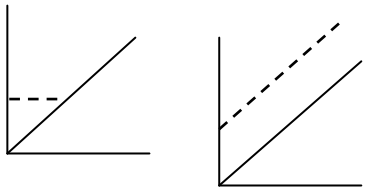
Inequalities and inequities
- Not everyone has good health/healthcare
    - Even in developed countries, there are people with lower levels of health care
    - In Australia, healthcare is really good
        - Life expectancy increasing
        - Birth mortality decreasing
- Definitions
    - Inequality – a difference between two or more things that involves a comparison only (qualitative/quantitative)
    - Inequity – an inequality that is unfair/preventable that involves comparison and a value judgement (subjective)
        - Often involves societal organisation/social circumstances
        - Often linked with other non-health inequalities

Social determinants of health
- Environmental, physical/living, biological, genetic – age, sex, physique, behaviour
- ++Social
    - Determined by: income, wealth, education, housing, culture, gender, class, socioeconomic status, ethnicity, employment, social hierarchy, residence, social capital
    - Arise from social organisation
    - Influences
        - Layer model – individual, community, society
        - A fuzzy pie chart? –a combination of genetics, SES, risk factors, place, and health services

CVD
- Life expectancy at birth is proportional to income
- Factors for CVD – race, sex, income, SES
- *Inverse care law – availability of good medical care is inversely proportional to need*

Broad conclusions
- SES is related to health (the wealthy are healthy)
- There is a gradient through different levels of society
    - Inequalities cover all circumstances
- Lifestyle doesn't explain anything
- The health gap is not increasing



Explanations
- Psychosocial – social hierarchy
- Culture
- Behavioural
- Natural selection/divine will

WHO commission's recommendations:

1. Improve daily living conditions
2. Tackle the inequitable distribution of power, money and resources
3. Measure and understand the problem and assess the impact of action

Reducing inequity
- Individuals – focus on the very poor
- Communities – change the gradient
- Improve access to essential services – water, work, food, housing, health
- Change society – make it one of equal opportunity
- Different explanations imply different solutions to problems
- Changes in terms of health
    - Health systems are controlled by the government; services by the practitioners

Conclusions
- Remedial action needs to be taken at all levels
- Health workers can make a difference

Lecture 2: Prac exam overview

Structure

- 4x30 minute components
    - Gross and neuro anatomy and embryology
        - Gross anatomy may include CT, x-ray and pins
        - Neuro may include photos or gross specimens
        - Embryology may involve questions about the adult structure and explaining embryonic roots or models
    - Physiology and pharmacology
    - Histology and histopathology
    - Microbiology and biochemistry

Anatomy

- 10x2.5 minute stations
    - 1.25 mins on specimen, 1.25mins on theory questions
    - 10 specimens/models/x-rays
        - Each has 3-4 flagged structures + 1-2 theory questions
            - The structure the pin goes through first needs to be identified
- Identification is of the utmost importance, 50-60% of mark

Histology and histopathology

- 6 questions, 3 histology, 3 histopathology, 30 minutes
    - Draw key features

Physiology and pharmacology

- 30 minutes, 5x6minute questions
    - Data analysis, ECG, calculations

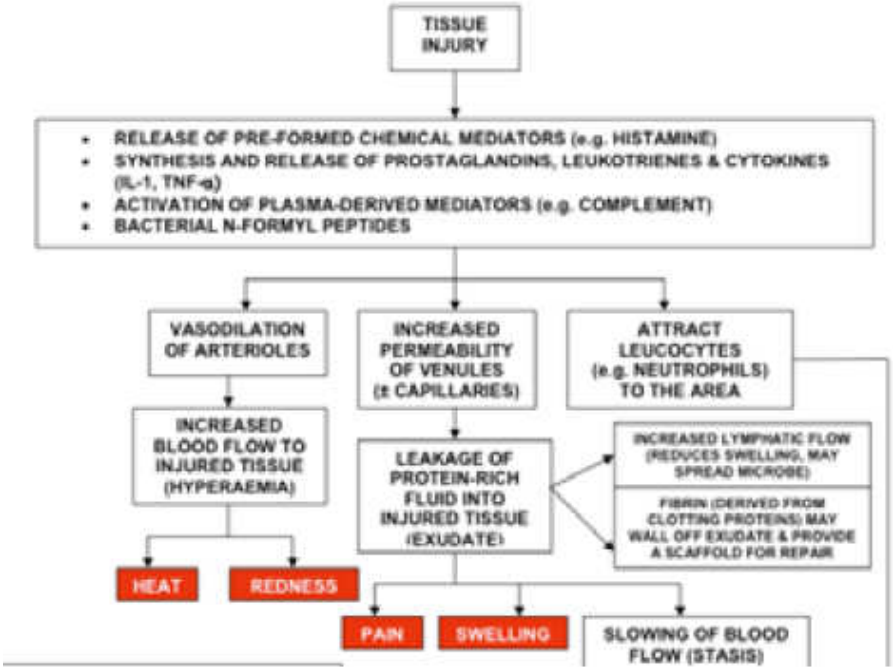
Microbiology/biochem

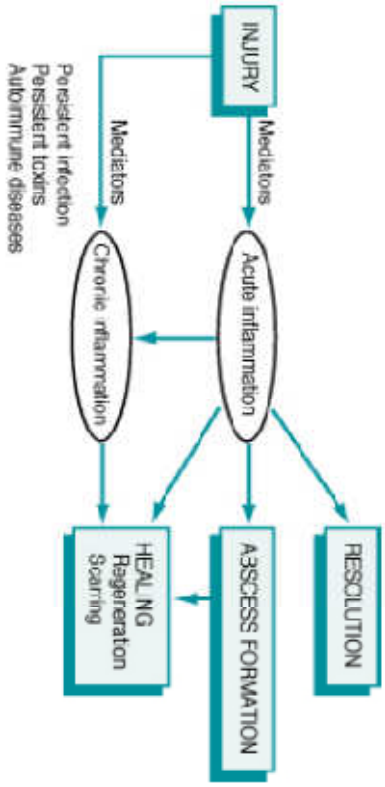
- 5 stations, 5 minutes each
    - 3 microbiology, 1 biochem, 1 molecular biology

Overall 40% required to pass

Introduction

- Inflammation: acute and chronic
    - Driven by chemical mediators leading to local changes that promote the healing process
    - Acute: inflammation then healing
    - Chronic: healing and inflammation run in parallel





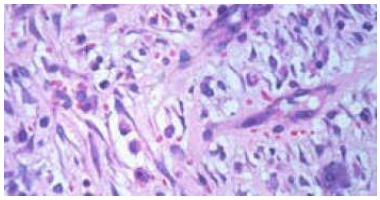
Definitions

- Healing is the process by which the body replaces damaged tissue with living tissue
    - Involves cell death which leads to inflammation

Regeneration

- Ideal way of healing
- Parenchymal cells that have died are replaced by replication of surviving cells
    - Several types of parenchymal cells that have different regeneration capacities
        - Labile – continuously replicating (eg: surface epithelia, skin, gut)
        - Stable – slow cell turn over by can proliferate with stimuli (eg. liver, renal tubules, secreotry glands, smooth muscle)
        - Permanent – cannot divide (eg. CNS nerves, skeletal muscle, cardiac muscle, hyaline cartilage)
            - Requires regeneration via adult stem cells – very limited
- Regeneration involves cell replacement and structural/architectural replacement
    - Otherwise tissue will not be functionally effective
    - Structural organisation ie, the extracellular matrix (CT) also needs to be regenerated

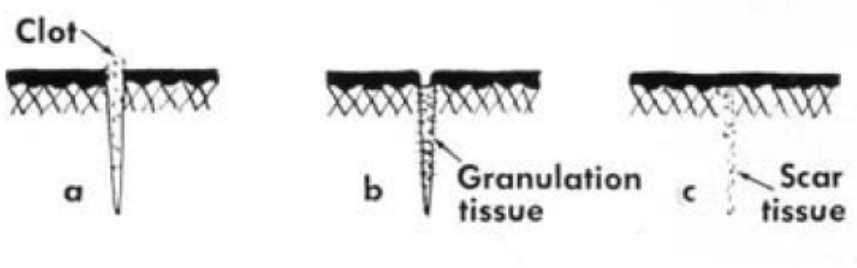
Repair

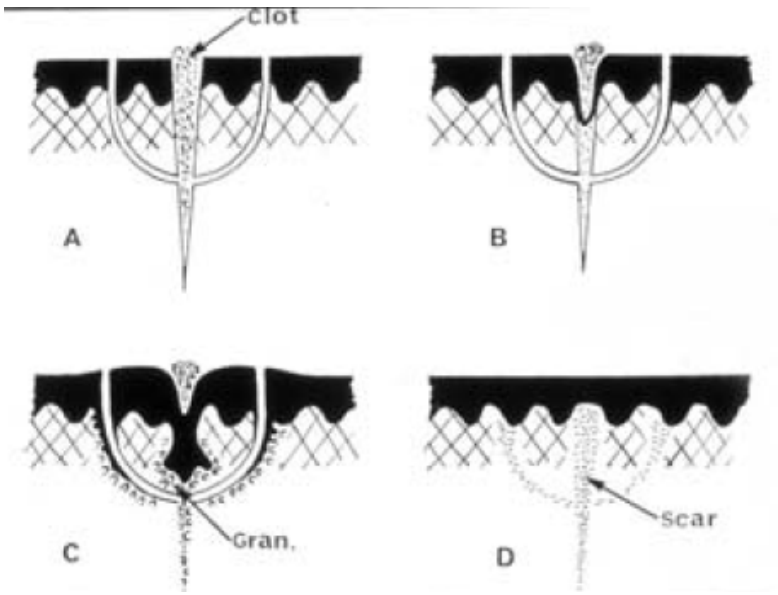


- When regeneration is not possible, parenchymal cells can be replaced by connective tissue - repair
    - Occurs in all tissues except in the bone and CNS etc via granulation tissue
- Granulation tissue has three main components
    - Inflammatory cells
        - Macrophages (phagocytose cellular and protein debris and coordinate via cytokines)
            - Keep granulation process going, induce cellular migration/differentiation and angiogenesis
        - Appear round
    - Activated contractile fibroblastic cells (myofibroblasts)
        - Make matrix proteins (extracellular matrix, collagen), proteoglycans and gluycosaminoglycans
    - Blood vessels – angiogenesis

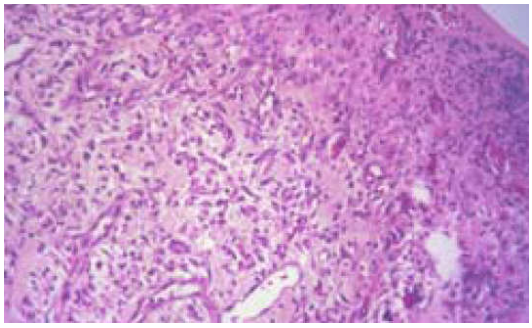
Healing in skin/mucosae – an example of repair

- Tissue injury leads to haemorrhage/haemostasis
    - This induces an acute inflammatory response
        - This triggers the healing process
- Healing involves restoration of the epithelial layer, requires:
    - Migration of adjacent epithelial cells
    - Proliferation to restore epithelial thickness
- Granulation process
    - Inflammation involves presence of macrophages that induce migration and proliferation of endothelial cells and fibroblastic cells
        - Endothelial cells proliferation forming vessels/capillaries – angiogenesis
        - Fibroblastic cells synthesise the extracellular matrix – collagen
    - Over time, the vascular supply regresses, collagen is broken down and remodelled (collagenases) and the scar contracts
- Eg: paper cut/shaving cut
    - Clot holds surfaces together
    - On the surface, cells migrate and proliferate
        - Granulation tissue collects and lays down collagen
    - Scar tissue forms, proliferation of endothelium complete
- Eg: large wound with sutures
    - Clot is not strong enough to hols the wound together so a suture provides strength
    - Epithelium migrates to undermine the wound (overshoots and is eventually broken down)
    - Granulation tissue forms below
    - Suture track begins the healing process with epithelial migration and granulation formation
        - Need to leave the suture in long enough for the granulation process to start but before epithelium forms in the suture wound itself
- Overall process of large wound with sutures
    - Post-operative – sutures holding epithelium together allowing granulation process to start
    - 1 week – sutures removed, dead epithelial cells are shed, vascularity due to granulation tissue and angiogenesis
    - 2 weeks – collagen remodelling reducing the size of the scar and its vascularity
    - 3 weeks – small scar, essentially invisible

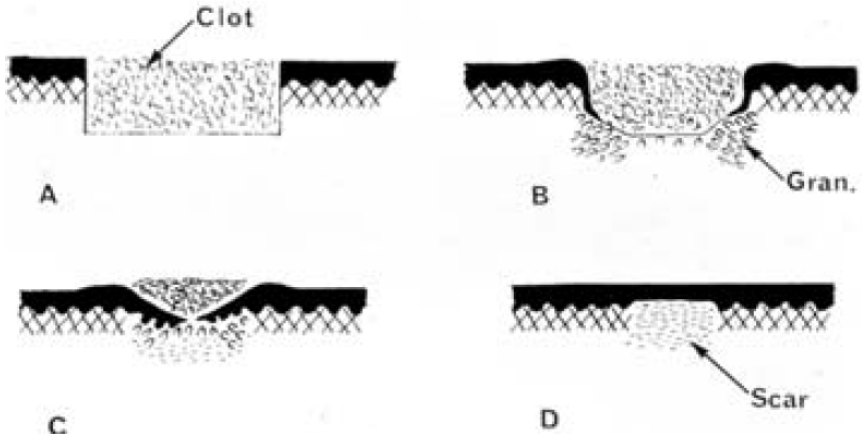




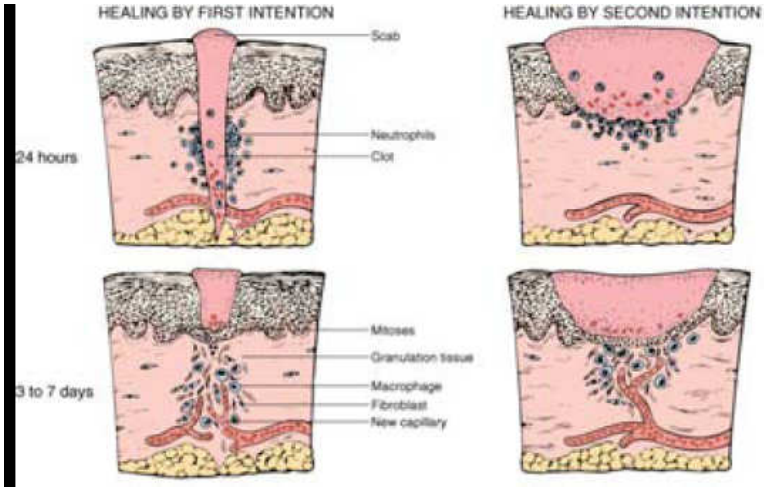
<u>Primary and secondary intention healing</u>



- Primary intention
  - Healing with an apposed incised wound
    - Limited inflammation, rapid restoration of epithelium by migration and proliferation
    - Little formation of granulation tissue
    - Minimal scarring
- Secondary intention
  - Healing with substantial tissue loss
    - Marked inflammation, delayed re-epithelialisation
    - Ingrowth of granulation tissue, wound contraction
    - Significant scarring
  - Slow process
    - Clot forms
    - Granulation tissue grows into base of wound
    - Minimal epithelial migration
    - With time, epithelium bridges gap and scar forms



- Granulation tissue
  - Can see BVs look to the surface and return
  - Myofibroblasts are oriented perpendicularly to hold wound together
- EG: lacerated wound
  - 3 weeks – clot, slow healing by second intention
  - 3 months – lack of hair, dense collagen and epithelium, crinkled due to scar contraction

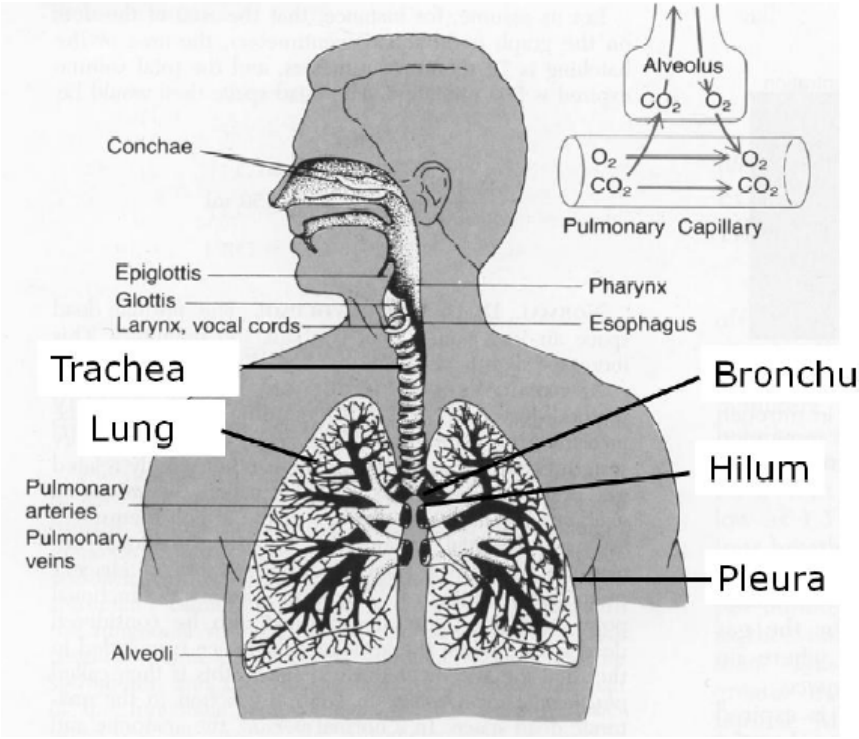


<u>Healing mediators</u>

- Mediated by sequential release of locally acting cytokines, platelets, macrophages and mast cells
  - Cytokines (proteins) in healing are often known as growth factors
- 3 types of chemical mediators
  - Autocrine
    - Same type of cells, eg: epidermal growth factor inducing epidermal proliferation
  - Paracrine
    - Adjacent cells, eg: macrophages affecting fibroblasts, vascular endothelium etc
  - Endocrine
    - Circulating hormones – not major in healing
- The mechanisms that stop granulation process are not well understood

<u>Factors affecting healing</u>

- Systemic and local factors
  - Local is dominant:
    - Vascularity (lack means slow healing)
    - Infection, mechanical trauma, chemical injury (eg: dressings)
    - Foreign bodies, irradiation, neoplasia
  - Systemic:
    - Age, nutritional status (protein, vitamin deficiency)
    - Other diseases (diabetes, neoplasia)
    - Hormonal status (steroid therapy, eg: glucocorticoid – anti-inflammatory)



Introduction

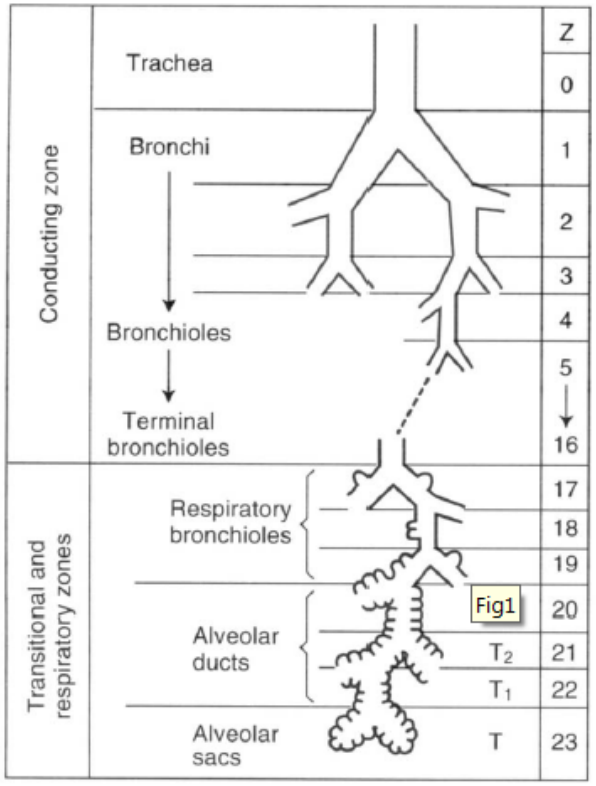
- Lung has many functions
  - Primary: gas exchange (CO_2 for O_2)
    - Exchange occurs at the blood-gas interface in the alveoli (air sacs)
  - Other functions:
    - Angiotensin converting enzyme, blood reservoir

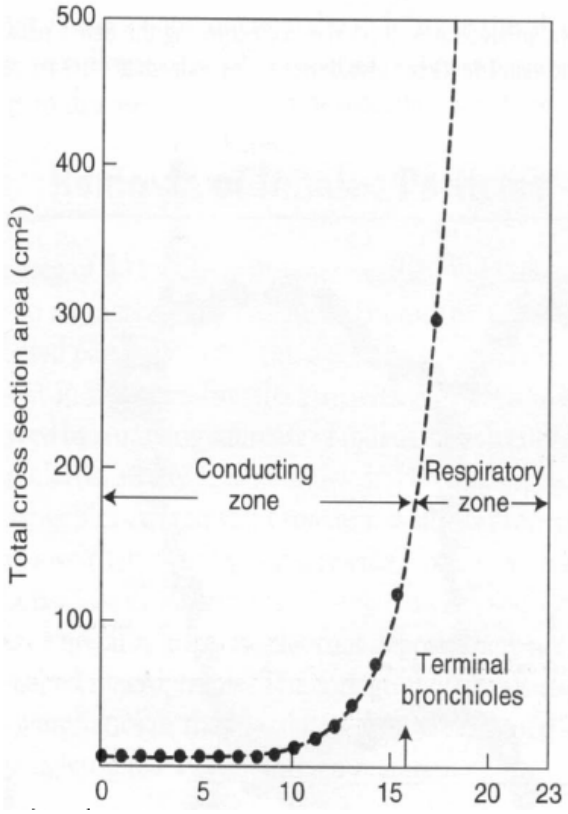
Alveoli

- Small air sacs (diameter 1-3mm)
  - Human lungs contain ~300 million
  - Look like aero chocolate bar
- Wrapped in capillaries
- Provides the blood-gas barrier
  - Thin: 0.3µm – allows easy diffusion
  - Large total surface area: 50-100cm^2

Airways

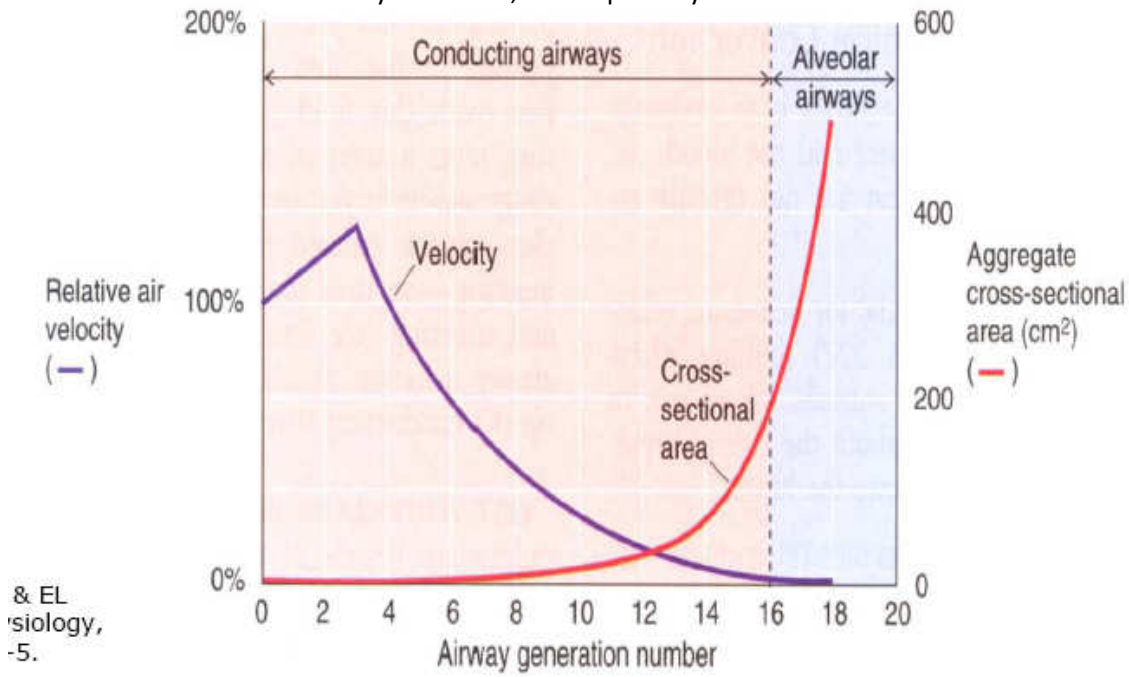
- Conducting zone and respiratory zone
  - Conducting zone transfers air to the alveoli
    - Made up of the trachea, bronchi, lobar bronchi (3R, 2L), segmental bronchi (10R, 8L), bronchioles
      - Up to the terminal bronchioles – the smallest bronchioles that have no alvolei
    - As you travel further into the lungs, the branches become narrower and shorter
    - Conducting zone also known as the anatomical dead space
      - Has a volume of ~150ml
      - Plays no part in gas exchange
  - Respiratory zone
    - Distal to terminal bronchioles, contains alveoli
    - Majority of lung
    - Made up of: respiratory bronchioles (alveoli in walls), alveolar ducts, alveolar sacs
  - When you reach the respiratory zone, cross-sectional area increases rapidly





Airflow

- Respiratory cycle has inspiration and expiration
    - Inspiration:
        - Thoracic cavity volume increases causing a negative P_{alv}
        - Air thus enters the lungs
    - Expiration:
        - Thoracic cavity volume decreases causing positive P_{alv}
        - Air thus leaves the lungs
- The driving force is due to the difference in atmospheric pressure and alveolar pressure:
    - Airflow = $(P_{atm} – P_{alv})/R$
        - P_{atm} – atmospheric pressure, P_{alv} – intra-alveolar pressure, R – airway resistance
- Air moves by bulk flow (convection) until terminal bronchioles
    - Air moves by diffusion in the respiratory zone
    - Dust settles where air velocity slows – ie, the respiratory zone



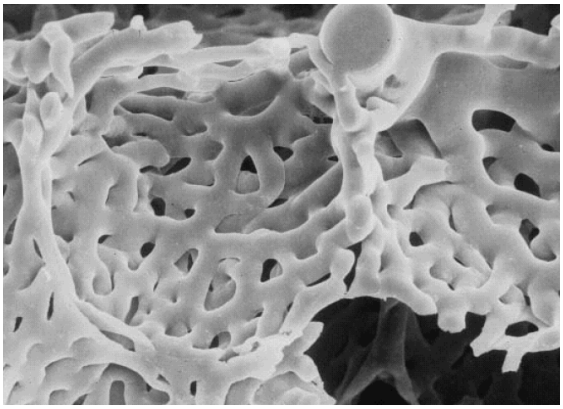
- Bump in velocity is explained by the trachea having a bigger diameter than the first few branches of the bronchi, so velocity initially increases
    - At the same time, cross-sectional area is not at a good enough scale to see the difference

Ventilation

- Total ventilation is the amount of air that enters the lungs
    - Total ventilation = tidal volume x respiratory frequency
        - Eg: 500ml/breath x 12 breaths/min = 6000ml/min
            - Which is the total ventilation at rest
    - Not all of this reaches the respiratory zone, of the 500ml, 150 remains in the anatomical dead space
- Thus, alveolar ventilation is the amount of fresh air reaching the respiratory zone/min
    - Alveolar ventilation = (tidal volume – dead space air) x respiratory frequency
        - Eg: 350 x 12 = 4200ml

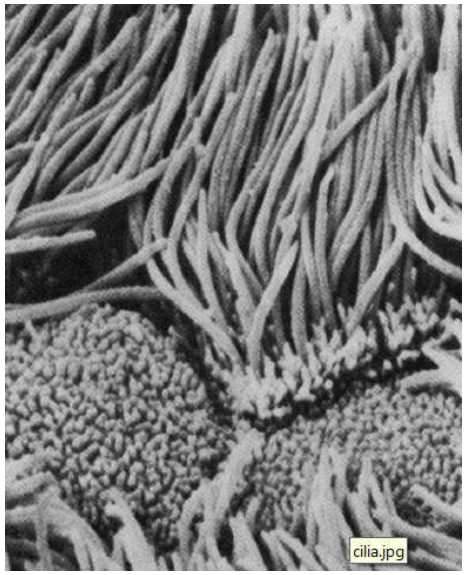
Blood vessels

- Vessels run from the pulmonary artery, branch into capillaries and exit via the pulmonary veins
    - Initially, arteries, veins and bronchi run close together
    - At periphery, arteries, bronchi are inside lobules, veins pass between
        - Dense capillary network
- Capillaries are susceptible to damage because there is very little supporting tissue
    - Inflation of lungs with pressure or an increase in capillary hydrostatic pressure can cause rupture



Blood flow

- Pulmonary
  - Whole cardiac output passes through pulmonary circuit ~6L/min
  - Mean pressure is ~15mmHg, vs systemic 90mmHg
    - Low resistance
  - Red cells spend <0.75s in the capillary network and complete equilibration in this time
- Bronchial
  - Bronchial arteries contain oxygenated blood and supply the conducting airways
    - Blood is drained by the pulmonary veins
  - Thought to be not that important – transplant patients

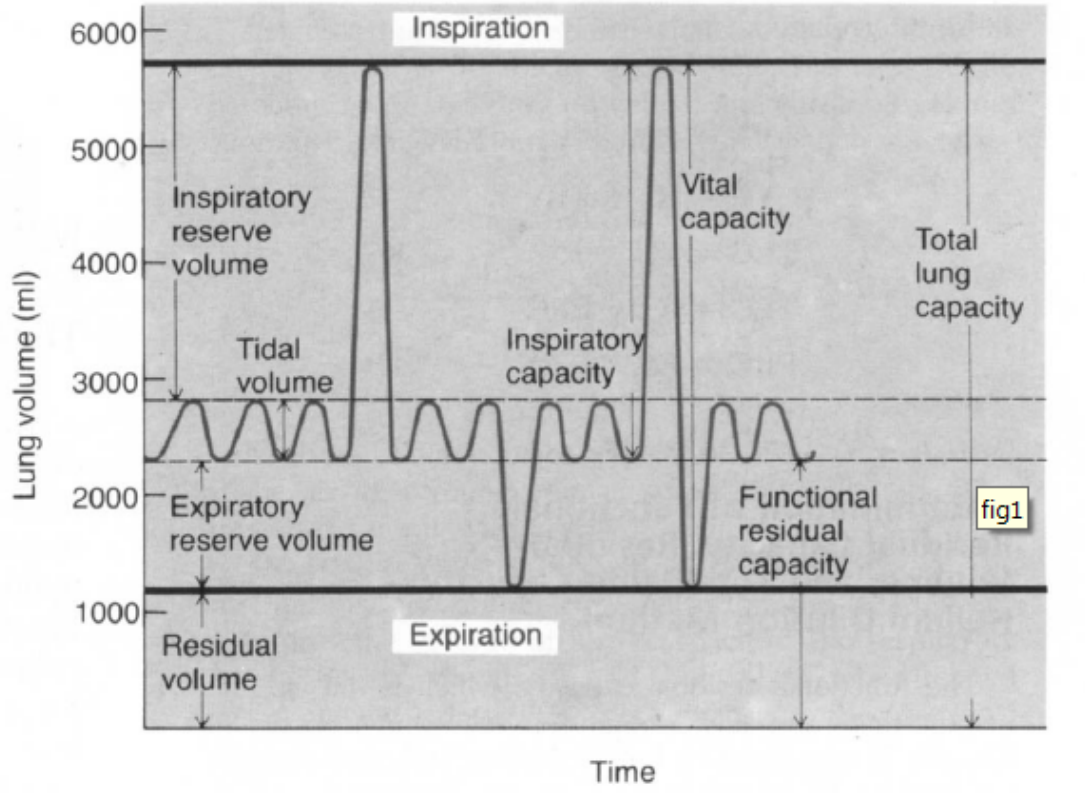


Removal of foreign bodies

- Nose filters large particles
- Smaller particles deposited where bulk flow stops (conducting airways)
  - Swept up in mucus (produced by goblet cells) and propelled by cilia up the trachea and swallowed
  - Ie: like a body surfer in a mosh pit
- Particles that enter the alveoli are engulfed by macrophages
- Coughing process
  - Inspiration (2.5L of air)
  - Epiglottis and vocal chords shut
  - Abdominal muscles and internal intercostals contract to build up lung pressure (>100mmHg)
  - Epiglottis and vocal chords open
  - Air under pressure explodes outwards at high velocity (800km/h) carrying foreign material
    - Sneeze is similar but clears the nasal passages instead

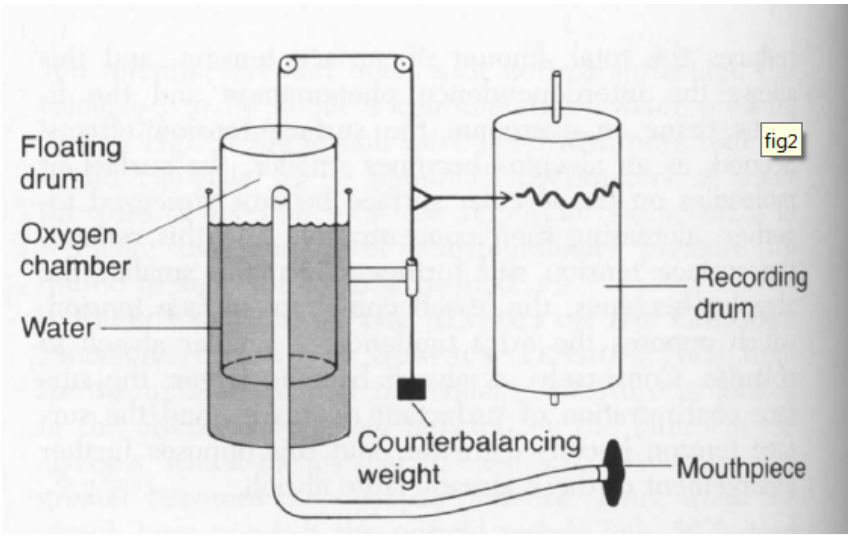
Lung volumes/capacities

- Definitions:
  - Tidal volume (500-600ml) – depth of breathing (amount of air normally breathed in)
  - Inspiratory reserve volume (amount of air we can breath in, more than tidal)
  - Expiratory reserve volume (amount of air we can breath out)
  - Residual volume, ~1L (amount left in lungs when all air breathed out)
  - Vital capacity – lung capacity minus residual volume
  - Functional residual capacity (~2L) – amount of air left in lungs on normal breath
  - Total lung capacity – whole lung volume

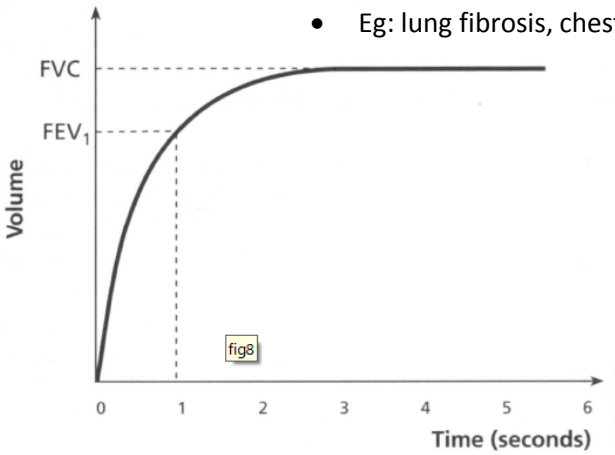


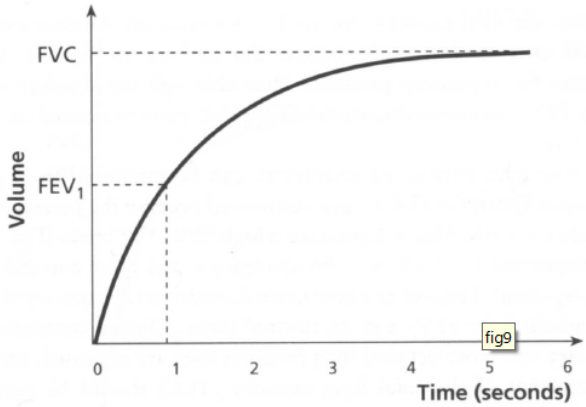
Spirometer

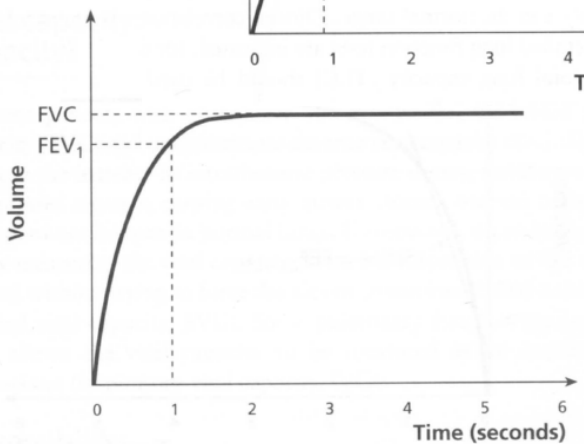
- A device that measures airflow and lung volume
    - Two types:
        - Volume displacement
            - Person breathes through mouthpiece and volume displaced is recorded
            - Flow is calculated by dV/dt
            - Advantages – simple, accurate, disadvantages – bulky, impractical for home/surgery
        - Flow sensing
            - Measures airflow over time and integrate to find volume
            - Various methods – needs calibration



- Useful measurements
    - All lung volumes/capacities except residual volume, functional residual capacity and total lung capacity
    - Forced vital capacity (FVC)
        - Volume of air exhaled in a single forced expiration after maximum inspiration
        - Often slightly lower than VC based on slow expiration
    - Forced expiratory volume in 1 second (FEV_1)
- Forced expiratory ratio (FER) or $FEV_1\%$ = FEV_1/FVC
    - Normally 70-80%
    - Can be altered in disease
        - Low FER is an obstructive pattern
            - Eg: asthma
        - Low FVC, FER high or normal is a restrictive pattern
            - Eg: lung fibrosis, chest wall disease (lungs not compliant, not expanding)







Wounds
- Evaluate via history and examination
- History:
    - Host factors (eg: age, medical history, co-morbidities, medications, vaccination status)
    - Injury factors (eg: type of wound, how the injury occurred, initial wound management)
    - Other factors (eg: social situation, occupation, activities of daily living)
- Examination:
    - Host factors (eg: general health, other conditions, venous/arterial disease)
    - Injury factors (eg: wound depth, bleeding/debris)
        - Does the wound need suturing? Should it be open or covered?
            - Suturing is not performed unless wound is clean and risk of infection minimal
    - Other factors (eg: can they care for the wound? Etc)

Types of healing
- Primary wound healing – 1st intention
- Delayed wound healing – left open, then healing by 1st intention
- Secondary wound healing – 2nd intention (deep burns, etc)
- Re-epithelialisation

Phases of healing
- Haemostasis → inflammation → granulation → remodelling
    - Maximum tensile strength of the wound is achieved by the 12th week
        - Resultant scar has only 80% of tensile strength of original skin

Johnny
- Assuming superficial graze
    - Should have:
        - Told mother
        - Cleaned wound with water, cleaned debris
        - Washed with antiseptic and covered with a non-occlusive bandage
        - Cleaned wound each day and watched progress to check for infection
- Assuming deep penetrating wound
    - Should have:
        - Told mother
        - Gone to see their GP
        - Checked tetanus immunisation status

When to suture
- Pros
    - Faster healing
    - Cleaner scar
- Cons
    - Infection
- Thus, may have to delay suturing until infection clears up

Impaired healing
- Mechanical injury, artery disease, infection (eg: staph)
- Vitamin C deficiency
    - Symptoms: easy bruising, gingivitis, dry/splitting hair, rough/dry skin, impaired healing
- Iron deficiency
    - Symptoms: fatigue, pallor, weakness, impaired immune response, impaired healing
    - Assessed by full blood count – can identify microcytic anaemia

Non-resolving infection

- Purulent wound with redness and swelling
    - Carbuncle/boil – caused by bacteria and infection
    - Treatment: drain to remove bacteria and swelling – thus allows the immune system to reach bacteria
- NB: pus is made up of neutrophils and inflammatory agents
- Lump around scar, explanations:
    - Another infection (deep fungal or mycobacteria)
    - Over responsive repair mechanism (eg: granulation)
- Immune-suppressed are particularly at risk of infection

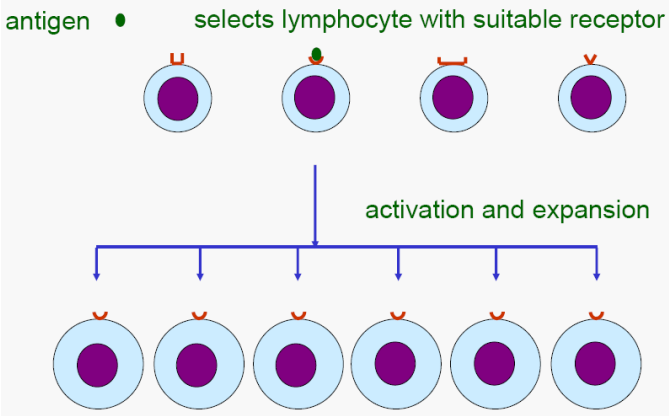
Diagnosis of infected wounds

- Skin swabs for surface bacteria
- Skin biopsy for deep infection

Note: Vaseline gauze may be effective to keep skin moist and encourage epithelial migration

Adaptive immunity

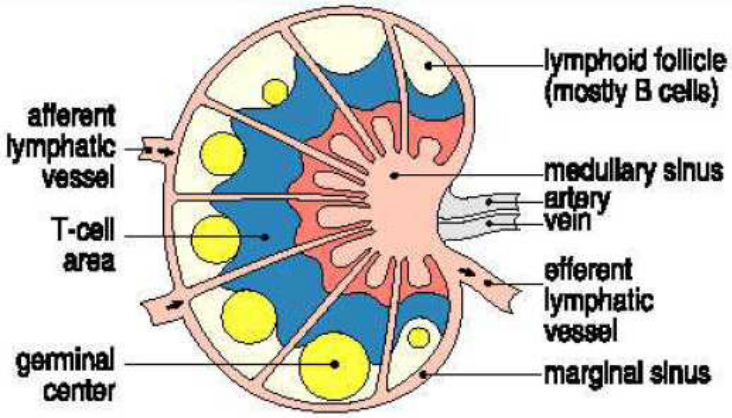
- Involves the process of clonal selection
  - T and B lymphocytes have surface antigen receptors
    - There are many generic types of T and B cell with different types of antigen receptors (naïve)
    - Each antigen receptor will only bind a select few antigens
  - When a T or B cell binds an antigen, it proliferates within a week
    - This creates clones of the particular T or B cell that was effective against that particular antigen



- When we are infected for the first time by a pathogen, there are few T and B cells that can respond
  - Over a week, the T and B cells that can respond multiply
    - This can be clinically seen by enlargement and tenderness of lymph nodes
  - Innate immunity attempts to deal with pathogen
    - If unsuccessful, pathogen will be quickly eliminated by the now numerous T and B cells specific to eliminating it – the acquired immune system
  - Thus, we get sick and then recover in about a week from infections
- Clonal memory
  - When the T and B cells multiply in response to a pathogen, memory T and B cells are produced
    - Survive for decades
    - Allow a fast response to the same pathogen if infected again
      - Lymphocytes will be more numerous, mature in function and faster to respond
  - Often pathogen is eliminated before we feel sick

Lymph nodes

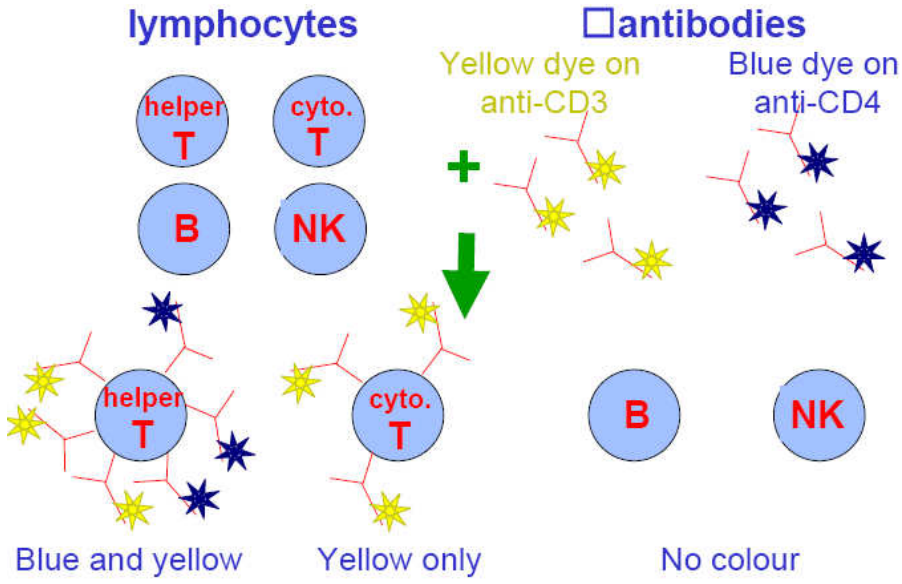
- Definitions
  - Secondary lymphoid tissue = lymph nodes, spleen and mucosa associated lymphoid tissue
  - T cell = Thymus-derived cell
  - B cell = Bone marrow-derived cell
- Anatomy
  - Cortex (outer) – follicles containing B cells
  - Paracortex (inside cortex) – sinuses with T cells
  - Medulla (inner) – blood vessels and efferent lymphatics
  - Process
    - In an immune response, germinal centres develop in the follicles with developing B cells
    - Afferent lymphatic vessels deliver lymph from tissues and upstream nodes to T and B cell areas exposing antigen to T and B cells
    - T and B cells undergo clonal selection and specific T and B cells begin to develop/multiply
    - Efferent lymphatic vessels drain lymph and lymphocytes to more nodes and blood stream
  - Spleen and other secondary lymphoid tissue have similar areas

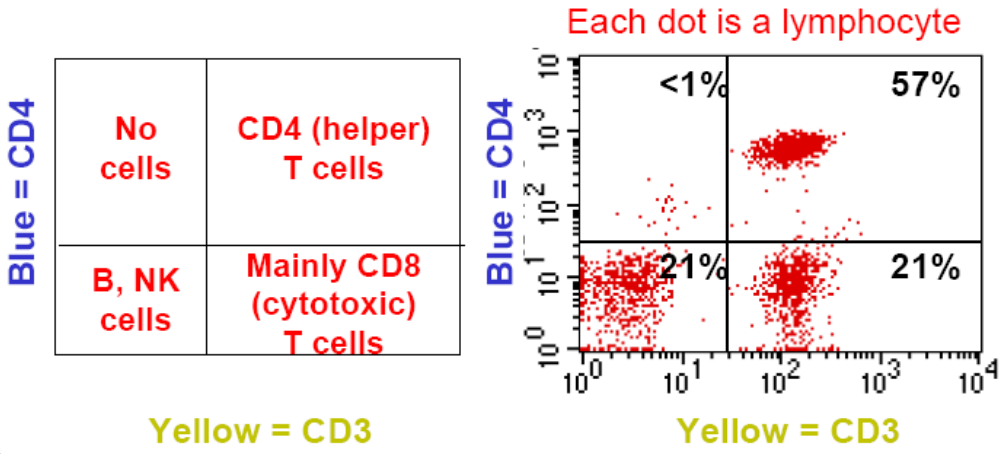


- Function
  - Facilitate exposure of as many T and B cells to antigen as possible
  - If receptors bind to antigen, migration stops and clones are produced in the sinuses/germinal centres
  - T and B cells enter via the afferent vessel or from the artery, then if they don't match the antigen, they leave via the efferent lymphatic vessel, travel to other nodes and return to the bloodstream

Lymphocytes

- Several types of T cells
  - T cells have surface molecules and this allows them to be classified
    - Most mature T cells have CD4 or CD8 (not both)
    - CD4 T cells are helper T cells – coordinate immune responses
    - CD6 T cells are cytotoxic T cells – kill virus infected cells
- Normal blood lymphocyte contents:
  - Mostly T cells – 2x CD4 than CD8
  - Some B cells (more abundant in secondary lymphoid tissue)
  - Natural killer (NK) cells
- At one time, only 2% of lymphocytes are in the blood, it is a dynamic process and lymphocytes are constantly entering and leaving
- Lymphocytes can be detected by antibody staining
  - In normal blood smears, CD4, CD8 and B cells look similar
  - Lymphocyte immunophenotyping (a standard lab test) allows differentiation
    - Types have different surface markers (molecules) that monoclonal antibodies labelled with fluorescent dies can attach to
    - Thus, blood can be passed through a flow cytometer which can perform a colour analysis and thus allow identification of lymphocytes





Natural killer cells

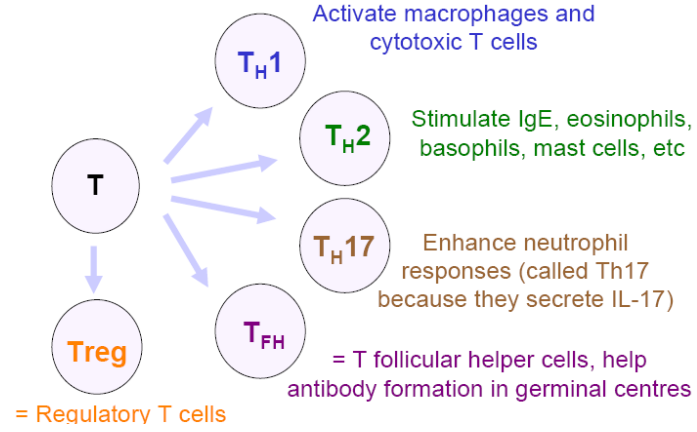
- Large granular lymphocytes – have a granular appearance and a large nucleus with small cytoplasm
  - Note: some CD8 T cells also have this appearance
- Make up 10% of blood lymphocytes, however, are very common in secondary lymphoid tissue
- Differences to T and B cells:
  - Part of the innate immune system
  - Do not have antigen receptors or surface antibodies but are activated by non-specific pathogenic features
- Particularly important in the early stages of viral infection

Naïve T cells and their activation

- T cells that have not encountered an antigen they react with are naïve
    - When a naïve T cell comes into contact with a compatible antigen, the T cell becomes activated via its TcR (T cell receptor) and begins to divide clonally
        - 2 types of clones:
            - Effector cells – migrate throughout body to counter pathogens
            - Memory cells – stored to allow a fast immune response in the case of a similar pathogen
    - Dendritic cells are important in initial T cell activation
        - Exist in an inactive form in areas that come in contact with the external environment – like the skin
            - Here, when they come into contact with a pathogen they are activated and travel via the blood stream to a lymph node where they activate T cells in the paracortex

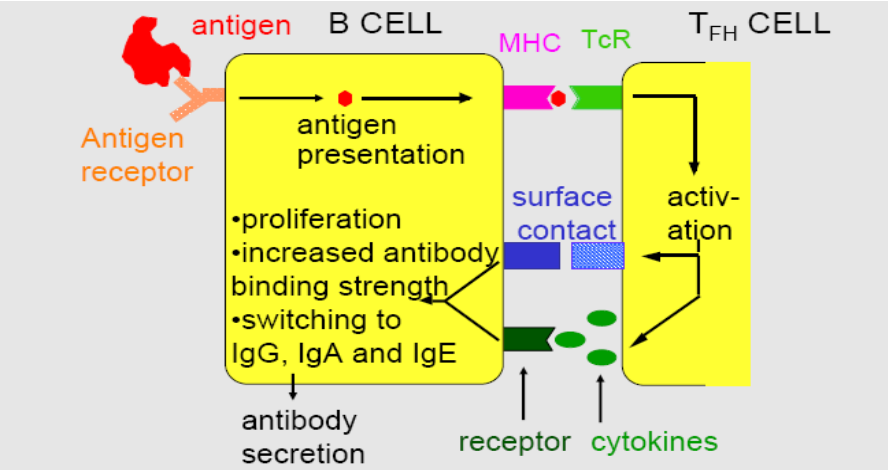
CD4 (helper) T cells

- Coordinate the immune response
    - Help other cells to attack pathogens
        - B cells – stimulate antibody production
        - Macrophages – activation
        - CD8 (cytotoxic) T cells – promoting antiviral function
    - Coordinate via secretion of cytokines (proteins) and expression of surface molecules
- Cytokines
    - Glycoproteins that are secreted and act locally
    - Egs:
        - Interleukins → between leukocytes
        - Interferons → antiviral activity
        - Tumour necrosis factors → inflammatory effects (kill by apoptosis and not tumours)
        - Colony stimulating factors (CSF) → promote hemopoiesis (formation of RBCs)
        - Chemokines → chemotactic activity
        - Growth factors → variety of other activities
    - Clinical Egs:
        - Interferon-α in Hepatitis C, Blockade of TNF-α in inflammatory disorders, G-CSF in neutropenia
- Differentiate into subsets that have different functions due to secretion of different cytokines
    - Types:
        - T_H1 – activates macrophages and cytotoxic T cells
            - Allows immunity to intracellular bacteria (TB) and viruses
            - Excessive function of this cell results in autoimmune diseases
        - T_H2 – stimulates IgE, eosinophils, basophils, mast cells etc
            - Allows immunity to multicellular melminth parasites
            - Excessive function results in allergic reactions
        - T_H17 – enhances neutrophil responses (secretes the cytokine IL-17)
            - Allows immunity to extracellular bacteria
            - Excessive function results in autoimmune diseases
        - T_{FH} – T follicular helper cells, helping formation of antibodies in germinal centres
            - Allows production of antibodies that are involved in most immune responses
            - Excessive function results in autoantibody production
        - T_{reg} – Regulatory T cells
            - Allows limiting of immune responses
            - Excessive function results in inhibition of anti-microbial and anti-tumour responses

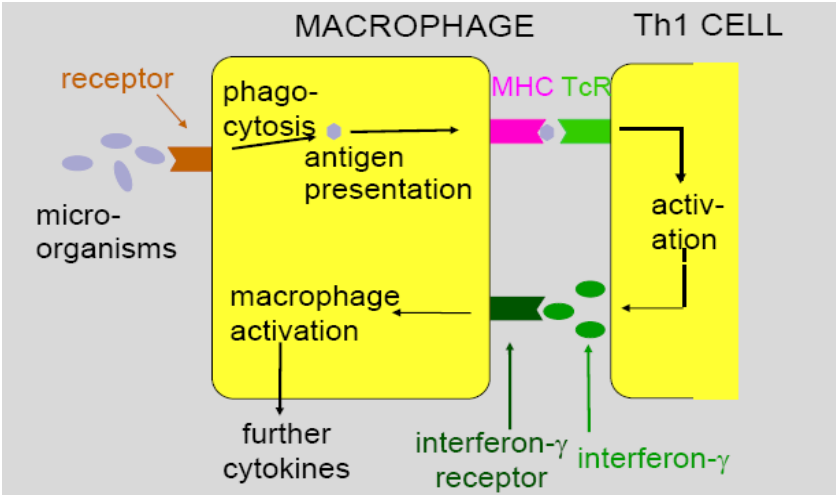


Interactions between T cells and other cells

- T cells and B cells
  - After T cells have been activated by dendritic cells, B cells can present antigens to helper T cells
    - T_{FH} cells help B cells make the optimal type of antibody and stimulate antibody production
    - This occurs in germinal centres of lymph nodes
  - T cells help B cells:
    - Make IgG, IgA and IgE antibodies
    - Improve the binding strength of these antibodies
    - Alone, B cells can only make IgM antibodies



- T cells and macrophages
  - After T cells have been activated by dendritic cells, macrophages can present antigens to the helper T cells
    - T_H1 cells induce local inflammatory reactions and activate macrophages via the cytokine interferon
    - This occurs in the tissue at the site of the antigen
  - T cells help macrophages with:
    - Phagocytosis
    - Lysis of intracellular pathogens
    - Secretion of enzymes that degrade extracellular proteins
    - Secretion of cytokines that increase inflammation

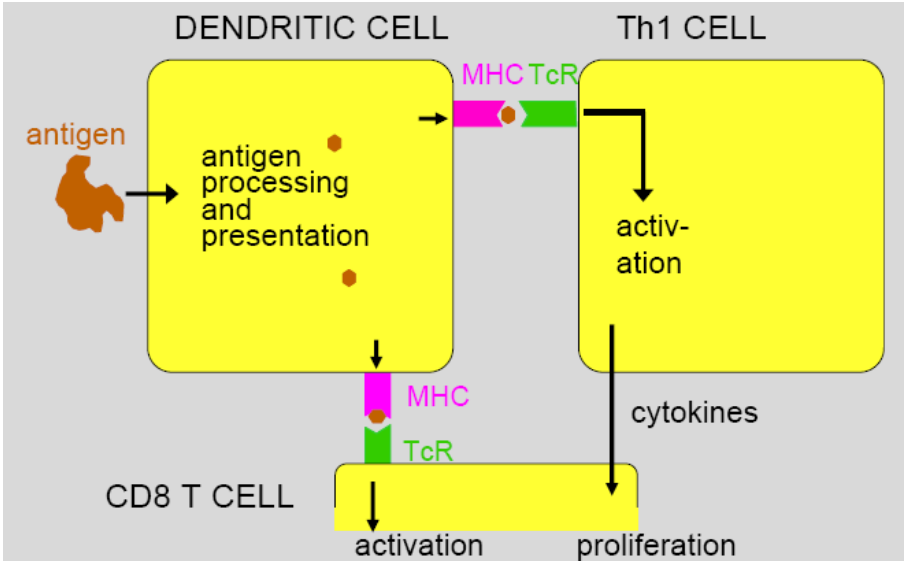


Cell-mediated hypersensitivity – an example of T cell and macrophage interaction

- Hypersensitivity – an exaggerated or inappropriate immune response
- Cell-mediated hypersensitivity (type IV/delayed hypersensitivity)
  - A delayed reaction to the local presence of an antigen in an immunised person
  - Peak reaction is at 24-48 hours
- Explanation:
  - Antigen presenting cells present antigen to Th1 cells, Th1 cells attract and activate macrophages which become numerous and cause an inflammatory response
- EGS:
  - Chronic infection (TB with macrophages that may cause damage), Mantoux test (TB antigen injection, 48 hours later check), contact hypersensitivity (chemicals), autoimmune diseases (insulin-dependent DM, Ms, Hashimoto's thyroiditis), Acute transplant rejection
  - Th17 may contribute

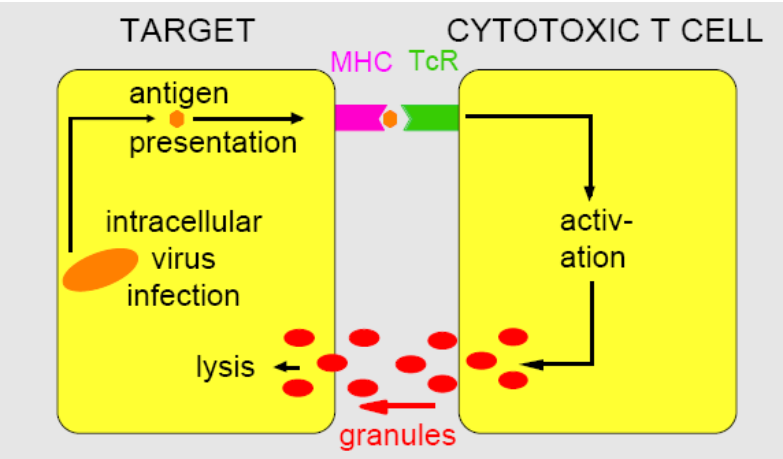
Interactions between T cells and other cells continued

- T helper cells and cytotoxic T cells
  - After Th1 cells have been activated by dendritic cells, they can stimulate cytotoxic T cells to multiply and to develop into mature effector cells
    - Th1 cytokines stimulate proliferation
    - Dendritic cells stimulate activation
  - This all occurs in T cells areas of secondary lymphoid tissue
    - Thus, cytotoxic T cells are activated and then leave the lymphoid tissue to destroy virus-infected cells



Cytotoxic T cells

- Process
  - Virus-infected cells present antigen to receptors of cytotoxic T cells
  - T cells are activated and release toxic granules that induce apoptosis
    - This normally occurs outside lymphoid tissue (eg: hepatitis virus cells are destroyed in the liver)
  - Virus-infected cells are killed so that they cannot spread virus to other cells thus controlling infection
- Cytotoxic T cells have other functions
  - Can kill some cancer cells (infected by a virus) and transplants
- NB: NK cells are activated differently to cytotoxic T cells but have similar kill mechanisms



- Appearance in action:
  - Toxin granules are scattered diffusely in cell then when a target is found, the granules move to the side of the T cell with the target in preparation for release onto the target thus inducing apoptosis

What is a virus?

- L: poison
- Definition:
  - A cellular organism with a nucleic acid genome that uses host cell metabolic machinery to reproduce
  - Offspring are produced in a protective form – the virion
- Properties
  - Smaller than bacteria, but larger than proteins
    - 20-350nm, can pass through 0.22µm (220nm) filters
  - Dependent on living cells for replication and existence
  - Has either single or double stranded RNA or DNA containing its genome
  - Able to attach/dock onto cells via external proteins (have the 'key' to the cell)
    - Thus can take over the cell and propagate
- Virion
  - Virus particles – inert carriers of the genome
  - Assembled inside cells using host cell machinery
  - The extracellular phase of the virus – the spaceship form
    - Protect the genome from inhospitable environments and transport it to other cells

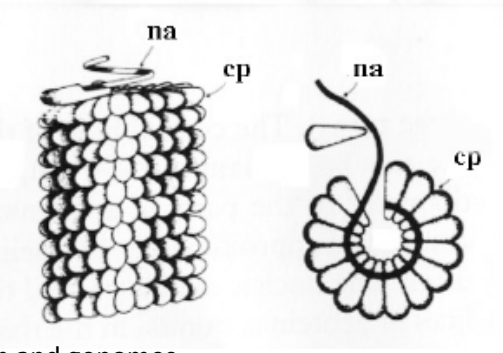
How common are viruses?

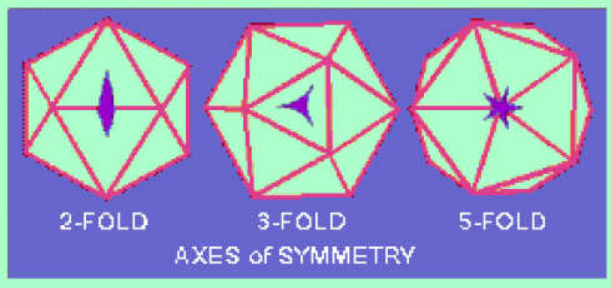
- Very, very common
  - Eg: CMV - <20 years of age, 30% have, 40-49, 70% have

Virus structure

- Nucleic acid is enclosed within a protein shell – the capsid
  - Sometimes this can be surrounded by a lipid envelope
    - All animal viruses with a helical shape have an envelope
    - The envelope is derived from the cell membrane via budding
- Envelopes contain two types of proteins:
  - Glycoproteins – projections known as spikes that aid attachment to potential host cells
  - Matrix proteins – a layer inside the envelope that aids rigidity (particularly helical viruses)
- Viruses without envelopes are known as naked = hydrophilic, thus protected from organic solvents
- Enveloped vs non-enveloped
  - Enveloped viruses
    - Released by budding and cell lysis
    - Sensitive to the environment – acid, detergent, heat, lack of moisture
    - Modify the host cell membrane during replication
    - Consequences:
      - Need moist environments
      - Spread in droplets/secretions/transplants
      - Can't survive the GIT
      - Does not always kill host cell
      - Protected from host cell immune system
  - Naked capsid viruses
    - Environmentally stable – temperature, acid, proteases, detergents, lack of moistre
    - Consequences:
      - Easily spread
      - Still infectious after drying
      - Resistant to detergents
      - Survive the GIT
      - Resistant to sewage treatment
      - Induce an immune response

- Shapes of virions – capsid/protein shell architecture:
    - DNA, ½ for genome, ½ for capsid
    - Sphere – icosahedron (a shell of equivalently bonded identical structures)
        - Strong structure with a maximum volume
        - 20 facets, each an equilateral triangle with 12 vertices
        - Egs: rotavirus, adenovirus, HPV,
    - Helix – cylindrical/spiral staircase shape
        - Forms as a hollow tube
        - Nucleic acid forms a spiral staircase within the capsid structure
        - Capsid is made up of capsomers that is a single individual protein
        - Egs: ebola, mumps, measles, rabies, SARS



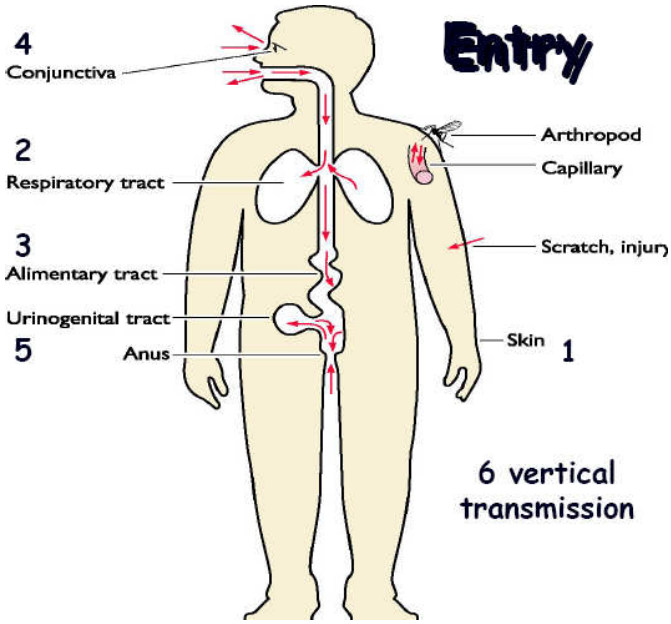


<u>Classification and genomes</u>

- International Committee on Taxonomy and Viruses (ICTV) established a naming system
    - Allows classification to predict replication/pathogenesis
- Classification
    - Order (-virales)
        - Family (viridae)
            - Subfamily (virinae)
                - Genus (virus)
                    - Species (eg: tobacco mosaic virus)
- Virus process involves replication and transcription
    - Replication in viruses involves 4 different polymerase
        - RNA viruses: RNA dependent RNA polymerase (RdRp), RNA dependent DNA polymerase (reverse transcriptase)
        - DNA viruses: DNA dependent DNA polymerase (DdDp), DNA dependent RNA polymerase (DdRd, not used in viral replication)
    - genome types:
        - single strand (+ and -), double strand,

<u>Ebola</u>

- Named after a river in the democratic republic of Congo in Africa
    - From the family filoviridae
- Causes Ebola hemorrhagic fever which is often fatal in humans
    - If get disease, 80% chance of dying
- Aetiology
    - 1 week incubation
    - Flu-like symptoms
    - Then virus attacks vital organs (liver, kidneys), blood & liver cells
        - Causes internal bleeding leading to shock and respiratory arrest then death

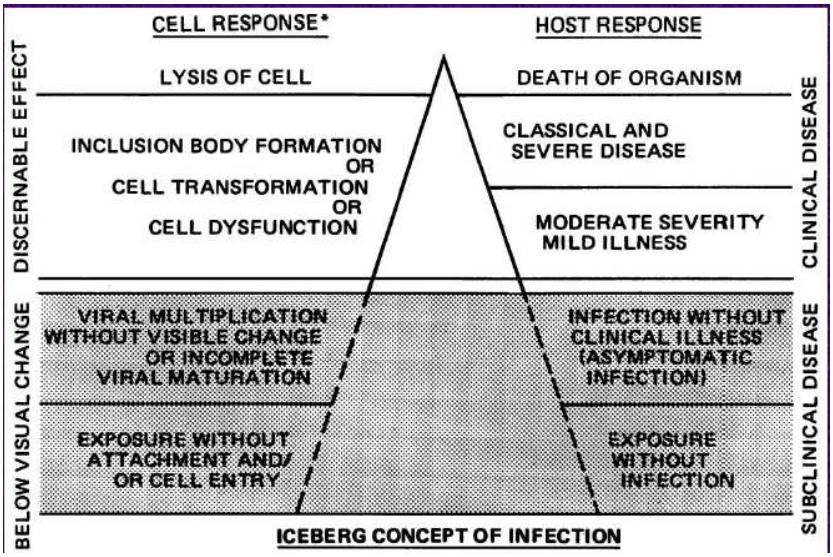


Transmission

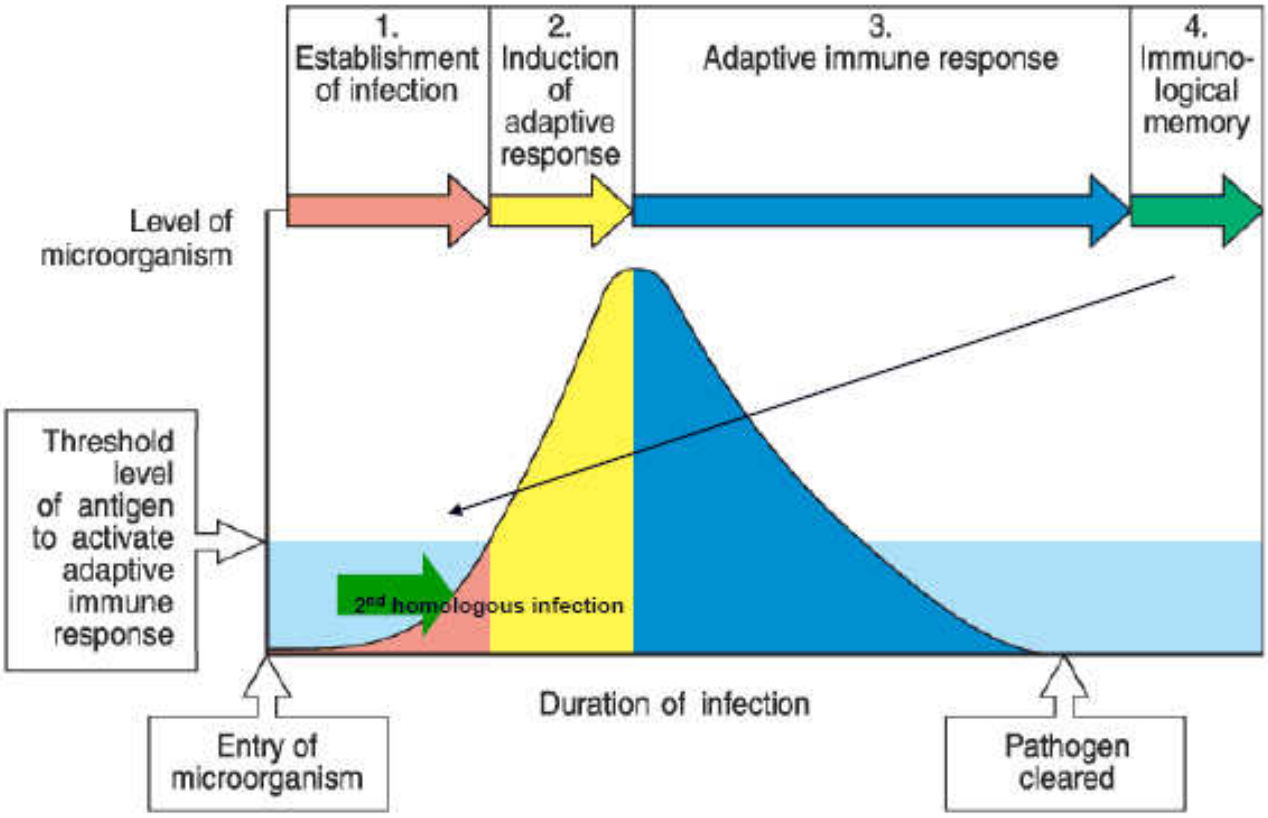
- Viral entry via:
  - Skin/wounds
  - Mucosal surfaces – eyes, mouth, nose, lungs, URT, genital tract, intestinal tract
  - Blood – injecting drug use, unsafe medical practices, insect vectors, eg: yellow fever virus
  - Vertical transmission – mother to baby
- Incubation times can be important
  - Short incubation (eg: common cold, influenza)
    - 1-3 days
  - Medium incubation (eg: polio, measles, rubella)
    - 14-16 days
  - Long incubation (eg: HepA, B, infectious mononucleosis, rabies)
    - 3-7 weeks
  - Very long incubation (eg: Creutzfeldt-Jakob disease)
    - Years
  - The longer the incubation time, the more serious the disease

Pathogenesis – how viruses cause disease

- Mechanisms of disease:
  - Cell death – apoptosis/immune mediated
  - Cessation of cell function – eg: hepatitis, myocarditis
  - The body's response to cell damage/loss of function – eg: mucus production
  - Local immune response – eg: rash
  - Systemic immune response – eg: fever
  - Trigger for auto-immune response – eg: post-infectious encephalomyelitis

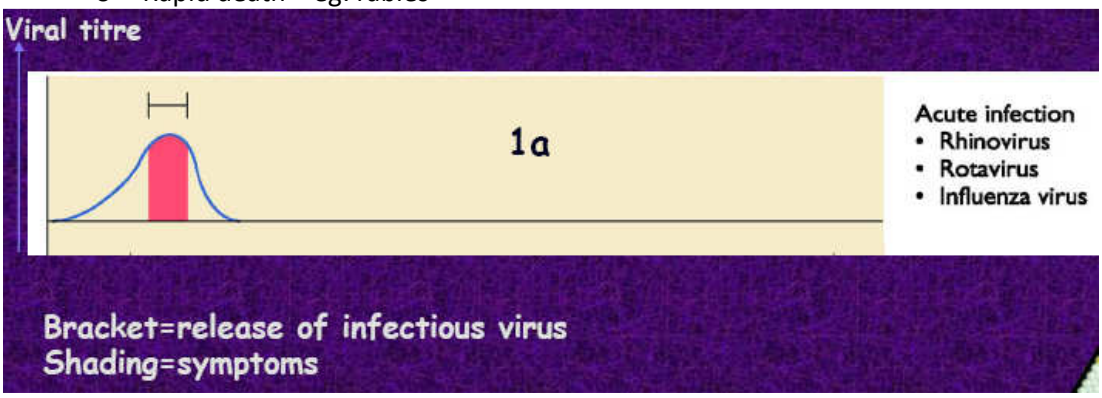


- Immune response and immunopathology
  - Immune system can be more damaging than the virus
    - Pro-inflammatory cytokines cause fever, rash, malaise
    - Cytotoxic T Lymphocytes induce apoptosis of cells an can cause damage to organs
    - Some viruses directly target the immune system, eg: HIV
- Effects with host cells
  - Cell lysis
  - Cell fusion – production of multi-nucleated syncytia
  - Inclusion bodies, aggregations of virions intracellular (in the cytoplasm or nucleus or both)
  - Transformation

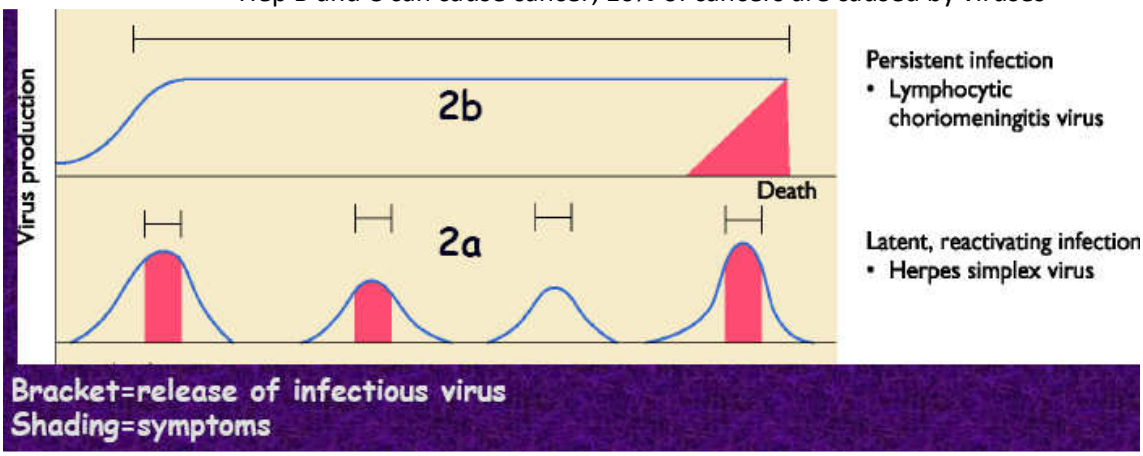

1.
Establishment of infection
2.
Induction of adaptive response
3.
Adaptive immune response
4.
Immuno-logical memory
Level of microorganism
Threshold level of antigen to activate adaptive immune response
2nd homologous infection
Duration of infection
Entry of microorganism
Pathogen cleared

Patterns of infection

- Infections can be acute or persistent
- Acute infection types:
    - Rapid recovery – eg: influenza
    - Apparent rapid recovery – eg: mumps, measles
    - Rapid death – eg: rabies



- Persistent infection types:
    - Latent
        - Eg: in nerve cells
            - Viral DNA can be maintained as an episome in the cell not being integrated into the genome
            - Reactivation may be spontaneous or in response to stimuli (eg: trauma, sunburn, stress)
    - Types:
        - Symptom free periods + reactivation (eg: herpes)
        - Long symptom free period followed by illness and death (eg: EBV, HIV)
        - Chronic disease (Eg: HPV, HCV, HBV)
    - May induce the development of tumours
        - Hep B and C can cause cancer, 10% of cancers are caused by viruses



RNA viruses	Chronic disease
Hepatitis C virus	Cirrhosis, liver cancer
Measles	SSPE (panencephalitis)
Rubella	Progressive panencephalitis
human immunodeficiency virus	AIDS
human T-cell leukaemia virus	Leukaemia
DNA viruses	
hepatitis B virus	Cirrhosis, liver cancer
herpesviruses -herpes simplex 1 & 2	Cold sores, genital recurrences
varicella zoster virus	Herpes zoster (shingles)
cytomegalovirus	Pneumonia, retinitis
Epstein- Barr virus	Lymphomas, carcinomas
Papillomavirus	Warts, genital and other cancers
polyomavirus JC	Encephalopathy
polyomavirus BK	Haemorrhagic cystitis
adenoviruses	None known

Note:

- Replication models of viruses use humans and chimpanzees

Introduction

- The upper respiratory tract is made up of the nose, paranasal sinuses, larynx and trachea

The nose

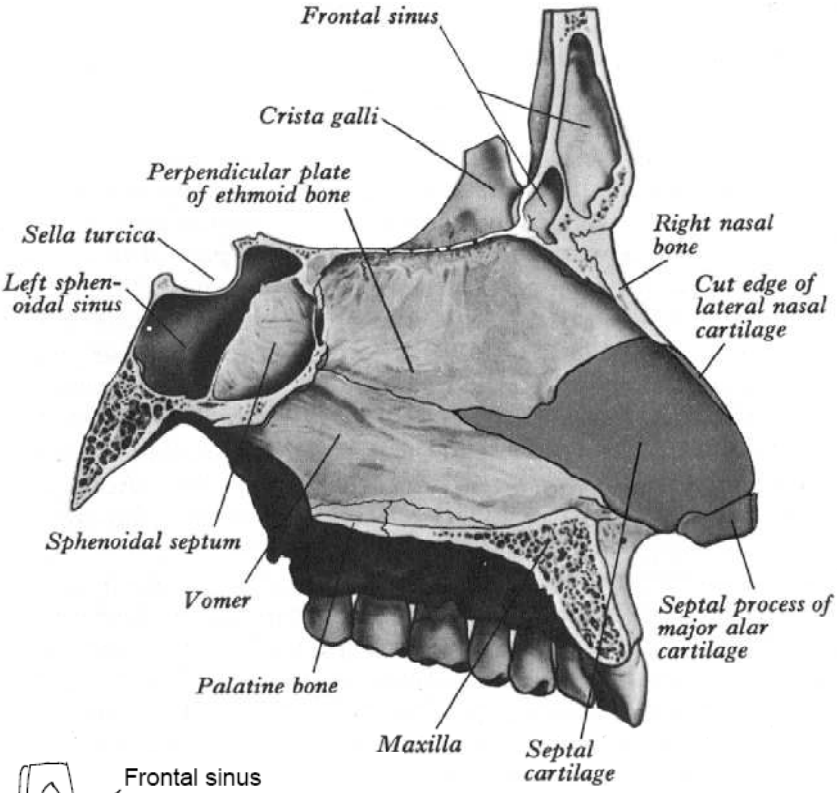
- Made up of two parts
  - External nose
  - Nasal cavity
- Four main functions
  - Facilitates the sense of smell
  - Provides an airway for respiration
  - Filters, moistens and warms inspired air
  - Removal of foreign particles

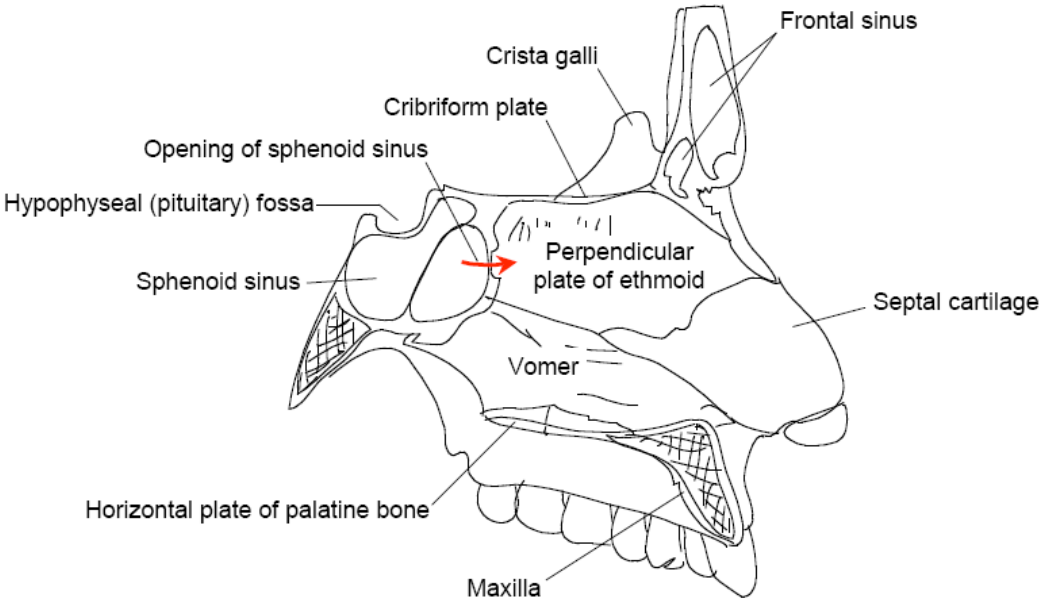
The external nose

- Made up of cartilage attached to a bony base – the piriform aperture
- Parts:
  - Nares (nostrils) – where air enters
  - Septal cartilage – septum dividing nares
  - Alar cartilages – lateral parts of external nose

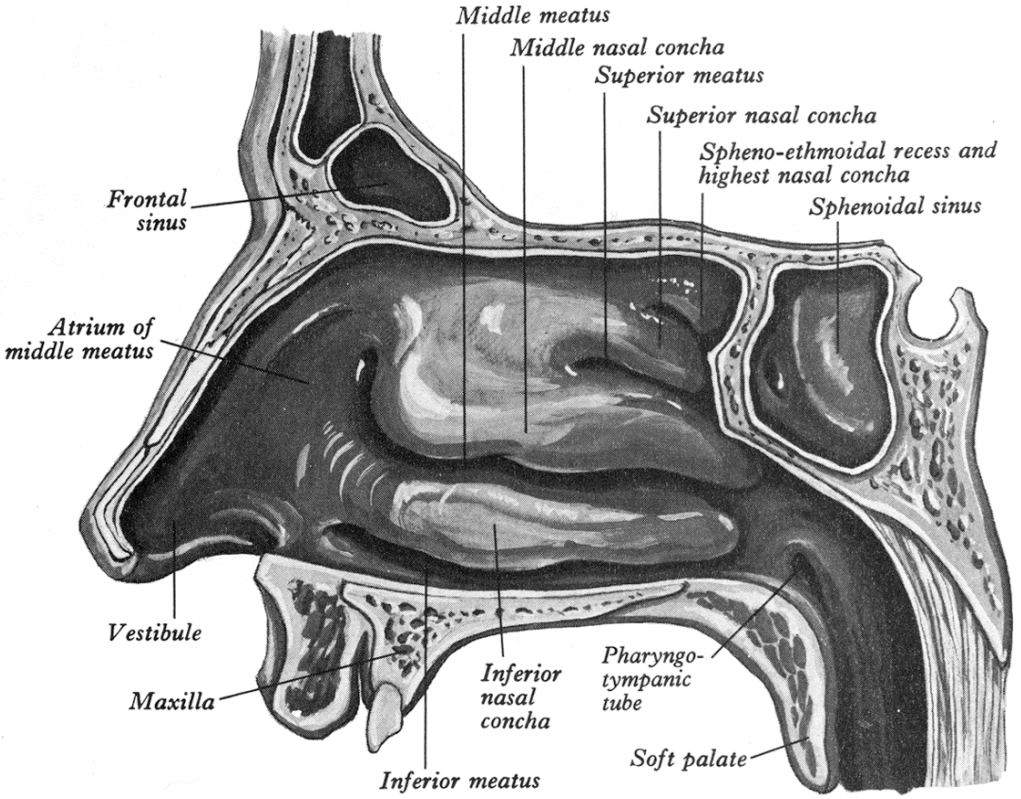
The nasal cavity

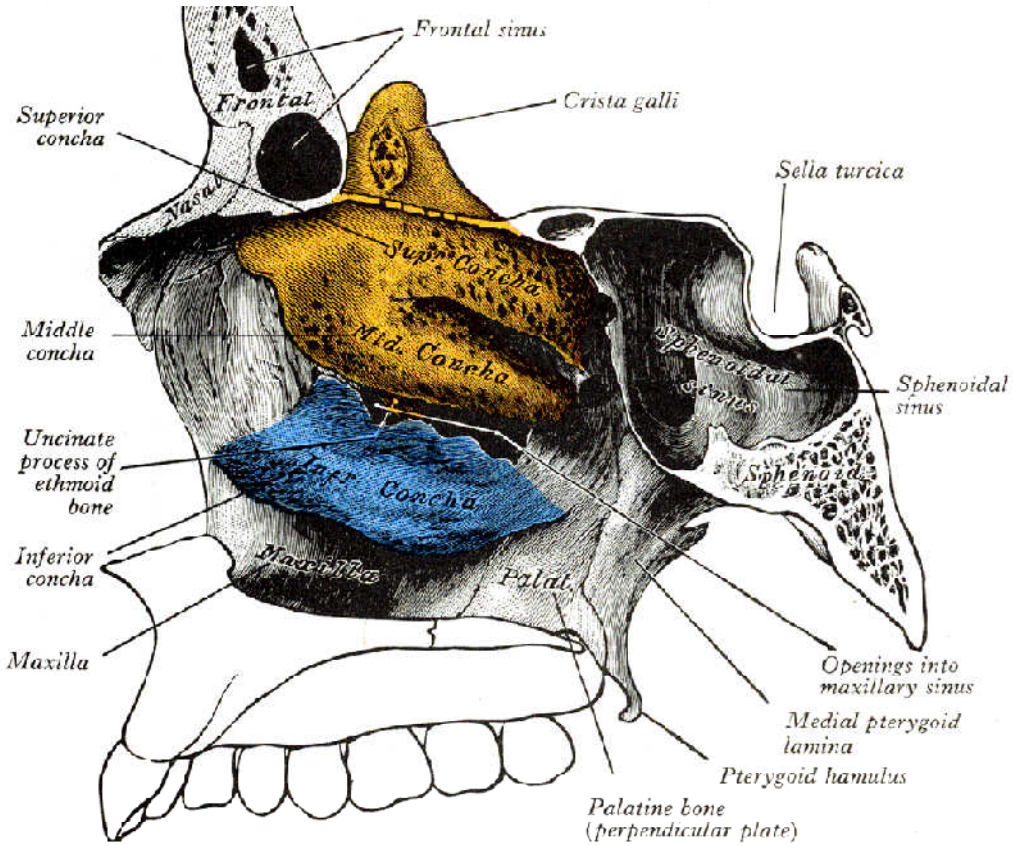
- Divided sagittally by the nasal septum
  - Two openings:
    - Anterior – nares
    - Posterior - choanae
  - The bony opening at the anterior is the piriform aperture
- Nasal cavity framework – bony and cartilaginous
  - Medial wall – nasal septum
    - Made up of nasal bones, the perpendicular plate of the ethmoid and the vomer
    - Anteriorly, made up of the nasal septal cartilages

