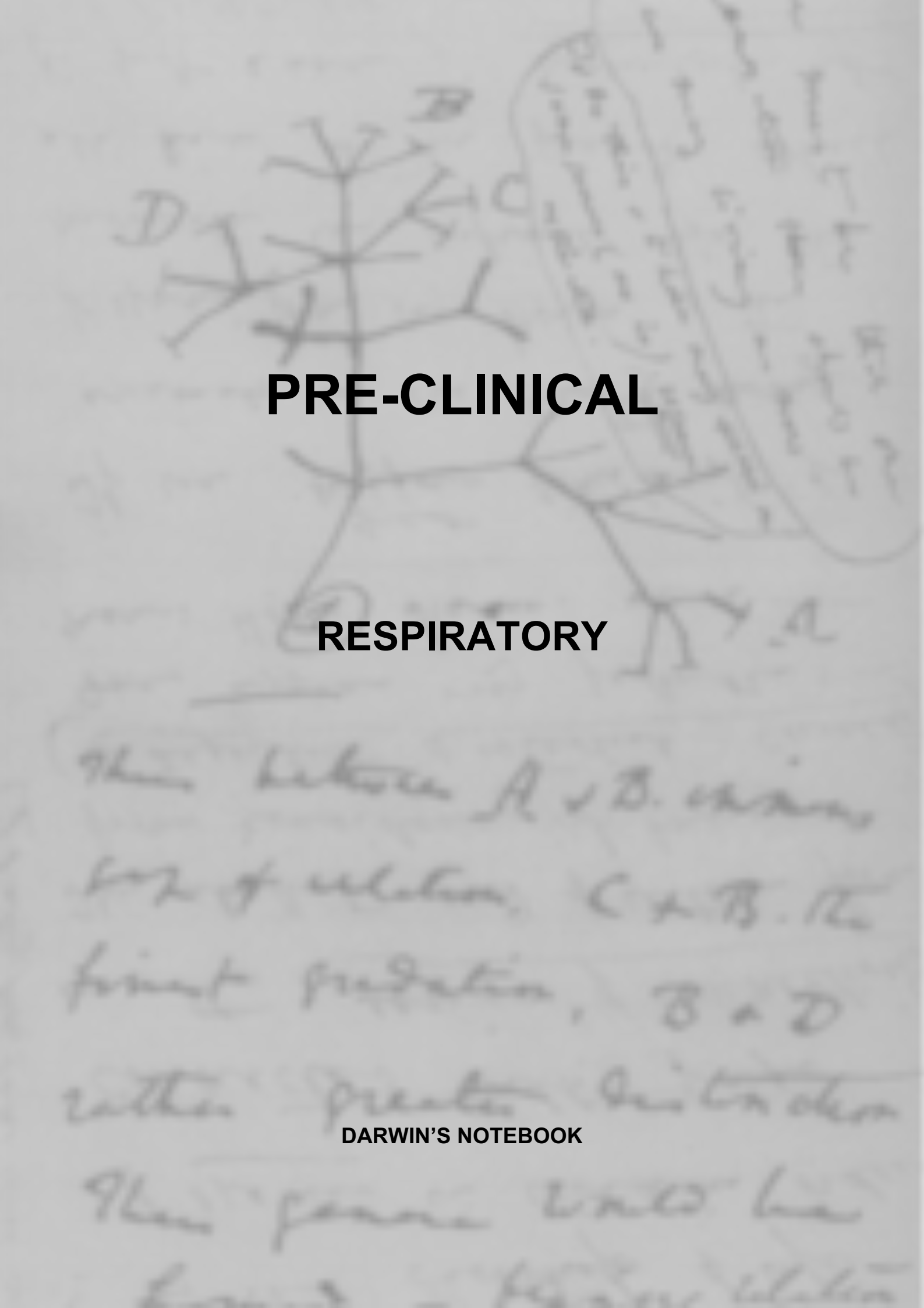


PRE-CLINICAL

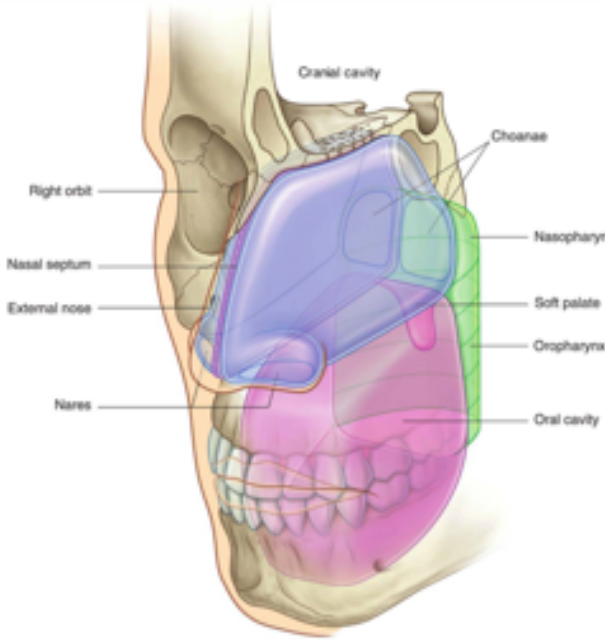
RESPIRATORY

DARWIN'S NOTEBOOK

TABLE OF CONTENTS

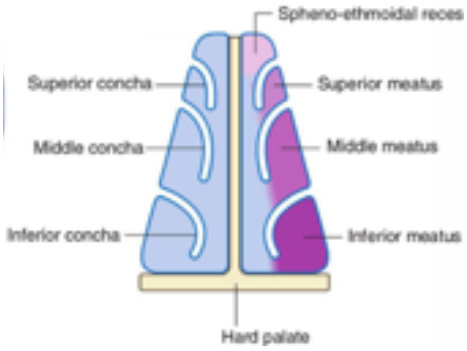
UPPER RESPIRATORY TRACT & PHARYNX

Describe the functions and boundaries of the nasal cavities



- The nasal cavities are the uppermost parts of the respiratory tract → contain olfactory receptors
- They have a large inferior base and narrow superior apex → held open by framework consisting mainly of bone and cartilage
- Superior 1/3 is lined by olfactory epithelium → inferior 2/3 is lined by respiratory epithelium (pseudostratified columnar ciliated epithelium with goblet cells)
- The smaller anterior regions are enclosed by the external nose → larger posterior regions are more central within the skull
- Anterior apertures are the nares → posterior apertures are the choanae, which open into the nasopharynx
- The nasal cavities are separated:
    - From each other → by a midline nasal septum
    - From the oral cavity below → by the hard palate
    - From the cranial cavity above → by parts of the frontal, ethmoid, and sphenoid bones
- Each nasal cavity has a floor, roof, medial wall (septum), and lateral wall

LATERAL WALL



- Characterised by three curved shelves of bone → conchae (or turbinates) → one above the other and project medially and inferiorly
- Superior and middle conchae are from ethmoid bone → inferior concha is its own bone
- Conchae separate each nasal cavity into inferior, middle, and superior meatuses, and a spheno-ethmoidal recess between the superior concha and the nasal roof
- The openings of the paranasal sinuses are on the lateral wall and roof of the nasal cavities
- Lateral wall also contains the opening of the nasolacrimal duct → drains tears from the eye into the nasal cavity

REGIONS

- Each nasal cavity consists of three general regions → the nasal vestibule, respiratory region, and olfactory region
- Nasal vestibule → small dilated space just internal to the naris → lines by skin and contains hair follicles
- Respiratory region → largest part of the nasal cavity → has a rich neurovascular supply, and is lined by respiratory epithelium
- Olfactory region → small and at the apex of each nasal cavity → lined by olfactory epithelium and contains olfactory receptors

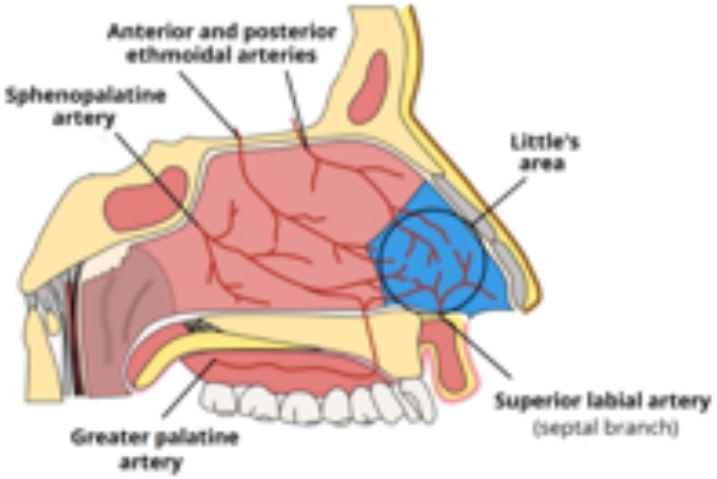
INNERVATION

- Innervation of the nasal cavities is by three cranial nerves:
    - Olfaction → olfactory nerve (CN I)

- General sensation → trigeminal nerve (CN V) → anterior region by ophthalmic nerve (V_1), posterior region by maxillary nerve (V_2)
- Glands → parasympathetic fibres in facial nerve (CN VII) → joins branches of maxillary nerve

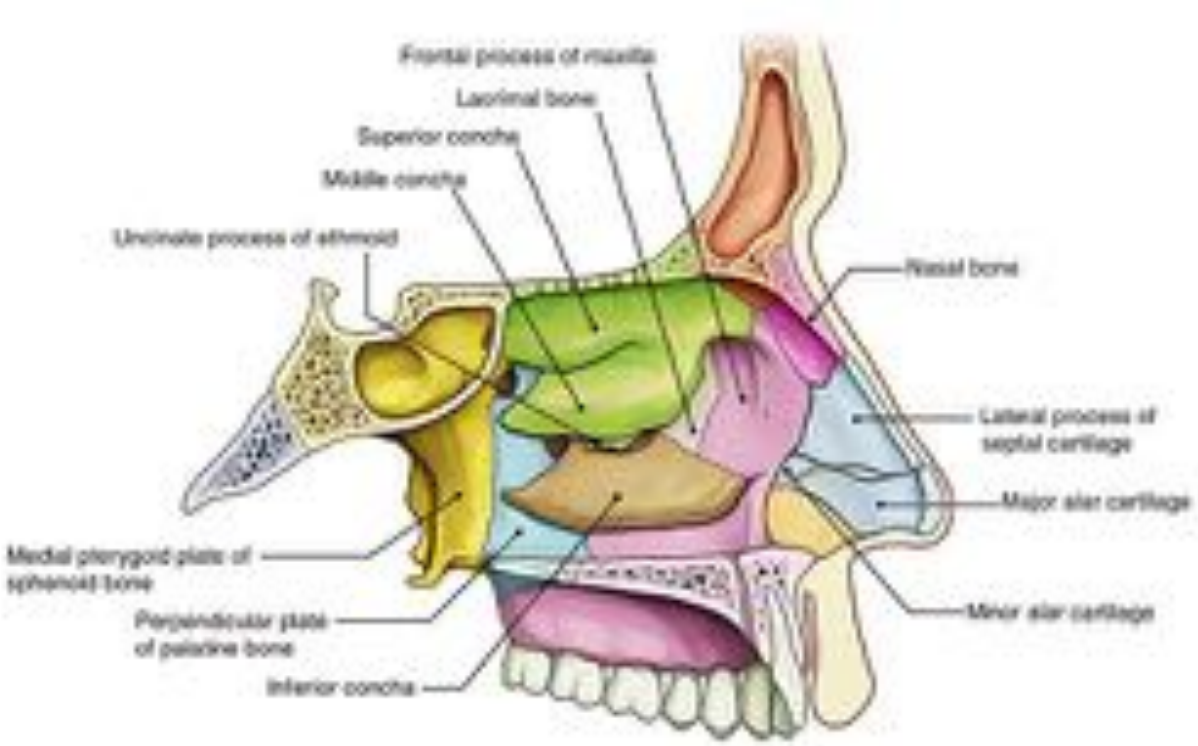
BLOOD SUPPLY

- Blood supply to the nasal cavities is by:
  - Terminal branches of the maxillary and facial arteries → branches from the external carotid
  - Ethmoidal branches of the ophthalmic artery → originates from the internal carotid artery
- Venous drainage:
  - The veins of the nasal cavities tend to follow the arteries
  - Drain into the pterygoid plexus, facial vein, or cavernous sinus



SKELETAL FRAMEWORK

- Bones that contribute to the skeletal framework of the nasal cavities include:
  - Unpaired ethmoid, sphenoid, frontal bone, and vomer
  - Paired nasal, maxillary, palatine, and lacrimal bones, and inferior conchae



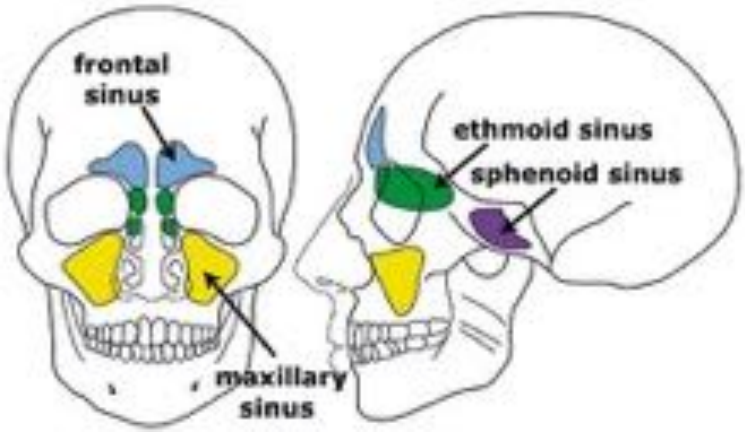
UPPER RESPIRATORY TRACT & PHARYNX

FUNCTIONS OF THE NASAL CAVITY

- Turbulence from nasal conchae and capillary plexus → helps epithelium to warm and humidify air
- Cleans inspired air and traps pathogens
- Olfaction
- Adds resonance to voice

Describe the functions and locations of the paranasal sinuses

- There are four paranasal air sinuses → ethmoidal cells, and sphenoidal, maxillary, and frontal sinuses → each is named according to the bone in which it is found
- All paranasal sinuses are:
    - Lined by respiratory epithelium
    - Open into the nasal cavities
    - Innervated by branches of the trigeminal nerve (CN V):
        - Frontal, ethmoidal, and sphenoidal sinuses → ophthalmic nerve (V_1)
        - Maxillary sinus → maxillary nerve (V_2)
- The paranasal sinuses make the skull lighter and add resonance to the voice



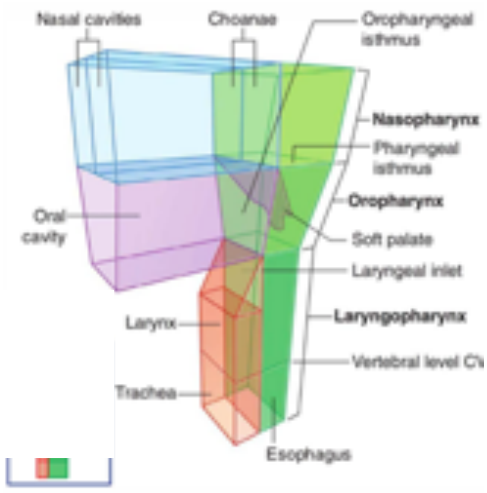
DRAINAGE

- Frontal → drains into hiatus semilunaris (shallow depression lateral to middle meatus)
- Ethmoid → anterior and middle parts drain into middle meatus → posterior part drains into superior meatus (via spheno-ethmoidal recess)
- Maxillary → drains into opening in inferior part of hiatus semilunaris
- Sphenoidal → drains into spheno-ethmoidal recess (adjacent to superior concha)
- Nasolacrimal ducts → drain into inferior meatus

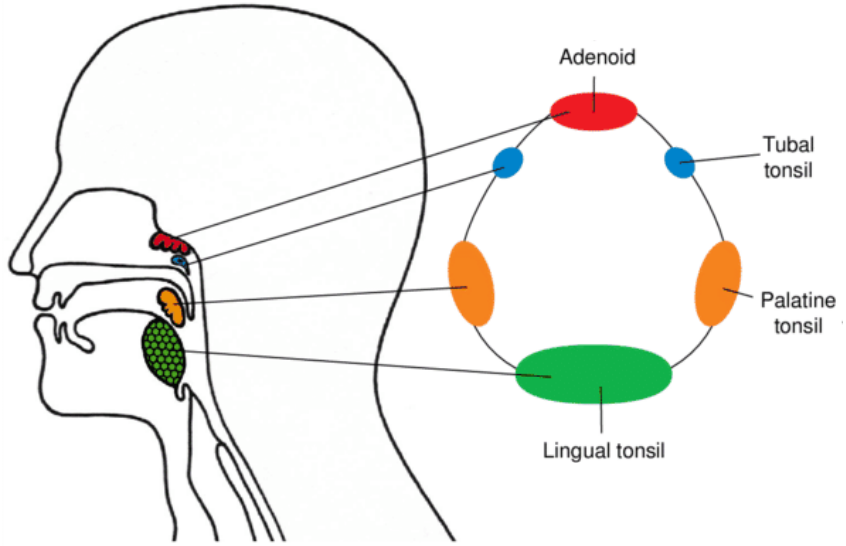
Describe the structure and function of the pharynx and its nerve supply

- Pharynx → a musculofascial half-cylinder → links the oral and nasal cavities in the head to the larynx and oesophagus in the neck
- Attached above to the base of the skull, and continuous below with oesophagus → to vertebral level C6
- Walls of the pharynx are attached anteriorly to margins of the nasal cavities, oral cavity, and larynx
- Subdivided into three regions → nasopharynx, oropharynx, and laryngopharynx:
    - Nasopharynx:
        - Anterosuperiorly → choanae (posterior apertures) of nasal cavity
        - Inferiorly → lower border of soft palate

- Oropharynx:
  - Superiorly → lower border of soft palate
  - Anteriorly → palatoglossus muscle
  - Inferiorly → tip of epiglottis
- Laryngopharynx:
  - Superiorly → tip of epiglottis
  - Inferiorly → cricopharyngeus muscle (at vertebral level C6)



- The Eustachian tube (pharyngotympanic tube) connects the middle ear to the lateral wall of nasopharynx
- Waldeyer's tonsillar ring → a ring of lymphoid tissue in the pharynx → surrounds the naso- and oropharynx → consists of:
  - Pharyngeal tonsils (adenoid) → on roof of nasopharynx under sphenoid bone
  - Tubal tonsils → on each side of nasopharynx near opening of Eustachian tube
  - Palatine tonsils → in the oropharynx
  - Lingual tonsil → on the back part of the tongue

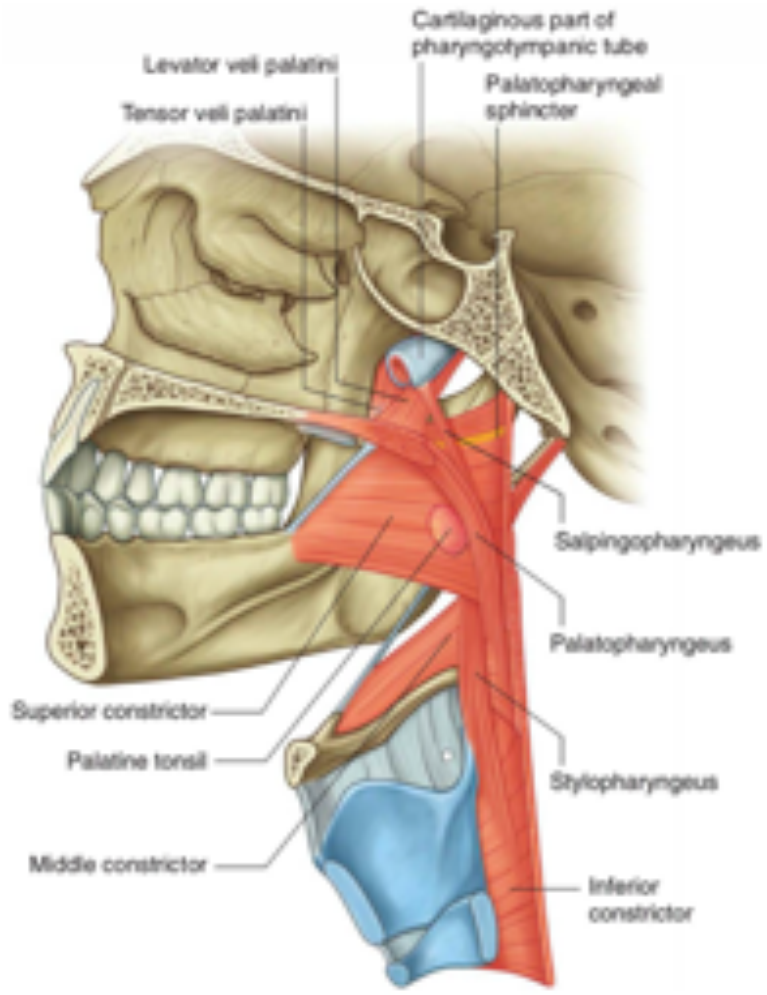


MUSCLES

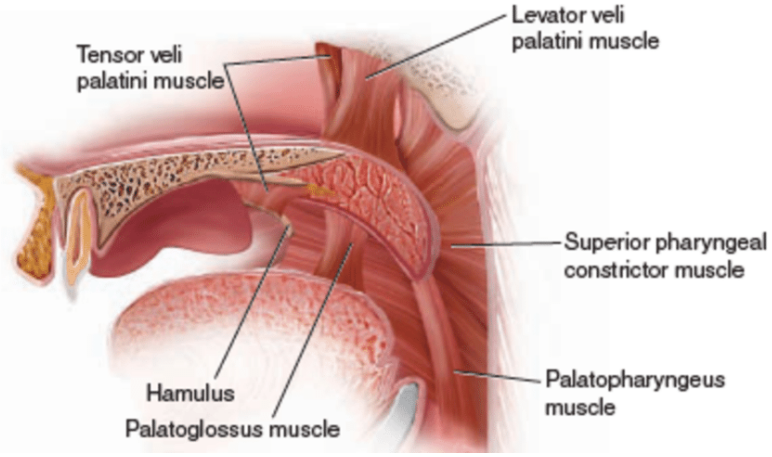
- The muscles of the pharynx are organised into two groups → constrictor and longitudinal muscles
- Constrictor muscles:
  - Three on each side → superior, middle, and inferior → muscles on each side are joined posteriorly by the pharyngeal raphe
  - Attach anteriorly to bones and ligaments related to lateral margins of nasal and oral cavities and larynx
  - Collectively, the muscles constrict or narrow the pharyngeal cavity
  - All constrictors are innervated by pharyngeal branch of vagus nerve (CN X)
- Longitudinal muscles:
  - Three on each side named according to their origins:
    - Stylopharyngeus → from styloid process of temporal bone
    - Salpingopharyngeus → from cartilaginous part of Eustachian tube
    - Palatopharyngeus → from soft palate

- All descend and attach into the pharyngeal wall
- These muscles elevate the pharyngeal wall, or pall the pharynx up during swallowing
- The salpingopharyngeus and palatopharyngeus are innervated by the vagus nerve (CN X) → stylopharyngeus is innervated by the glossopharyngeal nerve (CN IX)

- The pharyngeal fascia is separated into two layers → sandwich the pharyngeal muscles between them:
  - Buccopharyngeal fascia → thin layer → coats outside of the muscular wall
  - Pharyngobasilar fascia → thick layer → lines the inner surface

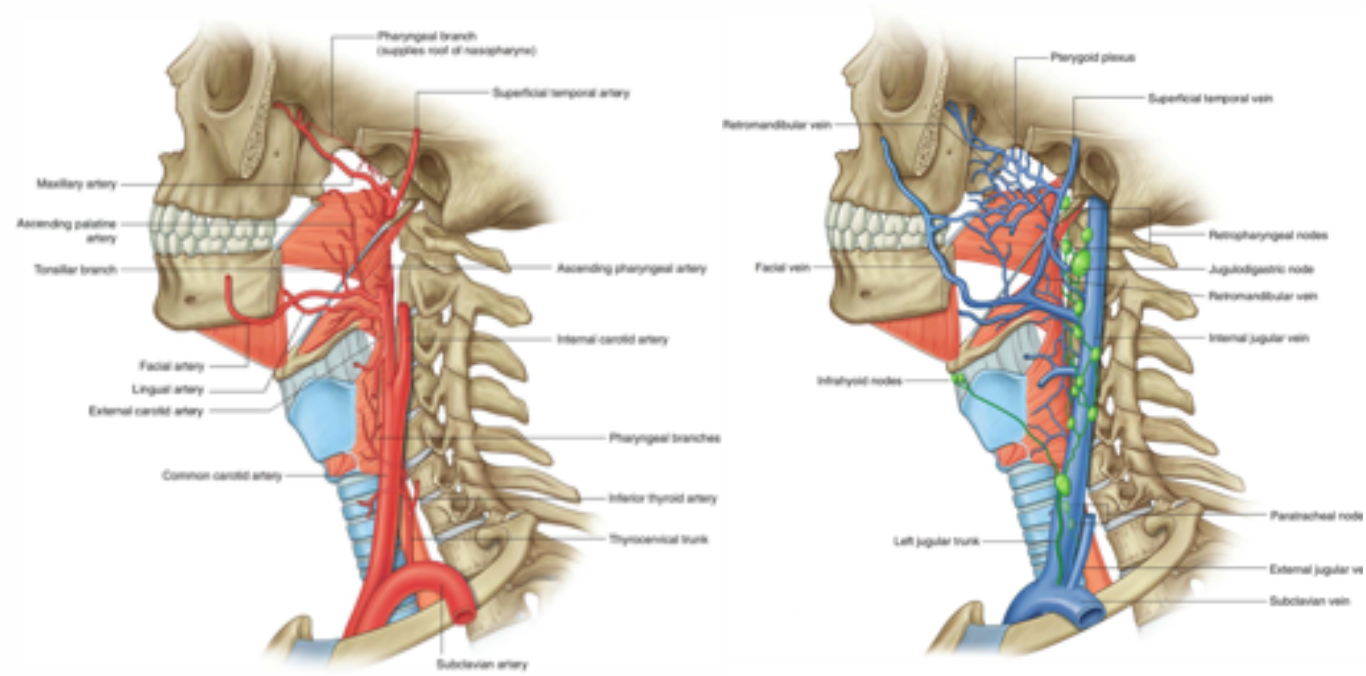


- Five muscles on each side form the soft palate → tensor veli palatini, levator veli palatini, palatopharyngeus, palatoglossus, and musculus uvulae



BLOOD SUPPLY

- Arteries that supply the upper parts of the pharynx are from the external carotid artery, and include:
  - Ascending pharyngeal artery
  - Ascending palatine and tonsillar branches of facial artery
  - Branches of maxillary and lingual arteries
- Arteries that supply the lower parts of the pharynx include pharyngeal branches from inferior thyroid artery → originates from thyrocervical trunk of subclavian artery
- Veins of the pharynx form a plexus → drains superiorly into the pterygoid plexus, and inferiorly into facial and internal jugular veins



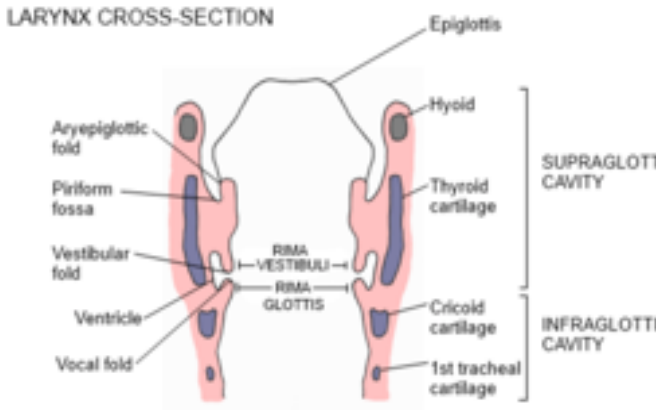
INNERVATION

- Motor and sensory innervation → mainly supplied by CN IX and CN X → form pharyngeal plexus:
  - Pharyngeal branch of vagus nerve
  - Branches from external laryngeal nerve from superior laryngeal branch of vagus nerve
  - Pharyngeal branches of glossopharyngeal nerve
- Motor supply to all pharyngeal muscles is from CN X **EXCEPT** stylopharyngeus (CN IX)
- Nasopharynx → pharyngeal branch of maxillary nerve (V_2) of trigeminal nerve (CN V)
- Oropharynx → glossopharyngeal nerve (CN IX) via pharyngeal plexus
- Laryngopharynx → vagus nerve (CN X) via pharyngeal plexus
- Gag reflex → via CN IX for sensory (afferent) and CN X for motor (efferent) → if constrictors fail to work it can cause loss of gag reflex

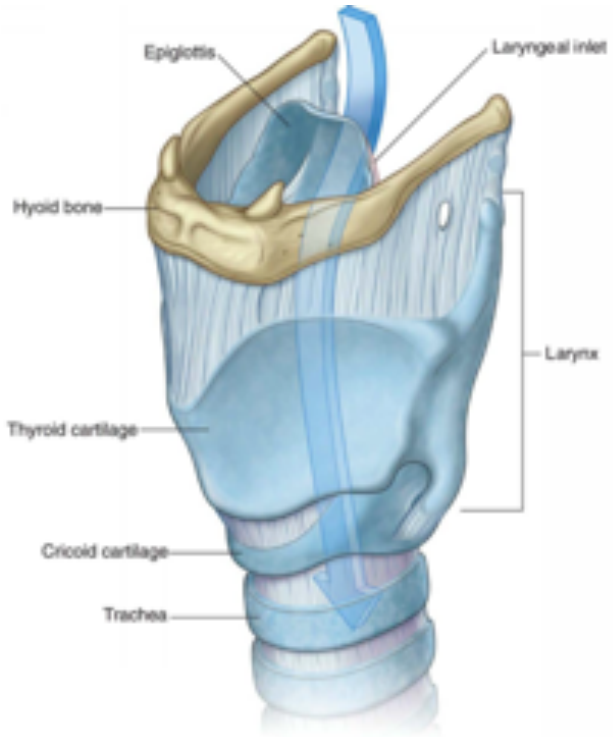
THE LARYNX

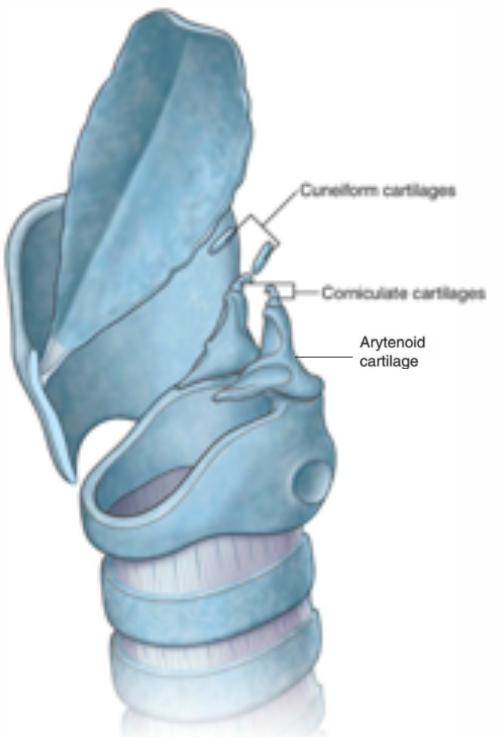
Outline the structure and function of the larynx and its key muscles

- Larynx → a hollow musculoligamentous structure with a cartilaginous framework → caps the lower respiratory tract
- Suspended from the hyoid bone → consists of:
    - 3 unpaired large cartilages:
        - Thyroid cartilage → hyaline cartilage
        - Epiglottis → elastic cartilage
        - Cricoid cartilage → hyaline cartilage → only cartilage in the airway to form a complete ring
    - 3 paired small cartilages:
        - Arytenoid
        - Corniculate
        - Cuneiform
    - Synovial joints → cricothyroid and cricoarytenoid
    - Fibroelastic membranes and ligaments:
        - Intrinsic membranes (between cartilages):
            - Cricothyroid membrane
            - Cricovocal (lateral cricothyroid) membrane → free upper border forms the vocal ligament
            - Aryepiglottic (quadrangular) membrane → free lower border forms vestibular fold
        - Extrinsic membranes (cartilage and bone) → connect the larynx to the surrounding structures:
            - Thyrohyoid membrane



- The larynx is lined with respiratory epithelium **EXCEPT** the vocal folds (stratified squamous epithelium)



