Guide for use of these notes

First of all thank you for choosing to download these notes to study from I hope you find them useful, please feel free to email me if you have any problems with the notes or if you notice any errors. I don't promise to respond to all emails but I'll do my best.

For the respiratory notes I used "Vander's physiology" and "The Respiratory System at a Glance".

I organise my notes so that you should read the learning objectives on the left then proceed down the right hand side for a few learning objectives and then cross back over to the left and continue like that.

Anything in this highlighted green is a definition or explains basically something's function.

🌟 Text highlighted in yellow or with a star is what I would deem important and key to your information.

Italics and bold just help to make certain terms stand out.

The notes are a bit quirky but I hope you like them and find some of the memory aides strange enough so that they stick in your head.

I provide them to you in OneNote format as that is how I created them, they can be saved as PDF but the formatting is not as nice. The one caveat with this is that these notes are freely copy able and editable. I would prefer if you didn't copy and paste my notes into your own but used them as a reference or preferably instead embellished these already existing notes by adding to them.

Good luck with first year
and enjoy the new Reynold's toilets

Stuart Taylor
Respiratory disease kills one in five people in the UK.

1. Lung Cancer
2. Pneumonia
3. COPD

Lung Cancer
- Cough
- Change in character of longstanding cough
- Haemoptysis
- Breathlessness
- Distal Infection
- Lobar Collapse

TB is particularly bad in London

Mesothelioma—Can be caused by asbestos exposure.

Chronic Obstructive Pulmonary Disease:
- Preventable and treatable
- Airflow limitation that is not fully reversible and is progressive
- Abnormal inflammatory response of the lung to noxious particles or gases.
- Significant extra-pulmonary effects.
- Exacerbations—particularly bad periods which causes an increase in severity of disease.
  - Infection—virus bacteria e.g. coronavirus
  - Very expensive ~£2130 cost of admission to hospital.

In 2020 it will be 6th biggest killer.

Risk factors:
- Susceptibility genes
- Poor lung growth and development
- Oxidative stress
- Female gender
- Age
- Respiratory infections
- Low socio-economic status
- Poor nutrition
- Co-morbidities

- Diagnosed by spirometry.
- Worried about becoming house and bed bound.

Airways diseases

<table>
<thead>
<tr>
<th>Localised obstruction</th>
<th>Due to disease within the lungs</th>
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<tbody>
<tr>
<td>Sleep apnoea</td>
<td>Sarcoïdosis</td>
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<tr>
<td>Laryngeal carcinoma</td>
<td>Asbestos</td>
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<tr>
<td>Thyroid enlargement</td>
<td>Extrinsic Allergic Alveolitis</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Fibrosing Alveolitis</td>
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<tr>
<td>Relapsing Polychondritis</td>
<td>Eosinophil pneumonia</td>
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<td>Tumours</td>
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<td>Post tracheostomy stenosis</td>
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<tr>
<td>Foreign bodies</td>
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<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
</tr>
</tbody>
</table>

Small lung disorders (also known as "restrictive disorders")

<table>
<thead>
<tr>
<th>Generalised obstruction</th>
<th>Due to disease outside the lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Pleural effusions</td>
</tr>
<tr>
<td>C.O.P.D.</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Scoliosis</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>Respiratory muscle weakness</td>
</tr>
<tr>
<td>Obliterative Bronchiolitis</td>
<td>Obesity</td>
</tr>
</tbody>
</table>

Infections

| Tuberculosis           | Pulmonary emboli               |
| Inferive bronchitis    | Pneumothorax                   |
| Pneumonia              |                                |
| Empyema                |                                |

Pulmonary vascular disorders

General Symptoms of Lung Disease

- Breathlessness
- Cough
- Sputum production
- Haemoptysis
- Hoarseness
- Stridor
- Weight loss, Anorexia, Fever.

Breathlessness

Onset

Within Minutes
- Pulmonary embolus, Pneumothorax, MI, cardiac rhythm disturbance

Over hours or days
- Pneumonia, pleural effusion, LVF, asthma, lobar collapse

Over Weeks:
- Infiltration (sarcoïdosis, fibrosing alveolitis, extrinsic allergic alveolitis), anaemia, valvular dysfunction

Over months:
- Same as weeks +obesity, muscular dystrophy, asbestos related conditions.

Over years:
- COPD, chest wall deformity,
Learning Objectives

- **Outline how the respiratory tract is protected against drying, cold and inhaled particles.**
- **Define alveoli, bronchioles, bronchi, trachea, larynx, pharynx, and nasal cavities.**
- **Sketch and name the cellular layers separating alveolar air from blood.**
- **Explain how the alveoli and airways resist collapse.**
- **Describe and sketch the organisation of the chest using the terms chest wall, diaphragm, mediastinum, pleural cavities, pleura, and lungs.**
- **Outline the blood circulation through the lungs making correct use of the terms double circulation, pulmonary circuit, right atrium, tricuspid valve, right ventricle, pulmonary valve, pulmonary trunk, pulmonary arteries, arterioles, alveolar capillaries, venules, pulmonary veins, left atrium.**

### The Nasal Cavities

- Septum divides the nose into two nostrils.
- Olfactory nerves are situated right at the top of the nasal cavity - Cranial nerves.
- Trigeminal nerve (5th cranial nerves) - three branches
  - Ophthalmic
  - Mandibular
  - Maxillary

### Nerves of Nasal Cavity

- Nasal septum
- Olfactory bulb
- Cribiform plate
- Olfactory tract
- Olfactory nerves
- Nasopalatine nerve (V2)
- Medial internal nasal br of ant. ethmoidal n (V1)

### Paranasal Sinuses

- Frontal sinus
- Ethmoid air cells
- Maxillary sinus
- Sphenoid sinus
- Nasal cavity
  - Nasal concha
  - Maxillary sinus' drainage is poor because middle nasal meatus is superior and lateral to it.
- Air spaces do not weaken the skull but allow it to be lighter

### The Pharynx

- Extends from back of the nose to the top of the larynx.
- Mixing of air- fluid and liquid
- Divided into 3 regions
  - Nasopharynx
  - Oropharynx
  - Laryngopharynx
- Entire area is pretty much an open tube.

### The Larynx

- Deviation indicates thoracic pathology.
- It is a cartilaginous structure which is attached to the floor of the oral cavity by the hyoid bone via a flexible membrane it also has trachea hanging from its inferior margin.
- Arytenoid cartilage - Sit on top of the cricoid - running from them are the vocal cords. Movement of arytenoid opens and closes vocal cords.
- Vocal cords were supposed to act as a sphincter to stop anything going down the trachea by immediately setting up a coughing fit to expel the object.
- Sound is generated by vibration of vocal cords when they are partly open.
Sinuses modulate resonance of the voice.

- Maxillary sinus drainage is poor because middle nasal meatus is superior and lateral to it.
  - The drainage would be much better as we were on all 4s.

- Air spaces do not weaken the skull but allow it to be lighter.
- Potentially acts as an insulator against cold and heat.
- Brain just behind specific sinuses.

- Protection against inhaled particles is mediated by the mucociliary escalator if very small and the cough reflex if larger.

### Trachea

- Deficient cartilage posteriorly which is filled with smooth muscle.
- Allows oesophagus to expand a little during swallowing.
- About 20 cartilage rings.
- Corina: Where bifurcation of the trachea occurs.

- Primary bronchi go towards the lung.
- RPB: shorter and more direct due to slight deviation of trachea from midline.
- Secondary/lobular bronchi: supply individual lobes of the lungs.
  - Only independent airway with its own blood supply.
  - Within the lobe the tertiary bronchi go on to supply the bronchio pulmonary segments.
  - No cartilage from bronchioles downwards and therefore susceptible to muscular spasms.

- Stuart's Respiratory System Page 4

### Sketch and name the cellular layers separating alveolar air from blood.

- There is the alveolar air sac which is where the inhaled air goes. It is composed of Type 1 alveolar cells which make up most of the surface area and are thin to aid diffusion and Type II alveolar cells which secrete pulmonary surfactant.
- There is also a small 0.5 micrometre gap which the air has to diffuse across dissolved in the alveolar fluid.

- This will probably be covered in the lung cell biology lecture and in some of the asthma practicals.

### Root/ Hilum of the lung

- Pulmonary ligament: Area of hilum with nothing in it.
- Bronchi: Will feel cartilage rings. Usually lie posterior.
- Low pressure system: Arteries are more superior but not as thick.
- Lymph nodes.
- Autonomic nerve plexuses.
- Bronchial arteries: supplying blood to the airways themselves.

### Right lung grooves

- Azygos Vein
- SVC: a little IVC
- Oesophagus

- This probably will be covered in the lung cell biology lecture and in some of the asthma practicals.
- There is the alveolar air sac which is where the inhaled air goes. It is composed of Type 1 alveolar cells which make up most of the surface area and are thin to aid diffusion and Type II alveolar cells which secrete pulmonary surfactant.
- There is also a small 0.5 micrometre gap which the air has to diffuse across dissolved in the alveolar fluid.
Describe and sketch the organisation of the chest using the terms chest wall, diaphragm, mediastinum, pleural cavities, pleura, and lungs.

**Diaphragm**
- **Position of Diaphragm**
  - Margin attached to costal margin (lower edge of rib cage)
  - Centre of dome bulges up because of pressure difference between pleural and abdominal cavities
  - Highest in expiration

**Phrenic Nerve**
- C3, 4 and 5 is motor to diaphragm.
- C3 4 and 5 keeps your diaphragm alive.
- Paraventricular sympathetic

**Explain how the alveoli and airways resist collapse.**
- Above the bronchioles the airways resist collapse due to muscle tone and the action of cartilage.
- Below the bronchioles pulmonary surfactant helps to reduce surface tension that would otherwise cause collapse of the airways. In addition the elastic pull of alveoli septae keeps bronchioles open as they do not have cartilage.

**Quiet inspiration - The diaphragm**
Intercostal muscles give flexibility to ribcage and stop lungs blowing out through chest wall.

Breathing in - They expand laterally
Deep breath - They expand anteriorly as well.

Abdominal muscles are important for forcing air out of the lungs. Provide additional force.

1 alveolar cells which make up most of the surface area and are thin to aid diffusion and Type II alveolar cells which secrete pulmonary surfactant.
- There is also a small 0.5 micrometre gap which the air has to diffuse across dissolved in the alveolar fluid.

**Left Lung Grooves**
- Aortic arch
- Heart
- Left brachiocephalic vein
- Thoracic aorta
- Anterior: L Common carotid
- Posterior: L Subclavian
• IVC - T8
• Descending Aorta - T12
• Oesophagus - T10
Learning Objectives

- To understand the continuum of lung growth and development from conception to adulthood and the factors that interfere with normal development.
- To understand how congenital lung defects arise.
- To be able to summarize the morphological and/or cellular events associated with the phases of intrauterine lung development.
- To summarize the main aspects of lung growth and the evolution of lung function in the postnatal period.
- To be able to give a brief account of the changes in the lungs and circulation that occur at birth to permit air breathing.
- To briefly describe the changes that occur at birth that facilitate the transition to air breathing. Comment particularly on the role and fate of lung liquid and the importance of pulmonary surfactant in stabilizing breathing.
- To understand the early life origins of susceptibility to lung disease.

Fetal circulation overview

- Pulmonary pressure is greater than systemic pressure on the RHS to force blood through the Ductus arteriosus and bypass the lungs.
- The Foramen ovale is a structure that allows blood to enter the left atrium from the right atrium in a fetus, and in adults once sealed.
- Most of the haemoglobin present within the fetus has a different oxygen association curve because of foetal haemoglobin, its structure makes it more likely to get oxygen than the mother.

To understand how congenital lung defects arise.

- Tracheal bud develops from the foregut at 4-5 weeks gestation.
- Bronchial branching is complete by 16 weeks gestation.
- Pulmonary artery branching follows bronchial branching.
- Alveolar development continues until 8-10 years of age.
- New baby has about 20-50% of adult alveoli.
- Ventilation is matched to perfusion therefore a poorly functioning lung doesn’t get as much of a blood supply.

Lung Embryogenesis

- Different tissues develop at different rates.
- Bronchial buds are supplied by systemic vessels from splanchnic plexus.
- Systemic vessels regress as pulmonary artery takes over principle supply.
- Bronchial artery development occurs independently.
- Malformation is influenced by the timing of the insult rather than its nature.

Influences on Lung development

- Hox genes
- Transcription factors
- Autocrine and paracrine interactions
- Peptide growth factors
- Thoracic cage volume
- Lung liquid positive pressure
- Amniotic fluid volume
- Maternal nutrition (i.e. Vit. A) - induced lung aplasia in a rat by withholding vitamin A.

To be able to summarize the morphological and/or cellular events associated with the phases of intrauterine lung development.
• reset chemoreceptors are respiratory centres.
• Aeration of lungs with high positive expiratory pressure. Taking a big breath doesn’t clear the lung fluid. Grunting with a closed larynx generates a positive pressure internally.
• Lung volume rises to optimum and airway resistance falls in first 2 hours.
• Lung compliance rise takes at least 24 hours.

To briefly describe the changes that occur at birth that facilitate the transition to air breathing. Comment particularly on the role and fate of lung liquid and the importance of pulmonary surfactant in stabilizing breathing.

- As alveoli mature, cells begin to get thinner and begin to generate intracellular structures known as lamellar bodies which reduces surface tension of fluid that is in alveoli. This is because it contains phospholipid called Surfactant.

Idiopathic Respiratory Distress Syndrome
- In this condition there is a deficiency within pulmonary surfactant.
- This causes an imbalance within the surface tension Lung Mechanics I + II and will cause the alveoli to collapse.

To understand the early life origins of susceptibility to lung disease.

- Maternal pregnancy smoking- impairs foetal respiratory movements and pacemaker function of smooth muscle.
  - Four-fold higher risk of infant wheeze.
  - High level of COPD
- Elastic pull of alveoli septae keeps bronchioles open as they do not have cartilage.
- Reduced level of alveoli means that any inflammatory conditions in the first year of two of life may cause bronchioles to collapse.

Factors influencing admissions for lower resp. tract infections in children aged 0-5 years.

- Social index
- Maternal smoking
- Birth weight
- Gender- Males
- Older siblings- Bring home infections
- Breast feeding (not significant)

Pseudoglandular period (5-16th weeks)
- The bronchial buds have now developed into the primordial left and slightly larger right primary bronchi, which subsequently divide by branching morphogenesis into five secondary (3 right and 2 left).
- At the 7th week these have started to divide progressively into 10 right or 5 left segmental (s) or tertiary bronchi each of which eventually forms a bronchopulmonary segment.
- By the 17th week most major structures of the lung have formed and are lined with columnar epithelial cells. Conducting blood vessels are present, but the gas-exchange surfaces have not yet developed and foetuses delivered now are not viable.

Canalicular period (17th-24th weeks)
- Bronchial cartilage, smooth muscle, pulmonary capillaries and connective tissue develop from the mesoderm. There is progressive differentiation and thinning of epithelial cells. The bronchi will have subdivided 17 times after 24 weeks, finally forming the respiratory bronchioles which themselves divide into three to six alveolar ducts and some thin-walled terminal sacs.
- These are lined by very thin walled Type II alveolar pneumocytes (squamous epithelium), which together with endothelial cells from capillaries form the future alveocapillary membrane (gas exchange surface). There are a few Type II alveolar pneumocytes which secrete surfactant.
- Not enough surfactant until 26th week to support unaided breathing: refer to Neonatal Respiratory Distress Syndrome. Some gas exchange can occur because of the terminal sacs and decent vascularization but the immaturity means that foetuses will normally die.

Saccular period (24th week-parturition)
- Associated with rapid development in the number of terminal sacs and the pulmonary and lymphatic capillary networks.
- Budding from terminal sacs and walls of terminal bronchioles and thinning of type I pneumocytes leads to formation of immature alveoli from around week 32.
- Sufficient surfactant and vascularisation are normally present between the 24th and 26th week to allow survival of some premature foetuses; although this is very variable. Surfactant increases significantly in the 2 weeks before birth.

Alveolar period (late fetal to childhood)
- Clusters of immature alveoli form during the early part of this period; mature-type alveoli with thin interalveolar septa and gas-exchange surfaces do not appear until after birth. Fetal breathing movements are present before birth, with aspiration of amniotic fluid, and these stimulate lung growth and development of respiratory muscles.
- More than 90% of the alveoli are formed after birth. At the end of lung development there are ~23 generations of airways with ~17 million branches.

To summarize the main aspects of lung growth and the evolution of lung function in the postnatal period.

- The problem with early birth is that there isn’t enough alveoli to allow gaseous exchange.
- Length from terminal bronchi to pleura increases with age as more alveolar ducts are formed.

Graph: 
- R. to L. shunting
- Deficient surfactant
- Pulmonary Vas- condensation
- Alveolar collapse
- Hypoxia
- Acidosis
- Alveolar hypo- ventilation

Graph: 
- Key to ventilation is ensuring that at the end of expiration there is a higher pressure than atmospheric pressure.
Apnoea - Temporary cessation of breathing from any cause.

- Defined by the reduction of nasal air flow to less than 30% of normal for ten seconds.
- A new baby usually tries to breathe through its nose, however the mechanisms aren't in place to open its mouth if its nose is blocked and thus it will asphyxiate.

