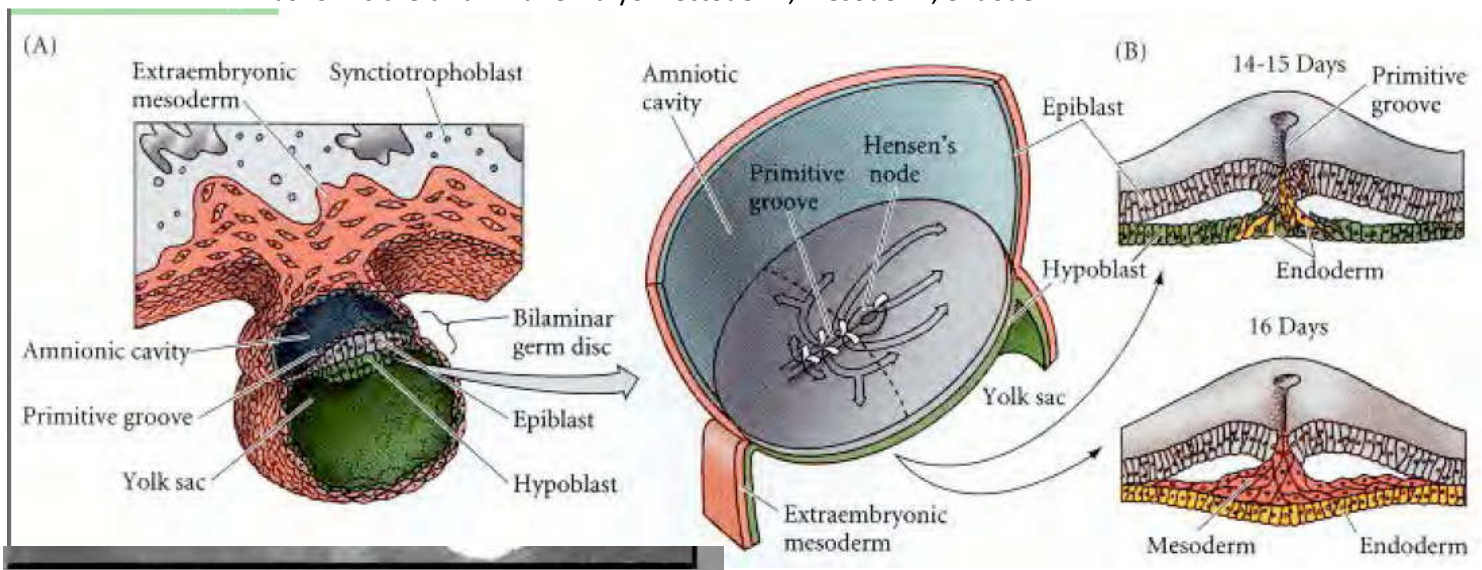
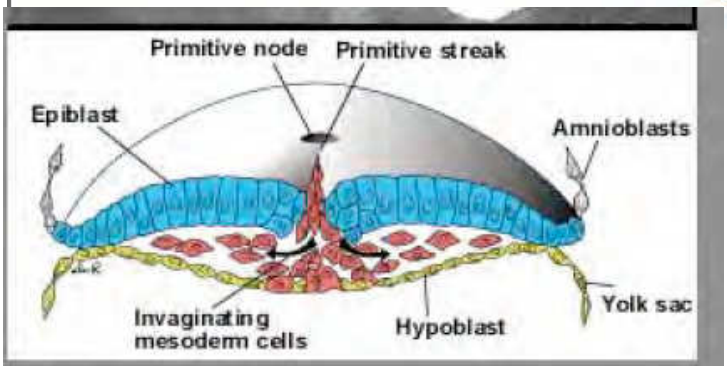
Trilaminar contributions

- Overview:
  - A simple tube is converted into a complex muscular, glandular and duct network that is associated with many organs
- Contributions:
  - Endoderm – epithelium of the tract, glands, organs such as the liver/pancreas/lungs
  - Mesoderm (splanchnic) – muscular wall, connective tissue
  - Ectoderm (neural crest – muscular wall neural plexus

Gastrulation

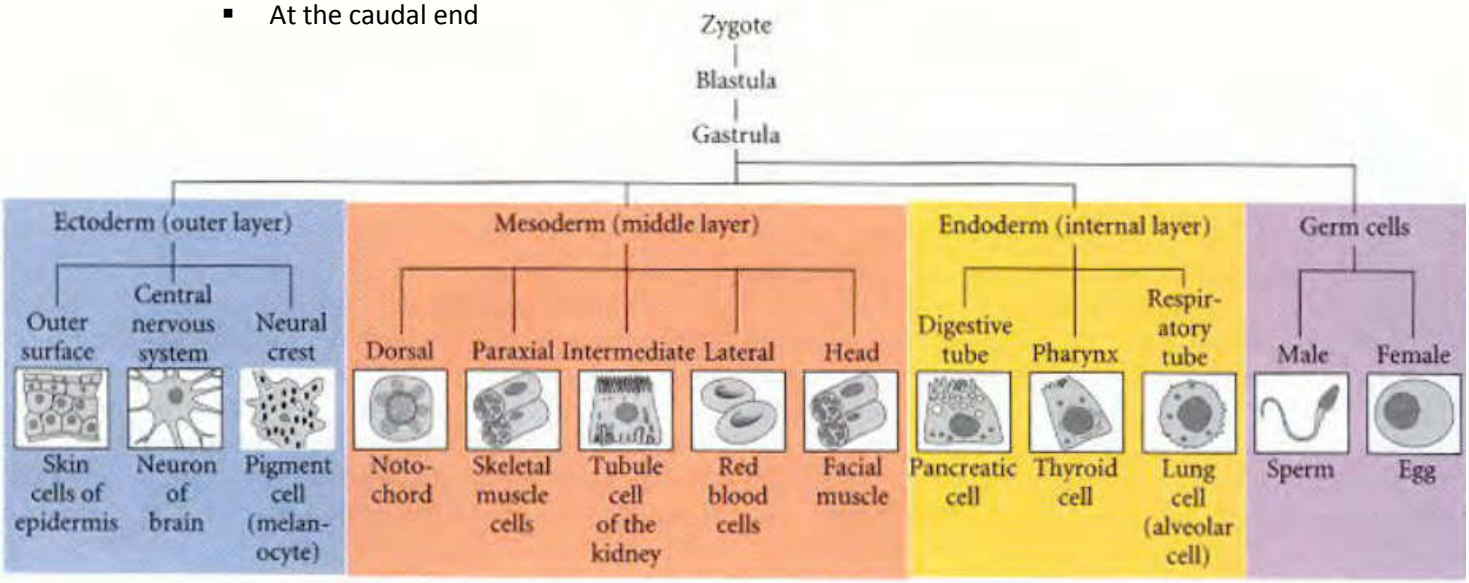
- Process of cell migration from the epiblast through the primitive streak
  - Primitive streak forms on the bilaminar disk
  - Primitive streak contains the primitive groove, the primitive pit and the primitive node
  - Primitive streak defines the body axis, the rostral caudal ends, and left and right sides
    - Thus forms the trilaminar embryo – ectoderm, mesoderm, endoderm





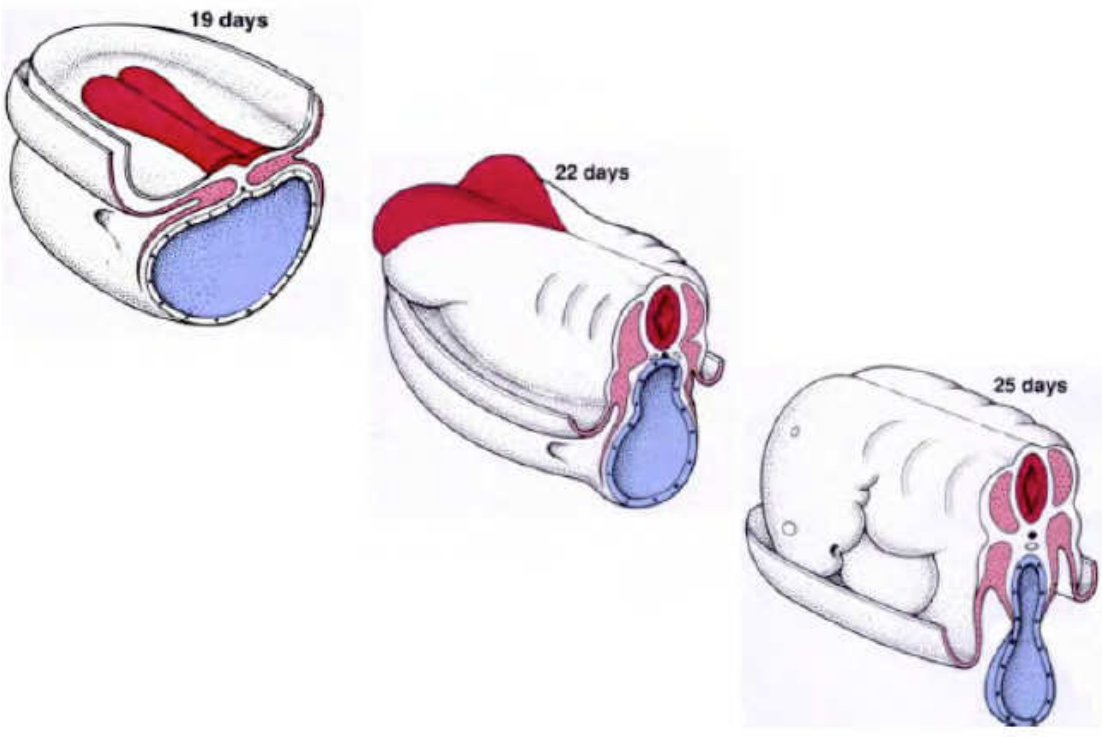
- Germ cell layers:
  - ectoderm – forms the nervous system and the epidermis epithelia
    - 2 main parts
      - midline neural plate – columnar epithelium
      - lateral surface ectoderm – cuboidal, containing sensory placodes and skin/hair/glands/enamel/anterior pituitary epidermis
  - mesoderm – forms the muscle, skeleton, and connective tissue
    - cells migrate second
    - migrate laterally, caudally, rostrally until week 4
  - endoderm – forms the gastrointestinal tract epithelia, the respiratory tract and the endocrine system
    - cells migrate first and overtake the hypoblast layer
    - line the primary yolk sac to form the secondary yolk sac

- Membranes:
    - Rostrocaudal axis
        - Ectoderm and endoderm form ends of the gut tube, no mesoderm
        - At each end, form the buccopharyngeal and cloacal membranes
    - Buccopharyngeal membrane
        - Breaks down to form oral cavity
        - At the rostral end
    - Cloacal membrane
        - Breaks to form the anus, urinary and genital openings
        - At the caudal end



<u>Folding</u>

- Stage 8: Week 3, days 17-19, 1-1.5mm
    - Folding of the flat disk
        - Folds ventrally, away from the amniotic side
        - Folds some of the yolk sac inwards, some stays outside
            - Embryo grows but yolk sac doesn't, thus after folding, it remains as a remnant
            - In animals, it is used for nutrition, but in humans it has been replaced by the placenta

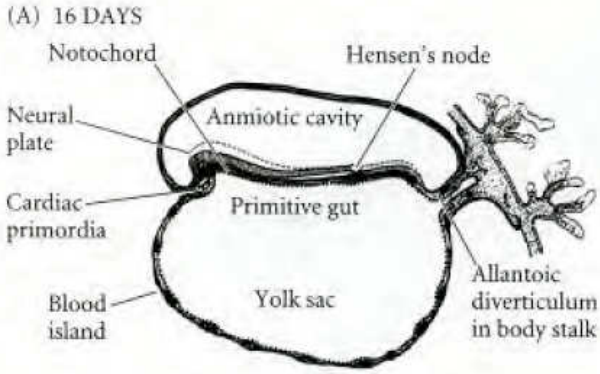


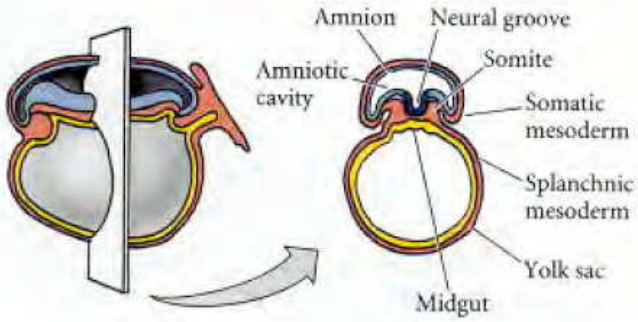
Endoderm

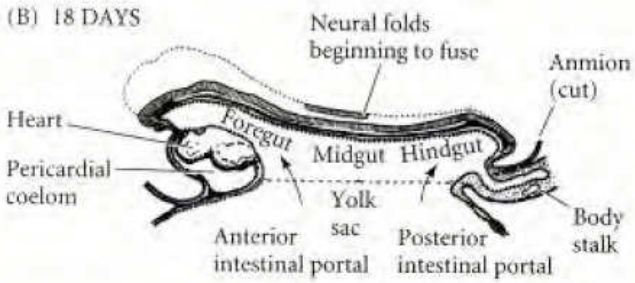
- Forms gastrointestinal tract
    - GIT doesn't carry out post-natal function until after birth
        - However, it is necessary developmentally for the fetus to practice: secretions/contractions
    - Note: allantois – structure of the endoderm that extends into the placental cord
- Forms the linings of two tracts:
    - Digestive tract
    - Respiratory tract
        - Outgrowth of the digestive tract: respiratory diverticulum
        - Bifurcates into two bronchi → lungs
    - Buds give ruse to the liver, gall bladder and pancreas
    - Pharynx – the common chamber in the anterior region
        - Endoderm gives rise to the tonsils, thyroid, thymus and parathyroid glands

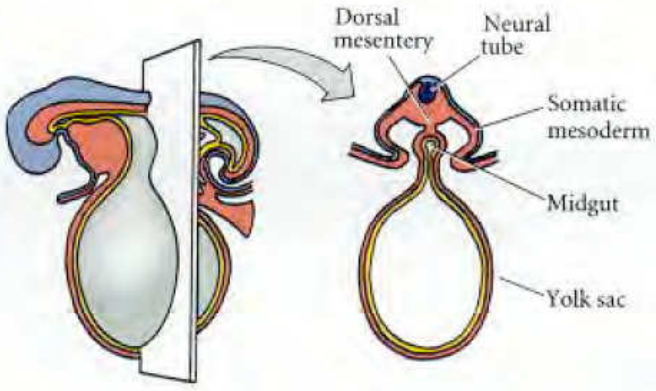
GIT

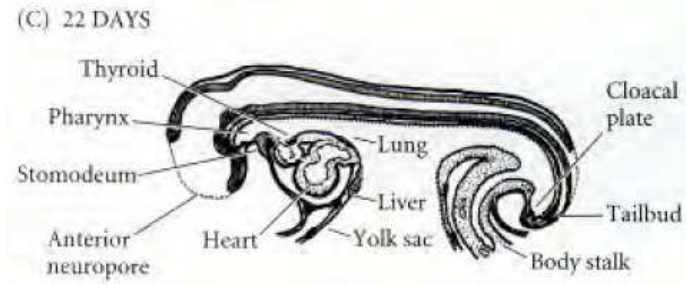
- By the 4th week:
    - 3 parts: foregut, midgut and hindgut
    - 2 specialised regions: buccopharyngeal membrane and the cloacal membrane
        - These are appositions of the ectoderm with the endoderm directly without mesoderm

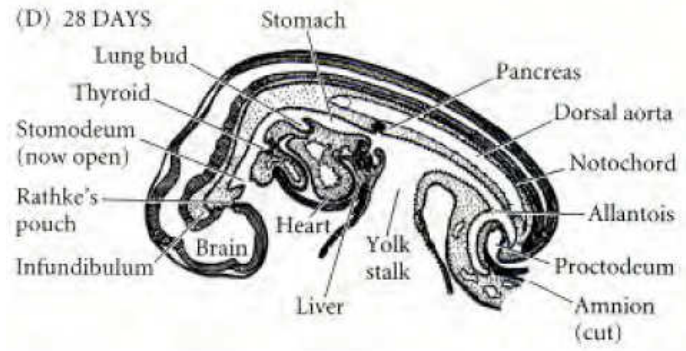


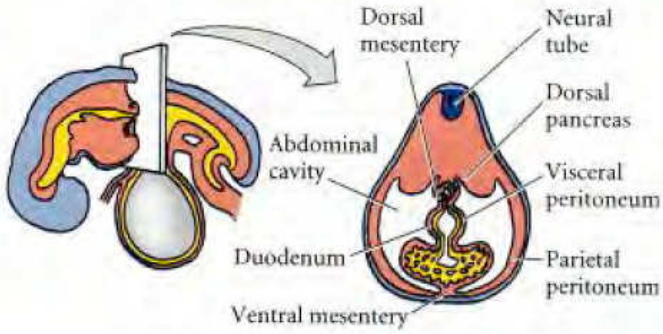










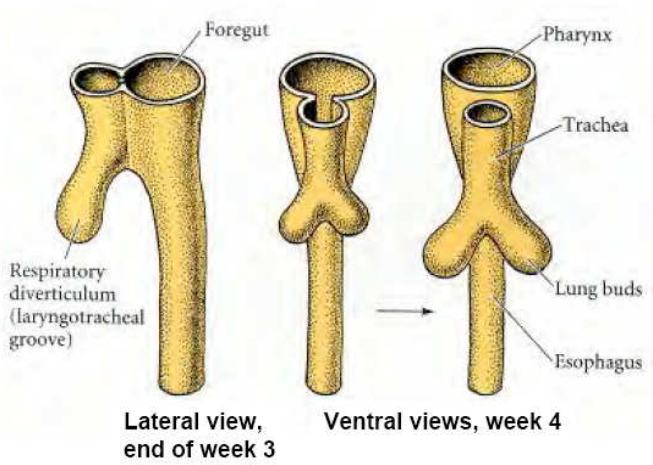


Oral cavity

- Forms through the breakdown of the buccopharyngeal (oropharyngeal/oral) membrane
    - Open to the amniotic sac
        - Allows swallowing of amniotic fluid which is important for muscular development
- Formed mainly from the pharynx lying within the pharyngeal arches

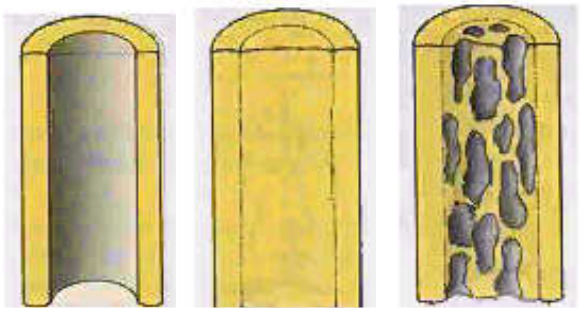
Foregut

- Partitions into the oesophagus and respiratory diverticulum during weeks 3 and 4



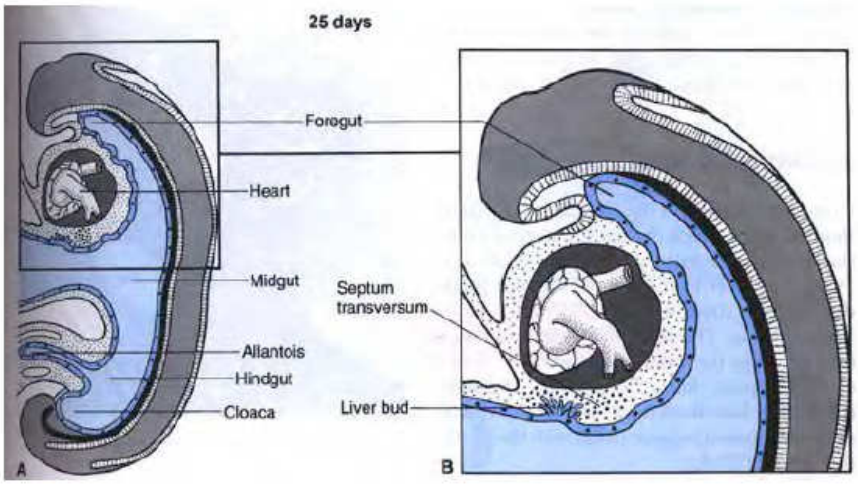
Canalisation

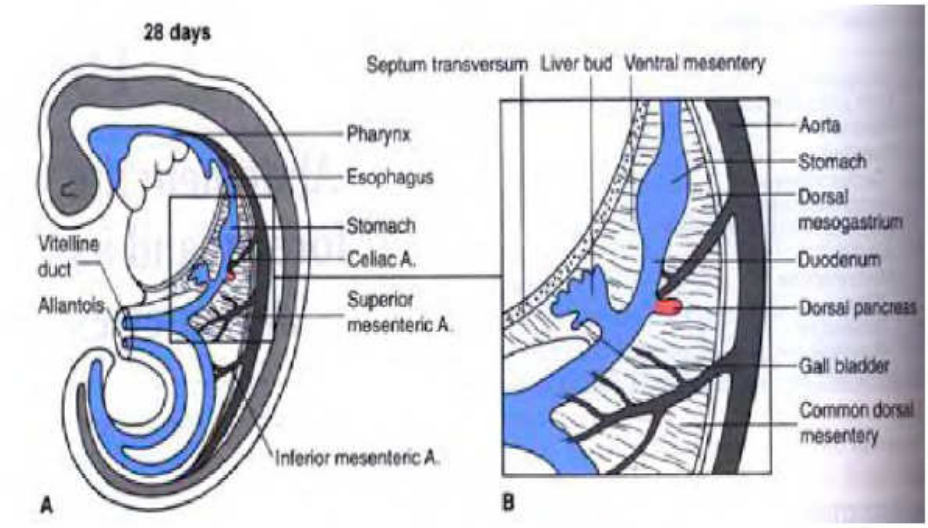
- Process:
    - Week 5 – endoderm in the GIT wall proliferates
    - Week 6 – endoderm proliferation results in total occlusion of the gut lumen
    - Weeks 7-8 – tissue degeneration results in reformation of the hollow gut tube
    - Week 8 – GIT endoderm is a tube once more
        - Ie: process is recanalisation – hollow → solid → hollow
- Abnormalities
    - Can lead to:
        - Duplications – two tubes
        - Stenosis – narrowing of tubes
        - Atresia – blockage of tubes



Liver

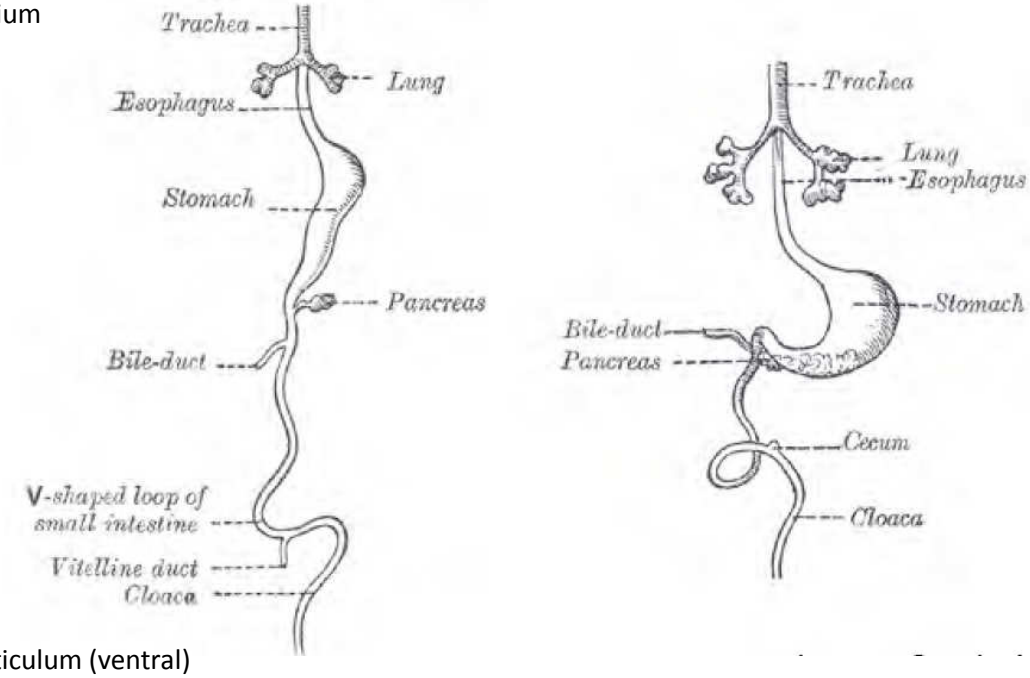
- Arises at the embryonic junction
    - Externally: where the ectoderm of the amnion meets the endoderm of the yolk sac
    - Internally: where the foregut meets the midgut
    - At the septum transversum – mesenchymal structure
        - Provides support where blood vessels and liver begin to form
- Liver bud
    - Derived from the endoderm
    - Differentiates to form the hepatic diverticulum which gives rise to ramifying hepatic primordium cells (hepatoblasts)
        - Hepatoblasts form hepatocytes and biliary cells
        - Diverticulum generates the gall bladder and then divides into right and left hepatic buds
    - 3 connecting stalks: cystic duct, 2 hepatic ducts
        - Fuse to form the bile duct
        - Reflects the liver's exocrine functions
- Hepatic buds
    - Left hepatic bud gives rise to: left lobe, quadrate lobe and caudate lobe of liver (anatomically left)
    - Right hepatic bud gives rise to the right lobe
    - Made up of hepatocytes
        - Produce bile from week 13 that accumulates in the hindgut
            - Forms the meconium of the newborn
                - Ie: the first stool which is made up of liver produce and debris from swallowing amniotic fluid
- Liver is richly vascularised
    - An important site of hemopoiesis in the embryo
        - Initially, yolk sac acts as primary site before stem cells migrate to the liver and then finally to the bone marrow
    - Majority of hemopoiesis is in fetal RBC formation
- Other structural origins
    - Vitelline veins form
        - Sinusoids – small blood vessels with a discontinuous endothelium
    - Mesenchyme forms
        - Connective tissue
        - Kupffer cells – specialised liver macrophages





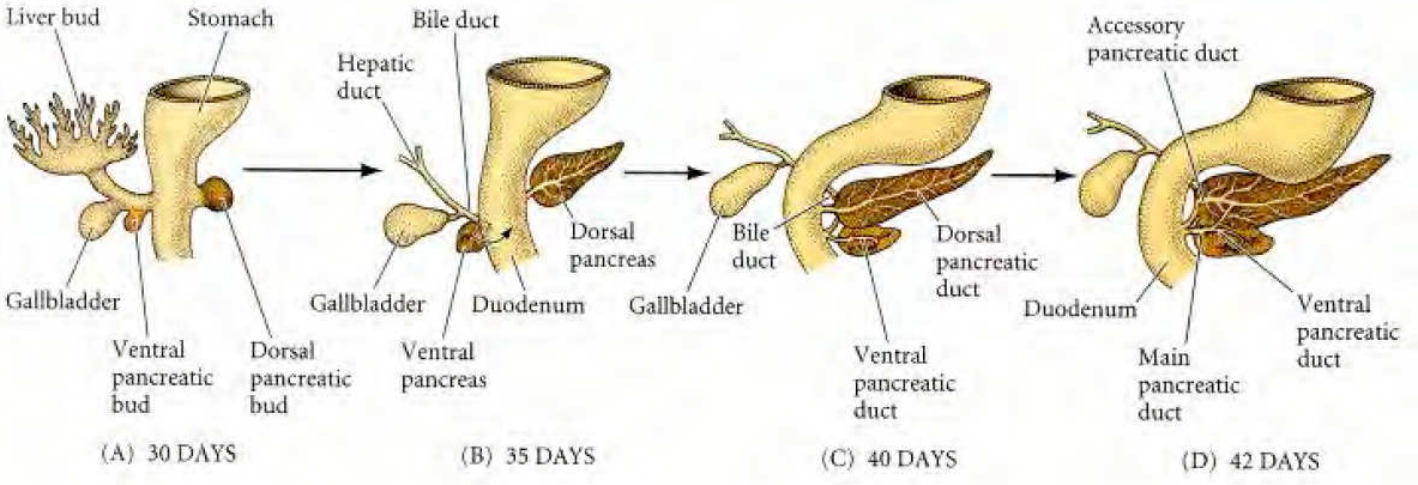
Stomach

- Foregut tube begins to dilate forming an enlarged lumen – week 4
- Dorsal border grows more rapidly than ventral
    - Establishes curvature of the stomach (1st rotation)
- 2nd rotation – in the longitudinal axis 90 degrees
    - Liver (ventral mesentery) and spleen (dorsal mesentery) are attached to mesentery and thus rotate with stomach
- Dorsal mesentery grows and hangs down as an apron-like fold: the greater omentum
- Embryonic mesogastrium



Pancreas

- Arises from 2 sources:
    - Hepatic diverticulum (ventral)
    - Duodenum (dorsal)
- Differentiates into specific cells for endocrine (hepatic) and exocrine (duodenal) functions
- Fusion arises from rotation
- Abnormalities
    - Dorsal pancreatic bud loses the duodenal duct, 10% of the population retain it and have a dual duct system

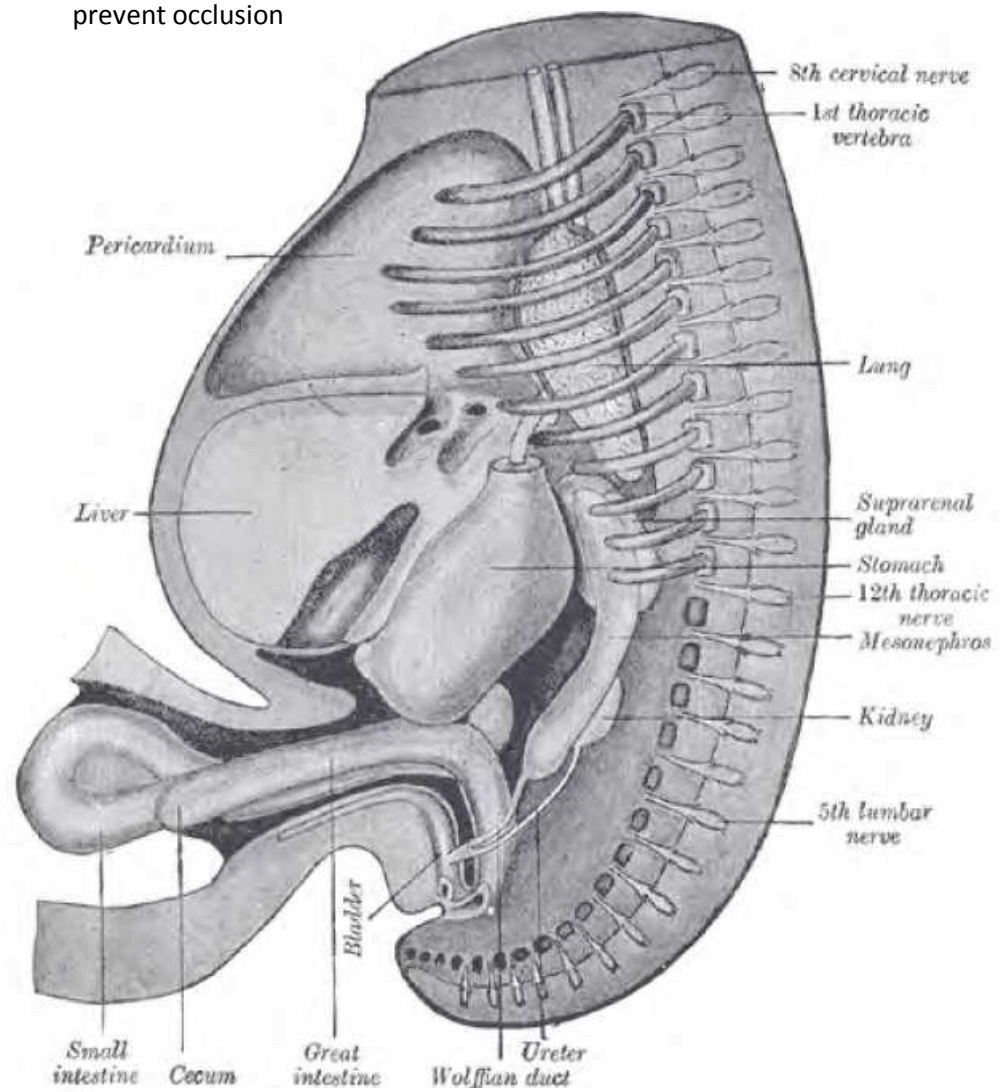


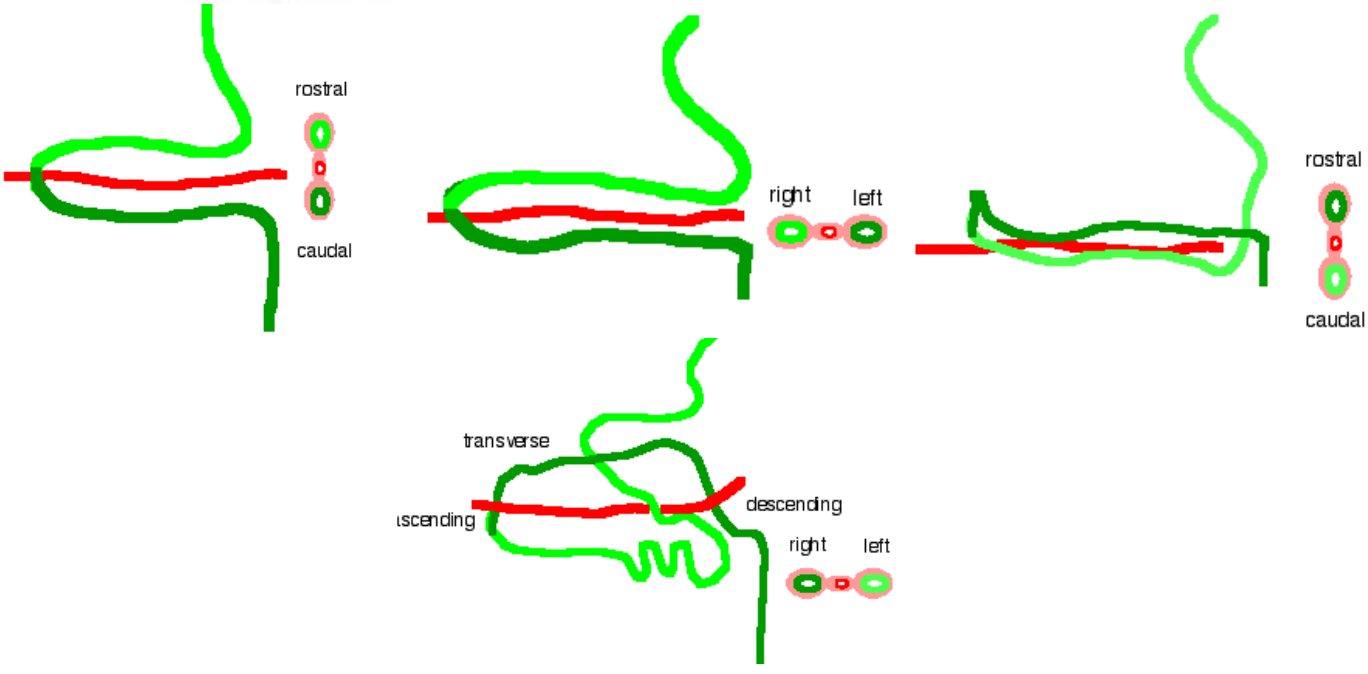
Spleen

- Arises within the dorsal mesogastrium as proliferating mesenchyme – week 5
- Hemopoietic function
    - Stem cells arise from the yolk sac wall
    - Generates red and white cells in the 2nd trimester

Midgut

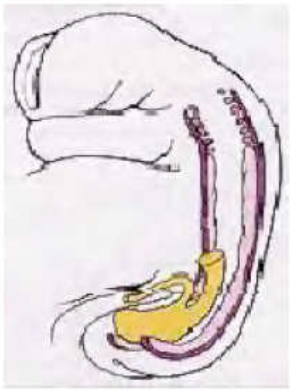
- Midgut herniation
  - The developing kidney and liver take up the abdominal space and so the developing midgut is forced outside the abdomen into the umbilicus
  - This herniation remains until week 11 of development
- Rotation occurs as part of the elongation of the GIT
  - This allows correct placement of the gut with its mesentery (dorsomesogastrium) in the abdominal cavity
  - Midgut is connected by the dorsal mesentry to the body surface – attached to the posterior body wall
    - Thus the vascular and nerve supply is maintained
      - Particularly important is the mesenteric artery thus rotation occurs around its axis to prevent occlusion

