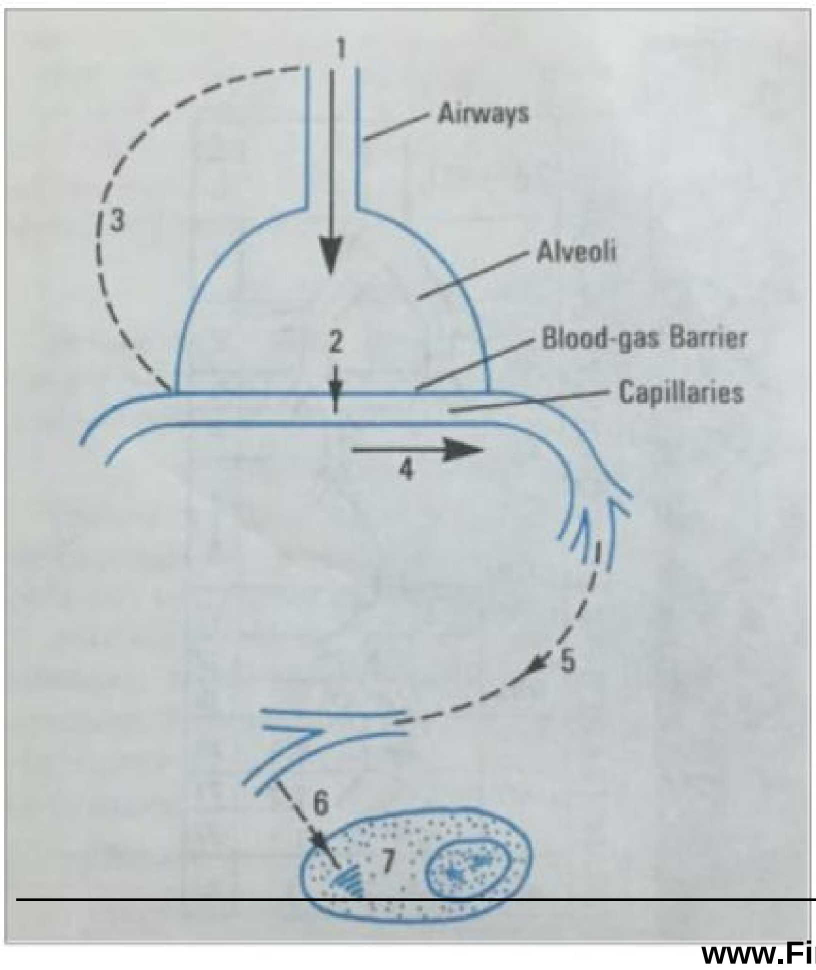
Introduction

to

Respiratory System

Schematic diagram showing delivery of oxygen to the tissues from air



1. Ventilation
2. Diffusion across the blood-gas barrier
3. Matching of ventilation and blood flow
4. Pulmonary blood flow
5. Transport of gas in the blood
6. Diffusion from capillary to cell
7. Utilization of oxygen by mitochondria