- There are two stages of apnoea
  1. **Primary apnoea**
     - If delivered here the baby will continue to make respiratory effects, it will stop gasping and attempt to cough with closed larynx to clear lungs.
  2. **Terminal apnoea**
     - If delivered in terminal apnoea the baby will not breathe spontaneously and the blood pressure rapidly drops off.

- If the time to resuscitate is longer than 30 mins then they will be seriously irreversibly brain-damaged proportional to length of asphyxia.

**Aspar score** - Allows you to determine the level of apnoea and asphyxiation.

![Graph showing lung function evolution](image-url)

![Diagram of respiratory system](image-url)
Learning Objectives

- Define the common lung volumes and describe how they alter in restrictive and obstructive disease
- Define anatomical and physiological dead space and give approximate volumes for both in a typical healthy adult
- Distinguish between alveolar and pulmonary ventilation.
- Describe the effect of increased breathing frequency compared with increased depth of breathing on alveolar ventilation
- Define Fick’s law of diffusion
- Relate Fick’s law of diffusion to gas exchange in health and disease
- Define the common lung volumes and describe how they alter in restrictive and obstructive disease

Lung Volumes and Capacities

- Maximal inspiration (V\text{\text{max}}) - Volume of air inspired during quiet respiration.
- Inspiratory reserve volume (IRV) - Volume of air inspired from VT to maximal inspiration.
- Residual volume (RV) - Amount of air left in lungs which cannot be expelled.
- Expiratory reserve volume (ERV) - Air expelled with forced expiration.
- Total lung capacity (TLC) - Volume maximal inspiration to residual volume (IRV + VT + ERV + RV).
- Functional residual capacity (FRC) - Volume of air at the end of normal quiet expiration (ERV + RV).
- Vital capacity (VC) - Volume of air maximal inspiration to maximal expiration (VC = IRV + ERV + TV).

Factors affecting lung volumes

- Body size
- Age
  - Less compliance in their lung system overall - even though alveoli are more compliant.
- Gender
- Muscle training
- Disease

Clinical Relevance

- Tidal Volume
  - Adequate V\text{\text{t}} - necessary to maintain oxygenation and CO₂ clearance
- Inspiratory reserve volume
  - Channels of Lambert - alveoli to small bronchioles
  - Channels of Martin- bronchiole to bronchioles.
- Air to area that would otherwise not get air.
  - Required during cough and undertaking exercise.

Vital capacity (VC) = IRV + ERV + TV

Maximal inspiration 5 L

Minimal ventilation (V\text{\text{t}}) - Is the volume of air entering the lungs each minute.

Factors influencing ventilation

- Influenced by age & sex, body size & posture, mechanical ventilation and pulmonary disease.

Vital capacity

- Not all tidal volume air is used in gas exchange.
- Dead space is term for that part of the tidal volume that is not involved in gas exchange.
- There are 2 types of dead space
  a. Anatomical
  - With each tidal volume 150mls remains in conducting zone up to terminal bronchioles.
  b. Alveolar
  - Inspiratory gas reaching alveoli unable to participate in gas exchange due to insufficient blood supply.
  - In healthy subjects alveolar dead space is almost zero.
  - In disease it is affected by PE.
    - Ventilation of non-vascular air spaces e.g. bullae.
  - Physiological dead space is the sum of all parts of tidal volume which does NOT participate in gaseous exchange.
    - PDS = AnDS + AlDS.
    - Influenced by age & sex, body size & posture, mechanical ventilation and pulmonary disease.

Distinguish between alveolar and pulmonary ventilation.

- Alveolar ventilation: The amount of minute ventilation reaching respiratory zone used in gas exchange.
- Pulmonary ventilation: The amount of air entering the lungs whereas alveolar ventilation is the amount of air entering the alveoli specifically.

Describe the effect of increased breathing frequency compared with increased depth of breathing on alveolar ventilation.

<table>
<thead>
<tr>
<th>freq/m</th>
<th>V\text{\text{t}}</th>
<th>VE</th>
<th>VTeh</th>
<th>VA</th>
</tr>
</thead>
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<tr>
<td>12</td>
<td>0.5</td>
<td>6</td>
<td>.35</td>
<td>4.2</td>
</tr>
<tr>
<td>24</td>
<td>0.5</td>
<td>12</td>
<td>0.35</td>
<td>8.4</td>
</tr>
</tbody>
</table>

A low FEV1, a low FEV1/FVC and a low peak expiratory flow rate are signs of obstructive disease.

Dead space = AnDS + AlDS

Classification of respiratory disease

Obstructive

- COPD
- Cystic Fibrosis
- Asthma
- Tumour
- Ankylosing spondylitis
- Chest wall isn’t as compliant and thus problems are noticed on attempting to inhale.

Restrictive

- Lung fibrosis
- Motor neurone disease
- Ankylosing spondylitis

Why assess spirometry?

- Diagnosis of respiratory disease
- Monitoring to assess
  - Deterioration
  - Drug efficiency
  - Efficient drug delivery system

http://en.wikipedia.org/wiki/FEV1/FVC_ratio
Define Fick’s law of diffusion

\[ \text{Diffusion rate} = \frac{\text{Q} \times \text{CvO}_2}{\text{CaO}_2 - \text{CvO}_2} \]

Relate Fick’s law of diffusion to gas exchange in health and disease

O2 consumption = O2 delivered – O2 returned

Which is ...

\[ \text{VO}_2 = (\text{Q} \times \text{CaO}_2) - (\text{Q} \times \text{CvO}_2) \]

\[ \text{VO}_2 = \text{Q} \times (\text{CaO}_2 - \text{CvO}_2) \]

Where

\[ \text{Q} = \text{rate of blood flow} \]

\[ \text{CaO}_2 = \text{O}_2 \text{ concentration in Arterial blood} \]

\[ \text{CvO}_2 = \text{O}_2 \text{ concentration in venous blood} \]

This is the Fick principle

- Gas exchange takes place in alveolar sacs across the alveolar membrane which is a boundary between the external environment and interior of the body.
- Gases cross the respiratory membrane by diffusion in accordance with Fick’s law.

Fick’s law states that the rate of transfer of a gas through a sheet of tissue is proportional to:

- Tissue area
- Difference in gas partial pressure between the two sides.
- Diffusion constant

And inversely proportional to the thickness of the tissue.

In accordance with Fick’s law diffusion is dependent upon:

Concentration / pressure gradient

- In the context of the respiratory gases concentration is described using the term partial pressure.
- Partial pressure describes the amount of gas dissolved in the plasma.
- E.g. PvCO2 is the amount of CO2 dissolved in the plasma of venous blood.
- Pulmonary capillaries have a low PdO2 (40mmHg) and a relatively high PCO2 (45mmHg) the greater the pressure gradient the faster diffusion occurs.
- The O2 transit time within the pulmonary capillaries is about 0.75 secs. However the O2 equilibrium is established within 0.25 secs, this safety margin allows for an increased velocity of blood flow in exercise without the RBC being under saturated.

Gas solubility

- CO2 is 20 times more soluble than O2.
- High solubility of CO2 facilitates rapid diffusion despite small CO2 gradient.
- This is explained by Graham’s law which says that the rate of diffusion of a gas is proportional to its solubility in the liquid and inversely proportional to the square root of its molecular mass.
- Equal amounts of CO2 and O2 diffuse across the respiratory membrane in the same time period.
- In respiratory disease when diffusion is impaired O2 will be primarily affected as it is less soluble whereas its has to be very severe to impair O2.

Thickness of alveolar membrane

- 0.5 to 1 μm thick which allows the fastest possible diffusion time.
- There is a greater distance between alveoli and capillary if the membrane is thicker which can lead to hypoxia.
- This may be caused by a. Inflammation b. Infection c. Fibrosis

Surface area of alveolar membrane

- Adult lung contains around 300million alveoli which gives a gas exchange surface of 70-80m².
- This is a huge capacity which can be utilised to maintain acid-base balance.
- However if this area is reduced then P2O2 will fall, PCO2 will rise and pH will drop.
- Temporary loss of surface area:
  a. Bronchial obstruction (tumour, mucous plug)
  b. Atelectasis- collapse of alveoli
  c. Consolidation
- Permanent loss surface area:
  a. Emphysematous bullae

Increasing of respiratory rate does not increase alveolar respiration and patients will run into respiratory fatigue.
- Not as effective doubling frequency as it is doubling VT.
- Increased depth causes an increased VT alv as air goes deeper into the airways.

Hyperventilation exists when the ratio of carbon dioxide production to alveolar ventilation increases above normal values caused by inadequate alveolar ventilation.
- Hyperventilation exists when the ratio of carbon dioxide production to alveolar ventilation decreases below normal values caused by excessive alveolar ventilation.

NOTE: This may seem the opposite of what you may think but consider it like this. Hyperventilation is the process of decreasing PaCO2 - a low CO2 production to alveolar ventilation ratio will serve to decrease CO2 concentration.

Regional redistribution of blood flow.

- Hyperventilation leads to poor CO2 excretion. Increased PACO2 (alveolar) and PaCO2 (artery).
- Respiratory alkalosis occurs due to CO2’s equilibrium which dissociates to give off H+ ions.

Hyperventilation

- Anxiety/fear
- Metabolic disease
- Airway obstruction
- Parenchymal lung disease
- Altitude

- Respiratory alkalosis occurs due to CO2’s equilibrium which means H+ ions are taken up.

Alveolar ventilation

- Determines O2 and CO2 levels in alveolar gas.
- Other factors are
  a. Rate of O2 consumption
  b. Rate of CO2 production
  c. Hb content of blood
  d. Hb affinity for O2
  e. Atmospheric pressure O2.

Ventilation- perfusion matching

- In respiratory physiology the V/Q ratio is the measurement used to describe efficiency and adequacy of matching two variables.

V- Ventilation- the air which reaches the lungs
Q- Perfusion- the blood which reaches the lungs

- The lungs are centred vertically around the heart.
- Part of the lung is superior to the heart and part is inferior.
- Lower part (dependent) of lung is better ventilated and better perfused than apex.
  a. This is because effects of gravity causes vessels at base of lungs to dilate which improves perfusion.
  b. Gravity also causes intrapleural pressure to be less negative at the base than the apex. This causes apical alveoli to be more expanded at FRC which reduces their ability to expand further.

For efficient gas exchange there needs to be maximum coupling between ventilation and perfusion.
- Inadequacy of either V or Q will have significant impact on removal of CO2 & oxygenation of blood.

Shunt

- Low ventilation- lung obstruction
- Sensors in arterioles cause Hyperic Pulmonary Vasconstriction- Regional redistribution of blood flow.

Alveolar Dead Space

- Low perfusion- vessel obstruction
V/Q mismatch occurs when some parts of the lung are underventilated relative to perfusion. The blood from these parts mixes in the pulmonary veins with blood from other parts of the lungs that are well ventilated. The resulting O₂ content is reduced and CO₂ content increased. Overventilating the well-ventilated regions to correct this is effective for CO₂ but not for oxygen. This is because blood from the well-ventilated units is already almost fully saturated (i.e. on the plateau of the sigmoid) and its O₂ content can only rise by a small amount (most of the oxygen is combined with haemoglobin and dissolved oxygen does not contribute much to O₂ content).

For CO₂, however, content rises almost linearly with PCO₂. Thus increasing the ventilation of already well-ventilated units will substantially reduce the CO₂ content in the blood from these units. When this mixes with the blood from under ventilated units, the resultant mix will have a normal or less than normal CO₂ content thereby bringing the resultant PaCO₂ back to normal or less than normal levels. The best answer is '2' but '4' is also possible.

**Qu. 2:** Which of the following statements about the rate of alveolar ventilation is correct?

- It is defined as the tidal volume multiplied by the respiratory frequency

Correct! There is no obvious reason why CO₂ production should be affected in moderate anaemia. Ventilation is largely controlled to keep arterial PCO₂ constant. Alveolar ventilation and arterial PCO₂ will be much as normal in a moderately anaemic subject.

- It is conventionally expressed in litres

Correct! The PO2 of mixed alveolar air depends on (i) the alveolar ventilation (ii) the rate of oxygen consumption and (iii) the composition of inspired gas. None of these will be changed in anaemia. The same ventilation that results in an alveolar PCO₂ of 5.3 kPa also results in a PO2 of roughly 13.3 kPa.

**Qu. 3:** Typically, obstructive disorders result in ...?

- A normal FEV1, a low FEV1/FVC and a low peak expiratory flow rate

A shunt shouldn't cause a V/Q mismatch because perfusion is matched to ventilation by a compensatory vasoconstriction and diversion of blood flow.

- A low FEV1, a low FEV1/FVC and a low peak expiratory flow rate

Alveolar dead space will because you can't stop breathing into the part of the lung with an obstructed vessel/low perfusion.

**REMEMBER IMPORTANT FACT NUMBER ONE**

Breathing an oxygen-enriched gas mixture is not very effective at increasing O₂ delivery to the tissues in anaemia.

**Qu. 5:** Which of the following statements about the rate of alveolar ventilation (forced expiratory volume in one second) is true?

- It measures the maximum flow rate achieved in a forced expiration

Correct! There is no obvious reason why CO₂ production should be affected in moderate anaemia. Ventilation is largely controlled to keep arterial PCO₂ constant. Alveolar ventilation and arterial PCO₂ will be much as normal in a moderately anaemic subject.

- It is achieved entirely as a result of the lung’s elastic recoil

Correct! The PO2 of mixed alveolar air depends on (i) the alveolar ventilation (ii) the rate of oxygen consumption and (iii) the composition of inspired gas. None of these will be changed in anaemia. The same ventilation that results in an alveolar PCO₂ of 5.3 kPa also results in a PO2 of roughly 13.3 kPa.

**REMEMBER IMPORTANT FACT NUMBER ONE**

Diffusion of gases across the alveolar-capillary membrane is very efficient. As a result the PO2 and PCO2 of the blood leaving a pulmonary capillary will be almost identical to that in the adjacent alveoli.

**IMPORTANT FACT NUMBER 9**

Breathing an oxygen-enriched gas mixture will NOT improve the raised PCO2 resulting from hypoventilation. Basically the only factors that determine alveolar PCO2 are (a) the ventilation and (b) CO₂ production. There is no obvious reason why either of these will change much when breathing O₂ and if they don’t, PACO2 will stay unchanged. However, in some patients with Chronic obstructive airways disease (i.e. COPD) who hypoventilate the arterial PO2 may be so low that it helps to drive breathing. So if then if you improve the PO2 by giving oxygen, this drive to breathe will be removed and the ventilation may fall to even lower levels - which in turn will result in a further (potentially dangerous) rise in PCO2 and fall in pH.
Learning Objectives

- Explain what is meant by elastic recoil.
- Define compliance.
- Explain how pulmonary versus chest wall compliances can vary in various respiratory diseases.
- Explain the concept of surface tension and the Law of Laplace.
- Explain how pulmonary surfactant affects lung volume and airway patency.

### Elasticity

Elasticity - Property of matter that causes it to return to its resting shape after deformation by an external force.

- The tissues of the lung and the chest wall are both elastic.
- Elastic Resistance vs Compliance
  - Connective tissues - elastin and collagen in lung
  - Surface tension generated at the air-liquid interface in the alveoli.

Typically the lungs tend to recoil inward away from the chest wall. If the chest is open the lungs collapse. This is because of:

- Connective tissues - elastin and collagen in lung
- Surface tension generated at the air-liquid interface in the alveoli.
- If the thorax is opened chest wall volume increases by 600-1000ml. Therefore the outward pull of the chest wall and the inward pull of the lungs would tend to separate the visceral from the parietal pleura.

- Incidentally the tendency for the lungs to pull away from the chest wall can be measured as the Pleural pressure (Ppl).

### Compliance

Compliance - Is the expression of pressure-volume characteristics of the respiratory apparatus (or of chest wall or of lungs) and determines the ability of the lung to stretch.

Lung compliance can be expressed via the formula:

\[ C_L = \frac{\text{Change in volume}}{\text{Change in pressure}} \]

A high compliance will mean a large change in volume for a given change in pressure, it is also the gradient of the pressure/volume curve.

#### Lung Pressure Volume Curve

For any given pressure the volume, during deflation is greater in inflation: hysteresis.

- Without any pressure there is still some volume in the lung due to airway closure.

#### Factors which affect elastic recoil

- Pressure difference between alveoli and pleural space
- Ptp=Palv-Ppl

#### Factors which stabilise the lungs

Forms relatively late in gestation (approx. 25 weeks)
- Surfactant

1. **Surfactant**

#### Measuring Ppl

- Directly by using a needle - risky may cause pneumothorax.
- Indirectly - Measure pressure in a thin walled balloon introduced into the middle third of the oesophagus.
  - Changes in the oesophageal pressure follow changes in the pleural pressure because the oesophagus lies between the lung and chest wall and because the walls of the oesophagus are thin and have little tone.

#### Pressure affecting the Respiration System

\[ P_{atm} = P_{alv} + P_{thoracic} \]

1. Surfactant
Factors that affect elastic recoil

- Lung volume history - important in shape of P/V curve
- Age (decreases with age)
- Nature of air-liquid interface and surface tension in the lung.
- During inspiration force is required to overcome the resistances of the respiratory apparatus, such as the elastic force of abdominal contents and resistance to airflow of the tracheobronchial tree, as well as the gas in the respiratory tract.