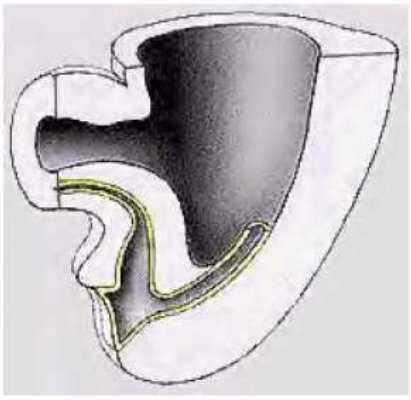




Hindgut

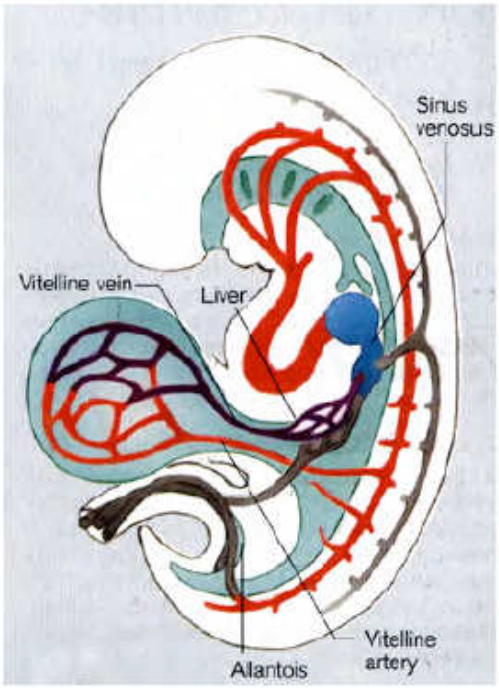
- Cloaca development
  - Begins as a common urogenital sinus
  - A septum bifurcates the sinus into urinary and rectal components

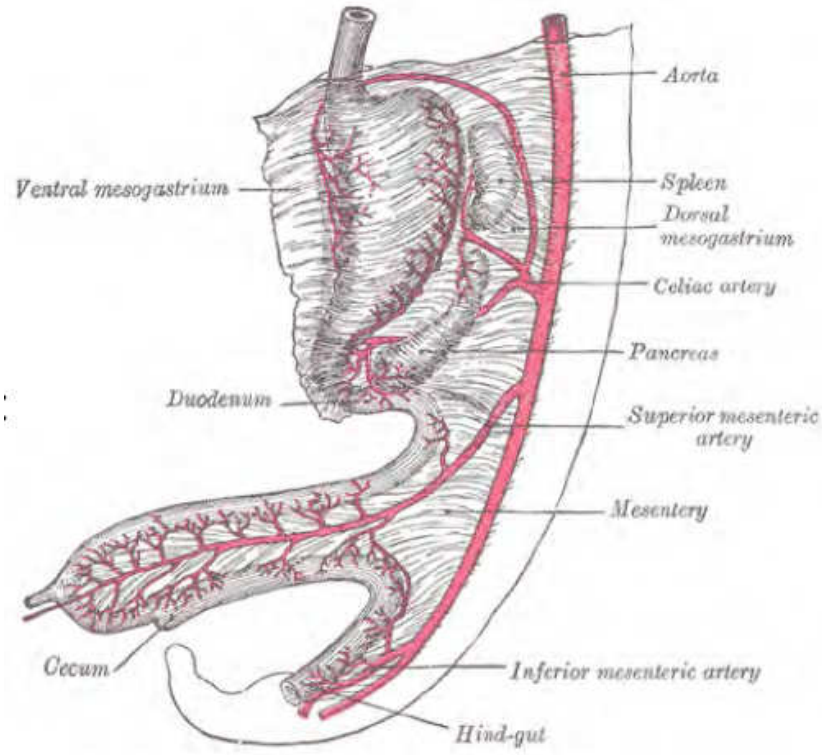




Blood supply

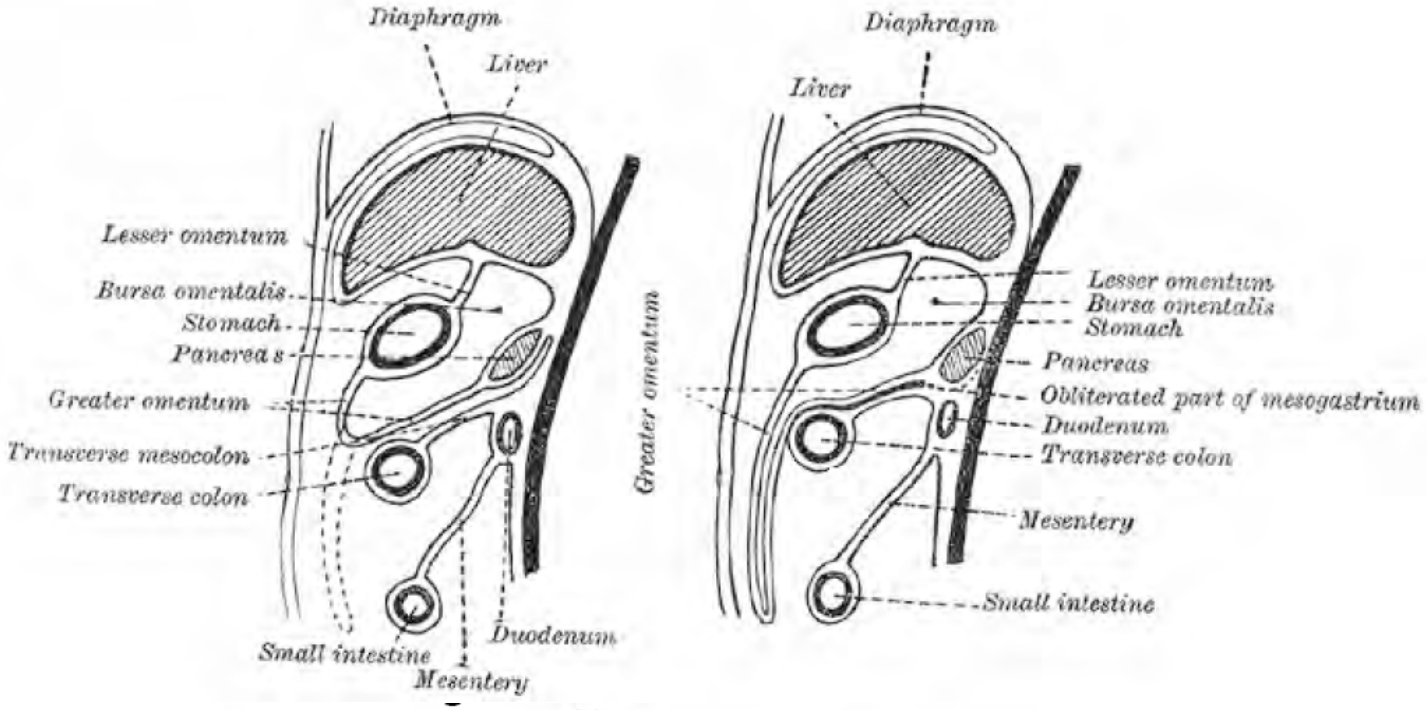
- Covers the entire surface of the yolk sac
  - Connects to the embryo through the yolk stalk
- Arteries
  - Arise from the dorsal aorta
  - Contribute to adult GIT arteries
- Veins
  - Empty into sinus venosus
  - Contribute to the adult portal system
- Arteries define areas of the gut:
  - Celiac artery – foregut
  - Superior mesenteric artery – midgut
  - Inferior mesenteric artery – hindgut

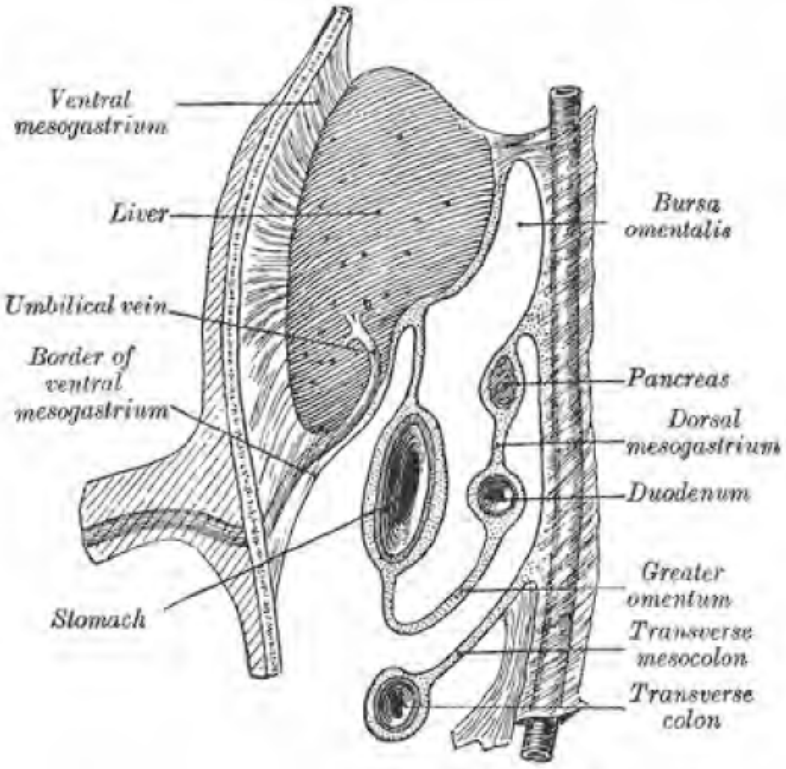




Mesentery

- Common dorsal mesentery generates the mesenteries of the GIT
    - Thus, gut is attached to the dorsal body wall, not the ventral
    - Embryonically, dorsal mesentery is made up of two folds, these fuse to form the greater omentum
        - Hangs down infront of the midgut like an apron carrying vascular and nerve supply
- Ventral mesentery
    - Remains at the level of the liver
    - Contributes to the lesser omentum and the falciform ligament





Abnormalities

- Impact on the GIT lumen
- Atresia – interruption of the lumen
    - Oesophageal, duodenal, extrahepatic-biliary, anorectal
- Stenosis – narrowing of the lumen
    - Duodenal, pyloric
- Failure of the midgut to return to the body cavity

Definitions
- Infant – young offspring of humans
- Neonate – newborn, less than a month old
- Toddler – 12-36 months, beginning to walk
- Child – human between the ages of birth and puberty

Growth
- Expected growth
  - Infants
    - Average birth weight 3.5kg
      - Initial weight loss of up to 10% body weight in first 5-7 days, regained by day 10-14
    - Average weight increases over the next 12 months
      - Months 0-3: 200g/week; months 3-6: 150g/week; months 6-9: 100g/week; months 9-12: 50-75g/week
      - Overall weight triples in the first 12 months
    - Length increases by 25cm
  - Toddler
    - 2nd year of life, gain of 2.5kg weight and 12cm length
      - Growth slows down and nutritional requirements decrease
    - Average growth rate from this point onwards continues steadily at 2kg/year and 10cm/year and declines with age to 6cm/year until puberty
  - Puberty – growth spurt
    - Occurs at 10-11 years in girls, 12-13 years in boys

Measuring growth
- Standards
  - Height
    - Children <24 months measure length
    - Children 24-36 months measure either length or height depending on behaviour of child
    - Children >36 months measure height
    - Length can be inaccurate because babies don't like being measured and don't sit still
  - Weight
    - Bare weight, 0-12
    - Light clothing, no shoes for older children
  - Head circumference
    - Measured until 2 years
    - Tape placed over the supraorbital ridges and over the external occipital protuberance
  - If a baby is not growing, measurements are affected in the order: weight → height → head
    - If head is affected, but not other two, there may be another problem
- Growth charts
  - Important to plot growth charts in 'Blue Book'
    - Parents are often pedantic with their 1st child, 2nd and 3rd not so much so
  - CDC published
    - Allows observation of normal growth and judging of standard growth based on percentiles
    - Presents a nationally representative sample using data from health examinations from 1963-94
      - Racially and ethnically diverse
      - Breast and formula fed babies (50% breast fed, 33% 3 months breast feeding or longer)
  - Other growth charts
    - WHO published
      - International representation using a breast-fed model
      - Follows birth to 5 years (1997-2003 data)
    - Preterm infants (Babson and Benda)
    - Disease specific (eg: trisomy 13, cerebral palsy, turner's, sickle cell, Prader-willi)
    - Culturally specific

Nutrition

- Defined by organisations such as the WHO, much controversy
    - Normal recommendation is 4-6 months, start infants on solids
        - Too soon (<4 months) problems:
            - Reduced breast milk production
            - Immature oral cavity development (should wait for tongue thrust)
            - Immature gut (no pancreatic amylase)
            - Pathogen exposure
            - ?food allergies
        - Too late (>6 months) problems:
            - Faltered growth
            - Immune protection compromised
            - Micronutrient deficiency (Fe and Zn) – iron stores are depleted after 6 months, need iron fortified food or can get iron deficiency
            - Developmental delay in developing motor chewing skills – harder to teach later
            - Decreased acceptance of new tastes/textures
            - ?food allergies
- How to introduce the first food
    - After breast/formula feed – already eating
        - At a good time
    - One food at a time and in small quantities (1-2 teaspoons at first)
    - No added flavourings – salt, sugar, butter, oil (infants have 300x the number of taste buds)
    - Mixed with water, formula or breast milk
    - Not too cold/hot
    - New food every 3-4 days + variety + distinct/separate
    - Persistence – children are neophobic (may need 12-20 times before children will eat)
- Types of food
    - 6-8 months: pureed
        - Reasons:
            - Early chewing possible
            - Increased strength of suck
            - Can sit without support allowing manipulation of food before swallowing
            - Exploration of new textures etc
        - Types of food:
            - Easily digestible, iron rich, low allergen; Gluten free cereal; vegetables, fruit; meat, legumes/beans
    - 8-12 months: mashed/chopped and finger foods
        - Reasons:
            - Clearing spoon with lips
            - Gums can bite and chew
            - Tongue and move laterally to move food to teeth
            - Pincer grip
            - Exploration of a variety of textures/foods
        - Types of food:
            - Well-cooked fish, minced meat; mashed, cooked vegetables/fruit; chopped, soft raw fruit/vegetables; egg yolk; cereals, bread, pasta; Dairy: cheese, custard, yoghurt (but not milk plain)
    - 12 months: family food
        - Reasons:
            - Rotary chewing movement and jaw stability
            - Able to self-feed
            - Can hold a cup
        - Food types:
            - Family foods cut up; plain pasteurised milk; avoidance of small, hard foods and tough meat

Calorie requirements

- Infants need more than adults
    - 6 months, need ~80kcal/kg/day
        - Decreases with age
    - Adults need 30kcal/kg/day

Concerns

- Certain foods:
    - Honey – can contain Clostridium botulinum spores
        - Delay until 12 months
    - Tea – Tannins bind iron and other minerals (which infants need)
    - Nuts – Inhalation and choking risk, allergy?
    - Fruit juice
        - Competes with breast milk and water, no fibre
        - Can cause gastro upset and failure to thrive, decreased appetite
        - Risk of obesity, dental problems
    - Reduced fat milk
        - Compromises growth, not before 2 years
- Commercial vs home cooked food
    - Commercial:
        - Advantages – convenient, portable, low in salt and sugar, well labelled for allergies, jars
        - Disadvantages – expensive, wastage, less texture, lumpy parts can be a problem
    - Home cooked
        - Advantages – food separated, sense-ational, minimal cost, can be pre-prepared, more texture
        - Disadvantages – preparation time
- Obesity
    - Hard to tell by looking who is obese/healthy
    - Need to look at BMI etc and compare to percentiles on growth charts

Dietary guidelines for children/adolescents

- Need a wide variety:
    - Vegetables, legumes, fruits
    - Cereals (whole grain preferable)
    - Lean meat, fish, poultry or alternatives
    - Dairy: milks, yoghurts, cheeses or alternatives
    - Water not juice
- Need to limit:
    - Saturated fat and total fat – low fat diets not appropriate for infants however
    - Salt
    - Sugars and foods with added sugars
- Specific guidelines vary with amount of growth occurring in that age group and their general energy requirements

Obesity myths

- Doing the gym class is more important than taking the stairs to get there
    - Children should be active all the time
        - Pedometers are helpful in monitoring activity
    - Everything is relative – exercise depends on the person
    - Good to establish a baseline of exercise within the family and foster competition
- 97% fat free foods won't make you fat
    - Obesity results when food input is higher than energy expenditure
    - 'fat free' foods still have calories and people feel like they can eat more. Lie!
        - In fact, when fat is taken out, food loses its flavour so sugars are added which adds to the calories
        - "diet" foods have artificial sweeteners and can have less calories
- Juice comes from fruit therefore it is healthy
    - Juice is low fibre, easy and fast to drink and can accompany a meal or snack
    - Not filling
    - A concentrated source of vitamin C – not hard to get enough vitamin C
    - Also a concentrated source of calories

Obesity myths continued

- All children need full cream dairy products
    - There is a perception that low fat dairy is nutritionally inferior
        - Reduced fat dairy is better for >2 years and skim dairy for >5 years
    - Amount of calories in full cream milk is important and can lead to weight problems
- Children are growing and need big/bigger portions than parents
    - Serves are often too large
    - Ratio of meat/carbohydrates to vegetables is often too low
    - There is an attitude of overeating

Fussy eaters

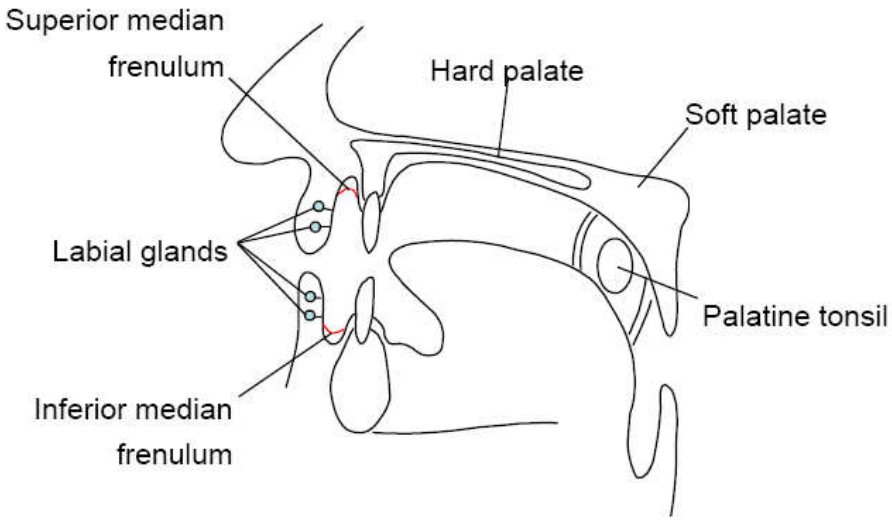
- Children test independent by their choice of food selection
    - Parents should not necessarily believe "I'm hungry"
- 1-5 growth slow and appetite is not as regular – normal for children to be erratic in eating patterns
    - Daily intake remains fairly constant, subconsciously know how much they need to survive/grow
- Parents should be persistent with new foods but respect the division of responsibility
    - Division of responsibility
        - Parents: provide food at appropriate time
        - Children: decide how much to eat or whether to eat
            - Thus if child pushes spoon away, stop feeding
- "No healthy child ever starved through refusing food. When your child is hungry enough, he will eat"

Nutritional deficiencies

- Iron deficiency
    - Infancy: important in development and cognition. Can result in anaemia
    - Adolescence: important in verbal learning/memory, muscle growth/menstruation. Can result in anaemia
    - Risk groups:
        - Maternal iron status low in breast feeding
            - Breast feeding exclusively past 6 months
        - Early introduction of cows milk/excessive drinking of cow's milk (1-2L/day)
            - Get full, not eating, no iron
        - Ethnic background/cultural issues
        - Late introduction of meat or vegetarian
        - Fussy eaters/ poor chewing, adolescence: restrictive eating patterns
    - Sources:
        - 5-20% of dietary iron is absorbed
            - Good sources (haem iron): meat, chicken, fish
            - Secondary sources (non-haem): eggs, dark green leafy vegetables, legumes
                - Not as well absorbed, but better if haem-iron present
            - Enhancers – vitamin C; inhibitors: tannins (tea), phytates (wholemeal cereals)
- Calcium deficiency:
    - Calcium:
        - Important in bone growth: 7x increase in bone mass 0-puberty, 3x increase during puberty
            - Calcium retention is 2-3x greater in adolescence – people stop eating properly at this time
        - Protects against osteoporosis
        - Need adequate intake through childhood
            - Ensures peak bone mass at 19-30
    - Risk groups: osteoporosis
        - Adolescent girls who minimise dairy, excessive juice/soft drink displacing milk, vegetarians, lactose intolerance, limited physical activity (disability), high protein/salt intake, excessive cola, fracture
    - Recommendations: 2-3 serves of dairy foods or fortified soy/day
- Constipation – common problem
    - Caused by: lack of high fibre foods (dislike/lack available fruits/veges), concentrated infant formula, low fluids, lack of exercise/immobility
    - Infant treatments: increase fluid, dilute fruit juice, dilute prune juice (not <9 months), increase fruit/veges
    - Older children treatments: less snack foods, more fruit/vege, wholemeal bread/cereal, fresh fruit instead of juice, adequate fluid intake, exercise

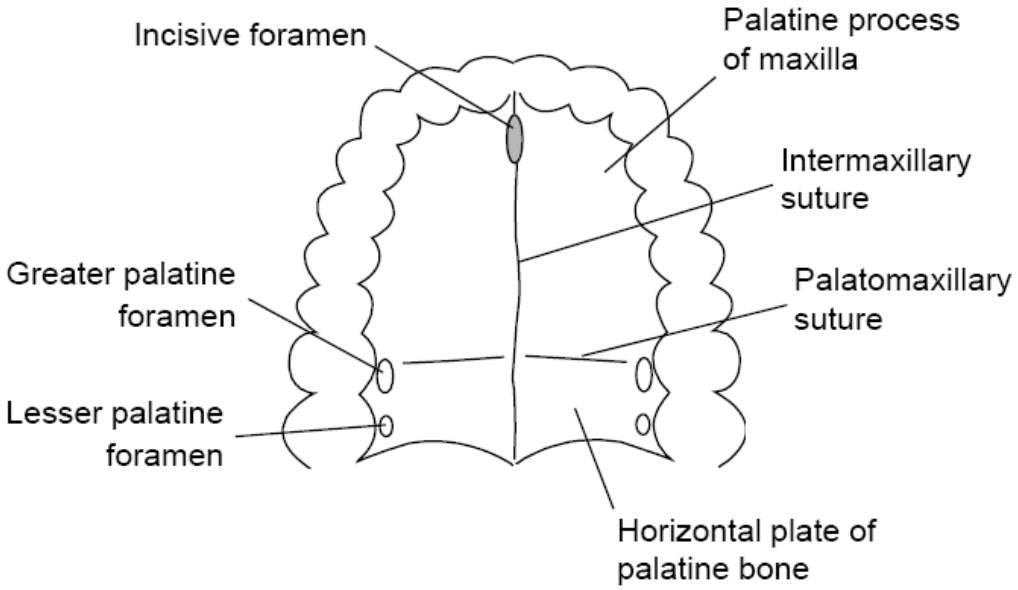
The mouth (oral cavity)

- Made up of 2 parts:
  - Small vestibule outside the teeth and inside the lips
    - Lips are covered by skin externally and a mucous membrane internally
      - Connected to the gum by a median labial frenulum
      - Obicularis oris lies between the mucous and epidermal layers (CNVII)
      - Labial glands are between obicularis oris and the mucosa, ducts opening into the vestibule
  - Inner oral cavity proper
    - Bound anterolaterally by the alveolar arches, teeth and gums
    - Communicates posteriorly with the pharynx via the oropharyngeal isthmus
    - Roof formed by the hard and soft palates
    - Floor is the anterior region of the tongue and the reflection of the mucosa from the inferior tongue to the internal mandibular surface

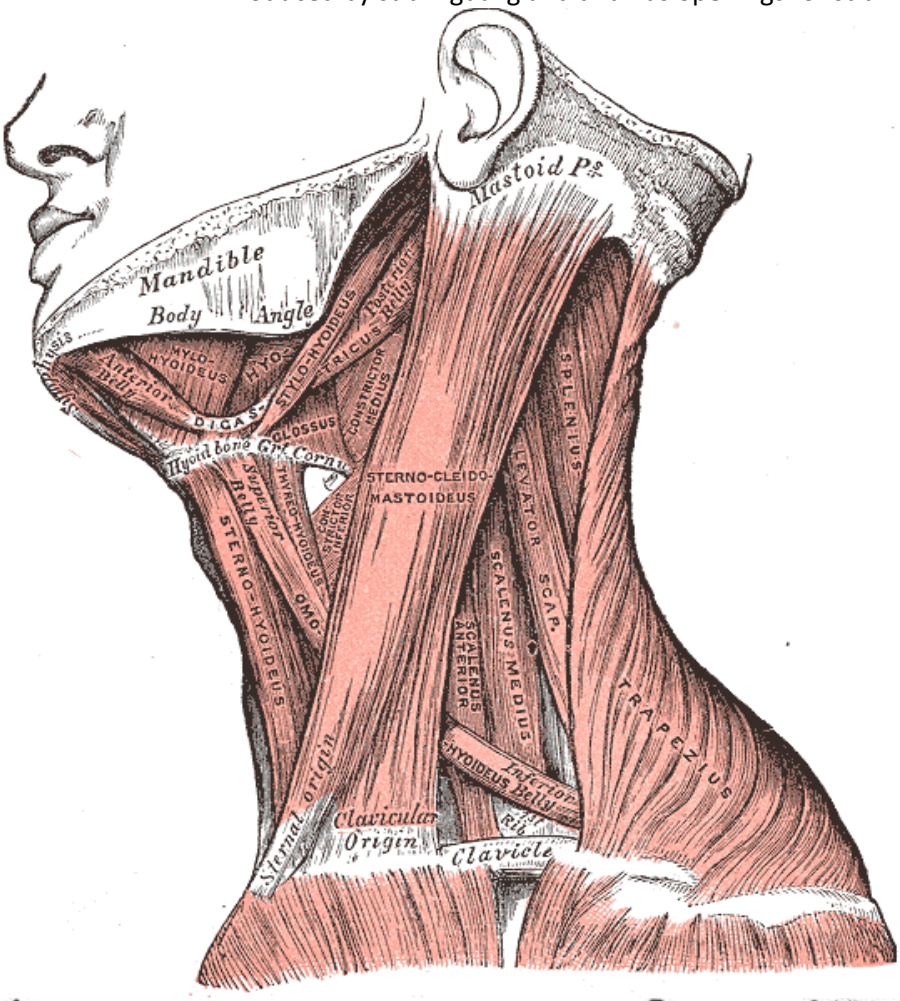


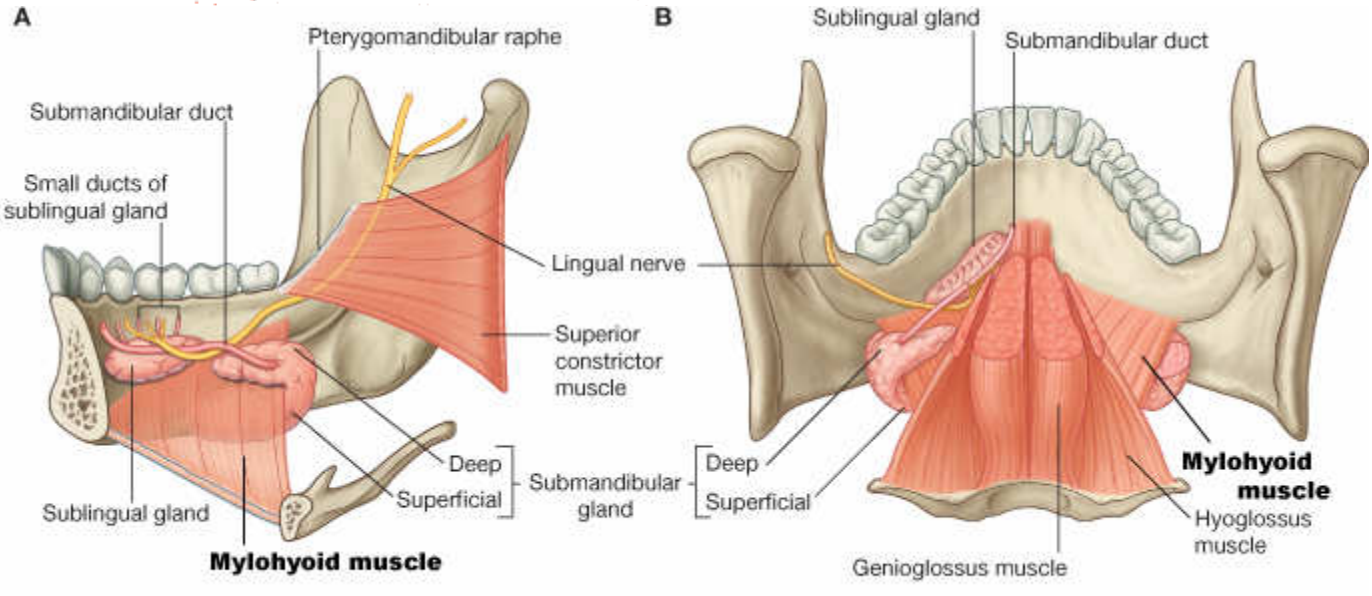
Cavity of the mouth

- Roof is made up of the hard palate (2/3) and soft palate (1/3) covered by mucosa – muscular tissue and CT
  - Bone part:
    - Palatine process of maxilla with the intermaxillary suture
      - Anterior is the incisive foramen with orifices of two incisive canals carrying nerves and vessels (sensory supply of the hard palate)
      - Posterior are the palatine foramina that carry the blood supply of the hard palate
    - Posterior is the paired horizontal plates of the palatine bones



- Floor
    - Muscles: from above downwards
        - Geniohyoid
        - Mylohyoid (diaphragma oris)
        - Anterior belly of the digastric – contraction opens the jaw via a pulley system
        - Stylohyoid
    - Frenulum of the tongue
        - Connects the lower surface of the tongue to the floor
        - Lower end has an elevation – the sublingual papilla where the submandibular duct opens
    - Sublingual fold
        - Produced by sublingual gland and has openings for sublingual ducts (salivary gland orifices)



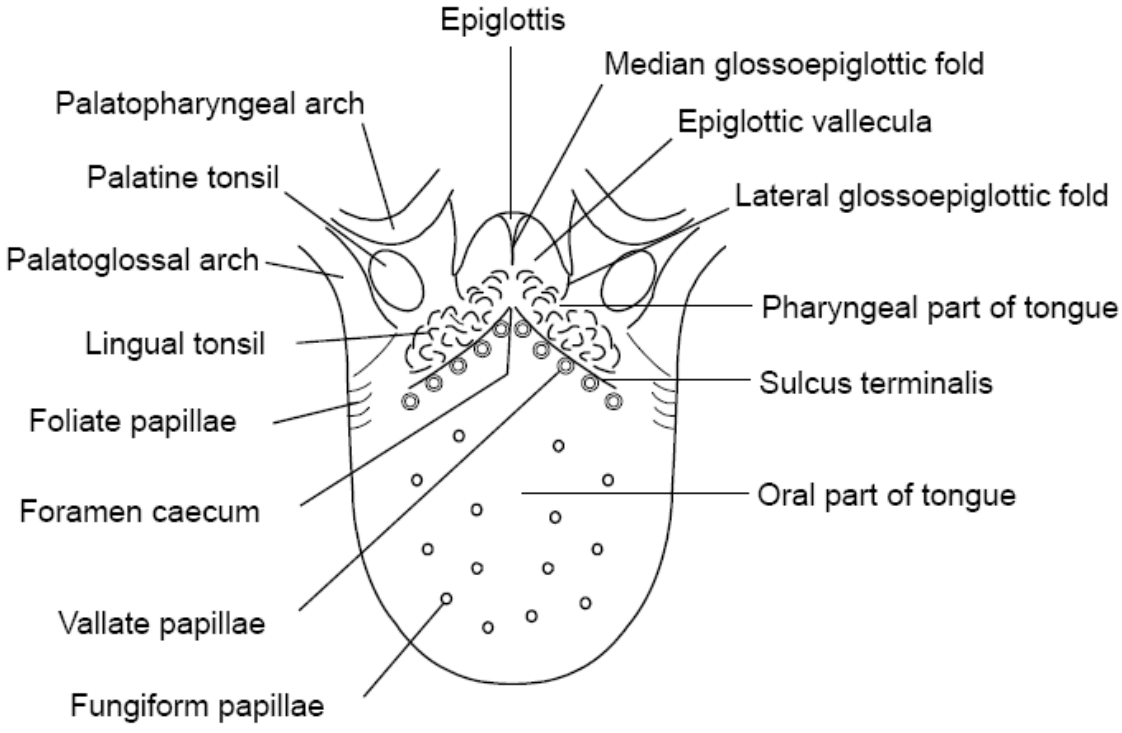


Tongue

- A highly muscular organ of swallowing, taste and speech
    - Has a root, apex, curved dorsum and inferior surface
- Has 2 parts separated by the sulcus terminalis (v-shaped groove running to the bases of the palatoglossal arches)
    - Oral (presulcal) part
    - Pharyngeal (postsulcal) part

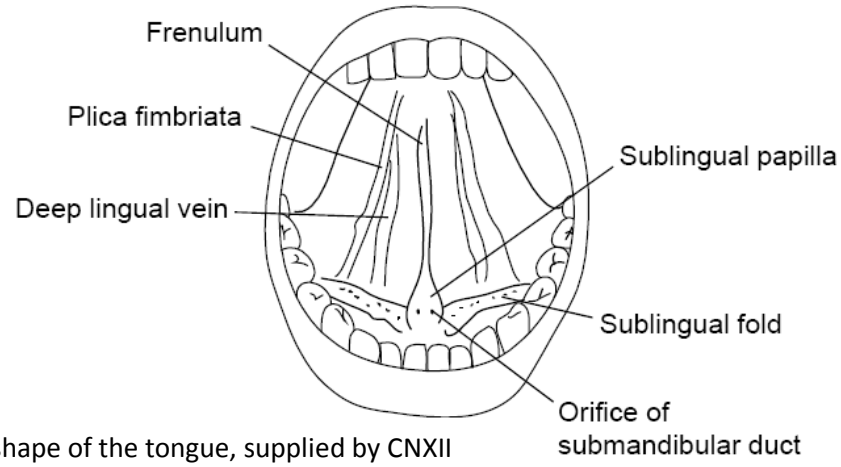
Tongue dorsum

- Foramen caecum – origin of the thyroid diverticulum during embryonic development
    - Located at the point of the sulcus terminalis "V"
- Median sulcus – extends from the median glosso-epiglottic fold to the apex of the tongue
- Lingual tonsil – multiple lymphoid nodules embedded in the submucosa (paved appearance)
    - In the postsulcal part
    - Palatine tonsil also seen in lateral wall – important because swelling can cause blockage of the GIT
- Epiglottic vallecula – space between the median and lateral glosso-epiglottic folds
    - In the postsulcal part
    - Important location for lodging of fish bones etc
- Lingual papillae (4 principal types)
    - Filiform
        - Small, conical or cylindrical
        - Arranged in rows parallel to vallate papillae
            - Cover much of the presulcal part of dorsum
        - Do not have taste buds but increase friction allowing gripping of food
            - Animals that groom fur (eg: cat) have prominent filiform papillae
    - Vallate (circumvallate)
        - 8-12 in number, 1-2mm in diameter
        - Arranged in front of the sulcus terminalis
        - Made up of papilla surrounded by a sulcus and then a wall (vallum)
            - Taste buds found in both sulcal walls
    - Fungiform
        - Found on the lingual margin
        - Large, round shape, deep red in colour
        - Have taste buds
    - Foliate
        - Grooves and ridges at the lateral margins of the tongue near the palatoglossal arch
            - Contain taste buds