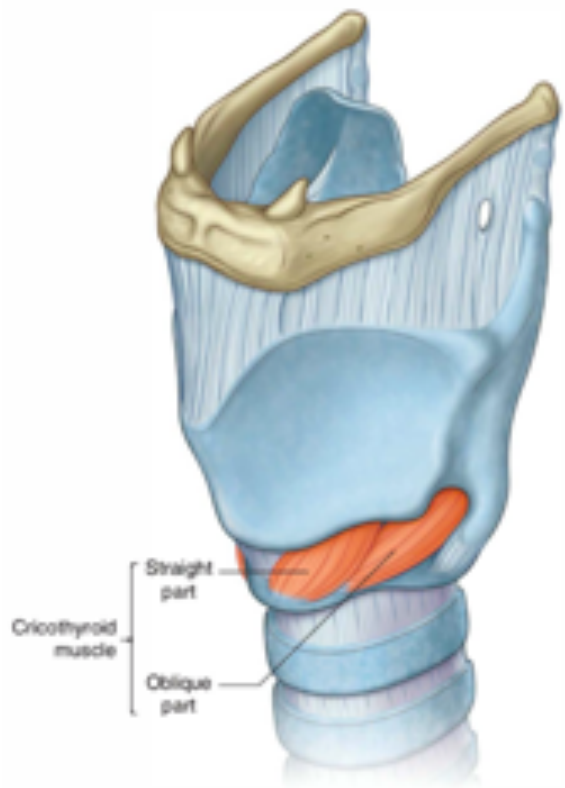


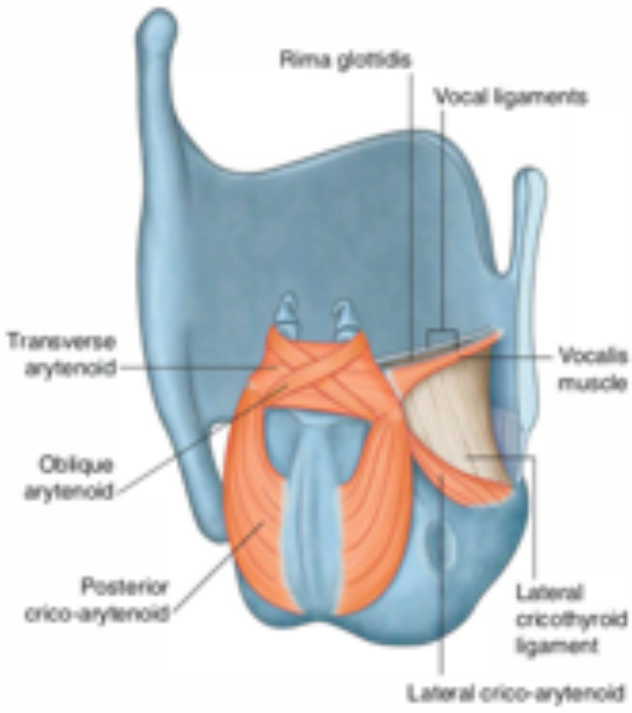
THE LARYNX

MUSCLES

- The intrinsic muscles of the larynx adjust tension in the vocal ligaments, open and close the rima glottidis (opening between vocal folds), and close the laryngeal inlet → they do this by:
    - Acting on the cricothyroid and cricoarytenoid joints
    - Adjusting the distance between the epiglottis and arytenoid cartilages
    - Pulling directly on the vocal ligaments
    - Forcing soft tissues associated with the quadrangular membranes and vestibular ligaments toward the midline

MUSCLE	FUNCTION
Oblique and transverse arytenoids	Adduct arytenoid cartilages
Posterior cricoarytenoid	Only muscle to abduct vocal folds
Lateral cricoarytenoid	Adducts vocal folds
Thyroarytenoid	Pulls the arytenoid anteriorly → relaxes vocal folds Approximates vocal folds
Vocalis	Continues along lateral aspect of vocal ligament → shortens vocal folds
Cricothyroid	Does not attach to arytenoid cartilages Has two bellies that run superior-inferior → superior belly attaches to inferior of thyroid lamina → inferior belly attaches to inferior horn of thyroid cartilage Lengthen the vocal folds
Aryepiglotticus	Adducts aryepiglottic folds
Thyroepiglottic muscle	Widens the inlet and causes depression of the epiglottis





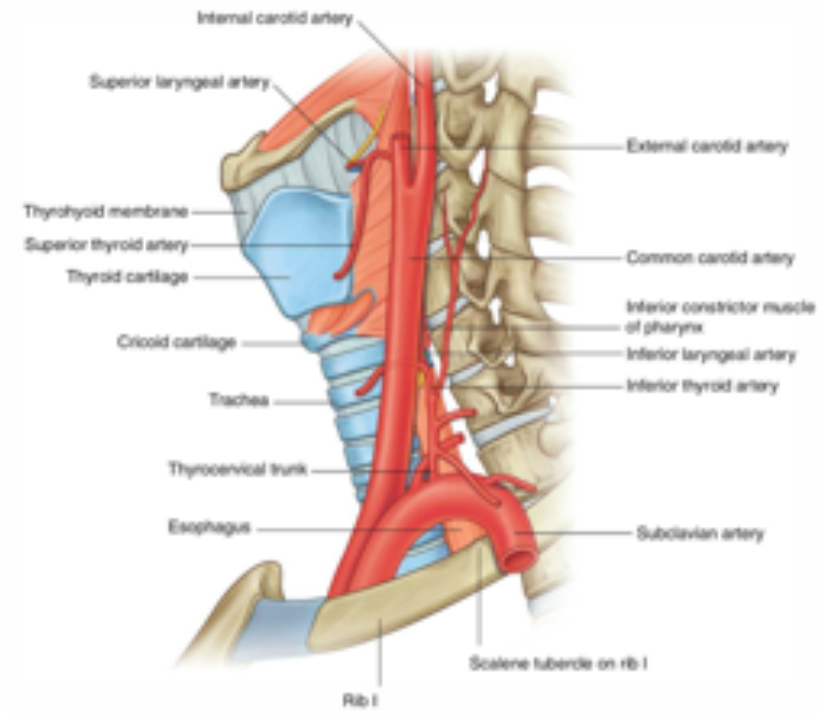
- During laryngoscopy, the vocal folds appear as glistening pearly white
- The gap between t

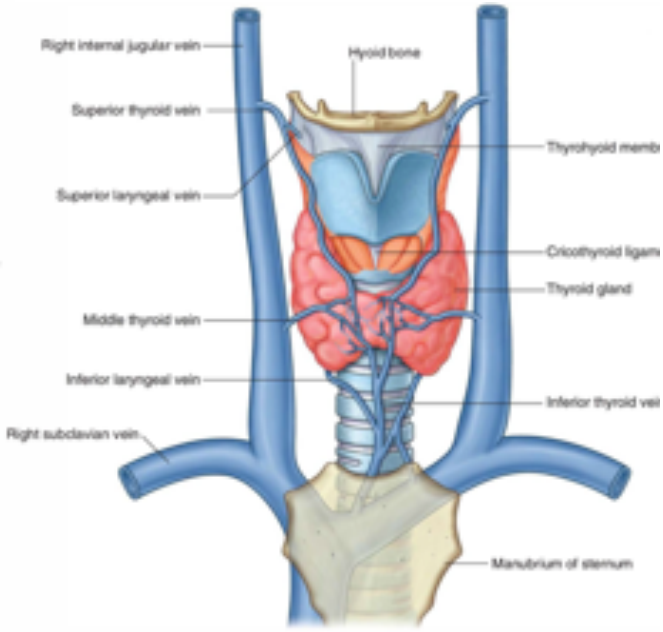
FUNCTION

- Guards the entrance to the tracheobronchial tree
- Prevents the ingress of fluids, particles, and foreign bodies into the airways
- Regulates airflow during breathing
- Vocalisation:
    - The unpaired cartilages protect the airway and vocal folds, and alter pitch of the voice
    - The paired arytenoid cartilages produce movement for voice production
    - The vocal folds are opened (abducted) and closed (adducted) by movements at the cricoarytenoid joints
- Raises intra-abdominal pressure → Valsalva manoeuvre
- Helps to fix the thorax when lifting objects
- Enables the modification of the flow of air during expiration to produce highly complex sounds → vary in loudness (intensity), frequency (pitch), and quality (timbre)

BLOOD SUPPLY

- The arterial supply to the larynx is via the superior and inferior laryngeal arteries:
    - Superior laryngeal artery → branch of the superior thyroid artery (from external carotid) → follows the internal branch of the superior laryngeal nerve into the larynx
    - Inferior laryngeal artery → branch of the inferior thyroid artery (from thyrocervical trunk from subclavian) → follows recurrent laryngeal nerve into the larynx
- Venous drainage is by the superior and inferior laryngeal veins:
    - Superior laryngeal vein → drains to the internal jugular vein via the superior thyroid vein
    - Inferior laryngeal vein → drains to the left brachiocephalic vein via the inferior thyroid vein

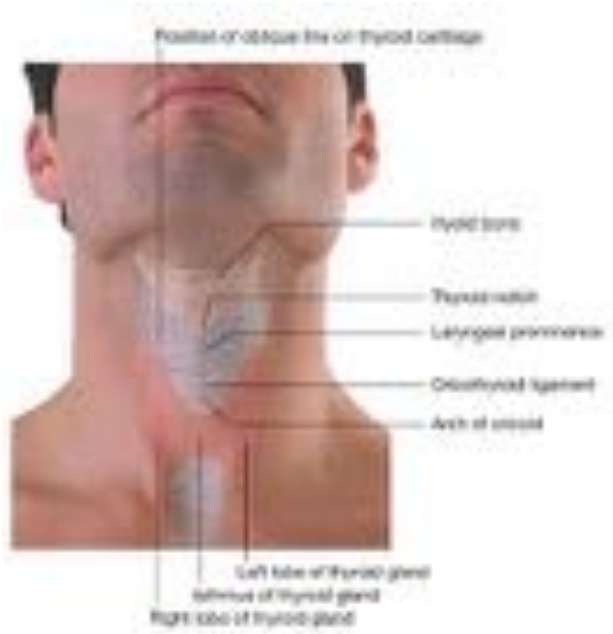




THE LARYNX

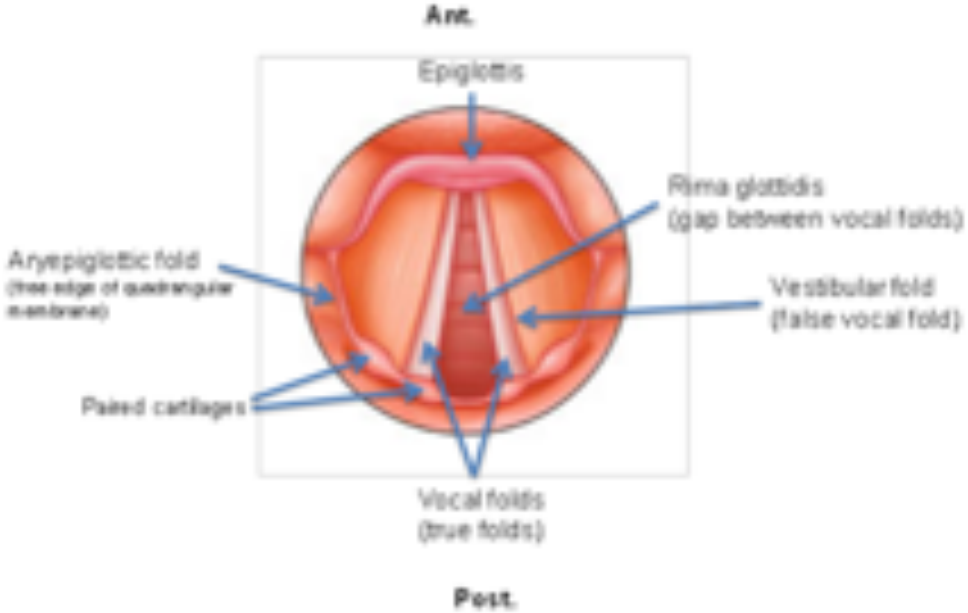
Identify the surface anatomy of the larynx and associated structures

- C3/4 → superior margin of the thyroid cartilage
- C5 → inferior margin of the cricoid cartilage → transition of larynx to trachea
- Cricothyroid membrane → between cricoid and thyroid cartilages → below laryngeal prominence of thyroid cartilage
- The isthmus of the thyroid glands sits antero-inferior to the larynx → superior portions of each lobe lie lateral to the cricoid cartilage



Describe the movements of the vocal folds and the muscles responsible for each movement

- During laryngoscopy, the vocal folds appear as glistening pearly white
- The gap between the vocal folds is the rima glottidis
- The glottis includes the vocal folds and processes, and the rima glottidis

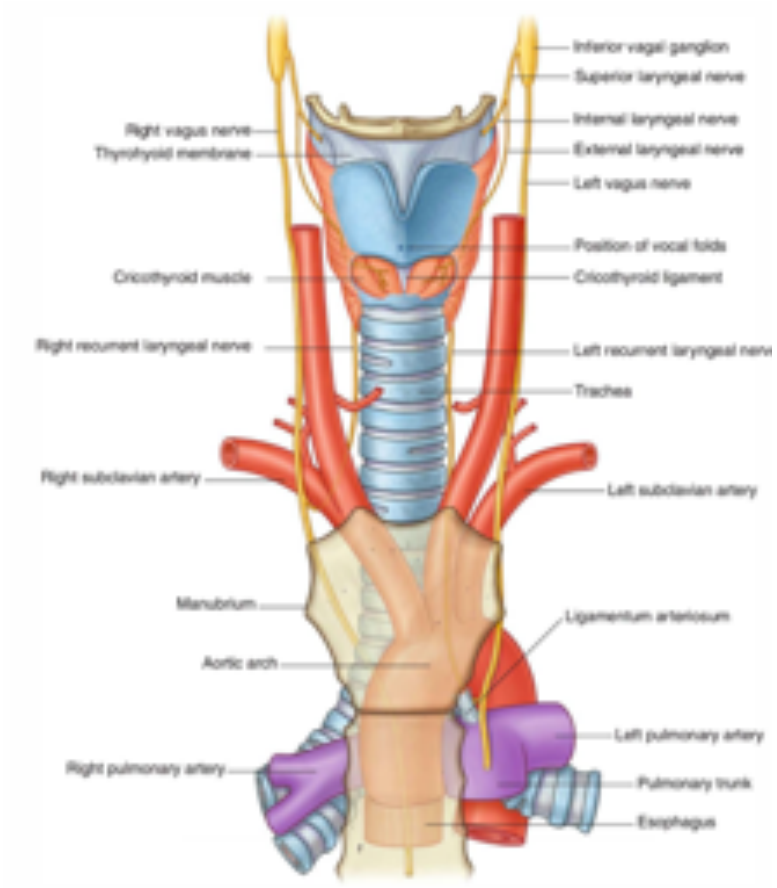


- Several muscles are responsible for the movements of the vocal folds:
  - Cricothyroid → lengthens and tenses the vocal folds
  - Posterior cricoarytenoid → abducts the vocal folds
  - Lateral cricoarytenoid → adducts the vocal folds
  - Thyroarytenoid → shortens and relaxes the vocal folds
  - Vocalis → tenses the anterior and relaxes the posterior of the vocal folds
  - Transverse and oblique artyenoids → close the intercartilagenous portion of the rima glottidis

THE LARYNX

Describe the origin and functions of the laryngeal nerves and the consequences of damage to these nerves

- All motor and sensory innervation of the larynx is from the vagus nerve (CN X)
- Motor branches to laryngeal muscles, and sensory to the mucosa
- Superior laryngeal nerve:
    - External branch → motor to cricothyroid
    - Internal branch → sensory to muscosa above vocal folds
- Recurrent laryngeal nerve:
    - Motor to all muscles except cricothyroid
    - Sensory to mucosa below vocal folds
    - The right RLN loops under the right subclavian artery → the left RLN loops under the ligamentum arteriosum (near aortic arch) before ascending posteriorly, adjacent to the trachea
- All nerves are ipsilateral → e.g. the right RLN supplies the ride side of the larynx
- NB: Vagus nerve has no autonomic function in the head and neck



DAMAGE TO RECURRENT LARYNGEAL NERVE

- RLN is a branch of CN X that supplies the laryngeal muscle sin control of vocal cord position
- A unilateral injury to this nerve may result in hoarseness of voice
- A bilateral injury may produce an absent voice (that can recover) → but patient is at risk of breathing impairment, airway obstruction, and asphyxiation

VIRAL INFECTIONS OF THE RESPIRATORY TRACT

List clinical terms used to describe infections of the respiratory tract

- Rhinitis → nose
- Pharyngitis → pharynx
- Sinusitis → sinuses
- Otitis media + otitis externa → middle and external ear
- Epiglottitis → epiglottis
- Laryngitis → larynx

Distinguish between upper and lower respiratory tract infections

- Upper respiratory tract infections (URTIs) → are common and relatively trivial → often viral in aetiology → secondary bacterial infections are common
- Lower respiratory tract infections (LRTIs) → potentially life threatening → can be viral or bacterial

Describe the cause of common viral infections of the upper respiratory tract

- Viral URTIs:
    - Rhinovirus → often called the common cold
    - Parainfluenza viruses 1-4
    - Coronavirus → also shows symptoms like the common cold → SARS/MERS
    - Respiratory syncytial virus (RSV)
    - Adenovirus
    - Enterovirus → coxsackie, echovirus
    - Secondary bacterial infections → sinusitis, otitis, bronchitis, pneumonia
- Pharyngitis/tonsillitis → can be caused by viruses or bacteria → adenovirus or *Strep. Pyogenes*

Describe the features and common aetiological agents of infectious mononucleosis

- Infectious mononucleosis → glandular fever → it is a syndrome → symptoms include pharyngitis, lymphadenopathy, fever and malaise → also atypical mononuclear cells in peripheral blood → can be caused by EBV, CMV, toxoplasmosis or HIV seroconversion

List the common viral causes of lower respiratory tract infection

- Common viruses include:
    - Influenza viruses
    - Respiratory syncytial virus
    - Rare → varicella zoster, measles, cytomegalovirus, SARS/MERS coronaviruses

Describe the clinical features and epidemiology of influenza infection

- Influenza virus → segmented, -ve ssRNA genome → 8 segments encode 11 proteins → 4^{th} = haemagglutinin → 6^{th} = neuraminidase
- There are 3 types of flu virus → A, B, and C → only A and B are pathogenic to humans → distinction based on internal proteins, nucleoproteins, and matrix
- Influenza A has subtypes → based on surface proteins haemagglutinin and neuraminidase → each differs by >20% in the AA sequence → H1N1, H3N2, etc.
- The definition of 'flu-like symptoms' varies → must contain the following two components:
    - Respiratory tract symptoms → rhinitis, cough, shortness of breath

  - Systemic symptoms → fever, headache, myalgia
- The influenza virus is a pneumotropic virus → affinity for the lungs → it is also lytic → strips off respiratory epithelium → therefore removes 2 innate defence mechanisms → mucous secreting cells and cilia
- In addition → the virus also initiates interferon production → it is the interferon that gives the systemic symptoms associated with the flu
- Complications with influenza:
  - Pneumonia → 1^{o} viral – mononuclear cell infiltrate → 2^{o} bacterial – PMNL infiltrate
  - Cardiovascular complications → unsure if myocarditis is a symptom or a risk factor
  - CNS complications → encephalitis → due to immune response not virus itself
- High risk patients → anyone with underlying comorbidities → anyone >65yrs → pregnant women and children <5yrs → most of these will be vaccinated
- Influenza presents in annual winter epidemics and is associated with excess death, hospitalisations, and other serious consequences → normal viruses have an epidemic every 2-4yrs once herd immunity has diminished again → influenza is different
- Influenza also shows an unpredictable pandemic pattern → both of which are due to antigenic drift and shift
- Influenza A reservoirs → can be animals including birds → often pigs as they support the growth of both human and avian viruses → mixing vessels
- Pandemic influenza:
  - 1918-19 → H1N1 → Spanish Flu
  - 1956-57 → H2N2 → Asian Flu
  - 1968 → H3N2 → Hong Kong Flu
  - 1976 → H1N1 → Russian Flu
  - 2009 → H1N1dpm → Swine Flu
  - ???? → ?H5N1 → ? next pandemic
- Key measures in combating pandemic flu → infection control → medical treatment → vaccination

List the mechanisms and describe the importance of antigenic drift and shift in influenza

- Antigenic drift → random spontaneous mutations in HA and NA → occurs in both type A and type B → accounts for interpandemic epidemics
- Antigenic shift → only occurs in type A → genetic reassortment between human and non-human viruses leading to new subtypes → often occurs in mixing vessels

Describe the clinical features and epidemiology of RSV infection

- RSV → enveloped paramyxovirus → -ve ssRNA → encodes 9 polypeptides (not segmented) → including 2 surface proteins F (fusion) and N (glycoprotein) → seasonal infection → extremely common → global infection by the age of 2
- Causes LRTI in infants → bronchiolitis and pneumonia → high hospitalisation rates → but low mortality (<0.5%) unless congenital heart/lung disease or immunocompromised
- It requires rapid diagnosis and appropriate infection control measures
- Re-infection occurs throughout life → due to antigenic drift

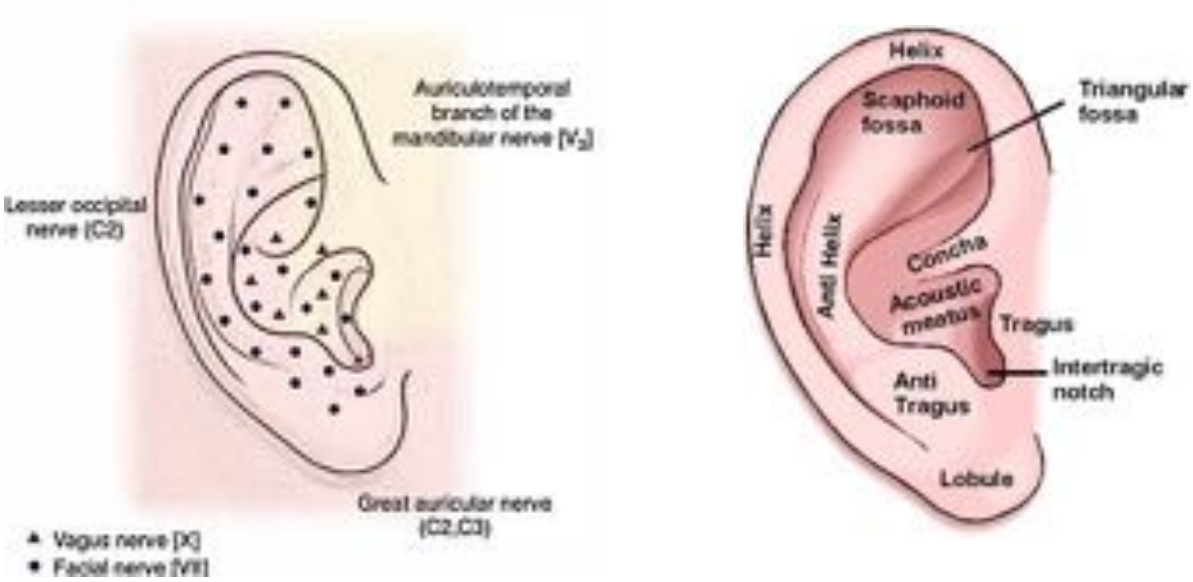
THE EAR

Describe the position, boundaries, and nerve supplies of the external ear and middle ear

- The ear is the organ of hearing and balance → it has three parts:
    - External ear → consisting of the part attached to the lateral aspect of the head and the canal leading inward
    - Middle ear → a cavity in the petrous part of the temporal bone → separated from the external canal by the tympanic membrane → connected internally to the nasopharynx by the Eustachian tube
    - Inner ear → consisting of a series of cavities within the petrous part of the temporal bone → between the middle ear laterally and the internal acoustic meatus medially

EXTERNAL EAR AND ACOUSTIC MEATUS

- Auricle → elastic cartilage covered by skin
- Complex multiple nerve supply → pain can be referred to the mandible/temporomandibular joint (via CN V_3) or the pharynx (via CN X)
- The cartilage is poorly vascularised → heals slowly → susceptible to infection
- A lobule may or may not be present



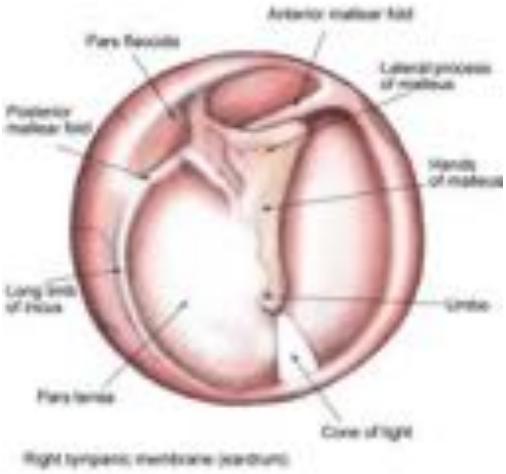
EXTERNAL AUDITORY CANAL

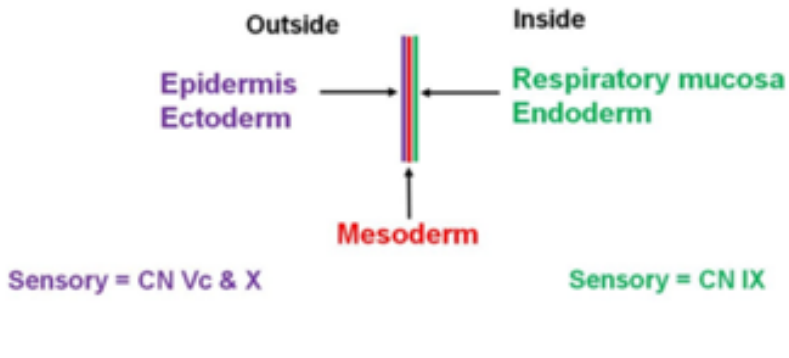
- From external auditory meatus to tympanic membrane → ~2.5cm long
- Lateral 2/3 → fibrocartilage continuous with auricle
- Medial 1/3 → osseous → contained within squamous and mastoid parts of the temporal bone
- Lined by skin attached to cartilage/periosteum of bone
- Continuous with the skin covering the external aspect of the tympanic membrane
- Skin secretes cerumen (wax)

TYMPANIC MEMBRANE

- Trilaminar composition → reflectes embryological origins:
    - Skin of EAC (ectoderm) → CN X/V_3/VII
    - Connective tissue (mesoderm)
    - Respiratory mucosa from pharynx (endoderm) → CN IX
- Epidermis → pain referral to/from mandibular teeth, TMJ, laryngopharynx
- Respiratory mucosa → pain referral to/from the pharynx

THE EAR



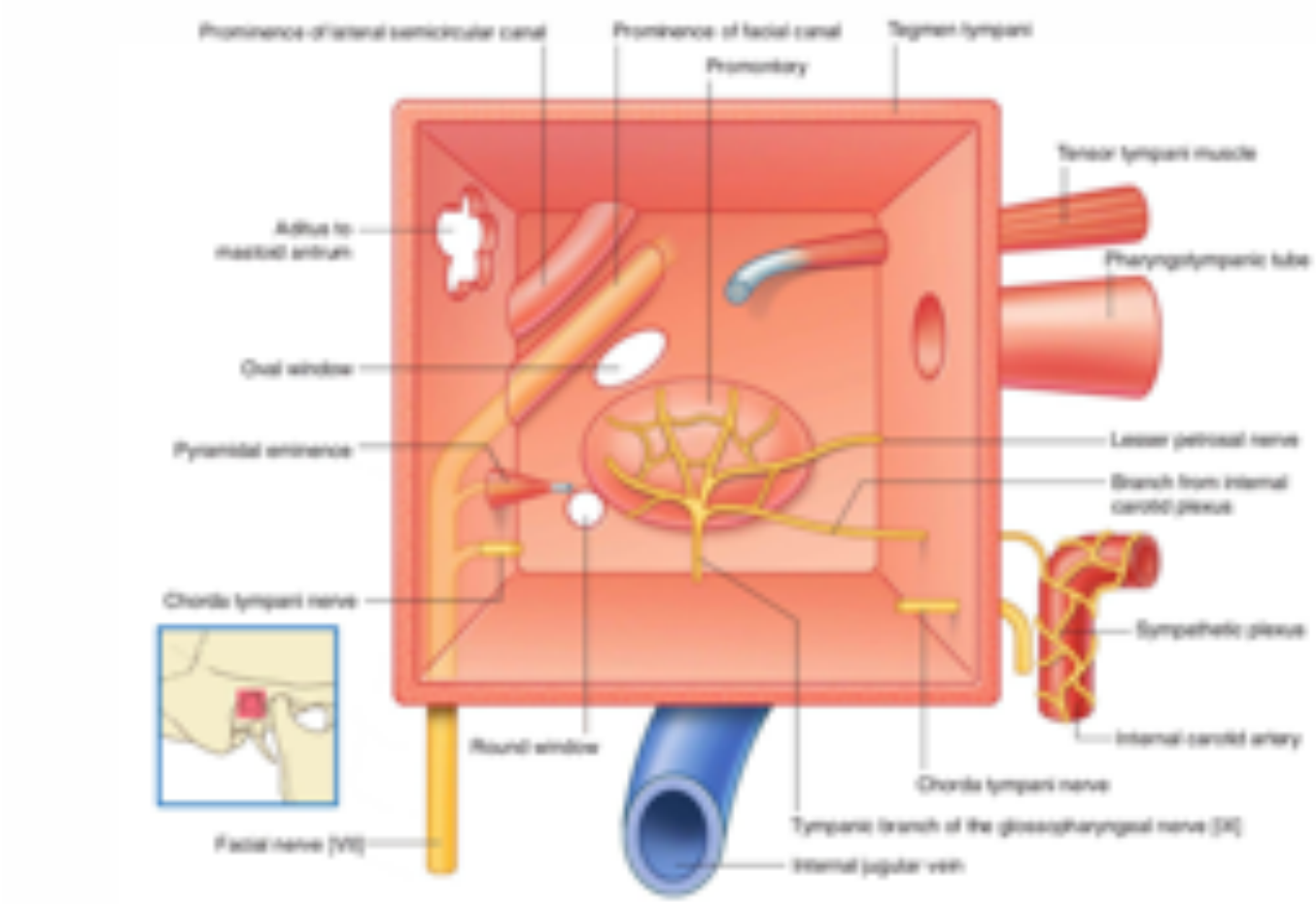


- Around the periphery of the tympanic membrane → fibrocartilaginous ring attached it to the tympanic part of temporal bone
- At the centre → concavity produced by attachment to the handle of malleus → point of attachment is the umbo
- Anteroinferior to the umbo is a bright reflection of light → cone of light
- Superior to the malleolar folds the membrane is thin and slack (pars flaccida) → the rest of the membrane is thick and taut (pars tensa)

MIDDLE EAR

- This is an air-filled, mucous membrane-lined space in the temporal bone
- Communicates with the mastoid area posteriorly (via aditus) and the nasopharynx anteriorly (via Eustachian tube)
- The middle ear has several boundaries:
    - Roof (tegmental wall) → thin layer of bone separating middle ear from middle cranial fossa
    - Floor (jugular wal) → thin layer of bone separating middle ear from internal jugular vein → tympanic branch of CN IX enters middle ear near medial border of the floor
    - Lateral (membranous wall) → consists of the tympanic membrane and bony epitympanic recess
    - Posterior (mastoid wall) → only partially complete → bony wall separates tympanic cavity and mastoid air cells → contains:
        - Aditus to mastoid antrum → infections of the middle ear can pass to the mastoid through this, resulting in mastoiditis
        - Pyramidal eminence → elevation through which stapedius muscle enters middle ear
        - Chorda tympani nerve (branch of CN VII) enters the middle ear
    - Anterior wall → only partially complete → thin layer of bone separates tympanic cavity from internal carotid artery → contains:
        - Opening of Eustachian tube
        - Opening for canal containing tensor tympani muscle
        - Chorda tympani exits the middle ear
    - Medial (labyrinthine wall) → also the lateral wall of the internal ear→ contains:
        - Promontory → bulge produced by the basal coil of the cochlea → covered by the tympanic plexus of nerves

