# Lecture 1: Diet and Nutrition

**What is a healthy diet?**

- A healthy diet should provide us with the right amount of energy (cal or kcal), from foods and drinks to maintain energy balance. Energy balance is where the calories taken in from the diet are equal to the calories used by the body – *British Nutrition Foundation*
- Men ~2500cal/day
- Women ~2000cal/day

**What is a calorie?**

- The amount of energy, or **heat**, that is required to raise the temperature of 1 gram of water by 1 degrees Celsius.

**What is obesity?**

- Obesity is generally caused by eating too much and moving too little
- Surplus energy is stored as fat
- '*Carrying excess fat to the point that it becomes detrimental to health*'

BMI can be used to identify obesity: >24.9 is said to be overweight, >30 is said to be obese.

- BMI is not accurate for muscular people
- BMI is also influenced by ethnic background

Alternatives to BMI:

- Waist circumference
- Waist to hip ratio
- Body composition

**Causes, Consequences and Treatment of Obesity**

Causes:

- Endocrine disorders
- Psychiatric disorders
- Medications
- Genetics
- Environmental factors
- Cultural normalities

Consequences:

- Cancer
- Stroke
- Osteoarthritis
- Poor mental health
- Cardiovascular diseases
- Respiratory problems.
- Premature death
- Diabetes
- Kidney problems
- Fatty liver disease

- In most cases, obesity is an entirely modifiable risk factor for disease

Treatment options:
- Lifestyle changes: e.g. reduced calorie diet, increased physical activity
- Bariatric surgery: e.g. gastric bypass, gastric band and sleeve gastrectomy
- Pharmacotherapy: e.g. appetite suppressors, fat absorption inhibitors

**Basal Metabolic Rate (BMR)**

- '*The rate of energy expenditure per unit time'*
- There are three basic physiological functions that need to be maintained:
    - Metabolic processes
    - Cell membrane pumps
    - Intracellular pumps
- Factors that affect BMR:
    - Age
    - Sex
    - Obesity
    - Climate
    - Medications
    - Disease
- BMT varies among people of equal height and weight, owing to ethnic and geographical differences
- Individual BMR remains fairly constant over a number of years.

**Measurement and Prediction of energy expenditure**

Indirect calorimeter
- Measurement of oxygen consumption and/or carbon dioxide production which is then converted to energy expenditure using formulae

Direct calorimetry
- Rate of heat loss from the subject to the calorimeter is measured

Non-calorimetric methods
- A number of techniques have been used to predict the energy expenditure and/or physical activity by extrapolation from physiological measurements and/or observations.
- These include heart rate monitoring, pulmonary ventilation volume and thermal imaging.

NB: There is a big variation between methods –
- Accuracy
- Reproducibility
- Reliability
- Complexity
- Cost

**Glycaemic index**

- Describes the glycaemic response of a food in relation to glucose
- Foods are classified as having a low, intermediate or high GI
- Low GI foods are recommended in diabetes management and in the general population

Factors affecting GI

- Size and nutrient composition of the meal
- Pectin to amylopectin ration in the food
- Degree of ripeness or preparation

High GI = bread, fruit juices and honey

Intermediate GI = granary bread, rice

Low GI = pulses, beans, peas, legumes and pasta

- There is currently insufficient evidence to suggest any particular diet is superior in treating overweight and obese patients with T2 diabetes
- Mediterranean, vegan and low-GI diets appear to be promising

## Lecture 2: Introduction to the GI Tract

**Overview**

Organs:

- Stomach – involved in protein digestion and contains HCl acid as well as pepsin enzymes
- Pancreas – endocrine function is to release protease enzymes, which are activated in the duodenum. Bicarbonate ions are also released from the pancreas.
- Small intestine – duodenum and jejunum are the primary sites for absorption
- Colon – site of water absorption

Structure:

- There is a common architecture but regional specification
- The innermost layer of the stomach contains glands which secrete acid – called gastric pits
- Mucous secretions protect the lining of the intestine – villi are either finger-like, leaf-life or broad. The size of villi decreases from duodenum to ileum.

Layers of the GI tract

1) Innermost layer is known as the mucosa, which is made of three layers:
    - Epithelium – involved in nutrient absorption
    - Lamina propria – largest part which contains loose connective tissue (blood vessels, muscle cells and nerves)
    - Muscularis mucosae – thin layer of muscle, NOT responsible for moving food but for moving folds

2) Submucosa: further connective tissue and contains glands (e.g. duodenal glands)

3) Muscularis externa: contains two layers of muscle; circular and longitudinal

Plexi:

- Myenteric – between the circular and longitudinal muscle and found from oesophagus to rectum
- Submucosal – between circular muscle and submucosa and only in SI and LI.

Levels of Amplification:

1st – folds (spiral OR Kerckring), referred to plicae circulares
2nd – villi
3rd – microvilli

**Histology** (covered in more detail in a later lecture)

Oesophagus
- Dense stratified squamous epithelium consisting of submucosal glands

Stomach
- Gastric pits in the mucosa filled with gastric glands
- Parietal cells which secrete HCl
- Contains oblique muscle

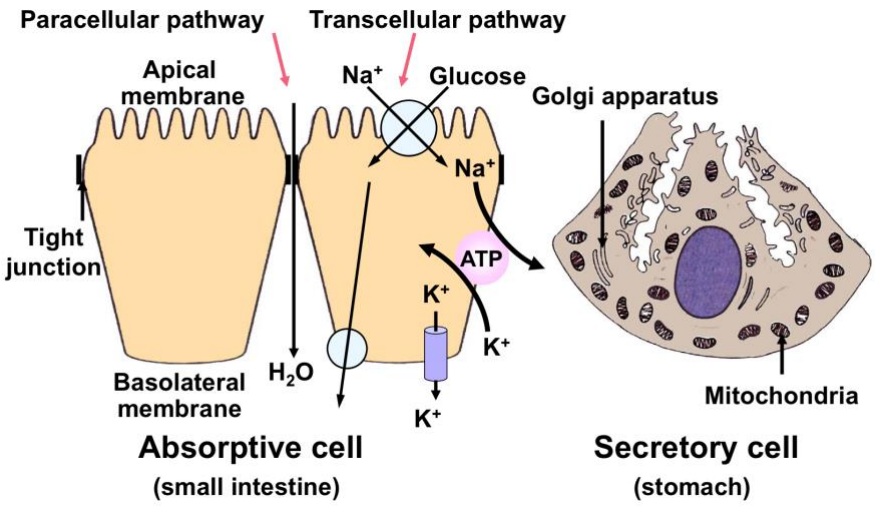
Duodenum
- Long 'finger-like' villi
- Crypts between villi contains Brunner's glands (glands in the submucosa)

Jejunum
- Villi (smaller and fatter than the duodenum)
- Crypts between villi

Ileum
- Smallest and fattest villi
- Crypts between villi
- Peyer's patches (Covered by flattened epithelium) – gut associated lymphoid tissue

Colon
- Crypts filled with mucus secreting goblet cells

**GI Epithelial Cells**




- Polarised cells – different ends have different functions and have two distinct membranes; absorption or secretion
- The top membrane is known as the apical membrane
- The base/sides are known as the basolateral membrane
- The secretory cells involved with acid secretion in the stomach are known as Parietal cells.

**GI Secretions**

Five major secretory tissues:

- Salivary glands
- Gastric glands
- Exocrine pancreas
- Liver-biliary system
- Intestine

Total secretion: ~8/9 litres/day

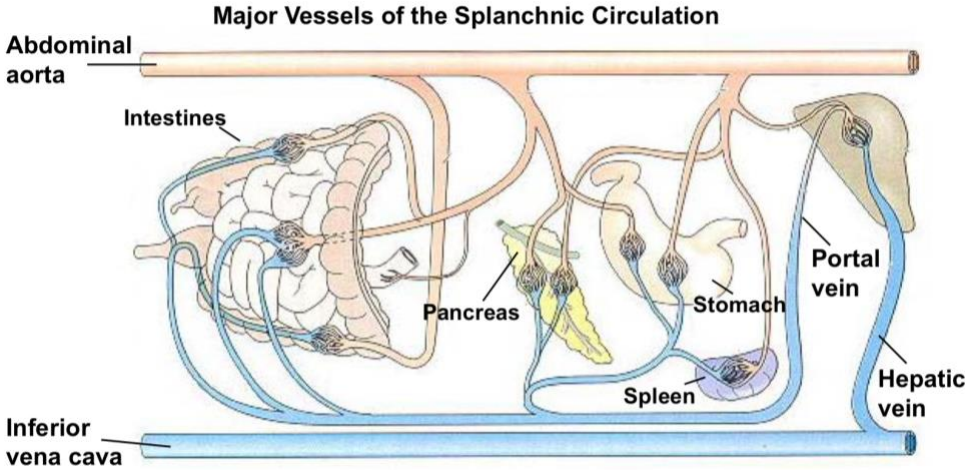
Secretions contain:

- Enzymes
- Ions
- Water
- Mucus

Functions:

- Breakdown large compounds
- Regulate pH
- Dilution
- Protection (bicarbonate and mucus)

**GI Blood circulation**




- There is an 8-fold increase to blood supply during digestion; progressive activation of blood supply – stomach to small intestine to large intestine

- Return of blood from GI system also important. Veins from SI are not always direct to the heart, products of carb and protein digestion delivered the liver via the portal vein.

- Villi have a rich capillary network, counter current mechanism in tip of the villi promotes efficiency of protein and carb absorption

- Drawback of counter-current mechanism – tips of villi are extremely sensitive to ischaemic damage

- Villous cells absorb fatty acids and then resynthesize them and then do not enter into the blood directly, only via the lymphatic system (thoracic duct).

# Lecture 1: Introduction to Respiratory Physiology

P: partial pressure
I: inspired
F: fractional composition
A: alveolar
a: arterial
$\bar{v}$: mixed venous
$\dot{V}$: volume per unit time

**Functions of the respiratory system**

• Gas exchange
• Filtering particulate matter (e.g. emboli) from venous blood
• Defence against inhaled particles and pathogenic organisms
• Processing of endogenous compounds by the pulmonary vasculature (e.g. Angiotensin I →Angiotensin II)

**Emergency Assessment**

1. A AIRWAY
2. B BREATHING
3. C CIRCULATION
4. D DISABILITY
5. E EXPOSURE
6. F Don't ever FORGET to measure blood glucose

**Rapid breathing rate**: tachypnoea
**Respiratory arrest**: apnoea

**Cyanosis**: abnormal blue-purple discolouration, caused due an elevated concentration of deoxyhaemoglobin indicative of low partial pressure of oxygen, process by which this occurs is called *hypoxaemia*

**Cheyne-Stokes respiration**: characterised by progressively deeper and sometimes faster breathing followed by a gradual decrease that results in a halt of breathing known as *apnoea*.

**Kussmaul Breathing**: deep and laboured breathing, caused by increase in acidity of arterial blood - *diabetic ketoacidosis*

**Auscultation of breath sounds**

*Vesicular*: normal breath sounds
*Wheeze*: heard during expiration
*Stridor*: heard during inspiration - airway obstruction, much greater pressure required for inspiration to occur
*Bronchial*: occurs in pneumonia, lung is full of fluid - *consolidation*

**Look** for flapping tremor: *hypercapnia*

- **Flapping tremor:** *asterixis*
- Rise in partial pressure of carbon dioxide in arterial blood
- Liver failure

Pulse oximetry

- Measures oxygen saturation using a pulse oximeter: 95-100%
- Only indicates occupation of binding sites NOT total oxygen content.

Measure **arterial blood gases (ABGs)**

- Arterial blood gas: needle contains heparin to prevent clotting
- Bright red/crimson colour
- Gas analyser
- ABG Report:

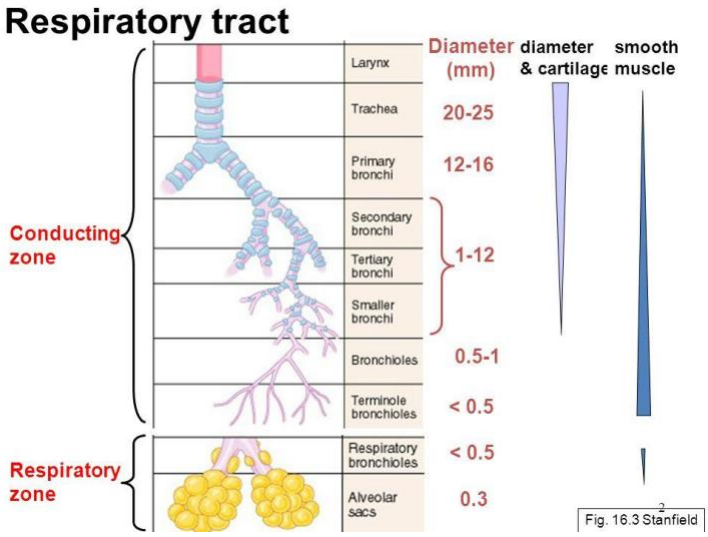
| SYRINGE SAMPLE | | | |
|---|---|---|---|
| ACID/BASE 37°C | | Units | Reference Rang |
| pH | 6.647↓ | | (7.350–7.450) |
| pCO2 | 3.75↓ | kPa | (4.67–6.00) |
| pO2 | 18.17↑ | kPa | (10.00–13.33) |
| HCO3 – std | 2.7 | mmol/L | |
| BEvt | –33.8 | mmol/L | |
| | | | |
| OXYGEN STATUS 37°C | | | |
| tHb | 12.3 | g/dL | (12.0–18.0) |
| Hct | 36 | % | |
| O2CT | 16.3 | mL/dL | |
| pO2 | 18.17↑ | kPa | (10.0–13.3) |
| O2SAT | 93.0 | % | |
| O2Hb | 94.8 | % | (94.0–97.0) |
| COHb | 0.3 | % | (0.0–1.5) |
| MetHb | 1.4 | % | (0.0–1.5) |
| HHb | 1.5 | % | (0.0–5.0) |
| | | | |
| ELECTROLYTES | | | |
| Na+ | 135.3 | mmol/L | (135.0–148.0) |
| K+ | 3.59 | mmol/L | (3.50–5.30) |
| Cl– | 101 | mmol/L | (98–106) |
| | | | |
| METABOLITES | | | |
| Glucose | 19.31↑ | mmol/L | (3.7–5.2) |
| Lactate | 18.56↑ | mmol/L | (0.50–2.00) |

↑ or ↓ = exceeds reference range

**Upper Respiratory Tract**

Nasopharynx: warms, humidifies and filters air, sneezing is a protective reflex - lined with (respiratory epithelium) *pseudostratified columnar epithelium.* Humidification causes the partial pressure of oxygen to decrease from the atmosphere into the respiratory system.

Laryngeal: function includes phonation, closing the airways during swallowing and the cough reflex




**Conducting zone role:**

- Provides a low-resistance pathway for airflow. Resistance is physiologically regulated by changes in bronchial smooth muscle and by physical forces acting upon the airways
- Defends against microbes, toxic chemicals and foreign matter - mediated by cilia, macrophages and mucus.
- Warms and moistens air
- Phonation - vocal chords in larynx.

**Dead Space**

- Volume of gas in the respiratory tract that is not involved in gas exchange
- Anatomical dead space includes the volume of gas in the upper airways and the conducting zone of the lower airways
- Physiological dead space is the anatomical dead space plus the volume of gas in the alveoli that have inadequate blood supply
- In healthy individuals: anatomical ~ physiological

**Factors affecting airway resistance**

- FRC: functional residual capacity - baseline from which you normally breathe, volume of gas which is constantly in your lungs when you breathe.
- Contraction of bronchial smooth muscle
- As lung volume decreases during expiration, dependent, small airways in the lung bases begin to close; this is known as the closing capacity
- Closing capacity increases with age eventually becomes equal to FRC at ~44 years (supine) and ~66 years in the upright position.
- Usually best to allow somebody with breathing difficulties to sit up rather than lay down

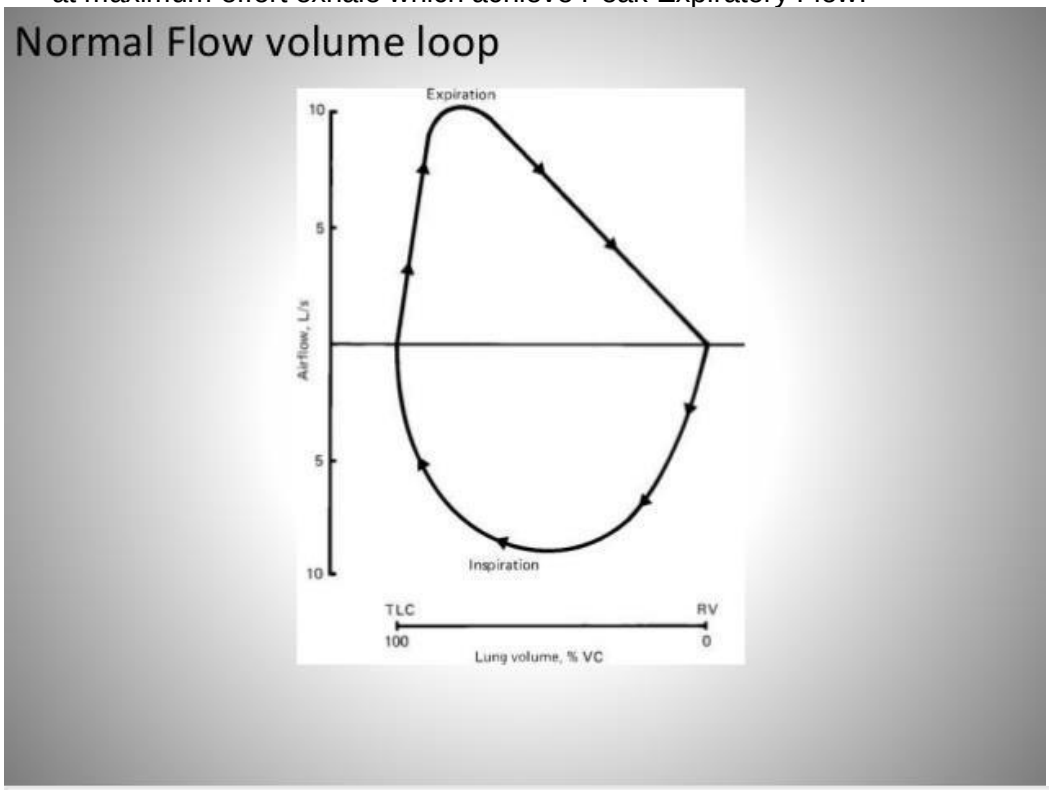
**Control of bronchial smooth muscle**

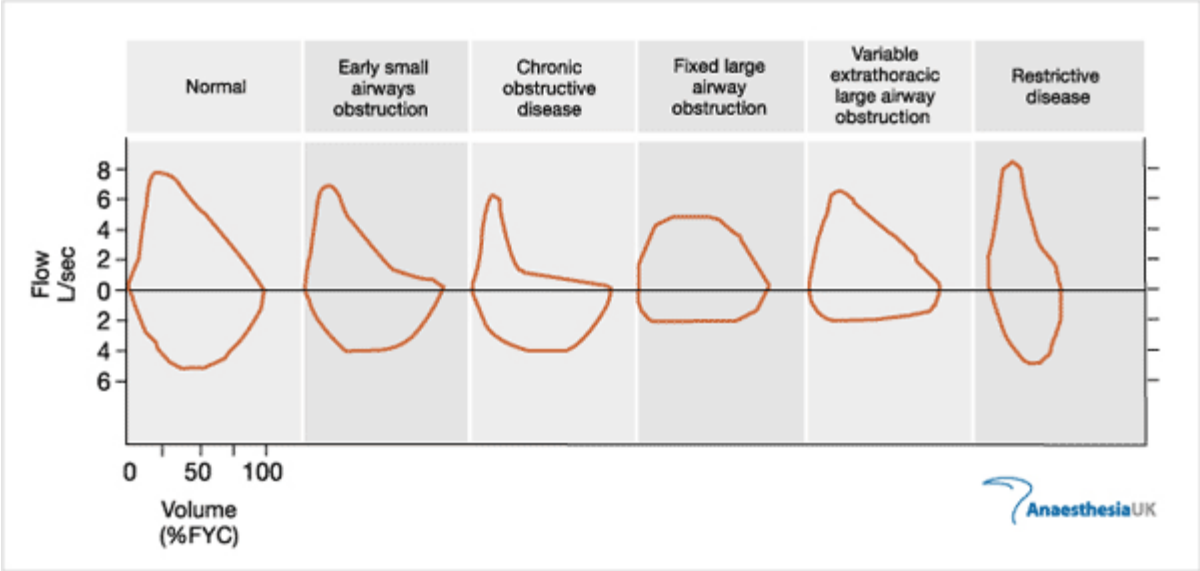
- Post ganglionic parasympathetic fibres release acetylcholine that agonises M3 muscarinic receptors to cause bronchial constriction
- Non-adrenergic non-cholinergic (NANC) is a *potential* bronchodilator system in humans
- Humoral (via blood) control
- Direct physical and chemical effects

- Direct physical contact: laryngoscopy

**Flow/Volume loop**

- Start at residual volume and inhale to fill the lung to Total Lung Capacity (TLC). Then at maximum effort exhale which achieve Peak Expiratory Flow.




Obstructive diseases

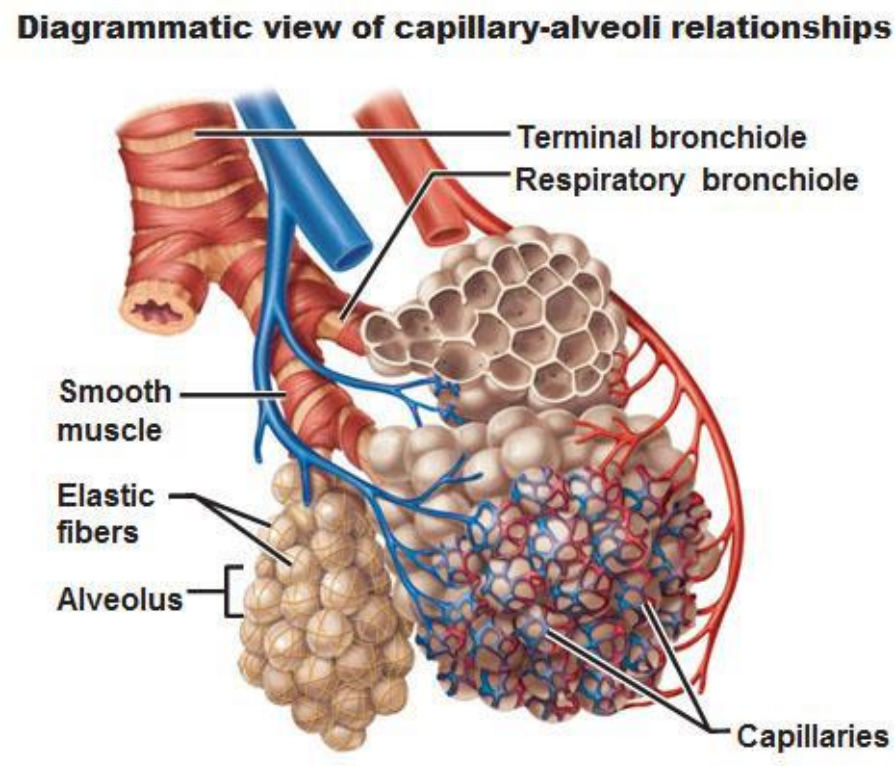
- When all the air is expired from the large airways, air from the smaller airways will be expired. With obstructive lung disease, these airways are partially blocked, so the air will come out slower.
- This will result in a lower flow and a (more or less) sharp fall in the flow-volume.

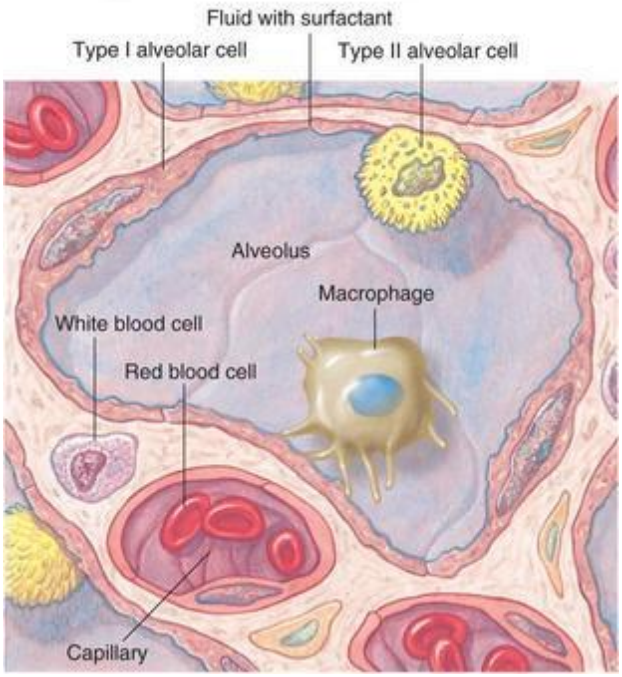
Restrictive disease

- Restrictive lung disease means that the total lung volume is too low.

- Since the airways are normal, the flow volume loop will have a normal shape: the curve will descend in a straight line from the PEF to the X-axis.

**Alveolar Structure**

- Elastin fibres mean that given the chance the lung will always collapse
- Type 1 alveolar cell: continuous layer of one cell thick flat epithelial cells.
- Type II Alveolar cell: produces a detergent-like surfactant, important in expanding the alveolus
- 

- 

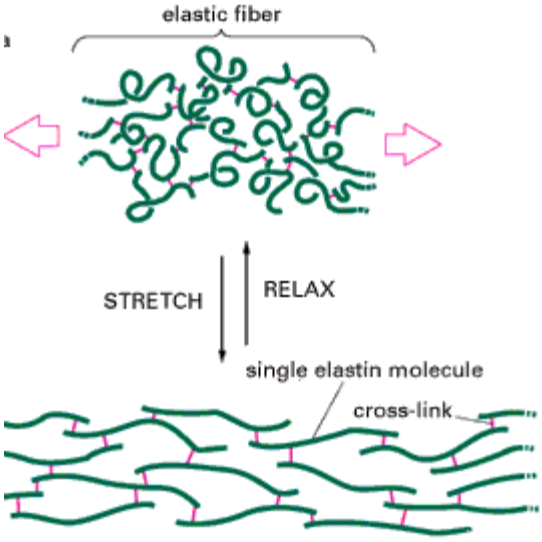
**Terminology**

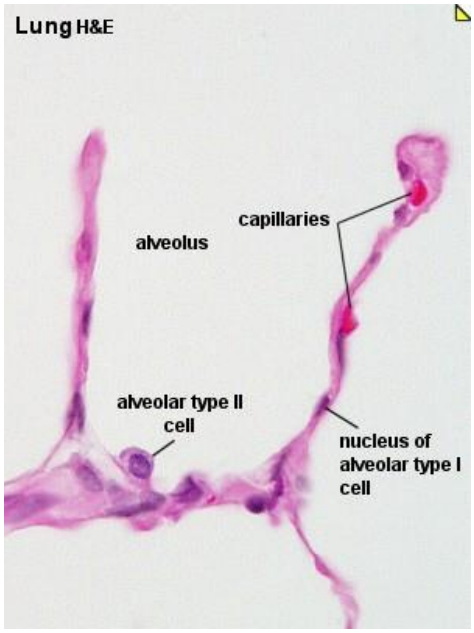
- Ventilation (V) refers to the *flow* of respiratory gases
- Perfusion (Q) is the *flow* of blood
- Minute volume ($V_E$) is the volume of gas exhaled in one minute
- $V_E$ = tidal volume x respiratory (breathing) rate
- Alveolar ventilation ($V_A$) is the amount of fresh gas delivered to the alveoli per minute
- $V_A$ = (tidal volume – physiological dead space) x respiratory rate

Ratio of alveolar ventilation ($V_A$) to perfusion is vital to gas exchange.