Elastic Forces

- At the end of normal expiration the resp. muscles are relaxed however there is still a volume of air remaining in the lungs which is called the Functional Residual Capacity.
- Above FRC the force of the lung tending to empty is more than the force of the chest wall in an inspiratory direction. Therefore RP is negative.
- Below FRC the pull of the chest in an inspiratory direction - the pull of lungs in expiratory direction. Therefore RP is positive.
- At FRC the forces exerted are equal but pulling in opposite directions. Therefore relaxation pressure is 0 at FRC.

Factors which stabilise the lungs

- Surfactant
  - Forms relatively late in gestation (approx. 25 weeks)
  - Can be assessed in amniotic fluid.
  - Glucocorticoids stimulate Type II cells to produce surfactant (can accelerate lung maturition)
  - Respiratory Distress Syndrome results from inadequate levels of surfactant.
- Interdependence of lung units
  - Adjacent alveoli share a common wall, therefore tendency of one alveolus or lung unit to collapse is opposed by the support of the surrounding units.

Explain the concept of surface tension and the Law of Laplace.

- Surface tension: Manifestation of attracting forces between atoms and molecules
- Units of force/unit length (dynes/cm)
- May be lowered by certain substances when placed in a liquid such as surfactant.

Law of Laplace

\[ P = \frac{2T}{r} \]

- Where \( P \) is the transmural pressure necessary to keep a spherical bubble of liquid inflated to a fixed size.
- \( T \) = wall tension
- \( r \) = radius of the bubble.

- There is a tendency for the lung to reduce volume due to:
  a. Elasticity of the lung parenchyma
  b. Surface tension at the alveolar air liquid interface
- If alveolar radius is reduced then alveolar pressure increases.
- Surface tension is dynamically altered and closely tuned to the alveolar radius.
- Reduced with expiratory decrease in alveolar radius.
- But increased with next increased expansion.
- Therefore surfactants are necessary to keep the alveolar pressure constant throughout the ventilatory cycle.

Explain how pulmonary surfactant affects lung volume and airway patency.

Pulmonary surfactant:

- Lipids 90%, protein 10%
- In lungs of all air-breathing vertebrates
- Formed in Type II alveolar epithelial cells.
- Surfactant is stored in characteristic osmiophilic lamellar bodies and secrete their contents into the alveoli lumen.
- Phospholipids and specific apoproteins.
- Without surfactant smaller alveoli would empty into larger ones if wall tension did not decrease. Due to law of Laplace small radius alveoli have a great pressure than large radius, therefore air would move between the two.

Further Detail:

- Synthesised by the cuboidal alveolar type II cell (less is produced in Clara cells, tracheal epithelium, middle ear)
- Continuous process of synthesis and degredation.
- Glucocorticoids, CAMP, oestrogens, thyroid, high volume lung inflation are all factors that increase its synthesis.
- Beta-receptor blockade inhibits surfactant synthesis.

Fates of surfactant:

- Recycled to Type II cells (most)
- Phagocytosis and degredation by alveolar macrophages
- Intra-alveolar catabolism
- Removal by mucociliary escalator.

Flow Resistance

- In addition to the elastic recoil of the lungs and chest wall the respiratory muscles encounter flow-resistance properties of the lungs and chest wall during breathing.
- The amount of force that must be applied during breathing depends on the amount of resistance to airflow:
  - Upper airways and tracheo-bronchial tree
  - Frictional resistance of tissues sliding over each other in lung parenchyma and chest wall.
- During inspiration - Force required to overcome flow resistance provided by inspiratory muscles. However normal slow expiration can be achieved just by the elastic recoil of the lung until level of FRC.
TLC: approx 6 litres
FRC: approx 40% TLC (2 components-a) ERV-15% TLC b) RV - 25% TLC
IC - approx 60% TLC
VC - approx 75% TLC (4.5 litres) = IC + ERV

Lung Mechanics 2 Learning Objectives

- Describe the relationship between alveolar and atmospheric gas pressures, airway resistance and airflow.
- Describe the factors that affect airway resistance centrally and peripherally.
- Name the two major components that contribute to the work of breathing and explain how each may be altered in disease states.
- Describe the relationship between mechanical work and oxygen cost of breathing in normal and patients with respiratory insufficiency.
- Describe the relationship between alveolar and atmospheric gas pressures, airway resistance and airflow.

Flow resistance = Pressure/Flow
- At any instant in the respiratory cycle:
  - \( P_r = P_{total} - P_{el} \)
  - Where \( P_r \) = Pressure required to overcome the flow resistance
  - \( P_{total} \) is total pressure applied
  - \( P_{el} \) = Pressure required to overcome the elastic resistance/tendency to recoil

**Airflow and resistance cont.**
- Vmax= Maximum airflow therefore:
  - Flow resistance (R) = Pressure (P)/Flow (V)
  - Once Vmax (flow) has been achieved then the resistance to airflow must rise in direct proportion to the driving pressure.
- The rise in airflow resistance that occurs at each lung volume is due to the dynamic compression of the airways.
- Flow resistance is normally between 1-3cm, water/litres/sec which can be increased 10-15 fold in Asthma or COPD.

**Pressure and dynamic compression**
- The pressure in the airways drops from the alveolar pressure to the mouth or Pao (atmospheric pressure).
- Pleural pressure and gradient of pressure in the airways - when interthoracic pressure is less than pleural pressure dynamic compression of airways occur.
- Equal Pressure Point (EPP) is the point at which intrabronchial and extrabronchial pressures are equal.

As lung volume increases airway resistance decreases
- This is because the airways are more distended at a higher lung volume due to a decreased transpulmonary pressure.

Airway calibre
- Whether or not they are large, larger = less resistance to flow.
- Airway generation
  - Airway generation refers to the number airway that it is i.e there are 23 generations of airway with higher numbers being smaller and more peripheral.
  - Highest regional resistance is at generation 4.
  - Medium sized bronchi of short length and frequent branchings result in highly non-laminar air flow with extreme turbulence.

Airflow profile
- Laminar vs turbulent vs transitional
- Pleural pressure and gradient of pressure in the airways: when intrathoracic pressure is less than pleural pressure dynamic compression of airways occur.
- Equal Pressure Point (EPP) is the point at which intrabronchial and extrabronchial pressures are equal. Further upstream from the EPP (towards atmospheric pressure) there is a transmural pressure tending to narrow or close the airway.

**Dynamic Compression of the Airways**

- Flow limitation occurs at specific sites of narrowing where the transmural pressures become negative, \( P_{pl} \neq P_{alv} \).
- When dynamic compression of the airways occurs the maximum driving force for flow will become the difference between \( P_{alv} \) and \( P_{pl} \) which will not be determined by effort but by the volume and compliance of the lung.
- The major factor contributing to a positive airway transmural pressure is a high lung static recoil pressure (high lung volume) because this contributes to a greater pressure within the airspaces relative to pleural pressure.

**Resistance to airflow**

- At high lung volumes: Maximum expiratory flow increases with increasing effort.
- At lower lung volumes: Increasing pressure raises the airflow rate to a maximum & further effort produces no further increase in flow (presumed to be because of airway compression).

**Mechanical work and alveolar ventilation**

1. **Increase in flow-resistive work** (e.g., in asthma)
   - Elastic energy stored during inspiration is not enough to produce airflow during expiration.
   - Therefore expiratory muscles tend to do extra work.

2. **Increase in elastic resistance** (e.g., pulmonary fibrosis)
   - Work required to overcome flow resistance is barely altered.
   - Much more work is required to overcome the high elastic resistance of the "stiff lungs".
   - The work of breathing can affect the pattern of breathing and therefore the amount of ventilation taking part in gas exchange.
   - For any given alveolar ventilation there is an optimal respiratory rate and tidal volume at which the total mechanical work of breathing is minimal.
Dynamic Compression of the Airways

- For any given alveolar ventilation there is an optimal respiratory rate and tidal volume at which the total mechanical work of breathing is minimal.

Mechanical work and alveolar ventilation

When the respiratory rate is less than optimal
- Flow resistive work is less but larger tidal volumes are required to achieve a given alveolar ventilation.
- Therefore the amount of work required to overcome the elastic resistance increases considerably.

When the respiratory rate is more than optimal
- Total ventilation must increase if the same ventilation is to be maintained.
- Therefore the amount of work required to overcome the elastic resistance is less however the flow-resistive work will increase roughly proportionally to the increase in respiratory rate.

Flow-volume loops in obstructive disorders

- At very high ventilation oxygen consumption increase considerably and may become a significant proportion of the total body oxygen consumption. This is due to increased oxygen demand by respiratory muscles.
- Emphysema: oxygen cost even at low ventilation may be increased by 4-10x.
- Respiratory insufficiency: oxygen consumption increases disproportionately even at very low ventilation.

Pulmonary fibrosis/kyphoscoliosis
- Elastic resistance is increased which causes curve to be shifted up.
- The work is minimal at increased frequency.
- Therefore respirations tend to become rapid and shallow.

Bronchial obstruction
- Flow resistance is increased and causes curve to shift up.
- Work is minimal at lower respiratory frequencies.
- Therefore respirations tend to become slower and deeper.

Qu. 2: Which of the following muscles plays no role in inspiration in either health or disease?

- Rectus abdominis
- Scalene
- Sternoceleidomastoid
- External intercostal

Best Option: Rectus abdominis

The abdominal muscles are recruited for forced expiration: the diaphragm and external intercostals are the main muscles of inspiration; the scalene and sternoceleidomastoids are recruited when demand is increased (e.g. in lung disease).

Describe the relationship between mechanical work and oxygen cost of breathing in normal and patients with respiratory insufficiency.

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Learning Objectives

Compare the systemic and pulmonary circulations with respect to

- (i) the structure of the arteries and arterioles
- (ii) the mean arterial blood pressure and flow
- (iii) the overall resistance to blood flow.

Explain how differences in the arterial blood pressures of the two circulations influence the structure of the two ventricles of the heart.

Describe and explain the relative difference in blood flow to the bases and apices of the lungs in a standing human.

Explain, with reference to the pulmonary circulation, the meaning of the terms vascular recruitment and hypoxic vasoconstriction.

Explain the importance of hypoxic vasoconstriction in the foetus. Give one advantage and one disadvantage of this response in an adult suffering from chronic lung disease.

Explain what is meant by pulmonary oedema. Identify 3 pathophysiological mechanisms that may lead to this state.

Explain the term "pulmonary embolism" and state the typical site of origin of such emboli. Describe the consequences of a large embolus with respect to

- i) the right side of the heart and the pulmonary circulation
- ii) the viability of the lung tissue and
- iii) the implications for gas exchange.

Give two reasons why lung disease may lead to pulmonary hypertension.

Appreciate, in the context of the pulmonary circulation, the concept of shunting. Identify the potential deleterious effects of an increased pulmonary shunt.

Describe and explain the relative difference in blood flow to the bases and apices of the lungs in a standing human.

- Gravity tends to send blood down to the bottom of the lungs.
- Bottom of lungs are a little squashed by abdominal contents - hence strange peaks.

![3 zone model diagram]

- 3 zone model
- Blood within the alveoli are more exposed to alveolar pressure due to really thin walls that aid diffusion.

![Blood flow volume graph]

- 3 zone model
- Zone 1: \( P_a > P_v > P_{au} \) - Top of lung
  - Alveolar pressure doesn’t change which is denoted as \( P_{au} \)
  - Arteriole pressure changes - major resistance vessels.
  - Alveolar pressure stricture arterioles and blocks blood vessels.
- Zone 2: \( P_{au} > P_v > P_a \)
  - On the arteriole side the pressure is great enough that it keeps the vessel open.
  - At the venous end of the system pressure is lower and hence the vessel closes under the influence of the arteriole pressure.
- Zone 3: \( P_a > P_{au} > P_v \)
  - Alveolar pressure isn’t high enough to close the vessels.

Compare the systemic and pulmonary circulations with respect to

- (i) the structure of the arteries and arterioles
- (ii) the mean arterial blood pressure
- (iii) the overall resistance to blood flow.

Explain, with reference to the pulmonary circulation, the meaning of the terms vascular recruitment and hypoxic vasoconstriction.

Vascular recruitment: This is the process of causing more blood vessels to have blood flowing through them.

Distension: The blood vessels which have blood flowing through them dilate to accommodate more blood flow.

- Capillary recruitment and distension both cause a fall in PVR.
- Automatic recruitment of zone 2 vessels.
- HPV: Hypoxic Pulmonary Vasoconstriction
  - If alveolar oxygen tension falls, blood is diverted to areas of the lungs which are adequately aerated - think ventilation-perfusion matching.
  - Alveolar oxygen sensor that is dependent upon Hypoxia-inducible factor which regulates systemic changes.
  - Tibetans have polymorphism that allows them to live better at altitude.

Explain how differences in the arterial blood pressures of the two circulations influence the structure of the two ventricles of the heart.

- In the foetus due to both R and L ventricles pumping against systemic circulation both ventricles are similar in size.
- Right ventricle atrophies as the pressure it is subjected to decreases. Right ventricle also loses the ability to pump blood into very high pressure.

Embryology

- Brachial arches that are reminiscent of when we were fish.
- Pulmonary outpouching of the 6th branchial arch.
- Ductus arteriosus - communication between pulmonary trunk and aorta.
- Foramen oval is communication between atria.
- RV pressure is greater in fetus thus blood passes through ductus arteriosus.

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  - Alveolar oxygen sensor that is dependent upon Hypoxia-inducible factor which regulates systemic changes.
  - Tibetans have polymorphism that allows them to live better at altitude.

Explain the importance of hypoxic vasoconstriction in the foetus. Give one advantage and one disadvantage of this response in an adult suffering from chronic lung disease.

Advantages

- Hypoxic vasoconstriction means that blood isn’t wasted by sending too much of it to the lungs where the oxygen supply is poor, instead it is sent to the placenta for oxygenation.
- Likewise in pneumonia the lung that is filled with fluid is bypassed.

Disadvantages

- In widespread lung disease it is unhelpful as blood does need to reach the alveoli even if they are functioning poorly.
- Altitude - see Hypoxia lecture

Explain what is meant by pulmonary oedema. Identify 3 pathophysiological mechanisms that may lead to this state.

- Pulmonary system doesn’t have to pump anywhere near as hard as the systemic.
- Arteries and veins have thinner walls and less smooth muscle than the systemic.
- Also the capillaries in the systemic circulation are like a network structure, whereas in the pulmonary system they are more like a mesh - posts in car park analogy...
Explain what is meant by pulmonary oedema. Identify 3 pathophysiological mechanisms that may lead to this state.

- **Pulmonary oedema**: Fluid infiltration into pulmonary tissue
  - **Interstitial oedema**
  - **Alveolar flooding**
  - Perivasular cupping and better defined interstitial structures indicate Pulmonary Oedema.

- Fluid leaves interstitial fluid and enters the alveoli which causes impaired gas exchange, reduced lung compliance and increased pulmonary venous pressure.

**Pathophysiological mechanisms**

1. Increased hydrostatic pressure causes high pulmonary venous pressure.
   - Left sided heart failure
   - Mitral stenosis
2. Decreased plasma colloid pressure - reduced plasma proteins
   - Starvation
   - Abnormal leakage from kidney or gut
3. Increased capillary permeability
   - Adult respiratory distress syndrome (ARDS)

**Qu. 8:** Which of the following statements about the tracheo-bronchial circulation is untrue?

- √ The rate of blood flow to the airway mucosa is relatively low compared to most other tissues
- Venous blood from the bronchial circulation returns to the heart via the pulmonary veins
- Venous blood from the bronchial circulation returns to the heart via the systemic veins
- It contributes to the humidification of inspired air
- It helps to clear inhaled drugs

**Best Option:** The rate of blood flow to the airway mucosa is relatively low compared to most other tissues

Blood flow in the tracheo-bronchial circulation is amongst the highest to any tissue. Venous return from these vessels returns to the heart via both systemic and pulmonary veins.
Learning Objectives

1. Know the structure of the mucosa (epithelium + underlying matrix) from the large conducting airways through to the alveoli.

2. Know the cell biology and function of the mucociliary escalator in normal lung defence and against inhaled toxins and microorganisms.

3. Know the role of Clara cells (non-ciliated secretory epithelial cells) and alveolar type II cells in lung defence and repair.

4. Know the role of the alveolar macrophage and polymorphonuclear neutrophil in normal lung and after inhalation of cigarette smoke, particles, microbes, noxious gases etc.

5. Know the role of the interstitial cells in connective tissue synthesis (brief).

6. Know what pathology causes obstructive lung disease, especially the role of uncontrolled inflammation, abnormal tissue repair and mucous production (tutorial).

7. Know the role of Clara cells (non-ciliated secretory epithelial cells) and alveolar type II cells in lung defence and repair.

- Full of granules that aid detoxification by secreting lysozyme.
- 20% of epithelial cells and is lower in smokers. Clara cells are destroyed by the cigarette smoke.
- Secretary cells and are very important in replacing and repairing damaged epithelium.
- Detoxification and repair/progenitor cells.
  - Pores of Kohn: Pores between adjacent alveoli that function as a means of collateral ventilation. In disease septae disappear and walls of alveoli have massive holes.

Alveolar:

- Type I epithelial cells are very large, and flattened: 40-80 microns in diameter. Wrap themselves around capillaries the gas can diffuse across them as they are very thin. Covers 95% of the alveolar surface.
- Type II epithelial cells are responsible for secreting surfactant and repair/progenitor cells. These cells sit in the corners of the alveoli and contain lamellar bodies full of pulmonary surfactant. Precursor of Type I cells.
  - Fibrotic lung disease: Type II divide but cannot differentiate into Type I. Fibroblast which are multiplying release factors which cause this mechanism. Only 5% of surface area because only tip of cell is protruding.
  - Stromal cells (myo) fibroblasts: produce ECM containing collagen and elastin which allows lung compliance and also make the extracellular matrix.
- Ratio of Type 1: Type II= 1:2 in number
- 1 or 2 macrophages per alveolus.
- Macrophages compensate for having no muco-ciliary escalator by phagocytosis. Either crawl back up the lung or go into the lymphatics system.