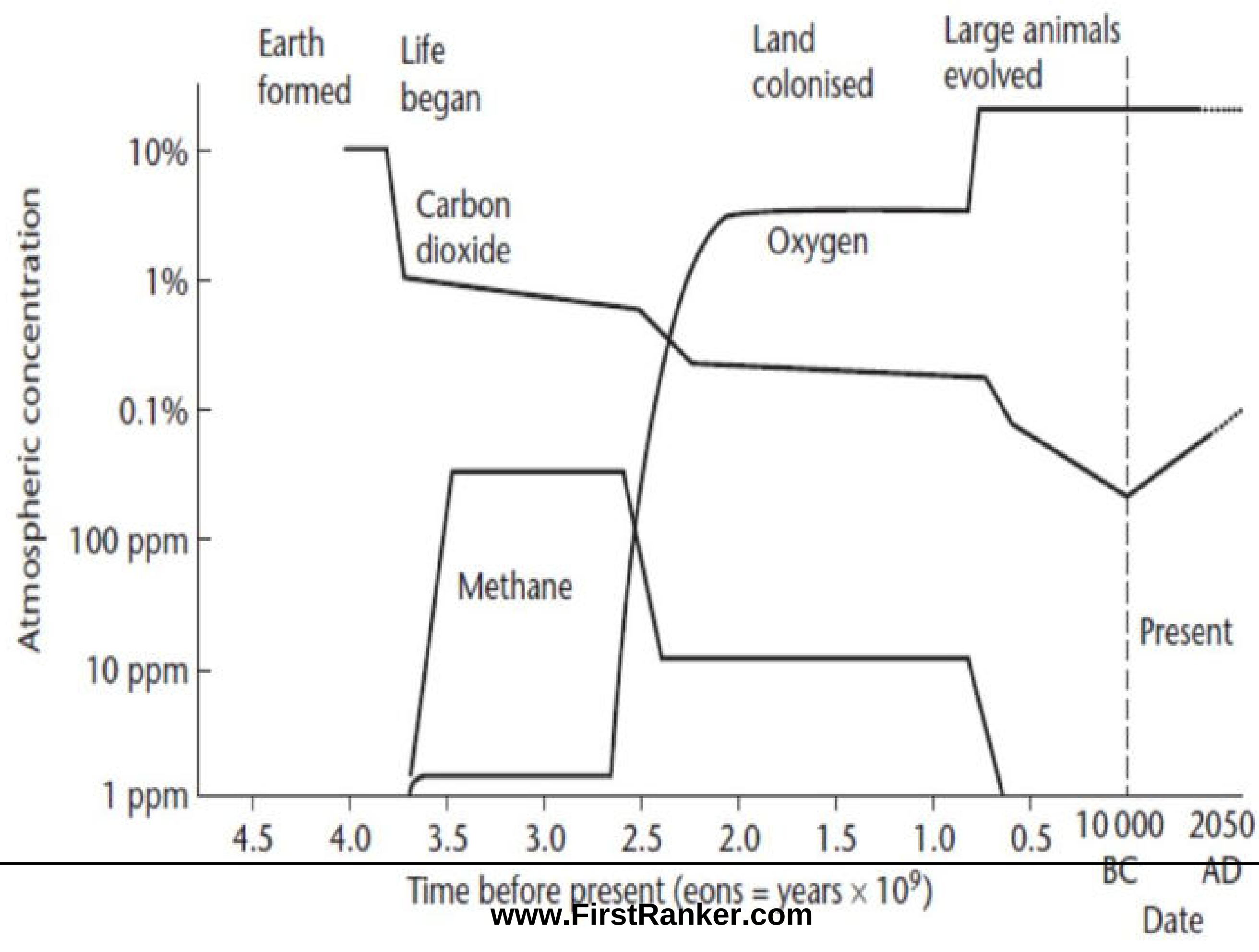
Gas Exchange in "Animals"

Cells require O_2 for aerobic respiration and expel CO_2 as a waste product.

Claude Bernard's concept:

A 'milieu interior' that remains constant and stable despite changes in the environment

Approximate timescale for the evolution of the gaseous environment



Oxygen: a paradoxical molecule

Oxygen first appeared in significant quantity some 2 billion years ago

Anaerobic prokaryotes

2 billion years ↓

Aerobic eukaryotes

700 million years ↓

Multicellular eukaryotes

- Oxygen is the fire of life

Max Kleiber (1961)

- Aerobic metabolism yielded more free metabolic energy than was achievable through anaerobic pathways.

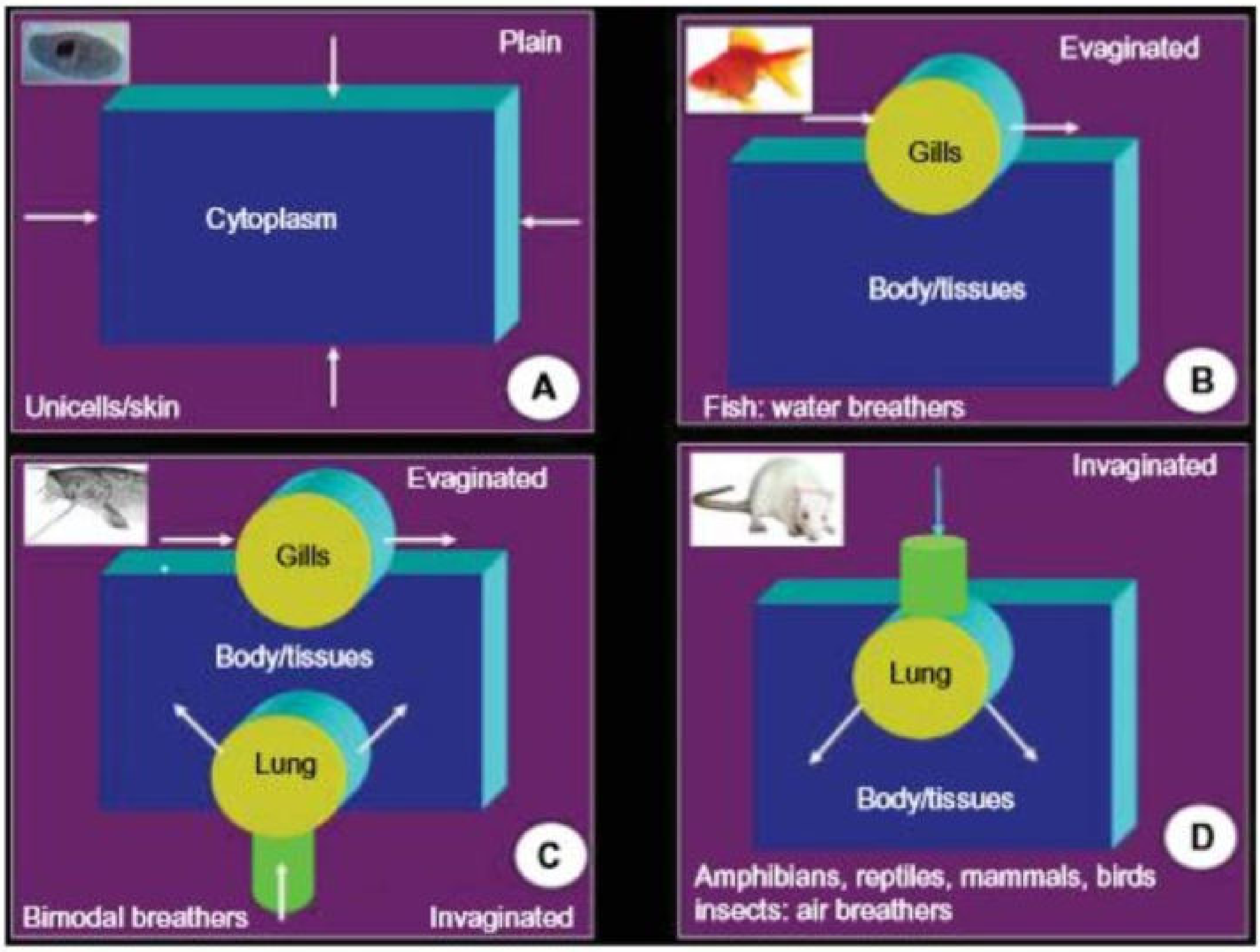
- About 350-400 million years back: A hyperoxic episode (atmospheric O_2 rose to a high of 35%) allowed development of exceptionally large animals such as the giant dragonfly.

