Hi freshers! These notes are for the lecture structure introduced in 2012/2013.

I aimed to be helpful when explaining concepts and to be concise rather than painstakingly extensive. They’re not organised by learning objective, but instead written in an order which makes more sense to learn. If there’s a section which seems out of place, it’s because that lecturer mentioned something we’ve already covered but added some more details. I have covered all the lectures in these notes, there are other sources to help with the practicals and other bits like the ‘workshop’. Terms in red are either new or important in resp, and bold is just used for emphasis.

Please email me at tca12@ic.ac.uk if you have any ICE, questions, or spot an error!

I: Introductory lecture(s)

Functions of the respiratory tract
- gas exchange
- metabolism
- self-defence
- self-repair
- vocalisation

A resting adult needs 250 ml O₂.min⁻¹.

Gas exchange
Oxygenating and removing CO₂ from the blood is the most important respiratory system function. For gas exchange to occur successfully, the respiratory tract must
- be open to the atmosphere
- increase the temperature and humidity of air inside it
- deliver air to the alveoli (we inhale enough air to fill a large swimming pool every day)
- have a large gas-permeable surface area (tennis court size)
- have lots of deoxygenated blood close to the gas-permeable surfaces
Metabolism
Specialised epithelial cells can break down many inhaled (exogenous) molecules. The respiratory tract and its capillaries’ endothelium also metabolise various endogenous molecules, including
- local hormones: angiotensin I $\rightarrow$ angiotensin II via ACE
- inflammatory mediators: leukotriene and prostaglandin removal, bradykinin inactivation
- neurotransmitters: noradrenaline and serotonin removal

Self-defence
The respiratory tract is a main portal of entry for pathogens and is vulnerable to many environmental agents, from viruses to pollen to asbestos. Defence is provided by
- mucus and cilia in the upper airways trapping and removing particles
- cells producing mediators in response to foreign organisms
- leukocytes in the pulmonary vasculature (macrophages, neutrophils, lymphocytes)

Self-repair
Complete recovery is possible from some forms of damage like pneumococcal pneumonias. However, the formation of fibrotic scars or degradation of gas exchanging units (emphysema) by cigarette smoke leads to permanent damage and loss of lung function.

Respiratory disease epidemiology
- respiratory disease is the most common reason for GP visits
- the most common chronic paediatric illnesses are respiratory (think asthma)
- one in five deaths in the UK are due to respiratory disease
- one in eight medical admissions is for chronic obstructive pulmonary disease (COPD)
- 5.2 million people in the UK have asthma, and it’s increasing in prevalence

Figure 1.2 Respiratory disease deaths by cause. United Kingdom, 2004
**Possible lung disease symptoms**
- breathlessness (*dyspnoea*)
- coughing, including coughing up blood (*haemoptysis*)
- sputum production
- wheezing, including due to large airway problems (*stridor*)
- hoarseness e.g. due to a tumour obstructing the *recurrent laryngeal nerve*.

**Dyspnoea**
“A sensation of difficult, laboured, or uncomfortable breathing.”

*Physiological causes:*  
- exercise
- pregnancy (even in 1st trimester)

*Pathological causes:*  
- lung disease
- heart disease
- pulmonary vascular disease
- neuromuscular disease e.g. diaphragm weakness / phrenic nerve paralysis
- systemic disorders e.g. anaemia, hyperthyroidism, obesity

*Psychological causes:*  
- stress
- anxiety
- panic attack

It can be classified by the clinical / **MRC dyspnoea grade**:
1. normal
2. able to walk and keep up with people of same age on the level, but not hills/stairs
3. able to walk 1.5 km on the level at own pace, but can’t keep up with people of same age
4. able to walk 100 m on the level
5. breathless at rest / minimal effort

**Measuring lung function**
A common method shown here is a *pneumotachograph*, displaying a *flow-volume loop*.

In this case, the patient inhaled, exhaled, inhaled, and then exhaled as much as they could. *Forced expiratory measurements* are very common.
2: **Pulmonary circulation**

**Bronchial circulation**
A systemic arterial supply of oxygenated blood to the lung tissues, stemming from the aorta and drained via bronchial veins and small bronchopulmonary anastamoses, which are links between the bronchial and pulmonary circulations. It aids tissue viability but is not essential; in lung transplant patients the bronchial circulation is not reconnected. It takes 1% of the cardiac output. Functions:
- helps warm and humidify air
- clears inflammatory mediators and inhaled drugs
- supplies tissue with inflammatory cells and plasma

**Requirements of the pulmonary circulation**
- accommodate the entire cardiac output every cycle
- accommodate increased cardiac output e.g. during exercise
- filter out small emboli e.g. air, blood, fat

Standard pulmonary blood pressure is **25/8** (120/80 systemic)
Standard pulmonary vascular resistance is **2 mmHg/l.min** (18 mmHg/l.min systemic)

**Pulmonary vascular resistance** (PVR) = \( \frac{\text{pulmonary arterial pressure} - \text{pulmonary venous pressure}}{\text{cardiac output}} \)

**Distribution of blood flow**

Thanks to gravity, less blood goes to the top of the lung than the bottom. This means the blood pressure in the bottom of the lung (Zone 3) is greater than that at the top (zone 1), whereas the air pressure is relatively constant. In **Zone 1**, the pressure exerted on the alveolar walls is greater than the blood pressure in the capillaries lining them, and the capillaries are **forced shut**. However, in
Zone 3, there is sufficient blood pressure that the capillaries are kept open. Between them, in Zone 2, the alveolar pressure is between the arterial and venous pressures so the capillaries are open up to a certain point, and then shut.

At rest, much of the lung is unused. This gives us the capacity to oxygenate more blood when necessary e.g. during exercise, blood pressure is raised and therefore more capillaries in the lungs are kept open (recruited), so despite the increased cardiac output the lungs can still oxygenate all the blood. By contrast, the systemic circulation copes with increased cardiac output by allowing more blood through the same vessels via distension. Vessels in the lungs can also distend.

**Regulation of blood flow**

If alveolar oxygen tension falls locally (less $O_2$ reaching some alveoli), there is active vasoconstriction of pulmonary arteries of diameter <1 mm. This diverts blood to better ventilated regions of the lungs, and is called hypoxic pulmonary vasoconstriction (HPV – not just the virus!). The alveolar oxygen sensor is dependent on hypoxia-inducible factor (HIF), which “regulates systemic changes in haematopoeitic, respiratory, and cardiovascular physiology that combine to restore adequate oxygenation.”

An example of when HPV is beneficial is in pneumonia, where blood will be redirected away from ineffective alveoli for better oxygenation elsewhere. HPV is also beneficial in utero: no oxygen is getting to the alveoli, so generalised HPV helps more blood be redirected into the systemic circulation via the ductus arteriosus.

HPV is not beneficial if infection is widespread, or you’re at high altitude.

**Disease states**

Pulmonary oedema, embolus, hypertension, and shunts.

**Pulmonary oedema**

“Fluid infiltration into pulmonary tissue.” Primarily an increase in volume of interstitial fluid, and can also result in alveolar flooding. Its causes are:

- raised pulmonary venous pressure due to mitral stenosis or LV failure
- lowered [plasma protein] due to starvation or abnormal leakage from kidney or gut
- raised capillary permeability due to endothelial cell damage

And its effects:

- impaired gas exchange
- reduced lung compliance due to them being ‘wet’ or ‘stiff’
- increased pulmonary venous pressure

Clinically, a patient with acute pulmonary oedema will be terrified and present with:

- severe breathlessness
- pink frothy sputum
- crackling sounds during auscultation
Pulmonary embolism
A pulmonary embolism can range in severity from never being noticeable to almost instant death depending on the size of the embolus and where it lodges. The most common embolus is a clot formed in the deep veins of the lower legs or pelvis, a condition called deep vein thrombosis.