Cigarette smoke increases apoptosis, necrosis and blocks repair of cells.

Functions of Secretory cells

- All secrete a protective lining layer which differs between areas of the lungs.
- Synthesise and release antioxidants such as glutathione, superoxide dismutase.
- Synthesise and secrete antiproteases such as SLPI
- Release lysozyme.
- Carry out xenobiotic metabolism

Miscellaneous

- Macrophages from people who smoke are much darker brown.
- People exposed to asbestos. Castrated phagocytosis.
- Cigarette smoke contain procarcinogens.
- Phase I enzymes make active compounds but phase II enzymes cannot metabolise to water soluble metabolite which is excreted. What happens instead is that the carcinogen binds to DNA and mutates it.

Qu. 5: Which of the following statements about the airways is untrue?

- Serous submucosal glands secrete mucins
Epithelia cells in the wall may secrete inflammatory mediators

Smooth muscle cells in the wall may secrete inflammatory mediators

Ciliated cells help to clear inhaled particles

A major part of the oxygen supply to the airways is obtained via the bronchial arteries

Mark = 1 (conf=1)

Best Option: Serous submucosal glands secrete mucins

Serous submucosal cells secrete antibacterials; mucus cells secrete mucins.
Awake—Control of breathing
16 March 2012
6:16

Learning Objectives

- Describe the timing and neural drive components of a tidal breath
- Know in outline the central organisation of breathing, and the principal inputs and outputs.
- Be able to describe the ventilatory sensitivity to CO₂ and hypoxia.
- Be aware of the neural response to “loaded” breathing.
- Realise that “breathlessness” is a complex sensation, and know that its quantity can be measured by Borg or Visual Analogue scales.

The organisation of breathing control

- There is no single pacemaker as in the heart.
- c. 10 groups of neurons in medulla near nuclei of IX and X nerves.
- Ventral groups are responsible for neural drive and dorsal groups are responsible for timing.
- Nucleus parahyoidalis—inspiratory
- Nucleus retrohyoidalis—expiratory
- Early and late firing inspiratory and expiratory groups, with augmenting or decrementing patterns.
- “Braking” produced by adducting larynx in early expiration or by inspiratory activity persisting.
- Inspiratory drive assisted by laryngeal and pharyngeal dilators.
- Pre-Bötzinger complex central rhythm generator.
- Complex array of neurotransmitters involved.

Reflex control

Cranial nerves

- Vth nerve: afferent from nose and face (irritant)
- IXth nerve: from pharynx and larynx (irritant)
- Xth nerve: from bronchi and bronchioles (irritant and stretch)
- Spinal nerve: from chest wall and respiratory muscles (spindles—“stretch”) (pain, startle) may influence the metabolic centre.
- Hering-Breuer reflex from pulmonary stretch receptors sense lengthening and shortening and terminates inspiration and expiration, but weak in humans (ventilatory responses in denervated lungs—post transplantation are normal).

What is being controlled?

- Metabolic controller has two parts
  i. Central part in medulla responding to H⁺ ion of ECF
  ii. Peripheral part at carotid bifurcation, the H⁺ receptors of the carotid body.

- CO₂ is very diffusible, and H⁺ changes mirror PCO₂ changes very rapidly for the hyperperfused carotid body, but more slowly in the ECF bathing the medulla. Thus, fast and slow responses exist.

- Normal alveolar PCO₂ is 5.3 kPa (40mmHg)
- Normal alveolar PO₂ is 13±kPa (100mmHg)

Functions of the respiratory muscles

- Maintenance of arterial PO₂, PCO₂ and pH (H⁺ ion), but pH is probably most important.
- Defence of airways and lungs: cough, sneeze, yawn.
- Exercise: fight and flight
- Speech, sing, blow.
- Laugh, cry, express emotions.
- Control of intrathoracic and intra-abdominal pressures, e.g. defecation, belch, vomiting.

Describe the timing and neural drive components of a tidal breath

- T: timing with subscript “I” meaning inspiration.
- V: volume with VE meaning ventilation.
- V/I: Mean inspiratory flow determined by neural drive.
- T/TOtot: Respiratory frequency per minute.
- VE: Ventilation

VE= VT x 60/TOT or VE= VT/I x T/TOtot

What are the determinants of a tidal breath in disease?

- In chronic bronchitis the total time for a tidal breath is about half of normal and the slope of VT/TI is steeper than normal due to relative hyperventilation. However VT is markedly reduced.
- In emphysema the tidal breath time is 3/4 of normal with tidal volume peak being only slightly less than that of normal. However the graph is shifted left by a greater VT/TI ratio which is a result of the quicker expansion by increased lung compliance.

CNS Control of breathing

- Involuntary or metabolic centre is located within the medulla.
  o This responds to metabolic demands for and production of CO₂ (VCO₂) and determines, in part, the “set point” for CO₂, generally monitored as PaCO₂.
- Voluntary or behavioural centre is located in the cerebral cortex.
  o Controls acts such as breath holding and singing.
  o Note that the metabolic will always override the behavioural.
- Other parts of cortex not under voluntary control, influence the metabolic centre.
- Sleep via the reticular formation also influences the metabolic centre.
- The limbic system (survival responses [suffocation, hunger, thirst]) and frontal cortex (emotions) and sensory inputs (pain, startle) may influence the metabolic centre.
1. Automatic Bulbopontine controller in the brainstem
2. Behavioural Suprapontine control which is widely distributed.
   * The stem suffix pontine refers to the Pons area of the brainstem.

Be aware of the neural response to “loaded” breathing.

- Dyspnoea is the medical term for breathlessness but with the connotation of discomfort or difficulty.
- There are three types of breathlessness.
  1. Tightness
     - Difficulty in inspiring due to airway narrowing; a feeling that the chest is not expanding normally.
  2. Increased work and effort
     - Breathing at a high minute ventilation, or at a normal minute ventilation but at a high lung volume, or against an inspiratory or expiratory resistance.
  3. Air hunger
     - Sensation of a powerful urge to breathe, e.g. a breath hold exercise
     - Mismatch between VE demanded and achieved.
     - Cerebral cortex compares two different afferent inputs.
       - Demand: A copy (corollary) of signal sent by metabolic controller to spinal motor neurones.
       - Afferents from lung, chest wall and chemoreceptors (carotid body) - output.

Realise that "breathlessness" is a complex sensation, and know that its quantity can be measured by Borg or Visual Analogue scales.

- See practical on dyspnoea Borg Scale is nothing at all to slight to maximal etc. Visual analogue scale is "not at all breathless" to "extremely breathless".

**Hyperventilation conditions**

**Central**
- Acute: metabolic centre poisoning (drugs, anaesthetics)
- Chronic: Vascular/ neoplastic disease of metabolic centre
  - Congenital central hypoventilation syndrome
  - Obesity hypoventilation syndrome
  - Chronic mountain sickness

**Peripheral**
- Acute: Muscle relaxant drugs, myasthenia gravis.
- Chronic: Neuromuscular with respiratory muscle weakness

**COPD**
- Mixture of central (won’t breathe) and peripheral (can’t breathe).

**Hyperventilation conditions**

- Chronic hypoxaemia
- Excess H+ (metabolic causes)
- Pulmonary vascular disease
- Chronic anxiety (psychogenic)

**Respiratory Acidosis**

- Acute: Hypoventilation causes decreased PaO2, PaCO2 and H+ rise which stimulates metabolic centre (and carotid body) to increase minute ventilation and restore blood gas and H+ levels.
- Chronic: Ventilatory compensation may be inadequate for PaCO2 homeostasis but renal excretion of weak acids (lactic and keto) returns H+ to normal, even though PACO2 remains high.

\[
[H^+] = \text{Constant} \times \frac{\text{PaCO}_2}{\text{HCO}_3^-}
\]

Strong ion difference= [Na+ + H+] - Cl-

**Metabolic acidosis and alkalosis**

- **Acidosis**: excess production of H+
  - Compensatory mechanisms
    - Ventilatory stimulation lowers PaCO2 and H+
    - Renal excretion of weak acids.
    - Renal retention of chloride to reduce strong ion difference.
- **Alkalosis**: excess HCO3_ moves H+.
  - Compensatory mechanisms
    - Hypoventilation raises PaCO2 and H+
    - Renal retention of weak acids
    - Renal excretion of chloride to increase strong ion difference.
Ciliated, intermediate, brush, basal tissue which is amongst the Nerves, ganglia, neuroendocrine cells, neuroepithelial bodies. Mediators, cytokines and chemokines. (produced by nitric oxide synthase, NOS)

Contraction and relaxation of the smooth muscle

Capillary

Fibroblast, interstitial cell (elastin, collagen, cartilage)

different areas of cilia are slightly out of sync that allows mechanism controlling ciliary beating

Mast cell, dendritic cell, lymphocyte, eosinophil, macrophage, neutrophil

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13:56

Airways Function

[Image 34x111 to 44x117]

[Image 34x540 to 44x545]

[Image 34x581 to 44x587]

[Image 34x625 to 44x630]

[Image 34x712 to 44x717]

[Image 34x755 to 44x760]

Smooth muscle cells:

Secretory:

- Mucous cells secrete mucus.
- Serous cells secrete antibacterial proteins such as lysozyme.
- Glands also secrete water and salts (e.g. Na and Cl).
- Smooth muscle around the base of the gland contracts and pushes the mucus out.
- It is thought that less viscous secretions from serous cells wash the mucus to the collecting ducts.
- Mucin granules contain mucin in high concentrations which is a precursor of mucus.

Cilia:

- Complex 9+2 arrangement of microtubules with dynein arms that provide ATP for movement.
- Apical hooks which engage with mucus.
- Metachronal rhythm - different areas of cilia are slightly out of sync that allows progressive movement of particles.

Epithelial cells:

- Secretions of mucins, water and electrolytes.
- Movement of mucus by cilia-mucociliary clearance.
- Act as physical barriers.
- Production of regulatory and inflammatory mediators:
  - NO (produced by nitric oxide synthase, NOS) - mechanism controlling ciliary beating as putting NO on cilia causes them to speed up.
  - CO (by hemeoxygenase, HO)
  - Arachidonic acid metabolites, e.g. prostaglandins (COX)
  - Chemokines e.g. IL-8
  - Cytokines e.g. GM-CSF
  - Proteases

Smooth muscle cells:

- Contributes to
  - Structure - hypertrophy or proliferation of the smooth muscle cells can affect the airway
  - Tone or airway calibre - contraction and relaxation of the smooth muscle under stimuli by adrenaline.
  - Secretion - Mediators, cytokines and chemokines.
- In diseases such as asthma where there is inflammation which causes enlargement of the layer and section of inflammatory mediators.
- They respond to bacterial products and cytokines to produce NO, COX, cytokines, chemokines and adhesion molecules.

Describe the humoral control of the function of the airway cells

- Nerves:
  - Parasympathetic (cholinergic)
  - Sympathetic (adrenergic)
  - Sensory
- Regulatory and Inflammatory mediators:
  - Histamine
  - Arachidonic acid metabolites (e.g. prostaglandins, leukotrienes)
  - Platelet activating factor, PAF

Airway vasculature: Tracheo-bronchial circulation

- 1.5% of cardiac output
- Blood flow to airway mucosa- 100-150 ml/min/100g tissue which is amongst the highest to any tissue.
- Bronchial arteries arise from many sites on aorta, intercostal arteries and other arteries.
- Blood returns from tracheal circulation via systemic veins.
- Blood returns from bronchial circulation to both sides of heart via bronchial and pulmonary veins.

Massive perfusion due to plexus just under the epithelium.

Functions of Tracheo-bronchial circulation

- Good gas exchange to airway tissues and blood.
- Contributes to warming and humidification of inspired air.
- Clears inflammatory mediators.
- Clears inhaled drugs.
- Supplies airway tissue and lumen with inflammatory cells and proteinaceous plasma.

Mechanism of plasma exudation in the airways

Regulatory-inflammatory cells in airways

Histamine

Neutrophil

Eosinophil

Serotonin

Adenosine

Prostaglandins

Leukotrienes

Smooth muscle (airway, vascular: contraction, relaxation)
- Regulatory and inflammatory mediators:
  - Histamine
  - Acetylcholine metabolites (e.g. prostaglandins, leukotrienes)
  - Chemokines
  - Proteinases (neutrophil elastase)
  - Reactive gas species (e.g. O₂, NO)

Describe the neuronal control of the function of the airway cells

Innervation of the airways
- Sympathetic or adrenergic pathways isn't present in human beings.
- Cholinergic constrict the airways instead we can relax our airways via adrenergic pathways.

- Vagus nerve
- Adrenal gland (adrenaline)
- Nodose ganglion

- Sensory nerve

Briefly outline the altered functions of airway cells to the pathophysiology of respiratory diseases

Asthma
- A clinical syndrome characterised by increased airway responsiveness to a variety of stimuli which leads to airway obstruction.
- Airflow obstruction is reversible and varies over short periods of time.
- Dyspnoea, wheezing and cough.

Pathology
- Mucus plug full of eosinophils.
- Epithelial fragility little gaps where cells should have been.
- Thickening of the basement membrane.
- Vasodilation of blood vessels.
- Contraction of airway smooth muscle throws epithelium into folds.

Pathophysiology schematic
- Sets up a cholinergic reflex resulting in constriction of smooth muscle and increased mediators or particles.
- Bronchodilators increase bronchi diameter but does nothing to affect the underlying oedema.

- Blood vessel
- Adrenal gland (adrenaline)
- Airborne irritants

Briefly relate changes in control mechanisms to the pathophysiology of respiratory diseases

- Asthma, COPD and cystic fibrosis all of which are common conditions involve control mechanism issues.
- Asthma~ 5% of population in industrialised countries
- COPD- 4th cause of death in UK and USA
- CF -cystic fibrosis autosomal recessive gene defect (~1:20 gene frequency; affect ~1:2000 Caucasians): CTFR
- Airway inflammation, airway obstruction...
- Airway remodelling

- Epithelial fragility exposes sensory nerve endings which are tickled by inflammatory mediators or particles.
- Sets up a cholinergic reflex resulting in constriction of smooth muscle and increased airway mucus secretion.
- Goblet cell hyperplasia causes increased mucus secretion.
- Fibroblasts contribute to increased thickening of the basement membrane.

- Airway inflammation causes retraction of airway smooth muscle.
- Airway obstruction increases mucus production.
- Airway inflammation, airway obstruction.
- Airway remodelling.

- Smooth muscle (airway, vascular: contraction, relaxation)
- Secretion (mucins, water, etc)
- Plasma exudation
- Neural modulation
- Chemotaxis
- Remodelling

- Parasympathetic 'Motor' pathway
- Parasympathetic (cholinergic)
- Sympathetic or adrenergic pathways isn't present in human beings.
- Vagus nerve
- Adrenal gland (adrenaline)
- Nodose ganglion

- Sensory nerve

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Diagnosis of cancer

Types of lung cancer and how they develop

Describe the link between cigarette smoking and the incidence of lung cancer. Also explore other aetiologies of lung cancer.

Describe the main histological types of lung cancer, their different biological behaviour, and the significance this has for prognosis and treatment.

Summarise how lung cancer is staged.

Increasing importance of molecular pathology

Describe the different local and systemic complications of lung tumours.

Explain what is meant by a paraneoplastic syndrome with examples.

Describe the risk factors and basic pathology of mesothelioma

Types of lung cancer and how they develop

- Tumours can be broadly split into benign and malignant lung tumours.

Benign
- These tumours do not metastasise but can cause local complications such as airway obstruction. An example of this is a chondroma.

Malignant
- These tumours have the potential to metastasise to other areas but their behaviour can vary from relatively indolent to aggressive. The commonest malignant tumours are epithelial tumours.

Common malignant tumours of the lungs

Small cell carcinoma- 20%

"Non-small cell carcinoma"
- Squamous cell carcinoma 20-40%
- Adenocarcinoma 20-40%
- Large cell carcinoma- uncommon

Development of Carcinoma

- Multistep pathway of changes from metaplasia, dysplasia, carcinoma in situ to invasive carcinoma.
  - Bur for some lung tumours a precursor lesion is not identifiable e.g. small cell carcinoma
  - Associated with accumulation of mutations.
  - Pathways different for different tumour types.

Describe the main histological types of lung cancer, their different biological behaviour, and the significance this has for prognosis and treatment.

Squamous Cell Carcinoma

- Irritants such as smoke cause cells to change and adapt in an initially preventive way.
- 25-40% pulmonary carcinoma.
- Closely associated with smoking.
- Traditionally central arising from bronchial epithelium, but recent increase in peripheral SqCC
- Local spread, metastasize late.

- The histology of SqCC shows evidence of squamous differentiation which includes keratinisation and intercellular "prickles" representing desmosomes.

Adenocarcinoma

- Atypical adenomatous hyperplasia- proliferation of atypical cells lining the alveolar walls. Increase in size and eventually can become invasive
- Type 2 cells proliferate and can become invasive.

Describe the link between cigarette smoking and the incidence of lung cancer. Also explore other aetiologies of lung cancer.