- The high intracellular diffusivity due to its '**small**' size and ability to act as an electron acceptor in the energy production pathways of the tricarboxylic cycle where it mops up protons (H^+) to form water.

The paradox!

- Utilization of oxygen is accompanied formation of reactive oxygen species (RORs).
- The assault by the RORs on the DNA, proteins and other macromolecules is profound..
- Oxygen toxicity could have necessitated the evolution of the nucleus and the nuclear membrane in the eukaryotic cells to minimize assaults by RORs: The mitochondrial DNA has more than 10 times the level of oxidative DNA damage than does the nuclear one.

Gas exchangers



Ideal Gas Exchanger?

1. **There are no rules in respiration, but only necessities**.

2. Gas exchangers have developed on a need-to-have basis.
3. **Brain v/s lung**

4. There are no tissues or cells that are unique to gas exchangers e.g. a neuron, osteocyte, a podocyte etc.

5. **The type II (granular) pneumocyte**

6. Surfactant-like phospholipids are produced in many tissues and organs, including **the stomach, the intestines**, the swim bladder, the gas mantle of an air-breathing snail (Helix aspersa), **the prostate gland, the female reproductive tract, the lacrimal gland, the mesothelial cells of the pleura, the pericardium, the peritoneum, and the Eustachian tube epithelium**

'A clear historical record documents for us the evolutionary design process. Looking into that record in detail can help us understand why certain things are the way they are and help us understand how things in general come to take the forms that they do.'
Petroski (2000)

'The only law that holds without exception in biology is that exceptions exist for every law'
Stebbins (1984)

Quantum leaps in morphological and physiological transformations of the gas exchangers and the respiratory processes happened at:

1. change of anaerobiotic to aerobiotic life
2. accretion of diffusion-dependent unicells into multicellular organisms.
3. formation of a closed circulatory system from an open one.
4. evolution of metal-based carrier pigments that improved oxygen uptake and transfer by blood/ haemolymph.
5. formation of invaginated respiratory organs ('lungs'), a transition that was requisite for water conservation .
6. physical translocation from water to land.
7. development of double circulation from a single one, a transformation that granted efficient delivery of oxygen to the tissues.
8. shift from buccal-force-pumping to suctional breathing.
9. progression from ectothermic-heterothermy to endothermic-homeothermy, a high-level metabolic state that required evolution of efficient respiratory organs.
10. capacity for highly energetic lifestyles (e.g. flight), performances that exacted singularly efficient respiratory organs.

- In the biosphere, over the biological range of temperature and pressure, the only two naturally occurring respirable fluids: water (a liquid) and air (a gas).
- Gills and lungs have evolved for respiration in the respective media.

Gills in air: closely packed, delicate, leaf-like respiratory units

i.dry out and become impermeable to oxygen.

ii.cohere due to surface tension and collapse under their own weight.

iii.creates large diffusion distances in the lamellae

Lungs in water: High viscosity of water → the ventilatory rate is much slower.
Liquids physically destroy alveoli , dissolve and mechanically displace the surfactant, osmotically interfere with the composition of the body fluids, cause pathological changes such as interstitial oedema and produce intrapulmonary froth and atelectasis upon re-exposure to air .
Macrophages are lost and airway constriction increases.