## Lecture 2: Compliance and Pulmonary Circulation

Lungs stretch due to a protein called **elastin**






**Laplace Equation**

*Transmural pressure = 2 x Surface tension/radius*

Transmural pressure
= alveolar pressure - intrapleural pressure
= 0 $cmH_2O$ -(- 5$cmH_2O$)
= +5$cmH_2O$

- A penetrating chest injury will allow air to be sucked into the intrapleural space
- $P_{ip}$ will become equal to atmospheric pressure i.e. 0 cmH2O
- Transmural pressure = 0 – 0 = 0 cmH2O
- Lung will collapse causing severe respiratory distress
- Known as a *traumatic pneumothorax* - requires emergency treatment

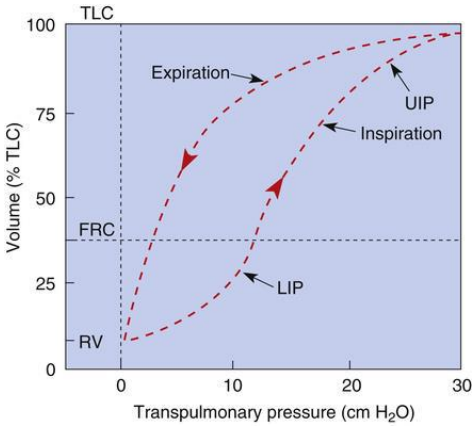
Surfactant reduces surface tension, increase ease of lung expansion and inflation

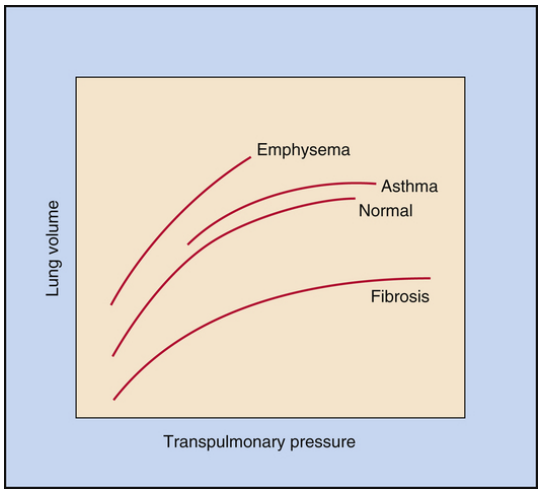
**First breaths**

- The ability to produce surfactant develops between 24 and 35 weeks' gestation
- Premature babies may lack surfactant and develop respiratory distress (Neonatal respiratory distress syndrome)
- Treatment includes giving artificial surfactant

**Compliance**

- Describes the distensibility of the lungs and the chest wall
- = change in volume / change in transmural pressure
- Difference between inspiratory and expiratory limbs is known as *hysteresis*

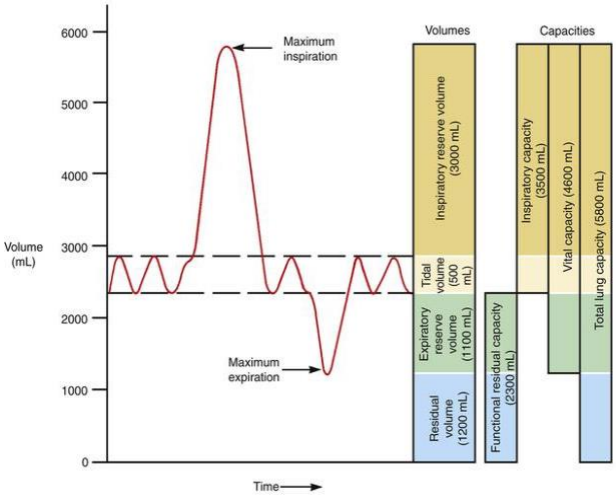



## Changes in compliance

- **Fibrotic** lung (restrictive) diseases lead to a scarring of the lungs and a reduction in compliance it results in a reduction in compliance and a reduction in FRC
- **Emphysema** (obstructive lung disease) results in a loss of elastin fibres and increase in compliance and an increase in FRC, the clinical description for this is a barrel-shaped chest

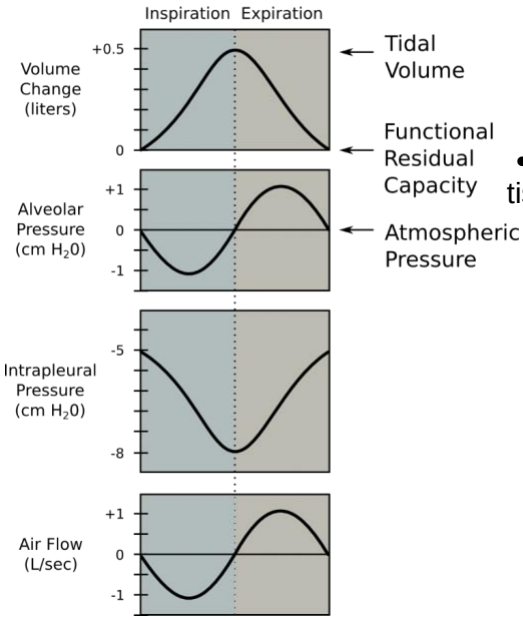
## Spirometer




## Boyle's Law

Pressure = k / Volume, where k is the constant of proportionality

If volume increases, pressure must decrease




**Work of breathing**

- Respiratory muscles require energy to do work
- Work must overcome resistance of airways and elasticity of tissues/effects of surface tension
- At rest the elastic energy stored during inspiration allows expiration to be passive

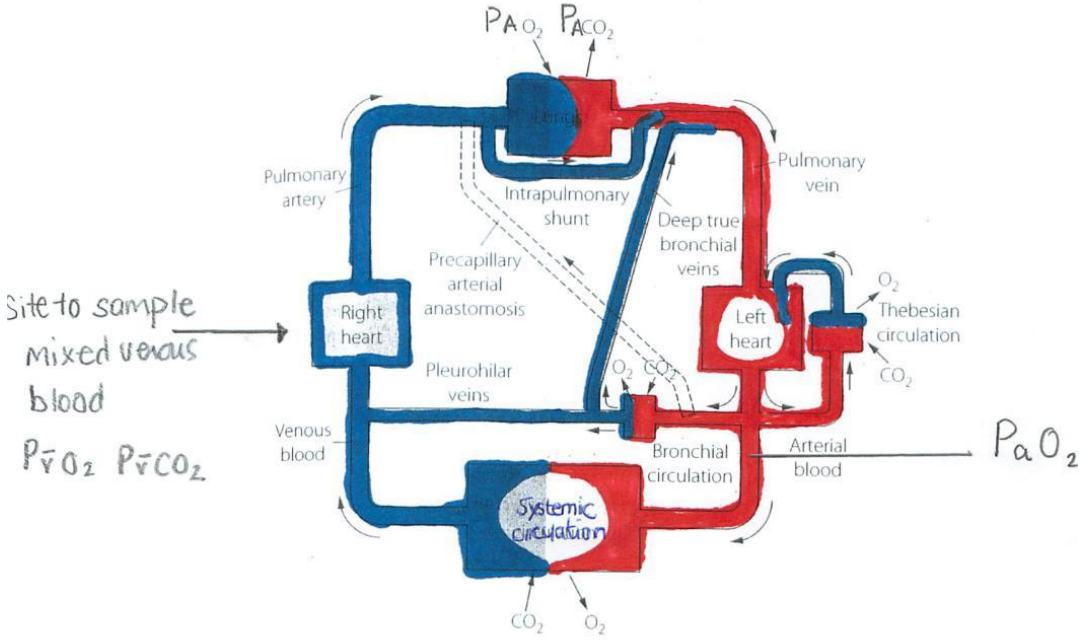
**Comparison of pulmonary and systemic circulation**

| | **Pulmonary circulation** | **Systemic circulation** |
|---|---|---|
| Pressure generated by | Right ventricle | Left ventricle |
| Systolic and diastolic pressures (mmHg) | 25/8 | 120/80 |
| Resistance | Lower (pulmonary vascular resistance) | Higher (total peripheral resistance) |
| Blood flow | Slightly less than 5 L/min | 5 L/min |
| Response of small arteries/arterioles to hypoxia | Vasoconstriction | Vasodilatation |

**Physiological Shunts**

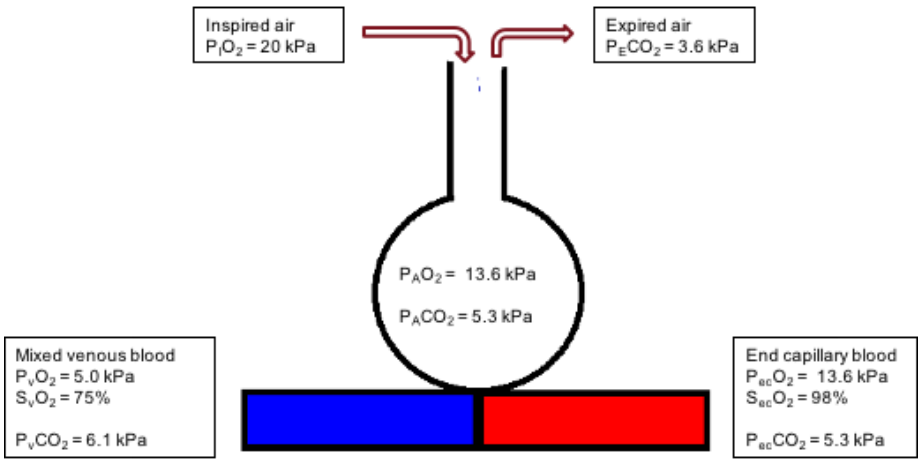
- Some deoxygenated blood drains in to the pulmonary veins from the bronchial circulation
- Some deoxygenated blood drains in the coronary circulation (5%), Thebesian veins from the drains in to the left ventricle
- This means $P_AO_2$ is > $P_aO_2$ and venous return to the left ventricle is greater than to the right ventricle

# Physiological Shunt (venous admixture)



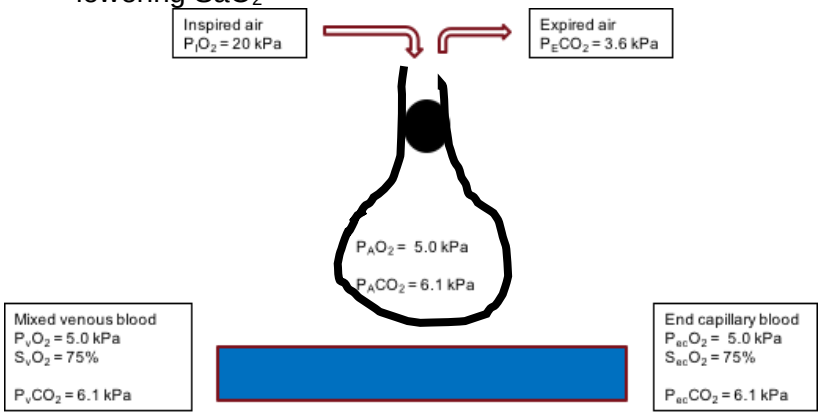

**$V_A$:Q = 1**

- The amount of ventilation with fresh gas equals perfusion with blood
- End capillary blood is fully arterialised/oxygenated



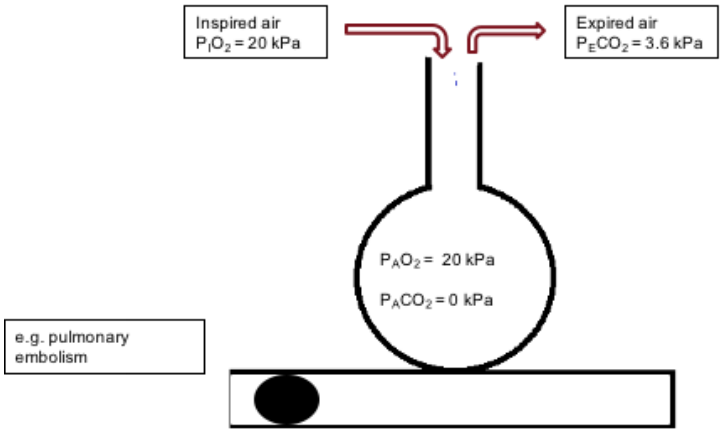
**$V_A$:Q = 0**

- Normal perfusion but complete absence of alveolar ventilation
- End capillary blood remains deoxygenated
- This is known as shunt/venous admixture
- It can lead to arterial hypoxaemia (hypoxic hypoxia) potentially causing **cyanosis** and lowering $SaO_2$

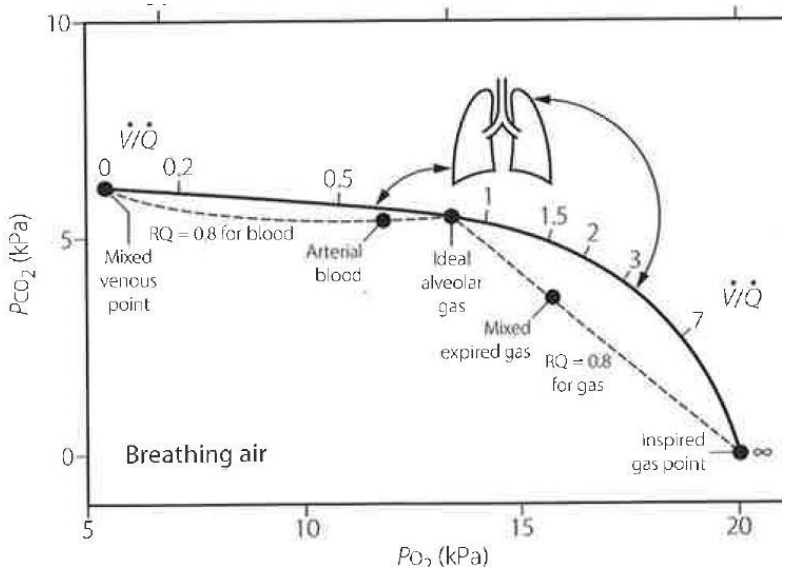



**$V_A$:Q = infinity**

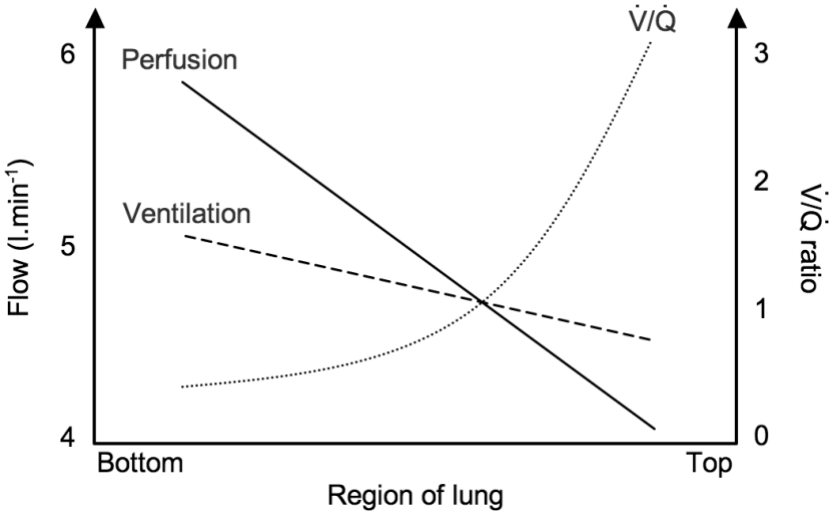
- Normal ventilation but complete absence of perfusion
- No gas is transferred this is wasted ventilation resulting in increased physiological dead space
- Pulmonary embolus leads to an increase in physiological dead space and wasted ventilation - increased A:a ratio



**Variation in $V_A$:Q ratios**




**Effect of Gravity**




- At the top of the lung there is relatively more ventilation than perfusion, the $V_A$:Q ratio is high and the $P_AO_2$ will be highest.
- This may explain why secondary foci of TB (tuberculosis) occurs in the apices in man and the bases in bats.

**Hypoxic Vasoconstriction**

Disadvantages

1. On ascent to altitude atmospheric pressure $P_B$ decreases leading to a fall in $P_AO_2$ throughout the lungs and a significant rise in pulmonary vascular resistance the response involves hypertrophy of the right ventricle to generate higher pressures
2. Chronic Obstructive Pulmonary Disease (COPD) can also lower $P_AO_2$ and cause right ventricular hypertrophy. In some patients the right ventricle fails resulting in *cor pulmonale*

   *Cor pulmonale is right sided heart failure due to hypoxic lung disease - cyanosis, raised internal JVP and hepatomegaly are signs*

A 76-year-old male patient with COPD complains of bilateral swelling of the legs. On examination he was cyanosed and had a barrel shaped chest. His SaO2 was 88% breathing air. His jugular venous pressure was elevated. What is the most likely cause of his leg oedema?

A: Cor pulmonale

## Lecture 3: Carbon Dioxide and Oxygen transport around the body

Alveolar ventilation = (tidal volume - physiological dead space) x respiratory rate

**Alveolar Ventilation Equation**

The partial pressure of carbon dioxide in alveolar gas and arterial blood is *directly proportional* to the rate of carbon dioxide production by metabolism and *inversely proportional* to the rate of carbon dioxide removal by alveolar ventilation.

$$P_ACO2 = P_aCO_2 \propto \frac{\text{Rate of carbon dioxide by metabolism}}{\text{Rate of carbon dioxide removal by alveolar ventilation}}$$

If the rate of CO2 production remains constant:

- *hyper*ventilation must lead to hypocapnia (↓ PaCO2)
- *hypo*ventilation must lead to hypercapnia (↑ PaCO2)
- Reference range = 4.67 – 6.0 kPa

**Dalton's Law**

- Partial pressure of oxygen inhaled into the nasopharynx?

$$P_IO_2 = F_IO_2 \times [P_B - P_{H2O}]$$
$$= 0.21 \times (101-6.3)$$
$$= 20 \text{ kPa (to 0 decimal places)}$$

Thus humidifying air causes a fall in the partial pressure of oxygen

**Diffusing Capacity**

- Measured using a single breath with a gas mixture containing a low concentration of carbon monoxide (CO)
- Decreased in emphysema, pulmonary oedema and pulmonary fibrosis and anaemia
- Increased during exercise because increase capillary perfusion in the apices increases the surface for gas exchange

**Oxygen Transport in Arterial Blood**

- Dissolved in plasma (2%): exerts a partial pressure and drives diffusion
- Bound to haemoglobin as oxyhaemoglobin, can't exert a partial pressure (98%)

Henry's Law: amount of oxygen dissolved in plasma = partial pressure x solubility

Binding capacity: maximum amount of oxygen that can bind to haemoglobin per unit volume of blood (mL $O_2$/100 mL blood)

**Calculating the total oxygen content of blood**

*Total content (C)*

= Amount bound to haemoglobin + amount dissolved in plasma (mL $O_2$/100 mL blood)

= (Oxygen binding capacity x $SaO_2$) + ($P_aO_2$ x solubility)

**Rate of Oxygen Delivery to Tissues**

O2 delivery = Cardiac output (Q) x O2 content *(C)*

*How can doctors increase Q in order to increase rate of oxygen delivery?*

- *Normal saline*
- *Inotropes*
- *Antidiuretics*
- *Raise legs when lying down to increase CVP to increase SV hence increasing Q*

**Haemoglobin**

- 4 subunits
- Subunits contain a haem moiety and a polypeptide chain (alpha or beta)
- Haem moiety is an iron-binding porphyrin with iron in the ferrous state (+2 oxidation state
- Each subunit can bind to one molecule of oxygen

*Variant 1*

- Fetal haemoglobin (HbF)
- Two alpha and two beta subunits
- Higher affinity for oxygen than HbA
- Ensure oxygen moves from maternal to foetal blood in the placenta
- Replaced by HbA with first year after birth

*Variant 2*

- Methaemoglobin
- Iron moiety oxidised for ferrous (Fe2+) to ferric (Fe3+) state
- Does not bind oxygen
- Congenital form due to deficiency of methaemoglobin reductase
- Blue skin and chocolate blood (blue Fugates of troublesome creek)
- Poisoning by some fertilizers and amyl nitrite, prilocaine etc.

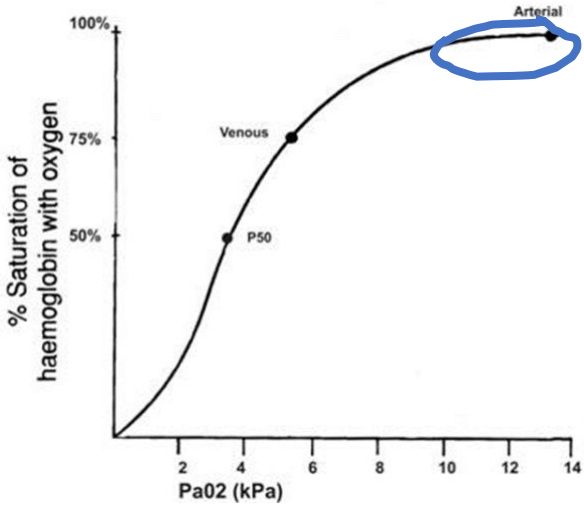
*Variant 3*

- Haemoglobin S Abnormal β submits Sickle cell disease
- Deoxygenated state HbS forms sickle shaped rods that distorts the red blood cells
- Causes anaemia and painful sickle cell crises due to blockage of vessels leading to ischaemia

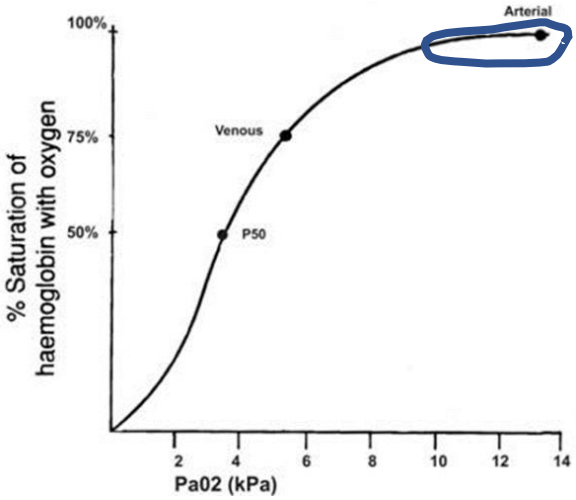
**Loading and Unloading of Oxygen**

- In alveolar gas and pulmonary capillary blood PO2 is 13.3 kPa. This results in almost 100% saturation to due high affinity
- In tissues the partial pressure of oxygen in venous blood is 5.3 kPa

- This results in 75% saturation due to lower affinity and facilitates unloading
- Pulse oximeter is used to detect arterial hypoxaemia before the clinical sign of cyanosis can be detected

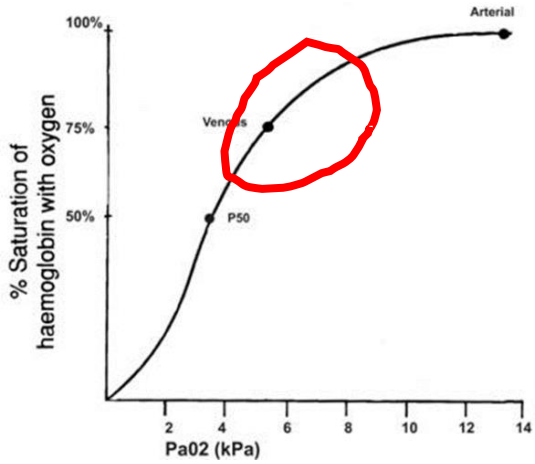



In this zone decreases in $P_aO_2$ do not cause major changes in $S_aO_2$



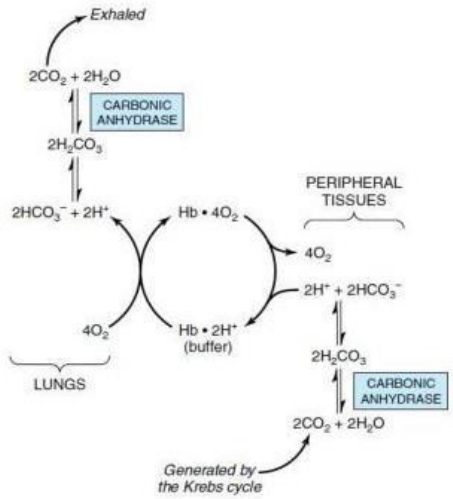

In this zone an increased $P_aO_2$ does not cause a significant increase in $S_aO_2$

This means that well- ventilated alveoli cannot compensate for under- ventilated alveoli and prevent hypoxaemia




In this steeper zone a fall in $P_aO_2$ causes a significant decrease in $S_aO_2$

**Bohr Effect**




- Changes in affinity due to change in $PCO_2$ and pH
- $CO_2$ produced by peripheral tissues results in the generation of $H^+$ ions
- $H^+$ ions bind to HbA and decrease affinity for $O_2$ facilitating unloading
- In lungs $O_2$ binding releases $H^+$ ions that react with $HCO_3^-$ to produce $CO_2$ that is exhaled

**2,3-Diphosphoglycerate (DPG)**

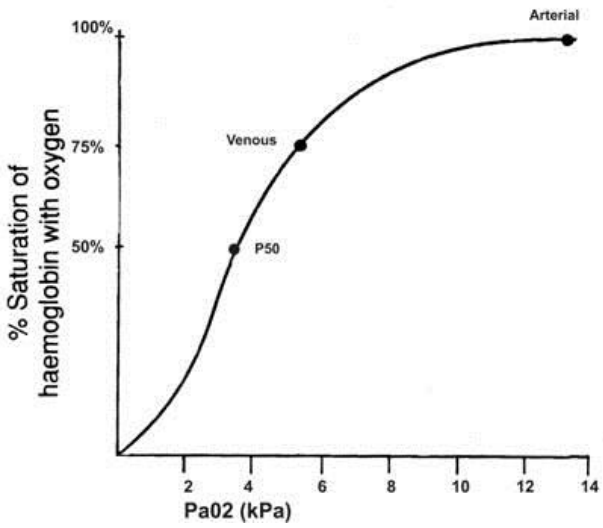
- Living at high altitude stimulates the production of 2,3-DPG by glycolysis in red blood cells
- It binds to the β submits and reduces affinity and facilitates the unloading of oxygen in peripheral tissues

**CO Poisoning**

CO binds to HbA with affinity 250 times higher than oxygen

1. Decreases the amount of $O_2$ binding sites
2. Causes a leftward shift in the curve making it more difficult to unload O2 in peripheral tissues

Increase partial pressure of oxygen to increase oxygen content of the plasma - *hyperbaric chamber*




**Carbon Dioxide Transport**

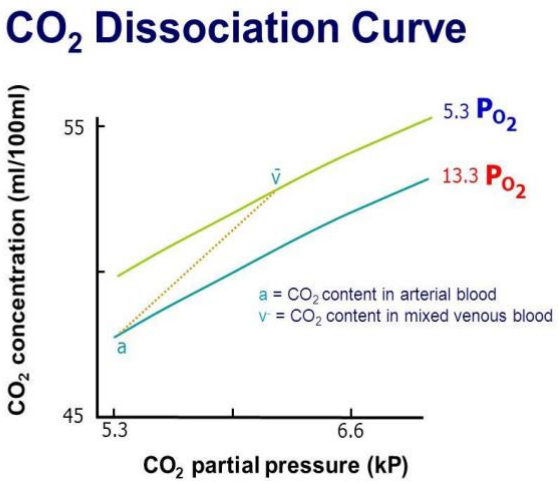
1. Dissolved in plasma
2. Bound to HbA forming carbaminohaemoglobin
3. Converted to bicarbonate ($HCO_3^-$), negative charge balanced by chloride shift into the red blood cell

**Dissociation Curve of Carbon Dioxide**

- Deoxygenated venous blood can carry more CO2 than arterial blood - this is the Haldane effect
- It is LINEAR

- This means that alveoli that are hyperventilated can compensate for alveoli that are hypoventilated in terms of CO2 elimination.

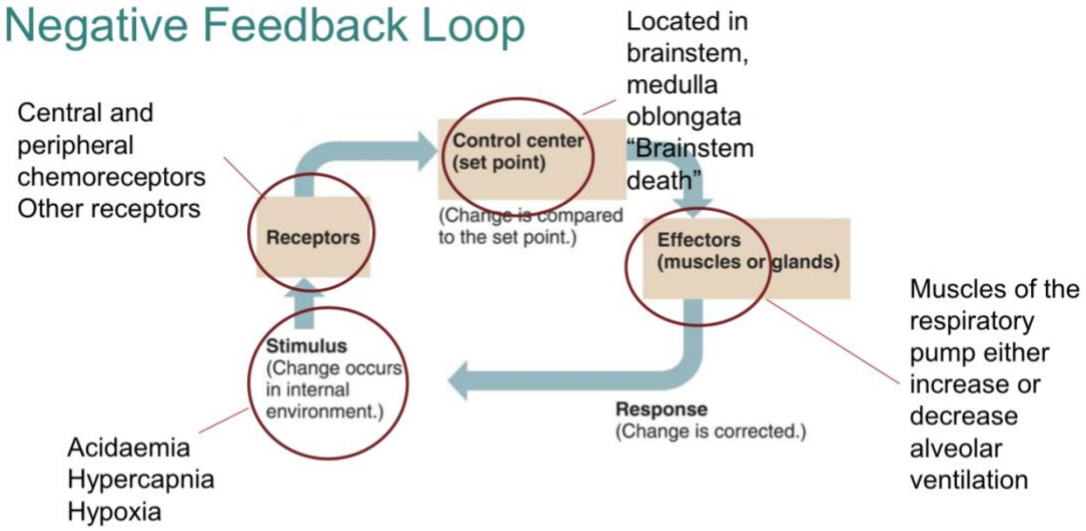
- Thus, VQ mismatch causes hypoxaemia but an increase in total alveolar ventilation prevents it causing hypercapnia.




## Lecture 4: Control of Respiration

The *negative feedback loop* determines the control of respiration – a change in stimulus drives a response:

- In terms of respiration, the stimulus may be *acidaemia, hypercapnia or hypoxia*.
- Central and peripheral chemoreceptors detect changes in blood pH levels due to the above stimuli, as well as other receptors.
- The control center is located in the brainstem, specifically the medulla oblongata
- The effectors are the muscles of the respiratory pump which either increase or decrease alveolar ventilation to ensure the change is corrected.




If the rate of $CO_2$ production remains constant:

- Voluntary hyperventilation (panic attack) must lead to an excess amount of carbon dioxide excretion, hence leading to *hypocapnia* (low $P_aCO_2$)
- Voluntary hypoventilation (breath-holding) must lead to hypercapnia due to reduced carbon dioxide excretion (high $P_aCO_2$)

**Carbon Dioxide and pH**

$\uparrow CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$ $\downarrow pH = -\log_{10}[\uparrow H^+]$

- Hypercapnia increases the $P_aCO_2$, driving the equilibrium to the right and increases the concentration of hydrogen ions.
- This results in *acidaemia*, and the process by which this occurs is called *respiratory acidosis*.
- Respiratory acidosis is a *pathological rise* in the partial pressure of carbon dioxide, leading to a fall in arterial blood pH.

$\downarrow CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$ $\uparrow pH = -\log_{10}[\downarrow H^+]$

- Hypocapnia (e.g. due to a panic attack) drives the equilibrium to the left and decreases the concentration of hydrogen ions.
- This results in *alkalaemia* and the process by which this occurs is known as *respiratory alkalosis.*
- Respiratory alkalosis is a *pathological decrease* in carbon dioxide leading to an increase in arterial blood pH.

Dangers of *acute* respiratory acidosis

- Decreased cardiac contractility
- Cardiac arrhythmias and potential cardiac arrest
- Alterations in pH-dependent biochemical pathways

Symptoms and signs of acute respiratory alkalosis

- Reduced cerebral blood flow due to vasoconstriction and causes patients to fell light-headed
- The decrease in plasma proton concentration results in an increased binding of calcium ions to albumin and a fall in free/ionized calcium ions. This leads to hyper excitability of nerves as free calcium prevents spontaneous action potential firing – membrane stabilizing effect.
- This causes tingling and numbness around the mouth and extremities

**Chemoreceptors**

Central chemoreceptors

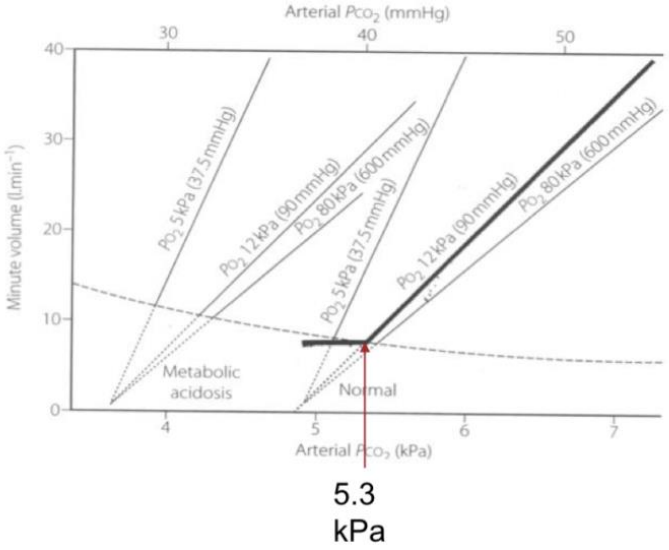
- Found on the ventral surface of the medulla
- Respond to high proton concentration (low pH) but since protons cannot cross the blood brain barrier, $CO_2$ diffuses across and is converted to protons via the action of carbonic anhydrase.
- (this is compensated by a rise in bicarbonate ion concentration in the CSF)

Peripheral chemoreceptors

- Found in the carotid bodies
- Stimulated by acidaemia, hypoxia, hypercapnia and decreased perfusion with blood (e.g. hypotension)
- Especially important in the ascent to altitude.