A smaller PE can become a chronic issue. Gas exchange happens normally at rest but the spare capacity of the lungs might be easily overwhelmed. In a larger one, gas exchange is impaired, right atrial and right ventricular pressures go up, and very occasionally lung infarction can occur. The cases that pulmonary embolisms are infamous for, however, are when a large embolus blocks a very early pulmonary artery. The right ventricle failing causing circulatory collapse leads quickly to death.

A perfusion scan (following injection of radioactive tracer) can demonstrate an embolism well.

Pulmonary hypertension
Any of the following causes can lead to RV failure. Usually, a cardiac defect will cause pulmonary venous hypertension, whereas an arterial defect will cause pulmonary arterial hypertension.

- **left** atrial, valvular, or ventricular disease
- chronic thrombotic and/or embolic disease
- defects in pulmonary arteries e.g. vascular diseases, congenital heart disease, toxins, drugs
- **hypoxia** or other respiratory disorders (called cor pulmonale if RV failure follows)

Pulmonary shunts
The alveoli are perfused with blood as normal but air isn’t reaching it. The most common cause is fluid in the alveoli e.g. due to pulmonary oedema. HPV then reduces the blood flow to that region. Shunting is the main cause of not enough oxygen in the blood (hypoxaemia).

Development
The fetus does not need its lungs until after it is born. The foramen ovale links the left and right atria, and the ductus arteriosus allows blood to pass between the pulmonary artery and aorta. Helped by the fact that the fetal pulmonary arterial pressure is high due to HPV and the systemic pressure is low due to the placenta, 90% of blood from the right ventricle goes into the systemic circulation and 10% to the lungs. The right ventricle’s wall is as thick as the left ventricle’s.

**Note:** It is better to think of the foramen ovale as a valve than a hole. If the pressure is higher in the RA then blood will pass into the LA; it is not as if there is one atrium.

**Note:** A mother taking aspirin or steroids late in pregnancy can stop the ductus arteriosus closing.
3: Lung development

Overview

4-5 weeks gestation: tracheal bud emerges from foregut
16 weeks gestation: bronchial branching finishes, leading to pulmonary artery branching
8-10 years of age: alveolar development finishes

- different lung tissues develop at different rates
- bronchial circulation development occurs independently
- bronchial buds are originally supplied by systemic vessels, which regress as the pulmonary artery takes over
- malformation is influenced more by the timing of an insult than its nature
- prematurity, birth weight, and smoking determine lung function the most through life
- an example of a congenital lung defect is cystic adenomatoid malformation, which leads to disorganised and non-functional lung tissue

Influences on lung development

- homeobox (HOX) genes
- transcription factors e.g. TGF-β stimulates fibroblasts to lay collagen
- peptide growth factors
- thoracic cage volume
- lung liquid pressure causing a trophic effect for growth down and outward into branches
- amniotic fluid volume
- autonomic stimulation of smooth muscle contraction and relaxation around airways to direct development by changing pressures
- maternal nutrition e.g. vitamin A
- and maternal smoking…

Maternal smoking

If the baby’s mother smokes while pregnant, it causes noticeably reduced lung function from birth. The airways’ radius is reduced, there are fewer alveolar attachments, and increased lymphocyte proliferation causing more inflammation in response to even the commonest allergens like house dust mites. This puts the baby at a higher risk of asthma and COPD later in life, as well as a 4x higher risk of wheezing as an infant.

Squeezing a normal baby’s chest results in increased inspiration and expiration, but in a baby whose mother smoked, there is no increase upon squeezing: their lungs are already doing as much mechanically as possible.

Birth events

Immediately:
- massive CNS stimulation
- low pressure placental circulation cut; causes a rise in systemic pressure
- lung aeration causes vasodilation: pulm. artery pressure falls, pO₂ rises, pCO₂ falls
The first day:
- blood flow to the lungs increases 5x
- chemoreceptors and respiratory centres ‘reset’
- lung volume rises to optimum and airway resistance falls (first 2 hours)
- lung compliance rises (but takes at least 24 hours)

There may be problems with the commencement of breathing. For example, the first gasp may fail (primary apnoea). The baby will be blue, as the circulation is fine but oxygenation is not occurring. Primary apnoea generally occurs if the baby was strangled by the umbilical cord. If the baby ever comes out feet-first, then this is very likely.
If the failure to commence breathing continues, blood pressure will fall and the baby will go pale. This is known as terminal apnoea and death will almost always follow.

<table>
<thead>
<tr>
<th>Table 15.4 Apgar score</th>
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<tbody>
<tr>
<td>Clinical feature</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0</td>
</tr>
<tr>
<td>Absent</td>
<td>Gasiing or irregular</td>
</tr>
<tr>
<td>Respiration</td>
<td>Diminished, or normal with no movements</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Limp</td>
</tr>
<tr>
<td>Response to pharyngeal catheter</td>
<td>Nil</td>
</tr>
<tr>
<td>Colour of trunk</td>
<td>White</td>
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</tbody>
</table>

The Apgar score is used to determine severity of apnoea and need for resuscitation:

What can go wrong?
Surfactant lining the alveolar walls is essential for reducing the surface tension of the fluid on the alveoli, which stops them collapsing every time you breathe out. Hormonal stimulation is required for surfactant release from lamellar bodies in the epithelium. Deficient surfactant causes the following cycle, which describes Infant Respiratory Distress Syndrome (IRDS):
- alveolar collapse
- alveolar hypoventilation
- hypoxia and acidosis
- pulmonary vasoconstriction (HPV)
- shunting
- even less surfactant stimulation…

The baby is treated with oxygen, continuous positive airway pressure (CPAP) to help reinflate the alveoli, intravenous fluids for stability, and surfactant via the breathing tube. IRDS often occurs after a premature birth or an elective caesarian section, as they can result in stimulation not occurring.

The cilia lining the airways can also be dysfunctional. In primary ciliary diskinesia (Kartagener’s syndrome), the ciliary motor protein dynein is missing so they can’t beat. Organ development in utero is dependent on microtubule function which is adversely affected by PCD, so patients often have right lower lobe collapse, dextrocardia (i.e. the heart is on the right), and sometimes even total situs inversus (all organs mirrored). Note: PCD patients have very low nasal nitric oxide levels.
4: Ventilation and gas exchange

Volumes and capacities
Two or more volumes make a capacity. This is an essential diagram to know off by heart.