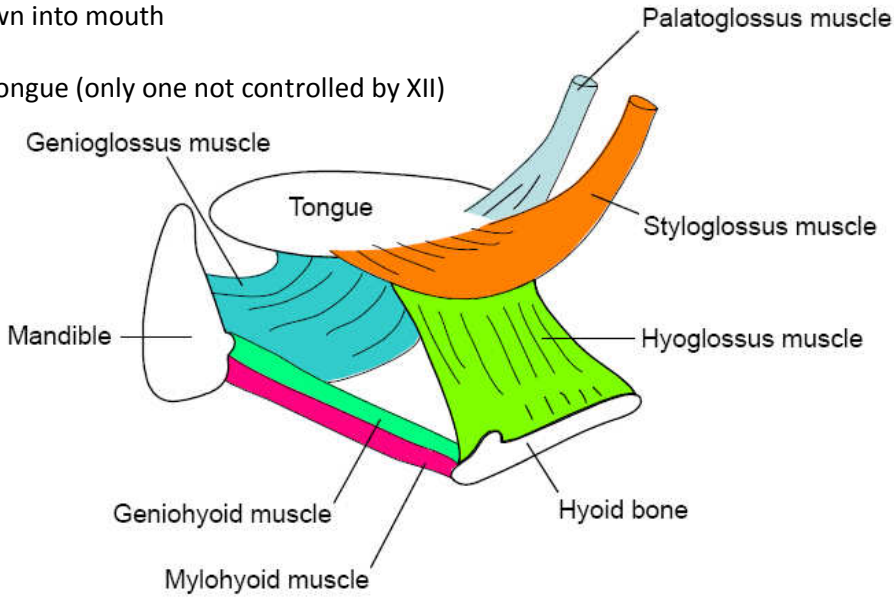
Inferior tongue surface

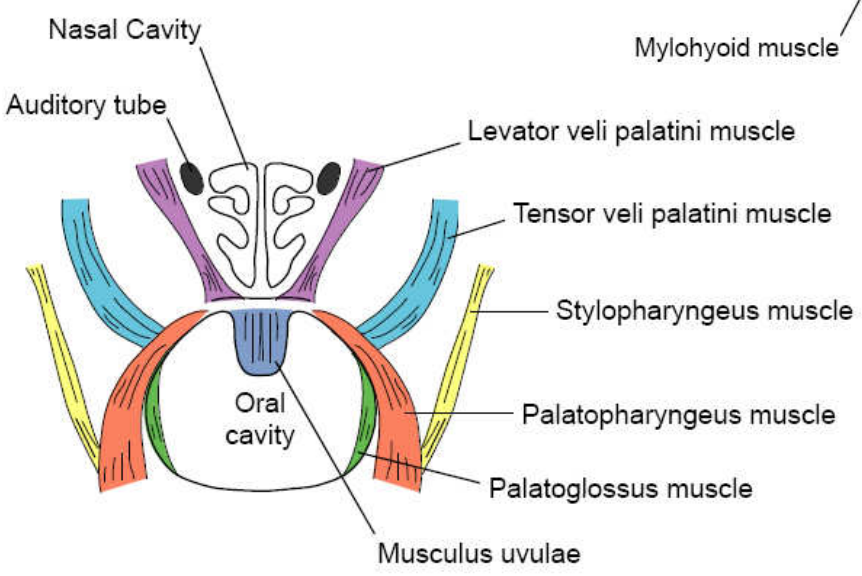
- Frenulum of the tongue – connects the tongue to the floor of the mouth
- Profunda linguae vein (deep lingual vein) – visible on either side of the frenulum
- Plica fimbriata – a fold of mucous membrane on either lateral side of the vein



Muscles of the tongue

- Intrinsic – alter the shape of the tongue, supplied by CNXII
    - Superior and inferior longitudinal
        - Shorten the tongue
        - Superior also turns the apex and sides upwards
        - Inferior also turns the apex down
    - Transverse
        - Narrow and elongate the tongue
    - Vertical
        - Makes tongue flatter and wider
- Extrinsic – paired, alter the position of the tongue, stabilise the tongue
    - Genioglossus – pulls tongue forward
    - Hyoglossus – pulls tongue down into mouth
    - Styloglossus – retracts tongue
    - Palatoglossus – elevates the tongue (only one not controlled by XII)





Sensory innervation of the tongue

- Oral part:
    - Lingual nerve – general sensation
        - From the mandibular division of CNV
    - Chorda tympani – taste
        - From CNVII
- Pharyngeal part and vallate papillae
    - Lingual branch of CNIX for both taste and general sensation
    - Near the epiglottis, internal laryngeal from CNX provides general sensation and taste

Soft palate

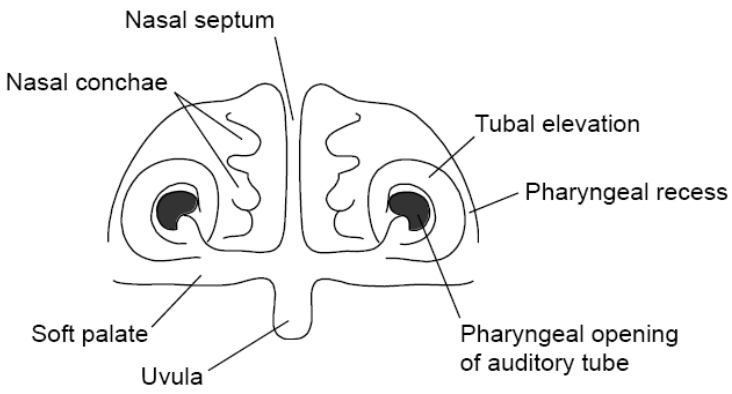
- Suspended from the hard palate
    - Partitions the nasopharynx and oropharynx
- Structures:
    - Uvula – median conical process on the posterior edge
    - 2 paired curved mucosal folds containing muscle extend laterally from the base of the uvula
        - Palatoglossal arch
        - Palatopharyngeal arch
    - Between these arches is the palatine fossa with the palatine tonsil
    - Palatine aponeurosis (thin and fibrous)
        - Supports the muscles and strengthens the soft palate
        - Attaches to the posterior border and inferior surface of the hard palate
            - Proceeds from here to thin and then enclose the uvulae muscle in the midline

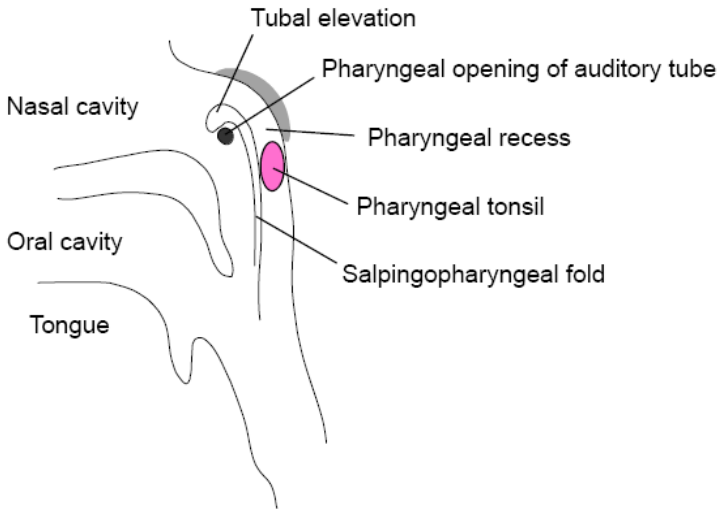
Pharynx

- 3 parts: nasopharynx, oropharynx, laryngopharynx

Nasopharynx

- Behind the nose and soft palate
- Communicates with the oropharynx by the pharyngeal isthmus
    - Bound by the soft palate and posterior pharyngeal wall
    - Closed during swallowing by elevation of the soft palate and contraction of the palatopharyngeus
- Pharyngeal opening of the auditory tube
    - Located on the lateral wall
    - Used to equalise the pressure of the ear with the external environment
        - Important for protecting the tympanic membrane
    - Bacteria can communicate with ear via the nose and cause a middle ear infection
    - Opening is bound above and behind by a tubal elevation
        - Pharyngeal recess is behind the tubal elevation
- Salpingopharyngeal fold descends from tubal elevation vertically and covers the salpingopharyngeus muscle
- Pharyngeal tonsil – lymphoid tissue
    - In the submucosa of the posterior wall
    - Also known as the adenoids



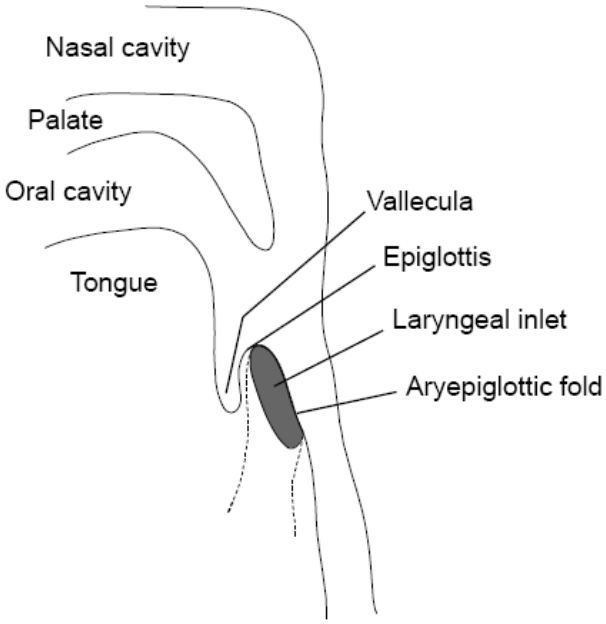


Oropharynx

- Extends from the soft palate to the upper border of the epiglottis
- Lateral wall made up of:
    - Palatopharyngeal arch
    - Palatine tonsil
        - Lies in the tonsillar fossa (sinus) between the palatoglossal and palatopharyngeal arches at the level of the 3rd lower molar tooth
        - Chief component of Waldeyer's ring – palatine, pharyngeal, tubal and lingual tonsils
            - Ring of lymphoid tissue that forms an annulus around the entrance to the digestive and respiratory tracts
            - Provides humoral and cellular defences against infection of the oral and nasal cavities and pharynx

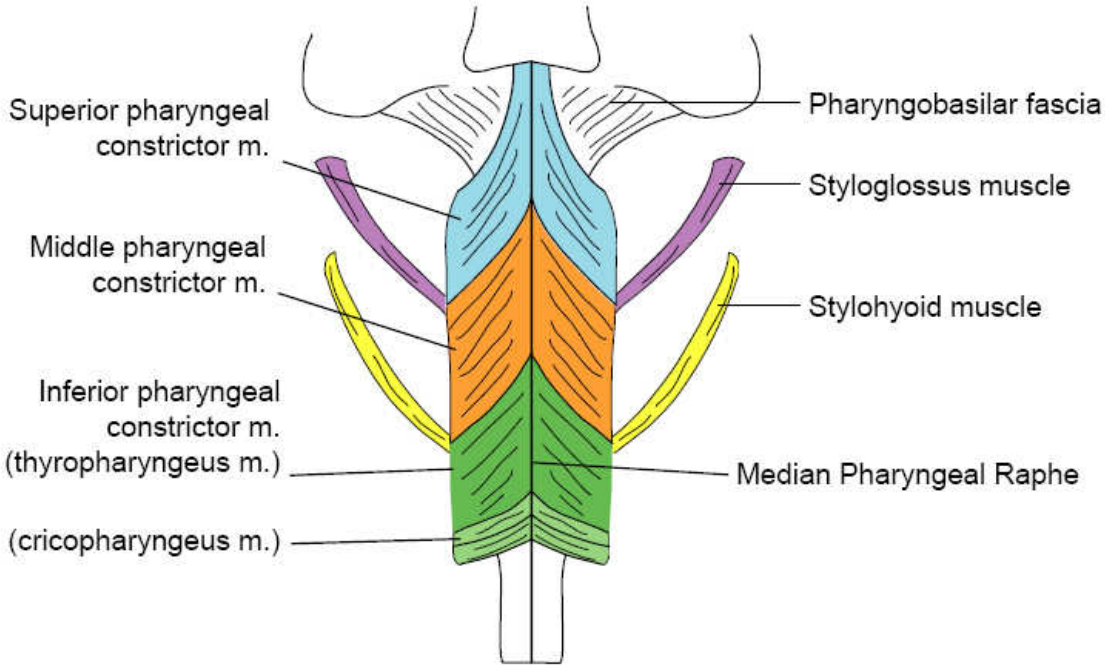
Laryngopharynx

- Extends from the cranial border of the epiglottis (lower CV3) to the inferior border of the cricoid cartilage (CV6)
    - Continuous with the oesophagus at CV6
- Anterior wall has the laryngeal inlet
    - Bound by the aryepiglottic folds
    - Either side is the piriform fossae – important place for lodging of fish bones



Pharyngeal musculature

- Corresponds to the various parts of the pharynx – act to propel food down to the oesophagus
    - Superior pharyngeal constrictor – nasopharynx
    - Middle pharyngeal constrictor – lower oral pharynx
    - Inferior pharyngeal constrictor has 2 parts: - laryngopharynx (possible action as a sphincter to prevent air entering the oesophagus)
        - Thyropharyngeus muscle
        - Cricopharyngeus muscle
- Has a median pharyngeal raphe – a CT band in the midline



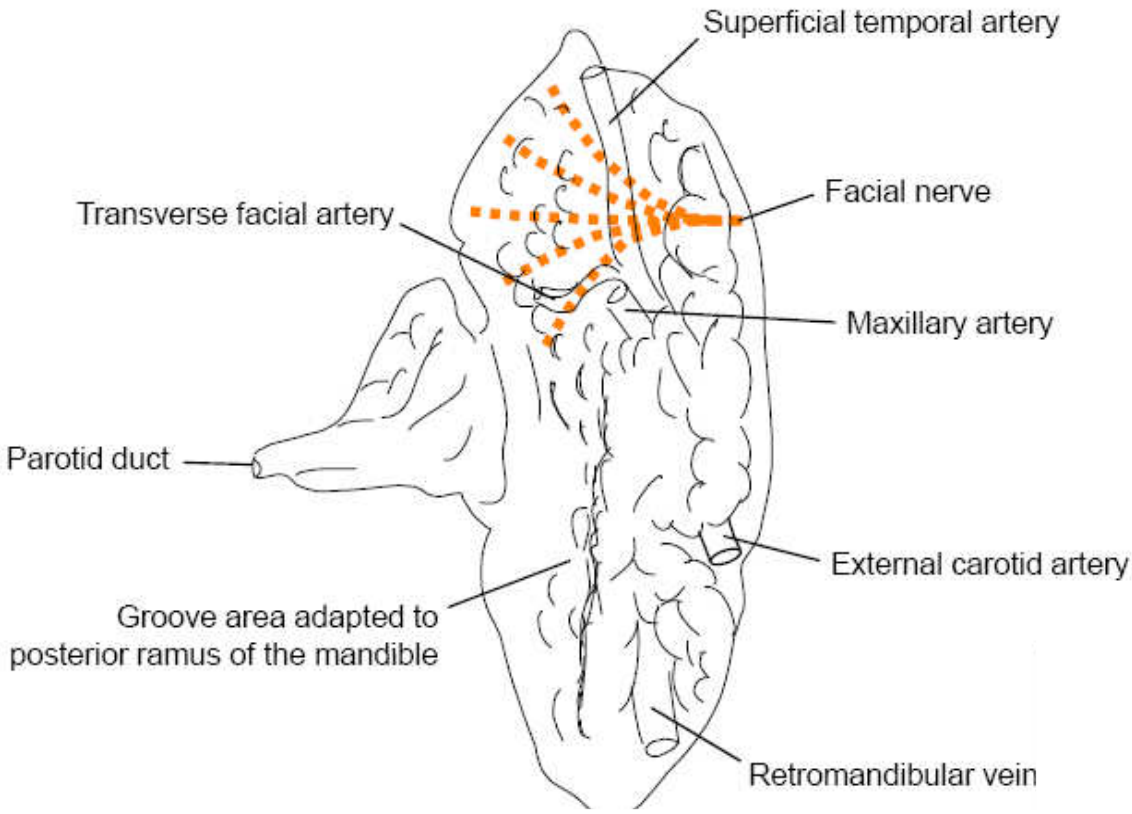
Anatomy

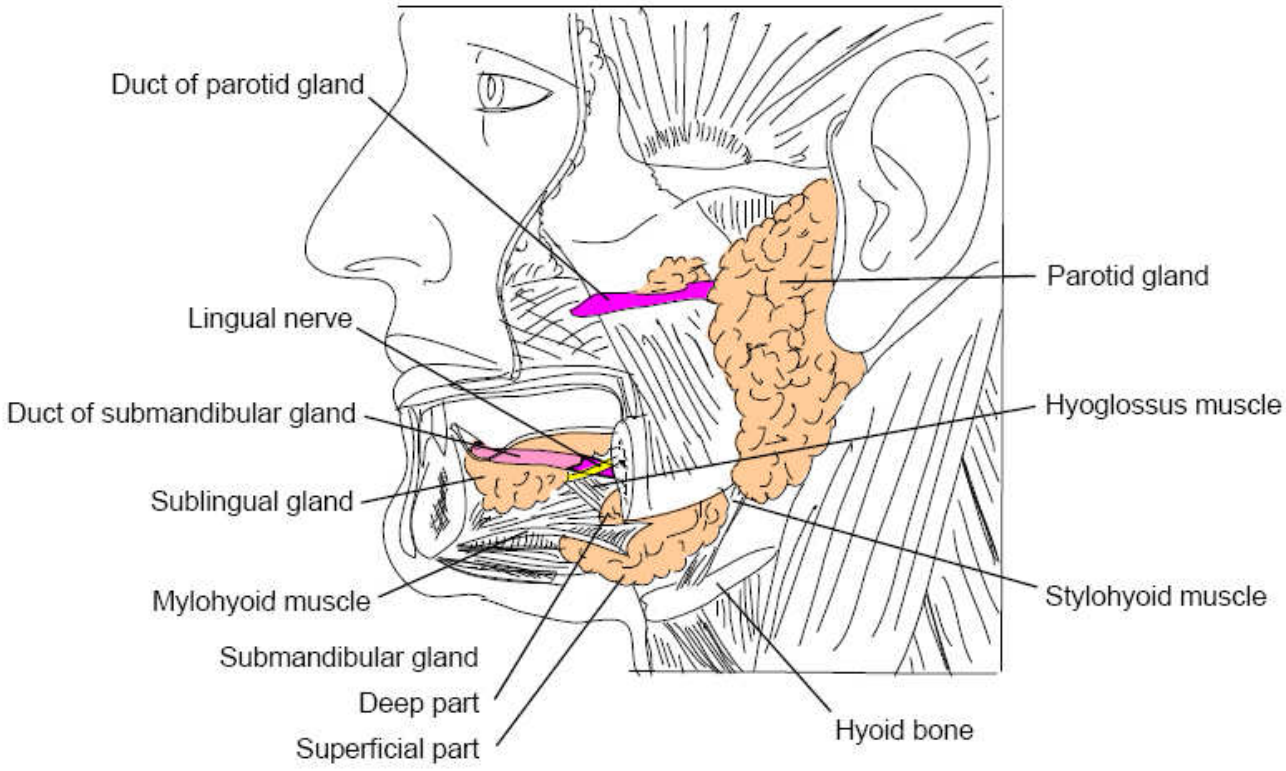
Salivary glands

- Functions
  - Lubrication of food to aid swallowing (deglutition)
  - Moistening of the buccal cavity (cheeks)
  - Aiding speech
  - Secretion of antibacterial agents (IgA)
  - Provide an aqueous solvent for molecules that stimulate taste receptors
  - A fluid seal for sucking and suckling
  - Secretion of digestive enzymes
- Two types:
  - Major salivary glands – located some distance from the oral mucosa
    - Parotid, sublingual and submandibular glands
  - Minor salivary glands – in the mucosa and submucosa of the tongue and walls of the oral cavity

Major salivary glands

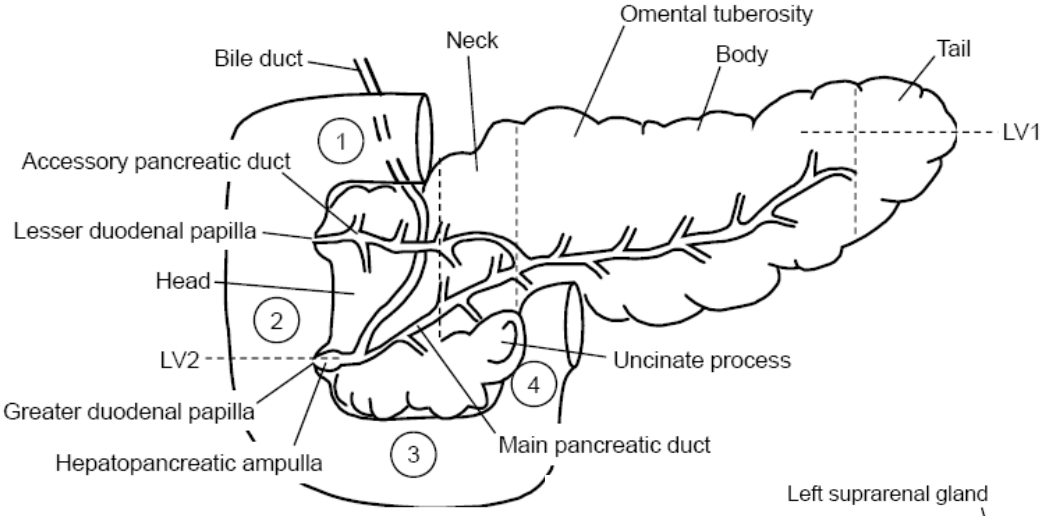
- Parotid gland
  - Weighs 25g
  - Located below the external acoustic meatus
    - Between the zygomatic arch and parotid duct
  - Penetrated by clinically significant structures:
    - External carotid artery with divisions
      - Maxillary artery (supplies cheek)
      - Superficial temporal artery (supplies from temple to vertex of the head)
    - Facial nerve and branches – from stylomastoid foramen and controls muscles of facial expression
    - Branches of the mandibular nerve (CNV_3)
    - Deep and superficial lymph nodes
  - Parotid duct carries saliva from the gland to the oral cavity
    - Ends at a papilla (skin flap in mouth) opposite the crown of the 2^{nd} molar
  - Pathology
    - A tumour or infection (eg mumps) in the parotid gland can affect associated structures
      - Eg: facial nerve – can present with facial weakness
- Submandibular gland
  - Superficial and deep parts separated by the mylohyoid muscle
  - Submandibluar duct carries saliva from the gland to the mouth
    - 5cm long
    - Opens in the floor of the mouth on the sublingual papilla at the base of the frenulum of the tongue
    - Associated with the lingual nerve (branch of CNV_3) that crosses it
- Sublingual gland
  - Located beneath the oral mucosa in contact with the sublingual fossa (on the lingual aspect of the mandible)
  - 8-20 sublingual ducts that open directly into the floor of the mouth (sublingual fold) and the submandibular duct

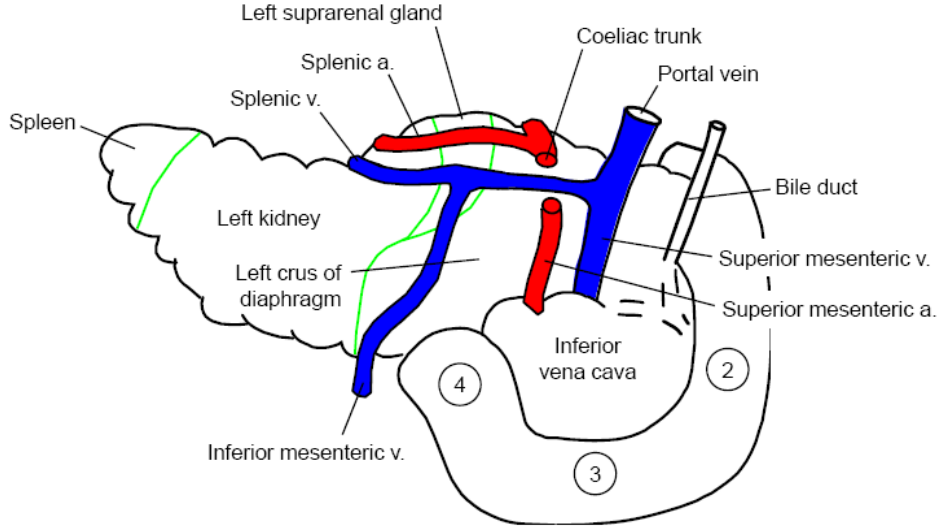

Superficial temporal artery
Facial nerve
Transverse facial artery
Maxillary artery
Parotid duct
External carotid artery
Groove area adapted to
posterior ramus of the mandible
Retromandibular vein


Duct of parotid gland
Parotid gland
Lingual nerve
Hyoglossus muscle
Duct of submandibular gland
Sublingual gland
Stylohyoid muscle
Mylohyoid muscle
Submandibular gland
Deep part
Hyoid bone
Superficial part

Pancreas

- Retroperitoneal structure
  - Extends transversely across the posterior abdominal wall from duodenum to spleen
  - In the epigastrium and left hypochondrium
- 12-15cm long
- Parts:
  - Head, neck, body tail
  - Uncinate process – projects from the lower left part of the head
    - Passes posterior to the superior mesenteric artery and vein
  - Body has surfaces and borders:
    - Surfaces: anterior, posterior and inferior surfaces
    - Borders: superior, anterior and inferior
- Functions
  - Endocrine (metabolic) – products of secretion are injected directly into the blood/body cavity
    - Hormones – islets of Langerhans
      - Glucagon – gluconeogenesis, glucose production and glycogen breakdown
      - Insulin – glucose uptake by cells and glycogen production/storage
  - Exocrine – secretions into the GIT via ducts
    - Pancreatic juices into the duodenum
      - Via main and accessory pancreatic ducts
      - Contains:
        - Enzymes for protein and fat digestion
        - Alkaline fluid with bicarbonate ions for neutralising stomach acid
- Ducts
  - Main pancreatic duct – drains into the greater duodenal papilla (8-10cm from pylorus of the stomach)
  - Accessory pancreatic duct – drains into the lesser duodenal papilla (4-5 cm from the pylorus)
  - Bile duct – carries bile from the liver. Bile emulsifies fat allowing its breakdown by pancreatic enzymes
- Pathology
  - Pancreatitis – enzymes damage the pancreas itself
  - Pancreatic cancer
  - Blockage of the bile duct can result in a build up of bile in the blood leading to jaundice





Histology

Salivary glands

- Compound exocrine glands that empty secretions (saliva) into the oral cavity
- Classification:
    - Size (major and minor groups)
    - Location (submandibular, sublingual, buccal (cheek), labial (lips), palatine)
    - Nature of secretions (serous, mucous or mixed sero-mucous)
- Size:
    - Minor salivary glands
        - Intrinsic, found in the structures of the oral cavity (labial, buccal, lingual, palatine)
        - Secrete saliva continuously keeping mucous membrane of mouth moist
    - Major salivary glands
        - Extrinsic, larger, found outside the oral cavity and have excretory ducts connecting to the mouth
        - Parotid, submandibular and sublingual glands

Acini (secretory portion of gland)

- The secretory unit of a salivary gland
- Small, round, sac-like dilation at the start of intercalated ducts
    - Narrow lumen with simple cuboidal epithelium – serous or mucous
        - Serous glands are more pink staining and have central nuclei
        - Mucous glands are pale staining and have peripheral nuclei
    - Basal lamina encloses acinus
        - Partially surrounded by myoepithelial (basket) cells – compress glandular cells to expel secretions into the lumen

Duct system (plumbing/tubing of glands)

- Extensive leading from each gland
- Process:
    - Myoepithelial cells contract and expel saliva from each acini into the intralobular duct system
        - 1st part: intercalated duct – inserted between secretory and excretory parts of the gland
            - Lined with simple squamous or low cuboidal epithelium
            - Cells increase in height leading into the striated duct (intralobular duct)
        - 2nd part: striated duct
            - Simple columnar cells
            - Basal striations due to basal infoldings of the plasmalemma (cell membrane)
                - Contain mitochondria
            - Secretory ducts that modify the ionic composition of saliva – reabsorb Na^+ and excrete K^+
            - Distally, becomes stratified columnar as it enters the interlobular septa becoming the interlobular duct
        - Interlobular ducts combine to form a lobar duct that drains an entire lobe
            - Lobar ducts join to form a single excretory duct that empties into the oral cavity

Parotid salivary gland

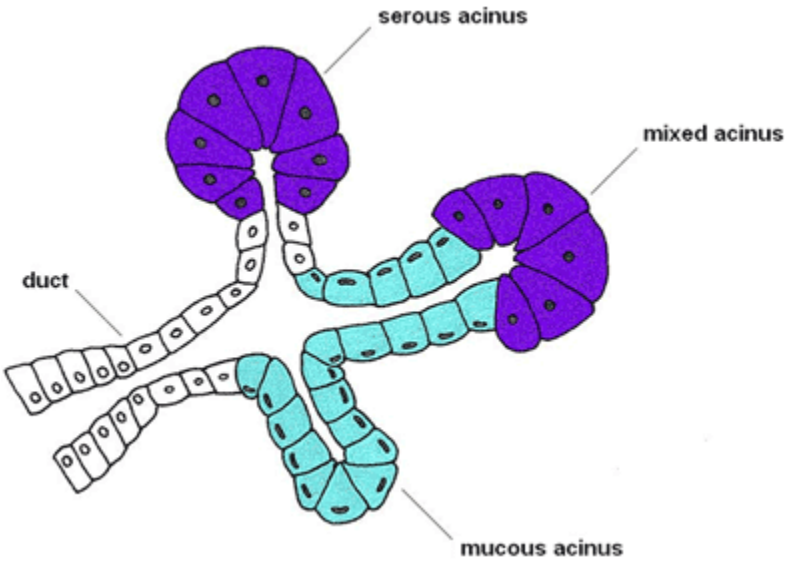
- Largest of the paired salivary glands
    - Located anterior and inferior to the external ear
- Enclosed in a CT capsule
    - Septa divide the gland into lobes/lobules
        - Made up of entirely serous acini that have a product rich in enzymes (proteins)
- Intercalated ducts are longer and more numerous, secretory (striated) ducts are less prominent

Submandibular salivary glands

- Smaller, paired glands
    - Located under each side of the mandible in the floor of the mouth
- Compound tubuloacinar glands
    - Mixed serous-mucous
    - Mucous acini are often capped with a semicircle of serous cells (serous demilune)
- Less dense CT capsule than parotid
    - Septa penetrate the gland parenchyma and divide it into lobes/lobules
- Has a large excretory duct (Wharton's) that opens near the frenulum of the tongue on the sublingual papilla
    - Intercalated ducts are shorter and striated ducts are longer (than parotid)

Sublingual salivary glands

- Smallest of the major salivary glands
- Aggregates of small glands found under the mucous membrane of the tongue near the midline of the mouth floor
- No capsule divided into many lobes by CT partitions
    - Lobes are very different in size and composition
        - Most are made up of mucous acini and serous demilunes, others are entirely mucous
        - Serous acini are rare
- Duct system is deficient, almost entirely lacks striated and intercalated ducts

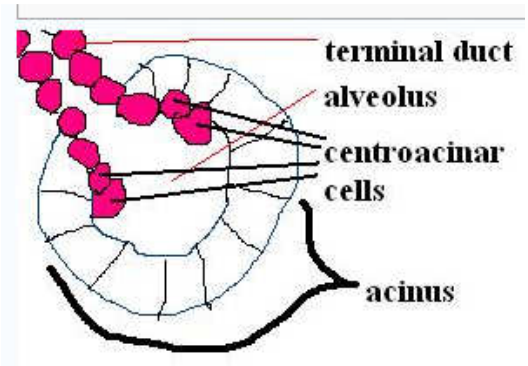


Pancreas

- Large, soft, greyish pink, lobulated, tubuloacinar gland (branching tubules with acini)
    - Located in the upper abdominal cavity behind the stomach
- Has a flimsy CT capsule that forms septa and divides the gland into lobules
- Has both exocrine and endocrine functions
    - Endocrine – secretes hormones directly into the blood
        - Islets of Langerhans (make up 2% of pancreas) are scattered among the exocrine secretory acini
    - Exocrine – secrete substances via ducts into the duodenum

Exocrine pancreas

- Compound tubuloacinar gland
    - Produces 1.2L/day of bicarbonate-rich fluid with digestive proenzymes
- 40-50 acinar cells form a round-oval acinus
    - Centrally there are 3-4 centroacinar cells
    - This begins the pancreas duct system
- Acinar cells - secretory
    - Shaped like a truncated pyramid
        - base positioned on the basal lamina (separates acinar cells from CT compartment)
        - apical cytoplasm has spherical acidophilic globules – zymogen secretory granules
            - contain inactive enzyme precursors
- Duct system
    - Centre of the acinus leads into the terminus of the intercalated ducts – pale, low cuboidal centroacinar cells
        - Intercalated ducts then join and form larger intralobular ducts that then converge to form interlobular ducts
        - These lead to the main pancreatic duct that joins the common bile duct and opens into the duodenum at the papilla of Vater (the hepatopancreatic papilla)
            - At the termination of the common duct, smooth muscle fibres form the sphincter of Oddi
                - This permits intermittent bile and pancreatic secretion flow into the duodenal lumen
- Exocrine pancreas vs parotid gland
    - Ducts begin with low cuboidal centroacinar cells that become the first part of the intercalated ducts
    - No striated ducts
- Histophysiology
    - Acinar cells manufacture, store and release enzymes:
        - Trypsinogen – converts proteins to amino acids
        - Amylase – converts starch and glycogen to maltose (which is then converted to glucose by maltase)
        - Lipase – breaks down fats into fatty acids and glycerol
- Hormonal control
    - Secretion control from the pancreas is regulated by duodenal (enteroendocrine) mucosal cells
        - Released in response to acid chyme in the duodenum
        - Ie:
            - Secretin – stimulates pancreatic centroacinar cells and intercalated ducts to secrete water with low protein and enzyme content but high bicarbonate ions
                - Neutralises chyme to activate enzymes
            - Cholecystokinin (pancreozymin) – causes acinar cells to release proenzymes, eg: zymogen granules

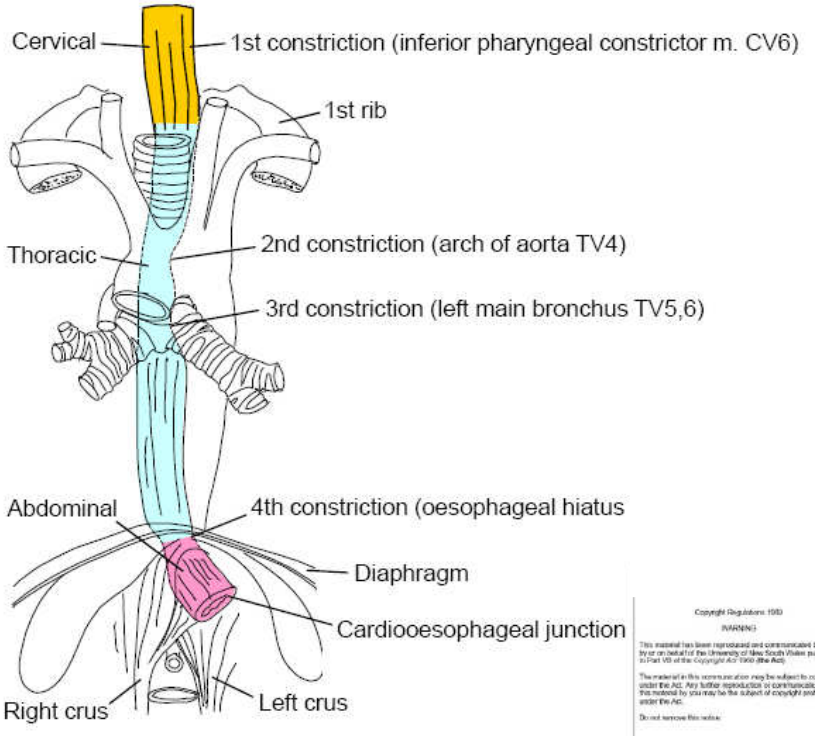


Endocrine pancreas

- Islets of Langerhans (up to 200µm in diameter) are richly vascularised spherical conglomerations of ~3000 cells
  - Endocrine pancreas is made up of ~1 million Islets (1-2% of pancreas)
    - Interspersed between exocrine cells
  - Surrounded by reticular fibres that enter the Islet and encircle the network of fenestrated capillaries
- Cells inside the Islets of Langerhans
  - Alpha cells (20%)
    - Large cells
    - Found at the periphery of an Islet
    - Produce glucagon (a peptide hormone) in response to low glucose
  - Beta cells (70%)
    - Most numerous, small cells
    - Found in the centre of the Islet
    - Produce insulin in response to increased blood glucose levels (eg: after consumption of a carbohydrate-rich meal)
      - Insulin is released into intercellular spaces and promotes glucose uptake
    - Plasma membranes have glucose transport proteins (glucose permease) that take up glucose when activated and decrease blood glucose levels
  - Delta cells (5%)
    - Largest cells
    - Manufacture somatostatin
      - Reduces motility alimentary tract and gall bladder by affecting smooth muscles
  - G cells
    - Release gastrin
      - Stimulates gastric release of HCl
      - Stimulates gastric motility and emptying
      - Increases the rate of cell division in gastric regernative cells
  - Pancreatic polypeptide cells
    - Produce pancreatic polypeptide
      - A hormone with an unknown function
  - Delta cells, G cells and PP cells are uncommon and scattered in Islets
- Capillaries
  - Islets are full of capillaries to allow direct delivery of hormones into the blood stream
- Pathology
  - Diabetes – loss of insulin leads to high glucose levels in blood, this feeds sugar and increases risk of infection