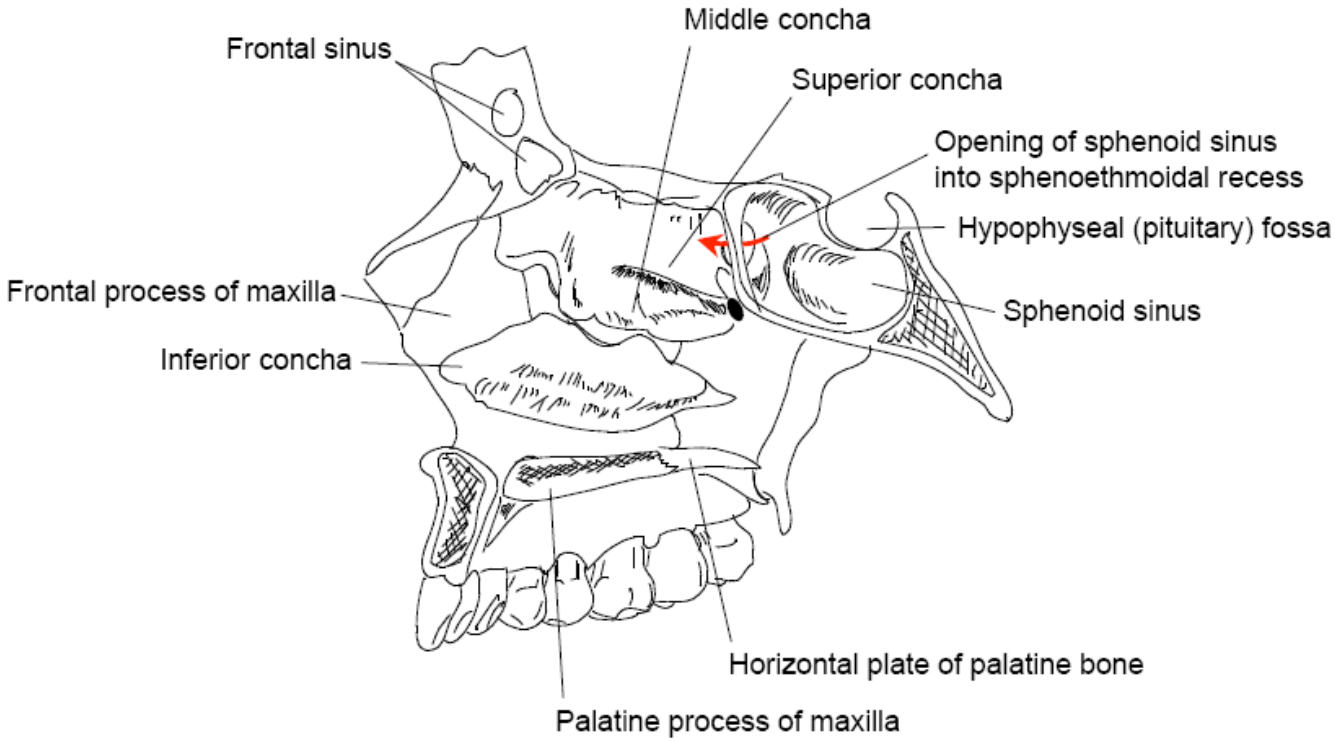


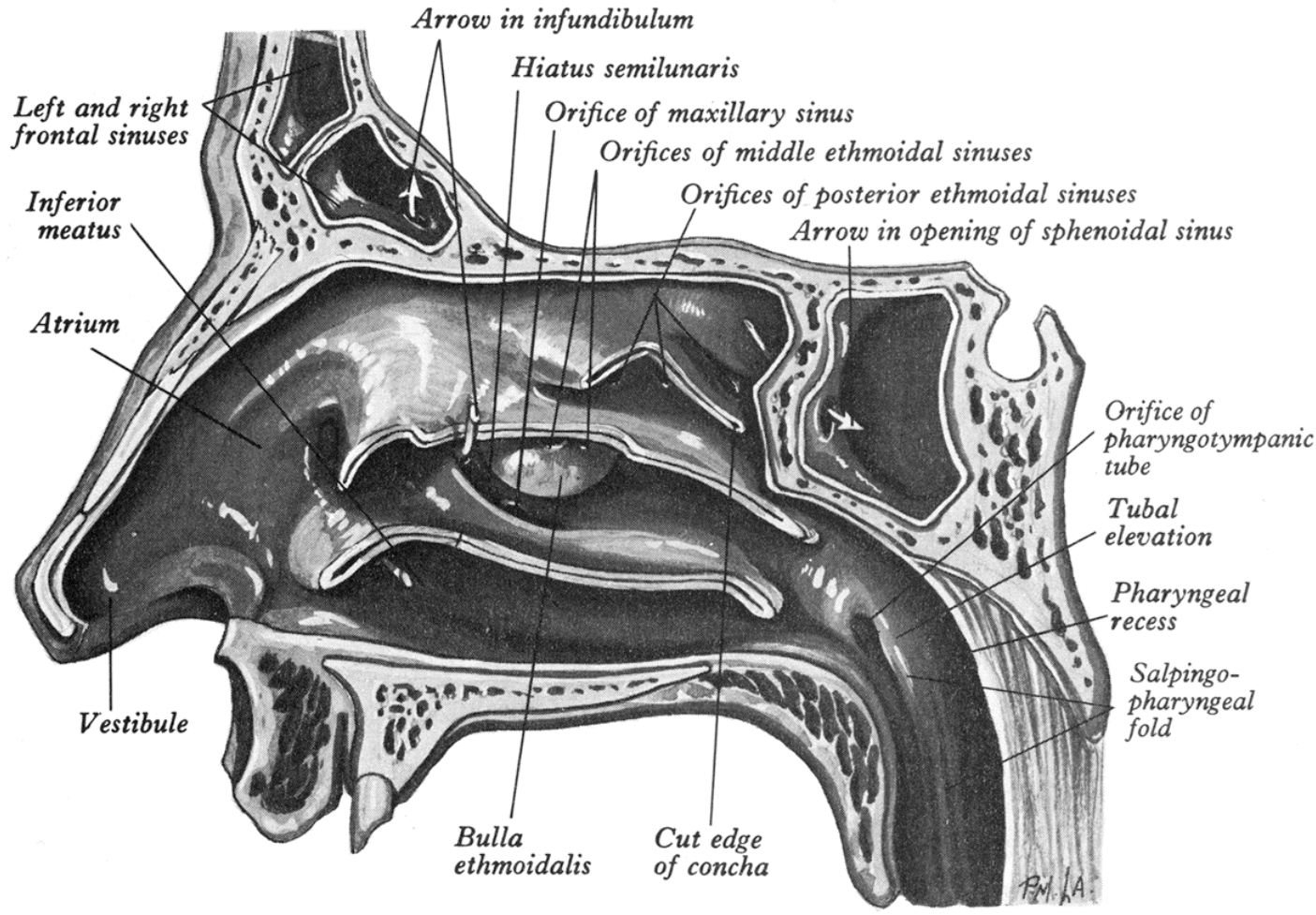


- Lateral wall
  - Made up of several bones: inferior concha, maxilla (frontal process), perpendicular plate of the palatine, ethmoidal labyrinth and lacrimal
  - Has three projections: inferior, middle and superior nasal conchae
    - Spaces between concha + below is called the superior, middle and inferior meatuses
      - Sinuses and cuts drain into these meatuses
    - These projections increase SA for warming the air and removing pathogens
  - Posterior to the superior concha is the sphenopalatine foramen
    - Contains (from the pterygopalatine fossa):
      - Sphenopalatine artery
      - Nasopalatine and superior nasal nerves



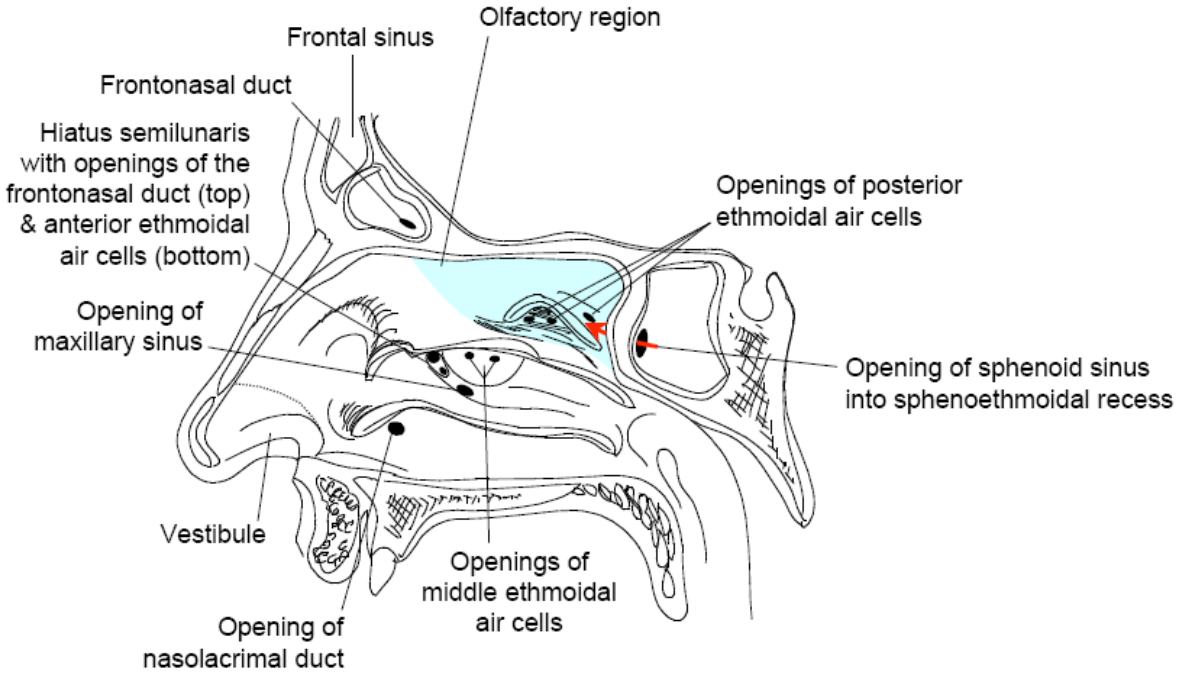






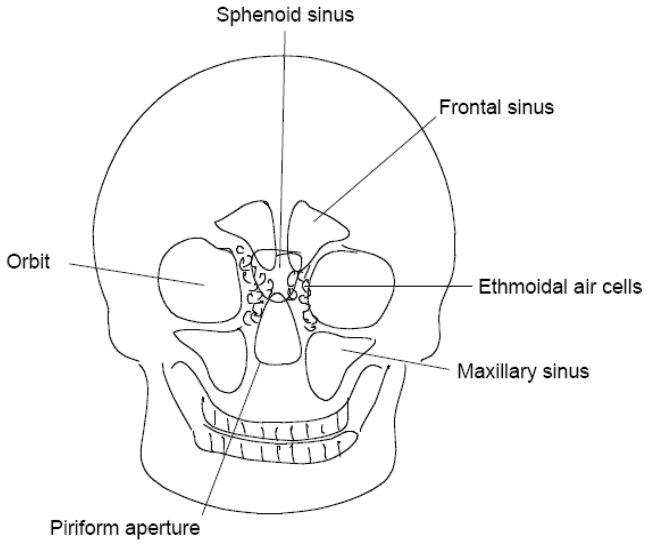
- Roof
  - Formed by:
    - Anterior – the frontal and nasal bones
    - Middle – cribriform plate of the ethmoid
    - Posterior – sphenoid body
      - Orifice of the sphenoidal sinus interrupts this posterior roof on both sides
- Floor
  - Formed by palatine and maxillary bones

- Nasal cavity features
  - Three regions
    - Nasal vestibule
      - Lined with skin with course hair
      - Forms a barrier and prevents the entrance of dust and pathogens
    - Olfactory region
      - Found on the superior nasal concha, the opposing area of the septum and the intervening roof
      - Contains micro cilia with nerves that respond to odours
        - Axons project through the cribriform plate and enter the olfactory bulb as the olfactory nerve
        - Has a continual replacement of nerve cells
    - Respiratory region
      - Makes up the rest of the cavity
      - Lined by pseudostratified columnar epithelium, goblet cells, serous and mucous glands
      - Functions to warm and moisten the passing air
- Nasal cavity openings
  - Spheno-ethmoidal recess
    - Opening of the sphenoidal sinus from behind the superior concha
  - Hiatus semilunaris
    - Drains the anterior ethmoidal and frontal air cells
      - Frontal air cells via the fronto-nasal duct and infundibulum
  - Orifice of maxillary sinus
    - Found in the middle meatus behind hiatus semilunaris
  - Orifice of the middle ethmoidal air cells
    - Found below the middle concha
  - Opening of nasolacrimal duct
    - Opens into inferior meatus
  - Orifices of posterior ethmoidal air cells
    - Found above and below the superior nasal concha



Paranasal sinuses

- Not found or underdeveloped at birth
  - Enlarge when permanent teeth are grown and after puberty
- Lined by respiratory epithelium
  - Thin mucosa which is less vascular and more adherent to the bone
  - Mucous secretions drain to nasal cavity – if drainage is obstructed, problems can be caused
- Function
  - Lighten the skull
  - Add resonance to voice
  - Thought to be a manifestation of unusual growth patterns of bone
- Groups
  - Frontal
  - Ethmoidal
  - Sphenoidal
  - Maxillary

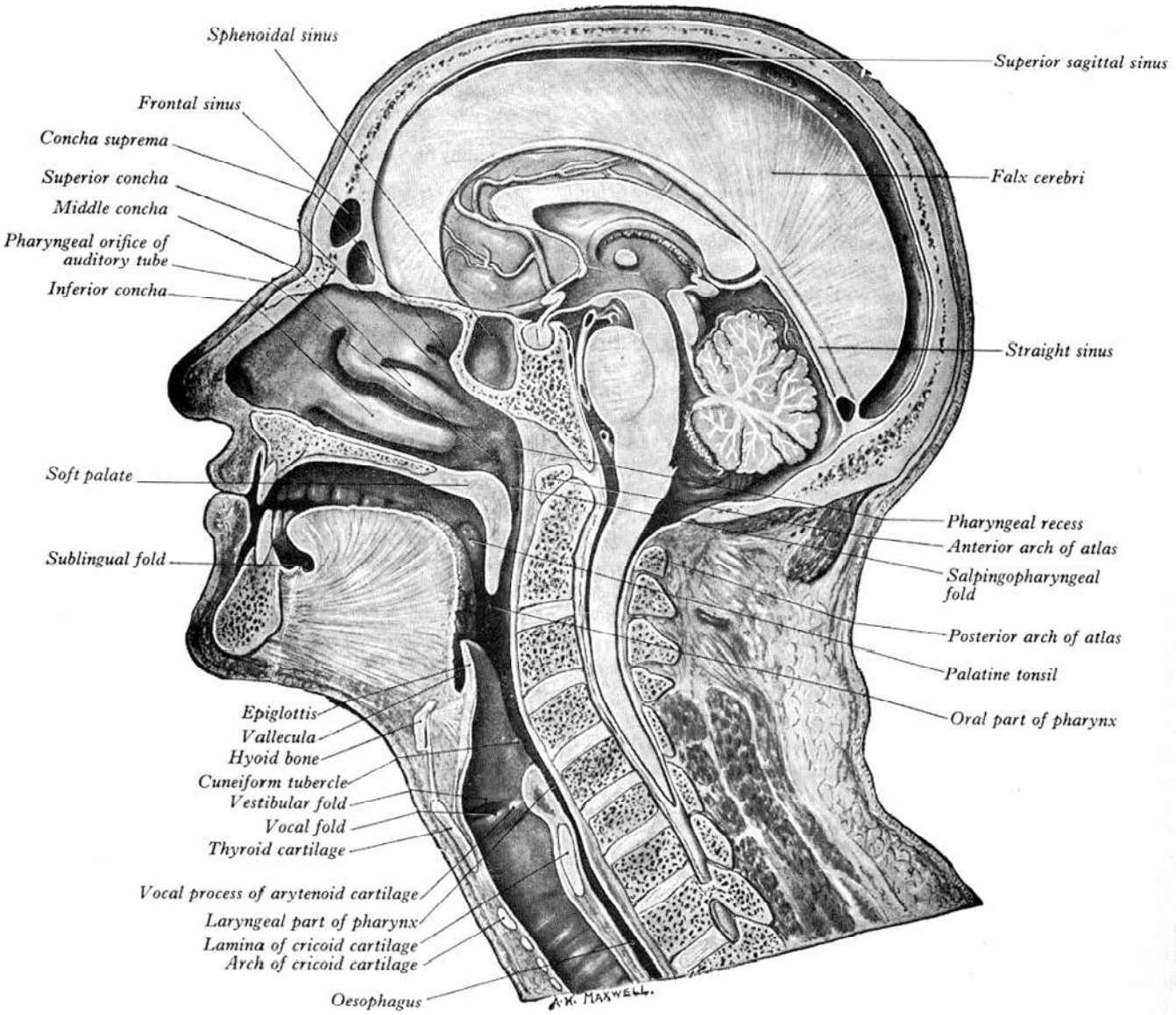


The larynx

- Stretches from the tongue to the trachea
  - Mostly made up of cartilage thus it is mobile and soft
- Location:
  - Adult males – level with the 3rd to 6th cervical vertebrae, can be higher in children and females
    - Males have a larger larynx due to increased pubertal growth of the cartilages causing the thyroid cartilage to project anteriorly

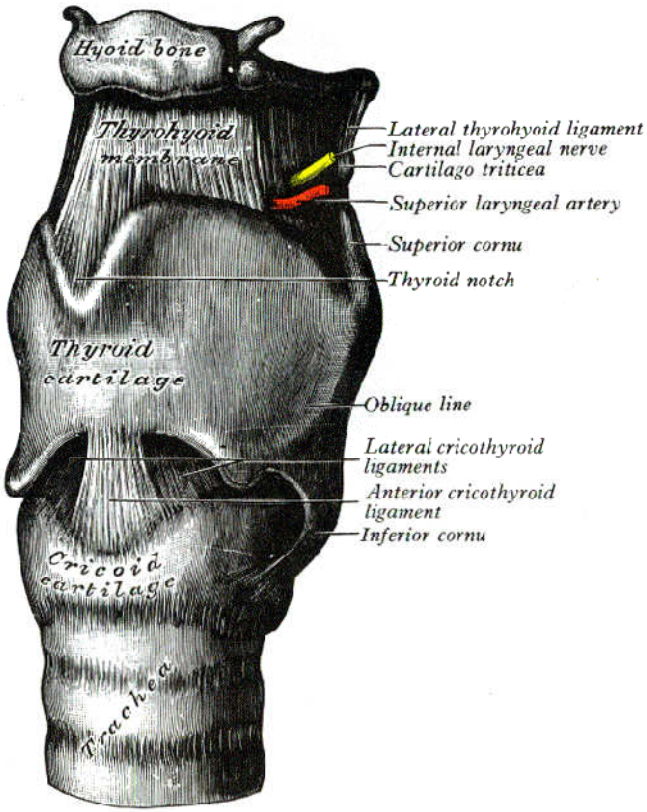
Laryngeal cartilages

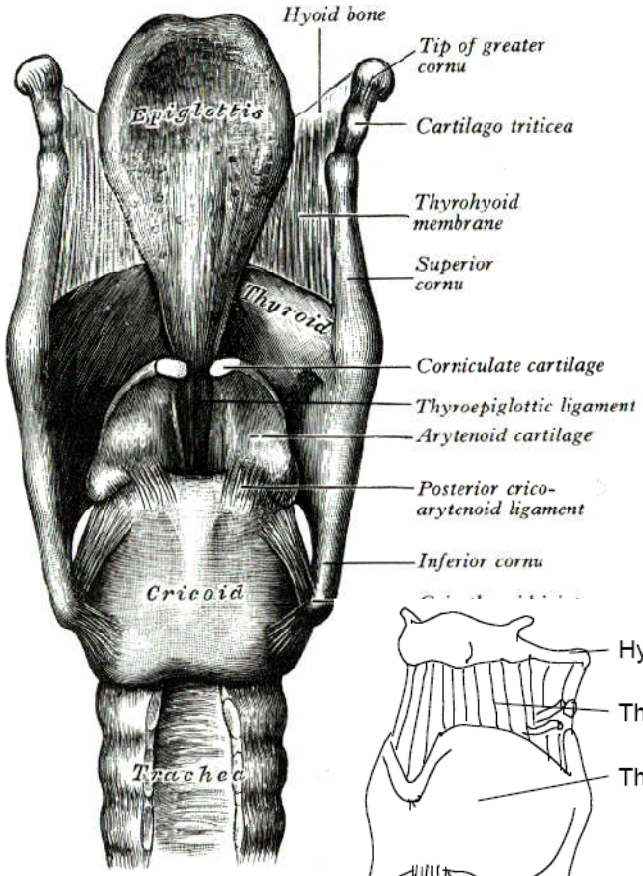
- Thyroid cartilage
  - Made up of two quadrilateral pieces of cartilage
  - Anteriorly, they are fused to form the laryngeal prominence (Adam's apple)
    - In men: an angle of 90^{o} is formed and 120^{o} in women
    - The prominence corresponds with the length of the vocal folds and thus the depth of the person's voice
      - The smaller the angle, the deeper the voice
- Cricoid cartilage
  - Shaped like a signet ring
  - Articulates with the thyroid cartilage at the cricothyroid joint – important for vocal production
- Arytenoid cartilages (2)
  - Pyramidal with 3 surfaces, an apex and a base
    - Base contains lateral muscular processes and anterior vocal processes
- Corniculate cartilages (2)
  - Found posterior to the aryepiglottic mucosal folds and strength the airway entrance
- Cuneiform cartilages (2)
  - Elongated elastic fibrocartilages that are in the aryepiglottic folds
  - Found anterior superior to the corniculate cartilages and also strengthen the airway entrance
- Epiglottic cartilage
  - Elastic fibrocartilage
  - Projects upwards behind the tongue and infront of the laryngeal inlet
  - Sides are attached to the arytenoid cartilages by the aryepiglottic folds

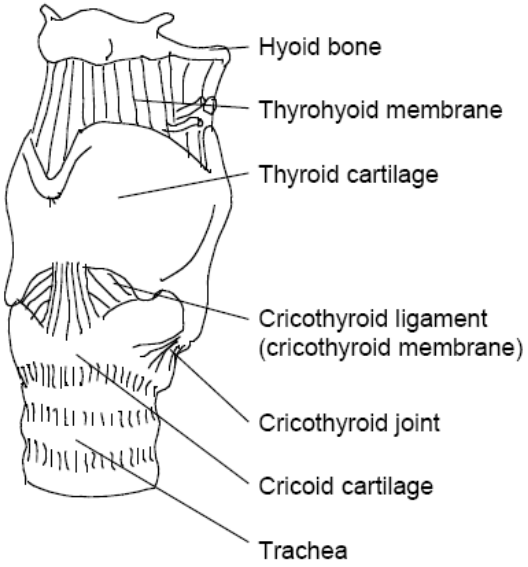


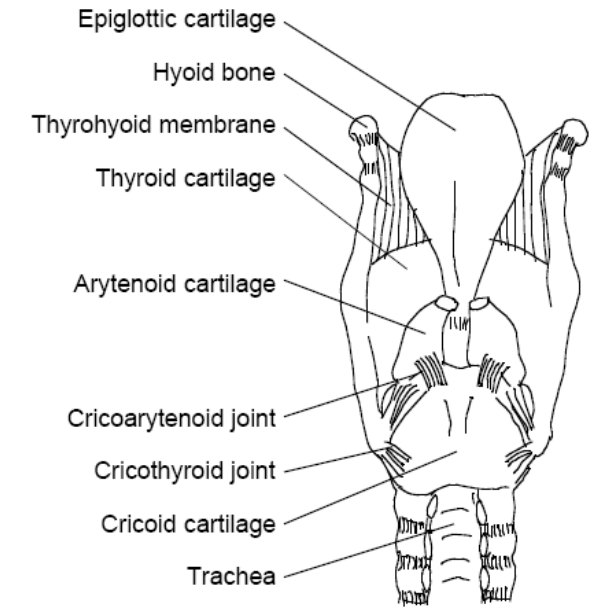
<u>Internal features of the larynx</u>

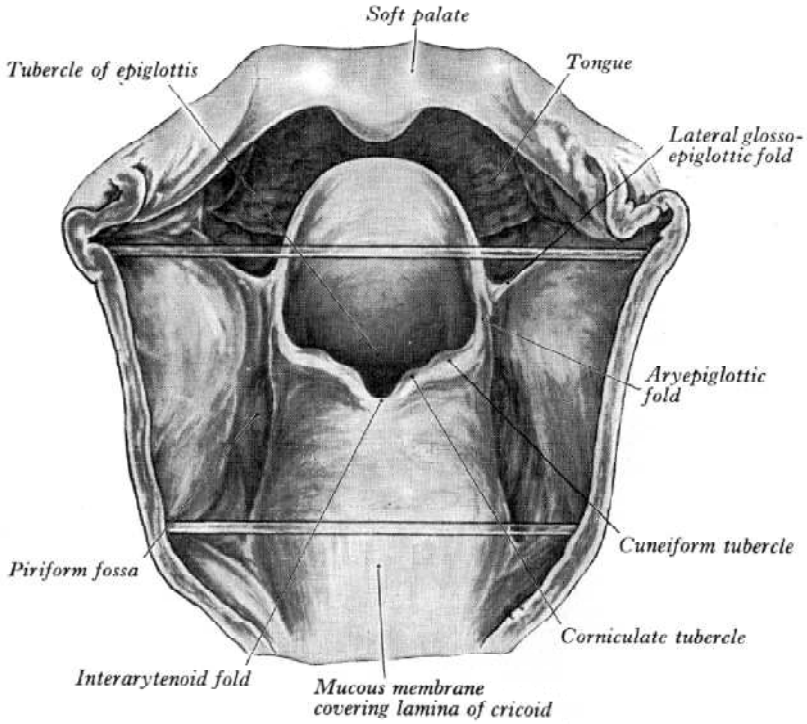
- Laryngeal cavity – extends from the laryngeal inlet to the lower border of the cricoid cartilage
    - The cavity has several parts divided by paired folds of mucosa (vestibular and vocal folds)
        - Laryngeal vestibule – above the vestibular folds
        - Middle part – between the vestibular and volca folds
        - Lower part – from the vocal folds to the lower border of the cricoid
- The laryngeal inlet is bound by:
    - Anterior – upper edge of epiglottis
    - Posterior – mucosa between the arytenoids and laterally by the aryepiglottic folds
        - Laryngeal inlet has two functions:
            - Protecting the airway
            - Production of sound
- Aryepiglottic folds have oval swellings anterosuperior and posteroinferior swellings – cuneiform and corniculate cartilages
    - Contain muscles that allow the airway to close
- Vestibular folds have a fissure between them – the rima vestibuli
    - Vocal folds have a fissure between them – the rima glottidis or glottis
        - Rima glottis is limited posteriorly by mucosa passing between the arytenoid cartilages
- The laryngeal sinus is between the vocal and vestibular folds laterally
    - Anteriorly – opens into the laryngeal saccule
        - This ascends between the vestibular ligament and thyroid cartilage
- Other notes:
    - Voice is created by air being pushed through the vocal folds
    - The epiglottis can be large in children so an infection can cause swelling and obstruction
    - The vestibular fold is important for voice modulation
    - The laryngeal saccule is the oil gland of the larynx lubricating the vocal folds

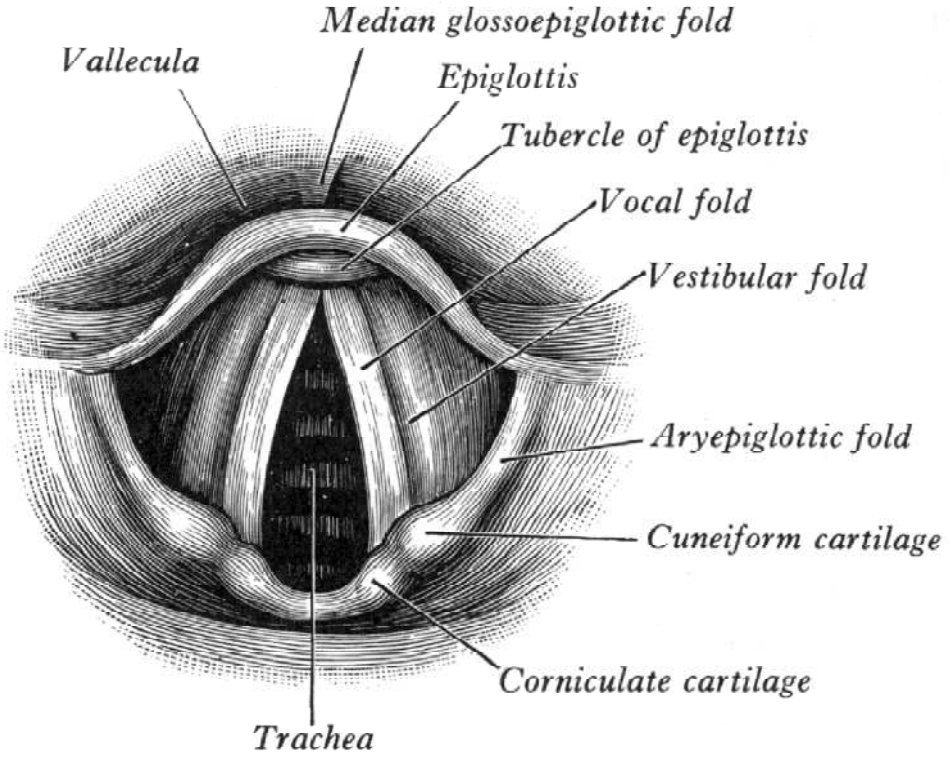

Hyoid bone
Thyrohyoid membrane
Lateral thyrohyoid ligament
Internal laryngeal nerve
Cartilago triticea
Superior laryngeal artery
Superior cornu
Thyroid notch
Thyroid cartilage
Oblique line
Lateral cricothyroid ligaments
Anterior cricothyroid ligament
Inferior cornu
Cricoid cartilage
Trachea


Hyoid bone
Tip of greater cornu
Epiglottis
Cartilago triticea
Thyrohyoid membrane
Superior cornu
Thyroid
Corniculate cartilage
Thyroepiglottic ligament
Arytenoid cartilage
Posterior crico-arytenoid ligament
Inferior cornu
Cricoid
Trachea

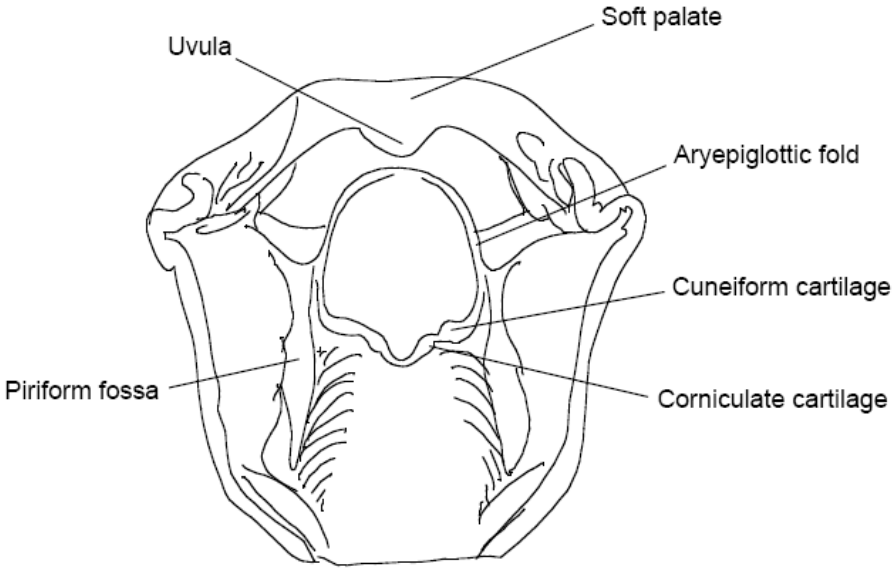

Hyoid bone
Thyrohyoid membrane
Thyroid cartilage
Cricothyroid ligament (cricothyroid membrane)
Cricothyroid joint
Cricoid cartilage
Trachea


Epiglottic cartilage
Hyoid bone
Thyrohyoid membrane
Thyroid cartilage
Arytenoid cartilage
Cricoarytenoid joint
Cricothyroid joint
Cricoid cartilage
Trachea

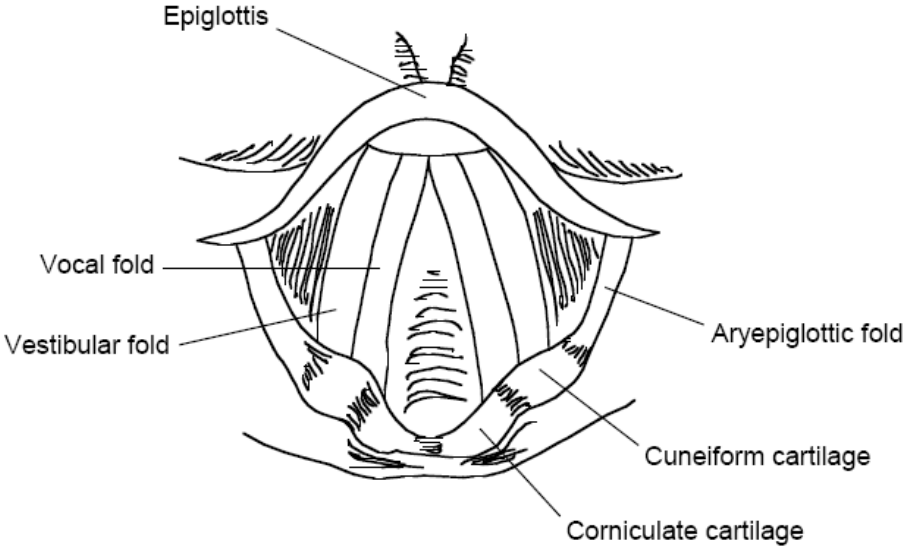


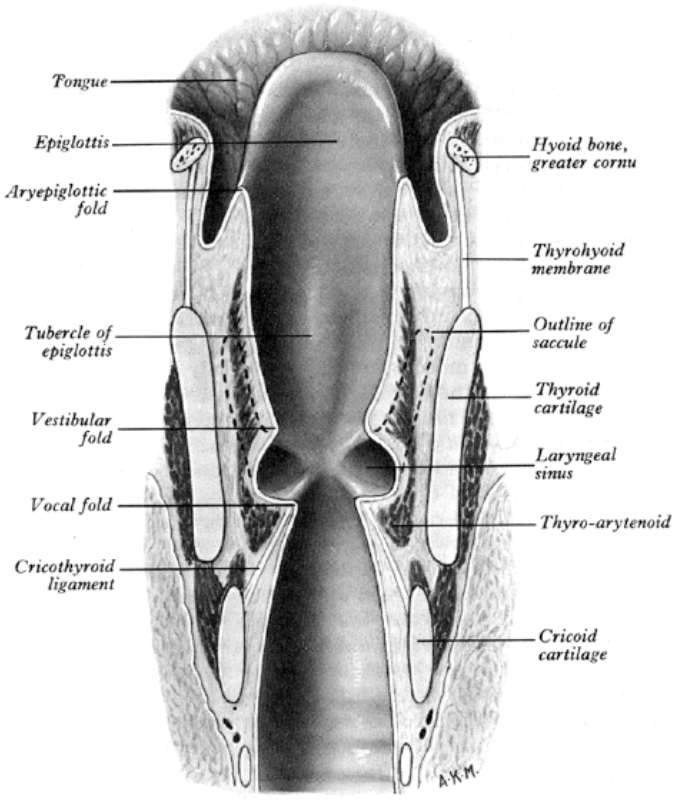


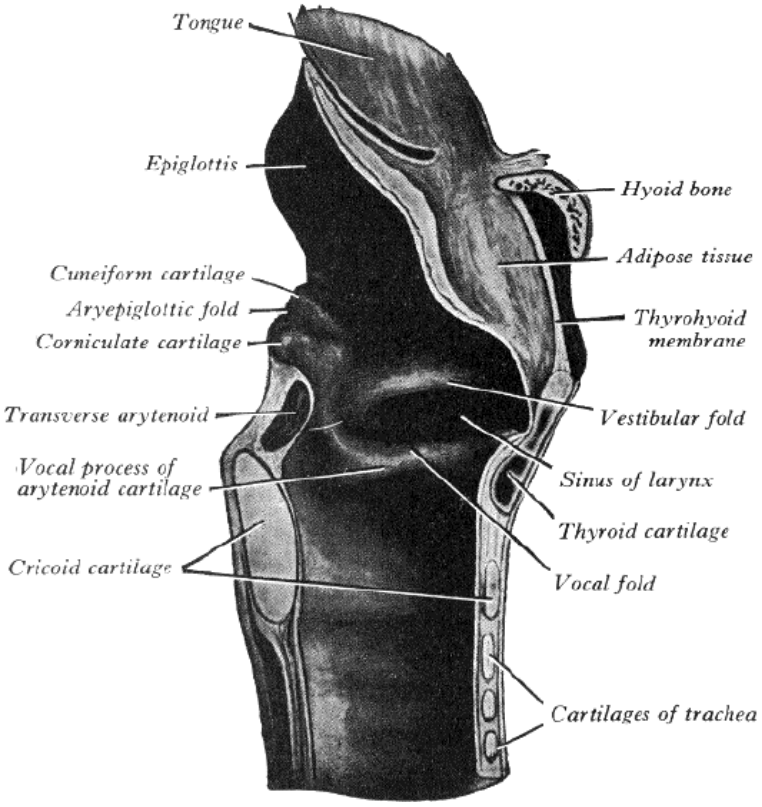
Posterior Aspect

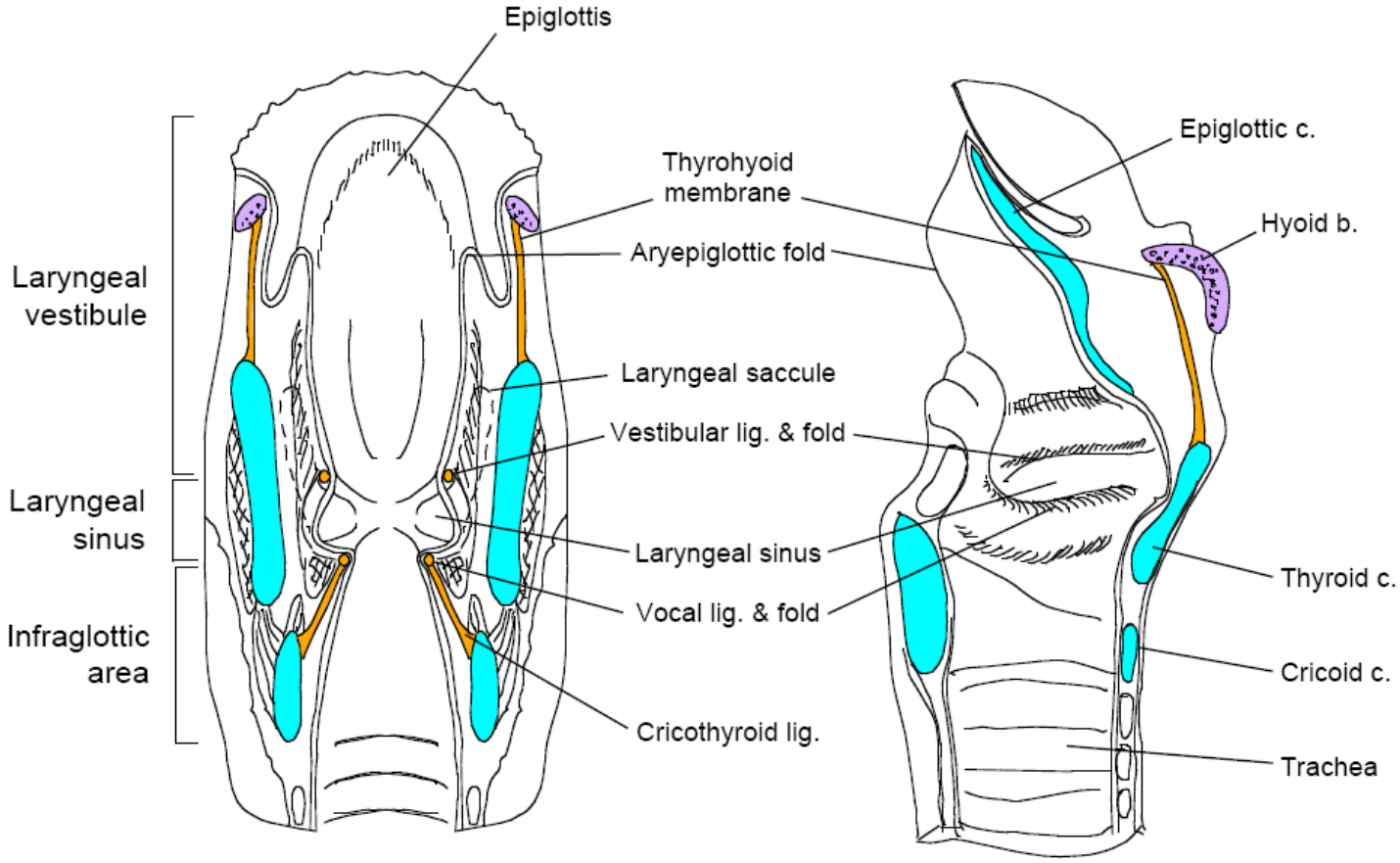


Superior Aspect



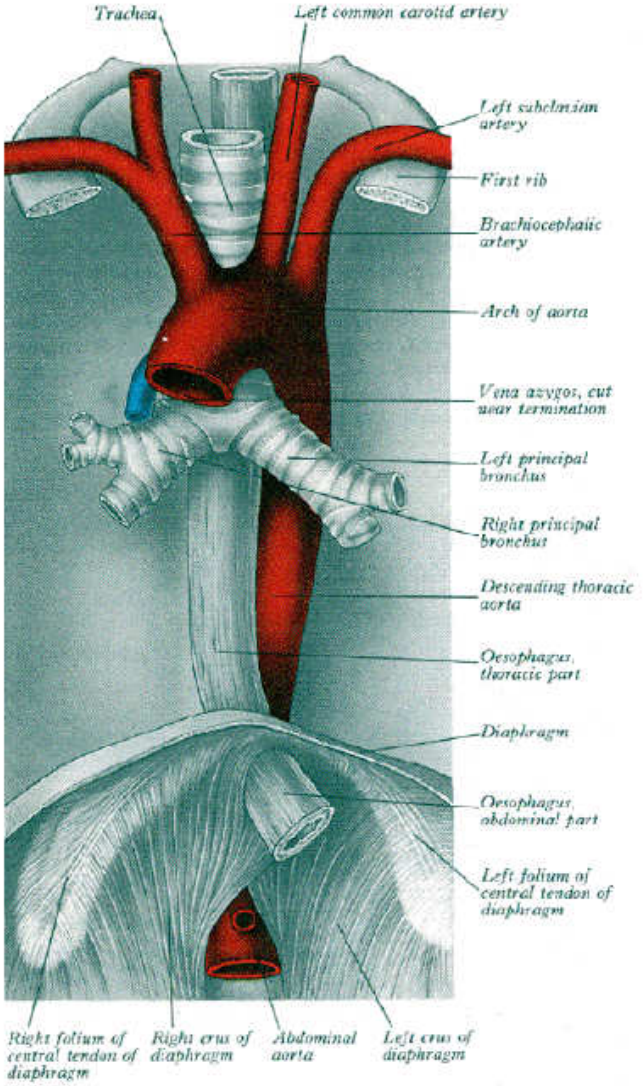

Tongue
Epiglottis
Aryepiglottic fold
Tubercle of epiglottis
Vestibular fold
Vocal fold
Cricothyroid ligament
Hyoid bone, greater cornu
Thyrohyoid membrane
Outline of saccule
Thyroid cartilage
Laryngeal sinus
Thyro-arytenoid
Cricoid cartilage
A.K.M.

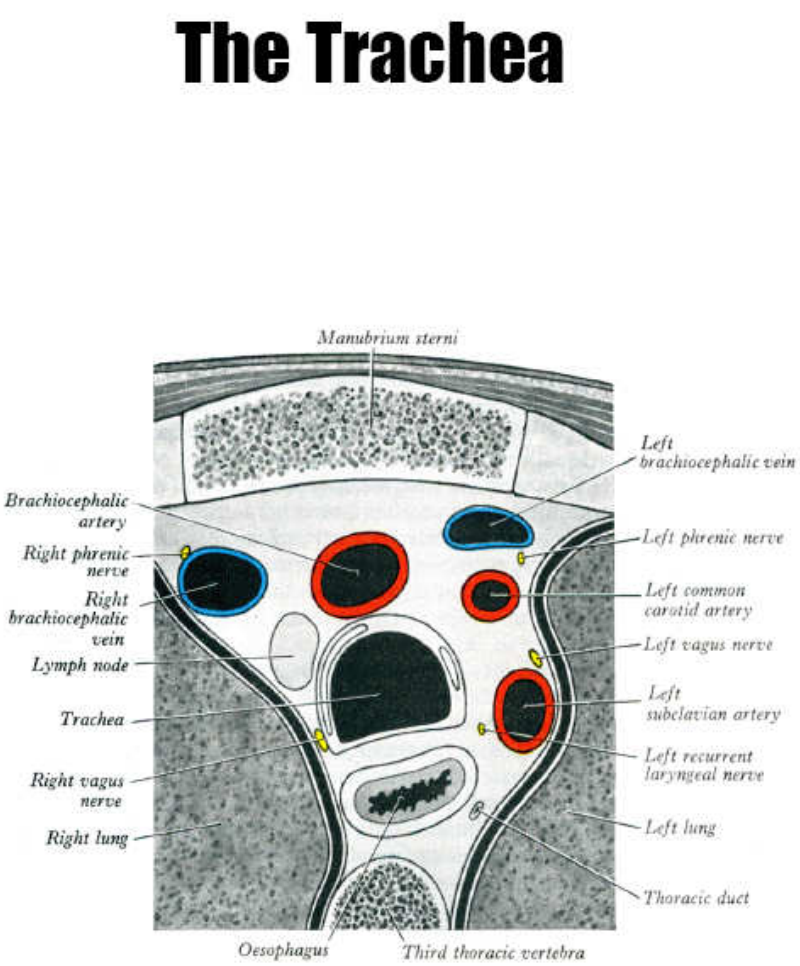

Tongue
Epiglottis
Cuneiform cartilage
Aryepiglottic fold
Corniculate cartilage
Transverse arytenoid
Vocal process of arytenoid cartilage
Cricoid cartilage
Hyoid bone
Adipose tissue
Thyrohyoid membrane
Vestibular fold
Sinus of larynx
Thyroid cartilage
Vocal fold
Cartilages of trachea

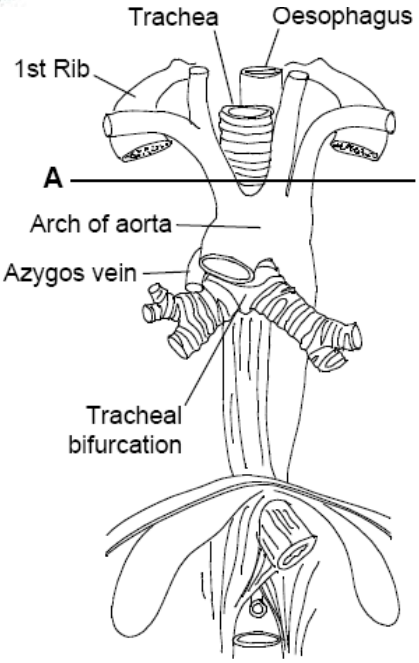

Epiglottis
Laryngeal vestibule
Laryngeal sinus
Infraglottic area
Thyrohyoid membrane
Aryepiglottic fold
Laryngeal saccule
Vestibular lig. & fold
Laryngeal sinus
Vocal lig. & fold
Cricothyroid lig.
Epiglottic c.
Hyoid b.
Thyroid c.
Cricoid c.
Trachea

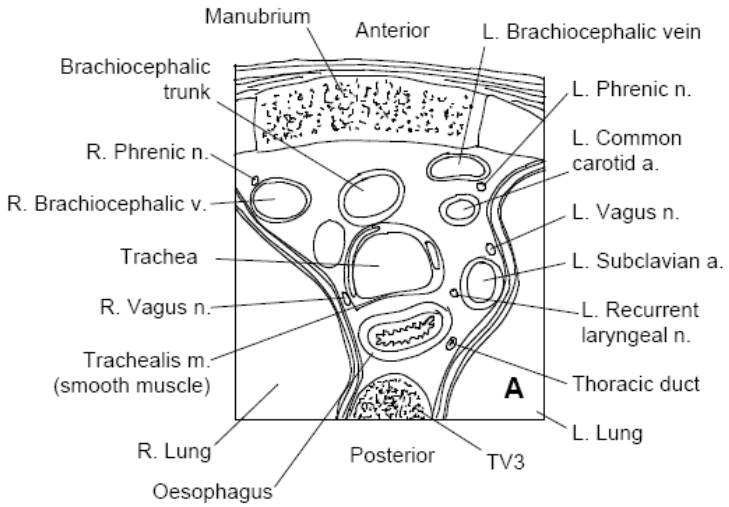
The Trachea

- 10-11cm long, beginning at the larynx (CV6)
    - Divides into main/principle/pulmonary bronchi at the upper border of TV5
    - On deep inspiration, tracheal bifurcation can descend to TV6
- Consists of 16-20 U-shaped cartilaginous rings
    - These are discontinuous posteriorly where the open part of the U is filled by the treachealis muscle (sm m.)
- At the bifurcation, there is an internal ridge known as the carina (L. keel)
    - Acts to trigger the cough reflex
- Other notes:
    - Bronchogenic carcinoma presents with a hoarse voice and paralysis of the diaphragm
        - Due to pressure on the phrenic nerve within the area near the tracheal bifurcation



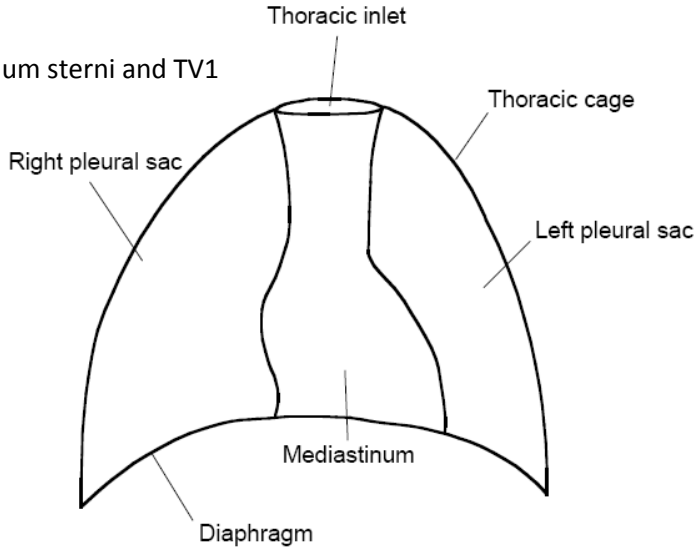






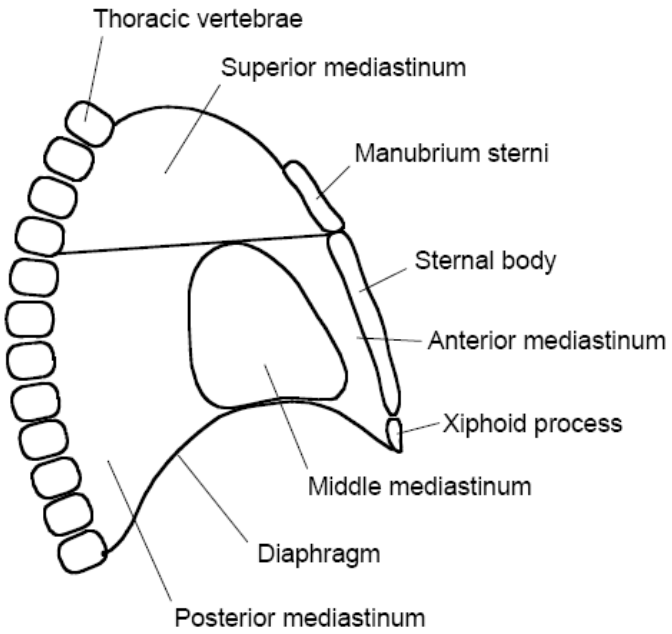
The thoracic cavity

- Borders
  - Superior – thoracic inlet (rib 1 on both sides, manubrium sterni and TV1
  - Posterior – thoracic vertebrae
  - Laterally – ribs and costal cartilages
  - Anteriorly – sternum
  - Inferior – diaphragm
- Three subregions
  - Cavity for the right lung – right pleura and lung
  - Cavity for the left lung – left pleura and lung
  - Mediastinum – see below



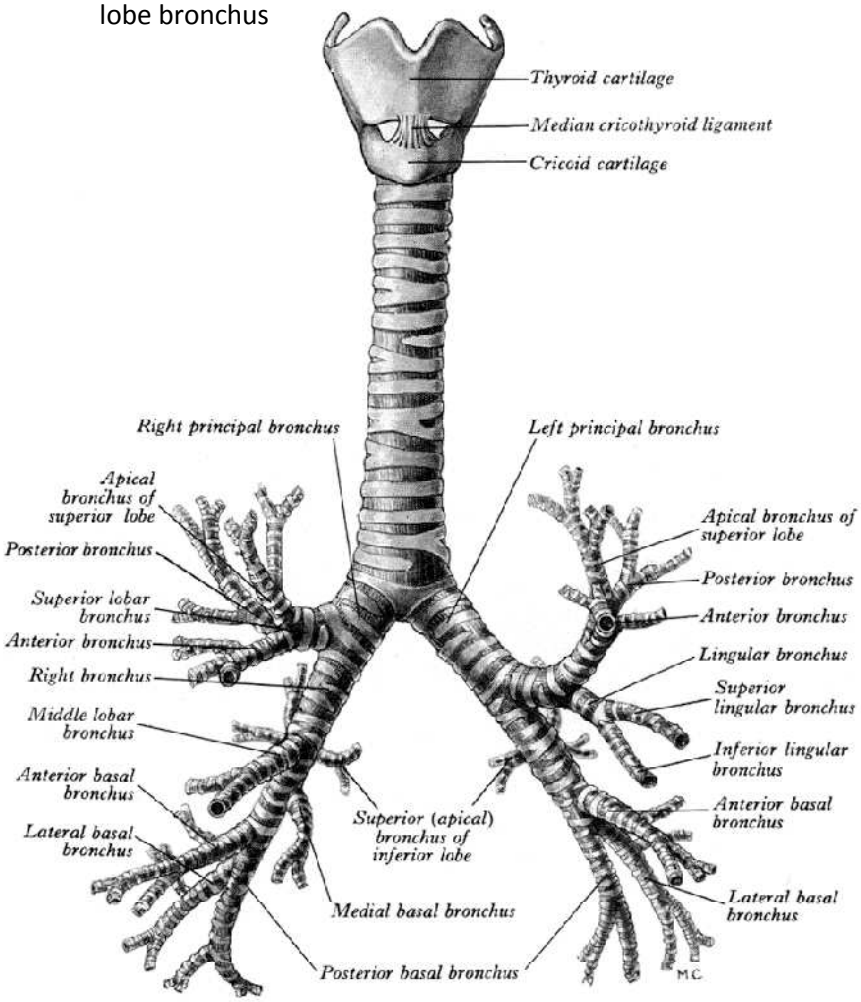
The Mediastinum

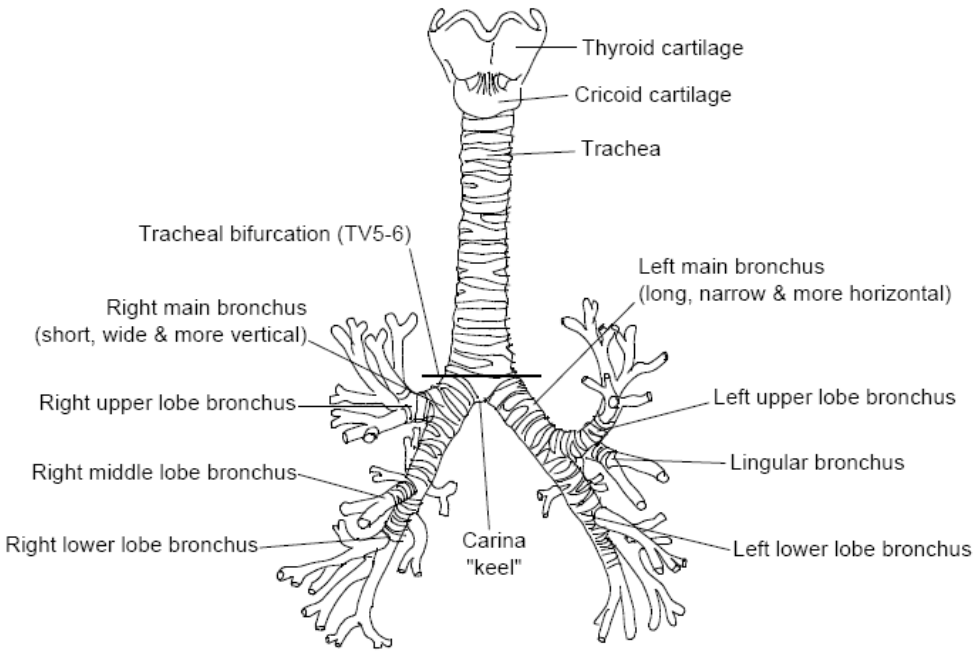
- Borders
  - Between the pleural sacs
  - Superior – thoracic inlet
  - Inferior – diaphragm
- Several sections
  - A transverse plane between the manubriosternal joint and the inferior margin of TV4 separates the superior and inferior mediastinum
  - Middle mediastinum contains the pericardial sac
  - Anterior mediastinum is anterior to the pericardial sac (retrosternal space)
  - Posterior mediastinum is posterior to the pericardial sac (retrocardiac space)
- Contents:
  - Superior mediastinum
    - Trachea, oesophagus, thymus
    - Aortic arch, brachiocephalic trunk, left common carotid, subclavian arteries, svc, brachiocephalic veins
    - Vagus nerve, recurrent laryngeal nerves, phrenic nerves, cardiac sympathetic nerves
  - Middle mediastinum
    - Heart and pericardium
    - Roots of great vessels
    - Proximal azygos vein, phrenic nerve
  - Anterior
    - Superior and inferior sternopericardial ligaments, internal thoracic vessels, lymph nodes, thymus
  - Posterior
    - Oesophagus, trachea, bronchi, thoracic aorta, thoracic duct, azygos and hemiazygos veins, vagus nerve, splanchnic nerves, lymph nodes



The bronchi

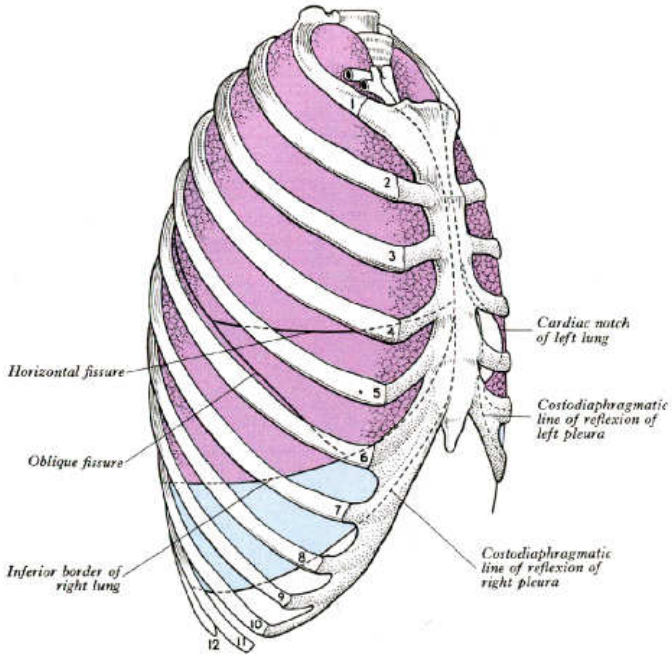
- Trachea bifurcates the TV5-6 into the left and right principal/main/pulmonary bronchi
    - At bifurcation is an internal ridge (carina) that triggers the cough reflex
    - Principle bronchi further divide to form lobar bronchi
        - The right principal bronchus is wider, shorter and more vertical than the left
            - Thus, foreign bodies tend to go to the right more often than the left
- The right principal bronchus
    - Gives off the right superior (upper) lobe bronchus, then enters the lung (extra-pulmonary portion)
    - After entering the hilum it divides into the right middle and inferior (lower) lobe bronchi
- The left principal bronchus
    - Longer (5cm vs 2.5cm)
    - Divides after entering the hilum into the left superior (upper) lobe bronchus and the left inferior (lower) lobe bronchus

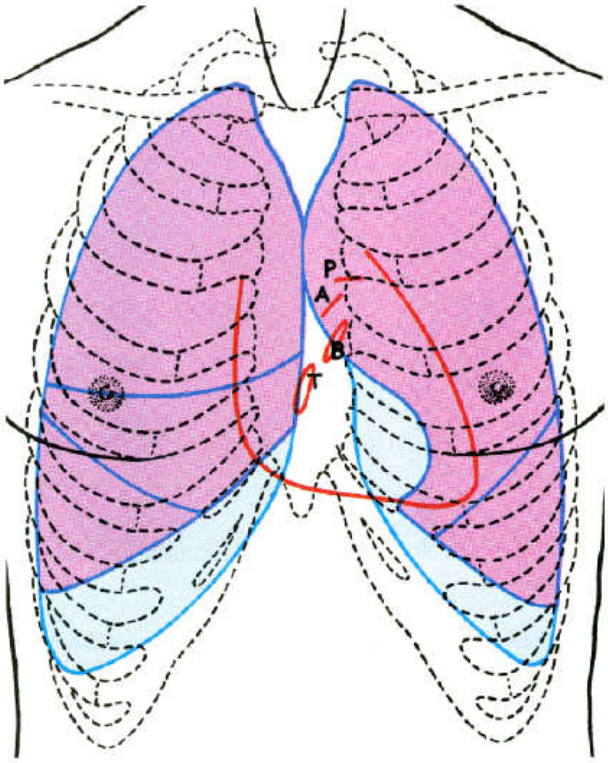


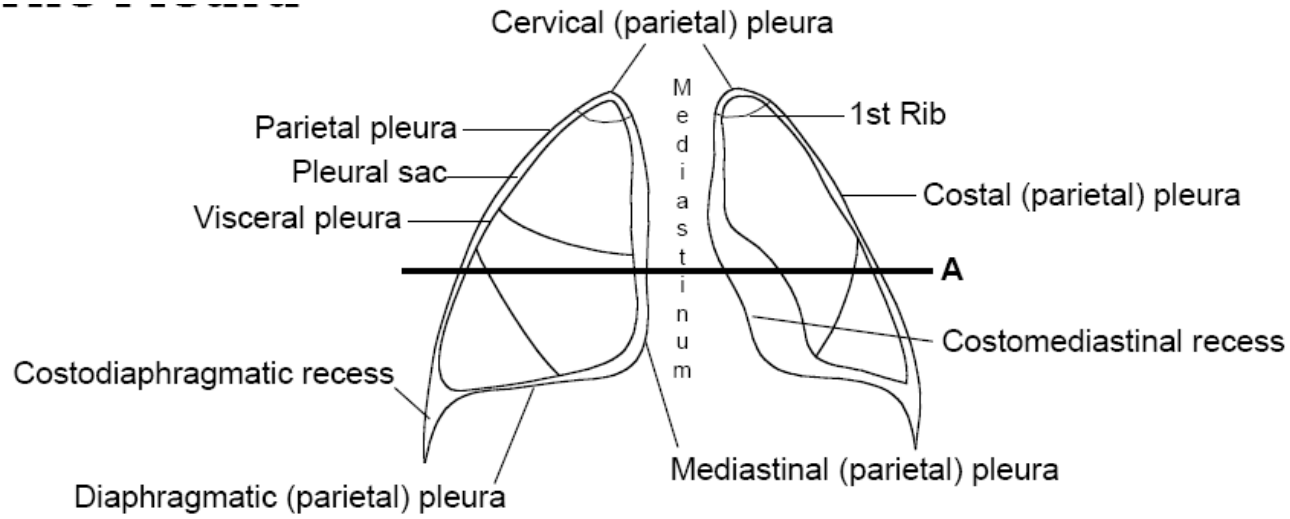


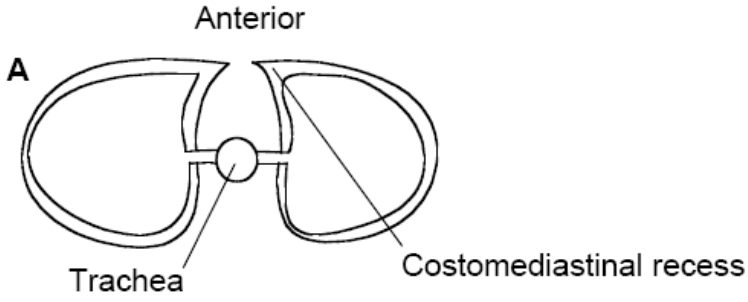
The pleura

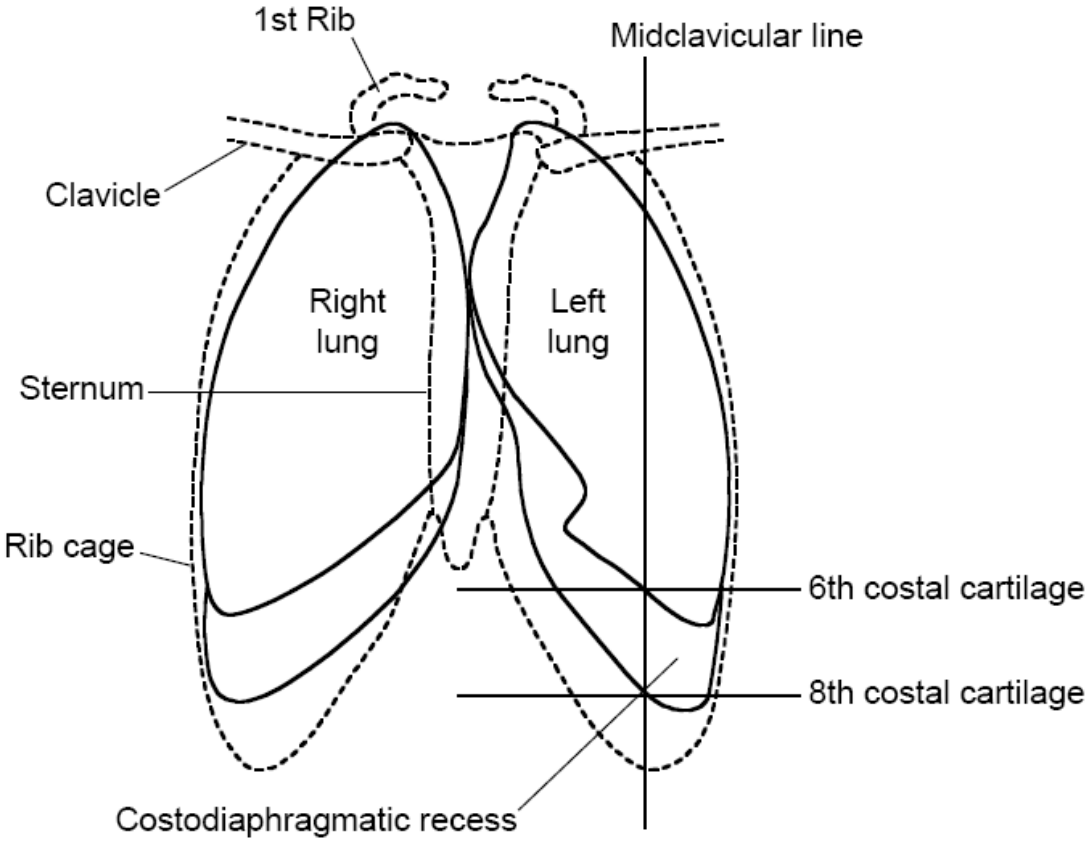
- The lungs are covered by pleura
    - Embryonically, the lungs are derived from a bud from the gut (endoderm)
        - They migrate into a fluid-filled space, the pleura which allow them to move freely
    - A sac-like serous membrane
        - Pulmonary/visceral pleura – part of the pleura adherent to the surface of the lung and fissures
        - Parietal pleura – lines the thoracic cavity, diaphragm and mediastinal contents
        - Pleural sac/cavity – potential space that separates the visceral and parietal pleura
            - Filled with a thin film of fluid
            - The pleural sacs touch just posterior of the sternal body
    - The parietal pleura has several regions
        - Costovertebral (costal) pleura – adjacent to the ribs and vertebrae
        - Diaphragmatic pleura – adjacent to the diaphragm
        - Mediastinal pleura – adjacent to the mediastinum
        - Cervical pleura (domes of the pleura) – over the spaces of the lungs and adjacent to cervical structures
    - Recesses
        - Occur at the reflexions of parietal pleura
        - Costomediastinal recess – between the costal surface and mediastinal surface
        - Costodiaphragmatic recess – between the costal and diaphragmatic surfaces
            - Not filled during quiet ventilation
            - On deep inspiration, lungs expand to fill these recesses
    - Parietal pleural innervation
        - Lateral cervical, costal and peripheral diaphragmatic pleura
            - T1-T11 intercostal nerves
            - Local pain in the adjacent external thoracic wall
            - Referred pain to other regions of the abdominal and thoracic wall
        - Medial cervical, mediastinal and central diaphragmatic pleura
            - Phrenic nerve (C3,4,5)
            - Referred pain to the neck, root of the neck and shoulder
    - Visceral pleura has no pain innervation






Cervical (parietal) pleura
Parietal pleura
Pleural sac
Visceral pleura
Mediastinum
1st Rib
Costal (parietal) pleura
A
Costomediastinal recess
Costodiaphragmatic recess
Mediastinal (parietal) pleura
Diaphragmatic (parietal) pleura


Anterior
A
Trachea
Costomediastinal recess

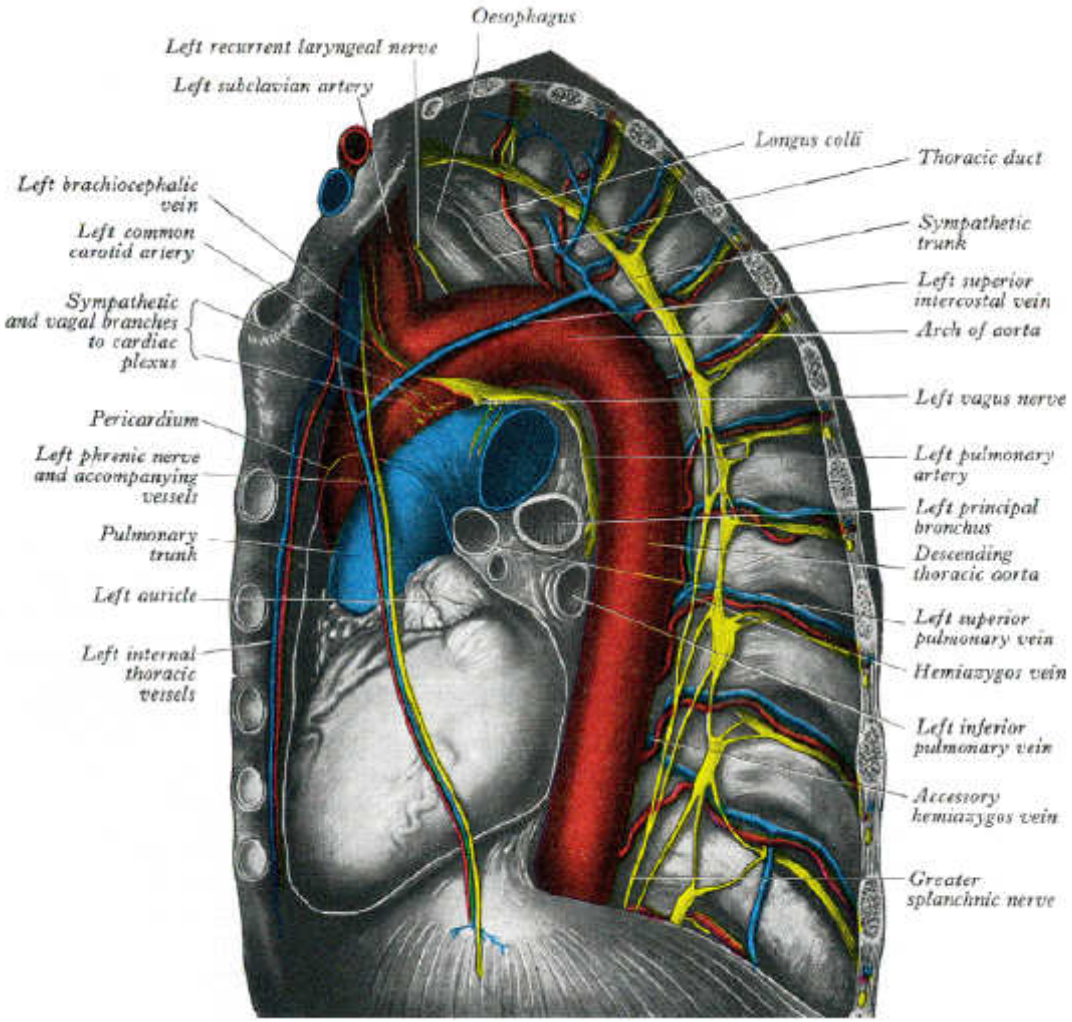

1st Rib
Midclavicular line
Clavicle
Right lung
Left lung
Sternum
Rib cage
6th costal cartilage
8th costal cartilage
Costodiaphragmatic recess

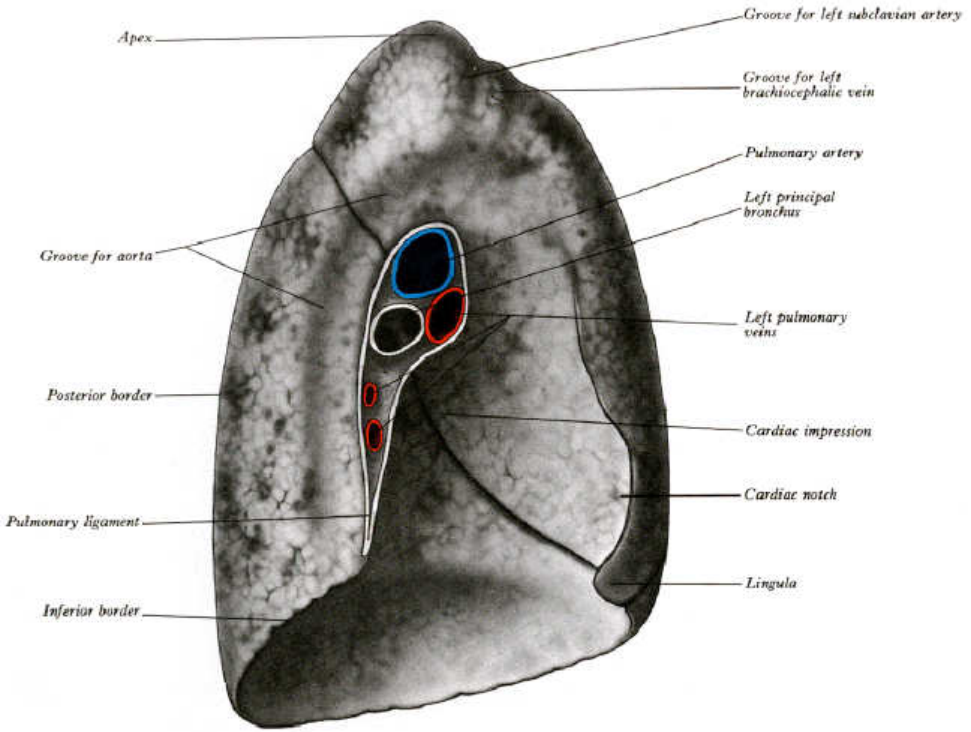
The Lungs

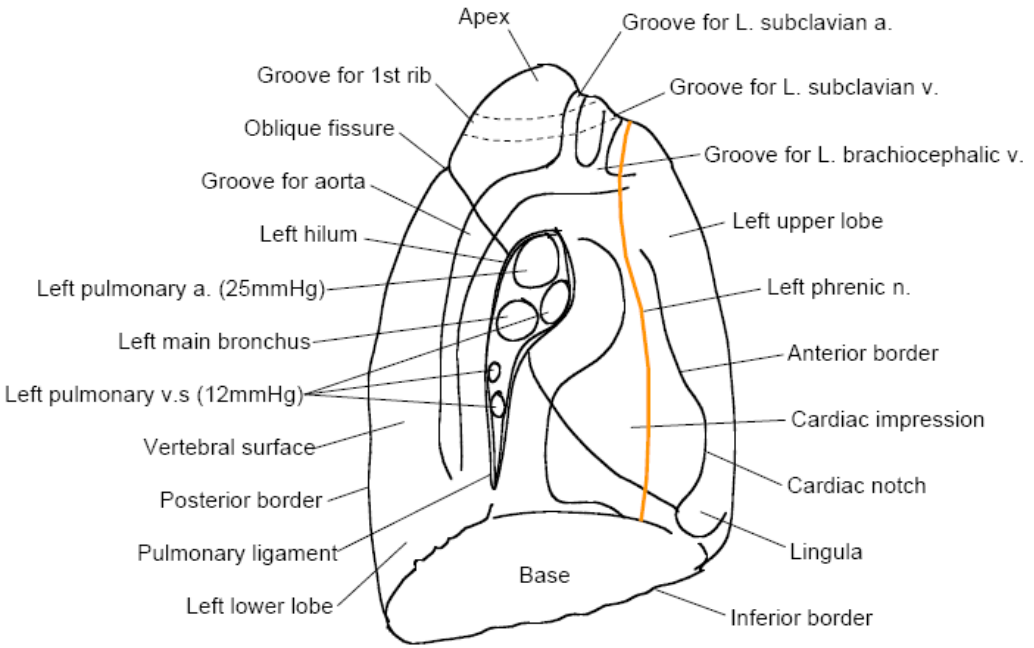
- Spongy and float in water
    - At birth – pink,
    - Adults – become discoloured by a dark mottling (accumulation of dark carbonaceous material deposited beneath the visceral pleura in loose CT)
        - Esp. lungs from smokers and people who live in industrialised areas
    - Stillborn infants – lungs are firm, non-crepitant and sink in water (lungs not expanded)
- The lung has several parts: apex, base, 3 borders, 2 surfaces

Parts of the lung

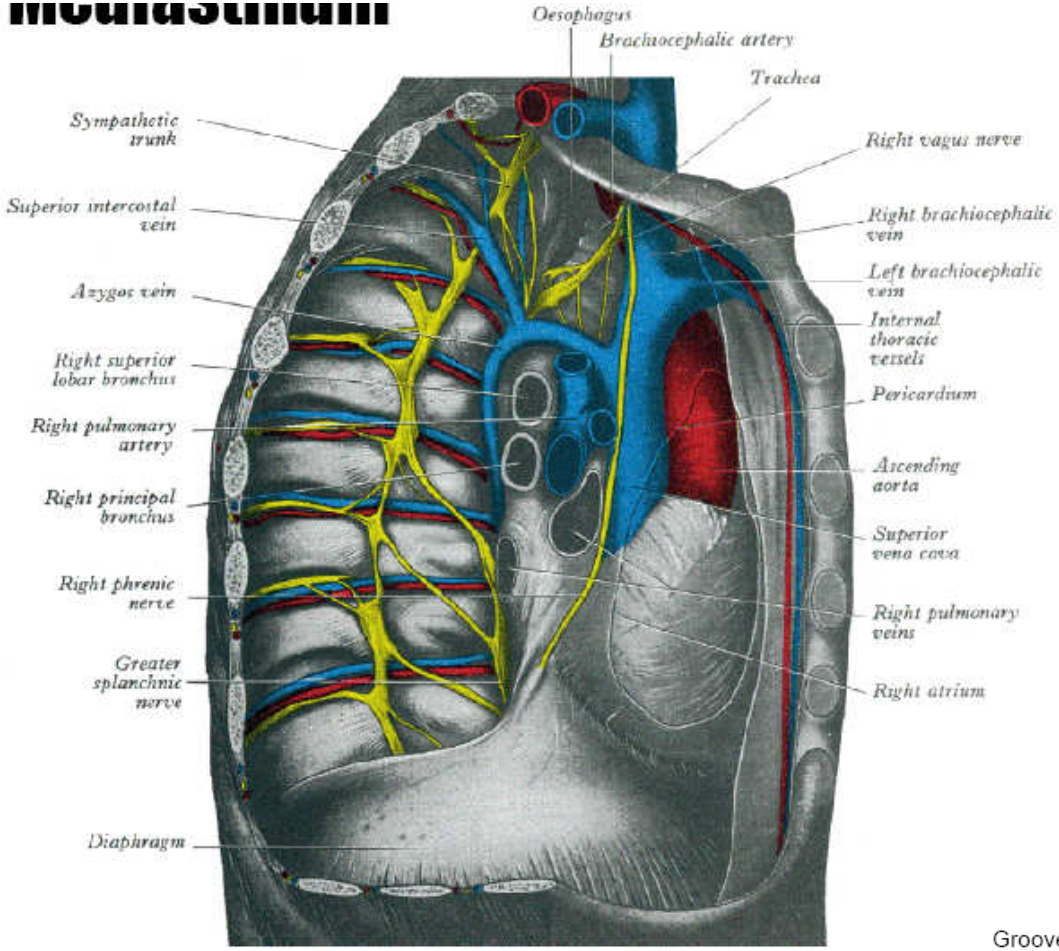
- Apex
    - Protrudes above the thoracic inlet and extends 3-4cm above the 1st costal cartilage to be level with the neck of the 1st rib
    - This is related to the cervicothoracic sympathetic ganglion posteriorly
        - An apical bronchogenic carcinoma here (Pancoast's tumour) can lead to Horner's syndrome
- Base
    - Semilunar and concave
    - Rests on the superior surface of the diaphragm
        - Diaphragm extends higher on the right than the left (due to the liver), thus concavity is deeper on the right
- Costal surface
    - Convex
    - Has the impression of the ribs due to its relation to the thoracic wall
- Medial surface
    - Has anterior (mediastinal) and posterior (vertebral) parts
        - Mediastinal part is shaped to the heart – cardiac impression
    - The hilum (comma-shaped) contains many important structures – pulmonary artery, veins, bronchi, bronchopulmonary lymph nodes
    - Important relations:
        - Left:
            - Pericardial sac, pulmonary trunk, aortic arch, left subclavian artery, thoracic duct, oesophagus, trachea, left brachiocephalic vein, vagus, phrenic and left recurrent laryngeal nerves
        - Right:
            - Pericardial sac, SVC, right brachiocephalic vein, azygos vein, oesophagus, trache and vagus and phrenic nerves
        - The pulmonary ligament extends inferiorly from the hilum reflecting the visceral pleura
- Inferior border
    - Separates the base from the costal and mediastinal surfaces
    - Extends into the costodiaphragmatic recess
- Anterior border
    - Has a variable cardiac notch on the left
- Posterior border
    - Separates the costal surface from the vertebral part of the medial surface
    - Corresponds to the heads of the ribs

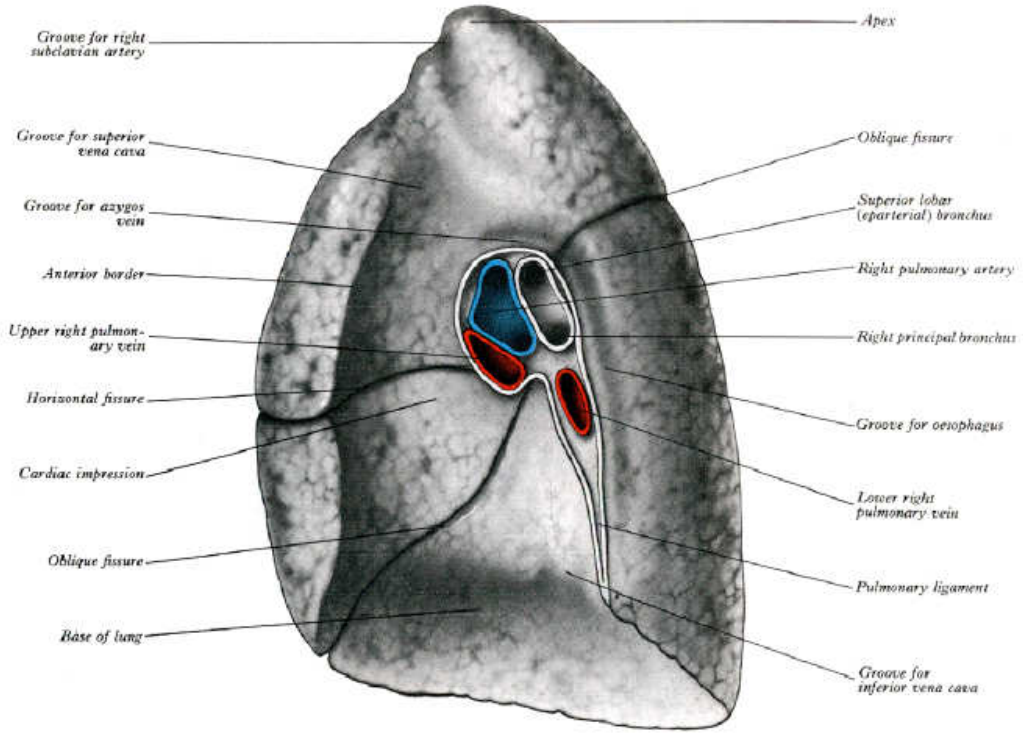

Oesophagus
Left recurrent laryngeal nerve
Left subclavian artery
Longus colli
Thoracic duct
Left brachiocephalic vein
Left common carotid artery
Sympathetic trunk
Sympathetic and vagal branches to cardiac plexus
Left superior intercostal vein
Arch of aorta
Left vagus nerve
Pericardium
Left phrenic nerve and accompanying vessels
Left pulmonary artery
Left principal bronchus
Pulmonary trunk
Descending thoracic aorta
Left auricle
Left superior pulmonary vein
Hemiazygos vein
Left internal thoracic vessels
Left inferior pulmonary vein
Accessory hemiazygos vein
Greater splanchnic nerve