- **Tidal volume** (TV or $V_T$): volume of air inspired during quiet respiration i.e. at rest
  - $V_T$ is determined by when adequate resting oxygenation and CO$_2$ removal occurs
- **Residual volume** (RV): the volume of air in the lungs which **cannot be expired**
  - can increase due to air trapping and alters lung mechanics
- **Inspiratory reserve volume** (IRV): volume between tidal volume and maximal inspiration
  - necessary to be able to cough or exercise
- **Expiratory reserve volume** (ERV): volume between tidal volume and residual volume
- **Functional residual capacity** (FRC): volume after ‘quiet’ expiration; $FRC = ERV + RV$
  - the lung is at its most compliant at FRC, which is after tidal expiration
- **Vital capacity** (VC): volume between maximal inspiration and maximal expiration
  - critical value of 1 litre identifies if patient can/not maintain spontaneous ventilation
- **Total lung capacity** (TLC): vital capacity added to residual volume; $TLC = VC + RV$

- **Minute ventilation** ($V_e$): volume entering lungs per unit time; $12 \text{ min}^{-1} \times 0.5 \text{ l} = 6 \text{ l.min}^{-1}$

Lung volumes are affected by
- gender
- age
- body size
- muscle training
- disease
Dead space and alveolar ventilation

There are two types of physiological dead space; anatomical and alveolar dead space.

About 150 ml of every 500 ml tidal breath does not reach alveoli; it occupies the space between the mouth/nose and the terminal bronchioles. This is known as the anatomical dead space, or the conducting zone. Note that in an intubated patient, external tubes increase anatomical dead space and need to be compensated for.

The alveolar dead space is the volume of air in the alveoli which is unable to participate in gas exchange due to insufficient blood supply. In healthy people it should be next to nothing. It is affected by pulmonary emboli and ventilation of non-vascular air spaces like bullae.

Physiological dead space is the sum of the parts of tidal volume which don’t take part in gas exchange, so, anatomical plus alveolar dead space. It’s influenced by

- age
- gender
- body size
- posture
- mechanical ventilation
- disease (increases it)
- holding your breath (decreases it)

Tidal volume – anatomical dead space = alveolar ventilation (AV)

Hypoventilation is inadequate alveolar ventilation; the CO₂ production to AV ratio is too high. The increase in $p_aCO_2$ and $p_aCO_2$ lowers blood pH leading to respiratory acidosis. Its causes include

- Generalised: - pain
  - reduced consciousness
  - reduced respiratory drive
- Scattered: - COPD
  - asthma
- Localised: - infection
  - sputum plug
  - lung collapse (atelectasis)

Hyperventilation is excess alveolar ventilation; the CO₂ production to AV ratio is too low. The decrease in $p_aCO_2$ and $p_aCO_2$ raises blood pH leading to respiratory alkalosis. Its causes include

- anxiety / fear
- metabolic disease
- airway obstruction
- parenchymal lung disease
Spirometry
It’s a simple, cheap way of measuring lung volume that is dependent on the effort the patient puts in. It’s used for diagnosing respiratory disease, and monitoring the progression and drug efficiency. The measurements taken are forced vital capacity (FVC), and then FEV$_1$ (maximum volume of air that can be forced out in 1 s) and FEV$_1$% (percentage of FVC expired in 1 s) are calculated from it.

Residual volume and functional residual capacity can not be measured with a simple spirometer because the RV cannot be expired. They can instead be measured by gas dilution, where
- a spirometer is filled with a known concentration of an inert gas not found in air
- the patient breathes in and out through the spirometer so the gas mixes in their lungs
- the concentration difference in the inspired vs expired gas is measured
- RV can be calculated using the dilution effect of the air already in the lungs on the gas

Classification of respiratory disease
Obstructive lung disease causes an increase in resistance. The pressure-volume relationship is normal during normal breathing, but when breathing rapidly greater pressure is needed because of the greater resistance. The extra effort can cause an overdistension of the lungs. TLC, FRC, and RV increase.
Obstructive diseases include asthma, bronchitis, emphysema, cystic fibrosis, and COPD.

Restrictive lung disease makes the lungs stiffer and limits expansion. A greater-than-normal pressure is required for the same increase in volume. TLC, FRC, and RV decrease.
Restrictive diseases include lung fibrosis, pneumonia, pulmonary oedema, and paralysis.

Fick’s Law
Rate of transfer of gas through tissue is proportional to
- surface area
- partial pressure difference
- diffusion constant
... and inversely proportional to thickness. The alveolar walls are 0.5-1 µm thick (2000x thinner than skin), but thickening can be caused by infection, inflammation, or fibrosis.

Following the above, diffusion also depends on
- gas solubility
- ventilation-perfusion coupling

Oxygen transit time
A red blood cell spends 0.75 s in the pulmonary capillaries, yet it only takes about 0.25 s for O$_2$ equilibration to occur at normal partial pressures. This spare time is a safety margin helping all blood to still be oxygenated during exercise. However, in pathological cases where the alveolar membrane is thickened then 0.75 s may not be enough and hypoxia can result.
Gas solubility
O₂ and CO₂ are both soluble, and equal amounts diffuse across the alveolar membrane in the same amount of time. CO₂ is 20x more soluble than O₂ but the CO₂ gradient is smaller. Because O₂ is less soluble, respiratory disease will affect oxygen diffusion well before it affects CO₂ transport.

Surface area
An adult lung has around 300 million alveoli, giving an exchange surface of 70-80m². Permanent loss of surface area can be caused by emphysema breaking down the walls of alveoli.

Ventilation-perfusion coupling
This is a central concept to respiratory medicine, matching the amount of air reaching the lungs (V) to the amount of blood reaching the lungs (Q). V/Q mismatch occurs when either is lacking, for example in pulmonary embolism (lack of perfusion) or an asthma attack (lack of ventilation).

Extra note: Fetal blood

<table>
<thead>
<tr>
<th>Blood</th>
<th>Fetal</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.2</td>
<td>7.4</td>
</tr>
<tr>
<td>pO₂</td>
<td>3-4 kPa</td>
<td>10 kPa</td>
</tr>
<tr>
<td>pCO₂</td>
<td>7-8 kPa</td>
<td>6-7 kPa</td>
</tr>
</tbody>
</table>

Note: A fetus can cope with reduced pO₂ as fetal haemoglobin has a higher affinity for oxygen (than normal haemoglobin): it carries enough O₂ for the fetus despite the lower partial pressure. On a graph of saturation against partial pressure, the sigmoidal curve for fetal Hb is further left. This is known as the Bohr shift.
5+6: Lung Mechanics

Note: 1 kPa = 10 cm.H₂O

Lung elasticity

**Compliance**: the ability of the lungs to stretch.

Lung compliance \( (C_L) = \frac{\text{change in volume}}{\text{change in pressure}} \)

Compliance is the gradient of the P/V curve.

**Pleural pressure** \( (P_{pl}) \) is the tendency for the lungs to pull away from the chest wall. The lung is kept very close to the chest wall by osmotic processes, so the elastic recoil of the lung pulling on the pleural space creates suction. That’s why the pressure is negative.

Due to gravity, the lung squashes the pleural space a bit at the bottom and pulls away at the top, so \( P_{pl} \) is more negative in apical regions than basal regions.

\( P_{pl} \) can be measured directly or indirectly:
- directly by a needle, which risks causing pneumothorax
- indirectly by a balloon in the oesophagus (mid 1/3), as it’s between the lung and chest wall

**Ventilation**

Less pressure is required to inflate a fluid-filled lung because the air-liquid interface is removed and so surface tension is too.

The graph shows that for an air-filled lung the volume is greater during deflation than inflation (hysteresis).