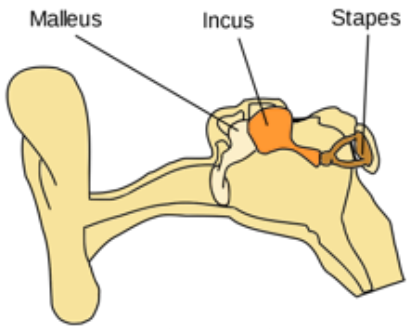
- Oval window → point of attachment for the base of stapes bone
- Round window
- Prominence of facial canal → ridge of bone produced by CN VII
- Prominence of lateral semicircular canal



- Tympanic membrane rupture can damage the chorda tympani (branch of CN VII) → resulting in loss of taste and sensation to anterior 2/3 of ipsilateral tongue (sensory to posterior 1/3 of tongue is via CN IX)
- Middle ear infections can affect the facial nerve, resulting in ipsilateral facial palsy
- Middle ear infections may affect the vestibular system, causing dizziness
- The Eustachian tube is the only route for air and fluid escape

Outline the arrangement of the auditory ossicles, and explain their role and associated muscles

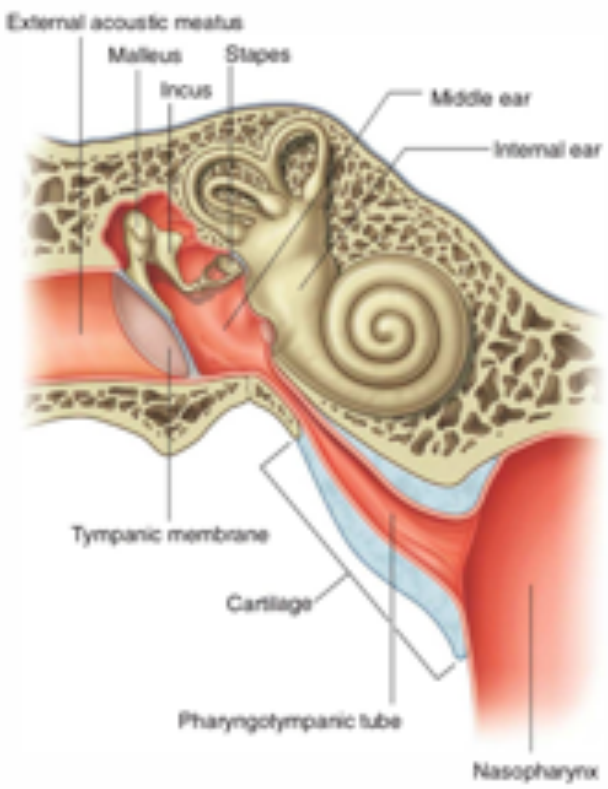
- The bones of the middle ear consist of the malleus, incus, and stapes → mediate hearing and amplify vibrations → ligaments prevent dislocation
- Form an osseous chain across the middle ear → from the tympanic membrane to oval window



- Two muscles associated with the auditory ossicles modulate movement during the transmission of vibrations → tensor tympani and stapedius:
    - Tensor tympani → originates from cartilaginous part of the Eustachian tube and inserts into upper part of handle of malleus → tenses the tympanic membrane, reducing the force of vibrations in response to loud noises
    - Stapedius → originates in the pyramidal eminence and inserts into posterior neck of stapes → contraction pulls the stapes posteriorly and prevents excessive oscillation, usually in response to loud noises → hyperacusis often results from facial nerve palsy (supply to stapes)

Explain the anatomy and role of the Eustachian (auditory) tube

- Eustachian tube → connects the middle ear with the nasopharynx → lined with respiratory mucosa
- Has osseous and cartilaginous parts → 1/3 nearest of the middle ear is osseous, 2/3 closest to nasopharynx is cartilaginous (trumpet-shaped)
- Equalises pressure in the middle ear with atmospheric pressure → pressure needs to be equal on both sides of the tympanic membrane for effective conduction of sound
- It is a natural drainage pathway for middle ear and mastoid secretions → route for URTI spread
- Opening in the nasopharynx is surrounded by pharyngeal tonsil tissue
- Innervation is from the tympanic plexus → primarily tympanic nerve (branch of CN IX)
- Normally in a closed position → isolates middle ear from URT → opened when swallowing by:
    - Tensor veli palatini
    - Levator palatini
    - Salpingopharyngeus



Outline the functional consequences of blockage of the auditory tube, URTI, damage to/absent ossicles, or damage to the joints between the ossicles

- Blockage of the auditory tube prevents drainage of middle ear epithelial secretions and prevents pressure equalisaiton → conductive hearing loss
- Inflammation of or damage to the mobile synovial joints between the ossicles interferes with the conduction of sound → conductive hearing loss
- Acute otitis media (suppurative otitis media) → infection spread from nasopharynx to middle ear → pain and swelling of the tympanic membrane → perforation of membrane can occur and provides relief
- Glue ear (secretory otitis media) → persistent mucoid accumulation → blocked pharyngotympanic tube → causes conductive hearing loss → often results in speech and language developmental problems
- Stimulation of auricular nerve (external acoustic meatus) elicits cough reflex or nausea

TESTING FOR CONDUCTIVE AND SENSORINEURAL HEARING LOSS

- Weber test:
  - Tuning fork (512Hz) placed in the middle of the forehead
  - Patient is asked to report in which ear the sound is heard louder
  - Conductive deafness → defective ear hears the tuning fork louder
  - Sensorineural deafness → normal ear hears the tuning fork louder
- Rhine test:
  - Tuning fork (512Hz) placed against mastoid process until no longer heard
  - The still-vibrating fork is then placed 1-2cm from the auditory canal until no longer heard
  - Conductive deafness → defective ear cannot hear sound when moved to the auditory canal
  - Sensorineural deafness → defective ear reacts normally, but sound diminished a lot earlier (clinician can still hear the sound)

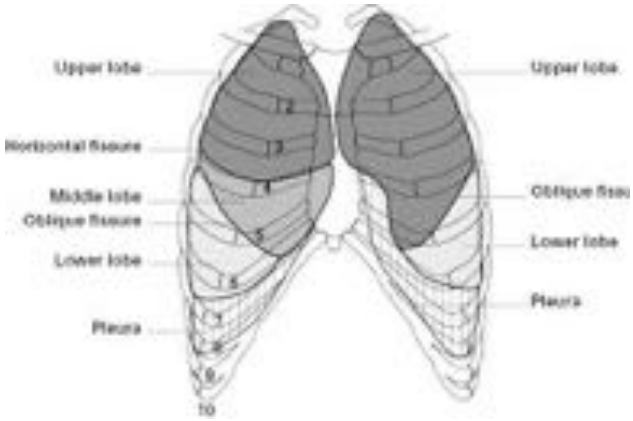
THE LUNGS & BRONCHIAL TREE

Outline the basic embryology of the lung

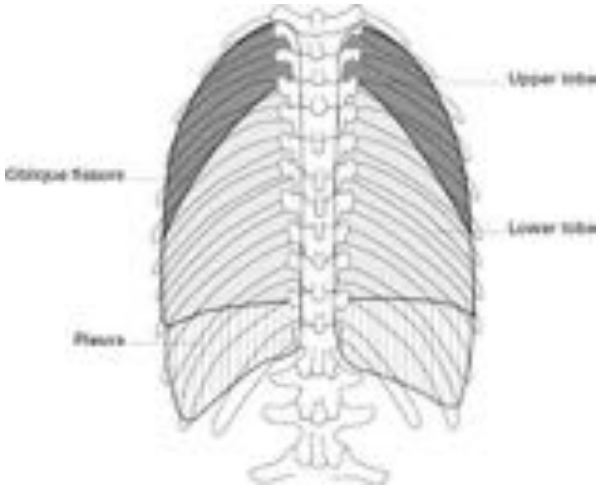
- Week 4 → laryngotracheal groove forms on the floor of the foregut
- Week 5 → left and right lung buds push into the pericardioperitoneal canals (primordia of the pleural cavities)
- Week 6 → descent of heart and lungs into the thorax → pleuroperitoneal foramen closes
- Week 7 → enlargement of liver stops the descent of the heart and lungs
- Month 3-6 → lungs appear glandular
- Week 24 → alveolar type II pneumocytes appear and begin to secrete surfactant
- Month 7 → respiratory bronchioles proliferate and end in alveolar ducts and sacs

Describe the surface markings of the lungs and pleura, and explain the structure and relevance of the costodiaphragmatic recess

- Knowing the lung surface markings is important for basic respiratory examination (auscultation and percussion)
- ANTERIORLY:
    - Apex → 2cm above medial 1/3 of clavicle
    - 2nd CC (angle of Louis) → T4:
        - Lungs are in closest proximity
    - 4th CC → T6:
        - Left lung → deviates to form cardiac notch
        - Right lung → horizontal fissure starts
    - 6th rib → T9:
        - Oblique fissures start
    - 8th rib → T12:
        - Lungs extend this far laterally
    - 10th rib → L1/2:
        - Parietal pleurae extend this far laterally



- POSTERIORLY:
    - T3 → oblique fissure
    - 10th rib → T10:
        - Lungs extend this far
    - 12th rib → T12:
        - Parietal pleurae extend this far
        - Costodiaphragmatic recess lies here



- Parietal pleura forms a deep recess between the thoracic wall and the diaphragm → the costodiaphragmatic recess
- The costodiaphragmatic recess is only filled with lung tissue on deep breathing
- Its function is for expansion room for deep inspiration → fluids may also collect here (e.g. during pleural effusion)

Describe the pleura, its reflections, nerve supply, and the pleural cavity

- Two pleural cavities, one on either side of the mediastinum, surround the lungs → superiorly they extend above rib I into the root of the neck → inferiorly they extend to a level just above the costal margin → the medial wall of each pleural cavity is the mediastinum
- Each pleural cavity is lined by a single later of flat cells (mesothelium) and an associated later of supporting connective tissue → together they form the pleura
- The pleura is divided into two major types:
    - Parietal pleura → associated with the walls of the pleural cavity
    - Visceral pleura → reflects from the medial wall and onto the surface of the lung
- Pleural cavity → the potential space between the two membranes → surface tension holds the two layers together
- The peripheral reflections of parietal pleura mark the extent of the pleural cavities:
    - Superiorly, the pleural cavity projects 3-4cm above the first CC
    - Anteriorly, the pleural cavities approach each other posteriorly to the upper part of the sternum
    - Inferiorly, the costal pleura reflects onto the diaphragm above the costal margin

INNERVATION

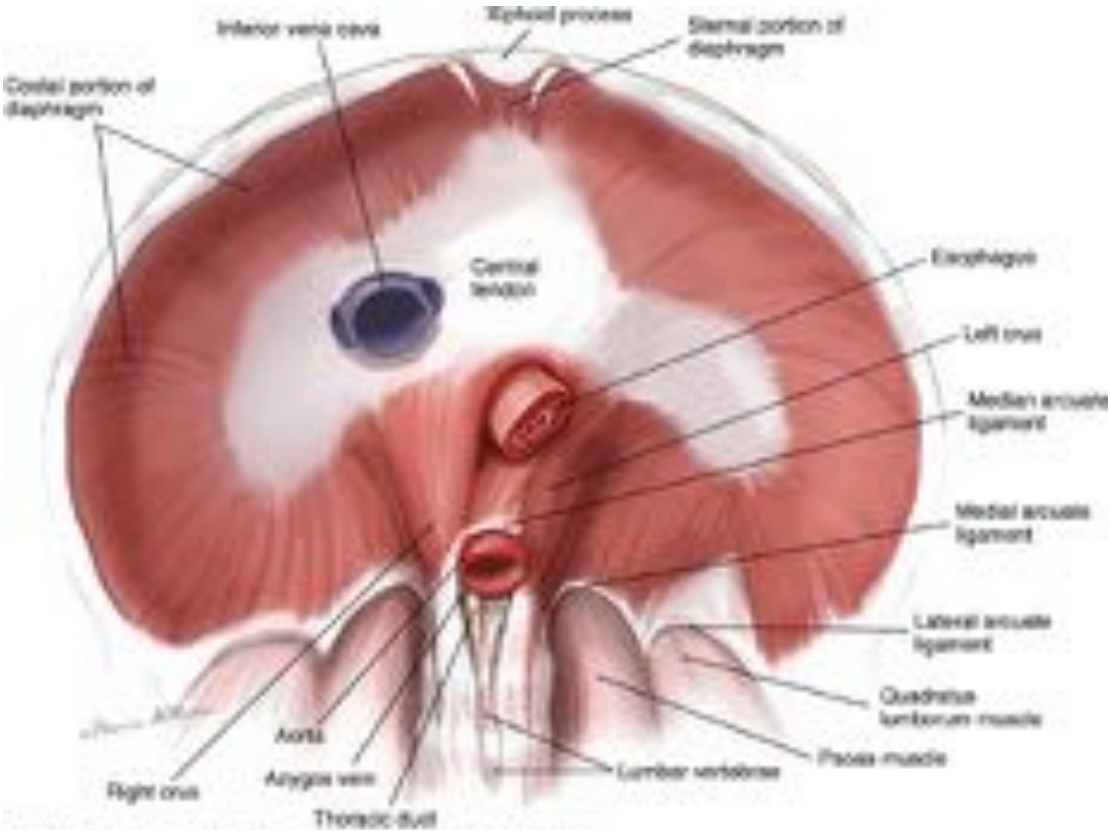
- Parietal pleura → the phrenic nerve (C3-5) for mediastinal and diaphragmatic pleura, and intercostal nerves for costal pleura
- Visceral pleura → visceral afferent nerves that accompany bronchial vessels
- Pain is sensed from parietal pleura, but NOT visceral pleura → visceral pleura is sensitive to stretch only

BREACH OF THE PLEURA

- The lung may collapse if the potential space between the pleura is breached
- Air or fluid entering the pleural cavity may compress the lung and collapse it (e.g. pneumothorax)
- In a tension pneumothorax → air that continues to enter the pleural cavity can't escape:
    - If trachea deviates towards the contralateral side and can form a "one-way valve" that prevents air entering the unaffected lung
    - Compresses superior and inferior vena cava and reduces venous return to the heart → leading to rapid death
- A haemothorax is blood in the pleural cavity → a pleural effusion is fluid in the pleural cavity
- As air/fluid is removed, the lung reinflates
- A chest drain is inserted in the midaxillary line, at the 5th of 6th IC space → to remove air (point upwards) or fluid (point downwards)
    - Needle thoracostomy → emergency decompression of pneumothorax → can be done via 2nd IC space in the midclavicular line
- Layers needed to pass through to insert a chest drain:
    - Skin
    - Superficial fascia (subcutaneous tissue)
    - Deep fascia
    - External intercostal muscles
    - Internal intercostal muscles
    - Innermost intercostal muscles
    - Parietal pleura

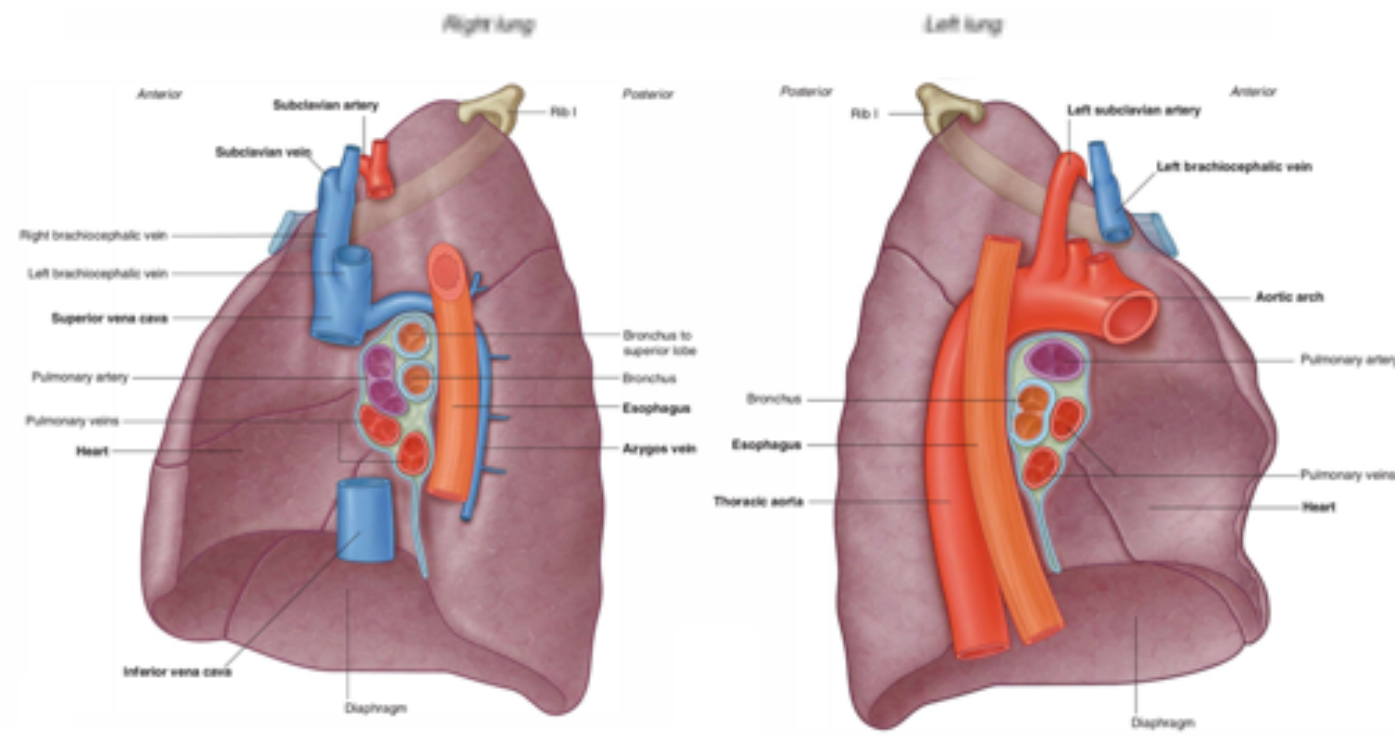
Describe the diaphragm, its attachments, and its innervation

- Diaphragm → a thin musculotendinous structure that fills the inferior thoracic aperture → separates the thoracic cavity from the abdominal cavity
- It is attached peripherally to the:
    - Xiphoid process of the sternum
    - Costal margin of the thoracic wall
    - Ends of ribs XI and XII
    - Ligaments that span the posterior abdominal wall
    - Vertebrae of the lumbar region
- It has a central tendon → trifoliate tendon
- The diaphragm has several apertures to allow the passage of structures:
    - IVC and right phrenic nerve → at T8
    - Oeophageal hiatus → oesophagus and CN X → at T10
    - Aortic hiatus → aorta, azygos vein, and thoracic duct → at T12
- The diaphragm is supplied by the phrenic nerves (C3-5)
- The arterial supply is from vessels that arise above and below the diaphragm:
    - Above → pericardiacophrenic and musculophrenic arteries, and superior phrenic and intercostal arteries
    - Below → inferior phrenic arteries
- Venous drainage is by veins that are generally parallel to the arteries → the veins drain into:
    - Brachiocephalic veins in the neck
    - Azygos system of veins
    - Left suprarenal vein and inferior vena cava



Identify the hila of the lungs and the structures passing through, and outline the lymphatic drainage of the lungs and the relevance of the carina and carinal lymph nodes

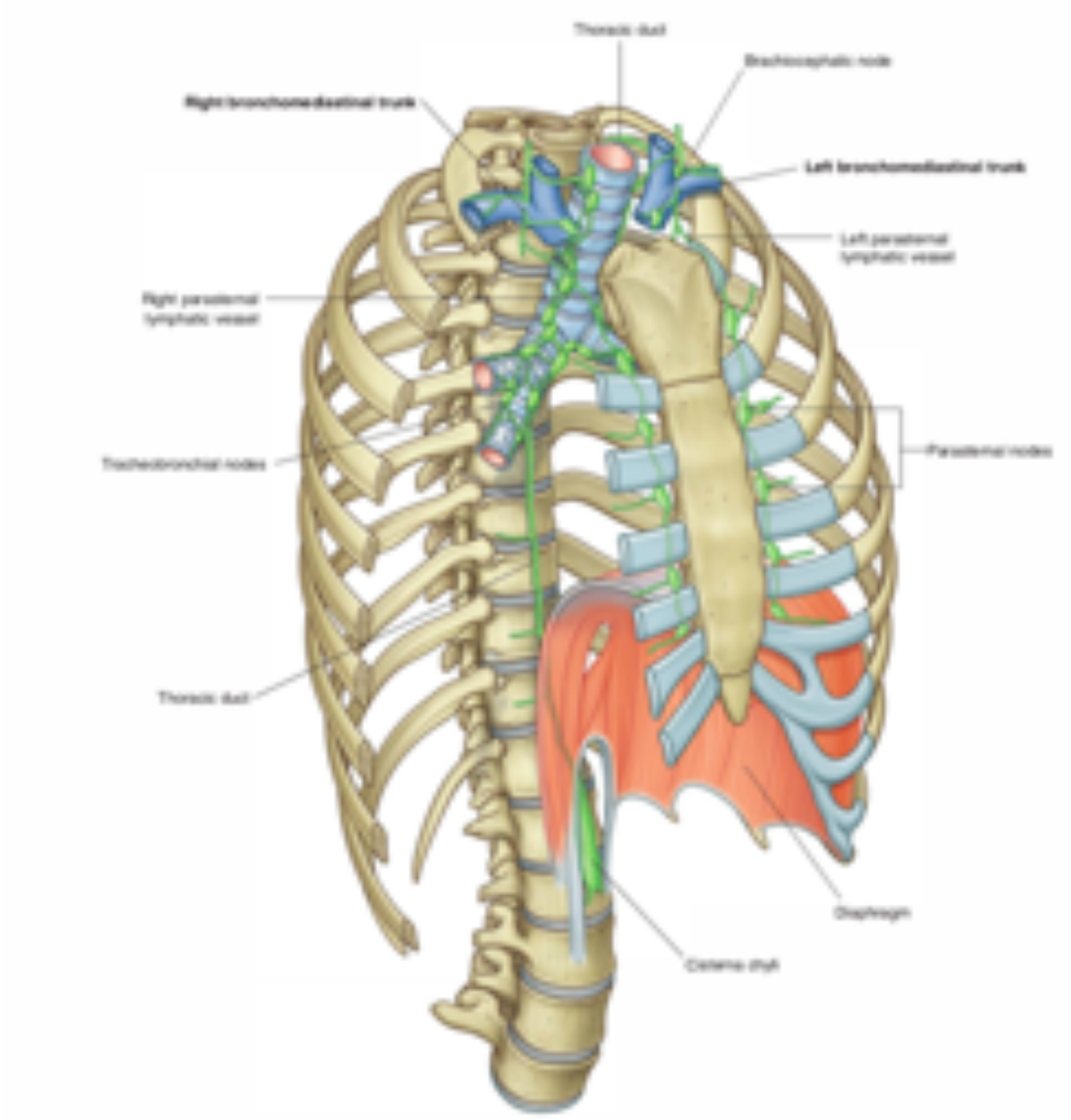
- The root of each lung is a short tubular collection of structures that together attach the lung to structures in the mediastinum → consists of the main bronchi and pulmonary vessels
- The hilum is where structures enter and leave the lung → important nerves are related to it
- A thin fold of pleura projects inferiorly from the root of the lung, and extends from the hilum to the mediastinum → the pulmonary ligament
- Within each root and located in the hilum are:
    - A pulmonary artery → anterior/superior
    - Two pulmonary veins → inferior
    - A main bronchus → two bronchi enter right hilum, one bronchus enters left filum
    - Bronchial arteries (branch from subclavian arteries) and veins
    - Pulmonary plexus of nerves → parasympathetic (CN X) and sympathetic
    - Lymphatics → bronchopulmonary lymph nodes
    - Point of pleural reflection and pulmonary ligaments
- Phrenic nerves (C3-5) → run anteriorly to the hilum to supply the diaphragm → referred pain to the shoulder
- Vagus nerves run posteriorly to the hilum



LYMPHATIC DRAINAGE

- The lymphatics of the lungs and visceral pleura → drain into the bronchopulmonary lymph nodes at the bifurcations of the larger bronchi
- The carina → a ridge of cartilage in the trachea at the point of bifurcation
- Carinal lymph nodes are several large nodes inferior to the tracheal bifurcation → receive afferents from the bronchopulmonary nodes and the heart → send efferents to the tracheobronchial nodes

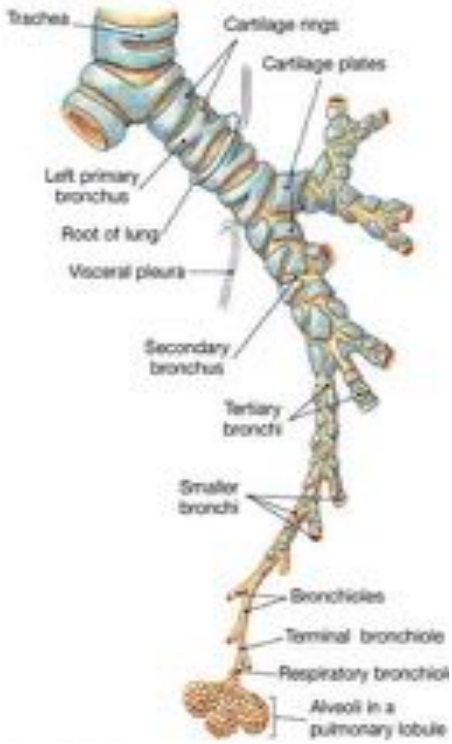
- As the carinal lymph nodes drain the bronchopulmonary nodes of the lungs, they are an important route of metastasis for lung cancer
- The tracheobronchial nodes pass superiorly along the trachea → unite with similar vessels from parasternal nodes and brachiocephalic nodes → form the right and left bronchomediastinal trunks → drain directly into deep veins at the base of the neck, or may drain into the right lymphatic duct or thoracic duct
- The left upper lobe drains into the thoracic duct → the left lower lobe and right lung drain into the right lymphatic duct



Describe the lobes of the lungs, the structure of the bronchial tree, and the bronchopulmonary segmentation of the lungs

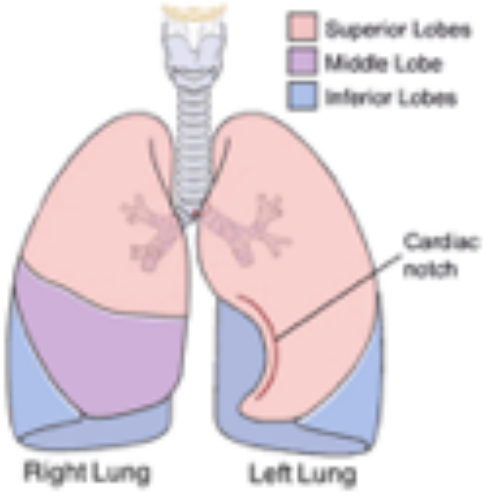
TRACHEA AND BRONCHI

- The trachea:
  - Situated anterior to the oesophagus and can be palpated above the suprasternal notch
  - Protected by incomplete cartilage rings
  - Has the trachealis muscle posteriorly → constricts during coughing in order to expel air with more force
  - A midline structure → relevant to x-ray and clinical examination
  - Starts at cricoid cartilage → C6
  - Bifurcates at T4 (sternal angle) in middle mediastinum → into right and left main bronchi
  - Enters lung hilum at T5/6
  - Innervation:
    - Sensory → CN X
    - Parasympathetic → CN X
    - Sympathetic → sympathetic trunk
- The left main bronchus passes under the arch of the aorta and is longer and narrower than the right → the right is more vertical → the right lung is therefore more vulnerable to aspiration pneumonia, as foreign objects are more likely to end up here
- The bronchial tree has many divisions:
  - Conducting zones → 0-16 divisions:
    - Main bronchi → left and right
    - Lobar bronchi
    - Segmental bronchi
    - Intrasegmental bronchi
    - Terminal bronchioles
  - Respiratory zones → 17-23 divisions:
    - Respiratory bronchioles
    - Alveolar ducts
    - Alveolar sacs



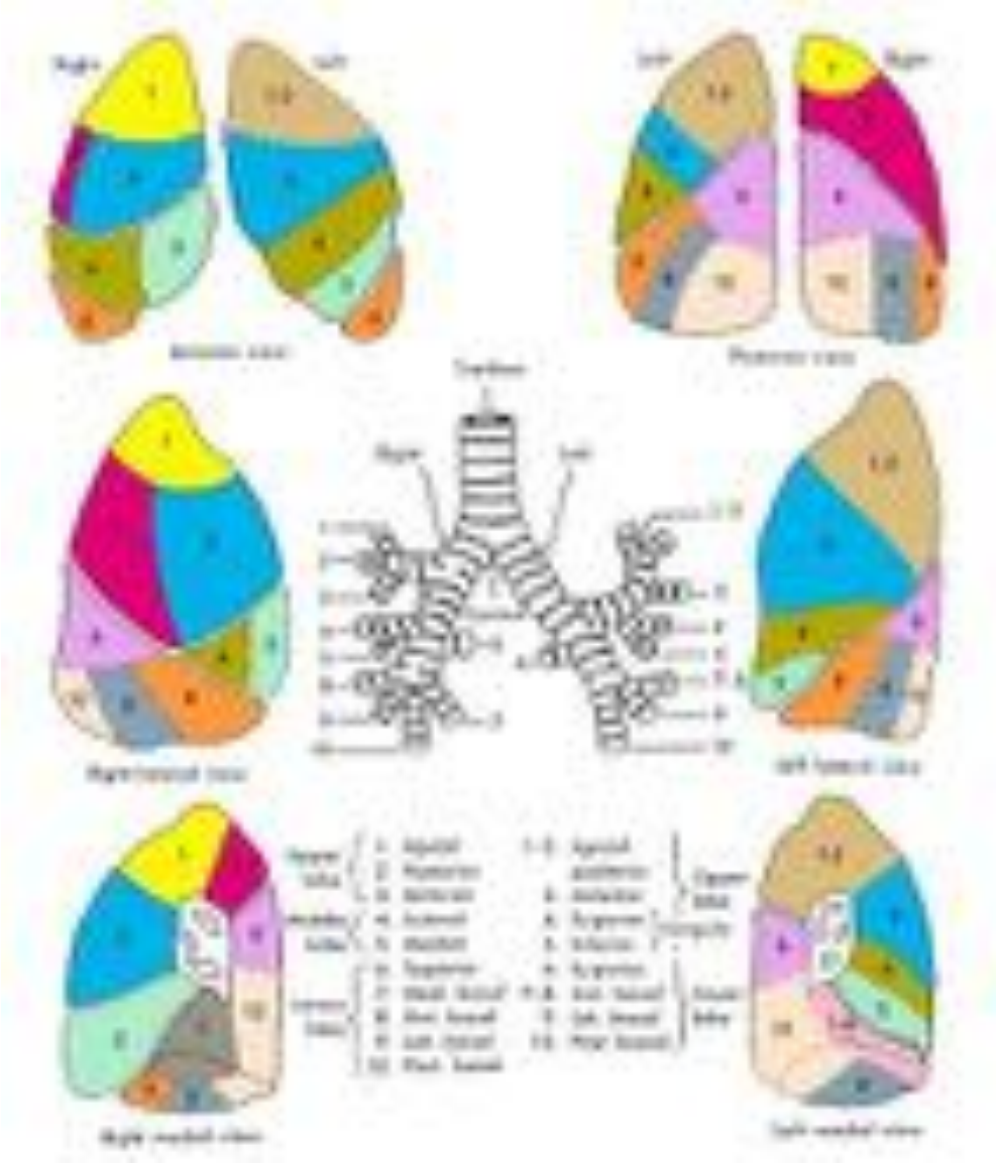
LOBES OF THE LUNGS

- The right lung has three lobes and two fissures → normally the lobes are freely movable because they are separated by invaginations of the visceral pleura → these invaginations form the fissures:
  - The oblique fissure separates the inferior lobe from the superior and middle lobes
  - The horizontal fissure separates the superior lobe from the middle lobe
- The left lung is smaller than the right lung and has two lobes separated by an oblique fissure → superior and inferior lobes



BRONCHOPULMONARY SEGMENTS

- Bronchopulmonary segments → an area of lung supplied by a segmental bronchus and its accompanying pulmonary artery branch → tributaries of the pulmonary vein tend to pass intersegmentally
- Each bronchopulmonary segment is shaped like an irregular cone → with the apex at the origin of the segmental bronchus and the base projected peripherally onto the surface of the lung
- A bronchopulmonary segment is the smallest functionally independent region of a lung → it is the smallest area of the lung that can be isolated and removed without affecting adjacent regions
- There are ten bronchopulmonary segments in each lung → some of them fuse in the left lung

