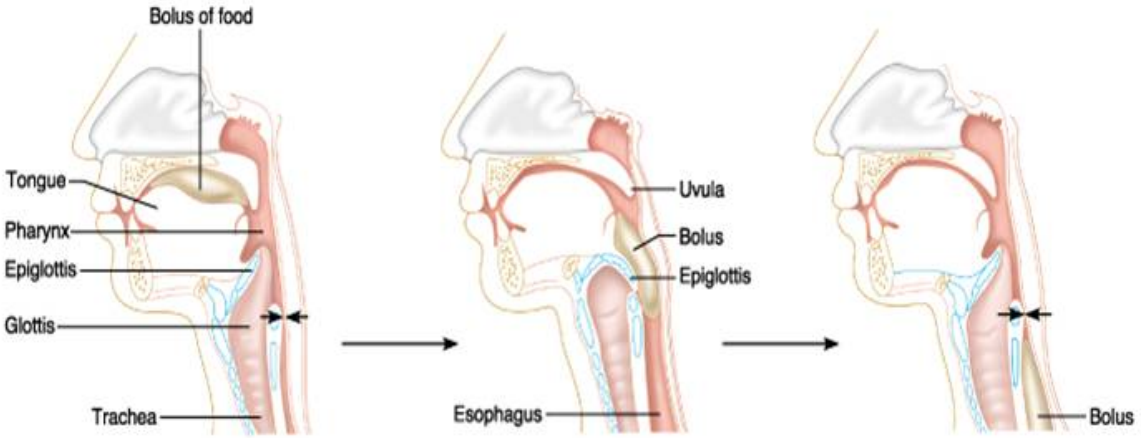
The Larynx: viewed from above



(c)

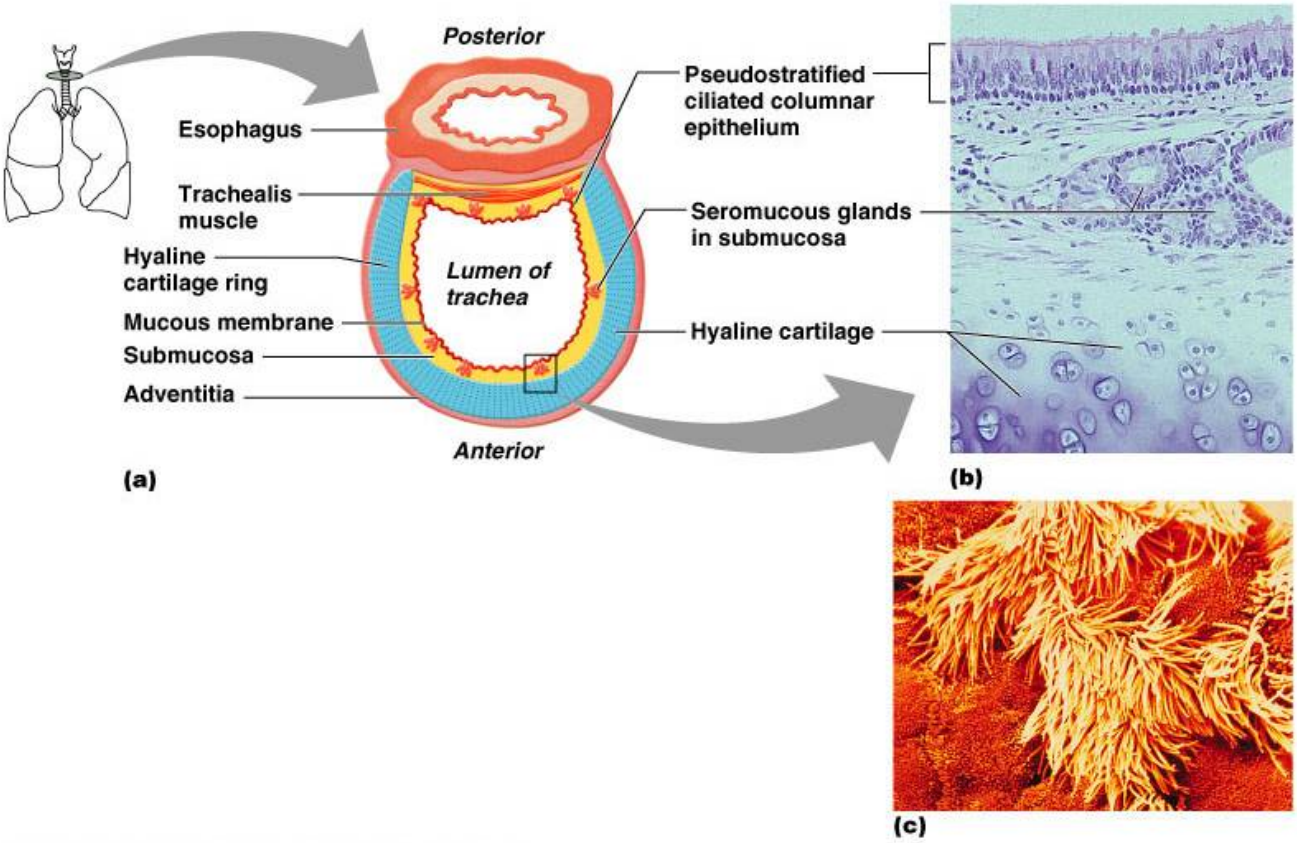
The opening to the larynx is called the glottis and it is protected by the elastic epiglottis. During swallowing, the epiglottis is pulled downward and covers the glottis, thus preventing food/drink from passing into the larynx and trachea.





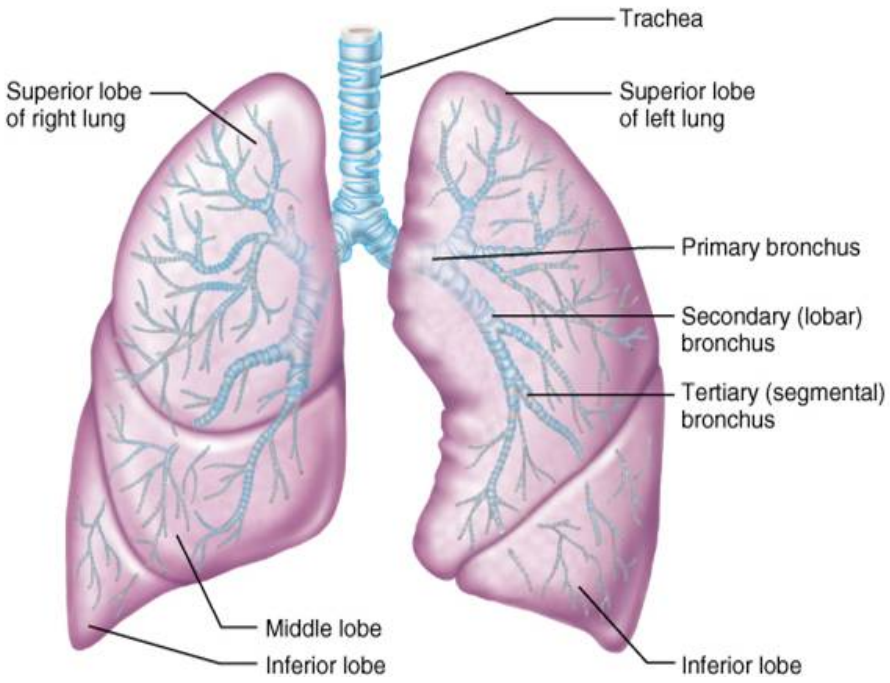
Trachea 

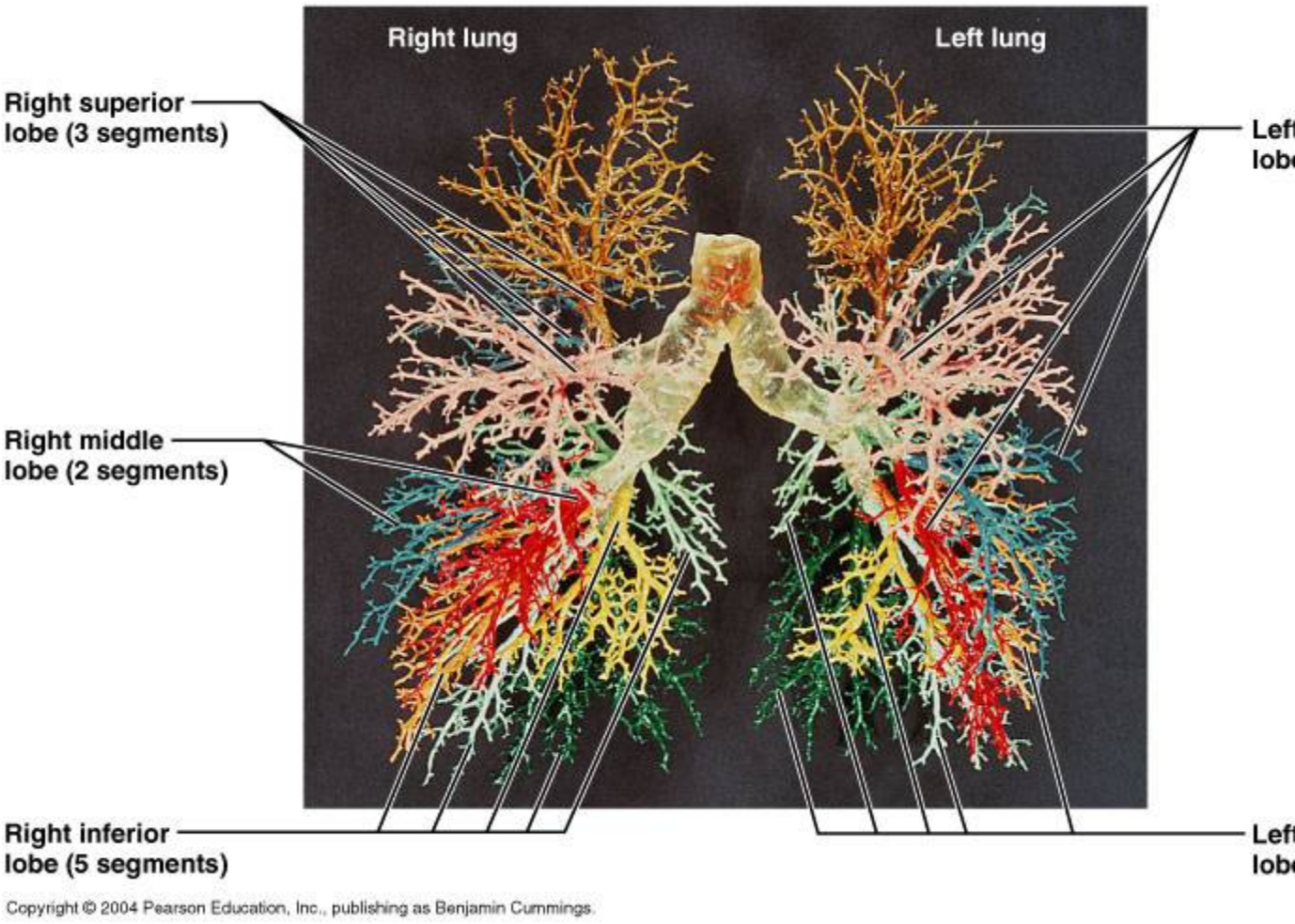
The trachea extends from the larynx to the mediastinum and ends by dividing into 2 primary bronchi. The trachea is reinforced by 16-20 C-shaped rings of cartilage. These rings prevent collapse of the trachea during inspiration. The lack of cartilage in the back of these rings allows for expansion of the esophagus during swallowing. The 2 ends of the cartilage C are connected by the trachealis muscle which is involved in coughing. The trachea is, not surprisingly, lined by respiratory epithelium. At the point where the trachea divides into the 2 primary bronchi, the last tracheal cartilage ring is expanded and a spar of cartilage extends posteriorly. This spar of cartilage is known as the carina and its mucosal lining is extremely sensitive to foreign matter.
Take a look at this cross-section of a trachea.



Bronchial Tree

Each primary bronchus runs obliquely before plunging into the hilus of the lung on its own side. Within the lungs, the primary bronchi divide into the secondary bronchi. Each secondary bronchus supplies one lobe of the lung. Since there are 2 lobes on the left and 3 on the right, there are 3 secondary bronchi on the right and 2 on the left. The secondary bronchi will divide into tertiary bronchi and then quaternary bronchi and so on until about 23 branchings have occurred. *As these branchings occur, what's happening to total cross-sectional area?*





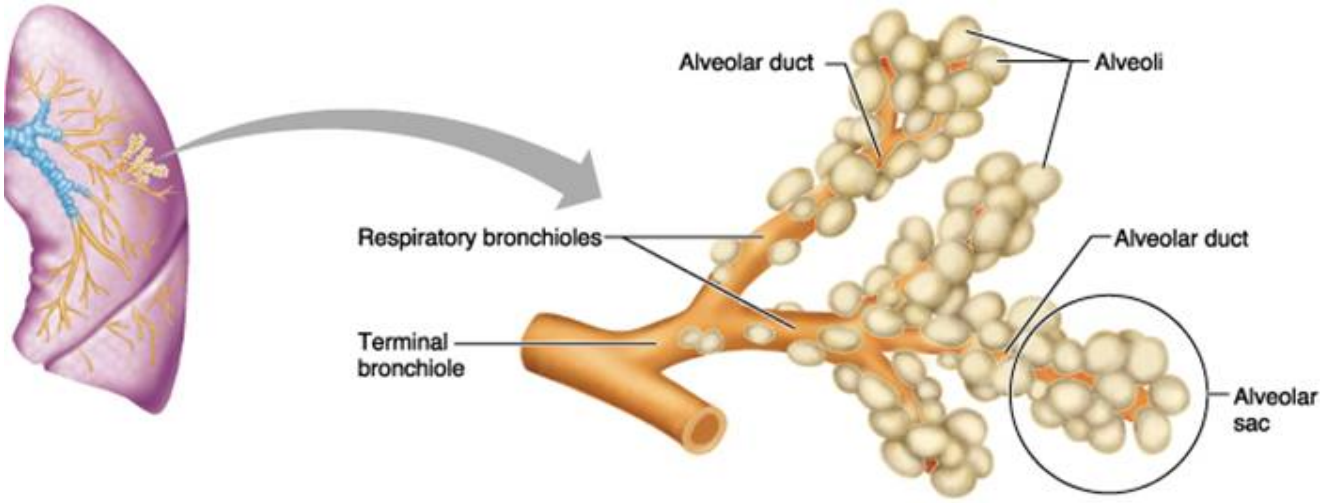
As the conducting tubes become smaller and smaller...

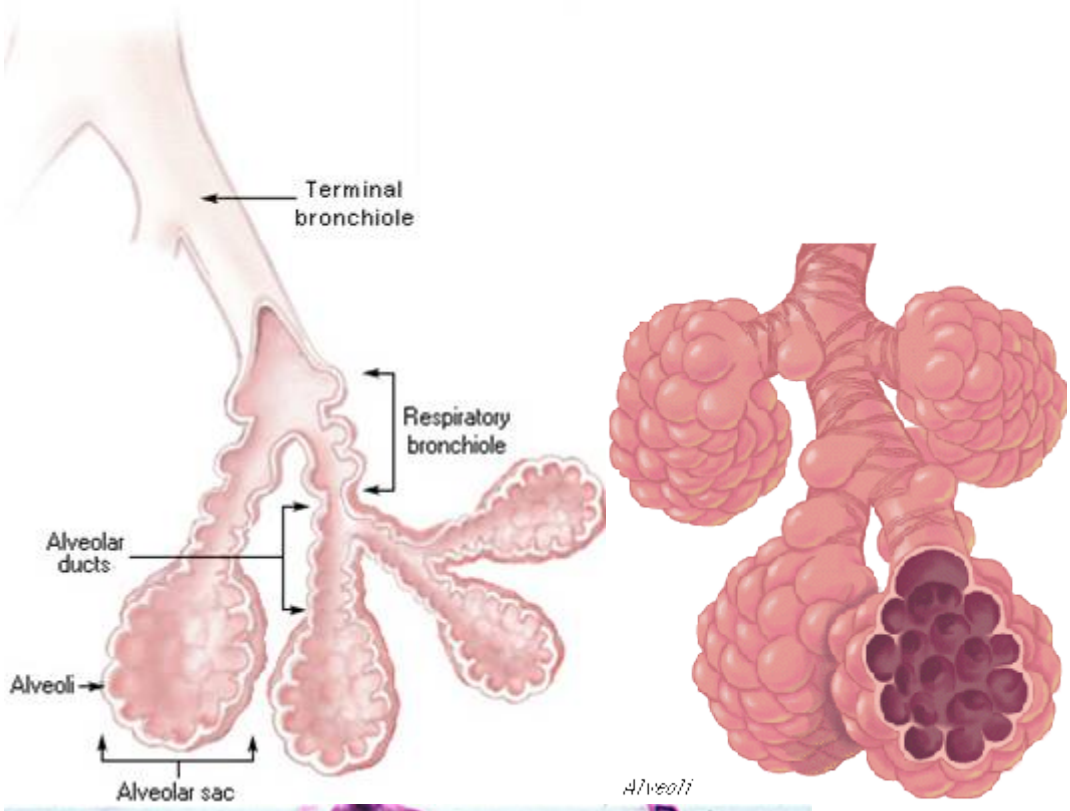
- The cartilage support changes. It goes from rings in the trachea to plates in the bronchi to none in the bronchioles. The cartilage must be absent by the time we get into the respiratory zone. It is not easy for gases to diffuse through a mass of hyaline cartilage.
- The epithelia changes. It goes from respiratory epithelium to simple columnar to simple cuboidal. Eventually, in the respiratory zone we will have simple squamous, which will facilitate diffusion.
- The amount of cilia and goblet cells decrease.
- The amount of smooth muscle increases. This will allow us to regulate the passage of air into certain areas of the lungs.

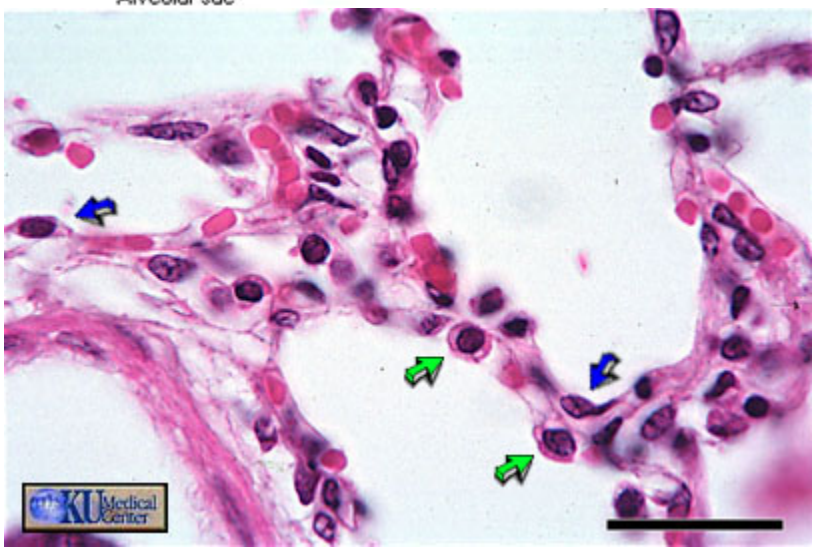
Passages with diameters of less than 1mm are bronchioles. Bronchioles lack cartilage. There are 2 types that we'll be concerned with: terminal bronchioles and respiratory bronchioles.

Alveoli

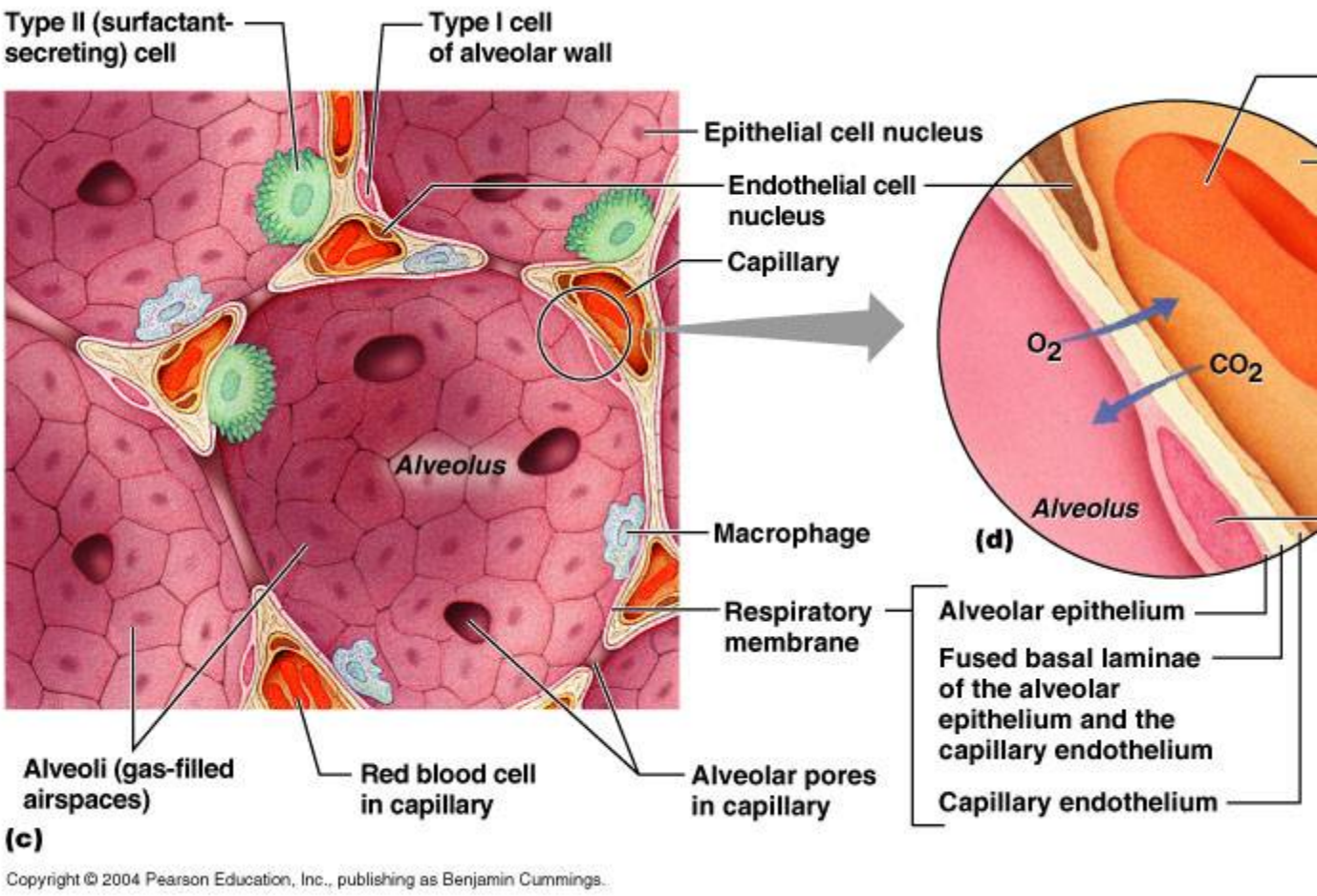
The respiratory zone is defined by the presence of thin-walled air sacs known as alveoli. Sporadic alveoli begin to appear in the respiratory bronchioles. Hence the respiratory bronchioles are the initial structures in the respiratory zone. The last bronchioles without alveoli are known as terminal bronchioles and are at the end of the conducting zone. Respiratory bronchioles lead into alveolar ducts which terminate in clusters of alveoli called alveolar sacs.



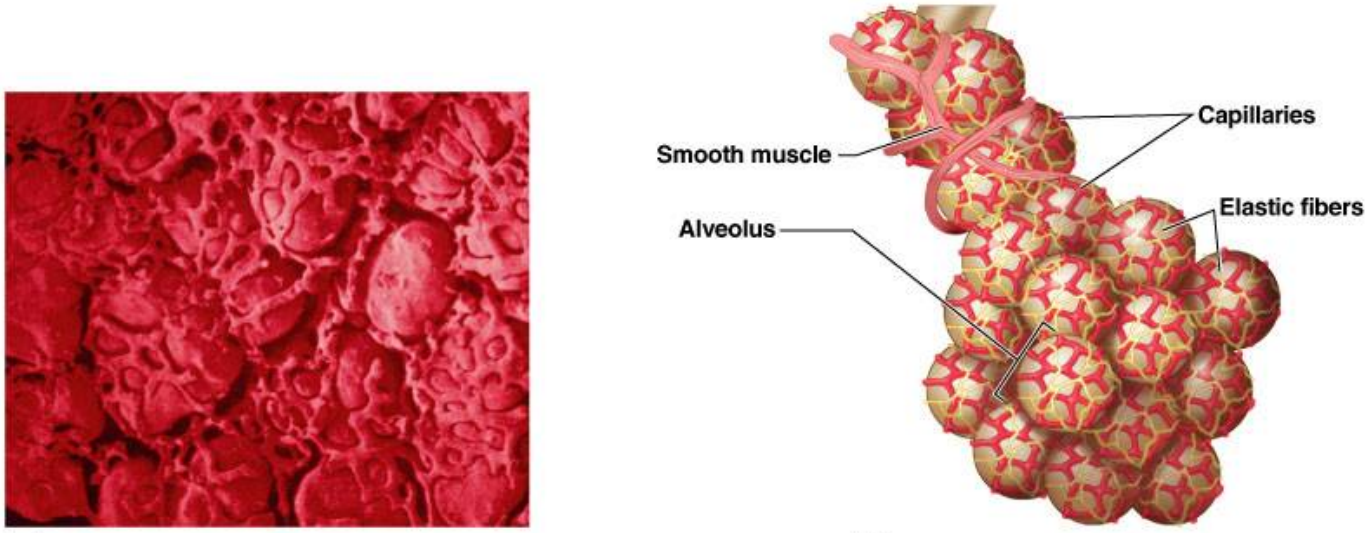




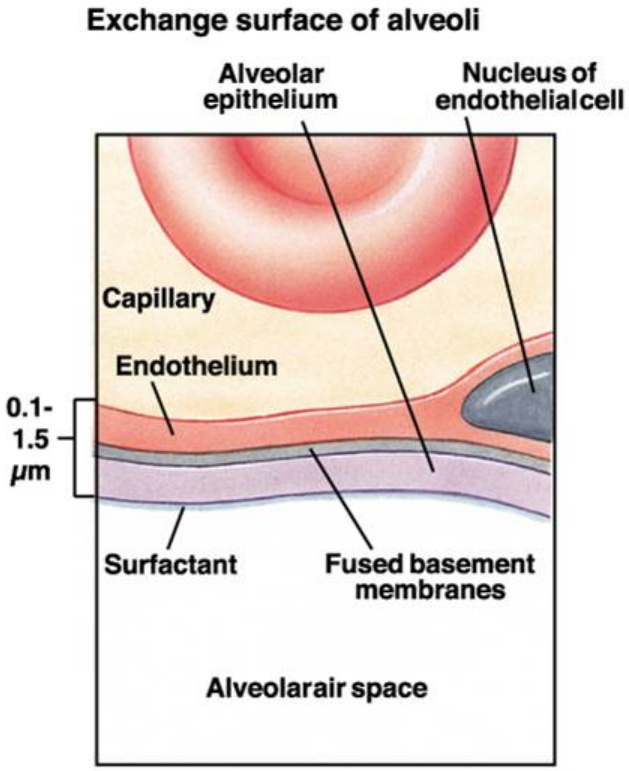
Alveoli are made of simple squamous epithelium consisting of 2 cell types: Type I and Type II alveolar cells.