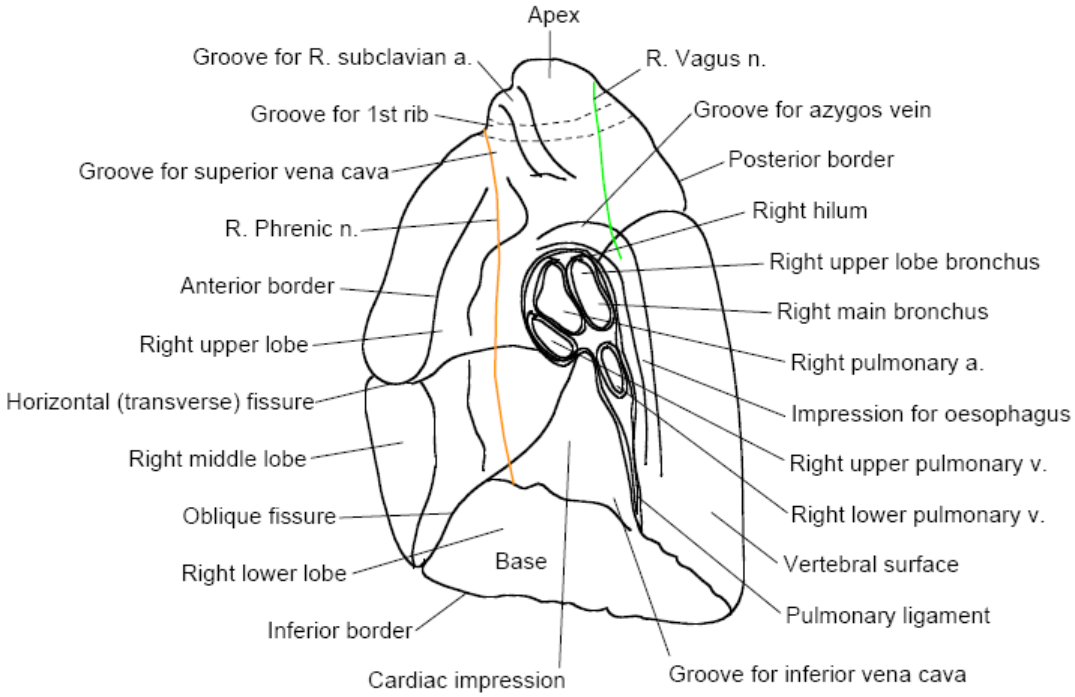

Apex
Groove for left subclavian artery
Groove for left brachiocephalic vein
Pulmonary artery
Left principal bronchus
Groove for aorta
Left pulmonary veins
Posterior border
Cardiac impression
Cardiac notch
Pulmonary ligament
Lingula
Inferior border


Apex
Groove for L. subclavian a.
Groove for 1st rib
Groove for L. subclavian v.
Oblique fissure
Groove for L. brachiocephalic v.
Groove for aorta
Left upper lobe
Left hilum
Left pulmonary a. (25mmHg)
Left phrenic n.
Left main bronchus
Anterior border
Left pulmonary v.s (12mmHg)
Cardiac impression
Vertebral surface
Cardiac notch
Posterior border
Lingula
Pulmonary ligament
Base
Left lower lobe
Inferior border

Mediastinum







Lobes of the lungs

- Each lung is divided into lobes
    - Left: upper and lower lobes
    - Right: upper, middle and lower lobes
- Lobes are separated by fissures
    - Oblique – left
    - Oblique and horizontal – right
    - Oblique on both sides starts at the level of the head of the 5th rib and follows the line of the 6th rib to the inferior border of the lung
    - Horizontal fissure starts at the oblique fissure at the midaxillary line at the level of the 6th rib before passing forwards to the right 4th costal cartilage meeting the anterior border
- Lobar branches divide into segmental bronchi (3rd order branches)
    - Bronchopulmonary segments are regions separated by fibrous tissue septa that represent the areas of the lungs supplied by various 3rd order branches
        - Septa are continuous of the visceral pleura
    - Pulmonary arteries tend to follow bronchi so they supply bronchopulmonary segments
        - Pulmonary veins are intersegmental and don't accompany bronchi
    - Diseases can be confined to a single segment
        - Eg: bronchoiectasis
        - Eg: malignant neoplasms often aren't cofined by septal boundaries
    - In each segment, airways are further divided (20-25 generations)
        - Cartilage makes up the walls of these branches until final bronchus
            - After this, it becomes a bronchiole which then will divide into 5-7 terminal bronchioles
                - Each of these supplies one or more respiratory bronchioles that are the start of the gas exchange (respiratory) area
                    - Further divisions include alveolar ducts, sacs and alveoli

Blood supply to the lungs

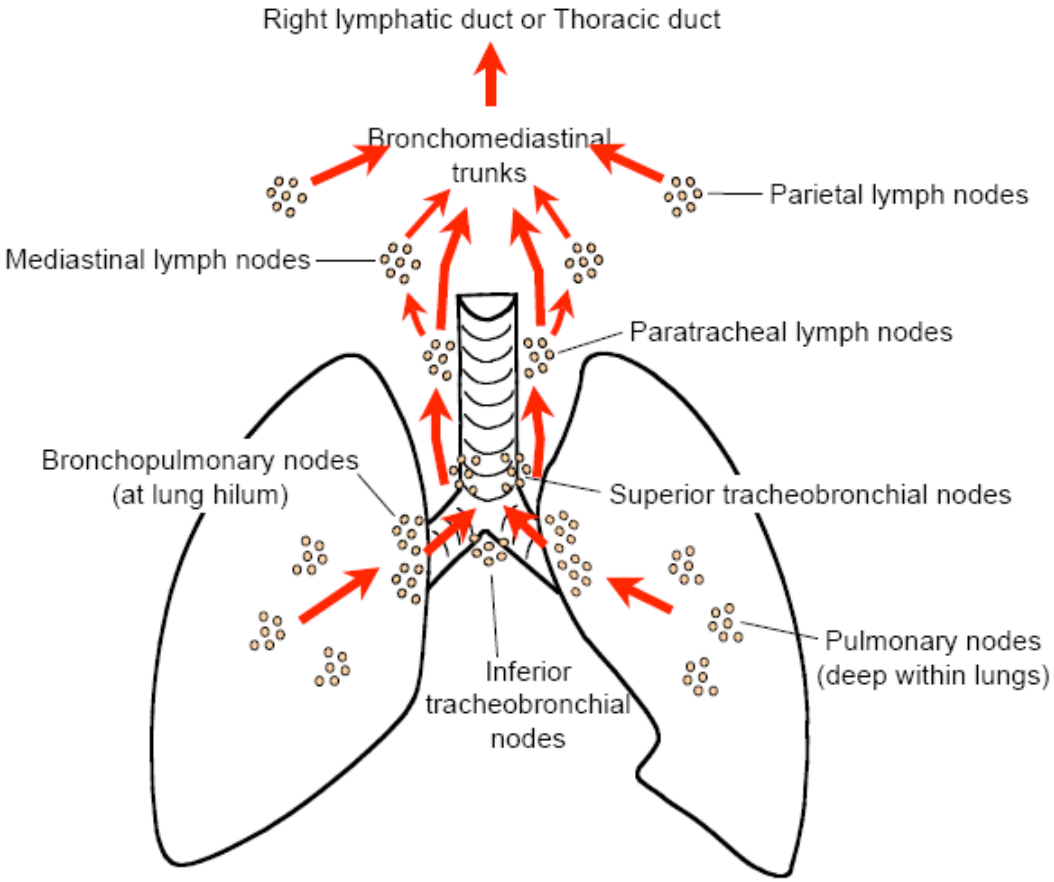
- Pulmonary circulation
    - Left and right pulmonary arteries carry deoxygenated blood
    - Pulmonary veins form near alveoli and carry oxygenated blood intersegmentally back to the heart
- Bronchial arteries
    - Supply oxygenated blood to the non-respiratory parts of the lungs
        - Ie: larger bronchi, nerves, walls of pulmonary vessels and some visceral pleura
    - Rest of the lung can receive oxygen directly from alveolar spaces
    - Left: two left bronchial arteries from the thoracic aorta
        - Right: one right bronchial artery arising in common with the right 3rd posterior intercostal artery from the aorta

Nerve supply to the lungs

- Anterior and posterior pulmonary plexuses infront and behind the roots of the lung
    - Receive fibres from several sources
        - Sensory
            - Vagus nerve
            - Sends afferent information from lung receptors to brainstem
            - Sensory endings are from walls of pulmonary vessels
                - Veins and visceral pleura, walls of bronchi, bronchioles and mucous membranes of bronchi (irritation – coughing)
        - Parasympathetic via vagus
            - Preganglionic fibres synapse in ganglion cells in the pulmonary plexuses
            - Cause constriction of smooth muscle and glandular secretion
        - Sympathetic from (T1 – 4/5) sympathetic ganglia
            - Direct fibres passing through pulmonary plexuses
            - Cause the relaxation of smooth muscle and inhibit glandular secretion

Lymphatic drainage of the thorax

- Generally, peripheral drains to the centre
    - Note: black nodes in the subpleural lymphatic plexus can be due to carbon in the air



Introduction
- HIV virus matures outside the cell

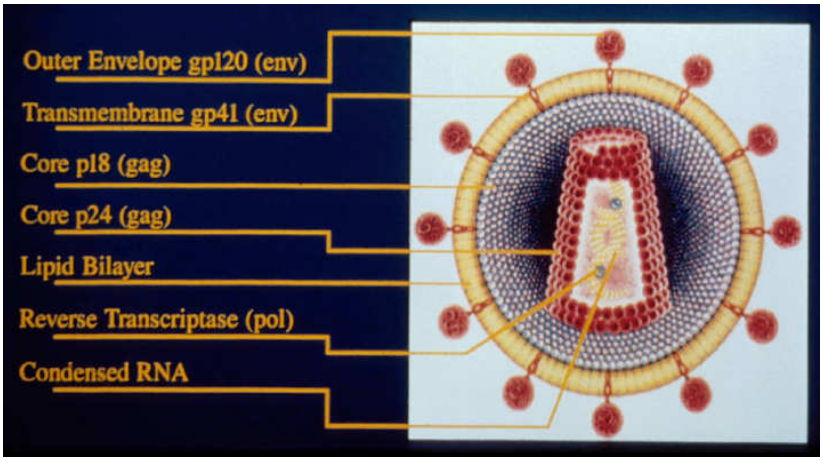
Epidemiology
- Australia
  - >800 new cases/year
  - >80% are in homosexual men
  - We are becoming complacent and incidence is on the rise
- South Africa
  - >400 cases new cases/day
  - Highest incidence is in 14-24 year old females

Definitions
- Types:
  - HIV-1 → majority of infections
  - HIV-2 → less pathogenic, limited to parts of West Africa
- AIDS – a state of immunodeficiency resulting from HIV
  - Was recognised/identified before the virus
  - Those with AIDS are susceptible to disseminated, recurrent infections (opportunistic infections)
    - Ie, low/non-pathological organisms
    - Eg: encapsulated bacteria, fungi, yeast, viruses, protozoa
  - May lead to increased susceptibility to certain malignancies
    - Ie: those diseases with possible virus triggers
  - Disease is a result of a depletion of CD4 + T cells (<200/mm^3), a loss of number and function

HIV-1, the time course
- Untreated
  - 7-8 years after infection, AIDS
  - 1-2 years from AIDS diagnosis, death
- Stages
  - Primary infection/seroconversion illness
    - Within 2-3 weeks lasting 5-21 days
  - Asymptomatic infection
    - 7-8 years
    - Not dormant, highly infectious
  - AIDS
    - <200 CD4 + T cells/mm^3 blood or an AIDS illness
  - HIV is a chronic/progressive infection that takes years to deplete the immune system

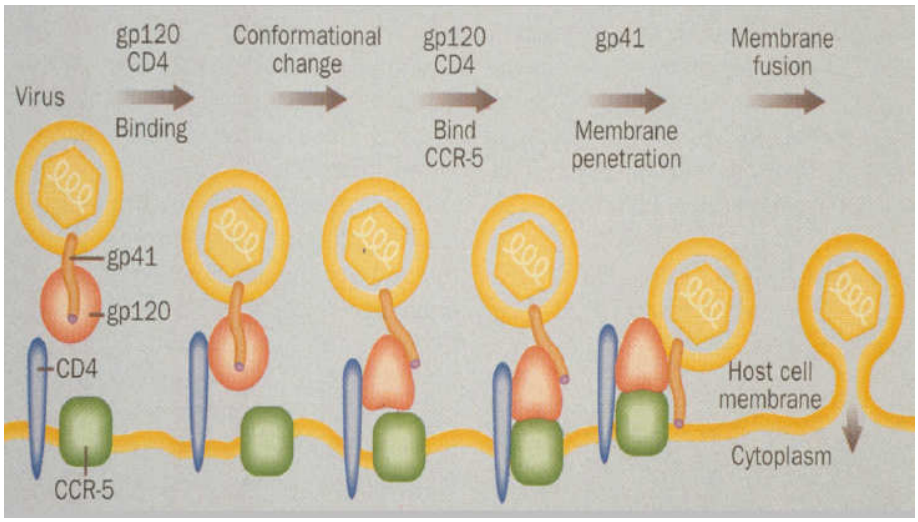
Viruses
- HIV is a retrovirus
  - Genome is made up of 2 ssRNA with 10 000 base pairs
  - RNA undergoes reverse transcription and DNA is integrated into the host cell genome

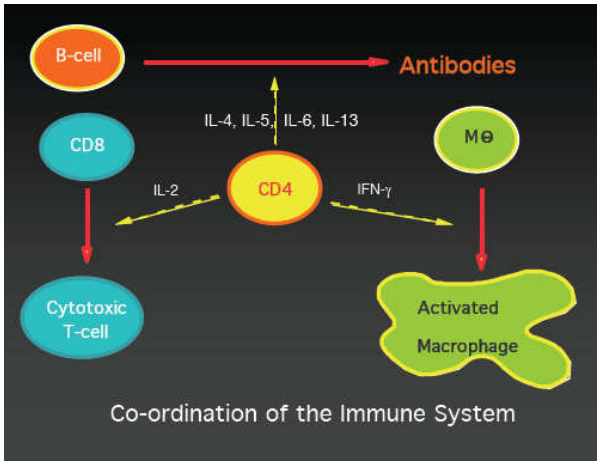
HIV-1 structure
- Outer envelope – containing gp120
- Transmembrane proteins – gp41
- Core – p18, p24 (gag)
- Lipid bilayer
- Cytoplasm containing reverse transcriptase, protease, integrase

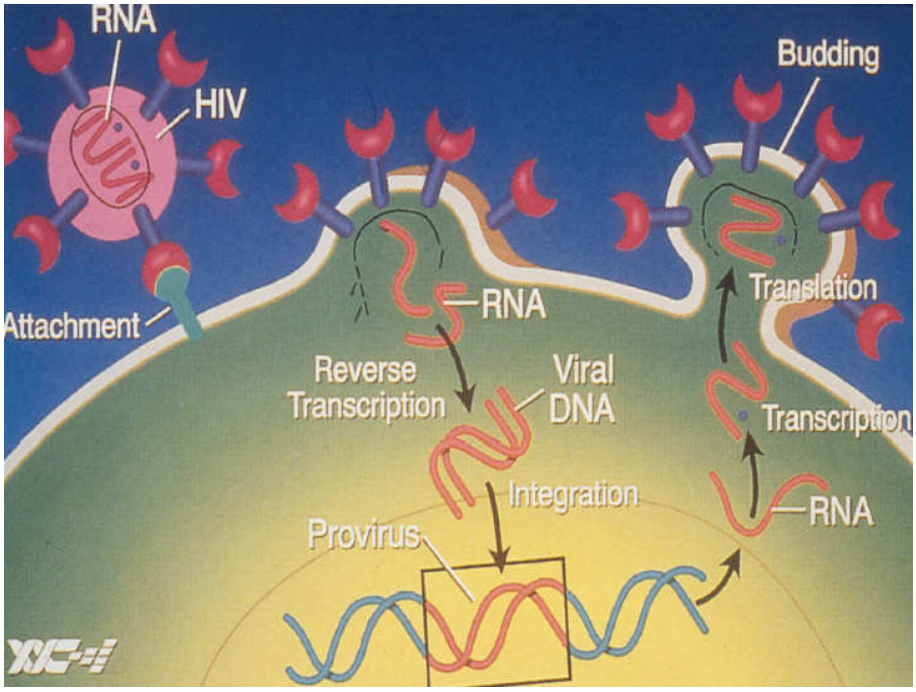


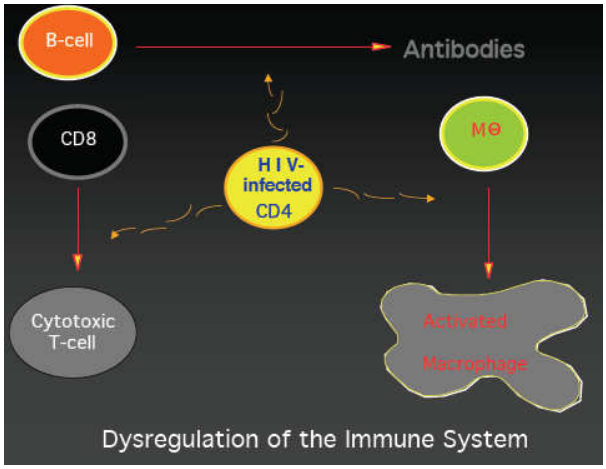
CD4

- Function – coordinate the immune response
  - Vital for the immune response
  - Egs:
    - IFN-γ activates monocytes to macrophages
    - CD8 cytotoxic T cells are for counteracting viruses, use IL-2
    - B cells mature using IL4,5,6 and 13
  - Ie: HIV infection causes cell death and non-activation of macrophages/CD8 (defective maturation)/B cells
- HIV-1 gp120 binds to CD4 molecule
  - Binds to chemokine receptors: CCR5, CXCR4
    - CCR5 is present on activated T-cells travelling to an infection – ie to the HIV infection site
- Process
  - CD4 binding
  - Conformation change in cirus
  - Binding to CCR5
  - Conformation change activating gp41
  - Fusigenic reaction allowing entrance of virus to cell
  - Reverse transcriptase changes RNA to DNA, double stranded
  - DNA integrates into cell DNA using integrase
  - Transcription, assembly of virus in the cytoplasm
  - Budding resulting in reproduction



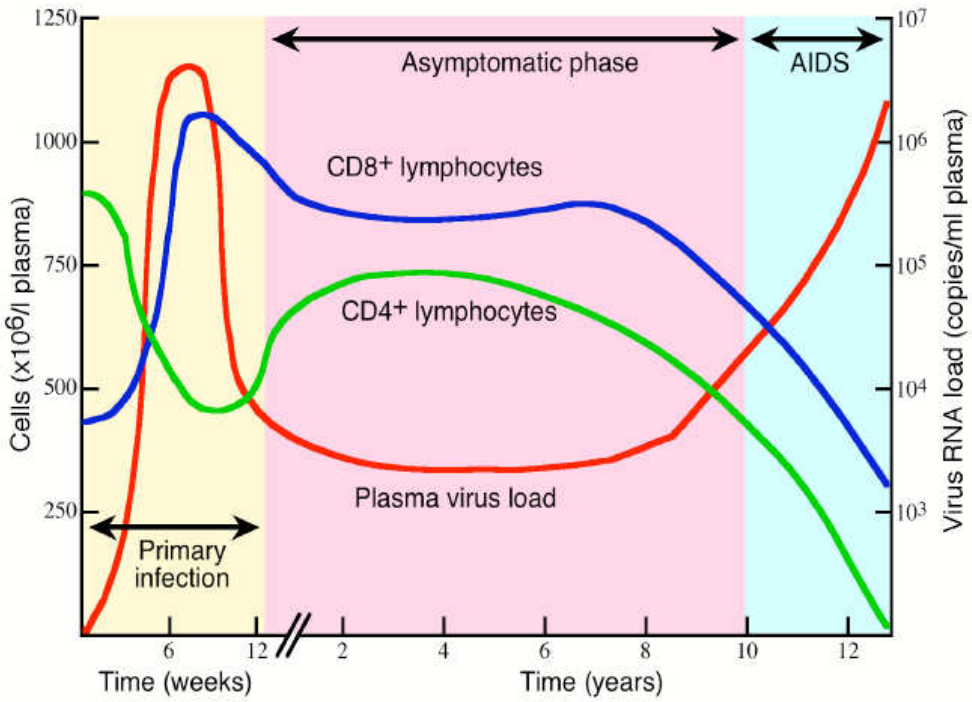






Monitoring the progression

- CD4 + T cell count – used to estimate how much of the immune system is left
    - Determines when to start antiviral therapy/prophylactic treatment
- Viral load – estimates the speed the immune reserve is being destroyed
    - High load means fast progression
- CD4+Tcell and viral load are used in tandem – want to drive down the viral load and to keep CD4+Tcell high
- Stages
    - Primary infection
        - High viral load = sick
        - CD4 low, CD8 high to fight infection
    - Asymptomatic
        - Plasma viral load drops
            - How much it drops is clinically important for outcome – how effective immune response still is after depletion
        - CD4 recovery, but not to previous levels
        - CD8 eventually drops in parallel to CD4
    - Normal ratio CD4:CD8 is 2:1, reversed in HIV



CD4+Tcell response

- CD4 count corresponds to susceptibility – best measure of immune deterioration
- Extent of decline correlates with disease progression
    - >500/µL is normal
    - <400 – TB/Kaposi's sarcoma
    - <200 – PCP (pneumocystis pneumonia)
    - <100 – CMV, Toxoplasmosis
    - <50 – Non-Hodgkin's lymphoma, MAIS (mycobacterium avium intracellular)
- As level drops, opportunistic infections are common – intracellular, viral, fungal

Critical parameters

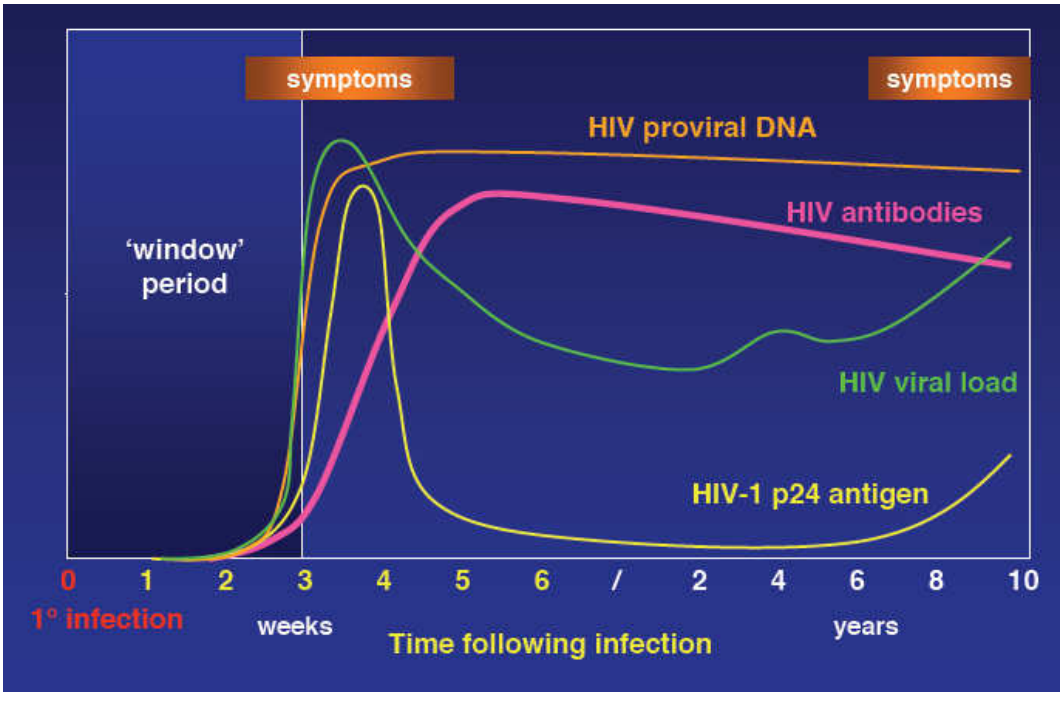
- Large virus amount
  - Average – 10^4-10^5/ml serum, asymptomatic
  - Seroconversion illness - >10^7 ml serum
  - Late - >10^6/ml serum
  - This measures virus in serum, but majority is not circulating in the blood
- Turnover rate - high
  - $T_{1/2}$ virus = 6 hours
  - $T_{1/2}$ infected cell = 2.5 days
- Mistakes
  - Reverse transcriptase makes lots of mistakes – lacks a proofreading function
    - Makes a mistake every 10 000 base pairs, thus 1 mutation/replication
- High viral turn over and high mistake rate results in many many mutations
  - Mutations lead to resistant strains of the virus
  - This constant mutation leads to exhaustion of the immune system
- Integrated virus is immunologically silent

Immune response to HIV

- Antibodies – used for diagnosis
  - Minimal neutralisation effect
  - Vaccine target
  - Possibly can be used to prevent infection?
- T-cells
  - Helper T cells – victim, directly attacked
    - Long term viral control needs HIV specific responses from these T cells
  - Cytotoxic T cells - effectors
    - Prevent infection? And progression?

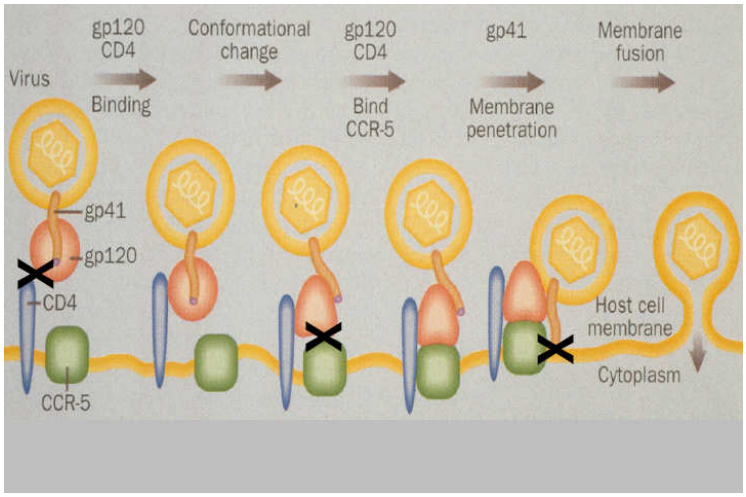
Diagnosis

- Serology – antibodies
  - 3 weeks to 3 months before antibodies are detectable
- Secondary tests
  - Viral DNA, viral RNA, viral proteins (nucleic acid tests)
  - Can be not useful due to mutations resulting in a high false negative rate
  - Other proteins and nucleic acids are detectable for different periods
- Western blot test
  - Detects antibodies to HIV proteins are present in the serum
  - There are a lot of ineffective antibodies



Clinical aspects of onset

- Seroconversion illness
  - Fever, rash, sore throat, lymphadenopathy, like glandular fever
- Reflected by:
  - CD4 low, CD8 high
  - Antibodies
  - CTL responses
  - Viral load detection – lower after seroconversion illness



Antibody targets

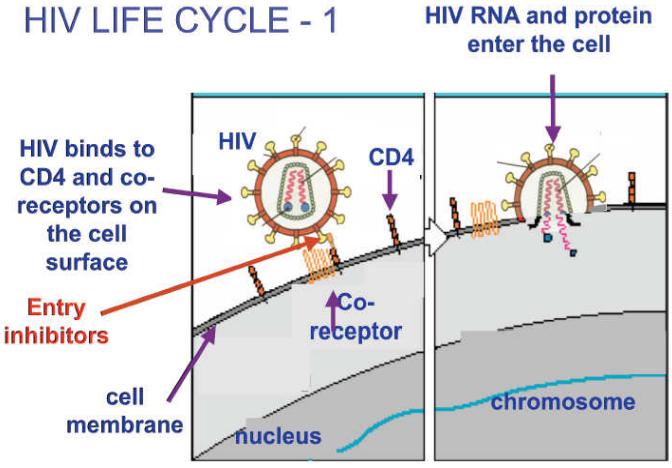
- V3 loop of gp120 – easy to target, however it mutates easily
  - Chemokine receptor binding face of gp120
    - Cryptic, only shown after conformational change and interaction with CD4
- Gp41g Fusigenic stage – looks like own body systems thus resulting in side effects

Antibodies

- Increased late, 3-6 months after infection
- Viral escape occurs – mutation and so antibodies have to keep being produced
  - Antibodies are always evolving to counter the virus – thus always chasing the virus
  - Many opportunities for neutralisation are cryptic and hidden deep in the envelope and protected by glycosylation and are thus only available for binding very transiently

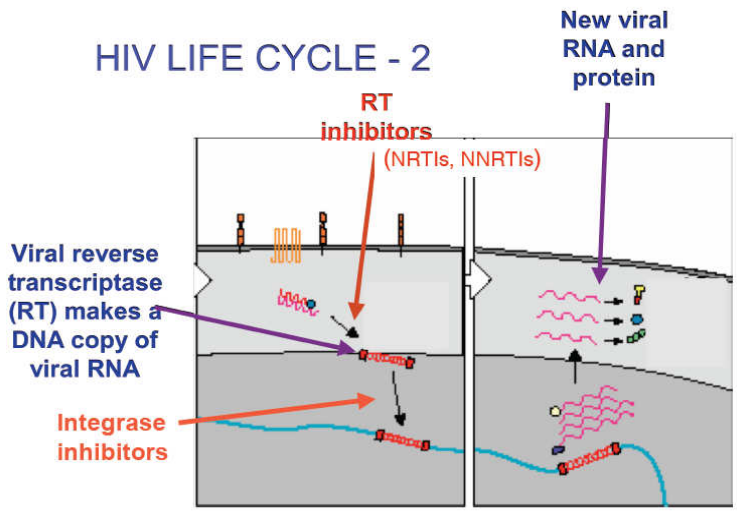
CD4

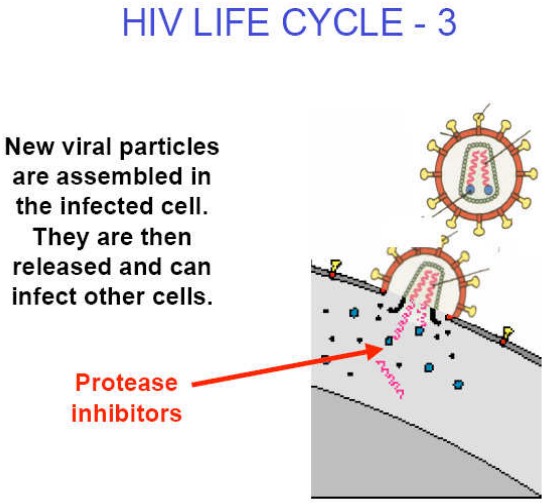
- Preferential infection of CD4 cells that counter the virus
  - Progressive reduction in IL2 production
  - Loss of proliferative function
  - Memory cells either lost or never generated



CD8

- Effective
- Can be detected day 7 post infection
- Eventual depletion is due to the fact that the disease progresses much faster than the CD8 can be produced
  - Places pressure on the virus and its mutation
  - CD8 adaptation is faster than CD4, thus less behind virus in chasing
  - Accumulation of escape mutations results in genetic escape





Antiretroviral therapy

- Therapies:
  - Entry inhibitors – gp120 and CCR5
  - Reverse transcriptase inhibitors – AZT
  - Integrase inhibitors – prevent DNA integration into genome
  - Protease inhibitors – prevents virus maturation
- Need combination therapy
  - Normally 2NRTIs (nucleoside reverse transcriptase inhibitor) and a protease/integrase/nnrti
- Aim is to reduce viral load and therefore turnover
  - Monotherapy – 7 days → 3 months results in resistance
    - With more drugs, more mutations are required to escape
- Therapy starts at CD4 350-200/μL, earlier if viral load high
  - Predicted 40 year survival
-

HIV summary

- HIV subverts the immune response
  - Targets the cells that would destroy it
- Rapid viral variation results in a high immune turnover and eventual exhaustion
- Effective cytotoxic T-cells kill CD4+T cells (infected) and thus further add to immune depletion

Summary

- Immune response controls virus – does not eliminate
  - Virus can be contained by a dynamic immune response – continually changing
  - Viral escape and variation contributes to loss of control of viral infection and thus progression to AIDS
- Therapeutic strategies need to be careful to avoid allowing the virus to become resistant to the drug, thus need combination therapy

Viruses

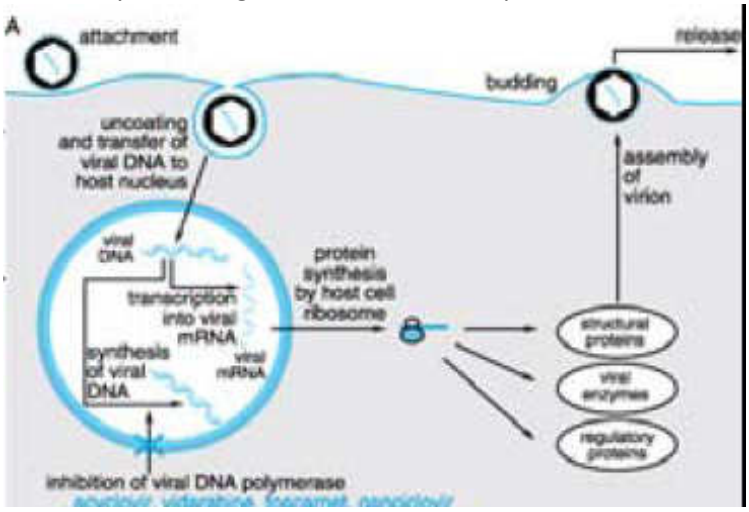
- Viral infections are common in humans
- Several types of viruses
    - DNA viruses
    - RNA viruses – esp. retroviruses (AIDS)
- Viruses have several ways of getting around host defences
    - Interference with cytokine signalling – trapping cytokines with pseudoreceptors
    - Inactivation of surface protein markers on infected cells to prevent detection of virus
    - Interference with apoptotic pathways
    - Tricking of NK cells by mimicking of surface protein markers of host cells
        - In most cases, host defences prevail and viral infections are resolved spontaneously
            - Exceptions: Lassa fever, Ebola, HIV

Immunomodulation

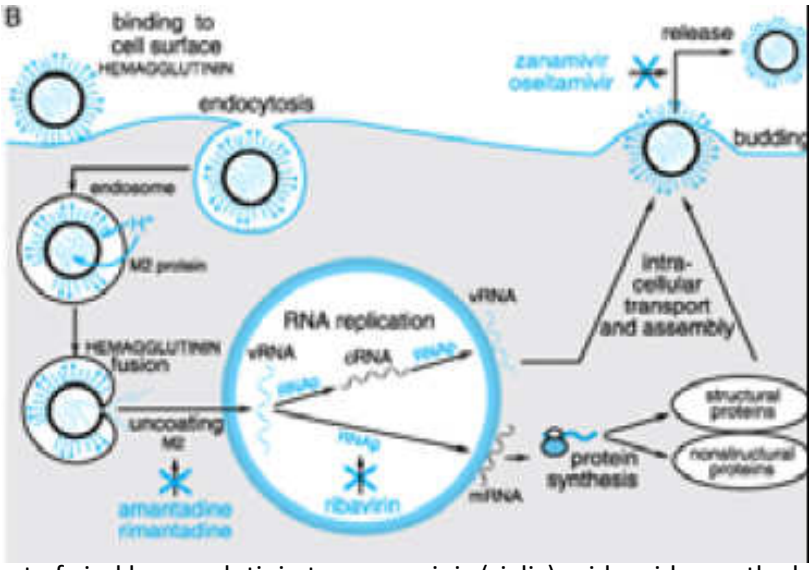
- Antibodies
    - Immunoglobulin contains antibodies that can protect against viruses
        - Antibodies neutralise viruses and prevent their attachment to host cells
        - A dose of immunoglobulin can prevent or attenuate measles, infectious hepatitis, rabies
            - However, needs to be given before the onset of symptoms
        - Can be highly specific to a particular disease
    - Eg: Palivisumab – a monocloncal antibody used against respiratory syncytial virus
        - Involves a intramuscular injection for infants
- Interferons (IFNs)
    - Proteins that are synthesised by mammals
        - Can be produced commercially using recombinant DNA technology
    - Involved in cell growth, regulation and modulation of immune reactions
    - IFN-γ is produced by T cells to coordinate the immune response (especially, activate macrophages)
        - IFN-α and IFN-β are also used in response to viruses
    - Bind to receptors on host cells and induce production of enzymes that inhibit translation of viral mRNA
    - Injected, don't cross BBB, short half-life
        - Side-effects because IFNs have many uses
- Vaccination
    - Successful for some diseases like polio, smallpox, influenza A and B, hepatitis B (based on memory T and B cells)
    - HIV vaccine unlikely because of antigenic drift – mutations lead to antigenic resistance

Virus replication

- DNA viruses
    - Process:
        - DNA enters host cell nucleus
        - Transcription is catalysed by host cell enzymes
        - Translation by ribosomes
        - Virus proteins are generated – enzymes for synthesising viral DNA, structural proteins
        - Assembly and release of virions



- RNA viruses
    - Process:
        - Viral RNA serves as its own mRNA
        - Host cell nucleus is not necessarily required for replication
        - Translation, assembly and release is the same as for DNA viruses
- Retroviruses have a different mechanism



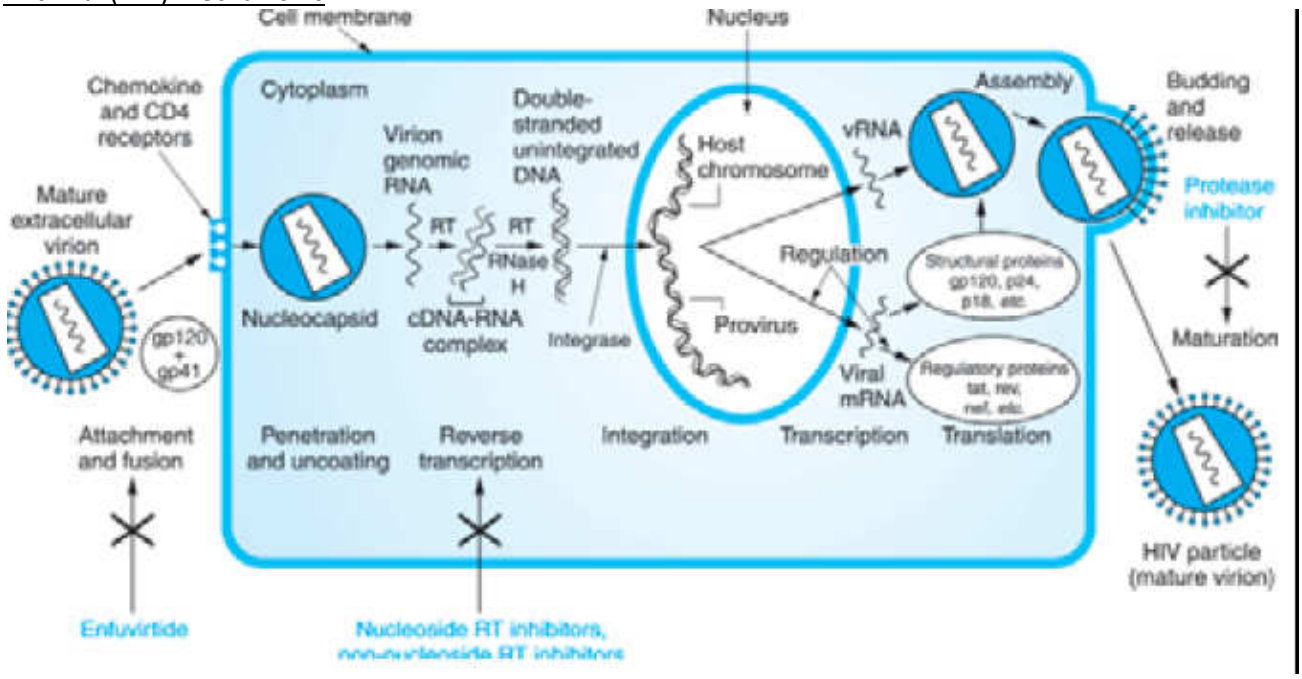
<u>Eg: Zanamivir, Oseltamivir</u>

- Influenza viruses begin infection by attachment of viral hemagglutinin to neuraminic (sialic) acid resides on the host cells (covalent bonds)
    - Virus then enters by endocytosis
    - Viral M2 protein (ion channel) acidifies endosome and the virion disassembles
        - For virion release, viral neuraminidase catalysese break the bonds between the particle coat and the host sialic acid
        - Thus, antiviral drug Azanmivir, oseltamivir inhibits viral neuraminidase and thus stops infection

<u>HIV</u>

- An RNA retrovirus – a lentivirus
    - Only one virion is required for sexual acquisition of infection
    - A chronic, persistent infection
        - Host CD4 + T cell count declines steadily increasing the risk of opportunistic diseases and death
        - Late onset of clinical symptoms (8-10 years)
        - In 'latent' period, silent replication occurs in the lymph nodes
- Two forms
    - HIV-1, most common
    - HIV-2, less virulent, confined to parts of Africa
- Fewer than 5% of people who would benefit from combination antiretroviral therapy receive it

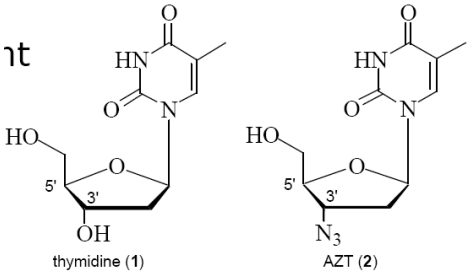
<u>Antiviral (HIV) mechanisms</u>



- Blocking entrance to the cell
  - Virus structure
    - Virion: nucleocapsid core with a lipid bilayer (envelope) derived from the host cell plasma membrane
    - Small regulatory proteins that enhance virion production and deal with host defences
    - Envelope has gp120 and gp41, proteins important for attachment and fusion
    - Nucleocapsid contains two copies of RNA genome (10 000 base pairs) and viral enzymes: reverse transcriptase, protease, integrase
  - Attachment and fusion
    - Virion binds through gp120 targeting CD4 receptors on lymphocytes and macrophages
      - Requires a coreceptor – chemokine receptor (CCR5, macrophages, initial attack) or CXCR4, T-cells, advancing disease
    - Fusion of virus lipid bilayer with host lipid bilayer, controlled by gp41
    - Capsid is uncoated releasing viral RNA and viral enzymes into cytoplasm
  - Entry inhibitors
    - Enfuvirtide – approved 2007
      - HIV entry inhibitor that selectively inhibits HIV-mediated membrane fusion
        - Binds and blocks gp41
      - Active against HIV-1 but not HIV-2
      - Expensive to manufacture and administered subcutaneously 2x/day
      - Resistance
        - Via mutations to gp41, a single AA substitution can result in 450x resistance
      - AE – injection site reactions
    - Oral alternatives are underdevelopment
- Reverse transcriptase inhibitors
  - Reverse transcription process:
    - Synthesis of a complementary DNA strand from viral RNA strand
      - Occurs at the polymerase active site
    - Reverse transcriptase has a 2nd active site – RNAse H
      - Allows degradation of original RNA
    - Synthesis of a complementary DNA strand
      - Occurs at the polymerase active site
      - Thus, a full-length double-stranded DNA copy of the virus is produced
  - RT is error-prone and lacks a proof-reading function, thus much mutation
    - Clinically, RTIs inhibit steps 1 and 3, the polymerase action
  - Integration
    - Viral enzyme integrase catalyses the reaction to integrate the viral DNA into the host chromosome
      - Complex, multistep process:
        - Processing of viral DNA in cytoplasm creating a reactive end
        - Transport into nucleus
        - Strand transfer reaction occurs and then host cell enzymes repair the new DNA
    - Raltegravir – integrase inhibitor approved for clinical use 2007
      - Inhibits strand transfer thus reducing toxicity since integrase has other uses in the body
- Protease inhibitors
  - After integration into DNA, virus may remain quiescent and reproduces as the cell divides (cell mitosis)
    - Once cells are activated, virus begins producing viral RNA and proteins
  - Viral proteins are synthesised as 3 major polyproteins that need a viral protease enzyme to be split further
    - Gag – structural proteins
    - Pol – 3 enzymes (RT, IN, protease)
    - Env – envelope proteins
  - Protease inhibitors prevent proteases cutting up the proteins and thus prevent virus function
  - Assembly of virions
    - Viral RNA copies are surrounded with structural proteins to form the nucleocapsid
    - Envelope proteins assemble on the cell surface and nucleocapsid cores are directed there
    - The virion buds through the cell membrane creating a new HIV particle
      - None of these processes associated with assembly has been successfully targeted for HIV therapy

Reverse transcriptase inhibitors

- Nucleoside analogues
  - Process:
    - Phosphorylated by host cell enzymes giving a 5'-triphosphate
    - Compete with equivalent substrate in reverse transcriptase action of creating DNA
    - Incorporated into DNA strand by RT or viral polymerases (DNA viruses)
      - Lack of the 3' OH groups causes chain termination
    - Side effects – inhibition of host cell DNA polymerases can lead to GIT disturbance (fast growing/dividing cells)
  - Aciclovir – specific for herpes simplex, can be given intravenously/topically
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
    - AZT (zidovudine) – first approved HIV treatment
    - 3TC (lamivudine), ABC (abacavir) – given orally
- Nucleotide analogues
  - Same mechanism as nucleoside analogues but requires fewer phosphorylation steps
  - Eg: tenofovir
- Non-nucleoside RT inhibitors (NNRTIs)
  - Allosteric inhibitors – causes enzyme to maintain the inactive conformation
  - Don't compete with endogenous nucleosides and don't need to be phosphorylated
  - Eg: nevirapine, Efavirenz – orally given
  - Side effects
- All RTIs have problems with resistance



Protease inhibitors

- Generally given orally
- Competitive inhibitors – compete for substrate
  - Mimic cleavage site of viral polyproteins
- Common side effects

Combination HIV therapy

- Known as HAART: highly active antiretroviral therapy
  - Normally involves 3 drugs from at least 2 classes
  - Commonly: two different NRTIs + (a NNRTI or a PI or an INI)
- Effects
  - HIV replication is inhibited
  - Presence of HIV in plasma is reduced
    - Thus patient survival prolonged
      - However, requires a complex, expensive regimen of drugs lifelong – often many side effects
  - Virus is not eradicated, lies latent in host genome of memory T cells, just reproduction stopped
  - HAART may have negative drug-interractions
  - Cross-resistance (resistance to one drug through exposure to another) not yet seen, but expected due to high mutation rate

Prophylaxis

- Difficult choices
- Pregnant women/breast-feeding women
  - Avoids damage/transmission to fetus/baby
  - Use: AZT (Zidovudine) or combination therapy
- Accidental exposure
  - Only if high risk of infection
  - Use: Zidovudine or combination therapy

Introduction

- For microorganisms to cause disease, it must be able to do two things
  - Multiply in the host
  - Spread from host to host (ie, enter and leave its host)
- There are many entrance and exit points for microorganisms
  - Mouth
  - Respiratory tract
  - Conjunctiva (host defences – lysozyme, blinking)
  - Skin – through scratches
    - Skin is regularly a very good barrier against infection
  - Urogenital tract
  - Alimentary tract

Success of spread

- The success of microorganism transmission is based on:
  - The number of microorganisms spread
    - The larger number of microorganisms shed, the greater the chance of them reaching a susceptible host
    - Most shed microorganisms die
  - The stability of the microorganisms in the environment
    - Changes in the environment cause the death of many microorganisms
    - Changes such as: desiccation (drying), temperature, chemicals
      - Microorganisms that can resist desiccation can spread rapidly
      - Microorganisms that can resist thermal/chemical inactivation can remain infectious for a long time in the environment
    - Some MO are very resistant
      - EG: mycobacterium tuberculosis (tuberculosis)
        - Can survive in air, dust, dried droplets for many months
          - In a microbiology lab, need to keep in a lamina flow cabinet
    - Some MO use an environmentally resistant spore form:
      - EG: Clostridium tetani (Tetanus)
      - EG: Clostridium perfringens (Gas Gangrene)
        - Gram +ve rods that in spore form can remain dormant in the soil for 60-70 years
        - When infected, bacteria is susceptible to O_2, however, it ferments sugars for growth which causes gas pockets
      - EG: Bacillus anthracis – causes anthrax, spores send in the mail
      - EG: Histoplasma spores – a yeast that can infect the lungs
  - The number of microorganisms required to infect a host
    - Eg: Shigella dysenteriae requires 10 microorganisms to infect – not affected by gastric acid
    - Eg: Salmonella needs 10^6 MO because it is destroyed by stomach acid
- Transmission can also be affected by host and microbial factors
  - Genetic factors in microbial strains (virulence factors)
    - Eg: genes that allow resistance to changes in pH (eg: shigella), temperature, chemicals
  - Host factors - some activities increase shedding and thus transmission
    - Coughing, sneezing, diarrhoea

Horizontal transmission

- The principle whereby an infected individual infects people they meet, and these people in turn become affected and also in turn infected more people they meet
- There are several types of horizontal transmission:
  - Respiratory and salivary spread
  - Fecal-oral spread
  - Venereal spread
  - Vectors – arthropod/zoonoses

Respiratory and salivary spread

- Spread of respiratory infections
    - Nasal secretions, sneezing, coughing, talking (ch, p)
- These infections are common in winter because people stay inside and are in contact with other people in cofined spaces
    - Ie, crowded conditions increase the spread of infection
- Inhalation localisation (ie, area first exposed) – determined by size of inhaled droplets
    - Large particles fall to ground
    - Particles 10µm are trapped by the nasal mucosa
    - Particles 1-4µm make it to the lower respiratory tract
    - Also depends on host defences:
        - Mucus + cilia
        - IgA, lysozyme protections
    - Area of infection in the respiratory tract depends on:
        - Presence of receptors
            - Need particular receptors on the host cells for attachment and invasion
        - Local temperature
        - Initial localisation
- Droplet transmission
    - Viruses: colds, influenza
    - Bacteria: meningitis (Haemophilus influenzae, streptococcus pneumoniae, Neisseria meningitidis)
- EG: Tuberculosis
    - Very serious infectious disease, kills ~2 million/year, infects 9 million others
    - Predisposing factors:
        - Poverty, malnutrition, poor housing (high density living with low hygiene)
    - However, TB is increasing in developed countries:
        - Immunocompromised, AIDS, chemotherapy
    - Mycobacterium tuberculosis can survive drying and thus it survives in dust and air
        - Has a waxy cell wall that withstands drying
            - Need an acid fast stain to visualise – pink on blue
    - Spread by inhalation of droplets or dust/aerosols containing mycobacteria tuberculosis
- Salivary spread
    - Respiratory pathogens – from upper and lower respiratory tracts
    - Viruses that infect the salivary glands
    - EGs:
        - Herpes simplex/paramyxovirus (measles) – childhood infection
        - Cytomegalovirus, infectious mononucleosis (Epstein-Barr virus) – adolescent/adult infection
- Prevention:
    - Flu vaccine, hygiene

Faecal-oral transmission – GIT infections

- Low public health measures and hygiene leads to easy spread of low intestinal infection
    - Ie: faecal contamination of drinking/bathing water (esp. developing countries)
- Diarrhoea
    - Eg: John Snow and the broad street pump
        - Outbreak of cholera (diarrhoea) in 1854
            - Snow performed interviews of sick people and mapped the infection
            - Found infectious were centred around broad street
            - Snow removed the broad street pump and showed that outbreak died down
            - Water demonstrated to be the cause
    - Diarrhoea allows aerosol spread and allows shedding of a very large number of organisms
- Faecal pathogens via food and fingers
    - Contaminates water that can then in turn contaminate food
    - Contaminates food
    - Viruses: Rotavirus; Protozoa: Giardia Lamblia
        - Bacteria: Campylobacter jejuni, salmonella typhinurium
            - Come on food – thus need to cook food properly and use different chopping boards
- Salmonella typhi – typhoid
    - Invades macrophages and can survive in these, travel into the lymphatics and then to the blood
        - Thus become a systemic disease
    - Human only host with enhanced ability to survive in water, sewage, certain food
        - 5Fs = flies, faeces, fingers, food and fomites (nonliving particles)
    - Typhoid Mary – cook, caused 7 typhoid outbreaks, jail, then more outbreaks, then jail again
        - A small population when they recover from typhoid become carriers where it lives in the gall bladder
            - Thus a full recovery is only declared after 3 clean stool samples
- Prevention
    - Increased hygiene: hand washing, supervision of food preparation, adequate refrigeration,
    - Detection of asymptomatic carriers, immunisation (where appropriate)

Urogenital transmission

- Urinary infections are not spread by urine
    - Urine can spread other infections by contamination – food, drink, living space
- EGs:
    - Schistosomiasis – parasite eggs are excreted in the bladder
    - Typhoid – bacterial persistence in bladder scarred by schistosomiasis
    - Polyoma virus infection – commonly excreted via urine in normal pregnancy
    - Cytomegalovirus infection – commonly excreted in infected children
- STDs – spread with less speed than respiratory and GIT infections because we don't have sex with crowds
    - Facilitation of transmission – increased sexual partners, contraceptive pill (unsafe sex)
    - Egs:
        - Viruses – papilloma virus (genital warts), HSV-1 (cold sores), HIV, Hep B
        - Bacteria – Neisseria gonorrhoea, Chlamydia trachomatis, Syphilis
        - Protozoa – Trachomatis vaginalis
- Transmission of urogenital tract STDs
    - Close sexual contact
        - Mucosal contact (eg: vagina mucus membrane broken)
        - Discharge (eg: Chlamydia and gonorrhoea)
        - Mucosal sores/warts (eg: HSV, papilloma virus)
    - Semen
        - Cytomegalovirus, Hepatitis B, HIV
- Prevention: Condoms

Transmission from skin

- Infection by:
  - Shedding
    - Normally shed $5x10^8$ skin cells/day
    - Normal flora can contaminate the environment
      - Eg: Dermatophytes (fungi), ringworm can infect broken skin
      - Eg: Tinea corpus, tinea pedes
  - Direct contact
    - Eg: Impetigo (Streptococcus pyogenes)
      - Common in children
      - Prevention – keep children at home away from others..
    - Eg: Staphylococcus aureus – common hospital acquired infection
      - Spread person to person by a lack of aseptic technique
      - Can live in dust particles for a long time

Transmission via blood

- Infection by:
  - Transfusions – contaminated blood products/clotting factors
  - Contaminated needles
    - Shared needles – drug injection
    - Needle-stick injuries
    - Problems in developing countries where needles are expensive and reused
- Commonly spread HIV, Hepatitis viruses
- Prevention
  - Education
    - No sharing of needles
    - Screening blood donations
    - Education to prevent needle-stick injuries

Vertical transmission

- Transmission of disease from parent to offspring
  - Can occur by:
    - Sperm/ovum –infection of human genome in germinal cells
    - Placenta, milk, blood – after conception
  - Pre-natal - transplacental egs:
    - Rubella, CMV – causes placental lesion, abortion, stillbirth, malformation
    - HIV – childhood AIDS
    - Hep B virus – antigen carrier infant, infections often peri/postnatal
    - Treponema pallidum – stillbirth, congenital syphilis with malformation
    - Listeria monocytogenes – meningoencephalitis – (uncooked food)
      - Generally only pregnant women/immuno-suppressed get this disease
    - Toxoplasma gondii (parasitic) – stillbirth, CNS disease
  - Perinatal - infected in birth canal
    - Gonococcal, Chlamydia conjunctivitis (blindness), HIV
    - Group B strep, E. coli – early onset meningitis
  - Postnatal – milk/direct contact
    - Cytomegalovirus, HepB, HIV, HTLV 1 (human t-lymphocyte virus)
  - Germline – viral DNA in human genome
    - Many retroviruses

Animal transmission

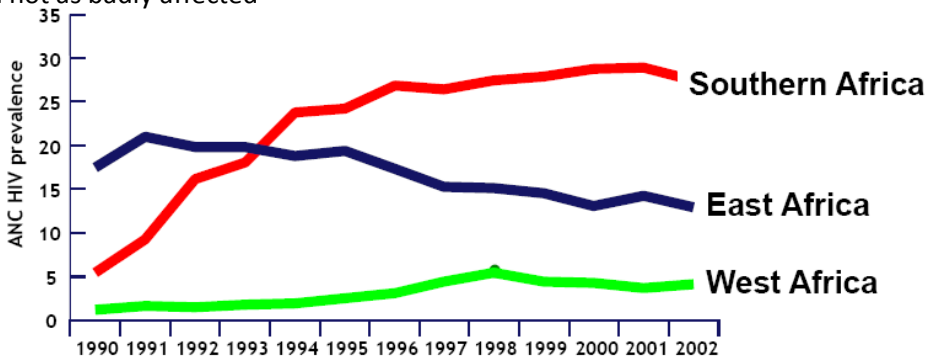
- Due to shared environments and common susceptibilities
- Transmission depends on:
    - Type of environment
    - Climate
    - Hygiene/sanitation
    - Type of contact
- Type categories
    - Arthropod and invertebrate vectors
        - Insects, ticks, mites
        - Viruses: yellow fever; Bacteria: Rickettsia; Protozoa: malaria; Helminths: lymphocytic filariases
        - Often passive transmission
            - Disease carried in mouthparts, on body, in the intestines
                - Then transferred onto food or directly to the host by:
                    - Feeding, regurgitation, defecation
        - Biological transmission
            - Insect bites infected host and ingests microorganism
            - Microorganism multiplies in insect and numbers increase
            - Insect bites next host where the microorganism passed on
        - Eg: Malaria – insect vector anopheles mosquito
            - Major impacts where anopheles mosquito breeds
            - ~35% world's population infected
            - 10million new cases/year, 2million deaths/year
        - Prevention:
            - Mosquito repellent, cover skin, light-coloured clothing bednets, anti-malaria drugs
    - Directly from vertebrates
        - Zoonoses – infections that animals pass directly to humans
        - Transmitted by:
            - Contact inhalation, bites, scratches, contamination of food/water, ingestion as food
        - Microorganisms involved: viruses, bacteria, fungi, protozoa, Helminths
        - From dogs and cats:
            - Bites/scratches – rabies
            - Vectors – Ticks, sandflies (rocky mountain fever, spotted fever)
            - Contact – dermatophyte/fungi
            - Faeces – worms (Hookworm), protozoa (toxoplasmosis)
        - Eg from food:
            - Contaminated animal feed, cow eats feed, slaughtered, meat product mishandled, individual eats and becomes infected

Global summary

- People living with HIV – 40.3 million
  - Vast majority in sub-Saharan Africa (25.8 million)
  - Also high numbers in Eastern Europe, south and south east asia and latin america
- New HIV infections (2005) – 4.9 million
  - Vast majority in sub-Saharan Africa (3.2 million)
  - Also high numbers in Easter Europe and south and south east asia
- Deaths due to AIDS (2005) – 3.1 million
  - Vast majority in sub-Saharan Africa (2.4 million)
  - Deaths in children (<15) total: 570000, Africa: 520000
- United states state of HIV is 10x worse than ours
  - Mostly due to injecting drug users (IDU)
    - we have a policy of needle exchange
- General trends:
  - 14000 new HIV infections/day (2005)
    - 95% of new HIV infections is in low and middle income countries
      - Due to inability to afford drugs/infrastructure to prevent transmission
    - 2000 in children (<15)
    - 12000 are adults (50% female, 50% 15-24)
      - An STD – affects people in their most productive years of their life

Africa

- Different in different parts of Africa
  - • Southern Africa the worst – HIV prevalence on the rise, 25-30% infected
  - East Africa has seen a decline recently, possible increasing again
  - West Africa not as badly affected



- Trends:
  - Prevalence in pregnant women is increasing especially in 20s-30s
  - Prevalence is higher in women than in med
    - Because: women often have sex for the first time with older men who have had several partners previously and thus get disease
- HIV is now the leading cause of mortality in sub-Saharan Africa, 1/5 of all death and 2x next highest
  - Projected population structure results in few people >35-40
    - Looks like a population pyramid of the 13th-14th century
    - Few parents are alive, grandparents from the previous generation look after orphaned children
- Biggest issue: treatment rollout
  - Pricing of drugs (too expensive, 1000-1500$/month in developed countries)
    - Produced through generic manufacturers in the developing countries (1$/day, still expensive)
    - Issues of intellectual property
  - Purchase of drugs – PEPFAR (Presidents emergency plan for AIDS research) in Africa, global funds
  - Lack of expertise/training
  - Prevention – education etc.

Asia

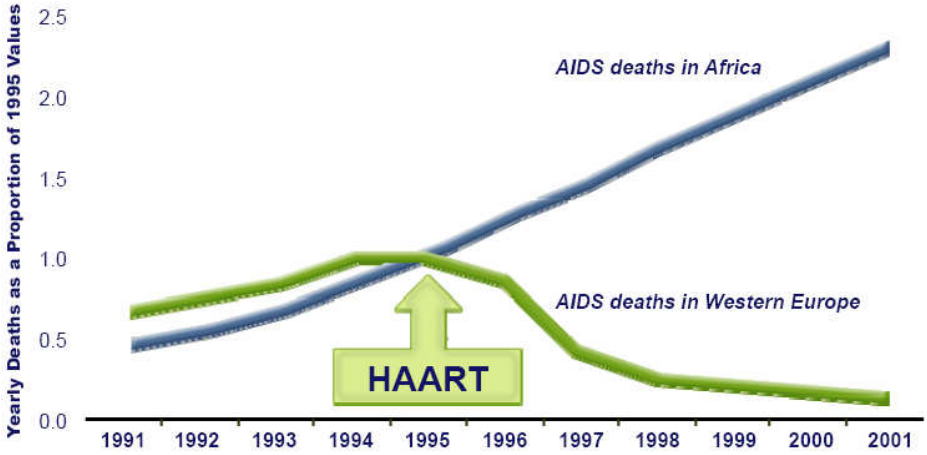
- Thailand
  - One of the first countries to have an effective HIV prevention response
  - 1990s – monitored conscription
    - 3% of young men were infected
    - Health minister (Mr Condom) brought in a 100% condom campaign and thus reduced HIV
  - Epidemic started in sex workers and spread to the general population
- Vietnam
  - Intravenous drug use, >80% in 2001 had HIV
- Indonesia
  - Sex workers
  - Avoided HIV until recently
  - IDU and sex workers intricately linked
- MSM – men who have sex with men
  - Not just western countries, does occur in Asia and spreads HIV, but cause is predominantly heterosexual

Eastern Europe

- Until the 1990s, no HIV
  - In the mid-late 90s, social events led to increased intravenous drug use that led to HIV
  - The soviet union broke down and increased poverty and social dislocation, thus increased IDU and spread of HIV
- Ukraine
  - Initially predominantly caused by IDU, then increase in heterosexual spread
    - which is not the dominant cause

Developed countries

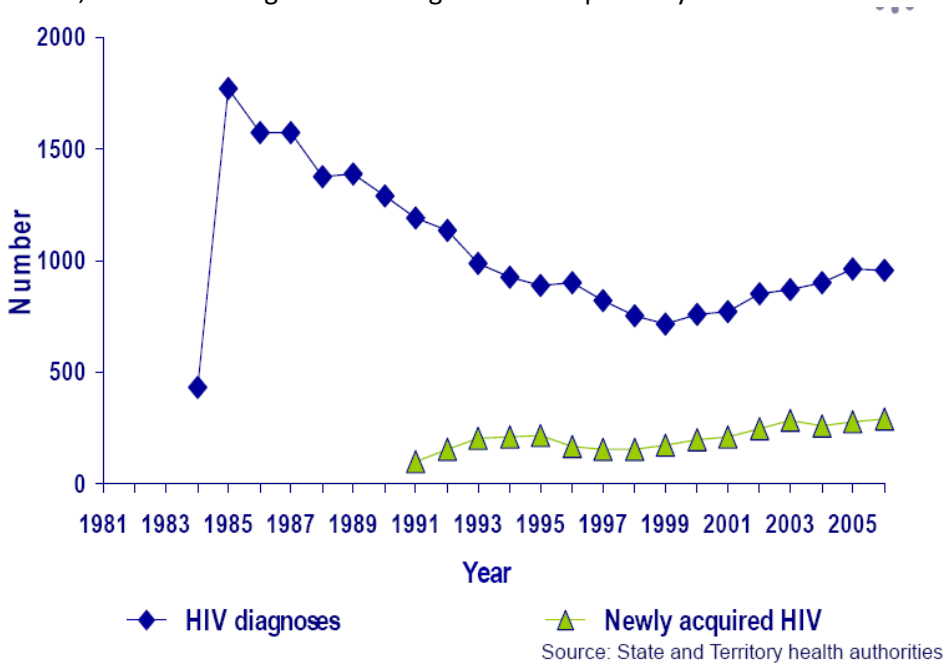
- Care prolongs a productive life
  - HAART – highly active antiretroviral treatment prolongs life by a large amount



- Western Europe
  - Heterosexually transmitted
    - Thought to bed due to migration patterns – especially out of Zimbabwe
  - UK has very good policies
    - Thus, low IDU and low vertical transmission
- Reduction in HIV rates has resulted in a complacency
  - The lack of threat has resulted in an increase in risky behaviours
- Social disadvantage, class inequity makes a difference in HIV rates

Australia

- Initial rise was due to the mobile population of Gay men that initially contracted virus
    - Good prevention policies reduced numbers slowly
    - In the late 1990s, peak of decline
    - In recent times, numbers are again increasing due to complacency



- Currently in Australia, HIV is viewed as a chronic illness rather than a fatal illness
    - 40 year expected lifespan
    - Ongoing mild immune deficiency
- NSW has highest rates of HIV but all have reduced
    - Risky behaviours are again on the rise however
- Men having sex with other men is the main cause of HIV in Australia because other categories are so well controlled
    - IDU spread is well controlled by needle-exchange programs
        - Surveys and monitoring occur – every year, blood is tested and a questionnaire taken
- Indigenous population has higher rates in heterosexual than homosexual activities
    - Trend follows that of developed countries
    - Needs education
    - Worry with PNG contamination – indigenous people can cross by canoes to PNG, thus HIV can enter country
- Australia has a recent increase in STDs (especially syphilis)
    - Thus, increased risk behaviour may result in these trends transferring to HIV rates

Globally: where to?

- Spread continues in Africa/Caribbean
- Asia/Eastern Europe may be emerging epidemics
- High income countries are having a resurgence in MSM risk
    - Also, there is higher risk in minority groups
- Delivery of care and prevention is essential

Australia: where to?

- Increasing risk behaviour
- Epidemics in neighbours – PNG(heterosexual)/Indonesia(IDU)
- No vaccine in the near future
- Drugs work for most – only in developed countries
    - Drugs result in more people with infection, more people on therapy and more people with immuno-deficiency

History of HIV

- Disease came to the world's notice through the gap population
    - Thought to be a disease of the gay man
    - Spread by rampant homosexual practices and promiscuous behaviours in the gay population
        - Especially in developed countries like the USA and Australia
    - Some famous people came out to have HIV – Rock Hudson
- Fear – based on a lack of knowledge
    - Children in schools
- Magic Johnson – famous basketballer, HIV positive
- Hope – data about antiretroviral treatment released
    - Recently, HIV has become a chronic disease rather than a fatal one
- 2000
    - People dying in 20s and 30s
    - Leaving orphans and social dislocation

Introduction

- Ethics is about relationships to others
    - Social perspective – ethics makes no sense without a community

Ethical perspectives

- Individual perspective values
    - Autonomy, choice, individual rights
- Population perspective values
    - Equity, justice, care for the community
- Sometimes these are in agreement, sometimes they're in conflict

EG: SARS

- Rights of the man who was isolated:
    - Autonomy, justice, benevolence, non-malevolence, human rights
- However, was kept in isolation, quarantine with no idea of what was going on because:
    - Community values outweighed those of the individual
        - Preventing spread of disease, community health, equity

Pneumococcal vaccine

- Who decides what vaccines are approved etc
    - ATAGI – publish the immunisation book, made up of scientists/ medical practitioners, doctor
    - ASVC – decide which are funded
    - Final decision lies with the health minister
- Diseases caused by streptococcus pneumoniae
    - Meningitis, septicaemia, pneumonia, otitis media
    - Especially in Aboriginal/outback communities
- Vaccination
    - Involves 3 shots, total cost of 400-500$
    - 83-89% effective, good and safe
- Other issues
    - Other costs due to lack of vaccination
        - Time off work, disability
    - Herd immunity
- Meningococcal vs pneumoncoccal
    - Pneumococcal is more common
    - Meningitis vaccine was funded
        - Where should we spend the money? – many factors

Burden of disease

- In Australia, very much due to CVD and risk factors for CVD
- Funding – if based on the burden of disease, we should be funding CV drugs, lifestyle programs and not vaccines
    - Why do we fund vaccines? CVD patients tend to be later in life, burden of disease important

EG:. Annie

- 4 years old, febrile, taken to GP/local hospital – sent home diagnosis: virus
- A few days later, not breathing, ambulance called, sent to ICU
    - Died a few days later, pneumococcus found in blood culture
- Family – effect was immeasurable, 1 year old child also febrile
- Ie. Individual perspective
    - Definitely want to have given vaccine, social/population view may be different – good for individual/community?
    - Other issues: political, economic, public opinion, advocacy, criticism, equity – eg: rural radiotherapy, priorities

Public health ethics

- Central ideas are:
    - Equity
    - Justice
- Individual rights are balanced with those of the community

Australia

- Health is worth in rural areas, overseas people, aboriginals, prisoners, the elderly etc.
    - Public health ethics – is this right? To have inequal health standards

Expenditure

- 9.3% of GDP is spent on health
    - Similar to other developed countries

Community care

- Reducing the burden of disease: weight, smoking, mental health
- Clinical practitioners – cultural sensitivity, aware of social perspectives, equity, community care

Health programs in indigenous communities

- Many people are sent out to areas of need and fail
    - Due to: inappropriate communication, structure
    - Community rejection/exclusion
- However, can be successful
    - Eg: strep infections causing scabies
        - Leads to renal failure
        - Itchy and scratchy program
            - Talked to community elders and involved them from the start
            - Program was effective because it was culturally and sensitively designed

Global perspectives

- Public health ethics
    - Money donations overseas?
    - “we are all part of the bigger picture”?

Introduction

- Respiratory tract function:
    - Gas exchange
        - Providing oxygen for cells and removing carbon dioxide generated through respiration

Morphological subdivisions

- Air conducting zone
    - Tubes that move air in and out of the lungs
        - Made up of the – nasal cavities, pharynx, larynx, trachea, bronchi and bronchioles ending at the terminal bronchioles
    - Improves the quality of inspired air
        - Warming/cooling – capillary beds, nasal venous plexuses
        - Moistening
        - Detoxifying by absorption of harmful gases (ozone, SO_2)
        - Entrapment of harmful bacteria and viruses (Goblet cell and mucous/serous gland secretions)
        - Cleansing – removal of particulate matter (cilia)
- Respiratory portion
    - Gas exchange occurs through thin-walled alveoli
        - Alveoli appear in airways distal to terminal bronchioles
- Musculo-elastic ventilation apparatus
    - Muscles of respiration
        - Eg: intercostals, diaphragm
    - Elastic fibres – provide elastic recoil of the lungs in expiration

Nasal cavities

- Divided into 4 regions
    - Vestibule
        - Narrow – in the nostrils
        - Lined by stratified squamous epithelium
            - An extension of the upper lip
        - External opening is lined by short, stiff hair (vibrissae) – have sebaceous glands
    - Respiratory area
        - Most of the cavity, lined by hard and soft palates
        - Lined by pseudostratified columnar ciliated epithelium with goblet cells (respiratory epithelium)
            - Ie the Schneiderian membrane
        - Has a medial and lateral surface
            - Medial surface (septal) is smooth
            - Lateral surface has three overhanging shelves of bone –superior, middle, inferior conchae
                - (otherwise known as turbinates)
        - Beneath the respiratory epithelium (especially on the larger conchae_ there is an extensive lamina propria with thin-walled venous plexuses for warming the air
    - Paranasal sinuses (frontal, maxillary, sphenoidal, ethmoidal)
        - In bones – draining into the nasal cavity
        - Lined by pseudostratified ciliated columnar epithelium continuous with nasal cavity lining
            - Thin lamina propria is attached to periosteum and has some seromucous glands
                - Secretions from these glands and goblet cells are swept into the cavity by cilia
        - Function: humidify air and resonate the voice
    - Olfactory area
        - Narrow roof of the nasal cavity extending over the superior concha and the adjacent septum
        - Epithelium resembles respiratory epithelium without the goblet cells
            - Pseudostratified columnar cells are taller with less cilia and an indistinct basal lamina

Olfactory epithelium

- Three cell types:
    - Sustentacular (supporting) cell – tall with long, slender microvilli on its tip
        - Covered in serous fluid
            - Fluid removes odiferous substances in preparation for new ones
    - Basal cells – small, rounded/cone shaped, single layer sitting on basal lamina
        - Undifferentiated stem cells that produce support cells and sensory cells
    - Olfactory/sensory cells – bipolar neuron wedged between basal and sustentacular cells
        - Spindle shaped cells with a lightly stained central nucleus
        - Apices are dilated into bulbs – olfactory vesicles
            - Vesicles extend to the surface between sustentacular cells
                - Each vesicle gives rise to 6-10 long, non-motile cilia (olfactory hairs) that lie on the mucosal surface
                    - Odor receptors
            - Basal segments narrow into axons and form bundles (fila olfactoria)
                - These pass through the cribriform plate of the ethmoid bone and synapse with neurons in the olfactory bulb
        - For olfaction, epithelium has to be kept moist by serous secretions
            - Produced by Bowman's glands in the lamina propria
        - In olfaction, small chemicals dissolve in the secretion causing an action potential that is transmitted to the olfactory bulb and is associated with memory etc

Nasopharynx

- Superiorly extends into the nasal cavity
- Respiratory epithelium lines most of this cavity
    - Exceptions: areas where epithelial surfaces are frequently in contact
        - Where the uvula and soft palate contact the posterior nasopharynx during swallowing
        - Here, there is stratified squamous non keratinising epithelium

Larynx

- Connects the pharynx to the trachea
- A hollow, bilaterally symmetrical chamber
    - Walls are made of rigid, irregularly shaped cartilages
    - Held together by ligaments, moved by skeletal muscle
        - Extrinsic muscles change the position of the larynx – swallowing
        - Intrinsic muscles alter the relative position of the vocal folds to produce sound
- Cartilage:
    - Hyaline cartilage:
        - External: thyroid and cricoid and the body of the triangular arytenoids
        - Internal: corniculates (horn shaped) and cuneiforms (wedged shaped)
    - Elastic cartilage:
        - The epiglottis, the tips of the arytenoids
- Central, midline cavity is the vestibule
    - Lateral extensions of the central cavity are ventricles
- Central cavity at the vocal cords is called the rima glottis
    - Lined by the true vocal cords
        - Covered in stratified squamous epithelium
        - Made up of bundles of elastic fibres – vocal ligaments
        - Contains the voluntary vocalis muscle which can vary the tension and length of the cords
    - Above the cavity are the false vocal cords (protective, ventricular folds)
        - Separated by the ventricle from the true cords
        - No muscle
        - Rich in seromucous glands and covered in respiratory epithelium

Trachea and primary bronchi

- Four layers
    - Mucosa
        - Respiratory epithelium
        - Prominent lamina propria containing lymphocytes in a matrix of elastic and reticular fibers
    - Submucosa
        - Loose CT with mixed serous and mucous glands
            - Ducts penetrate the mucosa to reach the lumen
    - Muscularis
        - Contains the involuntary trachealis smooth muscle that fills the open rings in the trachea and join the partial rings in the primary bronchi
    - Adventitia – dense
        - Contains thick collagenous CT bands with C/U-shaped hyaline cartilage
            - 16-20 in the trachea, 8-10 broken in each bronchus
            - An intermediate between bone and cartilage – avascular made up of chondrocytes
    - Pathology:
        - Smooth muscle in the lower bronchi can undergo bronchospasm involving a constriction of the airways
            - Goblet cells undergo hypersecretion further reducing lumen size

Intrapulmonary bronchi

- Extrapulmonary (primary) bronchi pierce the lung and divide into R: 3, L:2 intrapumonary (secondary) bronchi
    - These secondary bronchi undergo branching as they enter the lung forming segmental (tertiary) bronchi
        - These supply bronchopulmonary segments (R:10, L:8-10)
    - Secondary and tertiary bronchi have the same histology as the primary bronchi
- As bronchi decrease in size, changes develop:
    - Cartilage rings reduce to irregular cartilage plates and then reduce in size and number as the lumen decreases
    - Smooth muscle layer forms between the cartilage plates and mucosa
    - Goblet cells becomes less numerous
    - Epithelium is reduced in height and becomes simple columnar with fewer cilia

Bronchioles

- Tertiary bronchi terminate by forming two large bronchioles (0.5-1mm diameter)
    - Features:
        - Lack cartilage
        - Increase in size relative to the smooth muscle layers
        - Many non-ciliated Clara (bronchiolar epithelial cells) cells
        - Epithelial reduction from ciliated columnar to ciliated or non-ciliated low cuboidal in the terminal areas
        - Mucoserous glands in the lamina propria
        - Lack of goblet cells
    - Final bifurcation of bronchioles is forms terminal bronchioles (final part of air conduction zone)
        - Reduction in the muscle layer
        - Thin lamina propria
        - Epithelium is simple cuboidal with some ciliated, others non-ciliated Clara cells
        - Appear as a complete ring histologically

Respiratory bronchiole

- Transitional structure that separates conduction zone from the respiratory zone
    - At least two respiratory bronchioles divide from each terminal bronchiole
        - Mucosa is similar to terminal bronchioles but has respiratory alveoli
        - Has prominent tags of smooth muscle piercing the alveoli
        - Alveoli:
            - Prominent elastic fibres
            - Epithelium is continuous with the bronchiolar epithelium
            - Abundant Clara cells
        - Histologically identifiable by the long or junction tubes

Alveolar ducts and sacs

- Respiratory bronchioles divide into alveolar ducts
    - Walls are entirely made up of alveolar openings
        - Alveolar epithelium lines the alveoli and alveolar duct
        - Muscle layer no longer seen, but a thin tissue ring remnant remains
    - As ducts travel distally they become wider and terminate in a cluster of alveoli sharing a common chamber (alveolar sac)

Alveoli

- Functional unit of the lung
    - Missing the side net to the lumen allowing inspired air inside
- Thin-walled, outpocketings of respiratory bronchioles, alveolar ducts and alveolar sacs
    - Ducts and sacs are tightly clumped together and have common walls – alveolar septa
- Each alveoli has a capillary lined with flat endothelial cells and a continuous basal lamina
- Alveolus cells:
    - Type 1 Pneumocytes
        - Small alveolar epithelial (septal) squamous cells
        - Line 95% of alveolar surface area (only 40 % of alveolar cells are these however)
        - Have a flattened, central nucleus with broad, thin, winglike cytoplasm extension (0.1-0.3µm thick)
    - Type 2 Pneumocytes
        - Large alveolar cells (granular)
        - More numerous (60%) but are cuboidal cells without cytoplasmic extensions
            - Occupy 5% of alveolar surface
        - Lamellated inclusion bodies with microvilli
            - Lamellated bodies produce surfactant that contributes to the alveoli lumen
                - Surfactant stabilises the alveolar surface
    - Surfactant
        - Highly viscous and has low surface tension
            - Allows the alveoli diameter to stabilise and not collapse after expiration at birth
                - Thus air remains in the lungs and the residual capacity is established
        - Thus, if the alveoli remain open, less energy is required to expand them and the newborn can breathe easier
    - Macrophages (dust cells)
        - Large cells, 10-12 µm diameter
        - Lie in the alveoli and lumen (move around on pseudopods)
        - Clean the lungs of invading bacteria and particulate matter (eg: carbon, dust-borne debris)
            - Deficiencies/malfunction in macrophages increases virulence of pulmonary disorders
                - Eg: pulmonary tuberculosis, emphysema
            - The garbage collectors of the human body
        - Contain phosphotases and have the ability o hydrolyse particles/foreign bodies
            - If macrophages take up lead, silicon, asbestos, carbon – deposits can be seen in the lungs

Blood vessels

- Lungs have a dual blood supply
    - Functional (pulmonary arteries)
        - Less pressure than systemic arteries
        - Arteries and veins are histologically similar
        - Vessels accompany the bronchi and bronchioles
            - Supernumery arteries leave pulmonary arteries and travel directly to the alveoli and outer lung tissue
                - Important ancillary route minimising physiological insult (eg. embolism)
    - Nutritive (bronchial arteries - branches of the aorta)
        - Accompany and nourish the bronchi, terminal bronchioles and lung CT
        - Anastomose with the pulmonary circulation at the conducting/respiratory passage junction
            - Smaller diameter and thinner walls than pulmonary arteries
        - Bronchial veins follow larger bronchioles and bronchi to the root of the lung and empty into the azygos/pulmonary veins
        - Chronic inflammation/neoplasia can result in larger and more bronchial arteries

Pleura

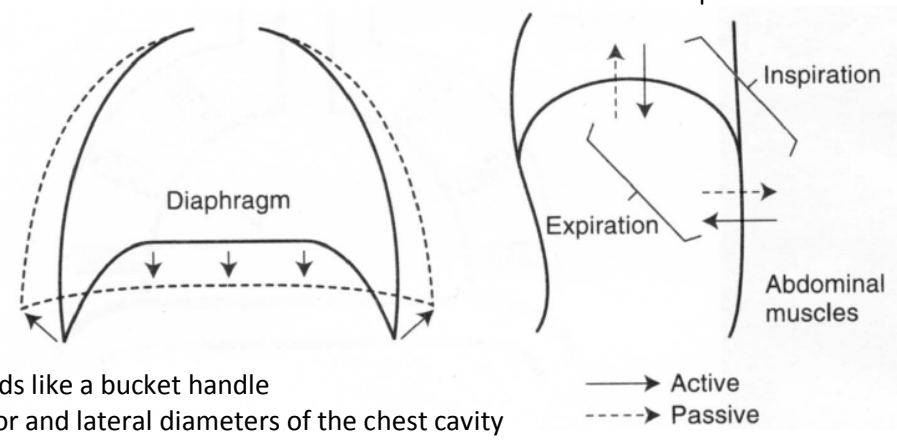
- Double-layered, serous, mesothelial membrane
    - Visceral pleura envelopes the lungs
    - Parietal pleura lines the internal surface of the thoracic cavity
- These layers are continuous at the hilum of each lung and form closed sacs (pleural cavities)
    - Sac is lined with mesothelium and contains fluid that lubricates the lung and pleural cavity
        - Allows frictionless movement during respiration
- Also has a layer of fibroelastic CT containing fibroblasts, macrophages, capillaries and lymphatics

Embryonic lung development

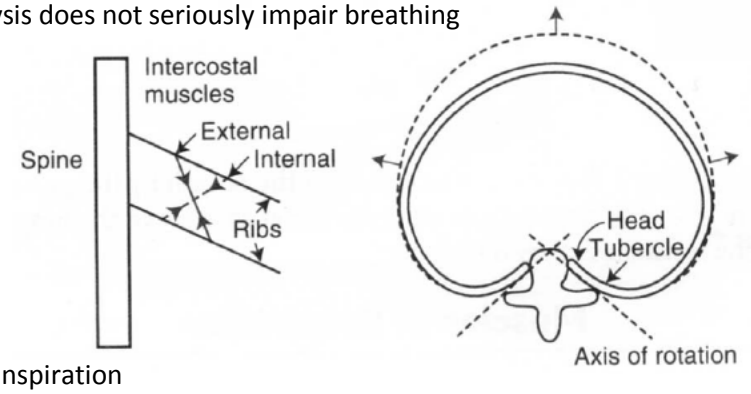
- Embryonic stage (2-7 weeks)
    - Respiratory diverticulum and bronchopulmonary segments
- Pseudoglandular stage (8-16 weeks)
    - Growth of duct system in the bronchopulmonary segments
    - Gland-like lungs
- Canalicular stage (17-26 weeks)
    - Formation of respiratory bronchioles and blood vessel growth
- Terminal sac stage (26weeks-birth)
    - Alveoli bud
    - Epithelial lining differentiates into two types → P1 (gas exchange), P2 (surfactant, from 32 weeks)
- Postnatal stage
    - 90% of alveoli are formed after birth

Muscles of respiration: inspiration

- Inspiration is an active process
  - Need to contract a muscle and do work
- Diaphragm – most important
  - A thin, dome-shaped sheet
  - Inserts into the lower ribs
  - Neural supply is via the phrenic nerves (C3-5)
    - Significant because it means that quadriplegics can still breathe
  - Excursion (expanding movement) – 1cm – 10cm (quiet – forced breathing)
    - Abdominal contents move down and forwards – nowhere else to go
    - Length of chest cavity increases – diaphragm descends increasing chest cavity volume and thus reducing pressure
    - Transverse diameter increases – lower ribs move outwards because abdominal contents push outwards



- External intercostal muscles
  - Connect adjacent ribs externally
  - Slope down and forwards
  - On contraction:
    - Ribs thus move up and forwards like a bucket handle
    - Increases the anterior posterior and lateral diameters of the chest cavity
  - Neural supply via the corresponding intercostal nerves
    - Paralysis does not seriously impair breathing



- Accessory muscles of inspiration
  - Contract in exercise, not used in quiet breathing
    - Scalene muscles – elevate ribs 1 and 2
    - Sternomastoids – raise the sternum
      - If used at rest, person is having trouble breathing
  - Others:
    - Alae nasi (flaring of nostrils) – reduces airflow resistance
    - Small muscles in the head and neck

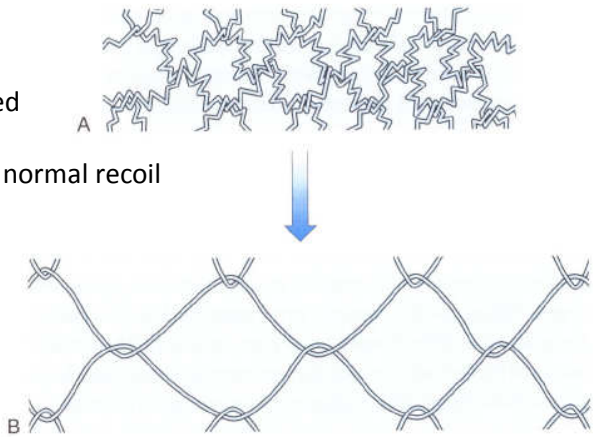
Muscles of respiration: expiration

- Expiration is passive in quiet breathing
  - Merely involves relaxation of the muscles of inspiration
    - The lung/chest wall are elastic and return to their original position
  - Can be active in exercise and voluntary hyperventilation
- Abdominal wall muscles – most important
  - Rectus abdominus, external and internal oblique and transversus abdominus
  - Contraction increases intra-abdominal pressure which then pushes the diaphragm up and increases the intra-thoracic pressure and forces air out
    - Involved in coughing, vomiting, defecation, labour
    - Explains why when we have a cough, we can have sore abdominal muscles

- Internal intercostals
    - Opposite to external intercostals, slope down and backwards and thus pull ribs down and inwards
    - Also stiffen the intercostal spaces to prevent bulging
- Neck and back muscles can also play a role

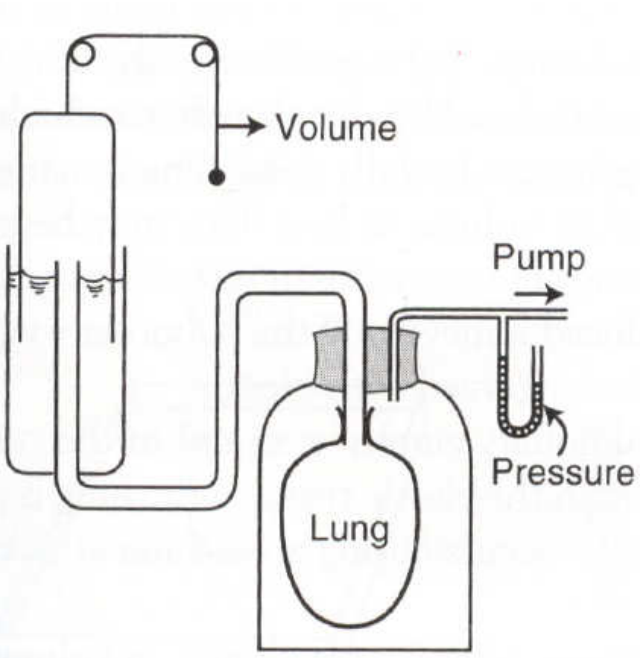
<u>Elasticity of the lung</u>

- Lung elasticity is the tendency for the lungs to return to their resting volume after distension (expanding)
    - Due to the arrangement of the tissue fibres elastin and collagen
        - Elastin allows stretchability and collagen prevents overexpansion
    - Arrannged in a criss-cross matrix (like a nylon stocking)
- In disease:
    - Emphysema – elastin degraded
        - Thus, not much recoil and chests become over inflated
    - Pulmonary fibrosis – over growth of the elastic fibres
        - Makes it harder to inflate the lungs although there is normal recoil

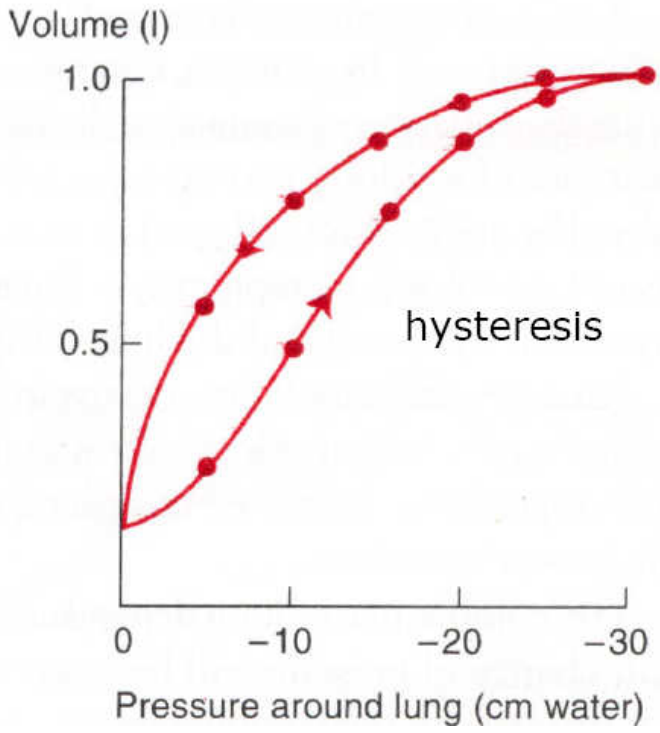


<u>Pressure in the lung</u>

- When lung pressure/volume is measured, a curve can be produced
    - As pressure decreases, the lung volume increases
    - Measured using a spirometer
- Observations:
    - Total volume = 1L
    - Volume doesn't start at zero because of residual volume
    - Inflation and deflation are different, the difference is known as hysteresis
        - (Gk. To lag behind)
        - Different is because inflating the lung takes more pressure to open airways while deflating just needs to keep airways open
- An alternate way to produce the curve is to inflate the lung with positive pressure (rather than reducing the pressure around the lung)
    - Ie, the x-axis would be airway pressure (and be +ve), rather than pressure around lung
    - This is because, the transpulmonary pressure is still equivalent whether you fill the lung with air or take air out of the container around the lung
        - Transpulmonary pressure is the difference in pressure between inside and outside the lung



Taken from JB West, Respiratory Physiology, The Essentials, 6th Edition, Lippincott Williams & Wilkins, 2000. Fig. 7-3.