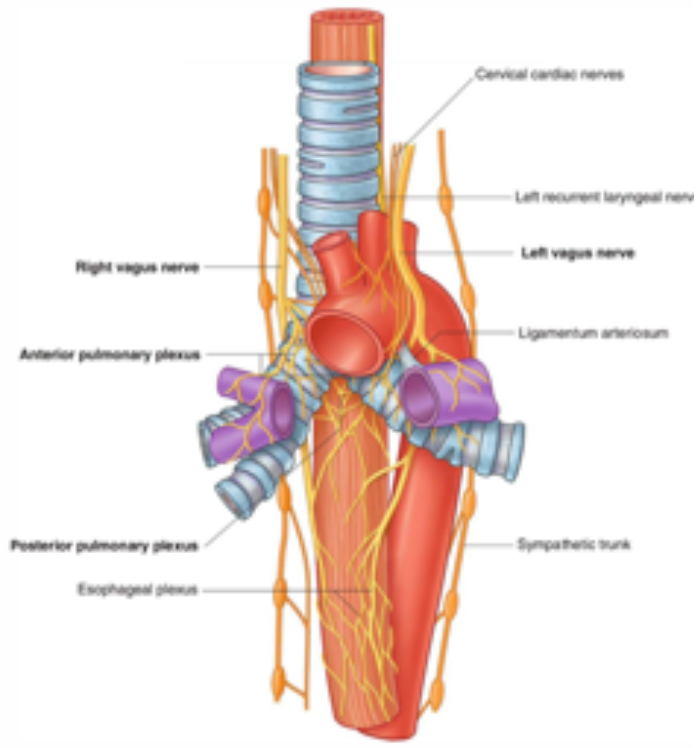


- Gravity affects drainage from the segments → e.g. to superior and posterior basal segments in the supine patient

Describe the basic organisation of the nervous system in relation to nerve supply of the respiratory system

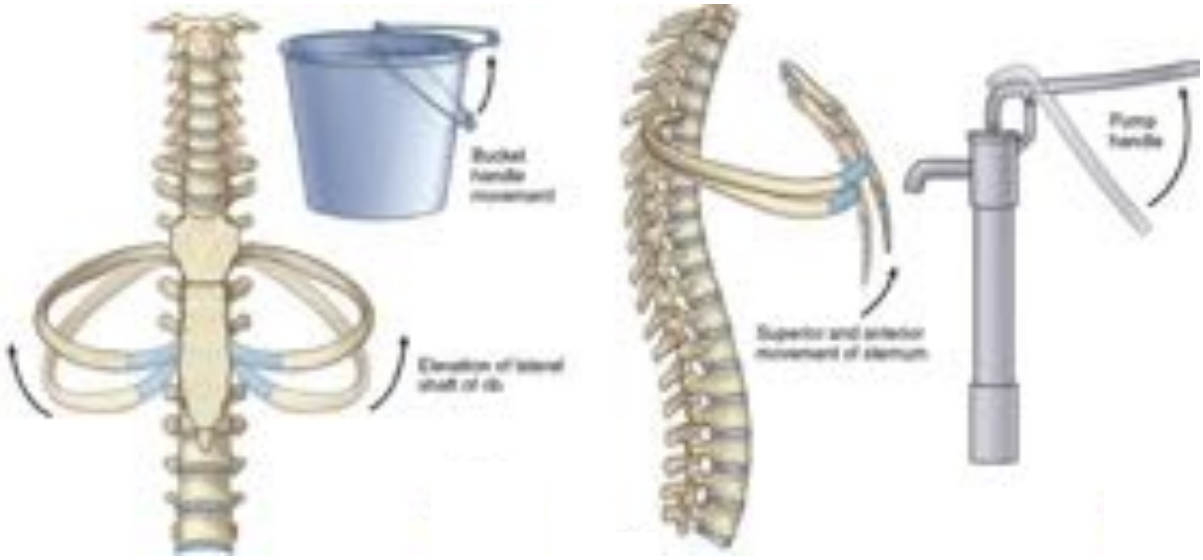
- Structures of the lung, and the visceral pleura, are supplied by visceral afferents and efferents distributed through the anterior pulmonary plexus and posterior pulmonary plexus

- The interconnected pulmonary plexuses lie anteriorly and posteriorly to the tracheal bifurcation and main bronchi → the anterior plexus is much smaller than the posterior plexus
- The pulmonary plexuses originate from the sympathetic trunks and vagus nerves → visceral efferents from the vagus nerve constrict the bronchioles → efferents from the sympathetic trunk dilate the bronchioles
- Branches of the plexuses are distributed from the airway and vessels



Outline the functional anatomy and clinical relevance of the thoracic structure with respect to respiration

- One of the principal functions of the thoracic wall and the diaphragm is to alter the volume of the thorax → moves air in and out of the lungs
- During breathing → dimensions of the thorax change in the vertical, lateral, and anteroposterior directions
- Elevation and depression of the diaphragm significantly alters the vertical dimensions of the thorax → depression results when the muscle fibres of the diaphragm contract, and elevation occurs when they relax
- Changes in the anteroposterior and lateral dimension result from elevation and depression of the ribs → when the ribs are elevated, the anterior ends of the ribs move the sternum up and forwards → this "pump handle" movement changes the dimensions of the thorax in the anteroposterior direction
- When the shafts of the ribs are elevated, the middles of the shafts move laterally → this "bucket handle" movement increases the lateral dimensions of the thorax
- Any muscles attaching to the ribs can potential move one rib relative to another → therefore acting as accessory respiratory muscles



SPECTRUM OF RESPIRATORY PATHOGENS

Describe the basic mechanism of infection of the respiratory tract

- URT is continually exposed to pathogens → while LRT is essentially sterile → the RT in general is a good route for transmission of infection, but it can take up to 2hrs for pathogens to settle
- The RT generally gets bacterial or viral infections → fungal infections tend to be limited to immunocompromised patients

Name some examples of physical host defences in the respiratory tract

- Mucociliary escalator
- Alveolar macrophages
- Coughing
- Surfactant proteins → SP-A and SP-D
- Lysozyme, lactoferrin, secretory leukoproteinase inhibitor

Describe some of the common or clinically important infective organisms of the respiratory tract

- *Streptococcus pyogenes* → group A strep → Gram +ve → non-motile, non-sporeforming coccus → occurs in chains or pairs → most frequents pathogens of humans → 5-15% of people are carriers → causes pharyngitis
- Group A strep → have an M protein component used to inhibit phagocytosis → also has haemolysins O and S, as well as DNAse, streptokinase, and pyrogenic toxins → can cause toxic shock and tonsillar abscesses
- Scarlet fever → caused by group A strep → rash over trunk and abdomen, then spreads to entire body → presents as pyrexia, lymphadenopathy, aches, and nausea
- *Corynebacterium diphtheria* → causes diphtheria → Gram +ve, anaerobic, non-motile, rod-shaped bacteria → irregular, club-shaped or V-shaped arrangements in normal growth → they undergo snapping movements just after cell division giving characteristic forms resembling Chinese letters → damage is caused by exotoxin A or B → severe pharyngitis and pseudomembrane that can cover the trachea → death can occur from multisystem toxaemia and myocarditis
- *Legionella pneumophilia* → causes Legionnaire's disease → facultative intracellular parasite that causes aggressive damage to lungs → necrotising pneumonia of alveoli and terminal bronchioles → infect macrophages and form endocytic vesicles before eventually killing the macrophages and being released → cannot be stained or grown using normal techniques → found in water and transmitted in humidified aerosol (not person-to-person) → most outbreaks occur in buildings with air conditioning cooling towers
- Symptoms of Legionnaire's disease include myalgia, fever, pleuritic chest pain, vomiting, and diarrhoea → mortality rate of 15% but up to 50% in hospital outbreaks → also produces β-lactamase
- *Pneumocystis carinii* (fungus) → generally limited to immunocompromised patients → causes lethal pneumonia → it has never been grown in culture, all information comes from clinical observations → resembles protozoa in shape, and contains cholesterol in cell walls rather than ergosterol → antibodies found in most humans by age 4 → low virulence in healthy hosts
- Symptoms of pneumocystis include dyspnoea, cough, alveolar infiltrates, cause sloughing of cells and fluid build-up → death is from progressive asphyxiation

- *Aspergillus* (fungus) → generally limited to immunocompromised patients → conidia small enough to reach the alveoli → after attachment extracellular proteases and phospholipases produced → colonisation leads to invasion of pulmonary tissues and penetration of blood vessels by septate hyphae → mortality for invasive aspergillosis is 100%

Review antibiotic prescribing guidelines for respiratory tract infections

- NICE guidelines → CG69 → most people will develop an acute RTI each year, presenting mostly in primary care → used to be prescribed ABs as presumed it was bacterial → now should not prescribe ABs
- In primary care → all previously stated infections should be offered a clinical assessment → this should include a history and examination to identify relevant clinical signs → a no AB prescribing strategy or delayed AB prescribing strategy should be used
- Depending on clinical assessment of severity → patients may be prescribed ABs:
    - Bilateral acute otitis media in children younger than 2yrs
    - Acute otitis media in children with otorrhoea (ear discharge)
    - Acute sore throat/acute pharyngitis/acute tonsillitis when 3 or more Centor criteria are present
- Centor criteria:
    - Presence of tonsillar exudate
    - Tender anterior cervical lymphadenopathy or lymphadenitis
    - History of fever → over 38 degrees
    - Absence of cough
- ABs may also be given if the patient is systemically very unwell → has pre-existing comorbidities → has symptoms and signs suggestive or serious illness and/or complications (pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications) → or if patient is older than 65yrs with acute cough and 2 or more of the following criteria → or if patient is older than 80yrs with acute cough and 1 or more of the following criteria:
    - Hospitalisation in previous year
    - T1 or T2 DM
    - History of congestive heart failure
    - Current used of oral glucocorticoids

Define pneumonia

- Pneumonia → inflammation of the tissue of either one or both of the lungs → most often bacterial or viral, but may also be chemical or fungal
- The most common cause in adults is *Strep. pneumoniae* → also caused by *Haemophilus influenza* and *Moraxella catarrhalis*
- Most common viral cause is RSV and sometimes influenza A or B → viruses are most common cause of pneumonia in young children
- Factors predisposing to pneumonia:
    - Anatomical defects → spinal or lung
    - Hyposplenia malignancy → bronchial carcinoma, Hodgkin's disease
    - Immunosuppression → congenital, iatrogenic, acquired (AIDS)
    - Alcohol abuse
    - Viral infections and 2^{o} bacterial infection
    - Advanced age
    - Chronic lung disease → emphysema
    - Chronic renal disease

- Diabetes
- Aspiration
- Nutritional status

- Bacterial pneumonia is a serious LRTI, particularly of lung parenchyma → can be community acquired (*S. pneumoniae*) or nosocomial (*S. aureus* or *P. aeruginosa*)
- Signs and symptoms of bacterial pneumonia include coughing (dry or productive), difficult breathing (rapid & shallow), tachycardia, fever, general malaise, sweating & shivering, loss of appetite, chest pain
- There are several factors that aid bacterial colonisation in hospitals → artificial ventilation → supine position and reduction in stomach acid, allowing migration of organisms from gut to oesophagus → unwashed hands of healthcare workers
- Diagnosis of pneumonia involves history, examination, chest X-ray, and sputum sample → as well as CURB65 → scored 0 (best) – 5 (worst):
    - **C**onfusion → altered mental state
    - **U**raemia → urea >7mmol/L
    - **R**espiratory rate → >30 breaths/min
    - **B**lood pressure → <90/60mmHg
    - **65**yrs or older

Outline the different causative agents of pneumonia

- Ventilator-associated pneumonia:
    - *Pseudomonas aeruginosa*
    - *Acinetobacter spp*
    - *Stenotrophomonas maltophilia*
    - *Haemophilus spp*
    - *Staphylococcus aureus* → esp. MRSA
    - *Escherichia coli/Klebsiella pneumoniae/Enterobacter spp*
    - *Streptococcus spp* → esp. *Strep. pneumoniae*
    - Fungi (*Candida spp, Aspergillus*)
- Aspiration pneumonia:
    - Gram –ve organisms (as above)
    - *Haemophilus spp*
    - Anaerobes
    - Mouth-related *Strep*
    - *Strep. pneumoniae*
- Pneumonia in the immunocompromised:
    - *Pseudomonas aeruginosa*
    - *Staphylococcus aureus* → esp. MRSA
    - *E. coli/Kleb. pneumoniae/Enterobacter spp*
    - *Candida* and *Aspergillus*
    - *Pneumocystis carinii*
- Pneumococcal disease is the term used to describe infections caused by *Strep. pneumoniae* → it can cause invasive pneumococcal disease (IPD) → IPD includes septicaemia, pneumonia, and meningitis → major cause of morbidity and mortality → esp. affects the young, elderly, and immunocompromised
- Non-invasive *Step. Pneumoniae* is more common than IPD → it spreads through RT including middle ear, sinuses, and bronchi
- *Strep. pneumoniae* → Gram +ve lancet-shaped cocci with a slightly pointed outer curvature → usually seen as pairs of cocci (diplococci) → but may also occur singly and in short chains

PATHOLOGY OF INFECTION

Define the terms pathogen, virulence, and infection, and describe the types of infection

- Pathogen → A bacterium, virus, or other microorganism that causes disease → rarely found in the absence of disease
- Virulence → a harmful quality possessed by microorganisms that can cause disease → disease-producing potential → related to:
    - Number of organisms required to cause disease
    - Capability of the organism to overcome host barriers
    - Factors causing damage to the barriers
    - Location of the organisms → always found on our body, but in the wrong environment they can become harmful
    - Status of the immune defences of the patient → high virulence will affect healthy, while low virulence will only affect a susceptible population
- Virulence factors → toxins (endotoxins and exotoxins), adhesion factors, evasive factors, and invasive factors
- Infection → the process of infection or the state of being infected → colonisation with a pathogenic organism producing harm
- Barriers to infection:
    - Non-specific → mechanical and secretory
    - Acute inflammation
    - Immune response → inadequate (immunodeficiency), excessive (hypersensitivity), or inappropriate (autoimmune)

Describe how microbes gain access to the body and how they do damage

- Routes of infection → inhalation, ingestion, sexual transmission, bites or injection → leads to infection of the RS, GI, genitourinary systems or skin
- Skin infections tend to get through at sires of damage to the skin → cuts, punctures, or burns
- Systems with mucosal membranes are penetrable only to more virulent organisms with the capacity to break the barrier → unless there is physical damage
- Breaching barriers:
    - Skin → penetration via cuts, burns, insect bites, infection
    - Respiratory system → lung defence mechanisms can be overcome (smoking, CF, etc.) and allow entry of bacteria causing pneumonia, TB, common cold, etc.
    - GI tract → ingestion of contaminated food/water (faecal-oral route) → but need to be able to survive at low pH of the stomach
    - Urogenital tract → STIs can colonise the UG tract by attaching to the cells during intimate contact, and therefore avoid flushing → affects women more than men
- The majority of damage caused by microbes is by killing cells or affecting the cell's function by:
    - Entering or binding to cells
    - Releasing endotoxins (lipopolysaccharide molecules in cell wall of Gram –ve bacteria) or exotoxins (proteins secreted by Gram +ve bacteria)
    - Releasing enzymes to break down tissue components or damage blood vessels
    - Inducing host immune response
    - Inducing inflammation → leads to tissue damage

PATHOLOGY OF INFECTION

Describe how microbes fool the body's defence mechanisms and how they are transmitted

- Microbes can hide from the immune system by:
  - Rapidly entering cells
  - Latency of viruses
  - Cloaking themselves in host proteins
  - Having a tough capsule
  - Dividing in the lumen or remaining in epidermis
- Microbes can also alter their antigens (variation) or inhibit recognition by affecting the adaptive immune response
- Some microbes have various methods to avoid them being killed by neutrophils and macrophages (innate immune response)
- Source:
  - Horizontal/vertical transmission
  - Fomites (objects likely to carry infection)
  - Zoonoses (animal transmission)
  - Community-acquired/nosocomial
- Movement within the body:
  - Locally proliferating
  - Breaching the epithelial barrier
  - Gaining access to the blood and lymph
- Person to person:
  - Skin shedding
  - Coughing and sneezing
  - Urination and defecation
  - Vertical transmission from mother to foetus

Describe the defence system employed by the lungs

Location	Host defence mechanism
Upper airways	
Nasopharynx	Nasal hair Turbinates Mucociliary apparatus Immunoglobulin A (IgA) secretion
Oropharynx	Saliva Sloughing of epithelial cells Local complement production Interference from resident flora
Conducting airways	
Trachea, bronchi	Cough, epiglottic reflexes Sharp-angled branching of airways Mucociliary apparatus Immunoglobulin production (IgG, IgM, IgA)
Lower respiratory tract	
Terminal airways, alveoli	Alveolar lining fluid (surfactant, Ig, complement, fibronectin) Cytokines (interleukin 1, tumour necrosis factor) Alveolar macrophages Polymorphonuclear leucocytes Cell-mediated immunity

- The respiratory tract is lined with ciliated pseudostratified columnar epithelial cells → appear pseudostratified as a result of basal neuroendocrine cells and stem cells
- Goblet cells are also found in the lining → these cells produce mucous, while serous cells secrete serous fluid
- The lungs are vulnerable to infection due to constant exposure to the external environment → constant inhalation of nasopharyngeal flora
- Organisms breathed in are trapped in mucous produced by goblet cells → removed via the mucociliary escalator → they can also be phagocytosed by alveolar macrophages and neutrophils recruited by macrophage factors
- Serum complement → such as C3b enhance phagocytosis by opsonising the organisms
- Some organisms → including those ingested by phagocytes → may reach the draining lymph nodes to initiate immune responses
- Upper RT → secreted IgA to block attachment of organisms to epithelium
- Lower RT → serum antibodies (IgM and IgG) present in the alveolar lining fluid → activate complement

Describe the aetiology, types, pathogenic features, and outcomes of pneumonia

- Pneumonia → inflammatory reaction in the alveoli and interstitium of the lung caused by an infectious agent → it is characterised by inflammatory exudate in the alveolar space that consolidates and leads to further inflammation of the alveolar septa
- Can be caused by bacteria, viruses, mycoplasma, fungi, and inorganic agents (inhaled dust or gases) → infection can also occur via aspiration of secretions/GI contents, or contamination from systemic circulation
- Pneumonia is classified by:
    - Anatomical site
    - Clinical setting in which the disease occurred
    - Microbiological → causative organism

ANATOMICAL SITE

- Lobar pneumonia → alveoli-alveoli → organisms access alveoli and rapidly spread via alveolar pores → occurs in alcoholics and those already ill
- Bronchopneumonia → bronchi-alveoli → organisms colonise bronchi and spread to alveoli → affected areas consolidate locally → lobules and eventually whole lobes → affects young, elderly, and immobile
- Distinction between the types can be blurred → similarities in confluent bronchopneumonia

CLINICAL SETTING

- Community acquired:
    - Typical:
        - *S. pneumoniae* → most common → 90% of lobar → Gram +ve diplococcus
        - *H. influenza* → COPD → Gram –ve coccobacillus
        - *Moraxella catarrhalis* → elderly/COPD → Gram –ve diplococcus
    - Atypical → often follows viral URTI → presents with fever, chills, chest pain (pleuritic), and productive cough → increased susceptibility with an underlying disease, immunoglobulin defect, or decreased splenic function → leads to patchy inflammation of interstitium → there is no exudate in alveoli, so no consolidation or sputum → only slightly raised WBC → mostly caused by *Mycoplasma pneumoniae* or viruses like influenza

- Hospital acquired → found in susceptible hospital patients who have severe underlying disease, immunosuppressed, on prolonged antibiotics or ventilation → most often caused by Gram –ve rod and *S. aureus*
- Immunocompromised → opportunistic infections are the biggest cause → bacteria, viruses (CMV), and fungi (*Pneumocystis jirovecii*)
- Aspiration pneumonia → caused by aspiration of gastric contents due to abnormal gag/swallow reflex (e.g. in stroke) → due to both bacteria and irritation by gastric contents → often necrotising leading to abscess formation and frequent death → caused by *S. pneumoniae, S. aureus, H. influenza,* and *Pseudomonas aeruginosa*

NECROTISING PNEUMONIA

- Lung abscess → tissue destruction as a result of acute inflammation with extensive infiltration of neutrophils/infection with pyogenic bacteria → infiltration of leucocytes resulting in pus → fibrous tissue surrounds → size = mms to 6cms
- Necrotising is the same but smaller and often develops into a lung abscess → caused by aspiration of infected material or gastric contents → more commonly right sided due to vertical airway
- Complications → ruptures into airways and pleural cavity or ruptures pulmonary vasculature → leads to embolus to brain and meningitis or brain abscess
- Anaerobic pathogens are often implicated → from oral cavity

CHRONIC PNEUMONIA

- Localised lesion → granulomatous inflammation
- Patients are often immunocompromised
- Caused by *Mycobacterium tuberculosis* → accounts for 6% of deaths worldwide → most common cause of death from a single infectious agent

SYMPTOMS, TREATMENT AND OUTCOMES OF ACUTE BACTERIAL PNEUMONIA

- Symptoms:
    - Fever, chills, dyspnoea
    - Cough with purulent sputum
    - Crackles on auscultation
    - Consolidation
- Diagnosis → sputum (Gram staining, culture), CXR, FBC
- Treatment → antibiotic → empirically, but can be changed on results of culture
- Outcomes:
    - Resolution → destruction of CT/vasculature is minimal/absent → neutrophils destroy organism, exudate liquefied by neutrophil enzymes (fibrin breakdown/phagocytosis of dead cells) → this is coughed up, reabsorbed by capillaries, or drained in lymph → epithelial stem cell proliferation and differentiation into type I and II pneumocytes
    - Organisation → scar tissue/fibrosis from destruction of connective tissue
    - Abscess formation
    - Empyema
    - Bacteraemia → meningitis/arthritis/infective endocarditis
    - Death

GAS EXCHANGE

Describe the functions of the conducting and respiratory zones and relate these to their anatomical and histological features

- Conducting zones → filters, warms, and moistens air → then conducts it to the lungs → also has a role in defence and phonation → 1st to 15th divisions → composed of:
    - Nose
    - Pharynx
    - Larynx
    - Trachea
    - Bronchi
    - Bronchioles
    - Terminal bronchioles
- Respiratory zone → site of gas exchange (O_2 and CO_2) → assumes pulmonary ventilation matches blood perfusion → 16th to 23rd divisions → composed of respiratory bronchioles and alveolar ducts (10%) and the alveoli themselves (90%)

Define the terms 'anatomical' and 'physiological' dead space

- Dead space → volume of air not participating in gas exchange → divided into anatomical and physiological
- Anatomical dead space → morphological and represents the volume of the conducting airways → approximately 150ml → air flushed out with each new breath → determined by anatomy, subject to size/posture, and the size of the inspiration
- Physiological dead space → functional and represents the total volume of gas in each breath that does not participate in gas exchange → includes anatomical dead space and unperfused/diseased alveoli → in health the volume is similar to anatomical dead space, but increases in disease
- Physiological dead space can be thought of as the volume that does not eliminate CO_2 → in health approx. 20-30% of minute ventilation is wasted

Explain the principles underlying gas flow and exchange across the alveolar-capillary walls

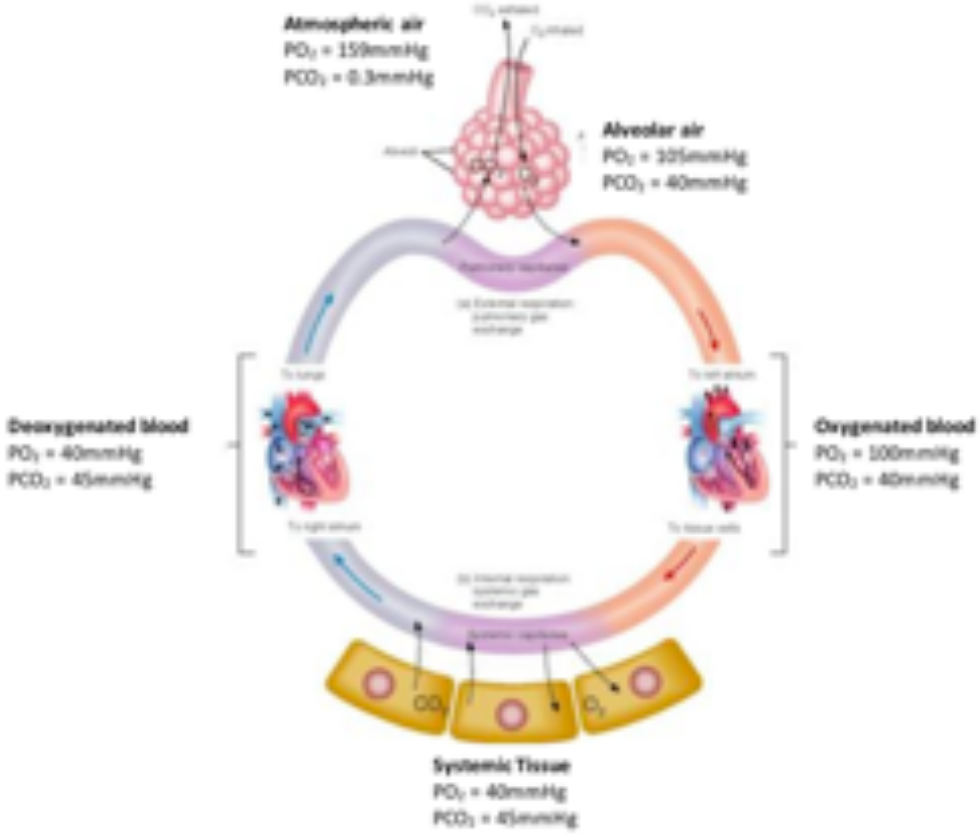
- Alveoli are the site for gas exchange → there are approx. 300 million, with a surface area of ~70m^2 → they are 1 cell thick, with a diameter of ~0.2-0.5mm
- Spongy mass budding from walls of respiratory bronchioles → containing alveolar ducts and sacs
- Ideal site for diffusion/exchange → short diffusion distance → highly perfused and highly ventilated → allows rapid equilibration (~0.25s)
- Diffusion capacity (D_L) → measures the rate of gas transfer across the air-blood barrier → single breath method:
    - Patient inhales test gas (CO) and holds breath for 10 seconds
    - Rate of disappearance from alveolar air is measure by comparing expired air with inspired air → infrared analyser
    - Normal value is ~25ml/min/mmHg

Describe the partial pressure gradients for O_2 and CO_2 exchange, and state their normal values

- In a mixture of gases, each gas has a partial pressure, which is the hypothetical pressure of that gas if it alone occupied the volume of mixture at the same temperature → the total pressure of an ideal gas mixture is the sum of the partial pressures of each individual gas in the mixture
- Henry's law → the amount of gas dissolved in the water (i.e. partial pressure) is determined by the temperature, its solubility in water, and its partial pressure in the air

GAS EXCHANGE

- In relation to respiratory physiology → the greater the partial pressure gradient, the more gas is loaded into the blood → e.g. the blood arriving at the alveoli has a higher PCO_2 than air, so blood unloads CO_2 into the air
- NB: Diffusion of one gas does not influence the diffusion of another
- The P_aO_2 is mainly determined by the P_AO_2 and the state of the air-blood barrier (air-liquid medium)
- Equal amounts of O_2 and CO_2 are exchanged despite CO_2 having a smaller partial pressure gradient → this is because CO_2 is ~20x more soluble than O_2, so can diffuse more rapidly despite it being 1.2x heavier
- Fick's law → describes influences on the rate of transfer of gases:
    - Rate is proportional to the surface area of the tissue and the difference in PP gradients
    - Rate is inversely proportional to the tissue thickness → thinner wall = faster rate
    - Rate depends on the diffusion constant (D) → which depends on the physical characteristics of the gas (solubility/molecular weight)
    - $Diffusion\ rate = \frac{alveolar\ surface\ area}{air-blood\ barrier\ thickness} \times pressure\ gradient \times D$
- PP gradient → increased metabolism or 100% O_2 increases rate of diffusion → altitude decreases rate of diffusion → 100% O_2 increases the gradient so speeds up delivery of O_2, helping to relieve breathing mechanisms
- Gas physical properties → heavier gases and less soluble gases decrease rate of diffusion → e.g. CO_2 is more soluble than O_2 so diffuses faster → therefore P_aCO_2 levels change before P_aO_2
- Alveolar-capillary membrane → can be affected by infection, fibrosis, etc. → the thicker the wall, the slower the diffusion
- Reduced gas exchange area → smaller surface area results in a slower diffusion rate → such as emphysema and pneumonia



GAS EXCHANGE

Explain the clinical relevance of ventilation-perfusion matching

- Gas exchange needs good ventilation (V) and perfusion (Q) of alveolar capillaries → V=5L/min and Q=6L/min
- V/Q matching in each alveolus maximises exchange → ranges from apex to base with the whole lung having a V/Q ratio of approx. -0.8 to 1
- Coupling diverts air and blood flow away from areas where one is diminished to maintain normal blood gas limits → reduced perfusion leads to reduced ventilation and vice versa → increased ventilation leads to increased perfusion and vice versa
- V/Q mismatch is the most common cause for a fall in PO_2 in respiratory diseases → in increases the area that is not used for gas exchange (physiological dead space) → in mismatch P_aO_2 falls so the P_A-P_aO_2 gradient increases, leading to an increase in breathing rate
- V/Q mismatch can be caused by a range of pathologies → common in emphysema, pneumonia, asthma, COPD:
    - Alveolar structural problems
    - Lack of inspired oxygen
    - Respiratory failure
    - Lack of circulation/blood flow
- Causes of Type I respiratory failure → decreased P_aO_2 only → might be due to:
    - Hypoventilation → low O_2 in inspired air (altitude) → V/Q mismatch
    - Decreased mixed venous O_2 content → increased metabolic rate (fever) → decreased CO (cardiac failure) → decreased arterial O_2 content
    - Anatomical intrapulmonary shunt → congenital cardiac defects (Tetralogy of Fallot) → section of lung is unventilated and blood bypasses the lungs
- Poiseulle's law → the principle of flow, pressure and resistance that governs air and blood flow → resistance to flow is inversely proportional to the radius → the smaller the radius the greater the resistance → therefore bronchioles provide the most resistance to airflow (V) and arterioles can readily increase or decrease local blood flow rates (Q)
- Altering respiratory bronchiolar and pulmonary arteriolar radius changes resistance and hence flow → bronchioles dilate in response to raised P_aCO_2 (hypercapnia) to improve airflow → pulmonary arterioles constrict in response to low P_aO_2 (hypoxia) to reduce flow and redirect blood to better perfused areas → opposite to systemic circulation response → there are continuous local changes throughout the lungs

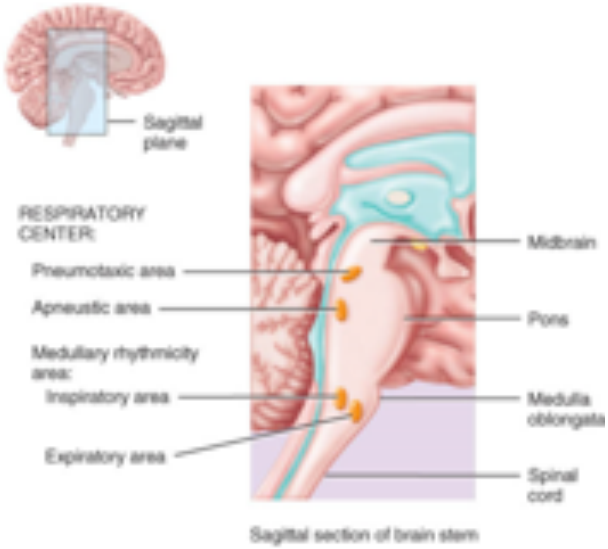
Additional information

- Arterial hypoxaemia → arterial P_aO_2 is below normal range → Type I respiratory failure when <6kPa
- Hypoxia → insufficient O_2 to carry out normal metabolic functions
- Hypercapnia → increase in P_aCO_2 above normal range
- Hypocapnia → abnormally low P_aCO_2

CONTROL OF BREATHING

Describe the location and role of the neural control centres in initiating and controlling ventilation