- **The foremost factors that have jointly prescribed the design of the gas exchangers include**

i. respiratory medium utilized
ii. habitat occupied
iii. phylogenetic level of development achieved
iv. body size
v. metabolic capacity and lifestyle pursued

- **Gas exchangers display certain or all of the following basic morphological features**

i. evagination or invagination from the body surface
ii. stratification or compartmentalization, means by which an extensive surface area is generated in a limited space
iii. thin partitioning between internal and external compartments, a property that promotes flux of respiratory gases
iv. vascularization, an attribute that increases the volume of blood exposed to external respiratory medium
v. geometric organization of the structural components, characteristics that determine the interaction between the respiratory media.

Stratification and compartmentalization of gas exchangers

- A large surface area is produced by internal subdivision of the parenchyma, giving rise to narrow terminal gas exchange components **alveoli** in the mammalian one.

- In the human lung, there are about 300 million alveoli of an average diameter of 250 µm, giving an overall alveolar surface area of 143 m^2.
- Increasing the internal subdivision and hence the respiratory surface area of the lung **occurs at a cost**: in a compliant lung, narrow terminal gas exchange components demand more energy to dilate on ventilation and have a high propensity of collapsing.
- **Saving grace**: Surfactant, a complex material consisting primarily of phospholipid material (dipalmitoylphosphatidylcholine), reduces surface tension, preserving stability of the narrow terminal respiratory units.
- A balance between maximization of respiratory surface area, ventilatory capacity, size of the terminal gas exchange components and overall respiratory efficiency must be established in every gas exchanger.

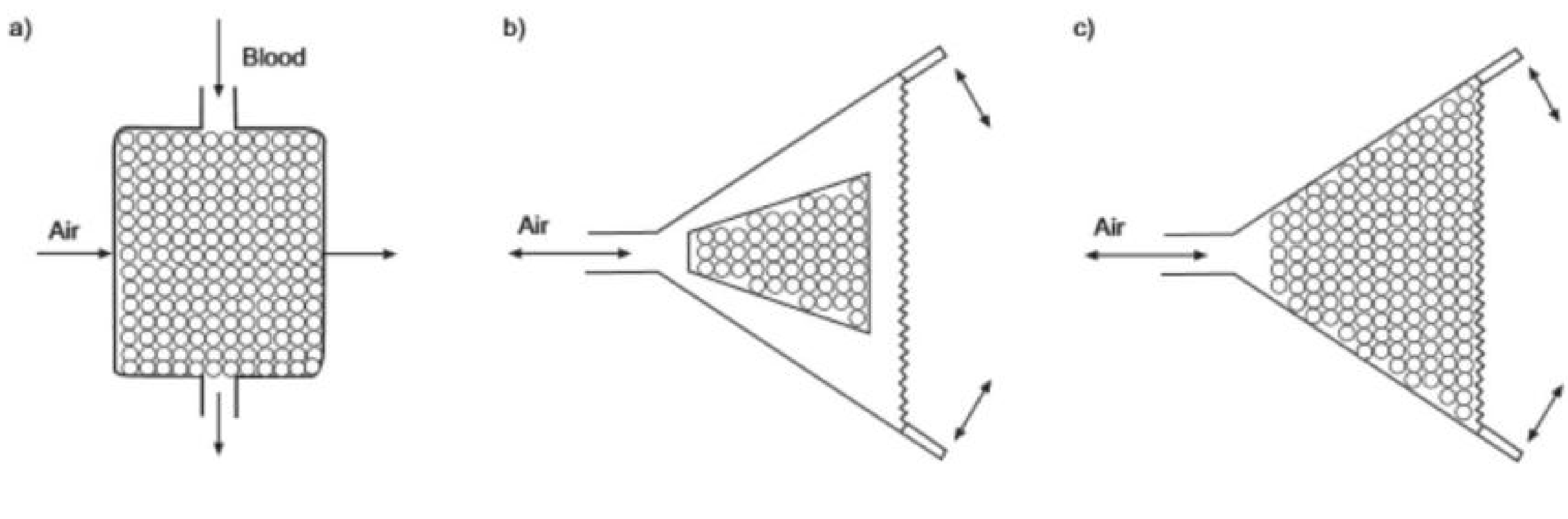
Evagination and invagination of gas exchangers

- requisite for successful terrestrial habitation: water loss across an extensive respiratory surface area was minimized.
- If the mature human lungs, of which the alveolar surface is 143 m^2 were designed like gills, **water loss** would be about 500 L per day.