**Full inflation** is at about 30 cm.H₂O in all mammals (ignore graph on this).

**Upper part of P/V curve**

**Normal**

**Emphysema** (top) / **Fibrosis** (bottom)

In emphysema, elastic recoil is lost so there is less force opposing stretch: higher compliance. Fibrosis is the opposite. More connective tissue means more elastic recoil: lower compliance.
**Distribution of ventilation**
In inspiration, the diaphragm causes a uniform decrease in pressure throughout the lungs. Despite the change being uniform, the basal parts of the lung expand more than the apical parts because they were under more pressure to begin with due to gravity (and gravity acting on blood). In some diseases, this distribution can be inverted. On exercise, ventilation increases everywhere and the expansion is more even throughout the lung.

**Interdependence of lung units**
Local variations have knock-on effects, mainly related to the alveoli surrounding the problem. Alveolar interdependence means if one alveolus is stiffer, the surrounding ones overexpand and vice versa, so if one alveolus is more distensible, the surrounding ones won’t expand as much. There is also airway and vascular interdependence, because airways and vessels are held open by surrounding alveoli, so if the airway is less stiff it will be overdistended.

This is a very relevant concept in diseases like emphysema because mechanical stress on one area transfers to adjacent ones, which can cause or help the spread of problems. However, the mutual support that alveoli provide each other with also helps stabilise the lung against collapse.

There are limits to how much tissue can strain, and lung tissue is particularly weak to shear forces. Any physical wave (like an impact e.g. in a car accident) will cause shearing damage to lung tissue.

**Airway closure**
As lung volume decreases, all airway diameters decrease, making the relationship between the surfactant lining (surface tension) and airway diameter change.

When diameter decreases to a critical level, radial tension overcomes surface tension, pulling the liquid lining shut. Closure happens at positive airway pressures, thus avoiding atelectasis (lung collapse).

Basal parts of the lungs are the first to close during expiration, and the last to reopen on inspiration.

**Work of breathing**
Normally, respiratory muscle work is about 5% of total metabolism. Lung disease can raise this due to gas transfer problems or mechanical problems.

\[
\text{Work} = \int P \Delta V = \text{integral of (pressure x change in volume)}
\]
Normal tidal breaths are the most efficient pattern for ventilating. If we double the frequency and halve the tidal volume (or the opposite), all that increases is the work needed.

As breathing demand increases (i.e. exercise), we take some steps.
- **first**, raise frequency by eliminating the breath hold time we have at rest
- **then**, raise tidal volume if necessary by ‘breathing deeper’
- if the exercise is sustained we can then further increase both frequency and tidal volume

Note: Don’t forget that we also switch from nasal to mouth breathing on exercise, but that’s not technically lung mechanics so the lecturer didn’t mention it here. He was an engineer, after all.

**Flow in straight tubes**

**Laminar flow** (also known as Poiseuille flow) describes the regular flow of fluid (liquid or gas) through a straight tube like an airway. If all the fluid enters at a constant velocity, it takes some time to become true laminar flow as the fluid in the centre accelerates relative to the outsides.
Airway resistance
Resistance \((R) = \frac{\text{pressure drop} (\Delta P)}{\text{flow rate} (\dot{V})}\)

The nose has very complex airflow patterns. Flow is usually steady, slow, and alternates between sides (usually you’re only breathing through one nostril). An exception is sniffing. In contrast, the mouth has a much larger diameter and lower resistance. The resistance in the mouth is also much less dependent on the flow rate (hence nasal \(R\) varies more). The larynx (vocal cords) creates a lot of resistance to flow. Usually, the lungs’ resistance is less than half of the total resistance, but during forced expiration the lungs’ resistance becomes very high.

\[
\text{Nose } R = \sim 1.4 \text{ cm.H}_2\text{O.l}^{-1}\text{s}^{-1} \\
\text{Mouth } R = \sim 0.25 \text{ cm.H}_2\text{O.l}^{-1}\text{s}^{-1}
\]

The resistance of each airway ‘generation’ is related to both radius and the number of branches.

A higher lung volume means greater airway radii so much lower airway resistance at TLC than RV.

Pressure drop \((\Delta P) = \Delta P_{\text{friction}} + \Delta P_{\text{convective acceleration}}\)

The point of the pressure drop is that it overcomes friction and accelerates or decelerates the air. \(\Delta P_{\text{conv. acc.}}\) is negative on inspiration (slowing air down), positive on expiration (speeding air up).

Note: Convective acceleration is more complicated because of the complex flows in the bronchi as they branch, this simple explanation is as if the respiratory tract was a trumpet shape.

Collateral ventilation
Alveoli can ventilate ‘parasitically’ if the primary airway is blocked, both from neighbouring alveoli via pores of Kohn and from small airways via channels of Lambert.

Mixing by diffusion
New and residual air mixes during inhalation: inhaled air does not enter in a ‘plug’.

Flow in collapsible tubes
Relevant examples:
- blood flow in veins
- Korotkoff sounds: measuring BP with a stethoscope and sphygmanometer cuff
- peeing
- blood flow in pulmonary capillaries (see page 4/5 to revise this example)

The three pressures to consider are the external, upstream and downstream. Tube possibilities are:
\[
\begin{align*}
P_{\text{ex}} &> P_u > P_d : \text{tube collapses; no flow} \\
P_u &> P_{\text{ex}} > P_d : \text{tube flutters; intermittent flow} \\
P_u &> P_d > P_{\text{ex}} : \text{tube open; normal flow}
\end{align*}
\]

Applying it to forced expiration
Involves interactions between
- characteristics of flow in airways
- elasticity of parenchyma
- elasticity of airways
Some diseases can be detected by looking at peak flow rate. This is the **maximum expiratory flow / volume** curve (MEFV curve). A peak flow rate of about 10-12 l.s\(^{-1}\) is normal. Peak flow depends on:

- chest wall / respiratory muscle strength
- airway resistance

It’s impossible to exceed the limiting envelope (~85% of VC). Most people’s FEV\(_1\) constitutes ~75% of their vital capacity.

**Mead model**

With the mouth **closed**, lung volume is fixed. \(P_{\text{alv}} = P_{\text{el}} + P_{\text{pl}}\) (elastic recoil + pleural pressure), and because there’s no net flow, \(P_{\text{alv}} = P_{\text{int}}\) too: air pressure is constant throughout the lungs. There is a ‘positive net outward pressure’ in the alveoli and airways.

With the mouth **open**, flow occurs and \(P_{\text{int}}\) falls towards the mouth. There will be a point along the airway where \(P_{\text{int}} = P_{\text{pl}}\). Further towards the mouth there’s a ‘negative net inward pressure’.

The Mead Model can explain the shape of the MEFV curve because the **maximum** peak flow rate is effort independent (though achieving your max does require effort): all that matters is \(P_{\text{el}}\). As lung volume falls, so does the amount of elastic recoil, which is why the limiting envelope exists: elasticity can only do so much.

**Airway distensibility**

You can calculate this with the formula \(D = \frac{1}{A} \times \frac{\Delta A}{\Delta P}\) where A is airway cross-sectional area.

So, the wider an airway the less distensible it is, and distensibility is also (unsurprisingly) related to how easily stretched the airway is, or change in cross per unit pressure (\(\Delta A/\Delta P\)).