Type I alveolar cells are extremely thin and occupy most of the alveolar surface area. Their external surfaces are cobwebbed with capillaries. Both the thinness and the "sheet" of capillaries around them make these alveolar cells ideal participants in the diffusion of gases. Also note the elastic fibers surrounding the alveoli. Their importance will become apparent soon.



The basement membranes of the alveolar I cells and the capillary endothelium are actually fused together. Thus the exchange surface (a.k.a. the respiratory membrane) consists of the alveolar I cell membrane, the endothelial cell membrane, and the fused basement membranes.

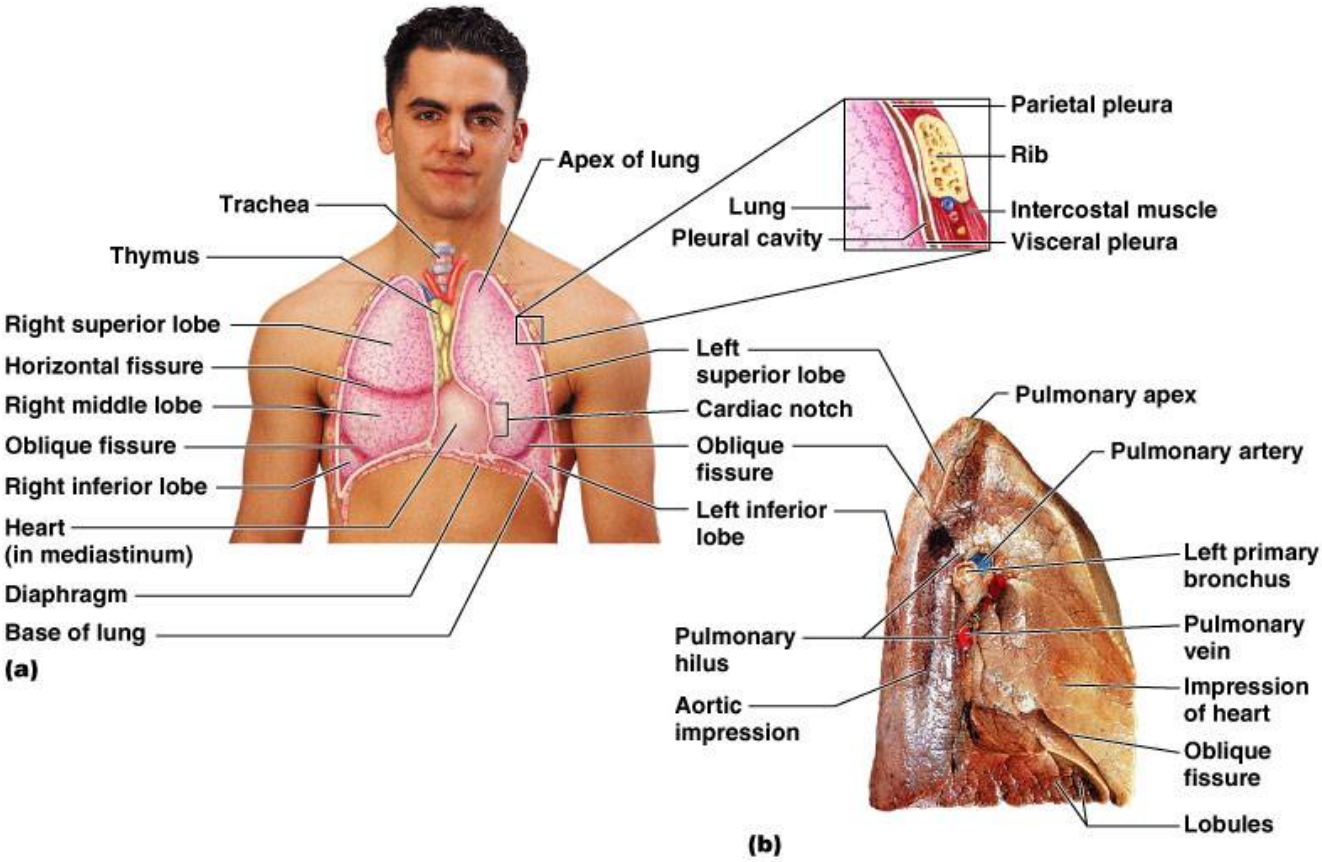


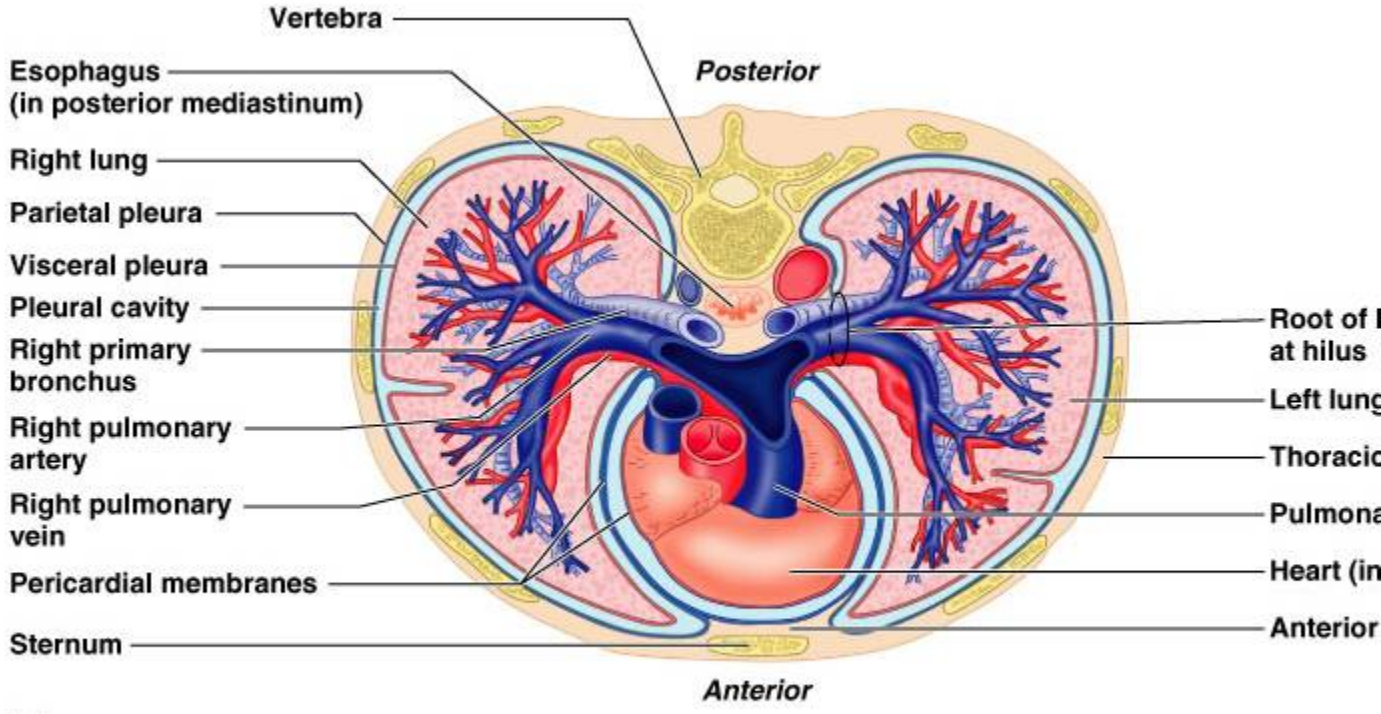
Scattered amongst the Type I alveolar cells are the Type II alveolar cells. Their primary function is the secretion of a chemical known as surfactant (more on it later). Crawling on and about both the Type I and Type II cells are the alveolar macrophages (dust cells) that deal with any foreign matter.

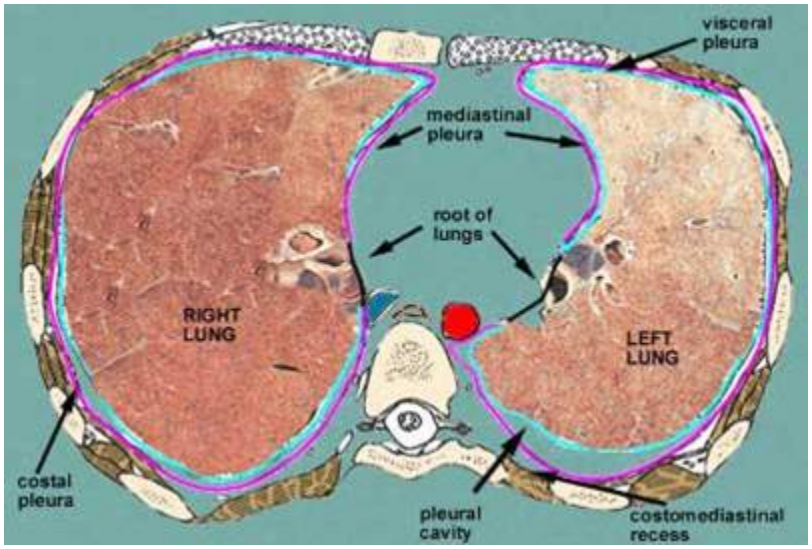
Lung Gross Anatomy

Let's now briefly discuss the gross anatomy of the lungs. The lungs occupy the entire thoracic cavity except for the mediastinum. The anterior, lateral, and posterior surfaces are all adjacent to the ribcage. The apex of each lung is just inferior to the clavicle and each base is superior to the diaphragm. On the medial surface is the hilus where the primary bronchi enter and the blood vessels and nerves enter/exit. The left lung is smaller than the right and has an indentation where the heart normally sits. The left lung is divided into 2 lobes whereas the right is divided into 3. The pulmonary arteries bring deoxygenated blood (for gas exchange) to the lungs while the bronchial arteries bring oxygenated blood (to supply oxygen for the structural tissue). The lungs are drained by the pulmonary veins.

The lungs are associated with a double-layered membrane - the pleurae. The parietal pleura covers the chest wall and the superior diaphragm. The visceral pleura covers the external lung surface. The pleurae produce fluid that fills the slit-like cavity between them. The pleural fluid helps affix the lungs to the chest wall and causes the lungs to move when the thorax does.

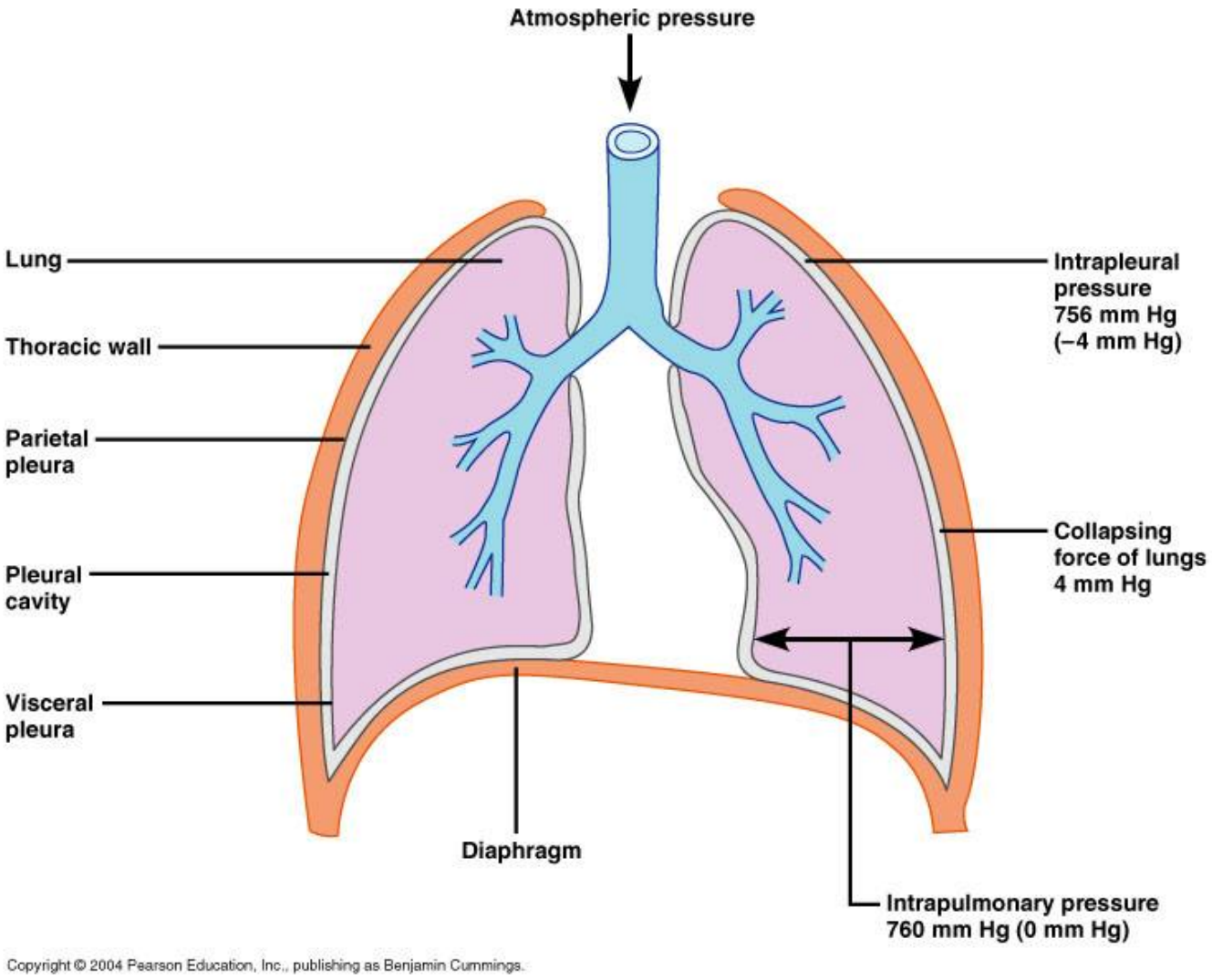






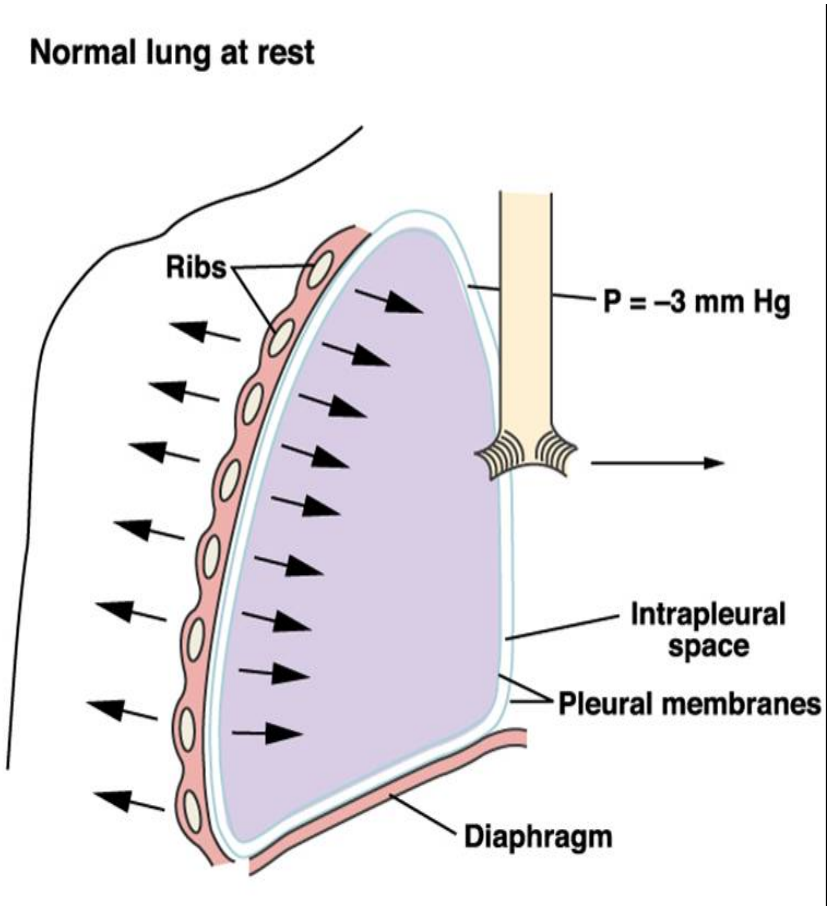
Pressure

Recall that blood flowed due to the pressure gradient created by ventricular systole. Air flow will also be governed by pressure gradients. Let's now discuss some important pressures.

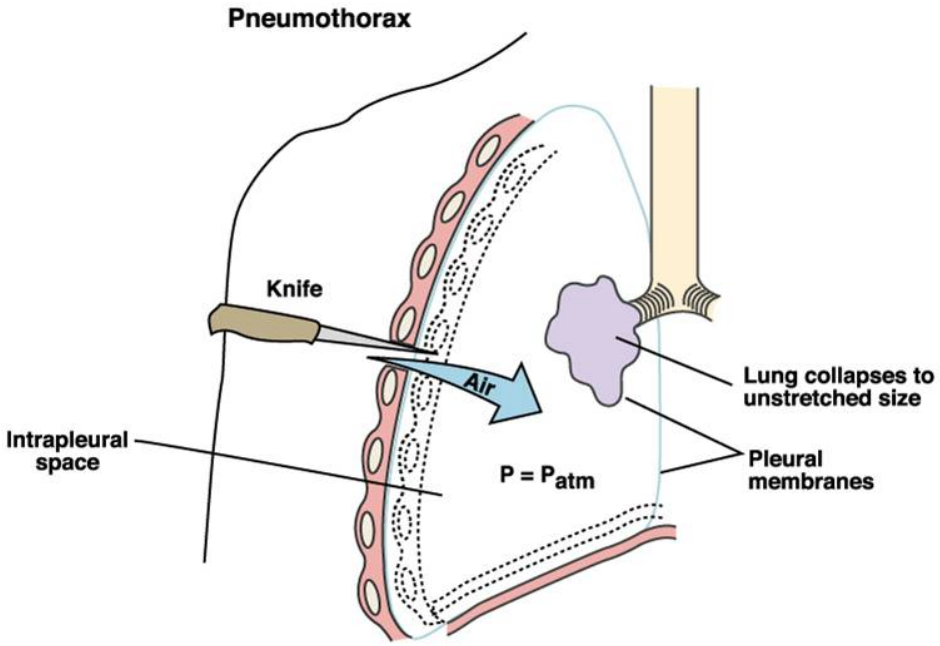


- Atmospheric Pressure (P_{atm}) - pressure exerted by the air surrounding the body. At sea level it's equal to 760mmHg. For our purposes, we'll assume it to be constant and assign it a value of 0mmHg.
- Intrapulmonary Pressure (P_{alv}) - pressure exerted by the air within the alveoli. It rises and falls during inspiration and expiration but it always equalizes with atmospheric pressure.
- Intrapleural Pressure (P_{ip}) - pressure within the pleural cavity. It is <u>always lower</u> than both atmopsheric pressure and intrapulmonary pressure.

Before we discuss the mechanics of inspiration & expiration, let's deal with the importance of the intrapleural pressure. The lungs are an elastic tissue and as such, they have a tendency to recoil - i.e., they want to collapse. The fact that the pressure in the pleural space is lower than the pressure within the alveoli prevents collapse. Because a pressure gradient exists between the alveolar pressure and pleural pressure, air *tries* to flow from the alveoli into the pleural space. It cannot, but by exerting force against the walls of the alveoli, it counteracts the tendency of the lungs to recoil.

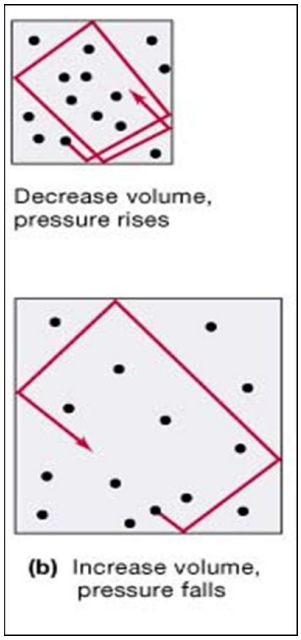


If the intrapleural pressure in the lungs rises (say due to a stab wound that opens the pleural cavity to the atmosphere and allows atmospheric and intrapleural pressure to equalize), the pressure gradient between alveoli and pleural space is abolished and the lungs collapse. This is known as pneumothorax. The difference between the pleural and alveolar pressures is known as transpulmonary pressure and is obviously quite important. Also, realize that because the lungs are each surrounded by their own pleural membrane, collapse of one does not necessarily affect the other.



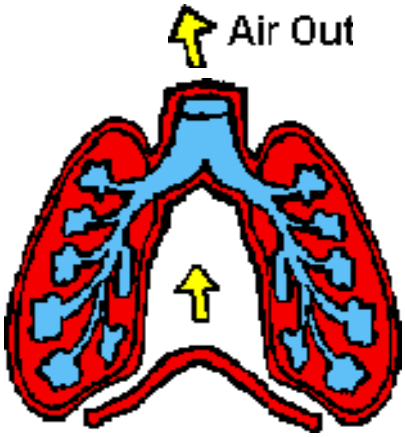
Pressure Volume Relationships

Before we delve any further, let's examine some basic relationships between volume and pressure. Boyle's Law states that pressure varies indirectly with volume. In other words, as volume decreases, pressure increases; and as volume increases, pressure decreases. This is due to the fact that pressure is caused by collisions of gas particles with the walls of the container (i.e., pressure equals force divided by area). If the volume increases, there will be fewer collisions with the container walls and the pressure will drop.

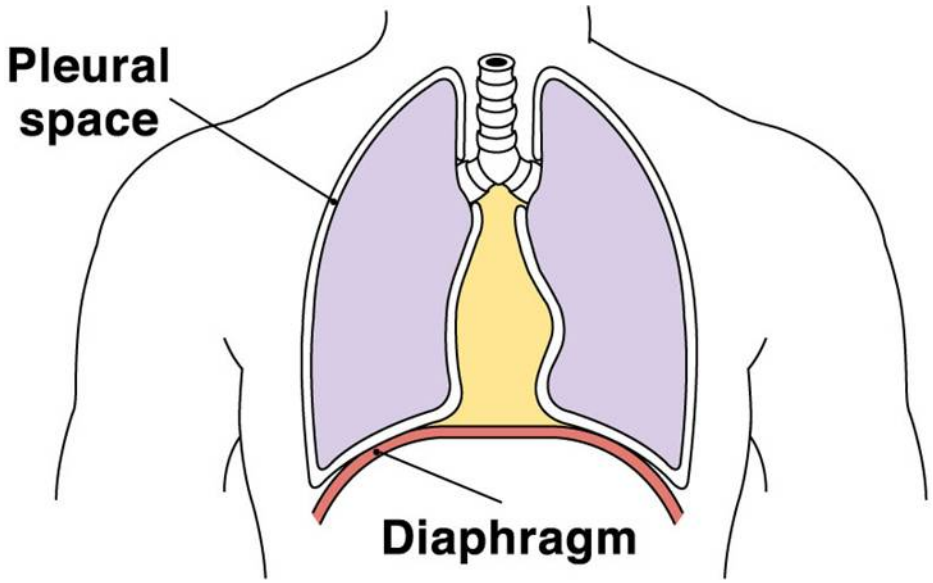


Inspiration and Expiration

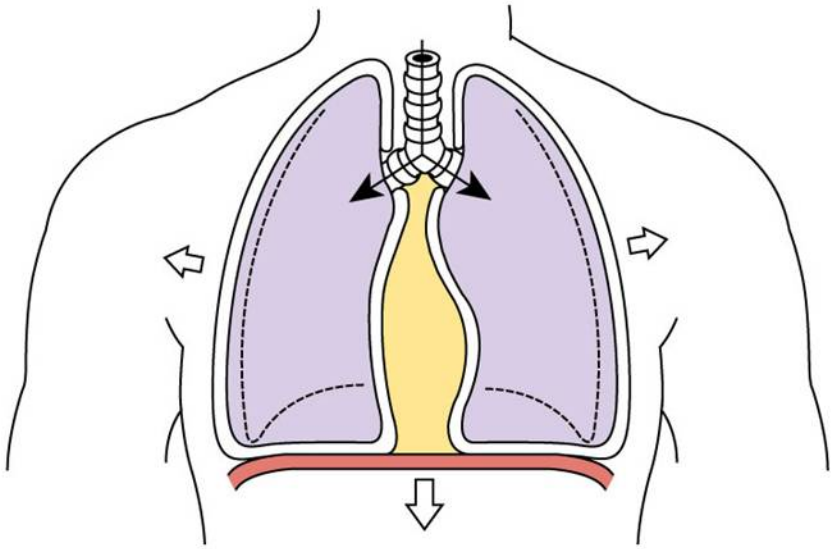
Inspiration begins with the contraction of the diaphragm and the external intercostals.



Compare the diaphragm at rest with the diaphragm contracting.



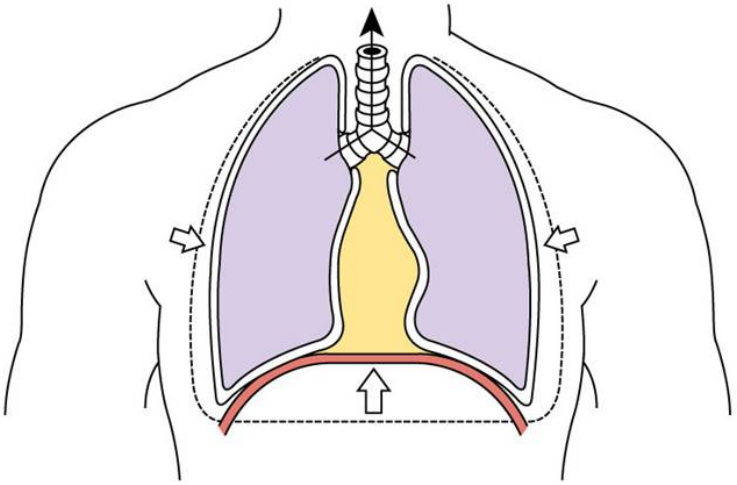
At rest, diaphragm is relaxed



Diaphragm contracts, thoracic volume increases.

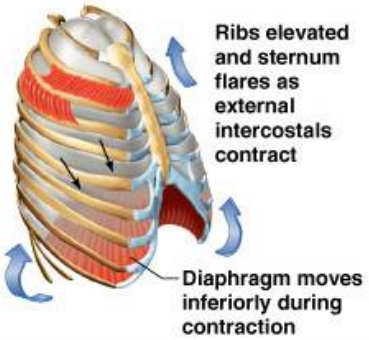
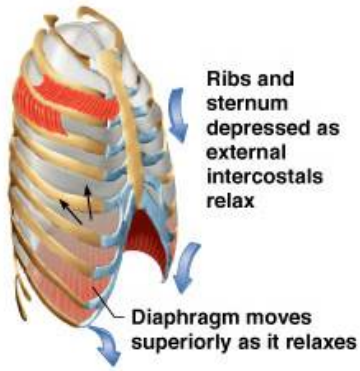
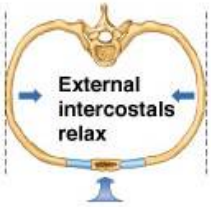
Contraction of the diaphragm causes thoracic volume to increase which causes lung volume to increase. This causes alveolar pressure to decrease. Now intrapulmonary pressure is less than atmospheric pressure and we have a pressure gradient. Air then flows in until the pressures are equalized. Remember - throughout the inspiration intrapleural pressure also changes so that it is always lower than intrapulmonary pressure. During forced inspiration (e.g., during exercise), other muscles (scalenes, sternocleidomastoids, and pectoralis minor) can come into play to create a larger change in thoracic volume and thus a larger pressure gradient.