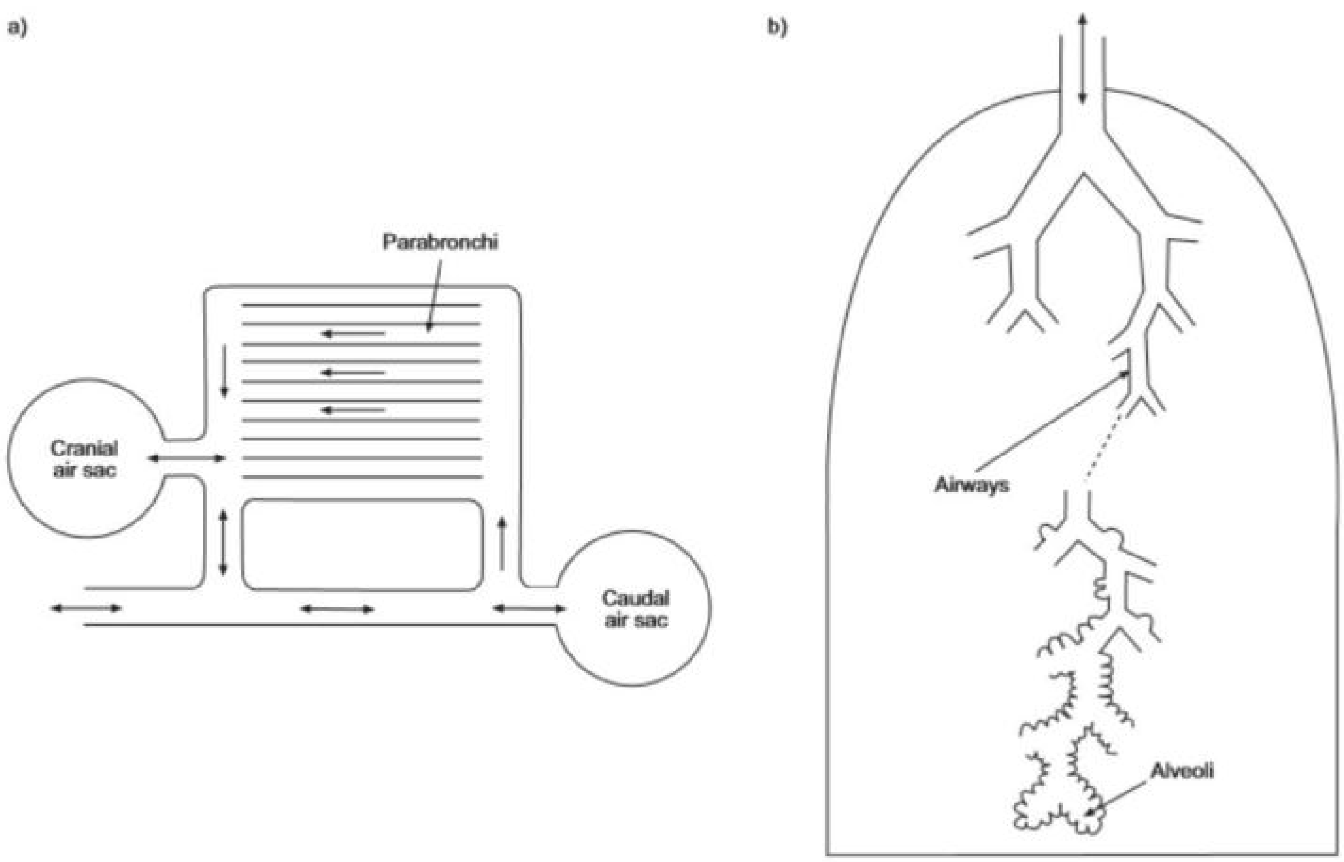
- **~~Dead space creation:~~**

i. While evaginated gas exchangers can be ventilated continuously and unidirectionally, lungs are invaginated organs.
ii. Thus having a narrow entry/exit point to the ambient milieu, they can only be ventilated tidally, i.e. bidirectionally (= in-and-out).
iii. In a resting person where the dead space is about 140 cm^3, about 28% of the 500 cm^3 of the inhaled air (tidal volume) does not reach the respiratory region of the lung.

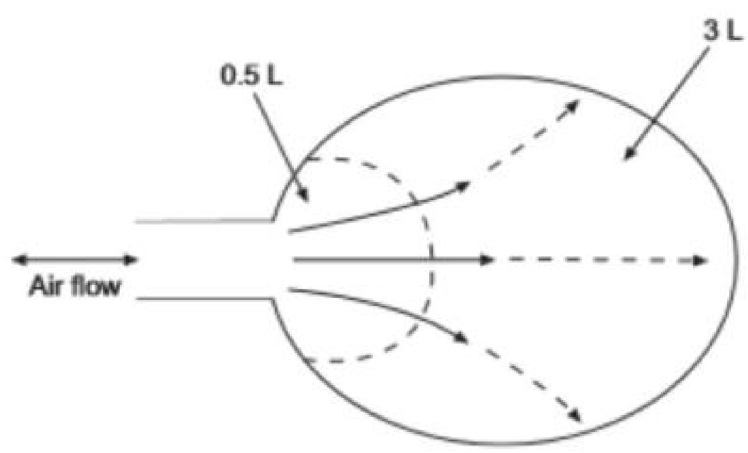
Possible configurations for a heat or gas exchanger



The flow-through arrangement for the gas-exchanging tissue in the bird,and the reciprocating pattern in mammals.