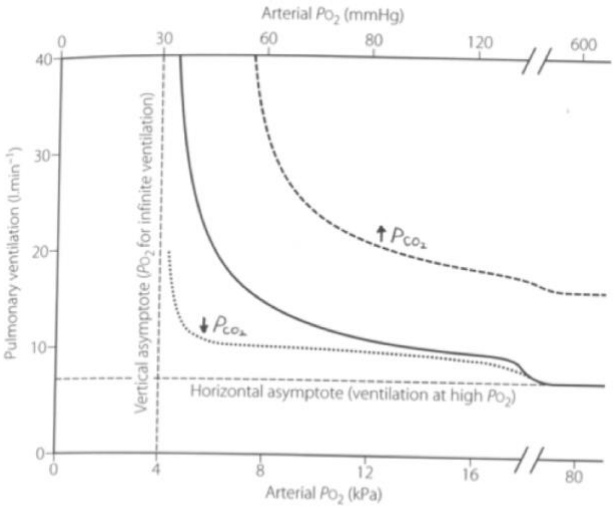
## Influence of Carbon Dioxide and Oxygen on respiratory control

### Carbon Dioxide




- This is a *linear relationship*
- A rise in arterial partial pressure of $CO_2$ causes an incremental rise in minute volume
- A maximum is reached between 13.3-26.7 kPa after which $CO_2$ narcosis occurs with respiratory fatigue
- Hyperventilation resulting in $P_aCO_2$ less than 5 kPa can lead to apnoea until $CO_2$ levels return to normal
- The gradient increases (shifted to become steeper) if there is coexisting hypoxia.

### Oxygen




- The relationship is linear until $SaO_2$ further decreases providing a powerful stimulus for minute volume.
- Curve is shifted upwards by coexisting hypercapnia
- Moment-to-moment control depends on $P_aCO_2$ not $P_aO_2$.
- Severe hypoxia can lead to gasping pattern of breathing.

## Influence of pH on Respiratory Control

$$pH \propto \frac{[HCO_3^-]}{P_aCO_2}$$

- Simplified form of the Henderson – Hasselbach equation
- Arterial pH depends upon the ration of bicarbonate ions to arterial partial pressure of oxygen

$$\downarrow pH \propto \frac{\uparrow[HCO_3^-]}{P_aCO_2}$$

- A pathological decrease in bicarbonate ion concentration is termed *metabolic acidosis* and causes a fall in blood pH -acidaemia.
- This is often seen in uncontrolled type 1 diabetes mellitus – diabetic ketoacidosis.

$$\downarrow pH \propto \frac{\downarrow [HCO_3^-]}{\downarrow P_aCO_2}$$

- The acidaemia will stimulate peripheral chemoreceptors in the carotid bodies resulting in an increase *alveolar ventilation*
- This results in a compensatory decrease in $P_aCO_2$
- Therefore, the disturbance in pH becomes a lower magnitude than before the compensation.
- The change in alveolar ventilation is seen as a deep, sighing breathing known as *Kussmaul breathing*.

Influence of Opioids on Respiratory control

$$\downarrow pH \propto \frac{[HCO_3^-]}{\uparrow P_aCO_2}$$

- Opioids such as morphine and diamorphine bind to the μ-opioid peptide receptors (MOP) and depress alveolar ventilation.
- The pathological rise in $P_aCO_2$ causes a respiratory acidosis and a fall in arterial pH.
- This can be reversed using the antagonist naloxone.
- This is known as *acute* respiratory acidosis as the onset is rapid (seconds to minutes).

Breath holding

- The 'breaking point' is the point at which you cannot hold your breath any longer
- This tends to occur when $P_ACO_2$ and $P_aCO_2$ are around 6.7 kPa and $P_AO_2$ is around 6.5 kPa.
- This depends on gas pressures but ALSO signals from respiratory muscles.
- The breaking point can be extended by:
    1) Prior hyperventilation
    2) Breathing 30% oxygen beforehand
    3) Removing the carotid bodies

**Comparing the Iron lung and the bag-valve-mask**

Iron lung

- A negative pressure technique which places the patient's body into a chamber to lower alveolar pressure below atmosphere and suck air in.

Bag-valve-mask

- A positive pressure device that generates pressures higher than atmospheric pressure and blows air in.
- Connected to a supply of 100% oxygen
- The bag self inflates

**The Relationship between $P_ACO_2$ and $P_aCO_2$**

$$P_ACO_2 = (P_aCO_2) \propto \frac{rate\ of\ carbon\ dioxide\ produced\ by\ metabolism}{rate\ of\ carbon\ dioxide\ excreted\ by\ alveolar\ ventilation}$$

- The partial pressure of carbon dioxide in alveolar gas is directly proportional to the rate of carbon dioxide production by metabolism and inversely proportional to the rate of carbon dioxide removal by alveolar ventilation.
- If the rate of carbon dioxide production remains the same:

    a) Hyperventilation will result in a reduced arterial partial pressure of carbon dioxide as the rate of removal of carbon dioxide increases, decreasing alveolar partial pressure of carbon dioxide. This results in a rise in arterial pH and therefore causes alkalaemia through respiratory alkalosis.

    b) Hypoventilation will result in a higher arterial partial pressure of carbon dioxide as the rate of removal of carbon dioxide decreases, increasing alveolar partial pressure of carbon dioxide. This results in a fall in arterial pH and therefore causes acidaemia through respiratory acidosis.

## Lecture 5: Anaerobic Metabolism

Anaerobic metabolism – lactate production

- Glucose is converted to pyruvate via glycolysis
- Then pyruvate accepts electrons from 2 NADH molecules to form 2 NAD+ molecules and lactate

Skeletal muscle energy metabolism

- Glucose-6-phosphate is the main energy source for muscle cells.
- Creatine phosphate is converted to creatine, synthesising ATP. This is a rapid system and an immediate source of energy for muscles (e.g. sprints).

**Glucose Transport (facilitated diffusion)**

GLUT (Glucose transporter):

- Different isoforms in different tissues ensure glucose is conserved for the brain during fasting.

| | $K_m$ Glucose | Affinity for glucose |
|---|---|---|
| GLUT1: red blood cells and many other tissues | 3 mM | medium |
| GLUT2: liver, islet β cell | 17 mM | low |
| GLUT3: brain | 1.4 mM | high |
| GLUT4: muscle, adipose tissue | 5 mM | medium |

- Under fed conditions muscle can use glucose as a fuel – normal blood glucose is kept at ~5mM through glucagon and insulin (see GI and Endocrine)
- There is no need for the liver to take up glucose when one of its main functions is to secrete it
- GLUT 4 is only present in muscle when glucose levels begin to rise.

**Glycolysis**

- Glucose is converted to two pyruvate molecules and yields 2 ATP, 2 NADH and 2 H+

- Occurs in the cytosol
- Is an anaerobic process as it does not require oxygen; however *aerobic glycolysis* yields more ATP as NADH is oxidised in the mitochondria.
- In aerobic conditions, pyruvate enters the mitochondria and is converted to acetyl CoA. In anaerobic conditions, pyruvate is converted to lactate.

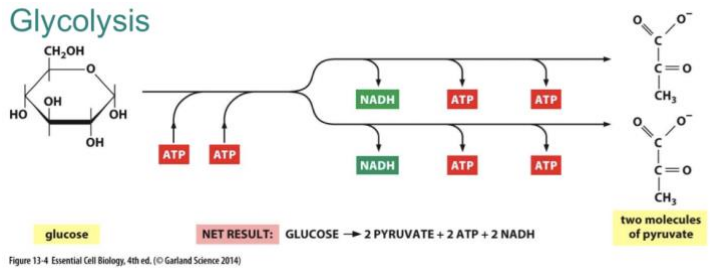


Figure 13-4 Essential Cell Biology, 4th ed. (© Garland Science 2014)

**The Transfer of NADH from glycolysis into the Mitochondria**

Malate-aspartate shuttle

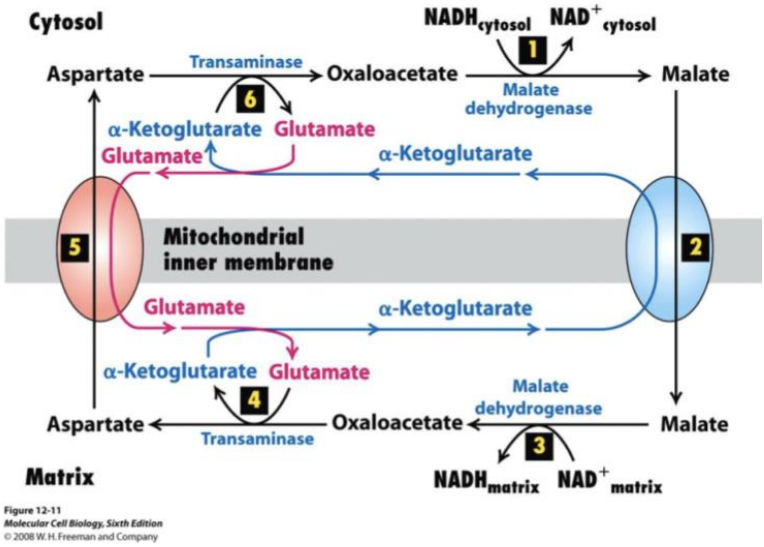


Figure 12-11
*Molecular Cell Biology, Sixth Edition*
© 2008 W.H. Freeman and Company

• No direct transport of NADH, malate-aspartate shuttle allows regeneration of NADH due to the action of malate dehydrogenase converting malate to oxaloacetate.

**Glycolysis (I)**

Most reactions in glycolysis are reversible but control is provided at 3 steps by irreversible reactions which are mediated by 3 large -ΔG enzymes:

i) Hexokinase
ii) Phosphofructokinase-1
iii) Pyruvate kinase

*Hexokinase*

Glucose phosphorylation by hexokinase in muscle and erythrocytes is irreversible. Low $K_m$ value of 0.1mM.

- Ensures glucose is phosphorylated and trapped within the cell
- Maintains large concentration gradient of glucose
- Inhibited by its product

*Phosphofructokinase-1*

Most important regulatory step – commits glucose to glycolysis. Sensitive to the energy state of the cell. Mediates the conversion of fructose-6-phosphate into fructose-1,6-bisphosphate. If ATP is plentiful, glycolysis is slowed down, however if it is not, the activators cause AMP and ADP to be converted to ATP

*Activators of PFK-1*:

- Fructose-2,6-bisphosphate
- AMP
- ADP

*Inhibitors*:

- ATP
- Citrate – an intermediate of the TCA cycle which signals the 'fed' state
- H+ - accumulates during anaerobic metabolism, prevents glycolysis continuing during hypoxia.
-

**Glycolysis (II)** – the energy yield 2 ATP molecules and 2 NADH molecules

Pyruvate kinase - mediates formation of pyruvate

In muscle:

- Fructose-1,6-bisphosphate is an activator
- ATP is an inhibitor

**Production of Lactate**

- Pyruvate is converted to lactate via the enzyme lactate dehydrogenase, which requires NADH and H+, forming NAD+ in the process.
- This is a reversible reaction and therefore not regulatory.
- Lactate production occurs under anaerobic conditions, but some always occurs normally in muscle contraction, especially during starvation. Needs to be removed efficiently in the blood.
- Lactate can be used by the heart as fuel by converting it back into pyruvate.
- Lactate can also be used for glucose synthesis in the liver (see GI lectures)
- Glycolytic ATP production is important during brief high intensity exercise.
- Lactate acidosis occurs when oxygen is limiting, either due to defective tissue perfusion (ischaemia/hypoxia) or during severe exercise.

**Fuel use in a sprint**

1-2 sec = ATP
2-5 sec = creatine phosphate
5-15 sec = glycogen

- First 15 seconds is anaerobic, unsustainable and is high power – type II glycolytic fibres.
- Muscle glycogen decreases when 'hitting the wall', increasing fatty acid consumption.

## Lecture 6: Aerobic metabolism and mitochondria

**Energy yield from anaerobic and aerobic glycolysis**

| Cell compartment | Type | Reaction | | ATP yield |
|---|---|---|---|---|
| Cytosol – glycolysis | Aerobic or anaerobic | glucose → | 2 pyruvate | 2 (substrate level phosphorylation) |
| Generated in cytosol and shuttled to mitochondria | Aerobic | 2 NADH → | 2 $NAD^+$ | 5 |
| Mitochondria | Aerobic | 2 pyruvate → | 2 acetyl CoA +2 NADH | 5 |
| Mitochondria | Aerobic | 2 acetyl CoA → | 2 $CO_2$ +6 NADH + 2 $FADH_2$ + 2 GTP | 15 +3 +2 = 20 |
| | | | | Total = 32 |

**The oxidation of fuel**

Oxidation of glucose proceeds via a series of oxidation reactions requiring transfer of protons/electrons.

Reducing equivalents transduce the energy in fuel molecules to ATP:

- NAD+/NADH
- $FAD/FADH_2$

ATP is produced by

- Substrate level phosphorylation (10%)
- Oxidative phosphorylation (90%)

**The TCA cycle (overview)**

- Acetyl CoA $\rightarrow$ 2 $CO_2$ + 3NADH + $FADH_2$ + GTP
- Pyruvate is transported into the mitochondrion via a pyruvate transporter where it is converted to acetyl CoA using the enzyme pyruvate dehydrogenase.
- Fatty acids directly enter the TCA cycle and do not need to undergo glycolysis
- Amino acids are either converted to pyruvate or directly enter the TCA cycle by being converted to citrate.

**Pyruvate dehydrogenase**

*Function*

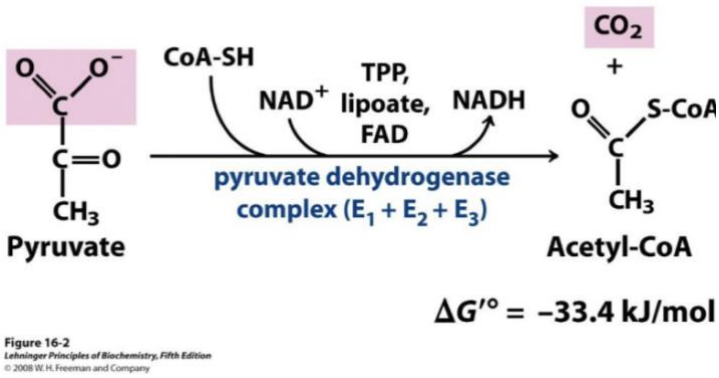
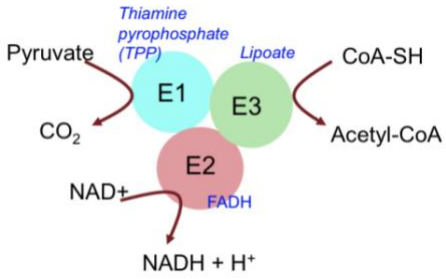



Figure 16-2
*Lehninger Principles of Biochemistry, Fifth Edition*
© 2008 W. H. Freeman and Company

- Converts pyruvate into acetyl CoA
- Produces $CO_2$ through the removal of the carboxylate ($COO^-$) group

*Structure*

Multisubunit complex (E1, E2 and E3 subunits):




- E1 - Requires thiamine pyrophosphate as a cofactor.
- E2 - Requires FADH as a cofactor to produce NADH.
- E3 - Requires lipoate as a cofactor to produce acetyl coenzyme A.

Thiamine (vitamin B1) deficiency – Beri Beri

- Starvation
- Alcoholism – severe deficiency results in Wernicke's encephalopathy (see Neuro)
- People existing on diets of refine carbs (white rice)
- Effects Nervous and CV systems

**The tricarboxylic acid (TCA) cycle – in depth**

Occurs in the mitochondrial matrix

- ONLY REQUIRED TO KNOW WHICH STEPS PRODUCE NADH AND $FADH_2$

Mnemonic for the intermediates in TCA:
A – acetyl CoA
Certificate – citrate
In – isocitrate
Karma – $\alpha$-ketoglutarate
Sutra – succinyl-CoA
Sometimes – succinate
Furthers – fumarate
My – malate
Orgasms – oxaloacetate

Enzymes:

- Citrate synthase
- Aconitase
- Isocitrate dehydrogenase
- $\alpha$-ketoglutarate dehydrogenase
- Succinyl thiokinase
- Succinate dehydrogenase
- Fumarase
- Malate dehydrogenase

Produces NADH – irreversible rate-limiting steps

Produces $FADH_2$

**Mitochondria**

*Outer membrane*

- Permeable to most metabolites due to the presence of porin
- Porin is a protein that forms a large pore

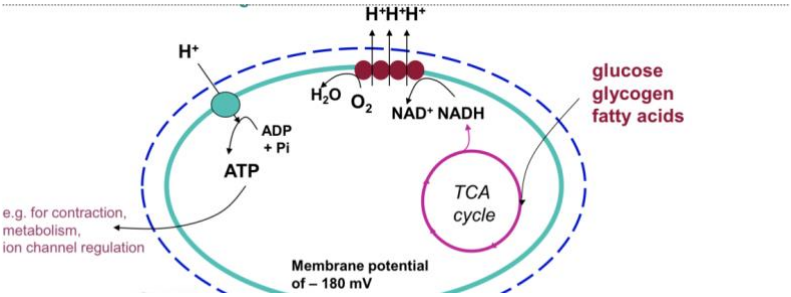
*Inner membrane*

- Permeable to oxygen, carbon dioxide and ammonia
- Made of ~75% protein

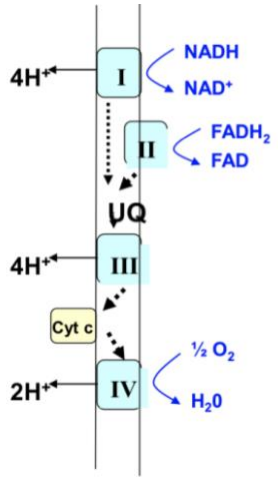
- Impermeable to ions and most metabolites
- Protein transporters/exchangers for pyruvate, malate, citrate and oxoglutarate
- Proteins of the electron transport train and ATP synthesis

*ATP production*

- Flow of electrons across the electron transport chain drives movement of H+ across the inner membrane creating an electrochemical and pH gradient – proton motive force/chemiosmotic potential.
- The movement of protons back through the ATP synthase drives ATP synthesis
- Any substance that provides an alternative route for protons uncouples electron transfer from ATP synthesis
- The source of electrons and protons comes from NADH, from the TCA cycle, originally from glucose, glycogen and fatty acids




*Electron carriers and the Respiratory chain*




**Complex I** – *NADH dehydrogenase*. Electrons are passed from NADH to FMN and then to an FeS centre.

**Complex II** - *succinate dehydrogenase. "succinate-Q reductase complex"*

**Ubiquinone** (UQ) also called coenzyme Q is reduced to $UQH_2$ by electrons from complex I or complex II

**Complex III** – *$UQH_2$-cytochrome c reductase*. Electrons from $UQH_2$ are passed to cytochrome b, then to cyt b1 within the complex, and finally to cyt c.

**Cytochrome c** is located on the outer surface of the inner membrane and transfers electrons from complex III to complex IV.

**Complex IV** – *cytochrome c oxidase*. Contains cyt. a and a3. cyt a3 passes electrons to oxygen.

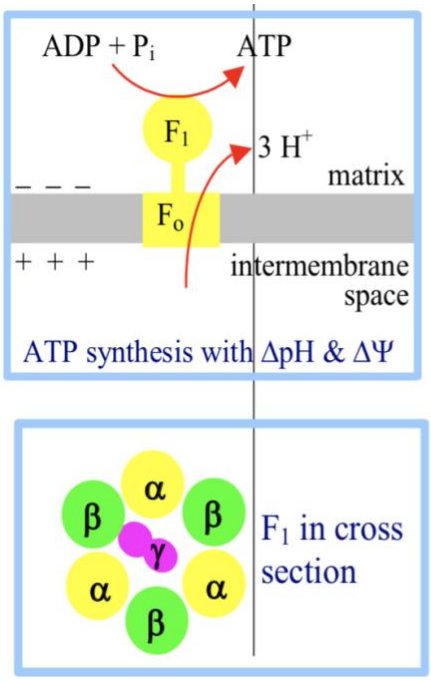
Each complex consists of many polypeptide units and electron carriers e.g. iron in cytochromes and iron-sulphur (FeS) proteins.

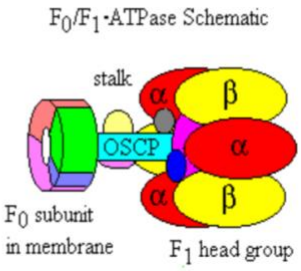
Mobile electron carriers shuttle electrons between complexes, electrons are also transferred within complexes.

- Protein complexes receive electrons so are therefore reduced, becoming reducing agents.
- Complex IV (cytochrome C oxidase enzyme) uses oxygen as a final electron acceptor.
- Membrane potential + pH gradient = proton motive force
- Oxidative phosphorylation is electron transport couple to ATP synthesis

*ATP Synthase*

- H+ movement causes a protein 'stalk' to rotate within the head group changing the conformation of the $\beta$ subunits.
- The $\beta$ subunits bind ATP and phosphate and form tightly bound ATP.
- This is then released by the proton-driven conformational change.



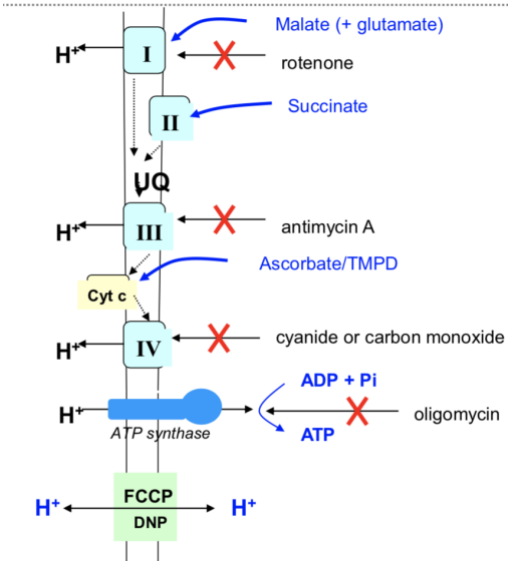




H⁺ movement causes a protein "stalk" to rotate within the head group changing the conformation of the β subunits. The β-subunits bind ATP and phosphate and form tightly bound ATP. This is then released by the proton-driven conformational change.

*OSCP oligomycin-sensitivity conferring protein*

- Oligomycin is an antibiotic which an inhibitor of ATP synthase by blocking the $F_0$ subunit (proton channel) which is necessary for oxidative phosphorylation.

*Inhibitors and uncouplers of oxidative phosphorylation*

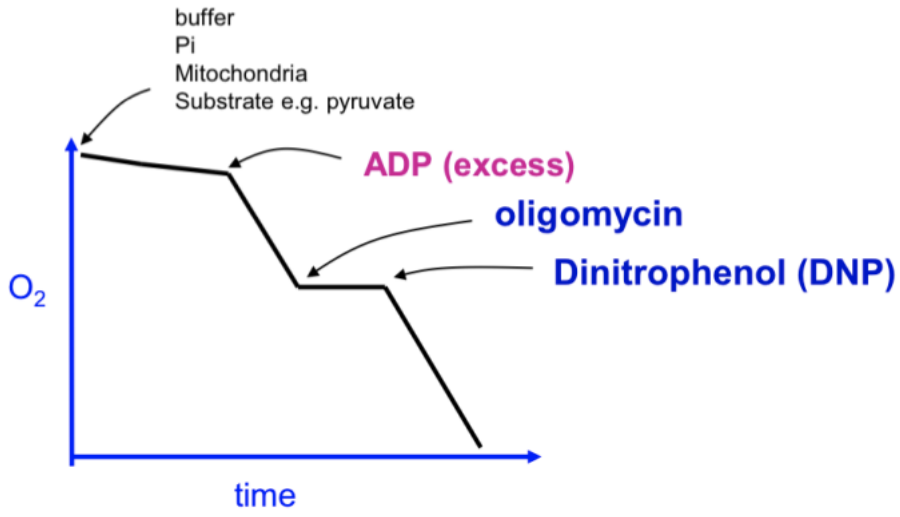



- Cyanide (CN) binds to the haem group of cytochrome IV and prevents oxygen acting as the final electron acceptor by preventing its binding. CO has a similar action.

- Dinitrophenol (DNP) is an uncoupler of oxidative phosphorylation. It is a weak acid and allows protons to move freely across the inner membrane, reducing the proton motive force. FCCP acts in a similar way.

- Rotenone, antimycin A and oligomycin are also inhibitors.

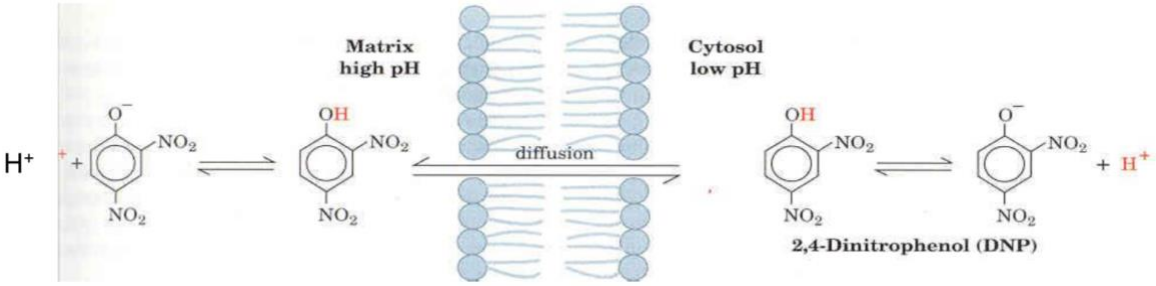
*Effects of inhibitors and uncouplers of oxidative phosphorylation on $O_2$ consumption*




- DNP stops ATP synthesis, but electron transport still continues, therefore oxygen is consumed. DNP is a lipid soluble molecule that can bind protons and transport them across the membrane, preventing the formation of a proton gradient and hence generation of a proton motive force.
- Oligomycin does not use up oxygen as it is in an inhibitor of the ATP synthase enzyme and prevents ATP synthesis. Therefore, since this is coupled to the activity of the electron transport chain, the activity of cytochrome IV ceases.
- Excess ADP increases oxygen consumption because ADP is used to form ATP and since there is an excess of ADP, there is also an excess of ATP. The electron transport chain utilises oxygen only when ATP is synthesising, hence the oxygen consumption increases.

*Action of uncouplers*

- Uncouplers increase metabolic rates by dissipating the proton gradient – therefore 'uncoupling' ATP synthesis from electron transport'



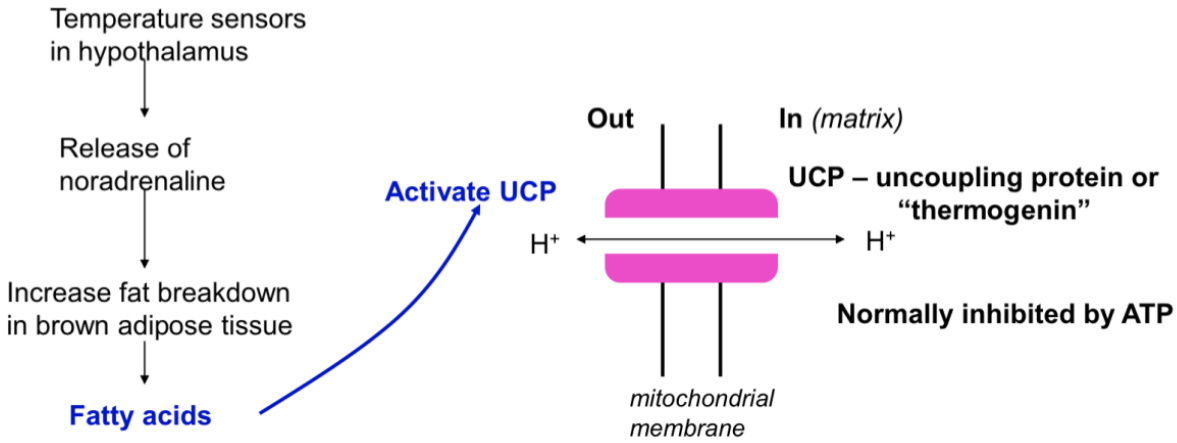

- DNP was used in 1929 as an anti-obesity drug, but '…in some cases the treatment eliminated not only the fat, but also the patients…'

**Heat production in brown adipose tissue**

- Non-shivering thermogenesis – heat production to maintain body temperature
- Brown adipose tissue is found in the neck, upper back and around the kidneys
- Important in newborn humans and hibernating animals.

*Mechanism of action*

1. Thermoreceptors in the skin send signals to temperature centres in the hypothalamus.
2. Noradrenaline is released
3. Increased fat breakdown occurs in brown adipose tissue, leading to fatty acid production
4. Fatty acids activate the uncoupling protein, thermogenin (UCP)
5. Thermogenin is found in the inner mitochondrial membrane of brown adipose tissue and allows protons to flow back into the mitochondria without having to enter the ATP synthase.
6. This therefore uncouple electron transport and ATP synthesis, generating heat.




*Diseases of the respiratory chain complexes*

Human mtDNA:

- Contains 37 genes
- 13 for oxidative phosphorylation
- 22 for tRNA
- 2 for rRNA

Complexes I-IV, except II:

- Consist of many subunits
- 57 subunits encoded by nDNA
- 11 encoded by mtDNA

- Mutations can be inherited from either genome, or arise during ageing (oxidative damage).