Oesophagus

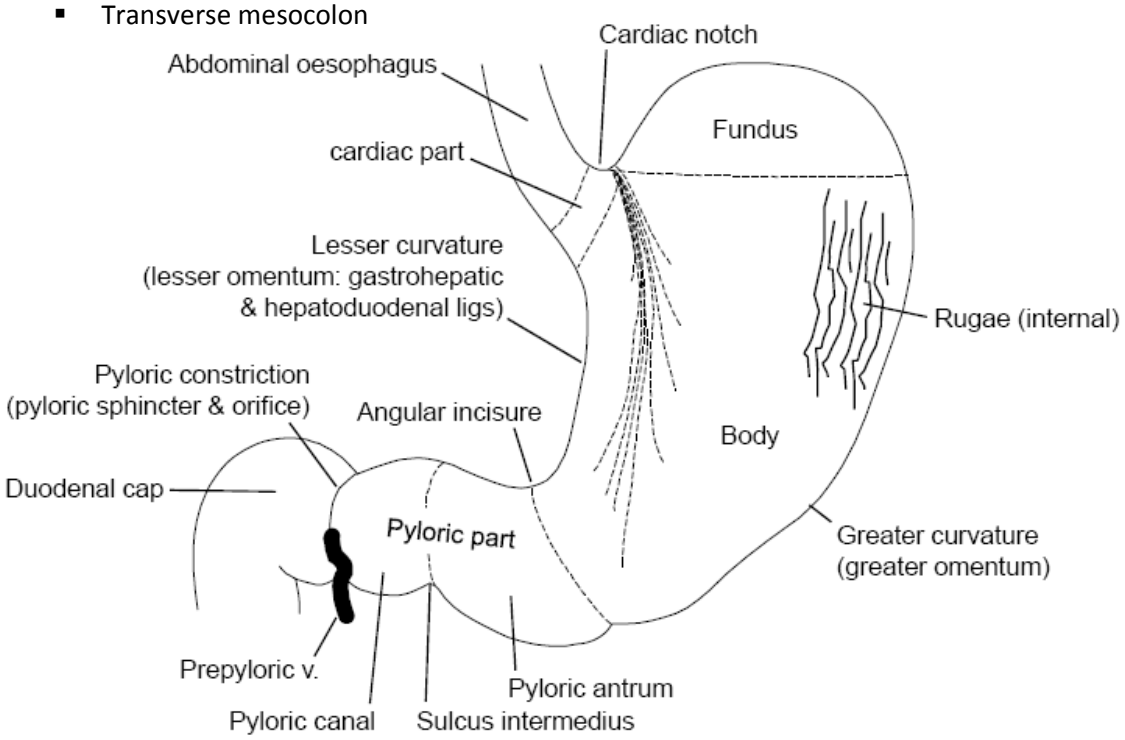
- Muscular tube that connects the laryngopharynx with the stomach
  - 25cm long
  - Extends from the pharynx to the cardiac portion of the stomach
- Begins at the lower border of the cricoid cartilage (CV6)
  - Passes through the diaphragm at TV10
  - Ends at TV11 in the gastric cardiac orifice
- Muscles:
  - Upper 1/3: striated, middle 1/3: mixed striated and smooth, lower 1/3: smooth
- Narrowest part of the GIT
  - 4 major constrictions:
    - Inferior constrictor muscle – CV6
      - Formed by inferior pharyngeal constrictor muscle of the pharynx
    - Aortic arch – TV4
    - Left main bronchus – TV5-6
    - Oesophageal hiatus – TV10
  - Constrictions are important sites for obstruction and scarring after swallowing caustic substances
- Three parts:
  - Cervical
  - Thoracic
  - Abdominal

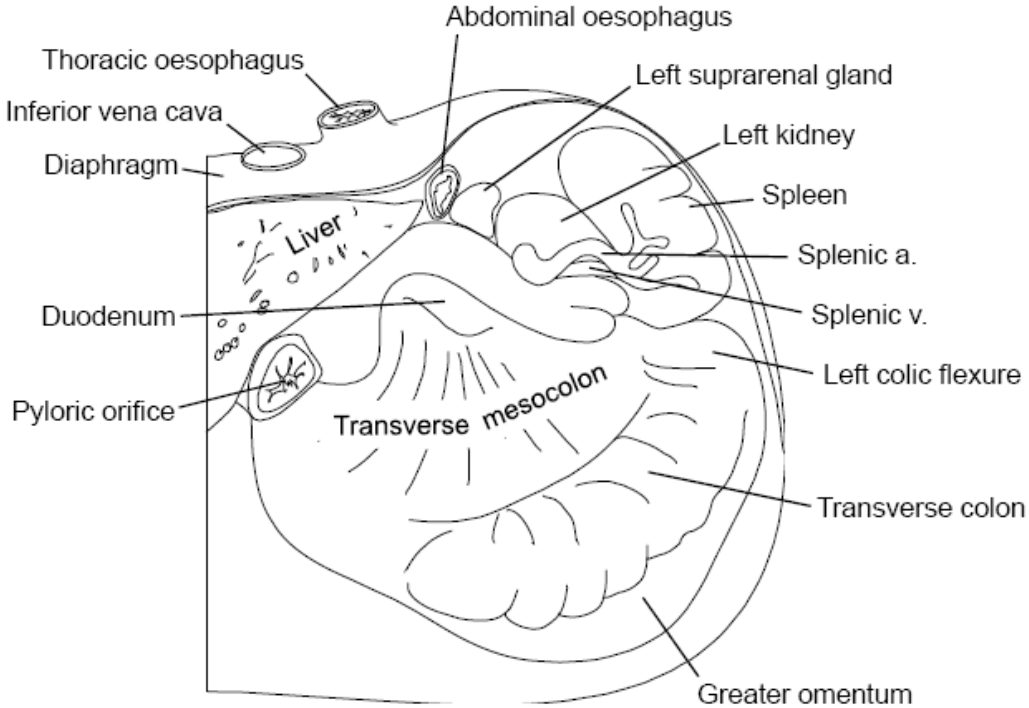


The stomach

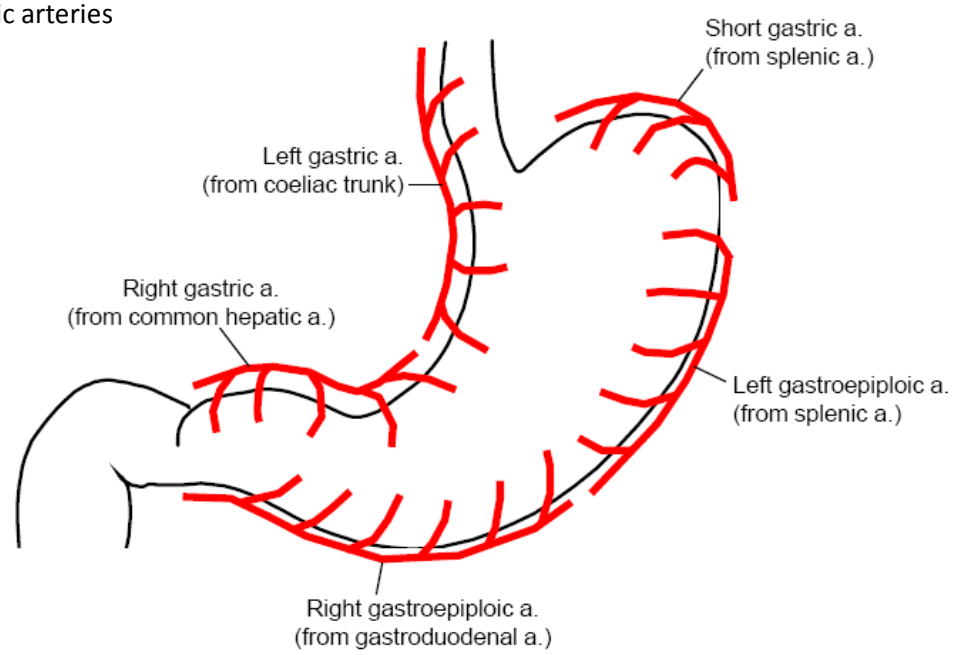
- Most dilated part of the GIT, capacity of 1500ml
- Two surfaces: anterior and posterior
  - Two borders/curvatures: greater and lesser curvature
  - Two openings: cardiac and pyloric
- Functions
  - Mechanical (churning) , chemical (acid) and enzymatic digestion (pepsin)
- Parts:
  - Cardiac part
    - Has Cardiac orifice
    - Located Left of the midline behind the 7th costal cartilage
      - 2.5cm from the sternal junction at TV11
  - Fundus
    - Part of the stomach above the cardiac orifice
    - Separated from cardiac part by cardiac notch/incisure
  - Body
  - Lesser and greater curvatures
    - Lesser – right border, attaches to the lesser omentum, gastrohepatic and hepatic duodenal ligaments, has the angular incisure
      - (note ligaments join similar-type tissue structures
    - Greater – left border, attaches to the greater omentum and gastrosplenic ligament
  - Pyloric part
    - Pyloric antrum leading to the pyloric canal and pyloric orifice
      - Orifice is surrounded by the pyloric sphincter – circumferentially arranged smooth muscle
    - Pyloric orifice is marked externally by the circular pyloric constriction
      - Prepyloric vein crosses the anterior surface vertically
      - Located about 1.2cm right of the midline in the transpyloric plane (LV1) when stomach is empty and patient is supine

- Muscles:
    - Oblique, circular and longitudinal (rest of GIT doesn't have oblique)
- Relations
    - Anterosuperior surface
        - Left costal margin
        - Left dome of the diaphragm
        - Gastric surface of the spleen
        - Left and quadrate lobes of the liver
        - Anterior abdominal wall
        - Transverse colon
    - Posteroinferior surface (stomach bed)
        - Diaphragm – left crus
        - Left suprarenal gland
        - Upper pole of left kidney
        - Splenic artery
        - Anterior pancreatic surface
        - Left colic flexure
        - Transverse mesocolon



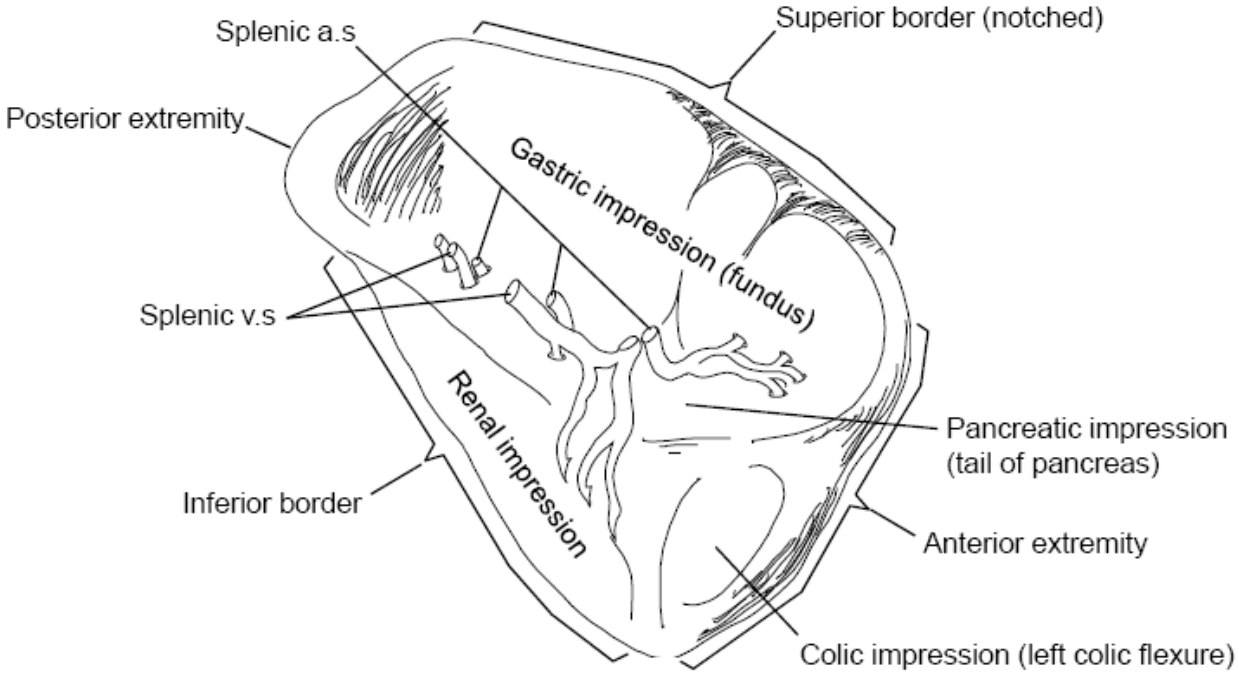


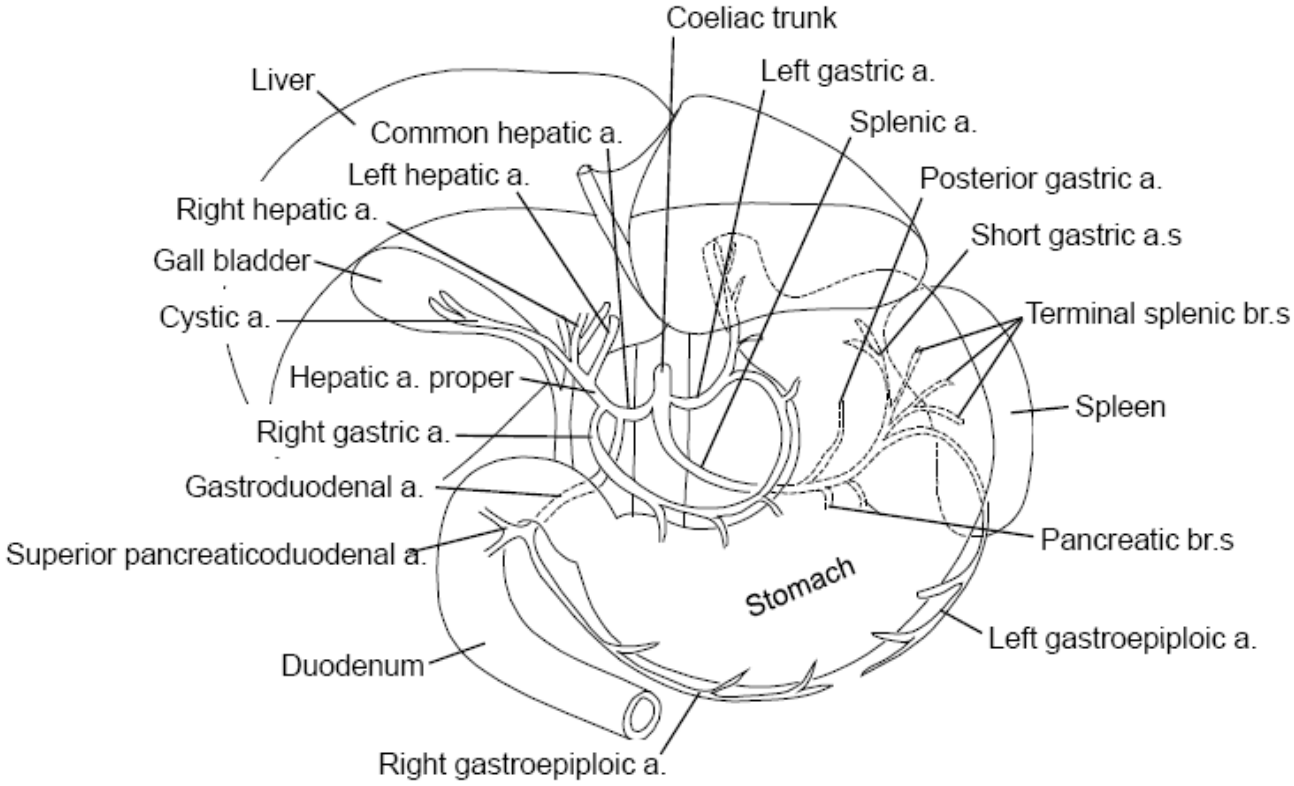
- Interior
    - Longitudinal mucosal folds – rugae
        - Lead from high in the body to the pyloric antrum and canal
- Arterial supply
    - Stomach is derived from the foregut, supplied by coeliac artery/trunk
    - Lesser curvature
        - Left gastric artery (coeliac trunk)
        - Right gastric artery (common hepatic artery, coeliac trunk)
    - Greater curvature
        - Left gastro-epiploic artery (splenic artery, coeliac trunk)
        - Right gastro-epiploic artery (gastroduodenal, common hepatic artery, coeliac trunk)
        - Short gastric artery (splenic artery, coeliac trunk) – supplies far left great curvature and fundus
    - Pyloric sphincter is supplied via the gastric and pyloric arteries (rami of the right gastric and right gastro-epiploic arteries



<u>Spleen</u>

- Located in the left upper abdomen between the gastric fundus and diaphragm
    - Dimensions
        - Long axis is on the 10th rib, short axis is from ribs 9-11
        - 12cm long, 8cm wide, 3.5cm thick, 150g weight in adults
    - Surface markers
        - Normally, anterior end does not extend more anteriorly than the midaxillary line
        - Superior border is normally notched – important orientation point
- Surfaces
    - Diaphragmatic surface – convex, smooth, related to abdominal surface of the diaphragm
    - Visceral surface – has 4 impressions:
        - Gastric impression – fundus and posterior stomach
        - Renal impression – left kidney: lowest and posterior, separated from gastric impression by a ridge
        - Colic impression – left colic flexure: anterior
        - Pancreatic impression – not always present, between colic impression and lateral part of the hilum
- Connected to the posterior abdominal wall by the lienorenal ligamen25-30t and the stomach by the gastrosplenic ligament


Splenic a.s
Superior border (notched)
Posterior extremity
Gastric impression (fundus)
Splenic v.s
Renal impression
Pancreatic impression
(tail of pancreas)
Inferior border
Anterior extremity
Colic impression (left colic flexure)

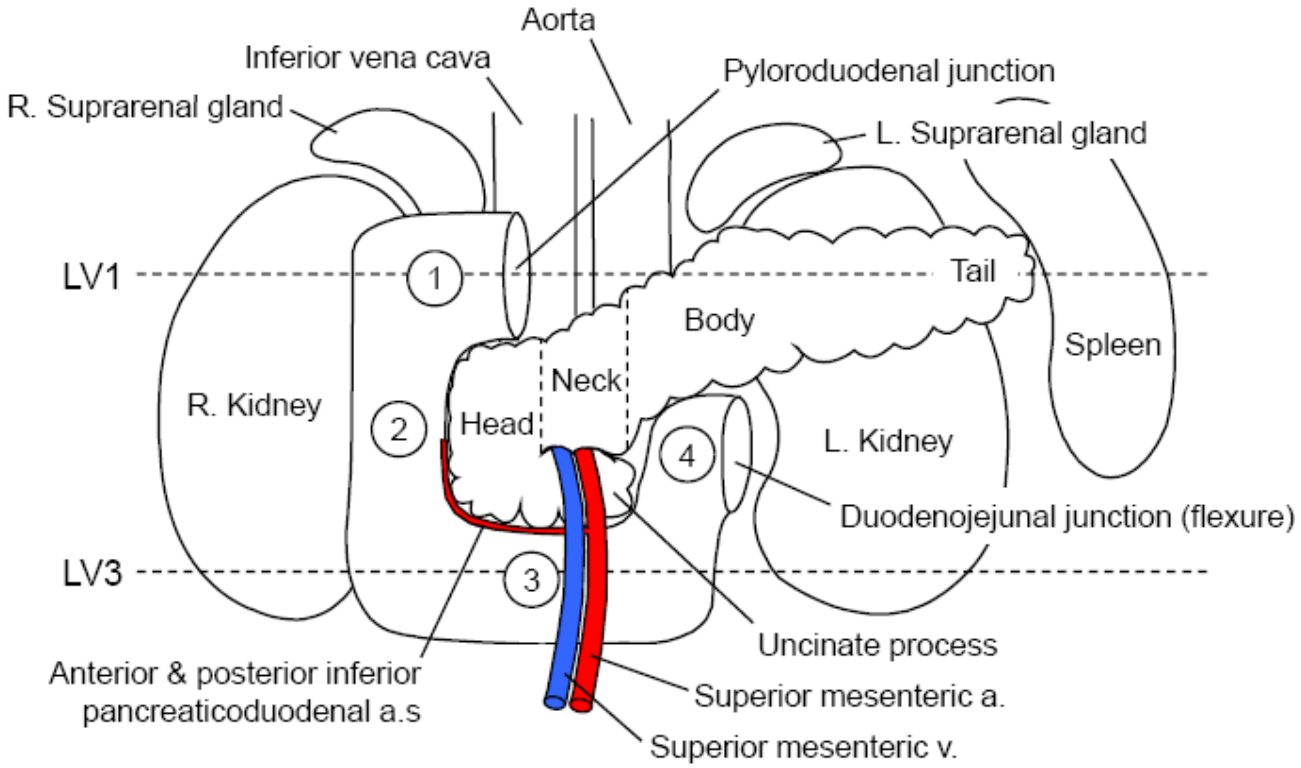

Coeliac trunk
Liver
Left gastric a.
Common hepatic a.
Splenic a.
Left hepatic a.
Posterior gastric a.
Right hepatic a.
Short gastric a.s
Gall bladder
Cystic a.
Terminal splenic br.s
Hepatic a. proper
Spleen
Right gastric a.
Gastroduodenal a.
Pancreatic br.s
Superior pancreaticoduodenal a.
Stomach
Left gastroepiploic a.
Duodenum
Right gastroepiploic a.

Small intestine

- Made up of the duodenum, jejunum and ileum

Duodenum – 12 thumb widths long

- Extends from the pylorus to the duodenojejunal junction
  - 25-30cm long
  - Arranged in a C-shape around the pancreas
  - No mesentery – except for 1st part
- 4 parts:
  - 1st (superior) – 2.5cm, LV1
    - Extends from the pyloric orifice to the superior duodenal flexure
    - Intraperitoneal part
  - 2nd (descending) – 8-10cm, LV1-3
    - Extends from the superior duodenal flexure to the inferior duodenal flexure
  - 3rd (horizontal) – 10cm, LV3
    - Extends to the left from the inferior duodenal flexure
  - 4th (ascending) – 2.5cm, LV2, to the left of the midline
    - Extends upwards to the duodeno-jejunal flexure
- Interior
  - Mucosa is made of circumferentially arranged folds – plicae circulares
    - Increase surface area to improve absorption
  - 2 papillae in medial wall of the 2nd part
    - Greater duodenal papilla (8-10cm from the pylorus)
      - Summit at the opening of the hepatopancreatic ampulla of Vater
        - Receives bile from the main pancreatic duct
        - Guarded by the sphincter of the hepatopancreatic ampulla
    - Lesser duodenal papilla (6-8cm from the pylorus)
      - Summit at the opening of the accessory pancreatic duct
      -

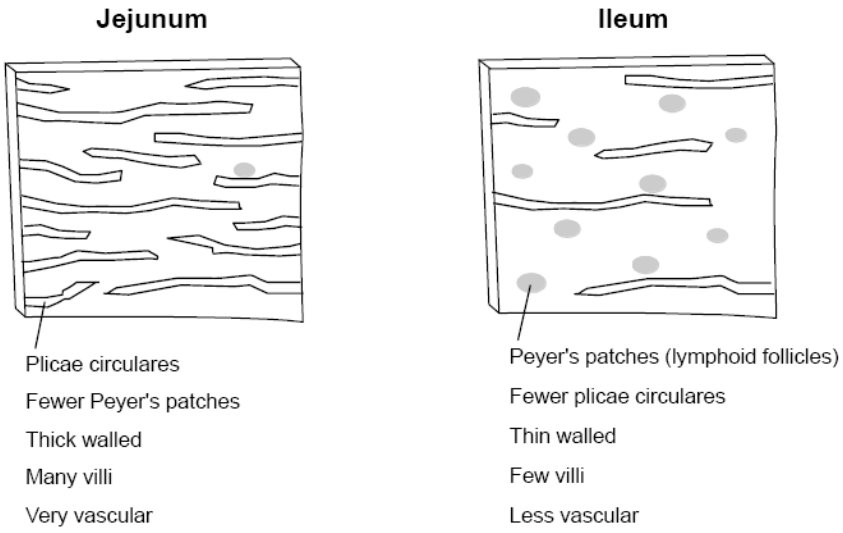


1. Superior 2. Descending 3. Horizontal 4. Ascending

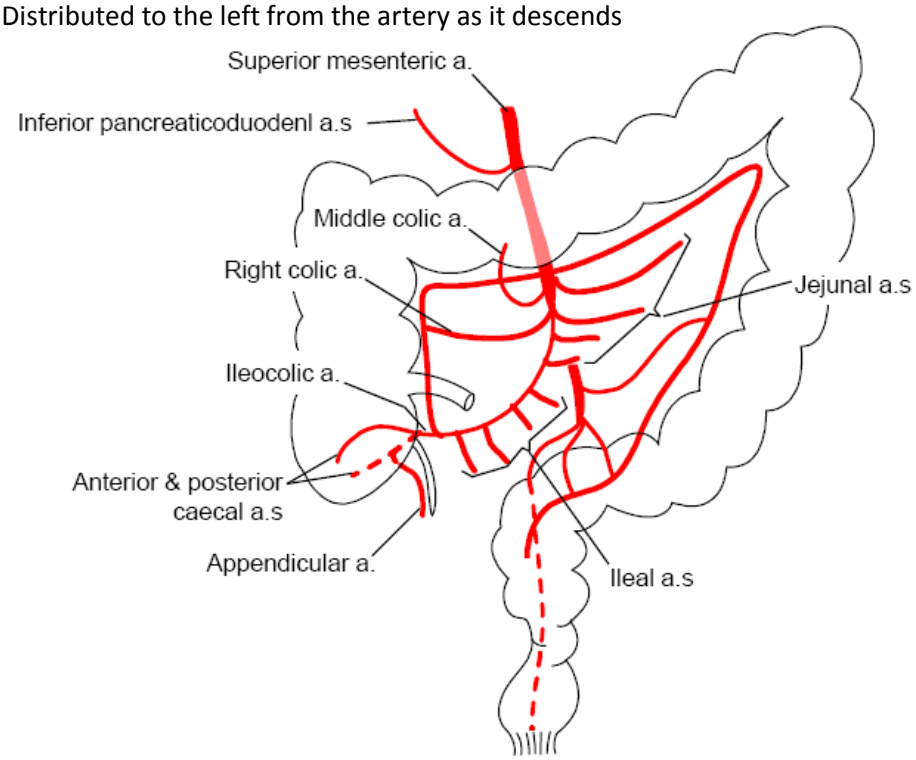
Jejunum and ileum

- Combined: 5-8m in length
- Jejunum vs ileum
    - Jejunum has:
        - More folds of the mucosa (known as plicae circulares or valves of Kerkring)
        - More villi
        - A thicker and more vascular wall
    - Distinguishing features:
        - Jejunum has more villi and is more vascular because most of nutrient absorption occurs here
        - Ileum has more Peyer's patches because it has a higher amount of natural microflora

Attributes	**Jejunum**	**Ileum**
Position	Upper left abdomen	Lower right abdomen
Abdomen extent	2/5	3/5
External feel and appearance	Thick, wide, vascular	Thin, narrow, pale
Peyer's patches (lymph follicles)	Few	Many
Vascular arcades	Few	Many
Vasa recti (allow maintenance of blood flow if gut moves and obstructs)	Long	Short
Mesenteric fat	Less	More



- Blood supply
    - Branches of the superior mesenteric artery (jejunal and ileal branches)
        - Distributed to the left from the artery as it descends



General structural plan of alimentary tract

- Alimentary tract: pharynx to anus has 4 layers (tunics)
  - Mucosa (mucous membrane)
    - 4 components
      - Epithelium
        - Oropharynx oesophagus and anus have simple squamous
        - Rest is simple columnar
      - Basal lamina
        - Variable thickness
      - Lamina propria (LP)
        - Loose CT with reticular fibres and lymphocytes
        - Compound glands found in certain regions (oesophagus and stomach)
        - Lymph nodules found in certain regions (ileum and colon)
      - Muscularis mucosae
        - Sheet of smooth muscle separating the LP from underlying submucosa
  - Submucosa
    - Fibroelastic zone of CT containing glands, blood vessels, lymphatics and nerves
    - Submucosal (Meissner's) plexus – nerve plexus of unmyelinated autonomic nerves
    - Compound glands – prominent in the duodenum (Brunner) and oesophagus
    - Lymph nodules – also present in the upper regions, but more so in the lower segments
  - Muscularis externa
    - In most of the GI tract, 2 prominent layers of smooth muscle
      - Inner circular
        - Modified at certain areas to form sphincters and valves
      - Outer longitudinal
    - Between layers is the myenteric (Auerbach's plexus) – nerve plexus of autonomic nerves and parasympathetic ganglion cells
      - Innervates the muscles to allow peristalsis
  - Serosa (adventitia)
    - Outermost layer made up of loose CT (collagen and elastic fibres), adipose, vessels and nerves
    - Serosa: outer layer of abdominal cavity organs that are suspended by a mesentery and covered by peritoneum (mesothelium)
      - Adventitia: outer layer of retroperitoneal organs that have no mesentery or mesothlium

Oesophagus

- Muscular tube about 20-25cm long transporting food from the pharynx to the stomach via peristalsis
  - Lies posterior to the trachea
- Pathology
  - Pregnancy: hiatus hernia, gastric reflux
- Layers:
  - Mucosa
    - Nonkeratinised stratified squamous that ends abruptly at the cardio-oesophageal junction
      - Then becomes simple columnar
    - LP has lymphoid nodules among CT fibres (fibroblasts/macrophages)
    - Mucous glands (small, known as oesophageal/cardiac glands)
      - Found in 2 limited areas: upper oesophagus and near the cardiac region of the stomach
    - Muscularis mucosa is a discontinuous layer of longitudinal smooth muscle
  - Submucosa
    - Loose collagenous and elastic CT zone
    - Acts as a shock absorber for rough boluses of food
    - Mucous oesophageal glands found here, empty onto the epithelial surface
      - Lubricate oesophagus and facilitate movement of food down the tube
    - Meissner's plexus also present+

Oesophagus continued

- Muscularis externa
  - Inner circular and outer longitudinal muscle layers
    - Upper 1/3 of oesophagus is voluntary – both layers have skeletal muscle fibres
      - Involved in voluntary swallowing (peristalsis not gravity)
    - Middle 1/3 – mixed smooth and skeletal muscle
    - Lower 1/3 – smooth muscle only
  - Auerbach's plexus present
- Adventitia
  - Outermost layer of loose CT
    - Contains blood vessels and nerves
  - Attaches the oesophagus to other structures in the neck

Stomach

- Fibro-muscular bag
- Function: mixing and partial digestion of food
  - Kneading action to mix gastric juices (HCl, mucin, digestive enzymes, water) with food
- Gastric regions (4):
  - Cardia – small zone near gastroesophageal junction
  - Fundus – large, dome-shaped above the level of the oesophageal opening
  - Body (corpus) – 2/3 of the stomach, extends from the fundus towards the pylorus
  - Pylorus – most inferior region, funnel shaped leading to the pyloric canal and the pyloric sphincter at the entrance to the duodenum
- Layers
  - Mucosa (mucous membrane)
    - Has longitudinal folds (rugae)
      - Function is to grip and move food around the stomach to mix with gastric juices
    - Simple columnar epithelium
    - Invaginations into the LP forming gastric pits for the emptying of gastric glands
    - Gastric glands
      - Mucosal thickness of 0.5-1.5mm is due to these glands
  - Submucosa
    - BVs and nerves (Meissner's submucosal plexus)
    - Loose collagenous and elastic fibres
  - Muscularis externa
    - 3 layers of smooth muscle
      - Inner oblique (at an angle), middle circular, outer longitudinal
      - Auerbach's myenteric nerve plexus found between circular and longitudinal layers
  - Serosa – covering around whole stomach of loose CT surrounded by mesothelium
- Gastric glands (mucosa)
  - 3 types: cardiac glands, gastric/fundic glands, pyloric glands
  - Types of cells lining glands:
    - Mucus-secreting surface epithelium (simple columnar)
    - Chief (zymogenic) cells (darker cells) – produce pepsinogen and lipase
      - pepsinogen produces pepsin that digests protein
    - Parietal cells (fried egg cells) – produce HCl
    - Mucous neck cells
      - Secrete mucin and are the stem cells for production of mucosa epithelium
      - Mucus protects stomach lining from acid
    - Enteroendocrine cells
      - Found in the base of gastric glands
      - Secrete gastrointestinal hormones: secretin, gastrin, cholecystokinin
  - Divided into segments
    - Initial segment (neck): lined with modified surface cells (mucous neck cells)
    - Intermediate segment (body): in fundus and body of stomach it is made up of basophilic chief cells and large eosinophilic parietal cells
    - Blind-ending terminal segment (base): lined with same cells as body + enteroendocrine cells

Stomach continued

- Regional differences
    - Cardiac region
        - Made up of a 25mm wide collar around the oesophageal orifice
        - Glands are least numerous
            - Wide, open, deep pits with mucous-type cells
            - Occupy most of the LP
            - Rest on a thin muscularis mucosae at their base
    - Fundic and body regions
        - Makes up ¾ of the stomach
        - Gastric glands/fundic glands most numerous in the stomach
            - Narrow, shallow pits
        - Cells of gastric glands
            - Lined with surface mucous cells
            - Has irregular mucous neck cells – pale secretory granules
                - Granules stain with mucicarmine that distinguishes from surface mucous cells
            - Body of gland is lined with parietal and chief cells (distinctive of fundic glands)
                - Chief cells – most numerous
                    - Granules contain the inactive proenzyme (zymogen) – pepsinogen
                - Parietal cells – most numerous in the neck region
                    - Large, oval, eosinophilic, HCl secreting
                    - Also secrete gastric intrinsic factor
                        - Glycoprotein that binds vitamin B2 allowing its absorption in the ileum
            - May have enteroendocrine cells – located in the base of glands between chief cells
                - G-type – produces and stores gastrin
                    - Gastrin: polypeptide hormone that stimulates gastric motility, HCl production and pepsinogen secretion
                - EC-type – produces serotonin: smooth muscle constrictor
                - EG-type – produces enteroglucagon: hormone that increases blood glucose levels
                - D cell – releases hormone somatostatin that locally regulates G and EG cells
    - Pyloric region
        - Makes up 20% of the stomach
        - Continuous with the duodenum
        - Glands resemble those of the cardiac region
            - Deeper pits, more branching and coiling of tubular glands
            - Has a few parietal cells and G-cells, no chief cells