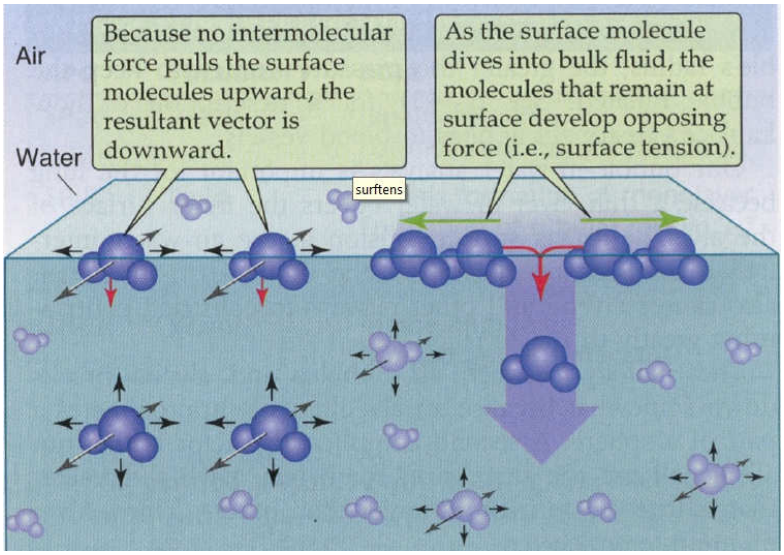


Compliance

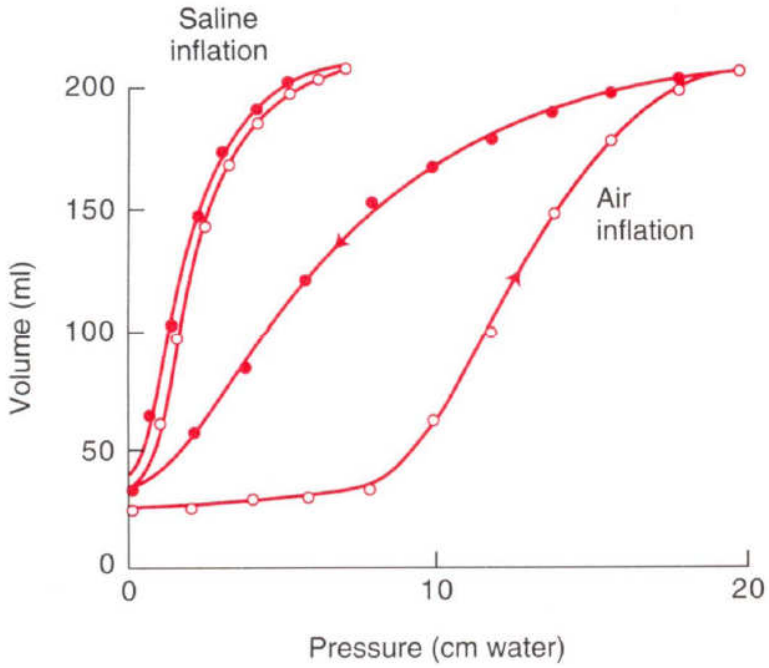
- Compliance = Δvolume/Δpressure
    - Ie, the gradient of the pressure/volume curve
- Measures how easy it is for the lung/chest wall to expand
    - Human lung is very compliant at normal pressures
        - Ie: -5 to -10cm water, with volumes 200ml/cm water
        - Less compliant at high pressures
    - Specific compliance is the compliance pre unit volume of lung
        - Ie: compliance/maximal lung volume
        - Used to allow for different lung sizes (eg. animals)
- Disease:
    - Reduction in compliance
        - Pulmonary fibrosis
        - Interstitial fluid
        - Local collapse of alveoli
        - High surface tension
    - Increase in compliance
        - Aging
        - Emphysema – lungs don't deflate again
            - Due to a loss of elastic tissue

Surface tension

- A measure of the force acing to hold a liquid surface together at an air-liquid interface
    - In the lungs, this air-liquid interface occurs in the alveoli
        - Ie, at the thin layer of fluid that lines the alveoli
    - To stretch the interface, work needs to be done
        - Thus, in the lungs, surface tension adds to elastic recoil (about half)

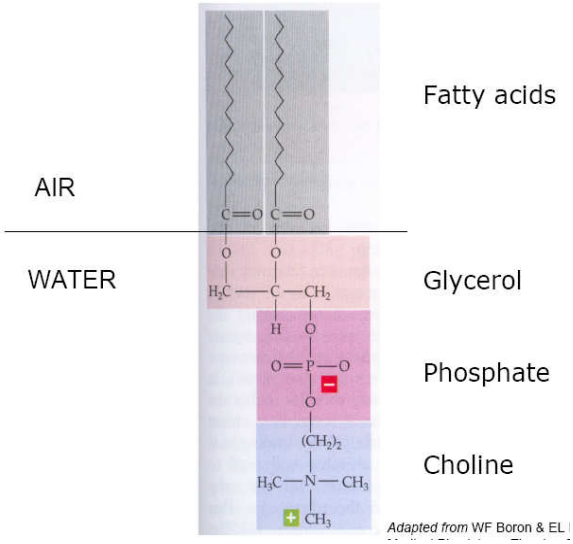


- To demonstrate importance of surface tension:
    - In an experiment using saline inflation, hysteresis is lost and there is no difference in inflation and deflation
        - This is because the lung is much more compliant without an air-water interface

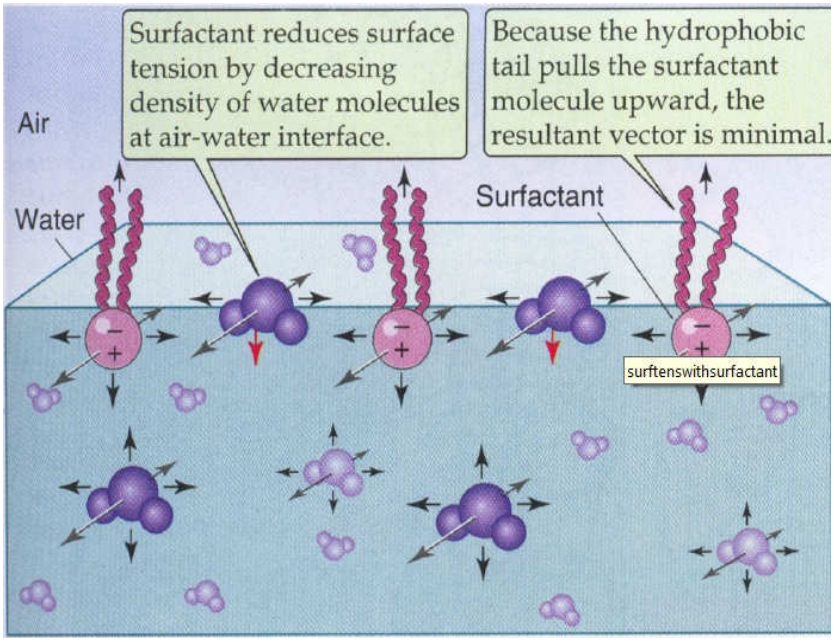


Surfactant

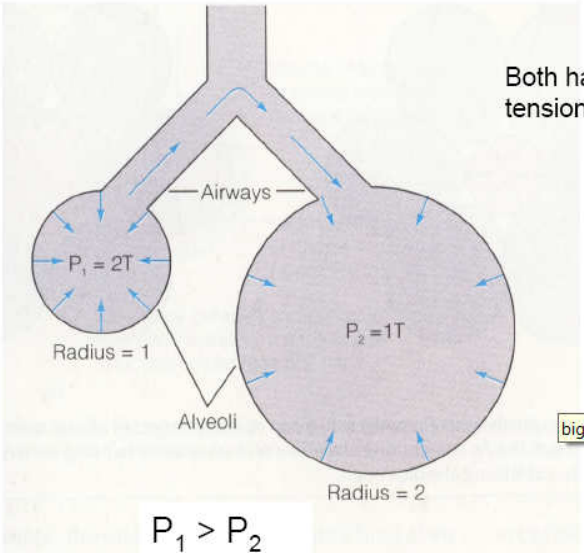
- A detergent-like mixture of lipids and proteins that lowers surface tension
  - In the lungs, mostly made up of – DPPC (dipalmitoylphosphotidylcholine)
    - Structure: fatty acid hydrophobic end and a protein hydrophilic end
- DPPC:
  - Secreted by alveolar type II cells (pneumocytes type 2) – contain organelles that make surfactant
  - Has a rapid turnover, and becomes depleted in areas that have no blood flow
    - Adaptive: no blood in lung, don't want air in there anyway
  - Can be deficient in premature babies causing respiratory distress syndrome
    - Mother can be treated with β-methasone before birth to stimulate surfactant production and newborn can be given surfactant doses directly into lungs
  - Mechanism of action
    - Molecules align on the surface of the water, the hydrophobic ends in the air
      - These cause repulsive forces that interfere with the hydrogen bonding in the water and thus reduce the surface tension
    - In smaller alveoli, surfactant molecules are crowded together and thus repel each other more, having a greater effect
- Advantages
  - Lower surface tension thus increasing compliance and reducing the work required to expand the lung
  - Stabilises the alveoli keeping them at the same pressure (small or large)
  - Keeps alveoli dry – with increased surface tension, the fluid flows out of the capillaries
- Without surfactant:
  - Stiff lungs
  - Atelectasis – collapse of areas
  - Transudate in the alveoli



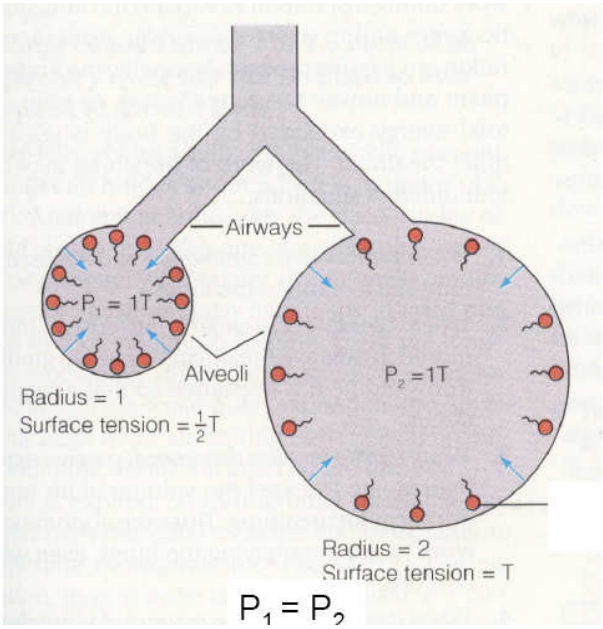
Adapted from WF Boron & EL



- Surfactant stabilising alveoli
  - Law of LaPlace: pressure = 2xsurface tension/radius P=2ST/R
  - Surfactant reduces the surface tension in smaller alveoli such that the pressure is the same and size will often be equilibrated

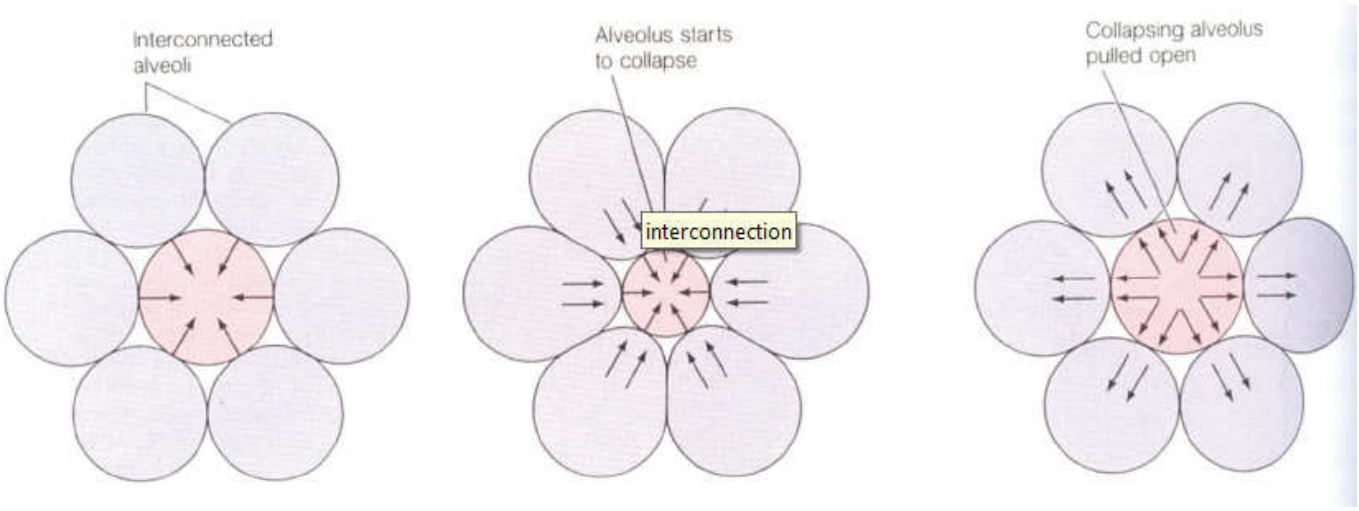


Taken from L Sherwood, Human Physiology From Cells to Systems, 2nd edition, West Publishing, 1993. Fig. 13-17 (b).



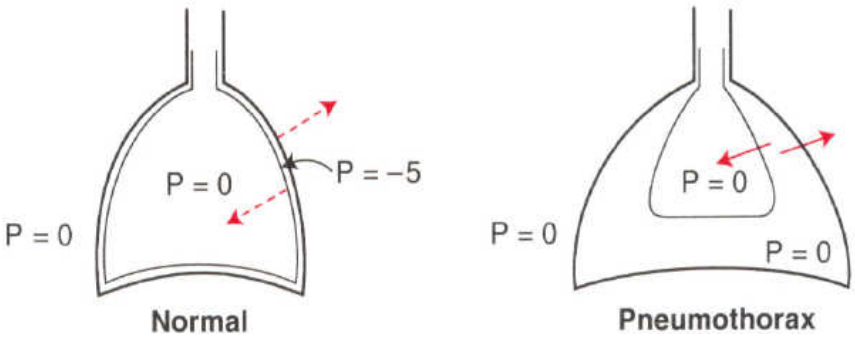
Taken from L Sherwood, Human Physiology From Cells to Systems, 2nd edition, West Publishing, 1993. Fig. 13-17 (a).

- Interdependence
  - Alveoli can stabilise each other
    - Surrounding alveoli can keep interconnected ones open



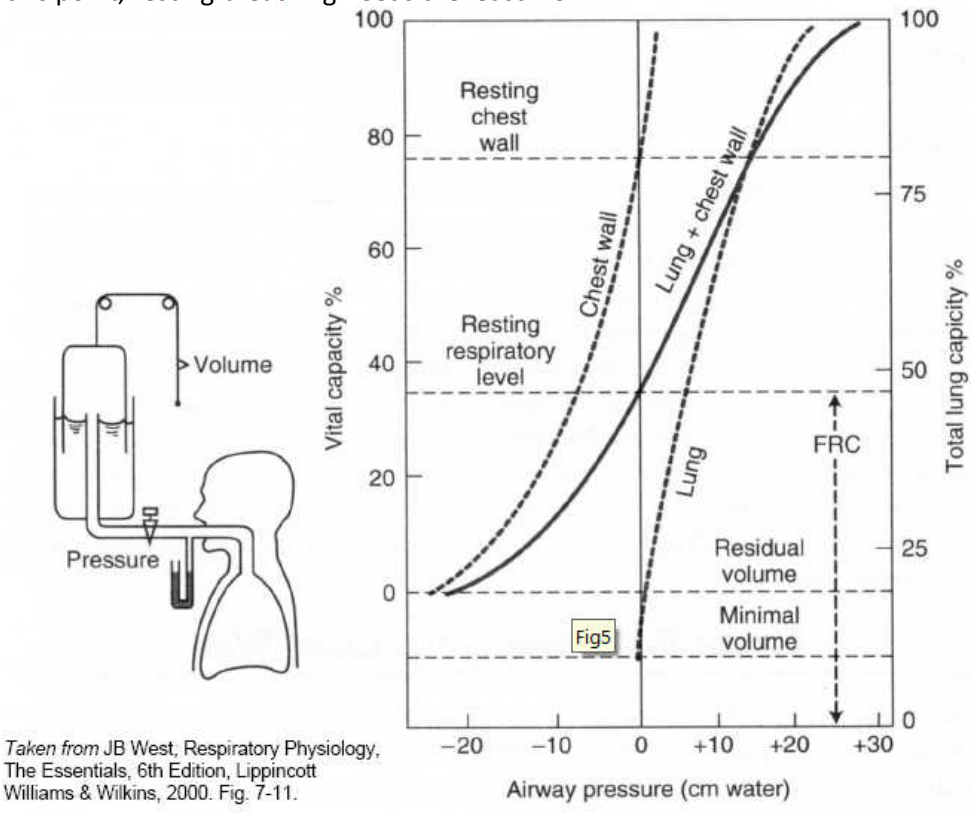
<u>Chest wall elasticity</u>

- At equilibrium:
  - Chest wall pulls outwards
  - Lungs pull inwards
    - Thus there is a negative (sub-atmospheric) pressure in the pleural space
- If air is introduced to the pleural space (pneumothorax) the lung collapses and the chest wall spreads out
  - Ie, the atmospheric pressure becomes zero and the chest cavity is no longer held in and the lungs can't expand and thus collapse



Relaxation pressure-volume curve

- Lung-pressure volume can be measured using a spirometer and varying pressure around the lung (see earlier)
    - Lung and chest wall pressure-volume (pleural space) can be measured using a balloon in the oesophagus
        - Oesophagus pressure is the same as that in the pleural cavity due to its location
    - Thus chest wall pressure can be calculated by subtraction
- Trends to notice
    - At 75% vital capacity, chest wall pressure stops increasing and reverses direction to decrease again
        - Ie, it begins to pull back in
        - General trend: as we breathe in the chest wall expands and pressure decreases causing air to rush in
            - When we reach a certain level of air in the lungs, the volume of air is enough that it makes the pressure equal to that outside
            - If the lungs continue to fill, it becomes harder because pressure gradient is in the wrong direction
    - FRC – functional residual capacity – ie when there is zero airway pressure based on chest and lung pressure
    - At zero airway pressure, very steep gradient means compliance is at its highest
        - Ie at this point, resting breathing needs the least work



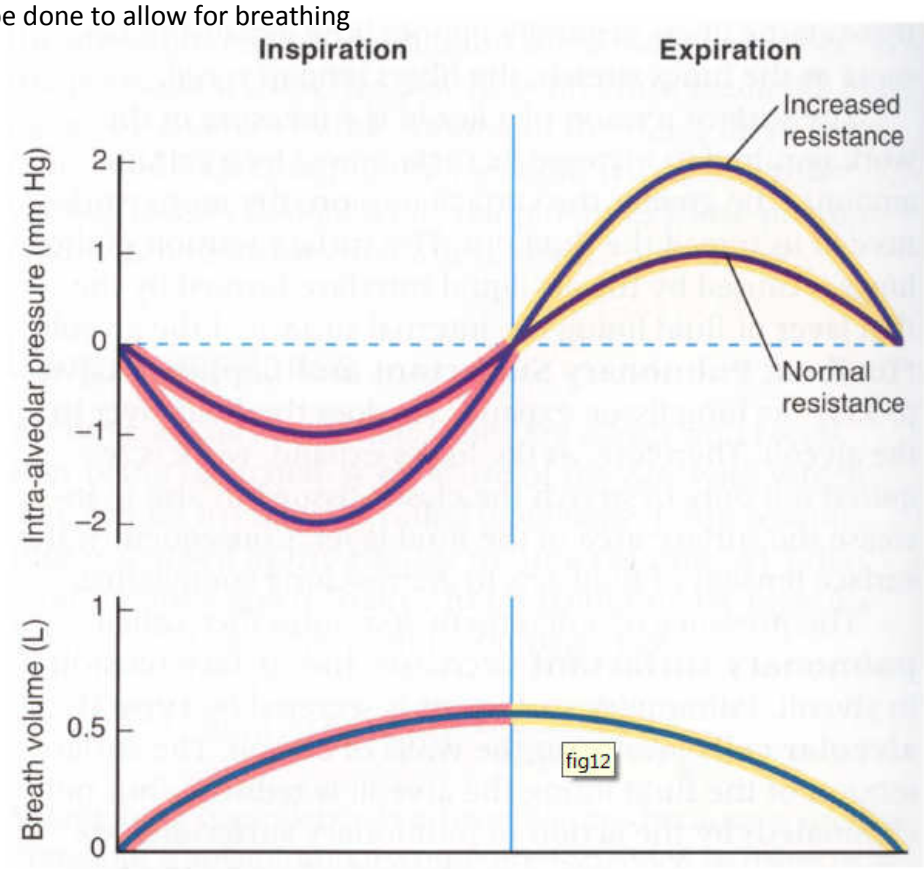
Taken from JB West, Respiratory Physiology, The Essentials, 6th Edition, Lippincott Williams & Wilkins, 2000. Fig. 7-11.

Total compliance

- Lungs are inside the thorax and behave like components in parallel
    - 1/Total compliance = 1/lung compliance + 1/chest wall compliance
    - $1/C_T = 1/C_L + 1/C_{CW}$
- Typical values in normal healthy human adults:
    - C_T = 0.1 L/cm water
    - C_L = 0.2 L/cm water
    - C_{CW} = 0.2 L/cm water

Airway resistance

- Increases with decreasing airway radius
- Laminar flow:
  - R = $\frac{8\eta l}{\pi r^4}$
  - R = resistance, η = viscosity of the gas, l = length of the tube, r = tube radius
  - 4^{th} power is important because it means that a small change in radius causes a large resistance change
- At rest, resistance is low but it increases with exercise
  - Important in asthma: airway decreases due to inflammation + muscle constriction
- Factors of airway resistance
  - Lung volume
  - Bronchoconstriction – asthma
  - Secretions/inflammation – parasympathetic nervous system, histamine, irritants
  - Density of gas
    - In scuba diving, Helium is mixed with oxygen because it has a low density thus reducing airway resistance
    - pCO_2, if low, not much blood is travelling to area therefore constriction – adaptive
  - Dynamic compression – forcible compression
- An increase in airways resistance means that a greater pressure gradient is needed to produce airflow
  - Thus, more work needs to be done to allow for breathing



Tissue resistance

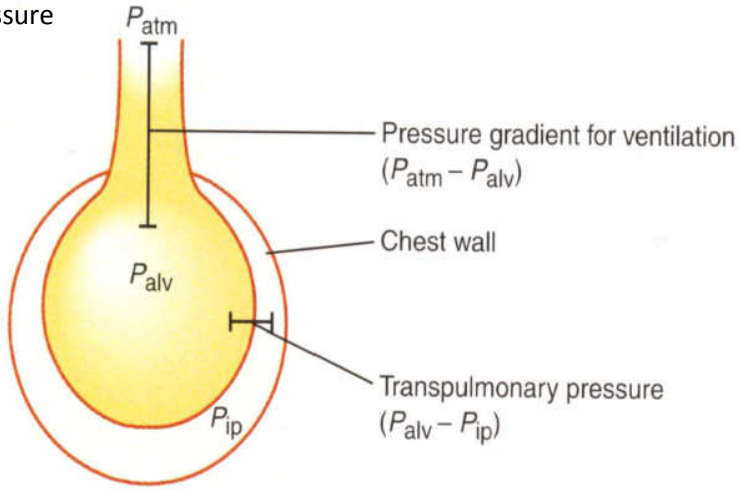
- The resistance that is due to tissues sliding past one anotherduring lung expansion and contraction
  - Makes up 20% of total resistance in young/healthy subjects

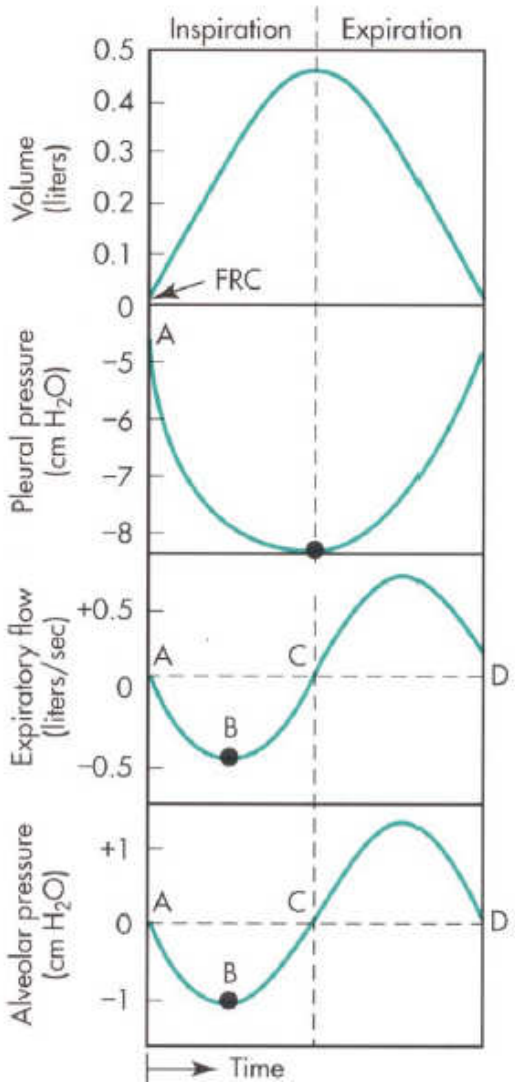
Pressures and flow – the breathing cycle

- If P_{alv} is less than P_{atm}, air flows in
  - If transpulmonary pressure is high, the lungs expand
- Intrapleural pressure
  - Defined as the pressure in the space between the lungs and chest wall (pleural cavity)
  - Measured with an oesophageal balloon
    - Always negative
    - Lungs pull inwards and chest wall pulls outwards
  - On inspiration, the thoracic cavity expands and thus the intrapleural pressure becomes more negative (volume increases)
  - Quiet breathing: varies from -5 to -8cm water

Breathing sequence of events

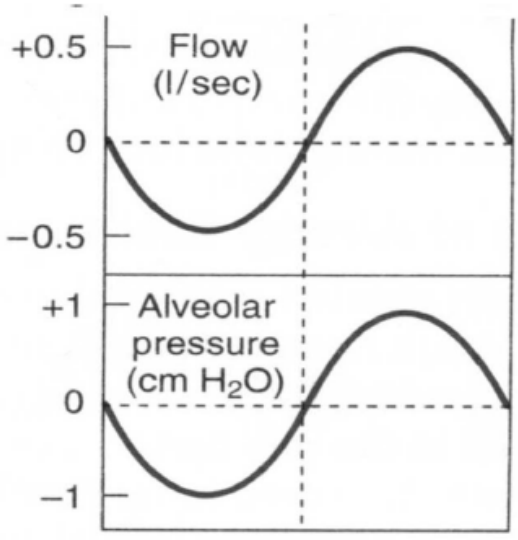
- Inspiratory muscles contract
- Thoracic cavity expands
- Pleural pressure becomes more negative
- Transpulmonary pressure increases
- Lungs inflate
- Alveolar pressure becomes sub-atmospheric
- Air flows into the lungs until alveolar pressure equals atmospheric pressure





Alveolar pressure

- Determined by:
  - The quantity of air molecules in the alveoli (moles)
  - The volume of the alveoli
- Varies with inspiration above and below atmospheric pressure
  - Inspiration – negative
  - Expiration – positive
    - These changes allow air to flow into and out of the lungs
  - At rest – varies from -1 to +1 cm water
- Process:
  - Inspiration, lungs expand and alveolar pressure falls
  - Air flows into lungs and number of molecules in alveoli rises
  - Pressure thus becomes less negative
- At zero pressure, there is no flow
  - Airflow matches the pressure trace



Respiratory symbols/abbreviations

- C – concentration of content of gas in a liquid
- F – fractional concentration of dry gas
- P – Pressure or partial pressure of a gas
- Q – volume of blood
- $\dot{Q}$ dot – volume of blood per unit time
- R – respiratory exchange ratio
- S – saturation
- V – volume of gas
- V dot – volume of gas per unit time

Modifier symbols

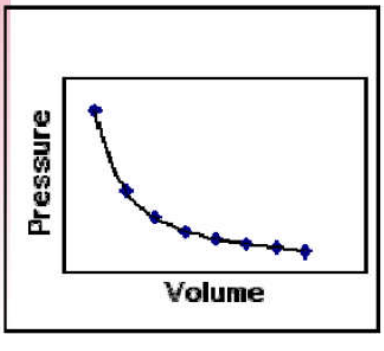
- Gas phase:
  - A – Alveolar
  - B – Barometric
  - D – Dead space
  - E – Expired
  - I – inspired
  - L – Lung
  - T – Tidal
- Blood phase
  - a – arterial
  - c – capillary
  - c' – end capillary
  - v – venous
  - v line – mixed venous
- Eg:
  - FE_{N2} – fraction of nitrogen in expired air
  - Pa_{O2} – partial pressure of O_2 in arterial blood

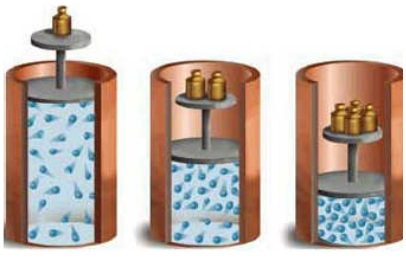
What is a gas?

- The kinetic theory of gases:
  - A gas is matter in a free molecular form (at everyday pressure and temperature)
  - Lacks shape, occupies available space
- Molecules are in continuous random motion
  - Collide with other molecules and their container walls
    - These collisions result in pressure
      - The magnitude of the pressure is dependent upon the number of molecules, their mass and speed

Gas laws:

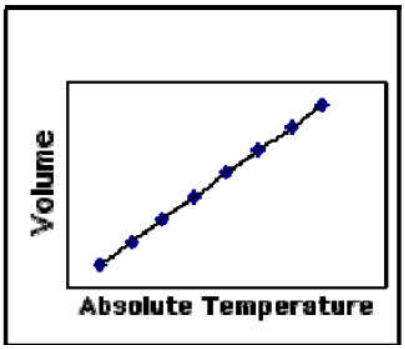
- These rules apply to the "ideal gas"
  - In body conditions, gases for the most part obey these laws
    - Exception – water vapour, often have to remove from calculations
- Gases don't follow laws at high pressures/low temperatures
  - Dispersion (Van der Waal's) forces are significant
  - Space occupied by gas becomes significant
- Boyle's law
  - For a constant temperature, pressure (P) is inversely proportional to volume (V)
  - $P \propto 1/V$
  - $P_1V_1 = P_2V_2$

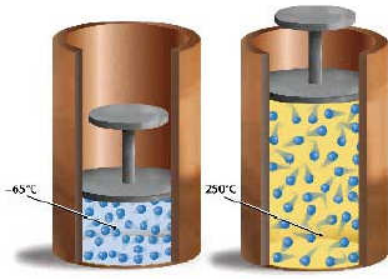




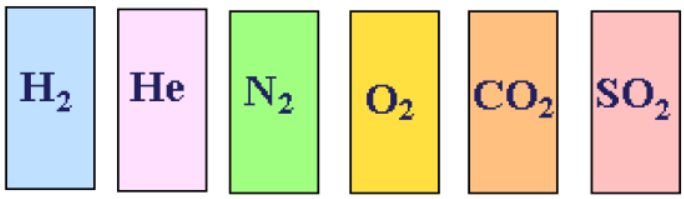
http://www.phschool.com/atschool/science_activity_library/images/solids_liquids_gases_boyle.jpg

- Charles's Law
  - For a constant pressure and a set amount of gas, volume (V) is proportional to the absolute temperature (T)
  - $V \alpha T$
  - $V_1/T_1 = V_2/T_2$



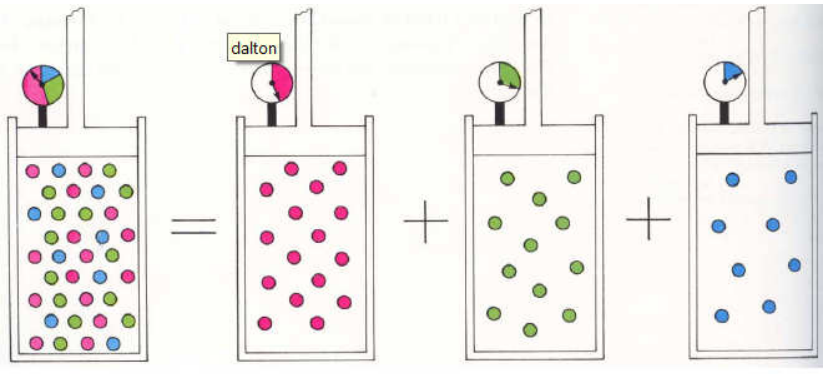


- Avogadro's Law
  - Equal volumes of gas at the same conditions (T and P) contain the same number of molecules
    - 0^oC, 1atm, 22.4L contains 1mol of any gas
    - 1 mole = 6.02×10^{23} particles

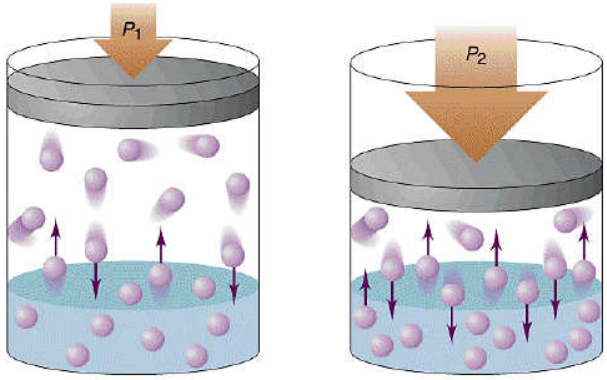


- Universal gas law
  - Combines Boyle's, Charles' and Avogadro's laws
  - $PV = nRT$
    - (P = pressure, V = volume, n = number of moles, R = universal gas constant, T = absolute temperature)
  - $P_1V_1/T_1 = P_2V_2/T_2$
    - This equation can correct gas volumes for different conditions
- Conditions:
  - STPD (standard temperature and pressure, dry)
    - 0^oC (273K), 760mmHg (1atm, 101.3kPa)
  - BTPS (body temperature and pressure, saturated with water vapour)
    - 37^oC (310K), 47mmHg
    - Water vapour saturation depends on temperature
  - ATPS (ambient temperature and pressure, saturated with water vapour)
    - 20^oC (293K), pressure given
  - ATPD (ambient temperature and pressure, dry) – not used very often
- NOTE:
  - Kelvin = $^oC + 273$
  - 1 mmHg = 1.36 cm water
  - 1 kPa = 7.5 mmHg = 10 cm water
  - 1 torr ~ 1mmHg

- Conventions:
  - Gas volumes of chemical significance is expressed as STPD
    - Eg: oxygen consumption, carbon dioxide production
  - Lung volumes normally expressed at BTPS
    - Eg: volumes that occupy the thorax
- Dalton's law of partial pressures
  - When gases exist as a mixture and occupy the same volume, total pressure is the sum of pressures each gas would exert if on its own in the same volume
  - $P_{total} = P_A + P_B + P_C$
    - Thus partial pressure of each gas is equal to the total pressure x the fraction of the gas
    - Ie: if 30% of a mixture is gases is oxygen and the total pressure is 760mmHg, the partial pressure of oxygen is 228mmHg



- Partial pressure (tension) of gas in a solution
    - Partial pressure of gas in a solution is equal to the partial pressure it would have in a gas mixture that is at equilibrium with the solution
        - Ie, liquid and gas partial pressures are the same
        - Eg: if we shake up water with oxygen and nitrogen until equilibrium is reached
            - P_{O2} = 275mmHg and P_{N2} = 440mmHg in the air and water
- Henry's Law
    - The concentration in solution is proportional to the partial pressure of the gas in contact wit the liquid
        - All for given gas, given liquid
    - Ie: the higher the partial pressure, the more gas dissolved
    - C_X = Sol x P_x
        - Sol is the solubility constant
    - Eg: O_2 37°C, solubility 0.03ml (STPD)/L plasma/mmHg
        - P_{O2} is 100mmHg, oxygen dissolved is 3ml/L
        - P_{O2} is 670mmHg, oxygen dissolved is 20.10ml/L



- "Givens"
    - Gases have different solubilities (eg: CO_2 is more soluble in plasma than O_2)
    - Gases have different solubilities in different liquids (eg: O_2 is 4x more soluble in oil than plasma)
    - Solubility changes with conditions
        - Eg: salts in solution lowers solubility of gas, increase in temperature lower solubility of gases generally

<u>Gas diffusion</u>

- Gases diffuse down their tension (partial pressure) gradient
    - This is not necessarily the same as the concentration gradient
    - Eg: oil with PO_2 100mmHg vs water with PO_2 200mg
        - Oxygen diffuses from water to oil until the tension is equal in spite of the fact that there is more oxygen in the oil (O_2 4x more soluble in oil than water)

<u>Composition of air</u>

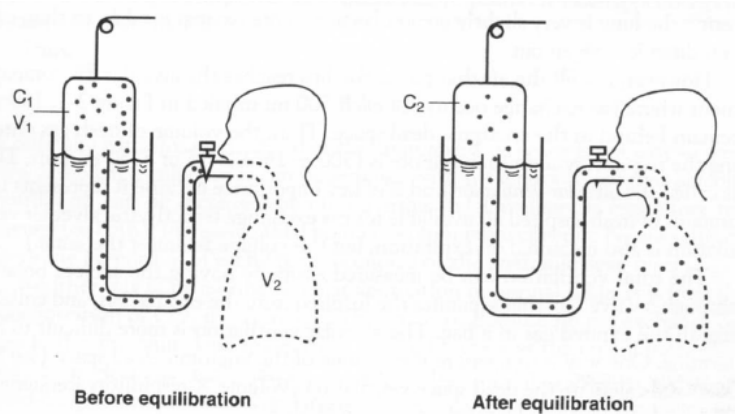
- Dry air
    - 20.93% oxygen
    - 0.03% carbon dioxide
    - 79.04% nitrogen and others (argon, helium etc)
        - Eg: barometric pressure 760mmHg, partial pressures follow fractions
- Inspired air
    - Air entering the lungs becomes fully saturated with water vapour
        - Most added in the nose – leaves the nose 75-80% saturated
    - At body temperature, vapour pressure of water is 47 mmHg
        - Thus, to calculate partial pressure in moist inspired air, take off 47 from barometric then calculate fractions
    - Eg: P_{O2} = 0.2093 x (760-47) = 149mmHg
        - P_{CO2} = 0.2mmHg, P_{N2} = 564mmHg

<u>Alveolar air</u>

- Average:
    - Oxygen – 100mmHg (pO_2 drops because it is taken by the blood)
    - Carbon dioxide – 40mmHg (increased, blood gives up CO_2)
    - Water vapour – 47mmHg
    - Nitrogen – 573mmHg
- Not uniform – variation in the respiratory cycle
- Varies in different alveoli

Measuring residual volume

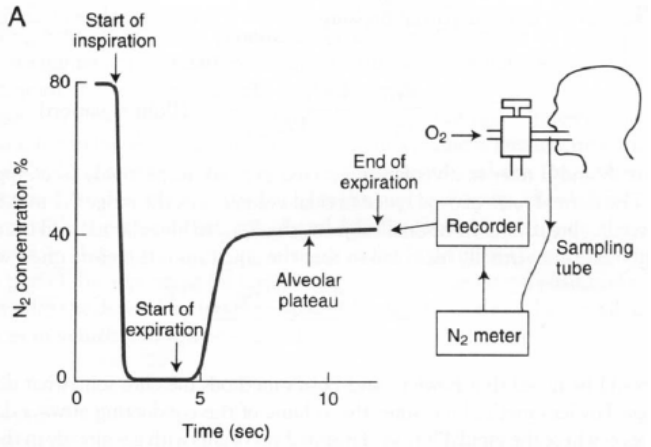
- Can't be measured using spirometry
- Measure using:
    - Body plethysmography
    - Gas dilution (He or N)
- Body plethysmography
    - Sit in sealed box with nose clip and breathe through a tube
    - Two volumes of gas are important: volume of the box (outside the body) and volume in the chest
    - Process
        - Patient breathes normally
        - At the end of maximum expiration (when only residual volume left, a shutter closes the mouthpiece and the subject tries to inhale
        - Failed inhalation causes chest volume to expand and the air in the lungs decompress
            - This increase in chest volume reduces the box volume and thus increases the pressure in the box
        - Use Boyle's law to determine residual volume:
            - First need to find the change in pressure in the box:
                - $P_1V_1 = P_2(V_1-\Delta V)$
                - P1 = box pressure before inspiratory effort
                - P2 = box pressure after inspiratory effort
                - V1 = volume of box before inspiratory effort
                - ΔV = gas volume change in the box
            - Then find residual volume using the ratio between the chest (mouth) pressure
                - $P_3V_2 = P_4(V_2 + \Delta V)$
                - P3 = mouth pressure before inspiratory effort
                - P4 = mouth pressure after inspiratory effort
                - V2 = residual volume
- Gas dilution (He or N)
    - Helium:
        - $C_1V_1 = C_2(V_1 + RV)$
        - Rearrange to find RV
    - Nitrogen
        - Bag filled with a known volume of pure oxygen (V_B)
        - After maximum expiration, subject takes 5 breaths into and out of the bag
        - Gas sample is taken from bag and measured for nitrogen



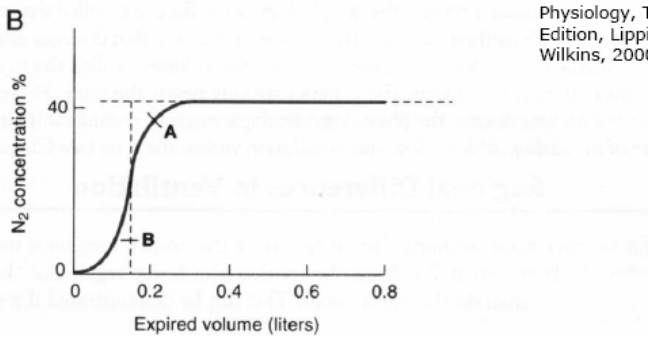
        - The only nitrogen in the bag should be that which was in the residual volume in the lungs
        - Thus, $RV \times F_{RN2} = F_{BN2} \times (RV + V_B)$
            - Rearrange for RV
            - $F_{RN2} = F_{AN2}$ which can be measured
            - F_{BN2} can be measured by sampling the bag
- Note – these methods can also measure FRC (functional residual capacity) and TLC (total lung capacity) depending on when the method is started
    - FRC – at the end of normal expiration
    - TLC – at the end of maximal inspiration

Measuring dead space

- Conducting airways play no part in gas exchange – the anatomic dead space
  - Volume is normally ~150ml
  - Can be measured using Fowler's method
- Fowler's method
  - Subject takes a breath of 100% oxygen and exhales through a one-way valve with a N_2 meter
    - Initially, value of N_2 is zero because subject is exhaling from the dead space
    - As the alveolar air mixes with the dead space air, the curve climbs and plateaus (alveolar air)
    - Thus, we plot N_2 concentration against expired air volume
      - The dead space is determined by drawing a vertical line where the area below the curve on the left is equal to the area above the curve on the right
      - Ie, the vertical line marks where the anatomical dead space volume finishes
        - (assumes that the mixture of N_2 to O_2 will be roughly half-half)



Taken from Physiology, Edition, Lippi Wilkins, 200



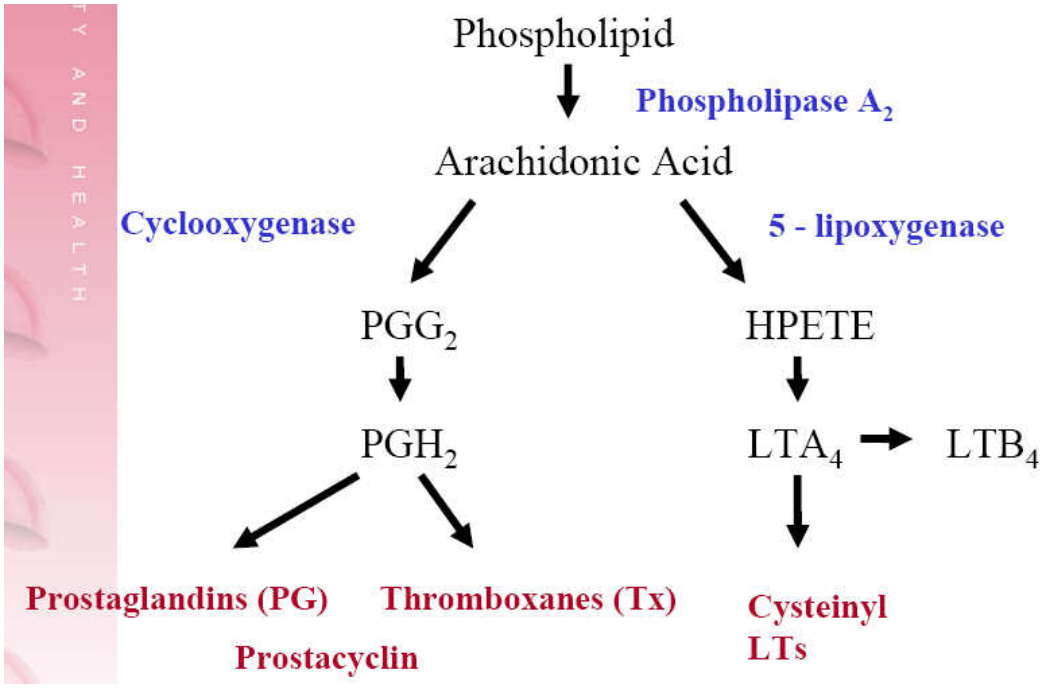
- Bohr's method
  - Based on the fact that expired CO_2 comes from the alveolar gas and not from the dead space (minimal amounts in atmosphere)
- Thus:
  - $V_T \times FE_{CO2} = V_A \times FA_{CO2}$
  - $V_T = V_A + V_D$
  - Substitute:
    - $V_T \times FE_{CO2} = (V_T - V_D) \times FA_{CO2}$
  - Rearranging
    - $V_D/V_T = (FA_{CO2} - FE_{CO2})/FA_{CO2}$
    - Or: $V_D/V_T = (PA_{CO2} - PE_{CO2})/PA_{CO2}$
  - In normal subjects, this ratio is 0.2-0.35 at rest
- Bohr's method measures the volume of the lung that does not eliminate CO_2
  - This is the physiological dead space
    - Ie: the total volume not participating in gas exchange + non-functional/poorly functioning alveoli (maybe due to impaired blood flow)
  - Normal people: physiological dead space is similar to anatomical dead space
    - Lung disease – physiological dead space may be much larger due to ventilation-perfusion mismatching

Introduction

- Inappropriate inflammation can cause disease
    - Via various mediators, eg: interleukins, peptides, cytokines etc
    - Examples of diseases: asthma, rheumatoid arthritis

Eicosanoid biosynthesis

- Eicosanoids are signalling molecules formed from phospholipids
    - Important in inflammation



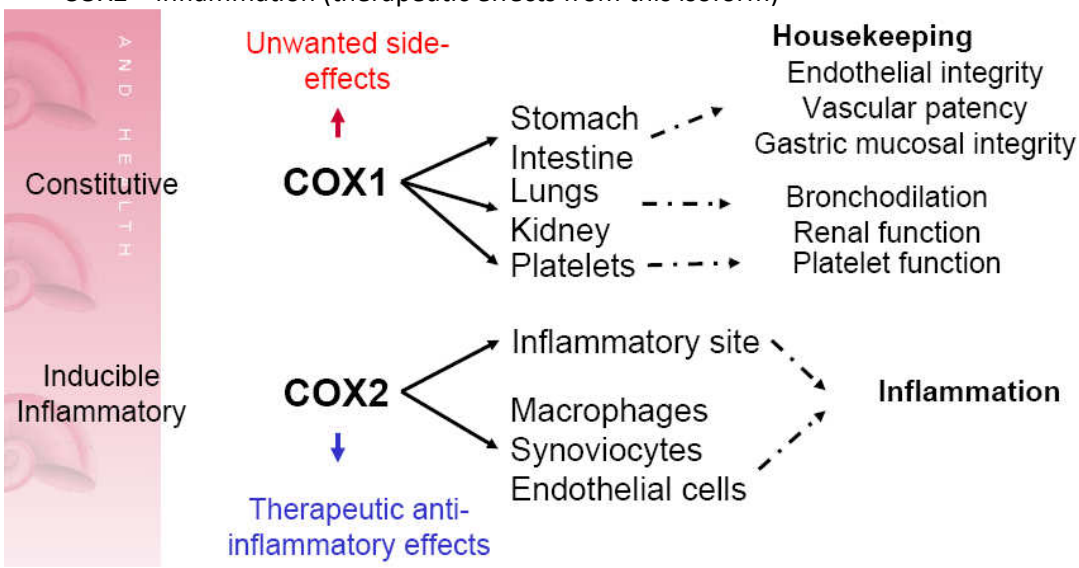
- Eicosanoids are divided into two groups:
    - Prostanoids formed by cyclooxygenase
        - Classical prostaglandins (PGD_2, PGE_2, PGF_2)
            - Increase vasodilation and vascular permeability
            - Sensitise nociceptive fibres to stimulation by other inflammatory mediators
        - Thromboxane A_2 (TXA_2)
            - Platelet aggregation and vasoconstriction
        - Prostacyclin (PGI_2)
            - Inhibition of platelet aggregation and vasodilation
    - Leukotrienes formed by 5-lipoxygenase
        - Eg: LTB_4, LTC_4
            - Increase vascular permeability
            - Promote leukocyte chemotaxis
            - Cause contraction of bronchial smooth muscle

Anti-inflammatory therapeutic strategies

- NSAIDS (non-steroidal anti-inflammatory drugs)
- Paracetamol
- Glucocorticoids
- DMARDs (disease modifying anti-rhematic drugs)
- Anti-cytokine therapy
- Anti-histamines

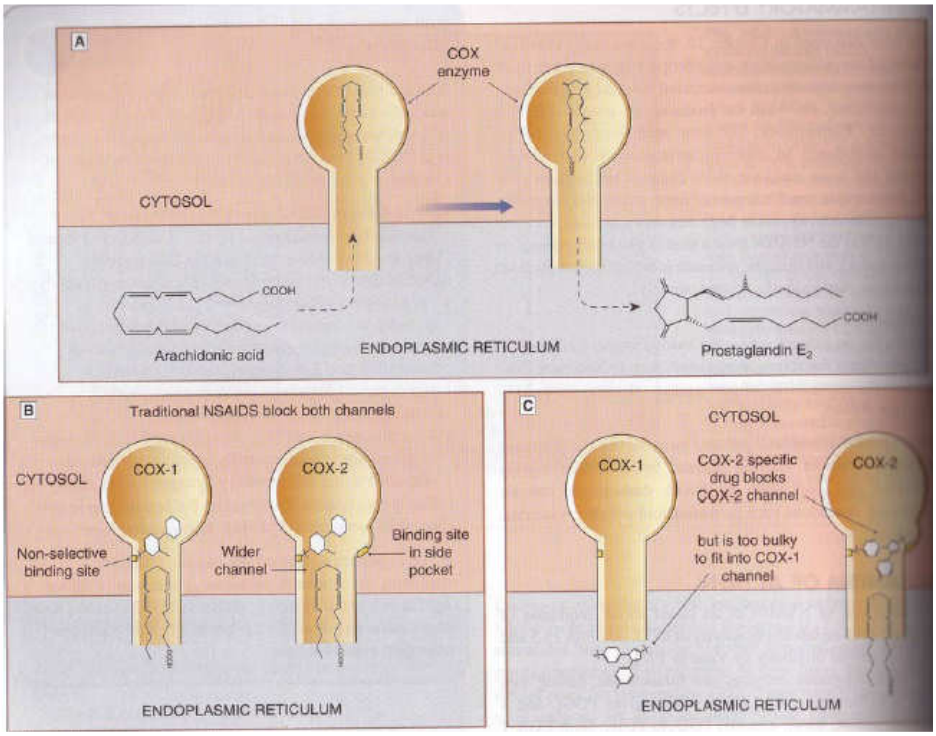
NSAIDs

- Three effects:
  - Modification of the inflammatory reaction
  - Analgesia – reducing pain
  - Antipyretic – lowering a raised temperature
- Examples:
  - Salicylic acids – aspirin
  - Propionic acids – ibuprofen
- Mechanism of action
  - Modulate cyclooxygenase
    - COX1 – housekeeping (unwanted side effects from this isoform)
    - COX2 – inflammation (therapeutic effects from this isoform)

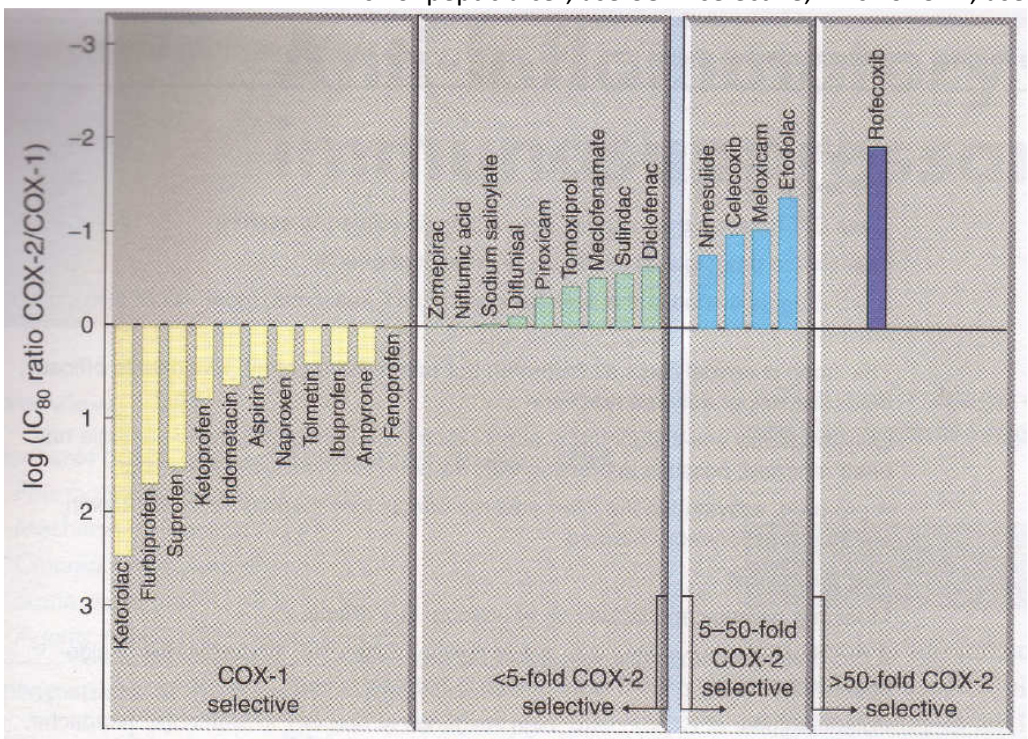


- Modulation of COX
  - Irreversible inhibition – Aspirin (acetylation of COX, inactivating it)
  - Competitive inhibition – most NSAIDs
  - Reversible non-competitive inhibition – paracetamol (thought to trap free radicals and thus interfere with hydrooxygenases)
- Anti-inflammatory action
  - Prostaglandins increase vasodilation, vascular permeability and thus oedema
    - Inhibition of prostaglandin synthesis reduces this
- Anti-pyretic action
  - In response to IL-1, E type prostaglandins are produced
    - PGEs elevate the hypothalamic set point to cause fever
      - NSAIDs inhibit prostaglandin synthesis
  - Note: NSAIDs only affect temperature in fever, not in normal circumstances or heatstroke
- Analgesic
  - Prostaglandins sensitise nociceptors so that they are receptive to bradykinin and histamine
    - NSAIDs inhibit prostaglandin synthesis
      - NSAIDs are particularly effective against pain that has an inflammatory component because they also reduce inflammation
- Side effects
  - GI
    - Dyspepsia (upset stomach), nausea, vomiting – protective actions of prostaglandins on the gastric mucosa are inactivated
    - Ulcer formation and haemorrhage risk – PGE_2 and PGI_2 inhibit gastric acid secretion, increase mucosal blood flow (restorative), + have a cytoprotective action
  - Renal
    - Renal damage/failure – PGE_2 and PGI_2 mediate vasodilation in the renal medulla and glomeruli
  - Other
    - Bronchospasm, skin rashes, other allergic reactions – hypersensitivity reaction/allergy to drug
      - Bronchospasm – COX pathway blocked, arachidonic acid shunted to the other pathway that causes bronchoconstriction

- Reducing side effects
    - Need a selective COX2 inhibitor
        - COX2 has a larger channel, thus selectively inhibit with a larger NSAID



        - There are different degrees of selectiveness
            - Rofecoxib – Vioxx is highly COX2 selective
                - COX1, however, inhibition stops platelet aggregation and is therefore protective against heart disease
                - Thus, don't want drug to be too selective
                    - If risk of peptic ulcer, use COX2 selective, if risk of CVD, use non-selective



<u>Aspirin – acetylsalicylic acid</u>

- Non-selective inhibitor of both isoforms
- Irreversibly inhibits COX and inhibits platelet aggregation (for about 8 days, CVD protective)
    - Used to manage mild to moderate pain
    - Used as a protection against CVD for its anti-platelet properties
- Side effects
    - GIT bleeding
    - Contraindicated in children under 16, may cause liver damage and encephalopathy

Ibuprofen and other non-selective NSAIDs

- Reversible COX inhibitors
- Treatment for mild to moderate pain
    - Used for initial rheumatoid arthritis treatment, doesn't stop joint damage however, so other drugs needed
- Side effects
    - GIT: nausea, vomiting, diarrhoea, bronchospasm

COX-2 selective inhibitors – coxibs

- Similar analgesic, antipyretic and antiinflammatory actions as non-selective NSAIDs
    - Fewer GIT side effects
    - No cardioprotective effects, thus associated with higher incidence of cardiovascular thrombotic events
- Egs: celcoxib, meloxicam, rofecoxib

Paracetamol –acetaminophen

- Analgesic, antipyretic, no anti-inflammatory effects
    - Not really considered an NSAID
- Reversible non-competitive inhibitor
- Preferential for COX-2
- Side effects
    - Overdose can result in hepatotoxicity – paracetamol poisoning → death
    - 3x or more than therapeutic dose can result in overdose

Topical Ophthalmic NSAIDs

- Used to treat:
    - Corneal abrasions (corneal surface pain)
    - Decrease postoperative ocular inflammation
    - Decrease allergic inflammation
    - Photophobia
- Eg: diclofenac, ketorolac

Glucocorticoids

- Steroidal anti-inflammatory drugs
    - An anti-inflammatory and immunosuppressant
- Used to treat:
    - Rheumatoid arthritis, inflammatory bowel condition, bronchial asthma, inflammatory skin conditions
- Mechanism of anti-inflammatory actions
    - Induce the production of Lipocortin
        - Lipocort inhibits the formation of arachidonic acid by inhibiting phospholipase A2
        - Also inhibits the formation of prostaglandins and leukotrienes
- Mechanism of immunosuppressant effects
    - Inhibits the accumulation of neutrophils and monocytes
    - Decreased antigen processing by macrophages
    - Decreased T-helper cell function
    - Decreased phagocytosis
    - Decreased antibody production
    - Decreased IL-2 production
- Glucocorticoids are corticosteroids
    - Other corticosteroids
        - Hydrocortisone (cortisol), cortisone, prednisone
        - Betamethasone (stimulates surfactant production in neonates), dexamethasone
- Side effects – especially if taken for long periods and in high doses
    - Suppression of the immune system
    - Altered bone metabolism → osteoporosis
    - Decreased wound healing
    - Development of diabetes and peptic ulcers
    - Growth suppression in children
    - Cushing's syndrome

DMARDs – Disease modifying anti-rheumatic drugs

- Inhibit joint damage
- Can lose efficacy and thus patients are rotated through the drugs

Disease-modifying anti-rheumatic drugs (DMARDs)	
Class	**Example**
Gold salts	Sodium aurothiomalate, auranofin
Penicillamine	Penicillamine
Antimalarials	Chloroquine, hydroxyquinine
Sulfasalazine	Sulfasalazine
Immunosuppressants	Cytotoxic drugs: methotrexate, azathioprine, ciclosporin

Anti-cytokine therapy/biological therapy

- Anti-cytokine agents are biological preparations that target the action of TNF-α
    - Eg: infliximab (an antibody that mops up excess receptors), etanercept
- Monoclonal antibodies selective against the chain of the IL-2 receptor
    - Eg: basiliximab, daclizumab
        - Note: ab meaning antibody

Anti-histamines

- H_1 receptor antagonists
- Clinical uses:
    - Allergic reactions:
        - Allergic rhinitis (hay fever)
        - Insect bites
        - Drug hypersensitivities
    - Antiemetics for motion sickness
    - Sedation
- Side effects: GIT disturbance
- Egs: Mequitazine, fexofenadine, cetirizine

History of HIV

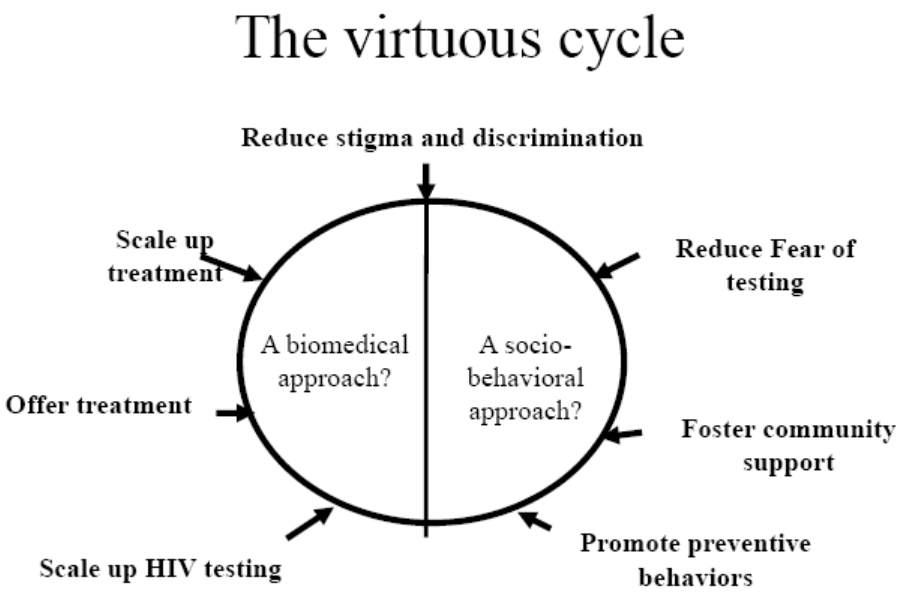
- 1980s, in the USA, young gay man with a rare form of pneumonia
  - Another with Kaposi's Sarcoma – used to be found in Jewish/Mediterranean population
  - Immune deficiency was blamed
- 1981 – first diagnosed case
  - Labelled as the 'gay cancer', the 'gay plague', 'gay pneumonia'
  - GRID – gay-related immune deficiency
  - HHHH – homosexual, heroin, haemophilia, Haitian
  - AIDS
- 1983 – virus isolated, HIV
- 1984 – diagnostic test
  - Commercial conflicts of interest
- 1980s
  - Approach to control of this communicable disease
    - Look at:
      - Host, agent, clinical/biomedical manifestations
      - Diagnostic test
      - Prevention – ST, blood transfusion, factor VIII (haemophilia)
      - Care and treatment: AZT etc

A global issue

- Defining the issue (how we define a problem determines the solution brought against it):
  - Need to consider:
    - Threat to public health, social well-being, economy, national security
    - Moral imperative
  - There was a lot of reluctance to make it a global issue
- To make HIV a global issue:
  - Need a clear concept formed by evidence
    - HIV causes AIDS
    - HIV is transmitted by sexual contacts, blood, injection equipment and from mother to child
  - Need concise objectives
    - Reduce transmission
    - Reduce impact on individual communities
    - Provide a supportive environment
  - Need political commitment
    - Governments: individually and through global forums, eg: UN, WHO
      - At UN general assembly 2000, the goal no. 6 was HIV/AIDS, malaria and other diseases
    - Sectors of government: health/social/police/finance/military/justice departments
    - Civil sector – people with HIV, people at risk, NGOs
    - Private sector – health industry, business
    - Media – education/awareness
  - Need dedicated resources
    - Technical – prevention, care, treatment methods (eg: condoms)
    - Human – trained personnel, deployed and supported
    - Financial – more money and better used
      - Sources: governments, private sources, philanthropy, world bank
  - Need to get the job done!
    - Need to reduce risk, vulnerability and impact
      - Vulnerability – individual, society, programme-related (design of responses to HIV)
      - Risk – human rights, ie increase equity, justice, security
    - Human rights: the legal claims a person has on society simply by being human
      - "what governments can do for you/what governments can't do for you and should for you"
      - Obligations to: respect rights, protect rights, fulfil rights
      - "human rights are universal, indivisible, inalienable and interdependent"
- Health can be optimised by the balance between public health and human rights

Obstacles to HIV response

- Stigma and discrimination
    - Definitions:
        - Stigmatization – a social practice that brands individuals or groups disgraceful and devalues them due to actual or perceived characteristics
        - Discrimination – action against a person based on a group, class or category rather than individual merit
    - Stigmatisation and discrimination can be countered with education, information, community attitude, knowledge, just policies etc



- Insufficient access to care and treatment
- Competing priorities

The way forward

- Good public health practice in terms of HIV testing
- Better workforce
    - Support, incentives etc
    - Involve the community
    - Education/training
    - Restructuring
- Think globally, act locally
    - LEAP
        - Leadership
        - Equity
        - Accountability
        - Partnerships
    - Eg: food crises, climate change

Summary

- A successful global response to HIV requires:
    - Global leadership
    - Political commitment
    - Resources
    - Partnerships
    - Action
- Optimising the response to HIV requires good public health practice and respect for human rights
- Need to think globally, act locally and work together as a global community

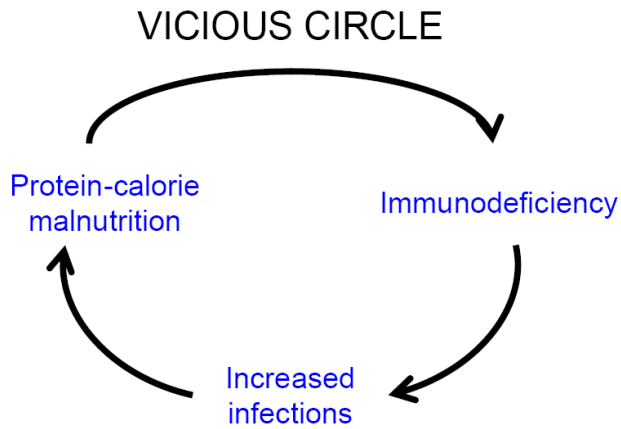
Definitions
- Immunocompromised host – an individual with an impaired immunity
- Immunodeficiency disorder – a condition associated with impaired immunity
- Immunosuppression – therapeutic measures that reduce the activity of the immune system
    - Immunosuppression is a cause of immunodeficiency

Causes of immunodeficiency
- Primary immunodeficiency – congenital (usually a single gene disorder)
- Acquired immunodeficiency – more common

Primary immunodeficiency
- Congenital
- If severe, often present a year after birth
    - In utero, immune system is not needed
    - Maternal antibodies from the placenta and lactation provide a few months protection
- Can affect T cells, B cells, neutrophils, etc
    - T cell disorders (or combined disorders) often have defects in antibody production
- Most disorders involve a single gene
    - Several are X-linked
- EG: boy in a bubble
    - Combined immunodeficiency, can't make T-cells
    - Died 12 years, from EBV from a bone marrow transplant from his sister
- Management:
    - Diagnosed and treated aggressively
        - Primary antibody deficiency responds well to immunisation with iv or sc IgG from blood donors
        - Primary T-cell deficiencies and neutrophils can be treated with haematopoietic stem cell transplants with a matching donor
    - Primary immunodeficiencies are good candidates for gene therapy
        - Some patients have responded well, others have developed leukaemia

Acquired immunodeficiency
- AIDS
- Protein-calorie malnutrition
- Old age
- Medically caused
- Associated with other diseases – malignancy, tuberculosis, DM (defective neutrophils), renal failure
- Reduced/absent spleen

Protein-calorie malnutrition
- Malnutrition leads to immunodeficiency which can cause increased infections and along with this, infections may lead to malnutrition



Old age and immunodeficiency
- Have increased infections
    - Eg: pneumonia is known as "the old man's friend", a common way for lives to end
- Older people have poorer vaccine responses
- T-cell function is affected
    - Numbers don't decline, but the thymus has shrunk and produces fewer naïve T cells
    - Memory cells are specific for only a limited number of pathogens
- Established antibody responses are not so affected

Medical causes of acquired immunodeficiency

- Glucocorticoids (steroids)
    - Used to inhibit unwanted immune responses
        - Autoimmune diseases, eg: rheumatoid arthritis
            - Acts systemically
        - Allergic disorders, eg: steroid puffers for asthma
            - Acts locally, and thus limits adverse effects
        - Transplantation – to prevent organ rejection
- Immunosuppressive drugs, eg: cyclosporin A
    - Used in transplantation and severe autoimmune disease
- These drugs inhibit all immune responses, especially T cell-dependent responses
- Cytotoxic drugs in cancer chemotherapy
    - Kill rapidly dividing cells – malignant and non malignant
        - Neutrophil precursors proliferate rapidly during infection
        - Lymphocytes proliferate rapidly after antigen activation

Reduced/absent spleen

- Causes:
    - Surgical removal – abdominal trauma, lymphoma
    - Sickle cell disease (causes infarcts in the spleen)
    - Congenital absence
- Spleen plays an important role in filtering and trapping encapsulated bacteria
- Patients without spleens are at increased risk of:
    - Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis
        - These can lead to overwhelming sepsis
- Management
    - Rapid and vigorous treatment
    - Vaccination against encapsulated bacteria

General features of immunodeficiency

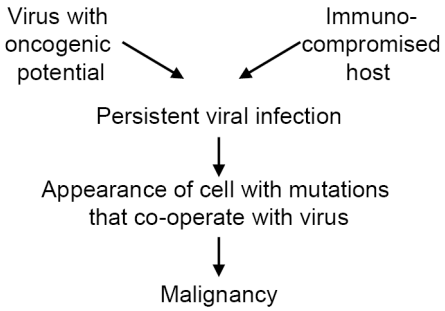
- Major consequence: increased risk of infection
- Increased risk of certain cancers
    - Especially those virus induced
- Increased risk of autoimmune disorders
    - Paradoxically caused by loss of regulatory Tcells?