**The Mitochondrial genome**

- mtDNA encodes proteins in all complexes except for II
- mtDNA is circular, like bacterial plasmid DNA
- Mutations in tRNA are potentially more damaging

*Inheritance*

- All maternally inherited (<0.01% paternally)
- Genomes of mitochondria with a single cell can vary (heteroplasmy)

- Relative abundance of a particular mutation within a cell depends on the number of mitochondria having that mutation.
- An effect of the mutation on the whole organ will depend on the number of cells containing the mitochondria with that mutation – 'Threshold effect'

*Prevalence of mitochondrial disease*

- Affects 1 in 8500 people

Symptoms include:

- Muscle wasting and exercise intolerance
- Cardiomyopathy
- Deafness
- Blindness
- CNS disorder

Severity varies on:

- Relative abundance of the mutant DNA
- Tissue distribution of the mutant DNA
- Vulnerability of each tissue to impaired oxidative metabolism

## Lecture 7: Respiratory Embryology

### Gastrulation and Germ Layer derivatives

- Formation of a trilaminar disc from a bilaminar disc.
- Epiblast and hypoblast become three germ layers
- Ectoderm, mesoderm and endoderm formation


Ectoderm

- Forms CNS and PNS and epithelium of the skin
- Neural innervation to the respiratory tract is derived from this germ layer

Mesoderm

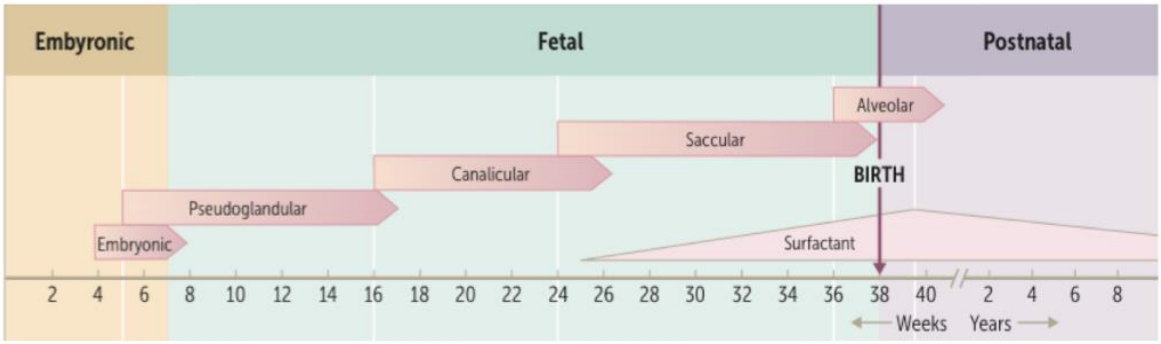
- Forms body connective tissue (blood, bone, muscle, connective tissue of the skin) and GI and respiratory tracts
- Lung tissue
- Muscular diaphragm
- Pleural cavities

Endoderm

- Forms GI tract organs and epithelium of the GI and respiratory tracts
- Respiratory epithelium
-

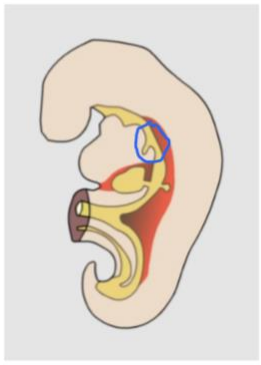
### Lung development

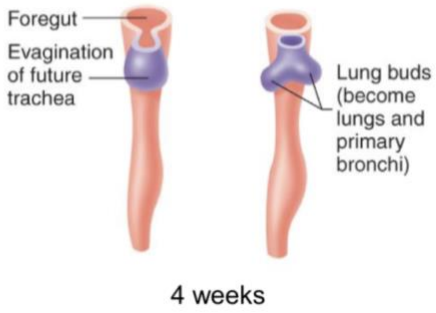
- Birth occurs before completion of lower respiratory tract development – alveolar development is incomplete at birth




*Embryonic Period – Weeks 4-8*

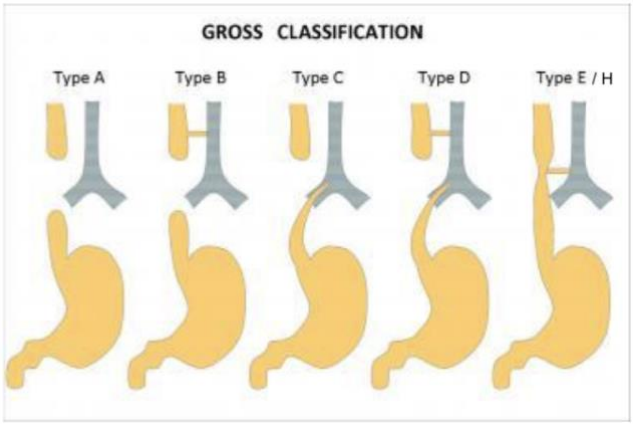
- Gut tube (made by endodermal cells) runs through the embryo, connected to the yolk sac
- Evagination (marked in blue on figure) – trachea and lung tubes push out from the gut tube then become the bronchial tree (primary bronchi and lungs)






Tracheoesophageal Fistula:

- Connection between the gut tube and the lung tube must be closed.
- A fistula is an *abnormal connection* between two hollow spaces.
- Atresia is an abnormal narrowing or absence of an opening/passage in the body




Type C: proximal atresia and distal fistula

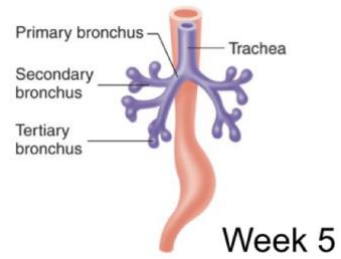
Type A: double atresia

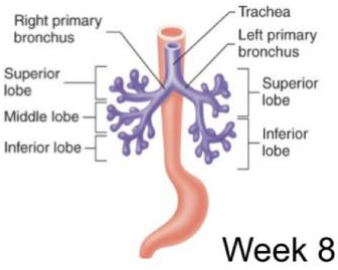
90% of TF cases are Type C

Type H: food may enter the lungs leading to respiratory distress syndrome

Polyhydramnios – caused by fluid build-up in the amniotic cavity due to fistula/atresia.

*Pseudoglandular period (week 5-17)*




Conducting airways:

- Branching occurs
- Epithelium adopts a glandular appearance – tall columnar and cuboidal

By week 8 all segmental bronchi are formed

- 14 more generations to reach terminal bronchioles

*Canalicular Period (week 16-26)*

Canalisation – input of CVS alongside respiratory system

Distinguishing between conducting airways and gas exchange areas

Moving towards viability ~24 weeks

Differentiation of epithelium
- Formation of respiratory bronchioles

Canalisation of lung parenchyma by capillaries
- Formation of future air-blood barrier

Distinguishing between future gas exchange regions and future conducting airways

*Saccular Period (weeks 24-38)*

Terminal sacs (primitive alveoli) form
- Cuboidal cells flatten (type 1 pneumocytes) – reduces diffusion distance, Fick's law
- Increase in surface area in future gas exchange region
- Intimately associated with blood vessels

Vascular tree
- Increase in length and diameter

Surfactant production by type 2 pneumocytes – this is required to open airways and reduce surface tension, very important

*Surfactant Deficiency*

- Results in respiratory distress syndrome
- Affects ~50% of infants born at 26-28 weeks, causes by inadequate production of surfactant by type 2 pneumocytes
- Causes air sacs to collapse on expiration and increases energy required for breathing

Treatment includes providing exogenous surfactant

- Reduces mortality by 30%
- Reduces pulmonary air leaks by 50%
- Surfactant is given via an endotracheal tube – high risk of pneumothorax.

*Alveolar Period (week 36 to 8 years)*

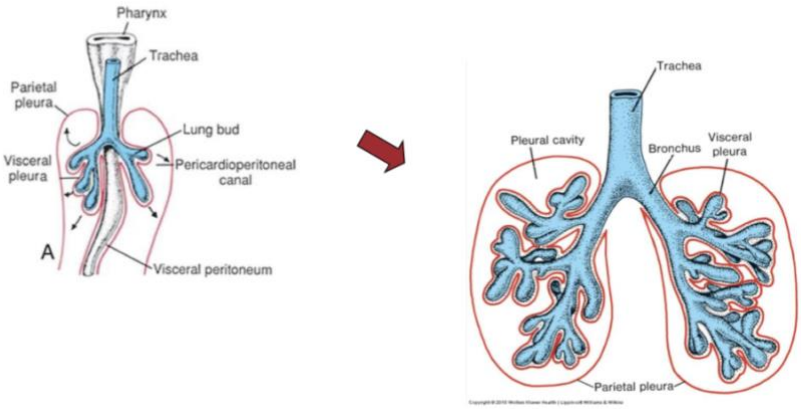
- Terminal saccules replaced by mature alveoli
- Only 16% of alveolar cells are present at birth
- Process continues after birth
- Maturation of respiratory system occurs until ~16 years

*Maturation*

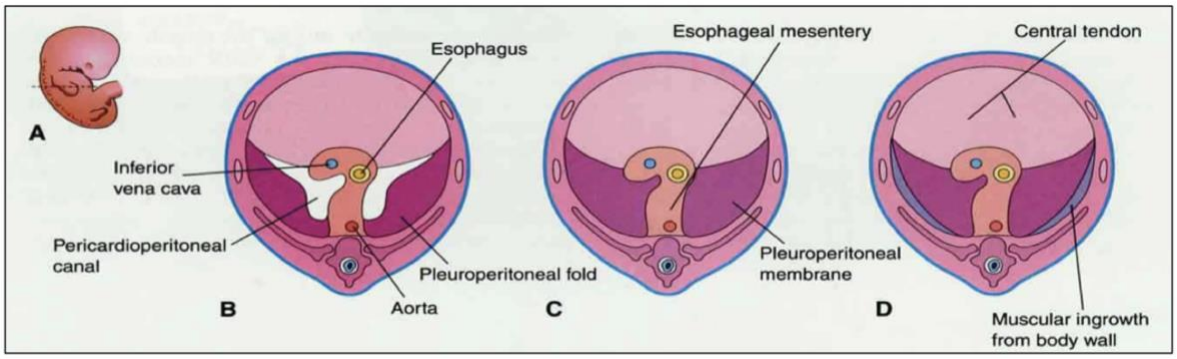
- Foetus makes respiratory breathing motions
    - This helps develop respiratory muscles
    - Also aids in lung maturation
- At birth lung fluid is rapidly resorbed
- Obligate nasal breathing – allows feeding and breathing to occur simultaneously, occurs for the first few months after breath. Breathing only occurs through the mouth when crying.

**Development of Pleural Cavities**

- Derived from mesoderm
- The separation of a single body space results in the formation of three cavities – pleural, pericardial and peritoneal




- The lung buds grow into the medial walls of the pericardioperitoneal canals (primitive pleural cavities), and the pleural cavities expand around the heart into the body wall.
- This splits the mesenchyme into an outer layer that becomes the chest wall and an inner layer forms the fibrous pericardium
- The pleural cavity and the pericardium separate in what is known as pleuropericardial separation.
- Pleuroperitoneal separation results in the development of the diaphragm.
- This occurs towards the end of week 6.

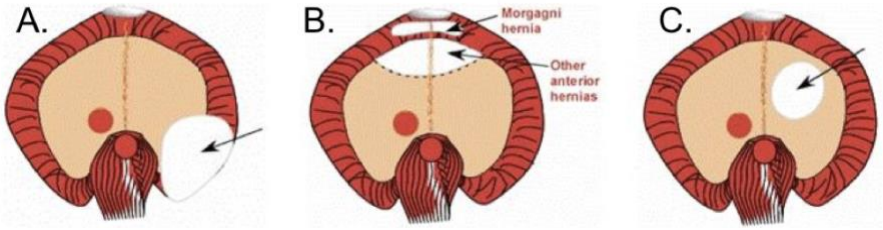



**Congenital Diaphragmatic Hernia**

- An abnormal opening between the chest (pleural cavity) and the peritoneum leading to peritoneal contents appearing in the pleural cavity, caused by an error in the development of the diaphragm.

Three types:

- A – Posterolateral (95%), of which (85%) on the left.
- B – Retrosternal (2 to 3%), 1% anterior
- C – Central (1%)




## Lecture 8: The Respiratory System During Exercise

Oxygen consumption rate if referred to as $VO_2$:

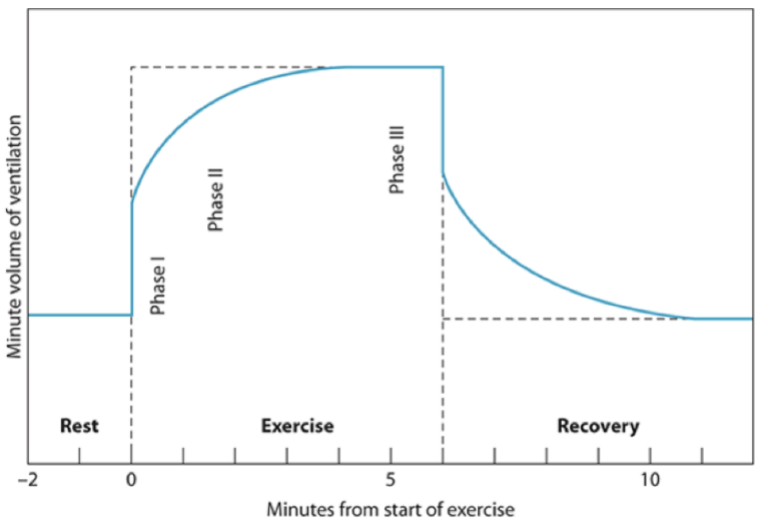
- Measured using a spirometer filled with 100% oxygen
- Value is approximately 200-250 ml/min at rest

**Changes in minute volume over time**

- There is an instant increase in ventilation slightly before or at the start of exercise – phase I
- During moderate exercise there is a further increase – phase II
- An equilibrium level is reached within approximately 3 minutes – phase III
- These changes are also seen in $VO_2$

To summarise, from rest to exercise there is a 3-phase change in minute volume:

1. Rapid
2. Slight increase
3. Plateau



During phase II some of the energy need to exercise is achieved through anaerobic metabolism:

- This leads to the generation of lactate
- This is known as the oxygen debt
- This oxygen debt continues until alveolar ventilation and minute volume reach their peak
- At rest, lactate is metabolised aerobically by the liver to repay the oxygen debt.

During recovery, minute volume and $VO_2$ remain elevated to allow lactate to be metabolised aerobically via the TCA cycle.

**Maximum Oxygen Consumption Rate $VO_{2\ max}$**

- This is the oxygen consumption rate when a subject is exercising as hard as possible
- A young healthy adult might achieve 3 l/min, but this decreases to 2 l/min by 70 years of age.
- A sedentary existence can reduce $VO_2$ max by 50% of expected whereas training increases it.
- The highest levels (>6 l/min) are attained by rowers who utilise a greater muscle mass than other athletes.
- This a good measure of cardiorespiratory fitness.

*Achieving higher intensity than $VO_{2\ max}$*

- A subject can exercise at higher intensity than $VO_{2\ max}$, but the extra energy is produced by anaerobic metabolism, which produces lactic acid.
- The point at which there is a sudden rise in the plasma concentration of lactate is known as the *anaerobic threshold.*
- This is also the build-up of lactate at $VO_{2\ max}$.
- There is a 250ml/min to 3000ml/min increase in minute volume from rest to $VO_{2\ max}$.
- The fall in arterial pH stimulates chemoreceptors, which leads to an increase in minute volume and alveolar ventilation.
- Lactate causes distress at levels above 11mmol/l and is a limiting factor for sustained heavy work.

**Oxygen Delivery During Exercise**

$O_2$ delivery = Cardiac output (Q) x $O_2$ content (C)

- In order to determine cardiovascular fitness, it is essential to consider supply AND usage of oxygen
- Oxygen delivery depends highly on cardiac output.
- As blood is almost completely saturated with oxygen at rest, it is not possible to exceed it and increase $O_2$ content during exercise.
- Therefore, the increase in oxygen delivery therefore relies upon the increase in cardiac output and pulmonary blood flow.

*Effects of Increased Mean Pulmonary Artery Pressure*

- Increases pulmonary blood flow
- Increases perfusion to lung perfusion
- Reduces physiological dead space and improves $V_A$:Q matching

As cardiac output increases, pulmonary pressure increases. This improves the V:Q ratio as more blood flows to apices of the lungs - reducing physiological dead space.

**Limiting Factors of $VO_{2\ max}$ and the Fick Equation**

$VO_{2\ max}$ = Maximum cardiac output x ($CaO_2$ – $CvO_2$)

v is mixed venous blood

$CaO_2$ -$CvO_2$ = arteriovenous difference in oxygen content

- Shows how much oxygen you can extract from blood
- The greater the AV difference, the greater the extraction of oxygen by tissues
- The AV difference depends upon the ability of tissues to extract oxygen from blood

**AV difference at Rest and during Exercise**

AV difference at Rest
= $CaO_2$ – $CvO_2$
= 20 ml $O_2$ per 100ml of blood – 5
= 15

- Mixed venous blood returning to the right ventricle at rest has a saturation around 70%

AV difference during Exercise
= $CaO_2$ – $CvO_2$
= 20 ml $O_2$ per 100 ml of blood – 15
= 5

- Mixed venous blood returning to the right ventricle during exercise has a saturation around 20%

- There is a 50% difference in saturation between rest and exercise
- Patients can be monitored on their venous blood saturation, the higher the better.

**How is increased oxygen extraction achieved?**

1. Oxygen haemoglobin dissociation curve shifted to the right
2. Decreases affinity of haemoglobin for oxygen
3. Facilitates unloading of oxygen

- Increasing $PCO_2$
- Decreasing pH
- Increasing temperature

**Effects of training on the heart**

- Increased number of myocardial capillaries
- Increased size of ventricular chamber due to hypertrophy of myocardial wall
- Increased vagal tone results in resting bradycardia

This allows an increase in the cardiac output that can be achieved during exercise. Some elite athletes have a resting heart rate of 40bpm

**Effects of training upon skeletal muscle**

- Increased number of capillaries
- Greater number of mitochondria
- Increased number of myoglobin

This allows an increase in the oxygen extraction that can be achieved during exercise. The anaerobic threshold increases, and the liver may increase its ability to clear lactate – trained athletes can also tolerate lactate levels as high as 20mmol/l.

NB: Cardiorespiratory fitness is an independent predictor of mortality and length of hospital stay. Its more accurate than age alone. However, a more objective method is needed.

**What drives the increase in ventilation during steady exercise?**

- Exercise does NOT result in acidaemia, hypercapnia or hypoxia
- The arterial blood gases remain unchanged
- The central and peripheral chemoreceptors remain unstimulated.

There are other receptors and reflexes that causes an increase in alveolar ventilation:

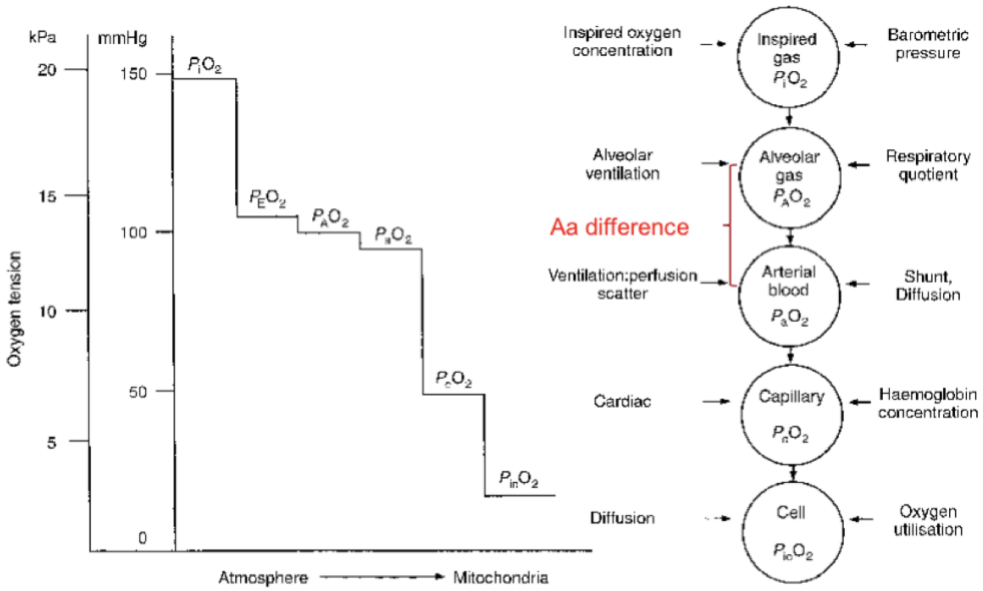
- Passive movements of the limbs trigger mechanoreceptors, which lead to an increase in alveolar ventilation
- Metaboloreceptors in the skeletal muscle detect metabolites and send sensory input to the medulla oblongata, resulting in an increased alveolar ventilation.
- Cortical output to muscles might also influence the respiratory control centres and initiate the increase in ventilation in anticipation.

NB: Mixed venous blood is sampled from the right atrium by inserting a Swan Ganz catheter into the jugular vein and then into the heart.

## The Respiratory System at Altitude

**The Oxygen Cascade**

- The partial pressure of oxygen in dry air at sea level is 21.2 kPa
- It moves down its partial pressure gradient until it reaches the mitochondria where it is consumed
- The partial pressure of oxygen in mitochondria is around 0.5 – 3.0 kPa
- The steps by which $PO_2$ decreases from air to cell are shown in the oxygen cascade along with the determining factors.
- A pathological disturbance in any one or more of these steps can lead to tissue hypoxia and dysfunction.




- Normal arterial $P_aO_2$ is roughly 13.6 – 0.044 x age in years
- Several studies show a progressive decline with age

**Hypoxia and Hypoxaemia**

*Hypoxaemia*

- Also known as hypoxic hypoxia
- Defined as an abnormally low $P_aO_2$
- Associated with the clinical sign of central cyanosis

There are *5 possible pathophysiological* causes and can be compared on their effects on the alveolar-arterial difference:

Aa difference = $P_AO_2 – P_aO_2$

$P_AO_2$ is calculated using the alveolar gas equation
$P_aO_2$ is measured by performing an arterial blood gas analysis.

- The difference in health subjects can be 2 kPa in young adults and 5 kPa in the elderly.
- This is due to the physiological shunt/venous admixture and the normal scatter of $V_A$:Q ratios

1. High Altitude

➢ Fall in barometric pressure leads to a decrease in $P_iO_2$ and $P_AO_2$
➢ This also leads to a fall in $P_aO_2$
➢ The Aa difference remains normal as the falls in $P_AO_2$ and $P_aO_2$ are relative to one another
➢ Supplementary oxygen helps increase $P_AO_2$ and subsequently $P_aO_2$.

2. Hypoventilation

➢ Leads to a decrease in $P_AO_2$
➢ This also leads to a fall in $P_aO_2$

- The Aa difference remains normal
- $O_2$ helps raise the arterial and alveolar partial pressure of oxygen

3. Diffusion defect (e.g. fibrosis)

- This also leads to a fall in $P_aO_2$
- The Aa difference is increased as alveolar partial pressure of oxygen remains normal but arterial falls
- Supplementary oxygen helps raise alveolar $PO_2$ so that the arterial $PO_2$ also increases to a normal level.

4. VA:Q mismatch (e.g. pulmonary embolism)

- Leads to a fall in $P_aO_2$
- This increases the Aa difference due to the increase in physiological dead space, which in turn reduces the oxygenation of the blood in the pulmonary veins, and hence the arterial blood
- Oxygen via a facemask does help as it raises the oxygenation of the vessels leaving the lungs that were not affected by the pulmonary embolism.

5. Right-to-left cardiac shunt (e.g. congenital cyanotic heart disease)

- Shunted blood bypasses the alveoli and cannot be ventilated resulting in a very low $P_aO_2$
- The Aa difference is increased as the arterial $PO_2$ decreases due to mixing of venous and arterial blood as well as reduction in lung perfusion, whilst the alveolar $PO_2$ remains normal.
- Oxygen via a face mask has a limited effect, only acts on non-shunted blood.

*Hypoxia*

- Defined as low tissue partial pressure of oxygen either due to reduced supply of oxygen or the inability to utilise it
- May be localised to a single organ or global
- Results in organ/tissue dysfunction or even cell death.
- Hypoxaemia is one of the causes of tissue hypoxia

What are the causes of tissue hypoxia?

Stagnant hypoxia

- Hypoxia that occurs due to abnormally low rate of blood flow
- Total oxygen content (C)

= amount bound to haemoglobin + amount dissolved in plasma
= (oxygen binding capacity x $SaO_2$) + ($P_aO_2$ x solubility)

- Rate of oxygen delivery ↓ = cardiac output ↓ x oxygen content
- Therefore, as cardiac output decreases, rate of oxygen delivery decreases despite oxygen content being unaffected.
- Heart failure is a cause of stagnant hypoxia, as the heart cannot pump sufficient cardiac output at normal filling pressures.

Local hypoxia

- May occur due to arterial occlusion leading to painful ischaemia and eventual infarction
- A plug in the coronary artery is known as a thrombus.
- The plaque exposes collagen to blood, initiating the coagulation cascade and causing blood to clot.

Hypoxaemia

- Total oxygen content (C) ↓

= amount bound to haemoglobin + amount dissolved in plasma
= (oxygen binding capacity x ↓$SaO_2$) + (↓$P_aO_2$ x solubility)

- Rate of oxygen delivery ↓ = cardiac output x ↓oxygen content
- Hypoxaemia leads to a decrease in the total oxygen content of the bloods

Anaemic Hypoxia

- Total oxygen content (C) ↓

= amount bound to haemoglobin + amount dissolved in plasma
= (↓oxygen binding capacity x $SaO_2$) + ($P_aO_2$ x solubility)

- Rate of oxygen delivery ↓ = cardiac output x ↓oxygen content
- The oxygen binding capacity is reduced when the concentration of haemoglobin falls (i.e anaemia) in carbon monoxide poisoning and poisoning resulting in an increase in methaemoglobin
- Iron-defiency anaemia can result in breathlessness and fatigue as symptoms.

Histotoxic hypoxia

- In histotoxic hypoxia the rate of oxygen delivery is normal, but the tissues are unable to utilise it.
- This results in an elevated $CvO_2$ and a low AV difference in the oxygen content of blood.
- The classic cause is cyanide poisoning and should be considered in victims of smoke inhalation.

Symptoms of hypoxia

- Anxiety
- Euphoria
- Confusion / poor judgement / irritability
- Lack of coordination
- Tachypnoea, use of accessory muscles
- Tunnel vision
- Loss of consciousness
- Seizures

**High Altitude**

*ABG ANALYSIS*

pH = ↑7.53

$P_aO_2$ (kPa) = ↓3.28

$P_aCO_2$ (kPa) = ↓1.77

$[HCO_3^-]$ (mmol/L) = ↓10.8

$S_aO_2$ (%) = ↓54

[Hb] (g/L) = ↑19.3

[Lactate] (mmol/L)

- *Hypoxaemia* stimulates *carotid chemoreceptors* resulting in an increase in alveolar ventilation
- The increase in alveolar ventilation causes profound *hypocapnia*
- The hypocapnia results in *respiratory alkalosis* which increases blood pH, producing *alkalaemia*
- There is a compensatory decrease in bicarbonate, which indicates that this is chronic respiratory alkalosis
- Hypoxia stimulates increased renal production of erythropoietin to increase production of red blood cells (polycythaemia) and [Hb] to increase oxygen carrying capacity.
- Despite severe chronic hypoxaemia none of the subjects had significantly raised lactate suggesting that the energy generation was *still predominantly aerobic*.

*ACCLIMITISATION*

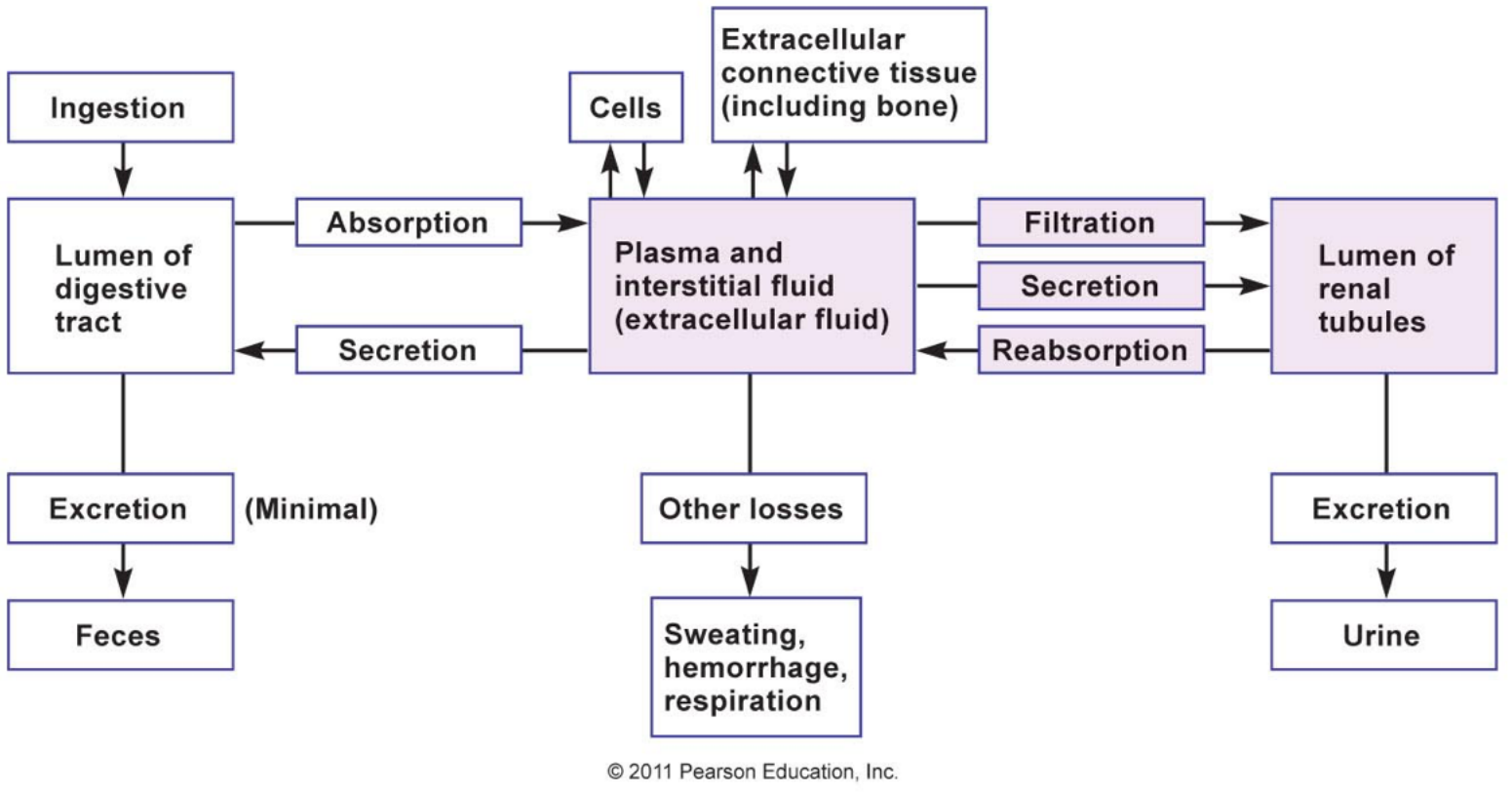
- Tolerance and performance improve over hours to weeks after living in high altitudes:
- Ventilatory changes
- Polycythaemia
- Raised pulmonary artery pressure and right ventricular hypertrophy
- Raised 2,3-diphosphoglycerate, formed by the Rapoport-Luebering shunt off the glycolytic pathway in erythrocytes and decreases the affinity of haemoglobin for oxygen and facilitates unloading.