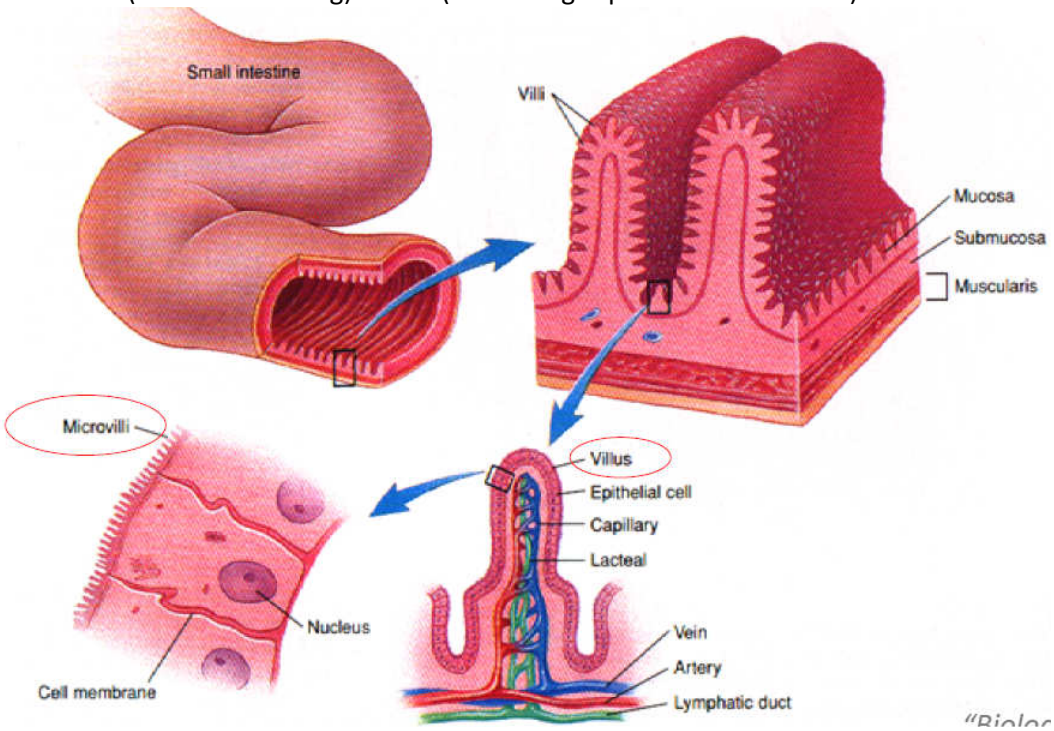
Small intestine

- Extends from the pyloric sphincter to the its union with the large intestine at the ileocecal valve (6-8m)
- Functions:
    - Completion of the digestion of food by various enzymes
    - Selective absorption of digested products into the blood and lymph
- Layers:
    - Mucosa (mucous membrane) [plicae circularis → villi → microvilli]
        - Two specialisations to increase SA and enhance absorption: plicae circularis and villi
        - Permanent, spiral (circular) mucosal folds – plicae circularis (valves of Kerckring)
            - Have a central core of submucosa
            - Maximum development reached in the lower duodenum and upper jejunum, disappear in the lower ileum
        - Villi – finger-like projections of the mucosa extending into the lumen, 0.5-1mm long
            - Covered by simple columnar epithelium, rest on a definite basement membrane
            - Have goblet cells (make mucus) – more numerous distally
            - Central core of LP, not submucosa
                - Contains free cells: lymphocytes, neutrophils, plasma cells, macrophages
            - Lacteal – lymphatic vessel at the core
                - Facilitates the absorption of fats
                - Protein and carbohydrates are absorbed into the blood stream → portal system → liver → stored as glycogen, converted or passed on
            - Fine nerve plexus lies among blood vessels and lacteal
        - Microvilli – very small villi on the top of each epithelial cell
    - Lamina propria
        - Loose reticular CT forming the core the villi
        - Contain collections of lymphocytes forming solitary lymph nodules
            - Increase in number and size distally until the ileum where they form Peyer's patches
                - Large aggregations of >20 nodules
    - Muscularis mucosae
        - Layer of smooth muscle separating LP from submucosa
        - Contains blood and lymph vessels, ducts and autonomic nerves from Meissner's plexus
            - If lymph nodules extend to mucosa and submucosa, muscular mucosa may not be present
    - Submucosa
        - Composed of areolar CT with large blood, lymph vessels and nerve plexuses
            - Nerve plexuses are parasympathetic submucosal (Meissner's) plexuses
        - Adipose cells
        - Peyer's patches (ileum) extending also in the LP
        - No glands except Brunner's glands in the duodenum
    - Muscularis externa
        - Inner circular and outer longitudinal smooth muscle
        - Between 2 layers are parasympathetic ganglia – myenteric plexus of Auerbach
            - Motor innervation of the muscles of the gut facilitating peristalsis
    - Serosa
        - Most of the SI is suspended by mesentery and covered by a single cell layer of mesothelium + thin layer of loose CT, collectively the serosa
        - Exception: retroperitoneal duodenum – covered by adventitia
- Intestinal glands (Cryptos f Lieberkuhn) (mucosa)
    - Tubular glands (0.3-0.5mm in depth)
        - Located between the bases of villi
        - Extend as deep as the muscularis mucosae
    - LP of villus extends downwards and surrounds these glands
    - Surface epithelium of villus lines crypts
        - Goblet cells are found in the upper half of the gland and at the base are replaced by Paneth cells
            - Paneth cells: have deeply staining eosinophilic zymogen granules - precursors for bacteriocidal enzyme lysozyme (may regulate SI mucosa bacteria)
        - Enterendocrine cells may also be found secreting hormones like secretin and cholecystokinin

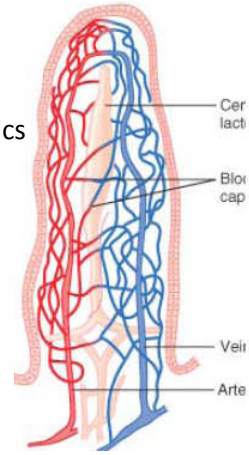
- Regional differences
  - Duodenum
    - Prominent Brunner's glands in the submucosa
      - Mucous glands restricted largely to the submucosa
      - Have alkaline secretions (pH 8.8-9.3) to neutralise acidic chyme of the stomch and protect the duodenal mucosa from autodigestion
      - Submucosa has few lymphatic nodules
    - Abundant villi
    - Incomplete serosa replaced with an extensive adventitia
      - Duodenum lies behind the peritoneum, serosas covers only the anterior wall
      - Otherwise, it is replaced by the adventitia
    - Terminations of bile and pancreatic ducts
  - Jejunum
    - Tallest villi, less profuse, lacteals are well developed for maximum fat absorption
    - No Brunner's glands
  - Ileum
    - Many lymphoid nodules (Peyer's patches) in the LP
    - Most of the Paneth cells reside here
      - No Brunner's glands, villi least numerous

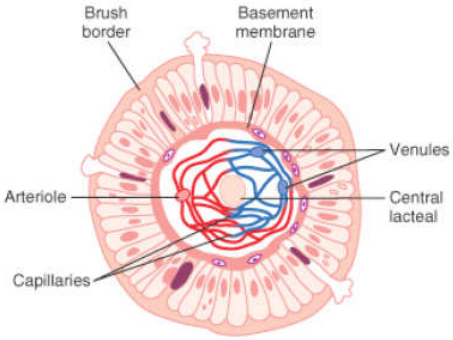
Overview

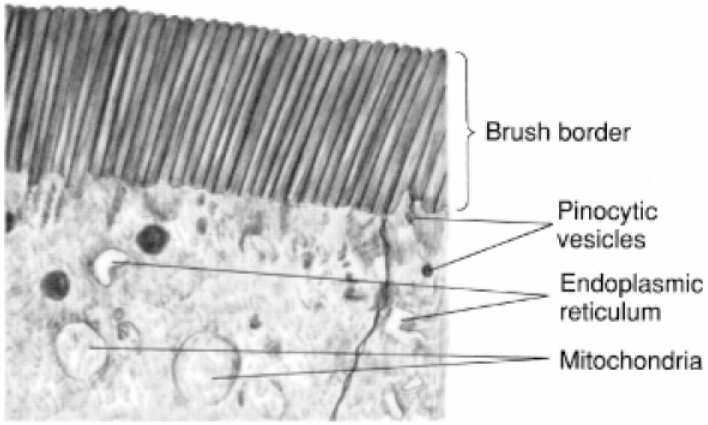
- Small intestine tissue structure:
  - Plicae circularis (folds of Kerckring) → villi (containing capillaries and lacteals) → microvilli



- Inside the villus
  - Arterial and venous blood flow
  - Lacteal → for fat absorption via chylomicrons
- Areas of absorption are maximised
  - Villi contain absorptive vasculature and lymphatics
    - Lined by enterocytes
  - Enterocytes are lined by a brush border containing microvilli
    - Actin filaments within allow movement







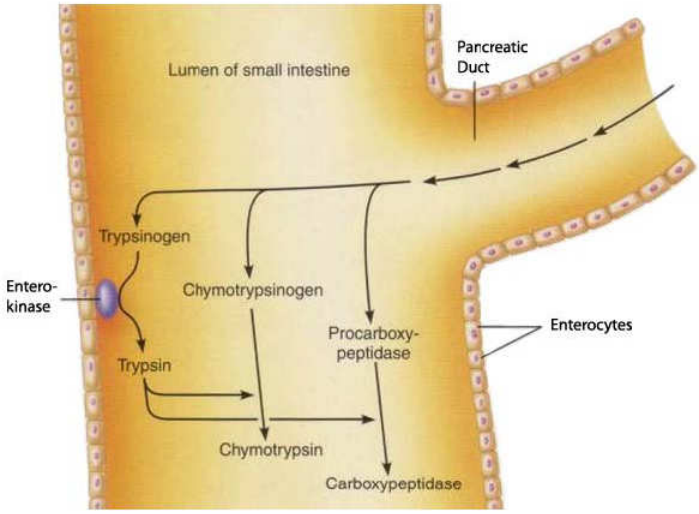
Functions of the small intestine

- Absorption of nutrients
  - Carbohydrates, protein, fats
  - Ions, vitamins, water
- Digestion – by luminal and brush border enzymes that facilitate transport into the bloodstream

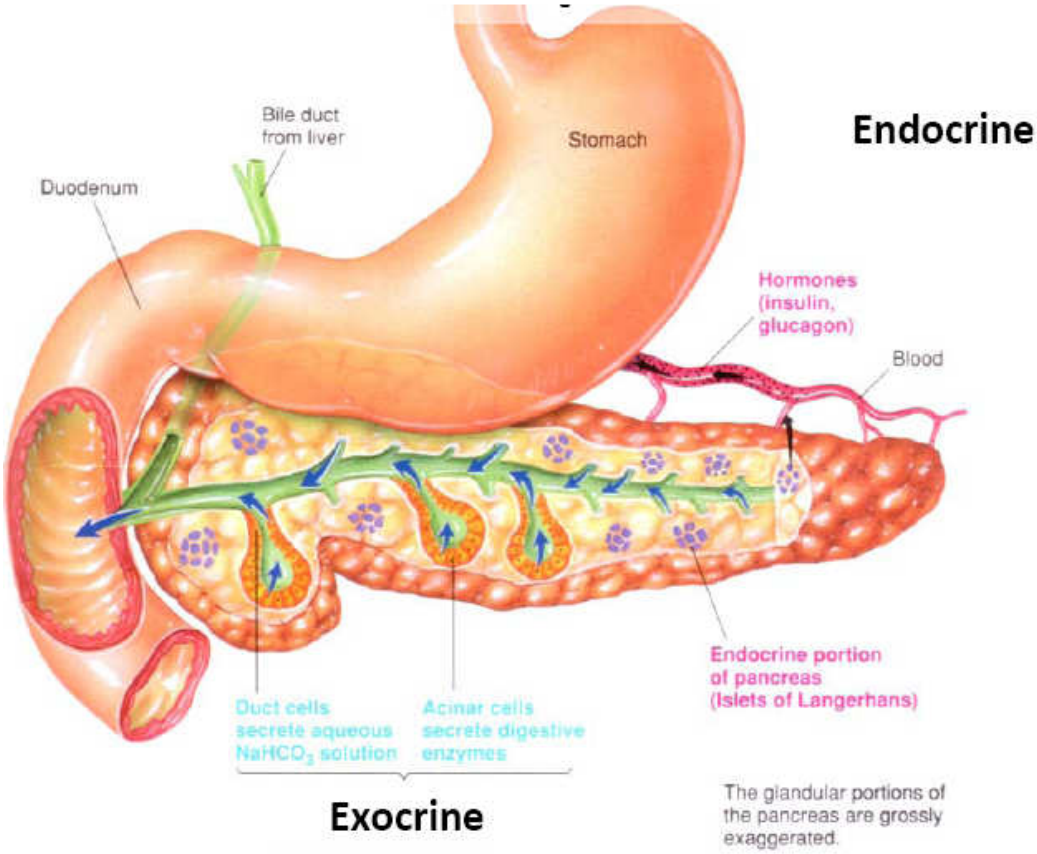
Digestive enzymes

- Pancreatic enzymes do most of the work
    - Many are secreted in inactive forms and are activated by the duodenum

Mouth	Amylase – minor CHO digestion Lingual lipase – minor fat digestion
Stomach	Pepsin – minor protein digestion
Pancreas	Amylase – CHO digestion Trypsin, Chymotrypsin – protein digestion Carboxypeptidase, elastase – protein digestion Lipase, colipase – fat digestion Phospholipase A2, cholesterol esterase – fat digestion
Small intestine	Enterokinase (activates trypsin) – protein digestion Disaccharides – CHO digestion Peptidases – protein digestion

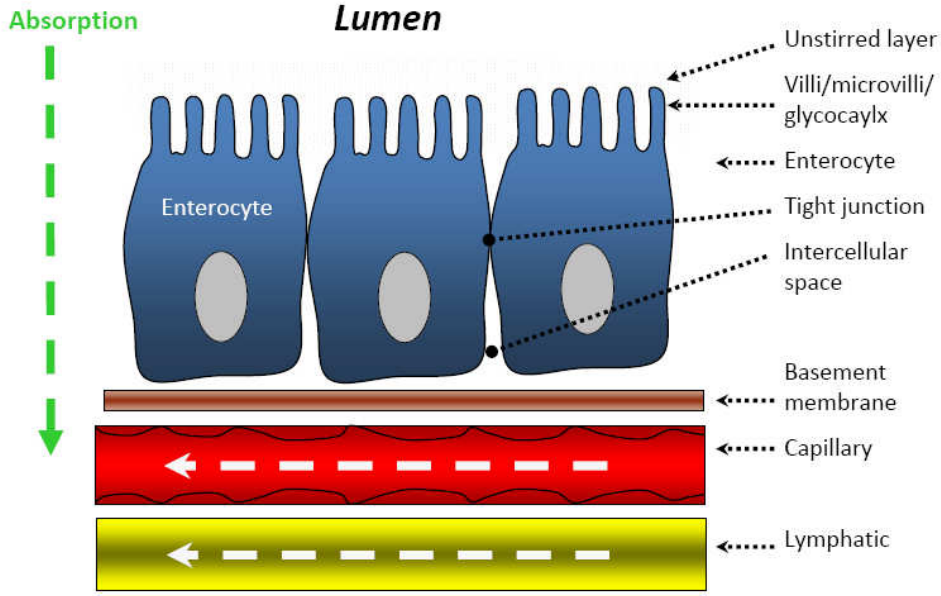


- Pancreatic secretions
    - Watery alkaline secretions rich in HCO_3^-
        - Neutralises acidic stomach contents as it enters the small intestine
    - Digestive enzymes
        - Complete the digestion of carbohydrates, protein and fats
            - Broken down into small constituent molecules that can be absorbed



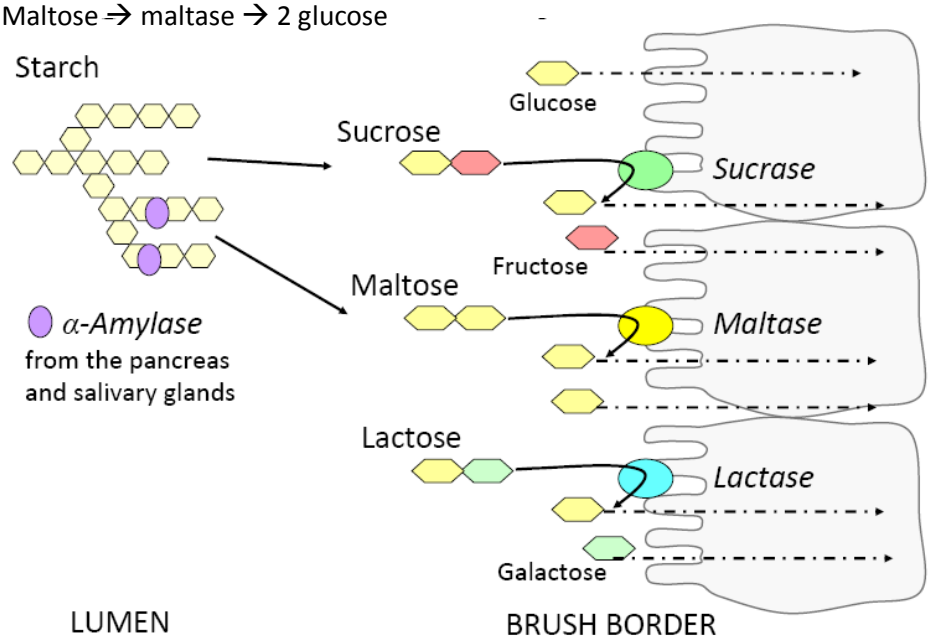
Digestion and absorption of nutrients

- Absorption – process whereby molecules cross barriers of the gut lining/wall and enter the blood stream
    - Some substances absorbed without digestion (water, ions, vitamins)
- Absorption barrier
    - Mucosal – enteroctyes joined by tight junctions that can't be passed easily by anything but water
    - Physical and chemical nature of nutrients determines how they cross the GIT wall
        - Hydrophobic/hydrophilic:
            - Eg: hydrophobic fats can perfuse the lipid bilayer, ie cholesterol, short chain lipids
        - Molecule/particle size:
            - Eg: large proteins can't get through easily



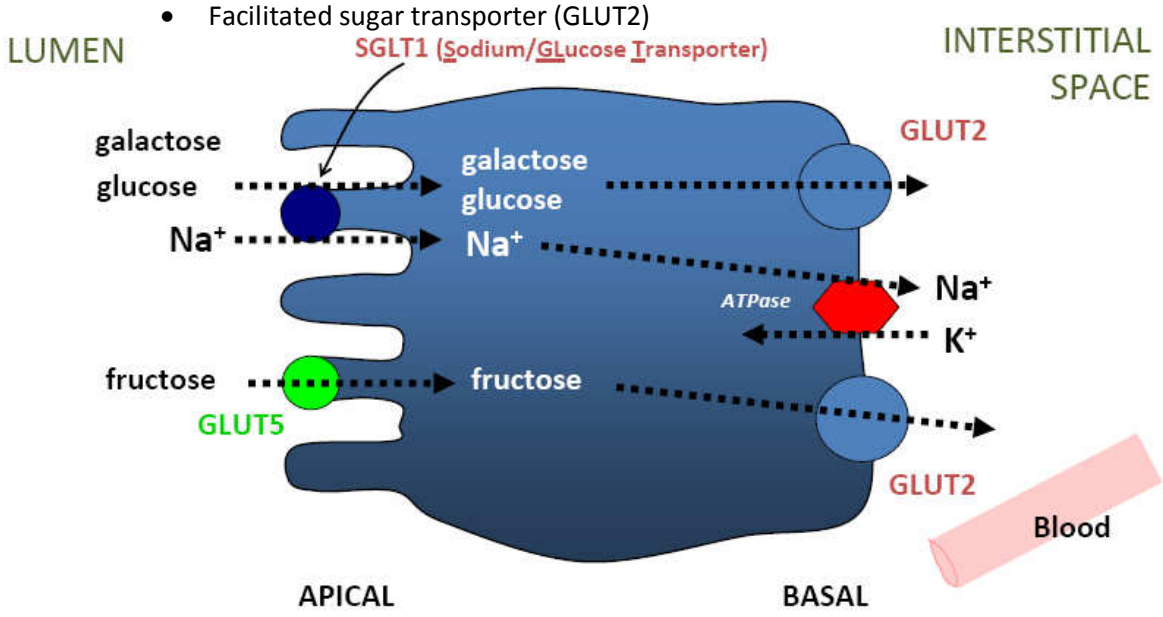
Sugars

- Carbohydrates in the diet
    - 60% are complex carbohydrates – starch (polysaccharides)
    - 30% are disaccharides – sucrose and lactose
    - 10% are monosaccharides – glucose, fructose (simple sugars, absorbed directly)
- Monosaccharides are absorbed across the small intestine epithelium
    - Other carbohydrates need to be digested before absorption
- Digestion of carbohydrates
    - Polysaccharides are digested luminally to disaccharides by:
        - Salivary amylases
        - Pancreatic amylases
    - Disaccharides are digested at the brush border to monosaccharides by:
        - Sucrose → sucrase → glucose + fructose
        - Lactose → lactase → glucose + galactose
        - Maltose → maltase → 2 glucose



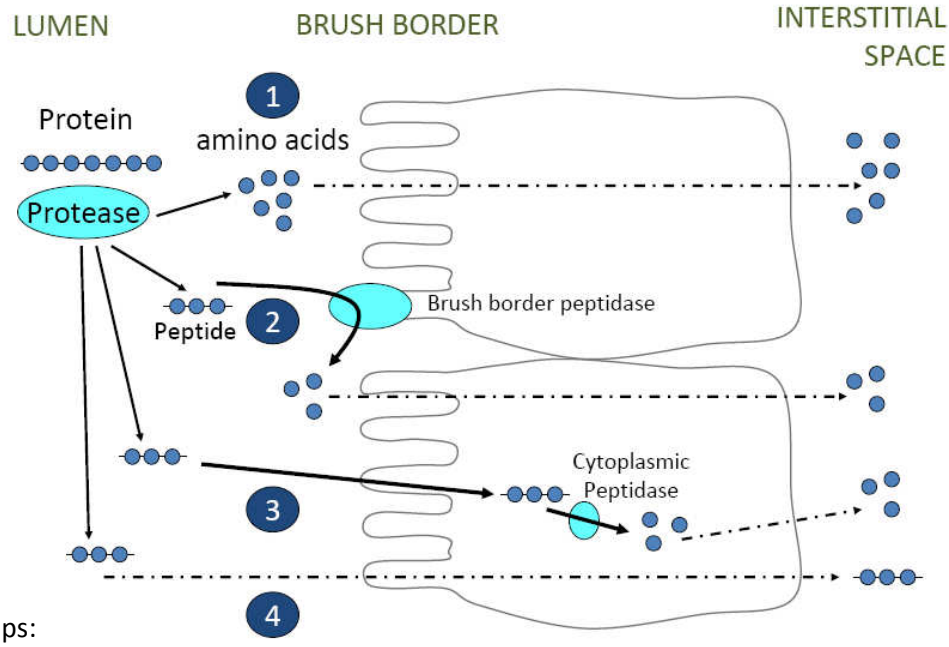
Sugars continued

- Abnormalities: lactose intolerance (enzyme)
  - Genetic or acquired where enzyme lactase is deficient (not an allergy)
    - Lactose is milk sugar
  - Lactose accumulates in the gut
    - Acts as an osmolyte (osmotic laxative trapping water in the lumen)
    - Acts as a nutrient for bacterial proliferation
    - Bacteria production of gas and osmotic induction of water in lumen leads to irritation, bloating and diarrhoea
  - Controlled by dietary modification or exogenous enzymes
- Absorption of carbohydrates
  - Monosaccharides produced through digestion (glucose, fructose, galactose) are absorbed in 2 steps:
    - Across apical membrane by active transporters:
      - Glucose and galactose Na^+/glucose cotransporter
      - Fructose facilitated sugar transporter (GLUT5)
    - Across the basal cell membrane:
      - Facilitated sugar transporter (GLUT2)

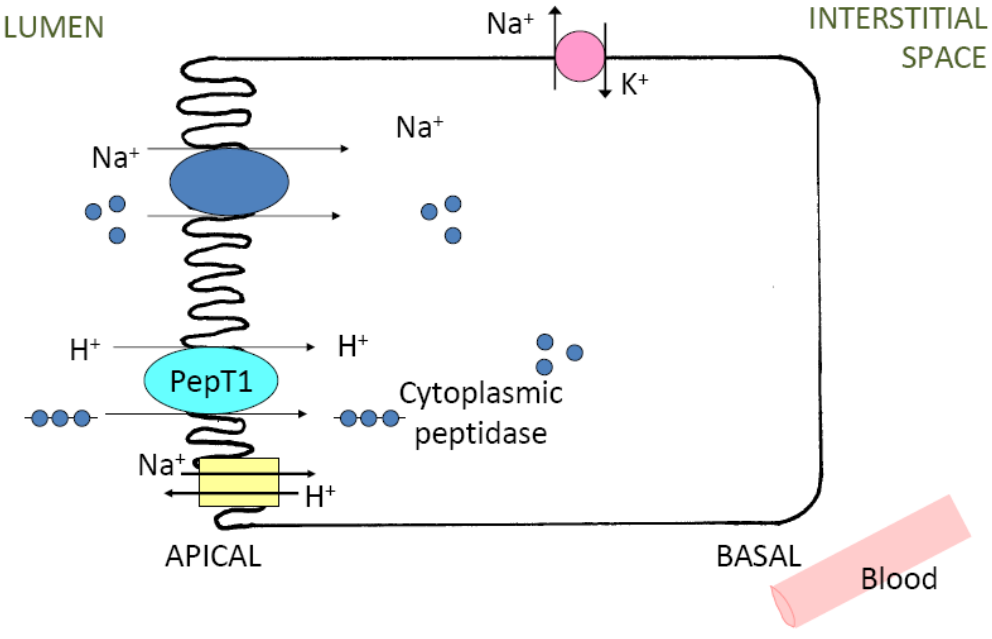


Proteins

- Protein in the diet
  - Eating requirements:
    - Adult: 0.6g/kg body weight/day
    - Child: 3-4g/kg body weight/day
  - Average diet – 90g protein/day
    - 10-30g of diet from GIT secretions (eg: pancreatic proteases)
    - 3g albumin
    - Stomach pepsin
- Digestion, 4 pathways:
  - Luminal proteases from stomach and SI hydrolyse proteins to peptides and amino acids
  - Brush border peptidase digests peptides to amino acids
  - Peptides broken down to amino acids by cytoplasmic peptidase
  - Peptides absorbed and cross directly into the blood stream

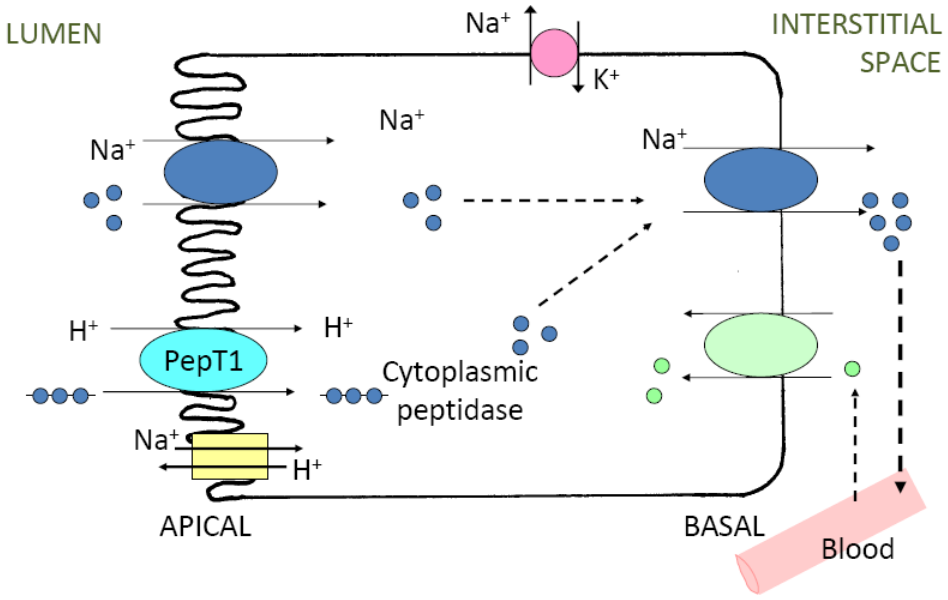


- Absorption, 2 steps:
  - Across the apical membrane
    - Na^+ dependent amino acid co-transporter
    - H^+ dependent peptide co-transporter (PepT1)
  - Across basal cell membrane
    - Na^+-dependent amino acid co-transporter
- Apical transport
  - Peptides: H^+/peptide co-transporter (PepT1)
  - Amino acids: 7 distinct transport systems that identify amino acid groups (acidic, basic, beta-amino acids)
    - Predominant AA transporter is Na^+-dependent AA co-transporter driven by Na^+ gradient inwards



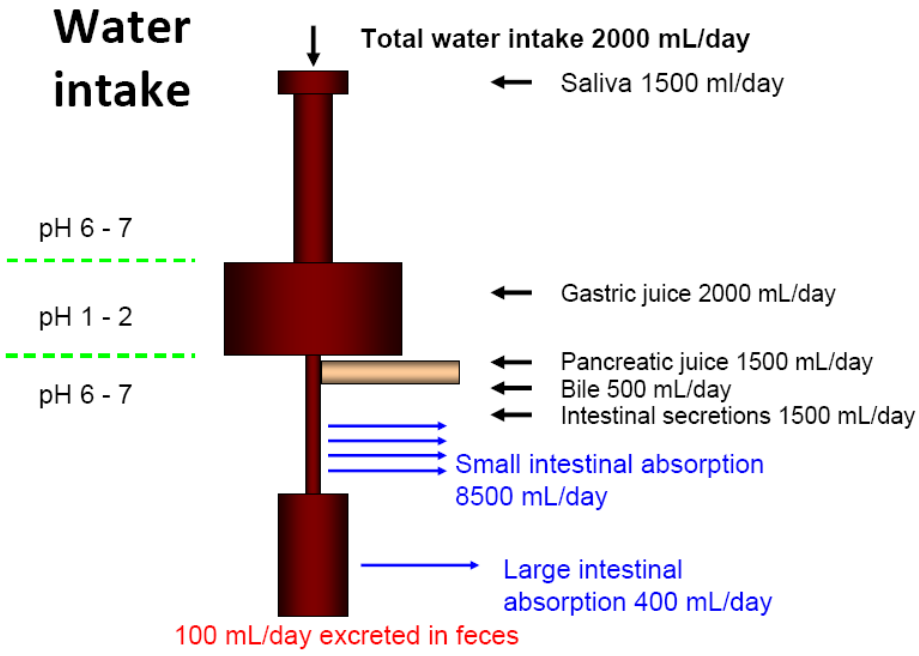
Proteins continued

- Basal transport
  - 90% of absorbed are transported across basal membrane and into circulation
    - Other 10% used by enterocyte itself for intracellular protein synthesis
  - At least 5 types of AA transporters are present in basolateral membrane
    - 3 mediate transport out, 2 absorb amino acids into the enterocyte
    - Transporteres are Na^+ depedent amino acid co-transporters



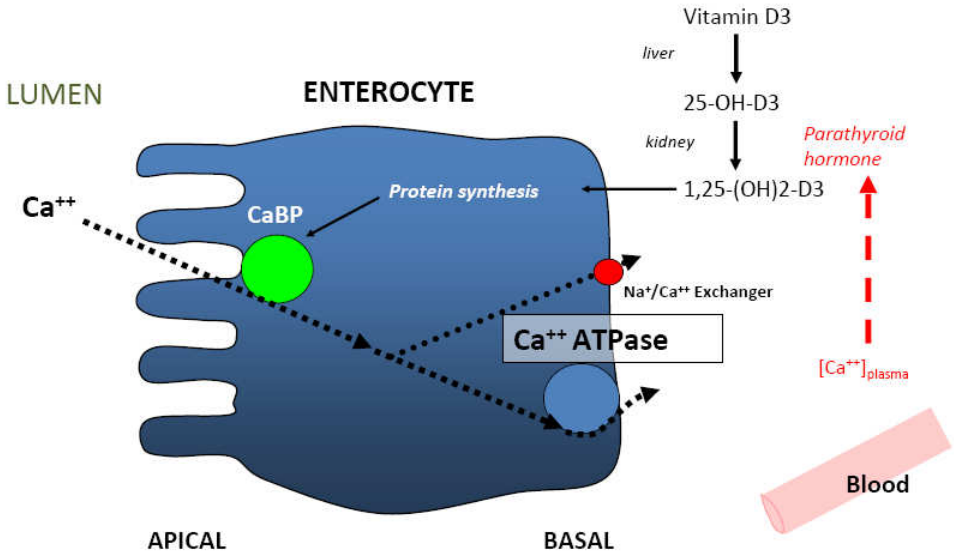
Absorption of water

- Diffusion
  - Continuous, driven bi-directionally by osmotic gradients
    - Gradient can be established by absorption of ions (Na^+, Cl^-) into intercellular spaces
      - Aided by tight junctions – permeable to water but not solutes)

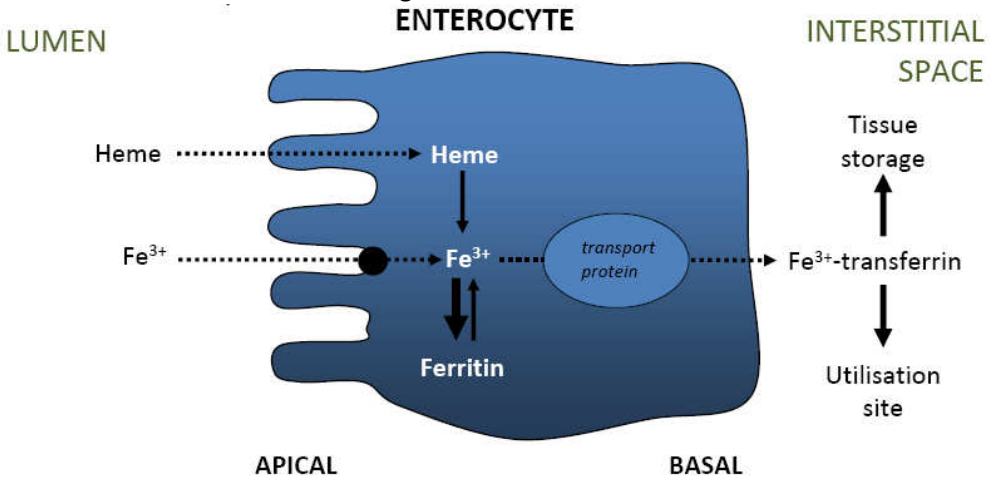


Absorption of ions

- Sodium
  - Co-transport with nutrients (glucose, amino acids)
  - Neutral co-transporter with Cl^-
  - Na^+/H^+ exchanger
  - Epithelial Na^+ channels
  - Gradients for Na^+ transport is provided by Na^+/K^+ ATPase on basolateral side of enteroyte
- Calcium
  - Some is regulated, some is unregulated
    - Half of absorption is regulated (transporters), the rest is unregulated paracellular (through the cell) absorption from the small intestine
    - Body can up-regulate Ca^{2+} production
  - Mainly in duodenum
  - Oxalate and some green leafy vegetables (eg. spinach) bind Ca^{2+} and prevent uptake



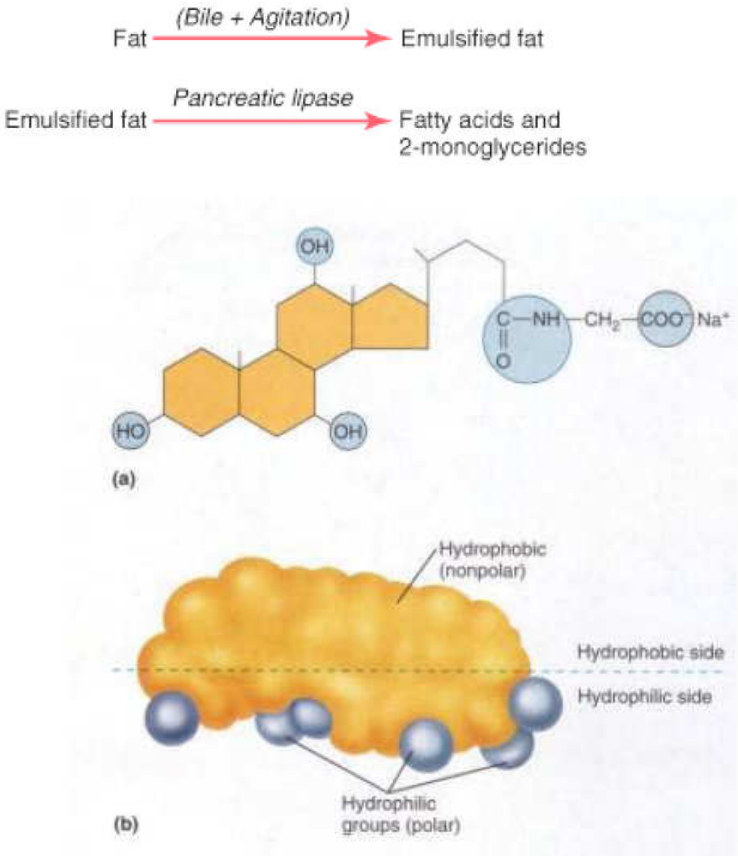
- Iron (Fe^{3+})
  - Requires binding protein tranferrin
    - Iron release from enterocytes is dependent on need/plasma levels
  - Absorption: transferrin-bound Fe^{3+}, Heme reabsorption
    - Iron is processed into ferritin for storage, can be bound to transferrin to allows transport out of the cell for utilisation or tissue storage