Reciprocating pattern of air movement in mammalian lung



Three shortcomings arising due to reciprocating pattern:

1. **Potential for uneven ventilation: increases during rapid breathing**
2. **Low alveolar oxygen tension:**
3. **Large terminal air units: to reduce resistance**

- Respiratory media must be brought into very close proximity to each other to optimize gas exchange by passive diffusion.
    - *the thickness of the blood–gas (tissue) barrier of the lung of the shrew (2.5 g)- 0.334 μm*
    - *the thickness of the blood–gas (tissue) barrier of the lung of the whale (150 tonnes)- 0.350 μm*

- In vertebrates, the thickness of the blood–water/air (tissue) barrier increases from fish, amphibians, reptiles, mammals to birds.

- In the avian lung, epithelial- and endothelial cells that constitute the blood–gas (tissue) barrier are separated only by a common basement membrane.

Separation of the gas exchange and ventilatory functions

- Gas-exchanging units require extremely thin walls because gas movement across them is by passive diffusion.
- The ventilating structures need to be freely distortable so that they can increase their volume during inspiration. In the bird lung, this is done by nonvascular air sacs, which are robust, in contrast to the alveoli of the mammalian lung, which are necessarily delicate because of their extremely thin-walled capillaries.

Shortcomings
- Occlusion of airways by aspiration or secretions
- Localised airway inclusion also commonly occurs in airway diseases such as chronic bronchitis and asthma.
- Is repetitive distortion of alveolar tissue a factor in its destruction? Emphysema, characterised by breakdown of the alveolar walls, Ageing etc.

Abbreviations and symbols used in respiratory physiology

V_T	Tidal volume
FRC	Functional residual capacity
ERV	Expiratory reserve volume
RV	Residual volume
IC	Inspiratory capacity
IRV	Inspiratory reserve volume
TLC	Total lung capacity
VC	Vital capacity
Raw	Resistance of the airways to flow of air into the lung
C	Compliance
V_D	Volume of dead space gas
V_A	Volume of alveolar gas
$\dot{V}_I$	Inspired volume of ventilation per minute
$\dot{V}_E$	Expired volume of ventilation per minute

$\dot{V}_I$	Inspired volume of ventilation per minute
$\dot{V}_E$	Expired volume of ventilation per minute
$\dot{V}_S$	Shunt flow
$\dot{V}_A$	Alveolar ventilation per minute
$\dot{V}o_2$	Rate of oxygen uptake per minute
$\dot{V}co_2$	Amount of carbon dioxide eliminated per minute
$\dot{V}co$	Rate of carbon monoxide uptake per minute
DLo_2	Diffusing capacity of the lungs for oxygen
DLco	Diffusing capacity of the lungs for carbon monoxide
P_B	Atmospheric pressure
Palv	Alveolar pressure
Ppl	Pleural pressure
Po_2	Partial pressure of oxygen
Pco_2	Partial pressure of carbon dioxide

Gas Laws

- Ambient (Atmospheric) conditions
  - Pressure is typically measured in mm Hg
  - Atmospheric pressure is 760 mm Hg
  - Atmospheric components
    - Nitrogen = 78% of our atmosphere
    - Oxygen = 21% of our atmosphere
    - Carbon Dioxide = .033% of our atmosphere
    - Water vapor, krypton, argon, …. Make up the rest
- A few laws to remember
  - Dalton's law
  - Fick's Laws of Diffusion
  - Boyle's Law
  - Ideal Gas Law

Dalton's Law

Law of Partial Pressures= $\mathbf{P_x = P_T * F_x}$

- "each gas in a mixture of gases will exert a pressure independent of other gases present"

  Or
- The total pressure of a mixture of gases is equal to the sum of the individual gas pressures.
- Conventionally, fractional concentration always refers to the dry gas.