ACUTE ALTITUDE SICKNESS

- Headaches
- Anorexia
- Fatigue
- Insomnia
- Definitive treatment is to move to a lower altitude.

## Factors Affecting the Plasma Composition

Solute and water content of plasma is affected by movement of materials **in and out of the body** and by movement of materials **between body compartments**.




Ways in which materials can be gained or lost from plasma:

1. By exchange with cells
2. Exchange with extracellular connective tissue including bone (Ca & P)

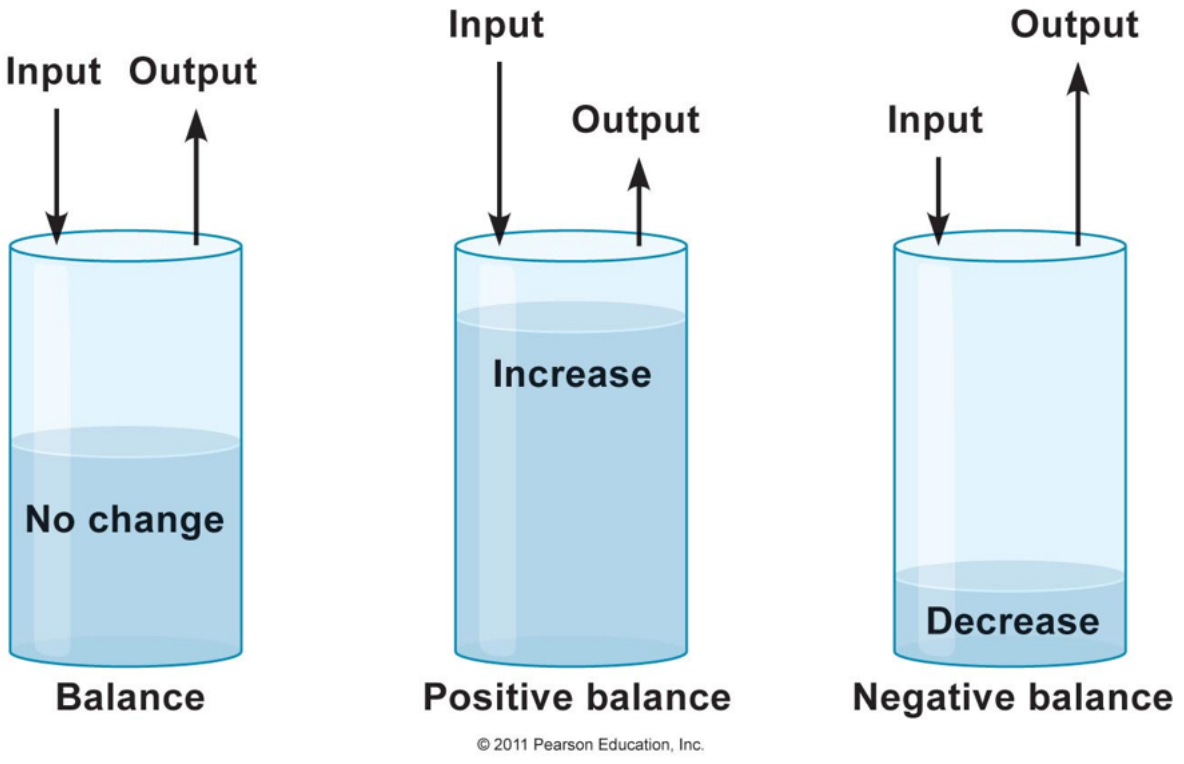
Outside exchanges:

1. Exchange with materials in the lumen of the GI tract
2. Exchange with materials in the lumen of the kidney tubules
3. Loss through sweating, hemorrhaging and respiration

The transport of materials across the **wall of the GI tract** normally involves a **net gain** of **water** and **solutes**. The transport of materials across the walls of the renal tubules amounts to a **net loss** of **water** and **solutes** by the body.

## Solute and Water Balance

**Balance** occurs when solutes and water enter and leave the plasma at the same rate. If a substance enters the plasma faster than it leaves and its **concentration increases** it is in **positive balance.** If a substance leaves plasma faster than it enters and its **concentration decreases** it is in **negative balance.**




Certain substances can exist with a negative or positive balance with no change in the plasma concentration when their concentration is controlled by specific **regulatory mechanisms**. **Glucose** is an

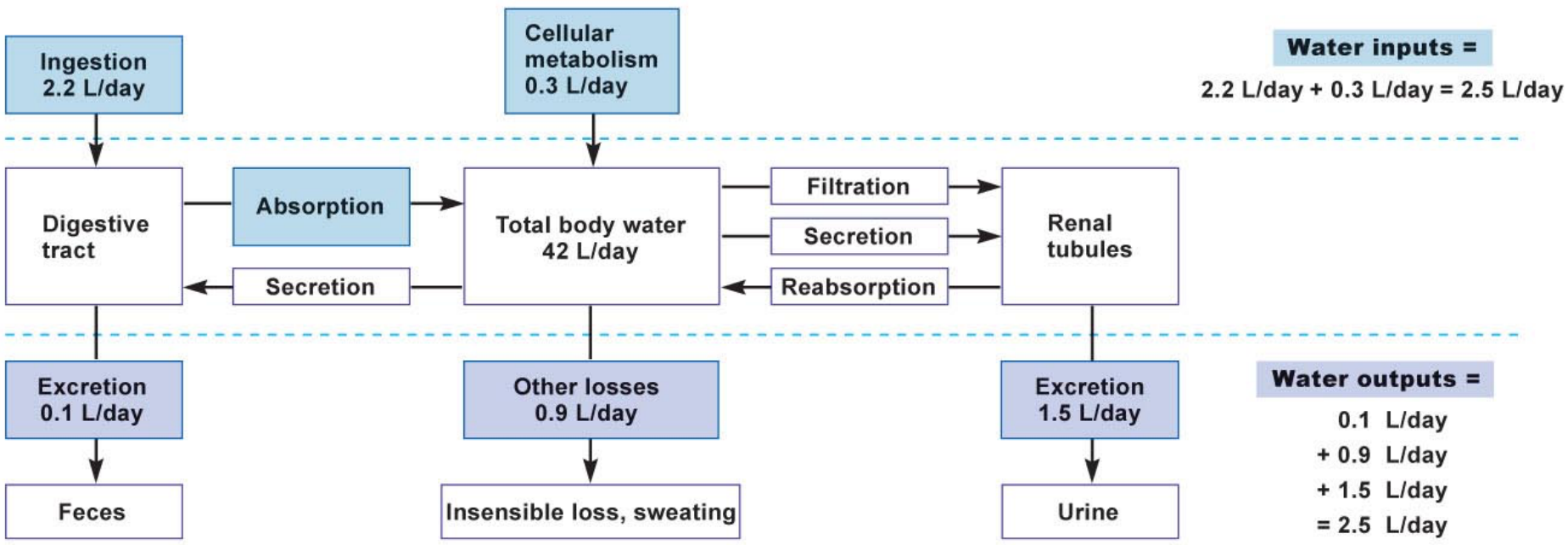
example.

In the kidneys 70% of filtered water and sodium is reabsorbed in the proximal convoluted tubules without regulation. The remaining quantity can be reabsorbed **depending upon** the **body's needs**. The kidneys can also regulate the **potassium**, **calcium** and **hydrogen ions** that are excreted.

**Principal cells** in the distal convoluted tubules and collecting ducts can adjust water and electrolyte excretion in response to hormonal influence. **Intercalated cells** in the same location can adjust **acid-base balance**.

## Water Balance

**Water balance** is the equality between the water that enters, or is produced in the body, with the water that exits, or is consumed by the body. Only the **kidneys** regulate the amount of water lost in order to maintain balance.





A state of normal blood volume is called **normovolemia.** When the amount of water taken in exceeds what is lost, the body is in a **positive fluid balance** and the body becomes **hypervolemic.** If more water is lost than gained, the body is in a **negative fluid balance** and the body becomes **hypovolemic.**

Water balance is important because plasma volume affects **mean arterial pressure** and changes in plasma osmolarity can cause fluid to shift from one body compartment to another and affect cellular functions.

### Osmolarity and the Movement of Water

Kidneys can vary the amount of water lost in the **distal convoluted tubules** and **collecting ducts,** but in order to do this, an **osmotic gradient** needs to be created in the kidney between the lumen of the tubule and the peritubular fluids, and **water permeability** needs to be regulated.

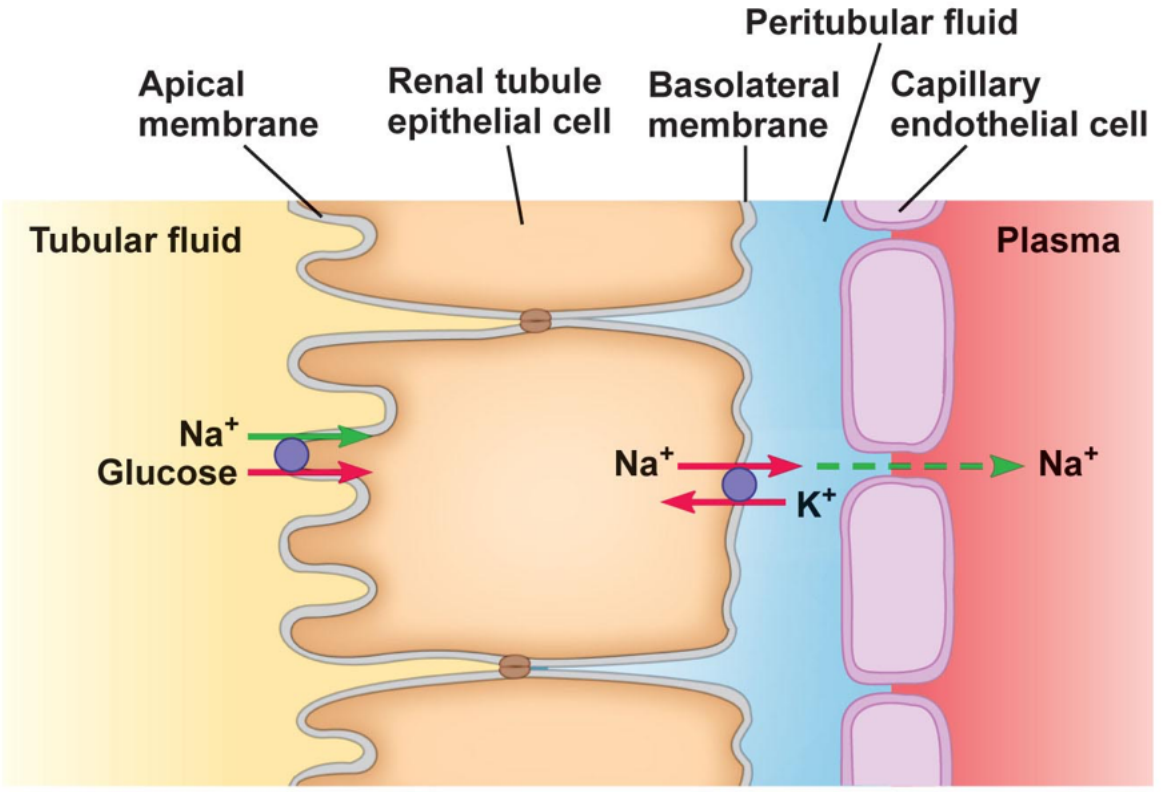
Under normal conditions the various fluid compartments in the body are in osmotic equilibrium with the osmolarity within the cells (intracellular), in between the cells (interstitial fluid) and in the plasma at about **300 mOsmoles**. If someone drinks a large quantity of water, the plasma volume expands and its **osmolarity decreases**. The water moves from the plasma into the interstitial fluid and into the cells because of the **osmotic gradient**. The movement of water into the cells would cause them to **swell**. The kidneys correct for this by producing a **large quantity** of **hyposmotic urine**.

If a person eats a very **salty food,** the salt is absorbed, enters the plasma and **increases plasma osmolarity**. Now the water movement is from the cells and interstitial fluid into the plasma and the cells would **shrink**. The kidneys correct for this by producing a hyperosmotic urine.

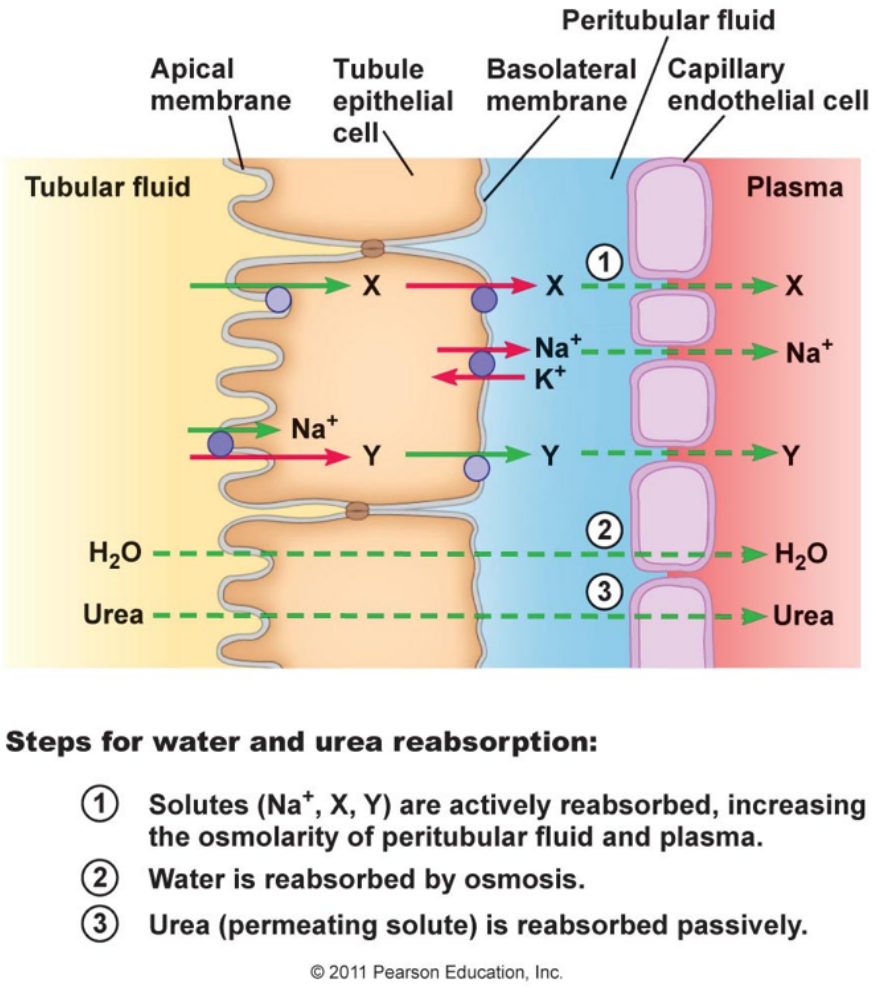
The kidney adjusts the osmolarity of the urine solely by varying the amount of **water reabsorbed** by the kidneys. Water reabsorption itself is a **passive process** that is driven by the osmotic gradients created by the **reabsorption of solutes**.

### Water Reabsorption in the Proximal Tubule

**Sodium** is the **most abundant** solute in the extracellular fluid. The active transport of sodium across the **basolateral membrane** of the tubular epithelium is primarily responsible for creating the osmotic gradient that causes movement of water.






**Steps for water and urea reabsorption:**

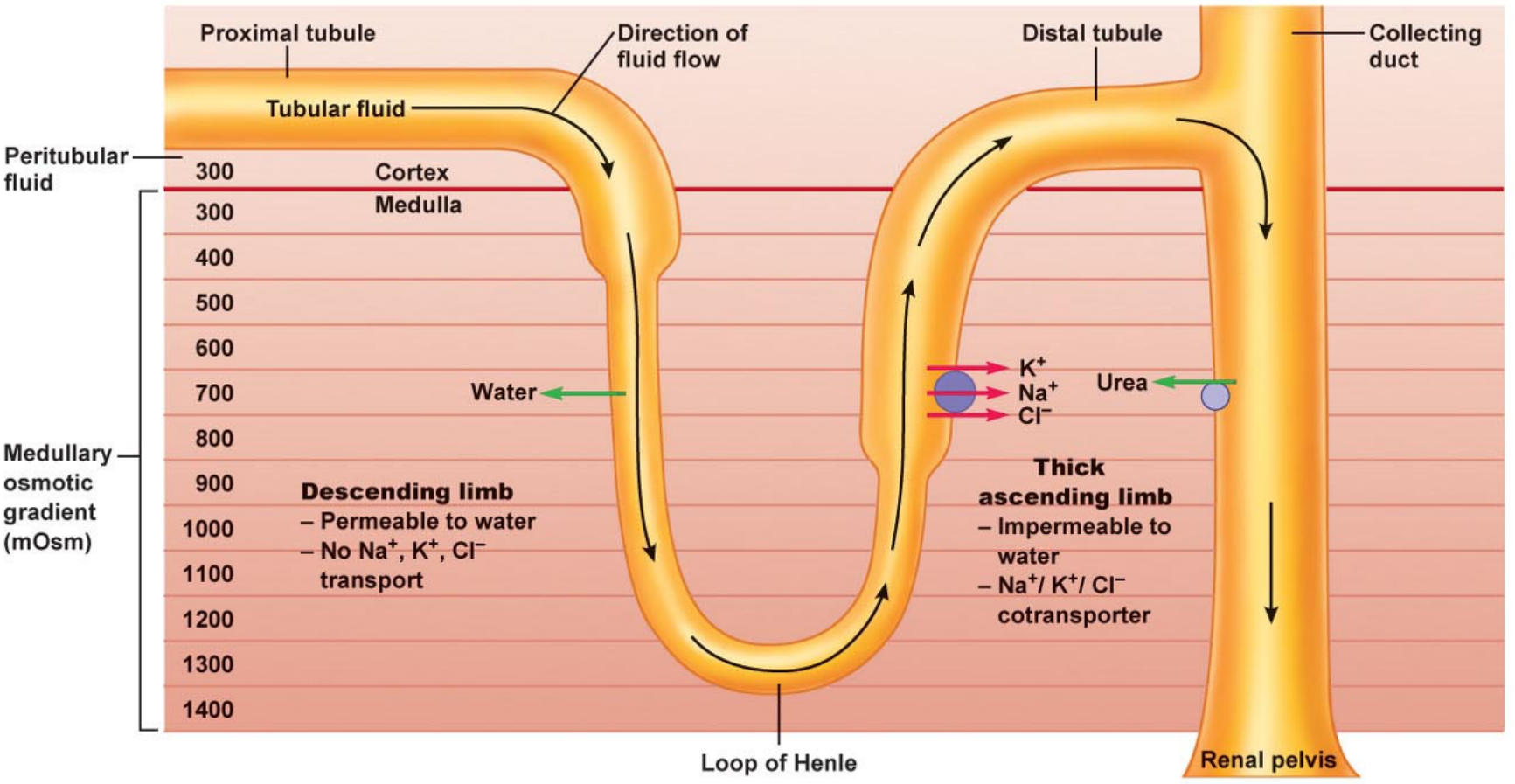
1. Solutes ($Na^+$, X, Y) are actively reabsorbed, increasing the osmolarity of peritubular fluid and plasma.
2. Water is reabsorbed by osmosis.
3. Urea (permeating solute) is reabsorbed passively.



In addition to sodium other solutes are actively reabsorbed contributing to the **osmotic gradient** that causes water to be reabsorbed. The movement of water from the lumen of the tubule into the plasma brings with it permeant solutes such as urea.

## Establishment of the Medullary Osmotic Gradient

The renal medulla has an **osmotic gradient** with the interstitial fluid being about **300 mOsmoles** near the cortex and increasing in osmolarity up to **1400 mOsmoles** towards the tips of the renal pyramids. This gradient is responsible for water reabsorption by the **collecting ducts**.

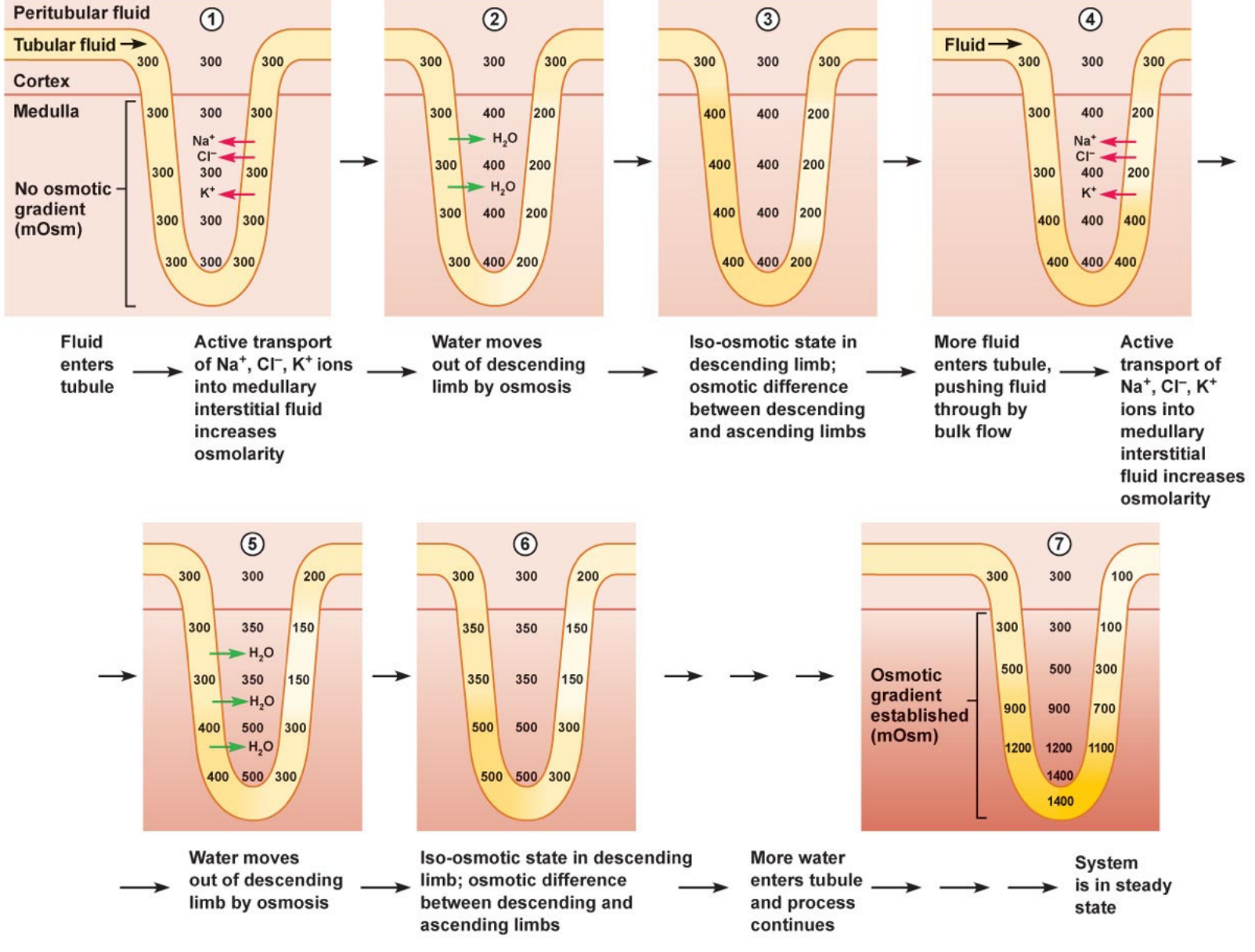


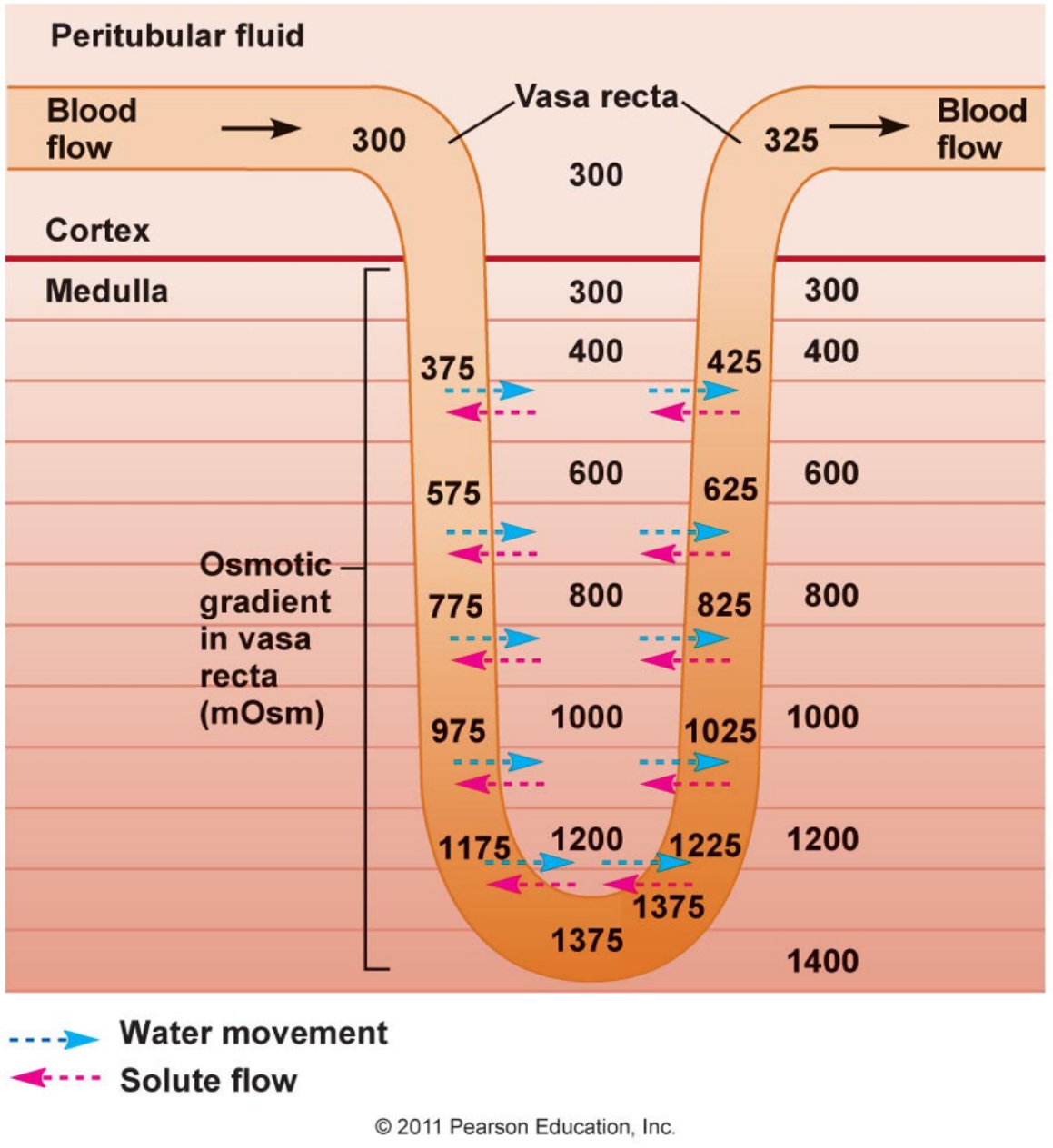



## Countercurrent Multiplier

The osmotic gradient is created by the mechanism of the **counter current multiplier** produced by the **loops of Henle** of the **juxtamedullary nephrons**. Study the figure below for an explanation of how the counter current multiplier establishes the medullary osmotic gradient.

**Urea** freely crosses most membranes but in the collecting ducts its movement is facilitated out of the collecting duct and it contributes about **40%** to the osmolarity of the gradient.