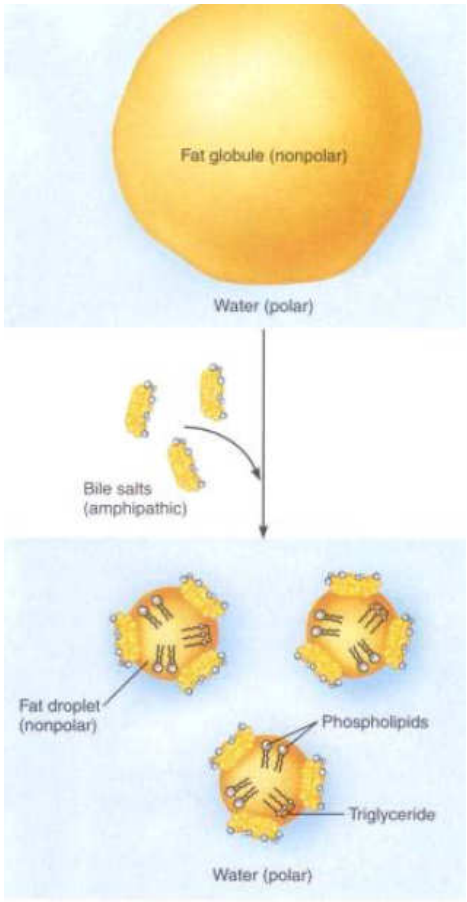


- Absorption of vitamins
  - Fat soluble (A, D, E, K)
    - Absorbed with lipids due to solubility in lipid droplets: micelles/chylomicrons
  - Water soluble (B-complex, C)
    - Require transport proteins (active transport or facilitated diffusion)
    - Eg: Vitamin B-12
      - Requires protection by intrinsic factor (IF) protein that is secreted by gastric parietal cells
        - IF-B_{12} complex is transported to the ileum for absorption
      - Abnormalities result in pernicious anaemia

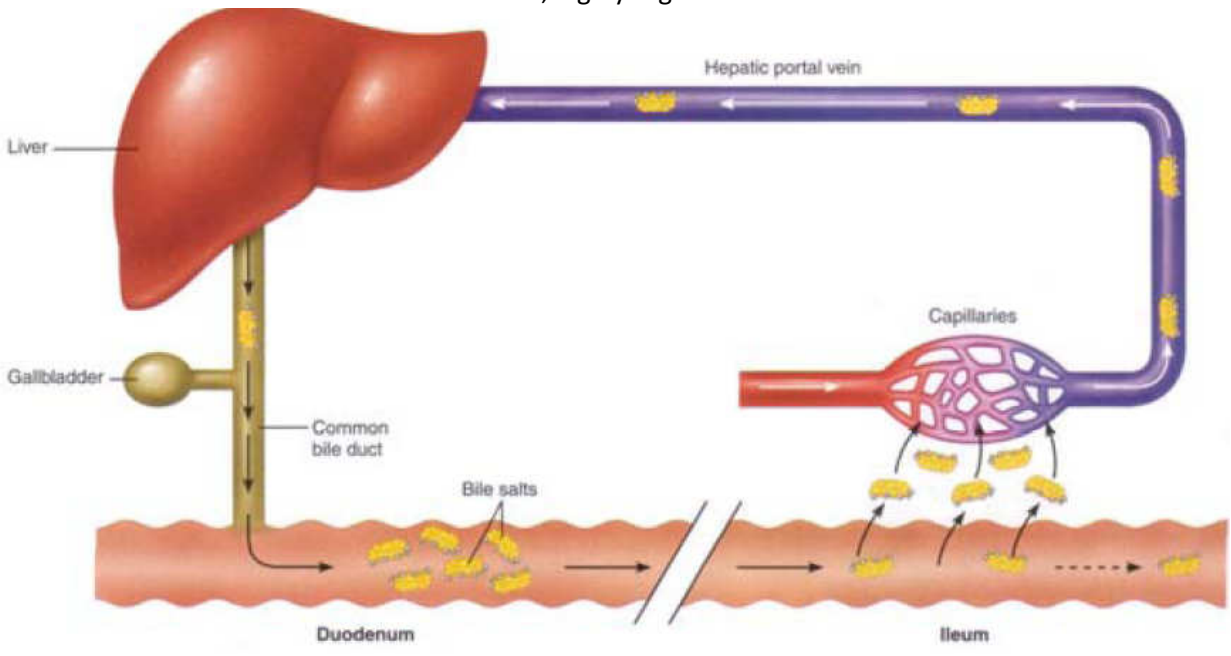
Fats (lipids)

- Fats in the diet
  - Average diet is 60-90g/day, approx 40% of daily energy intake
  - Different forms:
    - Triglycerides (90%),
    - Cholesterol esters (<5%), needed for steroid hormone synthesis and the lipid bilayer
    - Phospholipids (lecithin) in small amounts (<5%)
- Digestion
  - Hydrophobic and thus not soluble in the aqueous lumen of GIT
    - Therefore, fats are modified for passive diffusion
  - Process:
    - Emulsification into fine oil droplets by bile salts produced by liver and released into the duodenum
    - Hydrolysis catalysed by lipases in the salivary gland, gastric mucosa and pancreas



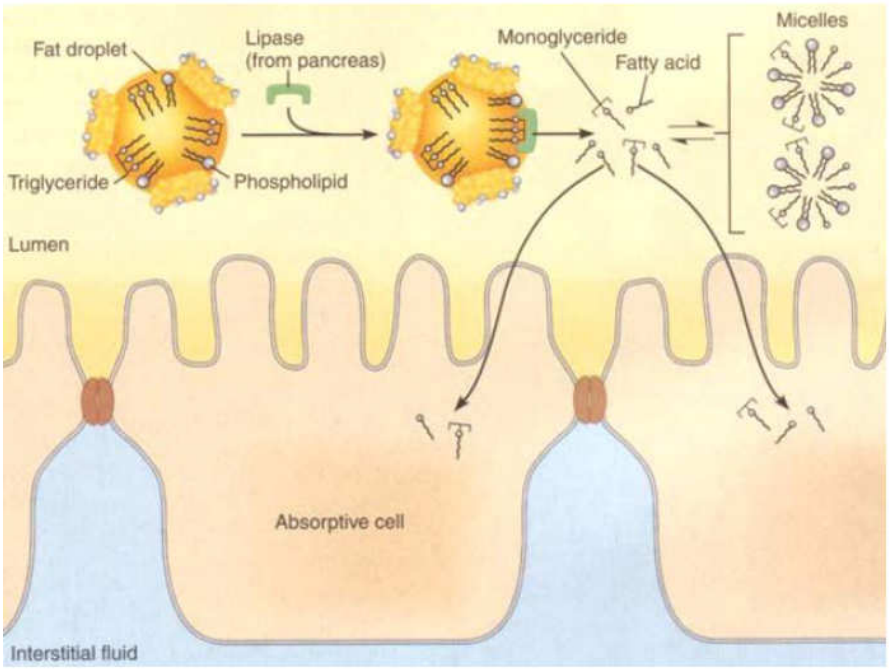


- Bile salts are recycled
  - Made from left over Hb in the liver, highly regulated



Fats (lipids)

- Solubilisation of lipids
    - Lipase, facilitated by bile salt-emulsification breaks down fat droplet (containing triglycerides and phospholipids) into monoglycerides and fatty acids
        - These form micelles and are absorbed by enterocytes before processing into chylomicrons and absorption into lacteals

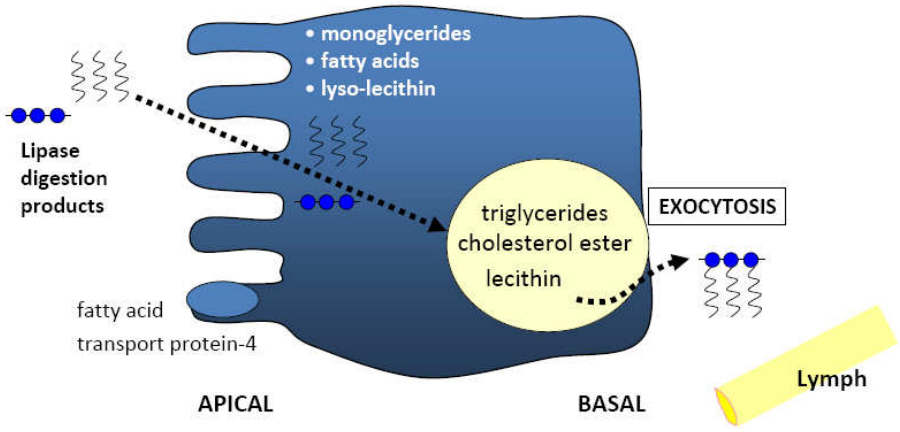


- Hydrolysis of fats

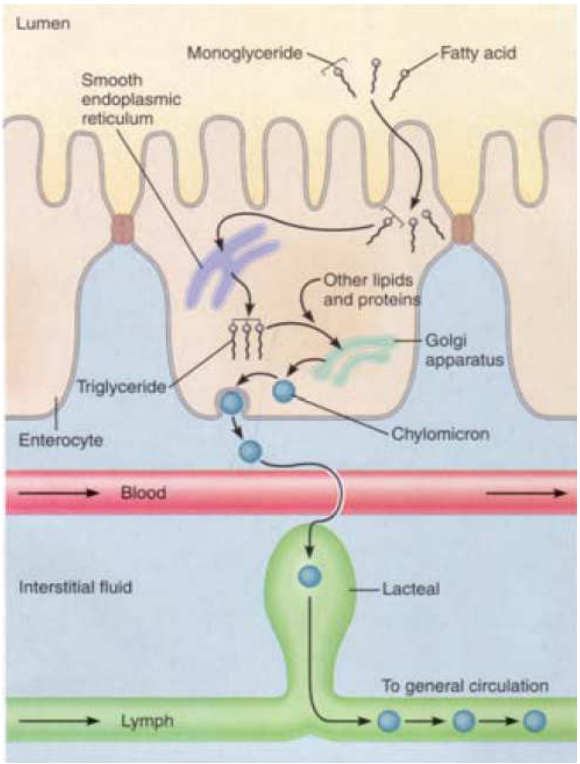
Ingested fats	Pancreatic enzymes	Digestion products
Triglyceride	Pancreatic lipase	Monoglyceride and 2 fatty acids
Cholesterol ester	Carboxyl ester hydrolase	Cholesterol and a fatty acid
Phospholipids, lecithin	Phospholipase A2	Lyso-lecithin and a fatty acid

- Absorption
    - Lipases break down fats into fatty acids, monoglyceride, cholesterol and lyso-lecithin
        - Then, these were thought to cross cell membrane by simple diffusion
        - Recently, transporters have been identified (eg. fatty acid transport protein-4)

LUMEN **ENTEROCYTE** LYMPHATICS

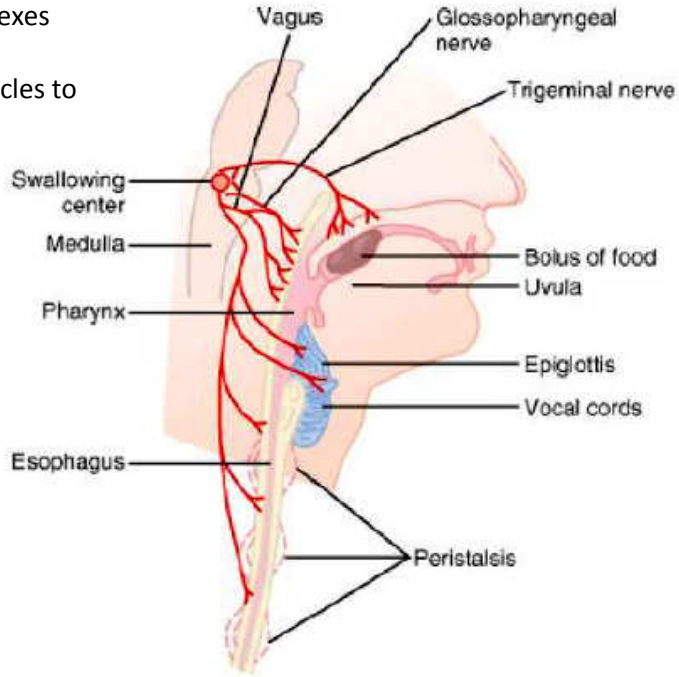


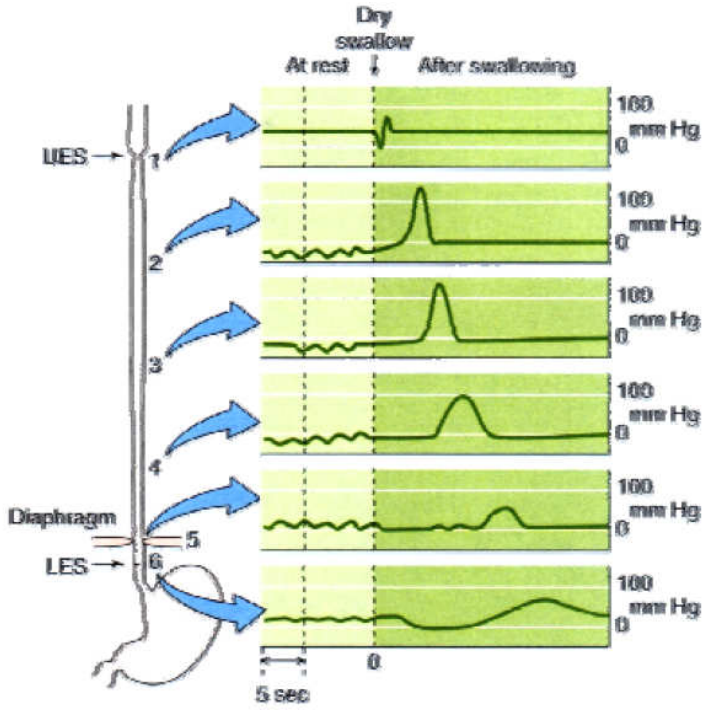
- Repackaging
    - Lipids are incorporated into chylomicrons for lymphatic transport (blood vessels don't have enough holes)
        - Chylomicrons are lipoproteins that are part protein and part lipid



Swallowing

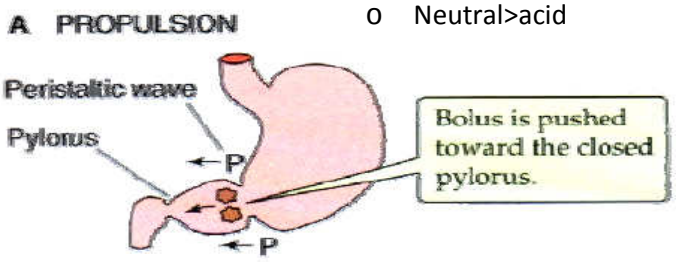
- A complex mechanism that allows food to be transported from the mouth into the oesophagus
  - Involves voluntary and involuntary phases and crosses the airway
- Phases of swallowing
  - Voluntary phase
    - Food moved by tongue upwards and backwards towards pharynx
  - Pharyngeal phase
    - Mechanoreceptors cause:
      - Closure of the trachea
      - Relaxation of the upper oesophageal sphincter
      - Initiation of the primary peristaltic wave
    - Involves the swallowing centre in the medulla and cranial nerves X, V and IX
    - Not voluntary, a reflex
  - Oesophageal phase
    - Food is conducted to the stomach assisted by:
      - Gravity
      - Primary and secondary peristaltic waves
      - Relaxation of the lower oesophageal sphincter
      - Receptive relaxation of the stomach
    - Involves local neural reflexes and extrinsic reflexes
- Movement down the oesophagus is by peristalsis
  - Alternating contraction, relaxation of oesophagus muscles to push food down

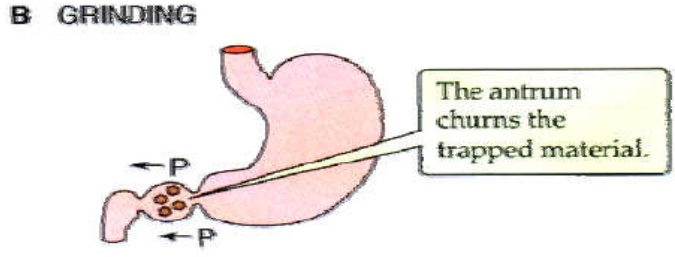


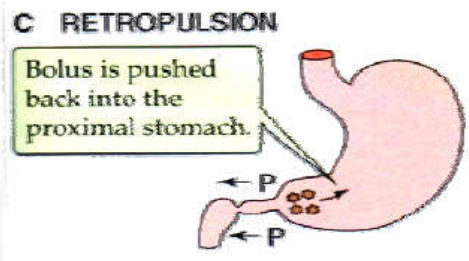


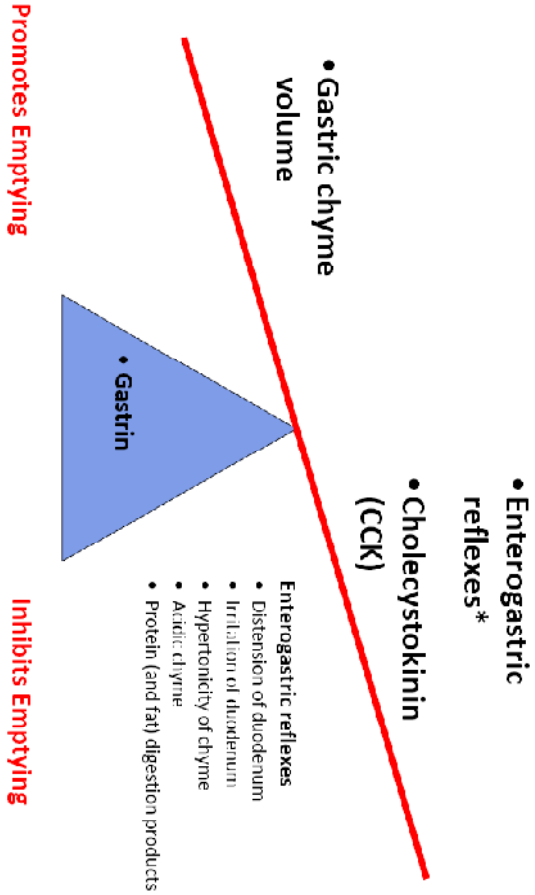
Stomach motility

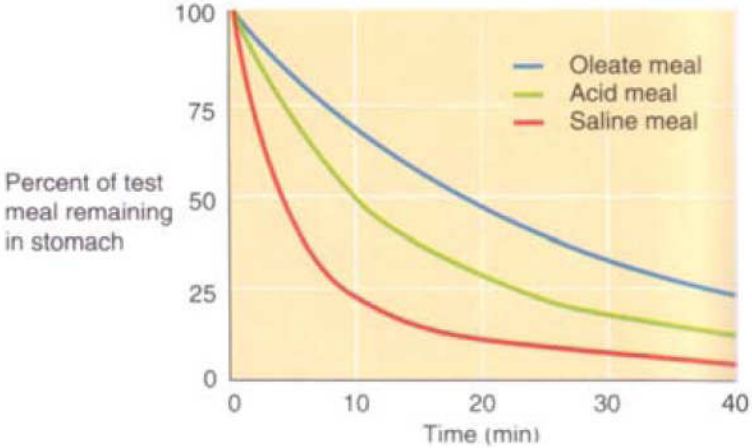
- There are 4 motor functions of the stomach in the process of gastric filling and emptying
  - Receiving and temporarily storing food and liquids
    - Provides a reservoir
    - Expands and accommodates for the increased volume without an increase in pressure
      - Accommodation reflex allows no pressure increase vs a muscular sac
        - A vagotomy causes this reflex to be lost – used as weight therapy in the 80s-90s
        - Now we use gastric banding/stapling as weight therapies
  - Mixing of food and liquid with gastric secretory products (pepsin, acid)
  - Grinding of food to reduce particle size enhancing digestion and allowing passage into the pylorus
    - Reduces the particle size and increases the mixing
    - 3 stages (the pyloric pump):
      - Propulsion
      - Grinding
      - Retropulsion
  - Regulating the exit of material from the stomach into the duodenum
    - Important because a small expansion of the duodenum can result in nausea
    - Balance between:
      - Gastric chyme volume – promotes emptying
      - Enterogastric reflexes / cholecystokinin (released when food is in the duodenum) – inhibits emptying
        - Enterogastric reflexes:
          - Distension/irritation of the duodenum
          - Hypertonicity of chyme
          - Acidic chyme
          - Protein/fat digestion products
      - Thus, rate is greater if:
        - Liquid>solid
        - Non-nutrient>nutrient
        - CHO>Protein>Fat
        - Neutral>acid





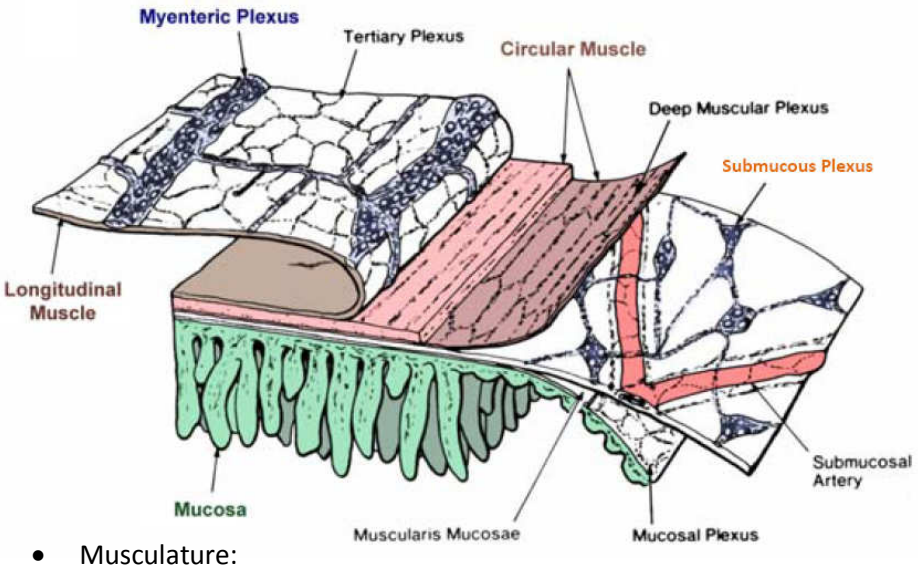


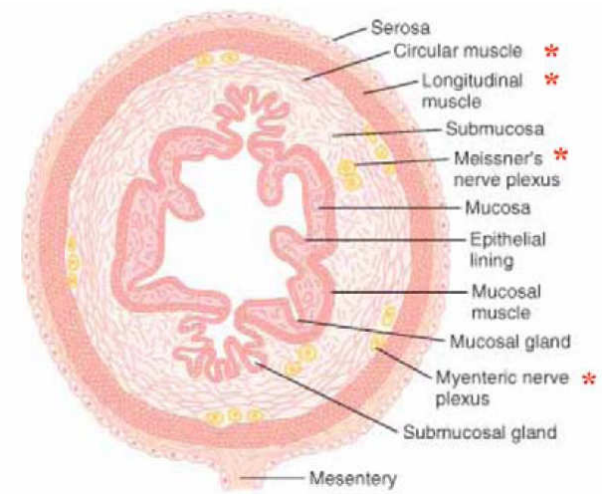




GIT motility

- Optimal exposure of segments of the GI tract is important for digestion and absorption
    - Motility allows mixing and propulsion
    - Function is highly regulated by neural, hormonal, local chemical and physical factors
        - SI is almost totally in control by local factors
- Structure of GIT:

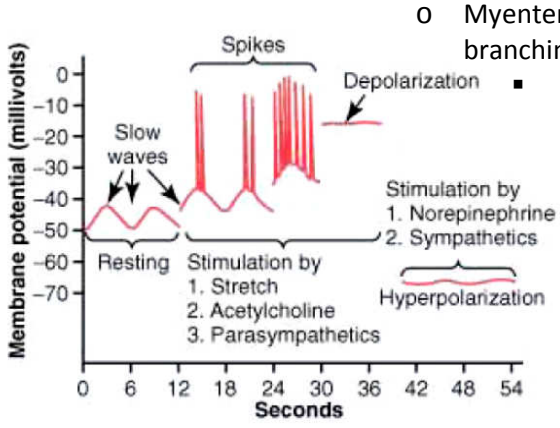




- Musculature:
    - Predominately smooth muscle
    - Exceptions:
        - Upper 1/3 of oesphagus including oesophageal sphinter
        - External anal sphincter
            - Both are skeletal muscle

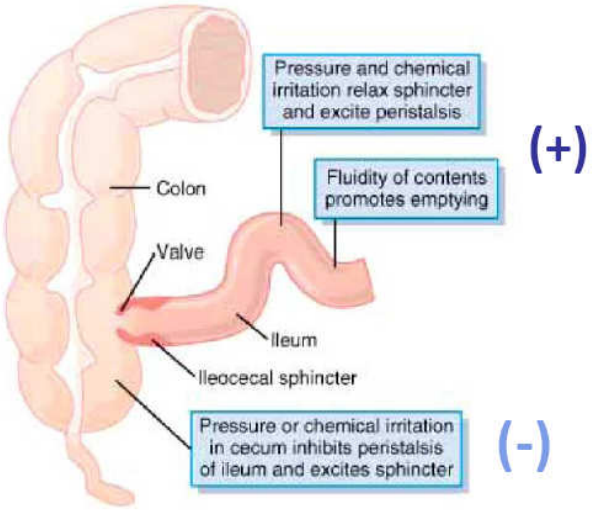
Slow waves

- Smooth muscle has continual oscillations in its membrane potential – it excites itself for no apparent reason
    - Frequency decreases down the intestine
        - Stomach: 3/s, duodenum: 12/s, ileum: 8/s, colon: 3/s
        - Gradient from top of small intestine to large intestine
    - With stimuli, a slow Ca^{2+} mediated creates a spike potential
        - Cytoplasmic Ca^{2+} increases and leads to smooth muscle contraction
- Generation of slow waves
    - Thought to comes from the interstitial cells of Cajal (ICC)
        - Found in smooth muscle layers
        - 2 functions:
            - Act as pacemakers – specialised ion channels that underlie slow wave activity
            - Transfer excitability – allows uniform contraction
                - Acts through gap junctions and spreads the excitation widely
        - Morphologically intercalated between nerves and smooth muscle cells
            - 2 classes:
                - Intramuscular ICC – spindle shaped, scattered in circular and longitudinal muscle layers, associated with nerve fibres
                    - Mediators between the ENS and SMC
                - Myenteric plexus ICC – triangular or irregular in shape, multiple processes with branching networks between longitudinal and circular muscle layers
                - Pacemaker generators
                    - Action potentials are caused by: stretch, ACh, PNS
                    - Hyperpolarisation is caused by NA, SNS



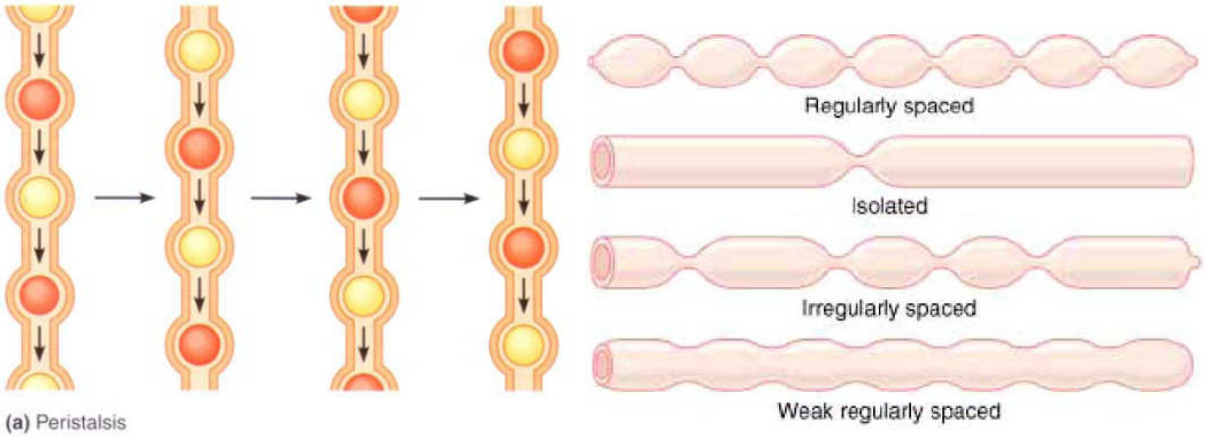
Tonic contractions

- A sustained muscular contraction without intervals of relaxation
    - Suited to the function of sphincters
    - Possible underlying electrical activity:
        - Repetitive spike potentials
        - Sustained depolarisation
        - "latching"
    - May need inhibitory transmission to relax smooth muscle (ATP, NO, vasointestinal polypeptide)
        - There are signals for release and relaxation
- Sphincter action: eg ileocaecal sphincter controls movement of chyme from small to large intestines
    - Relaxation – pressure, chemical irritation, fluidity of contents
    - Contraction – pressure, chemical irritation in caecum
        - Function: prevent bacteria entering small intestine and regulating flow of chyme to LI



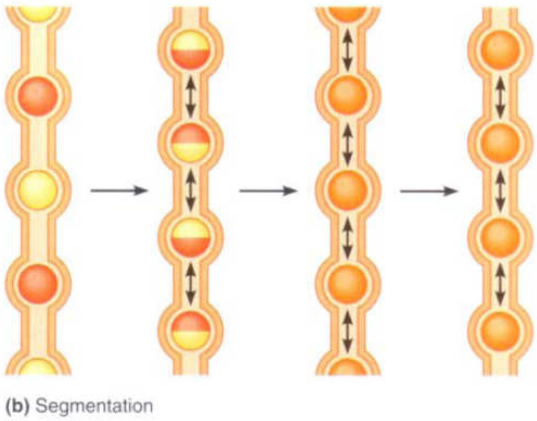
Peristalsis – moves contents

- Wave-like movement of muscles in the GI tract
    - Involves alternate contraction and relaxation of muscles to propel contents downwards
- Mediated by local, intrinsic enteric nerves (ENS)
    - Not affected by vagotomy or sympathetectomy
- Contractions travel short distances



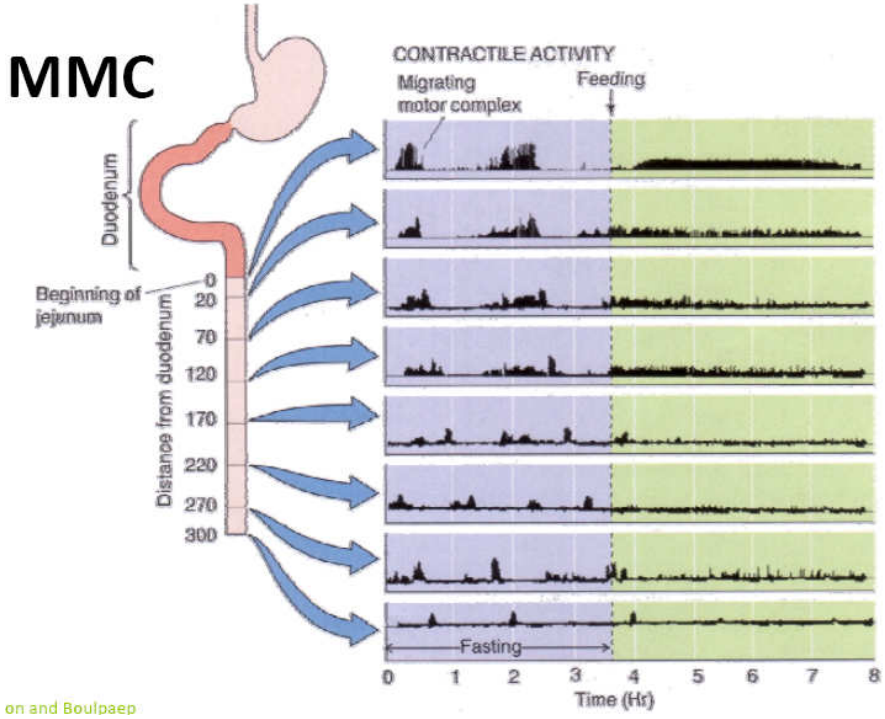
Segmentation – mixes contents

- A non-propulsive mixing motility seen often in the small intestine
    - Segmental rings of contraction chop and mix material to enhance digestion



Migrating motility complex (MMC) – housekeeping

- Occurs during a fasting state
- Contractile waves periodically move down the GI tract from mid-stomach to idleum
    - Associated with increased levels of motilin (intestinal hormone)
    - Removes dead epithelial debris, prevents bacteria entering SI from LI and clears the lumen
- Stopped by feeding



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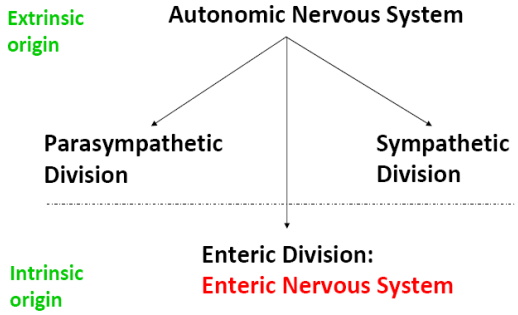
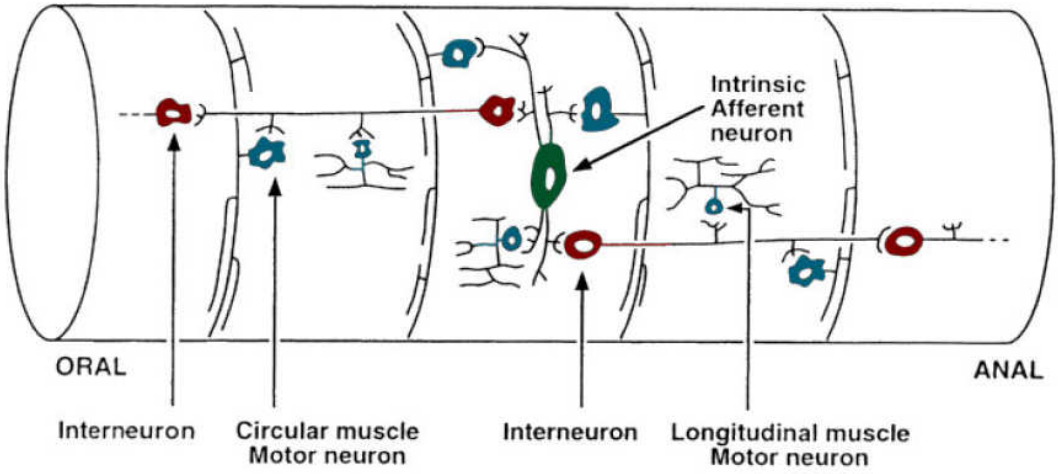
Neural control of intestinal motility

- Enteric nervous system
    - Complex network of neurons
    - Located in the gut wall form the oesophagus to the anus
        - Plexuses:
            - Myenteric plexus of Auerbach – motor and integrative functions
                - Forms a 2d plexus
            - Submucosal plexus of Meissner – secretion, vasodilation
                - Causes enterocytes to secrete fluid, BVs to vasodilate
    - Controls moment-to-moment motility and secretion of the GIT
    - Part of the autonomic nervous system
        - Third division of the ANS, ie: SNS, PNS, ENS (Langley, early 1900s)
        - Has reflex arcs
        - Has as many neurons as the spinal cord: 10^9 neurons
    - Only found in the gut
- Types of Git innervation
    - Intrinsic
        - ENS: sensory, interneurons and motor neurons
        - Mostly independent
    - Extrinsic
        - Afferent (vagal, DRG)
        - Efferent (sympathetic, parasympathetic)
        - Can interface through the ENS and receive information through it