Infection in immunodeficiency

- Opportunistic infections – those that do not normally cause disease
- Infections from conventional pathogens may have unusual features:
    - More severe/recurrent
    - Incompletely responsive to treatment
    - Unusual sites (eg. osteomyelitis)
- Pattern of disease reflect the degree and nature of the immunodefiency
    - Deficiency of Tcells/CD4 T cells
        - Impairment of macrophage, cytotoxic T cell function and antibody production
        - Susceptible to many pathogens: intracellular bacteria, viruses, fungi, bacteria, protozoa
        - Live vaccines can cause systemic infection
    - B cell, neutrophil, complement deficiencies
        - Susceptible to infections by extracellular bacteria

Malignancy

- Incidence of certain cancers is increased in the long-standing immunodeficient (AIDS, transplant recipients)
    - AIDS: 100x increase in risk of B cell lymphoma
    - Risk is proportional to reduction in CD4 cells
    - EGS:
        - B cell lymphoma – Epstein-Barr virus
        - Kaposi's sarcoma – Human herpes virus type 8
    - Common cancers have little incidence change



- Malignancy can arise from a single abnormal cell
    - Caused by abnormal genes
        - In theory, need at minimum 3 abnormal genes in the same cell
        - Viruses (oncogenic) can provide one abnormal gene that will cooperate with abnormal mutated cellular genes
            - Especially if virus is chronically infecting a cell
            - This thus reduces the number of mutations required for cellular genes to go malignant

Opportunistic infections in HIV

Definitions

- Opportunistic infection – infections that in general do not cause a symptomatic disease (provided there is a normal immune system)
    - Pattern of infection, malignancy etc are determined by the nature and extent of immune dysfunction

Immune defects

- T-cells – decreased number, cytotoxic response
- Neutrophils – decreased number, phagocytosis
- B-cells – decreased antibody responsiveness, number and increased autoimmune risk
- Macrophages – decreased phagocytosis and chemotaxis
- Natural killer cells – reduced IL-2, thus decreased T-cell mediation
- In HIV, CD4 count drops by 100/µL/year

Opportunistic infections in HIV/immunosuppressed

- Skin infections
- Respiratory infections
- Systemic viral infections
- Gastrointestinal infections
- CNS infections
- Haematological manifestations

Light immunodeficiency

- Dermatological manifestations
    - Rash associated with seroconversion illness – found on palms and souls of feet
        - Non-descript, flu-like symptoms
    - Staphylococcal infections – folliculitis (inflammation of hair follicles), superficial abscesses
    - Fungal lesions –increased extent and severity
    - Herpes zoster (shingles) – especially if in young adults or recurrent
    - Herpes simplex – recurrent or severe
    - Molluscum contagiosum, cutaneous cryptococcosis
    - Seborrhoeic dermatitis – like dandruff, + face affected
    - Kaposi's sarcoma – purple lesions
    - Lymphoma
    - Crusted scabies
    - Drug reactions – more allergic in general

- Mucosal lesions
    - Oral
        - Hairy leukoplakia – moss-like tongue
        - Oral candidiasis
        - Oral ulceration
        - Kaposi's sarcoma
    - Genital
        - Candidiasis
        - HSV
        - Cervical dysplasia
        - Carcinoma in situ
        - Perianal ulceration

<u>Moderate immunodeficiency</u>
- Bacterial infections
    - S. pneumoniae, S. aureus, H. influenzae, salmonella, Mycobacterium tuberculosis

<u>Advanced immunodeficiency</u>
- Bacteria – gram negative organisms like salmonella
- Fungi – Pneumocystis carinii, cryptococcosis, Candida
- Protozoa – Toxoplasma gondii
- Viruses

<u>Late stage HIV</u>
- Bacteria – mycobacteria tuberculosis, other mycobacteria
- Viruses – CMV
- Tumours – cerebral lymphoma, Kaposi's sarcoma

<u>Common opportunistic infections</u>
- Bacteria:
    - Pneumococcus
        - Incidence increased 20-50x in HIV infection
        - Can occur at any stage of HIV if CD4 <500
        - Presentation – lobar pneumonia, sinusitis, septicaemia, meningitis
        - Treatment – as for non-HIV
        - Prevention
            - Pneumovax (prevents against 23 most prevalent strains)
            - Penicillin prophylaxis
    - Non-typhi salmonella
        - Can occur at any stage of infection
        - More common in the developing world
            - most people can deal with 10^3-10^4 salmonella organisms because of stomach acid, if pH greater, increased risk
        - Presentation – septicaemia, shock, relapsing
        - Treatment – quinolones
        - Prevention – avoid uncooked food etc
    - Mycobacterium avium complex
        - A low grade systemic pathogen that doesn't normally cause harm unless CD4 <50
        - 1/3 will develop MAC without prophylaxis
        - Presentation – fever, sweats, weight loss, anaemia, lymphadenopathy, hepatosplenomegaly, generally unwell
        - Diagnosis – PCR, blood cultures
        - Treatment – raise CD4, suppression of bacteria

- Fungi:
  - Pneumocystis jiroveci
    - Most common AIDS defining illness, CD4<200
    - Rarer in the developing world because people die of TB first
    - Affects pulmonary and extra-pulmonary (skin, adrenals, sinuses)
    - Presentation – fever, dry cough, shortness of breath on exertion (SOBOE), clear chest
    - Diagnosis – chest x-ray (peri-hilar shadowing), arterial blood gas, PCR on sputum
    - Treatment – empirical (based on observation, or before diagnosis)
      - Steroids (if pO_2<70mmHg), cotrimoxazole, pentamidine, atovaquone, dapsone, clindamycin
      - Possible supportive CPAP (continuous positive airway pressure), to help ventilation
  - Cryptococcus neoformans
    - CD4<100
    - Inhaled encapsulated yeast
    - Affects: meninges, brain (rare), lung, skin, bone, prostate (important for reactivation)
    - Presentation: insidious – low grade fever, headache (vs bacterial meningitis with acute onset)
    - Diagnosis – CT brain with contrast, chest x-ray, lumbar puncture
  - Candida species p- candida albicans, tropicalis, glabrata, dubliniensis
    - CD4 200-350
    - Diagnosis – clinical, fungal culture, endocscopy
    - Treatment – azoles
      - Late stage – drug resistances, add terbinafine
- Protozoa
  - Toxoplasma gondii
    - CD4 < 100
    - Presentation – altered mental state, hemiparesis (weakness on one side), headache, fits, fever, confusion, coma
  - Cryptosporidium parvum
    - CD4<100
    - Transmission – water, person to person
    - Symptoms – diarrhoea, wasting, abdominal pain, nausea, URTI
    - Diagnosis – stool, small bowel biopsy
    - Treatment – no effective therapy
      - HAART to regenerate immune system and thus hope it can take care of itself
      - Symptomatic
- Viruses
  - Herpes viruses (CMV)
    - CD4<50
    - Sites – retina (visual loss, 'pizza retina'), gut (abdominal pain, diarrhoea, fever), spinal cord, brain (meningitis)
    - Diagnosis – clinical, plasma, biopsy
  - HSV-2 – genital herpes
    - Often coinfection with HIV
    - Reactivation occurs in immunodeficiency
      - These occurrences are more frequent, severe and prolonged
    - Also for HSV-1
  - Oncogenic viruses
    - Epstein-Barr virus, HHV8 (human herpes virus 8), HPV (human papilloma virus)
    - Multicentric Castleman's disease (MCD)
      - Lymph node hyperplasia, germinal centre formation and capillary proliferation
        - B-cell proliferation due to IL-6 production
      - HHV8 found in the HIV infected host who has this
      - Most cases of MCD in HIV positive dead in 6 months
        - Outlook can be improved with antiretroviral therapy
  - Hepatitis C
    - Adversely affects HIV outcome
    - HIV adversely affects Hep C outcome
    - HIV increases transmission risk of Hep C

- Syphilis
    - Active infection facilitates HIV infection and transmission 3-5x
    - Similar transmission risk factors
    - Syphilis occurs regardless of CD4 levels
    - With HIV:
        - Increased risk of neurological complications
        - Early ocular involvement, higher incidence of fever, GIT disturbance

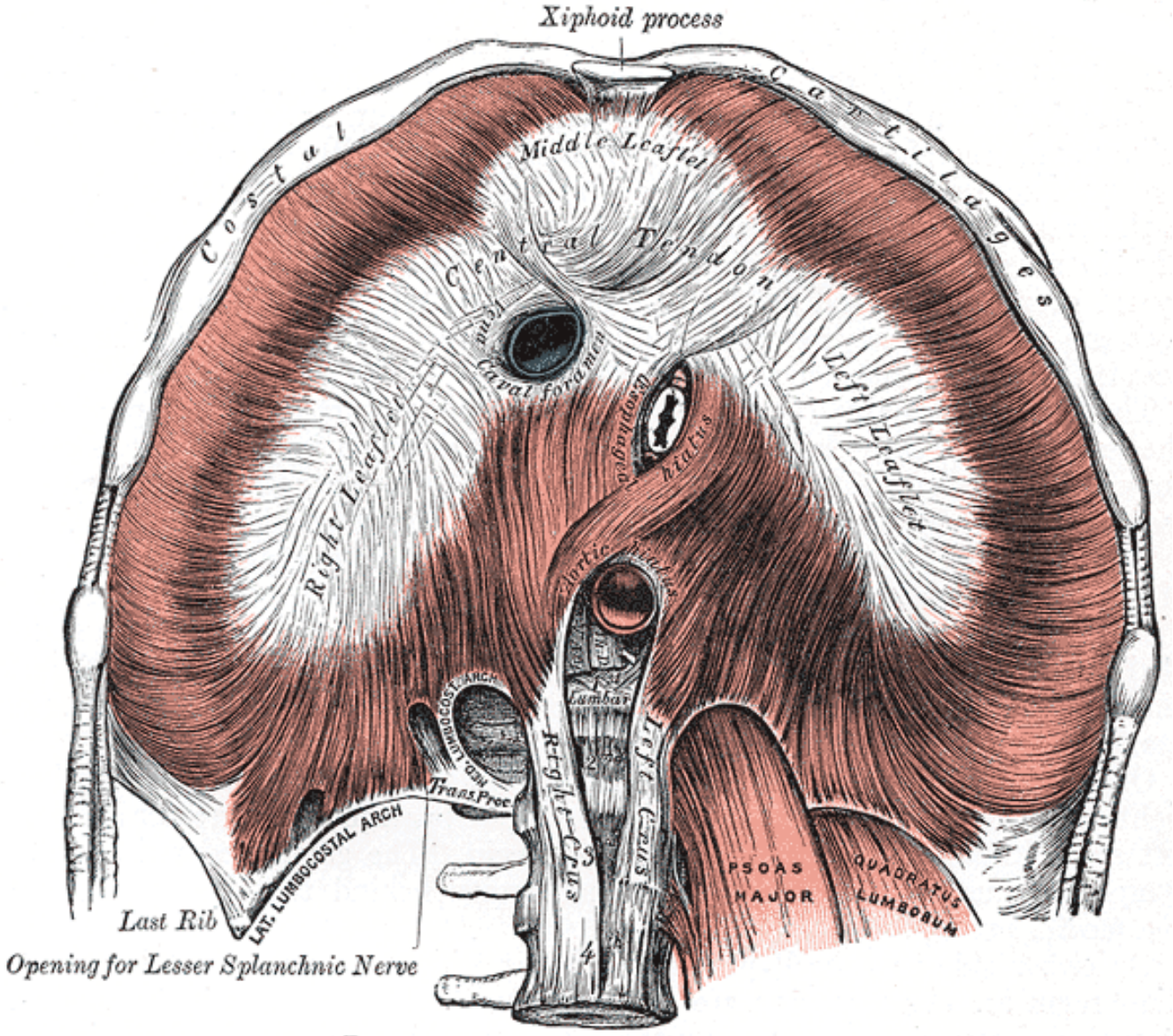
<u>Haemotological manifestations of immunodeficiency</u>

- Unexplained anaemia
- Thrombocytopenia
- Lymphopenia
- Hypergammaglobulinaemia
- False positive RPR (rapid plasma reagin, test for syphilis)

<u>General trends</u>

- Infections that normally would be easily dealt with by the immune system can take hold in immunodeficiency
    - Either this or regular pathogens are more effective
- Progression and how the body handles these diseases is based on the level of depletion of the immune system
- Treatment is to primarily try and boost own immune system via antiretrovirals
    - Secondarily, treatment may be symptomatic or auxiliary to the immune-system

SEE NOTES FROM AEB + HAND OUTS

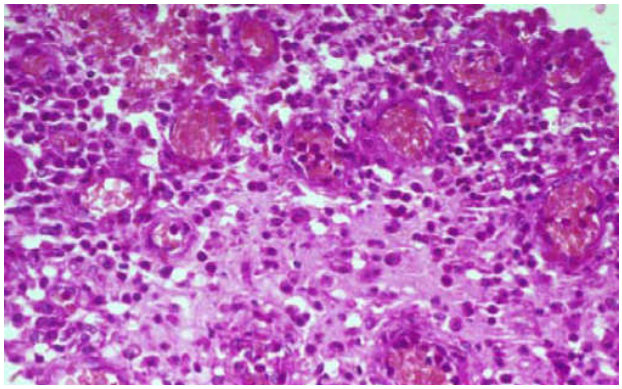


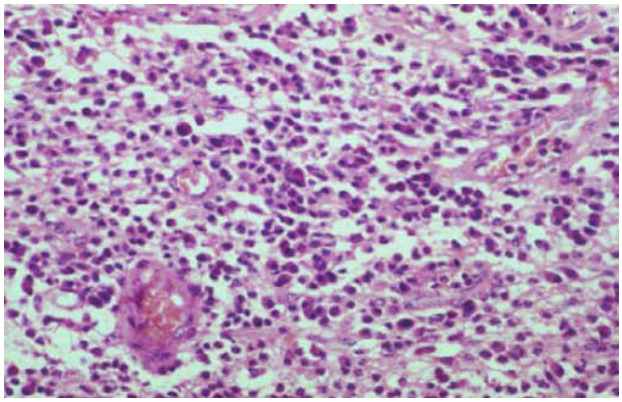
Chronic inflammation: definitions

- Based on duration
  - Arbitrary (said to be > or equal to 6 weeks), acute being <3 weeks
- Based on cellular response (mononuclear)
  - In acute inflammation expect neutrophils (polymorphonuclear)
  - In chronic inflammation, generally have macrophages/lymphocytes etc (mono morpho nuclear cells)
    - Ie: small round cells are lymphocytes and large round cells are macrophages
  - Problems with definition:
    - Acute inflammation due to pyogenic bacteria has neutrophils, but in acute upper respiratory tract infections, CD8 cells mediate acute inflammation (mononuclear)
- Based on processes (inflammation and repair)
  - Ie, inflammation followed by repair repeatedly is chronic inflammation
  - Problems:
    - Inflammation and repair can be simultaneous
    - Immunological response may contribute to inflammation and necrosis
- A better way of defining is by causes
  - Causes of chronic inflammation:
    - An acute irritant that is not eliminated
      - Persisting acute infections
      - Autoimmune diseases
    - A low intensity irritant of long persistence
      - Result in not much acute inflammation
        - Irritant is durable and causes healing and repair over time
      - Eg: Foreign bodies, chronic infections
- Major examples:
  - Asthma – acute episodes of inflammation that flares up on the background of chronic inflammation
  - Peptic ulcers – a mix of chronic and acute inflammation
  - Rheumatoid arthritis – chronic tissue disruption
  - Ulcerative colitis/Chrohn's disease
  - Renal disease – scarring leads to renal failure
  - Tuberculosis – tissue destruction and scarring + systemic manifestations

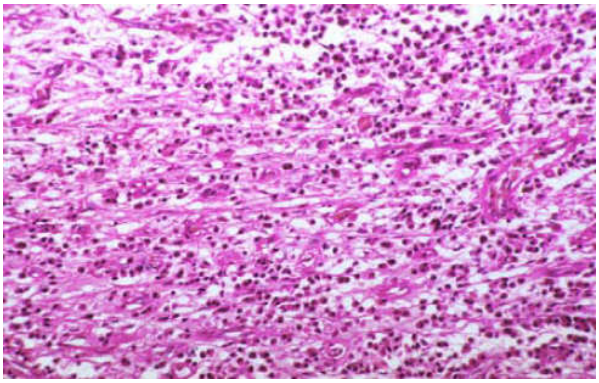
Chronic osteomyelitis

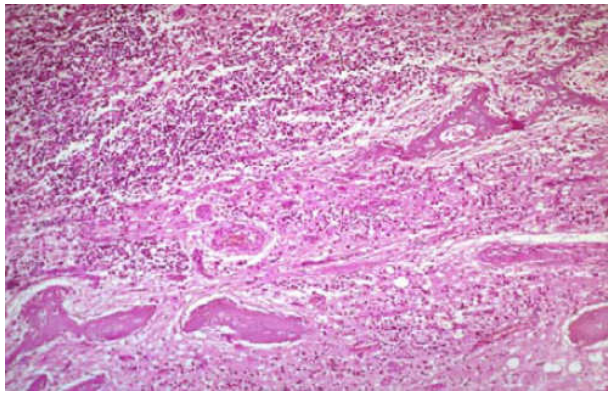
- An acute process leading to chronic inflammation
  - Vascular system bound to bone (rock), exudate increases and causes a rise in pressure
    - Vessels collapse, ischaemia, sinuses, bacteria hide in sinuses – healing and repair
      - Thus chronic inflammation
- Picture 1:
  - Higher power
  - Features: like those of acute inflammation
    - Dilated BVs, cells in extracellular space
    - Lobulated nuclei, neutrophils
    - Round, macrophages/lymphocytes
    - Proteinaceous fluid
- Picture 2:
  - Features:
    - Dilated vessels
    - Cellularity – cells are mostly round with an asymmetrical cytoplasm
      - Derived from B-lymphocytes: plasma cells – produce antibodies





- Picture 3:
    - Features: organisation of bone abscess
        - Fibres – collagen
        - Inflammation causes vascularity and healing by repair (granulation tissue)
- Picture 4:
    - Features
        - New bone formation (bone trabecula structures)
- Summary:
    - Chronic inflammation is due to a persistent acute inflammatory response
        - Centrally: there is an acute infection, peripherally, a chronic infection
            - Peripherally: ongoing healing and repair forming granulation tissue and new bone





<u>Histopathological differences in acute and chronic</u>

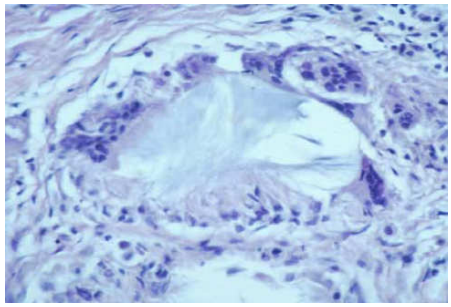
- Chronic inflammation:
    - Changes in cellular composition
    - Less marked vascular changes
    - Granulation tissue and other responses to healing

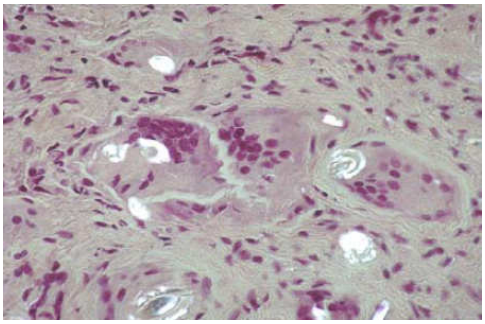
<u>Mechanisms of chronic inflammation</u>

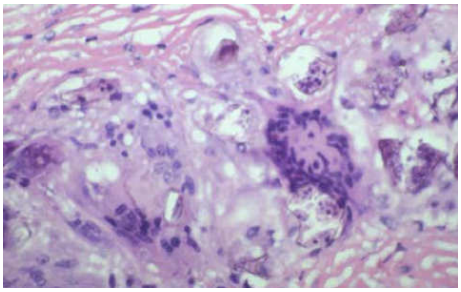
- Macrophage recruitment, replication, immobilisation (via lack of chemokines), activation
- Lymphocyte recruitment, activation, differentiation
- Granulocyte recruitment
- Endothelial cell and fibroblast migration and proliferation

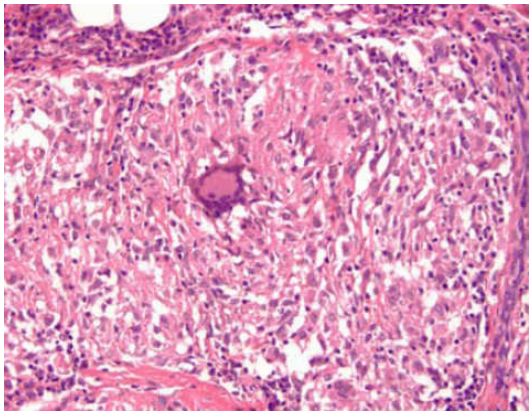
<u>Chronic inflammation by a persistent low intensity irritant</u>

- Eg: Acellular material in tissue surrounded by many cells
    - Eg: Gouty tophus (pic 1)
        - Gout – tissue deposition of monosodium urate
            - Low level chronic irritant that behaves like a foreign body
        - If a foreign body is too big, macrophages unite by fusion and form multinucleate cells – giant cells
            - Giant cell phagocytosis is characteristic of a persistent low level irritant
            - Form a granuloma
- Granuloma: a form of chronic inflammation consisting of a ball-like mass of inflammatory cells
    - Has a necrotic centre, an epithelioid cell layer and is often surrounded by a sea of lymphocytes
- Other examples of foreign body reactions:
    - Talc – silcate crystals (pic 2)
        - Giant cells have phagocytosed crystal aggregates
    - Schistosomiasis (pic 3)
        - Giant cells in reaction to parasitic ova
    - Sarcoidosis (pic 4)
        - Granuloma with epithelioid cells, giant cells and lymphocytes
- Epithelioid cells – syncytia of activated macrophages with increased cytoplasm



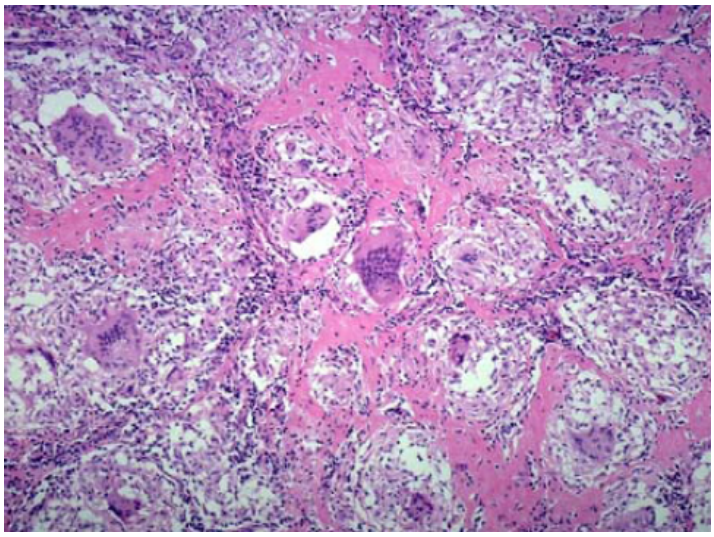


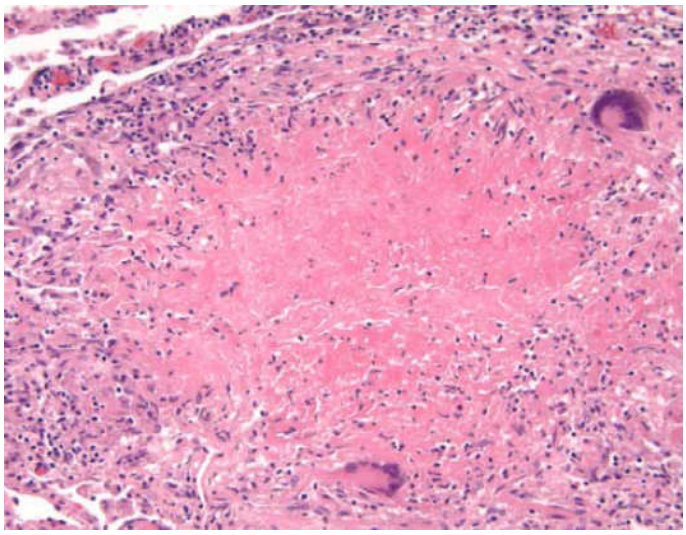




Necrotising vs non-necrotising

- Non-necrotising, eg: granulomas of sarcoidosis (pic 1)
    - Bands of collagen in between granulomas, healing and repair process started
- Necrotising granuloma, eg: tuberculosis (pic2)
    - Epitheliod cells lead to tissue destruction at the centre of the granuloma
        - Not quite coagulative or liquefactive necrosis, thus caseous (cheese-like) necrosis





Long term consequences of chronic inflammation

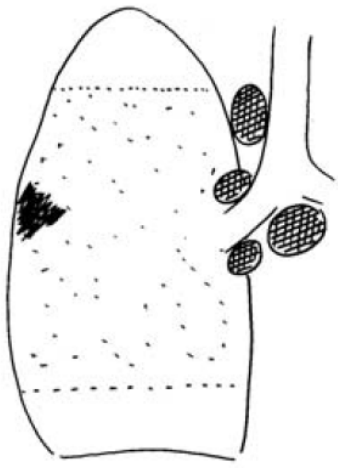
- Continuing effects of acute inflammation
- Destruction of tissue
- Scarring
    - Eg: inflammatory bowel disease can lead to bowel blockage through scarring
- Systemic effects
    - Eg: weakness, tiredness, weightloss etc

Tuberculosis

- Epidemiology
  - Number one cause of death from infectious disease
  - 1/3 people have been infected
    - Note: infected vs disease (disease is about 15 million cases)
  - HIV makes people particularly susceptible to TB
    - 50% of TB is due to HIV
  - Indigenous vs non-indigenous Australians
    - 8x more frequent
- Mycobacterium tuberculosis
  - No real toxins produced
  - Very tough, have to be destroyed by cells – live in phagocytes

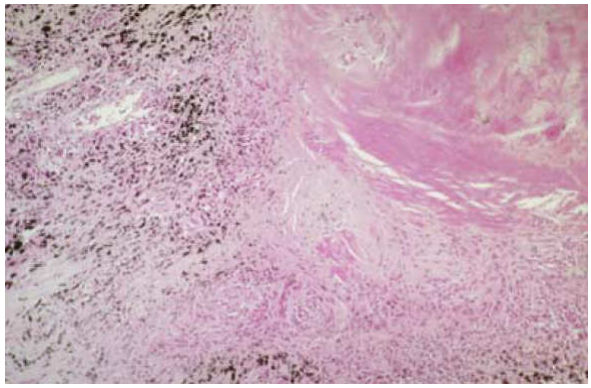
TB natural history – see diagram

- Immune response determines amount of damage:
  - Good immune response means tissue destruction is localised, marked caseation
  - Bad immune response means no tissue destruction, but TB spread
- Process:
  - Primary infection with bacteria
    - Pre-immune low-level bacteraemia
      - No neutrophils (because there is no trigger)
      - Macrophages, phagocytosis, MTB lives in macrophages and thus travels to get into the blood of lymph nodes
        - To destroy bacteria, macrophages need free radicals, but need to be activated to have these
      - Asymptomatic
    - 95% cases: typical Ghon complex (typical primary complex, localised caseation)
      - 2 sites of inflammation, initial site and lymph node
      - This can lead to healing or to a latent (decades) lesion (organism is dormant and viable)
        - Pulmonary or extrapulmonary
    - 5% of gases leads to progressive primary tuberculosis and thus massive haematogenous dissemination
  - Reactivation leads to post-primary tuberculosis
    - Due to decreased immune system:
      - HIV
      - Diabetes – macrophage function decreased
    - Leads to:
      - Localised caseating destructive lesions (most common clinical form)
      - Progressive post-primary tuberculosis (secondary TB)
      - Massive haematogenous dissemination

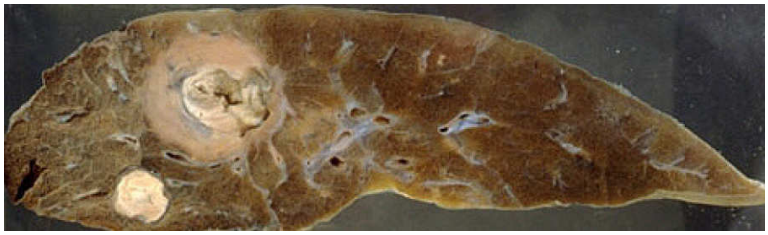


Primary lesions/foci

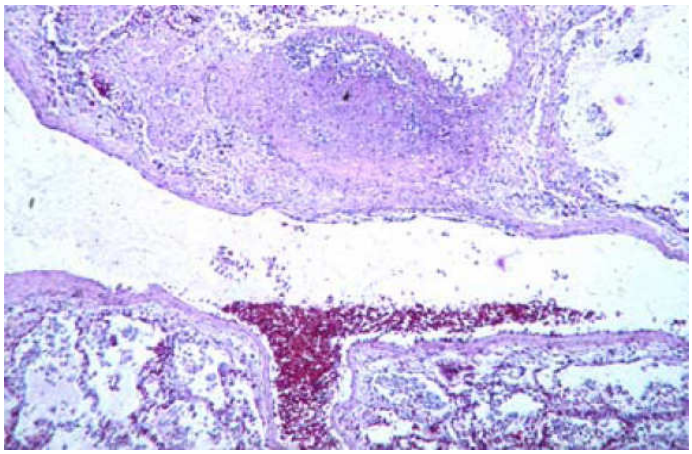
- Inhalation into middle 2/3 of lung
  - Carried away to lymph nodes
  - Ghol complex is infection involving primary focus and a local lymph node
- Identification:
  - Macrophages laden with acid-fast bacilli
  - Ziehl Neelsen stain using carbol fuchsin
    - Thus can identify rod-shaped TB inside macrophages
- Primary complex – involving lymph node
  - Lymph node may undergo early necrosis subclinically
- Primary focus and lymph node can leave remnants (eg: calcifications)
  - Focus may heal, but TB can still be present
  - Picture 1: carbon accumulation due to lymphatic blockage and necrotic tissue evident

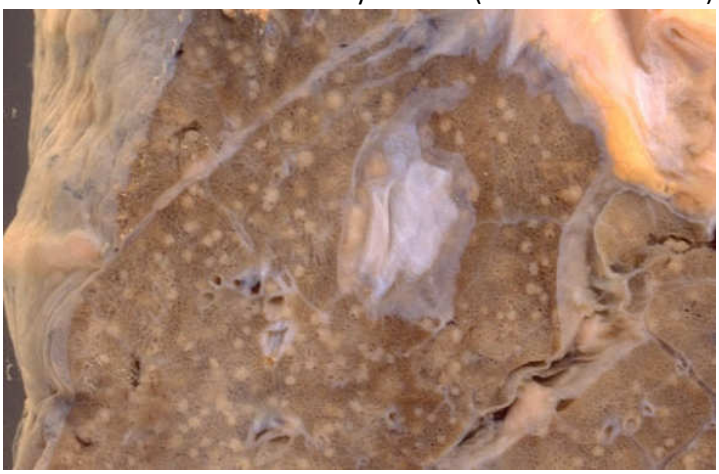


Progressive primary lesion



- If immunity is not adequate, lesion may spread – caseation (pic 1)
- Relationships to vessels are important (pic 2)
    - Access to vein may lead to haematogenous dissemination
- Haematogenous spread (pic3)
    - can lead to dissemination (white spots)
        - these are granulomatous tuberculous lesions
    - occur if host immunity is down (has little caseation)

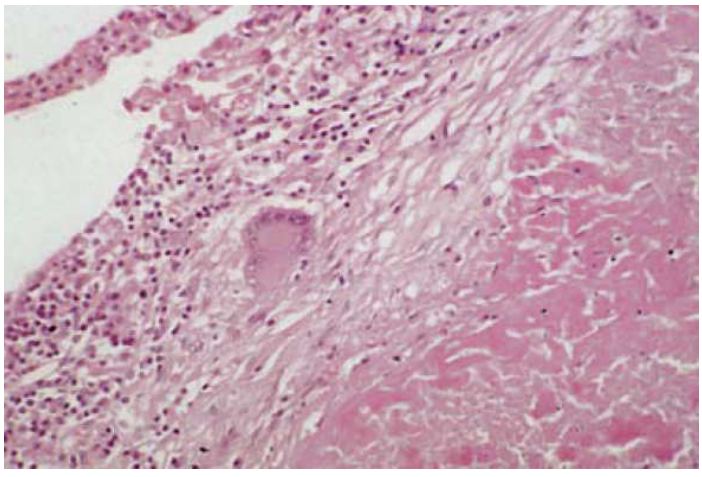




Post-primary lesion

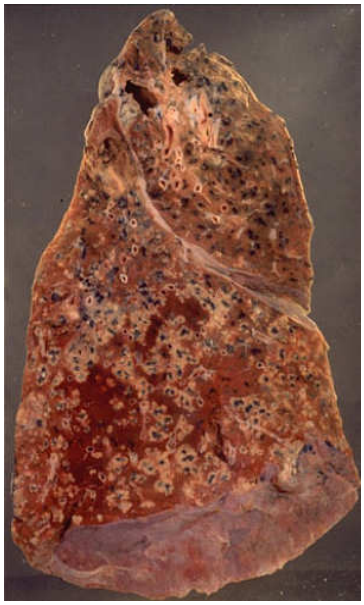
- Triggered by:
    - Age, malnutrition, diabetes (phagocytic function decreased), chronic alcoholics, HIV
    - Ie: direct/indirect immunological impairment
        - CD4 cells activate macrophages via gamma-interferon
            - Turns on free radicals (N and O) and causes formation of epithelioid cells
            - Impairment of this can lead to reactivation
- Can appear in many different places
    - Return at the best suited site
        - MTB is an aerobe thus the lungs are a common site
            - Especially in the apex of the lung that has less blood perfusion (gravity) and thus less O_2 extraction and thus higher O_2, which MTB likes

- EG:
    - Pic 1: post-primary infection in apex of lung
    - Pic 2: caseating apical post-primary lesion with high power
        - Langhan's giant cells (horseshoe arrangement of nuclei)
        - Note: granular mass and lymphatic cells
    - Neutrophils arrive later and can cause liquefactive necrosis, liquid can discharge into the bronchi spreading infection and causing cavity formation (can fill with carbon/soot)
    - Typical appearance of post-primary lesions is the cavitary apex (collapse of apex and formation of a cavity)



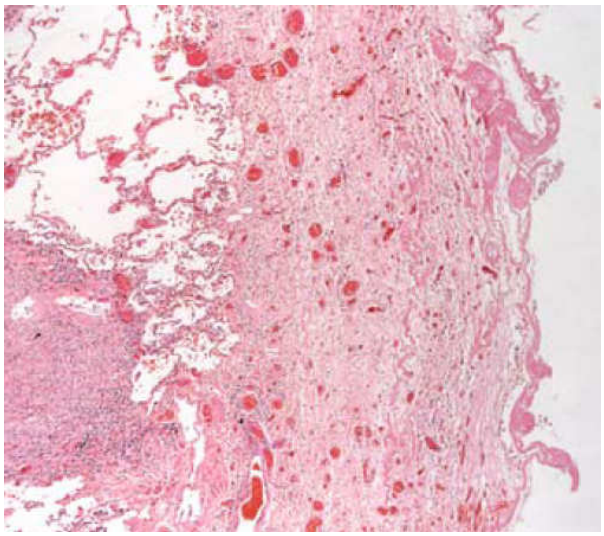
Other manifestations

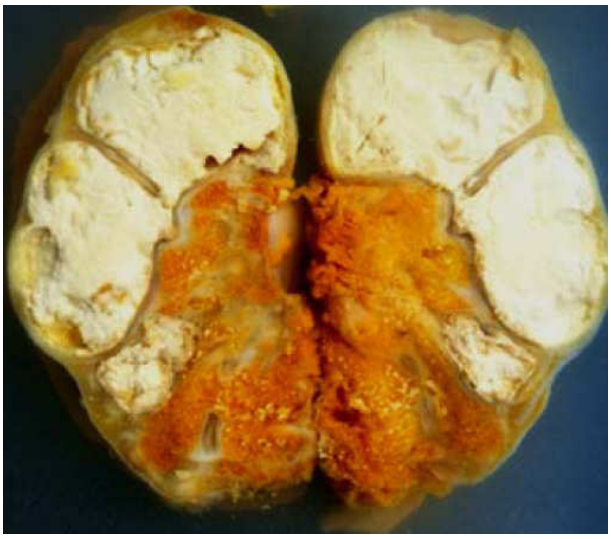
- Fibrocaseous TB: occurs with a very suppressed immune system
    - Apical cavitation and progression thus leading to growth of fibrous scar tissue
- Bronchogenic spread of TB: TB spreads throughout the lung via the airways
    - This can progress to haematogenous spread

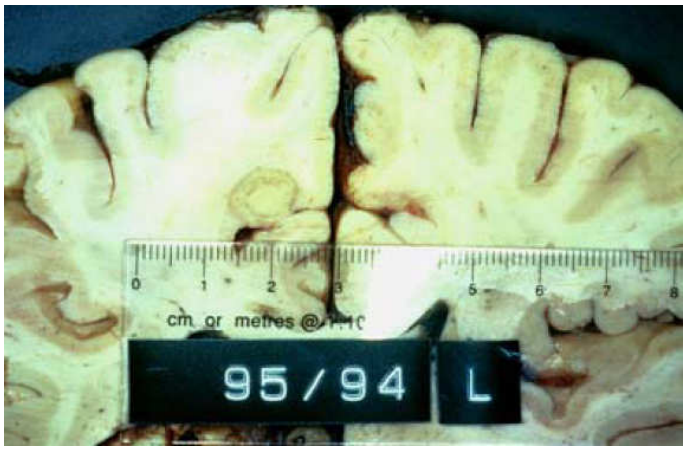


Extrapulmonary tuberculosis

- Reactivation occurring somewhere else, wherever TB survived after initial spread
- Make up 40% of notified cases of TB
    - Can happen with and without pulmonary TB
- Common sites:
    - Lymph nodes (36%)
    - Pleura (14%)
    - Skeletal (9%)
    - Genito-urinary (7%)
    - CNS (5%)
    - Miliary (disseminated) (2%)
        - Ie: massive haematogenous spread
        - (Size of millet seeds)
- EGS:
    - Tuberculous pleurisy
        - Granuloma/vasodilation/chronic inflammation in the pleura
    - TB or urinary tract
    - Renal TB
    - Cerebral TB
- "it's all about the host immune response"

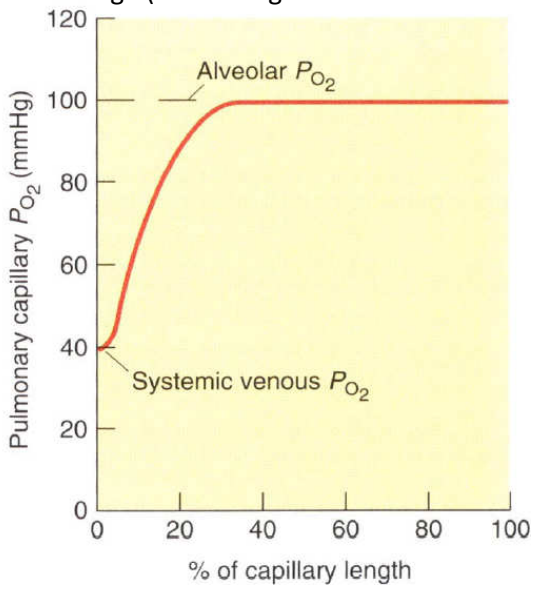






Normal gas values

- Normal mixed venous blood
  - P_{O2} = 40mmHg
  - P_{CO2} = 47mmHg
- Venous blood flows through capillaries and gas exchange occurs in the walls of the alveoli
  - After this, capillary gas tensions equilibrate with the tensions in the alveoli
    - P_{O2} = 100mmHg
    - P_{CO2} = 40mmHg
- Gas exchange occurs in the capillaries very quickly
  - Only uses about 1/3 of the capillary length and thus 1/3 of the capillary potential gas exchange
    - This means that in exercise, there is room for faster gas exchange ("breathing room" for equilibration)
- Arterial blood from the left ventricle is a mixture of:
  - Blood from the lungs
  - Blood from the bronchial veins
  - Blood from the left ventricle itself
    - Thus, gas tension is slightly lower:
      - P_{O2} = 95mmHg
      - P_{CO2} = 40mmHg

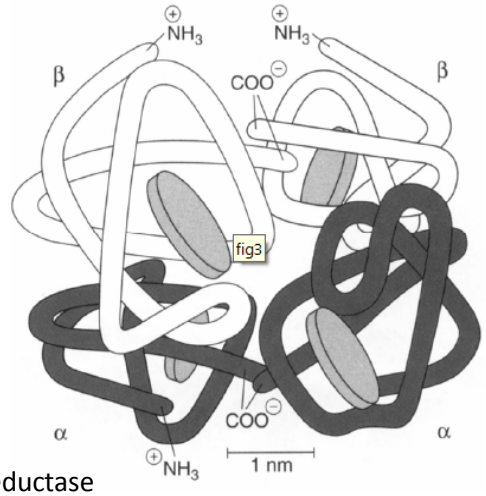


Oxygen carriage in the blood

- Two forms:
  - Dissolved
  - Combined with haemoglobin
- Dissolved
  - Some oxygen dissolves in plasma – quite a small amount (like physiological saline: ~0.023ml/ml/atm)
    - Ie: with P_{O2} 100mmHg, 0.3ml of O_2 (STPD) is carried in 100ml plasma
    - Ie, in 1L of cardiac output, dissolved oxygen gives 3ml/min of oxygen as compared to the resting O_2 consumption of 200ml/min
  - If dissolved oxygen was the only form, cardiac output would need to be ~83L/min to meet requirements
    - Thus a carrier is needed – haemoglobin

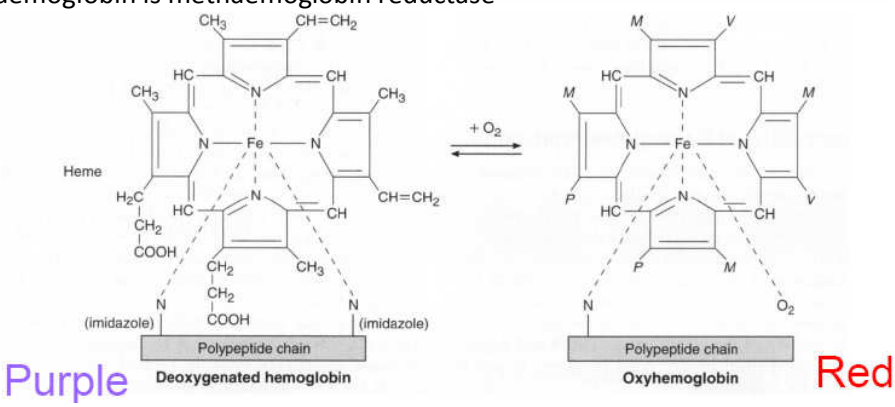
Haemoglobin

- A protein (MW 34450) made up of 4 subunits
  - Each subunit has a haem molecule attached to a polypeptide chain
  - Adult haemoglobin (HbA) has 2 α chains and 2 β chains
    - α chains are 141 amino acids in length
    - β chains are 146 amino acids in length



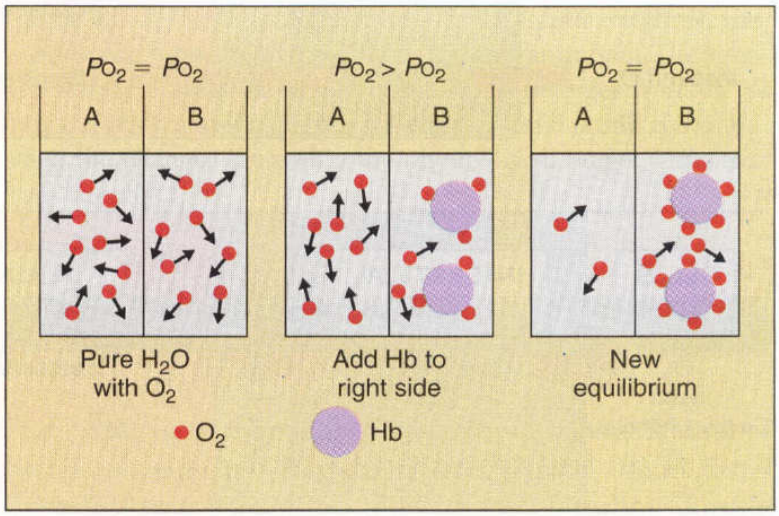
The Haem disc (moiety)

- Made up of a derivative of porphyrin and an atom of ferrous iron (Fe^{2+})
  - If the iron is oxidised into the ferric form (Fe^{3+}) it can no longer carry oxygen – known as methaemoglobin
    - Enzyme that removes methaemoglobin is methaemoglobin reductase
- Oxygenated form is red, deoxygenated form is purple
  - Cyanosis is blue-tinge to the skin due to deoxygenated haem moiety



Combination of oxygen with Hb

- O_2 combines reversibly with Hb to form oxyhaemoglobin
  - Ie: O_2 + Hb ←→ HbO_2
  - Purple ←→ red
- Each of the 3 subunits can bind one O_2 molecule thus forming Hb_4O_8
- Iron stays in its ferrous state
  - Reaction is oxygenation not oxidation
- Oxygenation and deoxygenation reactions are very rapid (<0.01 seconds)
  - Thus, they come to equilibrium very quickly
- Equilibrium:
  - If O_2 is attached to Hb, it stops contributing to the partial pressure and thus a new equilibrium forms
    - Thus increases speed of diffusion

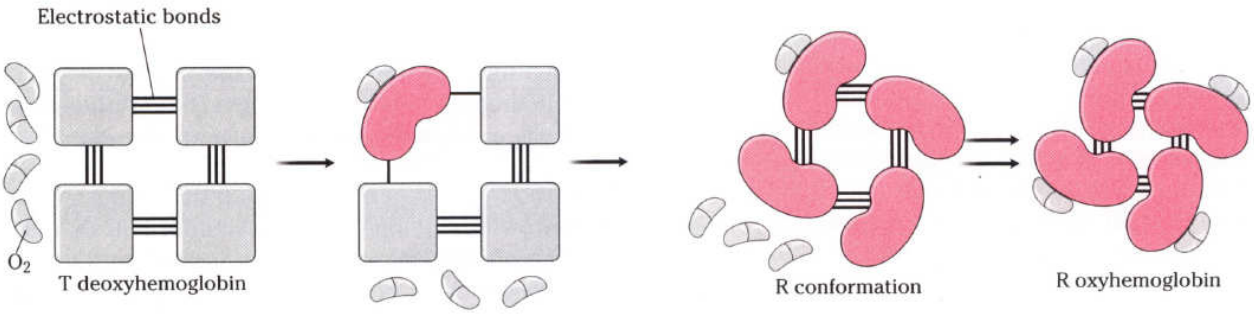


Terms for measuring oxygen in blood

- Oxygen capacity
  - Definition: the amount of oxygen (in vol% STPD) combined with Hb in a sample when all binding sites are fully occupied
    - Depends on the amount of Hb in the blood
  - 1g of Hb can combine with ~1.34ml of O_2
    - Thus, at normal concentrations of Hb (15g/100ml), oxygen capacity is about 20vol%
  - Hb can be lower in women of childbearing age than in men and children
  - Oxygen capacity does not include dissolved oxygen
- Oxygen saturation
  - Definition: the percentage of available binding sites of Hb, in a sample, that have O_2 attached
    - Saturation = O_2 combined with Hb/O_2 capacity x 100
  - Normal arterial oxygen saturation is ~97.5% with standard conditions (37°C, pH 7.4, PCO_2 40mmHg)
    - Mixed venous blood (going to the lungs) with PO_2 ~ 40mmHg has a 75% saturation
- Oxygen content
  - Definition: the amount of molecular oxygen (in vol% STPD or mmol/L) in solution or combined after binding power of Hb is destroyed and sample is put in a vacuum
    - Ie: oxygen in the blood that is either bound or dissolved
  - Assuming Hb is 15g/100ml
    - Normal arterial O_2 content is ~19.8vol%
      - Ie: 97.5% of 20vol% + 0.3vol%
    - Mixed venous O_2 content is ~15.2vol%
      - Ie: 75% of 20vol% + 0.12vol%
  - Equation: O_2 content (ml O_2/100ml) = (1.34 x Hb x saturation/100) + (0.003 x P_{O2})
    - Analogy: lecture theatre

Quaternary structure

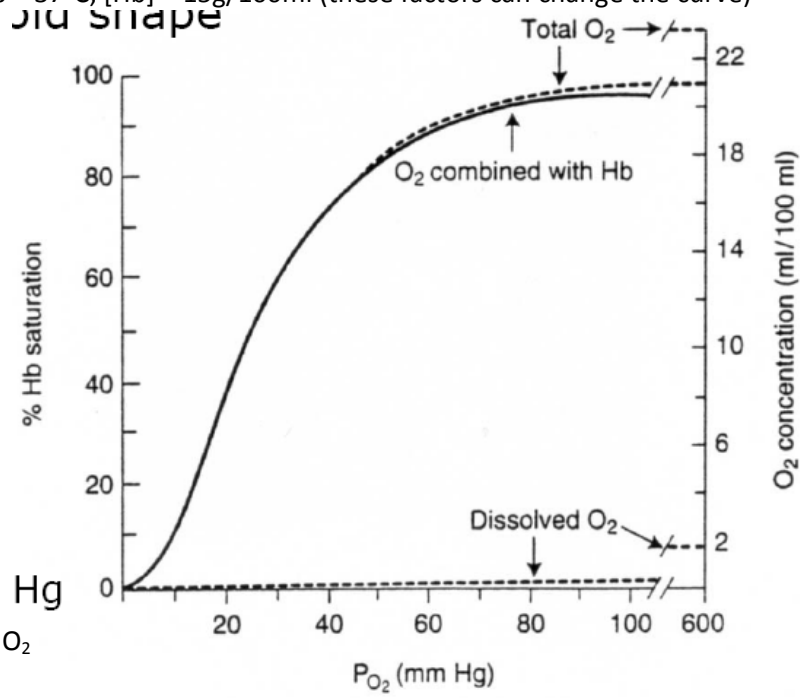
- The structure between protein subunits
  - Determines the Hb affinity for oxygen
- In deoxyHb, globin units are tightly bound by electrostatic interactions – a tense (T) configuration
  - When O_2 binds to the iron atom in the subunit core, a conformation change occurs
    - Thus that subunit takes on the relaxed ® configuration
      - This induces other subunits to change to the R form and thus easily pick up O_2 (500x)



Oxygen-Hb equilibrium curve (OEC)

- Also known as the O_2-Hb dissociation curve
  - Has a sigmoid shape
  - Conditions: pH: 7.4, PCO_2 = 40mmHg, Temp = 37°C, [Hb] = 15g/100ml (these factors can change the curve)
- Useful points:

PO_2	%Sat
0	0
20	35
27	50
40	75
100	97.5



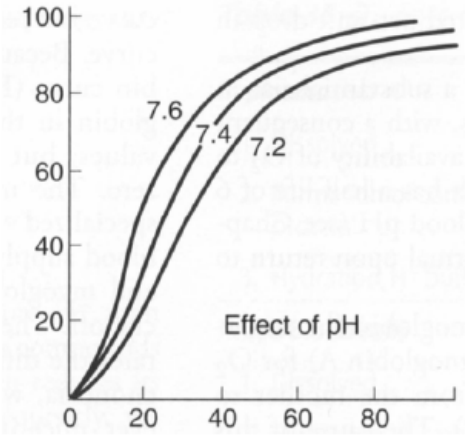
- Things to notice:
  - P_{50} = the PO_2 where Hb is half saturated by O_2
    - Gives an index of oxygen affinity
      - Ie: the higher the P_{50}, the lower the affinity
      - Increasing shifts the curve to the right, ie, higher PO_2 needed to increase saturation
  - Shape of the curve
    - Flat upper portion – O_2 loading at lungs aided
      - At lungs, easy to transfer oxygen and increase saturation, thus minimal diffusion required
    - Steep lower portion – O_2 diffusion into tissues aided
      - At tissue, as PO_2 drops, it remains at high saturation as long as possible to allow diffusion
  - Shape is sigmoidal because the quaternary structure has tense and relaxed phases

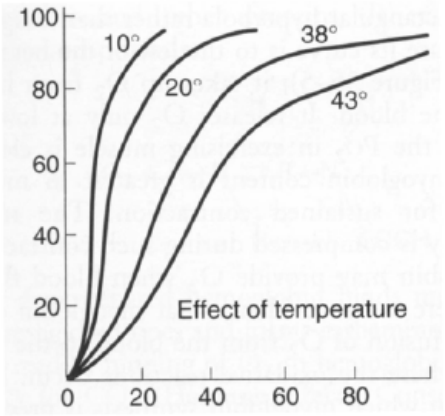
Haemoglobin and nitric oxide

- Nitric oxide causes vasodilation
- OxyHb binds NO tightly and thus scavenges it from the blood
  - DeoxyHb has no NO affinity
  - Thus, in hypoxic tissues, as oxygen is unloaded from Hb, NO is released also
    - NO causes local vasodilation and allows increased blood flow and thus increased oxygen flow to hypoxic tissues
- NO doesn't bind on haem moiety, but somewhere else on tetramer configuration

Factors that shift the curve

- Curve is shifted to the right (affinity is decreased) by:
  - Increased concentration of H^+ (decreased pH)
  - Increased PCO_2
  - Increased temperature
  - Increased 2,3 diphosphoglycerate (2,3 DPG)
- Acidity, PCO_2 and temperature are all effects of the exercising muscle
  - Thus, exercising muscle wants O_2 so if the affinity of Hb is decreased, O_2 more readily diffuses into tissues and supplies the muscle





The Bohr effect

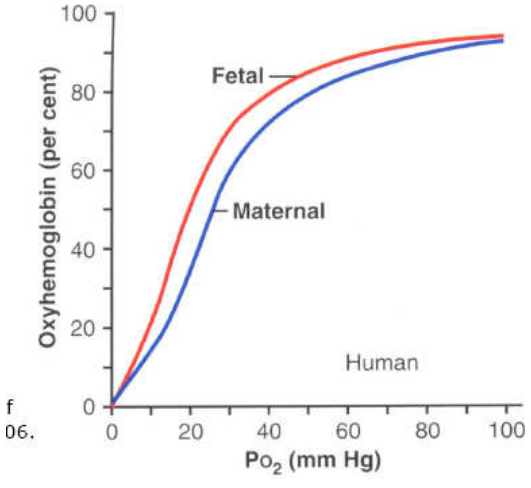
- The shift in OEC due to changes in blood CO_2 and pH (ie, increased H^+)
  - Due to H^+ binding to histidine residues on Hb
    - This causes a conformational change that decreases the affinity of Hb for oxygen
  - This enhances oxygenation of blood at the lungs and release of oxygenation at the tissues
    - At lungs, CO_2 is given up and there is a left shift causing increased affinity
    - At tissues, CO_2 enters the blood from the tissues and there is a right shift causes decreased affinity

2,3 DPG

- 2,3 diphosphoglycerate
  - Formed by glycolysis in red cells
  - Binds to β-chains in deoxyHb and stabilises the deoxy form lowering O_2 affinity
- With no 2,3 DPG, P_{50} for adult blood is 14mmHg (high affinity, O_2 will not diffuse easily into tissues)
- Normal concentrations of 2,3 DPG is 4-5mM
  - Can be altered by various factors:
    - Blood back storage, DPG falls and with increased affinity, Hb won't give up oxygen
    - Altitude, increased levels causing decreased affinity

Fetal Hb vs adult Hb

- HbF has 2 α and 2 γ chains
  - γ chain has 146 amino acids, 37 are different to the β chain
    - doesn't bind 2,3 DPG
- Fetal OEC is left shifted compared to the adults, this aids the movement of oxygen to the fetus across the placenta
  - In the first year of life, HbF is replaced by HbA gradually

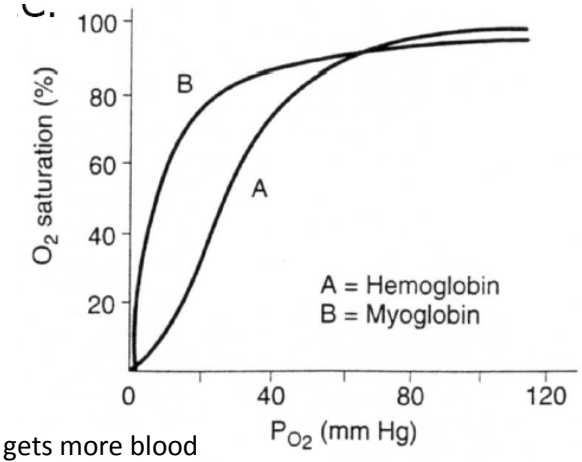


Pulse oximetry

- A machine that is used to measure Hb saturation and heart rate
  - Only gives saturation, not total content (ie, could have low oxygen content, but 100% saturation)
- Principles:
  - Hb and deoxyHb absorb light differently
  - Oximeter gives out 2 lights: IR and red
    - Measures absorption and thus can work out the ratio between purple and red Hb thus working out arterial saturation
- Uses and advantages
  - Accident and emergency, surgery, paediatrics
  - Minimises arterial blood samples

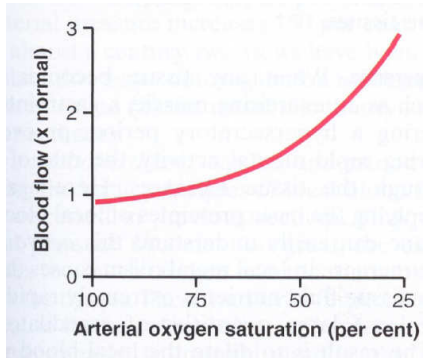
Haemoglobin and myoglobin

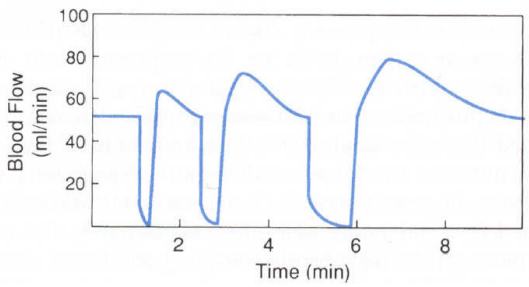
- Myoglobin is the oxygen-binding pigment in skeletal muscle
  - Binds 1 oxygen/molecule (instead of 4)
- Oxygen-myoglobin equilibrium curve is a rectangular hyperbola instead of sigmoidal
  - Left shifted as compared to the OEC
    - Thus, myoglobin takes up O_2 from Hb in the blood and releases it when there is low PO_2 in vessels supplying exercising muscles (because at low PO_2, it has higher O_2 saturation than haemoglobin)

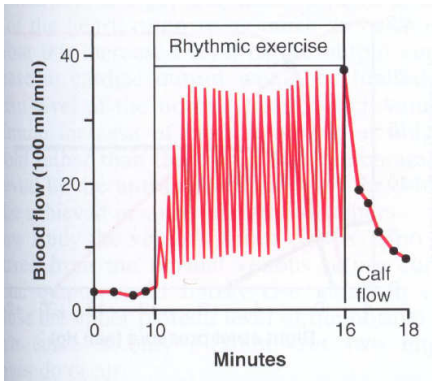


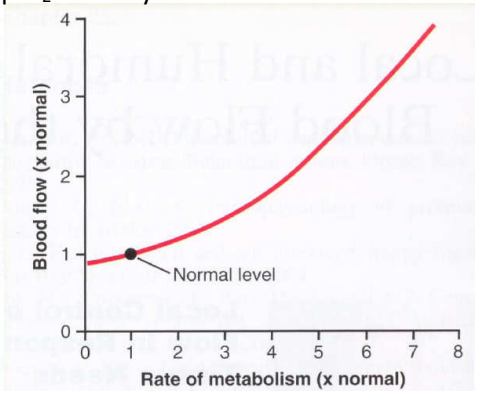
Control of blood flow

- Acute and long term
  - Acute – vasoconstriction/dilation of ateries/capillaries
  - Long term – BV number and size
- Acute:
  - Local
    - Tissue metabolism (O_2 needed) – tissue does more, gets more blood
      - Oxygen lack theory - smooth muscle cells in arterioles can't constrict without oxygen and thus dilate
      - Vasodilator theory – decreased oxygen and nutrients, vasodilator substances are produced
    - Autoregulation
      - Myogenic mechanism
      - Metabolic mechanism
    - Factors are released by endothelium
  - Neural – sympathetic nervous sytem
  - Humoral – eg: adrenaline, noradrenaline, angiotensin II
- Local metabolic – blood flow increases with rate of metabolism
- Reactive hyperaemia – occlusion of blood flow causes a transient increase in flow to pay back the oxygen debt
  - Eg: exercising muscle
    - Muscles contract and occlude the BV, each contraction is followed by reactive hyperaemia
- Oxygen saturation vs blood flow
  - If saturation decreases, blood flow increases to compensate and keep O_2 delivery the same



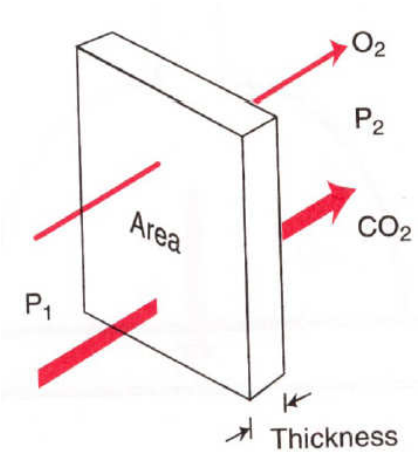






Gas movement through tissues

- Mostly move by diffusion
  - Volume of gas/unit time α A/T . D . (P_1-P_2)
    - D is the diffusion constant
    - T is thickness, open capillaries, 50µm, vs 0.3 µm in the lung alveoli
  - D α Sol/ Sqrt(MW)
    - Sol is the solubility of the gas
    - MW is the molecular weight

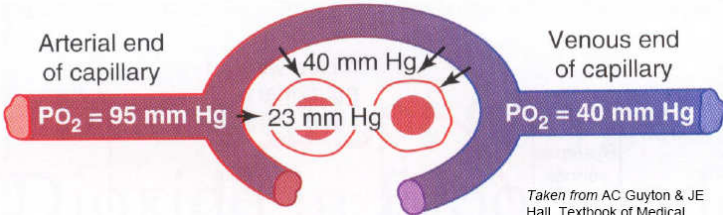


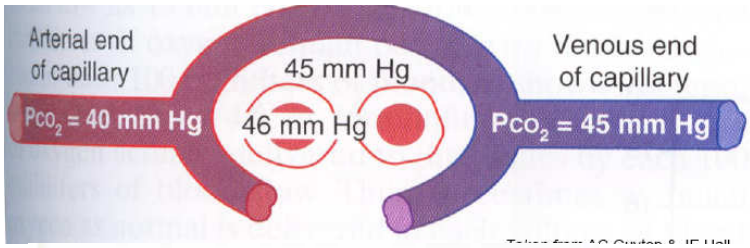
$$\dot{V}_{gas} \propto \frac{A}{T} \cdot D \cdot (P_1 - P_2)$$

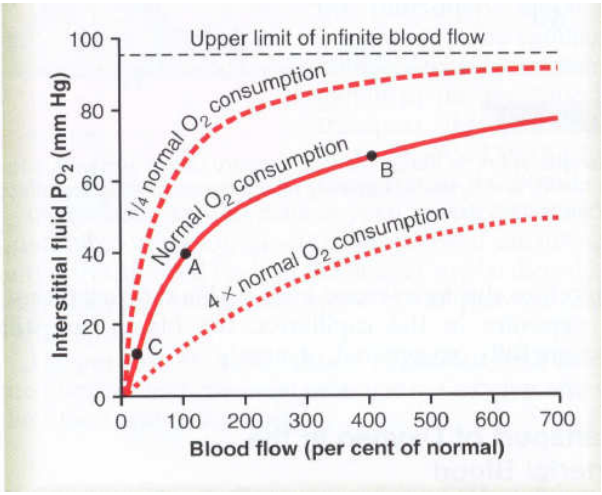
$$D \propto \frac{Sol}{\sqrt{MW}}$$

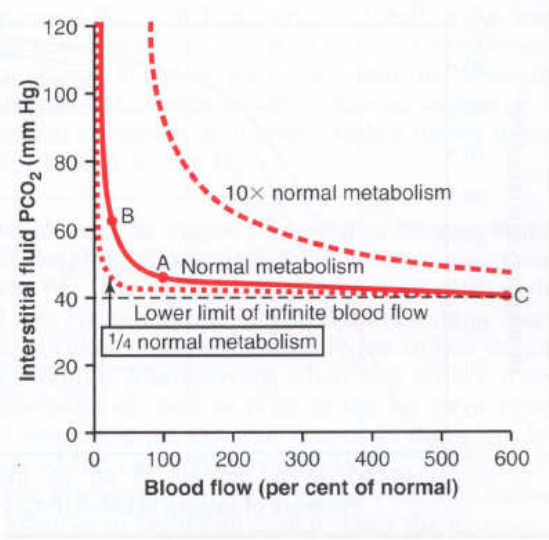
Oxygen levels in the tissues

- Oxygen diffuses from the systemic capillary blood to the interstitial fluid and then to the tissue cells by diffusion
  - This causes P_{O2} in the blood to fall
  - Reverse process for CO2

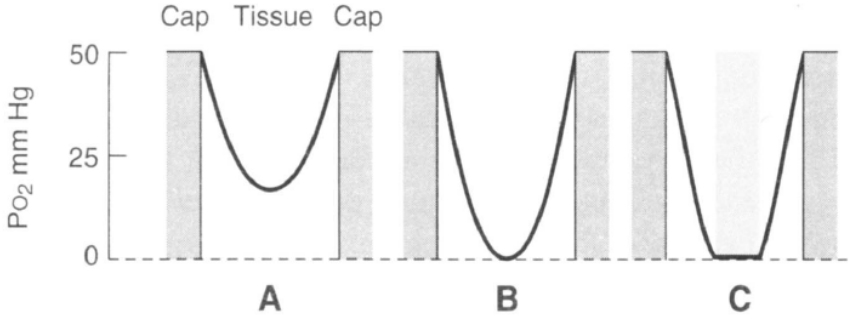








- Muscle cells
  - Often have very low (1-3mmHg) P_{O2}
    - This is due to myoglobin – reservoir for oxygen that supplies oxygen at low blood P_{O2} (exercise)
    - This enhances the diffusion gradient and allows O_2 to easily diffuse and feed muscle cells
  - During exercise, oxygen consumption increases and capillaries open up increasing the area for diffusion and decreasing the diffusing distance
  - CO_2 diffuses faster through tissue (20x) than oxygen, thus removal is not a problem vs oxygen delivery
- Oxygen delivery
  - A – oxygen delivery is adequate
  - B – oxygen delivery is JUST adequate (critical)
  - C – oxygen is inadequate for aerobic metabolism in the central core of tissue
    - Cell turns to anaerobic glycolysis and forms lactic acid
    - Glycolysis should lead to more blood flow and thus a return to aerobic metabolism



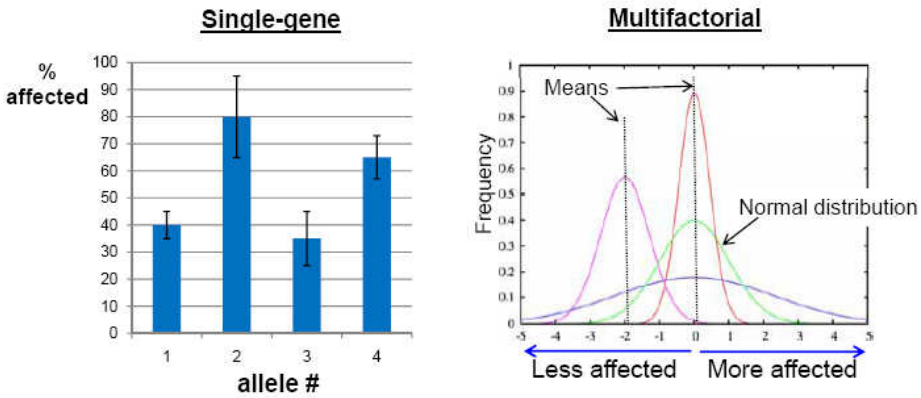
Lecture 24: Genetics and human health

Definitions
- Disorders – an abnormality in the genes resulting in a condition
- Disease – infectious diseases

The influence of genes
- Characteristics – in individuals and populations is defined by:
    - Genes
    - Environment
    - The interaction between these
- Studies:
    - Twin studies show a genetic component in diseases and disorders
        - Identical (monozygotic twins) have the same genes
        - Non-identical (fraternal, dizygotic twins) have different genes
        - Since monozygotic twins are more similar than dizygotic, genes have a strong influence
            - Ie MZ twins have genetics and environmental similarity while DZ have only environmental
    - Certain diseases are more determined by lifestyle/genes/combination of both
        - Eg: genes – psoriasis, diabetes, depression
        - Eg: lifestyle – MS, cancers
        - Eg: both – IQ, personality

More definitions
- Gene – the smallest unit of inheritance, a series of base pairs that encode a protein product
- Allele – an alternate version of a gene (come in abnormal/normal)
    - Particular genes can have many alleles
- Locus – the location of a gene on the chromosome
- Genotype – genetic makeup of an organism
- Phenotype – physical/biochemical characteristics of an organism, arise from genes/environment
- Population – a group of interbreeding individuals of the same species that inhabit the same place at the same time

Human disorders – due to genetics
- Can be due to problems with a single gene or can be multifactorial
    - Single gene – discrete data
    - Multifactorial – eg: traits like height



- Single-gene disorders
    - >12000 genes involved in known single-gene disorders
        - Catalogued by OMIM (online mendelian inheritance in man)
    - Eg: Sickel cell anaemia

Sickle-cell anaemia

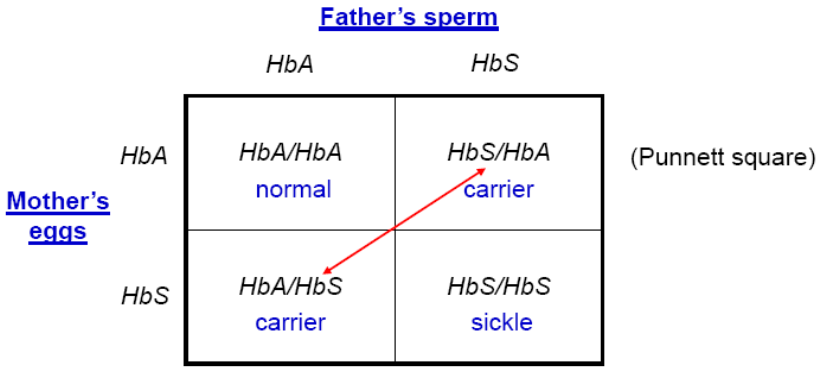
- Caused by a mutation in the gene for the haemoglobin β-chain
  - Thus the β-chain forms abnormally long cylindrical lines that causes sickle-shaped cells
- Each person has two copies of the Hb gene
  - Several alleles exist, some of which result in normal production (HbA) or sickle-cell production (HbS)
  - Thus, 3 phenotypes of individuals based on genotypes

Genotypes	HbA/HbA	HbA/HbS	HbS/HbS
Phenotypes	Normal	Carrier	Sickle

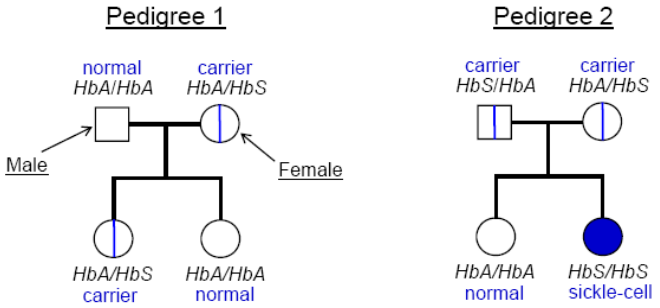
- HbS/HbS is often lethal
  - The HbS allele is kept in the population, however, because it has a selective advantage in its increased resistance to the malaria virus
  - Thus, HbA/HbS is common in malarial regions due to its selective advantage
    - However, HbA frequency is still greater because HbA/HbS causes slight disease

Single-gene inheritance

- Mendel's laws
  - Single genes are inherited in the Mendelian fashion (simple probability)
  - This is based on the nature of fertilisation – haploid gametes fusing to create a diploid organism
- Note: there can be maternal/paternal factors



- Pedigrees
  - Disease-causing mutations can be traced through families using pedigrees (family trees)

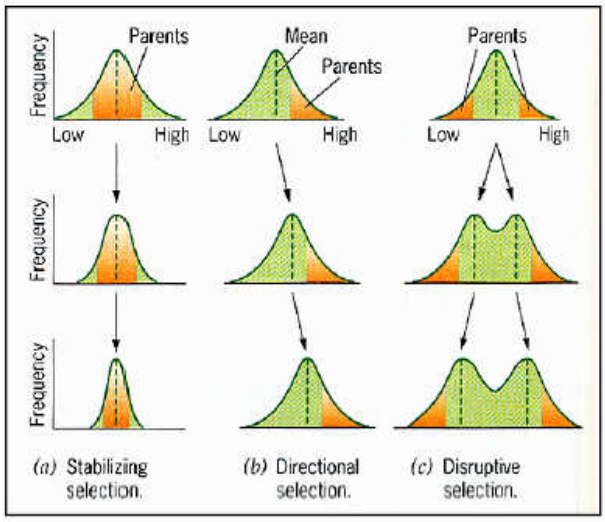


Inheritance of multifactorial disorders

- Very complex – many genes, many alleles
  - Strongly influenced by linkage of genes (whether genes are close together on the chromosome)
    - Linked genes are more likely to be inherited together (to do with crossing over during fertilisation)
- Genes involved in multifactorial disorders can be identified by linkage analysis and thus studies performed
  - Candidate gene studies
    - Often find nothing
    - Biochemical etc data on genes/disorders is analysed and thus possible responsible genes are identified
      - Thus, individuals are sampled and their phenotype/genotype compared
  - Genome screening
    - Take affected individuals and sequence their entire genome or certain markers
      - Expensive, but becoming more financially viable

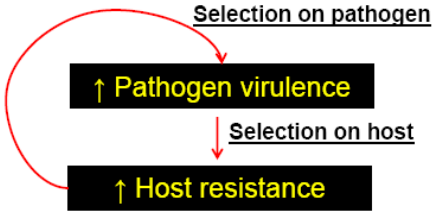
Frequency of genetic disorders

- Population size
  - Small populations are more susceptible to random changes and their genetics can be more easily changed
    - Founder effect – small population founded by a few people
      - Intermarriage and a lack of genetic diversity
    - Bottleneck effect – in event of a catastrophe, individuals that survive reproduce
      - Less genetic diversity and higher levels of genetic diseases
- Mating (marriage)
  - Random – no regard to characteristics
  - Assortative – find individuals that look like you
- Mutation
  - Vary in different populations, often environmental (eg: Chernobyl)
  - A source of new alleles
  - Mutations often result in increased problems/diseases/disorders and thus are often not passed far
- Migration
  - The world has essentially become one big population
    - This means that good and bad genes spread everywhere
  - Results in increased human diversity
- Natural selection
  - Stabilising selection – natural selection for those about the mean
  - Directional selection – gradual shift in populational mean (eg. height)
  - Disruptional selection – shift away from the mean, possible bimodal distribution
    - Huamns may override natural selection by mate selection and drift (random changes)



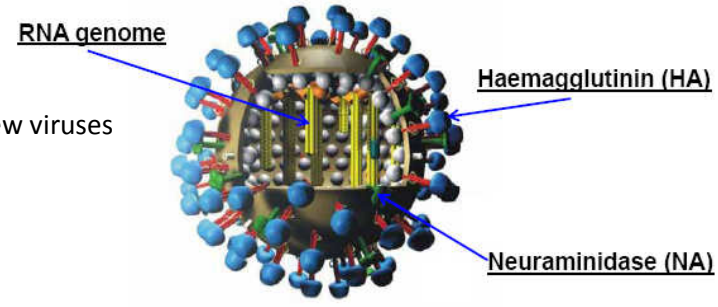
Human disease

- Pathogens and host defences are in a genetic arms race
  - Pathogen virulence and host resistance are based on genes/alleles



EG: influenza

- A virus that infects mammals and birds
  - Causes “flu”, chills, fever, muscle pain etc
- Structure:
  - Surface molecules:
    - Hemagglutinin (HA) – enables cell entry
    - Neuraminidase (NA) – allows budding of new viruses



Antigenic shift and drift

- To clear influenza, the immune system recognises the surface molecules (antigens)
    - HA and NA are important for influenza virulence
    - HA and NA are continuously mutating so as to not be countered by the immune system
        - These can change by antigenic drift/shift
- Small changes in the antigen – drift
    - Can lead to epidemics – several strains of the flu arise each year, can be countered with 'guess' vaccine
- Large changes in antigen – shift
    - Can lead to pandemics – human immune system is completely ineffective
- Shift can occur due to mixing of human and animal genomes
    - Eg: bird/pig infected by both human and animal strains, these infect the same cell and by chance the genome becomes mixed
        - Causes huge antigenic shift, human immune system has no counter causing a pandemic
    - This may occur with the avian flue strain H5N1

EG of antigenic drift/shift: antibiotic resitance

- Bacteria can become resistant to antibiotics
    - Mostly due to poor management of antibiotics:
        - Insufficient doses – need to be treated beyond asymptomatic or bacteria may not be completely destroyed and resistance develops
        - Inappropriate use – eg: antibiotics in farming
    - Bacteria can share resistance genes (via plasmids, conjugation etc)
        - Resistance genes can be combined and spread in DNA cassettes
- Human response:
    - Alleles in population influence susceptibility
        - Humans don't evolve fast enough for this resistance to be bred into genome
        - If selective pressure is high enough (eg. in a pandemic), natural selection may increase human resistance, many people will die however
    - Prevention is better than cure
- Study of resistance genes is important but difficult
    - Allow us to identify new drug targets
    - Allow us to better understand differences in disease susceptibility

Definitions

- Tuberculosis is an infectious disease mostly caused by Mycobacterium tuberculosis
    - Normally involves the lungs, can spread to other sites
        - Ie: extrapulmonary tuberculosis – eg: meninges, skin, GIT

Pulmonary tuberculosis

- Symptoms:
    - Cough
        - Cavitary TB may have haemoptysis
    - Chest pain
    - Weight loss
    - Night sweats
    - Fever
    - Malaise
    - Can be non-specific
- Transmission
    - Aerosol droplets nuclei
        - Ie: by coughing, sneezing, talking (one sneeze = 40 000 droplets)
        - Small droplets (1-5µm) can carry 1-10 bacilli
        - Dry dust particles can also carry bacilli for a long time (due to unique bacterial wall)

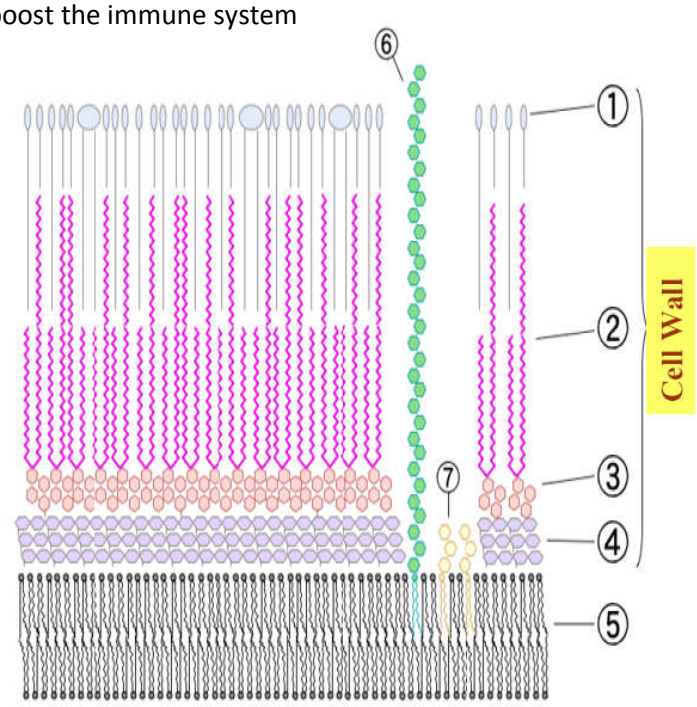
Epidemiology of tuberculosis

- Globally TB is quite a large health concern:
    - 2 billion people are infected
    - 14 million have active disease
    - Two million die/year
- Trends differ country to country
    - Africa, South-east Asia and the western pacific have much higher incidence, prevalence and mortality than the Americas, eastern Mediterranean and Europe
- Australia
    - Very low incidence – one of the lowest in the world
        - In 2006, 1201 notified cases (notifiable disease), made up of 1142 new cases and 59 relapses
    - Highest incidence is in indigenous Australians and migrants

Mycobacterium tuberculosis

- Mycobacterium genus has >70 species
    - Mycobacterium tuberculosis complex:
        - M. tuberculosis – main cause in humans
        - M. africanum, M. canettii – human TB in Africa
        - M. bovis – cattle/possible human transmission
        - M. microti – rodents
    - Mycobacterium Avium Complex (MAC)
        - M. avium subspecies avium, subspecies intracellulare, subspecies paratuberculosis (cattle)
    - M. leprae (Hansen's bacillus)
        - Causes leprosy, affects nerves
- Properties
    - Strict aerobe
    - Curved/rod shape – bacillus
    - Slow growing: doubling times:
        - M. tuberculosis – 15-20 hours
        - M. leprae – weeks
        - M. smegmatis – 3-4hours
        - E coli (for comparison – 20-40 minutes)

- Cell wall:
  - High lipid content, waxy
    - Thus resistant to chemical agents and desiccation (can survive in dry sputum for weeks)
    - Resistant to decolourisation with acid-ethanol thus gram stain is useless
  - Cell wall components stimulate immune system (non-specifically), ie induce macrophage response so they can live intracellularly
  - Cell wall components can be used as part of Freund's adjuvant – an antigen solution emulsified in mineral oil that can be used to boost the immune system
  - Components:
    - Outer lipids
    - Mycolic acid
    - Polysaccharides
    - Peptidoglycan



Mycobacterial cell wall:

1-outer lipids,

2-mycolic acid

3-polysaccharides (arabinogalactan)

4-peptidoglycan

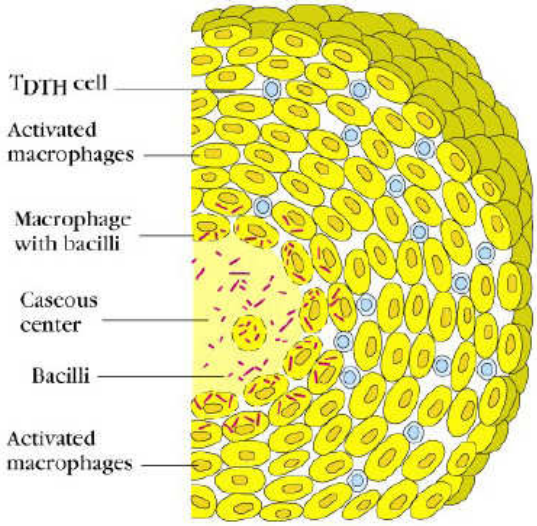
5-plasma membrane

6-lipoarabinomannan (LAM)

7-phosphatidylinositol mannoside

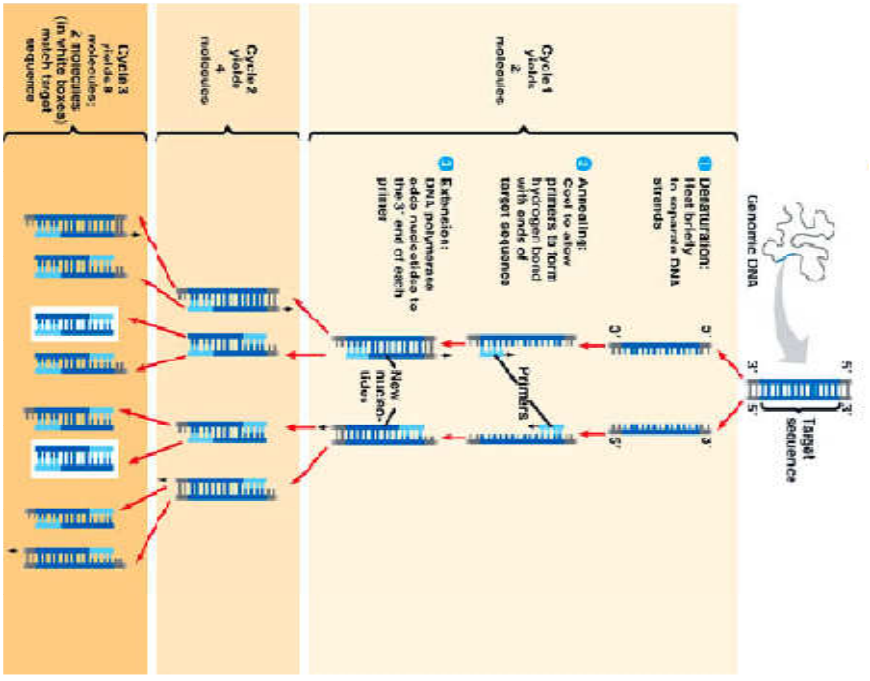
Pathogenesis

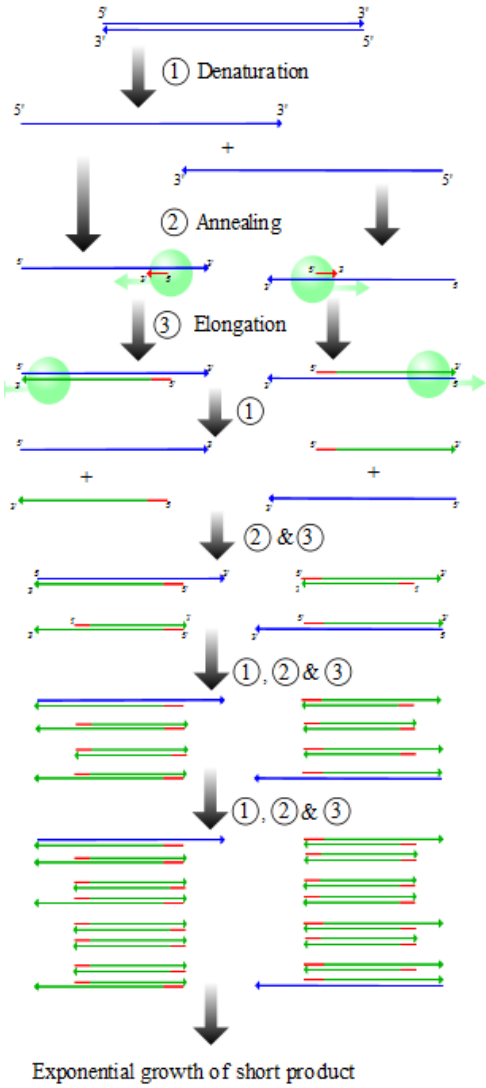
- See kumar's lecture
- Briefly:
  - Primary infection → survival and multiplication of TB in alveolar macrophages
    - Cell-mediated immune response induced → macrophages activated (3-4 weeks later) granuloma formed
      - Progressive disease
      - Infection resolved
      - Latent infection
        - Active disease later in life
- Lesions are caused by host immune response
  - Result from hypersensitivity reaction to the mycobacterial antigen
    - Granuloma – when there is less antigen and a good immune response
    - Tissue necrosis (enzyme) – when there is more antigen and thus a larger immune response
  - Cytokines cause pyrexia, cachexia and other symptoms
    - Eg: TNF, and IFN-γ



Diagnosis

- Sample collection
  - Pulmonary tuberculosis – sputum
  - Extra-pulmonary – specific to location
    - Eg: lymph node, tissue biopsy, cerebrospinal fluid, blood
- Direct microscopy
  - Ziehl-Neelsen staining (acid-fast staining)
    - Carbolfuchsin (red stain) dye while heating with steam to make cell wall more permeable
    - Decolourise with hydrochloric acid and ethanol
    - Counterstain with methylene blue
  - Standard lab protocols need 100 fields of view to confirm diagnosis, TB hard to find
    - A single acid-fast bacillus is diagnostic
    - To find a single bacillus, need quite high bacterial numbers (10^4/ml), thus test is not very sensitive
      - Thus, need care when reporting negative results: "no acid fast bacilli seen"
    - All mycobacteria are acid-fast, and other bacilli like Nocardia are weakly acid fast
  - Fluorescent staining
    - Requires special microscopy, not economically viable for developing countries
    - Auramine-rhodamine or auramine O
    - More sensitive and efficient
- Bacterial culture
  - Important for proper identification and antibiotic sensitivity testing
  - Solid media
    - Lowenstein-Jensen medium
    - 2-6 weeks for growth, 2-4 weeks for species identification)
  - Liquid media
    - Rapid identification (2 weeks)
  - Media may require inhibition of other organisms – malachite green
    - Bottle used to prevent drying
- Mantoux test (Tuberculin test, PPD)
  - PPD (purified protein derivative)
    - Crude extract from M tuberculosis
    - Injection intradermally
      - Size of reaction measured 48-72 hours later
    - Positive result means previous exposure to TB, doesn't have to be acute TB
      - Stimulates $CD4^+$ TH memory cells thereby determining whether immunological memory is present
- Molecular methods
  - Polymerase chain reaction
  - Nucleic acid probes – hybridisation using specific probes





Treatment

- Need to continue for 6 months
- First line drugs:
    - Isoniazid (INH)
    - Rifampin (RIF)
    - Pyrazinamide (PZA)
    - Ethambutol (EMB)
    - Streptomycin
- Second-line drugs
    - Less effective, or have toxic side effects
- Non-compliance can be a problem in treating TB
    - This can lead to drug resistance
    - WHO: DOTS – directly observed therapy, short course
        - Ensures that full course is taken and avoids relapse
        - Aims to reduce emergence of drug resistance
- Vaccination
    - BCG (developed from M. bovis)
        - On administration, it destroys macrophages and response elicited
        - Cheap and safe, but not necessarily effective
            - Controversial due to this variable efficacy (0-80%)
            - Doesn't prevent reactivation of pre-existing infection
        - Become Mantoux test positive
        - Not used routinely in Australia and USA

TB and HIV

- 40 million people have HIV
    - TB accounts for 13% of HIV-related death (can be higher in some regions)
- TB reactivation
    - HIV+ is 10%/year
    - HIV- is 10% lifetime
- Active TB is associated with a higher viral load and thus faster progression of HIV (CD4 drops faster)

Drug resistance

- Multidrug resistance TB (MDR-TB)
    - Defined as resistance to at least Isoniazid and Rifampicin
- Extensively drug resistant TB (XDR-TB)
    - MDR-TB that is resistant to quinolones and one of kanamycin, capreomycin or amikacin
    - Almost untreatable, serious public health threat
        - Eg: outbreak in South Africa in 2006 included 53 cases of XDR-TB
            - Average time of death was 16 days after sputum sample taken, all were HIV positive

Timeline

- 1882 – Koch identified causative agent
- 1921 – BCG vaccine produced, based on attenuated strain of M bovis that was cultured in the lab
- 1948 – streptomycin discovered, lowered TB rates
- 1980s – TB re-emerged with HIV
- 1993 – global emergency declared by WHO
- 1990s-today – multiple-drug resistant TB spreading

Definition

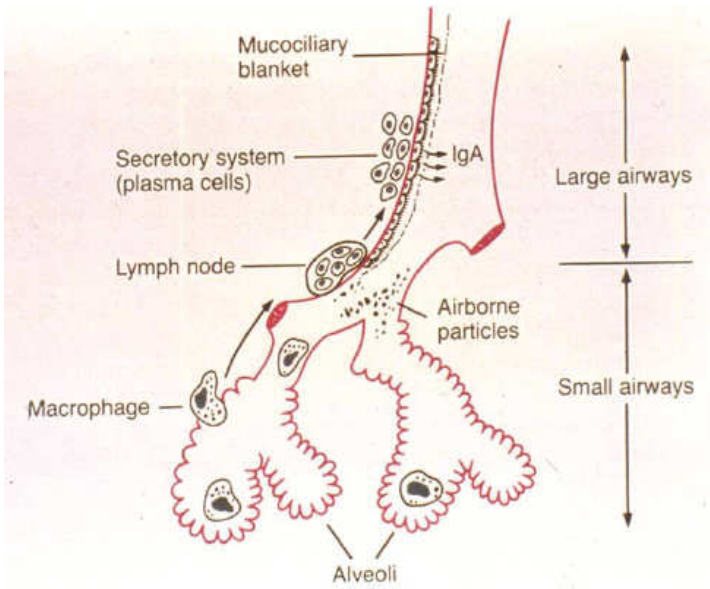
- Pneumonia (pneumonitis) - microbial invasion of the lung parenchyma and the associated host response
    - An expression of the acute inflammatory process
    - Parenchyma – the gas exchange part of the lung, distal to the terminal bronchioles
- Pneumonia can be particularly fatal for people with cancer or heart failure
    - "captain of the men of death

Classification factors

- Acute or chronic – not very useful except in defining pyogenic infection vs TB
- Typical or atypical – various microorganisms can express differently, and thus need different treatments
- Community acquired pneumonia (CAP) or nosocomial/hospital healthcare associated pneumonia (HCAP)
    - CAP – has a certain spectrum of microorganisms, therefore there are certain treatments
    - HCAP – often involves multi-drug resistant strains
- Normal/immunocompromised host – determines treatment/outcome
- Microbial agent - makes diagnosis easy and allows specific treatment
- Radiological (pathological) – eg: lobar, segmental, broncho-pnuemonia (Brisbane disease haha)

Causes

- Background and setting guides the likelihood of different species
- Bacteria
    - Streptococcus pneumoniae – pneumococcus (CAP)
    - Gram –ve bacteria like Enterobacteriaceae (E. coli, Klebsiella pneumoniae, Enterobacter sp.) – causes problems with ventilation
    - Pseudomonas aeruginosa – especially a problem in cystic fibrosis
    - Legionella species – can be spread by air conditioned cooling towers
- Bacteria-like
    - Mycoplasma pneumoniae
    - Chlamydia pneumoniae
    - Chlamydia psittaci – associated with birds
    - Coxiella burnetti – causes Q-fever
- Viruses
    - Influenza A and B
    - Adenovirus
    - Can predispose to bacterial infections because they lower lung defences
- Fungal
    - Especially affect immunosuppressed
    - Aspergillus
    - Cryptococcus neoformans – causes HIV meningitis
- Mycobacteria
    - Mycobacteria tuberculosis



Pathogenesis

- A fight between virulence and dose vs host defences
- Failure of host defences
    - Filtration/humidification of inspired air – filter larger particles
    - Epiglottic, gag/cough reflexes – prevent aspiration that can lead to pneumonia
    - Mucociliary transport – normally transport foreign material from the trachea and bronchioles
        - Have ciliated pseudostratified columnar epithelium with goblet cells
            - Cilia move particles out of the trachea where it can be coughed/swallowed
            - Mucus traps the debris
    - Innate immunity – alveolar macrophages, neutrophils, complement
    - Humoral immunity – B-cells, immunoglobulins (IgG, IgA), complement
    - Cellular immunity – antigens presented to T-cells in hilar lymph nodes
- Vs virulent organism and sufficient inoculum

Causes of defence impairment

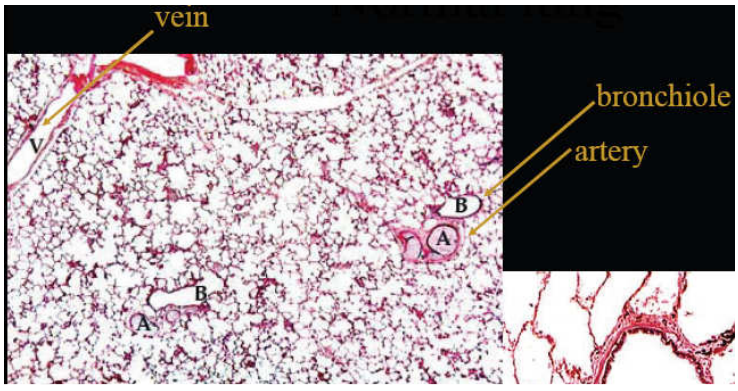
- Extremities of age – old age and very young
- Impaired mucus drainage – eg: CF, bronchiectasis (permanent dilation of the airways resulting in easy collapse and thus obstruction), obstructive neoplasm, foreign body
- Impaired mucociliary apparatus – eg: congenital, post-viral (damage to cells), cigarette smoke
- Impaired consciousness – cough/gag reflex suppressed (eg. anaesthesia, coma, narcotic drugs, EtOH)
- Static fluid in alveoli – cardiac failure: pulmonary oedema forms a liquid medium of nutrients
    - Macrophages are less effective in fluid (anoxia and hypoxia also affect macrophages)
- Immunodeficiency (innate, humoral, cell-mediated)

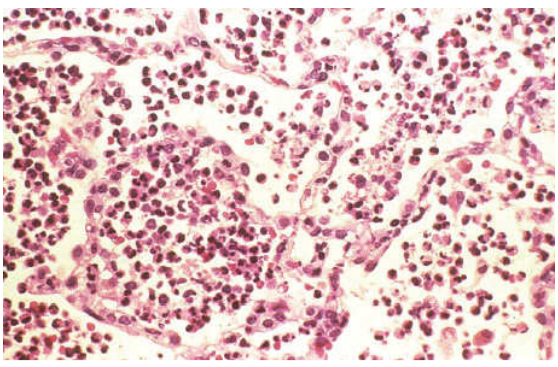
Pneumonia syndromes

- Acute, CAP – typical syndrome
- Atypical pneumonia
- Nosocomial (HCAP) pneumonia
- Pneumonia in the immunocompromised