Unlike normal inspiration which is an active process, normal expiration is a passive process due to the elasticity of the lungs and the relaxation of the inspiratory muscles. As the elastic lungs recoil and the inspiratory muscles relax, the thoracic volume decreases which yields a decrease in lung volume which yields an increase in lung pressure. Now the gradient has been reversed and air flows outward.

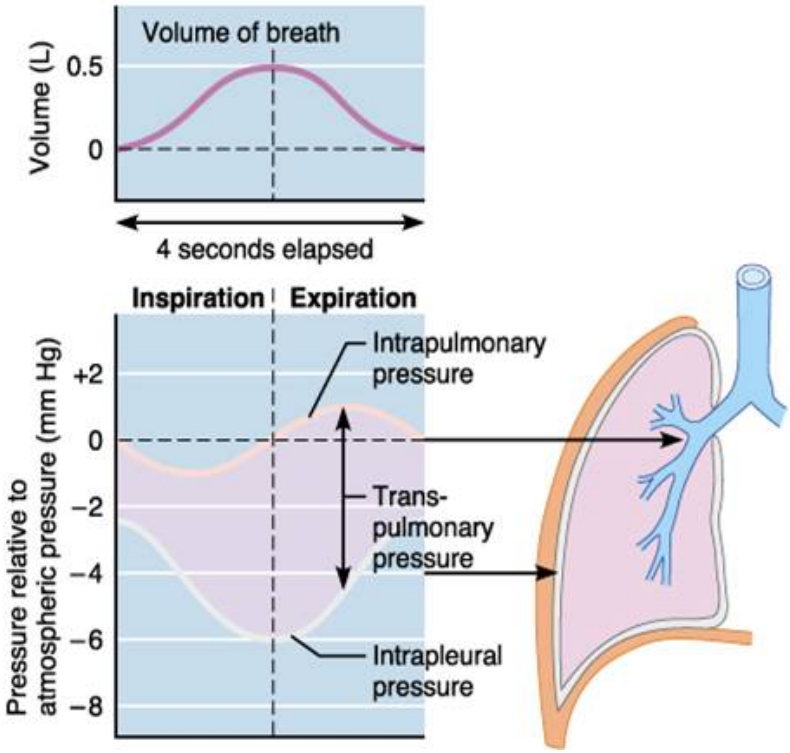


Diaphragm relaxes, thoracic volume decreases.

Forced expiration, on the other hand, is active and involves muscle contraction so as to create a larger pressure gradient. Such muscles include: external and internal obliques, transversus and rectus abdominus, internal intercostals, and latissimus dorsi.

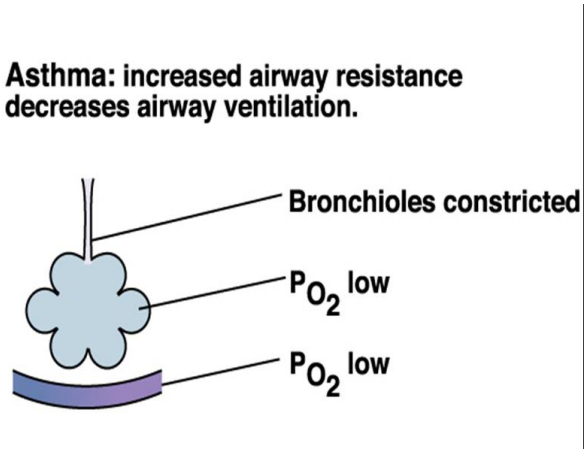
	Sequence of events	Changes in anterior-posterior and superior-inferior dimensions	Changes in lateral dimensions
Inspiration	① Inspiratory muscles contract (diaphragm descends; rib cage rises) ↓ ② Thoracic cavity volume increases ↓ ③ Lungs stretched; intrapulmonary volume increases ↓ ④ Intrapulmonary pressure drops (to –1 mm Hg) ↓ ⑤ Air (gases) flows into lungs down its pressure gradient until intrapulmonary pressure is 0 (equal to atmospheric pressure)		
Expiration	① Inspiratory muscles relax (diaphragm rises; rib cage descends due to recoil of costal cartilages) ↓ ② Thoracic cavity volume decreases ↓ ③ Elastic lungs recoil passively; intrapulmonary volume decreases ↓ ④ Intrapulmonary pressure rises (to +1 mm Hg) ↓ ⑤ Air (gases) flows out of lungs down its pressure gradient until intrapulmonary pressure is 0		

Take a look at this diagram depicting a single respiratory cycle.



Airway Resistance

Let's now switch topics and look at another similarity between air flow and blood flow. Air flow is not only directly proportional to the pressure gradient, it's also indirectly proportional to airway resistance. Airway resistance is due primarily to the diameter of the conducting tubes. For example, increased parasympathetic activity would cause a decrease in bronchiole diameter and thus an increase in airway resistance. Increased sympathetic activity would have the opposite effect. Other chemicals also exert effects; histamine can cause bronchoconstriction and thus greatly increase resistance. During asthma, bronchioles constrict - yielding a decrease in air flow.



Local accumulations of mucus, infectious materials or solid tumors are also sources of airway resistance.

Surfactant and Compliance

Let's return to something we briefly mentioned earlier: the production of surfactant by type II alveolar cells. Water molecules have a fantastic attraction for other water molecules. Water lines the surface of our alveoli. Because of the tendency for water molecules to hydrogen bond with and interact with other water molecules, there is a tendency for alveoli to collapse. Luckily, our type II cells produce surfactant. Surfactant is a detergent-like molecule that will interfere with the cohesion of water. This lowers the surface tension within the alveoli and helps prevent their collapse. Surfactant production does not normally occur until 34wks of gestation. Thus a premature baby is at risk of neonatal respiratory distress syndrome and will have much difficulty expanding her immature lungs.
Surfactant acts to increase the compliance of the lungs - the ease with which they expand. The higher the lung compliance, the more efficient the ventilation. Another factor that affects compliance is fibrosis. If inelastic scar tissue forms within the lungs, their compliance will decrease.

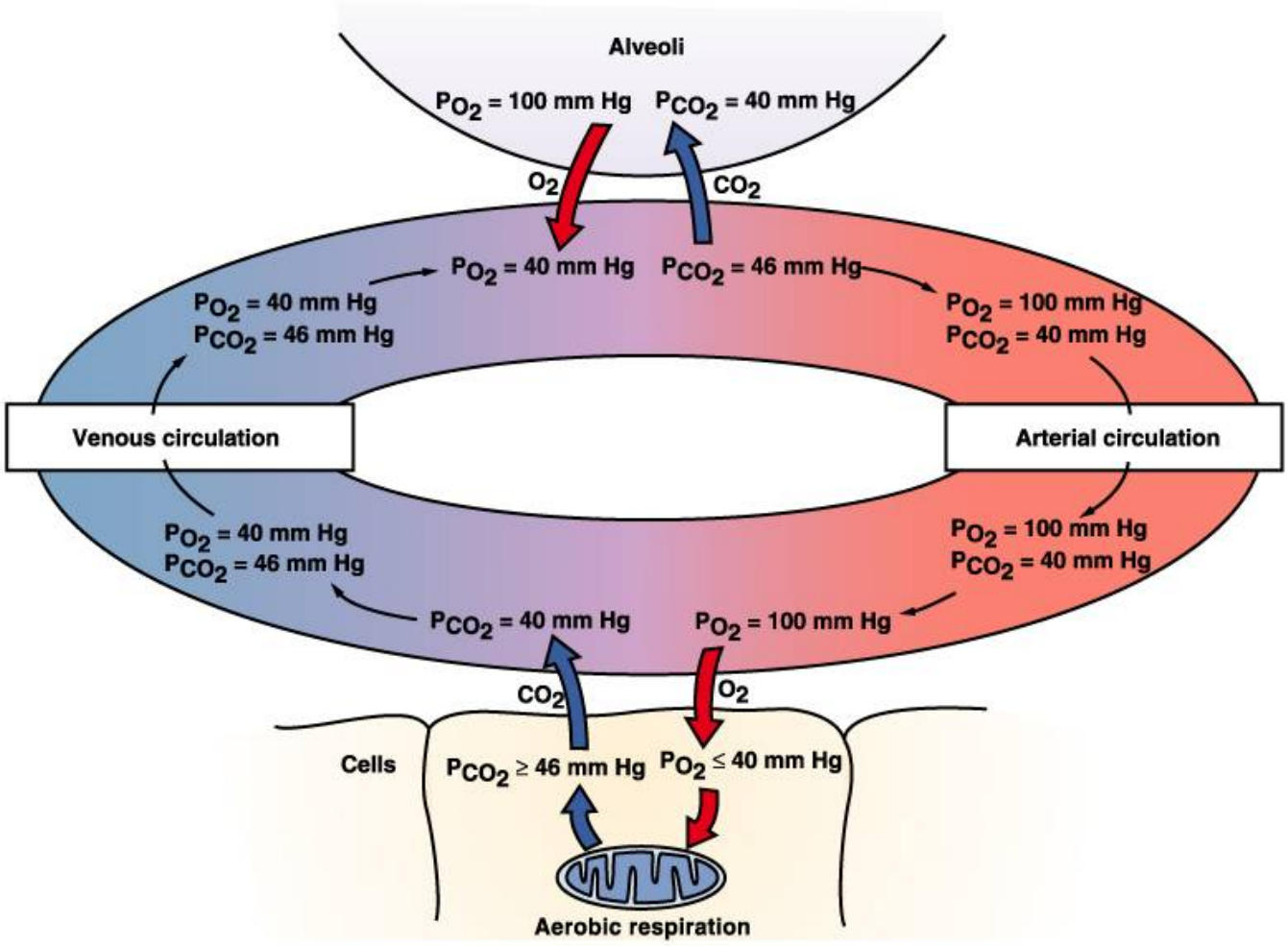
Gas Exchange

Now let's discuss the actual exchange of gases within the lungs. Factors that can influence the diffusion of O2 and CO2 across the respiratory membrane include:

- Partial pressures of O2 and CO2
- Thickness & surface area of the respiratory membrane
- Solubility of O2 and CO2
- Temperature

Partial pressure simply refers to the pressure of one specific gas in a mixture of gases (such as atmospheric air). O2 and CO2 move down their partial pressure gradients during gas exchange. The Po2 of systemic venous blood and pulmonary arterial blood is 40mmHg while the Po2 of alveolar air is an almost constant 100mmHg. This means that O2 will flow from the alveolus across the respiratory membrane and down its partial pressure gradient into the pulmonary capillaries. The Pco2 of systemic venous blood and pulmonary arterial blood is 46mmHg while the Pco2 of alveolar air is 40mmHg. This means that CO2 will flow across the respiratory membrane and down its partial pressure gradient from the pulmonary capillaries into the alveoli. Now let's examine exchange in systemic tissues. Pulmonary venous and systemic arterial blood has a Po2 of 100mmHg while the intracellular Po2 is typically 40mmHg at most. (Intracellular Po2 is kept low because O2 is continually being used in the ATP-generating processes of cellular respiration.) O2 will thus leave the capillaries and diffuse into the tissues. Pulmonary venous and systemic arterial blood has a Pco2 of 40mmHg and a Pco2 of at least 46mmHg. Thus CO2 will leave the tissues and enter the capillaries.

Take a look at this diagram depicting gas exchange.

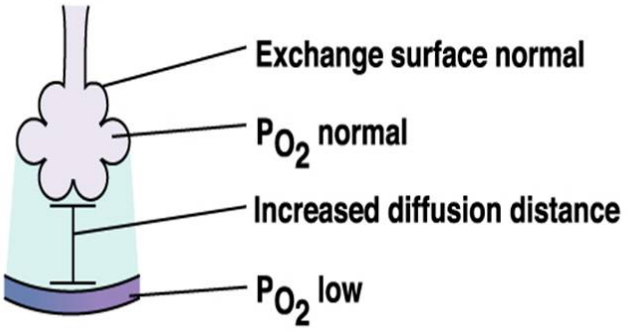


Even though the partial pressure gradient for CO2 is not as large as the gradient for O2, relatively equal amounts of the gases are exchanged because CO2 is much more soluble in plasma and alveolar fluid than O2.

An increase in temperature increases the kinetic energy and thus the movement of gases within the alveoli. This will result in an increased rate of gas exchange.

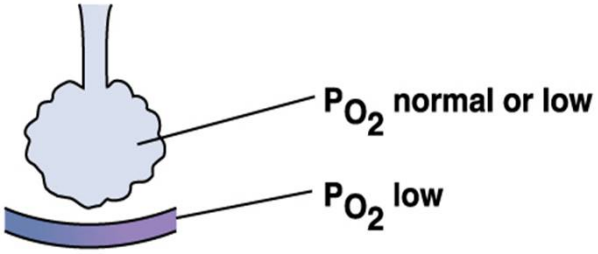
In healthy lungs, the respiratory membrane (alveolar membrane + endothelial membrane + fused basement membranes) is 0.5-1.0um thick and gases diffuse through it with ease. In pneumonia, the thickness of the RM increases due to mucus build-up. This decreases the efficiency of the diffusion. In pulmonary edema, fluid builds up between the alveolar membrane and endothelial membrane. This would also decrease gas exchange.

Pulmonary edema: fluid in interstitial space increases diffusion distance. Arterial P_{CO_2} may be normal due to higher CO_2 solubility.



The surface area of healthy lungs is enormous - 300 million alveoli! In emphysema, the surface area decreases, which of course impacts gas exchange.

Emphysema: destruction of alveoli means less surface area for gas exchange.



Oxygen Transport

Let's now examine the means by which O2 and CO2 are transported within the blood. 1.5% of transported O2 is dissolved within the plasma. The other 98.5% is bound to the hemoglobin in the RBCs. Each Hb can bind up to 4 molecules of O2 and this binding is quite reversible. Hb containing bound O2 is oxyhemoglobin while Hb w/o bound O2 is deoxyhemoglobin.

Look at this reversible equation that shows the loading and unloading of oxygen by hemoglobin:
$HHb + O_2 <- -> HbO_2 + H^+$

In the lungs, this reaction would proceed as written from left to right as hemoglobin picks up oxygen. It proceeds in this direction because the concentration of free oxygen is so high. In the tissues, it would proceed in the opposite direction as hemoglobin unloads oxygen. It proceeds in this direction in the tissues, because the concentration of free oxygen is low.

When inadequate amounts of oxygen reach the tissue it is known as hypoxia. Without oxygen, cells are unable to perform cellular respiration and produce ATP. Without ATP, cell death is inevitable.

Carbon monoxide has a greater affinity for Hb than O2 does. *Why is this so bad?*

O2 binding is cooperative. The binding of the 1st O2 molecule facilitates the binding of the 2nd which facilitates the binding of the 3rd which facilitates the binding of the 4th. In other words, as the loading of O2 proceeds, the affinity of Hb for O2 increases. If the Hb has 4 O2 molecules bound to it, it is saturated. If it has less than 4, it is unsaturated.

Hb is almost completely saturated at a Po2 of 70mmHg. At the tissue Po2 of 40mmHg, Hb is still 75% saturated. This means that on average, each Hb molecule in venous blood has 3 molecules of O2 bound to it. This is the so-called venous reserve and is particularly valuable during situations when O2 demand increases (e.g., aerobic exercise).

There are several factors that affect the binding of O2 to Hb. As cellular metabolism precedes, CO2, heat, and acids are all generated. All of these indicate a need for O2. They all cause the affinity of Hb for O2 to decrease - thus making Hb more likely to give up O2 when it arrives at the tissues.

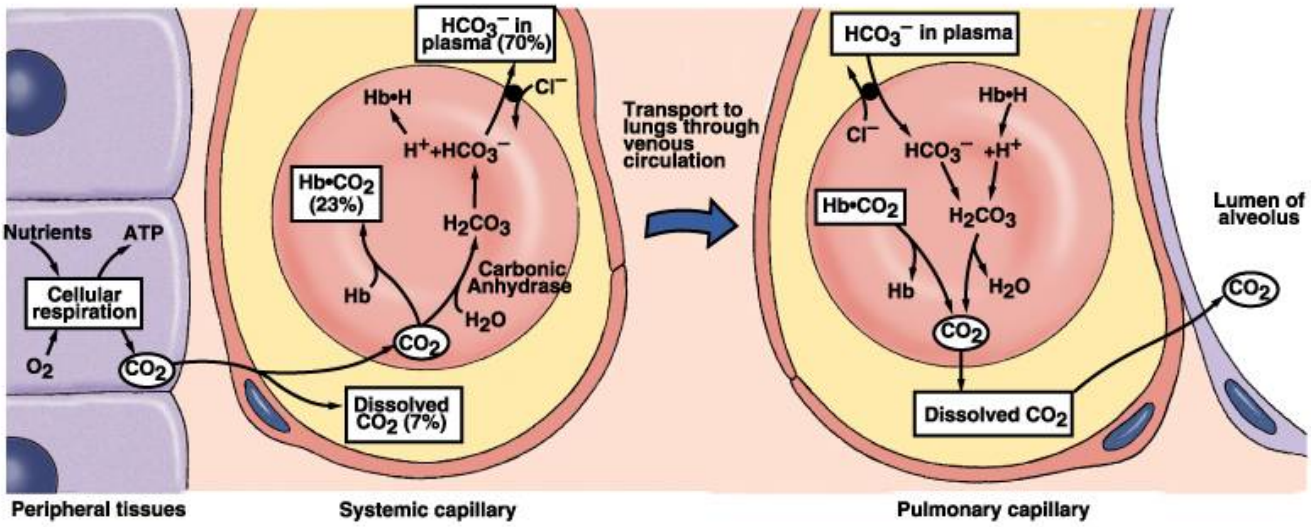
Carbon Dioxide Transport

Now let's turn our attention to CO2 transport. 7% is simply dissolved in plasma. 23% is bound to certain amino acids in hemoglobin (forming carbaminohemoglobin). 70% is transported as HCO_3^- , the bicarbonate ion.

Let's take a closer look. The CO2 made within tissue cells will diffuse into a capillary. 7% will dissolve in the plasma. The other 93% will diffuse into the RBC. In the RBC, 23% binds to Hb.
$CO_2 + Hb < -- > HbCO_2$

The other 70% reacts with water to form carbonic acid which will dissociate into the bicarbonate ion and a hydrogen ion: $CO_2 + H_2 <--> H_2CO_3 <--> HCO_3^- + H^+$.
This reaction occurs in the RBCs because the enzyme that catalyzes it (carbonic anhydrase) is in abundance there. Once generated, the bicarbonate ion exits the RBC and enters the plasma. In order to maintain the balance of charge within the RBC, a chloride ion enters the RBC from the plasma. This is known as the chloride shift.

In the pulmonary capillaries, the above processes reverse themselves and CO2 ultimately diffuses into the alveoli.



Carbon Dioxide and Plasma pH

Look again at the above equation describing how carbon dioxide is converted to bicarbonate. It should logically follow that if more CO2 is present in the blood, more HCO3- and H+ will be produced. Recall that we measure the acidity of a solution by determining the concentration of H+ in that solution.

Thus, we can assume that the blood level of CO2 will have an effect on the blood's pH. If breathing becomes shallow and slow, CO2 will accumulate in the blood. This will result in increased production of carbonic acid and then increased production of H+. Thus an increase in blood CO2 will yield an increase in blood acidity. This drop in plasma pH due to a rise in plasma CO2 is known as respiratory acidosis.

If hyperventilation occurs, CO2 will be eliminated from the body faster than it's being produced. This will decrease blood CO2 and thus decrease blood carbonic acid and decrease blood H+. This rise in plasma pH due to a decrease in plasma CO2 is known as respiratory alkalosis.

Obviously, changes in respiratory rate and depth can result in changes in plasma pH. It might be surprising to realize that the respiratory system can help correct and regulate the plasma pH. This occurs when there is a change in plasma pH that is not initially caused by the respiratory system itself. Examples of such situations are grouped into 2 categories: metabolic acidosis and metabolic alkalosis.

In metabolic acidosis blood pH and blood HCO3- are low. Typical causes include ingestion of too much alcohol (alcohol is metabolized to acetic acid), excessive loss of HCO3- in diarrhea, accumulation of excess lactic acid during exercise or shock, and the production of acidic ketone bodies as a result of starvation or diabetic crisis. In response to metabolic acidosis, the respiratory rate and depth will rise as the body attempts to "blow off" CO2. Ridding the body of CO2 will help raise the plasma pH.

In metabolic alkalosis blood pH and HCO3- are elevated. Typical causes include excess vomiting, excessive ingestion of antacids, or constipation. In response to metabolic alkalosis, respiratory rate and depth will be slow and shallow. This will enhance retention of CO2 and production of H+ and thus will lower pH.

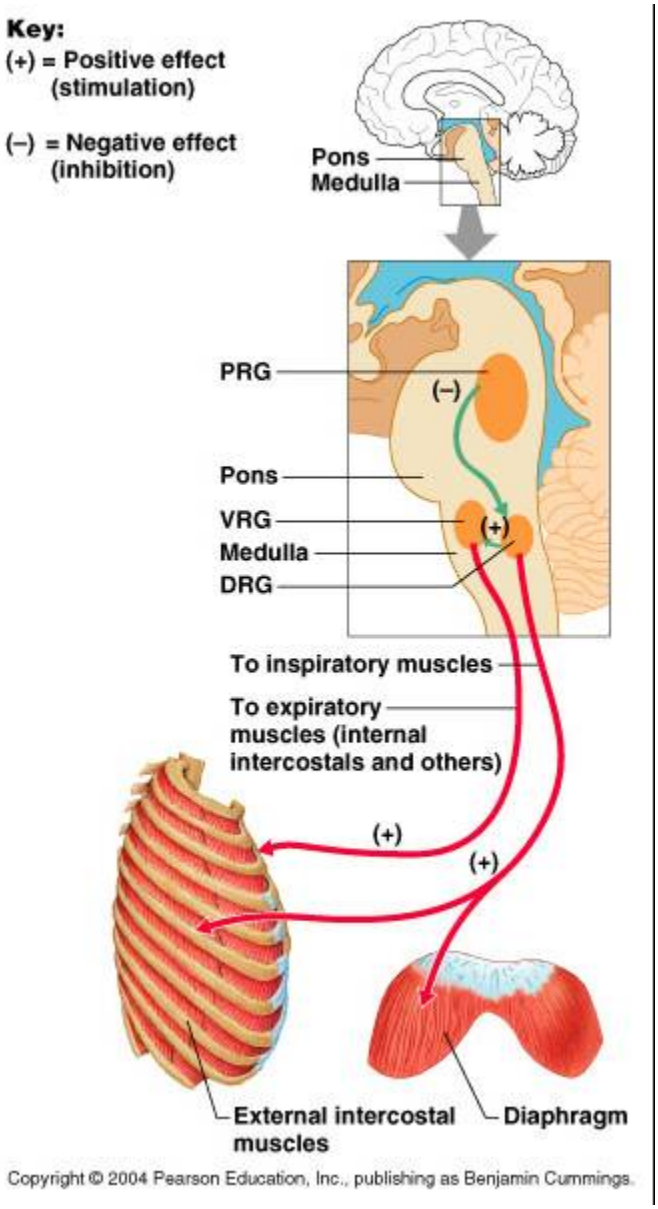
Control of Respiration

We now need to move to how we control respiratory rate. In the medulla oblongata, there are 2 main respiratory centers - the dorsal respiratory group (DRG) and the ventral respiratory group (VRG).

In many ways, normal respiration can be thought of as an autorhythmic process. The DRG contains neurons that innervate the diaphragm and external intercostals. They are active during quiet and forced inspiration. The VRG is only involved in forced expiration (remember, quiet expiration is a passive process) AND forced inspiration. Its neurons innervate the muscles of forced expiration, e.g., internal intercostals, and the muscles of forced inspiration, e.g., the scalenes. There is reciprocal inhibition between the inspiratory and expiratory neurons - so the 2 process cannot occur at the same time.

During quiet inspiration the DRG is active. During forced inspiration, the level of DRG activity increases until it activates the inspiratory portion of the VRG. At the end of active inspiration, the expiratory portion of the VRG becomes active.

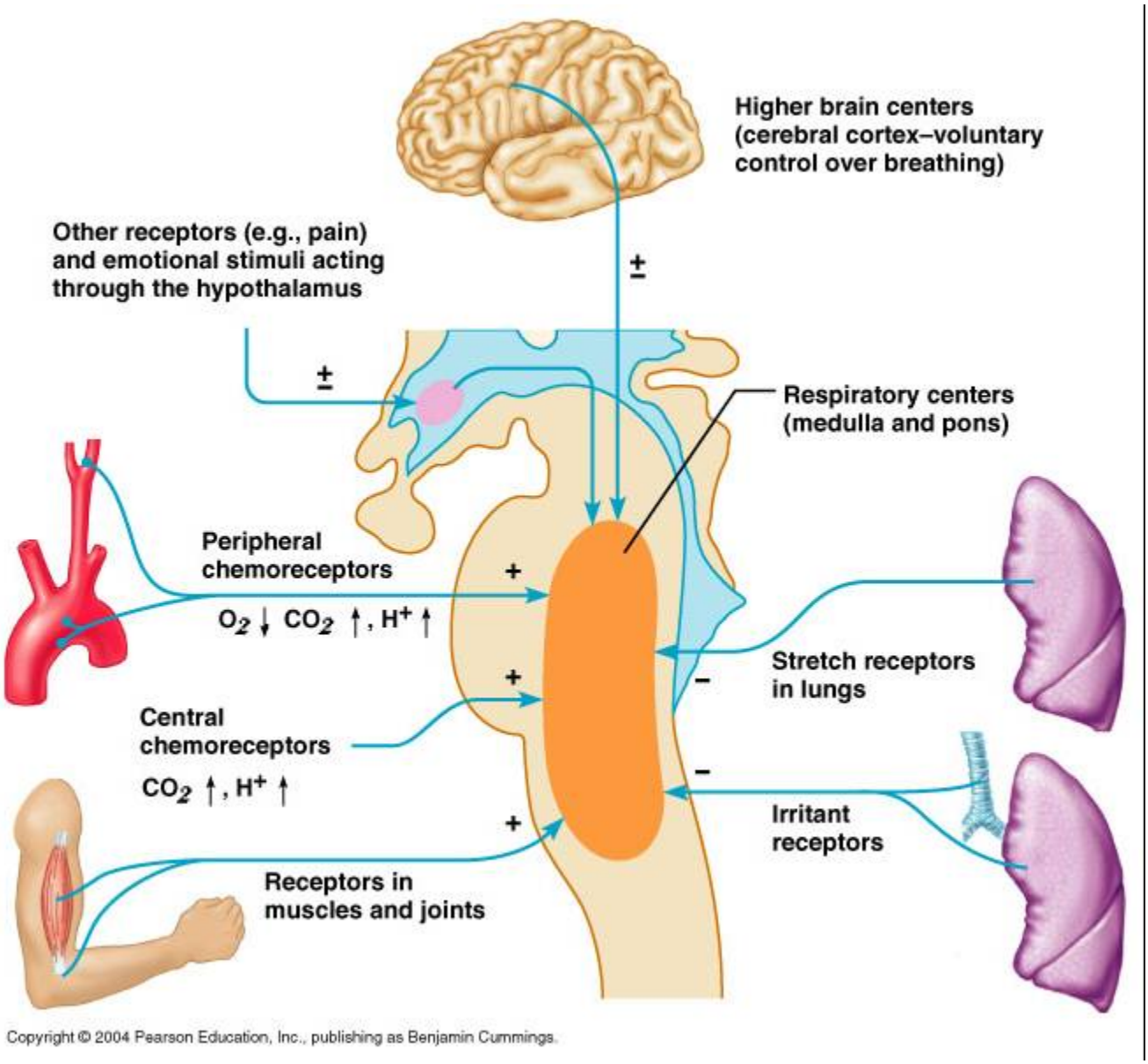
Note that the diaphragm is innervated by the phrenic nerve whereas the internal intercostals are innervated by the intercostal nerves.