**Note:** The overall learning objective for lung mechanics was just to “appreciate”. Bear that in mind!
7: Lung cell biology

Epithelium
- continuous barrier isolating body from external environment
- metabolises foreign and self compounds
- produces secretions, like surfactant and mucus, and mediators, like interleukins
- triggers repair
- clears airways via the mucociliary escalator

Goblet cells
- normally make up 20% of epithelial cells, though smokers have at least double the number
- synthesise and secrete mucus, which is more viscous in smokers and there’s more of it

Mucus
Mucus is made up of a thin ‘sol’ phase overlying the cells and a thicker gel phase on top. It contains
from goblet cells - mucin proteins, proteoglycans, glycosaminoglycans: provide viscoelasticity
from serum - albumin, alpha 1-antitrypsin: inhibit microbe and phagocyte proteases
from Clara cells - secretory leucoprotease inhibitor: “ “ “
from blood or cells - uric and ascorbic acid (blood), glutathione (cells): antioxidant against ozone, cigarette smoke, and oxidants released by activated phagocytes

Smokers’ mucus is more viscous and cilia can’t shift it very well, so infections can occur more easily.

Ciliated cells
- normally make up 80% of epithelial cells
- there are ~200 cilia per ciliated cell
- the cilia beat metasynchronously / in a metachromal rhythm like a field of corn in the wind
- the apices of cilia have ‘hooks’ in the sol phase of the mucus
- smoking causes a depletion of cilia but also causes ciliated cells to exist in bronchioles

Clara cells
- present in most airways, but more are towards the alveoli
- major role in breaking down foreign compounds (xenobiotic metabolism)
- make and release lysosyme and antiproteinases
- contain phase I and phase II enzymes

Phase I enzymes convert foreign compounds into a form that phase II enzymes can neutralise. Unfortunately, phase I enzymes (e.g. CYPIA1, a cytochrome P450 oxidase) can convert a precarcinogen like benzopyrene (BP) to the active carcinogen benzopyrene diol epoxide (BPDE).

Phase II enzymes (e.g. glutathione S-transferase) add a small molecule to BPDE which stops it being able to do anything. Some people don’t have this enzyme (they’re ‘null’ for it). If they also have a polymorphism of the CYPIA1 gene that causes high levels, their risk of lung cancer is 40x higher.
Type II pneumocytes
- found in the corners of alveoli
- produce phospholipid-rich **surfactant** which is stored in **lamellar bodies** before release
- produce antiproteinases
- precursors to type I pneumocytes, the cells which make up 95% of the alveolar surface

Fibroblasts
- found behind the epithelium
- produce extracellular matrix e.g. collagen, elastin

Normally, injury will cause some pneumocytes to die. Type II pneumocytes will then proliferate and differentiate into type I pneumocytes and fibroblasts, which also induces extra collagen deposition (fibrosis). Cigarette smoke blocks differentiation and so causes more cells to apoptose or necrose.

Alveolar macrophages
- recruit other immune cells like neutrophils via cytokines (e.g. IL-8)
- produce oxidants, antioxidants, and proteases (e.g. matrix metalloproteinase 9 (MMP9) which degrades alpha 1-antitrypsin and the extracellular matrix)
- contain phase I and II enzymes, like Clara cells and type II pneumocytes
- trigger growth and repair by fibroblasts and type II pneumocytes

Neutrophils
- similar function to macrophages
- produce proteases like **neutrophil elastase** (NE), which activates MMP9 as well as degrading the extracellular matrix

In non-smokers, the **macrophage : neutrophil ratio** in the large airways is 7:3, and in alveoli 9:1. In smokers, the ratio in the large airways is 3:7, and in alveoli neutrophil proportion goes up to 7:3.

**Cross-sectional area**
8: Structure

Note: This lecture is mostly diagrams, which can be found here: https://education.med.imperial.ac.uk/Years/1-1213/LSS/resp/index.htm

Upper airways
Larynx, pharynx (divided into laryngopharynx and nasopharynx), and two nasal cavities.

The nasal cavities are nearly triangular in cross-section. The medial and inferior walls are smooth, but the lateral wall’s epithelium covers three ‘scroll-like’ bony plates (conchae). Conchae warm and humidify air going in and retrieve moisture and heat as it passes out. Nasal hairs and mucus can trap anything from dust and pollutants to insects.

We use open-mouth breathing for exercise because the resistance to airflow in the nose is high.

Sinuses
The nasal cavities' lateral walls each connect to a frontal and sphenoid sinus (4 paranasal sinuses). Functions of these pockets of air may include
- weight reduction
- “crumple zone”
- vocal resonators
- temperature insulation

Lower airways
Trachea, bronchi (visible, cartilagenous), and bronchioles (microscopic, non-cartilagenous).
9: Breathlessness and breathing control (awake)

Control of breathing

Comes from two locations in the CNS:
- involuntary / metabolic centre in the medulla. Responds to CO₂ production/demand.
- voluntary / behavioural centre in the motor cortex. Controls breath holding, singing…

Metabolic control from the medulla comes from a response to pH changes in the extracellular fluid, but there is also a chemoreceptor in the neck, the carotid body (see diagram) which detects changes in p₅CO₂ (via pH) and p₅O₂. The carotid body works rapidly because it’s hyperperfused, whereas the ECF pH detector in the medulla is slower. Thus, fast and slow responses exist.

Another peripheral chemoreceptor is at the aortic arch.

p₅CO₂ and pH are more tightly controlled than p₅O₂. Oxygen saturation (SaO₂) is defended rather than p₅O₂. A fall in ventilation causes a rise in p₅CO₂ and fall in p₅O₂, the latter of which increases the sensitivity of the carotid body. Ventilation is increased so p₅O₂ rises and p₅CO₂ falls. Negative feedback!

If p₅O₂ and p₅CO₂ both fall, it’s because pO₂ of inspired air has fallen, not ventilation e.g. at altitude.

The metabolic centre is also affected by sleep, emotions, pain or surprise, and survival instincts via the limbic system such as suffocation, hunger, or thirst. It will always override the behavioural.

Control is coordinated in the medulla via “group pacemaker” activity from about 10 groups of neurons. One group, the pre-Botzinger complex, is necessary for generating the rhythm and is called the “gasping centre”. Converting gasping into regular rhythm is helped by other complexes.

Some groups of neurons discharge at different points in the respiratory cycle with different effects e.g. initiating inspiratory flow via respiratory muscles, or “braking” passive expiration by narrowing the larynx and pharynx.

Tidal breaths in health and disease

Obstructive (e.g. bronchitis/emphysema) and restrictive (e.g. fibrosis) disease both reduce tidal volume:
Note: Blood $[H^+]$ (and so pH) is proportional to $p_aCO_2 / HCO_3^-$. 
$[H^+]$ is also determined by the strong ion difference, $[Na^+ + H^+] - [Cl^-]$.

**Respiratory acidosis**

**Acute:**
- hypoventilation causes a fall in $p_aO_2$ and rise in $p_aCO_2$, so a lower pH
- metabolic centre is stimulated to increase ventilation and restore levels

**Chronic:**
- ventilatory compensation inadequate for maintenance of $p_aCO_2$ levels
- renal system compensates by excreting weak acids to maintain pH despite high $p_aCO_2$.

**Metabolic acidosis and alkalosis**

**Acidosis**, or excess production of $H^+$, is compensated for by
- increased ventilation
- renal excretion of weak acids
- renal retention of $Cl^-$ to reduce strong ion difference

**Alkalosis**, or reduced $[H^+]$ which can be due to excess $HCO_3^-$, is compensated for by
- decreased ventilation
- renal retention of weak acids
- renal excretion of $Cl^-$ to increase strong ion difference

**Conditions causing changes in ventilation**

**Hypoventilation** can be caused by

**Acute:**
- muscle relaxant drugs
- myasthenia gravis

**Chronic:**
- respiratory muscle weakness
- COPD

**Hyperventilation** can be caused by
- excess $H^+$ from metabolic problems
- hypoxaemia
- pulmonary vascular disease
- anxiety

**Breathlessness (also see page 3)**

Breathlessness can mean different things e.g. ‘breathless with excitement’, meaning suspended breathing due to an emotional cause, or ‘out of breath’ due to a comfort threshold being exceeded.