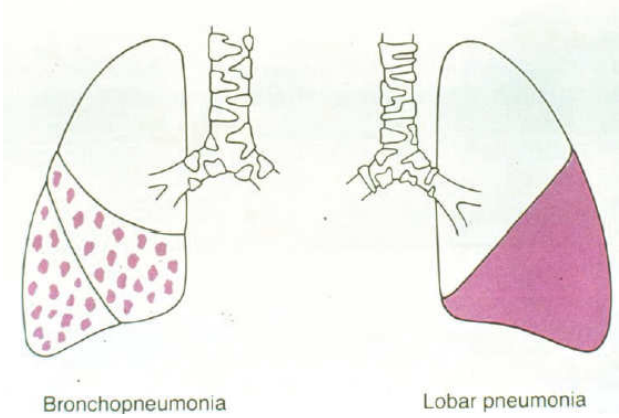
Community acquired pneumonia

- Epidemiology
    - Increased risk at extremes of age – all ages affected however
    - Increased incidence in mid-winter
    - Increased with underlying disease such as COPD (chronic obstructive pulmonary disease), diabetes mellitus and alcoholism
- Symptoms
    - Chills, rigors, productive cough, pleuritic chest pain
- Signs
    - Fever, tachypnoea, dullness to percussion,
    - Crepitations, bronchial breathing – due to alveoli not opening up because of consolidation
    - Pleural friction rub – inflamed lungs therefore rubbing on pleura
- Laboratory findings
    - Neutrophil leucocytosis, hypoxaemia (measured by oximetry),
    - Sputum with polymorphonuclear cells, gram stain or culture showing organism (gram +ve cocci)
- Pathology
    - Lobar – diffuse throughout a certain lobe
    - Bronchopneumonic – multifocal following terminal airways
    - Suppurative (due to pyogenic bacteria)
        - Bacteria releases myopeptides that are chemotactic to neutrophils
    - Classical stages – often not seen anymore due to antibiotics
        - Congestion – exudate into alveoli
        - Red hepatisation – looks like a solid piece of liver made up of neutrophils, fibrin and exudate
            - Red because capillaries are damaged and red cells leak into lung
        - Grey hepatisation – red cells degenerate
        - Resolution
- Histology:
    - Slide 1:Terminal bronchioles and sparse blood vessels are surrounded by alveoli, capillaries are dilated
    - Slide 2: PMNs, red cells, (red hepatisation), proteinaceous material causes consolidation of the alveoli via fibrin meshwork

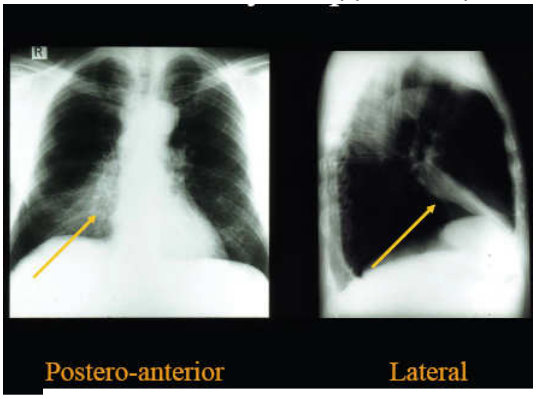


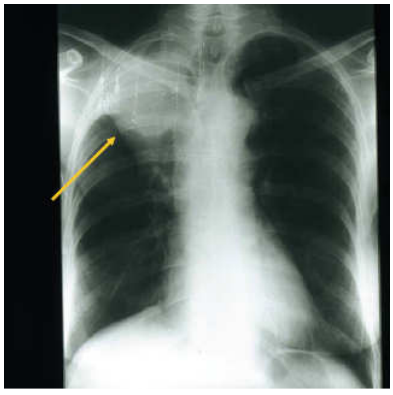


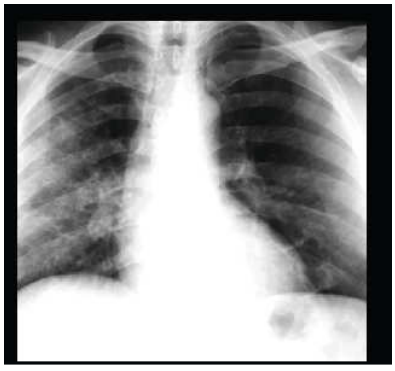
- Bronchopneumonia vs lobar pneumonia
  - Bronchopneumonia
    - Bacteria spread to multiple foci via the airways
    - Some parts are badly affected others are not
    - Can lead to confluent bronchopneumonia and this can appear like lobar pneumonia
  - Lobar
    - Particularly pathogenic strain of TB that can resist phagocytosis
    - Thus can spread in the exudate and infected entire lobe of lung



- Symptoms
  - Cough – stimulated by the inflammatory process
    - Purulent sputum if there is exudate
  - Shortness of breath – hypoxaemia (due to low saturation of the blood)
    - A perfusion/ventilation mismatch results in blood perfusing but not being oxygenated and thus causing cyanosis (effectively, lung is not oxygenating blood, blood shunt form R to L heart)
  - Pleuritic chest pain (maybe pain on inspiration)
    - Stimulation of sensory nerve endings in the parietal pleura by inflammation of the visceral pleura
- Signs
  - Tachypnoea – chemoreceptor mediated response to hypoxaemia
  - Fever – resetting of hypothalamic thermostat by IL-1, TNF-α
  - Crepitations – opening of fluid (pus)-filled alveoli
  - Dullness to percussion – consolidation of lung tissue (loss of resonance)
- Investigations
  - Imaging: chest x-ray (most important diagnostic investigation)
  - Cultures
    - Sputum – can't identify location of bacteria, can identify bacteria and determine antibiotic sensitivies
    - Blood – 20-30% of cases will turn up +ve
  - Ancillary tests:
    - FBC – neutrophil leucocytosis
    - Inflammatory markers – CRP (C-reactive protein), a systemic marker produced by the liver
    - Arterial blood gases – hypoxaemia
- Microbiology
  - Streptococcus pneumoniae (most common)
  - Haemophilus influenzae – especially in COPD, viral infection
  - Staphylococcus aureus – especially with previous viral infection
  - Legionella pneumophila – often found in epidemic settings
- Radiology
  - Can determine pattern: lobar or bronchopneumonia
    - Broncho – bilateral diffuse patterns, commonly in base of the lungs
      - More common in debilitated people, CHF, disseminated malignancy
      - Static secretions at base of the lungs provide medium for bacteria to grow
    - Lobar – isolated to one lobe
  - Consolidations appear as opacities



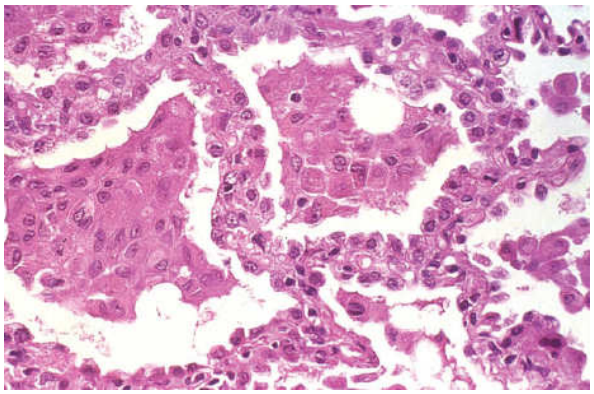


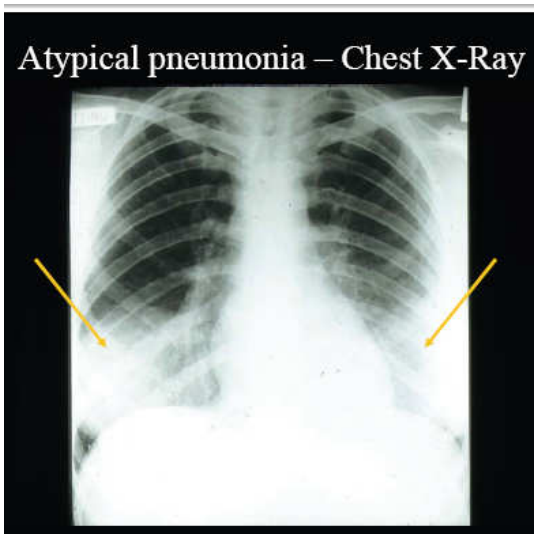


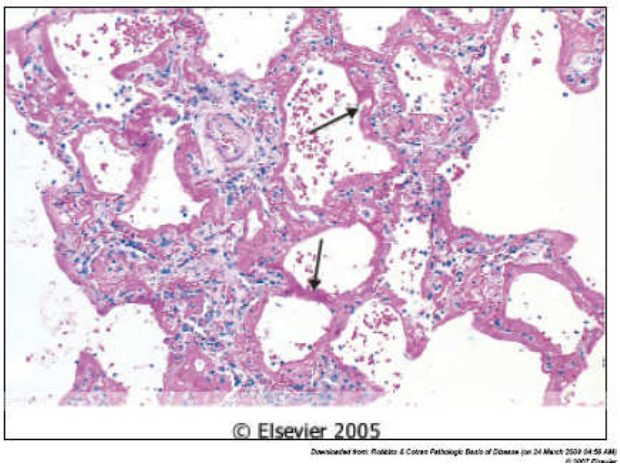
Slide 1: right middle lobe pneumonia, Slide 2: pneumonia in the right apex, Slide 3: multifocal bronchopneumonia

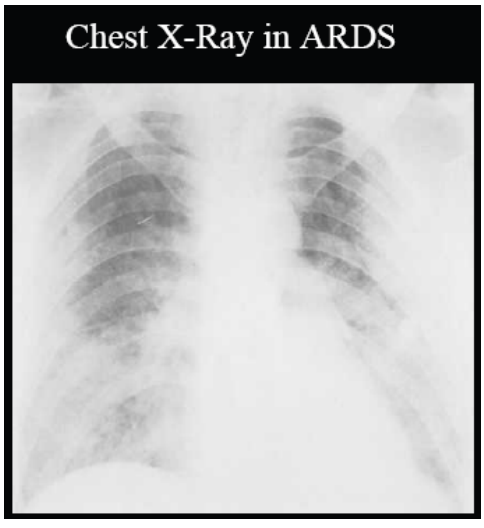
Atypical pneumonia – eg. mycobacterium pneumoniae (intracellular or viruses)

- Epidemiology
  - Children, adolescents, young adults, institutions
  - Year round occurrence
- Symptoms
  - 3-4 day prodrome of malaise
  - Then syndrome of headache, fever, and dry cough (non-specific symptoms)
    - Often mistaken for non-specific virus or bronchitis
- Signs – sparse, in the interstitium, not alveoli
- Laboratory tests – typically limited and unspectacular
- Pathology (interstitial pneumonia)
  - Inflammation in the alveolar septa (interstitium)
  - Infiltration of mononuclear leucocytes
    - Macrophage, plasma cells, T-lymphocytes
  - Proteinaceous exudate may occur
  - Hyaline membrane formation
    - Caused by alveolar epithelial damage
    - Made up of fibrin, surfactant proteins, and epithelial debris
    - Line alveolar walls and create a barrier between gas and blood causing hypoxaemia
      - This may lead to ARDS (acute respiratory distress syndrome)
- Slide: alveolar septa are full, there is shedding of epithelial cells into the spaces
- Microbiology
  - Mycoplasma pneumoniae (70%)
  - Chlamydia (Chlamydophila) pneumoniae
  - Viral: influenza A and B, adenovirus
  - Coxiella burnetti (Q fever)
  - Chlamydia psittaci
- Radiology
  - Hazy reticulonodular appearance
  - Slide: ARDS – diffuse alveolar damage
    - Eosinophilic membranes line damaged alveoli
    - Cause very opaque x-ray







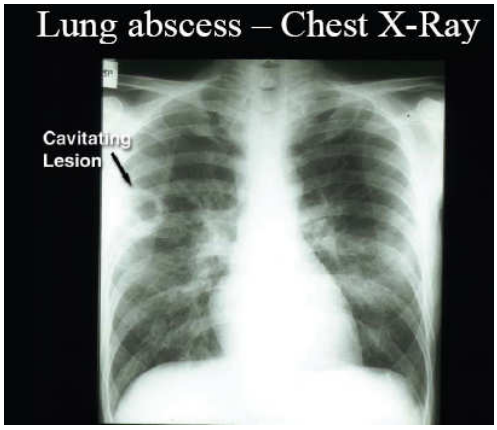


Nosocomial (healthcare associated) pneumonia

- Epidemiology
  - Elderly, unwell
  - Hospitals and nursing home
  - Recent surgery, intubation – gram –ve rods colonise ventilator tubing
  - Broad-spectrum antibiotic use – multi-drug resistant strains
- Symptoms
  - Fever, deterioration
- Signs
  - Tachypnoea, basal crepitations
- Laboratory findings
  - Leucocytosis, hypoxaemia
- Microbiology
  - Aerobic gram –ve bacilli (60%)
    - Klebsiella pneumoniae, E. coli, Serratia species, Enterobacter species, Pseudomonas aeruginosa
  - Staphylococcus aureus
  - Streptococcus pneumoniae
- Radiology
  - Variable, often patchy, widespread bronchopneumonia

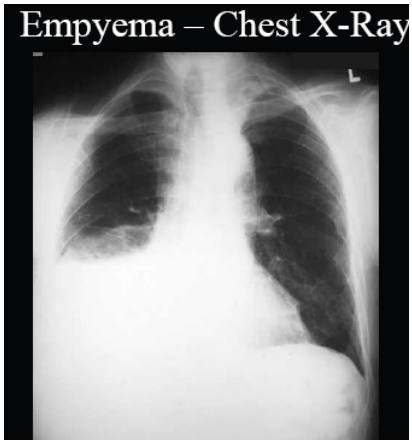
Pneumonia in the immunocompromised

- Features of pneumonia are often associated with immunodeficiency
  - HIV:
    - Diffuse, Interstitial pneumonia of insidious onset
    - Commonly due to Pneumocystis carinii (jirovecii) (PCP)
  - Acute leukaemia:
    - Focal pneumonia of insidious onset
    - Fever, productive cough
    - Often due to Aspergillus fumigatus
  - Bone marrow transplantation
    - Severe, diffuse, interstitial pneumonia
    - Often due to cytomegalovirus

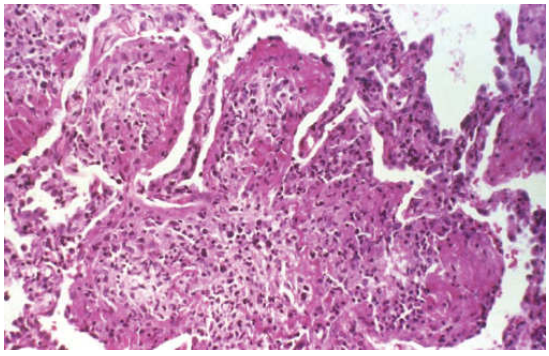


Complications of pneumonia

- Abscess formation
  - Pathogenesis:
    - Aspiration of infective material or gastric acid (most common)
      - Possibly due to impaired consciousness
    - Caused by certain bacteria associated with bronchopneumonia (esp. SA, Klebsiella pneumoniae, type 3 pneumococcus)
    - Septic embolism – of infective endocarditis or teeth gums
    - Airway obstruction
    - Penetrating injury to the lungs
    - Spread from adjacent organs
    - Haematogenous spread to the lung
- Empyema formation
  - A sinus into the pleural space is formed, pus collects and enters the pleural cavity



- Disseminated infection
  - Eg: meningitis, septic arthritis, infective endocarditis
  - Septic shock and multiple organ failure
- Respiratory failure
- Organisation of exudate – process of granulation – fibrous growth into exudate
  - Thus causes loss of gas exchange in the lungs



Introduction
- Causes of death globally:
  - TB – number 7
- Natural history: 50% die, 25% spontaneous cure, 25% chronic TB (continue to affect other people)

Global epidemic
- Epidemiology
  - 9.2 million new cases in 2006, incidence 139/100 000
  - 4.1 million were new smear positive cases (41% of cases)
  - 0.7 million are HIV positive (8%)
  - 14.4 million prevalence
  - 0.5 million MDR
- Number of cases
  - Top 5: India, China, Indonesia, South Africa, Nigeria
  - Africa has highest incidence of 363/100 000, HIV coinfection is an important factor
- Millennium development goal 6: to halt and reverse TB incidence by 2015
  - Stop TB strategy has 6 components:
    - DOTS expansion
    - Addressing TB/HIV, MDR-TB
    - Health system strength
    - Engagement of all care providers
    - Empowering of patients and communities
    - Enabling and promoting research

Australia epidemiology
- Prevalence: 2/100 000
- Incidence: 1000 cases/year, 80% born overseas
  - Most from SE Asia, Africa
- >80% are pulmonary TB – typical of a developed country
  - Developing countries – mostly extrapulmonary TB, women more prevalent
- In Australia, mainly reactivation disease
  - Compulsory screening of migrants – students are missed

Transmission
- >99% of transmission is via the respiratory route (pulmonary TB)
  - Requires prolonged close contact
    - Transmission can be increased by poor ventilation, crowded conditions etc.
  - Also dependent on the virulence of the organism
- Smear positivity determines infectiousness,
  - If there is smear positive, there are more TB organisms
  - If there it is smear negative, but culture positive, there are less TB organisms but still infection

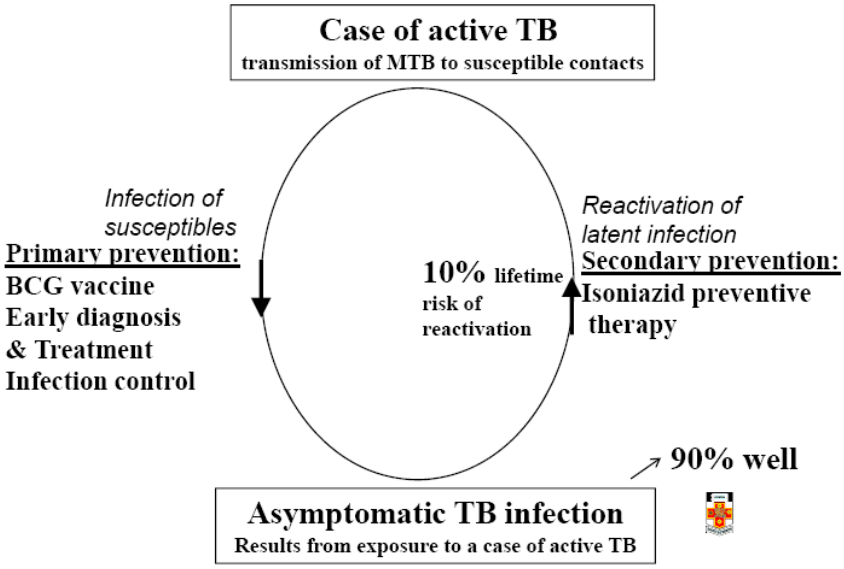
Notifiable diseases
- State laws make it compulsory to notify several diseases
  - Including: TB, small pox, SARS, pertussis, etc
- This facilitates contact tracing, screening and preventative therapy
  - Thus, need to screen household contacts and widen the contact circle using the “stone in the pond” model
    - Keep screening further and further out until get 5% prevalence (normal population prevalence)

Screening

- Principles
  - Screen for diseases of public health importance
  - Screen if intervention is possible
  - Screen if the results is a desirable change in outcome
    - Often these principles are not met, but screening occurs regardless
- Tools
  - Mantoux skin test
    - Sensitive, but false positives occur (BCG, environmental, mycobacteria)
    - PPV varies with prevalence
  - Chest x-ray
    - If there is a positive skin test or patient is symptomatic, perform chest x-ray
      - However, WHO stopped asymptomatic recommendation in 1970
    - Can identify cavities, consolidation, apical, hilar lymphadenopathy

Infection cycle

- Notes:
  - 10% lifetime risk, 5% in the first year, 5% the rest of life



Prevention

- Primary prevention
  - BCG, early diagnosis, treatment/infection control
    - Once on treatment, non-infectious after 2 weeks
- Secondary prevention
  - Used after identification of asymptomatic
    - Therapy to prevent reactivation: eg: Isoniazid, 300mg/day for 12 months
  - Isoniazid, 300mg/day for 12 months (Often 6 months given)
    - Side effects: hepatitis, especially >35
    - Problems: physician compliance, patient compliance

Compliance (adherence)

- Often not predicted by doctors
  - Can't be determined by age, sex, SES, education etc
- Decreases with:
  - Time of therapy
  - Number of drugs/tablets
  - Side effects
- Lack of compliance leads to MDR and XDR

MDR and XDR

- MDR – resistance to rifampicin and isoniazid
- XDR – these two and one of the quinolone family and one second line therapy (anti-TB injectable drugs, eg kanamycin)
  - Eg: in South Africa 2006, KwaZulu, 52/53 people died, average 16 day survival all had HIV
  - No previous infection, primary XDR infection vs XDR development during treatment
- Non-compliance can easily lead to relapse and transmission of TB that may be MDR

Quarantine act

- Individual liberty vs greater good
    - Quarantine can be affected to detain someone who is a threat to public health

DOTS – directly observed therapy short-course

- Need to watch patients taking tablets
    - Reduces drug resistance
    - Improves compliance
        - Compliance is important because:
            - Non-compliance higher on more pills
            - Non-compliance increases risk 16x of reactivation
    - Reduces relapse

Multicultural issues

- Most new TB patients in Australia will be born overseas, 80%,
    - 50% from SE Asia (Vietnam, Philippines),
- 7% of all new cases will be indigenous
    - Western Sydney >30% foreign birth, 20% non-English speaking background

Case 1 concerns

- Work, jobs
    - Shift work, treatment may have to be tailored
- Vietnamese – stigma is high
- Family, wife may react badly due to stigma
- Interpreter knows family, confidentiality
    - May need phone interpreter etc
- Denial
    - Start to feel better, deny having the disease
- Common to see patients post drugs overseas to help relatives at home

Case 2

- Female, request female doctor you are male.
    - Should reschedule appointment/allow transfer to another doctor
- It is important to be gender/culturally sensitive

Case 3

- Visual loss, denied having problems, known side effects of treatment
    - Patient wants to please doctor, and thus didn't tell that the treatment wasn't working

Case 4

- Halls Creek, WA
    - High Aboriginal population
    - Poverty, malnutrition, segregated pubs etc
- Issues
    - Hepatotoxicity, alcohol side effects
    - "White people medicine"
    - Elders in the community help is useful

Summary

- Cultural issues do exist
- Need to be sensitive
- Need to avoid moral judgement
- Need to be flexible and seek help if need be
- Need to overall, keep the patient's best interests in mind!

Blood CO2 carriage

- Blood CO2 is carried in 3 forms
  - Dissolved
  - As bicarbonate
  - As carbamino compounds

Dissolved

- CO_2 (similar to O_2) obeys Henry's law (ie, that with increased pCO_2, there is increased dissolved CO_2)
  - CO_2 is 20x more soluble than oxygen and thus dissolved CO_2 makes up a bigger proportion of blood carriage than dissolved O_2

Bicarbonate

- Bicarbonate (HCO_3^-) is formed in blood
  - $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$
  - The conversion to carbonic acid is slow in plasma and fast in red cells due to the enzyme carbonic anhydrase
    - CO_2 diffuses quickly into red cells
  - The conversion to bicarbonate is fast without enzyme
- HCO_3^- formation in the red cell causes:
  - A rise in intracellular HCO_3^- and H^+
  - HCO_3^- to leave the cell via Band 3 protein (an exchanger), replaced by Cl^-
    - If you remove RBCs from venous blood, they have higher Cl^- than arterial blood, due to higher CO_2 levels in venous blood
  - Some H^+ to bind to deoxyHb, more than to oxyHb
  - Swelling of RBCs– due to the increased osmolar content
    - Thus, RBCs are bigger at periphery and smaller at the lungs

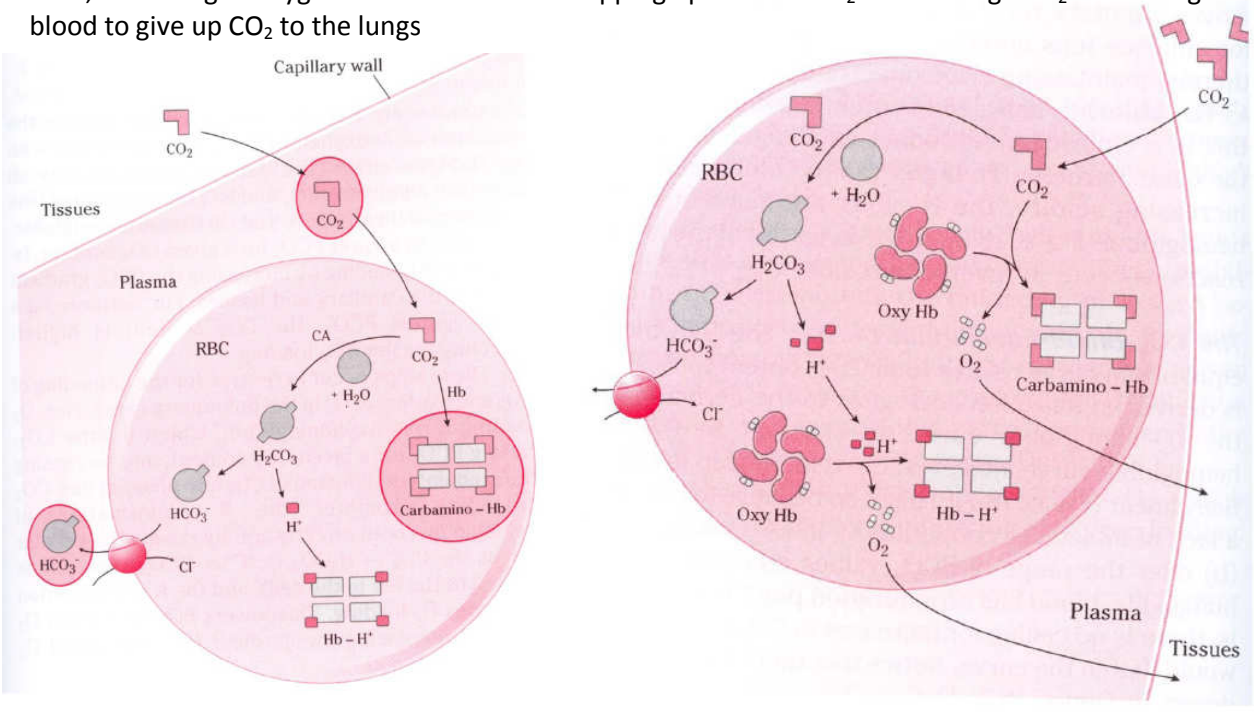
Carbamino compounds

- Carbamino compounds are formed when CO_2 combines with terminal amines in blood proteins like Hb
  - $CO_2 + HbNH_2 \leftrightarrow$ HB NH COOH
  - Reaction is rapid without enzyme
- DeoxyHb forms carbamino compounds easier than oxyHb

Bohr Effect	Haldane Effect
CO_2 and H^+ binding to Hb → decreased Hb affinity for O_2	Deoxygenation of Hb → increased Hb affinity for CO_2
Shifts O_2-hemoglobin curve RIGHT	Shifts CO_2-blood curve LEFT

The Haldane effect

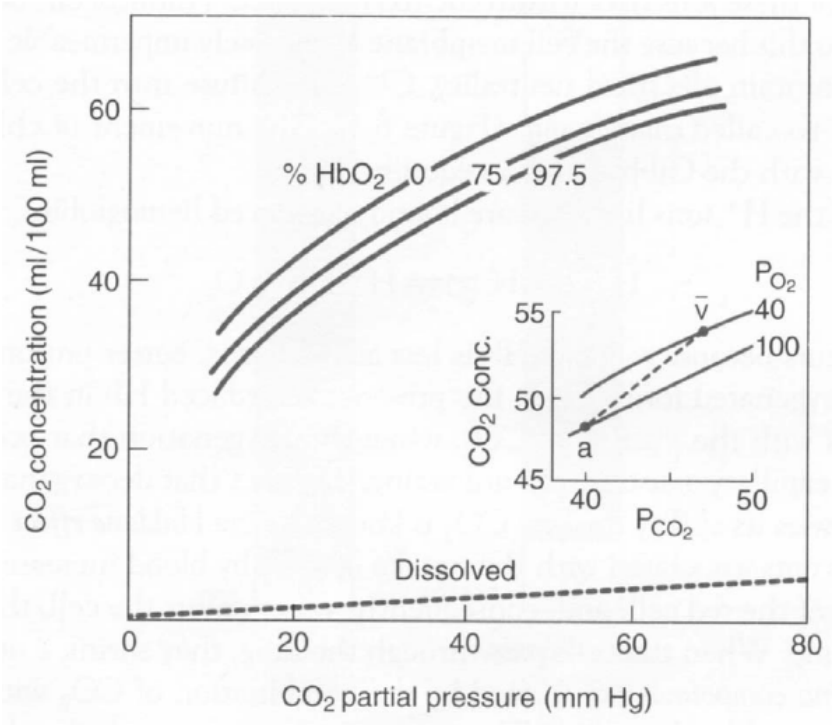
- Deoxygenated blood carries more CO_2 than oxygenated blood
  - Due to:
    - DeoxyHb binds protons more readily
    - DeoxyHb forms carbamino compounds more readily
  - Thus, unloading of oxygen into tissue allows mopping up of more CO_2 and loading of O_2 in the lungs causes blood to give up CO_2 to the lungs

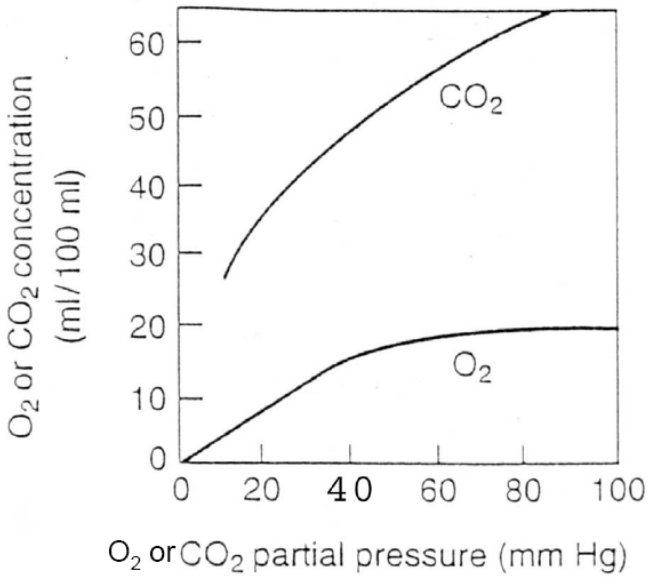


Relative amounts of CO_2 in each form

- Conversion from mol/L to vol%
  - 1mol gas = 22.4L
  - mol/L x 22.4 x 100 = vol%
- Arterial blood has a pCO_2 of 40mmHg which is 22mmol/L (49.3vol%) of CO_2
  - Proportions in blood:
    - 90% is HCO_3^-
    - 5% is dissolved
    - 5% is carbamino compounds
- Venous blood with pCO_2 of 47 mmHg contains 23.9 mmol/L (53.5 vol%)
- The venous arterial difference is 1.9 mmol/L (4.2vol%)
  - This is attributable to:
    - 60% HCO_3^-
    - 30% carbamino compounds
    - 10% dissolved

Blood CO_2 equilibrium curve





- Note:
  - CO_2 curve is more linear than the O_2 curve
  - CO_2 curve is steeper
    - In the range 40-50mmHg, CO_2 changes 4.7vol%, O_2 changes 1.7vol%
  - The lower the oxygen saturation of Hb, the greater the CO_2 content for given pCO_2 – the Haldane effect
  - Dissolved gas makes a bigger contribution to CO_2 content than for O_2 content
    - For arterial 5% vs 1.5%
  - Blood carries more CO_2 than O_2 even in arterial blood
  - ml/100ml = vol%

Rates of consumption

- Oxygen consumption depends on body size and activity level
  - Average adult – 70kg male
    - Basal O_2 consumption ~ 250ml/min (STPD)
    - Light walking ~ 700ml/min
    - Good exercise ~ 2L/min
    - Elite athletes ~ 6L/min
- Resting CO_2 production ~ 200ml/min
  - Normally (mixed diet) less CO_2 is produced than O_2 consumed
    - Thus, when you hold your breath, the volume of air in the lungs contracts
- Respiratory exchange ratio ®
  - R = CO_2 output / O_2 consumption
    - $R = V_{CO2} / V_{O2}$
  - Normal value for R = 0.8-0.85
  - R can vary with short term patterns of respiration
    - Eg: it can increase to >1 with hyperventilation or the onset of exercise because fast breathing washes out the body stores
  - R can vary on the long term by the nature of food being burned
    - Carbohydrates, R = 1.0
    - Fat, R = 0.7
      - Here, some O_2 is converted to H_2O instead of CO_2
    - Normal diet lies somewhere in between depending on ratio of carbs to fat
- Calculating O_2 consumption

$$\dot{V}_{O2} = O_2 \text{ inspired} - O_2 \text{ expired}$$
$$= \dot{V}_I * F_{IO2} - \dot{V}_E * F_{EO2}$$

note: $V_I > V_E$, less CO_2 comes out than O_2 goes in

  - There is no net consumption of molecular nitrogen by the body thus we can use inspired/expired N_2 to calculate V_I

$$\dot{V}_I * F_{IN2} = \dot{V}_E * F_{EN2}$$
Rearranging
$$\dot{V}_I = \dot{V}_E * F_{EN2} / F_{IN2}$$
Substituting
$$\dot{V}_{O2} = \dot{V}_E * F_{EN2}/F_{IN2} * F_{IO2} - \dot{V}_E * F_{EO2}$$
$$= \dot{V}_E (F_{EN2}/ F_{IN2} * F_{IO2} - F_{EO2})$$

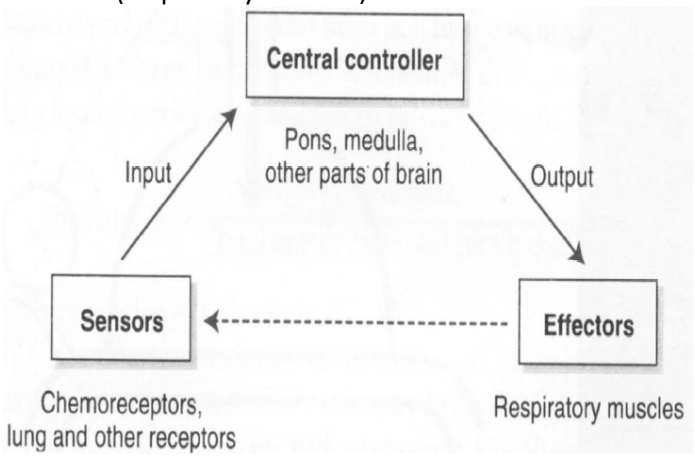
- Calculating CO_2 output

$$\dot{V}_{CO2} = CO_2 \text{ expired - } CO_2 \text{ inspired.}$$
$$= \dot{V}_E * F_{ECO2} - \dot{V}_I * F_{ICO2}$$

  - When air is breathed, we can assume $F_{ICO2} \sim 0$
    - Thus, $\dot{V}_{CO2} = \dot{V}_E * F_{ECO2}$

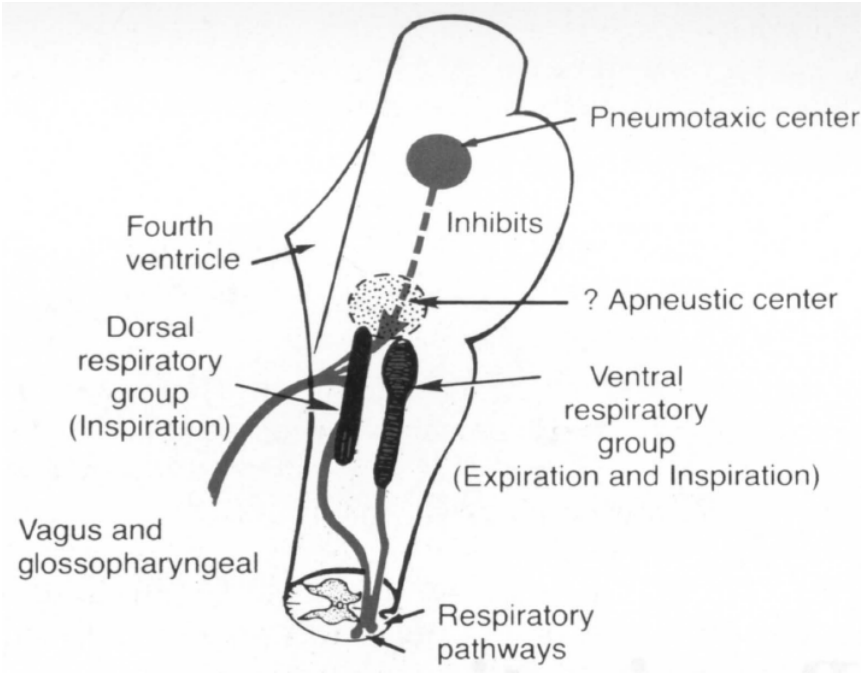
Introduction to respiratory control

- Arterial P_{O2} (95-100mmHg) and P_{CO2} (40mmHg) are kept within narrow limits
  - In spite of:
    - Changing metabolic demands (eg. exercise)
    - Changing posture (affects lung ventilation)
    - Episodic non-ventilatory behaviours (speaking, singing, whistling, eating, swallowing, sucking, sniffing, musical instrument, vomiting, straining)
  - Control of the ventilation levels allows us to keep arterial gases constant with these changes
- Overview:
  - Sensors such as chemoreceptors , lung and other receptors gather information (eg: about blood gases, about lung inflation)
  - Input information to the central controller in the pons, medulla and other parts of the brain
  - This outputs to the effectors (respiratory muscles) which feedback on the sensors



Central controller

- Breathing is automatic, but can be voluntarily overridden
- Automatic breathing is controlled by the respiratory centres of the pons and medulla
  - This can be demonstrated by:
    - Respiration stops with transection of the brainstem below the medulla
    - Automatic respiration is normal with transection rostral to the pons
- Main autonomic respiratory centres are in the medulla
  - This can be demonstrated by:
    - Respiration continues (gasping and irregular) after transection at inferior pons
  - Thus, something in the medulla is the most important but it is modulated by the pons
- Made up of several groups/nuclei
  - However, they are diffuse and poorly organised, possibly just collections of neurons

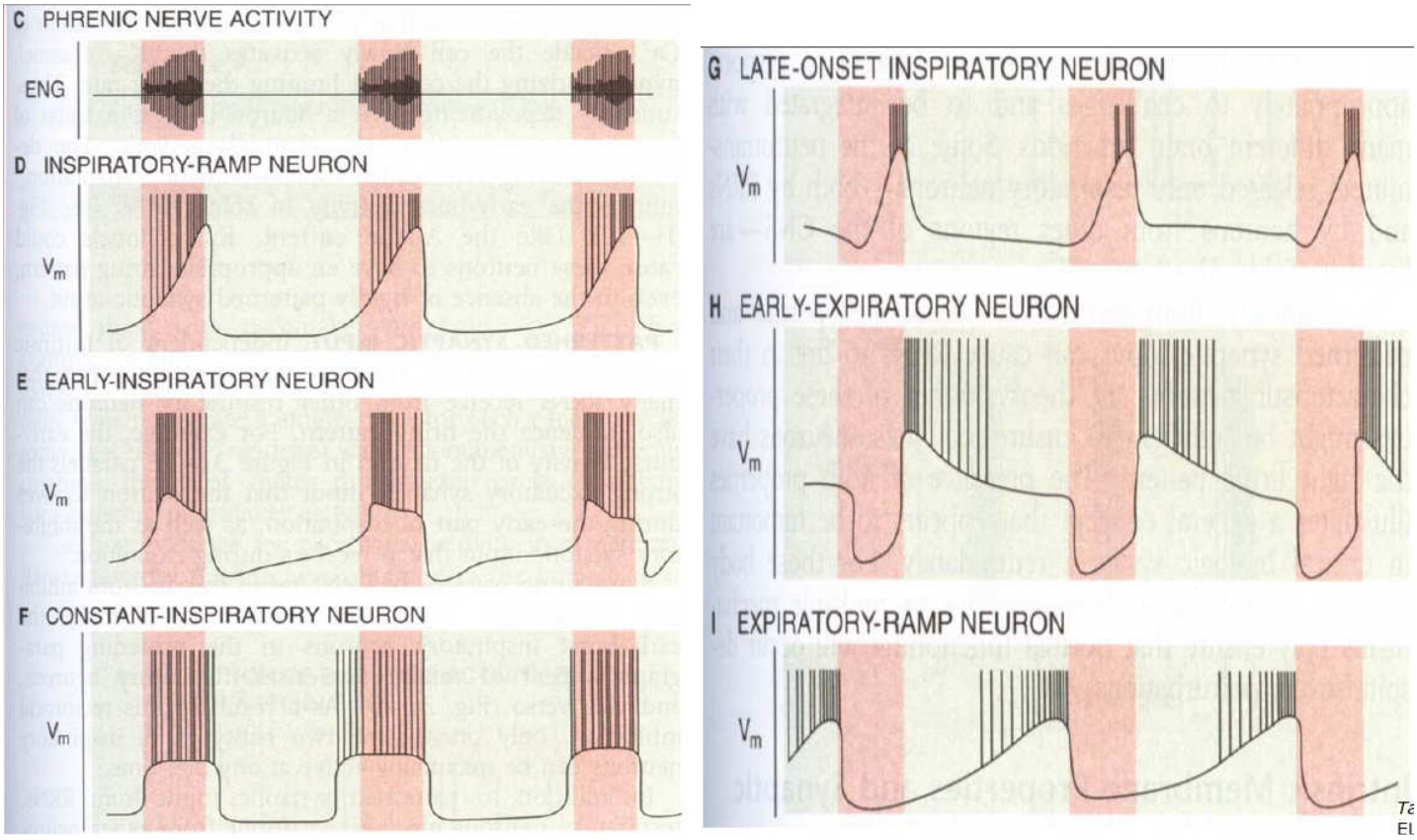


Medullary centres

- Two main neuronal groups in the medulla
    - Dorsal respiratory group (DRG)
        - Processes sensory information (arrive via the vagus/glossopharyngeal nerves)
        - Contains primary inspiratory neurons – has connections to the muscles of inspiration
    - Ventral respiratory group (VRG)
        - Primarily motor
        - Contains inspiratory (accessory muscles) and expiratory (expiratory muscles) neurons
    - Contain high densities of Respiratory-Related Neurons (RRN)

Respiratory related neurons (RRN)

- Neurons that fire in phase with the respiratory cycle
- Can be:
    - Interneurons – local connections
    - Premotor neurons – innervate motor neurons
    - Motor neurons – innervate respiratory muscles
- Individual types of RRNs fire at different times and rates during inspiration and expiration
    - Eg: inspiratory ramp neurons are important in determining inspiration and expiration



Expiration

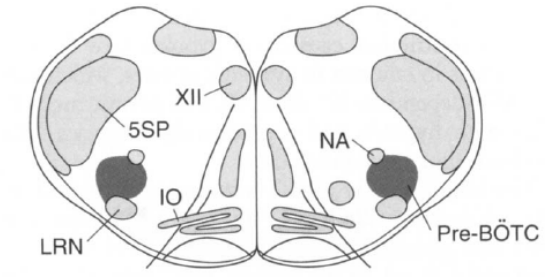
- Expiration is normal breathing is passive and cells in expiratory areas are quiescent
    - In forceful breathing (eg. exercise) expiration centres becomes active and cells fire
    - These activate the expiratory muscles and increase the speed of air outflow allowing an increase in the frequency of respiration

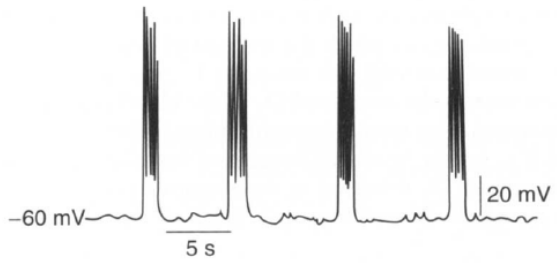
Pontine centres

- The pons contains two neuronal groups that modulate (are not essential for) normal respiratory output
    - Apneustic centre – lower pons
        - Thought to have an excitatory effect on the inspiratory centre of the medulla prolonging ramp action potentials
        - With transection above this site, apneuses results – prolonged, deep inspiratory gasps with a pause at full inspiration
            - Thought that the apneustic centre also functions to terminate inspiration and without it, the medullary inspiratory neurons fire excessively
        - Not known how important this is in humans
    - Pneumotaxic centre – upper pons
        - Switches off inspiration and shorten inspiratory time thus increases breathing rate
        - May cause switching between expiration and expiration

Generation of a central pattern

- Site of central pattern generation is unknown
    - For normal quiet breathing, it could be:
        - In a single site
        - Distributed about several sites
        - A property of the respiratory network – no one single site
    - Recent evidence:
        - May be located in a group of synaptically coupled pacemaker cells in the pre-Boltzinger complex
            - Found in the medulla (VRG – ventral respiratory group)
            - These neurons have been found to discharge rhythmically and cause rhythmic cahgnes in the phrenic nerve that supplies the diaphragm and hypoglossal nerve (controls tongue)





Taken from WF Ganong, Review Medical Physiolc 21st edition, Lanç 2003. Fig. 36-2.

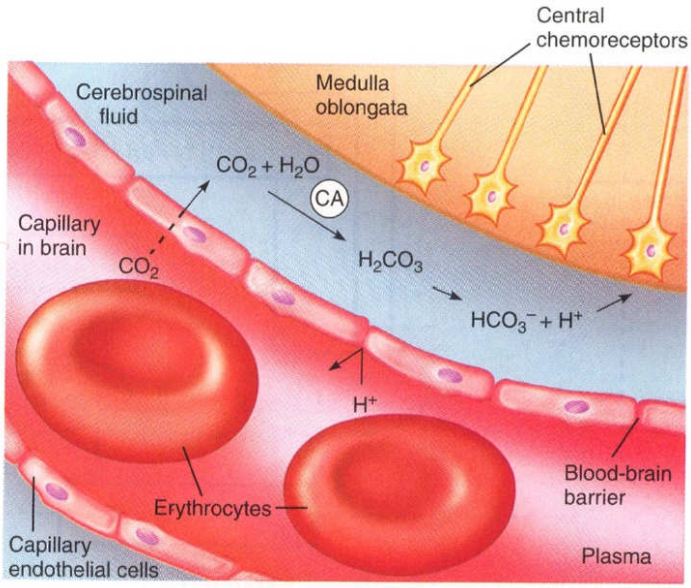
NA = Nucleus ambiguous; XII = hypoglossal nucleus
IO = inferior olive; LRN = lateral reticular nucleus
5SP = spinal nucleus of trigeminal nerve

Note:

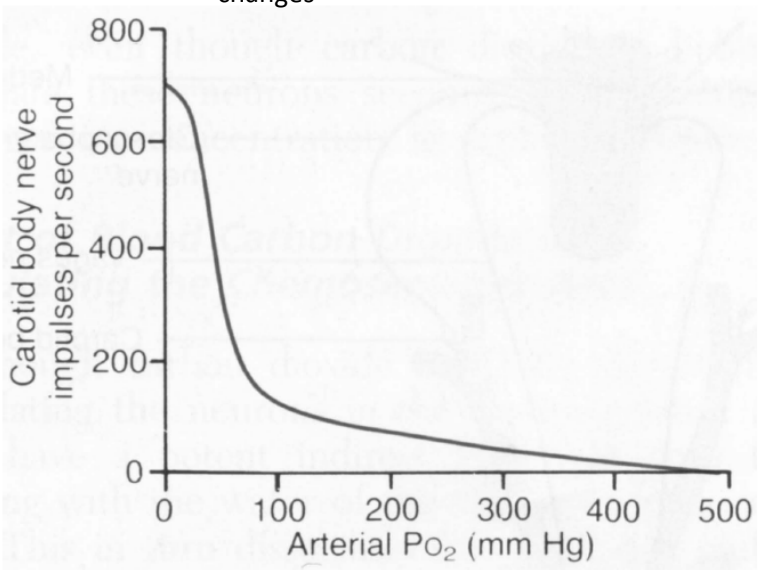
- Automatic breathing can be overridden easily by voluntary control
    - Hyperventilation – can halve arterial P_{CO2}
        - May cause alkalosis, tetani/spasms
    - Motivation can extend breath-holding time
- Other parts of the brain can influence respiratory rate:
    - Rage, fear, passion (limbic system)

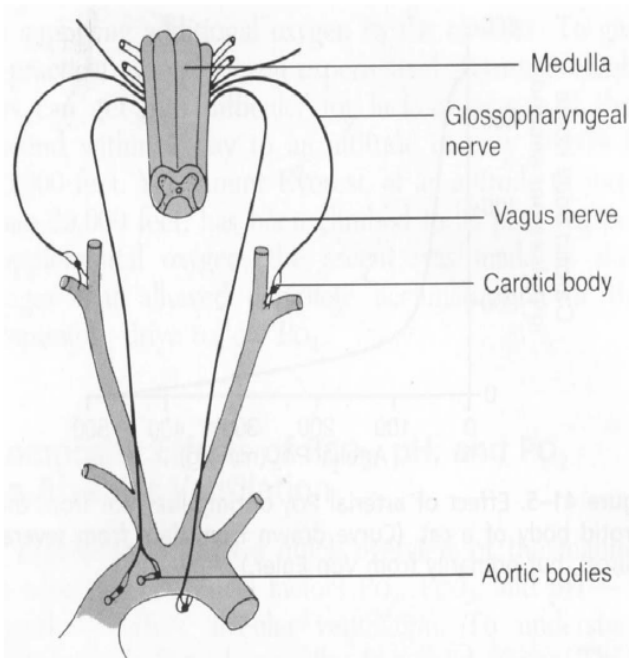
Chemoreceptors

- A sensory receptor that responds to a change in chemical composition of the blood/fluid around it
  - Two types: central and peripheral
- Central chemoreceptors
  - Most important for minute to minute control of ventilation (short term)
  - Located 200-400µm below ventral surface of medulla
    - Near exit of CN IX and X
  - Respond to changes in $[H^+]$ in CSF
    - Fall in pH leads to increased ventilation
    - Rise in pH leads to decreased ventilation
      - Ie: blood CO_2 regulates ventilation because it changes pH in CSF
  - CSF is more acidic than blood (7.32), has less buffering capacity (less protein)
    - Lowered buffer means there is a greater change in CSF pH for a given change in CO_2 than in blood



  - Patients that have lung disease and CO_2 retention, a compensatory slow diffusion of HCO_3^- across the BBB may occur
    - This returns pH and ventilation towards normal
    - A change in blood pH consequently has a potent acute effect, but a weak chronic effect
- Peripheral chemoreceptors
  - Information from the carotid body is carried up by the glossopharyngeal nerve
    - From the aortic bodies via the vagus
      - Both input the dorsal respiratory group
  - Peripheral chemoreceptors have an enormous blood supply (20x own weight/min)
    - This blood supply has the P_{O2} of arterial blood
      - Not influenced by own receptor extraction of oxygen even though they have a high metabolic rate
    - Respond to (increase firing):
      - Decreases in arterial P_{O2}
      - Decreases in arterial pH
      - Increases in arterial P_{CO2}
    - Respond quickly, discharge rate can vary during the respiratory cycle due to small cyclic blood gas changes

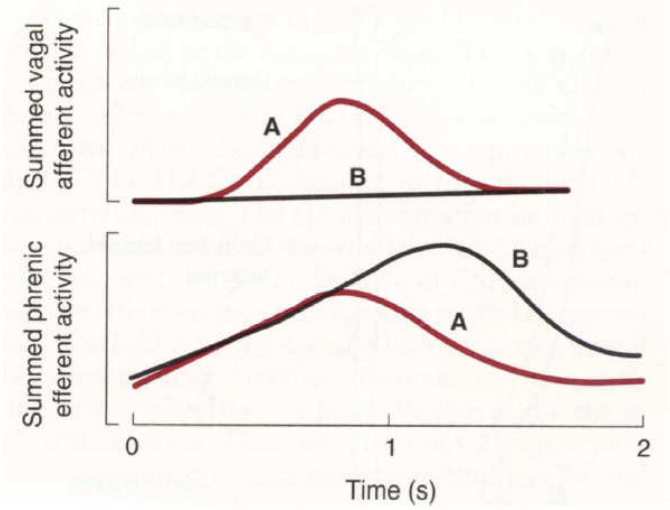




- Peripheral chemoreceptors (continued)
    - Responsible for increases in ventilation due to arterial hypoxaemia
        - Without these peripheral chemoreceptors, severe hypoxia depresses respiration
            - Ie: we don't have enough oxygen and central control becomes depressed
    - Less important than central chemoreceptors in response to arterial P_{CO2}
        - Cause less than 20% of the response to CO_2 in a normal subject, other 80% is via central receptors
        - However, response is more rapid so it may be used to match ventilation to abrupt changes like exercise
    - If arterial pressure falls below 80mmHg, peripheral chemoreceptors are stimulated
        - Ie, reduced blood flow means less oxygen availability and build up of CO_2 and H^+
- Note:
    - Chemoreceptors are different to baroreceptors
        - Arterial baroreceptors are in the carotid sinus and aortic arch and measure stretch as blood pressure rises
        - Chemoreceptors are located in the carotid body and aortic bodies and measure blood gases

<u>Lung receptors</u>

- Feed into central control
- Slowly adapting pulmonary stretch receptors
    - Located in the airway smooth muscle
    - Discharge when the lung is distended
        - Impulses travel via the vagus nerve (large myelinated fibres) to central control
        - With sustained inflation, they don't easily adapt
    - Cause termination of inspiration to protect the lung from over-inflation
        - Hering-Breuer reflex (becomes important in adults with ventilation >1L and newborns)
    - Graph: inspiration is prolonged when these receptors are blocked (B)



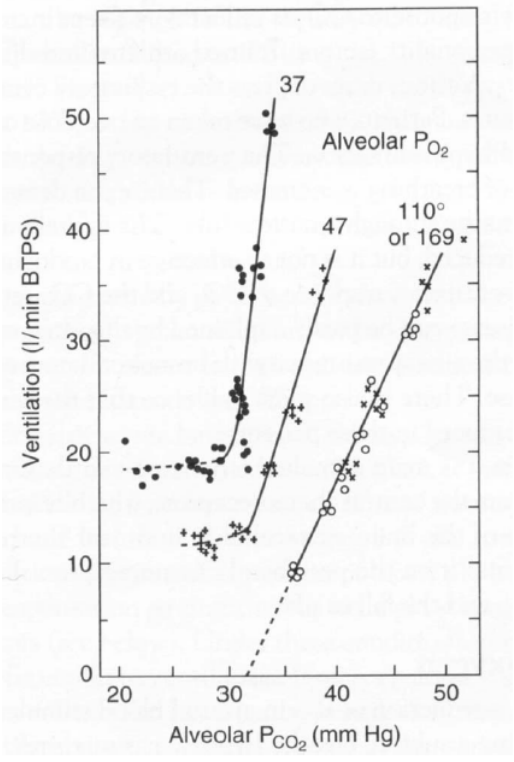
- Rapidly adapting receptors (irritant receptors)
    - Located between epithelial cells in the airways
    - Stimulated by noxious gases, cigarette smoke, dust, cold air, histamine, prostaglandins
        - Also respond to inflation with a rapid increase in firing (which almost instantly decreases again to 20% original rate)
            - Impulses travel by the vagus nerve in myelinated fibres
    - Reflexes result in hyperpnoea (increased depth of breathing, respiratory rate), bronchoconstriction, cough and mucus secretion
    - Has a possible role in asthma – responds to histamine
- Juxtacapillary receptors
    - Located close to blood vessels in alveolar walls and conducting airways
    - Respond to lung hyperinflation and chemicals like capsaicin, bradykinin, serotonin
        - Impulses travel in vagus in slow unmyelinated C fibres
    - Result in rapid shallow breathing
        - Intense stimulation causes apnoea
    - Possible activation by engorgement of pulmonary capillaries and increased interstitial volume (caused by left heart failure), leads to rapid shallow breathing and dyspnea

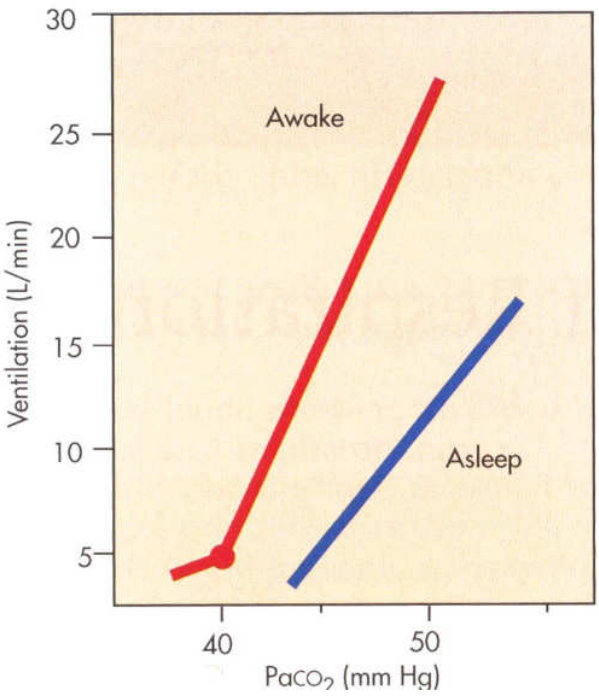
Other receptors

- Nose and upper airways
  - Nose, nasopharynx, larynx and trachea have receptors that respond to chemical and mechanical stimuli (similar to irritant receptors)
    - Result in reflexes like sneezing, coughing, laryngeal spasm and bronchoconstriction
- Joint and muscle receptors
  - Can stimulate ventilation especially in the early stages of exercising
- Gamma system
  - Intercostal muscles and diaphragm have muscle spindles that sense elongation
    - By reflex, this controls the strength of muscle contraction
  - Thought to be involved in the sensation of dyspnoea when a large respiratory effort is needed (and gamma receptors are stimulated)
    - Effort may be due to an airway obstruction
- Arterial baroreceptors
  - Increased blood pressure can cause hypoventilation
  - Decreased blood pressure can cause hyperventilation
    - Have little physiological importance (shock etc, are mediated via chemoreceptors)
- Pain and temperature
  - Pain can lead to apnoea then hyperventilation
  - Heating the skin can lead to hyperventilation

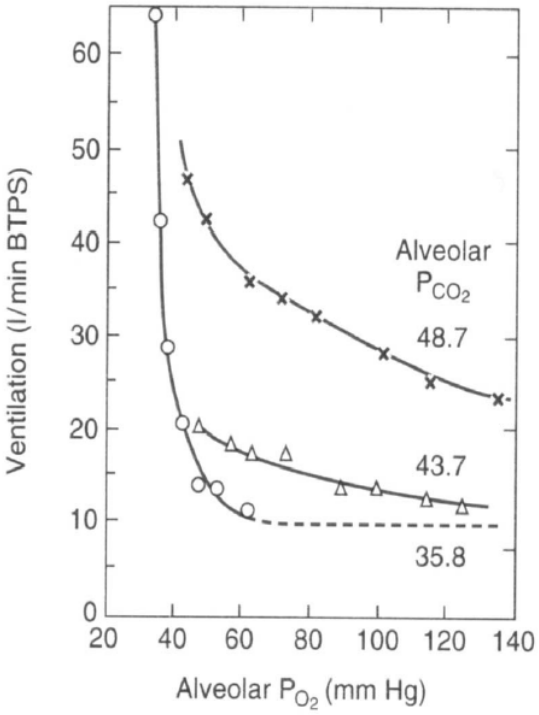
Integrated responses

- Response to carbon dioxide
  - Arterial P_{CO2} is the most important factor
  - Mediation of effect is by central and peripheral chemoreceptors
  - Arterial P_{CO2} is tightly controlled within 3mmHg during daily activity
    - Can rise more during sleep
  - Ventilatory response can be observed with a subject that inhales CO_2 re-mixtures or re-breathes from a bag
    - Normal oxygen levels, ventilation increases 2-3 litres/min for each 1mmHg rise in Pa_{CO2}
  - Graph: for a given P_{O2}, ventilation increases with increasing alveolar P_{CO2}
    - Also, if we decrease the alveolar P_{O2}, the ventilation starts higher and increases faster
  - Ventilatory response can be reduced by:
    - Sleep, age, genetic/racial factors, in athletes and divers, drugs that depress respiratory centres (morphine, barbiturates), increased work of breathing





- Response to oxygen
  - Ventilatory response can be determined by having a subject breathe hypoxic gas mixtures
  - Chemoreceptors that detect hypoxia are the peripheral chemoreceptors
    - Prolonged hypoxaemia can cause mild cerebral acidosis which also stimulates ventilation
  - If P_{CO2} is kept constant at ~36mmHg, P_{O2} can be reduced to ~50mmHg before ventilation increases significantly
    - This means that hypoxic stimulus is not that important for the day-to-day control of ventilation
      - Becomes important at high altitude and in patients with chronic lung disease and CO_2 retention
  - Graph:
    - A decrease in alveolar P_{O2} causes an increase in ventilation
      - When CO_2 is high, small changes in O_2 cause large ventilation changes
      - When CO_2 is low, small changes in O_2 don't change ventilation much



  - There is an important interaction between O_2 and CO_2 levels
    - High CO_2 and low O_2 stimulates ventilation more than each individually
- Response to pH
  - A reduction in arterial pH stimulates ventilation
  - Demonstration (separating response from response to P_{CO2}, ie, reducing pH and keeping P_{CO2} constant)
  - pH change is detected by peripheral chemoreceptors – the carotid bodies
    - Central chemoreceptors and respiratory centres in the brain can be affected by a large pH fall because BBB becomes partly permeable to H^+

Tuberculosis

- One of the leading causes of deaths from infectious disease
    - 2 billion people infected (1/3 world's population), a new person infected every second
    - 5-10% infected people get sick or transmit TB in their lifetime
    - 2 million deaths/year
- Caused by mycobacterium tuberculosis, known since 1000BC
    - Infectious disease of the lungs – can attack any part of the body
    - Transmitted person to person via air droplets
        - Optimal conditions: overcrowding, poor hygiene (personal and public)
    - In the 1960s, was considered an easilyi treated disease with rifampicin and ethambutol
        - A resurgence recently – late 1980s – has been due to strains with increased virulence and multi-drug resistance
- Infection can be asymptomatic
    - Disease is associated with:
        - Cough, haemoptysis, lethargy, loss of appetite and weight loss, fever, night sweats
- Australia
    - 2001, 997 cases reported, 771 lab confirmed
        - Incidence is those born overseas is thought to be about 4-5/100 000/year
        - Incidence in indigenous people was 9.8/100 000/year
        - Victoria: each year: 200-250 new lab confirmed cases

Mycobacterium Tuberculosis

- In humans, causative agent of TB
    - Observed and cultured by Robert Koch, 1882
    - Similar microorganisms isolated in diseased animals
        - Human strain thought to have evolved from ancestral bovine strain
        - Strains isolated in Africa thought to bridge this gap
- Mycobacteria are common
    - With genotypic taxonomy (that looks at 16s rRNA) there are >95 species of mycobacteria
        - 2 found to the major human pathogens:
            - Mycobacterium tuberculosis: Koch, 1882
            - Mycobacterium leprae: Hansen, 1874 (causes leprosy)
        - Other mycobacteria are environmental organisms – atypical mycobacteria
            - Responsible for opportunistic infections in AIDS and immunodeficiency
- Characteristically cause chronic disease and need prolonged treatment
    - Grow slowly, can be dormant in host for long periods
    - Often resistant to common antibiotics
        - Cell walls impenetrable to many antibiotics
        - Some can live inside macrophages
        - Easily develop resistance against a single chemotherapeutic agent

TB treatment

- Effective therapy needs:
    - A prolonged course (months to years)
    - Multiple drugs that work by different mechanisms
        - Problems with combination therapy:
            - Compliancy
            - Toxicity
            - Drug interactions – especially in HIV patients

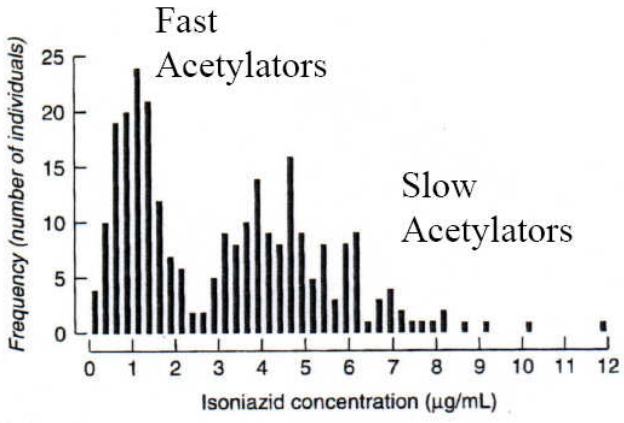
- First-line TB therapy
    - Four drugs are given for 2 months
        - Isoniazid + rifampicin + pyrazinamide + ethambutol
            - In HIV infected patientsm rifampicin can be replaced with rifabutin to minimise drug interactions with NNRTIs and protease inhibitors
    - Rifampicin and isoniazid are continued from months 3-6
        - This drug regime maximises efficacy and has an acceptable degree of toxicity
            - Thus majority of patients can be treated successfully
    - In non-drug resistant TB, treatment for 6 months
        - With HIV, or meningitis, extend to 9 months
    - May need to use second-line drugs if patient has a multi-drug resistant strain
        - Regimen needs to be tailored to patient individual needs
- Chemotherapy
    - Treatment of infection means we need selective toxicity
        - Drugs are toxic to invading organism and not the host
            - Ie, processes that are essential to the parasite and not the host are targetted
        - This selectivity is often relative

<u>Mechanisms of action</u>

- Possible targets:
    - Cell wall synthesis
    - Cell wall permeability
    - Inhibition of protein synthesis
    - Inhibition of nucleic acid synthesis
    - Antimetabolites – metabolic processes

<u>Isoniazid</u>

- Activity is limited to mycobacteria
    - A hydrazide of isonicotinic acid, discovered 1945
- Mechanism – unknown but inhibition of cell wall synthesis constituents has been shown
    - Thus, bacteriostatic for resting bacteria and bactericidal for growing bacteria
- Adverse effects: allergic skin reaction
- Kinetics – metabolised by acetylation (inactivated_
    - Genetics determine rate of acetylation
        - Distribution shown to be bimodal



<u>Rifampicin</u>

- Non-specific agent that is effective against other bacteria
    - Also known as rifampin
- Mechanism – inhibits DNA dependent RNA polymerase in prokaryotes and thus suppresses chain formation in RNA synthesis
    - Active against most gram +ve bacteria
- Kinetics
    - Well absorbed after oral administration
    - Distributes widely
    - Excreted through the liver into the bile
- Adverse effects
    - GIT: nausea, vomiting diarrhoea
    - Rash, fever, drug interactions (induces enzymes)
- Resistance – mutations can result in modifications of the target

Ethambutol

- Tuberculostatic, therefore used in combination
- Mechanism – inhibits cell wall synthesis by blocking arabinosyl transferase
- Kinetics – renal excretion
- Adverse effects – optic neuritis (visual disturbance, colour blindness), peripheral neuropathy
- Resistance – modification of target through mutation

Pyrazinamide

- Analogue of nicotinamide
- Mechanism - affects fatty acid synthase and thereby affects cell wall synthesis
    - Inactive at neutral pH, effective in acidic conditions
        - Thus effective against bacteria inside macrophages (with acid compartments)
- Kinetics – well absorbed from gut resulting in wide distribution
- Adverse effects – liver damage (historically, due to high doses), gout, GIT upset

Streptomycin

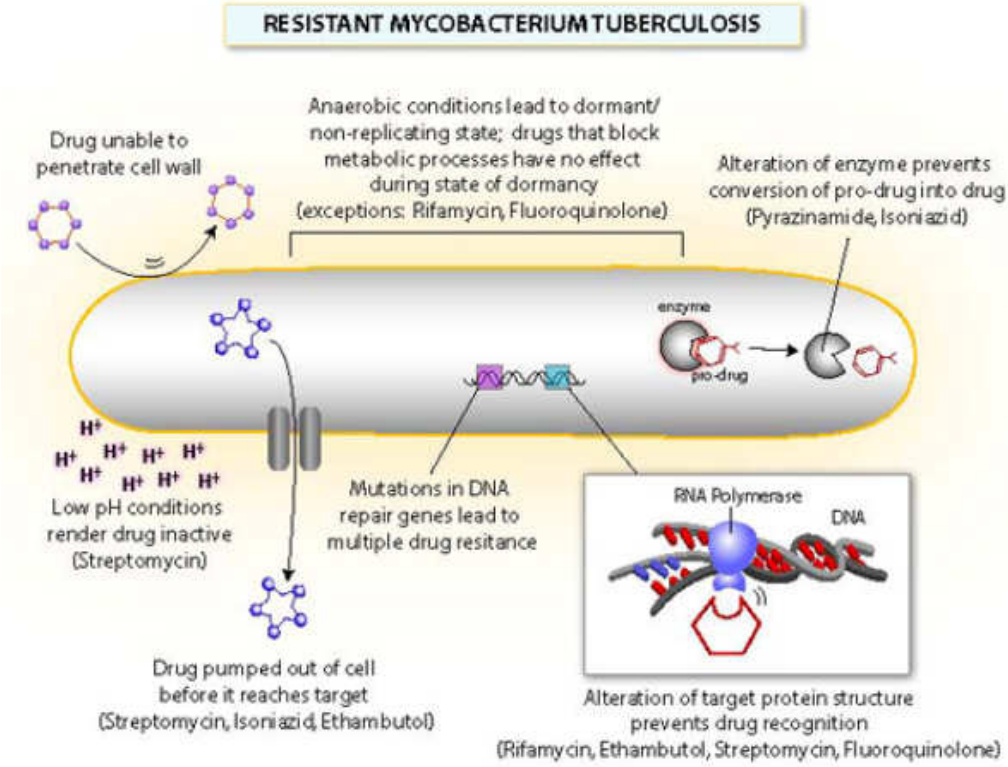
- First available TB drug, has other general uses
    - Rarely used now
- Mechanism – inhibition of protein synthesis (binds to 30s ribosomal subunit)
    - Bactericidal in vitro – suppresses in vivo
- Kinetics
    - Poorly absorbed from gut
        - Administered intramuscularly, or intravenously
    - Renal excretion
- Adverse effects
    - Ototoxicity, tinnitus, vertigo, nephrotoxic
- Resistance
    - Failure of permeation, reduced affinity for ribosome, inactivation

Chemoprophylaxis

- Used in high risk groups
    - Those exposed, (eg: the exposed household)
    - Those with infection
    - Those with a history of TB with a presumed inactive TB disease
- Usually treated with isoniazid

TB treatment issues

- In spite of BCG (bacillus Calmette-Guerin) vaccine and chemotherapies TB is still a significant infectious disease
    - Can be cured (6-9 month treatment) – long and laborious
        - Significant problems with non-compliance, toxicity and drugs resistance
    - Novel TB drugs are needed to target drugs resistant bacteria and drugs that reduce the length of treatment
        - Also, persistent bacteria are a problem – easily become resistant
- Drug resistance:
    - Dormant bacterial state
    - Cell wall penetration
    - pH
    - pumps
    - DNA repair genes
    - Target protein structure
    - Enzyme alteration to prevent drug activation



New developments

- Three new classes of anti-TB drugs are in clinical trials
    - Target different sites
- Better understandings of population pharmacokinetics and pharmacogenetics and microbial pharmacodynamics has lead to better dosing regimens
    - Eg: isoniazid
        - There is a difference in the population based on fast and slow acetylation of drug due to a single nucleotide polymorphism in the metabolising enzyme
        - Standard dose can be suboptimal in ethnic groups with fast acetylating gene
            - Thus dose needs to be altered
- Recent developments in pump mechanisms
    - Efflux pumps can limit the effectiveness of several drugs
        - Maybe agents can be developed to block pumps?

Introduction

- Definition of lower respiratory tract (LRT) – respiratory tract below the vocal cords
- Defence mechanisms of the lower respiratory tract
    - Muco-ciliary escalator
    - Cough
    - Vocal cords
    - Immune response – macrophages, dust cells, T and B cells
- Acute infections of the LRT: Acute bronchitis, Acute exacerbations of chronic bronchitis, Whopping cough, Bronchiolitis, Pneumonia

Acute bronchitis

- Symptoms:
    - Cough with sputum
        - Sputum is key symptoms
    - Low grade or absent fever
- Often caused by viruses
- Treatment is symptomatic because infections normally resolves naturally

Chronic bronchitis

- Definition: presence of a mucus producing cough most days of the month, 3 months of the year for 2 successive years without other underlying disease
    - Associated with smokers. >1pack/week means 60% chance of having chronic bronchitis
- Acute exacerbations of chronic bronchitis (AECB) – acute episodes
    - Chronic bronchitis predisposes to persistent bacterial infections
        - S. pneumoniae, H. influenzae, Moraxella catarrhalis
    - Symptoms:
        - Increase in volume and purulence of sputum
        - Worsening dyspnoea
    - Treatment – symptomatic
        - Aims to reduce obstruction and reduce volume and purulence of sputum

Whooping cough (pertussis)

- Characterised by one or more of:
    - Paroxysms of coughing – sudden severe coughing
    - Inspiratory whoop without other apparent cause
    - Post-tussive vomiting
    - Persistent cough lasting >2 weeks
- Severe disease of childhood
    - Adults and adolescents can get a milder form the disease, often not severe and therefore not diagnosed
- Spread by airborne droplets
- Caused by the gram –ve rod: Bordetella pertussis
- Epidemiology
    - Epidemics cycle through every 3-4 years
        - Eg: major epidemic in the early 90s
        - 2008, Australia had >14000 cases
- Vaccine can prevent disease, booster dose is used to boost waning dose
- Diagnosis
    - PCR for identification
    - Hard to culture
- Treatment
    - Early antibiotic treatment (after 3-4 weeks, not worth treating because organism no longer present)
        - Can limit spread of organism
    - Often symptomatic
    - Prophylaxis given
- A notifiable disease

Bronchiolitis

- Disease of childhood (<2) in the bronchioles
- Cause: 75% by respiratory syncytial virus (RSV), other 25% mostly by other viruses
- Diagnosis is clinical and treatment symptomatic

Pneumonia

- Definition: inflammation of the lungs
  - Entry of organism induces a host immune response that results in exudate and consolidation of alveoli and small airways
  - Consolidation: alveoli fill with fluid
- Epidemiology
  - Most common cause of infection-related death, 6th leading cause of death in USA
  - Australia: combined with influenza 7th underlying cause of death, 4th multiple cause of death
    - 50% of cases and majority of deaths due to bacteria (not virus, fungal etc)
  - Diagnosis is desirable but hard to obtain
- Transmission
  - Inhalation, aspiration (foreign material from oropharyngeal tract into lung)
  - Haematogenous spread
  - Exogenous penetration and contamination
- Clinical presentation
  - Fever, cough, chest pain, purulent sputum (not seen in all), tachypnoea
- Diagnosis
  - History
  - Clinical presentation
  - Diagnostic studies (imaging, culture)
  - Identification of organism is important but often does not happen (treatment after x-ray)
- Aetiology
  - Bacterial
    - Gram +ve bacteria: streptococcus pneumoniae, staphylococcus aureus
    - Gram –ve bacteria: H. influenzae, pseudomonas aeruginosa, Klebsiella pneumoniae, Legionella pneumoniae
  - Viral, fungal protozoan
- Types:
  - Typical – abrupt onset, productive cough with purulent sputum, pleuritic chest pain
    - Impressive physical findings, leucocytosis or leukopenia
  - Atypical – gradual onset, non-productive cough, substernal chest pain
    - Unimpressive physical exam, white cell count normal
- Other pneumonias
  - Viral pneumonia
    - Respiratory syncytial virus (RSV), parainfluenza virus, influenza virus, adenovirus
  - Aspiration pneumonia
    - Oropharyngeal contents
    - Involves: oropharyngeal flora, anaerobes (oropharyngeal secretions), enteric bacteria (stomach, intestines contents)
    - Diagnosis:
      - Chest x-ray shows consolidation at time of aspiration
      - Sputum culture is unreliable due to natural flora such as oral anaerobes
      - Blood cultures and pleural fluid cultures

Pneumonia classification

- Community acquired pneumonia
    - Aetiology: mostly S. pneumoniae and M. pneumoniae
    - Risk factors
        - Environment (eg: air conditioning towers may hold Legionella)
        - Lifestyle (eg: alcohols are predisposed to Klebsiella, gram –ve rod)
        - Age
            - Notes:
                - E. coli from faecal sample
                - Group B strep from mother's genital tract
                - Infants are mostly infected with viruses

AGE	Most likely organisms
Neonatal (0-1 months)	E. coli, Group B streptococcus
Infants (1-6 months)	C. trachomatis, RSV
Children (6months-5 years)	RSV, Parainfluenza viruses
Children (6-15 years)	M. pneumoniae, Influenza virus type A
Young adults (16-30 years)	M. pneumoniae, S. pneumoniae
Older adults	S. pneumoniae, H. influenzae

- Hospital acquired pneumonia
    - Aetiology: mostly S. pneumoniae and H. influenzae
        - Neonatal: Group B streptococcus, Chlamydia trachomatis
        - Assisted ventilation: Klebsiella, Staph. Aureus (particularly important in hospitals)
    - Consolidation
        - Lobular, segmental or lobar (Lobar pneumonia)
            - Streptococcus pneumoniae
        - Diffuse (Bronchopneumonia)
            - Mycoplasma pneumoniae
            - Chlamydia pneumoniae
            - Staph aureus
        - Pictures:

Investigations

- Sputum
    - Direct gram stain – see organisms if the ycan gram stain
    - Culture
        - Enable sensitivity test
        - May be interpreted wrong if contaminated
    - Sputum is hard to sample sometimes (kids, pneumonia that doesn't produce sputum)
- Blood culture
    - High specificity, (ie. a negative result is more likely to actually be negative)
    - low sensitivity (ie, a positive result may not actually be positive) 20-30% of people test positive
- Urine
    - Strep pneumoniae urinary antigen (a protein)
    - Legionella urinary antigen
- Serology – often used for confirmation rather than diagnosis
    - Legionella, Chlamydia, Mycoplasma

Streptococcus pneumoniae

- Gram +ve diplococci
    - Causes pneumococcus pneumonia
- An infection of the alveoli with many virulence factors such as the capsule
- Clinical features
    - Abrupt onset, fever, shaking chills
    - Productive cough, pleuritic chest pain
    - Dyspnoea, tachypnoea, hypoxia
- Risk factors
    - Chronic illnesses such as lung disease, heart disease, kidney disorders, sickle-cell anaemia, diabetes
    - Recovering from a serious illness
    - In a nursing home or other chronic care facility
    - >65 years – government recommends vaccine

Mycoplasma pneumoniae

- Features
    - No true cell wall
        - Doesn't stain with gram stain
        - Beta-lactams are ineffective against cell wall
    - Fastidious – slow growing (>7days to culture)
        - Slow eradication because antibiotics stop multiplication and it has a slow multiplication rate
    - Small self-replicating organism
        - Grows on special media, never found free in nature
    - Can't be seen with light microscope
- Epidemiology
    - Mostly in children >5 years, and young adults
    - Causes 15-20% of CAP
    - Incubation of 1-3 weeks, in which time host is a walking pneumonia
        - Symptoms develop over 2-4 days and persist for from a few days to more than a month
    - 2 million cases/year, 100 000 hospitalisation in US
- Laboratory diagnosis
    - Serology
    - PCR
    - Sputum culture – can't culture mycoplasma pneumoniae but still do culture in case another organism

Pneumonia severity index (PSI)

- A method of classifying CAP in terms of risk of mortality
    - Based on: risk factors, age, co-morbidity, physical exam results (temp etc)
- Classes I to V
    - Allows us to determine whether to hospitalise or not
    - Allows us to choose antibiotic use more carefully
        - Need to increase antibiotic coverage with increasing severity

Treatment

- Antibiotics
- Supportive treatment

Prevention

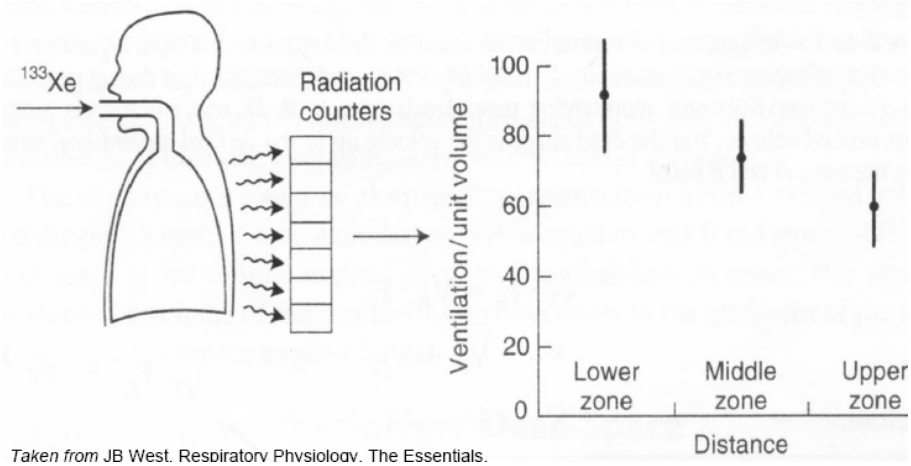
- Influenza vaccine – pneumonia is a common complication of influenza
- Pneumococcal vaccine
    - Normally given to people at risk:
        - Chronic illness
        - Recovering from severe illness
        - Nursing homes, chronic care facilities
        - >65 years

Cases

- Case 1:
  - 58, salesman with nasal congestion and a low grade fever
  - 2 days later, shaking chill, cough and severe pain on right side of chest
    - Temperature of 39.5^{o}C, respiratory rate of 40/min (tachypnoea)
  - Chest x-rays showed consolidation of right upper lobe
  - Gram stain of sputum showed PMN and gram positive diplococci
    - Diagnosis: streptococcus pneumoniae, typical pneumonia
      - Lobar pneumonia
- Case 2:
  - 7, fever, headache, dry cough
    - 12 year old brother had similar symptoms 2 weeks ago
  - 2 days later, temperature increased, cough worsened
  - Chest x-ray showed patchy infiltrate of left midlung field
  - Gram stain showed a few PMNs and no bacteria
  - Treated with erythromycin and fully recovered
    - Diagnosis: mycoplasma pneumoniae
      - Bronchopneumonia (diffuse), atypical pneumonia

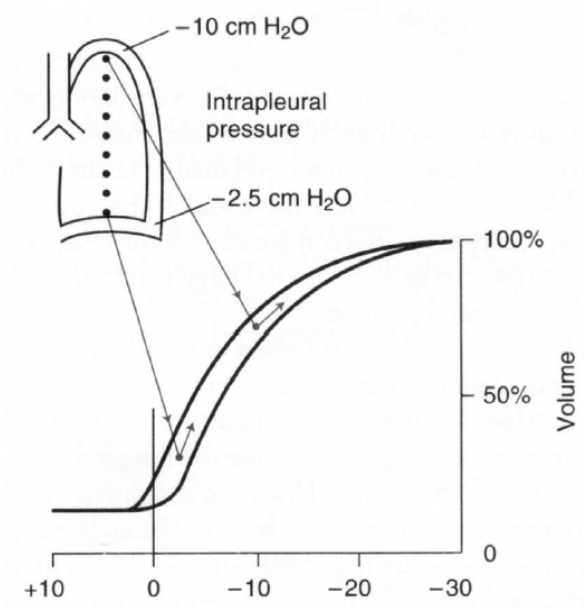
Ventilation regional differences

- In the upright lung, the lower zones ventilate more than the upper zones
    - Largely due to gravity
    - Ventilation is the change in volume per unit volume
- Demonstrate: radioactive xenon is inhaled and radiation counted at different areas



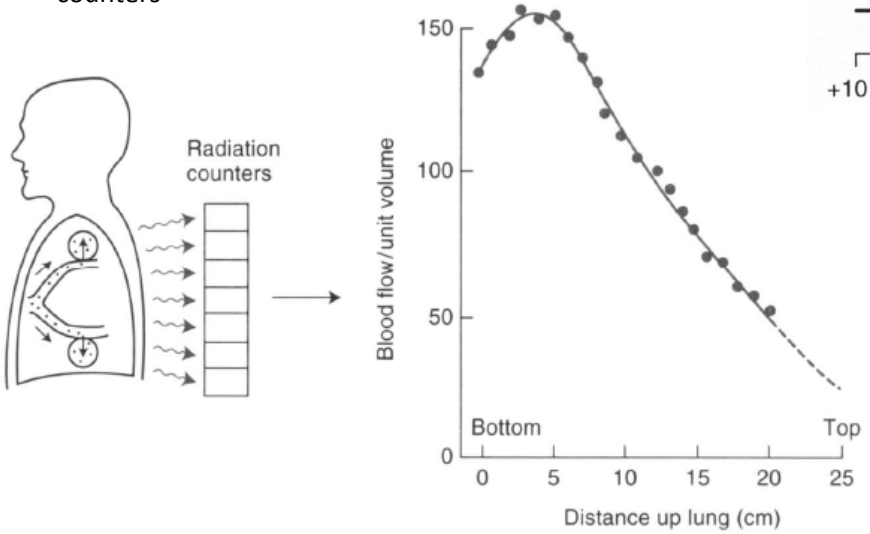
Taken from JB West. Respiratory Physiology. The Essentials.