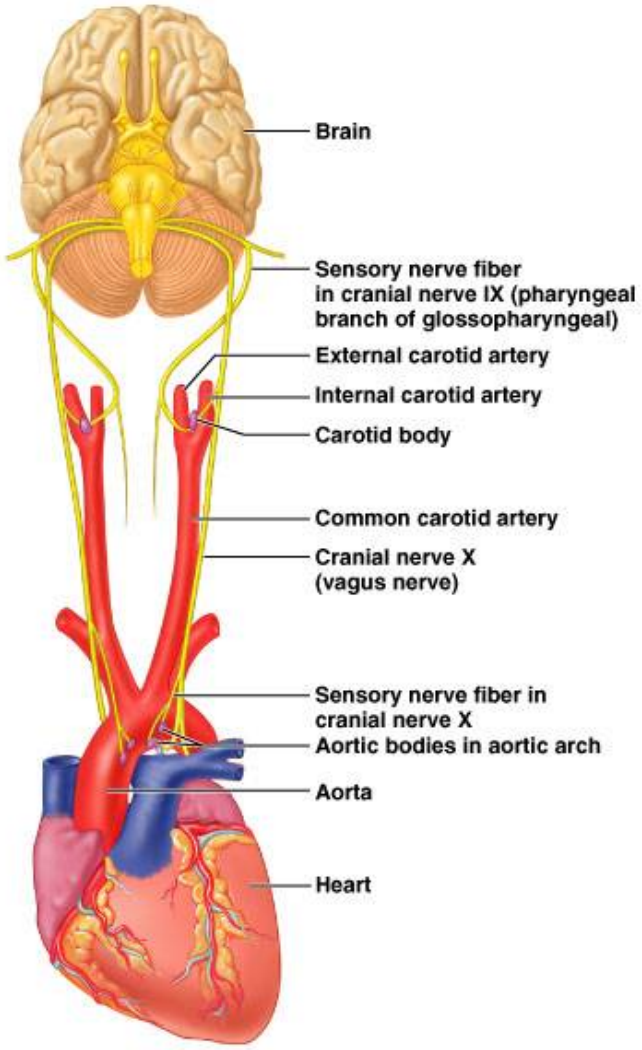
Let's now look at some other factors that can alter respiratory rates:

- Pain and emotions
- Irritating physical or chemical stimuli in the respiratory tract
- Overstretch of the lungs -- activates lung stretch receptors which act on brainstem centers to cause exhalation and prevent inhalation (this is known as the Hering-Breur reflex).
- BP changes as detected by carotid and aortic arch baroreceptors. A decrease in BP can result in an increase in respiration rate/depth

- Changes in plasma and CSF Pco2, Po2, and pH

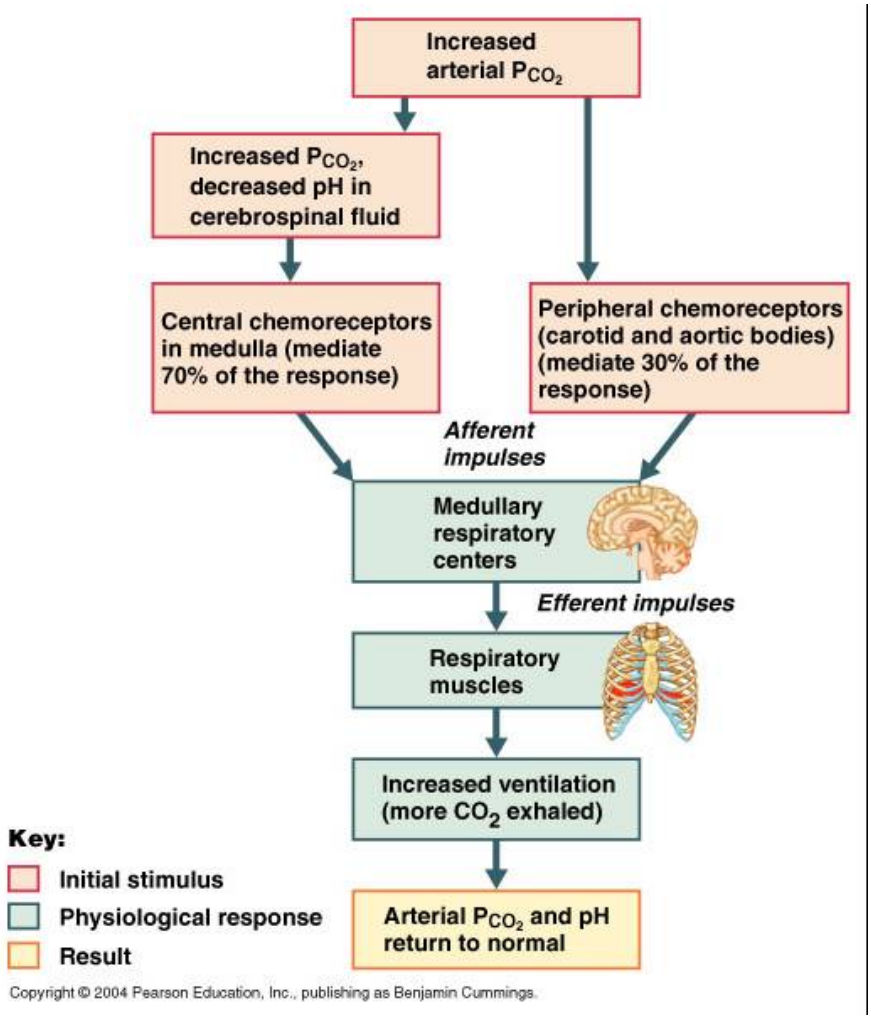


The most important of the above factors are the changes involving oxygen, carbon dioxide and hydrogen ions. There are chemoreceptors dedicated to monitoring Po2, Pco2, and pH. Peripheral chemoreceptors are found primarily in the carotid sinuses and the aortic arch. Central chemoreceptors are found on the medulla oblongata. The peripheral chemoreceptors monitor plasma Pco2, pH, and Po2. Central chemoreceptors primarily monitor pH of cerebrospinal fluid.



The most important receptors are the central chemoreceptors. pH changes can result in protein denaturation. If CSF pH goes too far from normal, brain proteins can be damaged and serious problems can occur.

An increase in plasma Pco2 will directly and indirectly activate peripheral chemoreceptors. It'll directly activate those that are sensitive to Pco2. Recall the carbonic anhydrase equation and notice that an increase in Pco2 will yield an increase in plasma [H+], i.e., a decrease in pH. Thus an increase in Pco2 will be detected by plasma pH receptors due to the change in [H+]. An increase in plasma Pco2 will also cause CSF Pco2 to increase. Since CSF contains carbonic anhydrase, the increase in CSF Pco2 will cause a decrease in CSF pH. This will be detected by the medullary chemoreceptors. The net response to the high CO2 will be an increase in respiratory rate and depth.



O2 & CO2 in Living Systems

- O2 & CO2 are transported in opposite directions in living systems & these processes have some commonalities:
- 1. both are transferred passively across body surfaces via diffusion
- 2. physical laws of gases pertain to both
- 3. for maximum rate of gas transfer of both, respiratory surface areas needs to be as large as possible & diffusion distances as small as possible
- while O2 needed & CO2 produces function as a factor of the animal's mass, rate of gas transfer is related to surface area = surface area of sphere increases as square of its diameter, volume increases as the cube (e.g. for very small animals such as protozoans, diffusion alone is sufficient however as animal size increases diffusion distances increase and ratio of surface area to volume drops

- large surface-area-to-volume ratios are maintained in larger animals by elaboration of special tissues for gas exchange
- some animals, whole body surface participates in gas transfer but large, active animals have specialized respiratory surface (respiratory epithelium) made up of thin layer of cells (.5 – 15 microns) – respiratory epithelium constitutes a major portion of total body surface area
- stagnation of gas-exchange (which could occur in cases of diffusion alone), avoided in most animals by ventilation (propels air or water over respiratory surface
- larger animals – relationship between CVS & RS transfer O2 & CO2 via blood flowing between respiratory epithelium & tissues – blood through extensive capillary network in both regions
- Graham's Law = rate of diffusion of substance down given gradient is inversely proportional to square root of its molecular weight (or density) – since O2 & CO2 are similar size, they diffuse at similar rates in air; also utilized or produced ~ same rate = the transfer system that meets the O2 needs will also ensure adequate rates of CO2 removal!
- Basic Components of gas-transfer system in many animals:
- 1. breathing movements = assure continual supply of fluid (air or water) to respiratory surface (e.g. lungs or gills)
- 2. diffusion of O2 & CO2 across respiratory epithelium
- 3. bulk transport of gases via blood
- 4. Diffusion of O2 & CO2 across cap. walls between blood & mitochondria of cells
- matching of capacities in this chain of events is called = symmorphosis
- interrelationship between rate of flow/supply, demands on body, number of mitochondria etc. limits are established by physical constraints and physiological function

O2 & CO2 in Blood

- Respiratory Pigments – O2 diffuses across resp. epithelium and binds to respiratory pigment (many different ones found across animal kingdom) & best known is hemoglobin (gives human blood red color) – NB because this binding greatly increases carrying capacity of blood for molecular O2 – in humans the capacity is 70% more than it would be without such binding
- Respiratory pigments = complexes of proteins & metal ions each with characteristic color (Hb = bright red when O2 loaded and maroon-red when deoxygenated) – Hb in most animals is contained in RBCs (erythrocytes) = contains 4-iron-containing porphyrin prosthetic groups (heme) associated with goblin (tetrameric protein) = its configuration (structure) is directly related to its ability to perform its function - Hb with O2 bound = oxyhemoglobin; when O2 absent = deoxyhemoglobin (normally binding of O2 to iron in heme doesn't oxidize Fe as it would when binding free Fe however it can occur under some conditions producing methemoglobin which does not bind O2 = non-functional
- Affinity of Hb for CO is > 200x than its affinity for O2 = CO will displace O2 & saturate Hb even at very low partial pressures = causing marked reduction in O2 transport – Hb saturated with CO = carboxyhemoglobin

O2 Transport

- Ea. Hb molecule can combine with 4 O2 molecules, one per heme – the extent of binding depends on partial pressure of O2 – when all four sites are occupied by O2 = 100% saturated & O2 content of blood is equal to its oxygen capacity
- Because O2 capacity of blood increases in proportion to Hb concentration, O2 content is expressed as % of O2 capacity i.e. <u>percent saturation</u>
- As Hb molecule is oxygenated, it goes through a conformational change from a tense (T) state to a relaxed (R) state & it has a higher affinity for ligands when in the T (deoxygenated) state
- NB property of respiratory pigments is their ability to combine reversibly with O2 over a range of partial pressures normally encountered in an animals
- Changes in chemical & physical factors in blood cause Hb to favor O2 binding at resp. epithelium & O2 release in tissues – Hb/O2 affinity is reduced by:
- 1. elevated temperature
- 2. binding of organic phosphate ligands (e.g. ATP) by Hb
- 3. decrease in pH (i.e. increase in H+ concentration)
- 4. increase in CO2
- <u>Bohr effect</u> = reduction in O2 affinity of Hb caused by decrease in pH
- When CO2 enters blood at tissues, it facilitates unloading of O2 from Hb; when CO2 leaves blood at respiratory surface, it facilitates uptake of O2 by blood
- NB point = while Hb of most animals is contained within RBCs, the values of blood parameters usually refer to condition in the plasma (not the RBC) e.g. normal Ph of mammalian arterial blood plasma at 37 degrees C is 7.4 (pH inside RBC is lower ~ 7.2)

- ## CO2 Transport

- $CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3$ (CO_2 rx with H_2O forming carbonic acid & it dissociates into bicarbonate and carbonate i.e. $HCO_3 = H^+ + CO_3$) & $H_2O = H^+ + OH^-$ $CO_2 + OH^- = HCO_3$ (CO_2 rx with hydroxyl to form bicarbonate) - CO_2, HCO_3 & CO_3 proportions depend on temp, pH & ionic strength
- In mammalian blood at pH 7.4, ration of CO_2 to H_2CO_3 is ~ 1000:1; ration of CO_2 to bicarbonate is ~ 1:20 = bicarbonate is predominate form of CO_2 in blood at normal pH
- Sum of all forms of CO_2 in blood (CO_2, H_2CO_3, HCO_3, CO_3) is total CO_2 content of blood NB = as partial pressure of CO_2 increases, the major change is in bicarbonate content of blood & formation of bicarbonate is pH-dependent
- RBCs constitute < 50% of blood volume (i.e. plasma volume is >RBC volume) & bicarb concentration is higher in plasma than in RBCs = most of bicarb in blood is in plasma

- Transfer of Gases to & from Blood summary:
- 1. CO_2 produced in tissues rapidly forms bicarbonate (HCO_3) in RBC in a hydration rx catalyzed by carbonic anhydrase (special note: carbonic anhydrase is absent from plasma therefore interconvesion of CO_2 & HCO_3 is slow in plasma)
- 2. HCO_3 leaves RBC in exchange for Cl^-, & excess H^+ are bound by deoxygenated Hb
- reverse process in lungs:
- 1. O_2 entering RBC displaces H^+ from Hb & CO_2 enters plasma (carbonic anhydrase in membrane of lung endothelial cells converts some of plasma bicarbonate to CO_2)
- 2. movement of CO_2 across respiratory surface is augmented by diffusion of bicarb & its conversion back to CO_2 at outer surface = facilitated diffusion of CO_2 (carbonic anydrase is embedded in endothelial cell membranes with its active site accessible to plasma so HCO_3 can be converted rapidly to CO_2 as blood perfuses lung caps. – oxygenation of Hb acidifies RBCs in lung caps, facilitating conversion of HCO_3 to CO_2 which then diffuses into plasma & across lung epithelium
- Excretion of CO_2 is limited by rate of bicarbonate-chloride exchange across RBC membrane.

- Regulation of Body pH
- 1. <u>H^+ Production & Excretion & H^+ Distribution</u>:
- H^+ produced through metabolism of ingested foods & excreted on regular basis i.e. largest pool of H^+ & greatest flux in H^+ traffic is associated with metabolic production of CO_2 (which at pH of body rx with H_2O to form H^+ + HCO_3) - at respiratory surface, HCO_3 is converted to CO_2 which is excreted
- (if CO_2 excretion < production & CO_2 accumulates = body will acidify; if the reverse, body pH will rise
- ingestion of meat usually results in net intake of acid, whereas ingestion of plant food often results in net intake of base
- if lung ventilation is reduced so CO_2 excretion drops below CO_2 production, body CO_2 levels rise and pH will fall = decrease in body pH = <u>respiratory acidosis</u>; reverse effect = rise in pH due to increased lung ventilation = <u>respiratory alkalosis</u> (using "respiratory" to differentiate changes otherwise related to metabolism of kidney function – e.g. anaerobic metabolism results in net acid production which reduces body pH = these changes = <u>metabolic acidosis</u> vs. vomiting = chloride loss & bicarb increase with increase in pH = <u>metabolic alkalosis</u>)
- body fluids are electroneutral = sum of anions = sum of cations – normal electrolyte status of human plasma is depicted in fig. 13-15 p. 541 (sum of bicarb, phosphates & protein anions = <u>buffer base</u>
- most cell membranes much more perm to CO_2 than H^+ or bicarb & cell membrane perm to H^+ > perm to K^+, Cl^- & Hco_3 (notable exception is RBC which is very perm to HCO_3 and Cl^- but not very perm to H^+)
- proton-exchange & anion exchange mechanisms in plasma membrane ply NB role in adjusting intracellular pH

- 2. Factors influencing intracellular pH:
- a. buffering by physical buffers (.g proteins & phosphates) located within the cell
- b. rx of HCO3 with H+ ions, forming CO2, which then diffuses out of cell
- c. passive diffusion or active transport of H+ ions from the cell
- d. cation-exchange mechanisms (Na+/H+ & Ha+/NH4+), anion-exchange mechanisms (HCO3-/Cl-) or both in plasma membrane
- pH influences many cellular activities – some positively, some negatively e.g. many enzymes are inhibited by low pH such as those involved with glycolysis
- many factors influence body pH also e.g. temperature since dissociation of water varies with temperature
- Ability of body to redistribute acid between body compartments has functional significance because some tissues are more adversely affected by changes in pH than others e.g. brain is particularly sensitive whereas muscles tolerate much larger oscillations in pH.

Gas Transfer in Air – Lungs

- functional anatomy – complex network of tubes & sacs with structure varying among species
- sizes of terminal air spaces in lungs becomes progressively smaller from amphibians to reptiles to mammals while total number of air spaces per unit volume become greater
- focus on mammalian lung – consists of millions of blind-ended interconnected spaces (alveoli) – main airway (trachea) subdivides to form bronchi & bronchioles which branch repeatedly leading to terminal bronchioles & respiratory bronchioles each of which is connected to terminal alveolar ducts & alveoli
- gases are transferred across thin-walled alveoli – airways leading to terminal bronchioles constitute nonrespiratory portion of lung – alveoli are interconnected by series of holes (pores of Kohn) which allow collateral movement of air = significant factor in gas distribution during lung ventilation
- air ducts leading to respiratory portion of lung contain cartilage & a little smooth muscle + lined with cilia – epithelium of ducts secretes mucus, which is moved toward the mouth by cilia ("mucus escalator") keeps lungs clean – in respiratory portions of lung, smooth muscle replaces cartilage
- diffusion barrier crossed by O2 moving from air to blood is made up of:
- 1. An aqueous surface film 2. Epithelial cells of alveolus 3. interstitial layer,
- 4. Endothelial cells of caps.5. Blood plasma and 6. membrane of RBCs
- 3 types of epithelial cells: 1. Type I (most abundant) = squamous cells with thin platelike structure extends between 2 adjacent alveoli 2. Type II = laminated body within cells and with surface villi; they produce surfactant 3. Type III = rich in mitochondria + numerous microvilli (NaCl uptake from lung fluid?) + Number of alveolar macrophages wander over surface of resp. epithelium.

- Lung Ventilation – Terms:
- 1. Eupnea = normal, quite breathing = at rest
- 2. Hyperventilation/Hypoventilation = increase (or decrease) in amount of air moved into or out of lungs by changes in rate/depth of breathing such that ventilation no longer matches CO2 production & blood CO2 levels changes
- 3. Hyperpnea = increase lung ventilation due to increased breathing in response to elevated CO2 production (e.g. during exercise)
- 4. Apnea = absence of breathing
- 5. Dyspnea = labored breathing
- 6. Polypnea = increased in breathing rate without increase in depth of breathing
- amount of air moved into or out of lungs with each breath = tidal volume
- air exchanged passes through nonrespiratory sections i.e. at end of exhalation (expiration) air in nonrespriatory sections is high in CO2/low in O2 & is first to be inhaled with next breath + at end of inhalation (inspiration) air in nonrespiratory sections is high in O2 & low in CO2 & is first exhaled – volume of air not involved in gas transfer = anatomic dead-space volume
- amount of fresh air moving into/out of alveolar air sacs = TV minus anatomic dead-space volume = referred to as alveolar ventilation volume & **only** this air is involved in gas exchange
- max amount of air moved into or out of lungs = vital capacity of lungs
- O2 & CO2 levels in alveolar gas are determined by both rate of gas transfer across rep. epithelium & rate of alveolar ventilation (alveolar ventilation depends on breathing rate, tidal volume & anatomic dead-space volume)

Pulmonary Circulation

- 1. pulmonary circulation = deoxygenated blood from pulmonary artery from heart (taking up O2; giving up CO2)
- 2. bronchial circulation = smaller supply = comes from systemic (body) circulation & supplies lung tissues themselves with O2 & other substrates fro growth & maintenance
- pulmonary circulation:
- birds & mammals = BP in pulmonary circulation < those in systemic circulation = this lower BP reduces filtration of fluid into lung – extensive lymph drainage of lung tissues also helps ensure that no fluid collects in lung = NB features because any fluid collecting in lung increases diffusion distance between blood & air & reduces gas transfer
- mammalian pulmonary circulation lacks well-defined arterioles, both sympathetic adrenergic & parasympathetic cholinergic fibers innervate smooth muscle around pulmonary blood vessels & bronchioles
- reduction in either O2 levels or pH cause local vasoconstricution of pulmonary blood vessels

Mechanisms for Ventilation of Lung

These vary by species – reflecting functional anatomy of lungs & associated structures – primarily consider mammals

Lungs = elastic, multi-chambered bags suspected within the pleural cavity (aka thoracic cavity) & open to exterior via single tube (trachea)– walls formed by ribs & diaphragm

Lungs elasticity creates pressure below atmospheric pressure in fluid-filled pleural space (fluid provides flexible, lubricated connection between outer lung surface & thoracic wall (thus, when thoracic cavity changes volume, gas-filled lungs do too

Pneumothorax = when thoracic cage is punctured & air is drawn into pleural cavity = lungs collapse

during normal breathing = thoracic cage is expanded & contracted by series of skeletal muscles, diaphragm & external & internal intercostals muscles – these muscle contractions are determined by activity of motor neurons controlled by the respiratory center within the medulla oblongata

volume of thorax increases as ribs are raised & moved outward by contraction of external intercostals & by contraction (lowering) of diaphragm fig. 13-30 p. 552 (contraction of diaphragm account for ~2/3 of increase in pulmonary volume – increase in thoracic volume reduces alveolar pressure & air is drawn into lungs – relaxation of diaphragm & external intercostals muscles reduces thoracic volume = raises alveolar pressure & forcing air out of lungs (generally, inhalation is controlled and exhalation is passive)

Pulmonary surfactants:

Lung wall tension depends on properties of wall & surface tension at the liquid-air interface – surface tension is a force that tends to minimize the area of a liquid surface causing liquid droplets to form a sphere – (makes surface film resistant to stretch)

Fluid lining is not simply water but surfactant = lipoprotein complexes that bestow very low surface tension on liquid-air interface – roles of surfactants:

1. Low surface tension of fluid lining alveoli = allows alveoli to expand easily during breathing & reduces effort of inflating lung (as noted above)
2. alveoli fold as their volume decreases & would stick/become glued together by surface tension if not for surfactant (reducing surface tension to allow easy inflation of collapsed alveoli) – when lung volume is reduced extremely, the lung will collapse = atelectasis however, due to presence of surfactant, even a collapsed lung can be re-inflated easily

3. Allow newborn babies to inflate their lungs (in mammals, surfactant appears in fetal lung prior to birth = without surfactant = babies cannot inflate lungs = called neonatal respiratory distress syndrome)

Reduce resistance to blood flow by increasing compliance of cap-alveolar sheet

Increase osmotic pressure of lung fluid = reducing water flux across lung epithelium

Heat & Water Loss

Increases in lung ventilation not only increase gas transfer but also result in creased losses of heat & water

- cool, dry air entering lungs of mammals is humidified (by H2O evaporation from surface of respiratory epithelium) & heated as air in contact with respiratory surface becomes saturated with H2O vapor & comes into thermal equilibrium with blood; exhalation of this hot, humid air results in considerable loss of heat & H2O – because evaporation of H2O cools nasal mucosa, temperature gradient exists along nasal passages (cool at tip of nose, warm towards glottis) – (cooling of exhalant air in nasal passages results in conservation of both heat & water) – structural variety in nasal passages among vertebrates

Regulation of Gas Transfer

- Energy is expended in ventilating respiratory surface with air(or water) & in perfusing respiratory epithelium with blood – significant selective pressure in favor of evolution of mechanisms for close regulation of ventilation & perfusion in order to conserve energy.

- ## Neuronal Regulation of Breathing:
- Medullary respiratory center – respiratory muscles activated by spinal motor neurons which receive inputs from neurons that constitute medullary respiratory center (such control can be very precise allowing extremely fine control of air flow e.g. whistling, singing, talking)

Inhalation of lungs stimulates pulmonary stretch receptors in bronchi & bronchioles which have a reflex inhibitory effect via vagus nerve on medullary inspiratory center & thus on inspiration = medulla contains a central rhythm generator that drives pattern generator within med. respiratory center to cause breathing movements.

Introduction to Blood Gas Basics

Two p.m., Bayside Community Hospital, the emergency room. A 29-year old female is complaining of chest pain and shortness of breath. The intern tells you her PaO2 is normal. Anxiety and hyperventilation, he says. Entering the room, you see a hyperventilating young lady with a cast on her right leg and a pack of cigarettes sticking out of her purse. On the chart, you see "Meds: BCP."

A quick calculation of the Aa gradient tells you that this patient's "normal" oxygen is not normal at all — it's depressed for her level of hyperventilation. Suspecting pulmonary embolism, you order a lung scan.

Time 3 p.m. The paramedics bring in a boy found hanging from the swing set. Rhythm is initially asystole, improving to sinus tach with epi and atropine. Pulse is very weak, and he remains unresponsive. Initial ABG's return with a pH of 6.91. Using the boy's weight and the base excess on the blood gases, you calculate an accurate and safe acidosis correction dose of sodium bicarbonate.

Time 4:30 p.m. Another tricyclic OD. ABG's show everything "out of whack." Using a simple method, you arrive at a diagnosis of "partially compensated respiratory alkalosis."

This software can help you get more clinical information from arterial blood gas analysis. It's intended for the physician who must make quick decisions based on ABG's, or the critical care nurse who wants to expand his or her understanding of blood gases. Our emphasis will be on rapid, easily remembered, "quick 'n dirty" methods — those methods most useful when the pressure is on and the books aren't around.

Why are blood gases done?

There are four good reasons for obtaining blood gases: 1) to assess the oxygenation capacity of the lungs for diagnostic reasons, 2) to assess the oxygen pressure in the blood for therapeutic reasons, 3) to assess respiratory adequacy, and 4) to assess acid-base status.

1) Assessment of oxygenation capacity

An example of this indication for drawing blood gases is the post-op patient with pleuritic chest pain. If the oxygenation capacity (as determined by calculating the arterial-alveolar (Aa) gradient) is absolutely normal, this is very strong evidence against a pulmonary embolism. Under these circumstances, blood gases would be drawn on room air to assure an accurate arterial-alveolar gradient.

Assessment of oxygenation can be valuable for a hyperventilating patient — by proving to the patient that his lung function is normal, i.e. a "therapeutic" blood gas.