## Role of the Vasa Recta

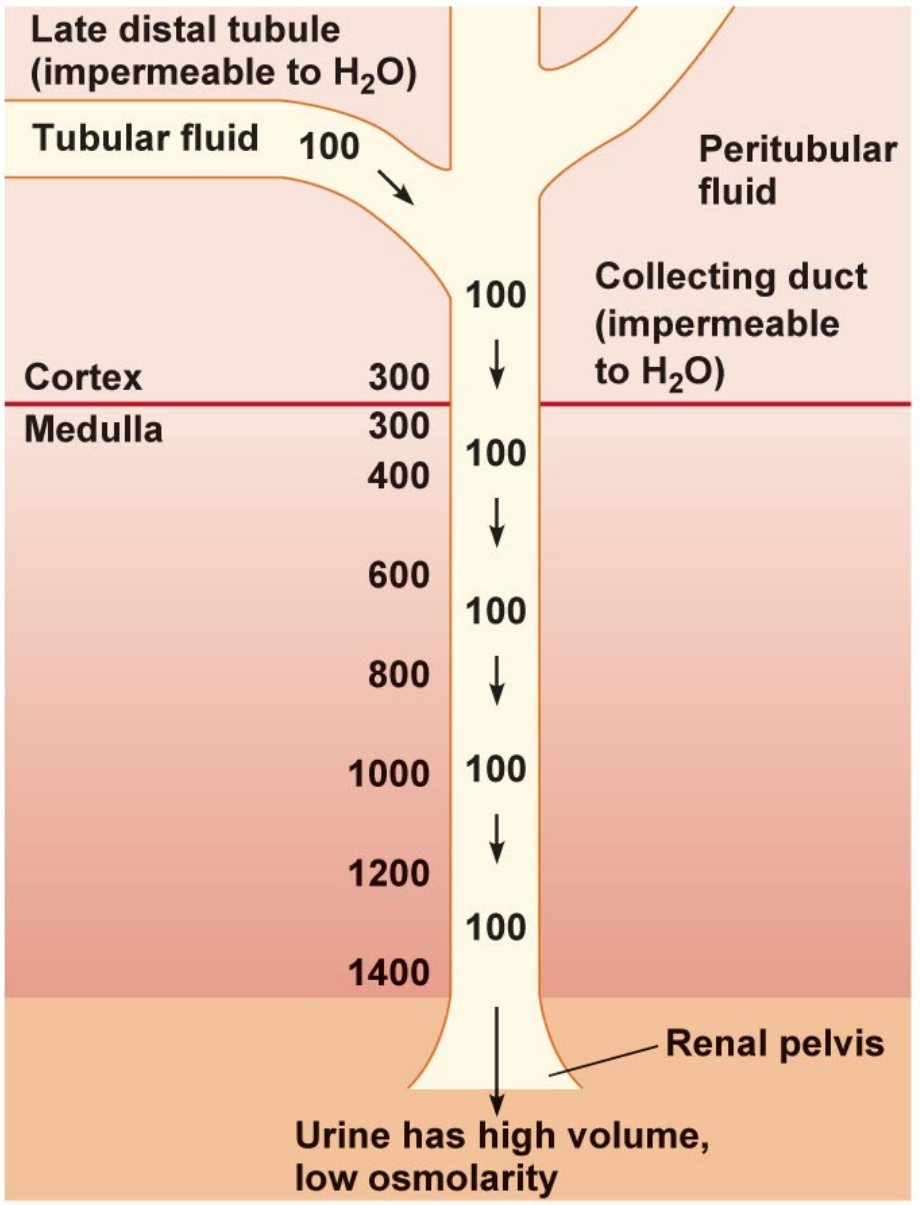
The **hairpin loops** of the **capillaries** of the vasa recta help to maintain the medullary osmotic gradient because the loss of water and gain of solutes that occurs as the descending limb goes towards the tip of the pyramid is counteracted by the gain in water and loss of solutes as the plasma ascends toward the cortex.

## Water Reabsorption in the Distal Tubule and Collecting Duct

Seventy percent of the filtered water is reabsorbed in the proximal tubule. Of the remaining **30%**, **20%** is reabsorbed by the **distal tubule** and **10%** by the **collecting duct**. The reabsorption in the distal part of the tubule results from the fact that the fluid in the lumen of the tubule is always hypo-osmolar compared to the peritubular fluid.

The tubular epithelial cells of the late distal tubules and collecting ducts have **tight junctions** between cells and the cell membranes are relatively **impermeable to water**. Water is able to pass only through water channels called **aquaporins** found in the cell membranes. **Aquaporin-3** channels are present in the basolateral membrane and **aquaporin-2** channels are present in the apical membrane when **ADH** is present.

When the distal tubules and collecting ducts are **impermeable** to water due to the lack of aquaporins in the apical membrane, the hypo-osmolar fluid entering the tubule **remains hypo-osmolar** even as it flows through the osmolar gradient created in the medulla and a dilute urine is excreted.




**(a)** Late distal tubule and collecting duct impermeable to water






**(b)** Late distal tubule and collecting duct permeable to water



When **aquaporin-2 channels** are present in the apical membrane of these tubules the tubules become **permeable** to water. The water flows down its osmotic gradient. As the collecting duct descends down the medulla, the peritubular fluid is increasingly hyper-osmotic and continues to draw water from the permeable

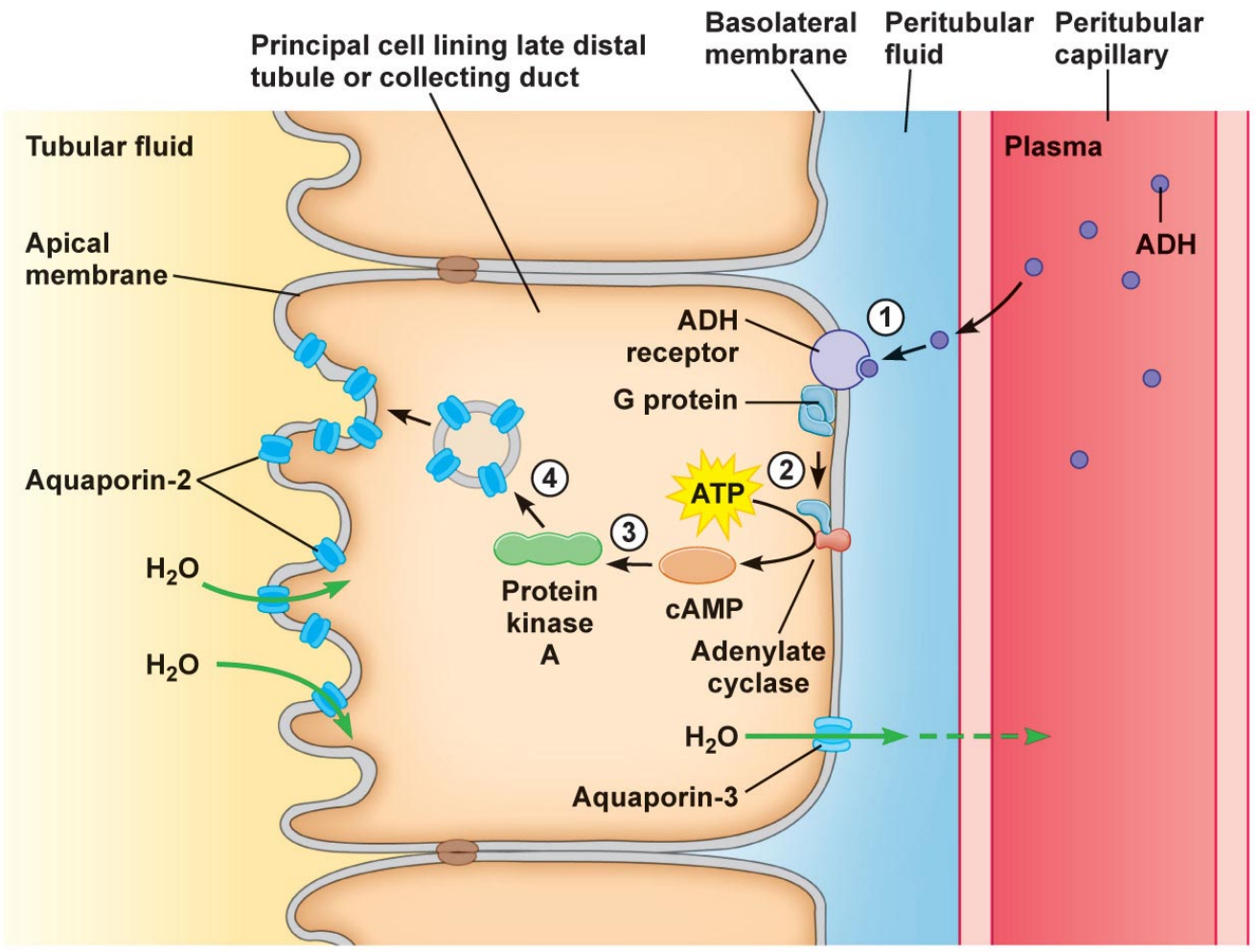
collecting duct. This continues until the fluid is **iso-osmotic** to the highly concentrated fluid at the tip of the pyramid which is **1400 mOsmole**. This is the most concentrated the fluid can get and the maximum concentrating ability of the kidneys. Hence, in order to rid the body of excess solutes there is always a certain volume of water that is lost (about 440 ml). This is called **obligatory water loss**.

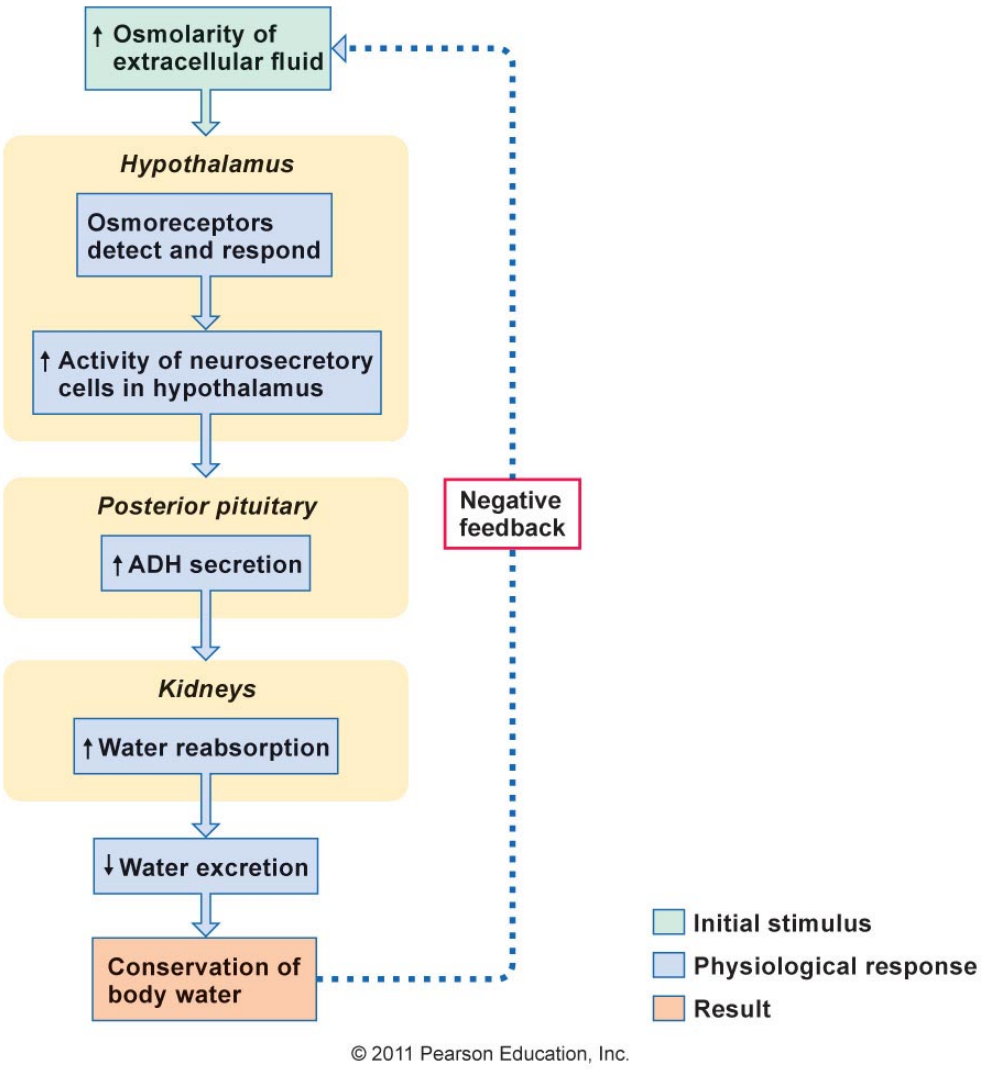
### Effects of ADH

**Antidiuretic hormone** or **ADH** regulates the permeability of the **late distal tubules** and **collecting ducts**. ADH stimulates the **synthesis of aquaporin-2** and its **insertion into the membranes** of the principal cells. Therefore, water reabsorption and urine volume are regulated by variations in the plasma levels of ADH.

ADH acts by binding to **receptors** on the plasma membrane. These receptors activate a **G protein** that activates the enzyme **adenylate cyclase** which catalyzes the synthesis of **cAMP**. cAMP causes the following effects:

1. Stimulates **insertion** of aquaporin-2 into the apical membrane by exocytosis.
2. Stimulates **synthesis** of aquaporin-2 molecules.



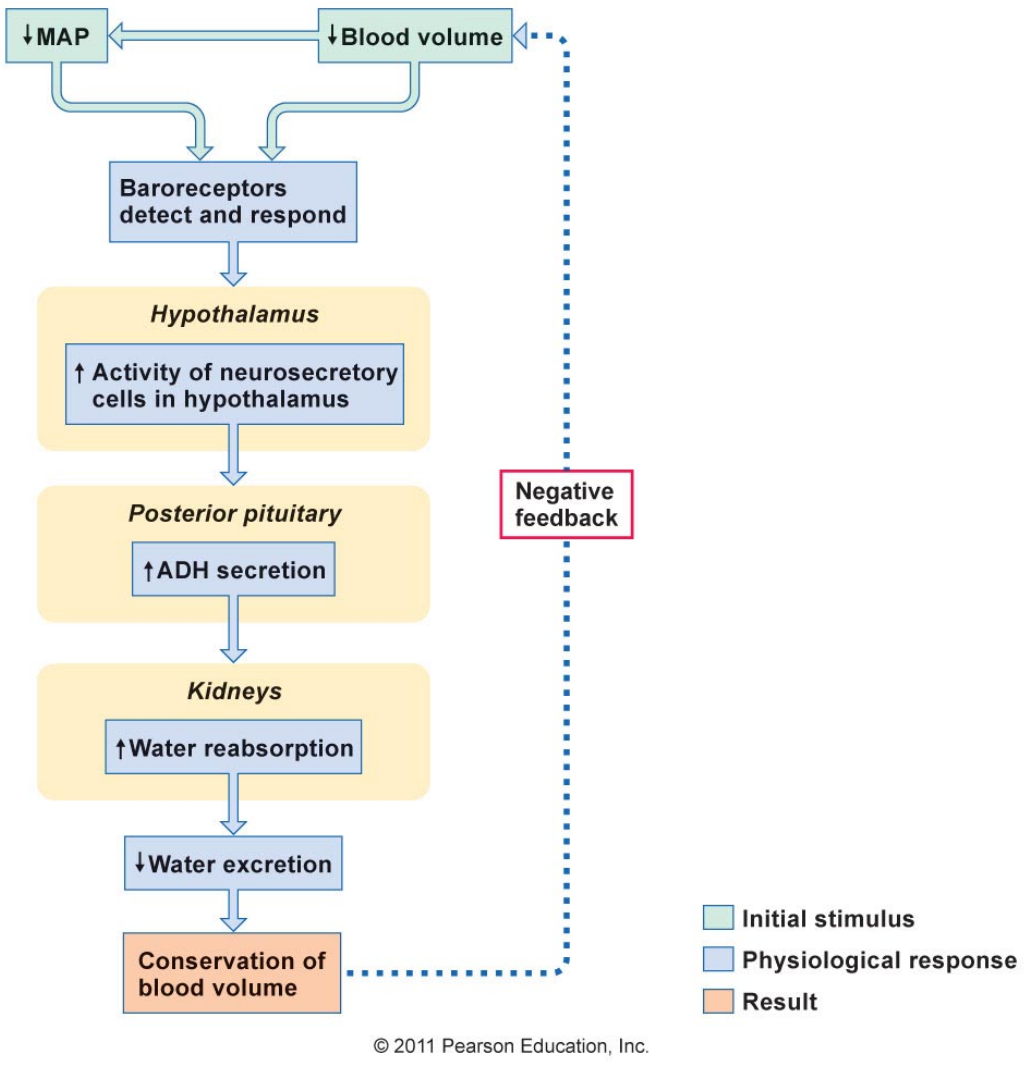



## Regulation of ADH Secretion

**Osmoreceptors** in the **hypothalamus** detect changes in osmolarity. When osmolarity **increases**, **ADH is secreted** by the pituitary and increases water reabsorption. When osmolarity **decreases**, ADH secretion is **inhibited**.

**Baroreceptors** in the **atria** responding to changes in blood volume, and **baroreceptors** in the **aortic arch** and **carotid sinus** responding to changes in blood pressure also regulate ADH secretion. When blood volume or pressure drop, ADH is **secreted** which helps to conserve plasma volume by increasing water reabsorption. When blood volume and pressure **increases**, ADH is **inhibited** with the opposite effects.

A deficiency in ADH secretion causes **diabetes insipidus** in which there is excessive urination (**polyuria**) and excessive fluid intake (**polydypsia**).




## GFR

When blood pressure drops below **80 mm Hg,** the **GFR** can no longer autoregulate and **GFR drops**. This

results in **less water** being filtered and **excreted**. When blood pressure is **greater than 180 mm Hg** the **GFR increases**. This **increases** the amount of water that is filtered and then **excreted**.

## Sodium Balance

Maintaining sodium balance is important for two reasons:

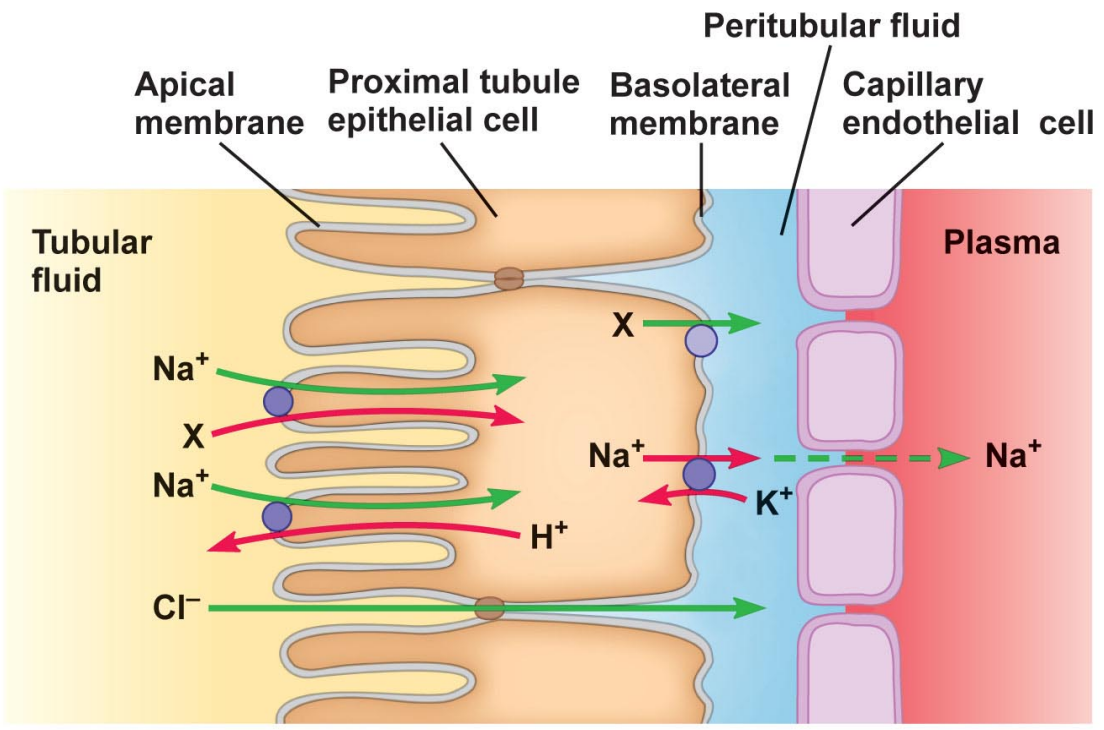
1. It is the primary ion **regulating osmolarity** of **extracellular fluid**. As such it is an important determinant of **plasma volume** and **MAP**. If sodium levels are high (**hypernatremia)** there is an **increase** in **blood pressure**, **hypertension**. If sodium levels are low (**hyponatremia)** there is a **decrease** in **blood pressure**, **hypotension**.
2. Sodium is also an important ion forming the **electrochemical gradient** of excitable cells.

## Mechanisms of Sodium Reabsorption

In all tubular segments sodium is **actively transported**. The reabsorption is due to **sodium/potassium pumps** located in the **basolateral membrane** of the tubular epithelial cells. The active transport of sodium at the basolateral membrane creates a concentration gradient across the apical membrane favorable for diffusion of sodium into the cell.

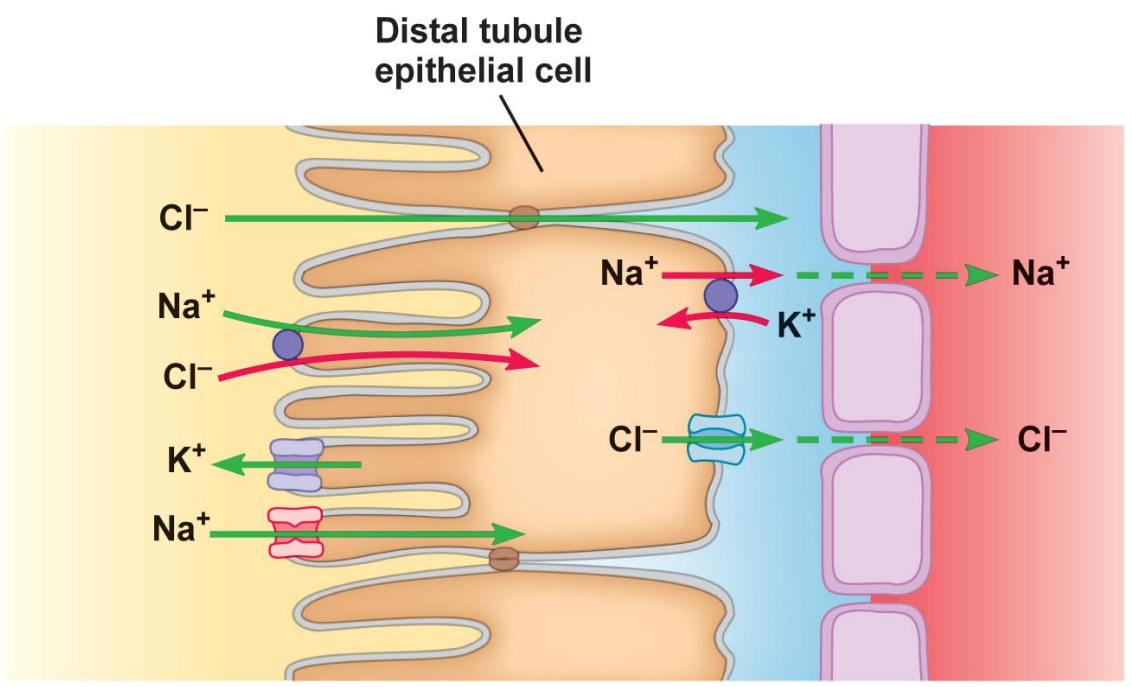
In the proximal tubule the entry of sodium into the cell is **coupled** with the movement of **other solutes**.

1. Sodium enters the cell **co-transported** with other molecules such as **glucose** and **amino acids**.
2. **Counter-transported** with the **hydrogen ion** leaving the cell and entering the tubular fluid.




**(a) Sodium reabsorption in the proximal tubule**






**(b) Sodium reabsorption in the distal tubule**



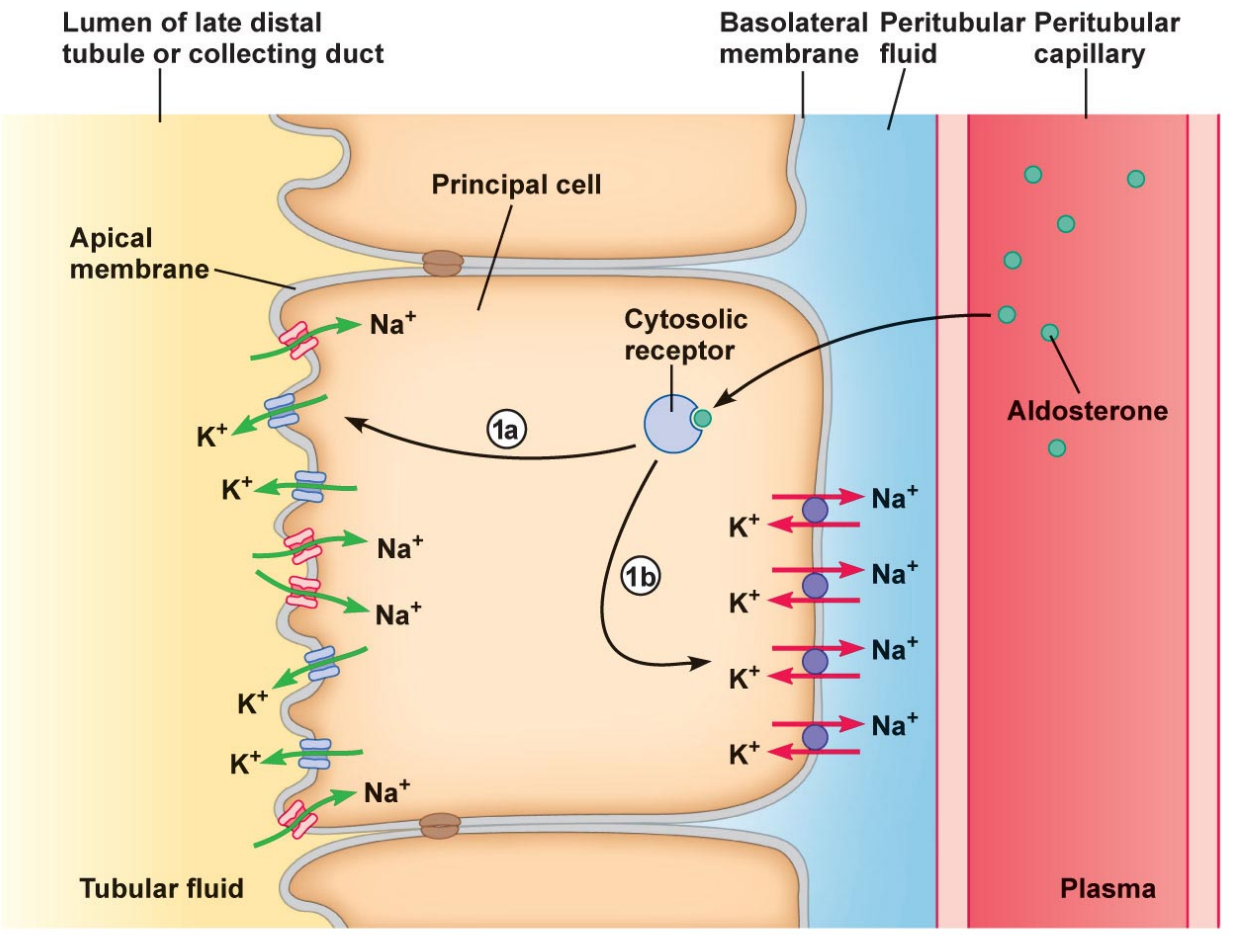
In the distal tubule the concentration gradient favoring movement of sodium into the tubular epithelial cell is the same but diffusion of sodium across the apical membrane is:

1. By co-transport with the anions **chloride** and **bicarbonate**.
2. Facilitated diffusion through **sodium channels**.

Sodium reabsorption in the distal tubules is often coupled with **potassium** and **hydrogen ions secretion**. This helps to minimize changes in the electrical potential across the membrane and facilitates the secretion of potassium and hydrogen ions.

### Effects of Aldosterone

**Aldosterone** regulates both **reabsorption of sodium** and **secretion of potassium**. Aldosterone (a permeant steroid hormone) enters the **principal cells** of the **late distal tubules** and **collecting ducts** and binds to cytosolic receptors. Its effects include:



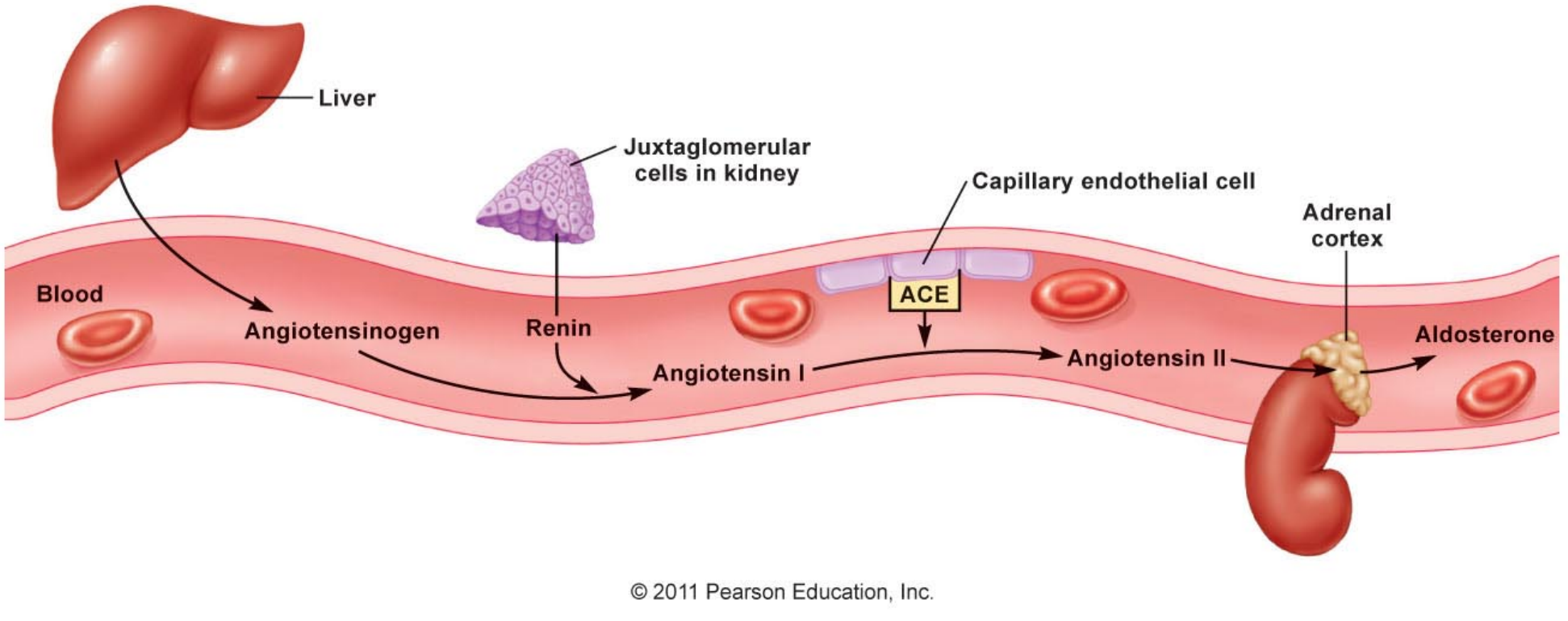


1. Increasing **sodium and potassium channels** in the **apical membrane** by causing channels to open and synthesizing new channels.
2. Increasing **synthesis** and **concentration of $Na^+/K^+$ pumps** in the **basolateral membrane**.