- 3 groups of neurons send impulses to the respiratory muscles:
  - Medullary rhythmicity centre → inspiratory (DRG) and expiratory (VRG) groups:
    - Dorsal Respiratory Group (DRG):
      - Input from the CN IX and CN X that terminate in the nucleus tractus solitarius
      - Input from the apneustic centre
      - Output is to the inspiratory muscles
    - Ventral Respiratory Group (VRG):
      - Inactive in normal, quiet breathing as expiration is passive
      - Output is to expiratory muscles
      - Activity increases with exercise, dyspnoea, and lung disease
  - Pneumotaxic centre → in pons → helps smooth the inspiratory and expiratory cycle
  - Apneustic centre → in pons → modulates aspects of the breathing cycle (e.g. gasping)



Sagittal section of brain stem

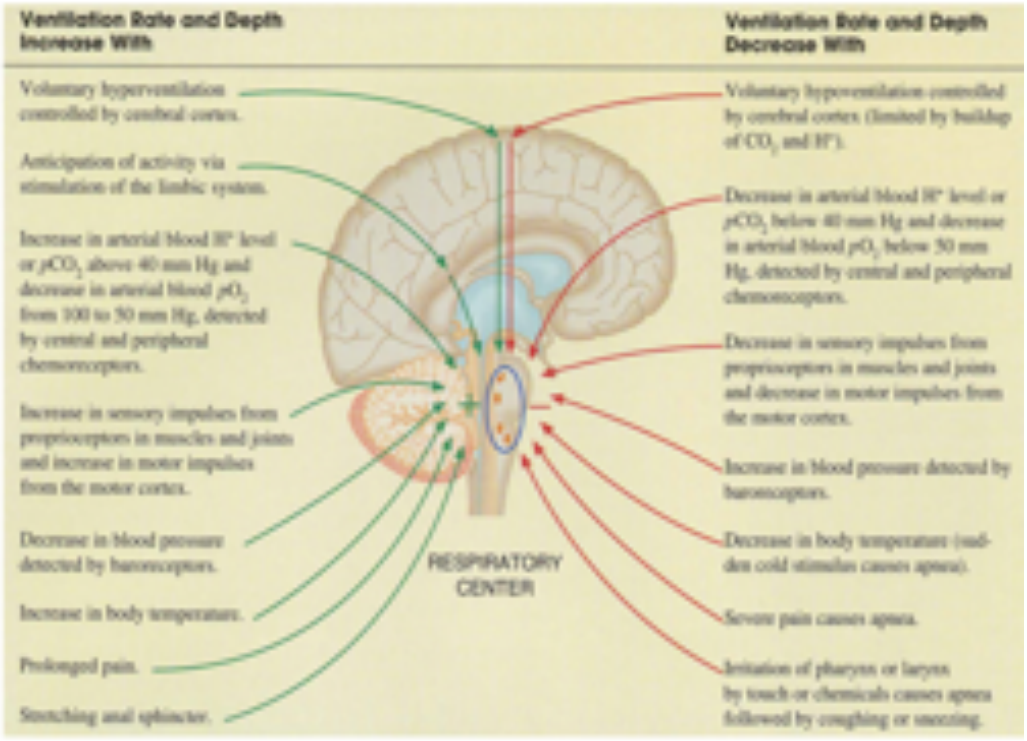
Describe influences on respiratory rhythm

- Basic respiratory rhythm is modified by:
  - Higher centres:
    - Cerebral cortex → voluntarily change breathing patterns → are overridden by stimuli of increased arterial H^+ and CO_2 concentration
    - Hypothalamus & limbic system → emotional changes
  - Baroreceptors, thermoreceptors, mechanoreceptors, stretch receptors, irritant receptorsm etc.
  - Chemoreceptors:
    - Arterial O_2, CO_2, and pH are the most important influences on breathing
    - Detected by two sets of chemoreceptors to stabilise these in health:
      - Peripheral chemoreceptors → in carotid and aortic bodies → primarily detect P_aO_2, but also sensitive to changes in P_aCO_2
      - Central chemoreceptors → on ventrolateral medullary surface → detect P_aCO_2 via pH of CSF only

PERIPHERAL CHEMORECEPTORS

- Respond by altering their nerve firing rate
- Carotid body → contain small nodules and have a high metabolic rate → type I/glomus cells are the chemosensitive cells of the carotid bodies → supported and protected by sustenacular cells
- Lie close to carotid sinus and aortic baroreceptors → elicit first 20% of ventilator change to P_aCO_2
- Carotid bodies exert the predominant, immediate effect on ventilation → primarily respond to a drop in P_aO_2 → aortic bodies respond more readily to haemodynamic changes (e.g. anaemia, hypotension)

CONTROL OF BREATHING



CENTRAL CHEMORECEPTORS

- Located in the medulla oblongata close to respiratory centres
- Primary source of feedback for assessing ventilation effectiveness
- Very sensitive to P_aCO_2 changes manifested as CSF pH changes
- Ventilation increases by 2-3L/min for every 1mmHg rise in P_aCO_2
- Elicit remaining 80% of ventilator change to P_aCO_2 → after initial peripherally-mediated effect
- Insensitive to hypoxia → also respond to severe metabolic acidosis

OVERVIEW

- Respiratory afferent fibres from the chemoreceptors in the thorax travel with CNX, and those from the upper airways travel with CNIX → both synapse in the DRG in the medulla
- Slowly adapting (mechanoreceptors) and rapidly adapting (irritant) pulmonary stretch receptors in the tracheobronchial tree → inform respiratory centre to alter breathing
- Ventilation is not altered significantly until <60mmHg (8kPa) → brain depression occurs below 30mmHg
- Acidosis also makes the carotid body more sensitive to hypoxia → alkalosis makes it less sensitive
- Chronic hypercapnia causes chemoreceptor adaptation and depresses ventilation:
    - Increased P_aCO_2 causes respiratory acidosis
    - Bicarbonate compensation returns the brain pH back to normal so central chemoreceptors are less sensitive to further changes in P_aCO_2
    - With central chemoreceptor drive depressed → minute ventilation depends on hypoxia via the carotid bodies
    - If pure O_2 given → this depresses carotid response output and will reduce hypoxic ventilation drive → this could depress ventilation, increase P_aCO_2, and induce coma (CO_2 narcosis)

NEGATIVE FEEDBACK CONTROL OF BREATHING

- For example → increase in P_aCO_2 → stimulates chemoreceptors → inspiratory centre (DRG & VRG) → muscles of respiration contract more frequently and forcefully → P_aCO_2 decrease

O_2 TRANSPORT IN BLOOD

Describe factors that affect gas transport

- Thickness of diffusion barrier, ventilation, perfusion, partial pressure, pH, temperature, and attitude

Describe the means by which O_2 is transported in the blood

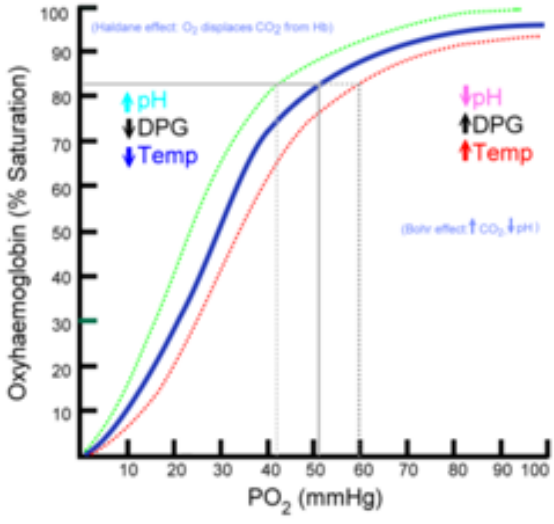
- O_2 can be carried in the blood by two methods:
    - Physically dissolved → O_2 has a lower solubility than CO_2 → carrying capacity is 0.3ml O_2/dL
    - Bound to haemoglobin in RBC (98.5%) → each mg of Hb carries 1.34ml O_2 → [Hb] = 15mg/dL → total bound is % saturation

Describe the structure and function of oxygen-binding proteins

- Haemoglobin → an Fe^{2+}-containing molecule → globular protein that contains 4 polypeptide chains, each containing a heme group → in adults this is 2α and 2β chains → in foetal Hb this is 2α and 2γ chains → γ chains have a higher affinity for O_2
- Hb has two states → oxyhaemoglobin and deoxyhaemoglobin
- O_2 binds to iron in the ferrous (Fe^{2+}) state
- Myoglobin → globular protein found in muscle tissue → contains 1 heme group instead of 4 → has a higher affinity for O_2 than haemoglobin
- Methaemoglobin (MetHb) → <1% of Fe in Hb exists in ferric state (Fe^{3+}) → dysfunctional form of Hb
- Methaemoglobin reductase → found in RBCs → changes Fe^{3+} back to Fe^{2+} → limits presence of MetHb → certain medications (ascorbic acid and gluthionine) can reduce the levels of methaemoglobin reductase
- Methaemoglobinaemia → excess MetHb → can be congenital (recessive) or acquired (nitrates) → results in blueish/brown blood and urine → Fe^{3+} has a reduced ability to unload O_2 at tissues

Understand the significance of the oxygen-haemoglobin dissociation curve

- The total % of sites bound to O_2 is constant for a given amount of O_2 → arterial blood, normal [Hb] – 97% saturation = 20ml O_2/100ml → venous blood (huge reserve) – 75% saturation = 15ml O_2/100ml
- NB: If a patient lost 50% of their blood → %HB-O_2 saturation would remain the same, but blood O_2 content would be halved
- There are certain factors that reduce Hb-O_2 affinity → these can help unload O_2 at tissues:
    - Acidic pH (Bohr effect)
    - Increased P_aCO_2
    - Raised body temperature
    - 2,3-bisphosphoglycerate (2,3-BPG) → metabolites whose levels increase in a hypoxic state
- These factors cause a right-hand shift in the dissociation curve → the affinity of Hb for O_2 is reduced → less O_2 bound to Hb so lower sats but more O_2 will unload at tissues
- There are certain factors that increase Hb-O_2 affinity → these prevent O_2 unloading at tissues:
    - Alkaline pH
    - Reduced P_aCO_2
    - Lowered body temperature
    - Foetal Hb



- These factors cause a left-hand shift in the dissociation curve → the affinity of Hb for O_2 is increased → more oxygen is bound tightly to Hb for any P_aO_2 leading to higher sats → it is more difficult for O_2 to unload at tissues

Appreciate the nature of haemoglobinopathies

- Anaemia → a state in which the concentration of Hb is below the normal for age and gender → leads to a reduced ability to transport O_2 → could be nutritional or haemolytic
- Haemoglobinopathy → a haematological disorder due to alteration in the genetically determined molecular structure of Hb → e.g. sickle cell anaemia, haemolytic anaemia, or thalassaemia
- Examples of haemoglobinopathies:
    - Mutations can cause MetHb → replacement of histidine makes the haem group inaccessible to methaemoglobin reductase
    - Spontaneous denaturation of Hb causes haemolytic anaemias → insoluble protein aggregates (Heinz bodies)
    - Mutations can affect O_2 binding affinity → makes it more difficult to unload O_2 at tissues
    - Mutations can alter processing or degradation of mRNA, or proteolytic degradation of α or β chains → thalassaemias
    - Hb with reduced H_2O solubility causes sickling disorders → sickle cell anaemia is a mutation of glutamate residues to valine in β chain → gives abnormal Hb (HbS) which has a decreased water solubility → RBCs sequestered in spleen for early destruction

Additional information

- Terminology:
    - O_2 pressure (P_aO_2) → amount of oxygen dissolved in plasma → 0.3ml O_2/dL
    - O_2 capacity → amount of oxygen bound to haemoglobin → 19.7ml O_2/dL
    - O_2 content → amount of oxygen bound to Hb + dissolved O_2 → 20ml O_2/dL
    - O_2 saturation → the percent of available binding sites bound to O_2 → stays constant with P_aO_2
    - O_2 capacity can be altered by [Hb] → as can O_2 content
- Oxygen transported dissolved and carried bound to respiratory proteins (mainly Hb)
- Adult and foetal Hb are allosteric proteins → 4 polypeptide chains → each with own haem
- Hb-O_2 binding is cooperative → giving a sigmoid dissociation curve that describes the % of Hb that is saturated with oxygen (SaO_2) → SaO_2 is therefore mainly determined by P_aO_2 → relationship can change due to temperature or pH
- The amount of Hb or its binding characteristics do not affect P_aO_2 → most common cause of reduced P_aO_2 is V/Q mismatch

HAEM

Define haem

- Haem is a complex organic molecule that contains iron at the centre of a ring → it catalyses electron transfer reaction, particularly involving diatomic gases (O_2) → this is due to iron acting as a good source or sink of electrons
- In the body haem is contained within proteins → haemoglobin, myoglobin, cytochromes, and some enzymes (catalase)
- Biosynthesis occurs in:
    - Most cells → cytochrome C → oxidative phosphorylation
    - Liver → cytochrome P450 → steroid/drug metabolism
    - Bone marrow → haemoglobin → transport of O_2
- Although haem protein metabolism is "essential" for protein metabolism → it makes up less than 3%
- Haem is made from glycine, but mainly in mitochondria

Define anaemia

- Anaemia → a condition in which there is a deficiency of red cells or of haemoglobin in the blood → results in pallor and fatigue

Give examples of nutritional defects which result in decreased levels of haem

- There are several nutritional problems that can prevent haem from being produced:
    - General nutritional deficit → leads to reduced glycine and succinyl-CoA for production
    - Iron poor diet → required for the iron in haem
    - Vitamin B6 deficiency → coenzyme required for the first reaction

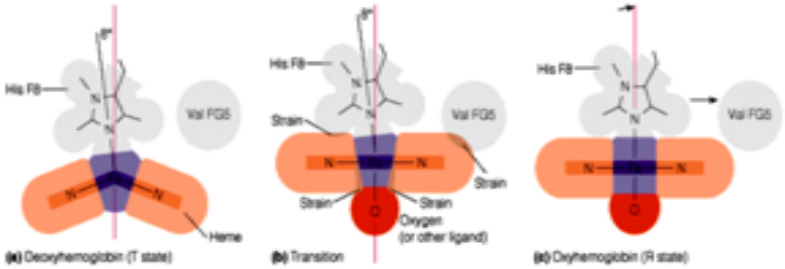
Describe how mutations in haemoglobin result in anaemia

- Mutations in Hb can affect function → over 200 AA substitutions have been documented → example is sickle cell anaemia
- Porphyrias → a collection of rare inherited (autosomal dominant) or acquired diseases of certain enzymes that are normally involved in the production of haem → manifest with either neurological (photosensitivity, dementia) or skin problems → diagnosis occurs via accumulation and excretion of porphyrias or via gene sequencing → an example of an enzyme is hydroxymethylbilane synthase
- An example of porphyrias → PBG (porphobilinogen) and δALA accumulate in urine → urine darkens with exposure (NOT photosensitive) → abdominal pain, neuropsychiatric disturbances → precipitated by drugs, EtOH which induce CYP450

Describe why the shape of haemoglobin is important

- RBCs contain the bulk of the haem in the body → lifespan of RBC is 60-120 days → senescent RBCs are phagocytosed and/or lysed
- The haem is contained in Hb → multi-subunit protein → 1 haem per subunit
- Thus, RBCs carry O_2 because they contain Hb which contains haem

- O_2 binding causes a major conformational change in Hb → can result in increased affinity for O_2 at other binding sites → this conformational change can be used to measure Hb saturation → it is the premise for pulse oximetry
- Other compounds that bind Hb can also affect how easy it is for the O_2 to bind → hydrogen, CO_2, and 2,3-BPG



Explain why toxins can result in decreased levels of haem

- Toxins can also impact on haem production → drugs such as griseofulvin (antifungal), sodium valproate and phenytoin (anticonvulsants), and ethanol → lead is also a toxin that can affect haem production
- Nutritional problems and toxins can also stop the production of Hb:
    - Anything that impedes haem production → nutritional deficit, iron poor diet, alcohol/other drugs
    - Similarly, anything that impedes Hb production impedes O_2 carrying capacity of RBCs, and thus causes anaemia
    - Anaemia can also be caused by defects that impair RBC development → vitamin B6 deficiency

CO_2 TRANSPORT IN BLOOD

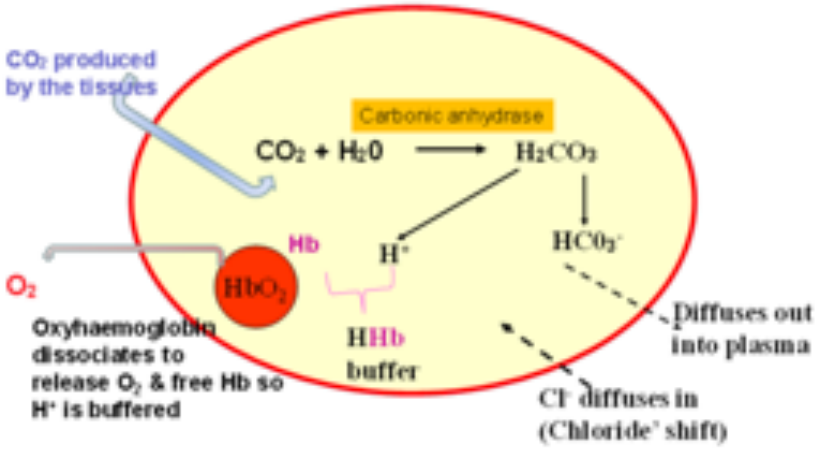
Describe factors that affect gas transfer

- Partial pressure difference
- Membrane thickness
- Surface areas of gas exchange
- Ventilation/perfusion ratio
- Temperature, pH, etc.

Describe the means by which CO_2 is transported in the blood

- CO_2 is produced in tissue by metabolism, exchanged with O_2, and transported to the lungs to be expired
- It can be transported in several different ways:
    - In solution in plasma (9%) → 20x more soluble than O_2 so contributes more to CO_2 content
    - Carbaminohaemoglobin (13%) → CO_2 + Hb ↔ $HbCO_2$ → inversely influenced by HbO_2 saturation → carried on globin chain
    - Bicarbonate ion (78%) → depends on reaction catalysed by carbonic anhydrase →

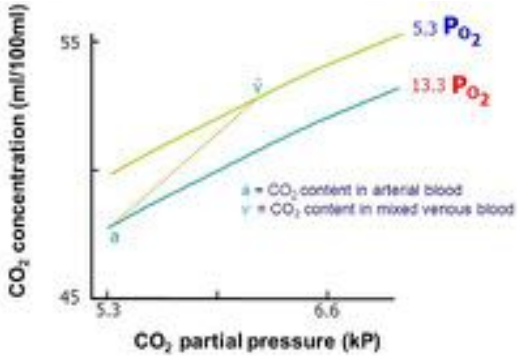
$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$



- In systemic circulation → CO_2 is produced in tissues and transported in the blood to the lungs
- In pulmonary circulation → the opposite reaction occurs which enables CO_2 to be expired

Understand the relevance of the carbon dioxide dissociation curve

- The dissociation of CO_2 from blood is linear → with saturation of Hb with O_2 having a major effect on the curve
- DeoxyHb has a greater affinity for CO_2 than oxyHb → forms carbamino compounds → so venous blood freely transports CO_2 more readily than arterial blood
- Hb prefers to carry CO_2 than O_2 when in the deoxygenated state → i.e. in venous blood
- The dissolved CO_2 content of blood is much greater than of O_2



Additional information

- Hyperventilation → P_aCO_2 decreases and P_aO_2 rises → O_2 content will not alter much as dissolved O_2 contributes minimally to the total O_2 carried in blood
- Hypoventilation → CO_2 cannot be exhaled so P_aCO_2 rises → $P_aCO_2 \propto \text{ventilation}^{-1}$

INTRODUCTION TO PH & BLOOD GAS ANALYSIS

Know the normal plasma pH range

- The normal pH range of systemic arterial blood is between **7.35-7.45**
- 'Normal' = 7.4 = 40nM/L H^+
- Acidosis → pH **below 7.35** → depresses CNS through depression of synaptic transmission → coma
- Alkalosis → pH **above 7.45** → over-excitability of the PNS then CNS through facilitation of synaptic transmission → spasms, convulsion and death

Arterial blood pH values	$[H^+]$	Clinical examples
6.8-7.3	160nmol/L – 50nmol/L	Metabolic/respiratory acidosis
7.35-7.45	45nmol/L – 35nmol/L	Normal range
7.5-8.0	32nmol/L – 10nmol/L	Metabolic/respiratory alkalosis

Describe the factors involved in pH homeostasis

- A solution's acidity or alkalinity is based on the pH scale
- pH = power of hydrogen = $- \log_{10}[H^+]$
- Metabolic production of acids can produce free H^+ → this can be due to:
    - Carbonic acid
    - Non-volatile acid produced from nutrient breakdown
    - Organic acids from intermediate metabolism

Outline the relationship between plasma pH, $[H^+]$, P_aCO_2, and $[HCO_3^-]$

- There are certain lines of defence against pH disorders:
    - Chemical buffers → intracellular and extracellular → fractions of a second
    - Adjusting ventilation to change P_aCO_2 → restores 50-75% of the way to normal pH → minutes
    - Adjusting renal acid and alkali excretion → long term regulation → hrs to days
- Buffer systems prevent rapid, drastic changes in pH → they don't get rid of free H^+, just bind it → mostly effective around the pK_a (50% ionised)
- 3 main extracellular buffer systems:
    - Protein buffer system → Hb and plasma proteins
    - Phosphate buffer system → bone
    - Carbonic acid-bicarbonate buffer system

THE CARBONIC ACID-BICARBONATE BUFFER SYSTEM

- It is quantitatively the most important ECF buffer system → though not the strongest
- Reaction is catalysed by carbonic anhydrase → $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$
- At pH 7.4 → bicarbonate ion conc (24mmol/L) is approx. 20x that of carbonic acid (1.2mmol/L)
- pK_a for the reaction is 6.1
- This system is tightly regulated → CO_2 is regulated by the lungs using chemoreceptors → HCO_3^- and H^+ are regulated by the kidneys → H^+ is excreted and HCO_3^- is reabsorbed or excreted
- Henderson-Hasselbach equation → chemical equation that describes the derivation of pH as a measure of acidity in biological and chemical systems
- At pH 7.4 → most H_2CO_3 exists as dissolved CO_2
- $pH \propto \frac{[HCO3-]controlled\ by\ kidneys}{PCO2\ controlled\ by\ lungs}$
- pH homeostasis can be disturbed if P_aCO_2, $[H^+]$ or $[HCO_3^-]$ are not maintained
- Respiratory and metabolic disturbances disrupt CO_2 and HCO_3^- conc. respectively, but can coexist

INTRODUCTION TO PH & BLOOD GAS ANALYSIS

Understand why respiratory and metabolic acid/base disturbances can arise

- Respiratory cause → if CO_2 is the main cause of pH disturbances
- Non-respiratory (metabolic) cause → if HCO_3^- is the main cause of the pH disturbance
- Compensation → refers to the physiological response to an acid-base imbalance
- Correction of the pH disturbance takes longer → uses kidneys
- Respiratory acidosis → cause is elevation of PCO_2 of blood → due to lack of removal of CO_2 from blood → emphysema, pulmonary oedema, etc. → renal compensation involves decreased excretion of HCO_3^- and increased excretion of H^+ → treatment is IV administration of bicarbonate and ventilation therapy to increase exhalation of CO_2
- Respiratory alkalosis → arterial PCO_2 is too low → due to increased removal of CO_2 from blood → hyperventilation (e.g. at high altitude), pulmonary disease, stroke, etc. → renal compensation involves decrease in excretion of H^+ and increased excretion of HCO_3^- → treatment is rebreathing expired air
- Metabolic acidosis/alkalosis → cause is a decrease/increase in HCO_3^- concentration, respectively → kidney disease, electrolyte disturbances, severe vomiting & diarrhoea, diabetes → compensation involves increasing/decreasing ventilation respectively to change P_aCO_2
- Normal values:
    - pH → 7.35-7.45
    - H^+ at pH 7.4 = 40nmol/L ($4x10^{-8}$ mol/L)
    - P_aCO_2 → 35-45mmHg (approx. 4.5-6kPa)
    - $[HCO_3^-]$ → 22-26mmol/L

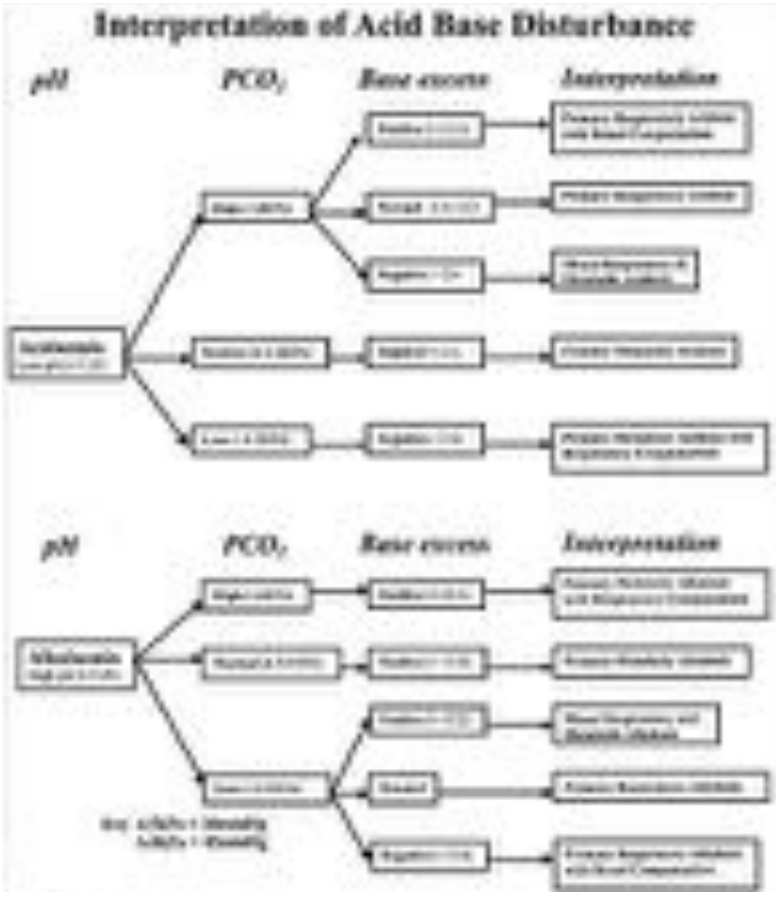
CLINICAL ACID-BASE DISTURBANCES

Outline the importance of acid-base disturbances

- Humans depend on complex chemical reactions to function → efficiency of these reactions is pH and temperature dependent
- Failures in acid-base defence can result in illness and death
- pH changes are associated with electrolyte disturbances which can be fatal independently
- Acid production and excretion:
    - Metabolism → CO_2 generation results in an acid load → approx. 15-20,000nmol/day H^+
    - Lungs → excrete 99.99% total as CO_2
    - Kidneys → excrete balance of H^+ with anions that cannot be metabolised → reabsorbs 4-5000nmol/day of HCO_3^- from glomerular filtrate
    - Liver → metabolises 1500nmol/day of lactic acid in TCA cycle and prevents net gain of H^+ in plasma → lactic acid is important for moving energy around the body
- Disturbances can be multifactorial in origin → aggressive intervention is often required to prevent patient death

Explain how disturbances are classified

- Acidosis:
    - pH <7.35 → $[H^+]$ >45nmol/L
    - Respiratory → failure to drive alveolar ventilation
    - Metabolic → net gain of H^+ or loss of HCO_3^-
- Alkalosis:
    - pH >7.45 → $[H^+]$ <35nmol/L
    - Respiratory → overdrive of alveolar ventilation
    - Metabolic → net loss of H^+ or gain of HCO_3^-
- Alkalosis is very rare in illness → normally acidosis → only cases are due to extreme vomiting of HCl
- Acidosis and alkalosis can get mixed up in severely unwell patients



RESPIRATORY FAILURE

Outline the pathophysiology of respiratory failure

- Respiratory failure → a failure of gas exchange (lung failure) → diagnosis normally relies on ABG analysis
- There are two types of respiratory failure:
    - Type I → hypoxaemia with a normal or low CO_2 → V/Q mismatch normally
    - Type II → hypoxaemia with a high CO_2 (>6kPa) → alveolar hypoventilation
- Hypoxaemia is defined as P_aO_2 <8kPa
- In practice → both types of respiratory failure can co-exist
- There are 4 main mechanisms of respiratory failure:
    - Alveolar hypoventilation → when ventilation is inadequate to perform needed gas exchange
    - Diffusion deficit → pathological process affecting the air-blood barrier
    - Shunting → blood is not properly being perfused with O_2
    - Ventilation-perfusion (V/Q) mismatch → ratio of air and blood reaching alveoli does not match → degree of shunt and degree of dead space in the same lung (not anatomical anomaly)
- Hypoventilation → leads to CO_2 retention, a reduction in minute ventilation and an increase in proportion of physiological dead space ventilation → it is often correctable with oxygen, but this may also have a detrimental effect in type II RF
- Causes of diffusion deficit:
    - Pulmonary oedema → acute
    - Pulmonary fibrosis → chronic
- Pulmonary shunt → often occurs when alveoli are filled with fluid → causes part of the lung to be unventilated although it is still perfused → in a shunt the venous and arterial blood mix:
    - Extrapulmonary shunt → mainly cardiac (paediatric) → shunt reversal occurs eventually
    - Intrapulmonary shunt → blood is transported through the lungs without taking part in gas exchange → commonest cause is alveoli filling and atelectasis (collapse or closure of part of the lung) → oxygen does not correct intrapulmonary shunt
- V/Q mismatch → due to the flat upper portion of the oxyhaemoglobin dissociation curve → blood leaving the relatively healthy alveoli will have an O_2 saturation of 97%, while blood leaving alveoli that do not have optimum V/Q ratios will have a much lower O_2 saturation → the mixture of this blood leaving the alveoli results in a low O_2 saturation and hypoxaemia

Outline the causes, symptoms, and signs of respiratory failure

- Common causes:
    - Acute asthma
    - Exacerbation of COPD
    - Pneumonia
    - Pulmonary oedema
    - Pulmonary embolism
    - Pleural effusion
    - Pneumothorax
    - ARDS/ALI
    - Respiratory depression
    - Drugs (e.g. opiates)
- Signs and symptoms:
    - Shortness of breath
    - Clues in history → speed of onset
    - Haemoptysis
    - Cyanosed lips
    - Pale, sweaty, and clammy
    - Stridor, wheeze, or crackle
    - Sitting up
    - SpO_2 <88%

RESPIRATORY FAILURE

List the common causes of type II respiratory failure

- COPD
- Respiratory depression → drugs (opiates)
- Neuromuscular diseases → Guillain-Barré syndrome and myasthaenia gravis
- Obesity hypoventilation
- Kyphoscoliosis
- Hypercapnoea is the end result of many causes of respiratory failure → indicates a tiring patient

Outline the principles of management of respiratory failure

- Management of acute respiratory failure requires emergency management and a definitive diagnosis → treatment of the underlying condition
- Emergency management → commences with an assessment of ABCDE:
    - Ensure airway is patent and protected
    - Note if stridor is present
    - Sit up (unless hypotensive) and give oxygen
    - Secure IV access → may need urgent fluids
    - If comatose → thing of drug-induced respiratory depression
- Controlled oxygen therapy → careful with patients in type II respiratory failure → may have lost hypercapnic drive:
    - Type I failure → 'high-flow', with a targeted SpO_2 of 94-98% → titrate down
    - Type II failure → 'low-flow', with a targeted SpO_2 of 88-92% → titrate up
    - Ventilation (if appropriate) → non-invasively