2) Assessment of oxygen pressure to guide therapy

Oxygen is toxic. High inspired concentrations of oxygen can damage lungs and eyes. For example, in the premature infant with lung disease, repeated blood gas determinations are performed so that the lowest possible inhaled oxygen concentration can be used that maintains the blood oxygen pressure at a level that keeps the infant alive.

(In most modern hospitals, a pulse oximeter is used for routine oxygenation monitoring. Blood gases are used as a baseline, and to monitor carbon dioxide retention and acid-base balance.)

Similarly, suppose you have a patient with a weak heart who's on a ventilator with positive airway pressure for ARDS (adult respiratory distress syndrome). The positive airway pressure gets more oxygen into his blood, but decreases the venous return to his heart. For two days you've been fighting a battle between inadequate cardiac output and inadequate oxygenation: increase his CPAP (continuous positive airway pressure), his cardiac output falls, he turns blue, but his oxygen looks great; decrease his CPAP, his oxygen falls down, he turns blue, but his cardiac output is great. Improvement of blood gases may allow you to decrease the airway pressure, getting the patient safely off his dangerous therapeutic tightrope.

3) Assessment of respiratory adequacy

When the decision is made to override the body's respiratory regulation system by intubating and artificially ventilating the patient, the blood gas machine must take the place of the carotid body chemical receptors. The level of arterial carbon dioxide and oxygen provide information on whether the rate or depth of ventilation, ventilator dead space, or airway pressure must be changed to preserve the patient's normal physiologic balance.

4) Assessment of acid-base balance

The measurement of serum pH and carbon dioxide pressure (and subsequent calculation of HCO3-) provide the means for identifying the presence of many diseases, especially when combined with determination of serum electrolytes. For example, the presence of severe acidosis in a comatose patient completely changes the clinical approach and subsequent evaluation. And of course, blood gases are used to monitor the therapy of acidosis in the unstable patient.

Why not get blood gases?

There are a lot of good reasons NOT to get blood gases. Perhaps the most important reason NOT to get blood gases is when the results won't change what you're going to do. For example, getting blood gases on every young asthmatic that comes to the ER is stupid. What's it going to change? If you just want to prove he's wheezing, or "monitor his response to therapy," get a PEFR (peak expiratory flow rate).

On the other hand, getting blood gases on a young asthmatic after he's had full doses of every possible therapy and is looking increasingly tired and blue is smart (if only to prove to his lawyers why you undertook the aggressive action of intubation and mechanical ventilation — when he gets a tension pneumothorax in the night and dies), even though your decision is based on the clinical picture.

Another reason NOT to get blood gases is “because the policy says to.” Protocols can be useful in helping you remember a solid, practical approach to a specific problem. But they should remain guidelines. Standard therapies and standard evaluation strategies should not be written into policies that force you to obtain unnecessary tests, and that can be used to “hang” you legally if — for very valid clinical reasons — you do not follow a long-forgotten obscure “policy” buried somewhere in that shelf of three-ring binders in the administration offices.

Another reason NOT to get blood gases is when something else less expensive or less unpleasant will get you the same information. Pulse oximeters have replaced the need for repeated sampling in cases where the primary interest is adequate oxygenation of the blood. Blood gases should also not be drawn where there’s a possibility of complications that outweighs the benefits of the test. For example, sticking a needle through the artery of a hemophiliac just to show he’s hyperventilating might not be such a good idea.

How are blood gases done?

Blood gases are drawn from an artery with a small needle attached to a syringe. The syringe contains a small amount of heparin to prevent clotting of the blood. If possible, the sample is obtained from the radial artery at the wrist. When repeated samples are necessary, an “arterial line” (a small catheter left inside the artery) is used. In newborns, the samples would be obtained through an umbilical artery catheter. When the radial pulse is unobtainable (blood pressure less than 60 systolic) the sample is usually obtained from the femoral artery in the groin.

Prompt flow of blood into the syringe (without pulling back on the plunger) shows that the sample is truly from the artery. However, during CPR the sample must often be aspirated from the femoral artery.

The sample is corked off immediately to prevent exposure to room air, and placed in ice. The site of the arterial puncture is kept under pressure (to prevent hematoma formation) for about ten minutes.

The sample is placed in a machine that measures the pH, partial pressure of oxygen (PaO2), and carbon dioxide (PaCO2). Usually the hemoglobin is measured in a separate machine. These are the “measured values,” from which other values are calculated. “Controls" (solutions of known pH) are used to insure the accuracy of the measurements.

Readings may need to be adjusted for the patient’s temperature. Oxygen, carbon dioxide, and pH are all affected by a change in patient temperature. The machine is calibrated for measurements on a patient with a temperature of 37.0 centigrade.

Measurements must be adjusted for temperature because:

1) Increased temperature changes the volume of the dissolved gas (not CO2 that has been converted to HCO3-) in the serum and red blood cells. The ideal gas equasion shows that volume of a gas (V) and temperature (T) are directly proportional.

PV = nRT

2) Increased temperature increases the vapor pressure of water, effectively lowering the partial pressure of oxygen in the blood stream.

3) Increased temperature changes the chemical reactions involving buffer solutions — the pK or dissociation constant is temperature dependant.

What values are returned from ABGs?

Only three to five values are actually measured when a blood gas analysis is performed. All remaining values are calculated from these measured values. The complexity of information returned to the clinician depends on the amount of computations performed.

At a minimum, the analysis will list values for pH, PaO2, and PaCO2 (these are measured directly), and serum bicarbonate (which is calculated). Most labs will also return values for hemoglobin and base excess.

Oxygen saturation can also be directly measured. Some labs, however, simply list the calculated saturation. Others will list both a measured and a calculated saturation. A large difference in these two values may indicate carbon monoxide poisoning.

Some labs routinely measure carboxyhemoglobin (carbon monoxide-complexed hemoglobin) with every blood gas.

An arterial-alveolar gradient may also be calculated for you by some newer blood gas software. The critical clinical information to be derived from the typical blood gas is: pH, PaO2, PaCO2, HCO3, base excess, Aa gradient, and sometimes hemoglobin.

The myth of normal values

My practice of emergency medicine spans three hospitals. Each has a different list of "normal ranges" on their blood gas slips. The values chosen as limits of normal are often arbitrary.

For example, is a person hyperventilating when he hits an arterial carbon dioxide of 34, or do you call 32 abnormal? Do you decide what normal oxygen is by measuring a whole bunch of people and using a standard deviation method? Or do you mathematically determine the lowest oxygen at which a person with a carbon dioxide of 40 could still have a normal arterial-alveolar (A-a) gradient?

Our lab (Salt Lake City) says 70 is the lower limit of normal oxygen. Yet a person with a "normal" A-a gradient of 10 and "normal" carbon dioxide of 40 will have an oxygen of 65! (The arterial-alveolar gradient means that the lungs are normal, making the "abnormal" oxygen meaningless.) Furthermore, a person can have a "normal" carbon dioxide, a "normal" oxygen, and yet have abnormal lungs as determined by the arterial-alveolar gradient calculation.

So what good are normal values? Well, they do provide a quick "ballpark" answer about the patient's status. But you must always keep in mind that you are evaluating the patient's respiratory status, not just his oxygen. You are evaluating his acid-base balance, not just his pH. Proper interpretation of the measured values on the Blood Gas test will tell you about the health of the lungs and the adequacy of ventilation, and about the nature of any acid-base disturbance.

Respiration and Ventilation

Definition of Respiration

Respiration is the total process of delivering oxygen to the cells and carrying away the byproduct of metabolism, carbon dioxide. Respiration includes gas exchange in the lungs, circulation of gases through the blood stream, and transfer of gases at the cellular level.

Air is drawn into the air sacs of the lungs, where oxygen from the air can enter the blood. Carbon dioxide exits from the blood into the alveolar air. The second half of respiration occurs when the blood reaches the tissues. Oxygen then diffuses into the cells, and carbon dioxide enters the blood. The blood then circulates back to the lung, where the process begins again.

Definition of Ventilation

Ventilation is the process of moving gases through the respiratory tract.

Inspiration (breathing in) occurs when the muscles of the diaphragm and chest wall contract. The contraction of these muscles increases the volume of the chest cavity, lowering the pressure inside. As the pressure in the airways decrease, air rushes in as the chest volume increases.

Expiration (breathing out) is a passive process. As the muscles relax, the elastic recoil of the lungs puts pressure on the gases inside. The pressure in the chest is now higher than outside pressure, so air rushes out. Expiration stops when the recoil of the lung and the "spring" of the ribs balance each other.

During quiet breathing, the decrease in pressure in the chest starts about 2.5 mm Hg (compared to the outside pressure), decreasing to around 6 mm Hg towards the end of inspiration. Strong breathing efforts can produce a pressure decrease (vacuum) in the chest as high as 30 mm Hg.

The muscles of the chest wall, including the diaphragm, contract to expand the volume of the chest. This “vacuum” is transmitted through the fluid-filled pleural space, lowering the pressure in the air sacs of the lung. This draws air in. As the muscles relax, the elastic recoil of the lung pushes air back out.

Lung Anatomy

Air can enter through either the mouth or nose, merging into a common chamber called the oropharynx. The function of the nose is to humidify and clean the air. From the pharynx, the air enters the larynx, the location of the vocal cords. The larynx is encased in the thyroid cartilage, with the epiglottis protecting the airway from foreign material at the upper margin and the cricoid cartilage providing circular support to the airway below.

The trachea is formed of semi-circular cartilage rings. The inner membrane of the trachea contains hair cells, mucous cells to continue the job of humidifying and cleaning the air. From the trachea, one major bronchus branches off to each lung. These further divide into smaller bronchi.

Beyond the bronchi, the smaller airways are called bronchioles. As the smallest bronchioles branch off to enter groups of air sacs, they’re called respiratory bronchioles. Multiple air sacs, called alveoli, form a branching complex at the end of the respiratory bronchiole. In the walls of each alveolus are capillaries. Only a very thin membrane (about 0.3 micrometers thick) separates the air from the red blood cells in the capillaries.

Lung Volumes

The amount of air that the lungs move in and out with respiration is called the tidal volume. With effort, additional air can be forced in with inspiration, and additional air can be expelled during expiration. The amount of air that can be inspired in excess of the tidal volume is called the inspiratory reserve volume; the air that can be expired after the normal tidal volume has been breathed out is the expiratory reserve volume.

Tidal volume, and especially the inspiratory and expiratory reserve volumes, are affected by processes that decrease the compliance (the “give” or flexibility) of the chest and lung. After all possible air has been forceably expired, the amount that still remains is called the residual volume. The residual volume increases in diseases that trap air in the chest, such as emphysema. Excess residual volume decreases the efficiency of gas exchange.

Another “volume” is the respiratory dead space, the amount of air within the chest that is not in contact with alveolar membranes and cannot exchange gases with the blood. The dead space becomes important in certain lung diseases, causing elevation of carbon dioxide levels. Respiratory dead space is NOT the same thing as residual volume. Residual volume includes the respiratory dead space, plus whatever volume is left in the alveoli.

The vital capacity is often measured clinically. It's the maximum amount of air that the patient can expire after a full breath — the sum of tidal volume, inspiratory reserve volume, and expiratory reserve volume. The amount of the vital capacity that can be expired in one second (sometimes called "timed vital capacity" or FEV1 — Forced Expiratory Volume in 1 second) gives information about diseases that increase airway resistance such as asthma.

Peak expiratory flow is a measure of the maximum speed of expiration in volume of gas per second. It provides an easily available (and portable) substitute for the FEV1 in assessing the severity and progress of airway diseases like asthma or chronic bronchitis.

Partial Pressure of Gases

Dry air is composed of 20.98% oxygen, 0.04% carbon dioxide, 78.06% nitrogen, and 0.92% other gases such as argon and helium. For purposes of blood gas analysis, the amount of a gas present is expressed in terms of "partial pressure." This is the amount of total gas pressure due to the substance being measured. For example, at sea level the total atmospheric pressure is 760 mm Hg. The amount of this pressure that is due to oxygen is 0.21 x 760 = 160 mm Hg. We would say that the partial pressure of oxygen at sea level in dry air is 160 mm Hg.

If atmospheric pressure is lower, the partial pressure of a gas will be proportionately decreased. In Salt Lake City, the atmospheric pressure is 647 mm Hg. The partial pressure of oxygen in dry air in Salt Lake is 0.21 x 647 = 136 mm Hg.

The partial pressure of carbon dioxide in dry air at sea level is 0.03 x 760 = 0.3 mm Hg. However, in the lung carbon dioxide exits the blood to raise the carbon dioxide content of the air. The partial pressure of carbon dioxide in the lung air sacs is around 40 mm Hg. Because this carbon dioxide gas must displace oxygen and nitrogen, the partial pressure of oxygen in the lung air sac will be lower than in outside air.

Water vapor enters the air when it's exposed to water. The maximum amount of water vapor in the air varies with temperature. At body temperature (37 centigrade) air can be saturated up to 47 mm Hg. As further water vapor enters the air, other water must condense out — the water content of the air is limited to 47 mm Hg. Therefore in the lung, where air is totally water-saturated, the partial pressure of water vapor would be 47 mm Hg.

Gas Exchange

during respiration, air becomes saturated with water vapor by the time it enters the alveolar sac. In the alveolus, it also mixes with carbon dioxide.

At the alveolar membrane, each gas diffuses in the direction where the partial pressure of that gas is less. In other words, oxygen diffuses towards the blood and is taken up by hemoglobin, and carbon dioxide diffuses towards the alveolus and mixes with the air. No "active process" is involved. Oxygen simply diffuses through the membrane and plasma, and is taken up by the red blood cells.

Although the diffusion occurs very rapidly, the gases do not have time to totally equilibrate. There will be a small pressure difference across the alveolar membrane for each gas. That is, oxygen partial pressure will be somewhat higher in the alveolus than in the blood, and carbon dioxide pressure will be slightly higher in the blood than in the air in the alveolus. In the case of oxygen, this pressure difference is calculated for the lung as a whole as the "arterial-alveolar (Aa) gradient."

About 2% of the blood flow through the lungs bypasses the pulmonary capillaries. This blood is not oxygenated, and forms a "physiologic shunt." Because of this blood that bypasses the alveoli, arterial blood will always contain less oxygen pressure than blood that has equilibrated with the oxygen in the lung alveoli. This "shunt" becomes part of the calculated "Aa gradient."

As blood circulates through the body, an opposite change occurs in the capillaries of the systemic circulation. Oxygen diffuses from the area of higher pressure — the blood — into the lower pressure of the cells. Carbon dioxide diffuses from the cells into the blood.

Oxygen Transport

Hemoglobin is a molecule composed of four subunits. Each subunit is a protein chain attached to a porphyrin ring containing one iron atom. As each iron atom can bind one oxygen (O_2) molecule, hemoglobin can carry one, two, three, or four oxygen molecules.

Normal blood contains about 15-16 grams hemoglobin per 100 ml. Each gram of hemoglobin can carry about 1.34 ml of gaseous oxygen. Fully saturated arterial blood will therefore contain about 20 ml of oxygen per 100 cc. The volume of oxygen in the blood is referred to as the O_2 content. Because O_2 content is dependent on the hemoglobin concentration, it doesn't provide a good measure of lung function. The partial pressure of oxygen (PaO_2), as measured in arterial blood, does provide an accurate picture of gas exchange in the lung.

The relative amount of oxygen in the blood compared to the carrying capacity of the hemoglobin is called the oxygen saturation, and is expressed as a percentage. It's directly proportional to the PaO_2 — the partial pressure of oxygen. The hemoglobin in arterial blood is only about 97% saturated with oxygen because of venous blood that passes directly through the lung (physiologic shunt). Venous blood is about 75% saturated.

Effects of Acid on Oxygen Transport

Oxygen status is affected by acid-base status. Oxygen affects the buffering capacity of hemoglobin through the Bohr Effect, but the opposite is also true. At a given oxygen pressure, oxygen saturation in the blood is lowered by increasing either carbon dioxide or hydrogen ion concentrations.

The presence of acid "shifts the curve to the left," meaning that less oxygen can be bound at a given PaO2. This mechanism assists hemoglobin in unloading oxygen in the capillaries, where acid concentration is higher. Raising the pH, conversely, increases the oxygen binding, allowing more total oxygen to be carried — a change that occurs in the alveolus as acid is eliminated through CO2.

Carbon Dioxide Transport

The gas carbon dioxide is transported through the blood stream by conversion to carbonic acid, which dissociates to hydrogen ion and bicarbonate. The hydrogen ion binds to hemoglobin, and is transported to the lungs. In this case, hemoglobin is acting as a buffer for the acid, but also is acting as an effective "transportation vehicle" for ferrying carbon dioxide to the lungs.

Hemoglobin and bicarbonate act as buffers for the acid produced by metabolism, effectively transporting this acid to the lungs for elimination. Read more about buffers in the "acid-base" section.

As carbon dioxide is formed in the cells (due to aerobic metabolism) it diffuses into the plasma of the capillary. As it enters the red blood cells (which contain carbonic anhydrase) it's quickly converted to H2CO3, which breaks down to H+ and HCO3-. About two-thirds of the HCO3- will diffuse out into the plasma (and is replaced by chloride in the red cell). Only small amounts of carbon dioxide remain dissolved or attach to other compounds.

About 50 ml of CO2 gas are contained in each 100 ml of arterial blood, almost all as HCO3-. As the blood goes through the capillaries, it picks up about 5 ml of additional CO2. With this addition of acidic CO2, the pH drops from 7.4 to 7.36. On reaching lungs, the process is reversed, and 5 ml of CO2 is converted back from H+ and HCO3- and discharged into the alveoli.

At rest, about 200 ml of CO2 is produced and excreted through the lungs. Over 24 hours, this is the equivalent of 12,500 milliequivalents of acid produced by metabolism and eliminated through CO2.

Chemical Control of Respiration

Special chemical receptors near the aorta and carotid arteries, called the aortic bodies and carotid bodies, are sensitive to an increase in carbon dioxide or acid concentration, or to a decrease in the pressure of oxygen (PaO2). When these receptors sense acidity or low oxygen, they stimulate the brain respiratory center to increase the speed and depth of breathing.

The area of the brain stem that controls respiration is directly responsive to increases in acid concentration in the cerebrospinal fluid, producing increased respirations. When acid buildup occurs, such as in diabetic ketoacidosis, strong stimulation of respiration results. The deep rapid breathing mixes alveolar air with increased amounts of low-CO2 air, leading to a decrease in the carbon dioxide in the blood as it passes by the alveolus. The reduction in CO2 raises the pH back towards normal.

When there is a rise in serum CO2, such as with the increased metabolism of exercise, ventilation is stimulated until the CO2 returns to normal levels. Lack of oxygen also acts as a respiratory stimulant, although a weak one. In healthy individuals at normal altitudes, oxygen levels play no role in regulation of ventilation. As arterial oxygen pressure falls, there is not much stimulation of respiration until the level is below 60 mm Hg. Patients suffering from severe chronic bronchitis and emphysema may come to rely on the “hypoxic drive” to stimulate respirations, as they become habituated to high levels of carbon dioxide.

Carboxyhemoglobin

Carbon monoxide binds tightly to hemoglobin, preventing it from accepting oxygen molecules. This CO-hemoglobin complex is called carboxyhemoglobin. Small amounts of carbon monoxide are normally produced by body metabolism. In city dwellers and smokers, the level is much increased. Heavy smokers may have as much as 10% of their hemoglobin bound by carbon monoxide.

Carbon monoxide reduces the oxygen saturation of hemoglobin at any given PaO2. The presence of carbon monoxide can be suspected, and a rough measure obtained, by comparing measured oxygen saturation with the oxygen saturation expected for the PaO2 and pH. Carboxyhemoglobin levels (usually expressed as a percentage of total hemoglobin) can also be directly measured.

Arterial Alveolar Gradient

There are times when the primary question to be answered from the blood gases is: are the lungs normal? Yet the values of oxygen and carbon dioxide, taken alone, can be misleading. For example, consider this blood gas, drawn in Salt Lake City on a seizure patient breathing room air:

pH = 7.225
paO2 = 62
PaCO2 = 51

Pretty bad lungs, huh? Probably aspirated, right? **No.** These lungs are perfectly normal. Calculation of the arterial-alveolar (Aa) gradient shows that no significant pulmonary problem is present. The Aa gradient is 8. (The barometric pressure in SLC is 647.)

Simply put, calculating the Aa gradient allows you to determine whether a measured oxygen value is normal for the patient's altitude, inspired oxygen percentage, and rate of respirations. The Aa gradient may help you decide whether a hyperventilating patient is simply upset, or has a pulmonary embolism. In this case a "normal" oxygen may turn out to be abnormal considering the low CO2 caused by hyperventilation.

What is the A-a gradient? It's the difference between the measured pressure of oxygen in the blood stream and the calculated pressure of oxygen in the alveolar sacs. It can be looked at as a measure of how well oxygen gets from air into blood. The higher the A-a gradient, the more problem there is with oxygen passage into the blood.

Calculating this "efficiency" of oxygen passage allows an accurate picture of overall lung health, because the effects of hyper- or hypoventilation on PaO2 are eliminated. A calculation is necessary because alveolar air doesn't have the same oxygen pressure as outside air. Some of the oxygen is displaced by water vapor, and by carbon dioxide exiting the blood into the alveolus. The partial pressure of all gases must add up to atmospheric pressure. If the CO2 goes down, the oxygen proportion will go up. Conversely, if the CO2 elevates, there can be less oxygen in the alveolus.

Calculating the Aa Gradient

The arterial-alveolar gradient is the difference between the measured pressure of oxygen in the blood stream and the calculated oxygen in the alveolus. The oxygen pressure in the alveolus can be calculated by:

1) Subtracting the partial pressure of water vapor at 37 degrees centigrade from the barometric pressure.

2) This result is multiplied by the oxygen percentage in the remaining air (it's the same as the outside air before it was humidified). This gives us the oxygen pressure in totally humidified air.

3) Because carbon dioxide displaces oxygen in the alveolus, the estimated alveolar CO2 must be subtracted. The alveolar CO2 is estimated by multiplying the arterial PaCO2 by a "respiratory quotient" fudge factor of 1.25.

Subtracting arterial oxygen from alveolar oxygen, the formula for calculating the Aa gradient is:

Aa = (BP - pH2O) x FiO2 - (1.25 x PaCO2) - PaO2

BP is barometric pressure, pH2O is the partial pressure of water at body temperature (47 mm Hg at 37 degrees centigrade), FiO2 is the fraction of inspired oxygen.

At sea level and room air, the formula simplifies to:

Aa = 150 - (1.25 x PaCO2) - PaO2

In Salt Lake City (home of the 2002 Winter Olympic Games), athletes breathing room air would have their Aa gradient calculated with the formula: to:

Aa = 126 - (1.25 x PaCO2) - PaO2

The A-a gradient merely reflects the gross difference between alveolar oxygen and blood oxygen. It says nothing about what caused that difference. An atrial septal defect that shunts unoxygenated blood through the heart can also elevate the A-a gradient. Like everything else in medicine, the A-a gradient must be evaluated while looking at the entire clinical picture.

Acids and pH

The pH is a method of expressing extremely small concentrations of acid in solution. The scale is exponential — a change of one unit is actually a ten-fold change. A solution with pH of 1 has ten times as much acid as a solution with pH of 2.

The pH scale allows the description of concentrations from 1 to 1/100,000,000,000,000 (10 to the minus 14) moles*/liter. pH is defined as the negative logarithm of the hydrogen ion (H+) concentration or activity.

pH = - log [H+]

Water has a pH of 7, with a hydrogen ion concentration of 0.0000001 M/L (-log[10 to the minus 7]=7).

Acids are substances that can provide a hydrogen ion. Strong acids hold their H+ ion weakly, so it's free to dissociate and act on other substances. Weak acids hold the hydrogen more tightly, so it doesn't contribute as greatly to free hydrogen ion concentration — and thus the solution has a higher (less acidic) pH.

*A mole is a unit of measure based on number of molecules rather than on weight or volume. It's 6.02246 x 10 to the 23rd power, the number of molecules required to make up a molecular weight in grams. For example, a mole of hydrogen (atomic weight 1.00797, two atoms per molecule) would weigh 2.01594 grams. An "equivalent" — from which the unit milliquivalent (mEq) comes — is the same thing in terms of ionic activity. An equivalent of a substance with a charge of +1 is a mole, while an equivalent of something with +2 charge requires only one-half a mole.

Acid Buffering

A buffer is a substance that resists changes in pH (acid concentration) by undergoing a reversible reaction — in other words, you add a bunch of acid, and the buffer undergoes a reaction so that only a small change in pH occurs. Add a bunch of alkali, the buffer changes back to its original state.

A buffer system consists of a weak acid combined with its salt. An example of a buffer is the carbonic acid (H2CO3) and bicarbonate (H+ HCO3-) system. When the H2CO3 / HCO3- system is at a pH that allows existence of significant amounts of both molecular (undissociated) and dissociated (hydrogen ion has split off) forms, it resists a change in pH by undergoing a change in relative concentrations. When acid is added to a buffer solution, the resulting change in pH is less than it would have been if the buffer were not present.

When hydrogen ion (H+) is added, much of the hydrogen is taken up by the salt of the buffering acid. With bicarbonate, H+ bonds to HCO3- to form H2CO3, which is a weak acid. With less hydrogen ion available, the solution is less acidic than it would have been without the buffer.

The second characteristic of a buffer is that the reaction is reversible — the hydrogen ion can be given back. When alkali is added to the solution, carbonic acid provides the proton to neutralize the alkali, again resisting the normally large change in pH that would occur with the addition of the hydroxide (OH-) ion.

Acid-Base Balance in the Body

The pH of the body must be maintained within a narrow range. Most body systems function optimally at a pH of near 7.4. As the pH changes (either higher or lower), enzymes may cease to function, nerve and muscle activity weakens, and finally all metabolic activity becomes deranged.

Hemoglobin is one of the most important buffering agents. Its buffering capacity is due to the imidazole chain of the hemoglobin molecule, which contains histadines. Imidazole can accept an extra proton or donate it back at the normal body pH.

Hemoglobin has an additional property that enables it to maintain pH within the capillaries, known as the Bohr Effect. When combined with oxygen, hemoglobin tends to release hydrogen ions that have attached to the imidazole chain (it becomes a stronger acid).

When hemoglobin is exposed to acid and lower oxygen concentrations in the capillaries, it gives up the oxygen. It then becomes a weaker acid, taking up extra hydrogen ion. This change maintains the pH in the capillaries essentially the same despite the higher CO2 concentration.

An opposite change occurs when hemoglobin is exposed to the higher oxygen concentration in the lung. As it takes up oxygen, it becomes more acidic (more prone to release the hydrogen ion). The hydrogen ions react with bicarbonate to form carbonic acid, which in turn is converted to carbon dioxide and released into the alveoli. Hemoglobin is therefore not only an oxygen-transporting molecule, but is also an acid-transporting system.

Carbonic Acid-Bicarbonate Buffering

The carbonic acid - bicarbonate system is a classic chemical buffer. In addition, the body has the ability to eliminate chemicals from either end of the chemical reaction to maintain the pH. In the case of bicarbonate, the chemical reaction is:

$H^+ + HCO_3^- = H_2CO_3 = H_2O + CO_2$

This buffering system is very effective because of the ability to convert carbonic acid to carbon dioxide (through the enzyme carbonic anhydrase) then remove CO2 from the body through respiration. For example, adding enough acid to lower the serum bicarbonate by half would normally drop the pH from 7.4 to 6.0 — but instead all the extra H2CO3 is removed by conversion to CO2. The drop in pH stimulates extra respirations so CO2 (and subsequently more H2CO3) is removed. The pH therefore falls only to 7.3 or 7.2.