Smoking- At least 75% of lung cancers can be attributable to smoking and 25% of cancers in non-smokers may be attributed to passive smoking. Risk is directly proportional to the number of cigarettes smoked, the duration smoked for, the age of initiation and the depth of inhalation and levels of tar and nicotine. Smoking a pack of cigarette a day for 20 years gives a lifetime risk of lung cancer of 10% which is 10-30 times greater than for lifelong non-smokers. Cigarette smoke contains a variety of chemicals that aids the development of tumours.

- Tumour initiators
  - Polycyclic aromatic hydrocarbons
  - Tumour promoters
    - N Nitrosamines
    - Nicotine
    - Phenols
  - Complete carcinogens
    - Nickel, Arsenic

Asbestos exposure- Asbestos + smoking= 50 fold increased risk of cancer in particular mesothelioma.

Radiation- radon exposure which is found naturally in rocks, soil and ground water, may also increase risk along with therapeutic radiation [Chromates, arsenic, nickel, mustard gas.

Genetic predisposition

- Familiar lung cancers are rare but there is evidence of increased risk for first degree relatives of young age, non-smoking cases.
- Susceptibility genes
  - Nicotine addiction
  - Chemical modifications of carcinogens
    - Polymorphisms in cytochrome p450 enzymes and glutathione S transferases which plays a role in eliminating carcinogens.
  - Susceptibility to chromosome breaks and DNA damage.

Summarise how lung cancer is staged.

Diagnosis of cancer

- Cancers can either be asymptomatic or symptomatic.
  - Less than 10% of lung cancers are discovered incidentally, instead the majority of patients are aged 50-70 and have some of the symptoms detailed below.

- Symptoms of lung cancer include:
  - Cough (which may change in nature over time)
  - Haemoptysis
  - Recurrent infections
  - Other

  - In addition symptoms due to haematogenous extrathoracic metastasis to bone, liver, adrenals and brain present in around one-third of patients at the time of diagnosis.

  - Another way to confirm a diagnosis other than X-ray is by looking at the histology (tissues) or cytology (cells) of the lungs.

Cytology

- Sputum samples
- Bronchial washings and brushings
- Bronchoalveolar lavage
- Pleural fluid
- Endoscopic fine needle aspiration of tumour/enlarged lymph nodes

Histology

- Biopsy at bronchoscopy- central tumours
- Percutaneous CT guided biopsy-peripheral tumours
- Mediastinoscopy and lymph node biopsy for staging of the cancer
- Open biopsy at time of surgery if lesion not accessible otherwise-frozen section.
- Resection specimen in order to confirm excision and staging.

Describe the link between cigarette smoking and the incidence of lung cancer. Also explore other aetiologies of lung cancer.

- Extremes fibrotic alveolar walls. Increase in size and eventually can become invasive.

- The histology of SqCC shows evidence of squamous differentiation which includes keratinisation and intercellular "prickles" representing desmosomes.
- Atypical adenomatous hyperplasia - proliferation of atypical cells lining the alveolar walls. Increase in size and eventually can become invasive.
- Type 2 cells proliferate and can become invasive.
- Extreme fibrotic - desmoplastic response.
- Arise from glandular epithelium and thus produces mucin vacuoles.
- Commoner in far east, females and non smokers.

**Histology**
- Increasing incidence currently making up 25-40% of pulmonary carcinomas.
- Peripheral and more often multifocentric.
- Extrathoracic metastases common and early.
- Histology shows evidence of glandular differentiation.
- Smokers are more likely to have a K ras mutation whereas non-smokers may have EGFR mutation.

**Large cell carcinoma**
- Poorly differentiated tumours composed of large cells. There is no histological evidence of glandular or squamous differentiation but on electron microscopy many show some evidence of glandular, squamous or neuroendocrine differentiation.
- It generally presents as a large peripheral mass, often with metastases.
- Poorer prognosis

**Small cell carcinoma**
- Very small, hyperchromic look very blue on histology.
- 20-25% tumours and very often associated with smoking.
- SC carcinomas arise from neuroendocrine cells in the bronchial submucosa and typically present as a central mass with lymph node enlargement.
- These are very aggressive tumours that invade lymphatics and blood vessels and thus 80% present with metastases such as brain and bone at diagnosis.
- Very chemo sensitive but have an abysmal prognosis.
- Paraneoplastic syndromes occur because the cancer arises from neuroendocrine cells.

**Significance for prognosis**
- It is very important to accurately diagnose whether or not a patient has small cell or non small cell lung cancer.
- After small cell carcinoma has been diagnosed survival is only for 2-4 months if left untreated. Chemoradiotherapy is undertaken but not usually surgery because most have spread by diagnosis.
- With non small cell carcinoma if the cancer is diagnosed at an early stage (1) then there is a 60% chance of surviving for 5 years. However if the cancer is diagnosed at a late stage (4) there is only a 3% chance of surviving 5 years. 20-30% have early stage tumours suitable for surgical resection. Less chemo sensitive than SC.
- In addition evidence has recently shown that it may be important to sub-type non SCC for treatment. Some adenocarcinomas respond well to anti-EGFR drugs (Tarceva).
- In contrast some patients with SC develop fatal haemorrhage with Bevacizumab.

**Explain what is meant by a paraneoplastic syndrome with examples.**

**Paraneoplastic Syndrome** - Systemic effect of tumour due to abnormal expression by tumour cells of factors not normally expressed by the tissue from which the tumour arose.

**Endocrine**
1. Antidiuretic hormone
   - Syndrome of inappropriate ADH causing *hyponatraemia* (especially SCC).
2. Adrenocorticotropic hormone (ACTH)
   - Cushing’s syndrome (SCC).
3. Parathyroid hormone-related peptides
   - Hypercalcaemia (SCC).
- Others include
  - Calcitonin causing *hypocalcaemia*.
  - Gonadotrophin resulting in *gynecomastia*.
  - Serotonin – Carcinoid syndrome (especially carcinoid tumors, rarely SCC).

**Non-endocrine**
- Haematologic/coagulation defects, skin, muscular.

**Increasing importance of molecular pathology**
- In advanced stage NSCLC ERCC1 positive tumours have poor response to cisplatin based chemotherapy.
- ERCC1 protein removes Drug-DNA adducts.

**Targets of Treatment - EGFR**
- Membrane receptor tyrosine kinase
  - Regulates angiogenesis, proliferation, apoptosis and migration.
- Mutation/amplification in NSCLC
  - Non smokers, females and Asian.
  - Adeno 46% vs Squam 5%
  - Target of tyrosine kinase inhibitor

**Describe the different local and systemic complications of lung tumours.**

**Local effects of Bronchogenic Carcinoma**
1. Bronchial obstruction
   - Collapse of distal lung causing shortness of breath.
   - Impaired drainage causing pneumonia, abscess and infection.
2. Invasion of local structures
   - Haemoptysis, cough
   - Invasion around large vessels - Superior vena cava syndrome - venous congestion of head and arm oedema and ultimately circulatory collapse
   - Oesophagus - dysphagia
   - Chest wall - pain
   - Nerves - Horner's syndrome
3. Horner's syndrome - cancer affecting sympathetic nerves causing drooping of eyelid and unchecked parasympathetic activity also resulting in pupillary constriction.
4. Extension through pleura or pericardium
   - Pleuritis or pericarditis with effusion
   - Cardiac tamponade.
5. Diffuse lymphatic spread within the lung
   - Very poor prognosis with SOB.

**Systemic effects of bronchogenic carcinoma**
- Physical effects of metastatic spread
  - Brain fits
  - Skin lumps
  - Liver pain and deranged LFTs
  - Bones (bone pain, fracture)
- Paraneoplastic syndromes

**Describe the risk factors and basic pathology of mesothelioma**
- Malignant tumour of pleura
- Aetiology - asbestos exposure
- <1% of cancer deaths, but increasing incidence due to times of regulation.
- Essentially a fatal disease because it grows around the lung and into the chest wall.
- Lung lag time as the tumour develops decades after exposure and the sex ratio is with males> females, approx 3:1.
- Epithelioid and sarcomatoid types
Describe the effect of sleep on breathing and blood gases and in healthy people.

Specifically how does sleep effect oxygen and carbon dioxide levels. What are the mechanisms that lead to these changes?

Describe the apnoeic threshold which, in some people leads to central sleep apnoea.

Describe the influences of sleep on the upper airway which, in some people leads to obstructive sleep apnoea.

Know at least two upper airway muscles that reduce their activity during sleep.

Know the other major cardio-respiratory diseases (one cardiac, one respiratory) that are exacerbated by sleep-related changes in the control of breathing; briefly explain why sleep is detrimental to these patients.

Describe the apnoeic threshold which, in some people leads to central sleep apnoea.

- Hypoxemia- High levels of CO2 >6.4kPA
- Apnoeic Threshold. The level above which your CO2 has to go to maintain breathing during sleep.

<table>
<thead>
<tr>
<th>PCO2 (mmHg)</th>
<th>Awake</th>
<th>Sleep</th>
<th>REM</th>
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- A reduced CO2 reserve will mean that one's CO2 levels are closer to the apnoeic threshold. This means that another drop in CO2 levels potentially caused by:
  1. Apnoea induced hypoaxemic hyperventilation
  2. Vagal input from pulmonary stretch receptors.
  3. Circulating catecholamines.

will result in cessation of breathing. [See BMI Sleep Apnoea]

Describe the influences of sleep on the upper airway which, in some people leads to obstructive sleep apnoea.

- Central congenital hypoventilation syndrome - Ondine's curse
  - Have to be artificially ventilated every night of their lives.
- Obstructive sleep apnoea

Definition
- A sleep condition in which airflow from the nose and mouth to the lungs is restricted during sleep. It is defined by the presence of more than five episodes of apnoea per hour of sleep associated with significant daytime sleepiness.

Causes
- Muscles at the back of the throat relax which causes the airway to collapse. Alcohol makes this worse because it is a muscle relaxant.
- There is no cartilage above the larynx and instead muscle tone is required to keep the airway open.

Ventilatory sensitivity to CO2

- Changing V̇ₐ has no effect on oxygen saturation, this is because you are on the flat part of the oxygen dissociation curve.
- A respiratory illness can cause particular problems in sleep because you are dropping off the steep part of the curve.
- No equivalent for CO2 which means that when you go to sleep carbon dioxide levels go up.
- Overall reduction in number of neural inputs or less sensitive to input means CO2 levels rise.
- CO2 has to go up by about 2-3mmHg in order for you to breathe. Only 1/2kPA between breathing and not breathing.

Obstructive Sleep Apnoea

Definition
- A sleep condition in which airflow from the nose and mouth to the lungs is restricted during sleep. It is defined by the presence of more than five episodes of apnoea per hour of sleep associated with significant daytime sleepiness.

Causes
- Muscles at the back of the throat relax which causes the airway to collapse. Alcohol makes this worse because it is a muscle relaxant.
- There is no cartilage above the larynx and instead muscle tone is required to keep the airway open.
There is a negative interlumenal pressure at the back of the throat. Upon sleeping muscles relax or are paralysed if in REM sleep. The negative pressure generated in the lungs causes air to be sucked through compliant airways which causes their collapse.

- As the airways are shut, much more pressure is needed on expiration to open the airway again.
- Excess adipose tissue in obesity compresses neck if lying supine. This is more likely to affect males due to where we deposit fat.
- Uvula can also get sucked into the airway, blocking it.

The large intrathoracic pressure needed to ventilate the body is also exerted on the heart. The causes a massive increase in preload and afterload which can contribute to cardiac failure.

Presents with sleepiness as they have to wake up to restore airway. Could potentially result in a car crash during the day when they are still tired.

Extra detail

- There is a negative interlumenal pressure at the back of the throat. Upon sleeping muscles relax or are paralysed if in REM sleep. The negative pressure generated in the lungs causes air to be sucked through compliant airways which causes their collapse.
- As the airways are shut, much more pressure is needed on expiration to open the airway again.
- Excess adipose tissue in obesity compresses neck if lying supine. This is more likely to affect males due to where we deposit fat.
- Uvula can also get sucked into the airway, blocking it.

Effects on subject

- The large intrathoracic pressure needed to ventilate the body is also exerted on the heart. The causes a massive increase in preload and afterload which can contribute to cardiac failure.
- Presents with sleepiness as they have to wake up to restore airway. Could potentially result in a car crash during the day when they are still tired.

Treatment

- Stent isn’t applicable because you need to swallow which would block the oesophagus.
- CPAP - continuous positive airway pressure.
- Lose weight.

1. COPD
   - Increased hypoxia causes increased sympathetic nerve activity which causes a much worse prognosis as it will lower CO₂.

2. Heart Failure run a low CO₂
   - Pulmonary congestion irritate J receptors in lungs causing hyperventilation and running of a low CO₂.

Effects on subject  

- CO₂ increases with apnoea.

Effects on subject  

- Increased hypoxia causes increased sympathetic nerve activity which causes a much worse prognosis as it will lower CO₂.

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Learning Objectives

- Understand how respiratory symptoms are generated and perceived
- Discuss the importance of measuring respiratory symptoms in clinical medicine and clinical research

**Cough:**
- Describe the mechanics of a cough with reference to inspiration, expiration and closure of the glottis. Briefly explain how this manoeuvre serves to (i) protect the lungs from inhaled noxious materials and (ii) clear excess secretions from the lower respiratory tract.

- Describe the type and location of sensory receptors with the airways indicating how they are stimulated to give rise to cough. Identify the neural pathways which transmit this afferent (sensory) neural information to the brain.

- Describe in outline which regions in the brain are involved in generating the co-ordinated neural activity that results in the act of cough. Identify the efferent (motor) neural pathways and the main muscle groups which produce cough.

- Outline the clinical causes and the pathophysiological basis of these respiratory symptoms: cough, chest pain and dyspnea. (Dyspnea will be covered in detail in another presentation).

- Explain the concept of the sensitised cough reflex in disease as the basis for chronic cough.

- Discuss ways of controlling unnecessary cough.

- **Chest pain:**
  - Identify the type and location of sensory receptors with the thoracic cavity that when stimulated give rise to chest pain. Identify the neural pathways which transmit this afferent neural information to the brain.
  - Describe in outline which regions in the brain are involved in the perception of pain.
  - Discuss the concept of referred pain in the chest.
  - Describe different typical patterns of chest pain that can help in diagnosing the cause of pain.

- **Dyspnoea:**
  - Review the terms used by patients to describe the troublesome symptom of shortness of breath and its measurement.
  - Discuss the importance of measuring respiratory symptoms in clinical medicine and clinical research
  - Describe the mechanics of a cough with reference to inspiration, expiration and closure of the glottis. Briefly explain how this manoeuvre serves to (i) protect the lungs from inhaled noxious materials and (ii) clear excess secretions from the lower respiratory tract.

- Identify the type and location of sensory receptors with the airways indicating how they are stimulated to give rise to cough. Identify the neural pathways which transmit this afferent (sensory) neural information to the brain.

**Medicine and Clinical Research:**

- Cough is the third most common complaint heard by the GP with 10-38% of patients in respiratory outpatients complaining of it.
- Chest pain most common pain for which patient seeks medical attention 35% including acute chest pain.
- Shortness of breath: 6-27% of general population, 3% of visits to A&E.

- Identify the type and location of sensory receptors with the airways indicating how they are stimulated to give rise to cough. Identify the neural pathways which transmit this afferent (sensory) neural information to the brain.

- Cough receptor may be located between a goblet cell and a columnar epithelial cell and transmits information to the vagus nerve and brainstem.

- Rapidly adapting irritant receptors which are located within airway epithelium.

- Most numerous on posterior wall of trachea.

- At main carina, and branching points of large airways, less numerous in more distal airways. Absent beyond the respiratory bronchioles.

- Also in pharynx. Possibly also in the external auditory meatus, eardrums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium, and stomach.

- Stimuli: laryngeal and tracheobronchial receptors respond to chemical and mechanical stimuli.

**Afferent neural pathways for cough**

- Superior laryngeal nerve
- Vagus nerve
- Carina
- Main bronchi
- Accessory muscles of inspiration
- External intercostal
- Diaphragm
- Glottis
- Cough centre

**Efferent neural pathways for cough**

- Central cortex
- Clotis
- Accessory muscles of inspiration

**Type of receptors**

1. Slowly adapting stretch receptors
   - Located in airways smooth muscle
   - Myelinated nerve fibres
   - Predominantly in trachea and main bronchi
   - Mechanoreceptors
   - Respond to lung inflation

2. Rapidly adapting stretch receptors
   - Naso-pharynx, larynx, trachea, bronchi
   - Small, myelinated nerve fibres
   - Mechanical, chemical irritant stimuli, inflammatory mediators

3. C (chemical) fibre receptors
   - Free nerve endings
   - Larynx, trachea, bronchi, lungs
   - Small unmyelinated fibres
   - Chemical irritant stimuli, inflammatory mediators
   - Release neuropeptide inflammatory mediators Substance P, Neurokinin A,
Discuss the main important causes of shortness of breath and approach to management.

Cough

Acute infections such as viral pneumonia, tracheobronchitis.

Chronic infections: bronchiectasis, tuberculosis.

Airway diseases including asthma, chronic bronchitis and chronic post-nasal drip.

Parenchymal disease such as interstitial fibrosis and emphysema.

Tumours: bronchogenic carcinomas, alveolar cell carcinoma, benign airway tumours.