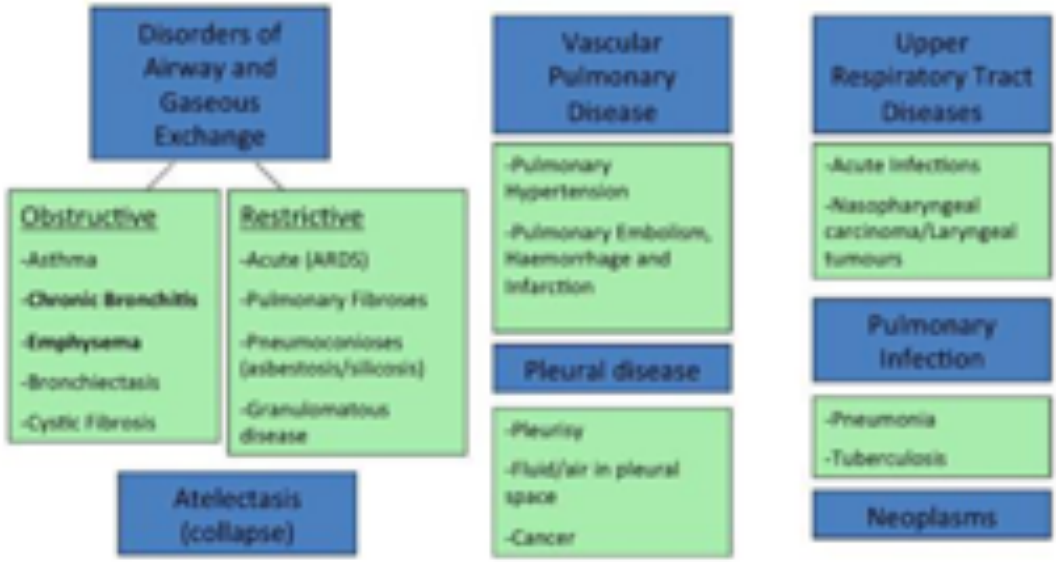
OBSTRUCTIVE & RESTRICTIVE PATHOLOGIES

Describe the structure of the respiratory system in the context of understanding lung disease

- The respiratory tract is lined by pseudostratified ciliated columnar epithelial cells with goblet cells → they appear pseudostratified due to basal neuroendocrine cells and stem cells
- Goblet cells produce mucous → serous cells secrete serous fluid
- Layers of the lining of the respiratory system:
    - Respiratory epithelium
    - Basement membrane
    - Vascular lamina propria → loose CT
    - Smooth muscle
    - Glandular submucosa
    - Cartilage
- Trachea → held open by rings of C-shaped cartilage → trachealis muscles control tracheal diameter
- Bronchus → more prominent smooth muscle layer → cartilage plates
- Bronchioles → no cartilage or submucosa → terminal and respiratory bronchioles have Clara cells instead of goblet cells → less than 1mm
- Alveoli → lined by flattened squamous epithelial cells (type I pneumocytes) and rounded cells → with prominent secretory granules (type II pneumocytes) for the secretion of surfactant

List the categories of lung disease and the main diseases in each

- Restrictive disease → occurs in the interstitium
- Obstructive disease → occurs in the tubule structures



Describe the pathological features and diagnosis of obstructive and restrictive lung disease and differentiate between the two

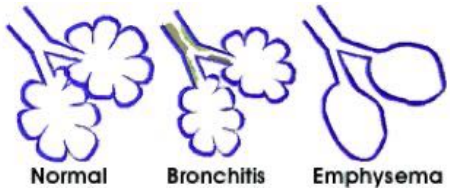
- Obstructive → limitation of airflow due to obstruction → causes increased airway resistance
- Examples of obstructive diseases:
    - Airway narrowing → asthma
    - Loss of elasticity → emphysema
    - Increased secretions → bronchitis and asthma

- Restrictive → restriction of normal lung movement during respiration → reduced expansion of lung tissue → decreased total lung capacity
- Examples of restrictive diseases:
    - Fibrosis → alveoli cannot expand properly into interstitium as it is solid
    - Pneumoconiosis
    - Other → nervous innervation, cancer, obesity

Describe the causes, clinical symptoms, pathological features, and underlying mechanisms of the major obstructive lung diseases

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- Chronic bronchitis and emphysema often coexist → known as COPD
- Characterised by chronic limitation of air low into and out of the distal respiratory tree → distal is more related to emphysema
- Patient can have a single condition but more commonly both
- Irreversible → often due to smoking and urban pollution → 4th leading cause of death in the UK



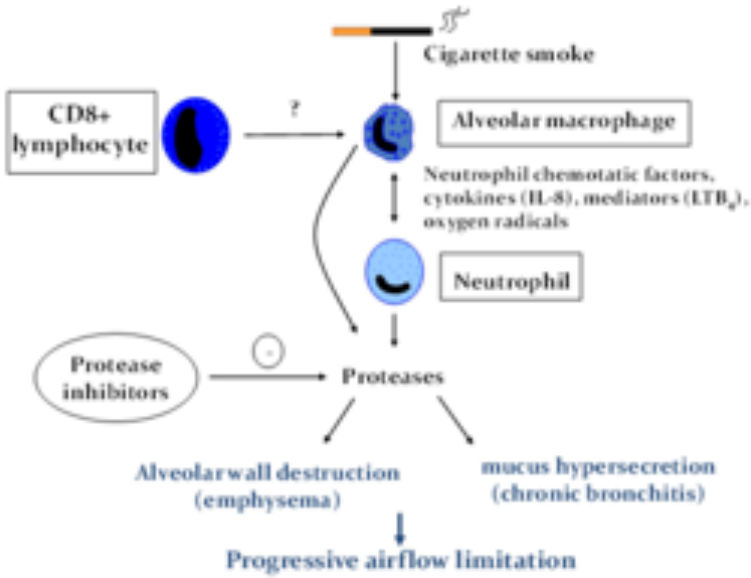
CHRONIC BRONCHITIS

- Mucous hypersecretion in large or small airways → different name if in small airways – bronchiolitis
- Involves inflammatory cells → T cells, macrophages, and neutrophils
- Defined clinically rather than morphologically → persistent productive cough for at least 3 consecutive months in at least 2 consecutive years
- Enlarged mucous secreting glands → increased goblet cells → increased mucous secretions in oedematous mucosa → brochiolar wall fibrosis → leads to luminal narrowing and airway obstruction
- Increased mucous secretion from chronic inflammation or smooth muscle hypertrophy causes obstruction
- Pure bronchitis → blue bloater

EMPHYSEMA

- Located distal to the terminal bronchioles
- Manifested by dilation of respiratory bronchioles and alveoli → destruction of elastic tissue → loss of elasticity causes difficulty in expiration and maintenance of the airway in respiratory bronchioles
- Coalescing of sacs causes loss of surface area for gaseous exchange
- Emphysema is classed by anatomical location:
    - Centriacinar (CA) or centrilobular:
        - Dilated respiratory bronchioles
        - Most common → smoking related
        - Most often seen in upper lobes
    - Panacinar (PA) or panlobular:
        - Dilated alveoli
        - Most often seen in lower lobes
        - Hereditary

- Main cause of emphysema is smoking (99%) → however there is a cause of inherited emphysema → α_1 antitrypsin deficiency (protease inhibitor) (1%) → cannot inhibit proteases produced by inflammatory cells
- Protease-antiprotease imbalance mechanism → normally protects lungs from enzymes that digest proteins → smoking stimulates alveolar macrophages to produce elastases, and stimulates attraction and activation of neutrophils which release granules rich in proteases → leads to uncontrolled proteolysis and destruction of elastic tissue → α_1AT-deficiency causes insufficient production of antiproteases so uncontrolled proteolysis



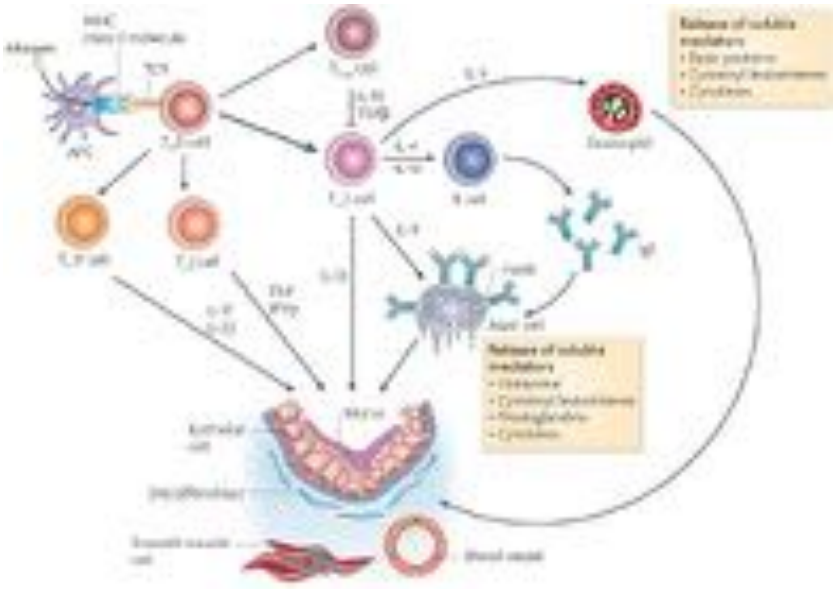
- Oxidant-antioxidant imbalance mechanism → normal lung contains abundant antioxidants → smoke contains abundant reactive oxygen species (free radicals) → oxidative injury causes tissue damage and inactivated antiproteases → functional deficiency
- Presentation:
    - Dyspnoea → prolonged expiration (prevent airway collapse) → barrel chest (muscle development)
    - Prolonged onset → >40yrs
    - Congenital α_1 antitrypsin deficiency will present earlier
    - Often co-presents with chronic bronchitis → cough and excess mucous production
    - Pure emphysema → pink puffer → pursed lip breathing

ASTHMA

- Asthma is a chronic inflammation of the airways → results in hyper-responsive airways → with episodic, reversible airway narrowing
- Often associated with a triad:
    - Intermittent and reversible airway obstruction
    - Chronic bronchial inflammation with eosinophils
    - Bronchial smooth muscle hypertrophy and hyper-reactivity
- Presentation:
    - Cough
    - Wheeze
    - SoB
    - Sputum production
    - Nocturnal cough or wheeze
- Precipitating an attack → URTI, environmental allergens, emotion, weather, aspirin, NSAIDs, β-blockers
- Asthma can be atopic/extrinsic or non-atopic/intrinsic
- Extrinsic → accounts for 70% of cases → caused by exposure to environmental allergens → e.g. house dust, pollen, animal, food
- Intrinsic → no obvious external allergen trigger → cold exposure, exertion, viral inflammation (reduces threshold to irritants)

- Intrinsic further divides into:
    - Childhood → viral infection and small airway size → frequently resolves with age
    - Occupational → repeated exposure to chemical irritant fumes, gases, or dust
    - Drug-induced → aspirin, NSAIDs in susceptible individuals

ACUTE PHASE

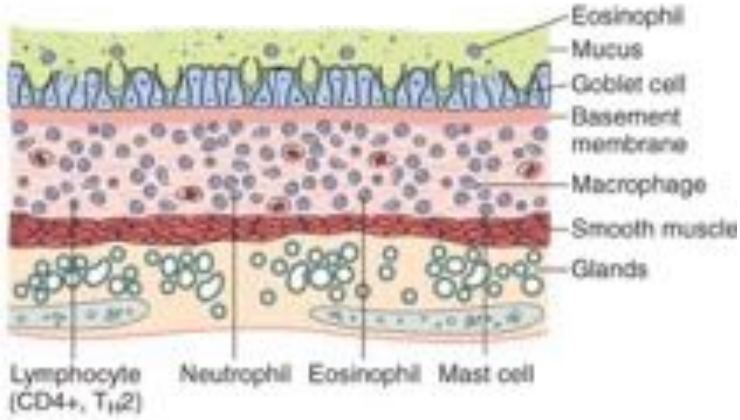


- T_H2 cells cause type I hypersensitivity reaction → cytokine production
- IL4 → stimulates IgE → activates mast cells which recruit eosinophils and neutrophils
- IL5 → stimulates eosinophils
- IL13 → stimulates mucous production
- Pneumocytes activated to recruit for T_H2 cells
- Bronchospasm as a result of ANS → parasympathetic
- Eosinophils amplify and sustain the inflammatory response

LATE PHASE

- Chronic inflammation of bronchi → airway remodelling
- Excess mucous production by goblet cells and glandular hypertrophy
- Bronchial wall oedema due to inflammatory exudate → eosinophil and mast cell accumulation
- Smooth muscle hypertrophy and fibrosis

ASTHMA OVERVIEW



- Reversible and intermittent
- Bronchoconstriction due to increased responsiveness of bronchial smooth muscle
- Hypersecretion of mucous leading to plugging of airway
- Mucosal oedema leading to narrowing of airway lumen
- Infiltration of bronchial mucosa by eosinophils, mast cells, lymphoid cells, and macrophages
- Morphological changes:
    - Excess mucous → production by goblet cell and glandular hypertrophy
    - Bronchial wall oedema → due to inflammatory exudate → eosinophil and mast cell accumulation
    - Smooth muscle → hypertrophy and fibrosis

OBSTRUCTIVE & RESTRICTIVE PATHOLOGIES

BRONCHIECTASIS

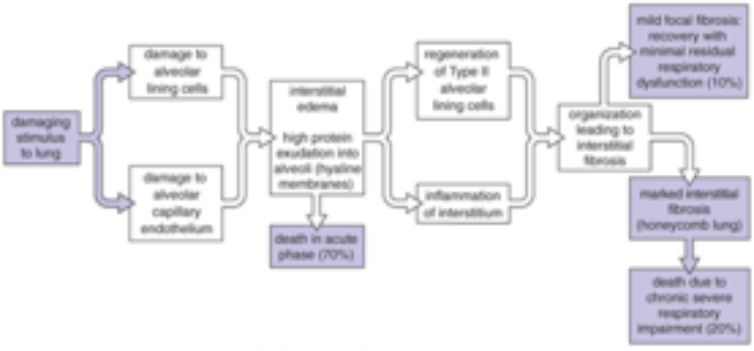
- Permanent dilation of main bronchi and bronchioles → from pulmonary inflammation and scarring due to recurrent infection, bronchial obstruction and lung fibrosis → airways then dilate as surrounding scar tissue contracts
- Secondary inflammatory changes lead to further destruction of airways
- Symptoms are chronic cough with dyspnoea and production of copious amounts of foul-smelling sputum
- Damage to epithelium causes bleeding (haemoptysis) and clubbing of fingers
- Secondary to primary obstructive disease or recurrent necrotising infections → both processes are involved in the pathogenesis, but either can come first
- Obstruction → clearance mechanism blocked → infection
- Infection → damage to walls → fibrosis → dilation
- Causes:
    - Infection → necrotising pneumonia, especially with virulent organisms e.g. TB → weakens bronchial walls and leads to fibrosis
    - Obstruction → tumours, foreign bodies, impaction of mucous → localised to that lung segment → as a complication of asthma/chronic bronchitis
    - Congenital/hereditary:
        - Cystic fibrosis → production of abnormally viscous mucous causes obstruction and predisposes to infection
        - Immunodeficiency → Ig deficiency predisposes to infection e.g. hypogammaglobulinaemia
        - Kartagener syndrome (immotile cilia syndrome) → cilia are abnormal → impaired mucociliary clearance → stagnation of secretions
- Morphology → affects lower lobes on both sides → particularly vertical air passages → can cause 4x expansion → shows signs of acute and chronic inflammatory exudate, epithelia ulceration, and fibrosis of bronchial and bronchiolar walls

Describe the causes, clinical symptoms, pathological features, and underlying mechanisms of the major restrictive lung diseases

- Restrictive lung disease can be:
    - Acute → acute respiratory distress syndrome (ARDS)
    - Chronic → pulmonary fibrosis and pneumoconioses

ACUTE RESPIRATORY DISTRESS SYNDROME

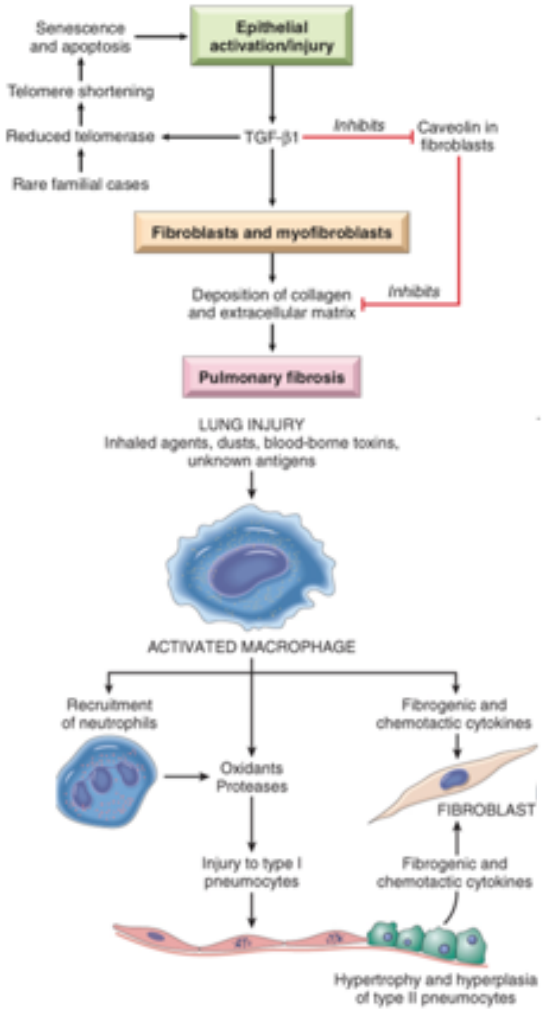
- Caused by diffuse alveolar damage as a consequence of direct (pneumonia/aspiration) or indirect (sepsis/trauma) lung injury
- Acute inflammation of alveoli rapidly damages capillaries and epithelium as a result of diffuse alveolar damage
- Under normal circumstances there is a balance of pro- and anti-inflammatory mediators → in ARDS there is uncontrolled inflammation



- Leads to acute onset of dyspnoea and hypoxaemia due to vascular leakiness and loss of surfactant → affects gaseous exchange and expansion of alveoli
- Organisation phase → can cause fibrosis of alveolar interstitium and proliferation of type II pneumocytes → leading to chronic reduced respiratory function
- ARDS is associated with a high mortality rate (60%)

PULMONARY FIBROSIS

- Persistent alveolitis → inflammation of alveolar walls and spaces → activation of pulmonary macrophages → attract and stimulate fibroblasts
- Damage to pneumocytes by macrophages and neutrophils causes proliferation of type II pneumocytes → these attract macrophages and secrete stimulatory factors for fibroblasts



PNEUMOCONIOSES

- Group of fibrosing diseases resulting from exposure to toxic inhaled particulates → e.g. asbestos, silica, and coal dust → asbestosis, silicosis, and coal worker's pneumoconiosis
- Particulate sizes → <1μm or >5μm are ok → 1-5μm reach distal airways, phagocytosed by macrophages, resulting in inflammatory response and fibroblast proliferation
- Immune response stimulated by particles → macrophages travel in lymphatics → lesions consist of pigmented /pale nodules of particle-laden macrophages and dense collagen

RESTRICTIVE OVERVIEW

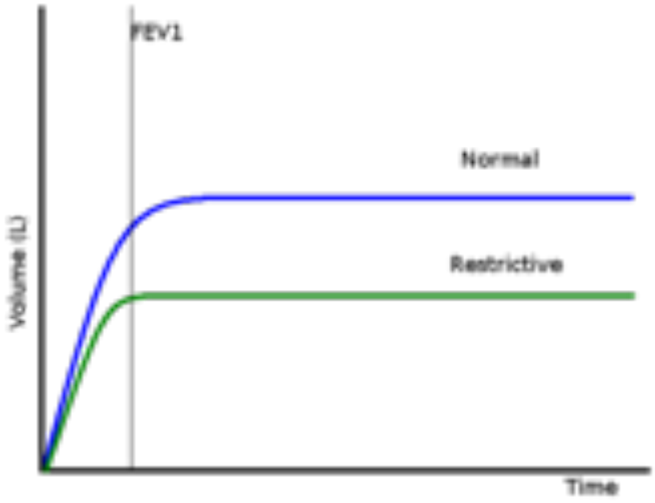
- Group of disorders affecting the lung connective tissue → especially alveolar wall interstitium
- Fibrosis causes reduced lung compliance → increased effort in breathing due to increased force required to expand lungs
- Cystic space → honeycomb lung
- Damage to pneumocytes and capillaries affects gaseous exchange → leading to hypoxia
- Acute or chronic interstitial lung disease → chronic includes pneumoconiosis, fibrosis, and infiltrative conditions (e.g. sarcoidosis)
- Can also arise due to chest wall disorders → lungs are normal → severe obesity, neuromuscular disorders, and diseases of the pleura

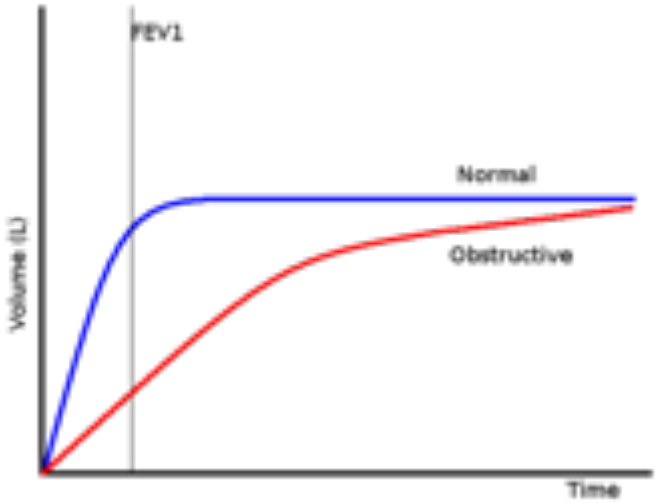
Outline how to differentiate obstructive and restrictive lung diseases

- Pulmonary function tests can be used to differentiate → specifically spirometry
- Spirometer → a device that measures lung volumes through the forced expiration of air in the lungs

OBSTRUCTIVE & RESTRICTIVE PATHOLOGIES

- Forced Expiratory Volume in one second (FEV1) → how much air can be exhaled in the first second of maximal expiration
- Forced Vital Capacity (FVC) → the maximum volume of air that can be forcibly expired
- Ratio of FEV1/FVC is given as a % → the proportion of total volume of air that can be expired in the first second of maximal expiration
- In obstructive disease → FEV1 is reduced, FVC is normal → FEV1/FVC ratio is reduced
    - Normal >80% → obstructive disease <70%
- In restrictive disease → FVC is reduced, FEV1 is reduced → FEV1/FVC ratio is maintained



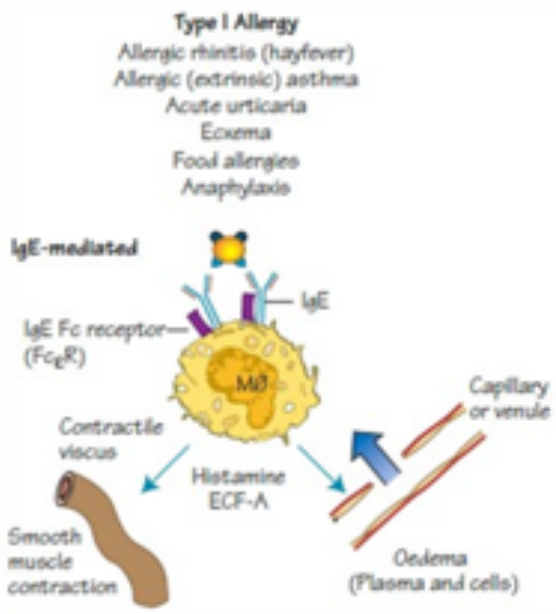


HYPERSENSITIVITY & ALLERGY

Distinguish the sources of the antigens recognised and material damaged by the adaptive response in antimicrobial immunity, allergy, and autoimmunity

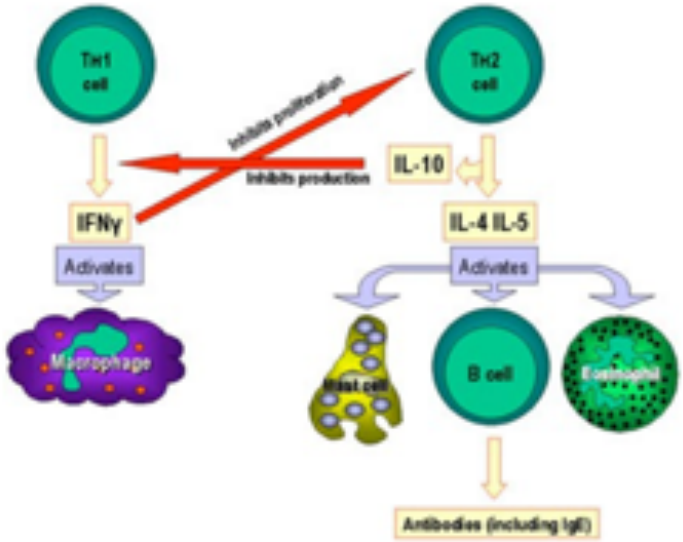
- Immunity → foreign material recognised → foreign material damaged
- Allergy → foreign material recognised → self material damaged
- Autoimmunity → self material recognised → self material damaged

Describe the role of IgE and mast cells in type I hypersensitivity



- Type I → immediate hypersensitivity
- Antigens bind to IgE molecules specific for the antigen → IgE bound to high-affinity IgE receptors (FcεRI) on the surface of mast cells
- Requires pre-sensitisation with the antigen → allows production of specific IgE by B cells
- Immediate reaction of allergen with surface bound IgE → causes release of mediates (e.g. histamine, leukotrienes, chemotactic factors, platelet activation factor) → induce smooth muscle contraction and increase capillary permeability → oedema
- Histamine stored in mast cell granules is released upon IgE receptor triggering → leukotrienes are synthesised *de novo* → peak effect at 4-6 hours later
- Allergic cascade → immediate phase – vasodilation, increased vascular permeability, increased adhesion molecules, bronchoconstriction → late phase – cellular infiltration, T cell activation

Explain the role of T_H2 cells in promoting IgE production and eosinophil development



- Antigen presenting cells (APCs – esp. dendritic cells) recognise antigen and present antigen to T_H2 cells → T_H2 cells release IL-4and IL-13 which encourage B cells to differentiate to plasma cells, and encourage class switching to IgE
- Activated T_H2 cells also produce IL-5 → leads to eosinophil growth and development → eosinophils express FcεRI → release cytotoxic molecules (e.g. major basic protein and eosinophil peroxidase) and cytokines → causes release of histamine from mast cells and basophils, and activates neutrophils and alveolar macrophages

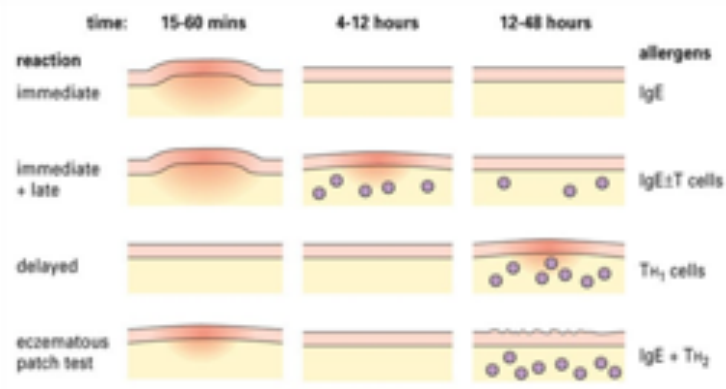
Explain how the route of exposure to allergens may influence the type of atopic disorder that results and describe atopic disorders that affect different tissues

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs, serum, venoms, peanuts	Intravenous (either directly or following oral absorption into the blood)	Oedema, increased vascular permeability, tracheal occlusion, circulatory collapse, death
Acute urticaria	Insect bites, allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis	Pollens, dust mite faeces	Inhalation	Bronchial constriction, increased mucous production, airway inflammation
Asthma	Danders, pollens, dust mite faeces	Inhalation	Bronchial constriction, increased mucous production, airway inflammation
Food allergy	Tree nuts, peanuts, shellfish, milk, eggs	Oral	Vomiting, diarrhoea, pruritis, urticarial, anaphylaxis (rarely)

- The route of entry determines the allergic response → IV, subcutaneous, inhalation, or oral
- Allergens are generally water soluble and relatively small → dust mites, cars, German cockroach, rat, grass, and fungi → all innocuous but produces hypersensitivity due to excessive immune response
- Having one allergy does not predispose to having multiple allergies → depends on antigen recognition by IgE

Outline the skin prick test

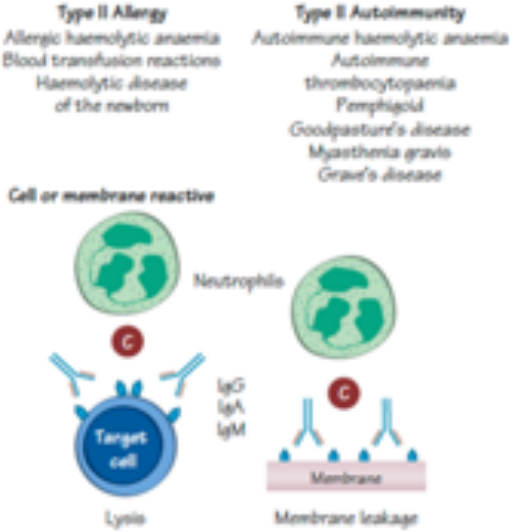
- Skin prick test → allergens used to determine what a patient is allergic to → 0.2ml of allergen inserted into the skin → associated with type IV hypersensitivity → type I hypersensitivity normally produces an immediate response (wheal and flare)



Describe the acute and chronic phases of atopic reactions

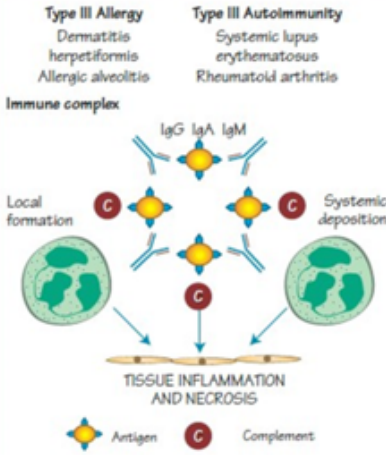
- There are two phases in the immune response:
  - Immediate phase → rapid inflammatory response, vasodilation, vascular permeability, increased adhesion molecules, and bronchoconstriction → attract other cells
  - Late phase → cellular infiltration due to adhesion molecules, T cell activation → other cells arrive

Outline the mechanism of type II hypersensitivity and how it is exemplified by haemolytic anaemia

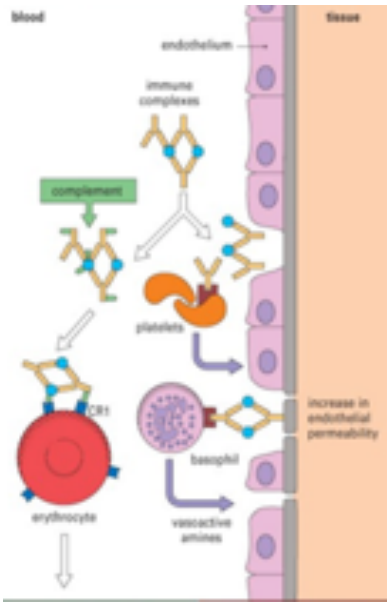


- Type II hypersensitivity → antibody-mediated hypersensitivity
- Associated with IgG, IgM, and IgA → complement and neutrophils are also important
- Neutrophils bind to target cells via Ab binding (IgG) → phagocytosis
- In hypersensitivity → neutrophils bind to innocuous substances → lytic enzymes get released causing damage to self
- Caused by IgG, IgA or IgM against cell surface and ECM antigens → Abs damage cells and tissues by activating complement and/or recruiting effector cells → damage to tissue is commonly produced by antibody to BM or to receptors → complement has a major role
- Complement → uses classical pathway → C1qrs
- Neutrophil tries to bind to something that is too big → like cell membrane → gets frustrated and releases its enzymes → resulting in tissue damage
- An example of type II → Rhesus haemolytic disease of the newborn → erythrocytes express Rhesus D (+ve) → if a mother is RhD- but have RhD+ baby→ ok during pregnancy, but when the baby is born the mother produces an Ab response → in second pregnancy this can cause problems as IgG can cross the placenta and cause RBC lysis in the baby → treatment is anti-D given to mother

Outline the mechanism of type III hypersensitivity and how it is exemplified by allergic alveolitis