On the other side of the equation, excess acid or excess alkali can be removed through the kidneys.

Changes in carbonic acid concentration occur rapidly (seconds) in response to hypo- or hyperventilation. On the other hand, changes in bicarbonate require hours or days through the relatively slow process of elimination by the kidney.

The ratio of bicarbonate to carbonic acid determines the pH of the blood. Normally the ratio is about 20:1 bicarbonate to carbonic acid.

This relationship is described in the Henderson-Hasselbach equation:

$$pH = pK + \log (HCO_3^-/H_2CO_3)$$

(pK is the dissociation constant of the buffer, 6.10 at body temperature. The change in pK with temperature is the reason pH determinations must be adjusted for patients with abnormal temperatures.)

As carbon dioxide is directly proportional to the carbonic acid (H2CO3), and can be directly measured, it will be substituted into the H-H equation.

$PaCO_2 = 33 \times H_2CO_3$ or $H_2CO_3 = .03 \times PaCO_2$

By substituting,

$$pH = pK + \log (HCO_3^-/(PaCO_2 \times 0.03))$$

Thus by measuring serum pH and PaCO2, the serum bicarbonate can be calculated:

$$\log (HCO_3^-) = pH + \log (PaCO_2) - 7.604$$

Total CO2

"Total CO2" is a value often reported on blood gas slips. Total CO2 is defined as the sum of the carbonic acid and the bicarbonate, or

$$TCO_2 = [H_2CO_3] + [HCO_3^-]$$

As the normal ratio of bicarbonate to carbonic acid at physiologic pH is around 20:1, total CO2 will therefore be about 5% higher than serum bicarbonate. When you observe a difference between total CO2 and bicarbonate that is larger than 5%, the patient will be acidotic.

The total CO2 is not particularly informative by itself. However it will be abnormal in cases of chronic (compensated) acid-base disorders, such as when chronicly elevated carbon dioxide levels cause bicarbonate retention.

For most clinical decisions, the serum bicarbonate, PaCO2, and pH are used to evaluate acid-base status. The typical clinician probably ignores the TCO2. The diagnosis of causes of acid-base disturbance is discussed later in this manual.

Base Excess

The "Buffer Base" is the total of all the anionic buffer components in the blood — such as bicarbonate, sulfates, and phosphates. The base excess is the amount of deviation of the patient's buffer base from normal — in other words, how much extra basic (anionic) chemicals the patient has in his blood, expressed in milliequivalents per liter.

The base excess is also defined as the amount of acid (in mEq/liter) that would have to be added to the patient's blood to bring it to normal pH of 7.4.

Base excess can be a negative value. If the patient is acidotic, acid would have to be taken away to bring the pH to normal. In this case, for example, a base excess of -8 would mean that 8 mEq per liter of base would have to be added to bring the patient's blood to normal pH.

Although many physicians use the difference between the patient's bicarbonate and average bicarbonate of 24 as an indication of the patient's need for bicarbonate replacement, the base excess is a more accurate measure because it also takes into account other buffers such as phosphate and hemoglobin. It remains accurate in cases where the buffering capacity of hemoglobin is decreased due to anemia.

Base Excess of ECF

The base excess of blood does not truly indicate the base excess of the total extracellular fluid (ECF). Because of different protein content and the absense of hemoglobin, ECF has a different buffering capacity. What's more, each extracellular fluid (for example CSF vs interstitial fluid) has a different buffer status.

The clinical determination of the amount of bicarbonate required for treatment of severe acidosis is usually based on the base excess of the blood. There is an unavoidable inaccuracy, however, due to several factors:

1) the time course of the acidosis makes the blood acid poorly reflect the total body acid burden in many cases.
2) Depending on the state of hydration, body fluid distribution varies.
3) ECF as a percent of body weight varies with age and fat content.

In general, however, recommendations for bicarbonate therapy are in the range of 0.1 to 0.2 mEq times the body weight times the base excess (ignoring the minus sign).

Bicarb = 0.1 x (-B.E.) x wt in kg

In other words, with the formula of 0.1 times weight, you're essentially neutralizing the calculated acid excess in a fluid compartment one-tenth of the body size. If you use a value of 0.2 times weight times BE, you're treating a fluid reservoir 20% body size. This fluid volume includes the blood, plus fluids that quickly equilibrate with it. Of course, more acid will be present elsewhere, especially if the acidosis is of more chronic nature.

Effects of Acid-Base Balance on Oxygen

Oxygen status is affected by acid-base status. Oxygen affects the buffering capacity of hemoglobin through the Bohr Effect (discussed previously), but the opposite is also true. At a given oxygen pressure, oxygen saturation in the blood is lowered by increasing either carbon dioxide or hydrogen ion concentrations.

The amount of oxygen carried by the blood is related to PaO2, but the relationship is not linear. Rather, the saturation of hemoglobin with oxygen is related to PaO2 by a sigmoid curve. As the oxygen pressure in blood exceeds 70 mm Hg, only small amounts of additional oxygen are added to hemoglobin.

The presence of acid "shifts the curve to the left," meaning that less oxygen can be bound at a given PaO2. This mechanism assists hemoglobin in unloading oxygen in the capillaries, where acid concentration is higher. Raising the pH, conversely, increases the oxygen binding, allowing more total oxygen to be carried — a change that occurs in the alveolus as acid is eliminated through CO2.

Approach to the Abnormal Blood Gas

Acid-base disorders can be approached with three questions:

What is wrong?
What caused it?
What's being done about it?

The answer to the first question, "What is wrong?" is obtained by simple inspection of the values on the pH, PaCO2, and HCO3-.

If all three values are normal, the answer to "What is wrong?" is "Nothing," and the other two questions can be ignored.

If either pH, PaCO2, or HCO3- are abnormal, check the pH. If it's below 7.4, the answer to "What is wrong?" is "Acidosis." If above 7.4, "Alkalosis."

If the pH is within the normal range, but the PaCO2 or HCO3- (or both) are abnormal, an acid-base derangement exists, but the body has fully compensated for it. For example, with a pH of 7.35 (normal) and decreased bicarbonate of 18, an acidosis exists.

Check pH, PaCO2, HCO3-.
Anything abnormal? If no, quit.
pH greater than 7.4 = alkalosis
pH less than 7.4 = acidosis

The second question is "What caused it?" The answer is "Metabolic" if bicarbonate has caused the observed change in pH from 7.4. If carbon dioxide caused it, the answer is "Respiratory." If both are guilty, the answer is "Mixed metabolic and respiratory."

First look at the bicarbonate. Is it guilty?

Increased bicarbonate raises the pH. Low bicarbonate lowers the pH. If you see a pH above 7.4 and the bicarbonate is elevated above normal, it means bicarbonate is guilty of raising the pH. So a metabolic alkalosis exists.

If the bicarbonate is above 7.4 and the bicarbonate is decreased or normal, bicarbonate is not guilty.

Similarly, if the pH is below 7.4 and the bicarbonate is below normal, it means lack of bicarbonate is responsible for lowering the pH. Therefore a metabolic acidosis exists.

Look at the CO2. Is it guilty?

Carbon dioxide is acidic. A high CO2 will lower the pH, while a low CO2 will raise it. If the pH is above 7.4 and the PaCO2 is lower than normal, lack of CO2 is responsible. A respiratory alkalosis exists.

If, however, the CO2 is normal or elevated while the pH is above 7.4, then CO2 can't be contributing to the disturbance.

If both PaCO2 and HCO3- are shifted in a direction that would contribute to the pH abnormality, both are guilty. A mixed metabolic and respiratory abnormality exists.

Check pH, PaCO2, HCO3-.
Anything abnormal? If no, quit
pH greater than 7.4 = alkalosis
pH less than 7.4 = acidosis
who's responsible?

HCO3- shifted in direction of pH = guilty
CO2 shifted opposite of pH = guilty

The final question is "What's the body doing about it?" We're checking for compensatory changes — changes the body has made to compensate for the abnormality. This is an inherently inaccurate question, as I'll discuss later. Consider your answer a "best guess."

Assume the body has only two mechanisms to affect pH: respiratory and metabolic. Respiratory is CO2 and metabolic is HCO3-.

After you've identified the guilty party (CO2 or HCO3-), look at the other value. If that other value is abnormal, but in a direction that would move the pH back towards normal, then compensation is present.

If you've found that both HCO3- and CO2 are guilty, then obviously compensation isn't present. As an example, assume blood gases that show pH=7.33, HCO3=16.5, and PaCO2=32. The problem is acidosis (any abnormality plus pH >> 7.4). The guilty party is metabolic (HCO3- is low, shifted in a direction that causes acidosis). Respiratory compensation is present (CO2 is abnormal in a direction that would raise the pH back towards normal.

Compensation by respiratory means is very fast, occurring within seconds or minutes. This compensation occurs via the body's control of respiratory rate through the brain respiratory center. Thus respiratory compensation for metabolic abnormalities is seen almost immediately.

Metabolic compensation, on the other hand, is slow. It occurs through elimination of acid or alkali by the kidney. Hours go by before significant compensation is seen. Metabolic compensation will occur for chronic respiratory disturbance, but also, metabolic correction through the kidney will be seen for metabolic disturbances.

Check pH, PaCO2, HCO3-.
Anything abnormal? If no, quit
pH greater than 7.4 = alkalosis
pH less than 7.4 = acidosis
Who's responsible?
HCO3- shifted in direction of pH = guilty
CO2 shifted opposite of pH = guilty
If only one guilty, check "innocent" value.
Shifted = compensation present.

Is this accurate? No. Identifying the source of acidosis and presence of compensation assumes that the same process has been going on all along. If body's state changes from one source of abnormality to another, or if two completely separate pathological processes are present, your "guess" will be wrong.

For example, Phil Smith has a heart attack and goes into V-fib. He develops both respiratory and metabolic acidosis. Then he gets defibrillated and wakes up. As he realizes that he has to give up his favorite cholesterol-rich foods, he hyperventilates. Now blood gases are drawn.

pH = 7.44 PaCO2 = 28 HCO3 = 18.6

Looking at these gases, you diagnose “fully compensated (chronic) respiratory alkalosis.” Not true. Phil has an acute respiratory alkosis superimposed upon a “slightly less acute” metabolic acidosis. Remember that bicarbonate abnormalities cannot change quickly.

Computer interpretation (such as that used in Mad Scientist Software's Blood Gases program) look for "zones" of blood gas values where clinical disturbances tend to fall. This gives a 95% level of certainty about mixed disorders and compensation. At the bedside however, you're on your own.

Whenever you diagnose a respiratory cause for an acid-base abnormality, with metabolic compensation, consider whether the abnormal bicarbonate could be a “leftover” or separate metabolic abnormality of the opposite type.

For example, in aspirin poisoning, both metabolic acidosis and respiratory alkalosis occur as a result of the aspirin. Depending on whether the pH happens to be above or below 7.4 at the moment, you might incorrectly call it a “compensated respiratory alkalosis” or a “compensated metabolic acidosis.” Always consider the clinical history. Then you can correctly decide whether“compensation” is really compensation, or a separate abnormality.

Like most everything else in medicine, blood gas interpretation requires a consideration of the patient history and your examination findings. Let's review our completed "bedside" algorithm.

Acid-base Disturbance Diagnosis Algorithm
Check pH, PaCO2, HCO3-.
Anything abnormal? If no, quit
pH greater than 7.4 = alkalosis
pH less than 7.4 = acidosis
who’s responsible?
HCO3- shifted in direction of pH = guilty
CO2 shifted opposite of pH = guilty
If only one guilty, check “innocent” value.
Shifted = compensation present.
History compatible with mixed disorder?
Not true compensation.

Metabolic Acidosis

Clinical causes of metabolic acidosis

Tissue metabolism normally results in about 12,500 milliequivalents of acid production per day. This acid is in the form of CO2, and after circulation to the lungs, is removed from the body in expired air. If aerobic metabolism ceases (due to lack of oxygen or inability to use available oxygen due to metabolic poisoning), tissues are unable to completely oxidize sugar to CO2. Instead, sugar is only partly oxidized to lactic acid. As this acid cannot be expired through the lungs as CO2 is, it remains in circulation, causing metabolic acidosis.

In untreated diabetes, normal sugar metabolism is deranged due to lack of insulin. In this case, acid buildup is due to acetoacetic and betahydroxybutyric acids.

A certain amount of acid is formed when dietary proteins are metabolized. These

proteins contain sulfate and phosphate groups that, after metabolism, form sulfuric and phosphoric acid. These acids amount to only about 150 mEq per day, however they must be excreted from the body through the slow process of kidney filtration. If the kidneys fail, acidosis results after several days. Ingestion of acidifying salts, and loss of bicarbonate through chronic diarrhea, are less common causes of metabolic acidosis.

Example:
pH = 7.21 PaCO2 = 40 HCO3 = 15.6

Compensation for metabolic acidosis

as the blood becomes more acidic, the brain's respiratory centers are stimulated to increase the rate and depth of breathing. This lowers the CO2 in the blood, decreasing its acidity.

The kidney then begins to remove the excess acid. As the plasma is filtered, acid anions enter the urine. In the kidney tubules, hydrogen ion is secreted. For each hydrogen ion that enters the urine, a sodium ion and a bicarbonate ion are put back into the plasma. In this way, acid is eliminated from the body.

Example of compensated metabolic acidosis:
pH = 7.34 PaCO2 = 28 HCO3 = 14.7

Metabolic Alkalosis

Causes of metabolic alkalosis

Fruits are the normal source of alkali in the diet. They contain the potassium salts of weak organic acids. When the anions are metabolized to CO2 and removed from the body, alkaline potassium bicarbonate and sodium bicarbonate remain. Metabolic alkalosis may be found in vegetarians and fad dieters who are ingesting a low-protein, high fruit diet.

A more efficient way to get alkali into the body is to consume sodium bicarbonate. This common heartburn remedy is probably the most common cause of symptomatic metabolic alkalosis.

If acid is eliminated from the body, it has the same effect as adding alkali. Persons with protracted vomiting of acidic stomach juices will often develop metabolic alkalosis, as acid is secreted into the stomach then vomited out of the body.

Example:
pH = 7.51 PaCO2 = 39 HCO3 = 30.4

Compensation for metabolic alkalosis

Short term, a decrease in respiratory rate leads to an increase in serum carbon dioxide levels. (The carbon dioxide is transported as hydrogen ion — buffered by hemoglobin — and bicarbonate.) This lowers the pH towards normal, partially compensating for the additional alkali present in the blood.

The slow process of eliminating bicarbonate through the kidney then begins. Hydrogen ions are transported from the filtered urine back into plasma, with sodium ions and bicarbonate left behind. Alkaline sodium bicarbonate is thus eliminated.

Example:
pH = 7.45 PaCO2 = 46 HCO3 = 31.2

Respiratory Acidosis

Causes of respiratory acidosis

Buildup of carbon dioxide occurs when ventilations are inadequate. This is usually due to absense of adequate respiratory effort — such as when central control of respiration is depressed due to narcotics or barbiturates. When respiration ceases due to cardiac arrest, of course, respiratory acidosis is an immediate result.

Respiratory acidosis can also result when obstruction of air motion leads to carbon dioxide buildup. Severe asthma and foreign body obstruction are examples.

Example:
pH = 7.21 PaCO2 = 55 HCO3 = 22

Compensation of respiratory acidosis

whereas respiratory changes can occur within seconds or minutes, metabolic changes take hours to days. Compensation for respiratory acidosis must occur through elimination of acid through the kidney, as discussed above under metabolic acidosis. Only in chronic respiratory problems, such as severe obstructive airway disease, will compensation be seen.

Example:
pH = 7.34 PaCO2 = 56 HCO3 = 29.5

Respiratory Alkalosis

Causes of respiratory alkalosis

Respiratory alkalosis occurs due to hyperventilation. The hyperventilation may be due to psychological causes — in fact, this is the most common cause.

In other causes, the hyperventilation may be due to abnormal stimulation of ventilation due to disease. Changes in the lung due to pulmonary embolism, asthma, or pulmonary edema often trigger increased respiratory rate, resulting in respiratory alkalosis.

Central stimulation of respiration occurs in aspirin poisoning. This respiratory alkalosis is a separate effect from the metabolic acidosis produced by aspirin.

Example of respiratory alkalosis:
pH = 7.57 PaCO2 = 24 HCO3 = 21.5

Compensation of Respiratory Alkalosis

Respiratory alkalosis must exist for hours before metabolic compensation can be seen. Alkaline sodium hydroxide is eliminated by the kidney, returning the pH back towards normal, as discussed above under metabolic alkalosis.

Example:
pH = 7.46 PaCO2 = 22 HCO3 = 15.3

Therapy of Respiratory Acidosis

the treatment of respiratory acidosis isn't difficult — in theory. All you have to do is increase the ventilation of the lungs. This removes carbon dioxide from the blood stream, raising the pH. The increase in ventilation may be easy in the intubated cardiac arrest or drug OD patient. Just turn up the ventilator, or tell the "bagger" to bag a little faster and deeper.

In the conscious patient with severe asthma or pulmonary edema, a decision must be made whether to await results from conservative therapy, or to take control the airway through intubation and assisted ventilation. (This decision, in practice, is based more on "gestault" of the clinical picture rather than on the level of carbon dioxide.) You either improve air motion with drugs, or force better air motion with an artificial airway.

In a patient with poor gas exchange due to intrapulmonary causes — that is, disease within the lung itself — increasing ventilatory rate and depth may be only marginally helpful. In this case, only improvement of the disease process will help.

Some cases of carbon dioxide retention are better untreated. For example, consider this patient with CHF and emphysema:

pH = 7.32 PaCO2 = 78 HCO3 = 39.3 PaO2 = 43

Review of past hospital records consistently shows a CO2 around 70 at discharge. This patient has a chronic (compensated) respiratory acidosis. Trying to "normalize" this patient's blood gases would be dangerous. And even if you succeeded, once the patient was breathing on his own he would retain CO2 again acutely, resulting in a severe acute respiratory acidosis of pH =7.1! If the patient must be intubated, sufficient "dead space" must be provided within the ventilator tubing to keep the CO2 in the patient's usual range.

Therapy of Metabolic Acidosis

Mild cases of metabolic acidosis are best left alone. Usually no treatment is needed if the pH is above 7.1, and rarely is it needed if the pH is above 7.2, although the patient's level of discomfort and compensating hyperventilation must be considered.

Metabolic acidosis is treated with sodium bicarbonate, given intravenously.

There is considerable question, however, how beneficial acidosis treatment is for certain patients.

For the semi-comatose diabetic in ketoacidosis, there's no question that bicarbonate will raise the serum pH. But as the acid is neutralized in the blood, CO2 is formed (you remember the chemical reaction). The increase in pH decreases respiratory drive, which slows the elimination of this extra carbon dioxide. The CO2 diffuses into the cerebrospinal fluid, causing a paradoxical lowing of pH around the brain, with deepening of coma. The moral: give bicarb slowly and maintain the hyperventilatory state, even if bag-valve assist or intubation is required.

For the patient in cardiac arrest, raising the pH hasn't been shown to improve the ultimate outcome. And alkalosis caused by too much bicarbonate is positively deadly for the arrest victim. On the other hand, since the American Heart Association changed its standards to eliminate the routine use of bicarbonate, I'm seeing a lot of arrested patients from the field with pHs of 6.9 — which may lengthen the "code time" if there's pulseless electrical activity because the patient can't be declared dead until he's both "warm and dead" and "acid-base normal and still dead." For now, treat the cardiac arrest patient with bicarbonate only based on proven need by blood gases.

Bicarbonate dosage recommendations vary widely — most sources recommend from 0.1 to 0.3 times the weight of the patient in kilograms times the (negative) base excess (BE) expressed in milliequivalents per liter. In my experience, 0.2 x weight x BE is about right for the typical patient. The calculated result of this formula will have units of milliequivalents — the number you calculate is the dose in milliequivalents.

However, the recommendation I'll give to you (and the formula given in both the Blood Gases disk and the ACLS training software) is based on the more conservative recommendation of the American College of Emergency Physician's textbook. This formula is 0.1 x weight x BE. The minus sign on the base excess is ignored.

Bicarb Dose = 1/10 of weight in kg times base excess

Bicarb = 0.1 x wt x BE

After giving bicarbonate, a repeat blood gas analysis should be performed (after a couple of minutes to "blow off" the CO2 that is formed). Often, an additional dose must be given. If you decide that use of bicarbonate is needed in a situation where blood gases are NOT available, for example with a tricyclic overdose or diabetic patient in coma far from a hospital, you need a reasonable way of calculating an empiric dosage.

In this situation, give the patient one mEq for every kilogram of body weight:

Empiric Bicarb = 1 mEq x weight in kg

in the cardiac arrest victim, a continuing dosage may be necessary IF BLOOD GASES ARE NOT AVAILABLE. This dose is 1/2 mEq per kilogram every 10 minutes. However, you'll probably never use this 1) because you should be getting blood gases, and 2) because if your CPR is so ineffective that acid continues to build up at that rate you'll never save the patient anyway. The final words on bicarbonate therapy are: Have a good reason for using it, be aware of its problems and complications, and monitor your therapy with repeat blood gas analysis.

Blood Gas Analysis and Critical Care Medicine

Critical care medicine is one of the newest and most rapidly growing medical specialties. Surprisingly new, in fact, because critical care medicine is, basically, applying physiologic principles to the care of seriously ill patients, something physicians have been trying to do for centuries. Modern critical care medicine is distinguished from its predecessors by incredible products of technology, advances in biochemistry, and astonishing know-how. We now have at our disposal sophisticated monitoring devices that provide moment-to-moment information about key circulatory and respiratory physiologic variables, how they are deranged by disease, and how they respond to intervention. We also have available an astonishing variety of high-tech instruments and powerful medications that we use to remedy ailing physiology, ventilators for breathing, machines to rid the body of excess fluid and impurities, vasopressor drugs to shore up flagging blood pressure, and even instruments to supplement a failing heart. Another distinguishing feature of critical care medicine is that it is practiced in specialized facilities, intensive care units, within acute care hospitals; these focal points for costly instrumentation are also headquarters for the expertly trained and knowledgeable physicians, nurses, and other professionals who care for desperately ill patients.

This paper retraces the history of the development of knowledge about blood gas transport, including the discovery of oxygen and carbon dioxide, the evolution of techniques to measure respiratory gases in the blood, and finally, how all this came together in Blegdams hospital, Copenhagen, on August 25, 1952, when an ingenious anesthetist, Bjorn Ibsen, came out of the operating room and started the modern critical care movement. We conclude with some comments about the remarkable changes that have occurred during the 45 years between then and now, and we make a few speculations about what the future might have in store.

BLOOD GAS TRANSPORT

According to Hippocrates (460-377 BC), good health resided in a proper balance among the four humors: blood, phlegm, black bile, and yellow bile, a balance that depended on the generation of life-giving heat within the left ventricle. Aristotle (384-323 BC) concluded that arteries carried air, but Erasistratus of Cos (about 330-250 BC) taught that "pneuma," created within the left ventricle from lung air, was the substance pumped through arteries to the tissues. Galen (130-199 AD) believed that the heart sucked blood-cooling air from the lungs into the left ventricle where the vital heat was generated, that pneuma was transported in arteries to the tissues, hence to veins via anastomoses, and that after arriving back in the heart, blood passed through minute pores in the septum from the right into the left ventricle for replenishment. These ideas went unchallenged by physicians until the 16th century.

Michael Servetus (1511-53) studied and practiced medicine, but his principal interest became theology. In *Christianismi Restitutio* (1553), Servetus contradicted Galen, concluding that the communication between the right and left sides of the heart was "not through the middle wall of the heart . . . but by a very ingenious arrangement the subtle blood is urged forward by a long course through the lungs," the first postulate of the existence of pulmonary capillaries. Severtus sent his book to John Calvin, who considered it heresy, had him arrested, jailed, and burned at the stake within the year of publication.

It remained for William Harvey (1578-1657), a brilliant anatomist and physician, to describe the circuit of blood flow around the body, including its circulation through the lungs. In his monumental *De Motu Cordis* (1628), Harvey flatly stated that blood was pumped from the right ventricle through the pulmonary circulation to the left ventricle, passing through "the invisible porosities of the lungs and the minute connections of the lung vessels." These theoretic pulmonary porosities became anatomic reality when first seen by the celebrated Italian microscopist Marcello Malpigi (1628-94). Thus, the anatomy of the circulation was concisely described, but the nature of the vital ingredient by which breathing fed the inner life-giving flame remained elusive. It took over 100 years to find it.

Discovery of Carbon Dioxide

Joseph Black (1728-99), who became Professor of Chemistry in Edinburgh, showed while he was a medical student that large quantities of a gas, which he called "fixed air" (carbon dioxide), were generated by heating or acidifying chalk. He was the first to prove that the same gas was present in exhaled air.

Discovery of Oxygen

Robert Boyle (1627-91) established the fact that the long-sought, life-sustaining substance was contained within air itself. His assistant, Robert Hooke (1635-1703), demonstrated in 1667 that a dog whose exposed lungs had multiple pleural punctures could be kept alive by providing a constant flow of air through the trachea without any movement of the lungs. Hooke showed, as had Richard Lower (1631-91), those arterializations of blood in the lungs occurred through the introduction of fresh air. No one noted that something was taken out of the air and something else was added.

The English Unitarian "dissenting" minister and amateur chemist, Joseph Priestley (1733-1804), who lived next door to a brewery, got interested in the waste gas product of fermentation and started investigating gases. He discovered that the gas given off by heating mercuric oxide caused a much brighter flame than plain air. In 1774, he showed that this gas was essential not only to combustion, but also to respiration and to the greening of plants. Priestley was the first to demonstrate that ordinary air, in which a candle would no longer burn and a mouse no longer live, might regain its former vital properties if green plants were kept within the sealed chamber. He eventually managed to isolate 10 new gases, including nitrous oxide and carbon monoxide, invented carbonated beverages, gum rubber erasers, and refrigeration. In 1791 his Birmingham home was burned and his laboratory trashed by a royalist-sectarian mob incensed by his support of the French revolution. He immigrated with his family to Pennsylvania in 1794.

Priestley was one of the great social and political minds of the Enlightenment. He had a significant influence on his good friend Thomas Jefferson, and had his portrait painted by the most famous American painter of the time, Gilbert Stuart.

The Swedish pharmacist, Carl Wilhelm Scheele (1742-86), also discovered the gas we call oxygen about 1772, but delayed publishing his findings until 1777. Neither he nor Priestley understood that their gas combined with fuel in burning or respiration, because they believed in phlogiston as the fiery substance that came out of combustible materials during burning.