Foreign body

Cardiovascular: left ventricular failure, pulmonary infarction and aortic aneurysm.

Other disease: reflux oesophagitis, recurrent aspiration.

Drugs: ACE inhibitors.

Complications

- Pneumothorax with subcutaneous emphysema
- Cough syncope
- Cardiac dysrhythmias.
- Headaches
- Intercostal muscle pain
- Rupture of rectus abdominis muscle
- Social embarrassment
- Urinary incontinence
- Wound dehiscence

Discuss ways of controlling unnecessary cough.

<table>
<thead>
<tr>
<th>Cough</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Inhaled corticosteroids</td>
</tr>
<tr>
<td>Cough variant asthma</td>
<td>(inhaled b-adrenergic agonists)</td>
</tr>
<tr>
<td>Eosinophilic bronchitis</td>
<td></td>
</tr>
<tr>
<td>Rhino-sinusitis/post nasal drip</td>
<td>Topical steroids</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux</td>
<td>Topical vasoconstrictors</td>
</tr>
<tr>
<td>Angiotensin Converting Enzyme</td>
<td>Medical therapies</td>
</tr>
<tr>
<td>variant asthma</td>
<td></td>
</tr>
<tr>
<td>Inhaled ACE inhibitor cough</td>
<td>Stop ACE inhibitor</td>
</tr>
</tbody>
</table>

Identify the type and location of sensory receptors with the thoracic cavity that when stimulated give rise to chest pain. Identify the neural pathways which transmit thisafferent neural information to the brain.

Chest pain

Sensory input from lungs, airways and chest wall

- Nose
- Trigeminal - Cranial nerve V
- Pharynx
- Glossopharyngeal (IX)
- Vagus (X)
- Larynx
- Vagus
- Lungs
- Vagus
- Chest wall
- Spinal nerves

Describe in outline which regions in the brain are involved in the perception of pain.

- Insular cortex
- Ventral premotor cortex - Brain is suggesting that the body be removed from the hot water stimuli.

Dyspnea

Troublesome shortness of breath reported by a patient

- Occurs at inappropriately low levels of exertion, and limits exercise tolerance.
- Can be associated with feelings of impending suffocation.
- Poor perception of respiratory symptoms and dyspnoea may be life threatening.

Describe in outline which regions in the brain are involved in the perception of dyspnea.

- Insular cortex
- Ventral premotor cortex - Brain is suggesting that the body be removed from the hot water stimuli.
Discuss the main important causes of shortness of breath and approach to management

- There is a scale created by the American Thoracic Society from 0-4 with 4 being most severe that they are breathless when getting dressed.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 None</td>
<td>Not troubled by breathlessness except with strenuous exercise</td>
</tr>
<tr>
<td>1 Slight</td>
<td>Troubled by shortness of breath when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>2 Moderate</td>
<td>Walks slower than people of same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level</td>
</tr>
<tr>
<td>3 Severe</td>
<td>Stops for breath after walking about 100 yards or after a few minutes on the level</td>
</tr>
<tr>
<td>4 Very Severe</td>
<td>Too breathless to leave house or breathless when dressing or undressing</td>
</tr>
</tbody>
</table>

- In addition there is the modified Borg scale which measure dyspnoea.

**Causes**
- Impaired pulmonary function
  - Obstructive: Asthma, COPD, tracheal stenosis
  - Neuromuscular weakness e.g. Phrenic nerve paralysis
  - Extrathoracic pulmonary restriction e.g. Kyphoscoliosis or pleural effusion.
- Impaired cardiovascular function
  - Myocardial disease leading to heart failure
  - Valvular disease
  - Pericardial disease
- Altered central ventilatory drive or perception
  - Systemic or metabolic disease
  - Metabolic acidosis
  - Anaemia

**Treatment of dyspnoea**
- Treat the cause itself if possible.
- Treating dyspnoea itself is difficult.
  - Add bronchodilators e.g. anticholinergics or beta adrenergic receptors agonists.
  - Drugs affecting brain e.g. morphine, diazepam
  - Lung resection e.g. lung volume reduction surgery.
  - Pulmonary rehabilitation - improve general fitness, general health, psychological well being.

**Discuss the concept of referred pain in the chest.**
- Visceral pain of the internal organs is not the same as somatic pain and the mechanisms are less well understood.
- The vagueness of visceral pain causes overlap of location and quality of pain and possible difficulty in diagnosis.
- Chronic pain is more complicated than acute pain and depends on poorly defined neural mechanisms.
- For a more detailed explanation of referred/visceral pain look in the anatomy of the abdomen section.

**Describe different typical patterns of chest pain that can help in diagnosing the cause of pain.**
- Chest wall: muscular or rib fracture
- Pleural pain
- Deep seated, poorly localised pain
- Nerve root pain/intercostal nerve pain
- Referred pain: shoulder-tip pain of diaphragmatic irritation.
- Chest pain and non-respiratory disorders
  - Cardiovascular disorders: MI, pericarditis, dissecting aneurysm
  - Gastrointestinal: oesophageal rupture, gastrooesophageal reflux
  - Psychiatric disorders: Panic disorder
Learning Objectives

- Oxygen delivery to the body tissues. Relationship of oxygen delivery to tissues and oxygen consumption. The development of tissue hypoxia when delivery fails to meet demand with onset of anaerobic metabolism (lactic acid production)
- Definition and causes of hypoxaemia.
- Haemoglobin and blood gas transport.
- Factors which change oxygen affinity
- Oxygen delivery to the body tissues. Relationship of oxygen delivery to tissues and oxygen consumption. The development of tissue hypoxia when delivery fails to meet demand with onset of anaerobic metabolism (lactic acid production)

Haemoglobin and blood gas transport.

- 2 alpha and 2 beta chains each having a haem molecule composing of a porphyrin and a ferrous ion.
- Very difficult to get the oxygen to the haem in the crevices of the haemoglobin. Once one molecule of oxygen has bound it causes haemoglobin to relax which makes the next oxygen molecule easier to bind.
- PO2 of 11 is nearly 100% saturation of the haemoglobin.
- Each gram of haemoglobin combines with up to 1.34mL oxygen, so with a [Hb] of 150g/L blood contains a maximum of 200mL/L oxygen bound to haemoglobin.
- Oxygen Content. This is the sum of the haemoglobin bound oxygen and the small amount of dissolved oxygen.
- Oxygen Saturation. The percentage of available binding sites to oxygen.
- The formula for this is: Oxygen capacity (mL/L) x 100%
- Factors affecting binding of oxygen to the haem group include pH, temperature, PCO2 and 2,3-DPG. This shifts the O2 dissociation curve resulting in something known as the Bohr effect.
- 50% of oxygen carried in the blood is wasted due to influence of CO2 on pH

Oxygen delivery

- O2 delivered = Cardiac output X O2 content (Litres/min) (ml/litre)
  = 5 x 200
  = 1000ml/min
- O2 uptake = CO X Arterio-Venous difference (consumption) 60ml
  = 5 x 60
  = 300ml/min
- R.Q = CO2 Output/ O2 uptake = 250/300 = 0.83

Decrease in oxygen affinity

- Good excess of delivery over consumption.
- Hypoxia means a lack of oxygen.

Definition and causes of hypoxaemia.

- Hypoxia means a lack of oxygen.
- Arterial O2 saturation <93%
- Arterial O2 content reduced

Causes:

- Alveolar hypoventilation
- Increased CO - cardiac output
- Imposed pulmonary perfusion
- Changes in regional blood flow
- Polycythaemia increase in red cells and haemoglobin concentration produced by secretion of erythropoietin from kidney
- Anaerobic metabolism

Compensatory mechanisms:

- Alveolar hypoventilation
- Increased CO - cardiac output
- Improved pulmonary perfusion
- Changes in regional blood flow
- Polycythaemia increase in red cells and haemoglobin concentration produced by secretion of erythropoietin from kidney
- Anaerobic metabolism

Compensatory mechanisms:

- Alveolar hypoventilation
- Increased CO - cardiac output
- Improved pulmonary perfusion
- Changes in regional blood flow
- Polycythaemia increase in red cells and haemoglobin concentration produced by secretion of erythropoietin from kidney
- Anaerobic metabolism

The relationships between content and gas tension in blood for oxygen (O2) and carbon dioxide (CO2) i.e. the O2 and CO2 dissociation curves. Factors affecting these curves with particular reference to oxygen uptake in the lung and the downloading of oxygen in the tissues.

Oxygen delivery

- O2 delivered = Cardiac output X O2 content (Litres/min) (ml/litre)
  = 5 x 200
  = 1000ml/min
- O2 uptake = CO X Arterio-Venous difference (consumption) 60ml
  = 5 x 60
  = 300ml/min
- R.Q = CO2 Output/ O2 uptake = 250/300 = 0.83

Factors which change oxygen affinity

- 80% of CO2 is carried by bicarbonate, 20% is carbamino.
- Carbon dioxide can bind to haemoglobin.

Factors which change oxygen affinity

- Decrease in oxygen affinity
- Increase in oxygen affinity

<table>
<thead>
<tr>
<th>Decrease in oxygen affinity</th>
<th>Increase in oxygen affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall in pH, rise in PCO2 and temperature.</td>
<td>Rise in pH, fall in PCO2 and temperature.</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Store blood</td>
</tr>
<tr>
<td>Pregnancy- due to foetal haemoglobin</td>
<td>Foetal blood</td>
</tr>
<tr>
<td>Increase in 2,3 diphosphoglycerate- DPG</td>
<td>Decrease in DPG</td>
</tr>
<tr>
<td>Shift in O2 dissociation curve to the right</td>
<td>Shift in O2 dissociation curve to the left</td>
</tr>
</tbody>
</table>

Hypoxia means a lack of oxygen.
Carbon monoxide affinity for Hb is 250 times higher for Hb than Oxygen. An inspired CO of 0.2% will saturate 80% of the Hb. Note that in the presence of CO the oxygen dissociation curve is shifted to the left (high affinity purple line) impairing oxygen unloading in the tissues. Note the lower affinity in anaemia (red line) and the difference in shape.

Anaemia and Carbon Monoxide

- In anaemia at any given partial pressure of oxygen the oxygen content is reduced because the lower concentration of haemoglobin results in a reduced concentration of binding sites.
- Alveolar PO2 is normal in anaemia and therefore arterial O2 content is 100mL/L. (75g/l x 1.34mL)
- At rest the tissues need to remove about 50mL/L ox oxygen from the blood passing through them.
- In exercise when there is an increased oxygen consumption there may be an inadequate partial pressure gradient driving diffusion of oxygen into the tissues which results from the reduced venous and capillary PO2.
- Although there is the same oxygen content in the anaemic and COHb graph, due to CO increasing binding affinity for oxygen (in the CO free Hb) there is an altered shape and leftward shift of the dissociation curve. This impairs oxygen release into the tissues resulting in hypoxaemia.
- At about 50-60% carboxyhaemoglobin symptoms of cerebral hypoxaemia such as headache, convulsions, coma and death are very severe. Interestingly though anaemic patients at the same arterial oxygen content level are typically asymptomatic at rest.

Point A: This shows the PO2 level after the tissues have removed the 50mL/L from a (Hb) of 150g/L

Point B: This shows the PO2 level after the tissues have removed the 50mL/L from a (Hb) of 75g/L [Anaemic]

Point C: This shows the PO2 level after the tissues have removed the 50mL/L from a (Hb) of 150g/L but with 50% occupied by carbon monoxide.

NOTE that above is g/L and thus a concentration of 150g/L is normal. In other modules we use g/DL and there a concentration of 15g/dl is normal.

High altitude pulmonary and cerebral oedema

- HAPE and HACE are serious medical emergencies with an untreated mortality of about 50%
- Approximately 1% of lowlanders suffer from these conditions usually proceeded by AMS.
- Patients with HAPE suffer from severe breathlessness, dry cough, chest pain and occasionally with haemoptysis. A chest X-ray shows patchy pulmonary oedema.
- The alveolar hypoxia leads to reflex pulmonary artery constriction and pulmonary hypertension which may lead to right heart failure.
- It is postulated that the oedema is due to "Capillary Leak" due to endothelial damage from hypoxia. There is no evidence of left ventricular failure.
- HACE usually follows AMS with severe headache, impaired cognition and physical function with clouding of consciousness which may proceed to coma. On ophthalmoscopy retinal haemorrhages are often seen and less commonly papilloedema.
- Successful treatment of HAPE and HACE depend on transferring the patient on oxygen before the alveolar hypoxia and ventilation and PaO2.
- Acclimatisation occurs over the next 2 to 10 days with resolution of symptoms and PAO2.
- Definition of respiratory failure and effect on arterial gas tensions.
- Respiratory failure: An arterial oxygen tension less than 60mmHg (47kPa), and a carbon dioxide tension above 50mmHg (6.7kPa)

Types of respiratory failure

Type 1 Hypoxaemic failure

- Decreased ability to transport oxygen with a normal (or low) PaCO2.
- The disorder of function in this condition is a disturbance of ventilation to perfusion relationships within the lung, whilst overall alveolar ventilation remains normal

Type 2 Ventilatory failure

- Low PaO2 and a low PaCO2 (or normal PaCO2) due to inadequate ventilation.
- Type 3 Combined hypoxaemic and ventilatory failure
- Features of type 1 and 2 are mixed, the deficit including both alveolar hypoventilation and a disturbance of V/Q relationships.
- Respiratory Acidosis - Note that in the graph.

The ventilatory and symptomatic effects of moving from sea level to high altitude. Description of the process of acclimatization on ascent to high altitude.

Hypobaric hypoxia

- 15,000 ft hypoxia develops as a result of the inverse relationship between oxygen partial pressure and altitude, resulting in a decrease in the partial pressure of arterial and arterial oxygen during ascent, and leads to reduced oxygenation of arterial blood.

Respiratory Response to a fall in barometric pressure at high altitude

- The primary need is to ensure an adequate uptake of oxygen in the lungs at the reduced PO2 (PaO2), alveolar ventilation increase with a corresponding fall in PaCO2 (and a rise in pH with an increased arterial oxygen affinity).
- The disadvantage of this situation is that the rise in pH (respiratory alkalasia) puts a 'brake' on the respiratory response to the hypoxia. Over the next few days at high altitude renal compensation for the alkalaemia leads to a return of the pH to normal, removing the inhibition of breathing.
- The result is a further increase in alveolar ventilation and rise in PaO2. Oxygen affinity tends to return to the same level as that which operated at sea level due to:
  - Correction of the alkalaemia by renal compensation
  - Increased production of 2,3 DPG

Respiratory System at a Glance Chapter 8 Carriage of Oxygen

- The alveolar hypoxia leads to reflex pulmonary artery constriction and pulmonary oedema. Occasionally with haemoptysis. A chest X-ray shows patchy pulmonary oedema.
- In exercise when there is an increased oxygen consumption there may be an inadequate partial pressure gradient driving diffusion of oxygen into the tissues which results from the reduced venous and capillary PO2.
- At altitudes above about 5500m (18,000ft) the strength of the hypoxic stimulus leads to increased production via diphosphoglycerate synthase and hence accumulation in the red cells.
- Deoxyhaemoglobin is able to bind to DPG which decrease oxygen affinity and aids unloading of oxygen in the tissue.

Acclimatisation of lowlanders to high altitude

- Lowlanders do not have a response that can restore the normal PaO2 level therefore they are hypoxic.
- On arrival at altitude lowlanders often feel unwell with headache, anorexia, photophobia and poor sleep. These symptoms are mild but when severe it is termed Acute Mountain Sickness.
- Acclimatisation occurs over the next 2 to 10 days with resolution of symptoms and improved physical and mental performance. It is associated with a gradual rise in ventilation and PaO2.
- At altitudes above about 5500m (18,000ft) the strength of the hypoxic stimulus leads to a marked respiratory alkalasia with increased oxygen affinity and uptake of oxygen in the lung. However this impairs oxygen unloading in the tissues and limits exercise capacity.
- The initial unpleasant effects of ascent to altitude can be ameliorated by slowing the ascent to 2 days or longer for higher altitudes. Drug prophylaxis against the unpleasant effects is achieved with acetazolamide leading to a mild metabolic acidosis with respiratory compensation and a rise in PaCO2.

The relationship between CO tension (PCO2) and arterial oxygen tension (PO2) within the lung. The effect on the relationship of changes in alveolar ventilation and perfusion relationships within the lung.
Add PO2 to PCO2 should always come to above 16kPa.

Example: A: Type 2 (ventilatory failure). (PCO2 10kPa, PO2 7.5kPa)
- Treatment is giving oxygen to try and target the low ventilation areas.

Example: B: Type 1 (hypoxaemic failure) (PCO2 3.5kPa, PO2 8.0kPa)
- Example: C: Combined type 1 and 2 failure (PCO2 7.5kPa, PO2 5.0kPa)

N(5kPa) is the PO2 and CO2 content of blood leaving a normal lung with normal VA/Q ratios averaged at 0.8. In diseases of the lung there are low VA/Q areas (L PaCO2 7.5kPa) and normal and high VA/Q areas (H PaCO2 2.5kPa). When blood from these areas mix in the left side of the heart the areas of high VA/Q compensate for the low VA/Q areas and resulting arterial PCO2 is slightly raised (5.2kPa) but within the normal range. This normality is achieved because the CO2 dissociation curve is nearly linear and also because any rise in PCO2 stimulates the chemoreceptors leading to an increase of ventilation of the high VA/Q areas.