Types of enteric neurons

- Intrinsic primary sensory neurons (IPANs
    - Found in the myenteric and submucosal plexuses
    - Receive information from the sensory receptors in the mucosa and muscle
        - Receptors respond to mechanical, thermal, osmotic and chemical stimuli
            - In muscle, can also respond to stretch and tension
    - Neurotransmitters: fast: ACh (nicotinic), slow: tachykinins
- Interneurons
    - Types: descending (anal) and ascending (oral)
    - Integrate information from sensory neurons and provide programming to enteric neurons
    - Neurotransmitters: fast: ACh, 5-Ht, ATP (ionotropic); slow: Tachykinins, ACh, 5-HT, ATP (metabotropic)
- Motor neurons
    - Types: inhibitory motor neurons and excitatory motor neurons, secretomotor and vasodilator neurons
        - Innervate circular and longitudinal muscles
        - Affect blood vessels and enterocytes
    - Control secretion and motility by acting on smooth muscle, secretory cells and endocrine cells
    - Neurotransmitters
        - Excitatory – ACh (Muscarinic), Substance P (SP) – Neurokinin (NK) receptors
        - Inhibitory – ATP (fast), Nitric oxide NO (medium), Vasoactive intestinal peptide VIP (slow)
- ENS circuits
    - Cells link up in a complex pattern that repeats throughout the gut and gives rise to the complex coordinated movements: peristalsis, segmentation, migrating motility complex

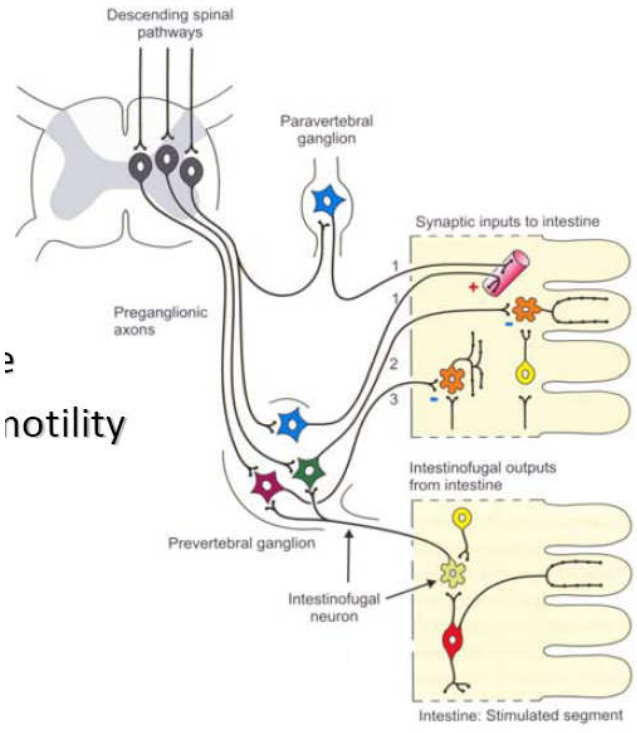


EG: neuronal control of peristalsis

- Distension activates ENS via the myenteric plexus to cause a contractile ring and a leading wave of relaxation
    - Contractile ring: ACh, SP
    - Leading wave of relaxation: NO, ATP, VIP

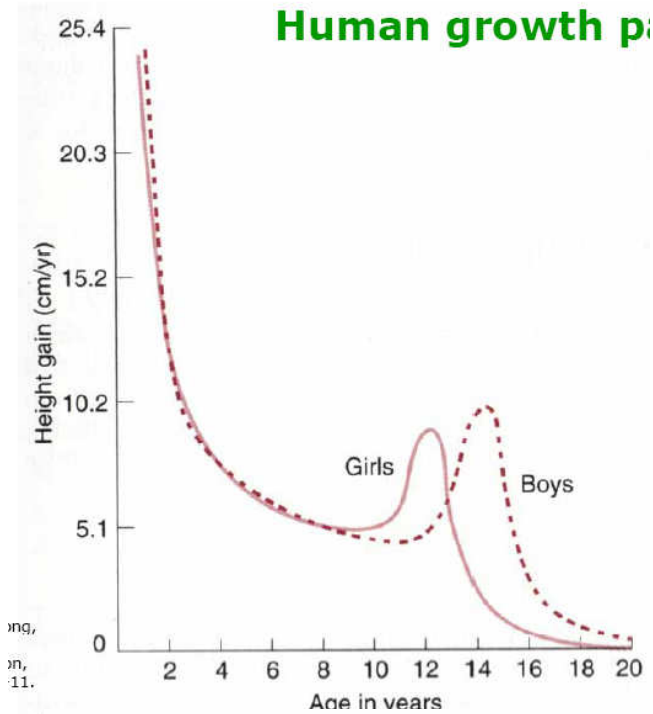
Sympathetic innervation of ENS

- Inhibits motility
    - Works via noradrenaline
- Interacts with the enteric nervous system, not the muscles directly
    - Thus gut can communicate via the SNS instead of via the ENS to respond to stimuli



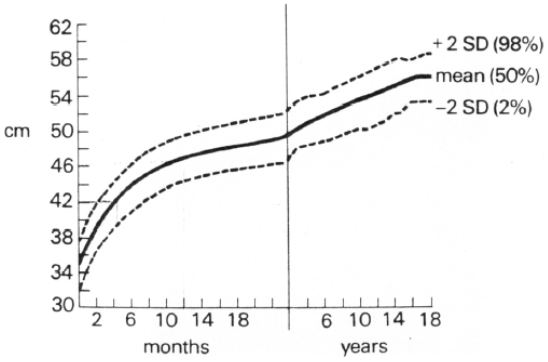
Definition of growth

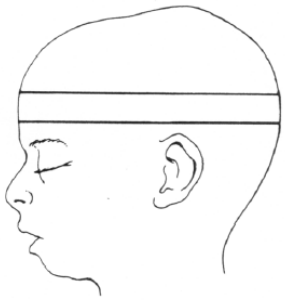
- A complex process involving hyperplasia (increase in number) and hypertrophy (increase in size)
    - Requires accumulation of protein
    - Individual increases in length and size – weight gain is not considered growth, however
- Often accompanied by sequential maturational changes

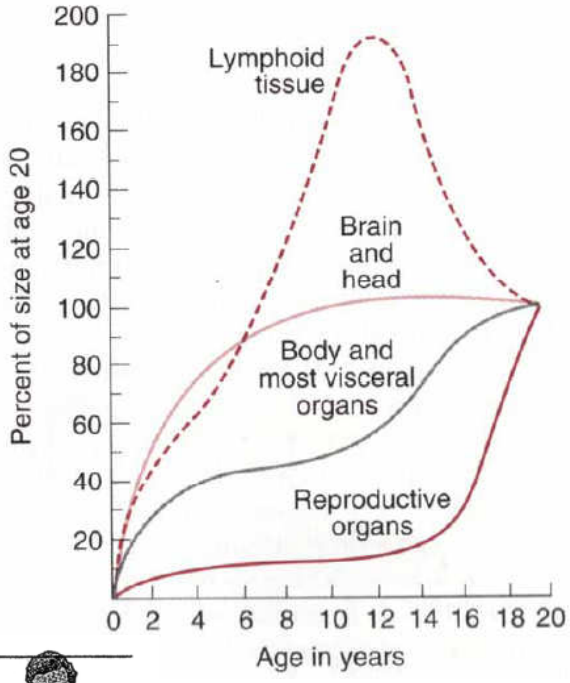


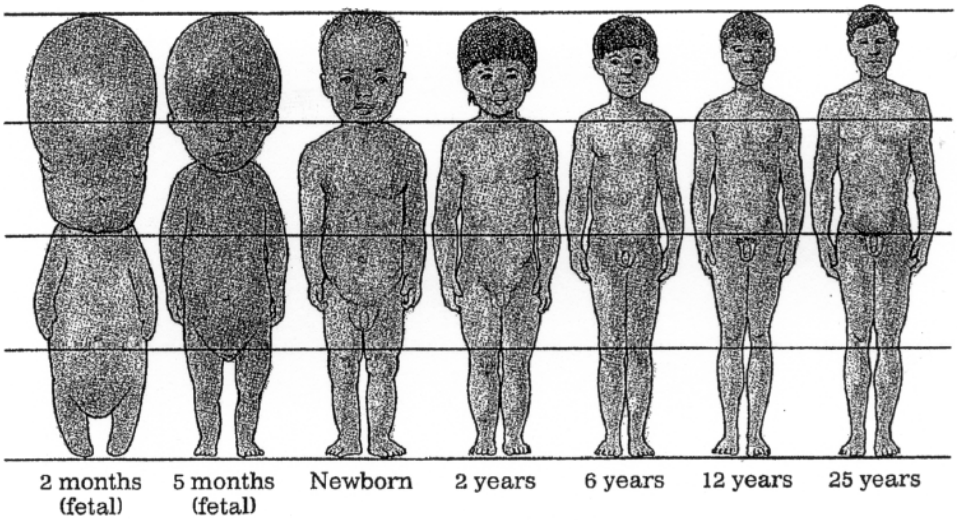
Growth patterns

- Human growth patterns
    - Growth spurt as an infant, and at puberty
    - After puberty, the epiphysial plate fuses and growth no longer occurs
        - Girls have puberty earlier than boys
    - Length: 2x by 4 years, 3x by 13 years
- Growth of varies tissue types
    - Lymphoid: larger at 12 than in adults
    - Brain: at 7 years old, approximately adult size
    - Body and visceral organs mostly follow the pubertal trend
    - Reproductive organs don't grow until puberty
- Head circumference
    - At birth, head circumference is ¾ that of adult
        - Brain and head grow in infancy
- Body proportions
    - Baby's head is ¼ body at birth
        - 44% of body is below umbilicus
            - 2 years old, 50%, adult: 60%
    - Adult head is 1/8 body



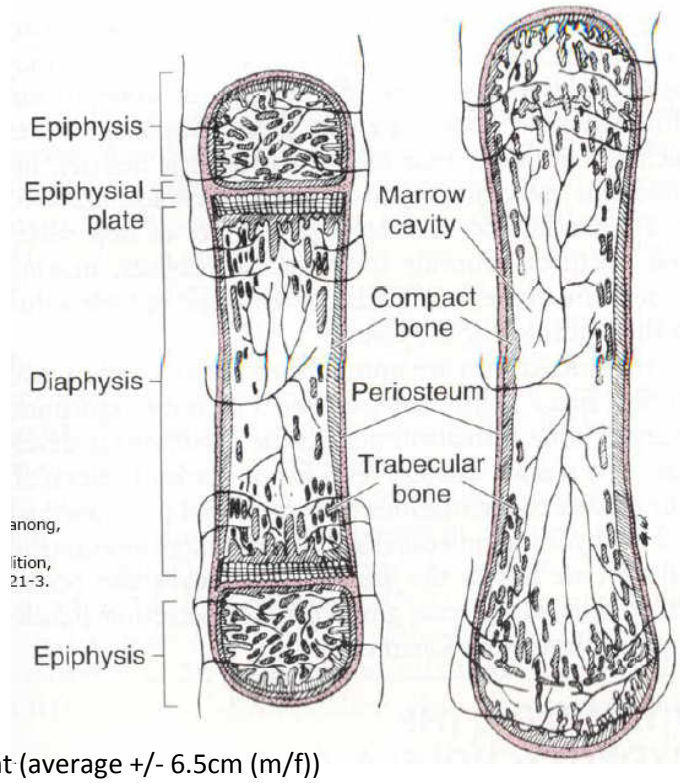






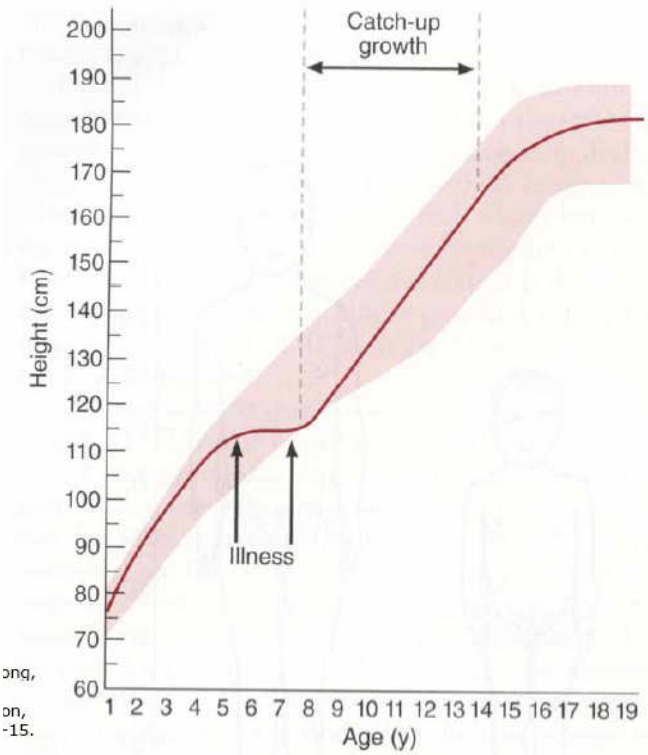
Bones

- Epiphysial plate is made up of cartilage cells that multiply and put out hyaluronic acid and collagen
    - This becomes cartilage that becomes bone
    - At puberty, estrogen causes fusion of the plate and bone closure stopping growth
- In a bone that has stopped growing, there is continual resorption and deposition of bone, it has not "stopped"
- Bone age
    - Important for assessing sexual maturity
    - X-ray can be used to assess
        - Higher the bone age, the less space left between the bones



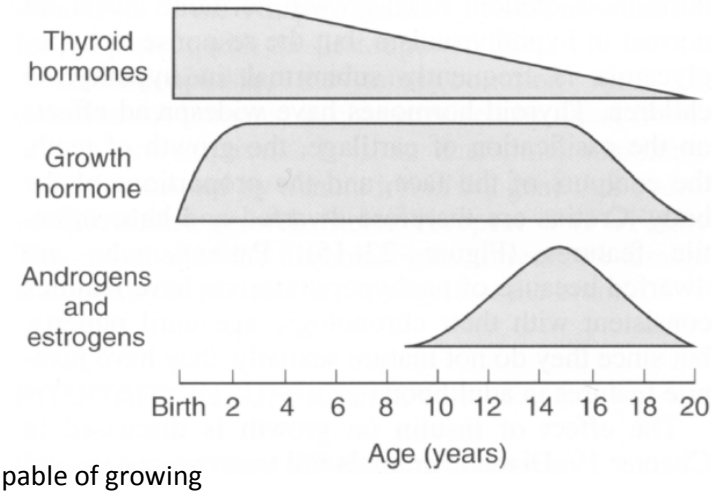
Factors affecting growth

- Genetics
    - Mid parental height (average +/- 6.5cm (m/f))
- Nutrition
    - Developing nations vs developed nations
        - Developed nations, genetics is main determining factor, developed: nutrition
        - Eg: 4yo in Sweden vs 6yo in Bangladesh, 4yo is taller
            - Bangladesh has a 65% stunted growth rate due to malnutrition
    - The wealthier are taller
    - Timing is important
        - If after puberty has started, the effect is less than before
- Psychological factors
    - Hormones can be interrupted by abuse, etc
- Injury and disease
    - Disease/injury can stunt growth, if temporary "catch up growth" can recover difference



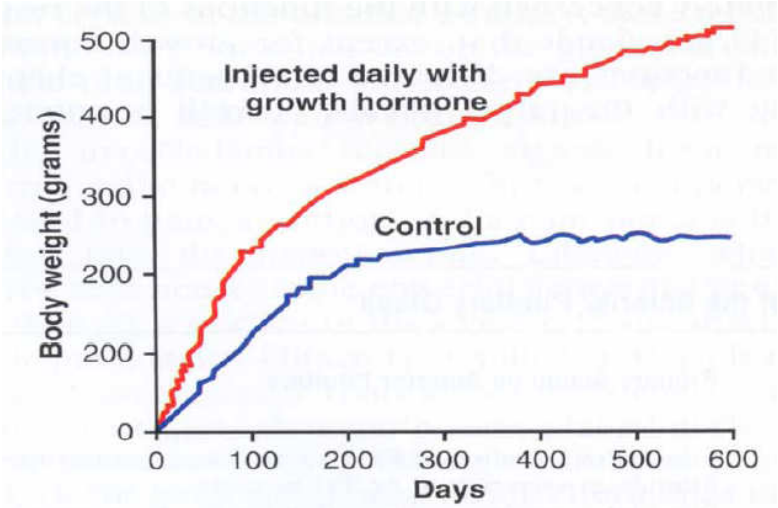
Factors affecting growth continued

- Hormones
    - Importance at different ages (timing is important)
        - Thyroid hormones – childhood
        - Growth hormone – throughout
        - Androgen sand estrogens – puberty

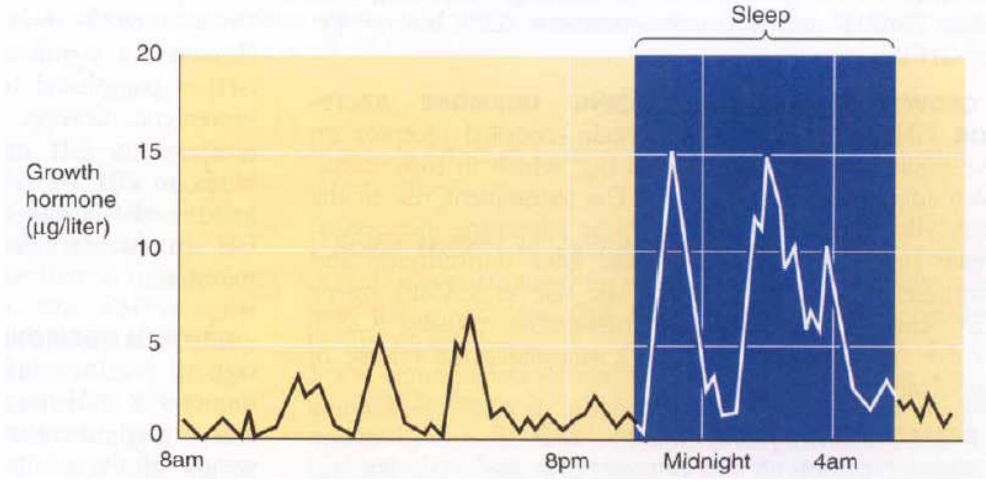


Growth hormone

- Promotes growth of almost all tissues in the body that are capable of growing
    - Ie, promotes:
        - Increased cell size
        - Mitosis
        - Differentiation of certain cell types of cells (eg: osteoblasts, early muscle cells)

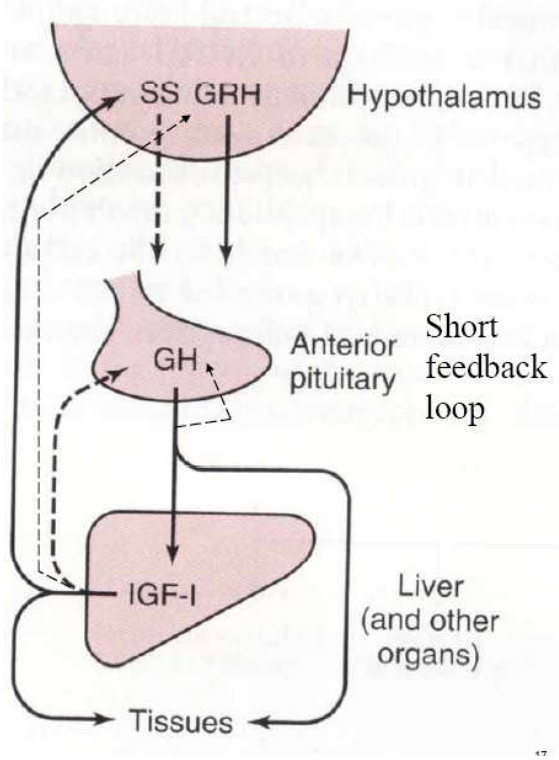


- Production and release
    - Produced in somatotrophs (particular cells) in anterior pituitary
        - Stored in secretory granules
        - Release occurs in bursts throughout the day, especially during sleep
            - Increased release in exercise, stress, high protein meals and fasting
    - Main form is 191 amino acids (a peptide hormone)



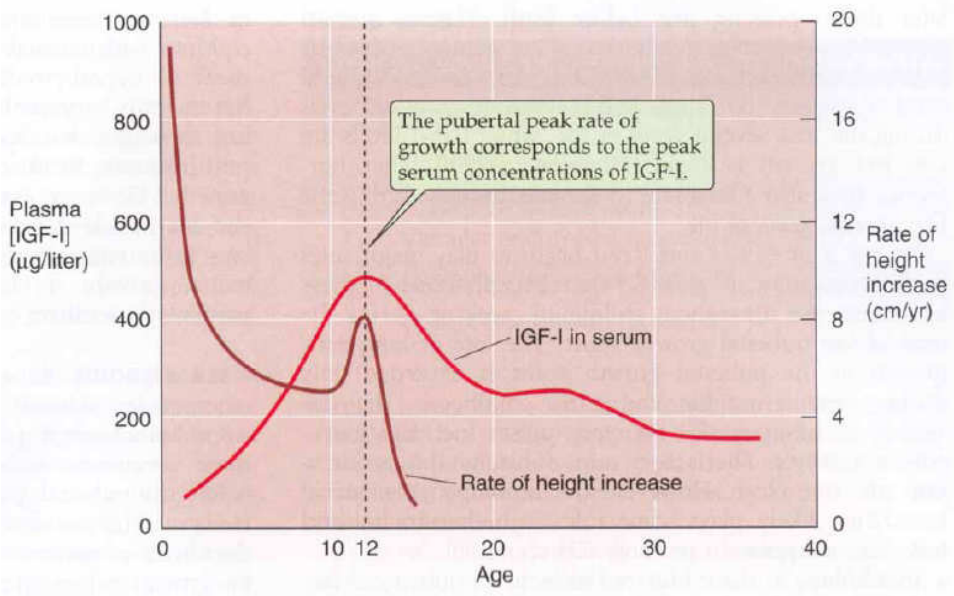
Growth hormone continued

- Control of release
  - Regulated by GHRH (growth hormone releasing hormone)
    - GHRH stimulates release
    - SS (somatostatin) inhibits release
      - Stimulation is more important because if dissected, growth is affected
- Plasma levels
  - Circulates free or bound to binding protein – 40%
    - Ie. can be bound to a large fragment of the extracellular domain of the GH receptor
  - Elevated levels in newborns
    - Average resting levels fall but spikes are larger at puberty
    - Mean level is 2-4ng/ml in adults, 5-8ng/ml in children
- Acute effects
  - Metabolic
    - Decreased glucose uptake by muscle
    - Increased lipolysis in fat
    - Increased gluconeogenesis in liver (making glucagon)
    - Insulin resistance (in the muscle, fat, liver)
      - Insulin normally makes glucose go into cells as glucagon, thus leads to hyperglycaemia
      - Thus also known as anti-insulin or diabetogenic
  - GH alone doesn't make cartilage grow, needs mediators



Insulin-like growth factors (IGFs)

- Mediate long term effects of GH
  - Known as somatomedians: IGF-I, IGF-II
- Produced by target tissues, especially in the liver
  - Levels are stable over 24 hours because they are bound to proteins
- Not seen in infancy, peak at puberty
  - Still present at old age and still regulated
    - Important for muscle mass, fat mass and nitrogen levels
    - Minimises the effects of ageing

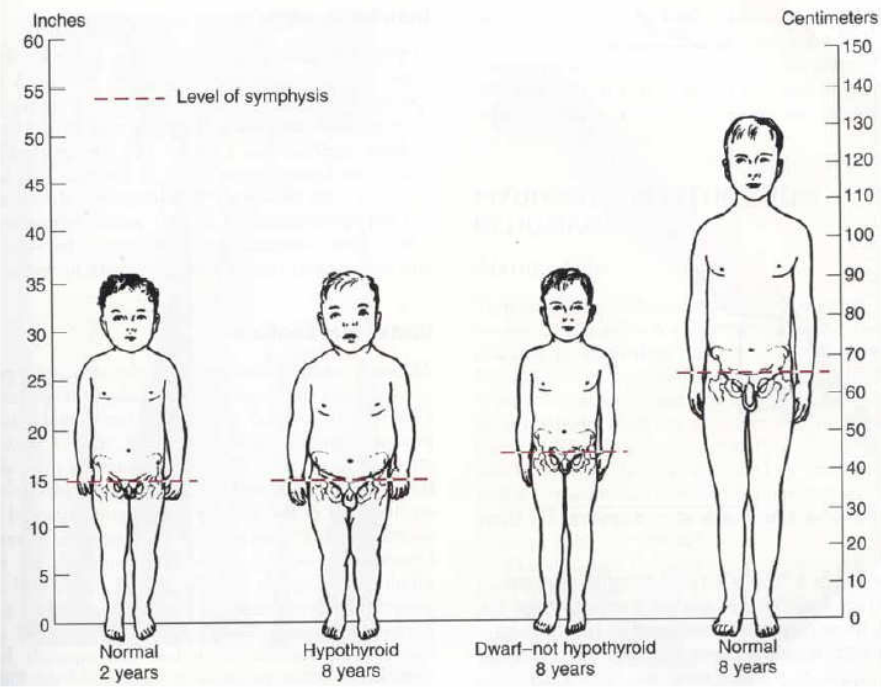


Sex steroids – estrogen and testosterone

- Important for growth spurt at puberty
    - Effects on growth are due to:
        - Protein anabolic effects (tissue growth) of androgens
        - Increased GH response to stimuli like insulin and arginine
        - Increases plasma IGF-I levels (if GH present)
    - Estrogens terminate growth by fusing the epiphyses in long bones
        - Sexual precocity (early puberty) – rapid growth, stop growing earlier, shorter
        - Castration (before puberty) – grow for a longer period, tall

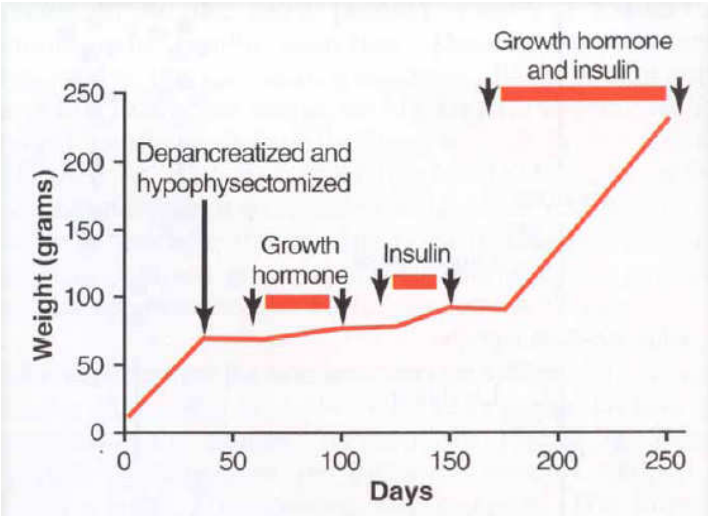
Thyroid hormone

- Permissive (enhancing) role on GH effects
    - Ie shown by growth in hypophysectomised animals is faster with GH + T4 than GH alone
    - Necessary for GH secretion
- Affects:
    - Ossification of cartilage
    - Growth of teeth
    - Contours of face
    - Proportions of the body
        - Ie. Congenital hypothyroidism (Cretinism) causes short stature and infantile proportions
            - Vs: dwarfism – proportions are normal
- Important for growth and development of the brain
    - Cretins have small brains, mental retardation



Insulin

- Synthesised in the pancreas
- Necessary for synthesis of proteins
    - If lacking, growth is stunted
- Important in utero and in combination with GH



Adrenocortical hormones

- Eg: aldosterone, cortisol
- Permissive action on growth
    - Ie. adrenalectomised animals don't grow well
    - If normal levels are not present, BP is low and thus growth inhibited
- Glucocorticoids can inhibit growth in high doses
    - Eg: high dose steroids for asthma – not used anymore

Other growth factors

- Nerve growth factor (NGF)
- Fibroblast growth factor
- Angiogenesis factor
- Vascular endothelial growth factor (VEGF)
- Epidermal growth factor (EGF)
- Hepatocyte growth factor (HGF)
- Precise roles are not completely understood
    - Tend to be tissue specific and work at local sites (paracrine, autocrine)

Causes of short stature

- Bone/cartilage diseases
    - Achondroplasia – commonest cause of Dwarfism in humans
        - Autosomal dominant
        - Mutation in Fibroblast growth factor receptor 3
        - Long bones don't grow, limbs are short, trunk is normal
- Endocrine disorders
    - Problems in the GH-IGF axis
        - Eg: GHRH deficiency, GH deficiency, GH insensitivity
    - Hypothyroidism – cretinism
    - Precocious puberty
- Chromosomal disorders
    - Down's syndrome (trisomy 21)
        - Simian crease, epicanthal fold
    - Turner's syndrome (45, X0)
        - Deep voice, stunted growth
- Chronic diseases and malnutrition
- Constitutional delayed growth (no known cause)

Causes of tall stature

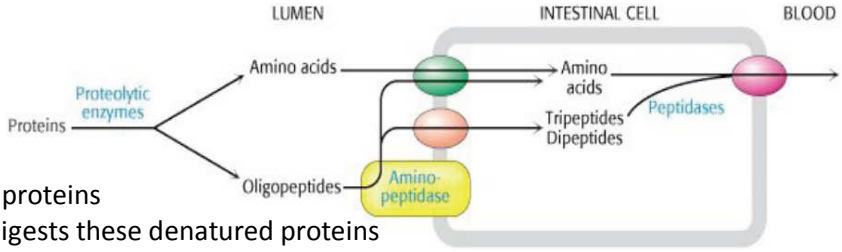
- Marfan's syndrome
    - CT disorder to do with fibrilin and the TGF-beta receptor
    - Abraham Lincoln was thought to have this disease
    - Patients show positive thumb sign
        - Have long fingers and toes
        - Often have cardiovascular problems especially in the arch of the aorta
- Endocrine disorders
    - Excess GH, eg tumours of anterior pituitary
        - Giantism – excess GH early in life
            - Can be treated early these days
        - Acromegaly (extremity) – excess GH late in life after long bones stop growing
            - Coarsening of facial features, jaw, facial bones, hands, feet
                - These continue to grow because they can still respond to GH
    - Androgen/estrogen deficiency or resistance (eg: testicular feminisation)
- Disorders with sex chromosomes
    - Eg: Klinefelter's syndrome (47, XXY)
        - Tall males, look male with female body shape
        - Common, 1/600
    - Eg: Supermale, (47, XYY)

Proteolysis

- The breakdown of peptide bonds
  - Peptide bonds link amino acids to form proteins
- Functions:
  - Control of protein activity by activation/deactivation
    - Eg: activation of proteins, many exist in inactive precursor forms
  - Release of amino acids from proteins for use as building blocks for new proteins
    - Eg: proteins in diet
- One function in more depth: activation by specific proteolytic cleavage
  - Some proteins are produced in an inactive form
    - Require cleavage by specific proteolytic enzymes and folding to create 3D conformation
    - An inactive precursor is called a zymogen (proenzyme)
  - Cleavage does not require energy (ATP) because there is enough energy in the peptide bond
    - Can occur outside the cell
      - Sometimes want to produce proteins and not activate them until at the target site
        - Eg: proteases
    - Occurs once in the life of a protein
- Examples:
  - Digestive enzymes – eg: proteases
  - Blood clotting – components are in the blood and activated when needed (eg: cut)
  - Some hormones – eg: insulin that is produced as a linear protein, needs cleaving/folding
    - Explains problems with artificial insulin synthesis (bacteria don't cleave produced proteins)
  - Some structural proteins – eg: collagen
  - Developmental processes – activation at the right stage in development
  - Apoptosis (programmed cell death – caspases, want appropriate activation

Digestive enzymes

- Ingested proteins are not absorbed as they are (we don't want animal proteins, non-functional)
  - Need to be broken down into amino acids and di/tripeptides for absorption and transport



- Protein digestion process
  - Stomach: acidic environment denatures proteins
  - Pepsin (protease that is active at pH 2) digests these denatured proteins
  - Intestine: continued digestion by proteolytic enzymes from the pancreas (highest producer of proteins)
  - Aminopeptidases in plasma membrane of intestinal cells complete digestion
- Don't want activation of proteases until:
  - At the correct location (not at place of synthesis)
  - There are target proteins to digest (prevent autodigestion)
- Eg: gastric and pancreatic zymogens

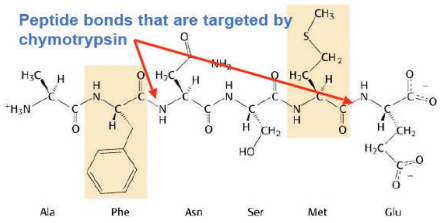
TABLE 10.3 Gastric and pancreatic zymogens

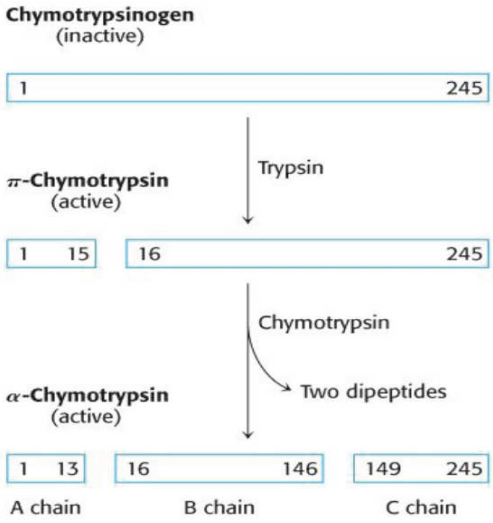
Site of synthesis	Zymogen	Active enzyme
Stomach	Pepsinogen	Pepsin
Pancreas	Chymotrypsinogen	Chymotrypsin
Pancreas	Trypsinogen	Trypsin
Pancreas	Procarboxypeptidase	Carboxypeptidase
Pancreas	Proelastase	Elastase

- Pancreas – exocrine part
  - Very active organ in the synthesis and secretion of proteins in the body
  - Zymogens are synthesised in acinar cells and stored in granules
    - Process:
      - Zymogen proteins produced by ribosomes attached to the RER
      - Modification in the golgi complex and packaging into granules
      - Accumulation of granules at apex of acinar cells in pancreas
      - Hormonal signalling or nerve impulse causes release into duct and then to duodenum

Chymotrypsinogen

- A zymogen of 245 AA
  - Lacks enzyme activity
- Activated by proteolysis, becomes chymotrypsin
  - 2 stage process
    - Cleavage of a single peptide bond by trypsin resulting in π-chymotrypsin (active)
    - Autocatalysis to produce α-chymotrypsin that is the stable and active form of the enzyme
      - Made up of 3 polypeptide chains (A, B, C) joined by disulfide bonds
- Proteolysis allows movement of amino acids into correct configurations
  - Allows formation of the substrate binding site (movement of Ile 16 closer to Asp 194)



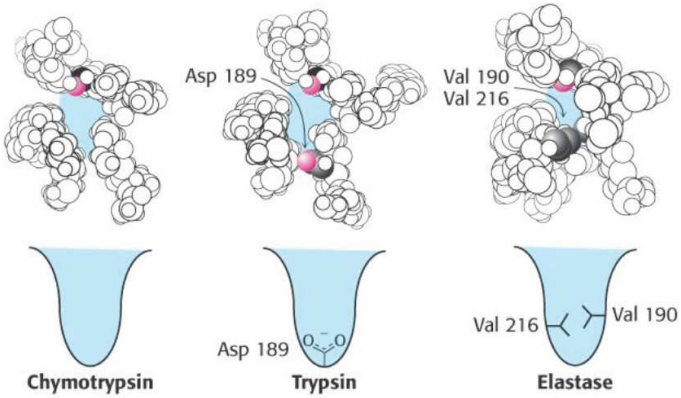


- Specificity
  - Very specific
  - Amino acids have the structure: amino group → alpha-carbon → carboxy group
    - Chymotrypsin targets the peptide bonds on the carboxy-side of neutral, aromatic, large amino acids

Other proteolytic enzymes

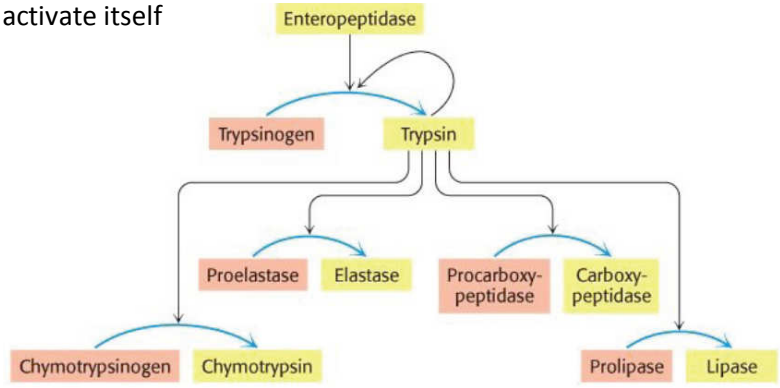
- Trypsin and elastase are homologues of chymotrypsin
  - Structures are very similar
  - Have different substrate specificities due to differences in substrate binding site
    - Chymotrypsin – has no charged AAs in site thus hydrophobic
      - Allows uncharged, large amino acids to enter
    - Trypsin – has aspartic acid in binding site, thus –ve charge
      - Allows positively charged amino acid side chains to enter
    - Elastase – bulk groups in binding site
      - Allows small amino acid side groups to enter