Antoine Lavoisier (1743-94), France's greatest chemist reported to the French Academy on April 14, 1774 that metals like phosphorus and sulfur gained weight when burned by combining with a constituent of air. Later that year, Lavoisier was visited in Paris by Priestley, who described generating his new gas in which a candle could burn with a much brighter flame than usual. Lavoisier then realized that it was Priestley's gas in ordinary air that had combined with his phosphorus and sulfur, and that combined with all fuel when burning takes place. Air, he realized, contained two distinct constituents: one that was respirable, which he called "air éminemment respirable," and another that was nonrespirable. In 1777 he realized that Black's "fixed air" must be a compound of coal, and that it was produced both by respiration and by combustion. Together with the mathematician Pierre Simon de Laplace (1749-1827), Lavoisier concluded that the generation of heat in a coal fire was in principle of the same nature as that taking place in the body. Both processes required Priestley's new gas, which Lavoisier now called oxygen, and led to the production of carbon dioxide and water, ultimately yielding the same quantity of heat per unit of oxygen consumed. Lavoisier's tremendous achievements immediately revolutionized chemistry and had a profound influence on medicine and physiology.

Gas Exchange in Lungs and Blood

The first to document the presence of both oxygen and carbon dioxide in blood was (Sir) Humphrey Davy (1778-1829), who published the results of his extraction process in 1799. Thirty-eight years later, in Berlin, Heinrich Gustav Magnus (1802- 70), using quantitative techniques, found more oxygen and less carbon dioxide in arterial blood than in venous blood, and he concluded that carbon dioxide must be formed in or added to the blood during its circulation. He upset the standard idea that heat production occurred in the lungs by showing that blood gas exchange took place within the lungs, whereas the oxidation and generation of body heat occurred elsewhere in the body.

Magnus was unable to measure the solubility of oxygen and carbon dioxide in blood because he did not understand that chemical binding was occurring. The discovery of the high affinity of oxygen for hemoglobin at low partial pressures was made in his thesis research by Lothar Meyer (1830-95). Meyer dedicated his dissertation to Professor Carl Ludwig (1816-94), which stimulated Ludwig to investigate blood gas exchange himself. Ludwig eventually concluded that the respiratory gases were actively secreted by the lungs, whereas Eduard Pflüger (1828-1910) claimed all exchange could be explained solely by diffusion.

Their heated debates in the 1870s were sufficiently inconclusive to lead to further studies in Copenhagen by Christian Bohr (1855-1911), a former pupil of Ludwig's. Using improved methods for measuring P_{O_2} in blood, Bohr was convinced he had shown active pumping of oxygen. After spending time working with Bohr, John Scott Haldane (1869-1936) joined the secretionists, and remained convinced, despite later proof to the contrary, until his death. The controversy ended with a brilliant series of seven papers in a single issue of the *Scandinavian Archives of Physiology* in 1910 by August Krogh (1874-1949), with the help of his wife Marie (1874-1943). With apologies for disproving the secretion theory held by his mentor, Christian Bohr, Krogh proved to everyone except the stubborn Haldane that the mechanism of gas exchange in the lungs was uniquely explained by the physical forces of diffusion.

Hemoglobin and Oxyhemoglobin Dissociation

Vincenzo Menghini (1704-59), at the University of Bologna, was the first to show that erythrocytes contained considerable quantities of iron whereas plasma did not. In Stockholm, Jöns Jacob Berzelius (1779-1848) was able to split the red material in blood into a protein called "globin" and a colored component containing iron oxide. Johannes Mulder (1802-80), Professor of Chemistry in Utrecht, determined the chemical composition of the pigmented portion, which he named "hematin," and showed that it took up oxygen. In 1862, this red pigment was renamed "hemoglobin" by Felix Hoppe-Seyler (1825-95) after he was able to crystallize it and describe its spectrum. He demonstrated that the crystalline form differed from one animal species to another. Using his own newly constructed gas pump, he found that oxygen formed a loose, dissociable compound with hemoglobin, which he called "oxyhemoglobin."

Carl Gustav von Hüfner (1840-1908), who succeeded Hoppe-Seyler as Professor of Physiological Chemistry in Tübingen, reported experimental evidence that 1.34 ml of oxygen combined with 1 g of crystalline hemoglobin; this was precisely the same as his theoretic value based on the iron content that he had also determined. The agreement of the two numbers led to much skepticism, but it was later essentially confirmed: the current theoretic value being 1.39 ml/g.

By drawing blood samples from animals exposed to different barometric pressures and determining the oxygen content of the blood, the Frenchman Paul Bert (1833-86) produced the first *in vivo* relationships between oxygen pressure and oxygen content. More detailed descriptions were provided by Bohr, who showed the effect of carbon dioxide on the position of the oxyhemoglobin dissociation curve, known as the "Bohr effect," which he reported in 1904 together with Karl Albert Hasselbalch (1874-1962) and August Krogh. The dissociation of oxyhemoglobin was affected by the pH, ionic strength, and temperature of the solution.

In 1910, Archibald Vivian Hill (1886-1977) proposed a simple equation for the dissociation curve, with slope n of about 2.7, $S/(1 - S) = kP^n$, where S is saturation and P is P_{O_2}, mm Hg. It fit poorly at low saturation. Hill's equation was modified by John Severinghaus by using two terms, one with n = 3 and one, n = 1: $S/(1 - S) = k(P^3 + 150P)$. For the standard human dissociation curve at pH = 7.40, T = 37° C, k = 1/23,400.

This provided a remarkably accurate standard dissociation curve with maximum error of ± 0.5% saturation from 0 to 100%. Its accuracy may relate to the kinetics by which the last three oxygen molecules combine essentially simultaneously, because the second oxygen causes a shape and affinity change.

Hemoglobin has probably been studied more than any other protein. Yet it was not until after World War II that the Nobel Laureates Linus Pauling (1901-94), California Institute of Technology, and Max Perutz, University of Cambridge, working independently, defined the chemical structure of the hemoglobin molecule, explained the binding and release of oxygen, and documented the accompanying molecular conformational changes. Genetic disorders of hemoglobin were found to afflict millions of people and to be the most common single gene disorder of mankind. They are usually caused by the formation of a hemoglobin variant with a single amino acid substitution in either the alpha- or beta-globin chains. Some of the aberrant hemoglobin molecules interfere with oxygen transport, some impair red blood cell survival.

ACID-BASE BALANCE AND CARBON DIOXIDE

While fermentation and respiration were recognized as producing carbon dioxide in Black's time, the mid-18th century, and acids and bases were identified far earlier, the connection between them was slow to appear. The alkalinity of blood was discovered in Paris by Hilaire Marin Rouelle (1718-79), using titration and color indicators. In 1831, William B. O'Shaughnessy (1809-89), an Irish physician working in London and later in India, showed that cholera reduced the "free alkali" of the blood. Later, Henry Bence Jones (1813-78), a physician at St. George's Hospital in London, recognized the relationship between blood alkalinity and stomach acid secretion. The relationship between the carbon dioxide content of blood and its alkalinity was established in his 1877 thesis by Friedrich Walter (b. 1850), which made it possible to study acidosis and alkalosis by extracting from and quantifying the carbon dioxide in blood. Perhaps this association of carbon dioxide with alkali was responsible for the long delay in understanding its role as carbonic acid when dissolved in water.

In 1907 the remarkable ability of blood to neutralize large amounts of acid led Lawrence J. Henderson (1878-1942), then an instructor in biochemistry at Harvard University, to investigate the relationship of bicarbonate to dissolved carbon dioxide gas, and how they acted as buffers of fixed acids. It was his insight that helped chemists and physiologists to realize that when acids are added to blood, the hydrogen ions react with blood bicarbonate, generating carbon dioxide gas, which is then excreted by the lungs, almost eliminating the increased acid. Henderson rewrote the laws of mass action for weak acids and their salts. In the case of carbon dioxide and bicarbonate he defined the dissociation constant k as the hydrogen ion concentration at which half of the carbonic acid is dissociated: $k = [H+][HCO_3^-]/[H_2CO_3]$.

Assuming that all dissolved carbon dioxide was carbonic acid, the denominator became $SPCO_2$, where S is the solubility of carbon dioxide in mM/mm Hg. Following this lead, in 1917 Hasselbalch adapted Henderson's mass law for carbonic acid to the logarithmic form known as the Henderson-Hasselbalch equation, a staple of contemporary clinical acid-base analysis: $pH = pK' + \log[HCO_3^-/SPCO_2]$.

Hydrogen Ions

Physical chemistry began as a discipline about 1884, the year Jacobus van't Hoff (1852-1911), a student of the thermodynamic theories of Josiah W. Gibbs (1839-1903) and Henri Louis Le Chatelier (1850-1936), realized that the osmotic pressure generated by molecules (or later, ions) in solution was exactly the same as they would exert at the same concentration in a gas, thus linking solution theory to the long established laws describing the behavior of gases. New understanding of electrolyte solutions was provided by Svante Arrhenius (1859-1927), who used conductivity in his thesis research to infer the existence of ionization of salts as their concentration was reduced. The Arrhenius discovery stimulated Wilhelm Ostwald (1853-1932) to make the first electrometric measurement of hydrogen ion concentration by the potential on a platinum electrode in solutions saturated with hydrogen gas. He discovered that this potential was a logarithmic function of the strength of the acid. Ostwald's student, Hermann Nernst (1864-1941), discovered the energetic equivalence of Faraday's constant F to PV/n of the gas laws, thereby mathematically linking electrometric ion activity to the behavior of gases. After Nernst moved to Göttingen, his assistant Heinrich Danneel (1867-1942) discovered the reaction of oxygen with a negatively charged metal (cathode), the basis of oxygen polarography, later developed by Jaroslav Heyrovsky (1890-1967) in Prague. Nobel prizes in chemistry were awarded to van Hoff (1901), Arrhenius (1903), Ostwald (1909), Nernst (1920), and Heyrovsky (1959).

Use of pH for Hydrogen Ion Activity

The credit (or blame) for introducing the term pH, the negative log of hydrogen ion (H^+) concentration, goes to S. P. L. Sørensen (1868-1939), who apparently tired of writing seven zeros in a paper on enzyme activity and wanted a simpler designation. Although the use of pH instead of nanomoles of H^+ has been repeatedly challenged, pH has survived in large part because the behavior of a substance in a chemical system is proportional to its energy (chemical potential), and this, in turn, is a logarithmic function of the activity of the substance. A pH electrode responds to the chemical potential of H^+, and thus the instrument provides a precise and readily obtained measurement of the chemical behavior of H^+ in the system, exactly what the chemist, physiologist, and clinician need to know. The pH of blood, and of neutral water, changes linearly with temperature, whereas H^+ concentration is a log function of temperature.

pH Electrode

In 1906, Max Cremer (1865-1935) discovered an electrical potential proportional to the acid concentration difference across thin glass membranes. By 1909, Fritz Haber (1868-1934) and Zygamunt Klemensiewicz (1886-?) had constructed and studied glass H+ electrodes. A modified Ostwald platinum electrode was used by Hasselbalch in 1912 to measure blood pH at body temperature; to avoid the loss of carbon dioxide during hydrogen gas equilibration, he equilibrated a small bubble of hydrogen with successive samples of blood until P_{CO_2} in the bubble was equal to that in the blood sample. This method allowed Hasselbalch to advance the understanding and definition of clinical acid-base disturbances. The first blood glass pH electrode—specifically designed to keep carbon dioxide in solution—was constructed by Phyllis T. Kerridge (1902-40) in London in 1925. Seven years later, D. A. McInnes and D. Belcher replaced the cup with capillary tubing and added a clever three-way glass stop-cock for making a fresh liquid junction with saturated potassium chloride, thus creating the first truly precise blood pH electrode. The pH of blood is a strong function of the temperature of measurement, falling 0.015 unit per degree Celsius rise; to mitigate this effect, a thermo stated blood pH apparatus was invented in 1931, but did not become commercially available until the mid-1950s. Accurate temperature correction factors for blood pH were first published by T. B. Rosenthal in 1948.

BLOOD GAS ANALYSIS

Until the introduction of electrochemical methods of analysis in the mid-1900s, measurement of blood oxygen and carbon dioxide contents depended on vacuum extraction, usually in combination with acidification to liberate the contained carbon dioxide, and chemical alteration of oxyhemoglobin to liberate the oxygen. The freed gases were quantified volumetrically until Donald D. van Slyke (1883-1971) developed a more accurate manometric method, which became the gold standard of blood gas analysis for more than a quarter of a century.

P_{CO_2} Analysis by Equilibration

Blood carbon dioxide content is almost all bicarbonate. Since the formulation of the Henderson-Hasselbalch equation, it had been possible to calculate P_{CO_2}, but only after first measuring the blood pH with a glass electrode and the carbon dioxide content with the Van Slyke technique. This cumbersome and time-consuming methodology was used on a grand scale—clinically—for the first time in Copenhagen during the polio epidemic of the early 1950s to document the need for, and consequences of, breathing support (described more fully below). These exigencies led Poul Astrup to come up with a novel technique based on the principle that in the clinically relevant range, there was a linear relationship between the pH and log P_{CO_2} of blood. Astrup designed an apparatus in which one could first measure the pH of a blood sample, and then bubble gas of known P_{CO_2} through the sample, and measure the pH again. He did this at two different P_{CO_2} gas values, plotted the measured pH against log P_{CO_2}, drew a line between the points, and located the initial pH on this line, to identify the original P_{CO_2}. The deviation of this line from a normal position was used to define the acid-base imbalance of the patient.

Terms such as standard pH and standard bicarbonate were used at first, but later the term base excess, or its *in vivo* equivalent, standard base excess (SBE), came into widespread use. This system was promptly marketed by Radiometer A/S as the Astrup Apparatus, and shortly thereafter modified by Astrup's associates, especially Ole Siggaard Andersen, to use very small blood samples.

P_{CO_2} Electrode

In Columbus, Ohio, Richard Stow, who was also struggling with the care of polio patients, conceived of an electrode for measuring P_{CO_2}. Stow knew that carbon dioxide permeated rubber freely and that it acidified water. He constructed his own glass pH and reference electrode, wrapped it with a thin rubber membrane over a film of distilled water, and showed it responded to changing P_{CO_2}. Stow refused to patent the idea, because he believed his electrode would never be stable enough to be reliable. At the NIH in Bethesda, Severinghaus and A. Freeman Bradley showed that its sensitivity could be doubled and it could be stabilized by adding $NaHCO_2$ to the electrolyte.

P_{O_2} Electrode

Toward the end of the 19th century, both Pflüger and Krogh had developed methods for equilibrating small gas bubbles with large volumes of blood to permit analysis of the gas tensions in the bubble. In 1942, F. J. W. Roughton (1899-1972) and Per F. Scholander (1905-80) constructed a syringe with a calibrated capillary attached for analysis of carbon monoxide in blood. In 1945 Richard Riley adapted the Roughton-Scholander syringe method for measuring blood P_{O_2} and P_{CO_2}. The "Riley bubble method" was widely used by respiratory physiologists, particularly to study ventilation-perfusion relationships in the lungs, but it had virtually no clinical utility. That came with the development and perfection by Leland Clark of the P_{O_2} electrode. In 1952 Clark adapted polarography to measure performance of his blood oxygenator by covering a platinum cathode with cellophane to exclude protein. He also tried a polyethylene membrane successfully, but at first rejected it, believing it could not be dependable because the reference electrode was outside the membrane. On October 4, 1954, he suddenly realized he could put a reference anode under the polyethylene along with the cathode, and that day, he constructed the first modern P_{O_2} electrode.

Clark and Stow independently discovered the technique of using differentially permeable membranes to separate an electrochemical cell from the substance to be analyzed. Clark's P_{O_2} electrode required stirring and calibration with tonometered blood. In 1957, Severinghaus and Bradley constructed the first blood gas apparatus as a thermostated water bath in which their modification of the Stow P_{CO_2} electrode and a cuvette with stirring paddle for Clark's electrode were combined with a miniature tonometer, in which a blood sample could be equilibrated with known gas to calibrate the P_{O_2} electrode (32). The needs for stirring and tonometric calibration were eliminated by miniaturizing the cathode in 1959. Astrup's equilibration method gradually gave way to three-electrode systems for measuring pH, P_{CO_2}, and P_{O_2}, which are extensively used in clinical and research studies of cardiopulmonary physiology, and which are the current gold standard of respiratory monitoring in intensive care units throughout the world.

Transcutaneous Blood Gas Analysis

Beginning in 1972, Dietrich Lübbers (1918-) and several of his students in Marburg demonstrated that when skin was heated to 42-45° C, it was possible to measure transcutaneously a reasonable value for arterial P_{O_2}, especially in newborn babies. Shortly afterward, transcutaneous electrodes were developed for measuring P_{CO_2}. The development and evaluation of transcutaneous P_{O_2} and P_{CO_2} sensors in the United States was catalyzed in 1974 by the Division of Lung Diseases through the request for contract proposal mechanism. Currently, optical (fluorescence) techniques for measuring pH, P_{CO_2}, and P_{O_2} are competing with electrode methods for both laboratory and clinical (cardiopulmonary bypass apparatus control and intravascular measurement) applications.

Oximetry

The concepts underlying oximetry go back to Hoppe Seyler's connection of oxygen with hemoglobin's red color (above) and the spectroscope invented by Robert W. E. Bunsen (1811-99) and Gustaf R. Kirchoff (1824-87) in Heidelberg. Important contributions were made by an American, Glen Millikan (1906-47), and a German, Kurt Kramer (1906- 85), whose respective research was greatly accelerated during World War II by the need to monitor blood oxygen saturation because pilots of both the Allied and German air forces were blacking out at high altitudes. The concept of using multiple wavelengths to distinguish among pigments of carbon monoxide-, met-, and oxy-hemoglobins was introduced by Robert Shaw of San Francisco in 1964. Finally, in 1972 in Tokyo, Takuo Aoyagi invented the pulse oximeter, which is based on the equation he derived that makes it possible to compute arterial oxygen saturation without precalibration, independent of ear thickness, skin pigment, hemoglobin concentration, and light intensity.

For more detailed history of blood gas physiology and analysis, the reader may consult Astrup and Severinghaus and West's recent collection of essays.

INTENSIVE CARE MEDICINE

Clinical use of blood gas analysis of pH and P_{CO_2} began with the polio epidemics as described previously, but commercial devices able to also measure P_{O_2} came surprisingly slowly into common use. Not so intensive care medicine. Like the goddess Venus, it emerged fully grown and ready for action. The birth and instant maturation of intensive care medicine occurred in 1952 during the last worldwide epidemic of poliomyelitis, a scourge that in Copenhagen, Denmark, was unprecedented in its number of victims, in the high attack rate among adults, and in the severity of the accompanying paralysis. The lessons learned while ventilating hundreds of patients who were unable to breathe by themselves prompted the rapid design, manufacture, and extensive deployment of the prototypes of modern ventilators. The need for prompt and accurate pH and P_{CO_2} measurements forced the relocation of blood gas analysis from the research laboratory to the ward, and accelerated the development of new techniques purely for clinical application.

Finally, the fact that the newly developed team—anesthetist, internist, surgeon, and clinical physiologist, supplemented by nurses and medical students—was a better organization than the pre-existing hierarchical system for coping with the huge problem that presented itself was accepted and was here to stay. Thus, all the basic elements of modern intensive care were formulated in Copenhagen during the late summer and fall of 1952. Although its history has been nicely recounted by Wackers, the highlights are worth repeating here in view of their importance and relevance.

BLEGDAMS HOSPITAL, 1952

No one was ready for the epidemic of poliomyelitis that ravaged the earth in the early 1950s. And the staff at Blegdams hospital in Copenhagen, a center of medical and epidemiologic expertise in infectious diseases, was as ill prepared as everywhere else. During the first 3 wk of the epidemic, 31 patients with respiratory muscle paralysis or bulbar polio were admitted and ventilated with the then available respirators: one Emerson iron lung and six cuirass machines. Twenty-seven of the 31 patients died within 72 h, a mortality rate of 90%, and it was clear there was much more to come. A catastrophe was in the making.

The chief physician and epidemiologist at Blegdams hospital since 1939, Henry CIA Alexander Lessen (1900-74), later admitted, "Although we thought we knew something about the management of bulbar and respiratory poliomyelitis, it soon became clear that only very little of what we did know at the beginning of the epidemic was really worth knowing". After the disastrous first 3 weeks, Lessen knew he had to do something, but he was not sure exactly what. He was advised to consult Bjorn Ibsen, a free-lance anesthetist at Copenhagen's university hospital. Lassen not only had to overcome a certain degree of professional pride in seeking "outside" help, he was genuinely skeptical about the contribution that Ibsen, an anesthetist, could make. Anesthesiology was just then emerging as a medical specialty, and it was held in low regard; moreover, its activities were confined to the operating room. But Lassen did invite Ibsen to participate in a decisive conference on August 25, 1952, at which the hospital's leading physicians met to discuss the looming disaster.

One of the things that were considered at the meeting was that polio patients died with high total carbon dioxide contents in their blood, as measured by the Van Slyke manometric method. According to convention at the time, this meant the patients had metabolic alkalosis, but when this was said, Ibsen immediately commented that the high values could just as well be explained by retention of carbon dioxide. After the session, Ibsen examined some patients, studied their records, looked at specimens from four autopsies, and became convinced that the patients had died from lack of ventilation. Blegdams hospital's physicians had focused on assisting their patients' breathing and supplying oxygen when needed, using the presence of cyanosis as a guide; in the process, they had ignored the accumulation of carbon dioxide from inadequate exchange of air.

During the discussion, Ibsen proposed to use hand-supplied positive pressure instead of the customary machine-generated negative pressure, and to gain access to the airway with a balloon-cuffed tube inserted through a tracheotomy.

He intended to use a Waters to-and-fro rebreathing system in which the patient would be ventilated by hand; this required that someone had to be at the bedside to squeeze—over and over again, hour after hour—the rebreathing balloon into which oxygen or air was flowing. Such a system had never been tried at Blegdams hospital before.

Lassen gave permission to go ahead, and the next day, August 26, a 12-yr-old girl who was thought to be dying from severe polio was tracheotomized, intubated, and manually ventilated. It was stormy but it worked. The total carbon dioxide content of her serum fell from about 40 to less than 20 mM/L, which showed that Ibsen's prediction was correct. Using an instrument called a carbovisor that measured expired carbon dioxide, Ibsen demonstrated to the local physicians how he could manipulate the patient's carbon dioxide levels by varying the frequency and force of his manual compressions of the bag. He could also make the clinical manifestations attributable to carbon dioxide retention come and go. The *coup de grâce* was applied when the patient was returned to a negative pressure ventilator and her exhaled carbon dioxide gradually began to rise.

Poul Astrup, director of the clinical laboratory, prevailed on Radiometer A/S in Copenhagen to provide a pH electrode that they had recently developed for biologic measurements on small samples, including blood. The next day, Astrup was able to measure pH in blood directly with the new electrode, and he quickly confirmed Ibsen's conclusion that patients with terminal stage bulbar polio were acidotic, not alkalotic.

Jolted from his initial skepticism, Lassen, now convinced, devoted himself energetically to implementing the new treatment. Teams of internists, otolaryngologists, and anesthetists were organized to deal with the flood of new patients. And hands were needed, lots of hands, to squeeze the bags to ventilate the patients 24 h/d during the 2 to 3 mo it usually took for them to recover the ability to breathe. At the peak of the epidemic, 40 to 50 new patients were admitted every day and 70 hospitalized patients required manual breathing assistance. Initially, the "hands" belonged to medical students who worked four shifts of 6 h each. When the need exceeded the number of available medical students, dental students were recruited. According to one observer, in total, approximately 1,500 students contributed 165,000 hours of life-preserving service, squeezing rubber bags.

After Ibsen's persuasive demonstration of the real clinical hazards of underventilation, regular arterial blood samples were taken from manually ventilated patients for measurements of pH, using the new Radiometer electrode, and total carbon dioxide by Van Slyke's method. After calculating P_{CO_2} from the Henderson-Hasselbalch equation, the medical students were given instructions, when needed, about how to modify the frequency and intensity of their ventilatory efforts.

AFTERMATH

Primitive though it was, Ibsen's approach was highly successful. The mortality rate of ventilated patients dropped from 90% at the beginning to 25% at the end of the epidemic, and the world took notice. Physicians from all over Europe visited Blegdams hospital and were impressed by what they saw.

Everyone, though, locals and visitors alike, recognized the need to replace the medical students, good as they were, with machines capable of delivering constant positive-pressure ventilation. It turned out that the Swedish physician-engineer Carl-Gunnar Engström had designed and built a volume ventilator in 1950 that incorporated a negative-pressure "suck" during exhalation to compensate for any impairment of venous return imposed during the positive-pressure inspiratory phase.

Moreover, the machine had been successfully used in 1951 to treat a single patient with chronic poliomyelitis in whom a negative-pressure respirator seemed to be inadequate. In the autumn of 1952, Engström's volume-controlled, positive-pressure ventilator was taken to Blegdams hospital for the treatment of patients with bulbar polio. It performed extremely well, so well in fact that it persuaded Swedish health officials to plan for their own inevitable epidemic by ordering several machines. These were manufactured in time to be available the following summer when poliomyelitis struck Stockholm with a ferocity similar to that experienced in Copenhagen. But Stockholm was ready. All patients with bulbar or respiratory polio were treated with mechanical Engström ventilators and Swedish medical students were not needed.

As the word spread, new ventilators were designed, built, and marketed with extraordinary speed. By 1953, hospitals searching for positive-pressure machines could choose from among several different models and trademarks. Within a few years, the switch from negative pressure to positive pressure for mechanical ventilation was complete throughout Europe, but not in America. When polio swept through the United States in the early to mid-1950s, we had only old-fashioned tank respirators, and our patients were the worse for it.

Another formative lesson learned from the Blegdams hospital experience was the vital importance of the clinical laboratory in the care of critically ill patients. Monitoring the adequacy of ventilation proved crucial. Shortly after the epidemic in Copenhagen, Astrup completed work on his equilibration method for measuring P_{CO_2}, and Radiometer A/S began manufacturing instruments that were soon used throughout the world to measured pH and P_{CO_2}. Astrup and his colleagues also developed new conceptual insights for evaluating acid-base balance, such as "standard bicarbonate" and "base excess," which were rapidly assimilated and applied in intensive care units that were mushrooming everywhere.

As could be expected from the early successes, these prototype units began welcoming not just polio patients, but those with respiratory failure from any cause, lung disease, drug overdose, central nervous system impairment, and after thoracic or other surgery, in some instances using paralysis, sedation, and artificial ventilation for a few days while healing proceeded. And not long afterward, highly specialized units began to appear in which facilities and expertise were focused on single groups of patients: premature babies, patients with burns, patients with heart attacks or arrhythmias, patients after open-heart surgery, patients with neurosurgical or neurologic disorders, and on and on, depending on local needs and politics.

THE FUTURE

Groucho Marx's old lament that "even the future isn't what it used to be" has a heightened contemporary sting to it owing to the intrusion of managed care into modern medicine. It is difficult to predict how the struggle will play out between managed care's zeal to cut costs in order to make a profit and industry's unrestrained development of costly instruments and medications that American physicians and patients eagerly assimilate. On the one hand, there is bound to be increasing pressure to reduce beds and services in intensive care units, notorious guzzlers of funds. On the other hand, it is equally certain that there will be no let-up in the burgeoning number of high-tech expensive devices and products that enhance monitoring capabilities, minimize or eliminate human error, and provide new therapeutic benefits. Some sort of equilibrium will undoubtedly be reached.