Both of these effects cause the simultaneous reabsorption of sodium and secretion of potassium.

### Renin-Angiotensin-Aldosterone System

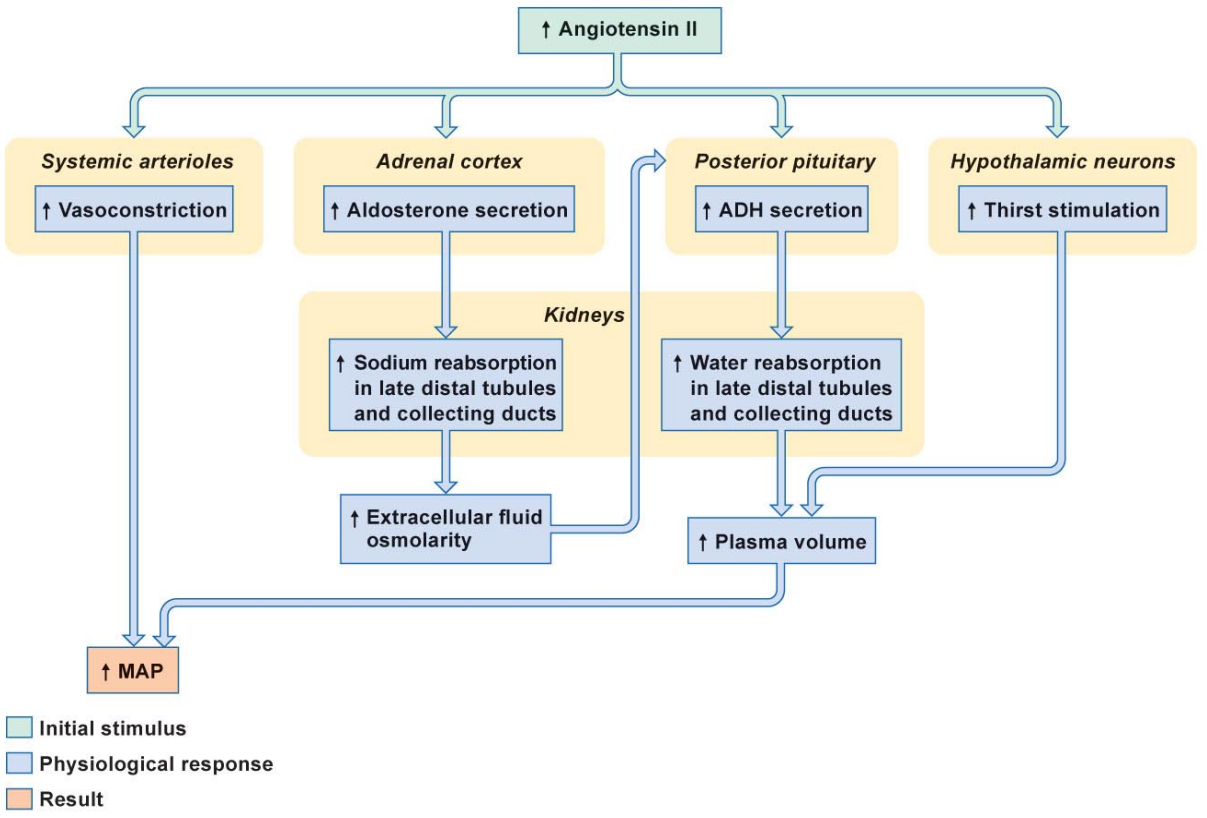
The walls of the afferent arteriole that contributes to the juxtaglomerular apparatus are granular cells that secrete **renin.** The nearby cells of the macula densa detect changes in the flow, and the **sodium and chloride concentration,** of the tubular fluid. A **decrease** in **sodium ion concentration** causes renin secretion to increase. Renin acts upon **angiotensinogen** which is secreted by the liver converting it to **angiotensin I**. **Angiotensin converting enzyme (ACE)** which is on the surface of the capillary endothelial cells throughout the body, but particularly in the **lung**, converts angiotensin I to **angiotensin II**.



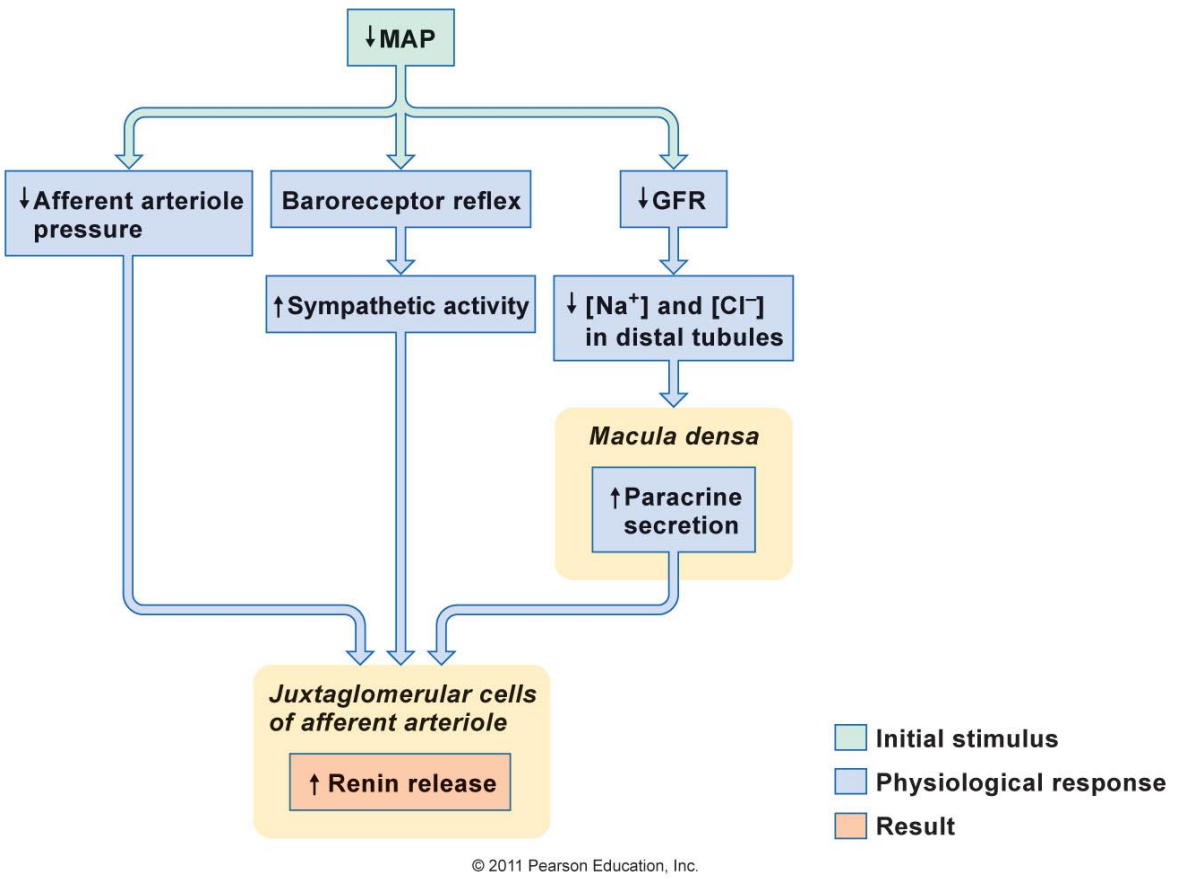


Angiotensin II increases MAP by the following effects:

1. acts as a **vasoconstrictor**
2. stimulates **release** of **aldosterone**
3. stimulates **secretion** of **ADH**
4. stimulates **thirst** and **fluid intake**







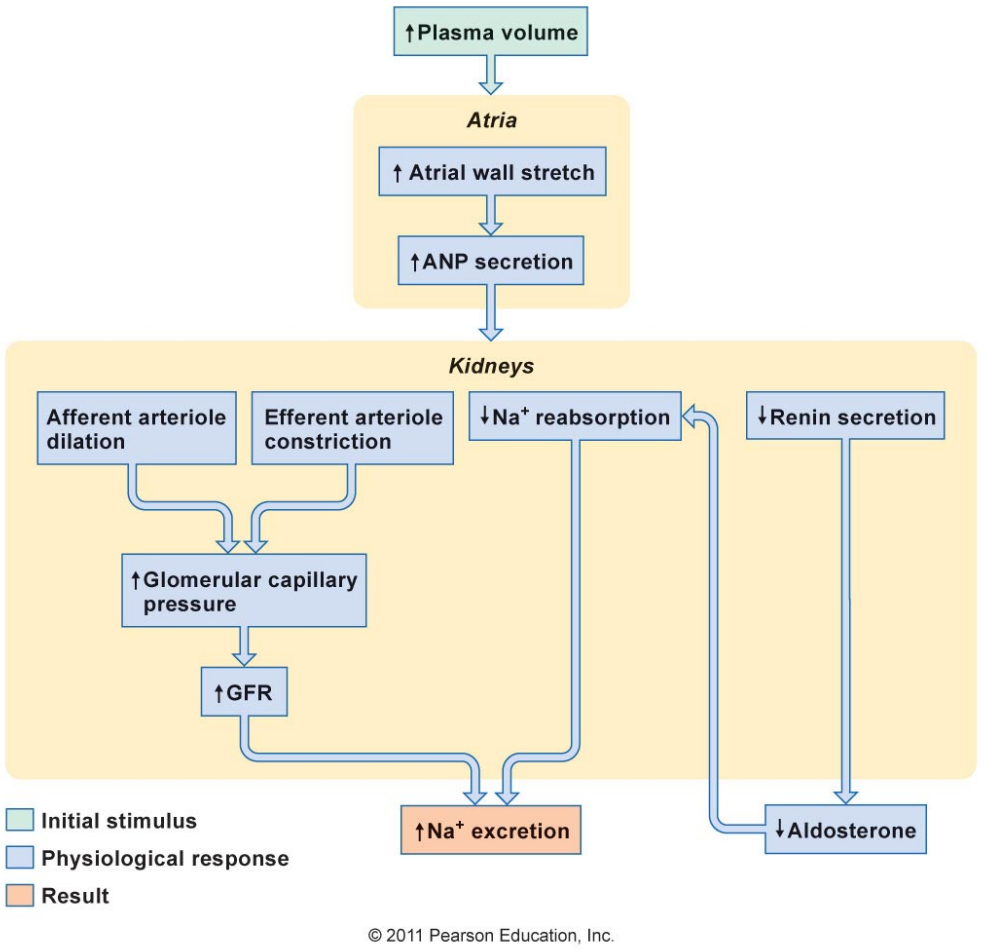

Renin release is stimulated by a **decrease in MAP** which is specifically detected by:

1. **Decrease** in afferent arteriole pressure
2. **Baroreceptor reflex** causing renal **sympathetic nerve stimulation**
3. A **decrease in GFR** leading to a **decrease** in **sodium and chloride concentration** in the distal tubule

**Atrial Natriuretic Peptide (ANP)**

This peptide is secreted by cells of the atrium when an increase in plasma volume causes its walls to stretch. ANP increases GFR by:

1. **Increasing** glomerular capillary pressure by **dilating** the **afferent arteriole** and **constricting** the **efferent arteriole.**
2. **Decreasing** sodium absorption by decreasing the number of open **sodium channels** in the principal cells.
3. **Decreasing** secretion of **renin** and **aldosterone**.





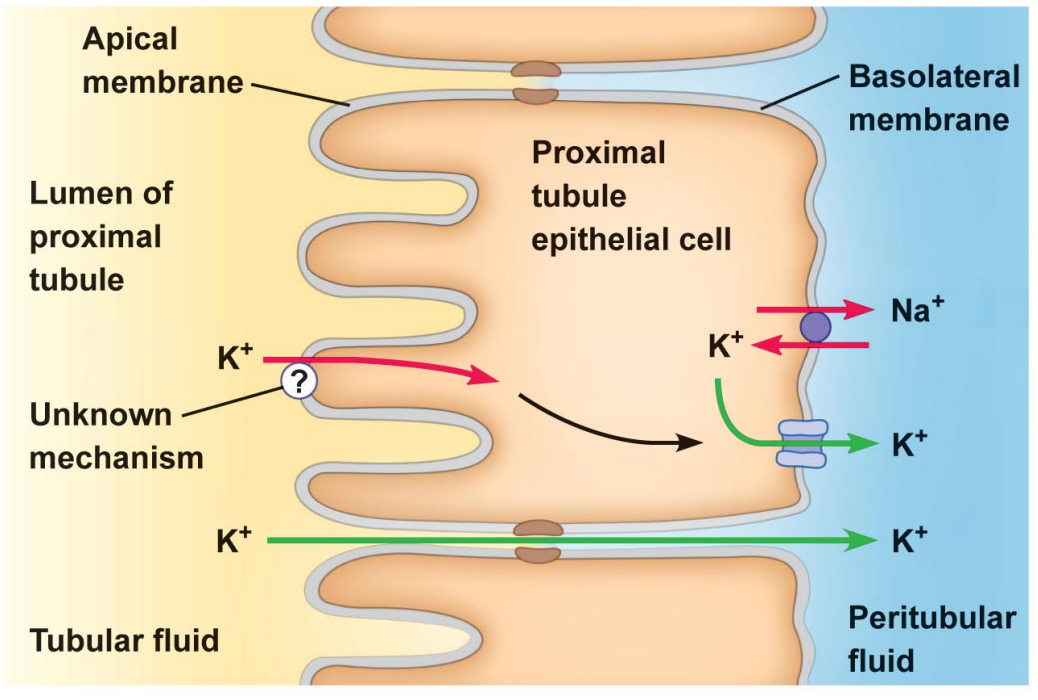
## Potassium Balance

The normal concentrations of potassium in the intra- and extracellular fluid is critical for proper functioning of excitable cells. **Hyperkalemia** is an increase in potassium plasma levels and **hypokalemia** is a decrease in plasma potassium levels.

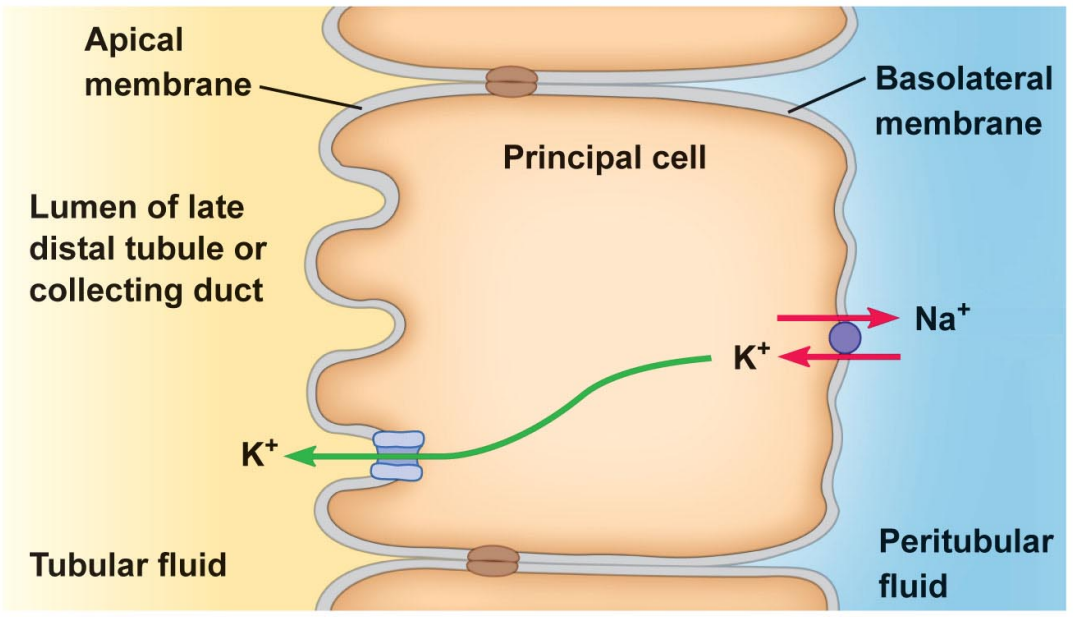
## Renal Handling of Potassium

Most of the potassium that is filtered is reabsorbed. However, potassium is regulated by varying the amount of potassium that is **secreted** by the **late distal tubule** and **collecting ducts**.

Potassium is absorbed in the proximal tubule by various mechanisms. Potassium is secreted in the distal tubules and collecting ducts by a **sodium/potassium pump** and **potassium channels** in the **apical membrane** of the **principal cells**.




**(a)** Potassium reabsorption in the proximal tubule




**(b)** Potassium secretion in the principal cells of the late distal tubule and collecting duct

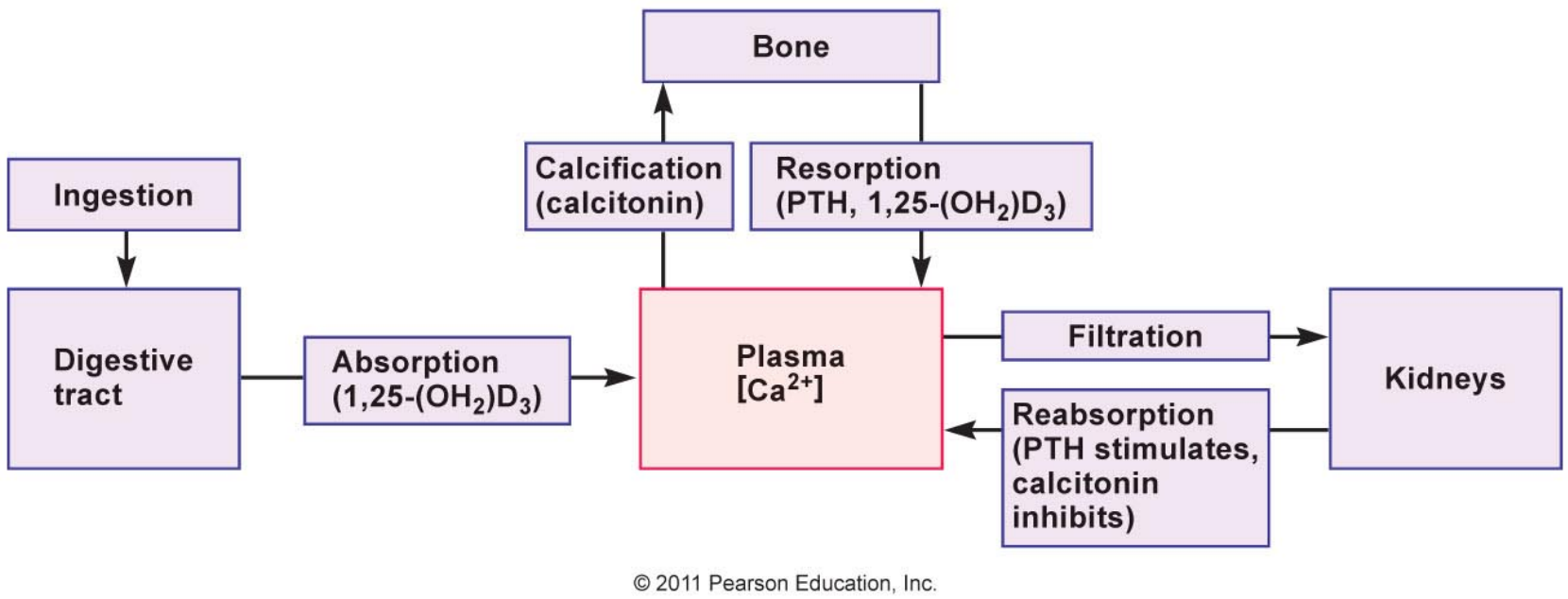


### Regulation of Potassium Secretion by Aldosterone

Aldosterone increases potassium secretion by **increasing $Na^+/K^+$ pumps** and **increasing $K^+$ channels** in the **apical membrane** of the distal tubules and collecting ducts. High potassium levels stimulate secretion of aldosterone by the adrenal cortex.

## Calcium Balance

**Hypercalcemia** is an increase in plasma calcium and **hypocalcemia** is a decrease in plasma calcium. Plasma calcium is regulated by a number of organs:






1. **Bone -** Calcium levels increase when resorbed from bone which serves as a reservoir. Excess plasma calcium can also be deposited in bone.
2. **Digestive -** Calcium can be absorbed from the digestive tract.
3. **Kidney -** Calcium can be excreted by the kidneys.
4. **Skin -** Participates in the formation of Vitamin D.

### Renal Handling of Calcium

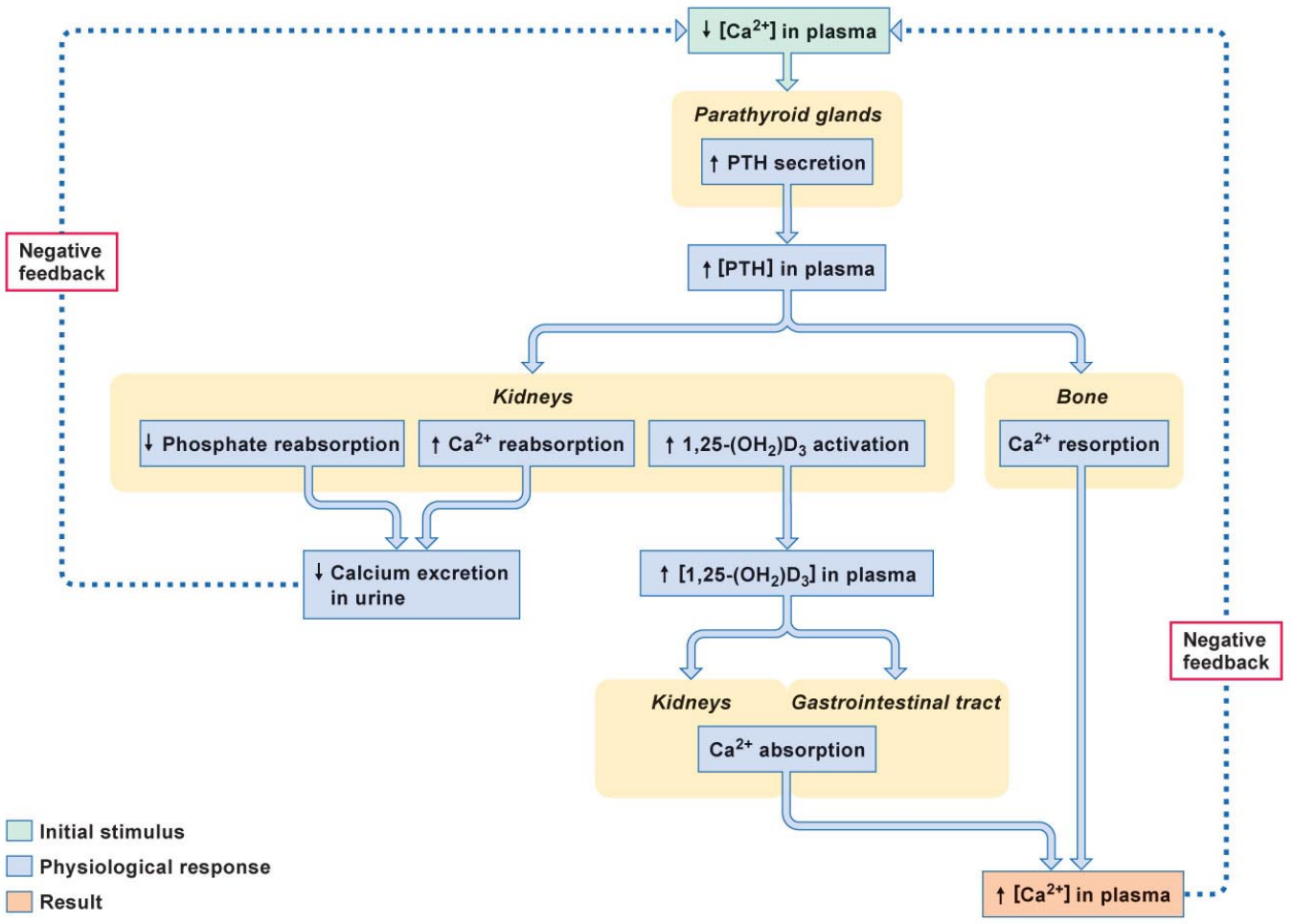
Calcium is transported in plasma both **free** and bound to **carrier proteins**. Free calcium is filtered at the glomerulus and normally 99% of it is resorbed: 70% is resorbed in the proximal tubules, 20% in the thick ascending limb of the loop of Henle, and 10% in the distal tubules. Hormones regulate reabsorption in the loop of Henle and distal tubules.

### Hormonal Control of Plasma Calcium

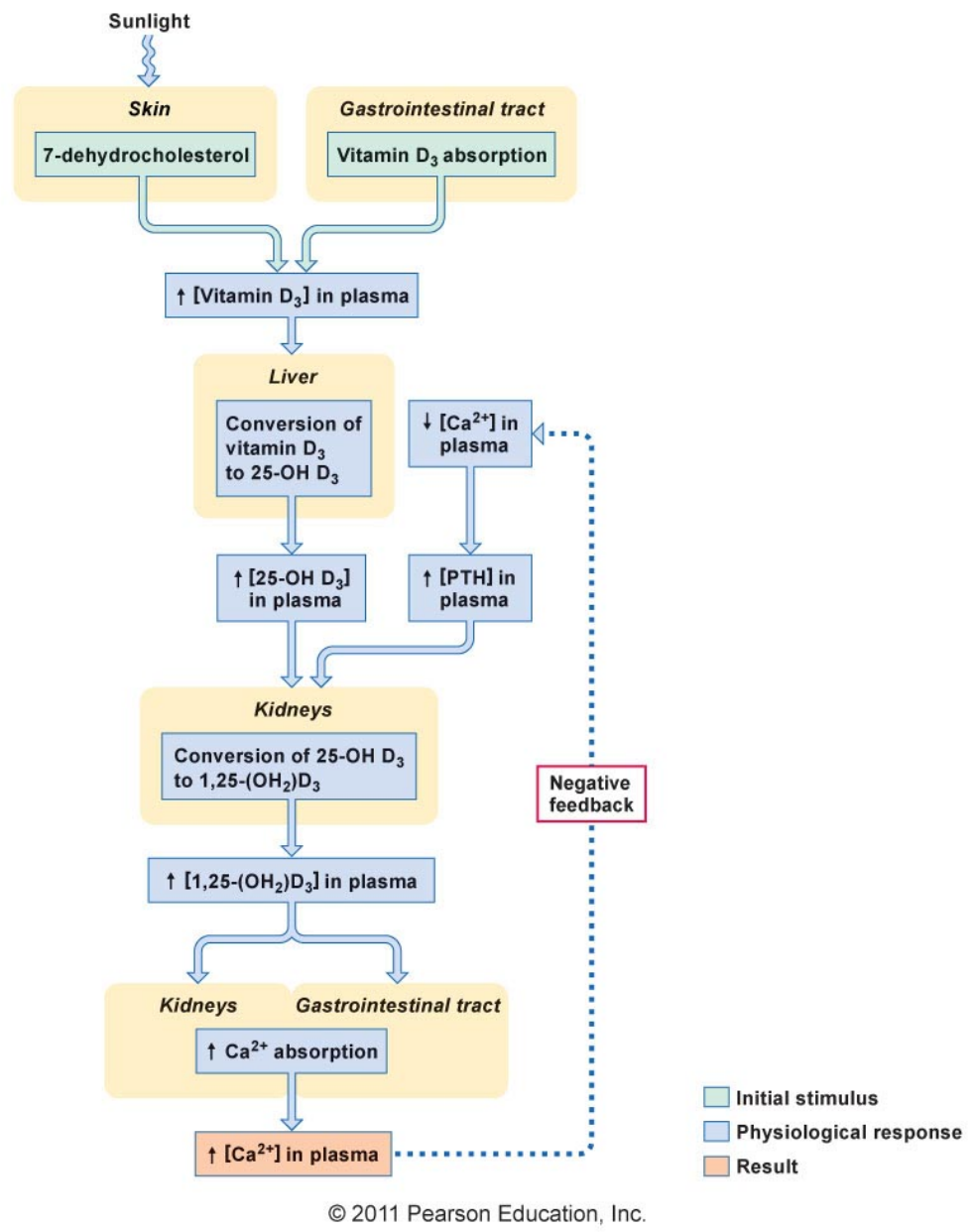
#### Parathyroid Hormone (PTH)

PTH is secreted in response to a decrease in plasma Ca. PTH:

1. Stimulates **calcium resorption** in the ascending limb of the loop of Henle and distal tubules.
2. Stimulates **activation of calcitriol** in the kidneys.
3. Stimulates **resorption of bone** & small increase in **absorption** from the **digestive tract**.








### Effects of Calcitriol

Calcitriol stimulates absorption of calcium from the digestive tract and kidney. **Vitamin $D_3$** can be converted from 7-dehydrocholesterol in the skin or absorbed in the diet. Vitamin $D_3$ travels to the **liver** and is converted to 25-OH $D_3$. From the liver 25-OH $D_3$ travels to the **kidneys** and in the presence of low calcium levels is converted to calcitriol.

### Calcitonin

Calcitonin **decreases** plasma calcium by **increasing** bone formation and **decreasing** reabsorption in the kidneys.

## Acid-Base Balance

It is essential to control pH within a narrow range of **7.38 to 7.42**. Control is performed by the combined action of the **lungs** and the **kidneys.**

Changes in pH can have profound effects:

1. Changes in pH **change** the shape of **enzymes** and their activities.
2. Activity of the **nervous system changes**:
   **Acidosis -** decreases excitability of neurons
   **Alkalosis -** increases excitability of neurons
3. Coupled to **potassium imbalances**:
   **Acidosis -** results in potassium retention or **hyperkalemia**
   **Alkalosis -** results in potassium depletion or **hypokalemia**
4. Acidosis causes **cardiac arrhythmias** and **dilation of blood vessels** of the skin.