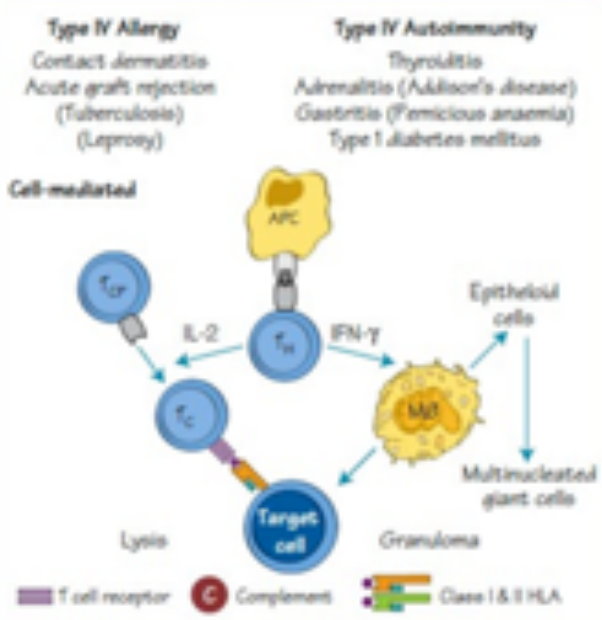


- Called immune complex hypersensitivity → immune complexes are normal and disposed of by the liver and spleen → in hypersensitivity these complexes are excessively produced but cannot be broken down fast enough so are deposited somewhere in the body → leads to tissue damage by inflammation
- Ab mediated → complement normally accumulates around these complexes to aid in breaking them down → due to continuous exposure to an allergen/antigen



- Presence of immune complexes in the circulation or in the tissue → location of immune complex depends on size, charge, antigen content, and complement → accumulation in tissue leads to activation of complement and accessory cells with consequent tissue damage
- The tissue where the infection is present is often the tissue that suffers from inflammation and necrosis → due to too many or too large complexes → deposition occurs
- An example is extrinsic allergic alveolitis → immune complexes against inhaled fungal spores → inflammation in the lung → leads to tissue damage and fibrosis → uses T_H cells and B cells, but different mechanism to type I hypersensitivity

Outline the mechanism of type IV hypersensitivity and how it is exemplified by contact dermatitis



- Like the other 3 types of hypersensitivity → it is a normal immune response, just in excess → called delayed type as it takes more than 12hrs to develop
- Chronic stimulation of macrophages by T_H1 cells → release excessive cytokines and overactivates → macrophages change into epithelioid cells → combine to form multinucleated giant cells → can then produce granulomas
- T_H1 cells have been previously exposed to these allergens
- Takes more than 12hrs to develop → involves cell-mediated immune reactions rather than humoral immune reactions → unlike other forms of hypersensitivity, it cannot be transferred by serum, but can be transferred by T cells → these T cells have been specifically sensitised by a previous encounter with the allergen → act by recruiting other cell types to the site of the reaction
- Examples of type IV hypersensitivity:
    - Contact → 48-72hrs
    - Tuberculin → 48-72hrs
    - Granulomatous → 21-28 days

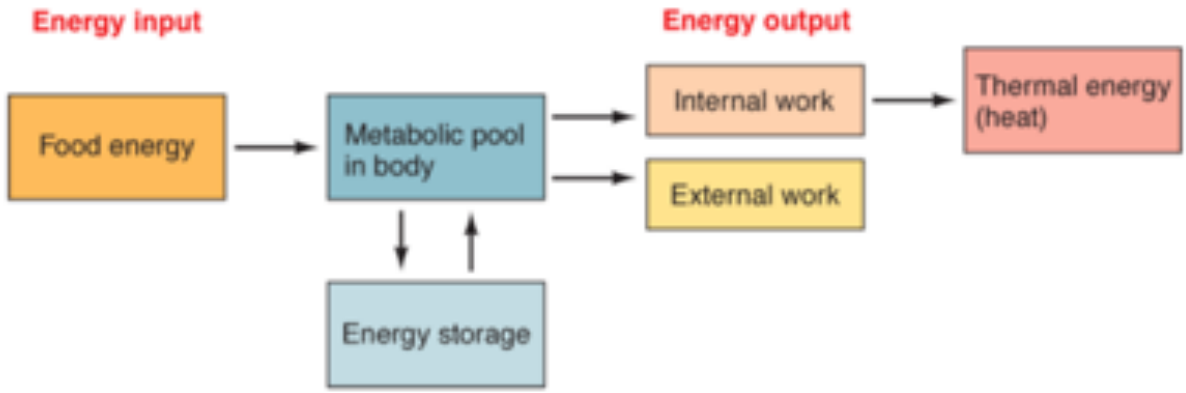
CONTACT DERMATITIS

- Characterised by eczematous reaction at the point of contact with allergen → primarily epidermal reaction → can be caused by e.g. nickel, poison ivy, or rubber → immunological active portion called hapten → haptens bind body proteins to become antigens, as they are too small alone to be antigenic
- Langerhans cells (APCs of skin) and keratinocytes (maintain structure of skin) → main cells involved in contact dermatitis
- Must have sensitisation phase before you get elicitation of response → only T cells with a T cell receptor for that specific hapten will form an immunological memory → on second exposure the Langerhans cell will activate memory T cells which produce IFN-α and therefore activate ICAM-1 in the epithelial cells → activating keratinocytes leads to cellular recruitment and an inflammatory response

Give examples of the major proteases

- Cathespins → cysteine, serine, aspartate proteases
- Zinc proteases

Describe nutritional balance via flow diagram



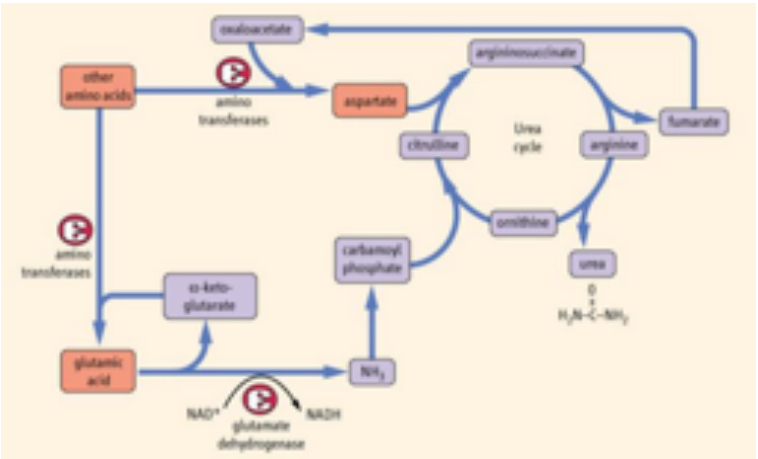
- The internal energy output is also known as the basal metabolic rate (BMR)

Outline the major energy stores of the body

- Liver → focal point for metabolic regulation and control → major glycogen reserve
- Adipose tissue → stores lipids primarily as triglycerides
- Skeletal muscle → substantial glycogen reserves → half of all protein in the body
- Neural tissue → must be supplied with a reliable supply of glucose
- Other peripheral tissues → able to metabolise substrates under endocrine control

Describe how muscle wasting occurs

- Muscle is the major nitrogen reserve in the body → wasting diseases may reflect issues with this storye → or may just reflect general insufficiency
- Types of muscle wasting:
    - Starvation → cancer (cachexia)
    - Injury/illness → AIDS, sepsis, renal failure
    - Immobilisation → sarcopaenia (elderly)
    - Nerve damage → spaceflight (???)
- Muscle wastage is caused by a difference in the nitrogen input (dietary protein) and nitrogen excretion mainly as urea → too little synthesis or too much degradation



Describe excretion of nitrogen

- Amino acids are broken down via amino transferases and glutamate transferases in aspartate and ammonia → ammonia is sent to the liver, where it enters the urea cycle → urea is then excreted via the kidneys → nitrogen is also lost through hair, skin, GI cells, mucous, nails, and body fluids

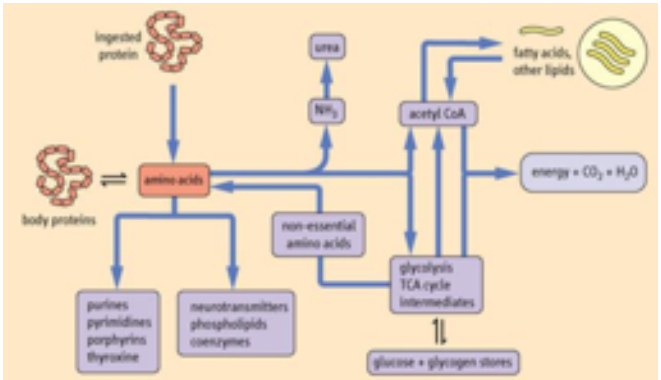
WEIGHT LOSS & NITROGEN METABOLISM

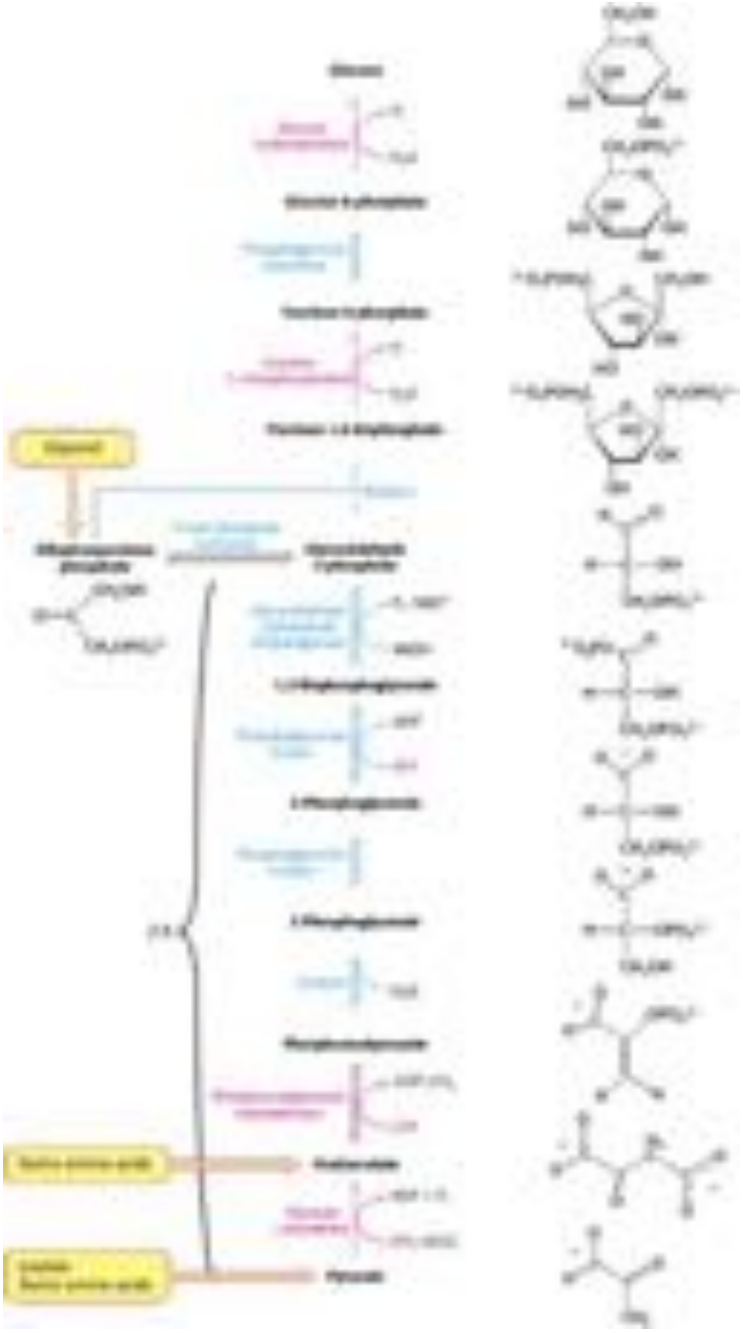
Describe the importance of urea

- Urea → small, neutral, non-toxic, and very water-soluble
- >80% of nitrogen is excreted as urea → the rest is excreted as creatinine, ammonium ions (toxic) and uric acid
- Urea is produced via the urea cycle → aspartate formed via transamination of oxaloacetate → oxidative deamination of glutamate to α-ketoglutarate
- Amino acids → produce oxaloacetate via the TCA cycle → this is also how AAs can be used to make glucose

Describe how glucose is made from proteins

- AAs are converted into pyruvate (or sometimes oxaloacetate) → enter into the TCA cycle → pyruvate converted to oxaloacetate, then to phosphoenolpyruvate (by pyruvate carboxylase) → then converted to fructose to glucose-6-phosphate and then finally to glucose



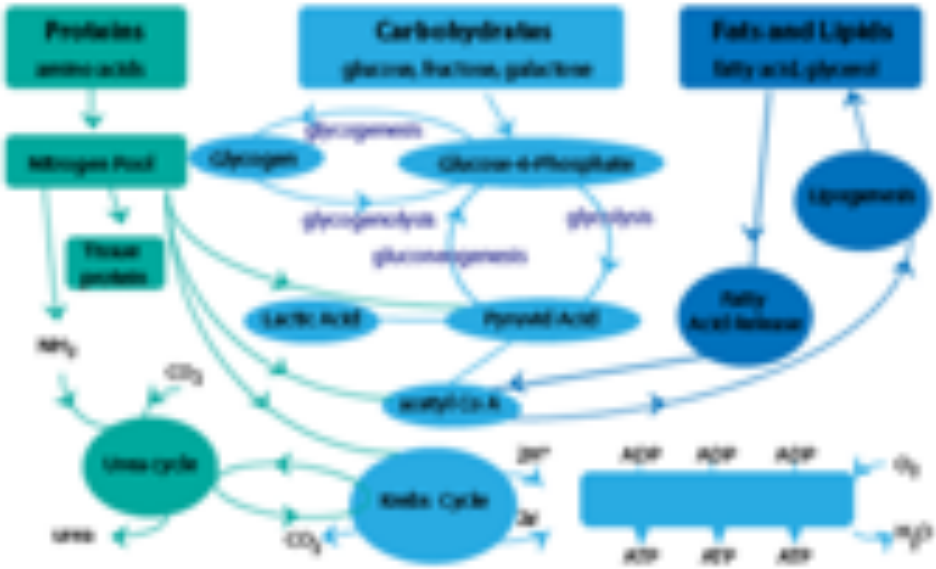


WEIGHT LOSS & NITROGEN METABOLISM

Explain the differential diagnosis of weight loss

- Decreased nutrient input → specific nutrient → specific energy producing nutrient deficit → general caloric deficit
- Genetic problem → decreased gene expression with age leading to malabsorption
- Increased demand for nutrients → illness
- Specific wasting disease → cachexia (cancer) or sarcopaenia (age)

Additional information



- There are two main pathways for proteolysis → lysosome pathway or ubiquitin-proteasome pathway
- Lysosome pathway → degrades extracellular and cell surface proteins via endosomes and most proteins via autophagosomes → common in starvation
- Ubiquitin proteasome pathway → degrades proteins from the cytoplasm, nucleus, and ER → common in stress
- Lysosomes → membrane-bound with a very low pH → contain multiple proteases, such as cathespins (cysteine/serine/aspartate proteases) and zinc proteases → has multiple entry mechanisms
- Proteasomes → barrel-like structures → use ubiquitination to break down proteins

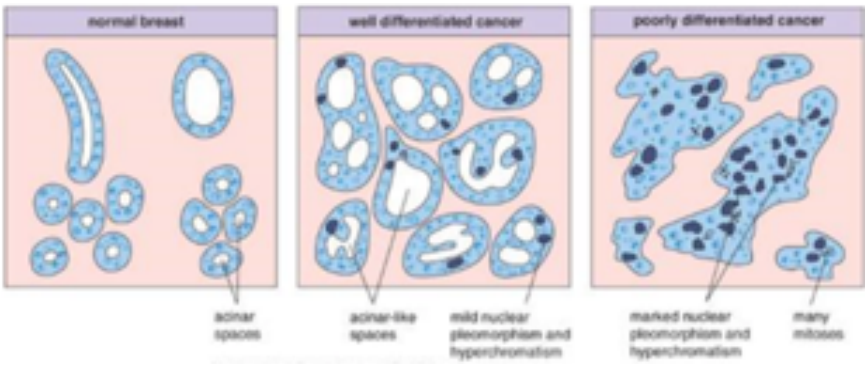
NEOPLASIA & LUNG CANCER

Distinguish the features of benign and malignant tumours

- There are 4 key differences between benign and malignant tumours:
    - Degree of differentiation (benign) or anaplasia (malignant)
    - Rate of growth → slow (benign) or fast (malignant)
    - Local invasion → benign tumours are not so invasive
    - Metastasis → normally only malignant tumours metastasise
- Differentiation → the features of a mature cell → well-differentiated tumours are similar to the parent cell → better prognosis
- Dysplasia → disordered growth, often pre-neoplastic
- Benign tumours can also be dangerous → depends on their location → if in a gland or brain, can cause increase in pressure or hormone release

Describe tumour differentiation, invasion, angiogenesis, and metastasis

DIFFERENTIATION AND ANAPLASIA



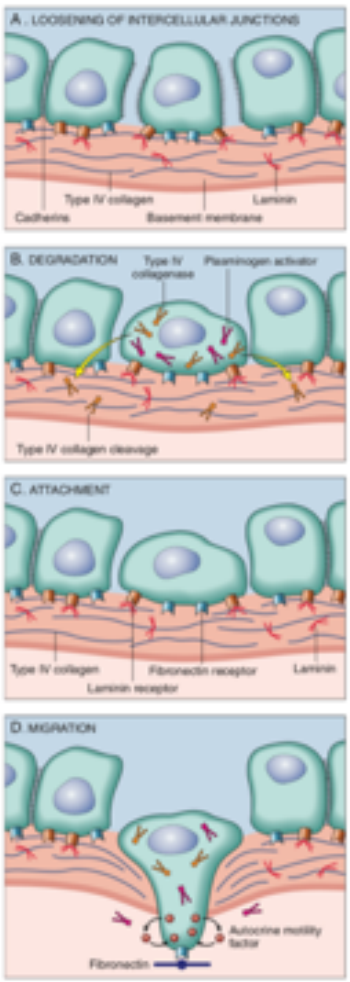
- One of the differences between benign and malignant cells is in differentiation or anaplasia of parenchymal tissue
- Anaplasia → loss of morphological and functional differentiation → most extreme alteration in cell growth
- Benign → well-differentiated morphologically and functionally → few mitoses
- Malignant → well-differentiated to undifferentiated (anaplasia) → due either to dedifferentiation of mature cells or growth of stem cells → more rapid growth = less differentiation
- Features include:
    - Cellular pleomorphism (variation in size and shape) → increased nucleus:cytoplasm ratio → giant cells with multiple nuclei → hyperchromatic nuclei
    - Nuclear abnormalities → increased mitotic figures → many abnormal
    - Failure to organise → polarity → lack of glands → stratification → grow in sheets
- Dysplasia → disordered growth (usually epithelial cells) → pre-neoplastic → does not necessarily lead to cancer → if stimulus is removed the tissue may return to normal
- Dysplasia is most easily illustrated in stratified squamous epithelium → basal cells appear in upper layers → inclusion of mitosis in upper layers

RATE OF GROWTH

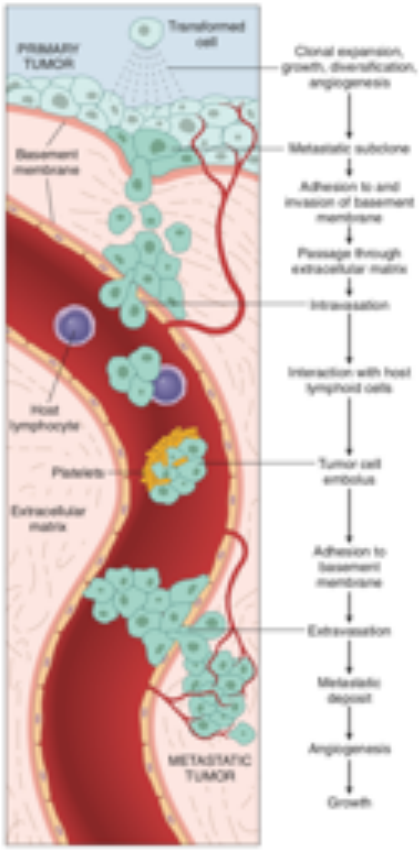
- Tumours grow over years before they are clinically evident as lesions
- Rapidly-growing tumours often have a necrotic core due to ischaemia → the mass of cells outgrows the blood supply available
- Generally benign tumours grow slowly and malignant tumours grow quickly → this depends on the differentiation of malignant tumours → poor differentiation = increased rate
- Benign tumours can grow quickly → e.g. under hormonal influence

NEOPLASIA & LUNG CANCER

LOCAL INVASION



- Benign tumours are rarely invasive → they do not infiltrate the surrounding tissue → often delineated by a fibrous capsule
- Malignant tumours progress by infiltration of surrounding tissues and invasion of adjacent tissue → they do this by breaching the BM
- While tumours are pre-invasive → contained by BM → they are called 'carcinoma in situ' or 'intraepithelial neoplasm'
- Surgical removal uses a wide margin → this is microscopically examined to ensure margins are clean → makes sure none of the cancerous cells remain → margins can be very blurry
- Invasion:
    - Breakdown of intercellular junctions → detach from neighbour → E-cadherins
    - Degradation of ECM and BM into connective tissue → proteolytic enzymes
    - Attachment to novel ECM components → proteolytically generated
    - Migration
- Cells need a blood or lymph supply to travel → secrete angiogenic factors to promote angiogenesis
- Support of tumours is essential for growth → such as stroma including blood supply
- Tumour will contain neoplastic cells and stromal tissue → excessive stromal growth is called desmoplastic response → excessive proliferation of neoplastic tumour cells will cause central necrosis due to ischaemia → this is the trigger for angiogenesis
- % of malignant cells = tumour cellularity
- Angiogenesis → the growth of new blood vessels via degradation and reformation of the vascular BM → angiogenic factors include VEGF and bFGF (basal fibroblast GF) → thrombospondin and thalidomide are anti-angiogenics
- Lymphangiogenesis → the growth of lymph vessels → VEGF-A and FGF2 can induce infiltration of bone marrow-derived inflammatory cells into tumours → which produce cytokines and lymphangiogenic factors → stimulate intratumoural lymphatic vessel growth and possible metastasis

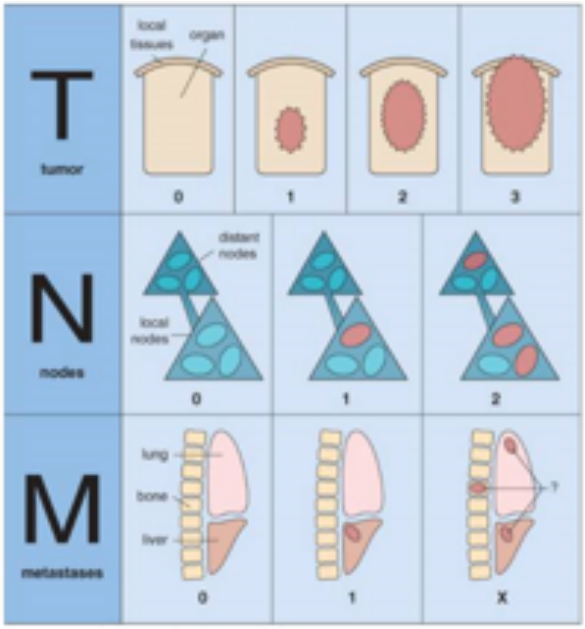


METASTASIS

- Benign tumours compress adjacent tissues or cause disease by uncontrolled hormone release → they do not metastasise
- Malignant tumours locally invade and then travel in the blood/lymph → establish secondary tumours at different sites
- Metastasis can occur in 3 ways:
    - Blood-borne spread
    - Lymphatic spread
    - Direct invasion of surrounding tissue

Describe tumour progression, grading and staging

- Grading of tumours can occur via histology/cytology → degree of differentiation → degree of pleomorphism (size and shape) → mitotic index
- There are also stages of tumours → defined using the TNM scale → tumour, node, and metastasis:
    - Tumour:
        - T0 = tissue free of tumour
        - T1-3 = refers to size and/or extent of main tumour → e.g. for breast cancer, T1 is <2cm, T2 is 2-5cm, and T3 = skin and/or chest wall involvement
    - Node:
        - N0 = no nodal involvement
        - N1 = local nodes involved
        - N2 = distant nodes involved
    - Metastasis:
        - M0 = no metastases
        - M1 = Demonstrable metastases
        - MX = Suspected metastases

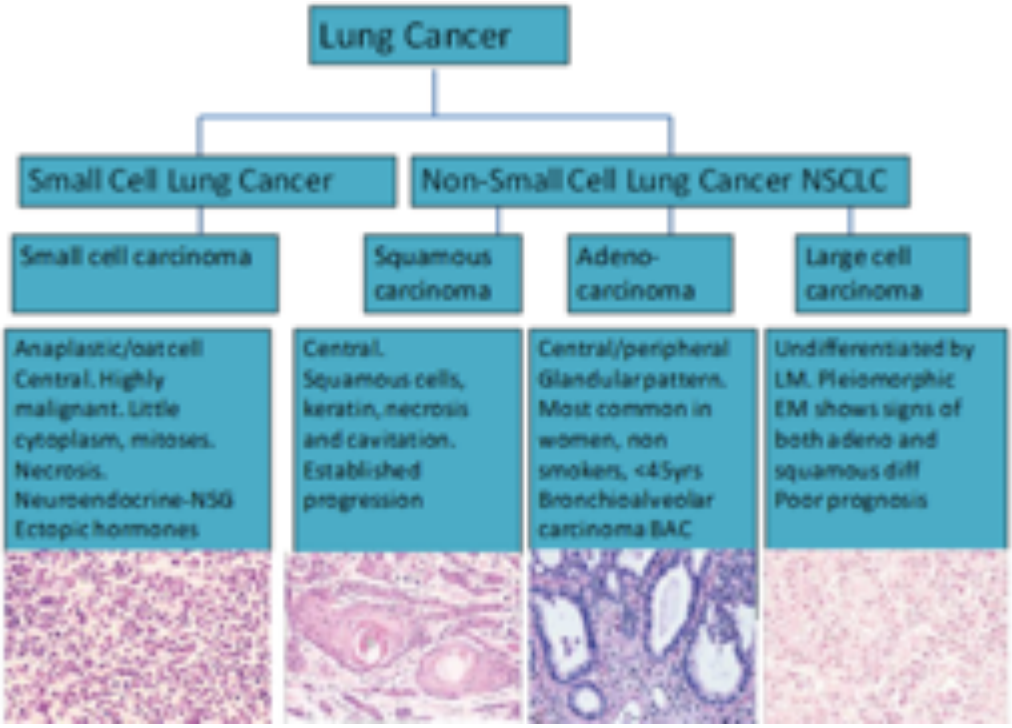


Understand the terminology relating to neoplasia and the nomenclature of tumours

Cell type	Benign	Malignant
Epithelial	-oma → prefixed with tissue of origin e.g. papilloma Adenoma → relating to gland	Carcinoma → prefixed with cell type e.g. basal cell carcinoma Adenocarcinoma → relating to gland
Mesenchymal (CT/muscle)	-oma → prefixed with tissue of origin → e.g. lipoma, chondroma, osteoma	-sarcoma → prefixed with tissue of origin → e.g. liposarcoma, chondrosarcoma
Embryonic	-blastoma → e.g. retinoblastoma	
Totipotent cells	Teratoma → from more than one germ layer	
Mixed tumours	Fibroadenoma	

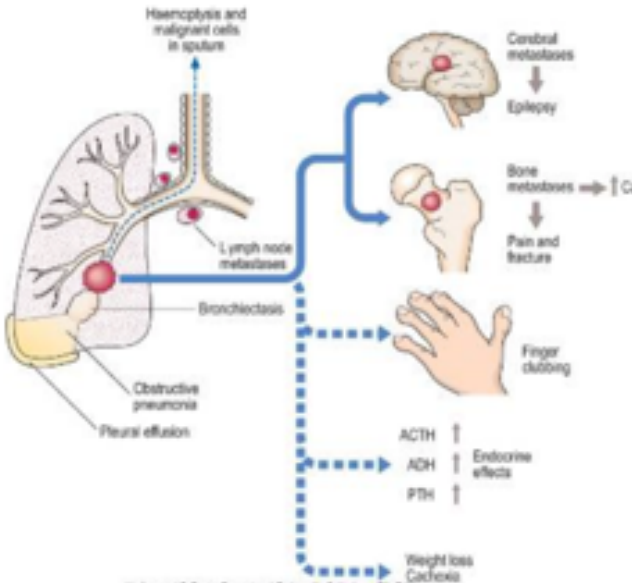
Describe the 4 main types of lung cancer, and distinguish small cell carcinoma from non-small cell carcinoma

- Classification → clinical and histological → 95% of primary malignant lung tumours are derived from bronchial epithelium → 5% from other areas
- Metastatic from breast, colorectal, prostate, testicular, and renal tumours
- Most common cause of death from cancer in industrialised nations
- Peak incidence 50-60yrs → but affects between 40-79yrs
- Smoking and industrial carcinogens are the main causes → smoking causes 90% of lung cancers
- Lung cancer can be subdivided into:
    - Small cell lung cancer (SCLC) → neuroendocrine and epithelial cells → small cell carcinoma
    - Non-small cell lung cancer (NSCLC) → epithelial cells → squamous carcinoma, adeno carcinoma, and large cell carcinoma



- Symptoms → chronic cough, hoarseness, chest pain, effusion (pleural/pericardial)
- 30% of cases present with symptoms of metastatic disease → fractures (bones), CNS symptoms (brain), jaundice (liver)
- Local spread to nodes is characterised by clinical syndromes:
    - SVC syndrome → compression of SVC from paratrachial nodes → obstruction of blood flow
    - Horner's syndrome → compression of cervical sympathetic chain
- Tests → imaging and tissue diagnosis → cytology of sputum, lavage, effusion, or aspirate → biopsy via bronchoscopy
- Screening is not possible as there are no early symptoms → X-ray screening trials did not improve survival → most tumours were inoperable
- Grading:
    - NSCLC → uses TNM
    - SCLC → either limited (confined to 1 hemithorax, mediastinum and supraclavicular nodes) or extensive (beyond this)

- Treatment:
    - NSCLC → surgery for TNM I and II → palliative radio/chemotherapy for TNM III and IV
    - SCLC → limited = radio/chemotherapy to affected site, possible prophylactic cranial irradiation → extensive = radio/chemotherapy for metastases
- Most tumours have metastasised to distant sites (70%) on presentation → 25% have regional lymph node involvement on diagnosis
- Prognosis:
    - 1 year survival → approx. 30%
    - 5 year survival → approx. 9%
    - 5 year survival for localised lung lesions → 45%



Lung cancer type	Location in the lung	Features
Adenocarcinoma (38%)	Peripheral	- Most common type of lung cancer in nonsmokers and more common in women - Arises from small airway epithelial and type II alveolar cells - Should test for EGFR mutation for possible targeted therapy - Sometimes appear at site of scarring - Tend to form glands and secrete mucin
Squamous cell carcinoma (20%)	$^2/_3$central and $^1/_3$ peripheral	- Strongly associated with cigarette smoking - Arises from large (proximal) airway epithelial cells - Tend to create obstruction and cause distal atelectasis - Intrathoracic spread rather than distant metastasis → therefore best prognosis
Small-cell lung carcinoma (14%)	Central (endobronchial) → neuroendocrine cells are located at bifurcation of small airways	- Strongest smoking association - Arises from pulmonary neuroendocrine cells, which are responsible for making neurotransmitters, growth factors, and vasoactive substances - Causes paraneoplastic syndrome → commonly secrete ADH or ACTH - Rapid growth and early distant metastasis (brain, liver, bone) → therefore worst prognosis
Large cell carcinoma (3-5%)	Peripheral	- Behave similar to adenocarcinomas but the lesions formed tend to be somewhat larger

PARANEOPLASTIC SYNDROME

- Paraneoplastic syndrome → side effects of cancer but not localised
- Up to 12% of patients have paraneoplastic syndrome
- Most are endocrine related to SCLC → Cushing's syndrome (ACTH) and syndrome of inappropriate ADH secretion
- Hypercalcaemia is also associated with squamous cell carcinoma
- Neuromuscular syndromes are also an example of paraneoplastic syndromes

CANCER OF THE PLEURA

- Malignant mesothelioma → tumour of the pleura → associated with asbestos exposure (50% of tumours) either directly or by living in close proximity to asbestos factory
- Long latent period → up to 50yrs (>25yrs)
- Asbestos exposure plus smoking → increased risk of carcinoma not mesothelioma
- Gross appearance → lung ensheathed by yellow-white tumour
- Histology → spindle cells or epithelial appearance or both
- Pleural effusion (exudate) → can be due to local tumour invasion or metastasis from lung/breast carcinomas via lymphatics