Dyspnoea appears in three forms:
- a feeling of **tightness**: chest not expanding well, or difficulty inspiring e.g. asthma attack
- **increased effort**: high minute ventilation or lung volume, or breathing against resistance
- **air hunger**: feeling a powerful urge to breathe (more); there is a mismatch between the minute ventilation demanded by the metabolic centre and the achieved minute ventilation
The **Borg scale** is used to ‘measure’ the **sensation** of breathlessness, unlike the MRC grade which measures capability. The patient is asked to rate their discomfort on this scale:

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>maximum</td>
</tr>
<tr>
<td>9</td>
<td>very very severe</td>
</tr>
<tr>
<td>8</td>
<td>very severe</td>
</tr>
<tr>
<td>7</td>
<td>severe</td>
</tr>
<tr>
<td>6</td>
<td>somewhat severe</td>
</tr>
<tr>
<td>3</td>
<td>moderate</td>
</tr>
<tr>
<td>2</td>
<td>slight</td>
</tr>
<tr>
<td>1</td>
<td>very slight</td>
</tr>
<tr>
<td>0</td>
<td>none</td>
</tr>
</tbody>
</table>

**Breath holding**

The time you can hold your breath for is a test of the strength of your behavioural controller versus your metabolic controller. The ‘break point’, where you give in and breathe, is an expression of **air hunger**.

Breath holding time can be increased by increasing lung volume or lowering $\text{p}_2\text{CO}_2$. Paralysing the thoracic muscles does **not** increase breath holding time.
10: Airway structure and function

Note: A lot of this lecture’s content was about topics covered elsewhere, so I’ve integrated it in.

Basic functions
To conduct O\textsubscript{2} in and CO\textsubscript{2} out. This is made possible by
- mechanical stability, thanks to cartilage
- calibre control, thanks to smooth muscle
- protection and cleansing, thanks to the mucociliary escalator and immune system

Airway submucosal glands
- mucous cells secrete mucus
- serous cells secrete antibacterials e.g. lysozyme
- glands also secrete water and salts e.g. Na\textsuperscript{+}, Cl\textsuperscript{-}

Cilia
In transverse section…

Control of airways

Nervous:
- parasympathetic (cholinergic)
- possibly sympathetic (adrenergic)
- sensory

Mediators:
- histamine
- prostaglandins and leukotrienes (both metabolites of arachidonic acid)
- cytokines e.g. GM-CSF \textit{(granulocyte macrophage colony-stimulating factor)}
- chemokines e.g. IL-8
- reactive gas molecules e.g. NO

Proteases:
- neutrophil elastase
- matrix metalloproteinase 9

Disease
Disruption of the control mechanisms is involved in asthma, COPD, and cystic fibrosis. The definition of \textit{asthma} is ‘a clinical syndrome characterised by \textit{increased airway responsiveness} to a variety of stimuli’. It leads to \textit{airway obstruction}.
II: Lung cancer

Epidemiology
- 3rd most common cause of death in UK
- kills over 40,000 per year in UK
- lung cancer causes 25% of all cancer deaths
- 80% of patients die within a year of diagnosis, and only 5.5% live 5 years after diagnosis
- causes of lung cancer are tobacco, asbestos, and radon.

Clinical features
The following suggest urgent referral for a chest x-ray, if unexplained or persistent (>3 weeks)
- cough
- chest / shoulder pain
- dyspnoea
- hoarseness
- finger clubbing (see diagram)
- abnormal chest signs on examination
- haemoptysis (not just if unexplained or persistent)

Choice of treatment is based on three factors:
- type of cell that has become cancerous
- stage of the tumour
- performance status of the patient

Histological cell type
The main distinction is between small cell lung cancer and non-small cell lung cancer, the latter comprising a variety of types including squamous cell or large cell carcinoma and adenocarcinoma.

<table>
<thead>
<tr>
<th>Cell Types</th>
<th>Volume Doubling Time (days)</th>
<th>Earliest Diagnosis (1 cm)</th>
<th>Usual Diagnosis (3 cm)</th>
<th>Death (10 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>88</td>
<td>7.2</td>
<td>8.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>161</td>
<td>13.2</td>
<td>15.4</td>
<td>17.6</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>86</td>
<td>7.1</td>
<td>8.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Small Cell</td>
<td>29</td>
<td>2.4</td>
<td>2.8</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Note: as shown above, small cell lung cancer kills much quicker than any other type.
Pathogenesis

The multi-step theory of tumour development is that cancer arises due to accumulation of genetic mutations which regulate cell proliferation, invasion, angiogenesis and senescence.

Precursor lesions to some types (but not small cell lung cancer, notably) have been recognised:
- squamous metaplasia, dysplasia, then carcinoma in situ precede squamous cell carcinoma
- atypical adenomatous hyperplasia precedes adenocarcinoma

Staging

All patients should have cross-sectional imaging done via a CT scan of the thorax, liver, and adrenals. Some may require a PET scan or bone scan. Staging is done with the TNM classification:

Primary tumour (T)

- **TX** can’t be assessed
- **T0** no evidence
- **Tis** tumour in situ
- **T1** <3 cm + surrounded by lung or pleura + no bronchoscopic evidence of invasion into a main bronchus
- **T2** >3 cm or involves main bronchus >2 cm from carina (tracheal bifurcation) or invades visceral pleura or collapse / inflammation affecting part of the lung
- **T3** invades chest wall or diaphragm or mediastinal pleura or parietal pericardium or main bronchus <2 cm from carina or collapse / inflammation affecting the entire lung
- **T4** malignant pleural effusion or invades mediastinum or heart or great vessels or trachea or oesophagus or carina or vertebral body

Lymph node (N)

- **NX** can’t be assessed
- **N0** no regional lymph node metastasis
- **N1** metastasis in ipsilateral peribronchial / hilar node
- **N2** metastasis in ipsilateral mediastinal / subcarinal node
- **N3** metastasis in contralateral mediastinal / hilar, ipsilateral / contralateral scalene, or supraclavicular node

Distant metastasis (M)

- **MX** can’t be assessed
- **M0** no distant metastasis
- **M1a** metastasis within lung
- **M1b** metastasis outside lung
12: Breathing control (asleep)

Sleep affects blood gases
Because your behavioural centre (in the motor cortex) and limbic system (in the frontal lobe) aren’t active during sleep, the only thing controlling breathing is the brainstem’s metabolic centre.

When you’re asleep, your breathing rate, tidal volume, and ventilation all fall, causing O₂ saturation to fall as well (only 1-2%). The fall in tidal volume causes pₐCO₂ to rise (hypercapnia), and that raised pₐCO₂ is what continues to stimulate breathing. The hypercapnic apneic threshold is the minimum pₐCO₂ necessary for breathing during sleep. If pₐCO₂ falls below it due to reflexes failing or being too slow, it can result in the subject ceasing to breathe (central sleep apnoea). This is one cause of ‘cot death’ or SIDS (sudden infant death syndrome).