Since the mid-1960s most critical care facilities have been able to obtain rapid blood gas analysis, usually using locally placed instruments. Because these devices were designed to be self-calibrating after about 1970, it became common practice for physicians, nurses, and respiratory therapists to withdraw blood samples from indwelling arterial lines, carry them over the apparatus, inject the sample, and read the answer usually as printed by the analyzer. This practice facilitated rapid therapeutic decision making and led to the widespread feeling that a blood gas analysis was the most useful laboratory test in critically ill patients.

Unfortunately, this situation was too good to last. There are changes taking place now that alter the availability and methods of blood gas analysis in many locations. Regulatory agencies have decreed that only licensed technologists may operate these automated blood gas analyzers, and this has resulted in reduced availability of rapid analysis in many locations, because the cost of keeping a licensed technologist at hand 24 hours per day cannot be justified. There may have been economic motivations behind this change, which has resulted in the transfer out of intensive care, operating rooms, and other locations of the blood gas service and resulting revenue to clinical pathology laboratories. Pressure on the regulatory agencies for this change is said to have originated with pathologists.

At the same time, technologic changes have permitted introduction of bedside, or hand-held blood gas analysis devices. These devices use disposable analytic cartridges, operate with newer optical sensors in some cases, and do not fall under the category of the installed blood gas analysis, so it can be performed by physicians, nurses and respiratory therapists, without laboratory technology certification. In general this change may have reduced accuracy because the devices are not calibrated automatically just before analysis is done and cost more per analysis. It remains unclear whether cost containment will further impede availability and accuracy in this field.

The introduction of pulse oximetry has greatly reduced the frequency of blood gas analysis for two reasons: because of the constant threat of hypoxia, and because acid-base status changes occur more slowly than oxygenation failure. An interesting technological development may lead to another change in practice.

Pulse oximeters are becoming so small, rapidly responding, and battery operated that they can be kept by the clinician (in a pocket or bag) and used whenever needed to assist in decision making, whether in an ICU or an office. Such devices were recently used by climbers on Mount Everest.

Pulse oximetry has also severely cut into the use of transcutaneous P_{O_2} and P_{CO_2} electrodes for monitoring. This dip seems to have partially reversed because the continuously available values from transcutaneous P_{CO_2} measurement have proved useful in both neonates and adults in some critical care situations, even when skin P_{O_2} is recognized to be an inadequate index of arterial oxygenation. Transcutaneous P_{CO_2} devices provide a very stable and sensitive monitor of changes produced by subtle manipulations of artificial ventilation, by the use of continuous positive airway pressure and positive end-expiratory pressure, and by the administration of sedative and opioid medications. Our prediction is that use of transcutaneous P_{CO_2} electrodes will increase.

A final comment relates to determination of gut P_{CO_2} in the critical care of patients who are in shock. The concept has been called gastric tonometry. It is based on the idea that mucosal P_{CO_2} is normally 5-10 mm Hg higher than arterial P_{CO_2}. In shock, as flow stagnates, mucosal surface P_{CO_2} rises far above arterial P_{CO_2}, for three reasons: (*1*) oxygen consumption and carbon dioxide production tend to remain normal, so as flow falls, the arteriovenous difference rises, elevating surface P_{CO_2}; (*2*) blood supply to mucosal surface in the gut consists of capillary loops that permit some countercurrent carbon dioxide exchange, so at low flow, carbon dioxide generated near the surface partly diffuses from venules into arteries, causing it to collect at the surface; and (*3*) as oxygen supply falls to some critical level, mucosal cells make lactic acid, and these hydrogen ions react with tissue bicarbonate to generate carbon dioxide gas in solution, raising local P_{CO_2}. With severe ischemia gut surface P_{CO_2} rises to the 200-300 mm Hg range. Various devices are being introduced to monitor this effect as a continuous index of gut, and hence body, circulatory adequacy. A new, disposable, inexpensive method of measuring P_{CO_2} has recently been invented (T. I. Tønnessen, Oslo, personal communication), which would be ideal for introduction on the tip of a nasogastric tube, inserted into either the stomach or the small intestine. We predict widespread use of this and similar devices in critically ill patients in the near future.

In other aspects of monitoring, there are sure to be new ways of assessing cardiovascular function noninvasively, continuously, and accurately, including such important variables as blood pressure, cardiac output, regional blood flow, especially to the brain, and even pulmonary arterial and left atrial pressures. Similarly, advances in the speed and fidelity of imaging methods, such as computed tomography and magnetic resonance, will make them safer and more readily available to patients in intensive care units. In the field of therapeutics, current efforts to construct a durable artificial heart and a simplified extracorporeal lung-replacement instrument will finally be realized. We can also predict that future progress will intensify the debate about what we are actually doing in our intensive care units: are we salvaging meaningful lives or are we prolonging inevitable deaths? We hope that along with the technological advances that are going to occur, more attention will be devoted to the personal and societal costs of critical care medicine and to its ethical underpinnings.

SUMMARY

Substantial progress in the acquisition of scientific knowledge concerning blood gas transport, which began in the 17th century, led to the discovery of oxygen in air and carbon dioxide in smoke, the presence of these gases in the bloodstream and the role of the lungs in getting them in and out of the body, and finally, how to measure them in blood. These basic research achievements were clinically applied in dramatic and successful fashion in 1952 during the polio epidemic that ravaged Copenhagen, Denmark. An inspired anesthetist, Bjorn Ibsen, after making the right deductions from scanty information, introduced a radical type of therapy that incorporated several novel features: a team approach by experts, a separate facility for trained personnel and special equipment, and a clinical laboratory for essential monitoring. This radical and effective way of treating seriously ill patients launched the proliferation of intensive care units and led to the inauguration of the now flourishing specialty of critical care medicine, where science and clinical medicine continue their powerful partnership.

Reference

JOHN W. SEVERINGHAUS, POUL ASTRUP, and JOHN F. MURRAY Am. J. Respir. Crit. Care Med., Volume 157, Number 4, April 1998, S114-S122 Departments of Anesthesiology and Medicine, and the Cardiovascular Research Institute, University of California San Francisco, and the San Francisco General Hospital Medical Center, San Francisco, California; and Department of Clinical Chemistry, Rigshospitalet, Copenhagen, Denmark

Glossary of Terms

a-A DC02
The arterial to alveolar difference for Co2. Also called the P(a-etCO2), normally 2-5 mmHg.

ABG
Arterial blood gas a test which analyses arterial blood for oxygen, carbon dioxide and bicarbonate content in addition to blood pH. Used to test the effectiveness of respiration.

ACLS
The American Heart Association's Advanced Cardiac Life Support

Acidosis
An abnormal physiologic process resulting in an increase in hydrogen ion concentration in the body; may be caused by either an excess accumulation of an acid or the loss of base.

Alveoli
Terminal air spaces that contain numerous capillaries in their septa, which serves as sites for gas exchange.

Analgesia
Insensibility to pain without loss of consciousness.

Analgesics
Agents that relieve pain without causing loss of consciousness.

Anesthesia
Loss of normal sensation or feeling. A drug used to produce anesthesia.

Anesthetic Gas
A compound (e.g. ether) that reversibly depresses nerve cell function, producing loss of ability to perceive pain and/or other sensations.

Antecubital
Relating to the inner or front surface of the forearm (the an·te·cu·bi·tal area of the right arm).

Apnea
Cessation of breathing

Asthma
A disease process that is characterized by paradoxical narrowing of the bronchi (lung passageways) making breathing difficult.

Treatment includes bronchodilators which are given orally or delivered as an aerosol (inhaled). Corticosteroids are reserved for more difficult cases. Symptoms include

wheezing, difficulty breathing (particularly exhaling air) and tightness in the chest. Factors which can exacerbate asthma include rapid changes in temperature or humidity, allergies, upper respiratory infections, exercise, stress or smoke (cigarette).

Bradycardia
A slowness of the heart beat, as evidenced by slowing of the pulse rate to less than 60 beats per minute in an adult patient and less than 70 beats per minute in pediatric patients.

Bronchodilator
A medication that acts to dilate the lumen of the airway to allow the unrestricted passage of air. These medications are commonly given to asthma patients who manifest wheezing.

Bronchospasm
An abnormal constriction of the smooth muscle of the bronchi resulting in an acute narrowing and obstruction of the respiratory airway. A cough with generalized wheezing usually indicates this condition. The most common cause of bronchospasm is asthma.

Bronchoscopy
An examination used for inspection of the interior of the tracheo-bronchial tree; taking of specimens for biopsy and culture and removal of foreign bodies

CABG (coronary artery bypass graft)
A surgical procedure, which involves replacing diseased (narrowed) coronary arteries with veins obtained from the patients lower extremities (autologous graft).

Capnogram
A continuous record of the carbon dioxide content of expired air

Capnography
Continuous measurement and graphical display of the carbon dioxide (CO2) level of a patient's exhaled breath.

Cardiopulmonary Resuscitation (CPR)
A life saving procedure that includes the timed compression of the anterior chest wall (to stimulate blood flow), alternating with mouth to mouth breathing (inflating another persons lungs when you exhale). Usually administered by one rescuer as 15 chest compressions to every 2 mouth-to-mouth breaths.

Cardiovascular System
The circulatory system, comprised of the heart, lungs, and blood vessels

Catheters
See catherterization

Catheterization
Use or insertion of a tubular device (catheter) into a duct, blood vessel, hollow organ, or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes. It

differs from intubation in that the tube here is used to restore or maintain patency in obstructions.

CCU
Critical Care Unit

Clinical Evaluation
Research pertaining to or founded on actual observation and treatment of patients, as distinguished from that gained by means of theoretical or basic sciences.

CHF (congestive heart failure)
A condition where the heart is not pumping effectively leading to an accumulation of fluid in the lungs. Typical symptoms include shortness of breath with exertion, difficulty breathing when lying flat and leg or ankle swelling. Causes include chronic hypertension, cardiomyopathy and myocardial infarction

Colonoscopy
An endoscopic examination of the large intestine (colon)

Colorimetric
Any of various instruments used to objectively determine the amount of a substance in a solution based on a color level.

Conscious Sedation
Light sedation during which the patient retains airway reflexes and responses to verbal stimuli.

COPD (chronic obstructive pulmonary disease)

Chronic obstructive pulmonary disease is comprised primarily of two related diseases - chronic bronchitis and emphysema. In both diseases, there is chronic obstruction of the flow of air through the airways and out of the lungs, and the obstruction generally is permanent and progressive over time.

Corticosteroids
Any of various adrenal-cortex steroids (as corticosterone, cortisone, and aldosterone) used especially as anti-inflammatory agents.

Electrophysiology
That branch of physiology that is concerned with the electric phenomena associated with living bodies and involved in their functional activity.

Endotracheal Intubation
Passage of a tube into the windpipe for maintenance of the airway during anesthesia, or in a patient with an impaired airway from any cause.

Endotracheal Tube
A flexible plastic tube introduced into the body through the mouth or the nose into the trachea to artificially respirate the lungs.

Extubation
Removal of a tube from an organ, structure, or orifice; specifically, removal of the tube after intubation

Fentanyl
A narcotic analgesic C22H28N2O with pharmacological action similar to morphine that is administered especially in the form of its citrate. Fentanyl is a potent synthetic (man-made) narcotic.. Fentanyl stimulates receptors on nerves in the brain to increase the threshold to pain (the amount of discomfort that a person must feel in order to be considered painful) and reduce the perception of pain (the perceived importance of the pain).

Hemodynamic
Relating to or functioning in the mechanics of blood circulation

Hemothorax
An effusion of blood into the cavity of the pleura

Hypercapnia
An excess of carbon dioxide in the blood

Hypocapnia
A deficiency of carbon dioxide in the blood

Hypoxemia
Below-normal oxygen content in arterial blood due to deficient oxygenation of the blood and resulting in hypoxia.

Hypoxia
Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood.

Hypoperfusion
Decreased blood flow through an organ

Hypertension
Persistently high arterial blood pressure. Hypertension may have no known cause (essential or idiopathic hypertension) or be associated with other primary diseases (secondary hypertension)

Hypotension

Abnormally low blood pressure, seen in shock but not necessarily indicative of it.

Hyperventilation
A state in which there is an increased amount of air entering the pulmonary alveoli (increased alveolar ventilation), resulting in reduction of carbon dioxide tension and eventually leading to alkalosis.

Hypoventilation
A state in which there is a reduced amount of air entering the pulmonary alveoli.

ICU (intensive care unit)
Advanced and highly specialized care unit provided to medical or surgical patients whose conditions are life-threatening and require comprehensive care and constant monitoring. It is usually administered in specially equipped units of a health care facility

IMV
Intermittent Mandatory Ventilation

Intubation
The insertion of a tube into a body canal or hollow organ, as into the trachea or stomach.

Isotopic Gas
A gas containing an isotope of a chemical element; isotopes differ only in their atomic mass, but are chemically identical. CO2-Gas, for example, contains almost 100 percent of the isotope Carbon 12 (12C). For diagnostic reasons CO2 can be artificially enriched with the heavier, non-radioactive carbon isotope ^{13}C.

Laparotomy
General term for abdominal surgery

Meconium Aspiration
Syndrome caused by sucking of thick meconium into the lungs, usually by term or post-term infants (often small for gestational age) either in utero or with first breath. The resultant small airway obstruction may produce respiratory distress, tachypnea, cyanosis, pneumothorax, and/or pneumomediastinum.

Metabolism
The sum of chemical changes whereby the function of nutrition is effected.

Midazolam
Midazolam is used to produce sleepiness or drowsiness and to relieve anxiety before surgery or certain procedures. It is also used to produce loss of consciousness before and during surgery. Midazolam is used sometimes in patients in intensive care units in hospitals to cause unconsciousness. This may allow the patients to withstand the stress of being in the intensive care unit and help the patients cooperate when a machine must be used to assist them with breathing.

Molecular Correlation Spectroscopy™ (MCS™)
A technology developed by Oridion to detect and monitor carbon dioxide levels in various medical applications.

Myocardial
Refers to the heart's muscle mass

Nasal Cannula
A device to be inserted in the nose of a patient in order to deliver oxygen and/or collect a gas sample from the patient's breath.

Necrotizing Enterocolitis (NEC)

Necrotizing enterocolitis (is an inflammation causing injury to the bowel. NEC may involve only the innermost lining or the entire thickness of the bowel and variable amounts of the bowel. Necrotizing enterocolitis affects mainly premature babies.

Neonate
A newborn baby

Neuromuscular
Pertaining to muscles and nerves.

Neuromuscular Blockade
The intentional interruption of transmission at the neuromuscular junction by external agents, usually neuromuscular blocking agents. It is distinguished from nerve block in which nerve conduction is interrupted rather than neuromuscular transmission. Neuromuscular blockade is commonly used to produce muscle relaxation as an adjunct to anaesthesia during surgery and other medical procedures.

Noninvasive
Descriptive of diagnostic procedures which do not involve the insertion of needles, cannulas, or other devices that require penetration of the skin.

Occluded
To close up or block off

OEM
Acronym for original equipment manufacturer; a firm that purchases complex equipment from other manufacturers and modifies or combines different components for resale.

Outpatient
A patient who comes to a hospital, clinic or dispensary for diagnosis and/or treatment but

does not occupy a bed.

Oxygenation
The process of supplying, treating or mixing with oxygen

PACU
Post Anaesthesia Care Unit

Palpation
A technique in which a doctor presses lightly on the surface of the body to feel the organs or tissues underneath

Peak Expiratory Flow Rate (PEFR)
Measurement of the maximum rate of airflow attained during a forced vital capacity determination.

Perfusion
The passage of fluid (usually blood) through out the body (organs and tissues).

Pharmacotherapy
The treatment of disease and especially mental disorder with drugs

Pneumoperitoneum
An abnormal state characterized by the presence of gas (as air) in the peritoneal cavity or the induction of pneumoperitoneum as a therapeutic measure or as an aid to roentgenography

Pneumothorax
An abnormal state characterized by the presence of gas (as air) in the pleural cavity.

Pulmonary Artery
The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs.

Pulmonary Embolism
The lodgment of a blood clot in the lumen of a pulmonary artery, causing a severe dysfunction in respiratory function. Pulmonary emboli often have origin in the veins of the lower extremities where clots form in the deep leg veins and then travel to the lungs via the venous circulation.
Symptoms and features include acute onset of shortness of breath, chest pain (worse with breathing) and rapid heart rate and respiratory rate. Some individuals may have haemoptysis.

Pulse Oximetry
Determination of arterial saturation of hemoglobin; the absorption of light by blood is measured spectroscopically.

Quadriplegia
Paralysis of all four limbs, both arms and both legs, as from a high spinal cord accident or stroke

Radiograph
Another name for an X-ray

Respiration
Breathing; gas exchange, specifically the exchange by a living organism of carbon dioxide (CO2), a waste product formed during the oxidation of food molecules, for oxygen (O2), which the organism needs to continue oxidizing its food.

Roentgenography
Photography by means of X rays

Sampling Line
A tube used to deliver a gas sample from a patient to a gas monitoring device.

SIMV
Spontaneous intermittent mandatory ventilation, synchronised intermittent mandatory ventilation.

Sinus tachycardia
A fast heartbeat (tachycardia) occurring because of rapid firing by the sa node, the natural pacemaker of the heart. Electrical signals initiated in the sa node are transmitted to the atria and the ventricles to stimulate heart muscle contractions heartbeats. Sinus tachycardia is usually a rapid contraction of a normal heart in response to a condition, drug, or disease as, for examples, pain, fever, excessive thyroid hormone, exertion, excitement, low blood oxygen level (hypoxia), or stimulant drugs such as caffeine, cocaine, and amphetamines. However, in some cases, it can be a sign of heart failure, heart valve disease, or other illness.

Spectrometry Equipment
Devices that measure emission or absorption of light as a function of wavelength.

Tachycardia
Relatively rapid heart action whether physiological (as after exercise) or pathological

Tachypnea
An abnormally rapid (usually shallow) respiratory rate. The normal resting adult respiratory rate is 12-20 breaths/minute.

Thoracotomy
A surgical procedure where an incision is made opening the chest cavity (wall)

Transthoracic Pacemaker
Crossing or having connections that cross the thoracic cavity (a trans·tho·rac·ic

pacemaker)

Transvenous Packemaker
Artificial pacemaker delivering stimuli through the chest wall usually applied as a temporizing measure in patients with atrioventricular block

Tracheostomy
The surgical creation of an artificial airway in the trachea (windpipe) on the anterior surface of the neck

V/Q ratio
The ratio of ventilation (V) to perfusion (Q)

V/Q Mismatch
Ventilation/Perfusion mismatch - an imbalance between ventilation compared to perfusion. Extremes are shunt perfusion and dead space ventilation.

Post-Test

Select the *best* answer to each of the following items. Mark your responses on the Answer form.

1. The term arterial blood gases refers to a measurement of the _____ and the oxygen and carbon dioxide concentrations in arterial blood; important in diagnosis of many respiratory diseases

a. Co2
b. pH level
c. HCO3
d. All of the above

2. HCO_3--This value is derived through the blood gas analyzer's manipulation of the _____.

a. pH data found on the test
b. Henderson-Hasslebach Equation
c. mixture of the bicarbonate concentration
d. None of the above

3. Metabolic alkalosis may be found in _____ and fad dieters who are ingesting a low-protein, high fruit diet.

a. persons over 60
b. vegetarians
c. persons of color
d. All of the above

4. Numerically the pH is approximately equal to the negative logarithm of hydrogen ion concentration expressed in molarity. PH 7 is neutral, above 7 is alkaline and below is _____.

a. indicative of possible drug use
b. and indication of diabetes
c. acidic
d. All of the above

5. In blood gas analysis, the pH, PO_2 and pCO_2 of the sample are measured with specific electrodes. By equilibrating the sample against different _____, mixtures the bicarbonate concentration is calculated.

a. CO_2
b. pH
c. blood serum
d. None of the above

6. PCO_2--This value is measured directly by the _____.

a. analyzing the pH level
b. CO_2 electrode
c. results of the blood platelet test
d. None of the above

7. Oxygen: the PaO_2 is the standard for measuring blood oxygenation. Decreases in PaO_2 are due to _____.

a. impairment of gas exchange
b. inspiration of hypoxic gas mixtures
c. hypoventilation
d. All of the above

8. These measure different aspects of acid-base balance:

a. HCO_3^-,
b. anion gap
c. pH
d. All of the above

9. Most blood samples can be collected routinely, on rounds, and kept and transported at room temperature until they are analyzed. Temperature does not affect their results. This is not true for _____.

a. arterial blood gases
b. samples for children
c. samples for persons over 60
d. All of the above

10. Arterial blood gases, as their name implies, must be drawn from an artery with a free-flowing, unimpeded flow of blood coursing through it. This procedure is known as an _____ and is usually performed on a palpable radial artery.

a. A/R stick
b. arterial stick
c. abg probe
d. None of the above

11. Modern blood gas analyzers are electronic marvels compared to the methods used for this purpose 20 years ago. On attaching the sample syringe to the cuvette, they automatically draw the sample into a heated sampling chamber with miniaturized electrodes that quickly and accurately (if properly calibrated) measure pH, PCO_2 and PO_2 values. Based on these three measured values, these units automatically calculate _____.

a. total CO_2
b. percent oxygen saturation and O_2 content
c. HCO_3
d. All of the above

12. "Respiration" is actually several distinct processes including _____.

a. Ventilation
b. External Respiration
c. Transport of gases between the lungs and the rest of the body tissues
d. All of the above

13. A(n) _____, directly measures percent oxygen saturation and hemoglobin, then accurately calculates oxygen content and carboxyhemoglobin, a value that reflects the degree of carbon monoxide in the blood in smoke inhalation victims.

a. PEFR
b. cuvette
c. co-oximeter
d. None of the above

14. The pulmonary arteries bring _____ (for gas exchange) to the lungs while the bronchial arteries bring oxygenated blood (to supply oxygen for the structural tissue). The lungs are drained by the pulmonary veins.

a. deoxygenated blood
b. PaO_2
c. pCO_2
d. None of the above

15. Factors that can influence the diffusion of O2 and CO2 across the respiratory membrane include:

a. Partial pressures of O2 and CO2
b. Thickness & surface area of the respiratory membrane
c. Solubility of O2 and CO2
d. All of the above

16. Arterial blood gas analysis is the gold standard for assessing respiratory function. The gas exchange capability of the lung can be _____ measured.

a. indirectly
b. directly
c. inferentially
d. None of the above

17. There can be no excuse for not being able to provide blood gas analysis rapidly and accurately on site at all times. Failure to do so can result in a potentially avoidable patient death.

a. True
b. False

18. There are a lot of good reasons NOT to get blood gases. Perhaps the most important reason NOT to get blood gases is when the results won't change what you're going to do.

a. True
b. False

19. Blood gases should also not be drawn where there's a possibility of complications that outweighs the benefits of the test. For example, sticking a needle through the artery of a hemophiliac just to show he's hyperventilating might not be such a good idea.

a. True
b. False

20. Blood gases are drawn from an artery with a small needle attached to a syringe. The syringe contains a small amount of heparin to prevent clotting of the blood. If possible, the sample is obtained from the radial artery at the _____.

a. posterior part of the forearm
b. midportion of the forearm
c. wrist
d. None of the above

21. At a minimum, the blood gas analysis will list values for _____.

a. pH
b. PaO2
c. PaCO2
d. All of the above

22. Respiration is the total process of delivering oxygen to the cells and carrying away the byproduct of metabolism, carbon dioxide.

a. True
b. False

23. One "volume" that is reviewed is the respiratory dead space, the amount of air within the chest that is not in contact with alveolar membranes and cannot exchange gases with the blood. The dead space becomes important in certain lung diseases, causing elevation of _____.

a. hemoglobin
b. carbon monoxide levels
c. carbon dioxide levels
d. None of the above

24. A mole is a unit of measure based on number of molecules rather than on weight or volume.

a. True
b. False

25. Regarding Acid-Base Balance in the body, the pH of the body must be maintained within a narrow range. Most body systems function optimally at a pH of near _____. As the pH changes (either higher or lower), enzymes may cease to function, nerve and muscle activity weakens, and finally all metabolic activity becomes deranged.

a. 6.5
b. 7.4
c. 8.4
d. None of the above

26. The clinical determination of the amount of bicarbonate required for treatment of severe acidosis is usually based on the base excess of the blood. There is an unavoidable inaccuracy, however, due to several factors:

a. the time course of the acidosis makes the blood acid poorly reflect the total body acid burden in many cases
b. depending on the state of hydration, body fluid distribution varies
c. ECF as a percent of body weight varies with age and fat content
d. All of the above

27. Oxygen status is affected by acid-base status. Oxygen affects the buffering capacity of hemoglobin through the Bohr effect, but the opposite is also true. At a given oxygen pressure, oxygen saturation in the blood is lowered by increasing either carbon dioxide or hydrogen ion concentrations.

a. True
b. False

28. Buildup of carbon dioxide occurs when ventilations are inadequate. This is usually due to absence of adequate respiratory effort — such as when central control of respiration is depressed due to narcotics or barbiturates. When respiration ceases due to cardiac arrest, of course, respiratory acidosis is an immediate result.

a. True
b. False

29. _____ is an abnormal physiologic process resulting in an increase in hydrogen ion concentration in the body; may be caused by either an excess accumulation of an acid or the loss of base.

a. ACLS
b. Acidosis
c. Hypoxemia
d. None of the above

30. _____ is a gas containing an isotope of a chemical element; isotopes differ only in their atomic mass, but are chemically identical. CO2-Gas, for example, contains almost 100 percent of the isotope Carbon 12 (12C). For diagnostic reasons CO2 can be artificially enriched with the heavier, non-radioactive carbon isotope ^{13}C.

a. Blood Gas
b. Isotopic Gas
c. CO2-Gas
d. None of the above

31. According to Hippocrates (460-377 BC), good health resided in a proper balance among the four humors: blood, phlegm, black bile, and yellow bile, a balance that depended on the generation of life-giving heat within the left ventricle.

a. True
b. False

32. _____ (1728-99), who became Professor of Chemistry in Edinburgh, showed while he was a medical student that large quantities of a gas, which he called "fixed air" (carbon dioxide), were generated by heating or acidifying chalk. He was the first to prove that the same gas was present in exhaled air.

a. Marcello Malpigi
b. William Harvey
c. Joseph Black
d. Michael Servetus

33. In 1907 the remarkable ability of blood to neutralize large amounts of acid led _____ (1878-1942), then an instructor in biochemistry at Harvard University, to investigate the relationship of bicarbonate to dissolved carbon dioxide gas, and how they acted as buffers of fixed acids.

a. Friedrich Walter
b. Lawrence J. Henderson
c. Bence Jones
d. William B. O'Shaughnessy

34. The credit (or blame) for introducing the term pH, the negative log of hydrogen ion (H+) concentration, goes to S. P. L. Sørensen (1868-1939), who apparently tired of writing seven zeros in a paper on enzyme activity and wanted a simpler designation. the chemical potential of H+.

a. True
b. False

35. Until the introduction of electrochemical methods of analysis in the mid-1900s, measurement of blood oxygen and carbon dioxide contents depended on vacuum extraction, usually in combination with acidification to liberate the contained carbon dioxide, and chemical alteration of oxyhemoglobin to liberate the oxygen. The freed gases were quantified volumetrically until _____ (1883-1971) developed a more accurate manometric method, which became the gold standard of blood gas analysis for more than a quarter of a century.

a. T. B. Rosenthal
b. Poul Astrup
c. Ole Siggaard Andersen
d. Donald D. van Slyke

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