**Sources of Acid-Base Disturbances**

Inputs include:

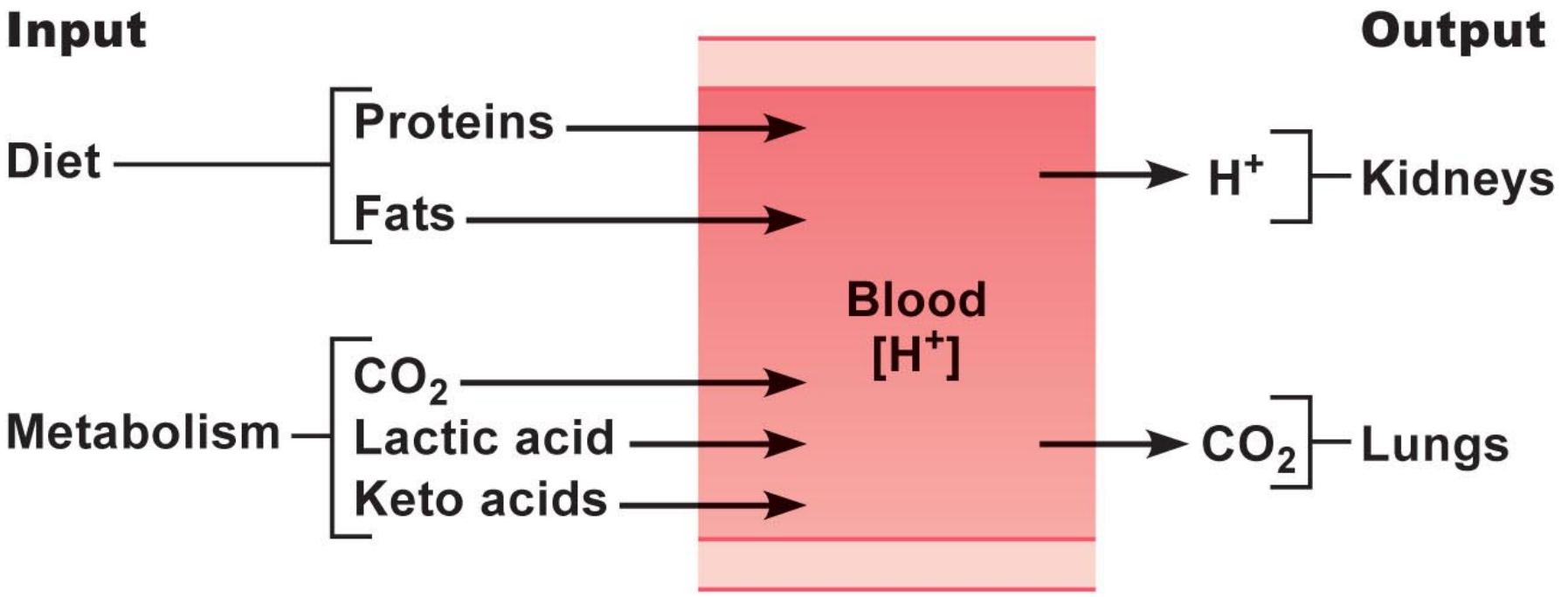
Dietary sources - proteins and fats

Metabolism - carbon dioxide, lactic acid, ketoacids

Outputs include:

Lungs - carbon dioxide

Kidneys - hydrogen ions






**Respiratory Disturbances**

The lungs regulate the amount of carbon dioxide in the blood which is continually produced by cellular metabolism. The normal **$P_{CO2}$ is 40 mm Hg**. This level is maintained by respiratory chemoreceptors. Diseases that **interfere** with the **exchange of $CO_2$** between the blood and alveolar air, or **hypoventilation**, lead to a buildup of $CO_2$ in the blood which results in **respiratory acidosis**. **Hyperventilation** causes $P_{CO2}$ to decrease and this leads to **respiratory alkalosis**.

**Metabolic Disturbances**

Metabolic Acidosis -

Causes:

**Loss** of **alkaline substances** from the body.

**Excess production** of **acid** in metabolism.

**Excess consumption** of **acids** in the diet.

Metabolic Alkalosis -

Causes:

**Loss of acids** from the body.

**Addition** of **alkaline substances** to the blood.

**Specific Causes of Metabolic Disturbances:**

1. **High protein diet -** Protein catabolism produces **phosphoric acid** and **sulfuric acid** that cause metabolic acidosis.
2. **High fat diet -** Catabolism of fats produces **fatty acids**.
3. **Heavy exercise -** When oxygen demands cannot be met and anaerobic metabolism is used to produce energy and **lactic acid** builds up.
4. **Excessive vomiting - Loss** of **hydrogen ions** in the stomach leads to metabolic alkalosis.
5. **Severe diarrhea - Loss** of **bicarbonate ions** can produce metabolic acidosis.
6. **Alterations in renal function -** Kidneys **secrete hydrogen ions** and **absorb bicarbonate**. Malfunction can produce either acidosis or alkalosis.

## Defense Mechanisms Against Acid-Base Disturbances

Three processes protect the body from dangerous shifts in pH. These processes only **compensate** for an imbalance and do not correct the cause of the imbalance.

### Buffering of Hydrogen Ions

The buffering of hydrogen ions is the first line of defense against changes in pH. **Bicarbonate** is the most important **buffer** in **extracellular fluid**. **Proteins** and **phosphates** are the most important **intracellular** buffers.

The law of mass action determines whether a buffer binds or releases hydrogen ions:

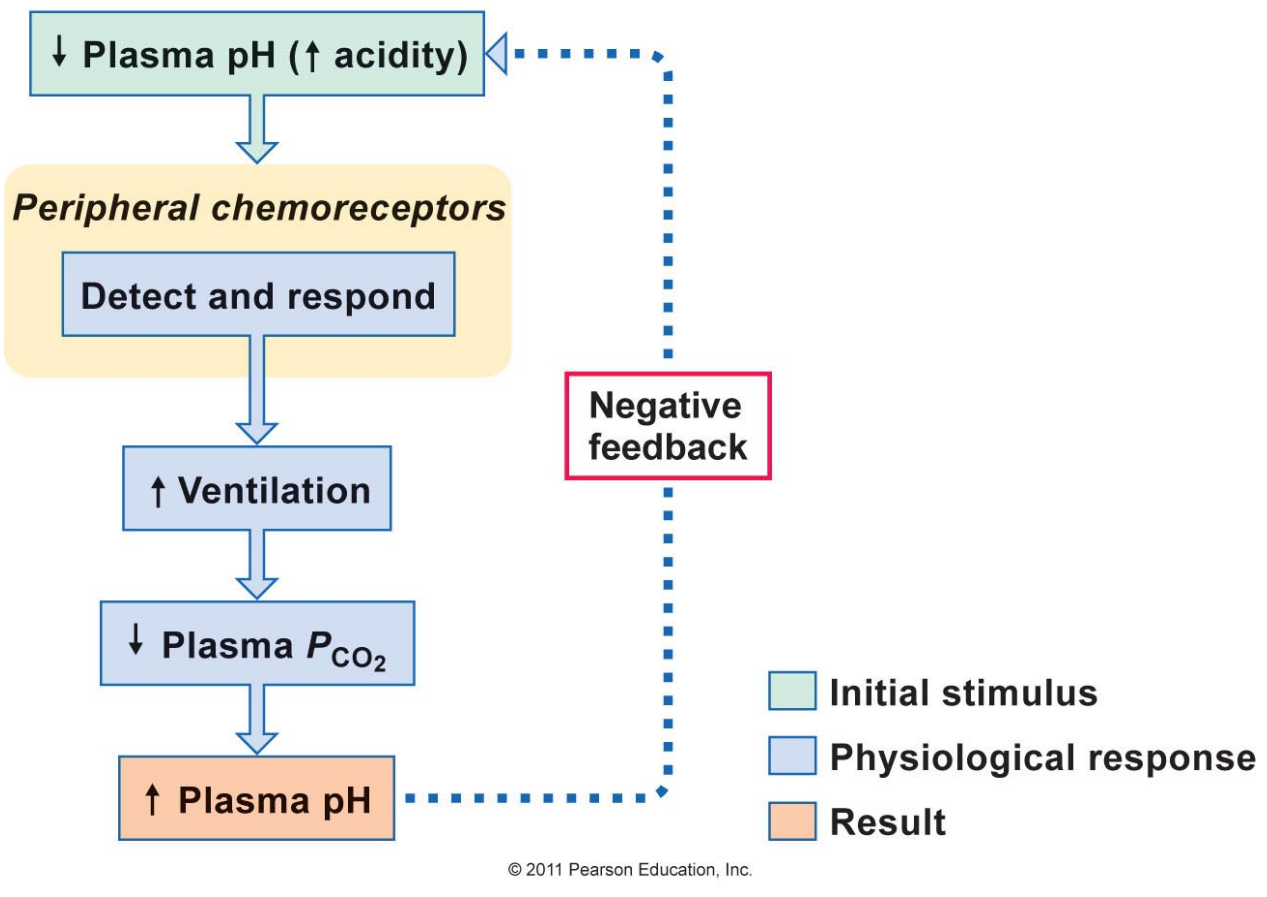
$$H^+ + A^- \rightleftharpoons HA$$

When $H^+$ is added, the reaction goes to the right as the $H^+$ binds with the anion form of the buffer. When $H^+$ is removed, the reaction goes to the left as $H^+$ disassociates from the acid form of the buffer.

Buffering is the **fastest defense** against alterations in pH but buffering can **only limit changes** in pH and cannot do the job alone. Once there is a deviation from the normal pH, renal and respiratory mechanisms help to compensate for it.

### Respiratory Compensation

Respiratory compensation is the second line of defense and acts in **minutes**. **Increasing** alveolar ventilation by blowing off $CO_2$ **increases** pH while **decreasing** alveolar ventilation **decreases pH**. Unlike buffers, ventilation can regulate pH by reversing a change. However, respiratory compensation alone cannot restore pH to normal.



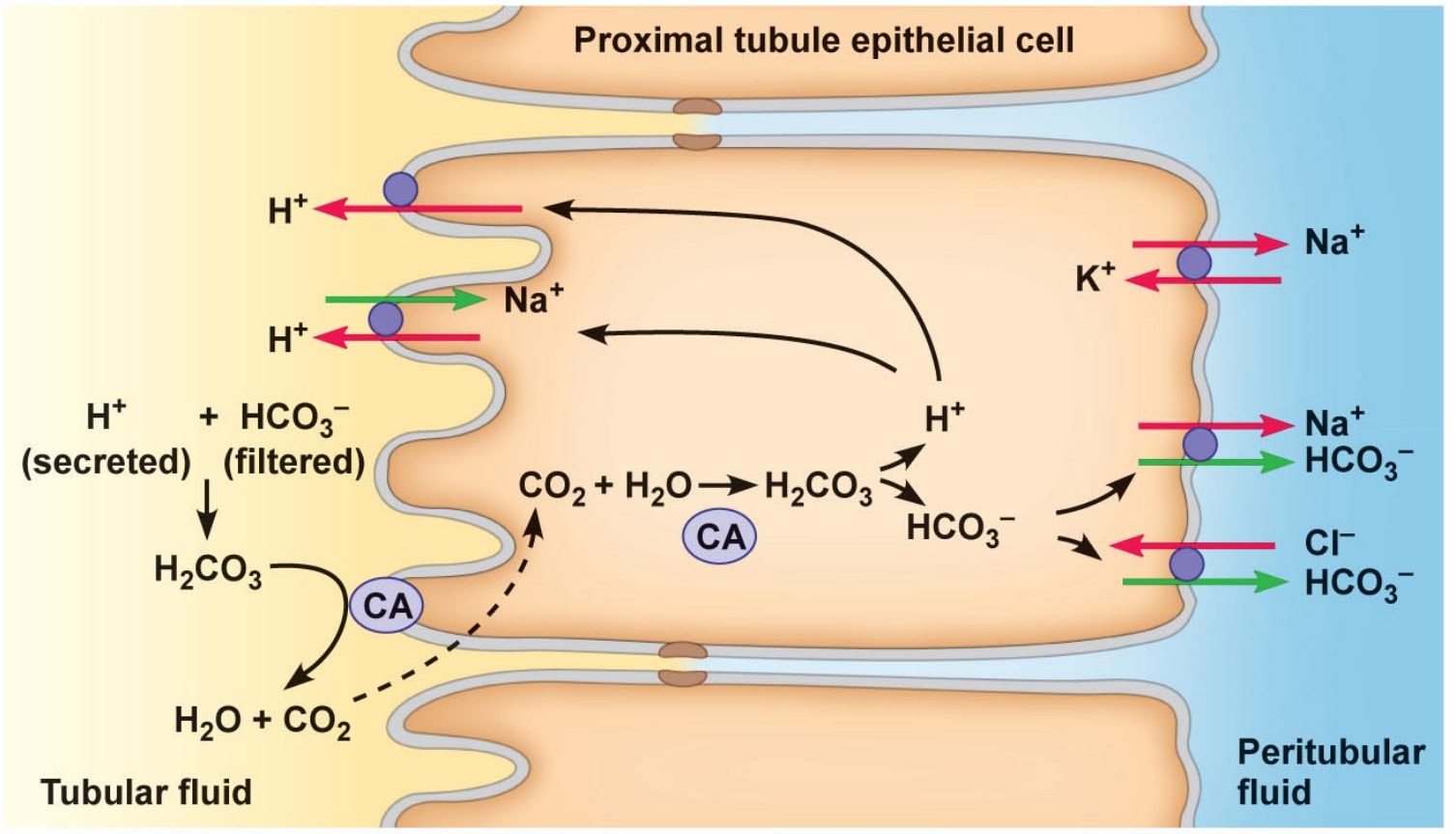


### Renal Compensation

Renal compensation is the third line of defense and takes **hours to days**. The basic mechanism of renal compensation involves **hydrogen ion secretion** and **bicarbonate reabsorption** and **synthesis**. If pH **decreases** the kidneys **secrete** hydrogen ions and **absorb bicarbonate** and **synthesize new bicarbonate**. If pH **increases** the kidneys **decrease** hydrogen ion secretion and bicarbonate reabsorption.

**Renal Handling of Hydrogen and Bicarbonate Ions in the Proximal Tubules**

The basolateral membrane of tubular epithelial cells have:






1. **$Na^+/K^+$ pumps**
2. **$Na^+/HCO_3^-$ cotransporters**
3. **$HCO_3^-/Cl^-$ counter transporters**

The apical membrane has:

1. **$Na^+/H^+$ counter transporters**
2. **$H^+$ pumps** that pump $H^+$ into tubular fluid

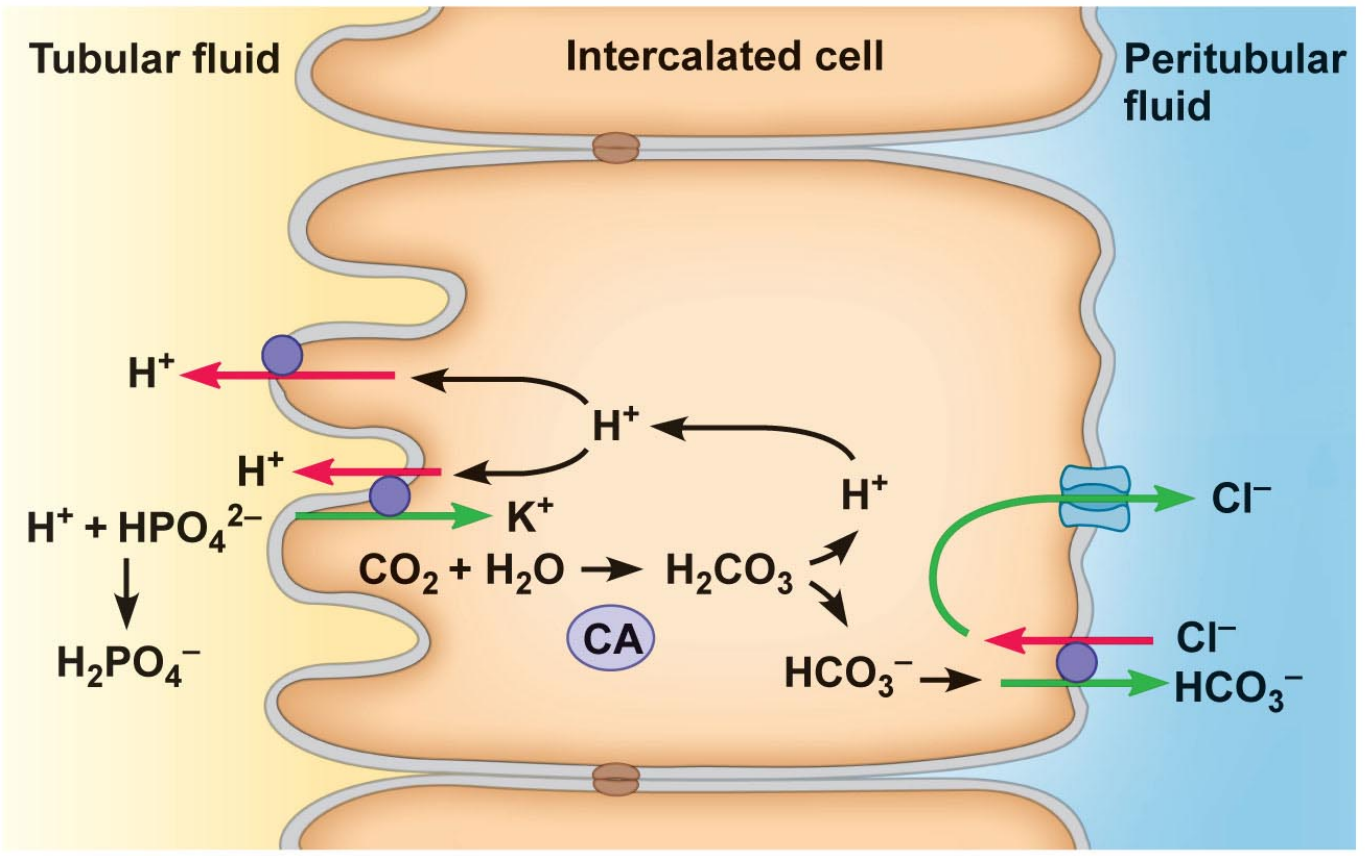
Also important is **carbonic anhydrase** which is located in the cytosol and on the apical membrane. Carbonic anhydrase on the apical membrane **converts** the filtered **$HCO_3^-$**, after it combines with $H^+$ to form carbonic acid, into **$CO_2$** and $H_2O$. The $CO_2$ **diffuses** into the **epithelial cell** and is converted back to **carbonic acid**. The $H^+$ inside the cytosol disassociate from the carbonic acid. **$H^+$** is pumped back into the **lumen** by the $H^+$ pumps and $Na^+/H^+$ counter transporter. The **$HCO_3^-$** is transported into the **peritubular fluid** by the **$Na^+/HCO_3^-$ cotransporter** and the **$HCO_3^-/Cl^-$ counter transporter**.

The net effects are to:

1. **reabsorb 80-90% of filtered $HCO_3^-$**
2. **secrete $H^+$**
3. **reabsorb $Na^+$**

**Renal Handling in Late Distal Tubule and Collecting Duct**

**Intercalated cells** in the late distal tubules and collecting ducts have different membrane proteins. The basolateral membrane has:






1. **$HCO_3^-/Cl^-$ counter transporters**
2. **Chloride channels**

The apical membrane has:

1. **$H^+$ pumps**
2. **$K^+/H^+$ counter transporters**

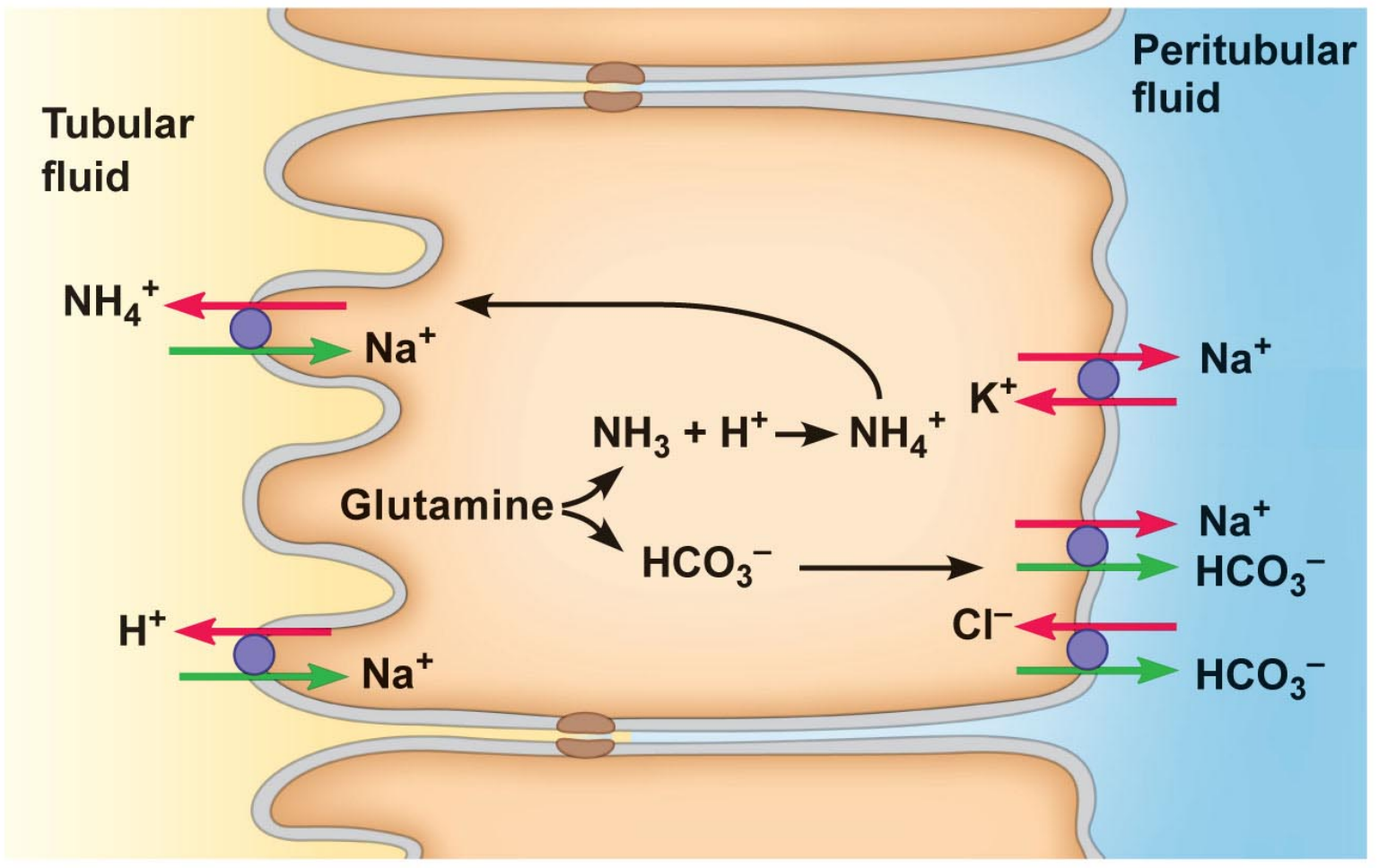
**Carbonic anhydrase** is in the cytosol. Carbonic anhydrase produces carbonic acid in the cytosol which disassociates to form hydrogen ion and bicarbonate ion. The **hydrogen ion** is **secreted** into the lumen and the **bicarbonate** is **secreted** into the **peritubular fluid**.

The net effect is to:

1. Form **new bicarbonate ions**
2. **Secrete $H^+$**

As $H^+$ are secreted into the tubular fluid an excessive decrease in pH is prevented by the buffering action of **phosphate ions** which are freely filtered at the glomerulus.

**Role of Glutamine in Renal Compensation during Severe Acidosis**



During **severe acidosis** another mechanism involving glutamine helps renal compensation in the **proximal convoluted tubule**. Glutamine is transported into the tubular epithelial cells and catabolized to produce **$HCO_3^-$** and **$NH_3$**. The $HCO_3^-$ is newly formed and is **secreted** into the **peritubular fluid**. The $NH_3$ combines with $H^+$ to form **$NH_4^+$** and is **secreted**. The net effect is new $HCO_3^-$ is added to the blood and $H^+$ is secreted in the form of the $NH_4^+$ ion.

**Compensation for Acid-Base Disturbances**

The acid-base status of the plasma is reflected by the **ratio** of bicarbonate ions to $CO_2$ in the plasma as determined by the **Henderson-Hasselbach equation**. When the pH is normal this ratio is **20 to 1** or 20 $HCO_3^-$ ions for every molecule of $CO_2$ in the plasma. The **respiratory system** regulates the concentration of **$CO_2$** in the plasma, while the **kidneys** regulate the concentration of **$HCO_3^-$** . The four basic acid-base disturbances are as follows:

**Respiratory Acidosis**

**Hypoventilation** due to lung disease, depression of the respiratory center or diseases of the respiratory muscles causes **$pCO_2$ to increase**. This decreases the ratio of bicarbonate to $CO_2$ . The acidosis is corrected by the **kidneys** which **increases** the **absorption of $HCO_3^-$** and **secretion of $H^+$**.

**Respiratory Alkalosis**

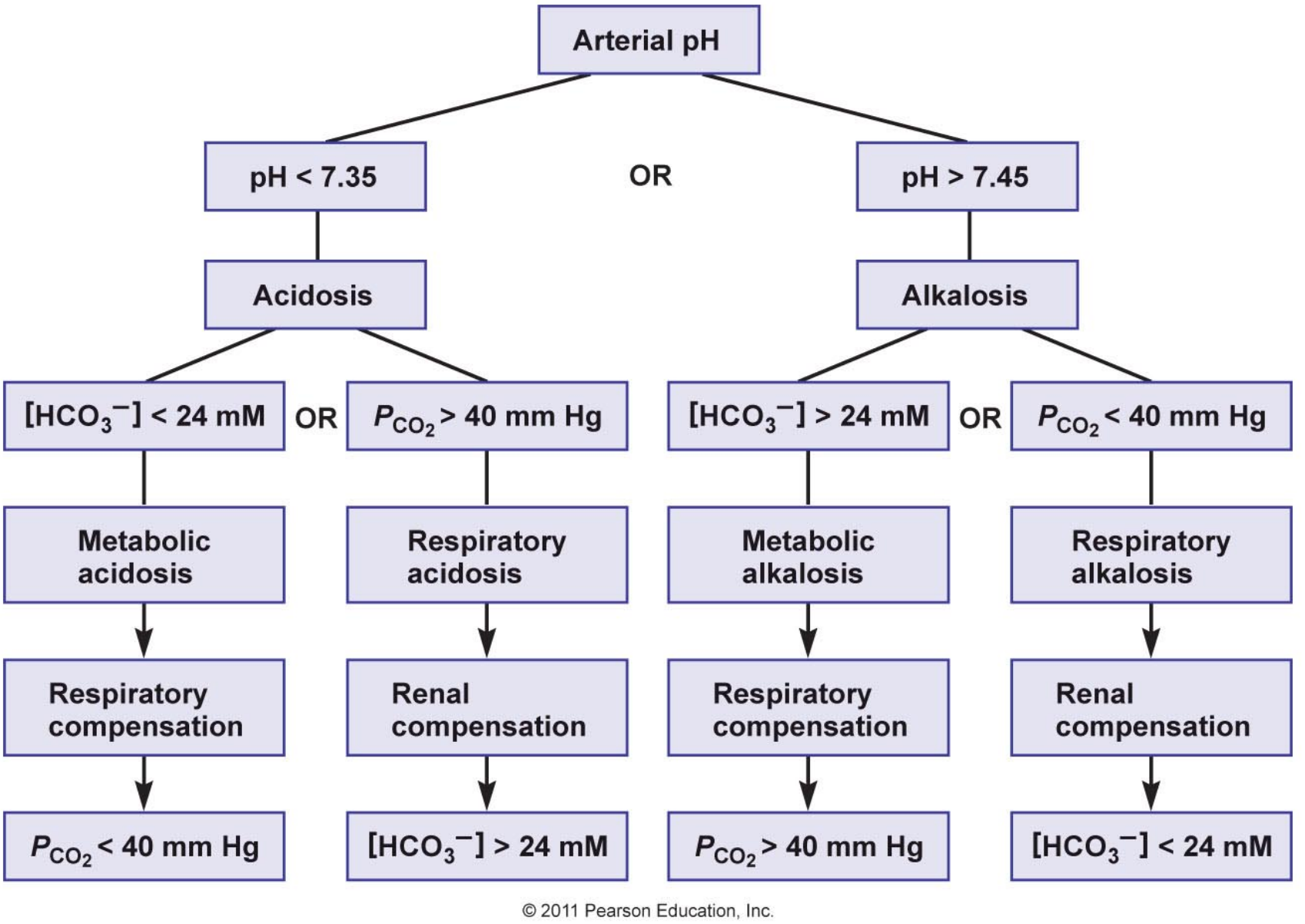
**Hyperventilation** due to fever or anxiety **decreases the $pCO_2$** thus increasing the bicarbonate to $CO_2$ ratio. Again the **kidney** corrects by **reabsorbing less $HCO_3^-$** and **secreting less $H^+$**.

**Metabolic Acidosis**

An **increase in $H^+$** is due to metabolic causes including diarrhea, diabetes mellitus, strenuous exercise, renal failure, etc. Compensation includes an **increase** in **ventilation** and renal compensation by an **increase** in **bicarbonate production** and an increase in the **secretion of $H^+$**.

**Metabolic Alkalosis**

A **decrease in $H^+$** due to vomiting, ingestion of alkaline drugs (sodium bicarbonate or antacids). Compensation involves both the lungs and the kidneys. Compensation includes a **decrease in ventilation** which **increases $pCO_2$** and in the kidneys an **increase** in the **secretion of bicarbonate** ions and a **decrease** in **secretion of $H^+$** .





**Evaluation of Acid-Base Disturbances**

Diagnosis of acid-base disturbances includes measuring:

1. plasma pH
2. $P_{CO2}$
3. plasma bicarbonate

| | |
|---|---|
| Metabolic Acidosis - | decrease in pH |
| | decrease in $[HCO_3^-]$ |
| | decrease in $P_{CO2}$ |
| Respiratory Acidosis - | decrease in pH |
| | increase in $[HCO_3^-]$ |
| | increase in $P_{CO2}$ |
| Metabolic Alkalosis - | increase in pH |
| | increase in $[HCO_3^-]$ |
| | increase in $P_{CO2}$ |
| Respiratory Alkalosis - | increase in pH |
| | decrease in $[HCO_3^-]$ |
| | decrease in $P_{CO2}$ |