LOW VA/Q means that ventilation is well matched to perfusion - High O2 low CO2
HIGH VA/Q means that ventilation and perfusion are not well matched - LOW O2 and low CO2 by compensation

This is a hypothetical example to illustrate the effect of ventilation to perfusion inequalities in the lung on arterial O2 tension and saturation.
- The normal VA/Q areas (N) contribute blood to the pulmonary venous system with a normal PO2 (11kPa) and saturation (96%).
- The low VA/Q (L) areas contribute blood with a PO2 of 5kPa and saturation 75% (20% drop from normal).
- The high VA/Q (H) areas contribute blood with a PO2 of 16kPa and saturation of 100% (rise from normal of only 4% see hatched area).
- The blood from the three regions of the lung with different VA/Qs mix in the pulmonary venous system and the left side of the heart. The resulting PaO2(F) is 7.5kPa with an O2 saturation of 75%.
- Thus the areas of high VA/Q do not compensate for the low VA/Q areas due to the sigmoid shape of the oxygen dissociation curve.
To define "Allergy" and to distinguish it from related terms such as "tolerance", "Atopy" and "Hypersensitivity".

To understand the fundamental immunological mechanisms operative in the major forms of allergic airway diseases (i.e. allergic rhinitis, asthma and extrinsic allergic alveolitis).

To appreciate the scope and burden of allergic airway disease.

To understand possible reasons for the rising trends in allergic disease.

To outline the principles of treatment of allergic airway diseases, including atopy.

Introduction and Definitions

Since the late 1950s the incidence of allergy in developed countries has risen steadily. In the United Kingdom the incidence of common allergic diseases has trebled in the last 20 years, to become one of the highest in the world. Recent estimates suggest about a third of the population will develop symptoms due to allergy at some point in their lives. No comparable increases in prevalence have been observed in developing countries, but although many hypotheses have been proposed, the true reason for the "allergy epidemic" in the westernised world has yet to be found.

The term "allergy" was first coined by Clemens von Pirquet in 1906 to describe an altered or changed reactivity of the immune system to foreign proteins, irrespective of whether this resulted in immunity or a harmful effect. However, today most clinicians restrict the use of the term to situations where an exaggerated sensitivity (hypersensitivity) results from a heightened or altered reactivity of the immune system in response to external substances. These foreign substances that provoke allergies are called allergens and enter the body either by inhalation, swallowing, injection, or contact with the skin, eye or airways. The common allergens include grass, weed and tree pollens, substances present in house dust (particularly the faeces of dust mites), fungal spores, animal products, certain foods, and various chemical agents found in the home and at work. It should be appreciated that allergy is not a disease but a mechanism which may play a role in a number of disorders.

Atopic (IgE-mediated) allergic conditions arise when individuals produce increased amounts of immunoglobulin E (IgE), a class of antibody which binds strongly to specific receptors on mast cells (specialised cells found in connective tissue and airways) and blood basophils. When the cell-associated IgE comes into contact with the specific allergen against which it is directed, the molecules of IgE become "cross-linked" by that allergen, and the mast cell becomes activated. This results in the release of inflammatory chemicals such as histamine and leukotrienes. Acute symptoms of allergy such as sneezing, spasm of the airways, itching, rash and tissue swelling are caused by histamine, and when there is a large release into the circulation, as in anaphylaxis, histamine causes a fall in blood pressure. Leukotrienes have a more prolonged course of action, causing airway narrowing and swelling which leads to shortness of breath and wheeze.

The symptoms of chronic allergic disorders, such as a continuous blocked nose or ongoing wheezing, may result from another molecular pathway involving immune cells known as T helper 2 (Th2). This pathway involves the release of cytokines and chemokines, small messenger proteins which recruit other cells into the reaction. The majority of people who suffer from IgE-mediated allergy are said to be "atopic". Atopy can be defined as a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and, as a consequence, to develop typical symptoms such as asthma, rhinoconjunctivitis or the atopic dermatitis syndrome (AEDS). This means that atopic individuals are more likely to develop these allergic conditions than non-atopic individuals.

Non-atopic (non-IgE-mediated) allergy

Some conditions are not dependent on IgE but still involve an abnormal immune response to a wide variety of external environmental agents. These conditions are known as non-atopic (non-IgE-mediated). The mechanisms of non-atopic disease are less clearly understood but some disorders (i.e. extrinsic allergic alveolitis) may involve tissue damage mediated by immune complexes.

Although many patients exhibit hypersensitive reactions to food, only some of these cases are caused by true IgE-mediated food allergy, such as an allergy to peanuts. In other cases there may be no evidence to suggest that their problem is associated with an alteration in the immune system, so their condition is known as "food intolerance". Examples of these are aromatics which wheeze after exposure to food additives such as sulphites and nitrates.

Molecular basis of IgE production

The T cell provides help for B cell activation and antibody production. Cytokines such as interleukin-4, interferon-gamma, transforming growth factor-beta and IL-10 produced by T cells act directly on B cells, via cell surface receptors, inducing proliferation and differentiation and also modulating the antibody response. Help is also provided through interaction of cell surface structures, particularly the CD40 ligand on T cells which interacts with CD40 on the B cell surface. Isotype switching of immunoglobulin is dependent upon this molecular interaction. Cytokines instruct B cells to switch from making IgM heavy chains to make other isotypes. IL-4 and/or IL-10 direct isotype switching to IgE and IgG4, IL-10 favours IgE production over IgG. IFN-gamma induces IgG1 and TGF-beta induces IgA.

Extrinsic allergic alveolitis (EAA)

Extrinsic allergic alveolitis (EAA) or hypersensitivity pneumonitis (HP) is a non-IgE T cell disease associated with alveoli and interstitium. EAA occurs in susceptible people following the repeated inhalation of certain antigens. These antigens typically include bacterial or fungal microorganisms in the workplace or bird antigens. Classical examples are Thermophilic actinomycetes in mouldy hay giving rise to Farmer’s lung and bird droppings and bloom causing pigeon breeders lung. Some antigens that cause asthma such as the mold, Alternaria, can also induce EAA. The prevalence of EAA varies and is related to the particular antigen and the host immune response. Studies have shown that, a minority of individuals exposed develop disease. Cytokine gene polymorphisms in the TNF-alpha promoter region appear to be a host susceptibility factor. Establishing the diagnosis of EAA is challenging requiring a high index of suspicion, a thorough history, careful examination, complete pulmonary function tests and radiographic studies. The histology reveals a lymphocytic infiltrate with a predominance of CD8+ lymphocytes, “foamy” alveolar macrophages, and non-caseating granulomas consistent with nonspecific interstitial pneumonia. Early identification of patients with EAA with subsequent avoidance of the causative antigen is the key to a successful outcome. An index case at a workplace is a sentinel event that should prompt evaluation for other affected workers and assess working conditions, identify causative antigens and remediate exposure promptly. Pharmacological treatment for acute EAA is limited to oxygen and oral corticosteroids. Oral steroids may not affect the long-term prognosis. The prognosis is generally favorable if intervention takes place before pulmonary fibrosis occurs.

Burden of Allergic Diseases

The burden of allergic disease is sometimes underestimated. In addition to the obvious health effects, allergic disorders can make social interactions difficult as even simple everyday activities can pose a major health risk (House of Lords Science and Technology Committee Report, September 2003). On a national scale, the treatment of allergy patients forms a significant part of the work of the health care providers and, in Western societies, the number of allergy-related work absences represents a large cost to the economy. Allergies affect all aspects of a patient’s life. However, severe allergic reactions in children’s sleep and may impair their performance at school and asthma has been associated with school absenteeism. Allergy patients often find it difficult to live a normal life. This is especially apparent in children, where special care has to be taken whilst engaging in everyday activities which in turn induces anxiety and impairs the quality of life.

In England approximately 3 million people (6% of the population) each year consult their primary care physician with conditions related to allergy and 72.6 million community prescriptions are issued (Department of Health 2006; Royal College of Physicians of London 2003). This included 38.9 million prescriptions for asthma and 4.5 million for nasal allergies. This amounted to a cost of £0.9 billion, which represented 13 per cent of the total drug budget (compared to 27 per cent spent on cardiovascular diseases and 8 per cent on gastro-intestinal disorders).

The prevalence of allergic disease has markedly increased over recent years. In the UK, by 2004, the scale of the “allergy epidemic” was such that 39 per cent of children and 30 per cent of adults had been diagnosed with one or more of asthma, eczema and hayfever, and 38 per cent of children and 45 per cent of adults had experienced symptoms of these disorders in the preceding 12 months. In fact by the end of 2005, one in 9 people had a recorded diagnosis of any allergic disease, including any one of asthma, hayfever, eczema, anaphylaxis or peanut allergy. This figure represented a 28% increase in prevalence over a four year period. Asthma, eczema and allergic rhinitis often occur together and this co-morbidity, or multiple allergic disease, often requires multiple referrals to different organ specialists. More than two million people in England are estimated to suffer from multiple allergic diseases, with an increase in the prevalence rate of 49% cent between 2001 and 2005. (QRESEARCH and The Information Centre for health and social care).

Rising trends in allergic disease

The marked increase in the prevalence of atopic disease in Western Europe, the USA and Australasia during recent years indicates the importance of environmental influences. It has been suggested that in Western countries the developing immune system is deprived of the microbial antigens that stimulate Th1 cells, because the environment is relatively clean and because of childhood vaccinations and the widespread use of antibiotics for minor illnesses in early life. This is often referred to as the "hygiene hypothesis". Atopy and allergic asthma were less frequent in people exposed to agents in soil, air and water such as K. pylori, T. gondii, hepatitis A virus. Therefore these microbes, by producing an IL-10 produced by T cells, may affect the development of atopic disease. Also a traditional lifestyle with a high gut bacterial richness environment dampen the allergic response. Such findings may explain, for instance, why in Europe and USA and Australasia during recent years indicates the importance of environmental influences. It has been suggested that in Western countries the developing immune system is deprived of the microbial antigens that stimulate Th1 cells, because the environment is relatively clean and because of childhood vaccinations and the widespread use of antibiotics for minor illnesses in early life. This is often referred to as the "hygiene hypothesis". Atopy and allergic asthma were less frequent in people exposed to agents in soil, air and water such as K. pylori, T. gondii, hepatitis A virus. Therefore these microbes, by producing an IL-10 produced by T cells, may affect the development of atopic disease. Also a traditional lifestyle with a high gut bacterial richness environment dampen the allergic response. Such findings may explain, for instance, why in Europe and
making IgM heavy chains to make other isotypes. IL-4 and/or IL-13 direct isotype switching to IgE and IgG4. IL-10 favours IgG4 production over IgE. IFN-gamma induces IgG1 and TGF-beta induces IgA.

Th1 and Th2 cells

T helper cells are sub-divided based upon the pattern of cytokines elaborated following activation. Cells secreting cytokines such as IL-2 and interferon-gamma (IFN-gamma) have been referred to as Th helper 1 cells (Th1). The cytokines produced by these cells promote cytotoxic T cell responses and inhibit allergic responses. Cells producing IL-4, IL-5, IL-9 and IL-13 are called Th helper 2 cells (Th2). These cells provide help for isotype switching to IgE and are the predominant Th helper phenotype associated with allergic inflammation.

IL-13 has been identified as a key cytokine in the induction and maintenance of bronchial hyperreactivity in animal models of asthma. Whilst in murine systems, differentiation of the two subsets is often clear, these populations are less well defined in humans. In reality, cytokine profiles are specific for the most frequent cell being of a Th0 phenotype capable of secreting both Th1 and Th2 cytokines. The recent identification of populations of regulatory or suppressive T cell populations secreting cytokines such as IL-10 (Th11 cells) and TGF-beta (Th3), adds to the complexity of the T cell subset issue, although at the same time providing tangible explanations for the suppressive effects of adoptively transferred T cell populations which have been described in many models over the past three decades. Recently, closer inspection of the cytokine secretion profile of CD8+ T cells has revealed a similar ability to synthesis polarised cytokine profiles giving rise to the Th1 and Th2 nomenclature.

The range of allergic airway diseases

There are three principle "types" of allergic airway disease. The first involves the upper airways (allergic rhinitis), the second effects the lower airways (asthma) and the third are allergic reactions in and around the alveolar spaces (extrinsic allergic alveolitis).

Allergic Rhinitis

Rhinitis can be either seasonal or perennial, and is characterised by a blocked or runny nose, sneezing, itching and streaming eyes. Seasonal allergic rhinoconjunctivitis (more commonly referred to as hayfever), is caused by allergenic substances contained within pollen. Commonly the causative factor is grass pollen but allergy to tree and weed pollen is also on the increase. Most hayfever patients suffer the worst symptoms at the height of summer when vast clouds of grass pollen become airborne. Due to mild winters and warmer springs, pollination of grasses in the United Kingdom is now starting earlier than it did 50 years ago. Therefore the worst symptom can be well established by the first week in June and tend to peak around mid-June to early July. When the pollen counts are very high, some wheeziness can also co-exist with rhinitis, in a condition known as seasonal allergic asthma.

Perennial allergic rhinitis involves troublesome chronic symptoms such as a blocked, runny nose and sneezing. Some patients have non-allergic causes of perennial rhinitis such as infection and structural abnormalities, and a small minority of patients have underlying immunodeficiency problems too. In the United Kingdom, allergy to the house dust mite (Dermatophagoides species) and allergens derived from animals such as cats, dogs, horses and pet rodents are the most important causes of chronic perennial allergic rhinitis.

Asthma

Asthma is a chronic disorder characterized by episodes of wheezy breathlessness, but which may also present as an isolated cough, particularly in children. The cause of asthma is still uncertain, but the pathology involves inflammation of the large and small airways (bronchi and bronchioles). The consequence is an irritant or twitch airway in which airflow obstruction results from exposure to a variety of non-specific irritants (bronchial hyper-responsiveness). A wide clinical spectrum of asthma symptoms result, ranging from mild occasional wheezing, which is usually controlled by the occasional use of inhaled bronchodilators, through to severe intractable disease which requires treatment using systemic corticosteroids. 

Allergy can trigger an attack in around 75 per cent of asthmatics, and this is most commonly due to sensitivity to house dust mites or pollen. However, even in patients who suffer from allergic asthma, there are usually other triggers such as viral infections, exercise, exposure to fumes and other irritants such as tobacco smoke, and certain drugs (especially aspirin and related compounds). Food allergens and additives are rarely responsible but can also occasionally be implicated in triggering asthmatic symptoms. In a few cases, the role of allergy in asthma is obvious, such as in patients who wheeze when the pollen count is high but not at other times of the year. But in many cases it is difficult to determine the exact role of allergy in asthma. A significant proportion of asthmatics (about 25 per cent) are not sensitised to common airborne allergens, and so are "non-atopic asthmatics". Their disorder often starts in later life and can be more severe than those who have asthma which begins in childhood.

development of atopic disease. Also a traditional lifestyle with a high gut bacterial turnover rate and intestinal colonisation with lactobacilli and bifidobacteria protect against allergy. Such a lifestyle is usually associated with "organic" food including spontaneously fermented vegetables.

Other related factors which may encourage the Th2 phenotype include a date of birth around the pollen season, and alterations in infant diet. Furthermore, atopic allergic diseases are less common in younger siblings and larger sibships and in those who have had measles and hepatitis A indicating that repeated "immune stimulation" (e.g. by viruses) may be protective.

The development of specific allergic diseases may be related to alterations in the target organ. For example, the co-factors required for the development of an asthmatic attack may include respiratory virus infections and exposure to increased allergens, tobacco smoke, and air pollutants. These factors alone, or in combination, may alter immunoregulatory mechanisms at mucosal surfaces in ways that promote a Th2 cell-mediated allergic inflammatory response.

The treatment of allergic airway disease

The basis of the treatment of allergic airway disease consists of avoidance of the allergen (where possible and practicable), anti-allergic medication and (in the case of allergic rhinitis) specific allergen immunotherapy – also called hyposensitisation or desensitization. Currently, the drugs usually used for treating allergic rhinitis are antihistamines (for relief of symptoms) and topical corticosteroids for suppression of allergic inflammation. Histamine H1-receptor antagonists such as loratadine, cetirizine and fexofenadine are less sedative and more pharmacologically selective than older antihistamines. Some H1-blockers such as cetirizine are claimed to have the additional property of inhibiting allergen-induced tissue eosinophilia, an effect which may be H1-independent.

Specific immunotherapy, which has been used in the treatment of allergic disease for nearly 100 years, consists of administering increasing concentrations of allergenic extracts over long periods of time. In seasonal allergic rhinitis, and to a lesser extent perennial rhinitis, specific immunotherapy is extremely effective and long lasting, especially when treatment is maintained for several years. Unfortunately, all patients receiving conventional specific immunotherapy are at risk of developing general, and potentially fatal, anaphylaxis, particularly during the induction phase. Attempts to minimize systemic reactions include pre-treatment of allergen extracts with agents like formaldehyde (resulting in the formation of so-called algaloids). However this results in reduced immunogenicity as well as a decrease in IgE binding.

The mode of action of specific immunotherapy is complex. IgE blocking antibodies that compete with IgE for allergen may prevent aggregation of FceRI IgE complexes. It has been proposed that SIT, as with other forms of infectious tolerance, may involve situations in which non-allergic antigens (e.g. by IL-10) to one epitope of a molecule confer tolerance either to (i) the whole molecule (linked suppression), (ii) other molecules being presented by the same, or adjacent, antigen-presenting cells (bystander tolerance) or (iii) is passed to the next generation of naive T cells (infectious tolerance).