- Explanations:
    - Lung is suspended in the chest and weight of lung (due to gravity) causes the intrapleural pressure at the bottom to be less negative than the top
        - Thus, volume is lower in the bottom of the lung (less pressure causing expansion)
        - At lower volumes, lung is easier to inflate (greater compliance), thus inspiration means greater increase in volume at base than at apex
            - Although low volume, there is still gas present (small airways close before gas is removed trapping air in alveoli)
        - Analogy: slinky, top is more stretched, bottom less (volume)
    - Apex has bigger resting volume because of greater expanding pressures, thus less change in volume on inspiration
- If lying down (supine/prone):
    - A different part of the lung becomes equivalent to the base (dependent) and thus better ventilated
        - However, in the upright position, the difference is greatest due to largest distance



Blood flow regional differences

- In the upright lung, blood flow decreases linearly from bottom to top, low values at the apex
- Demonstrated: radioactive xenon dissolved in saline is injected into a peripheral vein
    - Xenon is not very soluble and comes out in the lungs. If subject holds breath, can be measured using radiation counters

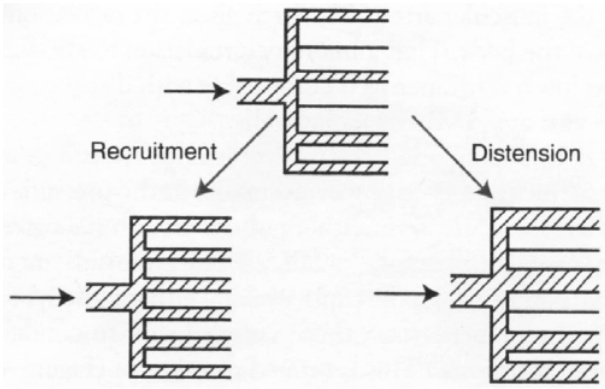


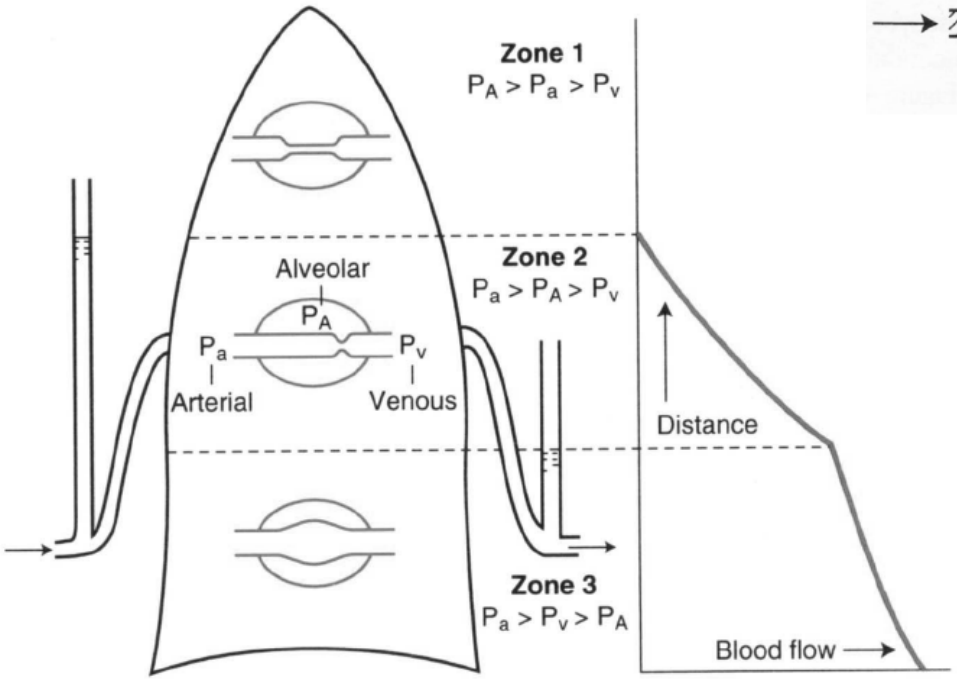
Blood flow regional differences continued

- Explanations:
    - Hydrostatic pressure, blood vessels closer to the heart have higher blood flow than those further away
        - The pulmonary vasculature can be considered as a column of blood
        - 30cm high lung, pressure difference from top to bottom is 30cm water (blood), 23mmHg
            - A large pressure difference for the pulmonary circulation
                - Mean pressure 15mmHg, systolic 25, diastolic 8
- Distribution can be changed by:
    - Posture – supine causes apical blood flow to increase so distribution of blood is more uniform, posterior (dependent) regions flow exceeds anterior parts (effect of gravity?)
    - Exercise – upper and lower zone increase blood flow reducing the regional difference

The zones

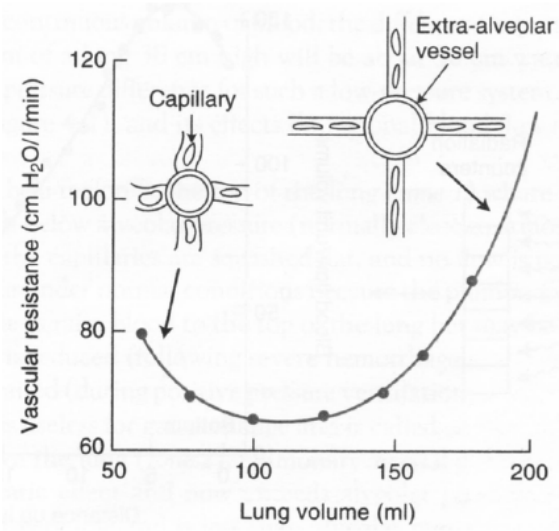
- Physiological zones, not anatomical
    - Size should not be equivalent and can change with circumstances
        - Ventilation causes a bigger zone 1, exercise causes a smaller zone 1 (zone 1 often not even seen)
- Pulmonary arterial pressure increases with decreasing distance from the heart
- Zone 1
    - Region at the top of the lung
    - Pulmonary arterial pressure < alveolar pressure, thus no capillary flow
        - Ventilated, but unperfused lung – useless for gas exchange
    - Normally not seen – present with severe hypotension (decreased artery pressure, eg. due haemorrhage) or with raised alveolar pressure by positive pressure ventilation
- Zone 2
    - Pulmonary arterial pressure > alveolar pressure, venous pressure < alveolar pressure
        - Thus, blood flow is determined by arterial vs alveolar pressure
            - Pressure difference is responsible for flow increase → leads to capillary recruitment
- Zone 3
    - Venous pressure > alveolar pressure, flow is determined as normal by arterial-venous pressure difference
        - Increase in flow is due to capillary distension
            - The pressure within the arteries/veins increases and alveolar pressure is constant causing increased width
            - Also may have more recruitment
- Recruitment vs distension
    - Recruitment – opening of previously closed vessels
    - Distension – increase in calibre (width) of vessels
        - Often caused by the same forces – increased blood flow, and thus can occur together





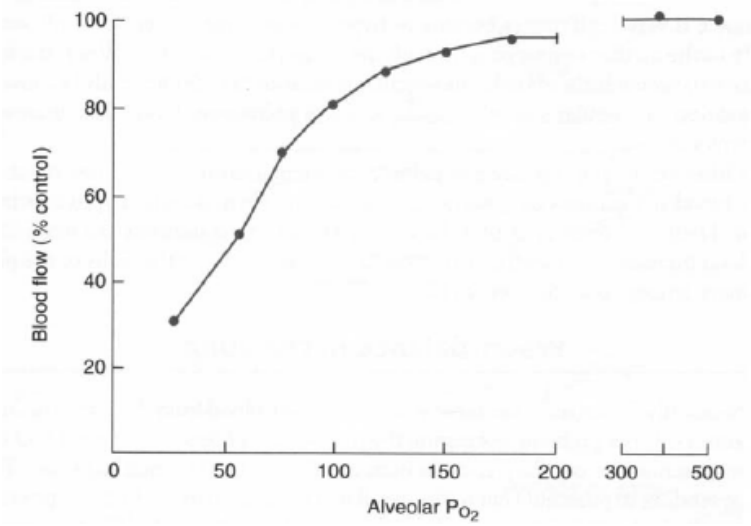
Zone 4

- A region of reduced blood flow that occurs at low lung volumes
    - At high volumes/pressures, capillaries are squashed reducing blood flow, increasing vascular resistance
        - (capillary bed provides 40% of vascular resistance in the lung)
    - At functional residual capacity, we have a minimum in the vascular resistance
    - Below functional residual capacity, the resistance increases again
        - Explanation: extra-alveolar vessels are squashed when the lung parenchyma around them is poorly inflated –not kept open by inflated lung
        - Mostly affects the bases of the lungs because these parts have low ventilation



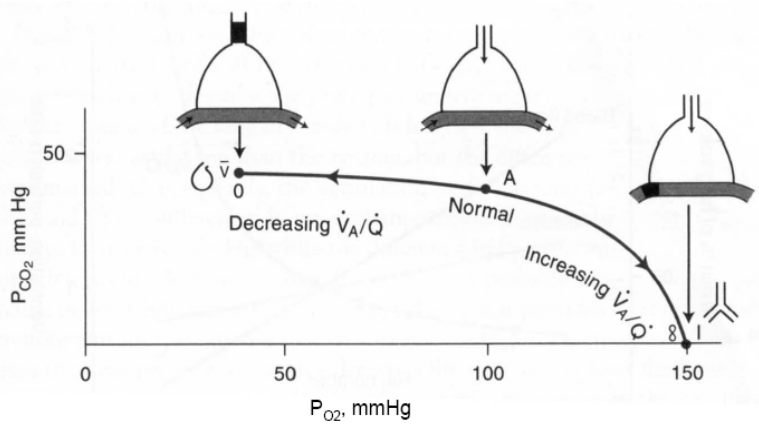
Other factors that influence pulmonary blood flow

- Hypoxic pulmonary vasoconstriction
    - When P_{O2} of alveolar gas is reduced, smooth muscle in vessel walls contract in the hypoxic region
        - Blood diverts away from poorly ventilated regions – adaptive response
            - Response is non-linear: certain high level of P_{O2} causes same blood flow
        - Vs rest of the body where low P_{O2} causes vasodilation to get more oxygen
- Low blood pH
    - Causes vasoconstriction, especially if associated with alveolar hypoxia
- Sympathetic outflow
    - Weak vasoconstrictive effect
- In some animals, some parts of lung intrinsically higher vascular resistance
- Blood flow decreases at the end of ducts (alveoli)
    - Peripheral parts less supplied
- Central regions are better supplied than peripheral
- Other (not important in day to day changes:
    - Histamine, angiotensin constrict BVs
    - NO_2 dilates BVs



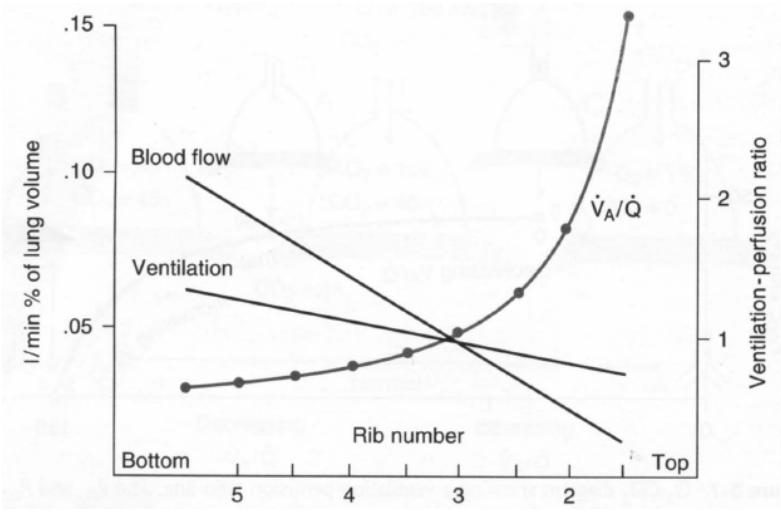
Ventilation-perfusion ratio

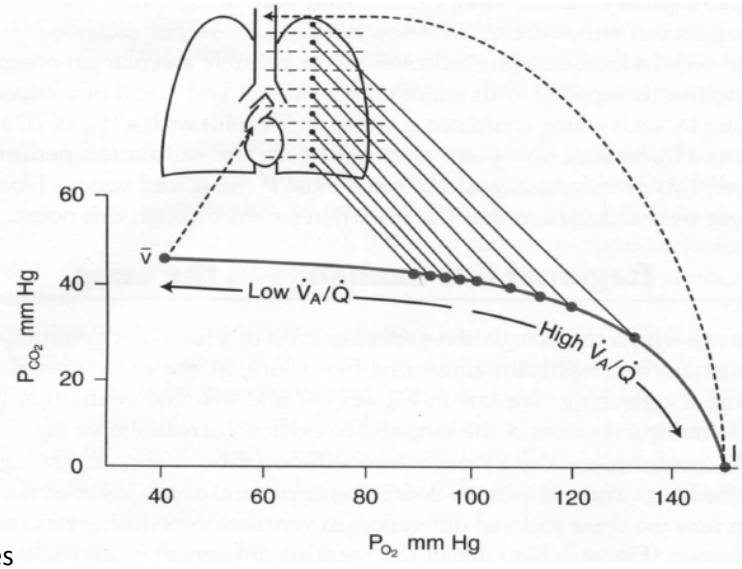
- Ratio is important for adequate gas exchange
    - Normally overall is 0.8-1.0 (EG: 4L/min ventilation to 5L/min perfusion)
    - Normally has PA_{O2} = ~100mmHg, PA_{CO2} = ~40mmHg
        - PA_{O2} is determined by the addition of new O_2 by ventilation and removal by blood flow
        - PA_{CO2} is determined by addition of new CO_2 from the blood and removal by ventilation
- Pathological changes:
    - Perfusion obstructed
        - O_2 tension approaches inspired (blood not taking away more oxygen)
        - CO_2 tension approaches zero (CO_2 not removed from blood)
    - Ventilation obstructed
        - O_2 and CO_2 tension approach venous blood
            - (no new O_2 for absorption by blood, CO_2 builds up because: no new air with no CO_2)



Regional differences in V-P ratio

- In the upright lung, ventilation-perfusion ratio increases base to apex (0.6 → 3.3)
    - Ie, much more ventilation than perfusion at apex, and more perfusion than ventilation at base
    - Note: $\dot{V}$ = ventilation, and $\dot{Q}$ = perfusion
- Thus, can match these ratios to the PCO2 vs PO2 graph
    - At apex, alveoli tensions are more like inspired air (not much perfusion, so gas exchange low)
    - At base, alveoli tensions are more like venous blood (lots of perfusion, high gas exchange)





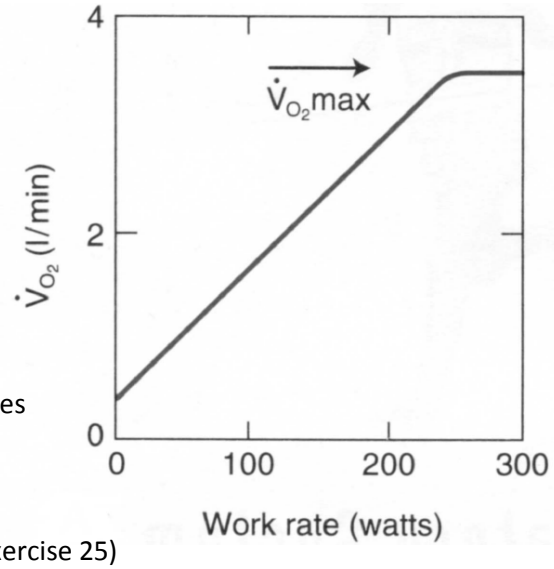
- Blood gas content due to ventilation/perfusion differences
    - Oxygen
        - Difference in tension from top to bottom >40 mmHg
            - Pathology: post-primary TB often affects apex due to increased O_2 tension (aerobe)
        - Oxygen-haemoglobin equilibrium curve has a plateau at higher P_{O2}, thus O_2 saturation does not change much
            - Thus, difference is like: 20ml O_2/100ml blood vs 19.2 O_2/100ml blood
    - Carbon dioxide
        - Difference in tension from top and bottom of lung is less ~14mmHg
        - CO_2 equilibrium curve is linear, thus bigger difference between content of CO_2 leaving blood in apex vs base
            - Apex ~ 42, Base 49ml CO_2/100ml
- Oxygen uptake and carbon dioxide output with ventilation/perfusion differences
    - Oxygen
        - Uptake is low at apex despite PA_{O2} high due to low blood flow
            - O_2 uptake is higher in the base
            - During exercise, apex contribution to O_2 uptake increases as blood flow becomes more uniform
    - Carbon dioxide
        - Less CO_2 output in the apex due to increased ventilation in base
            - Difference in CO_2 output is not as great as O_2 uptake difference
    - R (respiratory exchange ratio) is higher at the apex R = 2.0, than at the base R = 0.65
        - More CO_2 output at apex than O_2 input

Ventilation-perfusion mismatching

- Regional variations have minimal effect on gas exchange
    - Disease can cause severe disturbances
- Severe hypoxaemia (low Pa_{O2})
    - Ie: blood leaving regions with low ventilation-perfusion ratio have low O_2 saturation
    - Compensation by other regions with high v-p ratio cannot occur because OEC at top end is flat
        - Ie: with a lower P_{O2} saturation will remain similar
- Hypercapnea (high Pa_{CO2})
    - Unlikely to happen because blood CO_2 equilibrium curve is linear in the working range
        - Also, with high P_{CO2} we tend to hyperventilate which blows off excess CO_2

Exercise and respiration

- Exercise increases the demand for gas exchange
  - Moderately fit: V_{O2} can increase to ~4L/min
    - V_{CO2} can increase even more (eg ~ 8L/min)
    - Thus, R can increase to 1.0 or more
      - Exercise has a reliance initially on burning carbohydrates rather than fat
      - Lactic acid produced uses the HCO_3^- as a buffer and produces CO_2
      - Acidotic blood, chemoreceptors increase ventilation and thus we lose more CO_2
  - V_{O2} increases linearly with work rate until max is reached
    - At max, anaerobic metabolism kicks in
- Graph:
  - Starts above zero – baseline metabolic rate
  - Plateau – anaerobic metabolism kicks in
- Exercise limit is due to the CV system, rather than the respiratory system
  - In max exercise, heart is at 90% capacity, and respiratory at 65%

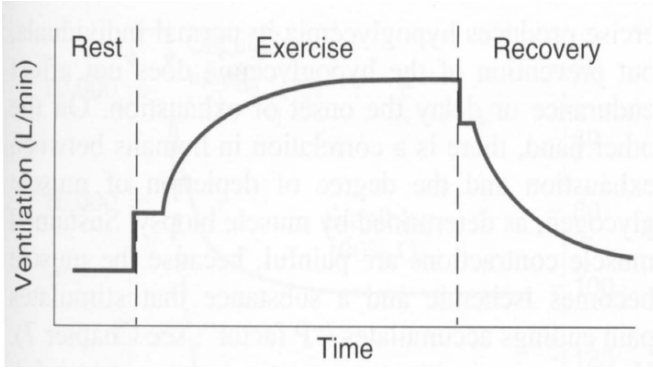


Blood gases in exercise

- Arterial PO2, PCO2 and pH are little effected in moderate exercise
  - Ie: we can ventilate sufficiently to compensate
  - If anything, PO2 rises and PCO2 falls, ventilation over compensates
- Severe exercise – pH falls due to lactic acidosis
- However (venous blood):
  - O_2 extraction from exercising muscles increases
    - PO_2 in mixed venous blood is lower (normal 40mmHg, exercise 25)
    - Causes alveolar-capillary gradient to increase and more O_2 to enter blood

Ventilation in exercise

- Abrupt rise (in anticipation), brief pause, further gradual increase
- In moderate exercise, ventilation is increased due to increased tidal volume and respiratory rate
  - Total ventilation (fit subject) with V_{O2} 4L/min is about 120L/min
- After exercise, ventilation remains high until oxygen debt has been repaid
  - Recovery is determined by how long it takes to replace O_2 debt ~90mins
  - Stimulated by low pH,
  - R can fall to 0.5 or less
    - Taking in more oxygen to pay off debts: lactic acid, ATP, replacement of O_2 in myoglobin



Stimulation of ventilation in exercise

- Impulses from brain
  - As motor cortex sends impulses to exercising muscles, collateral impulses to respiratory centres in brainstem
- Proprioceptive impulses
  - Passive limb movement can cause an increase in ventilation
    - Movement is detected by receptors in joints and muscles
  - Reflex is abolished if these sensory nerves are blocked
- Other factors like acidosis in prolonged exercise

Other cardiorespiratory changes

- Cardiac output rises – HR and SV increase
- Capillaries open in muscles
- Pulmonary capillaries undergo recruitment and distension improving lung diffusion
- Less inequality in ventilation : diffusion
- OEC shifts:
  - To the right in exercising muscles – allows O_2 from Hb into muscles
  - To the left in the lungs – allows O_2 into Hb from air

Introduction

- Definitions:
  - Ethics – to do with our relationship to other human beings
  - Social perspectives – take the opinion that ethics makes little sense without considering the community
- Social perspectives are in direct contrast to principle based/human rights ethics
  - Comparison:
    - Principle based and human rights:
      - Focus on the individual: autonomy, choice, personal care, individual rights, high standards for each patient
      - Give priority to the individual
    - Social perspectives:
      - Focus on the many: equity, justice, care for the community, rights for the whole community, higher standards overall
      - Give priority to the society/community

Example: pneumococcal vaccine

- Pneumonia and meningitis caused by Streptococcus pneumoniae – pneumococcal
  - Causes a huge burden of disease in aboriginal and rural communities
- Vaccine:
  - 400-500$/person, annual cost of 67.7 million dollars, about 40% of vaccine budget in Australia
  - 83-89% effective in preventing invasive pneumococcal disease
  - Good vaccine, and safe
- Other factors:
  - Costs – treatment, time off work, morbidity (neurological deficitis/disabilities)
  - DALYs/QALYs
  - Herd immunity, especially elderly
- Burden of disease
  - Do we define according to the absolute cost of disease?
  - Do we define according to the proportion of the population affected?

Other Issues to consider in determining who gets funding

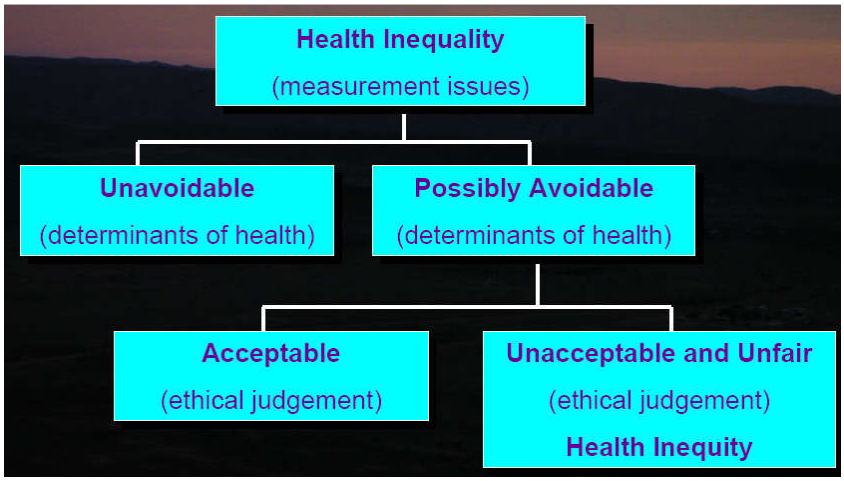
- Political issues
- Economic issues
- Public opinion
- Advocacy/criticism
- Equity
- Priorities

Public health ethics

- Focus on issues affecting people – considered as populations/communities
- Need to balance the rights of the individual and public
- Equity and justice are very important
  - This can be achieved by bringing up the minimum standards of a given community to an acceptable level
    - Globally, this is hard – TB, Malaria, HIV
    - Locally, this is hard – Pneumococcal, streptococcal infections

Introduction

- Inequality – generic term used to designate difference, variations and disparities in individuals and groups
  - Factual, descriptive
- Inequity – inequalities that are deemed unfair or stemming from an injustice
  - Ethical judgement, oriented by goals/targets



Principles of equity

- Need to ensure:
  - Services in disadvantaged populations is not of poorer quality or less acceptable
  - Allocation and application of resources are related to need
  - Extra effort is made to reach those who have worse health

Locational disadvantage

- Disadvantages that are due to limited access to services and opportunities based on location
  - Often arise from deficiencies and physical and social infrastructures
- Local variation persists, social groupings/ranking persist

Stressors on health

- Environmental factors
- Socio-economic factors
- Psycho-social factors

Australia: poorer health in some groups

- Certain groups within Australia have poorer health
  - Injuries
  - Mental disorders
  - Ulcers
  - Varicose veins
  - Nerves/tensions/emotional problems
  - Influenza
  - Bronchitis/emphysema
  - Arthritis

Interventions to reduce locational disadvantage

- Improve the physical environment
- Social/economic factors
- Improve access to health/social services
- Reduce social exclusion
- Reduce crime
- Build sense of community
  - Need to intervene at individual (micro), locational (meso) and societal (macro) levels

Equity

- In healthcare, 4 measures:
    - Access
    - Utilisation
    - Quality of care
    - Outcomes

EG: malaria

- HIGH morbidity, mortality in developing countries
    - Increased prevalence linked to road building, mining, logging, agricultural, irrigation projects (development)
- Prevention:
    - Can avoid malaria at lost cost (affordable)
    - Controllable in any country
- Problems:
    - Cheap treatments are produced in china, no one wants to fund treatment because it is not a problem in developing countries, therefore no money/profit involved

Local groups susceptible to inequities

- Aboriginal/Torres Strait Islanders
- Chronic mental health problems
- Prisoners
- Alcohol/drug abuse
- Low income
- Unemployed
- Chronic illness
- Refugees

"Our task must be to free ourselves from the prison by widening our circle of compassion to embrace all living creatures and the whole of nature in its beauty... We shall require a substantially new manner of thinking if mankind is to survive."
 Public health ethicist

Continuing the story

- 27 years of HIV
- Dental care
    - Candida destroys bone in the mouth
    - No HIV dental/general care until recently
    - Now has dentures
- 55th birthday
- Indinovir – causes kidney stones if not flushed with water – drinking lots of water
    - Since then
        - Has been very proactive with choices of drugs
        - Treatment has been tailored to person, individual wants and to increase quality of life
- HIV infected brain
    - Wasting down to 48kg
    - Libido dropped
    - Loss the use of legs, control of walk
        - Couldn't' walk straight
    - Tests/scans
    - Treatment change allowed virus to attack brain. Drugs kicked in and recovered
- Blind in one eye
    - Felt like grains of sand in eye, causing irritation
    - Over Christmas, so couldn't get into an HIV practice. Seen in early February at RPA
    - Eye didn't know it was blind and was sending signals that it wasn't getting blood and capillary regrowth
        - Thus drainage was blocked
    - Left eye is currently collapsing
- Wants to accept HIV as part of life, but not let it dominate his life
- Finished his writing degree at UTS
- Living life, following interests and doing things he always wanted to do
    - Cooking
    - Online Australian gourmet food products shop
- Ageing and other products not caused by HIV

Uses of odds, risks and ratios

- Direct comparison
  - Eg. new treatment group vs control/comparison group
- Effect size
  - Ie: how much worse/better is intervention
- Can be used to calculate measures that allow us to determine clinical significance
  - Note: useful for evaluating numbers needed to treat (NNT)
- Overall: instead of comparing means, it compares data and 'proportions'

Rates

- Event rate = number with symptoms better/ total treated
  - Compare experimental vs control
- Example 1:
  - 40 patients with severe influenza (respiratory failure requiring ventilation) assigned to a new antiviral treatment
  - 40 patients with severe influenza assigned to standard treatment
    - Assessment of whether symptoms improved over following 3 days (set criteria)
  - Experimental event rate (EER) = 22/40 = 55%
  - Control even rate (CER) = 7/40 = 18%

Anti-viral Treatment	Symptoms got better	Did not	Total number treated
New treatment	22	18	40
Standard	7	33	40

- Uses (measures incidence):
  - Morbidity rate
  - Mortality rate
  - Case-fatality rate
  - Attack rate
- Visualising:

intervention/risk

RCT/cohort study

	Disease Present D+	Disease Absent D-	
Risk present R+	a	b	a+b
Risk absent R-	c	d	c+d
	a+c	b+d	n

- Useful in presenting information from RCTs or cohort studies
  - Ie. can show chance of disease/change with different interventions/risks
  - Start with risk factor/intervention and show chance of developing disease/getting better

Odds

- Odds of an event = number of events/number of non-events
- Example 2:
  - If you roll a die, how likely are you to roll a 6?
    - Rate: 1/6 = 0.167
    - Odds: 1:5 = 20%
- Not probability or rates
  - If odds = 1, the event is just as likely to happen as not happen
  - If odds <1, the event is less likely to occur
  - If odds >1, the event is more likely to occur
    - If odds of event are certain = impossible (x/0)
    - If odds of event are impossible = 0 (0/x)
      - in these cases, odds are not useful
- Uses:
  - Polling, politics, gambling
  - Studies where there is no follow up over time
    - Eg: case control, cross-sectional studies
  - Harder for people to understand
- Visualising:

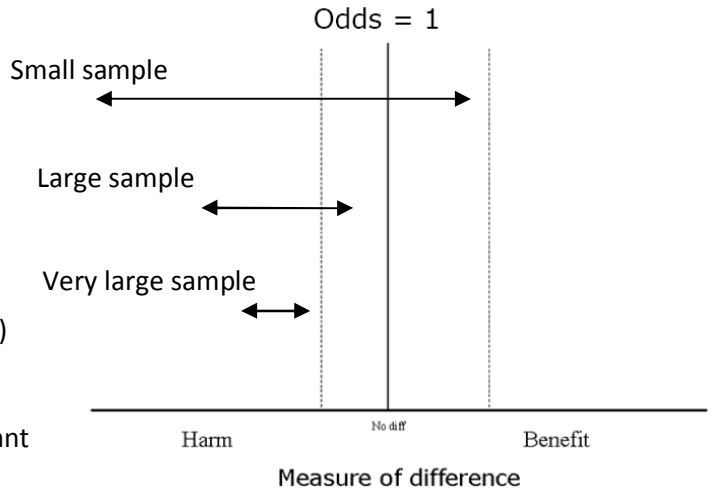
RCT/cohort study

	Disease Present D+	Disease Absent D-	
Risk present R+	a	b	a+b
Risk absent R-	c	d	c+d
	a+c	b+d	n

- Useful is presenting case control or cross-sectional studies
  - Ie: case vs control with a risk factor
  - Ie. can show proportion of people in case/risk factor/intervention group who have a certain disease/change
- Eg example 3:
  - 40 cases of severe influenza
  - 40 matched controls who did not have severe influenza
    - Looking for relationship between influenza and cigarette smoking

Treatment	Smokers	Non-smokers	Total number treated
Case	22	18	40
Control	7	33	40
Case Odds	22 / 18 = 1.2		
Control odds	7 / 33 = 0.21		

  - Case odds: 22/18 = 1.2
  - Control odds: 7/33 = 0.21
    - Odds ratio (Case odds: Control odds) = 1.2/0.21 = 5.7
      - Means 5.7x more likely to be a smoker if have influenza
- Interpretation of odds ratios
  - OR is a ratio
    - A point value
    - An indication of size of effect
  - Can use 95% confidence intervals



Confidence intervals

- Indicates the level of precision of an estimate
  - Narrow CI means great precision
  - Precision is related to variability (standard deviation) and sample size
- Not statistically significant if interval crosses the no-dif line
  - The larger the sample, the more statistically significant
- Not necessarily clinically significant

Risk

- Relative risk ratio
  - RR = EER/CER
- Relative risk increase or reduction (RRR) = (EER-CER)/CER as a %
  - Not encouraged because it is a clever way of presenting information → factors out the baseline risk
- Absolute risk reduction (risk difference) (ARR)
  - ARR = $|CER - EER|$

Anti-viral Treatment	Remission	No remission	Total number treated
New treatment	22	18	40
Standard	7	33	40
Experimental event rate EER	**22/40 = 0.55 or 55%**		
Control event rate CER	**7/40 = 0.18 or 18%**		
Relative Risk Ratio	0.55 / 0.18 = 3.1		
Relative Risk Reduction	100 ((0.55 – 0.18) / 0.18) = 206%		
Absolute Risk reduction	0.18 - 0.55 = 0.37 or 37%		

Odds ratio vs Risk ratio

- Risk ratio
  - Number of individuals having an event over a given time period / number of susceptible individuals at the start of the time period
- Odds ratio
  - Number of individuals having the state at the time of asking / number not having the state at that time
- Eg: Anti-viral clinical trial
  - RCT over 2 months
  - Rates, so use RR
- Eg: case control study for influenza and smoking
  - Case control – retrospective, no follow-ups
  - Retrospective, therefore use OR

Importance of results

- Factors:
  - Bias
  - Chance variation between groups (p-values, significance)
  - Effect of the treatment (quantify effect, look at clinical significance)
- RR – shows how many times more likely to contract disease/get change if in risk/intervention group
- ARR – shows the amount of reduction in risk of having disease/getting change if in risk/intervention group

Number needed to treat

- Number of patients that would need to be treated to benefit one patient or prevent one bad outcome
  - NNT= 1/ARR = 1/(EER-CER)

Treatment	Total number treated	Number whose symptoms remitted	Numbers who did not remit
New treatment	40	22	18
Standard	40	7	33
Experimental event rate EER	22/40 = 0.55 or 55%		
Control event rate CER	7/40 = 0.18 or 18%		
Absolute risk reduction	0.55 - 0.18 = 0.37 or 37%		

NNT = 1/(EER – CER)	1/(0.55 – 0.18) = 1 / 0.37 = 2.7 = 3

Introduction

- Prevalence of disease affects the likelihood of diagnoses
- Global causes of death
    - CHD, LRTI, Diarrhoea, HIV/AIDS, Stroke/CVD, COPD (smoking), TB, Neonatal infections, Malaria, Premature and low birth weight
    - CHD is the highest because:
        - Transition countries (like china and India) are experiencing lifestyle changes that increase risk factors
        - The population is ageing
- Burden of disease
    - Depression is an important cause of disability
    - Road traffic injuries are on the rise
- Risk factors – for diseases that increase the burden of disease
    - SES
    - Smoking
    - Sexual behaviour
    - Changing environments and habitat (road traffic)
    - Trends in developing/transition countries
- Trends in developing/transition countries
    - Eg: Smoking in China
        - 70% of men smoke, 4% of women (1/3 cigarettes around the world consumed in china)
        - 1/3 young men die from smoking
            - 3000 die/day
            - Contributes to 4/5 leading causes of death in China today
        - World's largest tobacco producer, ¼ global production
            - Chinese market is seen as a prize for tobacco multinationals

Malaria

- Caused by plasmodium parasite (falciparum, vivax, malariae, ovale) that is transmitted by the anopheles mosquito
- Mortality is rising due to drug resistance
    - A child dies every 30s
    - 247 million cases in 2006, 880 000 deaths, most cases are in African children <5
- Vulnerability (risk groups)
    - Travellers
    - Low income countries
    - Non-immune pregnant women
        - Malaria leads to miscarriage and maternal death, impaired fetal growth, anaemia
- Preventable and curable
- Clinical features
    - Fever, headache, chills, vomiting
    - Worry about cerebral malaria (caused by falciparum)
    - Other symptoms:
        - Disseminated intravascular coagulation, convulsions, respiratory distress, bleeding, jaundice
- Diagnosis
    - Light microscopy and rapid diagnostic tests
- Treatment
    - Chloroquine – mainstay in the past, now ineffective
    - Sulfadoxine-pyrimethamine
    - Artemisinin (+ Artemisinin combination therapy, ACT)
        - Aim is to eradicate parasite from liver and blood
- Resistance
    - Documented for falciparum (in all except ACT)
    - Vivax is developing resistance to sulfadoxine-pyrimethamine
    - Often localised, different areas have different resistances

- Prevention
    - Insecticide-treated nets
    - Pregnant women: preventative doses of s-p (clear placenta of parasites)
    - Indoor spray to kill mosquitos
    - Avoidance of dusk to dawn, long sleeve clothes, repellent, prophylaxis (Eg: Mefloquine, Chloroquine etc)

Causes of death in Australia

- IHD, Stroke, Trachea/lung cancer, Dementia/AD, Chronic LRTI, Colon/rectum cancer, Diabetes, Blood/lymph cancer, HF, Kidney disease/urinary disease

Rates

- Incidence – number of new cases over time
- Prevalence – total number of cases at a particular point in time

Surveillance systems – used to monitor disease trends

- CDC guidelines for use:
    - Guide immediate action for important public health cases
    - Measure burden of disease and risk factors (identification of populations at risk, new health concerns)
    - Monitor trends in burden of disease (direction of epidemics/pandemics)
    - Guide planning, implementation and evaluation of programs that prevent and control disease / injury / adverse exposure
    - Evaluate public policy
    - Detect changes in health practices and the effects of these
    - Allocation of health resources
    - Description of clinical course of a disease
    - Basis for epidemiological research
- Eg uses:
    - Influenza pandemic
    - Rotavirus → gastroenteritis, seasonal pattern
        - Vaccine available

Influenza

- U shaped curve by age

Meningococcal

- Bacterial, fulminating illness leading to death
    - Not very common, but has a very high death rate
    - Test – push a glass on the rash, look for blanching, absent – meningococcal
- Epidemiology
    - Spike in the very young 0-4, spike in the 15-25 age group (young adults/teenagers)
    - Transmitted in saliva

Pneumococcal

- Less public awareness
- Infant, immunocompromised, elderly
    - U shaped curve by age

Epidemic vs endemic

- Endemic – a disease that exists permanently in a particular region or population
- Epidemic – an outbreak of disease that attacks many people at the same time and spreads through several communities
    - Defined by rate of growth of the epidemic curve
- Pandemic – an epidemic that spreads throughout the world
- Misnomer: “obesity epidemic” → an endemic disease on the rise

Herpes zoster - shingles

- Dermatomal distribution
- Ophthalmic zoster (trigeminal nerve)
    - Antivirals are available but need to be given early
- Particularly common in the ageing population
    - Vs chicken pox in the young (vaccine available)
- HZ vaccine available but not funded

Comparing burden of disease of different diseases

- Like comparing apples and oranges
    - Need a common denominator/health outcome
- WHO designed: DALY a measure of overall disease burden to quantify diseases
    - DALY – disability adjusted life year
        - DALY = YLL (years of life lost) + YLD (years of life with disability)
        - Combines mortality and morbidity into a single, comparable measure
    - QALY – quality adjusted life year
        - Also takes into account quality of life
    - Thus we can use QALY and DALY to compare cost efficacy of different interventions
        - Used to allocate resources (drugs/acute health care funding)

Statistics

- $p < 0.05$ is significant
- CI – significant if it doesn't cross 1
- Chance
- Bias – systematic error (eg wrong ruler)
- Confounding factors (other factors that may influence results, eg: cholesterol in heart disease)

Association

- RR (relative risk, time factor), OR (odds ratio, no time factor) and Hazard ratio
    - Egs:
        - Risk of smoking causing lung cancer, OR = 5.4
            - Ie: of smokers, 5.4x increased chance of also having lung cancer
        - Risk of AMI in people on statins – RR = 0.5
            - Ie: people on statins are half as likely to develop an AMI than those not

Causation

- Dependent on many factors – Bradford Hill Criteria
    - Temporal relationship
    - Strength of the association
    - Dose response relationship
    - Consistency, biological plausibility, alternative explanations
    - Coherence/reproducibility
    - Experiment, specificity

Types of studies

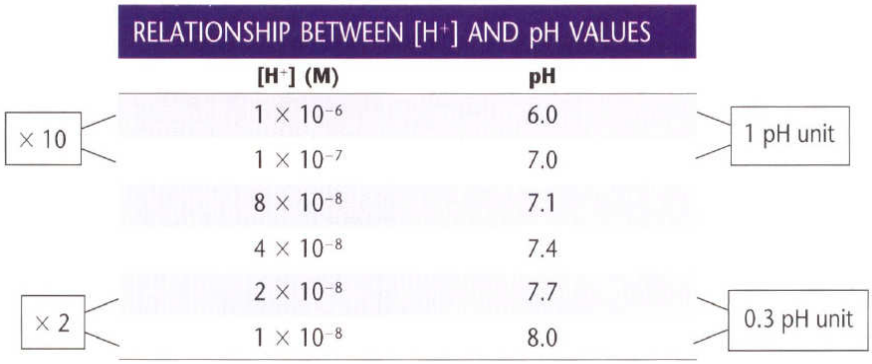
- Case series
- Descriptive – similar to cross-sectional studies
- Observational epidemiology (case control, cohort)
- Intervention studies (RCT)

Summary

- Patterns of disease are important for clinical practice
    - Assists us with clinical judgement and decision making
- Underpins all public health prevention programs
    - Involved in economic analysis which is important for obtaining funding

Fundamental concepts: pH

- pH
  - a measure of acidity
  - pH = -log[H^+]
    - thus if [H^+] = 10^{-7}mol/L, pH = 7.0
  - A hydrogen ion is a single free proton released from a hydrogen atom
- As [H^+] increases, pH decreases, acidity increases
  - Each pH unit less than 7.0, [H^+] increases 10x, less – decreases 10x
  - If you double the amount of [H^+], decrease pH by 0.3



- Normal arterial pH is ~ 7.40 (7.35-7.43)
  - Venous pH is slightly lower due to increased CO_2 (7.37)
  - Fluids are slightly alkaline
    - Even more so because at body temperature, neutral is at pH 6.8, vs 7.0 at 25°C
- pH is a better measure of acidity than [H^+] because protons are in very low concentrations in the body
  - ie, pH 7.4, = 40nmol/L vs [Na^+] in arterial is 145 mmol/L
    - note, 7.1 = 80nmol/L, 7.7 = 20nmol/L
- pH is tightly regulated in the body (6.8-7.8)
  - (in spite of protons in low concentrations)
  - Normal pH is important for normal metabolic function (enzyme activity, blood clotting muscle contraction)
    - Eg: phosphoric kinase with a change of 7.1 to 7.2 there is a 20x reduction/increase in activity

Fundamental concepts: acids and bases

- Acids are proton donors
  - Eg: Hydrochloric acid (HCl), carbonic acid (H_2CO_3), carboxyl groups (R-COOH)
- Bases are proton acceptors
  - Eg: Hydroxyl ions (OH^-), ammonia (NH_3), bicarbonate (HCO_3^-), R-NH_2 (amino groups)
  - Base is often synonymous with alkali
- Strong and weak acids
  - Strong acids completely dissociate into solution
    - Eg: HCl → $H^+ + Cl^-$
  - Weak acids don't completely dissociate into solution and form an equilibrium (typical of body)
    - Eg: Carboxyl groups: R-COOH ←→R-COO^- + H^+
  - The stronger the acid, the higher the K_A (equilibrium constant)
    - $K_A = [H^+][A^-]/[HA]$
      - The higher the K_A, the lower the pK_a (-logK_A)
- Strong and weak bases
  - Classification into strong/weak based on complete/incomplete combination
    - OH^- is a strong base
    - Bicarbonate is a weak base
- Acids and bases in extracellular fluid (to do with acid-base regulation) in the body are for the most part weak

Henderson-Hasselbalch equation

- Derivation
  - $K_A = [H^+][A^-]/[HA]$
    - Make $[H^+]$ the subject,
      - $[H^+] = K_A[HA]/[A^-]$
    - Take the negative log of both sides
      - $pH = pK_A - \log[HA]/[A^-]$
      - $pH = pK_A + \log[A^-]/[HA]$
  - note: if $[A^-] = [HA]$, $pH = pK_A$
- Carbonic acid-bicarbonate system
  - Notes:
    - $pK_A = 3.5$ for H_2CO_3 dissociation equation
    - H_2CO_3 concentration is hard to measure so we use CO_2 concentration because it is equivalent 1:400
    - Thus, $pK_A = 6.1$ for new dissociation equation using CO_2 concentration
    - 0.03 is the solubility coefficient
      - Ie for every mmHg of CO_2, there is 0.03mmol dissolved

$H_2CO_3 \leftrightarrow H^+ + HCO_3^-$

$pH = pK_A + \log[A^-]/[HA]$

$pH = 3.5 + \log[HCO_3^-]/[H_2CO_3]$

$H_2CO_3 \leftrightarrow CO_2 + H_2O$

$pH = 6.1 + \log[HCO_3^-]/[CO_2]$

$pH = 6.1 + \log[HCO_3^-]/0.03*P_{CO2}$

Normal arterial blood

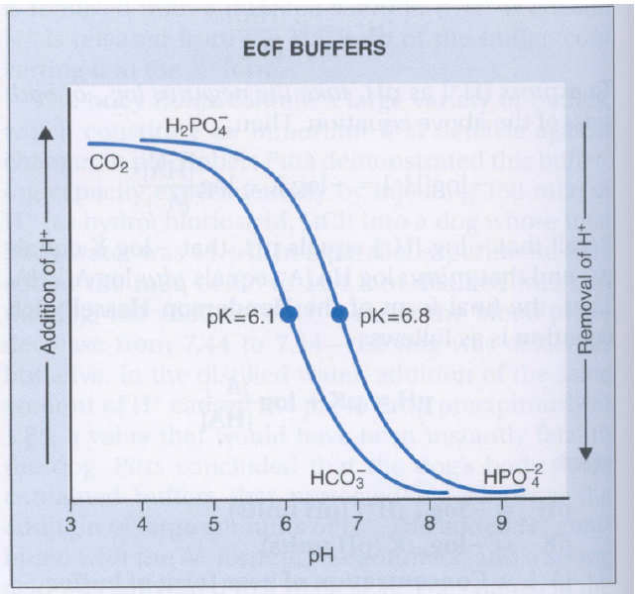
$pH = 6.1 + \log(24/0.03*40)$

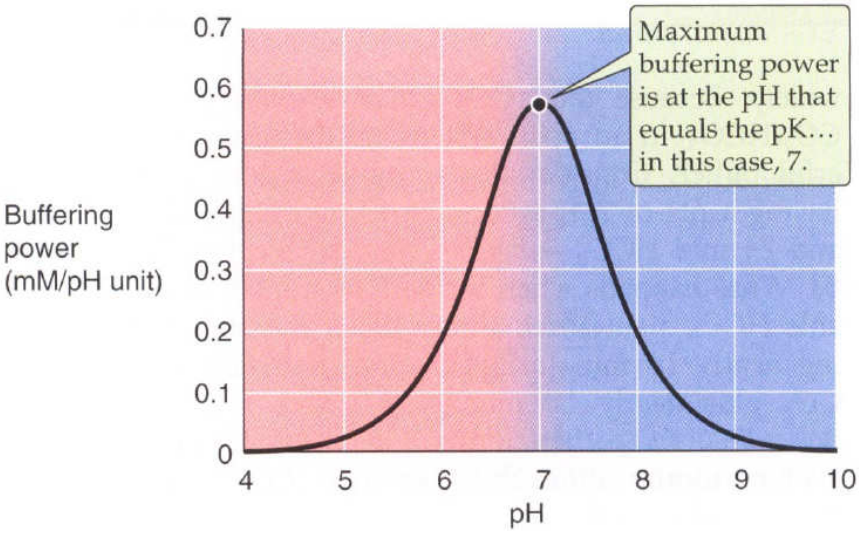
$= 6.1 + \log(20)$

$= 7.4$

Buffers

- Definition – any substance that reversibly consumes or releases H^+
  - Minimises the change of pH that occurs in an acid/base system
    - pH change is not prevented but minimised
  - Buffer is most effective when pH at equilibrium constant (pK) is within 2 or 1 of pH range
    - Ie, most effective around their standard equilibrium pH
- Graphs: a closed system



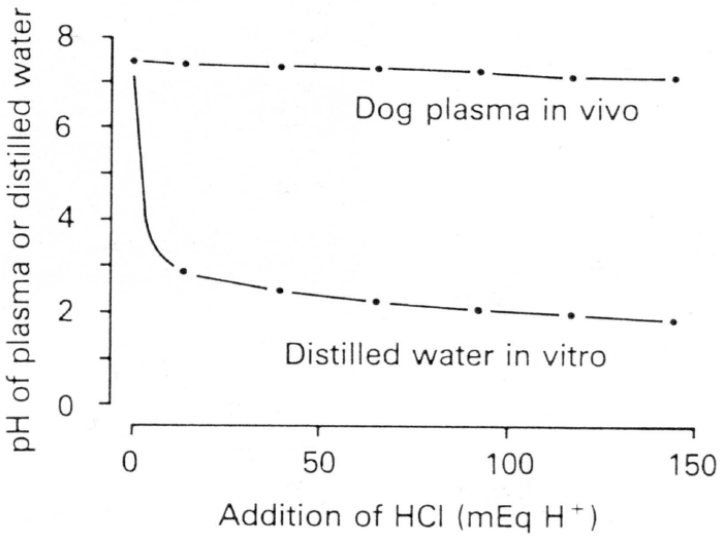


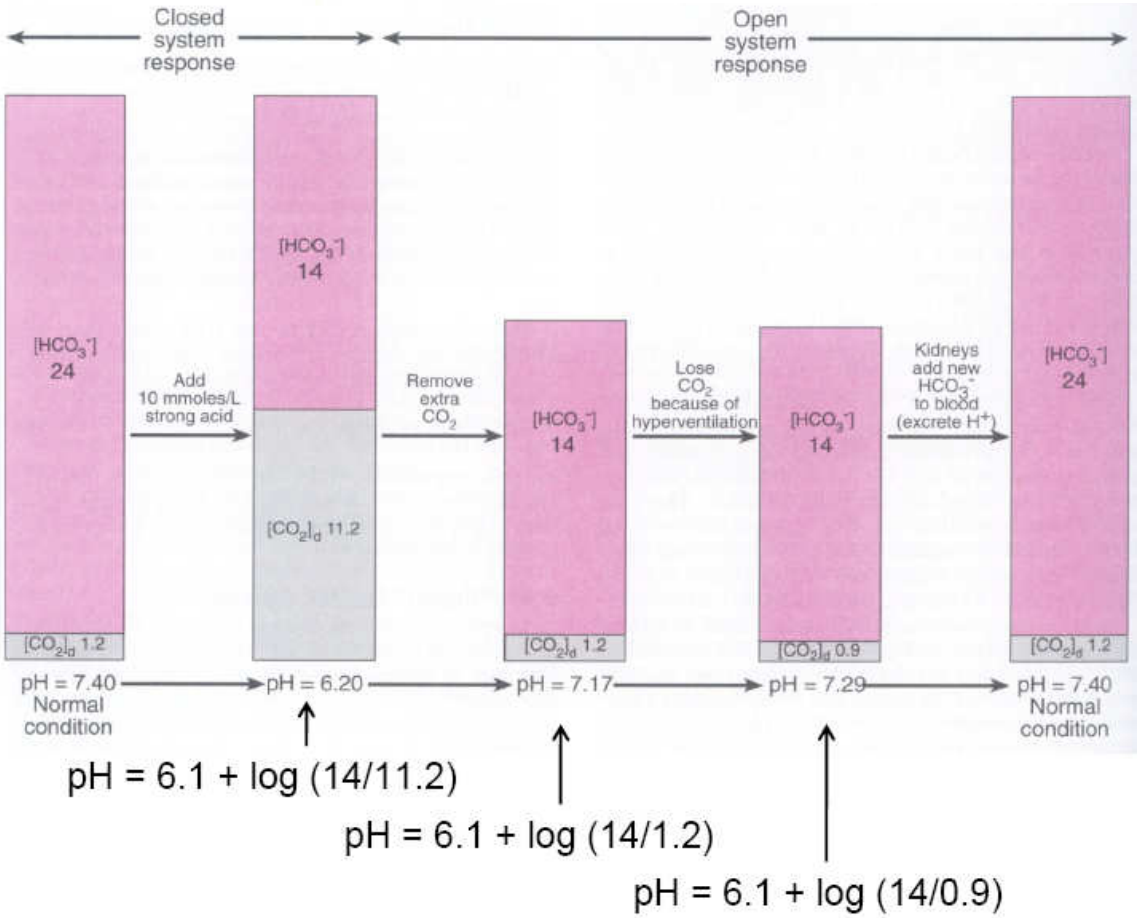
Body acid-base balance

- Metabolism produces acid every day
  - Cellular metabolism of carbohydrates and fats – 15-20 mol/day of CO_2 (volatile acid, can be lost from lungs)
  - Also:
    - Small amounts of non-volatile (fixed) (non CO_2) acids (~70mmol/day)
      - Sulfuric acid – metabolism of amino acids with sulfur groups (methionine/cystine)
      - Hydrochloric acid – metabolism of lycine, arginine and histidine amino acids
      - Phosphoric acid - metabolism of nucleic acids and phospholipids
    - Depend on diet – vegos have lower levels of these (less protein)
    - To produce just volatile and non-volatile acids, need to have sufficient perfusion and insulin
      - Not adequate perfusion – produce lactic acids
      - Not enough insulin – produce hydrobutyric acid and acetoacetate
  - In spite of these processes, normal pH range is maintained
    - Due to:
      - Buffering – quick, in seconds
      - Respiratory regulation of pH – minutes
      - Renal (kidney) regulation of pH – hours/days

Blood buffering

- Buffers are very effective
  - pH doesn't change that much around buffering pH
- Carbonic acid-bicarbonate system (an open system)
  - Not useful for CO_2 buffering
  - Important body buffer because CO_2 and bicarbonate can be regulated by the body
    - CO_2 can be eliminated in the lungs
    - Bicarbonate can be excreted or generated by the kidneys
  - Bicarbonate is present in relatively high concentrations (~24 mmol/L)
  - pK = 6.1





- Phosphates
  - Reaction: $H_2PO_4^- \leftrightarrow HPO_4^{2-} + H^+$, pK 6.8
  - Closer to plasma pH than bicarbonate system,
    - Not much organic phosphate in the blood (0.8-1.6mmol/L)
- Protein buffering
  - Major blood buffer for CO_2 produced by tissues
  - Method of action:
    - Acceptance or release of a proton by an amino acid residue side chain (esp. histidine)
      - pK of the side chain of histidine in a peptide chain is 6.1-7.1
    - Acceptance or release of a proton by the terminal NH_2-NH_3^+ or COOH-COO^- side groups
      - COO^- groups are ionised at blood pH so don't help buffering
      - pK for NH_2-NH_3^+ terminal groups is ~8.0
  - Main protein in blood is haemoglobin
    - 6x buffering capacity of plasma proteins
    - Present at a high concentration
    - Rich in histidine residues (38/molecule)
  - Haemoglobin
    - As it becomes more deoxygenated, it can take up more protons
      - For each mole of O_2 released by haemoglobin, 0.7 mol of protons can be taken up before pH changes
      - Thus, important for buffering in deoxygenated tissues (where CO_2 added to blood)
  - Buffering not only in blood – also in interstitial fluid (mainly bicarbonate) and in cells
    - Proportions: acid infusion results in: ~20% in blood (plasma proteins), 30% in interstitium, 50% intracellularly (proteins, incl. Hb, phosphates and bone tissue)

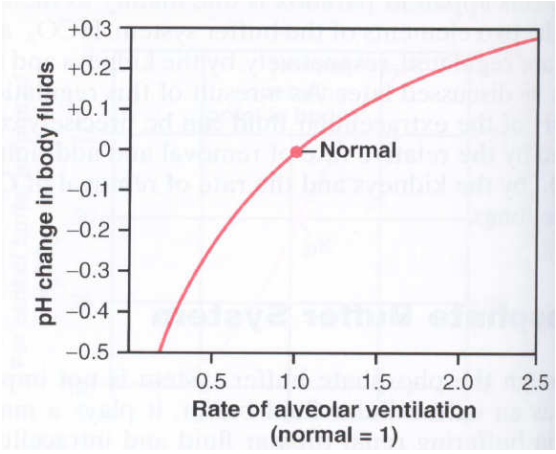
<u>Isohydric principle</u>

- In a common solution, all buffer pairs are at equilibrium with the same $[H^+]$ in their equation
  - If a condition changes the balance of the buffer systems, the other systems are also changed because they buffer each other by shifting hydrogen ions back and forth
  - The pH can be worked out from any of them

$$pH = 6.1 + \log[HCO_3^-]/0.03*P_{CO2}$$
$$= 6.8 + \log[HPO_4^{2-}]/[H_2PO_4^-]$$
$$= pK_3 + \log[Hb^-]/[HHb]$$
$$= pK_4 + \log[Prot^-]/[HProt]$$
etc.

<u>Respiratory regulation of pH</u>

- Involves the variation of CO_2 (volatile acid) elimination in lungs
  - Ventilation determines P_{CO2}
    - at maximum hyperventilation, can reduce P_{CO2} from 40 to 10 mmHg
    - hypoventilation often results in hypoxia before P_{CO2} can get much higher than 60mmHg



<u>Renal regulation</u>

- Bicarbonate buffering is limited in the long term
  - As it counters the acid, it is consumed and CO_2 is excreted
- Lost bicarbonate is replenished by regeneration in the kidneys
  - Acid excretion can also occur especially as phosphate and ammonium
  - If pH is too high, kidneys can secrete bicarbonate into the urine to lower the pH

<u>Acid-base disorders</u>

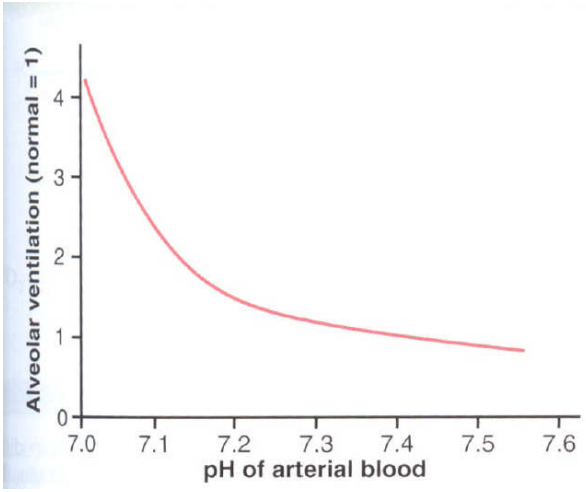
- Acidosis – plasma pH less than 7.35
- Alkalosis – plasma pH greater than 7.45
  - Acidaemia and alkalemia – same thing if you just look at the plasma pH (osis are processes)
- A primary change in P_{CO2} is a respiratory disorder
- A primary change in HCO_3^- is a metabolic disorder
  - Disorder may be mixed (eg: emphysema + diarrhoea)
  - The direction of the equilibrium change indicates which disease (respiratory/metabolic)

Respiratory acidosis

- Low pH and elevated P_{CO2} (>40mmHg)
  - Caused by failure to eliminate CO_2
    - Mechanisms:
      - Inadequate ventilation (eg. drug induced – eg. heroin overdose, depression of respiratory centres)
      - Inadequate gas exchange (eg. pulmonary oedema, ventilation-perfusion inequality)
  - Buffering is intracellular
  - If this is sustained, renal compensation will occur
    - Since this takes a few days to take effect, there are acute and chronic phases of respiratory acidosis

Respiratory alkalosis

- High pH and low PCO_2
  - Caused by hyperventilation
    - Mechanisms:
      - Stimulation of respiratory centres by drugs/neurological disorders
      - Anxiety/fear
      - Altitude (hypoxic)
  - Renal compensation
    - Reduces acid excretion (returns acids to the body)
    - Stimulates bicarbonate secretion into urine
  - Buffering is again intracellular

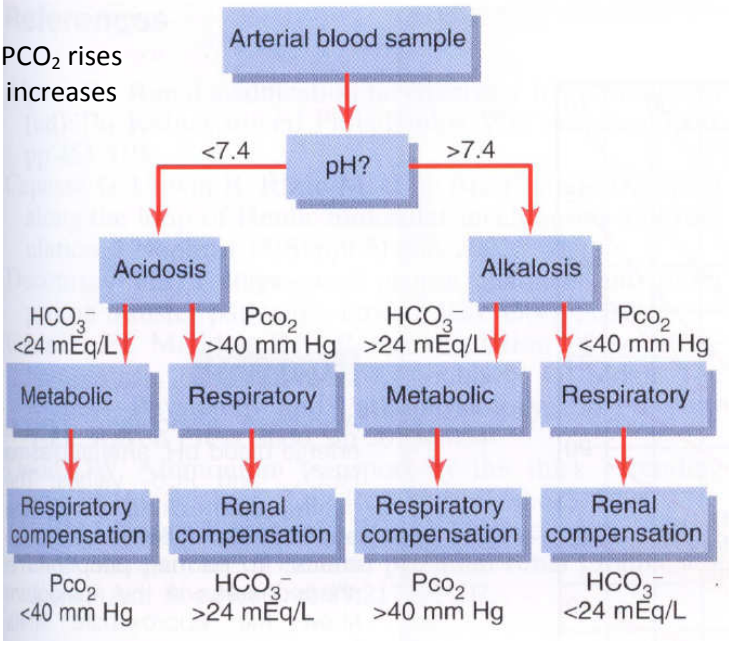


Metabolic acidosis

- Low pH and low plasma bicarbonate (<24)
  - Caused by:
    - Addition of non-volatile acid to body
      - Eg: diabetic ketoacidosis, ingestion of ammonium chloride
    - Loss of non-volatile alkali – diarrhoea – lose HCO_3^- from lower GIT
    - Kidneys fail to excrete sufficient acid (eg renal failure)
  - In response, ventilation rate is stimulated and PCO_2 falls minimising plasma pH fall
    - Also, renal net acid expression increases
    - Increased ventilation rate explains 'deep breathing/air hunger' in diabetic ketoacidosis
- Graph: less than pH 7.4, ventilation increases to remove CO_2

Metabolic alkalosis

- High pH and high plasma bicarbonate
  - Caused by:
    - Addition of non-volatile alkali (eg: ingestion of antacid mixture)
    - Loss of non-volatile acid (eg: loss of gastric HCl through vomiting, excess aldosterone – lose acid from kidneys)
  - In response, ventilation rate is reduced and PCO_2 rises
    - Also, renal excretion of bicarbonate increases



- Note: in diagram,
  <>7.4 really means <7.35 or >7.45

Anion gap

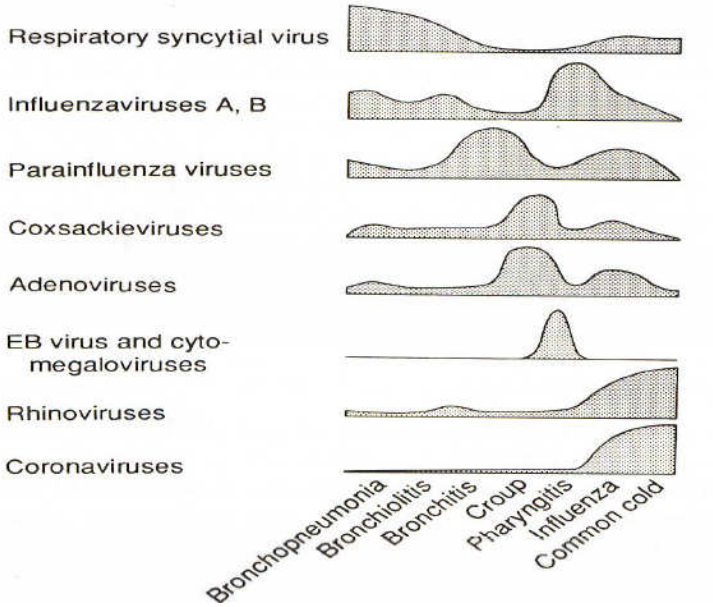
- Used to determine the cause of metabolic acidosis
  - Anion gap = $[Na^+] – ([Cl^-] + [HCO^-])$
    - Normally = 8-16 mEq/L = mmol/L (but to do with charge)
  - Electroneutrality is maintained
- Ie, full equation:
  - $[Na^+]$ + [unmeasured cation] = $[Cl^-]$ + $[HCO^-]$+ [unmeasured anions]
- If anion of the non-volatile acid is Cl^-, anion gap is normal
  - If it is not, (eg. lactate, beta-hydroxybutyrate) anion gap is increased
- Pathology
  - Normal anion gap (hyperchloraemic)
    - Eg: Diarrhoea, loss of HCO_3^-, kidney retains Cl^-
    - Eg. renal tubular acidosis, Addison's disease
  - Increased anion gap
    - Eg: diabetic ketoacidosis (increased beta-hydroxybutyrate)
    - Eg: lactic acidosis
    - Eg: chronic renal failure
    - Eg: poisonings – aspirin, ethylene glycol, methanol

ANSWERS TO ACID-BASE PROBLEMS

	pH	$[HCO_3^-]$	PCO_2	Disorder
(a)	7.34	15	29	metabolic acidosis
(b)	7.49	35	48	metabolic alkalosis
(c)	7.47	14	20	chronic respiratory alkalosis (Note: compare with f)
(d)	7.34	31	60	chronic respiratory acidosis (Note: compare with e)
(e)	7.26	26	60	acute respiratory acidosis
(f)	7.62	20	20	acute respiratory alkalosis
(g)	7.09	15	50	mixed acidosis (note: both the low HCO_3^- and the high PCO_2 are consistent with acidosis).

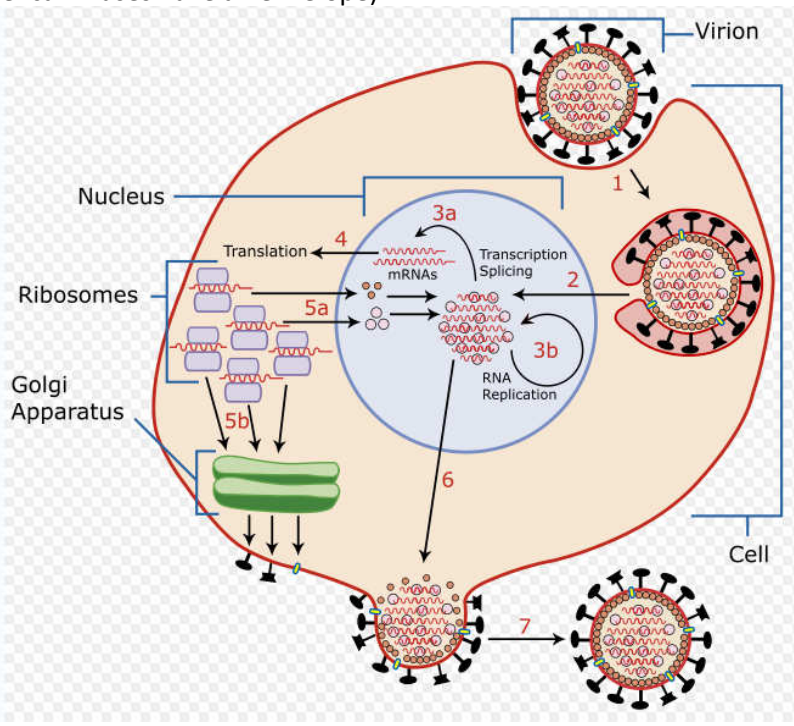
Background information

- Respiratory viruses (that cause respiratory infection)
  - Adenovirus, coronavirus (a strain of which causes SARS)
  - Human metapneumovirus
  - Influenza A and B
  - Parainfluenza 1, 2, 3 (4 – mild)
  - Respiratory syncytial virus (RSV)
  - Rhinovirus – causes 50% of all colds
- Children – common respiratory viruses
  - hRSV, influenza, etc
  - enteroviruses
  - HSV, VZV, EBV, Measles
- Many viruses cause respiratory disease, the worse is caused by Influenza A
- Virus locations
  - The further into the lungs, the more serious
    - The more common viruses/more mild viruses affect the nose/throat regions instead of lungs



Influenza introduction

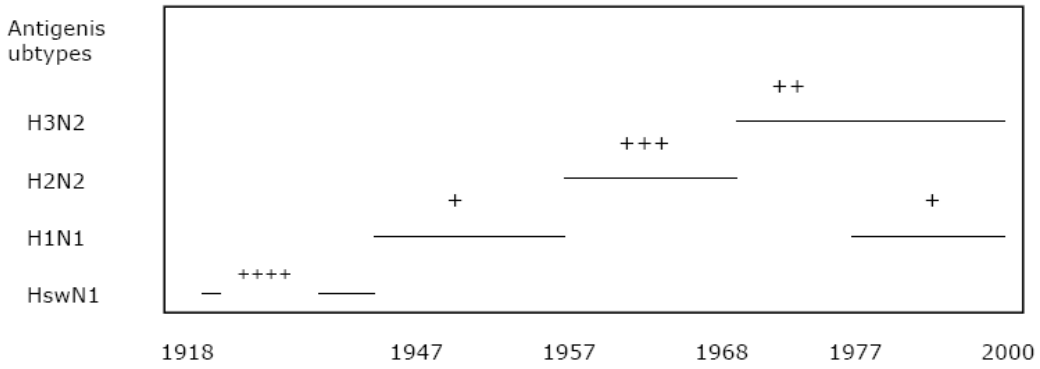
- Strikes in winter
  - Can be sick for up to 3 weeks
- True influenza is a potentially very serious infection that can cause an epidemic and kill many (especially the young/old)
  - Often used as a misnomer for common cold
- Treatments and vaccine are available
- Properties (Orthomyxoviridae family):
  - 3 genera: ABC
  - -ss RNA virus with 13.6 kb (HIV has 10kb), 8 segments (6 code for 1 protein, 2 for 2 proteins), 10 genes
  - Helical virus with an envelope (in humans, all helical viruses have an envelope)
- Epidemiology
  - Seasonality
  - Antigenic drift/shift
  - B genera is less pathogenic
- Pathogenesis
  - Transcription/replication in cell nucleus
  - 1-4 day incubation
    - Produces a large number of virions
- Taxonomy
  - Family/genus/species
  - Orthomyxoviridae /orthomyxovirus /ABC
- Nomenclature
  - Type /Town isolated /# isolates /year isolated /major type of HA/NA
  - Eg: A/Singapore/6/86/H1N1



Epidemiology

- Features of virus
  - Repeated infection throughout lifetime due to mutation and drift
  - Rapid spread via short epidemics (regular) and pandemics (occasional)
    - Epidemic influenza – seasonal in temperate zones, year round in tropics
    - Pandemic influenza – less seasonal
  - A new subtype replaces the previous subtype
- History
  - 1889-1892: H2N2, "European"
  - 1918-1919: H1N1, "Spanish" – 40 million dead
    - 1933 – first strains isolated
    - 1947 – variation detected
  - 1957: H2N2, "Asian" – 1 million dead
  - 1968: H3N2, "Hong Kong" – 1 million dead
  - 1977: H1N1 + H3N2 "Russian"

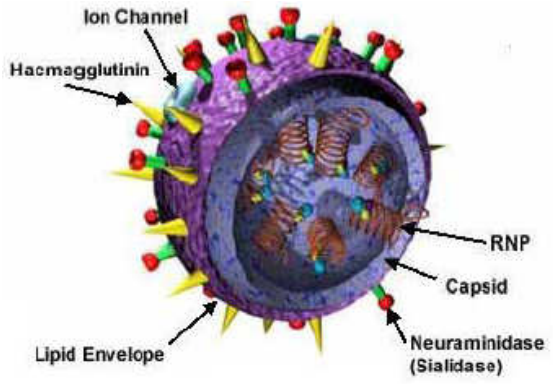
(Severity of pandemic + → ++++)



- Influenza increases general mortality rates
- Annual impact
  - 10-20% are infected
  - Large economic costs through medical services, work days lost and hospitalisations

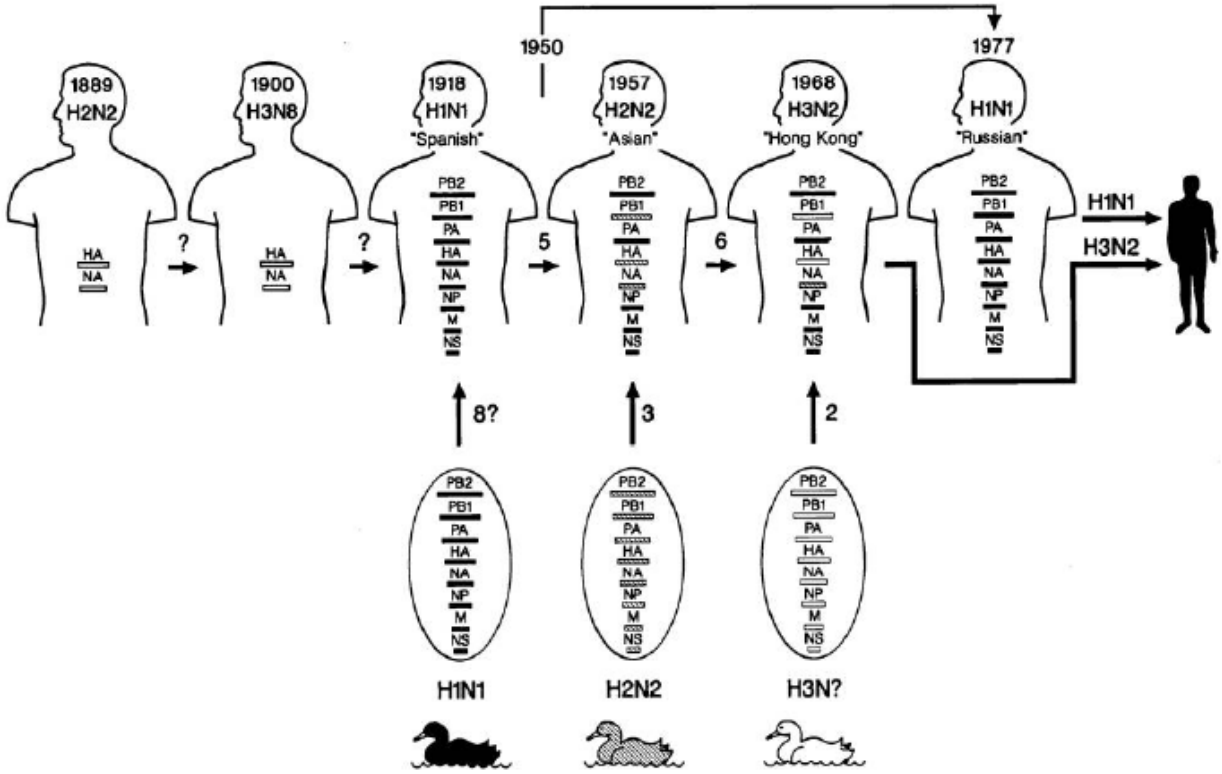
Structure

- 80-120nm spherical
- Lipid envelope surrounding a nucleocapsid core
  - Derived from the host cell membrane
  - Contains embedded glycoproteins haemagglutinin and neuraminidase
    - HA1 and HA2 recognise the alpha-2,6 sialic acid receptors on host cells in humans
- Nucleocapsid core contains:
  - Nucleoproteins
  - Single-stranded RNA (-ve strand)
  - From the RNP (ribonucleoprotein) complex
    - Contains polymerase proteins (P1, 2, 3) and non-structural proteins (NS1 and NS2) and matrix protein
- Note:
  - M2 channel protein is important for allowing H^+ into cell and lowering pH
    - This allows dissociation of the viral matrix which uncoats the virus and allows its contents to enter cell cytoplasm



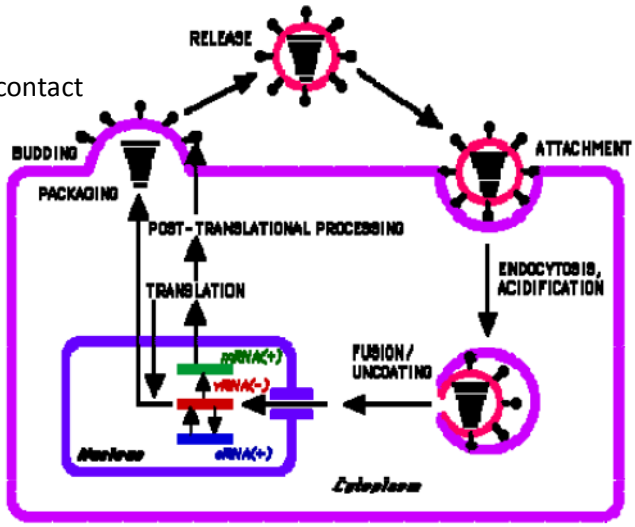
Viral evolution

- Viruses evolve by 3 processes:
    - Antigen drift
        - Virus doesn't change subtype and shows serological cross-reactivity but not complete
        - Gradual change that if different enough can cause epidemic
    - Antigen shift
        - New influenza subtype emerges with haemagglutinin that doesn't cross-react at all
        - Can cause pandemics (1957, 1968)
        - Population is entirely naïve, has no immunity
        - 2-3 segments of genome completely changed
    - Reassortment
        - Facilitates genetic variability and in this way changes immunological targets
        - May be facilitated by a coinfection (pigs, allow segment swapping between bird/human flu)
- Environmental and social conditions encourage mutation
    - Can facilitate transfer from animal to human
        - Economic development and land use – increased human/animal exposure
        - International travel an commerce
        - Poverty, war and famine
- Diagram: history of influenza
    - 1918, Spanish flu thought to have been caused by complete zoonotic transmission
        - Asian and HK due to a reassortment
        - Currently H1N1 and H3N2 are still in population



Pathogenesis

- Process:
    - Inhalation of respiratory droplets or mucosal membrane contact
    - Virus attaches to respiratory epithelium receptors via HA
    - Endocytosis and acidification
    - Uncoating
    - Fusion into nucleus
    - mRNA and cRNA are produced
    - cRNA and nucleoproteins assemble and are packaged
    - Virions are released from cell



Clinical features

- Abrupt onset: fever, sore throat, cough, myalgia, headache, malaise
    - Lasting 3-7 days
- Complications:
    - Vary with age
    - Egs: Otitis media, pneumonia, croup (laryngotracheobronchitis)
    - More detail:
        - Pneumonia – viral, bacterial
        - Reye's syndrome (children <18) – encephalopathy/ liver degeneration
        - Congenital malformation
        - Acute viral encephalitis
- Death is often from secondary bacterial superinfections
    - While the immune system is fighting the virus, bacteria take hold (EG: S. aureus, S. pneumoniae, H. influenzae)
- Influenza vs common cold
    - Causes:
        - Influenza: influenza A/B
        - Cold: many different viruses (rhinovirus, coronavirus, human metapneumovirus)
    - Locations
        - Influenza: systemic with fever, arthralgia, myalgia
        - Cold: local, nose and throat
    - Onset: influenza: abrupt, cold: gradual
    - Symptoms
        - Influenza: chills, myalgia, sore throat, cough
        - Cold: sneezing, sore throat, nasal congestion
    - Complications/mortality
        - Influenza: can be severe, esp pneumonia, especially at risk groups (diabetes, immunocompromised, 3rd trimester pregnancy, severe asthma, post transplantation)
        - Cold: complications rare (possible pneumonia), rare mortality
    - Timing: influenza: 1-2 weeks, epidemiology is seasonal, cold: rapid recovery, found all year
- Influenza B
    - Milder
    - Less nasal symptoms
    - Causes a mild respiratory tract infection in children and a mild URTI in adults
        - 2008 was an exception

Avian influenza (bird flu)

- 385 cases, 243 deaths (63% mortality)
    - Only Ebola (80-90% mortality) and variola major higher
- Conditions for a pandemic
    - New influenza subtype
    - Infection of humans causing serious illness
    - Spreads easily and sustainably human-human
- Various strains
    - H7N7, mild disease, conjunctivitis; H9N2, respiratory disease, no deaths; **H5N1, emerged in HK 1997**

HK 1997

- 18 people hospitalised, 6 deaths
    - Virus found in chickens, disease associated with poultry contact
    - All poultry culled December 1997 – stopped further cases

H5N1

- Currently entirely avian
    - binds to the alph-2,3 receptors, found in the lower respiratory tract of humans
        - victims so far have had contact with infected poultry
- symptoms in birds:
    - neurological signs, inability to stand, diarrhoea, death

Spanish flu: the mother of all pandemics

- H1N1 strain
- up to 50 million deaths worldwide
    - most people die of complications like pneumonia
    - many died in 15-34 age group
        - due to cytokine storm
        - similar pattern to H5N1
- Recreated 2006 from archived specimens and victims buried in permafrost
    - Good model because it was initially a purely avian virus that with a few mutations was able to successfully cross the species barrier and infect humans

Pandemic

- Is it possible?
    - Human-human transmission is deciding factor
        - Possibly has already happened:
            - Daughter to mother (Thailand); Woman to several people of family (Indonesia)

Vaccination

- Seasonal vaccination against influenza A/B
    - Types:
        - Whole inactivated virus
            - 30% efficacy, 1-5 year duration, SE: local pain, myalgia, fever
        - Split virus vaccine (eg. fluvax)
        - Subunit vaccine
    - Recommended for: >65yo, ATSI >50, immunodeficiency, chronic illness, pregnant women (2-3 trimester)
- Contents:
    - H1N1, H3N2, influenza B – various subtypes of these strains

Treatment

- Neuraminidase inhibitors
    - Prevents release of virus from cell
    - Eg: Zanamivir (Relenza), Oseltamivir (Tamiflu)
- Amantadines (Symmetrel) – oral
    - Effective if given within 24-48 hours after onset of symptoms
    - Resistance develops quickly after treatment
    - SE common in elderly – neurological (dizziness, confusion)
- Zanamivir (Relenza) – inhaler
    - Effective if given within 30 hours of symptom onset
    - Shortens illness by 1.5-2.5 days
- Oseltamivir – oral
    - Same as Zanamivir
- Efficacy
    - Shedding is reduced in 70% of people by day 4 compared to placebo
    - Therefore, effective

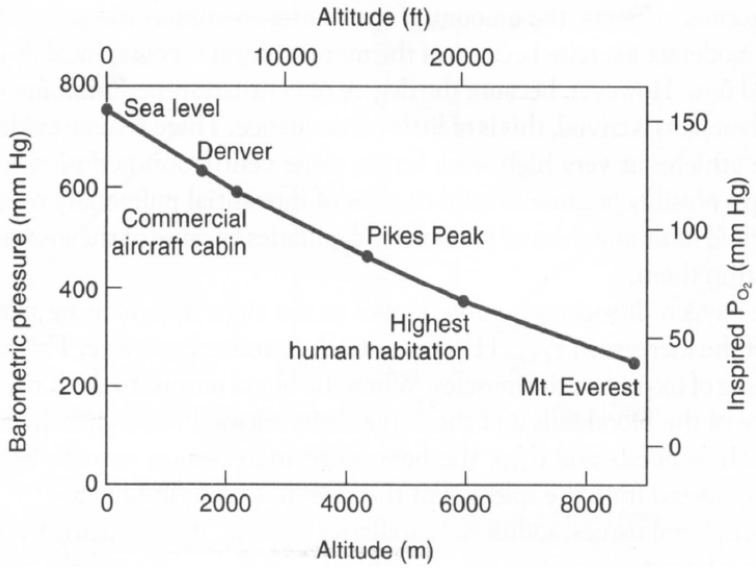
Definitions
- Hypoxia – oxygen deficiency at the level of the tissue
- Hypoxaemia – an abnormally low P_{O2} in the blood
    - Most common cause of hypoxia
- Cyanosis – a bluish discoloration of the tissues caused by the presence of an increased amount of deoxygenated haemoglobin
    - Oxygenated Hb is more red, deoxygenated is more purple-blue

Cyanosis
- Detected when deoxyHb rises to more than 5g/dl of blood
    - Rarely seen in anaemia (total Hb is low), more common in polycythaemia
    - Most often seen in mucus membranes, nail beds, lips, earlobes and fingers where the skin is thin
- Two types
    - Central
        - Indicates blood from the left ventricle is deoxygenated (for whatever reason)
    - Peripheral
        - Indicates that circulation is slow, more O_2 is taken out (or that there is a perfusion problem)
- Occurrence is dependent upon:
    - Hb in the blood
    - Hb saturation
    - State of capillary circulation

Types of hypoxia
- Hypoxic hypoxia – pO_2 is decreased causing arterial blood oxygen to be decreased
- Anaemic hypoxia – pO_2 is normal, there is less Hb and so the amount of O_2 carriage is reduced
- Circulatory/ischaemic hypoxia – pO_2 is normal, carriage is normal, tissue has low blood flow
- Cytotoxic hypoxia – normal pO_2, normal carriage, normal blood flow, cells can't use O_2 (eg. cyanide poisoning)

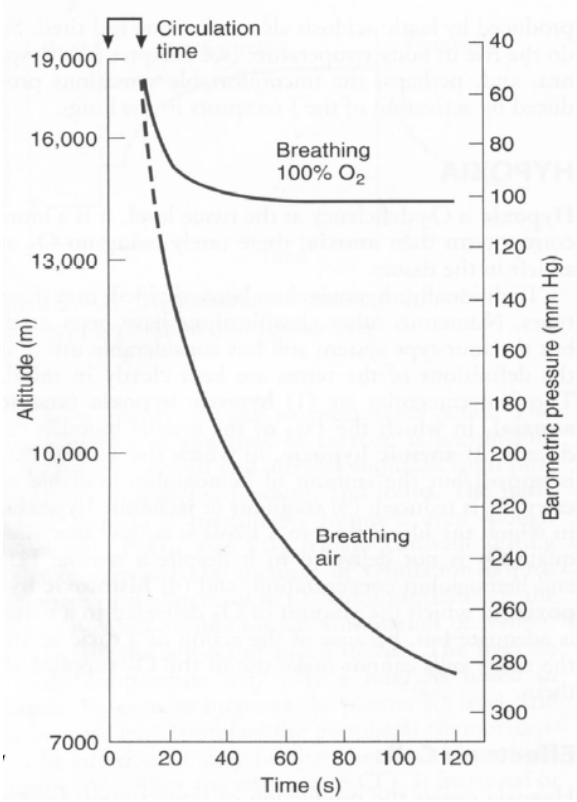
Causes of hypoxic hypoxia
- Reduced inspired O_2 (eg. altitude)
- Hypoventilation
- Diffusion impairment
- Shunt
- Ventilation-perfusion inequality

High altitude (reduced inspired O_2)
- The higher the altitude, the lower the barometric pressure (and thus the lower the partial pressure of oxygen
- Questions:
    - Denver, P_B = 600, P_{O2} of moist inspired air
        - P_{IO2} = (600-47) x 0.2093 = 116
    - 5800m, P_B = 380. Thus, P_{IO2} = 70 mmHg (less than normal arterial P_{O2}
    - 8848, Mt Everest, BP~225. P_{IO2} = 44 mmHg



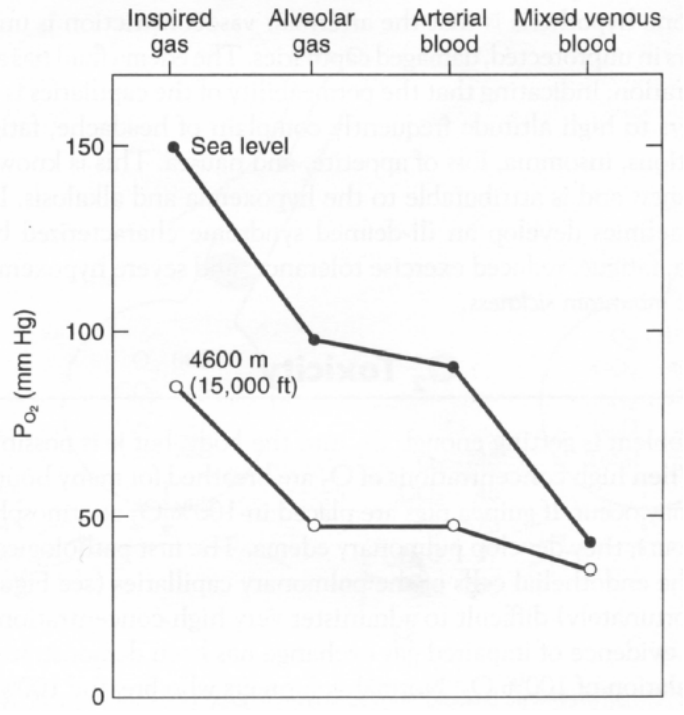
Adjusting to altitude

- Graph: duration of useful consciousness with sudden exposure to ambient pressures of various altitudes
    - With high altitude (and thus low pressure), there is a 10s window of useful time – time it takes the blood to go from the heart to the brain
    - Notice: as altitude decreases, increasing ability to remain conscious when breathing air
- Notes:
    - P_{O2} suddenly drops (eg. cabin pressure in an aeroplane lost – 10-20s unconscious, death in 4-5 minutes
    - Less severe hypoxia results in 'alcohol' effects – impaired judgement, drowsiness, dulled pain sensation, excitement, disorientation, loss of time sense, headache
    - 140 million people live >2500m, Andes: >4900m
        - Due to acclimatisation



Acclimatisation to altitude

- Hyperventilation
    - Hypoxic stimulation of peripheral chemoreceptors cause increased ventilation
        - This is then limited by resulting low P_{CO2} and alkalosis
    - After 1 day, CSF pH decreases due to movement of bicarbonate out of CSF
        - 2-3 days, arterial blood pH returns to normal (reduces pH) by excretion of bicarbonate by kidneys
    - This alkalosis limiting factor on hyperventilation is thus eliminated and ventilation can further increase
        - Also, carotid bodies increase sensitivity to hypoxia and respond slower
- Polycythaemia
    - An increase in the concentration of RBCs in the blood
        - Stimulated by low arterial P_{O2} – kidney releases erythropoietin that stimulates bone marrow
    - Increased RBCs means increased Hb which means increased O_2 carrying capacity
        - P_{O2} and O_2 saturation are going to be decreased, but arterial O_2 concentration may be increased
        - Eg: resident of Andes: [Hb] of 19.8g/100ml
            - Pa_{O2} = 45mmHg, S_{O2} = 81%
            - Arterial O_2 concentration = 22.4ml/100ml
            - P_{O2} of mixed venous blood also maintained, (only 7mmHg below normal)
    - Problem: increased blood viscosity
    - At high Hb levels, there is increased O_2 concentration in blood (see graph)



- Shifts in the oxygen-haemoglobin equilibrium curve
    - Moderate altitudes: increase in 2,3 DPG (partly due to respiratory alkalosis)
        - Causes a rightward shift of OEC and allows better unloading of oxygen in periphery
            - (also interferes with O_2 loading in pulmonary capillaries, however)
    - Extreme altitudes: EOC shifts to left due to marked respiratory alkalosis (due to hyperventilation)
        - This assists loading of Hb
    - Note: acidosis causes a right shift, alkalosis causes a left shift (to do with CO_2)
- Other features
    - Pulmonary diffusing capacity increases to maximise loading of oxygen
    - Pulmonary blood perfusion is low, however, so capillaries are constricted, causing increased pulmonary pressure → can lead to RV hypertrophy
    - Number of capillaries/unit of volume in peripheral tissues increases to increase ability to oxygenate tissue
        - Due to endothelial growth factor
    - Changes in oxidative enzymes inside cells (allowing better O_2 removal from blood)
    - Maximum breathing capacity increases since air is less dense
        - This helps in high ventilations (200L/min) that occur with exercise
    - Threshold – at 4600m, maximum oxygen intake reached, after this point, rapid decline
        - This can be corrected if oxygen is breathed (not completely, but mostly)

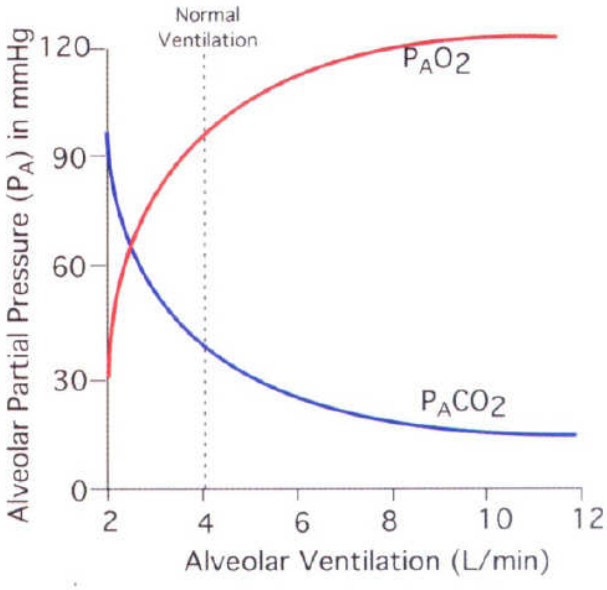
<u>Pathology associated with high altitude</u>

- Acute mountain sickness
    - Affects newcomers, develops 8-24 hours after arrival, lasts 4-8 days
    - Symptoms: vague: headache, fatigue, dizziness, palpitations, insomnia, loss of appetite, nausea
        - Cause: thought to be associated with cerebral oedema
            - Low P_{O2} causes arteriolar dilation, if cerebral autoregulation doesn't compensate, increased capillary pressure favouring transudation of fluid into brain
            - Those who do not develop have diuresis, those affected have decreased urine volume
                - This fits the fluid/retention loss theory
- Pulmonary oedema
    - Symptoms: severe dyspnoea, orthopnoea, cough, cyanosis, rales (crackles) in lungs
        - Can cough up pink frothy fluid
        - Life threatening, needs immediate descent
    - Mechanism unknown
        - Thought to be associated with high pulmonary artery pressure
            - Pulmonary vasoconstriction is widespread (due to hypoxia)
                - If uneven, leakage can occur in unprotected/damaged capillaries
            - Fluid has high protein – indicates capillary permeability is responsible
- Cerebral oedema
    - Symptoms: confusion, ataxia, irrationality, hallucinations, clouding and loss of consciousness
        - Needs immediate descent
    - Mechanism is unclear, end result is leakage of fluid into brain
- Treatment:
    - Diuretic acetazolamide – carbonic anhydrase inhibitor
        - Increases bicarbonate excretion in urine (proximal tubule) and stimulates respiration (via acidosis)
            - Thus reduces the formation of CSF (by vasoconstricting peripheral vessels)
- Chronic mountain sickness
    - Long term residents
    - Syndrome: ill defined: cyanosis, fatigue, reduced exercise tolerance, marked polycythaemia, severe hypoaxaemia, pulmonary hypertension (leading to right heart failure)
        - Blood viscosity is so high and pulmonary vascular resistance is so high that RH failure can develop
    - Best treatment is descent if possible

Hypoventilation

- The volume of fresh gas going intol alveoli/unit time is reduced (alveolar ventilation reduced)
  - Always associated with a rise in P_{CO2}
    - P_{CO2} is inversely proportional to alveolar ventilation
    - $P_{CO2} = \dot{V}_{CO2}/\dot{V}_A * K$ (K is a constant).

k = 863 mmHg



- Easily treated by increasing inspired O_2
  - Alveolar gas equation:
    - $P_{AO2} = P_{IO2} - P_{ACO2} [F_{IO2} + (1 - F_{IO2})/R]$

    OR
    - $P_{AO2} = P_{IO2} - P_{ACO2} /R + \text{correction factor}$

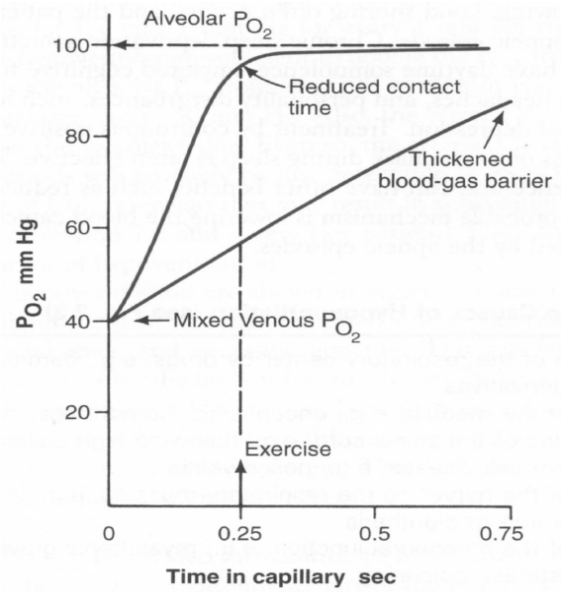
    small, ignored
  - Assume $P_{ACO2} = P_{aCO2}$
  - If P_{aCO2} and R remain constant, (they will if alveolar ventilation rate and metabolic rate are unchanged), mmHg rise in P_{IO2} causes a corresponding rise in P_{AO2}

- Question:
  - Man, normal lungs (no gas exchange problem, $P_{aO2} = P_{AO2}$)
  - P_{aCO2} = 40mmHg
  - Barbiturates overdose, halves alveolar ventilation, CO2 output the same
    - P_{aCO2} rises to 80mmHg to compensate (associated)
  - If R = 0.8, P_{aO2} falls to 49mmHg (using equation)
  - Fraction of O_2 required to increase P_{aO2} to 100mmHg is 0.28 (using equation)

- Causes of hypoventilation
  - Depression of respiratory centres by drugs (eg: barbiturates, morphine)
  - Diseases of the medulla
  - High spinal cord lesions
  - Diseases of anterior horn cells – poliomyelitis
  - Diseases of nerves to the respiratory muscles (eg: Guillain Barre syndrome)
  - Diseases of neuromuscular junction
  - Diseases of respiratory muscles
  - Thoracic cage abnormalities – eg crushed chest
  - Upper airway obstruction (eg. thymus gland tumour)

Diffusion impairment

- When equilibrium does not occur in the P_{O2} in the pulmonary capillary and capillary gas
  - Normally, equilibration takes 1/3 of the time available in the pulmonary capillary
    - This time can be prolonged with the blood-gas barrier is thickened (eg. interstitial fibrosis)
    - This can be further exaggerated in exercise where contact time is shortened
  - 100% O2 corrects problem quickly by increasing the gradient for gas flow (alveolar to capillary) overcoming the increased resistance
- P_{aCO2} is not raised because CO_2 crosses the blood-gas 20x more readily than O_2

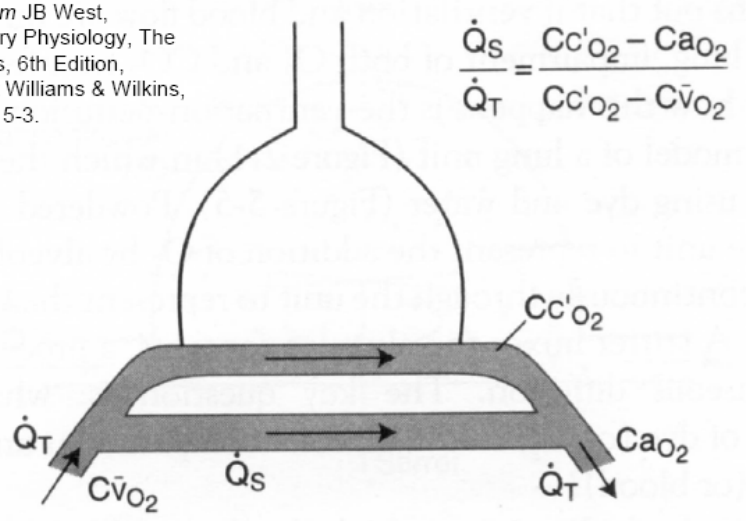


Shunt

- A shunt is when blood from the venous circulation enters the arterial circulation without oxygenation in the ventilated areas of the lung
    - Normal shunts: blood from the bronchi, coronary venous blood
    - Abnormal shunts: pulmonary arteriovenous fistula, septal heart defects
- The size of the shunt can be calculated
    - Total amount of O_2 leaving system is $Q_T \times C_{aO2}$
    - Thus equals the sum of the parts:
        - $Q_s \times C_{vO2}$
        - $(Q_T - Q_s) \times C_{C'O2}$
    - Rearrange to get equation

Taken from JB West, Respiratory Physiology, The Essentials, 6th Edition, Lippincott Williams & Wilkins, 2000. Fig 5-3.