TUBERCULOSIS

Describe the global and UK burden, aetiology, signs and symptoms, and key methods for diagnosis of tuberculosis

PREVALENCE

- TB is 2nd only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent
- In 2012 → 8.6 million fell ill with TB → 1.3 million died → 95% of deaths in low- and middle-income countries
- In 2012 → 530,000 children became ill with TB
- Leading cause of death in HIV → approximate ¼
- Multi-drug resistant TB has been found to be present in virtually all countries that have been surveyed → Ab resistant TB and TB resistant to all anti-TB drugs available (pan-resistant)
- TB death rate dropped 45% between 1990 and 2012
- Labs do not like handling TB samples → often get sent to specialist centres for analysis
- There are hot spots for TB prevalence around the UK → London is very high, followed by Birmingham → often very dense urban areas
- Found that a lot of people diagnosed with TB in the UK were not actually born in the UK → thought that when they visited family abroad they contracted the disease → high levels found in India, Pakistan, etc.
- Key statistics in the UK:
    - 8751 cases in 2012
    - 73% occurred in people born in high burden countries and concentrated to large urban centres
    - Cases born outside of the UK → almost half identified within 5 years
    - 7.3% had at least one social risk factors e.g. dense housing
    - 7.4% resistant to any first line drug → significant number due to number of cases diagnosed each year
    - 1.6% are multi-drug resistance

MYOBACTERIUM TUBERCULOSIS

- *M. tuberculosis* was first identified by Robert Koch
- It is a complex of organisms → can cause human diseases → consists of:
    - *M. africanum*
    - *M. bovis* → less common now milk is pasteurised → attenuated version used in BCG vaccine
    - *M. microti*
    - *M. canetti*
- Main agent now is now *M. tuberculosis* → it is an obligate aerobe → rod shaped bacillus → acid fast and non-spore forming
- It is very difficult to Gram stain → waxy outer coat and mycolic acid in cell wall → helps protect against antibiotic therapy and host defences
- Non-tuberculous mycobacteria and *Norcardia spp* → also contain mycolic acid so difficult to differentiate on sputum spear examination
- It has a slow division time → but like highly oxygenated tissues → hence likes the respiratory tract

TUBERCULOSIS

RISK FACTORS

- Risk factors include people who have recently been infected with TB bacteria → close contact with TB patients, migrated from high rate areas, homeless, drug users, HIV infected, or children under 5 with positive TB test → immunosuppression or weakened immune system also increases risk
- Risk factors:
    - HIV
    - Substance abuse
    - Diabetes mellitus
    - Severe kidney disease
    - Low body weight
    - Organ transplant
    - Medical treatment → corticosteroid or organ transplant
    - Specialised treatment → RA or Crohn's disease

TYPES OF TB

- Not everyone infected with TB bacteria becomes sick → divided into latent TB (no signs or symptoms, host defences are controlling infection) and TB disease
- Latent TB is not considered to be infectious → but will get positive blood/skin test but normal CXR → still needs treatment to prevent it moving on to TB disease
- TB disease shows signs and symptoms and patient feels sick → infectious and show a positive skin/blood test → may now have an abnormal CXR or sputum sample
- Both forms of TB need treatment
- Other sites of infection:
    - Skin/soft tissue → commonest type of non-pulmonary disease → diffuse swelling of the neck
    - Bones and joints → especially spine → Pott's disease
    - Genitourinary tract → prostatitis, orchitis or renal lesions → may cause infertility in women → sterile pyuria (WBC in urine but won't grow TB on culture)
    - Disseminated disease → many organs involved simultaneously

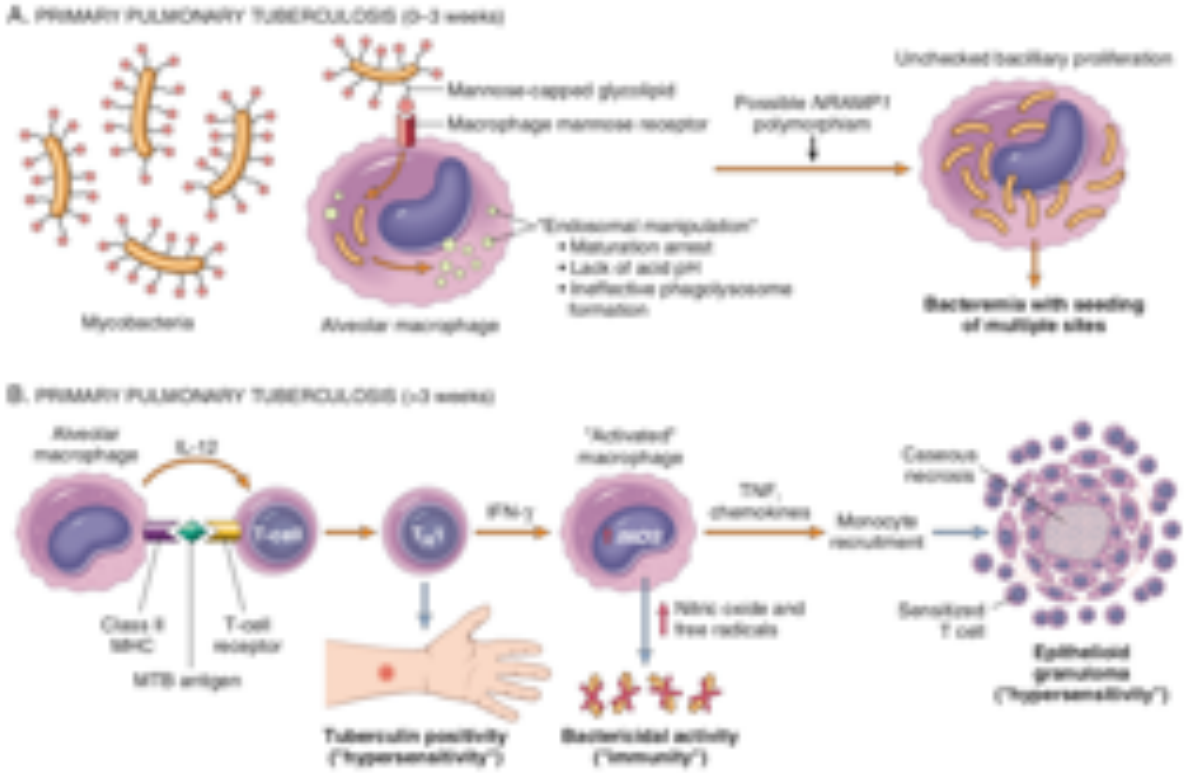
TRANSMISSION

- Transmission is most commonly through contact with active TB disease or aerosol droplets from cough → may be found on dust particles → waxy outer coating makes organism resistant to desiccation → can survive outside of a host for quite a long time

PATHOGENESIS

- 3 weeks after exposure → inhaled mycobacteria engulfed by macrophage → mycobacteria manipulate endosomes → defective phagolysosome formation → mycobacteria proliferate in macrophages → mild fly symptoms/asymptomatic
- Cell-mediated immune response → macrophages drain to lymph nodes → antigens presented to T cells, which are converted to T_H1 cells → T_H1 cells activated macrophages via IFN-γ → monocytes recruited and converted into epithelioid macrophages
- Ghon complexes form → ghon focus (primary lesion) plus affected lymph nodes
- Granulomatous inflammation → aggregates of epithelioid macrophages form, and giant cells may be present → these are surrounded by T_H1 cells which chronically activate macrophages → older granulomas have fibroblasts and collagen → hypoxia can cause core of caseous necrosis (unique to TB → yellow-white cheese-like amorphous granular lysed cells with no cell outlines or architecture)

- Caseating tubercle can erode into lung vasculature → systemic dissemination to any organ via pulmonary vein (commonly liver, spleen, and kidneys) → seeds expand, coalesce, and destroy large areas of organs → military TB → if pulmonary artery is involved, it causes military TB of lung
- Isolated organ (metastatic) TB → only a few organisms invade the blood stream → they are dealt with or can remain latent in an organ for years (e.g. brain, kidney, adrenals)



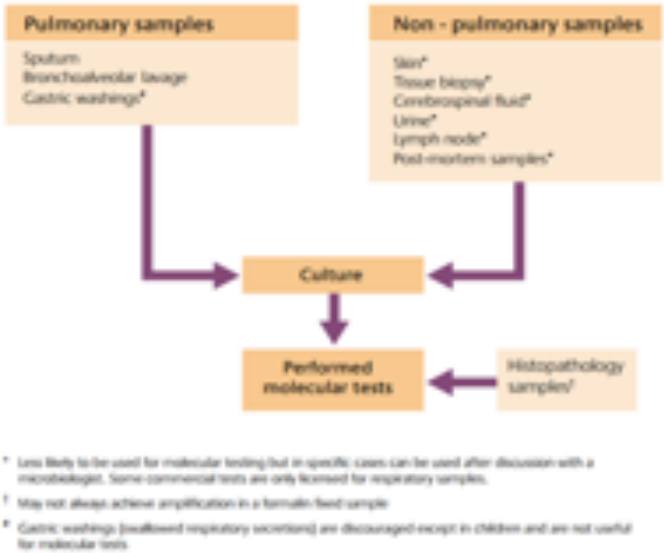
SIGNS & SYMPTOMS

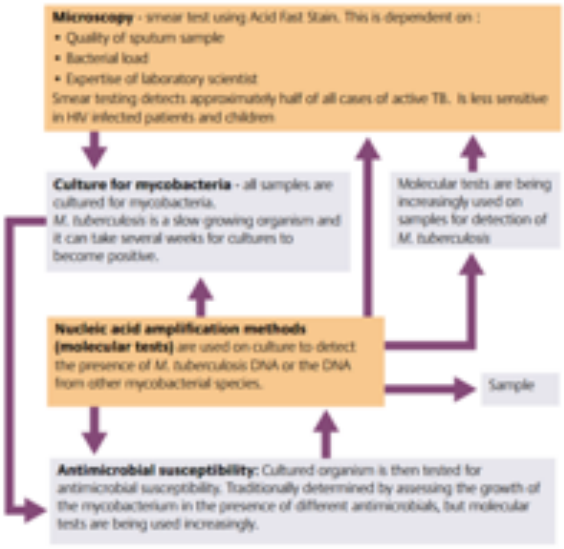
- Signs and symptoms for TB disease can take a long time to present → several months
- Examples of symptoms:
  - Fever and night sweats → indicative of TB
  - Persistent cough lasting longer than 3 weeks
  - Weight loss
  - Fatigue
  - Loss of appetite
  - Chest pain

DIAGNOSIS

- Diagnosis is normally by skin or blood test → as well as CXR (typically presents in apical lobes) and microbiological sampling → the latter requires culturing so takes a little longer
- Skin test (TST) is also called Mantoux test → 0.1ml of tuberculin-derived protein injected into the skin of forearm → results in a wheal (6-10mm) → measured 458-472hrs later and diameter classified depending on associated risk factors
- Blood tests → IFN-γ release assays (IGRA) → WBCs from infected persons release IFN-γ upon exposure to antigens derived from *M. tuberculosis* → rapid testing (approx. 24hrs) and BCG vaccination does not affect results → produces limited data on progression to TB disease → expensive

- TB cannot be Gram stained effectively so Ziehl-Neelsen stain is used → works on the same principle as Gram staining but works for TB





TREATMENT

- Treatment for latent TB should be initiated after the possibility of TB disease has been excluded
- Persons suspected of having TB disease should receive the recommended multi-drug regimen for treatment of disease until the diagnosis is confirmed or ruled out
- If exposed to and infected by a person with MDR TB or extensively (XDR) TB → preventative treatment may not be an option
- NICE guidelines for treatment of latent TB:
    - Either 6 months of isoniazid (6H) or 3 months of rifampicin and isoniazid (3RH) for people aged 16-35yrs not known to have HIV
    - Either 6 months of isoniazid (6H) or 3 months of rifampicin and isoniazid (£RH) for people >35yrs in whom treatment for latent TB infection is recommended
    - 6 months of isoniazid (6H) for people of any age who have HIV
    - 6 month of rifampicin (6R) for contacts, aged >35yrs, of people with isoniazid-resistant TB
    - People eligible for treatment of latent TB infection, but who decline to take this treatment, should be given 'inform and advise' information about TB and have chest X-rays 3 and 12 months later
- Treatment for active respiratory TB:
    - A 6 month, 4 drug initial regimen → 6 months of isoniazid and rifampicin (6RH) → supplemented in the first 2 months with pyrazinamide and ethambutol
    - In adults not known to have HIV, or who are HIV +ve, or children

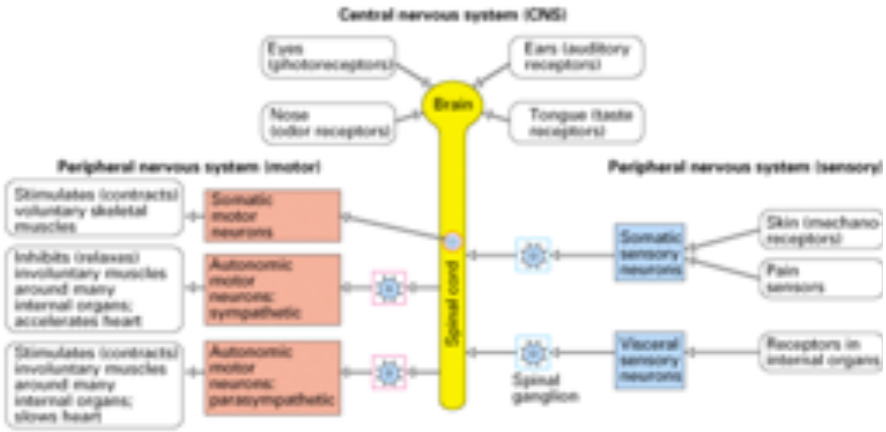
TB & HIV

- Risk of HIV is 10-20x greater in people with HIV
- At least 1/3 of 34 million people living with HIV worldwide are also infected with latent TB
- It is the leading cause of death in HIV +ve people → routing HIV testing should therefore be offered to patients with presumptive or diagnosed TB
- 3 I's for HIV/TB → intensified case finding for TB → isoniazid preventative therapy → infection control

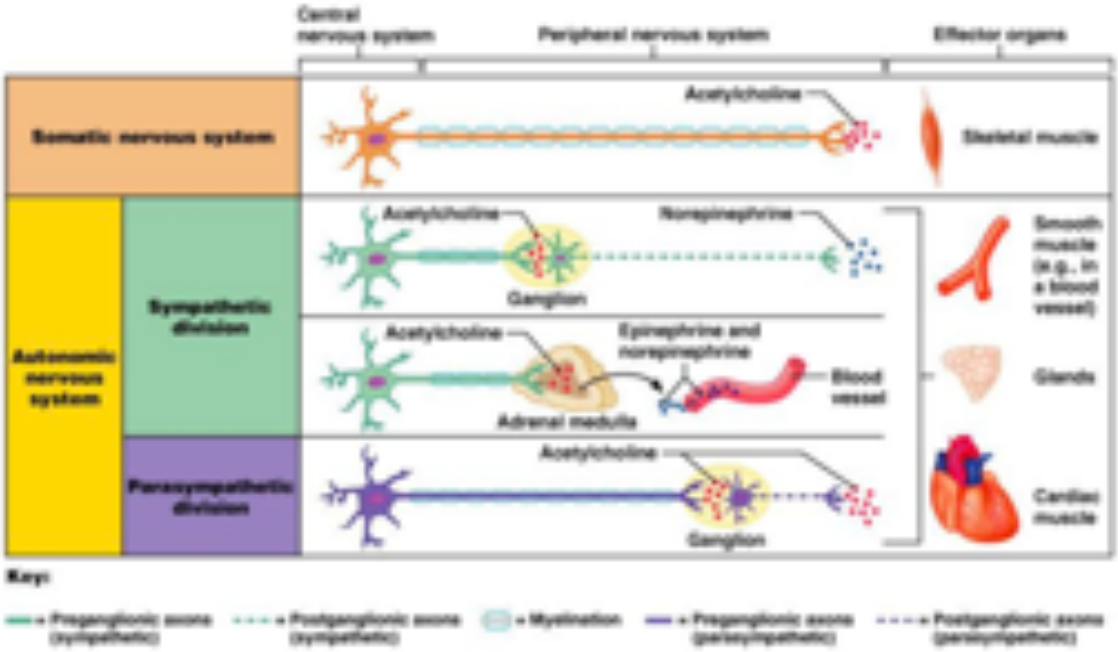
THE AUTONOMIC NERVOUS SYSTEM

Describe the basic organisation of the nervous system

- Central (CNS) → consists of the brain and spinal cord
- Peripheral nervous system (PNS) → consists of autonomic (sympathetic/parasympathetic) and somatic (motor/sensory)
- Sympathetic (SNS) → fight, flight, or fright
- Parasympathetic (PSNS) → rest and digest
- Enteric (ENS) → nervous system of the gut and influenced by SNS and PNS → cell bodies are within the walls of the gut → self-regulating



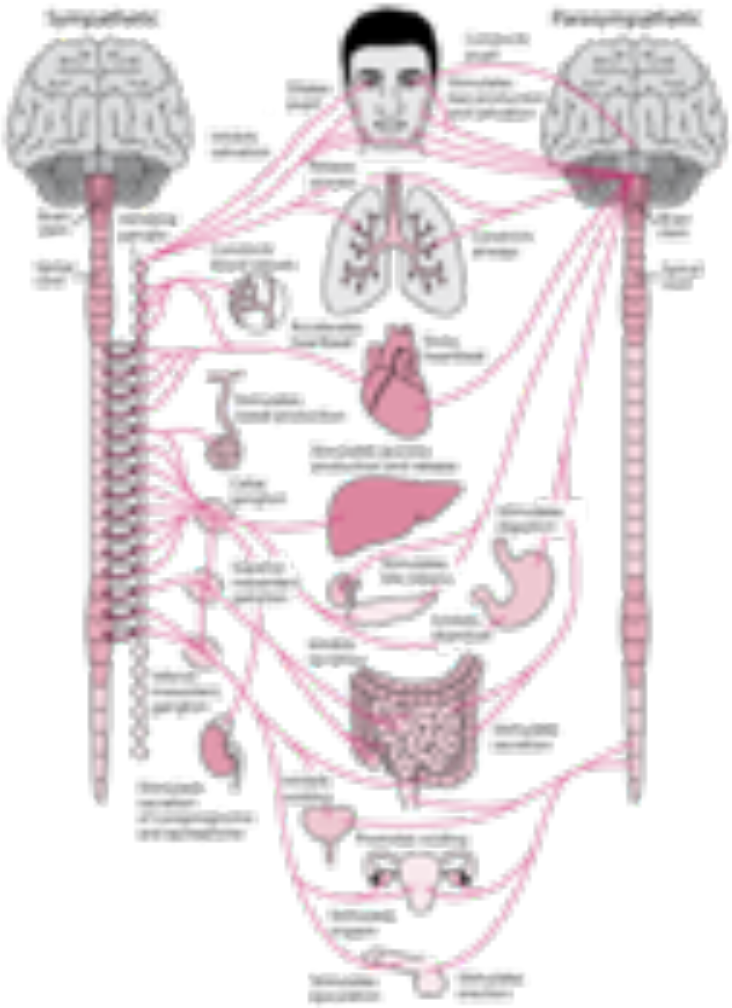
Describe in more detail the organisation of the autonomic nervous system



- Both branches of the ANS have pre-ganglionic cell bodies in the CNS and post-ganglionic cell bodies in the periphery
- The sympathetic chain → a line of sympathetic ganglia that sits very close to, and runs alongside, the CNS → it allows nerve fibres to travel to spinal nerves that are superior and inferior to the one in which they originate
- Parasympathetic NS synapses very close to the tissue it innervates → either in the surrounding tissue or even in the wall of the organ
- Sympathetic pre-ganglionic cell bodies are found in the thoracolumbar region of the spine → T1-L1/2 → myelinated pre-ganglionic fibres secrete ACh onto nicotinic receptors → unmyelinated post-ganglionic fibres secrete noradrenaline onto adrenergic receptors (except to sweat glands and arrector pilorum muscles → ACh to muscarinic receptors)

- Parasympathetic pre-ganglionic cell bodies are found in the craniosacral region of the spine → brain stem (cranial) → CN III, VII, IX, X and S2-4 → myelinated pre-ganglionic fibres secrete ACh to nicotinic receptors → unmyelinated post-ganglionic fibres secrete ACh onto muscarinic receptors
- The vagus nerve (CNX) arises in the medulla → it has no parasympathetic action in the head and neck → parasympathetic activities occur from the neck to the descending colon → everything after this is controlled by sacral nerves
- Adrenal medulla → post-ganglionic cell bodies without axons (chromaffin cells) → release Adr and NA into the blood stream

Describe the effects of autonomic activity on effector tissues such as the heart

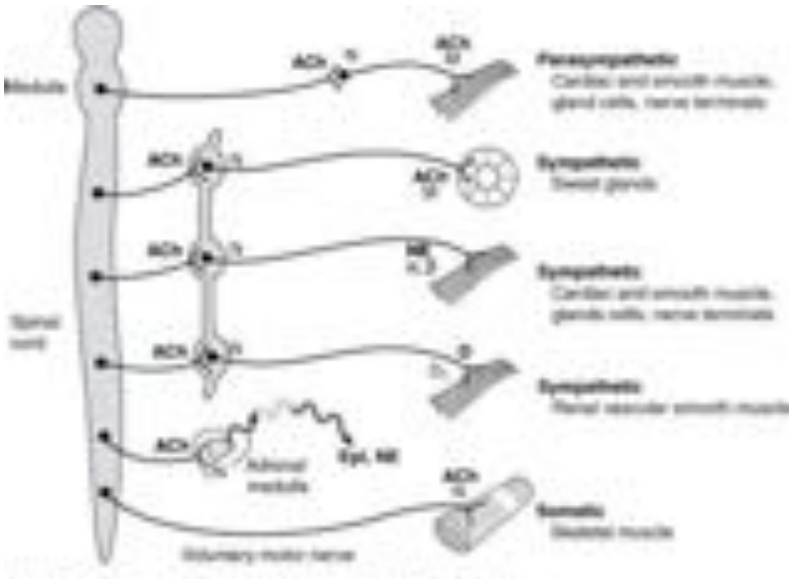


	Sympathetic	Parasympathetic
Heart	Increased HR Increased contractility	Decreased HR No effect on contractility
Blood vessels	Vasoconstriction	Vasodilation
Gut	Decreased activity	Increased activity
Sweat	Increased secretion	N/A
Airways	N/A	Bronchoconstriction

- NB: SNS causes bronchodilation, but via the release of Ad

AUTONOMIC PHARMACOLOGY

List the transmitters utilised and the receptors activated at the various locations of the ANS



- The autonomic NS is the branch of the NS that regulates involuntary movement and function
- Parasympathetic → routine maintenance
- Sympathetic → mobilisation and increased metabolism
- The main NTs are acetylcholine (parasympathetic) and noradrenaline (sympathetic) → not always true
- ANS uses two-neurone efferent pathway → pre-ganglionic and post-ganglionic
- Pre-ganglionic cell bodies in grey matter of CNS
- Post-ganglionic cell bodies in periphery
- SNS and PNS are not always opposing each other:
    - Antagonism → heart, pupil, gut, bladder, bronchi
    - Unopposed → blood vessels, sweat (SNS) and ciliary body, lacrimal glands (PSNS)

Describe the transmitters utilised and receptors activated at the various locations of the ANS

PARASYMPATHETIC TRANSMITTERS & RECEPTORS

- Pre- and post-ganglionic cholinergic neurones → ACh
- Nicotinic receptors in the ganglionic transmission
- Muscarinic receptors on effector tissue
- Muscarinic (M) receptors:
    - Metabotropic → G-protein
    - M1-M5
    - Post-synaptically in SM, cardiac muscle, glands
    - Agonists → ACh, muscarine
    - Antagonists → atropine
- Nicotinic (N) receptors:
    - Ionotropic → ion channel
    - ANS ganglia, motor end plate, CNS
    - Agonists → ACh, nicotine
    - Antagonists → curare (tubocurarine)

SYMPATHETIC TRANSMITTERS & RECEPTORS

- Pre-ganglionic → cholinergic neruones
- Post-ganglionic → noradrenergic neurones
- Ganglionic transmission → nicotinic receptors
- Adrenoceptors on effector tissues → metabotropic (G-protein) → α- and β-adrenoceptors
- α-adrenoceptors:
    - α_1 and α_2 (pre/post-ganglionic)
    - Blood vessels of organs and tissues → except skeletal muscle vessels
    - Agonists → NA>adrenaline>phenylephrine
    - Antagonists → phentolamine
- β-adrenoceptors:
    - β_1 (myocardium), β_2 (bronchi, uterus, muscle, and coronary vessels), and β_3 (adipose tissue)

  - Agonists → adrenaline>NA>isoprenaline
  - Antagonists → propranolol
- Drugs – adrenoceptor → agonist → use – antagonist → use:
  - $\alpha 1$ → phenylephrine → hypotension – prazosin → hypertension (rarely)
  - $\alpha 2$ → clonidine → hypertension (rarely) – yohimbine → erectile dysfunction
  - $\beta 1$ → dobutamine → cardiac failure (rarely) – atenolol → cardiac arrhythmias
  - $\beta 2$ → salbutamol → asthma/COPD
- NB: The effects of the SNS on sweat glands are mediated by muscarinic receptors → the post-ganglionic neurones are also cholinergic → M_3 receptors

Outline the second messenger cascades that may be set in place inside target cells by receptor activation

Nicotinic	Ion channel (Na^+/K^+)
Muscarinic M_1 Muscarinic M_2	Phospholipase C, reduced cell membrane K^+ conductance Adenylyl cyclase, increased cell membrane K^+ conductance
α-adrenoceptor	Phospholipase C, PIP_2 hydrolysis
β-adrenoceptor	Adenylyl cyclase

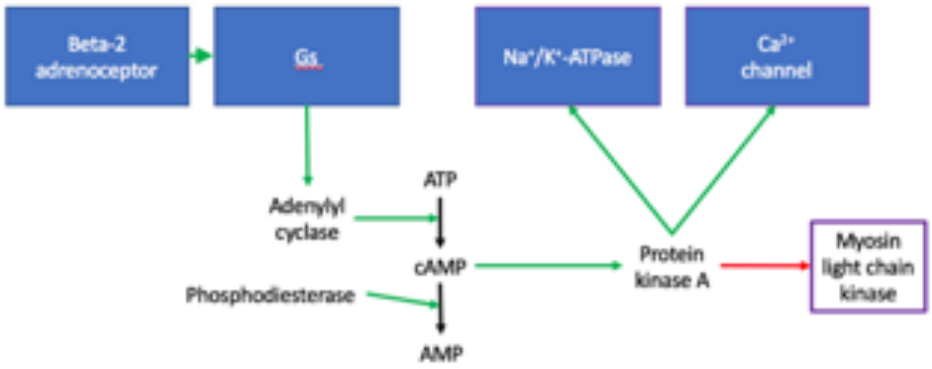
Outline the effects of local application of various drugs on the heart, blood vessels, gut, airways, and salivary glands

M_1	Salivary glands	Increased salivation
M_2	Heart	Negative chronotropy
M_3	Airway smooth muscle	Bronchoconstriction
M_3	Gut smooth muscle	Contraction
M_3	Bladder smooth muscle	Contraction
α_1	Blood vessels, vasa differentia	Vasoconstriction
α_1	GI smooth muscle	Relaxation
α_1	GI sphincteric muscle	Contraction
α_2	Presynaptic sympathetic neurones	Limits transmitter release
β_1	Heart	Increased inotropy & chronotropy
β_1	GI smooth muscle	Relaxation
β_2	Bronchi	Relaxation
β_3	Adipose tissue	Lipolysis

Describe the mechanisms of the various classes of drug used to treat asthma

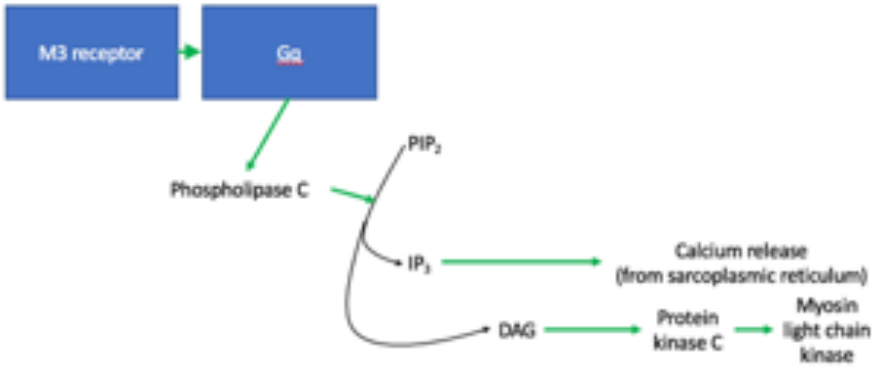
β_2 AGONISTS

- β_2 agonists activate the $G_{\alpha s}$ protein subunit, activating adenylyl cyclase → this converts ATP to cAMP, which then activates protein kinase A → PKA deactivates myosin light chain kinase (which causes contraction in smooth muscle) → relaxation of smooth muscle and bronchodilation → PKA also increases function of Na^+/K^+-ATPase to hyperpolarise muscle cell, and also inhibits release of Ca^{2+} (which activates calmodulin which activates MLCK) → PKA also upregulates MLC phosphatase to breakdown myosin light chain
- Are inhaled, and can be fast-acting (e.g. salbutamol) or long-acting (e.g. formoterol)
- Adverse effects:
    - Tachycardia/palpitations → due to activation of β_1 receptors in heart
    - Fine muscle tremor → due to activation of β_2 receptors in skeletal muscle
    - Hyperglycaemia/hyperinsulinaemia
    - Hypokalaemia
    - Paradoxical bronchospasm



MUSCARINIC ANTAGONISTS

- M_3 receptor activates $G_{\alpha q}$ protein subunit →activates phospholipase C, which cleaves PIP_2 to IP_3 and DAG → IP_3 causes Ca^{2+} release from sarcoplasmic reticulum to activate calmodulin, and DAG activates protein kinase C which activate MLCK → leading to bronchoconstriction
- Muscarinic antagonists block the M_3 receptor and so prevent this from occurring
- Are inhaled, and can be fast-acting (e.g. ipratropium) or long-acting (e.g. tiotropium)
- Adverse effects:
    - Blurred vision → due to inhibition of ocular reflexes mediated by PSNS nerves
    - Dry mouth → due to inhibition of M_1 receptors in salivary glands
    - Urinary retention → due to inhibition of M_3 receptors in bladder smooth muscle
    - Constipation → due to inhibition of M_3 receptors in gut smooth muscle



CORTICOSTEROIDS

- These freely cross the plasma membrane and bind to cytosolic receptors → move into the nucleus and affect transcription of genes → reduce phospholipase, so less formation of arachidonic acid derivatives such as leukotrienes (cause bronchoconstriction) and prostaglandins (promote inflammation) → reduced macrophages, interleukins, and cytokines
- Since they act by transcription their action is delayed, so they are not suitable as sole therapy in acute exacerbation
- Can be inhaled (e.g. beclomethasone), oral (e.g. prednisolone), or IV (e.g. hydrocortisone)
- Adverse effects:
    - Hoarse voice
    - Oral candidiasis → caused by local immunosuppression
    - Infection
    - Osteoporosis
    - Adrenal suppression → caused by negative feedback in the HPA axis
    - Cushing's syndrome → from excessive usage

METHYLXANTHINES

- These are non-specific phosphodiesterase inhibitors → prevent the conversion of cAMP to AMP → more cAMP to activate PKA and deactivate MLCK → bronchodilation
- Can be administered orally for chronic (e.g. theophylline) or IV for acute (aminophylline)
- Metabolised using CYP450, and have a narrow therapeutic window
- Adverse effects:
    - GI disturbance
    - Tachycardia
    - CNS stimulation
    - Hypokalaemia

LEUKOTRIENE RECEPTOR ANTAGONISTS

- Leukotrienes cause an inflammatory response, including bronchoconstriction (G_q-linked), vasodilation, mucous production, and eosinophil recruitment
- Leukotriene receptor antagonists are competitive inhibitors, making them unsuitable for treating acute exacerbations of asthma
- LTRAs should be considered early in children <5yrs to avoid high doses of ICS/LABA
- Adverse effects:
    - Headache
    - Dry mouth
    - GI upset
    - Hypersensitivity