Central to these effects is the influence of specific immunotherapy on T lymphocyte function. There is evidence that specific immunotherapy induces a shift from a Th2 to a Th1 cytokine profile: production of IL-4 and IL-5 decreases and the output of IFN-g and IL-12 increases. These changes can explain the marked inhibition of the late-phase allergic reaction caused by immunotherapy. After several months or years of treatment the early, immediate weal and flare response and total serum IgE concentration are also reduced.

The induction of IL-10 secreting T regulatory cells also appears to be critical. IL-10 has a wide range of inhibitory effects on allergy, including the induction of long-term anergy in allergen-specific CD4+ cells, decreases the number of mast cells and inhibition of eosinophilopoiesis. It has been proposed that SIT, as with other forms of immune modulation, may involve situations in which non-responsiveness induced (e.g. by IL-10) to one epitope of a molecule confers tolerance either to (i) the whole molecule (linked suppression), (ii) other molecules being presented by the same, or adjacent, antigen-presenting cells (bystander tolerance) or (iii) is passed to the next generation of naive T cells (infectious tolerance).
Learning Objectives

- To learn about the healthy lungs defences against infection. We are continually exposed to infectious agents during breathing, but the healthy lung is sterile from the first bronchial division.

- To understand how the host defences can be compromised; congenital or acquired. Three examples: primary ciliary dyskinesia, viral infection, cigarette smoking.

- To understand the differences in pathogenesis between acute and chronic lung infections. Two examples: pneumococcal lobar pneumonia and bronchiectasis.

- To understand how the host defences can be compromised; congenital or acquired. Three examples: primary ciliary dyskinesia, viral infection, cigarette smoking.

Survey by general practitioner college every fourth patient is a respiratory tract problem.

- 1 in 12 of people admitted to hospital with pneumonia die.
- Constantly breathing in pathogens.
- Multi-layered defence mechanisms
  - Mechanical: URT filtration, mucociliary clearance, cough, surfactant, epithelial barrier.
  - Local: BALT, sIgA, lysozyme, transferrin - neutralises bacterial toxins, antiproteinases, alveolar macrophage

- All airways are lined by ciliated epithelium, each cells has about 200 hair like projections.
- Each cilia has a specific movement mechanism at about 12 times per second. Bacteria are unable to get through the epithelium due to the cilia beating quickly.
- Little claws at the top of the cilia grab the mucous and push it along.
- Cilia move in a wave of movement - metachronously.
- Cilia are made up of microtubules, 9+2 arrangement, central pair and 9 outer pairs. Dynein arms provide the energy to allow the cilia to move.

- Right is normal, left is in a cold. The tight junctions are starting to fall apart.

- Pathogen virulent to get through defence mechanisms
  - Failure of defence mechanisms - Genetic reason or an acquired reason such as smoking.

- Secondary bacterial infection to a viral rhinitis. Bacterium has opened up the airway and caused tight junctions to fall apart.
- Compound cilia is where cilia join together and are ineffective.

- Indicators of disordered defence
  - Acute, overwhelming
  - Recurrent, acute, slow to resolve
  - Bronchial
  - Pneumonic
  - Daily purulent sputum only temporarily responding to antibiotics.

Primary Cilia dyskinesia - Carter Gaynor syndrome
- Failure of cilia function can cause dextro-cardio
- People who have ciliary dyskinesia exhale a small amount of NO.
- Beat in different directions and at different speeds.
- Ciliary dyskinesia can cause bronchiectasis

- Bacteria are either virulent or adapted for colonisation.

- Colonise - haemophilus influenza - has "hairs" which anchor bacteria on epithelial surface. This bacteria won’t invade and just grows. 1/3 would have bacteria in the airway.
- Not virulent enough to infect healthy epithelium in normal circumstances.

- Bacteria strategies to avoid clearance
  - Exoproducts impair mucociliary clearance.
    - Slow and disorganise ciliary beat, stimulate mucus production, affect ion transport and damage epithelium.
  - Enzymes
    - Break down local immunoglobulins
  - Exoproducts
    - Impair neutrophil, macrophage and lymphocyte function
  - Adherence
    - Increased by epithelial damage and tight junction separation
  - Avoid immune surveillance
    - Surface heterogeneity, biofilm formation, surrounding gel and electrolysis.

Causes of Chronic Bronchial Sepsis

1. CONGENITAL (e.g. pulmonary sequestration, bronchial wall abnormalities).
2. MECHANICAL OBSTRUCTION (e.g. foreign body, tumor, lymph node).
3. INFECTIOUS PNEUMONIA (e.g. gastric contents, caustic gas).
4. HEMATOSIS (e.g. CFA, sarcoid).
5. POSTINFECTIVE (e.g. TB, pneumonia).

Pneumococcal lobar pneumonia
- High chance of cough, fever and dyspnoea.
- Pneumolysin punctures holes into epithelial cells.

Bronchiectasis
- Extreme amount of mucus production.
- Very thickened walls due to inflammatory response.
- Recurrent respiratory infections.
Extreme amount of mucus production.
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• Recurrent respiratory infections.
• Breathlessness - asthma and small airways disease
• Fatigue - severe tiredness and lethargy and difficulty in concentrating.
• Can be caused by cystic fibrosis

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- Can be caused by cystic fibrosis

**Chronic inflammation**
- If inflammatory response fails to clear pathogen then it can cause tissue damage.
- Interferes with protease-anti-protease balance. Inflammatory cells release a small amount of proteases as they move. However anti-protease can neutralise this. Neutrophils can overwhelm anti-proteases. Proteases chew up the surface of epithelial cells.
- Neutrophil proteases can degrade elastin.
Learning Objectives

- To be aware of the “Barker hypothesis”, which encompasses the concept of foetal programming and the early life origins of health and disease.
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Maternal pregnancy smoking
- Intra-uterine growth retardation
- Increased pregnancy complications
- Sudden infant death
- Respiratory illnesses in infancy
- Poorer educational attainments

- Birth weight correlates with increased lung function in late adult life.
- Lung function later on in life is decreased if the baby has a low birth weight, the mother smokes and there are post-natal insults.

- Poor air quality is linked to a number of conditions that can cause adverse health effects. These include:
  - Premature death
  - Lung cancer
  - Exacerbation of COPD
  - Pre-term birth

- Diesel particles increases the response to common aeroallergens such as ragweed.

TNF and ozone
- Pro-inflammatory: neutrophil infiltration
  - TNF knockout mice have reduced inflammation
  - Neural sensitivity
    - TNF-a primes mast cells to release substance P.

- Certain polymorphisms protect against the effects of ozone.

- Genetic impairment of immune integrity and exposure to inflammatory stimuli.
- Genetic impairment of metabolic mechanism and exposure to metabolites.
- Epigenetics.

- Being nurtured in a completely different environment results in morphological changes.

Epigenetics: Defined as changes in phenotype or gene expression caused by mechanisms other than changes in the DNA sequence, which may be transmissible across generations.

- Diet can effect how well DNA is methylated which can silence a gene's expression.

Unifying Hypothesis

- TH1 down regulate TH1 cells which ensures the pregnancy goes full term.
- TH2 cytokines-IL-4 at the maternal-foetal interface which stops a full immune response and rejection occurring.

Learning Objectives

- To understand immune and airway ontogeny and the way in which genetic and environmental factors interact to affect life-long outcomes in relation to allergic and respiratory disease.

- To review the evidence that much Respiratory and Allergic disease has its origins in early life.

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- To consider the mechanisms of foetal programming and amplification of effects through life.

- To understand immune and airway ontogeny and the way in which genetic and environmental factors interact to affect life-long outcomes in relation to allergic and respiratory disease.
- Children with older siblings or early day care are less likely to have wheeze in later life.
- Being exposed to a parasite as an infant helps to protect against allergy.
- Higher level of antibiotics during pregnancy is associated with a higher risk of the baby having asthma. Modifies gut flora which will affect what the baby is exposed to.
- Exposure of mother to unpasteurised milk—lactose bacilli, a stable reduces chance of allergy.
- Diversity of microbiota in faeces in infants is associated with non-allergy.
- Oligosaccharides major important component of breast milk that helps reduce levels of eczema.

**Mechanisms**

1. DNA methylation to CpG motifs (30 million) which impairs transcription.
2. Histone modification on 30 million nucleosomes by acetylation, methylation, phosphorylation, ubiquination, open chromatin to aid transcription.
3. MicroRNAs in the cytoplasm mostly block mRNA transcription—viral RNA can also do this and thus affect human transcription.
Acid-Base Status

Anion is $\text{r}ve^-$ ion and cation is $\text{v}e^+$ ion.
It is important that the amount of acid produced equals the amount of acid excreted.

### Acids and their site of excretion

<table>
<thead>
<tr>
<th>Production</th>
<th>Excretion</th>
</tr>
</thead>
</table>
| Respiratory | Lungs: $\text{CO}_2$
| Metabolic  | Kidney: $\text{H}^+$
|            | Phosphate $\text{Sulphate}$

- Volatile means gaseous.
- Protein metabolism generates acids.

### Mechanism of pH balance

1. Blood buffer system: $\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}_2\text{O} + \text{CO}_2$
2. Respiratory system: Controls $\text{PCO}_2$ via chemosensors. Rapid response in minutes to hours.
3. Renal system: Very slow days to weeks. Absorption of $\text{HCO}_3^-$.

Presentation of patients:
- Kussmaul breathing in Diabetic Ketoacidosis.
- Glucose converted to keto acids.
- COPD may look normal but the blood gases give a different story.

### How to interpret blood gas

1. Look at the pH is it normal if so there may be a full compensation.
2. CO2 tells if there is a respiratory element i.e. cause or compensation.
3. Base excess to check for metabolic/ kidney.

#### Base excess

- Raised base excess= Excreting acid= alkalosis or compensatory for acidosis.
- Decreased base excess= Over production of acid= acidosis or compensatory for alkalosis.

Think of Base Excess as a measure of $\text{HCO}_3^-$, the greater the $\text{HCO}_3^-$ the more alkaline and thus alkalosis.

- Base excess ignores $\text{PCO}_2$: thus ignores lung function.

#### HCO3 levels

Gaseous: (due to carbon dioxide): $\text{HCO}_3^-$ rises and falls directly with the $\text{PCO}_2$.
Metabolic: Falls when acids are buffered in the blood.
Renal: Rises when acid excretion by the kidney increased and falls when there is kidney failure.

### RENAL COMPENSATION BASE EXCESS IS OPPOSITE TO WHAT YOU THINK IT WOULD BE

A positive base excess may make you think that it is a metabolic alkalosis i.e. $\text{HCO}_3^-$ levels are high. However it could be renal compensation for a respiratory acidosis i.e. $\text{HCO}_3^-$ levels are chronically raised as we are "producing" more bicarbonate to negate the effects of the respiratory acidosis.

$\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}_2\text{O} + \text{CO}_2$

#### Table of conditions and their effect on normal respiratory values

<table>
<thead>
<tr>
<th>Condition</th>
<th>pH</th>
<th>$\text{PCO}_2$</th>
<th>PO2</th>
<th>Base excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>7.37-7.45</td>
<td>4.7-6.4kPa (35-48 mmHg)</td>
<td>10.7 kPa (80mmHg)</td>
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### Examples

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### Conditions

#### Respiratory Acidosis
- Low pH
- $\text{PCO}_2$ is higher than expected.
- Can be caused by hyperventilation, CNS opiates, pneumothorax.
- Chronic problem may cause base excess to be raised as renal system compensates for increased acid load by excreting it.

#### Respiratory Alkalosis
- High pH
- $\text{PCO}_2$ is lower than expected.
- Hyperventilation, head injury, stroke, asthma.
- BE may be low if at high altitude for a long period of time.Renal compensation for high pH (alkaline) is to produce more acids hence lowered BE.

#### Metabolic Acidosis
- Increase in non-volatile acids i.e. lactate, phosphate, sulphate.
- High anion gap= Ketoacidosis ($H^+$ generation): Ketones increase $\text{r}ve^+$ anions.
- Normal anion gap= Diarrhoea (loss of $\text{HCO}_3^-$) Replaces with Cl-

Anion gap= Difference between anions i.e. normally sodium (occasionally potassium is taken into account) and the cations i.e. chloride and bicarbonate.

The anion gap should be about +10. This is not relevant for exams but is cool.

#### Metabolic Alkalosis
- Vomiting loss of $\text{H}^+$

Compensations: These can either be partial i.e. the pH is still outside the normal range or full if the pH is within the normal range.

### Normal important values for Respiratory System

**pH:** 7.37-7.45
**$\text{PCO}_2$:** 4.7-6.4kPa (35-48 mmHg)
**PO2:** over 10.7 kPa (80mmHg)

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#### Number 1

- pH is low= acidosis.
- $\text{CO}_2$: high
- PO2= low
- BE= very high

**Explanation**
- Because the pH is low you know it is an acidosis.
- Because there is hypoxia and hypercapnia you know there is Type 2 respiratory failure.
- Because BE is high it again confirms it is acidosis (of metabolic origin) or renal compensation.
- However you know it isn’t renal compensation for respiratory acidosis because the PO2 is low which is not normal.
- Also you know there has to be renal compensation because looking on the chart on the left it was normal metabolic acidosis base excess should be low, but it is very high. As a result there has to be renal compensation i.e. excretion of acid for this to be possible.

### Diagnosis

- Metabolic acidosis with Type 2 respiratory failure and renal compensation.
Annoying complication: However over a long period of time there may be renal compensation to excrete more acids (non-volatile) to restore pH which would make the base excess high as detailed above.

2* - In metabolic acidosis CO2 is not directly affected but there may be respiratory compensation which will cause hyperventilation to remove CO2 - get rid of acid and increase pH.

Metabolic acidosis/alkalosis + Respiratory compensation = Normal PO2 only CO2 changes.

**Examples**

<table>
<thead>
<tr>
<th>pH</th>
<th>PCO2</th>
<th>PO2</th>
<th>BE</th>
</tr>
</thead>
<tbody>
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<td>7.5</td>
<td>7.4</td>
<td>7.19</td>
</tr>
<tr>
<td>10.7</td>
<td>2.7</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Normal values

| pH= 7.37 - 7.45 |
| PCO2= 4.7 - 6.4kPa (35 - 48 mmHg) |
| PO2 over 10.7 kPa (80mmHg) |
| Base excess= -2 to +2 |

**Diagnosis**

| Number 2 |
| pH is high |
| PCO2 is very low |
| PO2 is normal |
| BE is low |

**Explanation**

- Because pH is high it has to be an alkalosis
- Because CO2 is low it means it is a respiratory alkalosis - i.e. hyperventilation breathing off all the CO2 and increasing the pH.
- Because base excess is low it means that there must be renal compensation i.e. we are over producing acid in kidney to compensate for blood being alkaline

**Diagnosis**

- Respiratory alkalosis with renal compensation

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Stuart's Respiratory System Page 43
By Neeraj Kalra and Joseph Simmonds

Sleep apnoea

- Brainstem- most important controller of breathing during sleep.
- Neurones in the pons and the medulla.
- Pre-Botzinger complex- Medulla

Sleep

- Causes changes to respiratory centres- changes in respiratory muscles adjusting
- Chemosensors- aortic arch is the main one, also the carotid sinus.

Awake- saturation is 100%.
REM sleep is around 95% saturation.

Lung disease- COPD base saturation is lower which whilst sleeping means the saturation of O2 is quite dangerously low.

Although O2 isn't driving breathing at sleep its still important not to be hypoxic.

We must have hypocapnia to sleep.

Sleep apnoea

Apnoea- transient cessation of ventilation.

Obstructive- Compression in the neck- trachea is compressed which means huge weight gain

Central

- Sensitivity to CO2 is decreased.
- Using O2 to drive respiration- dangerous to give O2 as this will remove that drive.

Differences between the two

- Obstructive- still contraction of muscles to cause gas exchange. Whereas in central there is no drive to breathe.

Obstructive- CPAP- continual positive airway pressure
Central- Treat associated medical problem, CPAP, motorneurone

Blood gases

3 levels of defence
- Buffering- metabolic (nearly instant)
- Respiratory (hours to days)
- Renal (slower days to maybe weeks)

Compensation of an acid-base misbalance is performed by either the lungs or kidneys.

Metabolic method
- Bicarbonate ions are important for metabolic acids
- Haemoglobin- important for carbon dioxide
- Plasma protein- Minor buffer

Lungs
- $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$
- More CO2 the more $H^+$ ions.

Kidneys
- They perform the same reaction where instead you can excrete the hydrogen ions.

Base excess
- Amount of theoretical HCO3- (based on CO2 levels) compared to the actual level of HCO3.
- Higher base excess means a higher HCO3- level- Alkalosis.

Looking at blood gases

- Read patient history, and decide if this maybe causing either a metabolic problem or a respiratory problem.
- Decide whether the patient is in acidosis or alkalosis based on pH.
- Look at PCO2 and decide if it is low or high and whether it is compensatory or metabolic.
- Look at BE and is low or high and whether this is compensating for a respiratory cause.

Type 1- Low PaO2 and normal PCO2
Type 2- Low PaO2 and low PCO2.
Asthma

- Increased mucous secretion
- Oedema
- Bronchoconstriction/smooth muscle constriction

Fig. 8.1 Diagrammatic representation of the pathophysiology of asthma: (a) longitudinal section and (b) cross section.