– **<u>Practical application?</u>**

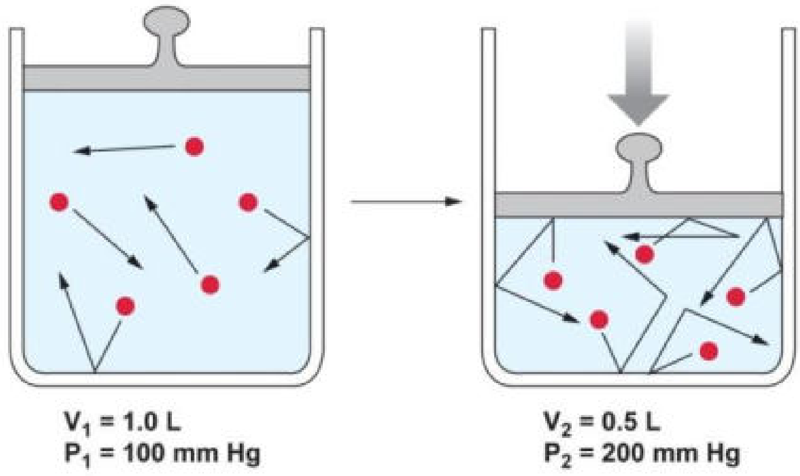
- If we know the total atmospheric pressure (760 mm Hg) and the relative abundances of gases (% of gases)
  - We can calculate individual gas effects!
  - P_{atm} x % of gas in atmosphere = Partial pressure of any atmospheric gas
    - » P_{O_2} = 760mmHg x 21% (.21) = **160 mm Hg**

Now that we know the partial pressures we know the gradients that will drive diffusion!

Boyle's Law

– Describes the relationship between pressure and volume
  - "the pressure and volume of a gas in a system are inversely related" at a constant temperature

$$P_1V_1 = P_2V_2$$

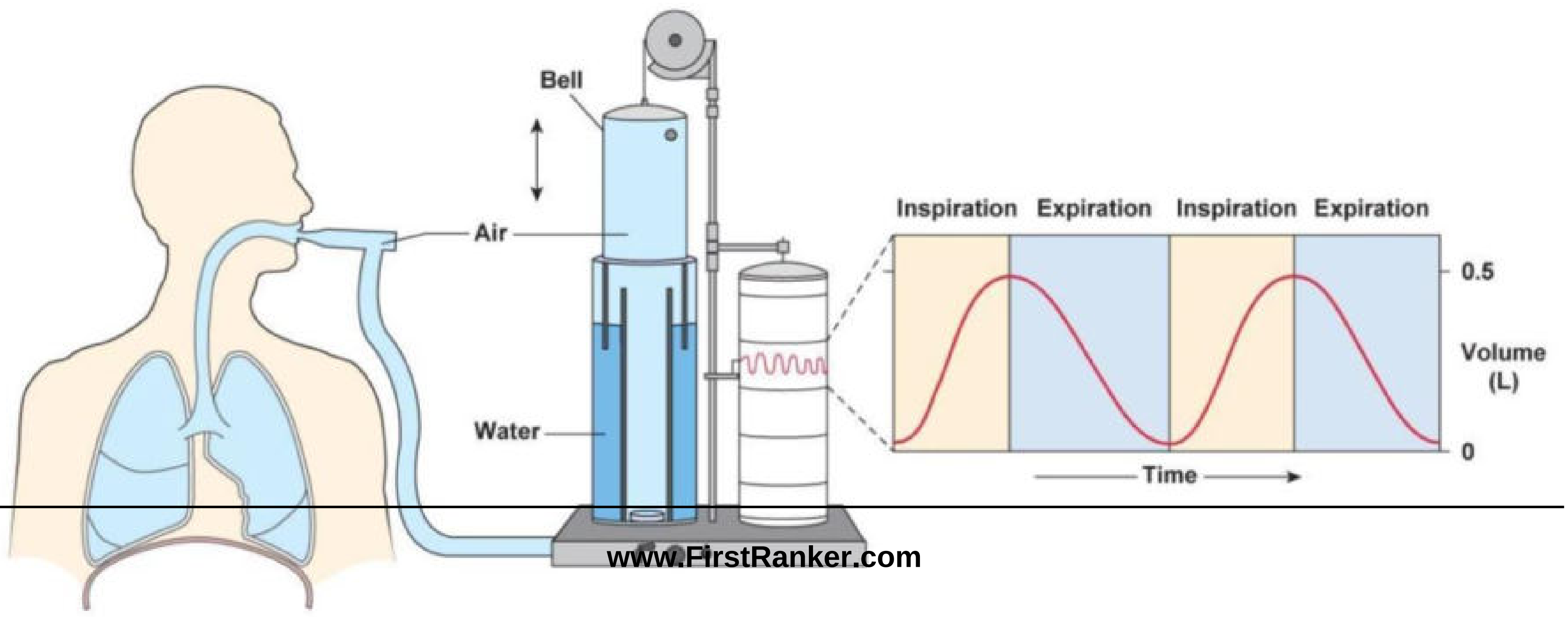


As the molecules are brought close together (smaller volume), the rate of bombardment on a unit surface increases (greater pressure).

- How does Boyle's Law work in us?

- Increase in lung volume decreases intrapulmonary pressure: **Air goes in.**
- Decrease in lung volume, raises intrapulmonary pressure above atmosphere: **Air goes out.**

- Principle of Spirometry



- **Charles Law**: at constant pressure, the volume is proportional to the absolute temperature

$$V/T = \text{constant}$$

A rise in temperature increases the speed and momentum of the molecules, thus increasing the force of bombardment on the container.