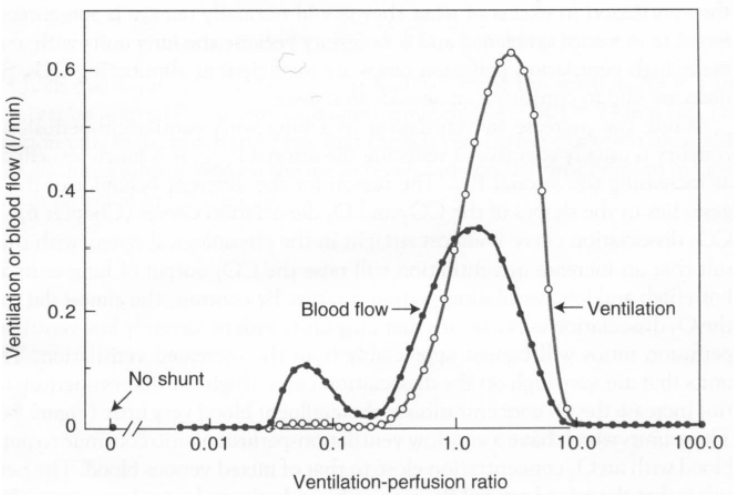
$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{Cc'_{O_2} - Ca_{O_2}}{Cc'_{O_2} - C\bar{v}_{O_2}}$$

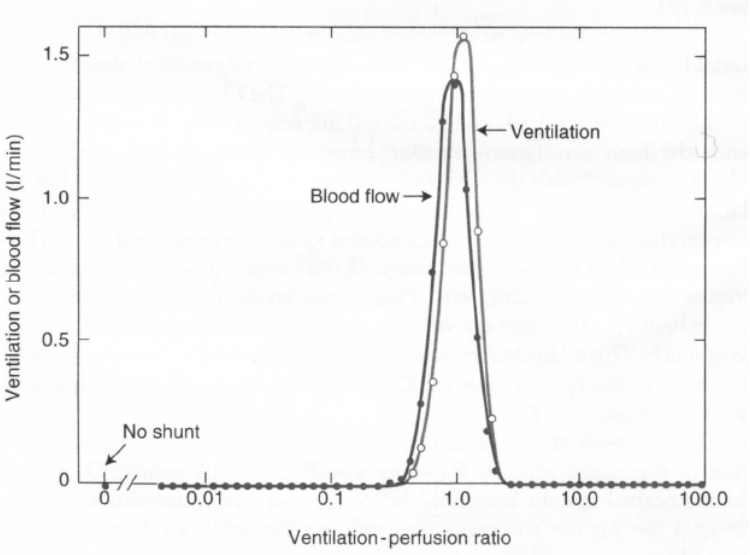


- Eg question:
    - Normal lungs, with right to left shunt
    - O_2 concentrations of arterial: 18, venous 14ml/100ml
    - Conc. leaving pulm. capillaries is 20ml/100ml, how large is shunt?
    - Using equation, sub in values
        - $Q_s/Q_T = 1/3$ (1/3 flow)
- 100% oxygen cannot fix because the shunted blood is never exposed to the higher P_{AO2}
    - A small rise in arteria P_{O2} does occur, due to increased dissolved O_2 in blood
- Raised P_{aCO2} doesn't occur because chemoreceptors will cause increased ventilation to blow off excess CO_2
    - Ie, the unshunted blood gets lower P_{CO2} to compensate for shunted blood
    - In fact, P_{aCO2} may be reduced because hypoxaemia also increases respiratory drive

Ventilation-perfusion inequality – a very important cause

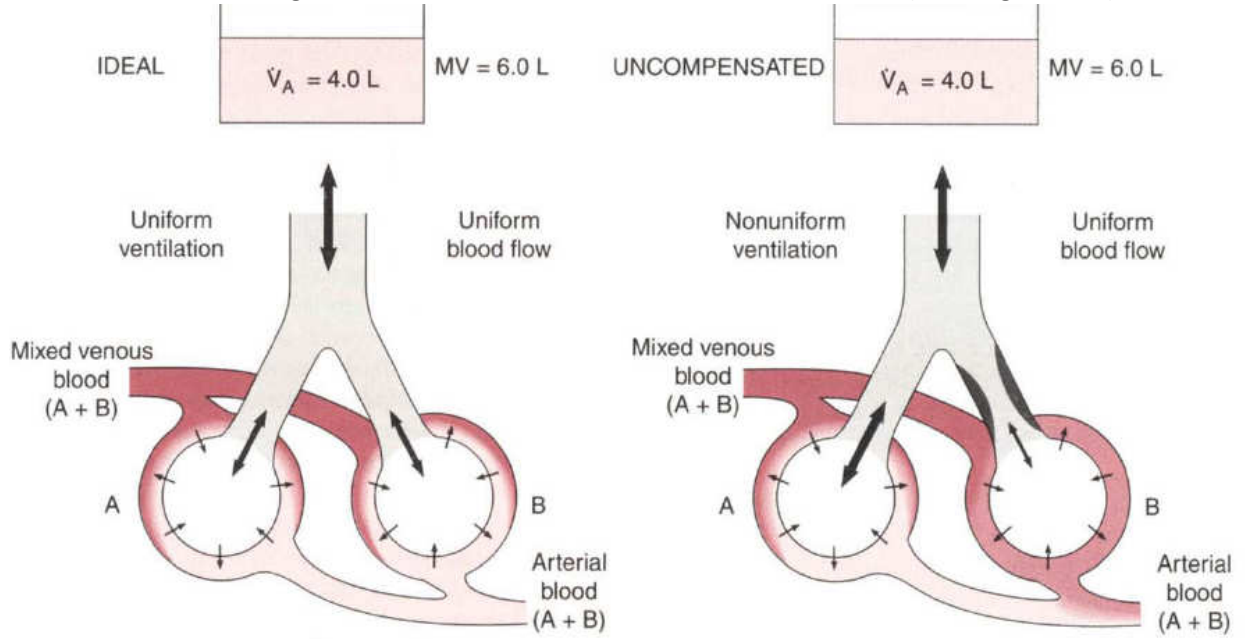
- A common mechanism of hypoxaemia
- Defined by: alveolar-arterial difference for P_{O2} is widened (ie, ventilation and perfusion are not equal)
    - Diseases: chronic obstructive pulmonary disease, interstitial lung disease, or vascular disorders like pulmonary embolus
    - Different to diffusion impairment because diffusion may have normal perfusion
- Often identified by excluding other causes: hypoventilation, diffusion impairment, shunt
- 100% oxygen improves hypoxaemia
    - Increases ventilation of blood that is perfused
- Graph: normal ventilation/perfusion ratios
- Graph: abnormal (chronic bronchitis and emphysema





Ventilation-perfusion inequality continued

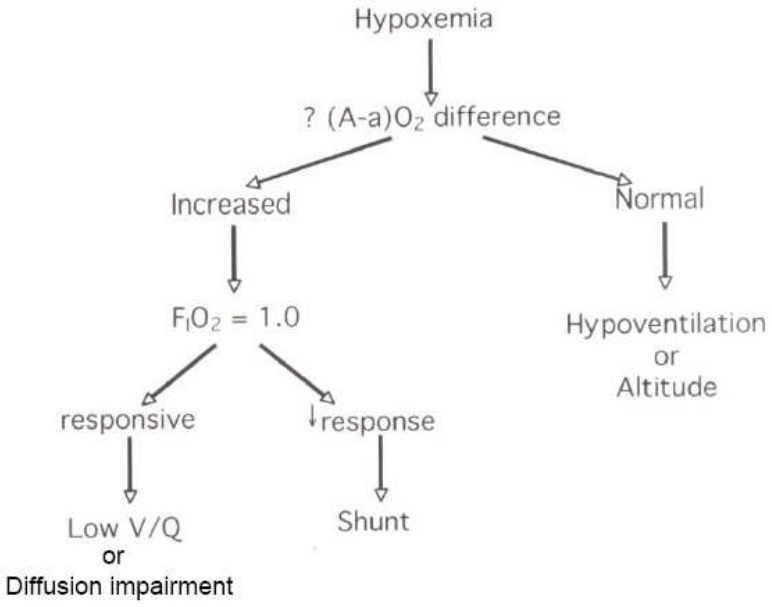
- picture notes:
    - in ideal, arterial O_2 saturation is the same in both capillaries
        - in uncompensated (inequality – ventilation lower), arterial saturation is compensated by other capillary, but not enough to reach normal levels
    - alveolar O_2 tension is compensated, increased on average
        - arterial tension is compensated, but not able to reach normal levels
        - there is a large difference between alveolar and arterial tension (defining feature)



	A	B	A + B
Alveolar ventilation (L/min)	2.0	2.0	4.0
Pulmonary blood flow (L/min)	2.5	2.5	5.0
Ventilation/blood flow ratio	0.8	0.8	0.8
Mixed venous O_2 saturation (%)	75.0	75.0	75.0
Arterial O_2 saturation (%)	97.4	97.4	97.4
Mixed venous O_2 tension (mm Hg)	40.0	40.0	40.0
Alveolar O_2 tension (mm Hg)	104.0	104.0	104.0
Arterial O_2 tension (mm Hg)	104.0	104.0	104.0

	A	B	A + B
Alveolar ventilation (L/min)	3.2	0.8	4.0
Pulmonary blood flow (L/min)	2.5	2.5	5.0
Ventilation/blood flow ratio	1.3	0.3	0.8
Mixed venous O_2 saturation (%)	75.0	75.0	75.0
Arterial O_2 saturation (%)	98.2	91.7	95.0
Mixed venous O_2 tension (mm Hg)	40.0	40.0	40.0
Alveolar O_2 tension (mm Hg)	116.0	66.0	106.0
Arterial O_2 tension (mm Hg)	116.0	66.0	84.0

Summary of hypoxaemia



Anaemic hypoxia

- Rarely severe at rest, unless [Hb] is very low
    - Can be compensated by 2,3 diphosphoglycerate increase (increased unloading of O_2 into tissue)
- During exercise, can have difficulty, however

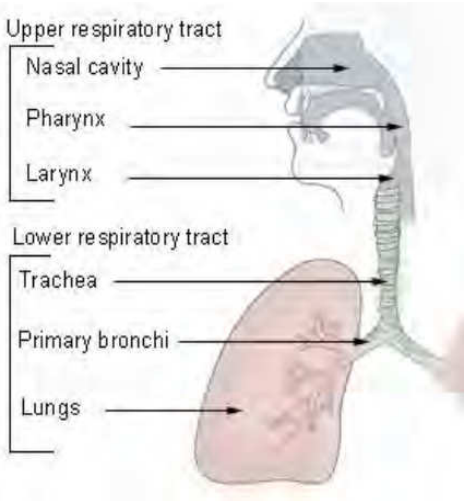
Carbon monoxide poisoning

- CO is formed naturally in small amounts in the body
    - May have functions as a chemical messenger in the brain etc
- Poisonous in large amounts
    - Formed by incomplete combustion of carbon
    - Binds with Hb forming carboxyhaemoglobin
        - Affinity for Hb of CO is 210x O_2
        - Thus, small amounts of CO can tie up a lot of Hb in the blood and make O_2 carriage impossible
- COHb shifs OEC to the left causing problems with O_2 unloading
    - Ie. an individual with 50% of normal Hb (anaemia) can perform moderate work, but a person with 50% of normal Hb (carboxyhaemoglobin) may not be able to

- Clinical:
    - Appearance – not cyanosed since COHb is cherry red in colour
    - Symptoms are like those for hypoxia – headache, nausea, arterial P_{O2} is normal so respiration is normal
        - Arterial P_{O2} is normal because CO prevents O_2 release into the tissue, so levels of O_2 in blood are normal or raised. Thus, chemoreceptors aren't stimulated and respiration is normal
        - Death results with 70-80% circulating Hb is COHb
    - Has other effects on cellular cytochromes – only important at higher than lethal doses
- Treatment
    - Termination of exposure
    - Ventilation and O_2
        - Hyperbaric oxygen is useful because high PO_2 allows better competition with CO for Hb binding sites, thus driving CO out of blood

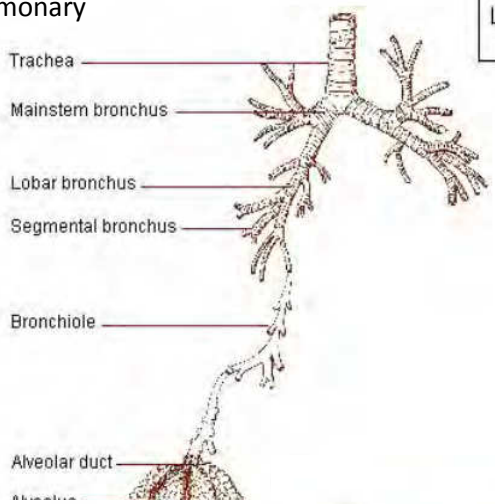
Introduction

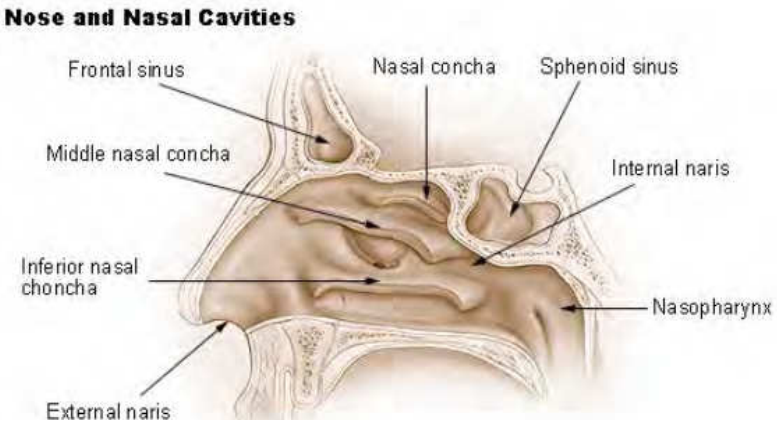
- Embryonic respiratory system
  - Does not carry out normal function (gas exchange) until after birth
    - Thus abnormalities may not be immediately apparent
- Lung development is a result of many complex interactions
  - Mechanical forces
  - Genetic factors
  - Endocrine influences
  - Cell-cell communication
- Overview:
  - Foregut (lung parenchyma) develops from the endoderm
  - Pleural cavity derived from the Intraembryonic coelom (mesoderm)
  - Pharynx develops with head
  - Diaphragm develops with muscle
  - Cardiovascular is linked with pulmonary

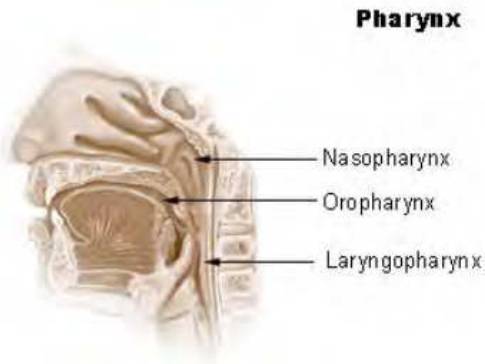


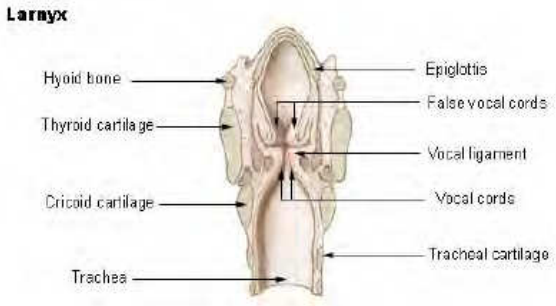
Respiratory tract

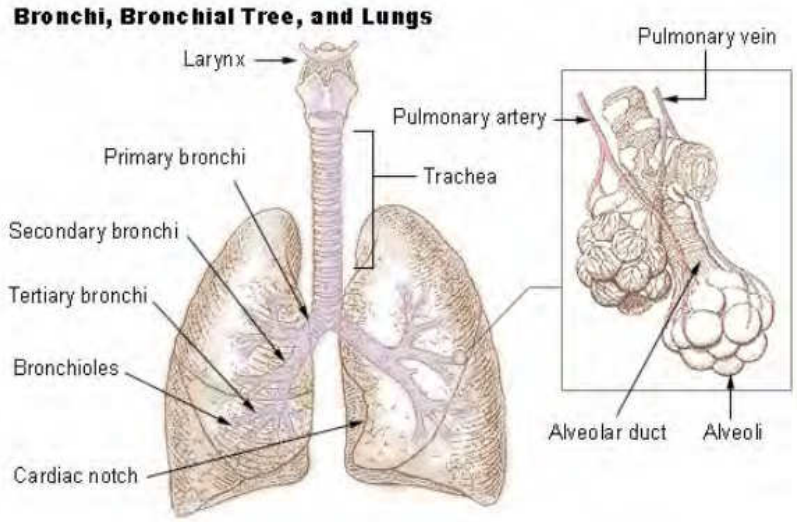
- Upper – nose and oral cavity to larynx
- Lower – trachea to lungs
- Anatomy :revision (see pics)





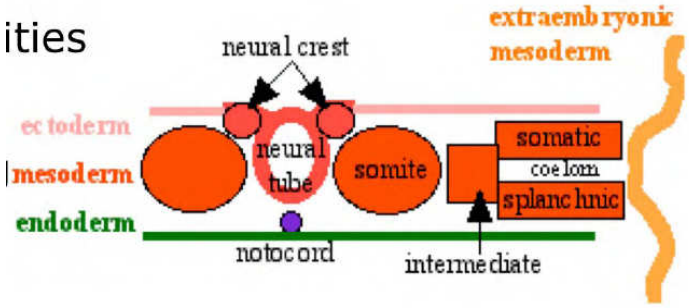






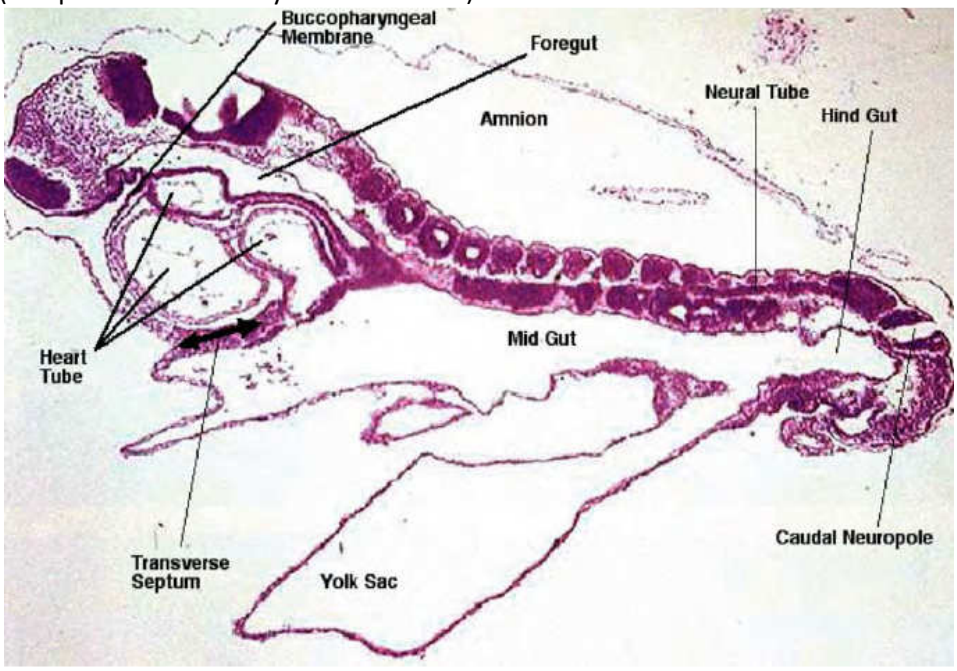
Mesoderm Development

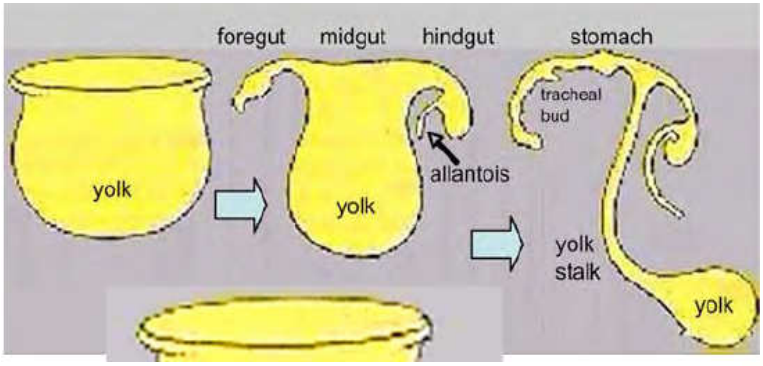
- Lateral plate differentiates into the somatic and splanchnic mesoderm and the intraembryonic coelom
    - Somatic mesoderm becomes the body wall
    - Intraembryonic coelom becomes the 3 major body cavities
    - Splanchnic mesoderm becomes several things including the mesoderm of the lung, alveoli septa and capillary beds

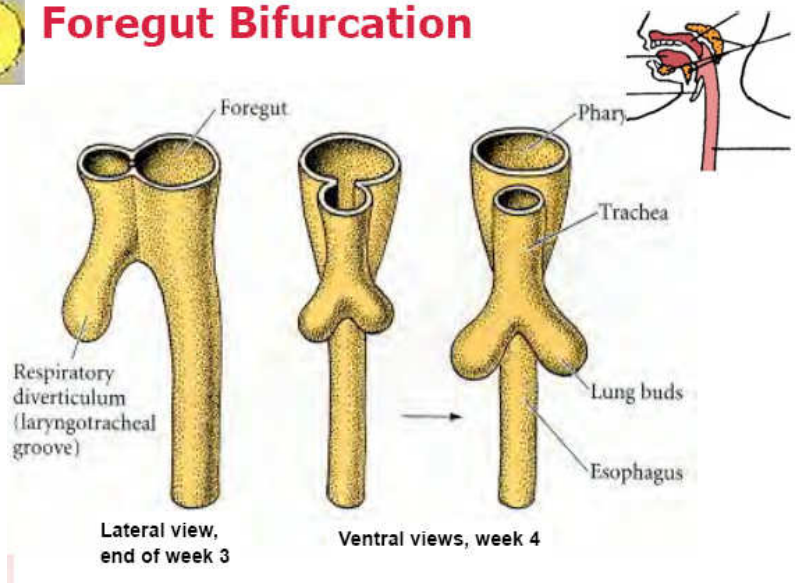


Further development

- Foregut extends into head region
- Septum transversum is present (origin of the diaphragm)
- Endoderm development:
    - Foregut separates and forms the tracheal bud
        - Blind-ended tube (respiratory diverticulum)
    - Weeks 3-4, bifurcation of bud
        - Grows down, interacts with mesoderm that stops growth in the midline causing bifurcation
        - Process is repeated for all branching
        - (an epithelial-mesenchymal interaction)

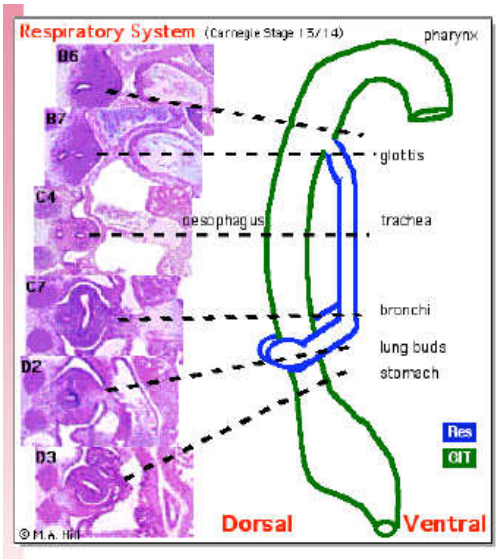


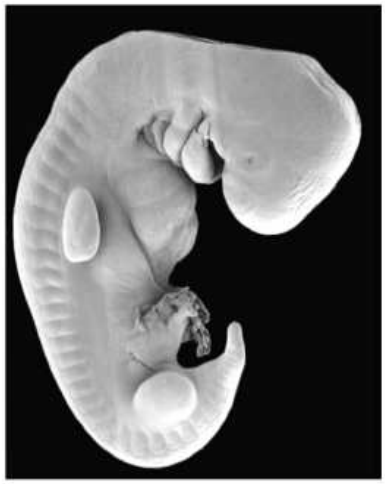




Stage 13-14

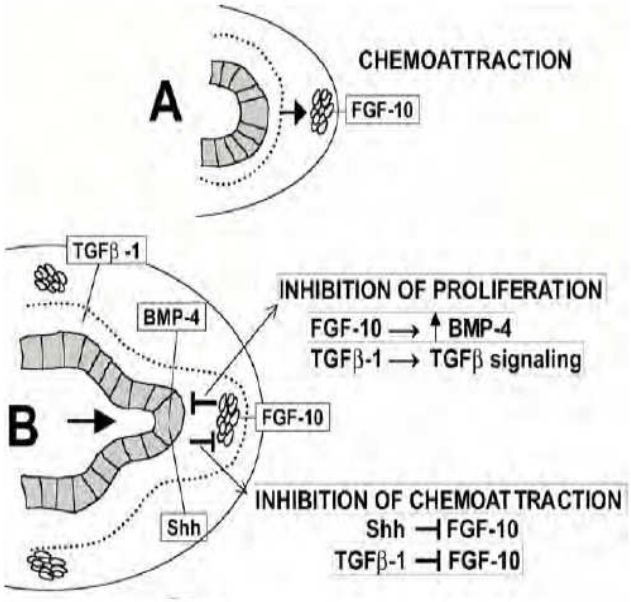
- Lung buds are present
  - Initially just very small tubes
- Pleura
  - Derived from mesoderm surrounding intraembryonic coelom
- Liver
  - Stops the descent of the lungs
  - The heart also pushes the lung buds backwards

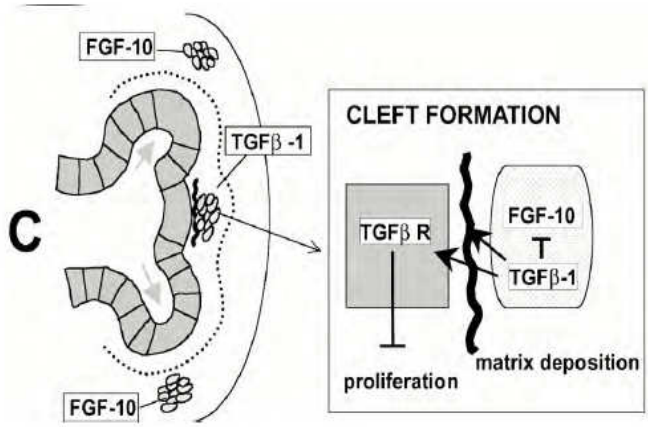




Molecular signalling in lung bud formation

- Fibroblast growth factor (FGF-10)
  - Mesenchyme expresses causing chemoattraction of epithelial cells
  - Induces growth of endoderm downwards
- Bud is induced
  - FGF-10 (chemoattraction) is inhibited by:
    - Shh (expressed at tips)
    - TGFβ-1 expressed in the subepithelial layers
  - Proliferation at tip of bud inhibited by: FGF-10-mediated up regulation of BMP-4 (bone morphogenetic protein-4)
- Limit of bud outgrowth and expansion – causes cleft and bifurcation
  - FGF-10 expressing cells at other sites induce new buds
  - Cleft is formed by maintenance of a low level of FGF-10 in appropriate regions (mediated by subepithelial TGFβ-1





Week 4

- Laryngotracheal groove forms on floor of the foregut
  - Median longitudinal groove in the ventral wall of pharynx
    - Groove deepens and lips fuse to form a septum that converts groove into a tube

Week 5

- L and R lung buds push into the pericardioperitoneal canals
  - Canals are the primordia for the pericardial, pleural and peritoneal cavities

Pleural cavity

- Pericardioperitoneal canals initially continuous
    - Canals become cavities by folding and growth the diaphragm (the pleuroperitoneal membrane)
    - Pleuropericardial fold
        - Restricts communication from pleural and pericardial cavities
        - Contains the cardinal vein and phrenic nerve
    - Pleuroperitoneal membrane
        - Forms inferiorly at the transverse septum and separates the peritoneum from the pleural cavity
    - Visceral pleura
        - Derived from splanchnic mesoderm

Late embryo to fetal stages

- Pseudoglandular stage (weeks 5-17)
    - Undifferentiated epithelium
    - Few buds, appear solid because the are filled with fluid
        - Amniotic fluid and epithelium secretion (needed for expanding lung volume)

Splanchnic mesoderm (mesenchyme)

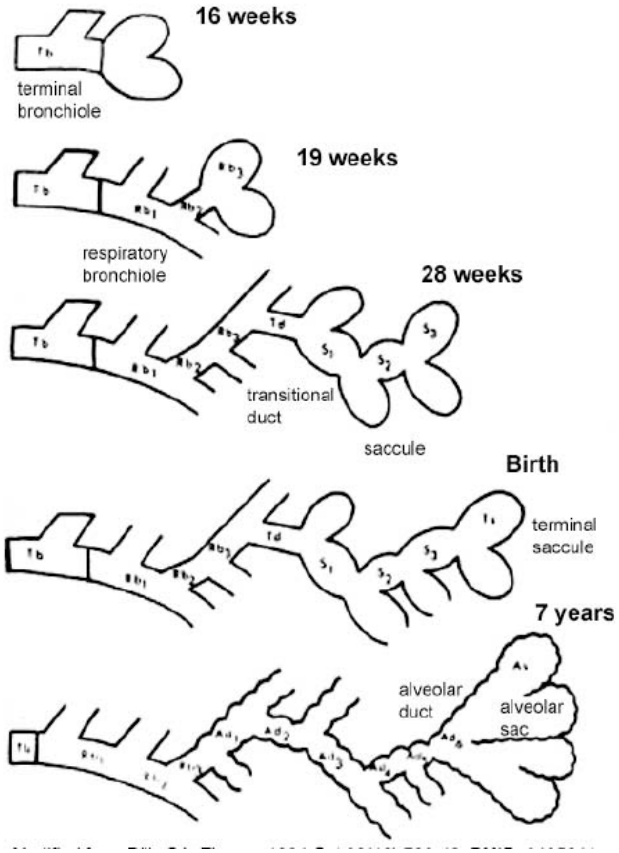
- Forms:
    - Cartilage for bronchi and bronchioles
    - Pulmonary smooth muscle
    - Connective tissue
    - Capillaries
    - Visceral pleura (parietal pleura is formed by mesoderm of the thoracic cavity body wall)

Week 6

- Descent of heart and lungs into the thoracic cavity
- Pleuroperitoneal foramen closes
    - Muscles descend to form the diaphragm (explains phrenic nerve innervation)

Week 7

- Liver enlargement
    - Stops the heart and lung descent (physical barrier)



Histological periods

- Embryonic
- Pseudoglandular (week 5-17)
- Canalicular (Week 16-25)
- Terminal sac (Week 24-40)
- Alveolar (Late fetal – 8 years)

Sacculation

- 2 types of epithelial cells form:
    - Type I – cells flatten, thin and spread
    - Type II – cells remain cuboidal, acquire surfactant-filled lamellar bodies (7 months onwards)
- Surrounding mesoderm differentiates
    - Vascular remodelling
    - Thinning and branching of mesenchyme (in preparation for gas exchange)
    - Alveolar volume and SA increases

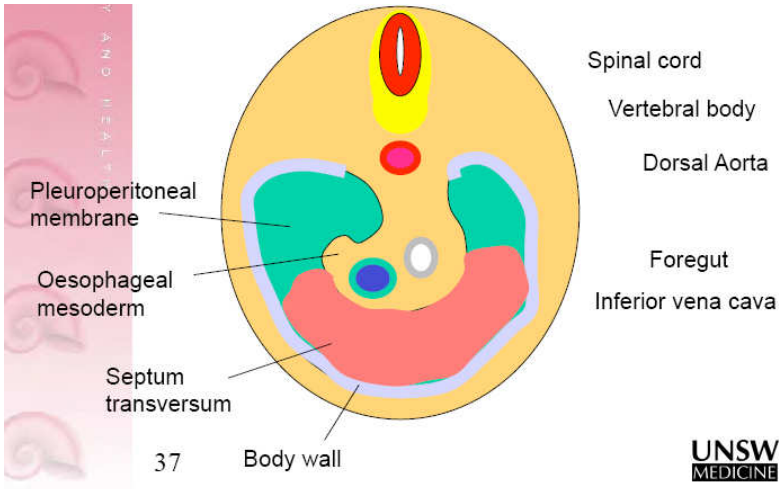
Fetal development

- Month 3-6: lungs appear glandular
- Month 6 (end): alveolar type II cells appear and begin to secrete surfactant
- Month 7: respiratory bronchioles proliferate and begin to end in alveolar ducts and sacs

Diaphragm

- 5 parts:
  - Central tendon – derived from the septum transversum
  - Musculature – from somites 3-5 (explains phrenic nerve innervation from neck, C3,4,5)
  - Connective tissue – ventral pleural sac
  - IVC, CT around oesophagus – mesentery of oesophagus
  - CT around central tendon – pleuroperitoneal membranes

- Innervation
  - Phrenic nerves, C3-5
    - Diaphragm motor neurons
    - Sensory nerves for other abdominal structures (mediastinum, pleura, liver, gall bladder)
- Fetal breathing movements (FBM) – 3rd trimester
  - Regular spontaneous muscular contractions
    - Prepare respiratory system for neonatal function
    - Expand thoracic volume and aid late stage of lung development



Ribs

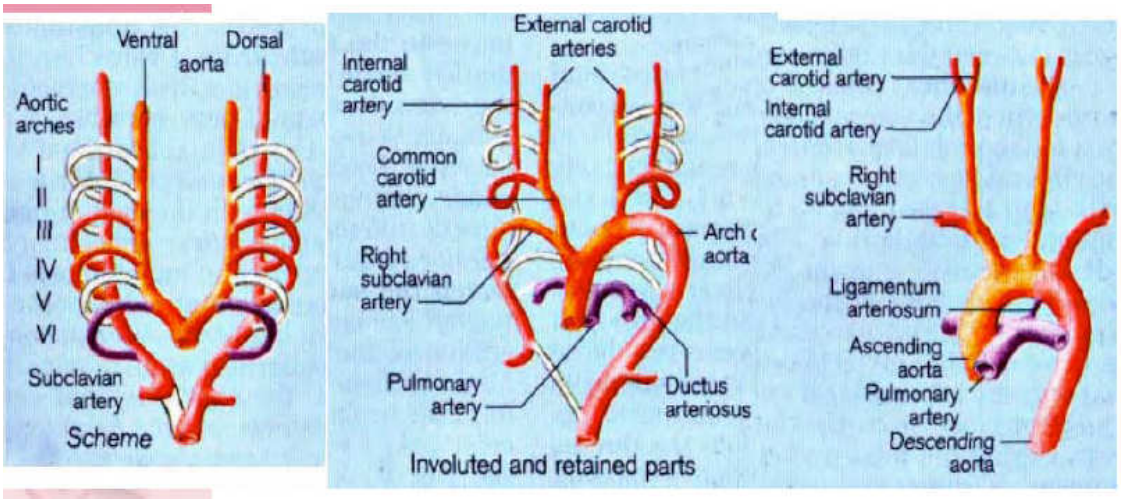
- Infant rib is horizontal
  - Breathing motions in neonate are only diaphragmatic, high rate: 30/min
- Adult rib is oblique causing bucket/pump handle types of inspiration

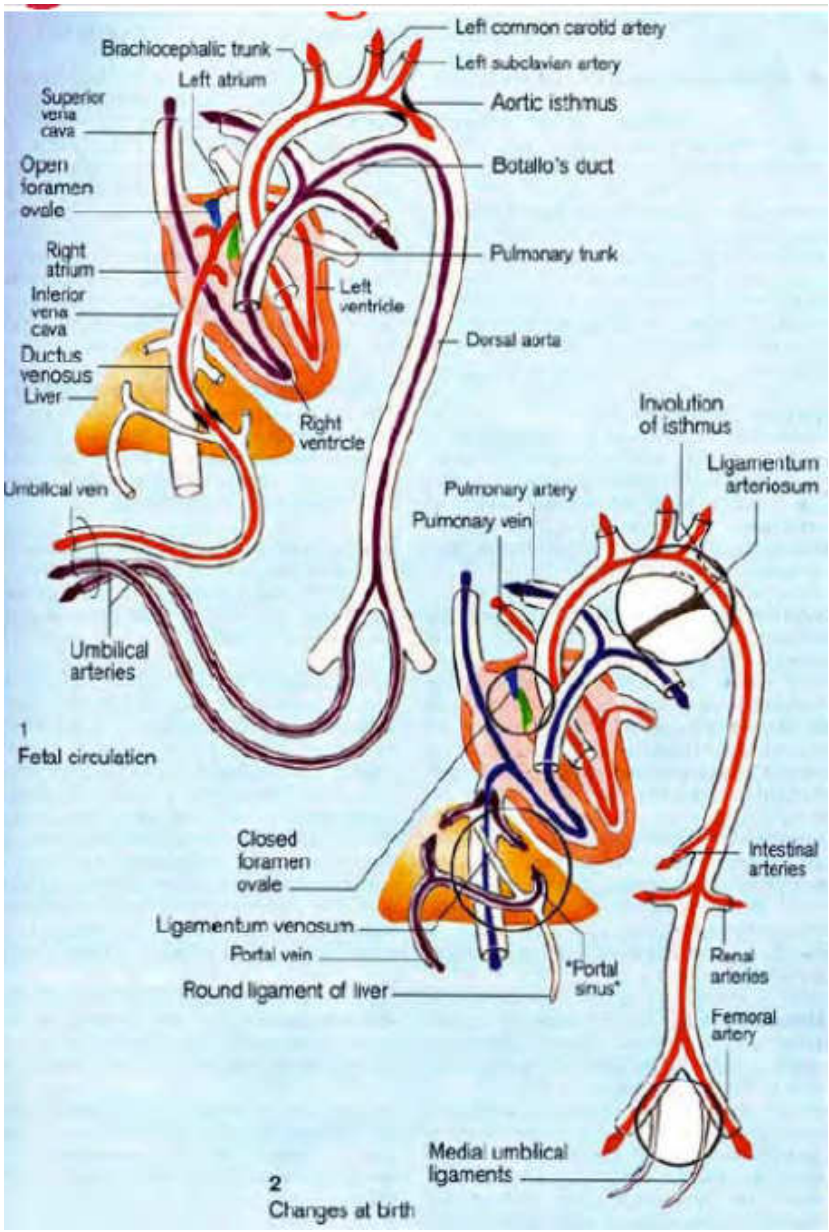
Postnatal lung growth

- Factors:
  - Hormones (thyroid, glucocorticoids) – important for stimulus of surfactant etc
  - Body growth – larger the body, larger the lungs
  - Respiratory movements (environmental effects) – if movements inhibited, lungs can be underdeveloped

Circulation and shunts

- Pulmonary circulation is not functional until after birth
  - Majority is derived from the 6th aortic arch arteries
  - Bronchial arteries are generated from dorsal aorta
- Thus, only a small amount of blood is in the pulmonary circulation, thus it is shunted past through the ductus arteriosus
  - Other shunts: ductus venosus (ligamentum venosum), ductus arteriosus (Botallo's duct, ligamentum arteriosus), Foramen ovale (fossa ovale)





<u>Birth – fluid to air</u>

- Fluid in the upper respiratory tract is expired (coughed up)
- Fluid in the alveoli is absorbed (lung is dewatered)
    - Facilitated by the lymphatics/pulmonary circulation

<u>Respiratory abnormalities</u>

- Congenital abnormalities, respiratory are quite common
    - Cleft palate – 7.3% of all congenital, respiratory 1.4%
- Abnormalities:
    - Tracheo-oesophageal fistula (incomplete separation of the foregut)
        - Causes oesophageal atresia (failure of oesophagus to be a normal opening/properly tubular)
    - Lobar emphysema
        - Overinflated lung (growth more rapid than lung/alveoli growth), too much space for number of alveoli
    - Newborn respiratory distress syndrome (often in premature infants)
        - Eg: hyaline membrane disease
        - Eg: lack of surfactant (type II alveolar cells)
            - Treatments: many
                - Endocrine stimulation
                - Artificial surfactant
                - Initial problem thought to be due to a lack of O_2, given 100% oxygen which damaged BVs in the retina → blindness
    - Congenital diaphragmatic hernia (musculoskeletal abnormality)
        - 5 contributors to diaphragm, if closure is incompletely, pressure changes lead to herniation of peritoneal contents
    - Azygos lobe – right lung upper lobe expands
        - Quite common, 0.5% of population has this abnormality
        - Harmless

Diaphragmatic hernia

- Occurs at the border between the pleural and peritoneal cavities
    - More commonly occurs on the left than right (the left pleuroperitoneal canal is larger)
        - L: Bochdalek hernia (stomach and intestines hernia)
        - R: Morgagni hernia (liver and intestines hernia)
        - Small parasternal region hernia (oesophageal hiatus)
            - L much more common, other two very rare
    - Lung (and organs themselves) are compressed
- Epidemiology: 2.1-3.8/10 000 births
- Often corrected surgically at birth or in fetus

Hyaline membrane disease

- Surfactant deficiency
    - Surfactant is a phospholipid (and surfactant protein) that reduces surface tension and thus aids lung inflation
        - Produced by alveolar type II cells
    - Causes:
        - Hereditary disease
            - Surfactant b deficiency (lethal)
        - Premature births
            - Lungs mature rapidly up to birth (from just before birth)
    - Treated with endocrine stimulation or artificial surfactant replacement

Tracheo-oesophageal fistula

- Results in oesophageal atresia
    - 2.5-3.6/10 000 births
    - 10% are stillborn, 20% of live born die during neonatal period
- More common in multiple births

Lobar emphysema

- Over-inflated lung
    - Commonly left upper lobe, or collapsed lower lobe
    - Left lung can herniate across the mediastinum
- Possible cause:
    - Congenital deficiency of cartilage in left upper lobe bronchus

Infections: bronchiolitis

- Most common LRTI in infants
    - 70% due to RSV
- Respiratory syncytial virus RSV)
- Symptoms:
    - Acute inflammation
    - Oedema
    - Necrosis of epithelial cells that line the small airways
        - Can damage post-natal growth of lungs, repair occurs in most cases
    - Increased mucus production
    - bronchospasm

Mantoux test: from CMI lecture

- An example of cell mediated hypersensitivity (delayed-typed hypersensitivity)
- Process:
  - TB protein antigens are injected intradermally
  - If circulating mycobacteria-specific memory T-cells are present, these are activated at the site and release cytokines (especially: IFN-γ)
  - Cytokines attract and activate macrophages
  - Inflammation results but is slow in onset and persists for several days (time line: 48 hours – 7 days)
  - Test is assessed 48 hours after injection when reactions peak and other hypersensitivities have subsided
    - Thus, at this time, the reaction is purely a cell mediated hypersensitivity reaction
- Events:
  - PPD (purified protein derivative) (tuberculin) protein is injected intradermally into the skin
  - An acute inflammatory response is induced causing increased adhesiveness of local endothelium (12 hours)
  - Leukocytes influx into the skin
  - Specific T-cells (if present) are activated by local dendritic cells or infiltrating macrophages
  - T-cells release cytokines such as IFN-γ
  - This induces influx and activation of macrophages (peak at 48 hours) causing a lesion
  - Diameter of this lesion is measured

Interferon-gamma release assay (IGRA)

- An analogue of the Mantoux test
- Process
  - Take blood sample
  - Add M. tuberculosis-specific antigens
  - Mix and incubate
  - Dendritic cells or monocytes in the blood present antigen to T cells and if specific T-cells are present, they are activated
  - Release of IFN-γ by T cells (24 hours)
  - Plasma collected
  - IFN-γ is measured by ELISA

Mantoux vs IGRA

- Similarities of IGRA to Mantoux test
  - Assess whether antigen-specific memory T-cells are present
    - Thus, can assess whether a latent TB infection is present
      - Doesn't distinguish between latent and active TB
  - Can give a negative result in advanced TB where there is an immunosuppressive effect or in immunocompromised patients (HIV/TB patients)
- Differences of IGRA to mantoux
  - IGRA is more quantitative and stops the process of the hypersensitivity reaction earlier than the Mantoux test
- Advantages of Mantoux vs IGRA
  - Inexpensive (been used for 100 years)
  - Doesn't need complicated lab work and can be performed easily by ancillary staff
- Advantages of IGRA vs Mantoux
  - More specific for M. tuberculosis (uses antigens that are absent in BCG)
    - IGRA is negative after BCG vaccine and other mycobacterial infections, mantoux can be +ve
  - More sensitive, especially in immunocompromised
  - Does not require injection or return for assessment (logistic hassles)

Innate viral immunity

- The general response to all kinds of viruses
    - Fast and doesn't improve with repetition

Type 1 interferons (cytokines)

- Interferon alpha and beta (IFN-α, IFN-β)
    - Characteristics:
        - Produced locally by many cell types within hours of a viral infection
        - Produced especially in response to viral double stranded RNA (appears very foreign)
    - Has been used therapeutically to treat viral hepatitis B and C (can cure in some)
- Note:
    - IFN-γ is a type 2 interferon – also has antiviral effects, but also other actions
        - Produced by T-cells, in a separate category
- Effects of type 1 interferons
    - Act on all cells → stimulate pathways that interfere with viral replication
    - In most cells → stimulate MHC Class 1 expression and antigen presentation to T cells
    - NK cells → activate to facilitate killing of virus-infected cells

Antigen presentation

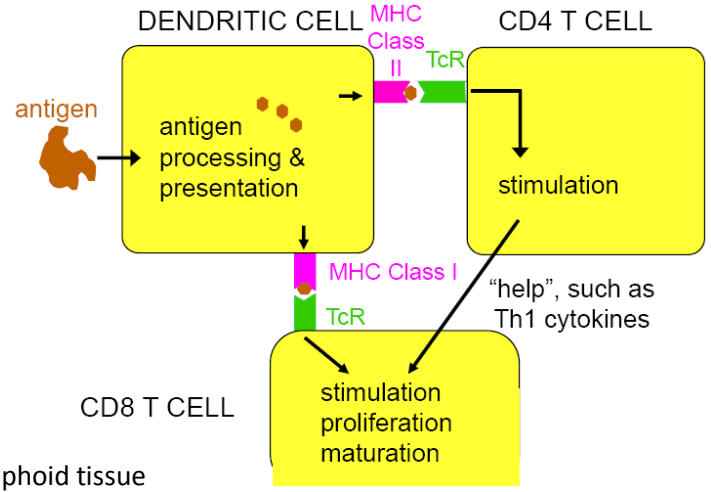
- Protein antigens synthesised inside the cell (eg: viral proteins) bind to MHC Class I receptors
    - Presented to CD8 (cytotoxic) T cells
- Protein antigens synthesised outside the cell (eg: extracellular bacterial proteins) bind to MHC Class II receptors
    - Presented to CD4 (helper) T cells
- Dendritic cells present antigen using both MHC Class I (CD8) and Class II (CD4)

Natural killer cells

- Develop in bone marrow, circulate in blood
    - Large ,granular lymphocytes (10% of lymphocytes in blood)
- Function: to kill cells infected with viruses
    - No antigen-specific receptors (eg. TcR, surface antibody)
    - Respond to non-specific features of infection:
        - Type 1 interferons and other cytokines
        - Cells that have reduced MHC Class I expression (counter a viral strategy that downregulates MHC I protein on the surface to avoid the immune system)
- Important in the early stages of viral infection before induction of the T-cell response

Adaptive viral immunity

- Cytotoxic T cells and neutralising antibodies

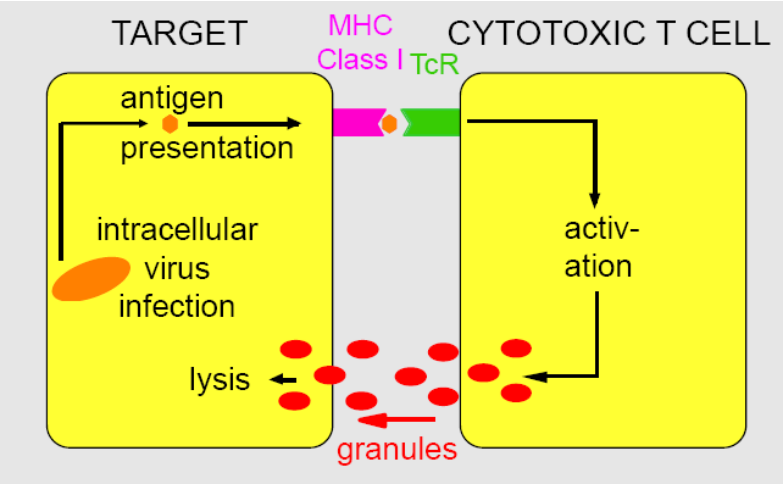


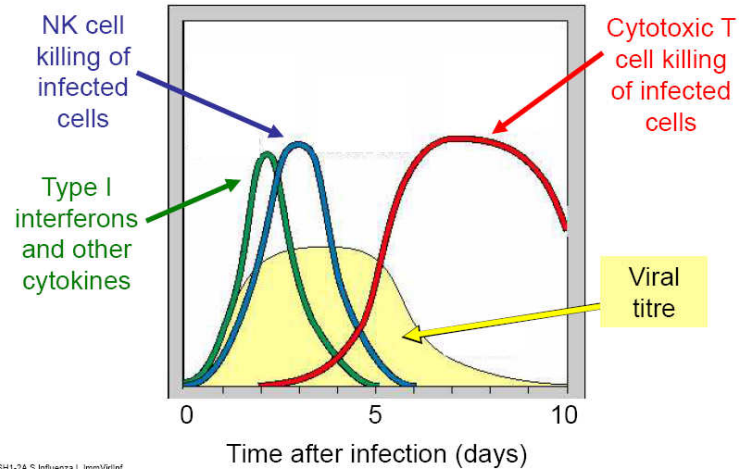
Cytotoxic T cells (CD8)

- Make up 1/3 of T cells
- After viral infection, dendritic cells carry viral antigens to lymphoid tissue
    - Here, they present them to CD8 (MHC I) and CD4 (MHC II) T cells
- Cytotoxic T cells with specific TcR that match the viral antigen form clones and cytotoxic granules mature
    - Helper T cells with specific TcR (T-cell receptor) also form clones
        - Differentiate into Th1 cells that help CD8 cells to proliferate and mature via cytokines
- This differentiation occurs in T-cell areas of secondary lymphoid tissue
    - When CD8 cells are mature, they leave the lymphoid tissue to search for virus-infected cells systemically

CD8: Cytotoxicity

- Virus-infected cells use MHC Class I receptors to present antigens to TcR of CD8 cells
    - CD8 cells respond and release cytotoxic granules to induce apoptosis in the virus-infected cell
        - Occurs outside lymphoid tissue (eg, in respiratory epithelium)
            - (CD8 cells don't destroy dendritic cells when presented initially because they are immature and not yet activated)
    - Destruction of a virus-infected cell before formation of mature viral particles stops spread of infection
        - Antigen can be presented on the surface of cell before virus spread
        - CD8 cells destroy own infected cells to prevent further infection
- CD8 cells, when they meet their target, granules migrate to the side closest to the target in preparation for release
    - Granules are released into the space between the CD8 cell and infected cell to induce apoptosis
- Can also kill some cancer cells (beneficial) and transplants (harmful)
- NK cells use a similar granular release method to kill cells, but are activated by different pathways





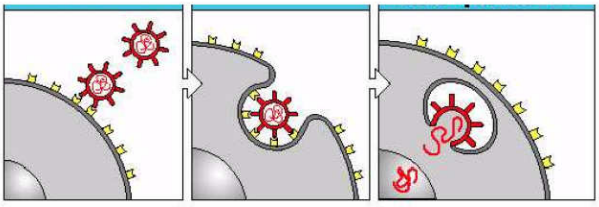
Course of viral infection

- <12 hours, type 1 interferons and other cytokines released by cells
- NK cells activated to kill infected cells
- 5 days, CD8 cells activated and kill infected cells (after several days of clonal expansion and activation)
    - As CD8 number increases, viral titre decreases (eliminated by CD8)

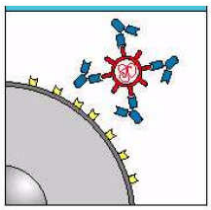
Neutralising antibodies

- Definition
    - Immune cells that bind to a target and thereby inhibit further function of that target
    - Important in combating viral infections and bacterial toxins
- In viral infection:
    - Viruses replicate inside cells and must bind to surface receptors to invade cells
    - Neutralising antibodies bind to viruses and prevent their binding to cell surface receptors
        - Most effective are IgG and IgA
            - produced several days after start of infection
    - Effects of neutralising antibodies:
        - Elimination of viruses
        - Prevention of reinfection (especially at mucosal surfaces)
            - Antibodies are already present on reinfection, CD8 cells can take days to redevelop new clones
- Process:
    - Neutralising antibodies coat the virus and prevent it binding to the cell surface

Virus (red) binds to receptors on cell surface (yellow) and enters cell (grey)



Neutralizing antibodies (blue) protect cells by coating the virus and preventing it from binding to cell surface

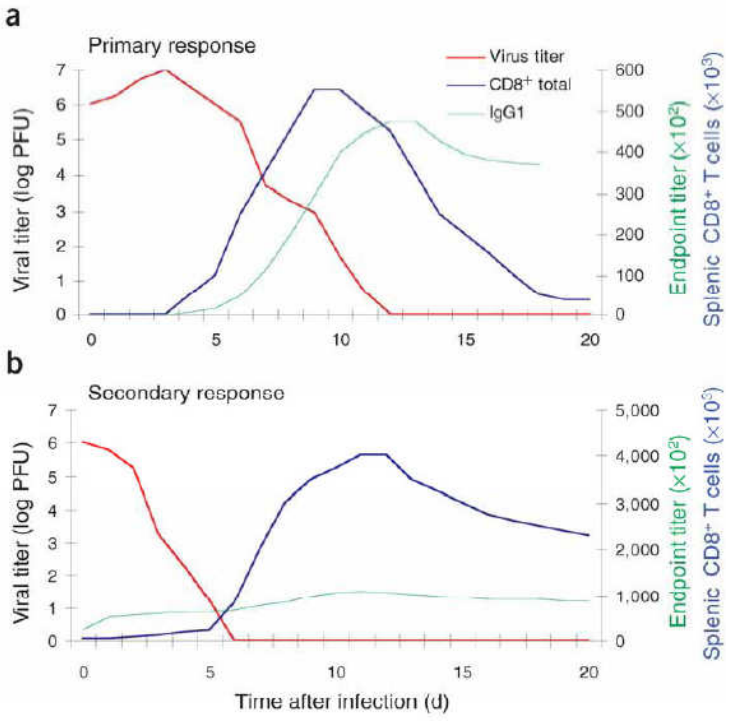


Vaccination against viruses

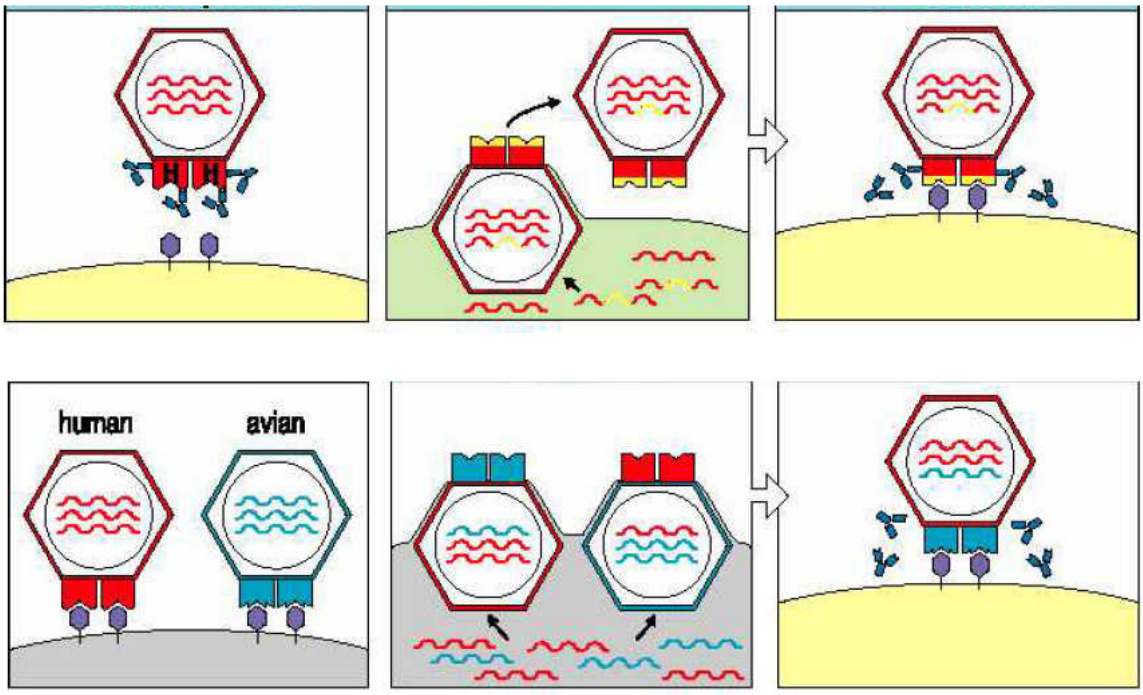
- Successful viral vaccines:
  - Smallpox: vaccine introduced 1796, eradication from the wild 1979
  - Polio: vaccine licensed 1955, eradicated in all but 3 countries 2008
- Types of vaccines
  - Live viruses: (polio, measles, mumps, rubella, smallpox)
    - Vaccine contains attenuated version of the virus – strains that have lost pathogenicity after growth in culture
    - Retain antigens
  - Killed virus: (influenza)
    - Standard flu vaccine in Australia
  - Viral subunits: (Hep B, Papillomavirus)
- Live viral vaccines
  - Advantages:
    - Virus mimics a natural infection accurately and thus induces a better immune response
      - Virus is still alive and thus replicates and delivers antigen over a long period of time
      - Antigens are presented to MHC (major histocompatibility complex) types I and II
        - (killed viruses only present to class II (CD4), thus inducing neutralising antibodies, but not much CD8)
      - At mucosal surfaces, can elicit good mucosal protection via IgA antibody
  - Limitations
    - Can cause mild symptoms of disease
    - Risk of serious infection in immunocompromised
    - Risk of reversion to wild-type v irus

EG: Influenza

- Immune response
  - Early, Type 1 interferons limit infection
    - NK cells role is unknown – important in other viruses ,however
  - First 36 hours, dendritic cells carry antigen from respiratory tract to lymph nodes (lymphatics) or spleen (blood)
  - 1-2 weeks, CD8 cells and neutralising antibodies clear the virus
    - Neutralising antibodies are directed against haemagglutinin (binds to sialated receptors) and neuraminidase
      - Mucosal IgA and systemic IgG play a role
  - CD4 cells are important to augment antibody and CD8 responses
- Primary infection, virus titre falls when specific CD8 levels rise
  - Secondary infection, virus titre falls immediately due to present neutralising antibodies before CD8 response can be fully mounted
- Normally we achieve 100% success in clearing the virus



- Influenza vaccination
  - Inactivated viruses (whole, killed) are used
    - Allow production of neutralising antibodies – especially to counter haemagglutinin
      - Antibodies produced are strain specific
    - There is no production of a good CD8 cell response
  - Influenza is an unstable RNA virus and thus mutates quickly
    - Influenza thus can escape immunity from previous vaccinations, thus each year a new vaccine is produced
- Antigenic shift and drift
  - Drift:
    - Influenza only needs 2 point mutations (changes in 2 AA) to cause drift
    - Antibodies that are effective against one strain may be less effective against another drifted strain
  - Shift (hasn't occurred since 1968):
    - Possible mechanism:
      - A host (eg: pig) is coinfected with human and avian strains of influenza
      - Viral RNAs recombine and via reassortment a new virus with a different HA is produced
      - Neutralising antibodies have no cross-reactivity
    - Other mechanisms: direct mutation?



Introduction
- We need to understand gender to understand health and provide equal healthcare
- Main problems for women: (MEN)
    - Menarche, menses, menorrhagia, menopause, hysterectomy, gynaecology, human papilloma virus

Definitions
- Sex – biological characteristics that define male and female
- Gender – the socially constructed roles, behaviours, activities and attributes that a particular society considers appropriate to men and women
    - The way cultures interpret and elaborate innate biological differences into social expectations, behaviours and actions
    - The economic/social and cultural attributes of males and females at a particular time
    - The roles of men and women that are socially determined and related to how are perceived and expected to behave
- Examples to illustrate
    - Sexual difference – women menstruate
    - Gender difference – in most of the world, women do more housework than men
- Gender equality – equal treatment in terms of laws and policies
- Gender equity – fairness/justness of benefits/responsibilities
- Gender discrimination – distinction/exclusion based on social constructs of male and female
- Gender mainstreaming – the process of increasing knowledge and awareness of gender and integrating it into all the actions of health professionals

Equity and equality
- Example to illustrate
    - Boys and girls are given compensation after sexual abuse
        - Equality: $10 to boys, $10 to girls
        - Equity: compensation is based on need, and the outcomes need to be considered
            - The health of boys/girls needs to be equal, this is not necessarily equivalent to $
            - Eg: girls may have been raped, more damage, STDs, pregnancy etc

Gender equity and women
- Western medicine is based on the 70kg white male
    - Children are different, therefore we have paediatrics
    - Women are different, but western medicine ignores many of these differences
- Cardiovascular disease
    - Women: heart attack presentation is often atypical
        - Nausea, back pain, shortness of breath, sweating
        - May not have chest pain, thus heart attack may be diagnosed late
- Women can often be defined/perceived by their female features, rather than as the gender: female
- Other: women more commonly get migraines, osteoporosis
- Drugs and alcohol – women metabolise alcohol and drugs differently to men
- Psychiatry
    - Attempted suicide is more common in women
    - Depression/anxiety is more commonly diagnosed in women
    - Men commit suicide more successfully than women
- Ophthalmology
    - Orbital fractures common – domestic violence
    - Eyelid lacerations
    - Eyelid contusions
    - Cataracts, 1/10 people > 60. Often need surgery, women incidence > men
        - Women are often not having cataract surgery
        - Women are often not being treated for diabetes, thereby aggravating cataracts
    - Eye injuries in men are most commonly due to fighting or workplace injury, women commonly injury is due to domestic violence (stats: 38%<15, majority 1st time when pregnant)

International determinants of health

- Income/social status
- Social support network
- Education
- Employment
- Social environment
- Physical environment
- Housing
- Personal health practices
- Health child development
- Biology and genetic endowment
- Access to health services
- Culture/ethnicity/immigration/refugee status
    - ALL THESE COME BACK TO GENDER
- Problem attitudes:
    - Improve men → improve country → then improve women
    - Cultural practices that cause degrading of women and women's health (eg. if husband dies)

Gender of medical students

- Are we representative of the population?
    - Sexual harassment: 46% of women, 24% of men
- Patient exposure
    - Do male students miss out on seeing female problems? Female patients?
        - Eg: in labour, 43% of women didn't want a male medical student over a female one
            - thus discouragement of men to do obstetrics and gynaecology
- Females do better at OSCE style exams
- Many more male doctors in higher positions (professors, etc)
    - Cultural stereotypes
    - Sexism
    - Family responsibilities – superwoman, supermum attitudes

Other: note

- Suicide rates, women 2-4x increased risk if medical student
- Gender of patient/doctor is important: preference, etc

Summary

- Gender differences are important for both men and women's health
    - We need to be gender aware/sensitive/competent

Introduction

- The body is in a constant battle between health and disease
    - Based on the host defences (immune system, antibodies, CD8 cells, phagocytosis, barriers (skin/mucosa)) vs microorganisms

Infectious disease

- The ability for microorganisms to cause disease depends on 2 factors:
    - Ability to spread from host to host
    - Ability to survive and multiply in the host
- Definitions:
    - Infectious disease: an infection that produces signs (eg. runny nose) and symptoms (eg. headache)
    - Pathogen: a microorganism that has the capacity to cause disease
- Regular pathogens vs opportunistic pathogens
    - Regular pathogens cause disease regularly (Corynebacterium diphtheriae – diphtheria, streptococcus pneumoniae)
    - Opportunistic pathogens cause disease rarely
        - Pseudomonas aeruginosa – gram –ve rod
            - Found in the environment,
            - Cystic fibrosis predisposes, often kills, creates a biofilm that is hard to get rid of
        - Candida albicans
            - Immunosuppressed are predisposed
            - Cant get systemic infection or with antibiotics, vaginal thrush
- Pathogenicity – capacity of a microorganism to produce disease
    - Depends on microorganisms ability to:
        - Gain entry to host
        - Attach to host cells
        - Survive in host and multiply
        - Evade host defences
        - Damage tissue (invade tissue) and produce disease symptoms
    - Dependent on virulence: a measure of pathogenicity or the likelihood of causing disease
        - Virulence factor: a bacterial factor or strategy that contributes to virulence

Urinary tract infection

- Host defence mechanisms
    - Mechanical:
        - Flushing effect of urination
        - Epithelial cell shedding
        - Sphincter action (prevent entry to bladder)
    - Biological:
        - Immune system is less important than mechanical processes
- Majority of infections infect via the ascending pathway
    - Enter via the urethra and multiply in bladder
        - May remain in bladder or ascend the ureters to the kidneys themselves
            - If damages blood vessels and enters blood stream, can cause sepsis
- Definitions:
    - Cystitis – infection of the urinary bladder
    - Pyelonephritis – infection of the kidney
- Several requirements for urinary tract infection:
    - A source of urinary pathogenic E. coli (UPEC) – a strain that can cause infection
        - Gram –ve rod common in normal GIT flora
        - Not all strains are the same, some can infect UT others can't
    - Entry and colonisation of vagina/urethra

- Adhesion
    - Important factor in facilitating colonisation of urethra
        - 10-36% of faecal E. coli adhere to vaginal, uroepithelial cells, 22-36% of asymptomatic bacteruria E. coli, 50-60% cystitis E. coli, 70-100% of pylonephritis bacteremia e. coli
        - Thus, adhesion is an important factor in determining invasiveness
    - Adhesion protects the bacteria from urinary lavage thereby allowing multiplication and invasion
        - Adhesins: Type 1 pili (fibrae); pyelonephritis associated pili (P pili)
- Type 1 pili
    - Produced by most strains of E. coli
    - Binds to mono-mannose residues/receptors on host cells
        - Found in the bladder, vaginal tract
        - Faecal isolates of e. coli interact poorly with mono-mannose receptors (GIT doesn't have receptors)
- Uroepithelial cells (bladder epithelium, umbrella cells)
    - Secrete uroplakins that sits on the top layer of the urepithelial cells
        - These are transmembrane proteins that cover the uroepithelial cell surface
        - Mannose receptors attach to the uroplakin
- Invasion process:
    - E. coli enters bladder, multiplies and attaches to mannose residues attached to uroplakins via type 1 pili
    - Binding leads to engulfment of e. coli allowing avoidance of the immune system
    - Bacterial invasion triggers cells to slough off rapidly and be excreted in urine
    - Inflammation
    - Symptoms – increased urine frequency (sphincter control loss) and dysuria (acidic urine irritation)
- P pili
    - Attach to the Globobiose receptor that is present in many cell types in the bladder/kidney
        - Attachment and damage to kidney cells leads to an inflammatory response
            - This may lead to damage to blood vessels, if bacteria in this way enters blood stream, can cause sepsis

<u>Respiratory tract infection</u>

- Defence mechanisms:
    - Nose
        - Nasal hairs – trap organisms/particles
        - Sneeze reflex – flush organisms/particles
    - Mouth
        - Flow of saliva
        - Antibacterial properties of saliva (lysosyme, antibacterial to gram +ve)
        - Resident microflora – take up nutrients/space
    - Mucous
        - Mucin – traps bacteria
    - Cilia
        - Ciliated cells in the respiratory tract, beat upwards to flush out foreign particles
    - Antibacterial action
        - Lysozyme
        - Secretory IgA – binds to bacterial antigens
        - Lactoferrin – iron acquisition (bacteria need iron, prevent this, bacteria have siderophores however)
        - Lactoperoxidase – antibacterial
    - Rapid turnover of mucosal cells
    - Immune system – Peyer's patches

Bacterial sore throat

- Normal major cause is viruses
- Streptococcus pyogenes can cause a bacterial infection
    - Gram +ve cocci
    - Virulence factors:
        - Non-fibrillar adhesins (doesn't use pili or fimbrae, uses proteins instead)
            - Attaches to Fibronectin (in the host cell) via Fibroenctin binding proteins F1 and F2
        - Hyaluronic acid (HA) capsule
            - Colonies freshly isolated appear mucoid
            - Aids attachment to pharynx
                - Attaches to CD44 receptor on epithelial cells
            - Antiphagocytic properties
                - Acidic (negatively charged),
            - HA appears similar to host cell CT and is not recognised as foreign
                - Thus, antigens are hidden below capsule
                    - Prevefns opsonised phagocytosis by neutrophils or macrophages
        - M-protein
            - Binds to mammalian proteins
                - Fibrinogen – results in fibrin production and walling off of the infection
                    - Causes pus formations to build up: fibrin, PMNs and cell debris
                - Fc region of IgG – prevents opsonisation by antibodies
            - Opsonisation: aided phagocytosis, neutrophils recognise the Fc region of IgG
                - M protein binds Fc, thus no phagocytosis
        - Extracellular enzymes
            - Streptolysins – damage membranes of susceptible cells (epithelial cells)
            - Streptokinases – activate plasmin to dissolve fibrin clots and facilitate spread
            - Hyaluronidase – digests host CT and facilitates spread

Streptococcus pneumoniae causing pneumonia (25-60% of pneumonia)

- Alpha haemolytic, gluggy, gram +ve dipolococci. Causes lobar pneumonia
- Virulence factors:
    - Polysaccharide capsule
        - >90 capsular serotypes, antibodies against one may be useless against another
        - Extremely thick
            - 200-400nm (vs: peptidoglycan 20nm, plasma membrane 9nm)
            - Conceals inner structures of S. pneumoniae
        - Anti-phagocytic – negatively charged
            - Anionic surface is not well recognised by host defences
            - Prevents complement activation
        - Allows bacteria to survive in the lungs, cause damage to epithelial cells and thus inflammation and an immune response
        - Fragments of the capsule shed in the replication process
            - These are bound by antibodies and activate the complement pathway away from the bacteria, causing inflammation and damage
    - sIgA1 protease
        - Breaks down the host secretory IgA_1 antibody at the hinge regions
            - IgA is the predominant immunoglobulin in mucosal defence
    - Pneumolysin
        - Stops beating of cilia
            - Leads to mucus build up in the lungs
            - Compromises the cough reflex – can't expel pneumococcus
        - Activates classical complement pathway
            - Binds Fc portion of antibody to lipotechoic acid, activates the complement system
            - Increases inflammation
    - Hyaluronidase
        - Enzyme, breaks down hyaluronic acid – the ground substance of CT
            - Thus promotes further bacterial dissemination

- Lung tissue damage
    - Influx of PMNs to site of infection
        - Need antibodies for phagocytosis, therefore ineffective
        - Alveoli become engorged with oedema and immune cells
    - Teichoic acid on the surface of bacteria activates the alternate complement pathway
        - Leads to production of C5a that further mediates the inflammatory response
            - Further influx of PMNs
    - PMNs release reactive oxygen species like H_2O_2 hydrogen peroxide
        - Causes damage to host cells
- Invasion process:
    - S. pneumoniae enters the lung and causes an inflammatory response
        - Capsule prevents phagocytosis and increases the inflammatory response
            - Pneumolysin further increases the inflammatory response
                - Hyaluronidase further facilitates the spread of the organism

<u>Staphylococcus aureus</u>

- Staphylococcal pneumonia – a lower respiratory tract infection
    - Rarely a primary event, often follows a previous viral infection
        - Eg: Spanish flu 1918, deaths were mostly due to secondary Staph. aureus bacterial pneumonia
- Virulence factors
    - Protein A
        - Extracellular protein (90% of strains)
        - Covalently bound to the cell wall
        - High affinity for Fc region of IgG
            - Prevents opsonisation of organism, and thereby facilitation of phagocytosis
    - Surface polysaccharide
        - Majority of clinical isolates have this factor
        - Impedes phagocytosis without complement system aid
    - Enzymes and toxins
        - Coagulase
            - Important virulence factor
            - Encloses S. aureus in fibrin and walls of the infection
                - Protects S. aureus from PMNs, fibrin deposition acting as a barrier
                - Abscesses form diffusely in the lung
        - Lipase
        - Staphylokinase (fibinolysin)
            - Produced by all Staph aureus
            - Dissolves fibrin clot allowing organism to spread
        - DNAase - reduces viscosity of abscess material and facilitates spread
            - Hyaluronidase - local dissolution of host extracellular matrix facilitating spread
        - Superoxide dismutase
            - Used to detoxify oxygen radicals used by PMNs to destroy bacteria
                - $2O_2^{\cdot} + H_2O \rightarrow SOD \rightarrow H_2O_2 + O_2$
        - Catalase
            - Used to protect cell from H_2O_2 that can cause DNA, protein, lipid damage
                - $2H_2O_2 \rightarrow catalase \rightarrow 2H_2O + O_2$
        - Leukocidin
            - Lyses neutrophils and macrophages
        - Alpha toxin
            - Forms pores in human cell membranes that disrupts the cells (esp. in the lungs)
                - Induces proinflammatory cytokine production:
                    - IL-1, TNF-α, → IL-8 → neutrophils
- Invasion process:
    - Coagulase leads to deposition of fibrin around the organism causing a walled-off abscess
        - Spread is facilitated by DNAase and staphylokinase (fibrinolysin)
        - Tissue damage is caused by leukocidin, alpha toxin and hyaluronidase

Flu and public health
- Health delivery systems
- Transmission of infection/patterns of disease

Viruses
- Most cases, host defences prevail and infections resolve spontaneously
    - Exceptions: Lassa fever, Ebola virus, HIV
- Virulence factors
    - Turn off protein markers allowing virus to remain undetected
    - Mimicking of protein markers in host cells to prevent detection

H5N1
- Needs a high attack rate and low virulence to be most effective

Prevalence and incidence
- Prevalence – frequency of condition at any one time in a population
- Incidence – number of new cases in a given time in a population

TB scenario
- Respiratory regulation of pH
    - Acidosis, low pH, high pCO_2
    - Alkalosis, high pH, low pCO_2
        - May be due to hyperventilation, at high altitudes
- pH is tightly regulated in the body

Access and adherence
- Dependent on SES, language, gender, age, stress, transport
    - These are all barriers to health care, need to study and see what we can do about them

Drug resistance – due to lack of adherence?
- Mutation – genetic code change (TB)
- Transduction – horizontal transfer (Staph)
- Transformation – DNA from the environment (Penicilin)
- Conjugation – genetic passage between cells (shigella)
- Prevention:
    - Right drug for the right bug, complete antibiotic course (DOTS), multidrug therapy
- Ethics → human rights vs social perspectives

HIV
- Stigma, epidemiology, pathology/microbiology
- Left lung has lingula + narrow base
    - Right lung has middle lobe and horizontal fissure (4^{th} ICC → 5^{th} ICS (mid axillary line))
- Limiting spread → condoms/needles/education
    - unknown agent in the 1980s
    - vs John Snow 1855, Broad Street pump and cholera

Antiinflammatory drugs
- NSAIDs, etc → many types, different groups

Healing and repair

- Social, cultural background of patient is very important
    - Need to look at factors that influence care-seeking
- acute inflammation: swelling, redness, pain, heat, loss of function (not: ulceration, induration – chronic inflam)
- Healing:
    - 30 mins → bleeding has slowed, haemostasis/platelet aggregation
    - 2 hours → yellow ooze/swelling, exudate
    - 6 hours → opaque covering, fibrin etc
    - 5 days → crusty scab, granulation tissue, collagen deposition, scarring
- Healing by second intention: dermis/subdermis layer is wavy: allowing islands of dermal cells to remain in injury
    - These can regenerate dermal layer

Tips

- 3 diseases:
    - How can they be prevented pharmacologically and socially
    - Process of transmission
    - Pathology/disease provoked
- Public health issues:
    - Individual/family/community response
    - Disease, treatment, prevention
    - Population context
    - Global context