Sleep affects respiratory muscles
Sleeping increases upper airway resistance, especially in the pharynx, due to muscle relaxation and the pull of gravity when lying down. In some people, notably the obese, their necks can actually crush the pharynx or trachea, causing obstructive sleep apnoea. This is different from the central kind in that, whilst airflow is stopped in both cases, in central sleep apnoea the patient stops trying to breathe whereas in obstructive sleep apnoea they’re trying but can’t. The fall in pₐO₂ and rise in pₐCO₂ causes the person to wake up so they can resume breathing.

The tongue and uvula being enlarged, or the jaw being further back, can increase the likelihood.

Other diseases affected by sleep apnoea
COPD patients already have a reduced SaO₂, which decreases further during sleep. The main problem, however, is that they retain additional CO₂ due to their reduced ventilation, and when combined with sleep apnoea this can cause respiratory failure more easily.

Half of heart failure patients hyperventilate because they have pulmonary congestion (blood backed up in the pulmonary circulation). Hyperventilation can cause pₐCO₂ to fall below the hypercapnic apneic threshold at night, resulting in central sleep apnoea.
**13: Sensory aspects of respiratory disease**

**Cough**
A defense mechanism protecting the lungs from *inhaled material* and *excess mucus*. A high velocity airflow is created by doubling the airway pressure. This happens as the *trachealis muscle* at the back of the trachea contracts and invaginates into the lumen, reducing the space and thus increasing the pressure.

Coughing is controlled by the ‘cough centre’ in the medulla of the brainstem, linked to the respiratory centre there. Neurone terminals in the upper airways might act as ‘cough receptors’, responding to mechanical (like inhaling food) or chemical stimuli (like inhaling tobacco smoke).

Causes of cough are in some way *irritant*, and include
- any respiratory disease
- foreign bodies e.g. crumbs
- cardiovascular diseases e.g. LV failure, pulmonary embolism, aortic aneurysm
- acid reflux
- post-nasal drip
- ACE inhibitors

Coughing can actually result in loads of complications:
- pneumothorax
- fainting (cough syncope) if the intrapulmonary pressure raise cuts off venous return
- headache
- cardiac dysrhythmia
- wound *dehiscence* (coming unstuck)
- urinary incontinence
- social embarrassment and depression!

Ideally we’d treat the underlying cause of a cough (e.g. asthma with a corticosteroid inhaler) but drugs to combat coughing itself (*antitussives*) exist. They can be narcotic, like codeine or morphine, or non-narcotic like *levopropoxyphene* or *dextromethorphan*, a synthetic derivative of morphine.

**Chest pain**
There are different types of pain, and not just in the sense of sharp or dull, acute or chronic, but also somatic or *visceral pain*. Somatic pain is felt at the surface, like a mosquito bite or a punch. Visceral pain comes from the internal organs, be it the heart, kidneys, or appendix, and it’s felt as a *diffuse* pain which is *difficult to localise* and is often *referred* to somatic structures, for example irritation of the diaphragm being felt in the shoulder. The viscera are far less well innervated than the skin with afferent fibres, and visceral pain from different organs can often manifest similarly in terms of referral location and quality, making diagnosis difficult.

*Note:* The dyspnoea part of the lecture is all stuff we already covered above. Hakuna matata.
14: Hypoxia

**Oxygen delivery**

\[ O_2 \text{ delivered} = \text{cardiac output} \times O_2 \text{ content of blood} \]

\[ O_2 \text{ uptake} = \text{cardiac output} \times \text{arterio-venous } O_2 \text{ difference} \]

**Respiratory Quotient**

\[ \frac{\text{CO}_2 \text{ output}}{O_2 \text{ uptake}} \]

**Haemoglobin**

Factors affecting oxygen binding to haemoglobin include:

- \( p_a O_2 \), in creating the sigmoidal curve of \( O_2 \) dissociation. It’s quite difficult for the 1st molecule to bind to the Hb, but once it does, it causes a conformational change which makes it far easier for the 2nd and 3rd \( O_2 \) to bind. The final \( O_2 \) again finds it more difficult.

- \( \text{pH} \), as in more alkaline conditions \( O_2 \) saturation is increased for the same \( p_a O_2 \) and likewise if the blood is more acidic, Hb’s affinity for \( O_2 \) decreases. This is the Bohr effect. It means that alkaline blood is much worse at giving up its oxygen to tissues. This occurs because \( H^+ \) competes with \( O_2 \) for space on Hb, causing more \( O_2 \) to dissociate.

- \( p_a \text{CO}_2 \) (and lactic acid concentration), in that when we exercise we produce more \( \text{CO}_2 \) and a greater \( p_a \text{CO}_2 \) causes Hb’s affinity for \( O_2 \) to fall so that more \( O_2 \) is released into the tissues, which is exactly what we want. This is the Haldane effect. It works in 2 ways.
  - higher \( p_a \text{CO}_2 \) means higher \([\text{HCO}_3^-] + [H^+]\), so more \( O_2 \) dissociation (see above)
  - \( \text{CO}_2 \) itself can compete for space on Hb too, forming carbaminohaemoglobin

- 2,3-bisphosphoglycerate (2,3-BPG, part of glycolysis) concentration in RBCs has the same effect, so a greater concentration of 2,3-BPG increases \( O_2 \) dissociation.

- higher temperature also aids \( O_2 \) dissociation, which is a factor as exercise produces heat.

The disadvantage of oxygen dissociating more easily into the tissues is that it isn’t taken up as well by the lungs. Increased ventilation when exercising makes up for it, preventing a fall in \( \text{SaO}_2 \).

**Altitude and compensation**

Another compensatory mechanism for hypoxia we haven’t mentioned before is polycythaemia, in which erythropoietin (the hormone which stimulates red blood cell production) is secreted from the kidneys. [Hb] in the blood can go up from a normal 13 g/dl to 18-20 g/dl. Polycythaemia (a form of renal compensation) is just one process combating the reduced atmospheric \( p_O_2 \) at altitude (hypobaric hypoxia). Initially, at altitude, ventilation increases to keep \( p_a O_2 \) up, but this reduces
p\textsubscript{a}CO\textsubscript{2} and thus raises pH, causing respiratory alkalaemia. Due to the lower p\textsubscript{a}CO\textsubscript{2}, additional ventilation is no longer stimulated. Correction of the alkalaemia by the kidneys happens over a few days, and oxygen affinity returns to normal (i.e. at sea level) thanks also to increased production of 2,3-BPG. It is also thought that the peripheral and/or central chemoreceptors become more sensitive to p\textsubscript{a}O\textsubscript{2} during this time, so the effect of p\textsubscript{a}CO\textsubscript{2} on the control of breathing is reduced.

While adjusting, someone who lives near sea level can experience poor physical or mental function. These symptoms are usually mild, but if severe are termed acute mountain sickness (AMS):

- headache
- anorexia
- nausea (and vomiting)
- photophobia
- sleeping poorly

AMS is not usually treated, though painkillers for the headache can be given. A useful prophylactic tactic is to give acetazolamide, which causes a mild metabolic acidaemia contrary to the respiratory alkalaemia caused by altitude. This decreases unpleasant effects and enhances acclimatisation.

1% of people who get mild AMS develop one or both of the serious medical emergencies called high altitude pulmonary oedema (HAPE) and high altitude cerebral oedema (HACE).