Avogadro's law: relates volume of a gas to the amount of substance of gas present.

or

"equal volumes of all gases, at the same temperature and pressure, have the same number of molecules"

For a given mass of an ideal gas, the volume and amount (moles) of the gas are directly proportional if temperature and pressure are constant.

- which can be written as: $V/n=K$

- A gram molecule (e.g. 32g of oxygen)occupies 22.4 liter at STPD

- **Ideal Gas law**: this law combines three laws
  - The pressure and volume of a container of gas is directly related to the temperature of the gas and the number of molecules in the container
  - PV = nRT
    - n = moles of gas
    - T = absolute temp
    - R = universal gas constant @ 8.3145 J/K·mol
    - When the units employed are milliliters of mercury, liters and degrees absolute, then R=62.4

- **Henry's law** : the amount of dissolved gas is proportional to its partial pressure in the gas phase.

$$C_x = K * P_{x},$$

where K is the solubility coefficient of gas in the liquid.

The partial pressure of a gas in solution is best defined as its partial pressure in a gas which is in euilibrium with that solution

Graham's Law

- the rate of diffusion of a gas is 1/ to the square root of its molecular weight

Atmospheric Air vs. Alveolar Air

- H2O vapor 3.7 mmHg
- Oxygen 159 mmHg
- Nitrogen 597 mmHg
- CO2 .3 mmHg

- H2O vapor 47 mmHg
- Oxygen 104 mmHg
- Nitrogen 569 mmHg
- CO2 40 mmHg

Gas Pressures in a Mixture of Gases—"Partial Pressures" of Individual Gases

The pressure of a gas acting on the surfaces of the respiratory passages and alveoli is proportional to the summated force of impact of all the molecules of that gas striking the surface at any given instant.

This means that *the pressure is directly proportional to the concentration of the gas molecules*.

. The rate of diffusion of each of these gases is directly proportional to the pressure caused by that gas alone, which is called the *partial pressure* of that gas. The concept of partial pressure can be explained as follows.

Consider air, which has an approximate composition of 79 percent nitrogen and 21 percent oxygen. The total pressure of this mixture at sea level averages 760 mm Hg.

Therefore, 79 percent of the 760 mm Hg is caused by nitrogen (600 mm Hg) and 21 percent by O_2 (160 mm Hg). Thus, the "partial pressure" of nitrogen in the mixture is 600 mm Hg, and the "partial pressure" of O_2 is 160 mm Hg; the total pressure is 760 mm Hg, the sum of the individual partial pressures.

Pressures of Gases Dissolved in Water and Tissues

Gases dissolved in water or in body tissues also exert pressure because the dissolved gas molecules are moving randomly and have kinetic energy. Further, when the gas dissolved in fluid encounters a surface, such as the membrane of a cell, it exerts its own partial pressure in the same way that a gas in the gas phase does.

Factors That Determine the Partial Pressure of a Gas Dissolved in a Fluid.

The partial pressure of a gas in a solution is determined not only by its concentration but also by the *solubility coefficient* of the gas. That is, some types of molecules, especially CO2, are physically or chemically attracted to water molecules, whereas other types of molecules are repelled. When molecules are attracted, far more of them can be dissolved without building up excess partial pressure within the solution. Conversely, in the case of molecules that are repelled, high partial pressure will develop with fewer dissolved molecules. These relations are expressed by the following formula, which is *Henry's law*:

Partial Pressures of Gases in Blood

- When a liquid or gas (blood and alveolar air) are at equilibrium:
  - The amount of gas dissolved in fluid reaches a maximum value (Henry's Law).
- Depends upon:
  - Solubility of gas in the fluid.
  - Temperature of the fluid.
  - Partial pressure of the gas.
- [Gas] dissolved in a fluid depends directly on its partial pressure in the gas mixture.

Diffusion in the gas phase: Gas molecules tend to distribute themselves uniformly throughout any available space until the partial pressure is same everywhere.

- Diffusion
- Light gases diffuse faster because mean velocity of the molecule is higher.

Diffusion of dissolved gases: rate is inversely proportional to the square root of the molecular weight of the gas.

- The amount of gas that moves through a film of liquid (or a membrane) is proportional to the solubility of the gas.

- Fick's Laws of Diffusion: Gas exchange involves the diffusion of gases across a membrane
  - Things that affect rates of diffusion
    - Distance to diffuse
    - Gradient sizes
    - Diffusing molecule sizes
    - Temperature

$$R = \frac{DA\ \Delta\ p}{d}$$

D= diffusion constant (size of molecule, membrane permeability, etc)

A= area over which diffusion occurs

Δ p = pressure difference between sides of the membrane

d = distance across which diffusion must occur

Question of the day!

Using Fick's law of diffusion through a tissue slice, if gas X is twice as soluble and 4 times a dense as Y then the ratio of diffusion rates of X to Y will be