In addition to the symptoms of AMS, patients with HAPE develop

- severe dyspnoea
- chest pain
- dry cough
- haemoptysis (sometimes)

The hypoxia causes HPV (hypoxic pulmonary vasoconstriction) and thus pulmonary hypertension which can cause RV failure. ‘Capillary leak’ causes the oedema.

HACE again follows on from AMS but causes severe headache and impaired cognitive and physical function which can lead to coma. Retinal haemorrhage and sometimes papilloedema can be seen.

The best and only immediate treatment for AMS, HAPE, and HACE is to get the patient to a lower altitude. Giving them oxygen to breathe also helps, as do diuretics and steroids though not on their own. Nifedipine can be crucial for HAPE, as it reduces pulmonary arterial blood pressure, reducing the afterload on the right ventricle. HAPE and HACE have a 50% mortality if untreated.

**Respiratory failure**

“Failure to maintain at rest p\textsubscript{a}O\textsubscript{2} > 8 kPa (>60 mmHg) and p\textsubscript{a}CO\textsubscript{2} < 6.7 kPa (<50 mmHg).”

**Type 1:** Hypoxaemic failure: low p\textsubscript{a}O\textsubscript{2} and normal or low p\textsubscript{a}CO\textsubscript{2}. There is V/Q mismatch but alveolar ventilation remains normal.

**Type 2:** Ventilatory failure: low p\textsubscript{a}O\textsubscript{2} but high p\textsubscript{a}CO\textsubscript{2}. Alveolar hypoventilation is occurring.

**Type 3:** Combined failure: mixed. Everything the same as type 2 but with V/Q mismatch.
15: Allergic airway disease

Definitions

**Hypersensitivity:** exaggerated sensitivity to any agent

**Allergy:** exaggerated sensitivity due to heightened or altered reactivity of the immune system to an external agent. Allergy is a mechanism not a disease.

**Atopy:** hereditary predisposition to produce IgE specific to common aeroallergens. Atopic diseases are allergic rhinitis, asthma, and atopic eczema.

**Intolerance:** having symptoms following exposure but with no immunological mechanism

What appears to happen in allergy is that the immune system recognises foreign proteins on things like pollen grains as if they were parasitic worms or ticks.

**Mechanism of allergy**

When a helminth (worm) comes into contact with an epithelial cell via the cell’s toll-like and NOD-like receptors, the cell secretes IL-25 and IL-33. These stimulate cells of the innate immune system like natural killer cells, to secrete the ‘classical Th2 cytokines’ IL-4 and IL-13 (stimulating IgE production by B cells) and IL-5 (eosinophil stimulating). These lead to the proliferation of mast cells and Th2 cells (see below).

The acute symptoms of allergy are caused by mast cells. The mast cells have IgE-coated cell membranes, and when the allergen reaches that IgE the mast cell degranulates, releasing histamine and other mediators like leukotrienes. Histamine triggers local vasodilation, sneezing (via C-fibres), and mucus hypersecretion (runny / stuffy nose): the classic allergic symptoms.

Sensitized Th2 cells can cause chronic symptoms of allergy. They receive stimulation via antigen-presenting cells like dendritic cells. Symptoms are caused via the Th2 cytokines released:

- IL-4: IgE synthesis
- IL-13: IgE synthesis, airway hyperresponsiveness
- IL-5: eosinophil maturation
- IL-9: mast cell maturation

**Appearance of allergic diseases**

The ‘allergic march’ is the progression in prevalence of allergic symptoms with age (see right).

We’re not sure what the reasons are for it, but we think early intervention would be key to stopping the development of allergic disease.
Hayfever, or seasonal allergic conjunctivitis, affects around 15% of the British population, which is the highest prevalence in Europe. It is an allergic reaction to proteins in/on pollen grains.

Common triggers of asthma and perennial allergic rhinitis (year-round unlike hayfever) include:
- dust mites
- cockroaches
- cats, dogs, and horses
- alternaria (a common plant fungus)

Asthma is a very broad, heterogeneous disease but its many phenotypes fall into 3 categories:
- intermittent and mild; allergy is often important
- persistent but manageable; allergy may be important
- chronic and severe; infection is important not allergy

The critical point to make about asthma is that it involves narrowing of the airways, via:
- oedema of the surrounding tissue
- contraction of smooth muscle
- plugging of airway lumen by secretions and debris

And these cause the cough, wheezing, and dyspnoea (of the chest tightness variety).

Anaphylaxis is a reaction following an allergen entering the circulation. The massive release of histamine causes relaxation of vascular smooth muscle and contraction of non-vascular smooth muscle. It thus causes vasodilation and makes lots of fluid leave the circulation, leading to massive hypotension, and simultaneously narrows the airways via oedema and bronchoconstriction. Treating anaphylaxis is primarily done by administering adrenaline, as its actions counter those of histamine, and also by giving intravenous fluids to combat the hypotension.

Extrinsic allergic alveolitis is the final allergic airway disease, occurring in just 0.1% of the population. It is caused by very small particles (<5 µm), hence why it can affect the alveoli, and it is generally occupational e.g. farmer’s lung from mouldy hay or miller’s lung from infested flour. In the alveoli, antigen-antibody complexes form with IgE and stimulate complement, neutrophils, macrophages, and so on which inflame the interstitium between the alveolar epithelium and vasculature. If untreated it can lead to massive fibrosis. Treatment is purely by avoidance.

Treatment
The fall in infectious disease prevalence mirrors the rise in allergic disease prevalence.

The ‘hygiene hypothesis’ suggests that being in an environment of relative cleanliness as an infant predisposes you towards allergies. So, having children with lots of siblings, attending day care, helminth or hepatitis A infections, and living on farms actually reduces the development of allergy. Other factors associated with the increase in allergy prevalence include obesity and stress (as they cause chronic inflammation), water sanitation, climate change (higher pollen counts), and genetics.

Treatment is via avoidance, medication (antihistamines and corticosteroids to reduce inflammation) and immunotherapy. The latter desensitizes the patient to the allergen by injecting increasing doses over time. It does not ‘cure’ the allergy but it reduces symptoms greatly for years.
16: Lung infection

Defense mechanisms

**Mechanical:** epithelium, surfactant, filtration (e.g. by nasal hairs), mucociliary clearance, coughing

**Local:** bronchus-associated lymphoid tissue (BALT), secretory immunoglobulin A (sIgA), lysozyme, antiproteinases, and alveolar macrophages

**Systemic:** neutrophils, complement, other immunoglobulin.

Ciliary beating

Remember that cilia have apical hooks. This is how they beat to push the mucus in one direction:

![Ciliary beating diagram](image)

Haemophilus influenzae

This bacterium causes about 70% of all chronic respiratory infections. Its long hairs (fimbriae) have receptors on the ends which adhere to the epithelium, anchoring it against mucociliary clearance so it can form colonies.

It is much easier for the bacteria to reach the epithelium in areas of damaged ciliated epithelium, however, hence why H. influenzae usually infects smokers or people recovering from a cold.

Pneumonia

Similar symptoms to bronchitis (coughing up phlegm, fever, dyspnoea), but much more severe. It’s most often caused by *streptococcus pneumoniae*, which are visible as *diplococci* under the microscope. It produces a toxin called *pneumolysin* which perforates cell membranes to kill the cell. The ‘pneumococci’ can then get through the epithelium and invade, even into the blood.