**+ draw diagram



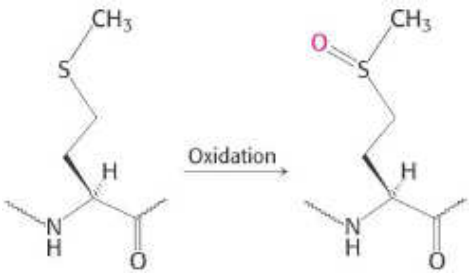
Digestion of proteins in the GIT

- Proteolytic enzymes all have different substrate specificity
  - Needs concurrent activation of several proteolytic enzymes
- Trypsin activates all pancreatic zymogens
  - Trypsin is itself a zymogen that is activated by enterokinase (enteropeptidase) that activates trypsinogen
    - Enterokinases are produced by cells lining the duodenum
  - Trypsin can also activate itself



Regulation of trypsin

- Conversion of trypsinogen (inactive) to trypsin is very precise but irreversible
    - Pancreas synthesises trypsin inhibitory protein to protect itself by inactivating trypsin
- Pancreatic trypsin inhibitor (PTI)
    - Polypeptide chain that has a site trypsin recognises as a substrate
        - Thus this part of the protein binds to the active site of trypsin
    - Poor substrate that is cleaved slowly and thus trypsin is inactivated
- Importance of PTI
    - Deactivates accidental trypsinogen activation
        - Activation of trypsin is particularly dangerous because it is the start of the proteolytic cascade of digestion enzymes
        - Trypsin can also self-activate
    - Trypsin activation in the pancreas or ducts can cause pancreatitis or tissue necrosis
- α1-antitrypsin
    - Another protease inhibitor
    - Binds irreversibly to elastase – the secretory product of neutrophils
        - Binding prevents tissue digestion
    - Genetic disorders can lead to a deficiency in this enzyme → causes emphysema
        - Elastase destroys alveolar walls in the lung by digesting elastic fibres and connective tissue proteins
- Cigarette smoke and emphysema
    - Cigarette smoke oxidises a methionine amino acid in the α1-antitrypsin
        - Thus the inhibitor can't bind elastase because methionine bait cannot selectively trap elastase
        - Ie, the addition of a single Oxygen group by oxidation results in deactivation of enzyme



Cellular protein turnover

- Proteins within cells are degraded also (not just proteins in food)
    - Thus cellular behaviour and metabolism can be regulated
    - Also, cells use this to detect and remove damaged/defective proteins
        - There are mechanisms to tag proteins for destruction)
- Intracellular proteins have different half-lives
    - Vary from minutes to weeks (Hb) to years (crystallin – lens protein in the eye)

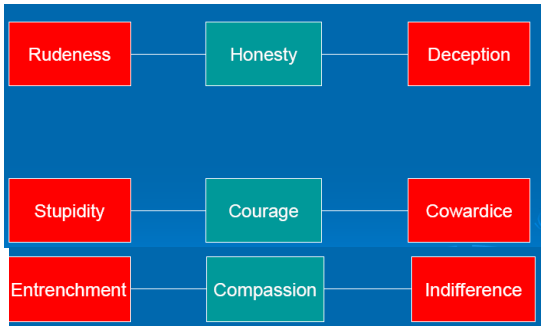
Introduction
- Definitions
  - Ethics – a system of moral principles that guides appropriate conduct
  - Morals – principles of right and wrong governing individual conduct
  - Values – acceptable principles or standards of a group or individual

What do you look for in a doctor?
- Graduate capabilities
- Virtues

Virtues and vices
- Generosity - greed
- Honesty - dishonesty
- Compassion - hate
- Courage - cowardice
- Temperance - lust
- Kindness - jealousy
- Integrity - pride
- Wisdom – short-sighted, ignorance

Hippocrates
- "to abstain from voluntary acts of mischief and corruption, and abstain from seduction of females and males, freemen and slaves"
  - Ie: we need balance of specificity/broadness and need to be contemporary when defining codes of conduct
  - Ie: "I will be focussed on my patient, honest, respectful and act with integrity" BMA

Virtue ethics
- Plato/Aristotle – justice, piety, courage
  - Greek epics made heroes/villains, virtues/vices
  - Ancient Chinese philosophy
- Emphasises virtues and moral character vs emphasising rules/consequences
  - Virtues often fall between vices
    - Eg: entrenchment – compassion – indifference



History of virtue ethics
- Cardinal virtues: prudence, justice, temperance, courage
  - Theological virtues: faith, hope, love
- Virtue ethics – what kind of person should we be?
  - Ideals towards which we should strive
    - Discovered by reflection on our potential
    - Virtues are traits that allow us to recognise these ideals
- Other schools of ethics focus on rules/consequences

Virtue ethics relevance
- Still relevant in what we aspire to be in becoming doctors and the expectations of society

AMA code of ethics
- Incorporates virtues and integrates codified rules of conduct
  - Patient well being - **consideration**
  - Respect – **compassion and respect**
  - Science and art of medicine to the best of our ability – **dedication**
  - Recognise professional limitations – **humility**
- Implications
  - Virtues are important but may not be enough to guide how we work as doctors

Problems with virtue ethics

- No codifying principles
- Non-functional/operational
- Not grounded in rules/outcomes
- Do not always guide actions
- Characters can be a complex mix
- Virtues can result in detrimental actions

Case: doctors selling records with de-identified personal data

- Legally right vs morally right? – who gains from information
- Trust vs simply confidentiality
- Right or wrong depends on virtue?

Case: complaints against doctors

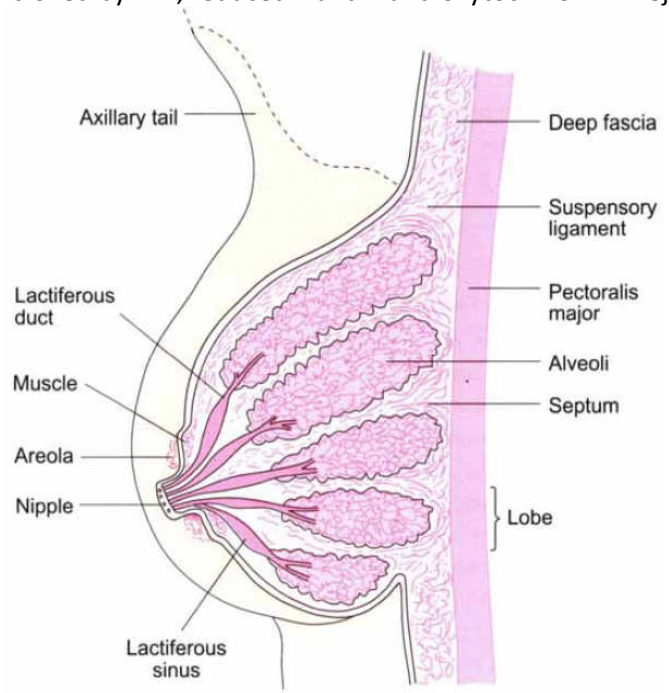
- Virtues – respect, communication, care are important
    - Better for doctor and patient
    - Competent doctor means whole patient care
- Doctors make mistakes, chance of being sued is related to relationship with the patient
    - Society now expects more virtuous doctors

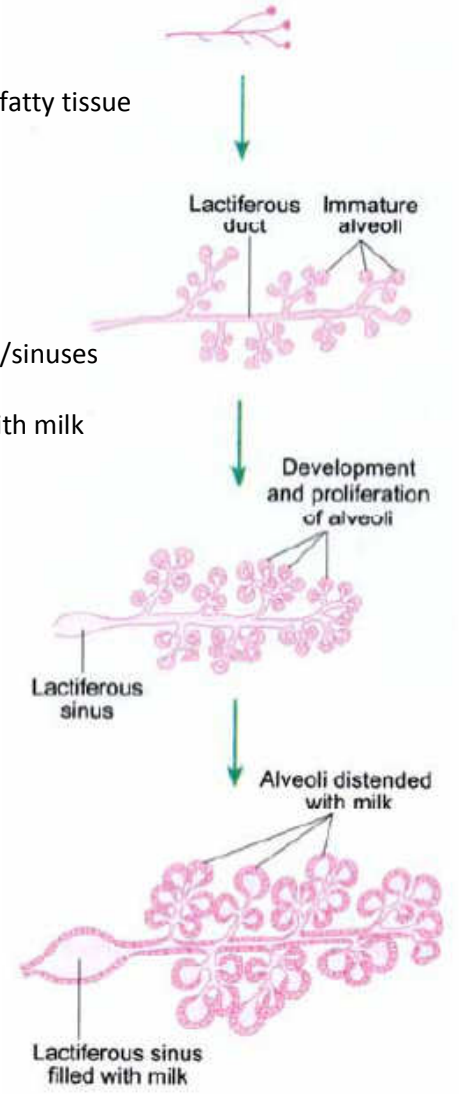
Case: sex-charge GP still working

- Charges were 30 years ago
    - Should the GP be stood down pending the hearing?
- Issues:
    - Innocent until proven guilty, law cases can be drawn out
    - Media
    - Stepping down voluntarily or notification to minors that case pending
    - Can people change, or do they still need to carry the burden of mistakes

<u>Mammary gland</u>

- Modified sweat gland
- Found in males (rudimentary) and females (developed)
    - In females it is mostly made up of glandular tissue draining into ducts and fatty tissue
- Breast development
    - Begins as a rudimentary gland
    - Non-pregnant adult has lactiferous ducts and immature alveoli
        - Alveoli → lobules → lobes (15-20)
        - Alveoli lined by cells and drain into ductules
        - Controlled by E and P
    - Pregnant has developed/proliferation of alveoli and development of ducts/sinuses
        - Controlled by E, P, PRL and hPL (insulin, cortisol)
    - Lactating breast has alveoli distended with milk and sinuses/ducts filled with milk
        - Controlled by PRL, reduced E and P and oxytocin for milk ejection





<u>Definitions</u>

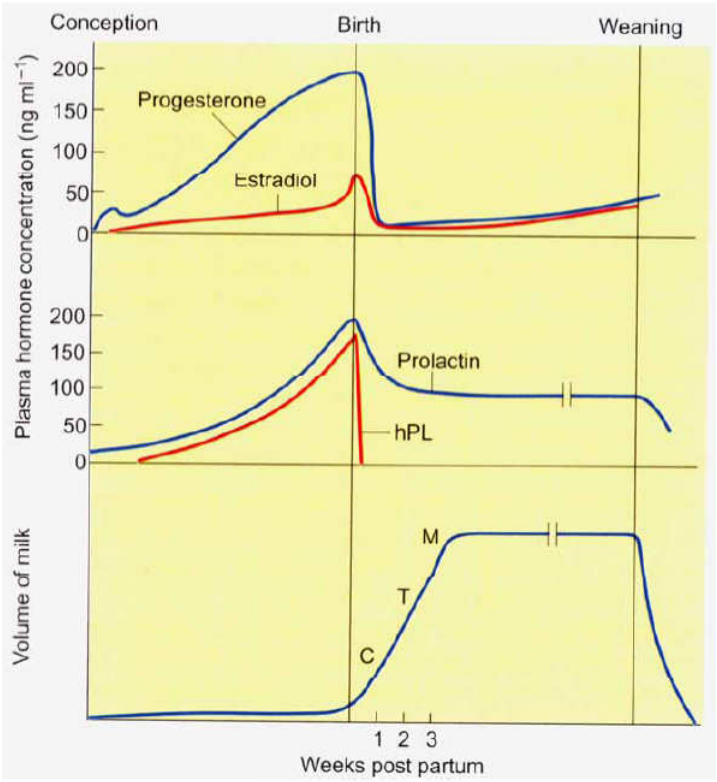
- Mammogenesis – differentiation and growth of mammary glands
- Lactogenesis – initiation of milk production
- Galactopoiesis – maintenance of milk production
    - Milk secretion and milk ejection

<u>Mammogenesis</u>

- Occurs during pregnancy
- Fat tissue in the breast is replaced by ductular-lobular-alveolar growth
    - Prominent lobules form
    - Duct system branches
    - Alveoli lumen dilate
    - Alveolar cells differentiate (have prolactin receptors)
- Controlled by estrogen, progesterone, prolactin, human placental lactogen
    - Permissive effect of insulin, adrenal steroids – not that important, but need to be present

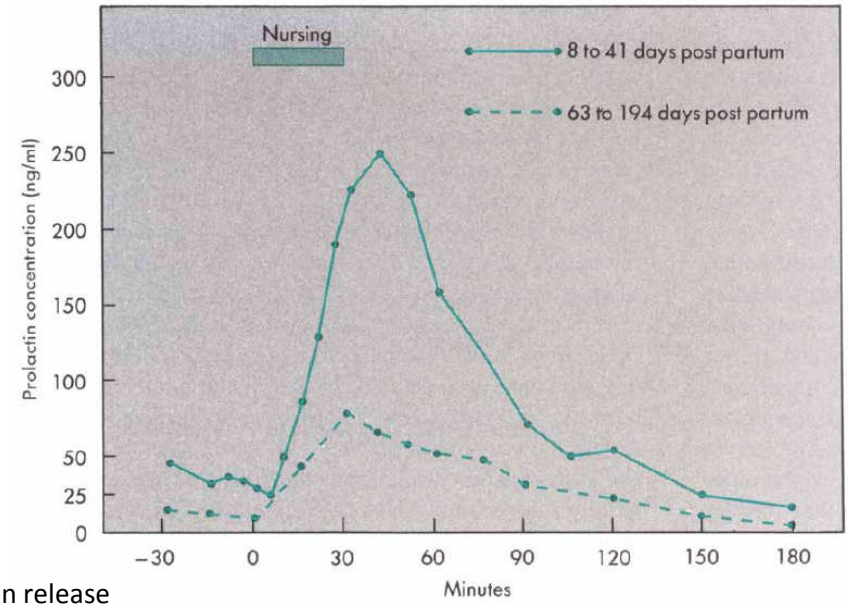
Lactogenesis

- Depends on:
  - High levels of prolactin
    - Levels fall slightly after parturition, but not as much as other hormones
  - Withdrawal of estrogen and progesterone
    - Alveoli are developed enough to secrete milk by 4 months of pregnancy but the breasts are not responsive to prolactin until after parturition because progesterone is still high
- Without suckling, milk secretion will only last 3-4 weeks
- Hormone changes:
  - Progesterone and estrogen fall after birth (prouduced by placenta)
    - hPL falls for the same reason
  - prolactin falls but not as much as others



Galactopoeisis – milk secretion

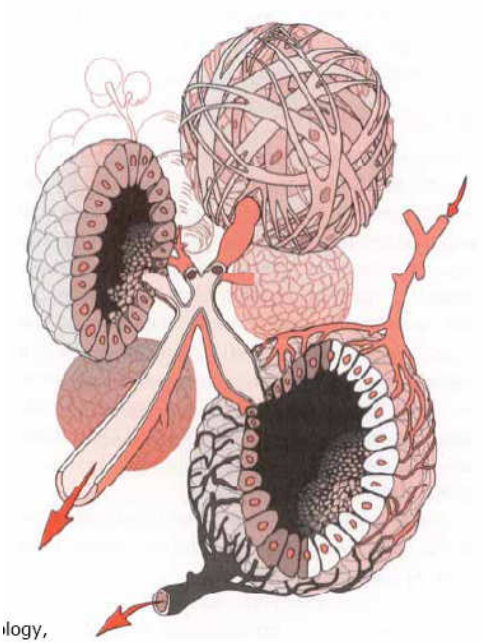
- Process of milk secretion
  - Synthesis of milk constituents in alveolar cells
  - Intracellular transport of constituents
  - Discharge of these into alveolar lumen
- Dependent upon secretion of prolactin from anterior pituitary
  - PRL release stimulated by suckling
    - Ie: baby orders next meal while feeding current one
    - Thus, supply = demand
      - During growth, feed more, more milk produced
- Graph: after feeding, serum PRL increases, increase is less further post-partum



- Prolactin release
  - Suckling → sensory nerves → synapse in spinal cord → neurons to hypothalamus arcuate nucleus → inhibits dopamine release → removes inhibition on lactotrophs in anterior pituitary → prolactin release → breast produces milk
    - Note: dopamine normally inhibits prolactin
- Effects of prolactin on alveoli cells – makes protein, carbohydrates, fats of milk
  - Increased uptake of amino acids (to make protein)
  - Induction of transcription of genes for milk proteins casein, lactalbumin and β-lactoglobulin
  - Induction of enzymes (galactosyltransferase and N-acetyllactosamine) to synthesise lactose – milk sugar
  - Stimulation of fatty acid and phospholipid synthesis
  - Upregulation of own receptors – thus makes cells more receptive next time

Galactopoiesis – milk ejection/removal

- Milk removal
  - Passive removal of milk from cisterns (pouch that holds fluid) and large ducts
  - Ejection of milk from alveoli (let down, draught)
- Oxytocin
  - Stimulates contraction of myoepithelial cells around alveoli forcing milk out into lactiferous ducts
  - This leads to increased intramammary pressure causing milk "let down" with milk spurting from nipple
- Milk ejection reflex
  - Suckling → neuroendocrine reflex → oxytocin release
- Oxytocin release reflex
  - Suckling → sensory nerves → synapse in spinal cord
    → neurons to hypothalamus: paraventricular and supraoptic nuclei → oxytocin production
    → oxytocin release from posterior pituitary → breast → contraction of myoepithelial cells
    - Note: cell bodies in the hypothalamus connect via axons to the pituitary
  - Reflex can also be conditioned to occur with other stimuli:
    - Baby's hungry cry
    - Rattle of milk bucket (cows)
  - Can be inhibited by physical and psychological stresses
    - Causes: adrenaline? → activation of SNS → inhibition of oxytocin release
    - Important factor when lactation is being established
      - Need to calm mother, reassure etc (eg: picture of baby)



Suckling – ie, not sucking

- Infant causes expression of milk
- Infant draws out nipple and alveoli to form a teat that it compresses between its tongue and hard palate
  - Relief of this pressure allows rapid refill

Contraceptive effect of lactation

- Lactation inhibits the ovarian cycle
  - Suckling → prolactin → fall in GnRH production
    → inhibition of FSH and LH release → inhibition of ovulation
  - Suckling → sensory nerves → synapse spinal cord
    → neurons to hypothalamus: arcuate nucleus and preoptic area → fall in GnRH production
    → inhibition of FSH and LH release → inhibition of ovulation
- Contraceptive effects
  - Lactational amenorrhoea
  - If not lactation after delivery, ovulation cycles can resume in 8-10-18 weeks
    - If at risk of pregnancy, at 6 week check up, doctor should advise other forms of contraception
  - If lactating, ovulatory cycles eventually resume
    - Especially in well nourished women
      - Malnourished: Bangladesh anovulation averages 18-24 months
    - Especially after solids are introduced because there is less suckling

Milk composition

- Colostrum – first week
  - Yellow, sticky
  - Less water-soluble vitamins (B, C), fat and lactose than mature milk
  - Contains more protein, more of some minerals, fat soluble vitamins (A, E, D, K) and immunoglobulins
  - Low volume
- Transitional phase – weeks 1-3
- Mature milk – after 3 weeks
  - There is variation between foremilk (watery) and hindmilk (feed)
    - Important in hot weather because infant will suckle more often but for not as long, thus gets fluid
  - Contents:
    - Water 90 g% (g/100g) - thus, women need to keep fluids up
    - Lactose 7g%
      - Promotes intestinal growth of lactobacillus bifidus flora (important natural flora
      - Galactose (product of lactose digestion) is essential for myelin formation in nervous tissue
    - Fat (fatty acids, saturated fatty acids, unsaturated fatty acids)
      - Main energy source
      - Almost completely digestible (well-emulsified, small fat globules)
    - Amino acids
    - Protein – lactalbumin, lactoglobulin, casein
      - Casein is 44% of total protein in human milk, 82% in cow's milk
        - Quite hard to digest, however
    - Minerals – calcium, iron (not a good source), magnesium, potassium, sodium phosphorus, sulfur
    - Vitamins: A, B_1, B_2, B_{12}, C, D, E, K
    - Cells (macrophages, neutrophils, lymphocytes)
      - Colostrum – 7-8x10^6/100ml, mature milk – 1-2x10^6/100ml
    - Other details:
      - pH 7.0
      - Energy value: 70 kcal/100ml, range 60-75

Lecture 12b: Infant formulae *Anna Pham*

Reasons to breast feed

- WHO recommends breast feeding for 4-6 months
  - Then solids + breast milk for up to 12 months
- For baby:
  - Breast milk is nutritionally complete: 20kcall/ml
  - Immunological benefits
  - Easier nutrient absorption (iron, proteins – content changes depending on baby growth, minerals)
  - Transmission of tastes from maternal foods – increased acceptance of new foods
- For mother:
  - Lack of menstruation
  - Reduces risk of breast/ovarian cancer later in life
  - Better return to pre-pregnancy weight
  - Lower obesity rates
- As adults, children who were breast fed have: lower BP, cholesterol, obesity, type 2 DM, better intelligence

Reasons to not breast feed

- Not all mothers want to/can
- Common reasons:
  - Previous difficult breast feeding
  - Nipple anomalies
  - Stress, anxiety, embarrassment
  - Smoking, illness
- Risks with breast feeding
  - If exclusive >6 months: iron deficiency
  - Vegan/vegetarians need to monitor own diet to ensure enough vitamin B_{12}, folate

Formula feeding for premature infants

- Premature babies have unique needs
  - Smaller nutritional stores
  - Underdeveloped digestion and absorption
  - Need for rapid growth
- Formulae
  - Low birthweight formula – easily digested
    - Increased protein, minerals higher: Na, K, PO_4 (transferred last trimester of pregnancy), Ca, Zn
    - 24 kcal/30ml (slightly higher than normal breast milk
  - Human milk fortifier – mother breast feeding as well, add to this
    - Powder supplement added to pre-term breast milk
    - Has added protein, Ca, PO_4
    - Increases breast milk up to the 24 kcal/30ml
  - Used until baby body weight ~2.5kg

Regular infant formulae

- Regulations on advertising (MAIF agreement)
  - Not allowed to advertise formula for <1
  - Need to encourage breast feeding on packets
- Comparison of infant formulae
  - Infant/starter/1
  - Follow on/2
  - Toddler/3

	Infant/starter/1	Follow on/2	Toddler/3
	Mimics human milk	Designed to meet the needs of older infants	
Suitable for:	Birth-12 months	6-12 months	1-3 years
Source:	Cows/soy/goat based	Cows/soy/goat based	Cows/soy based
Protein	13-15g/L	20-25g/L	27-32g/L
Calorie:	20kcal/30ml (840kJ)	20kcal/30ml (840kJ)	20kcal/30ml (840kJ), S26 higher, 30kcal/30ml
Protein source	Whey:Casein, 60:40	Whey:Casein, 20:80, 60:40	Whey:Casein, 40:60, 20:80
Carbohydrate	Lactose	Lactose	Lactose

Nutritional composition of different milks

- Trends:
  - Protein content increases with age
  - Why:casein ratio decreases with age
  - Infant formula is quite similar to human milk, higher iron and PO4
  - Follow-on milk is a halfway between human milk and cow's milk

	Human Milk	BMS	Cow's Milk	Follow-On
Protein (g)	10	15	34	21-25
Whey: Casein	60%:40%	60%:40%	18%:82%	20%:80%
Fat (g)	42	34-37	33	27-36
CHO (g)	74	70-76	47	67-83
Energy (kcals)	693	650-670	645	650-700
Na (mmol)	6	7-8	17.8	7.4-15
K (mmol)	15	14-18	39	15-29
PO4 (mg)	146	210-316	930	460-620
Fe (mg)	0.8	7-8	0.2	7-12

* Per litre

BMS-Breast Milk Substitute = Infant Formula

Soy formulae

- Indications:
  - Vegan, cow's milk protein allergy without soy protein allergy, permanent lactose intolerance, galactosemia
- Characteristics:
  - Lactose free
  - No nutritional advantage over standard formula
- Unproven reasons for use:
  - Atopic family history, FTT, asthma, irritable baby, reflux, previous child
  - Possible long term effects of phytoestrogens
- Australian college of Paediatrics
  - Policy statement – Soy protein formula (1997): unless really have to, don't use
    - Ie: avoid indiscriminate use, should not be used routeinely
    - Long term prescription of CMP free formula should only be given after definite diagnosis

Thickening formulae

- Uses
  - Dysphagia (can't swallow), ?reflux, to modify swallow (stays in mouth longer)
  - Should involve speech pathologists
- Commercial thickeners are available to manipulate formula
- Anti-reflux formula
  - Infant formula with a thickening agent
    - Eg: carob bean flour, rice starch, corn starch, or maltodextrin instead of lactose
  - Casein dominant for a more solid curd – 80:20
  - Risk of tube blockage

Specialised formulae

- Protein modified
  - Hydrolysed, protein with reduced MW
    - Indications: intolerance to milk proteins, enteropathy, maldigestion, malbsorption
    - Eg: Pepti-junior
  - Amino acid (protein-amino acid)
    - Indications: severe diarrhoea, eosinophilic esophagitis
    - Eg: neocate, elecare
- Carbohydrate modified
  - Lactose free
    - Indications: lactase deficiency
    - Eg: delact, Karicare, Soya
  - Sucrose free (cow/soy based)
    - Indications: sucrase – isomaltase deficiency
    - EG: karicare Soya, Pepti-junior, neocate, elecare
- Fat modified
  - Indications: chylothorax, intestinal lymphangiectasia, biliary atresia, fat malabsorption
  - Eg: monogen, caprillon
- Renal
  - Indications: acute renal failure, chronic renal failure, dialysis, pre-dialysis renal failure,
    - Eg: nepro, kindergen, suplena
- Metabolic
  - Indications: range of metabolic conditions like PKU (phenylketonuria)
  - Eg: various – modified proteins, carbohydrates
- PBS – some formulae are listed
  - Authority script required showing age and medical condition

Dieticians

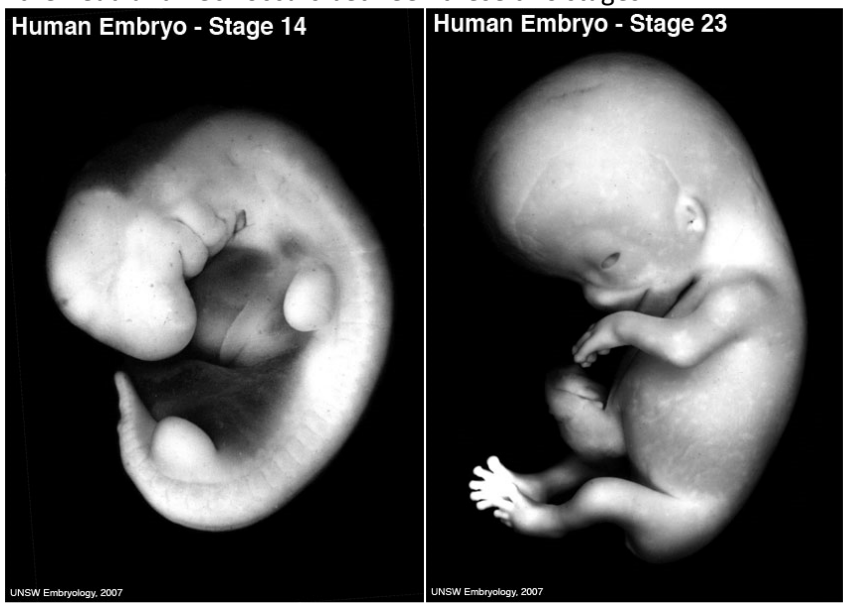
- Indications
    - Infant not getting adequate calories on current volumes of feeding
        - Fluid restricted (cardiac/renal)
        - Increased caloric requirements (CF, prematurity)
        - Hypermetabolic state (frequent infection, post-surgery)
        - Excessive losses (short gut syndrome, malabsorption syndromes)
        - Failure to thrive (to achieve catch up growth)
- What dietician will advise
    - Extra calories
        - Can increase standard infant formula of 20kcal/30ml to 30kcal/30ml
        - Assess requirements, current intake and make suggestions
            - Can increase volume, concentration or change method
            - Can add CHO or fat
- Dietician toolbox
    - Concentrate the formula
        - Add calories, proteins and nutrients
            - Maintains ratio of protein : fat : carbohydrate
        - May cause constipation
    - Extra CHO (eg. polyjoule powder – maltodextrin)
        - Adds extra calories
            - Easy and inexpensive
            - Minimal increase in osmolarity and renal solute load (RSL)
        - May cause osmotic diarrhoea
    - Fat (eg. Calogen, LCT (long chain triglyceride) emulsion or liquigen, MCT (medium CT) emulsion)
        - Easy, but expensive
        - MCTs have an alternate digestion route and may cause GIT upset
    - Combinations (eg. concentrated formula to 24kcal then additive to 30kcal)
        - Minimises disadvantages of one method
        - Maintains protein:fat:CHO ratio

Introduction

- External identity is your face
- The face and neck have the same origins
    - Arise from transient structures
- Facial abnormalities are important
    - Lip/cleft palate make up 7% of all birth defects
        - Rank 7th and 10th most common defects
    - Important because the appearance of the face and ear can determine internal defects – ie at which point in development, there was an interruption. Eg: kidney

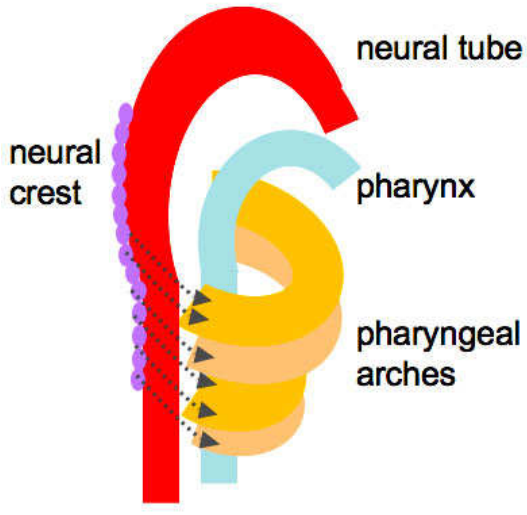
Embryonic overview

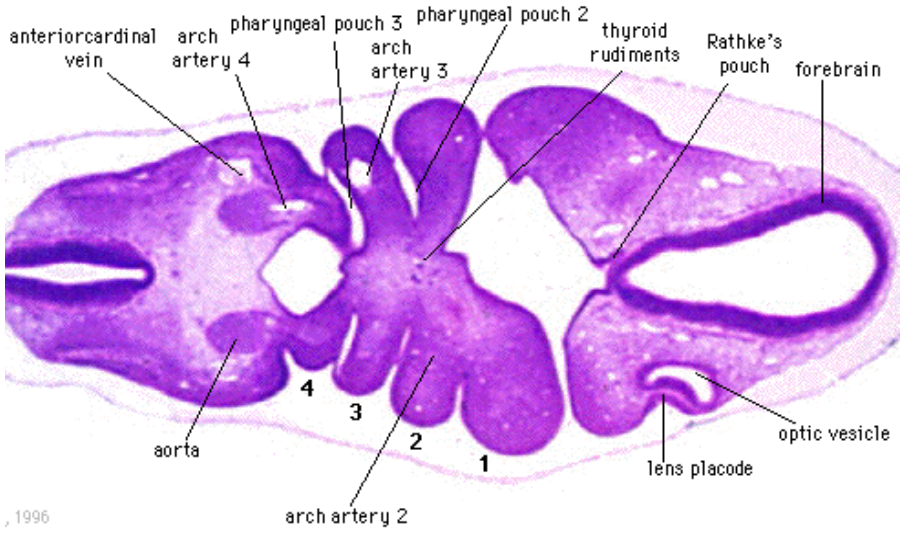
- Stage 14 (week 5 days 31-35) is approximately the midpoint of the embryonic period
    - No neck/face structures
    - "head" area is the brain fold – hind, mid and forebrain covered by a thin epidermis
        - Most rapidly growing part of the embryo at this point and folds ventrally
    - Pharyngeal arches 1, 2, 3 present
    - Cervical sinus – where the 2nd arch grows over the 3rd and 4th
- Stage 23 (week 9 days 56-60) is approximately the end of the embryonic period
    - Facial/neck features are identifiable
- Thus, development of the head and neck occurs between these two stages



Pharynx

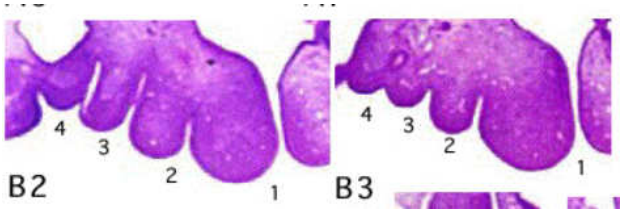
- The brain fold bends the pharynx and the buccopharyngeal membrane ventrally
    - Pharyngeal arches are wrapped around the pharynx
        - Top of which is known as the hypopharyngeal eminence, pharynx folds over this



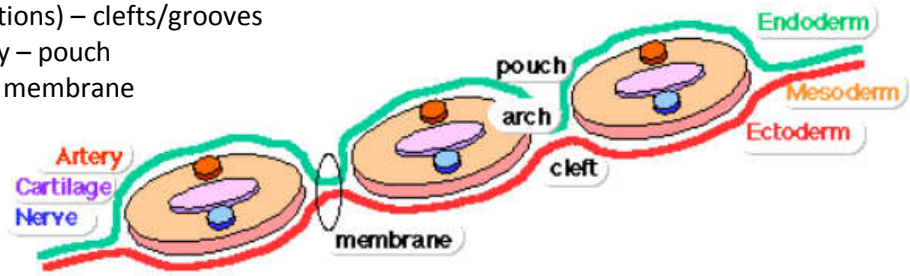


Pharyngeal arches

- There are 5 arches in humans: 1, 2, 3, 4, and 6
    - No. 5 is missing because it either fuses with 6 of regresses
        - later, no. 6 fuses with 4
    - Form from week 4 onwards (proliferate under the surface from week 3)
        - Form rostrocaudally sequentially and thus arches have different sizes and levels of development
        - Arches 1 and 2 appear at the closure of the cranial neuropore
- Arch 1 has 2 components: maxillary and mandibular parts
    - Bifurcates into upper and lower parts and allows communication through the gap – forms the mouth
        - A thin tissue layer separates inside form outside and connects the arches



- Composition of pharyngeal arches
    - Each arch has contributions from all 3 germ cell layers
        - Ectoderm – epidermis of face
        - Mesoderm – undifferentiated CT
            - Unique because there are no somites
        - Endoderm – lining of the pharynx
            - Neural crest cells migrate into the mesoderm from the hindbrain/midbrain region
    - Within each arch is an artery, nerve and some cartilage and a muscular component
- Parts:
    - Space between arches (indentations) – clefts/grooves
    - Space between arches internally – pouch
    - Endoderm meeting ectoderm – membrane



Neck and face

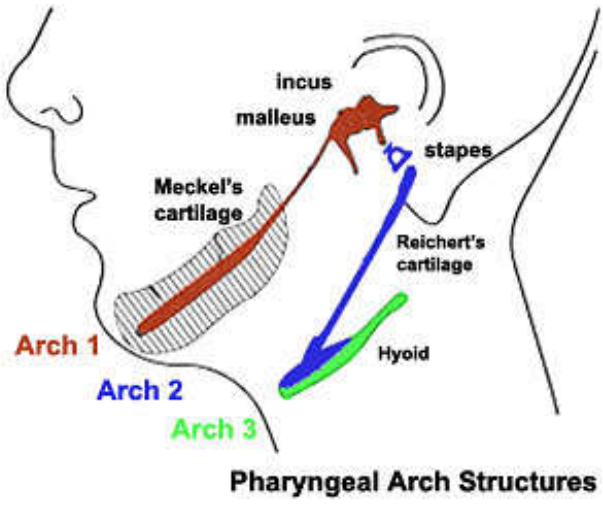
- Face is formed by arches 1 and 2
- Internal features of the neck are formed by arches 3 and 4

Neural crest cells

- Neural crest cells migrate into the mesoderm from the hindbrain/midbrain region
    - Contribute to CT of the head region:
        - Cartilage, bone, ligaments
            - Jaw cartilage and bone, middle ear (in mammals), frontonasal bones, teeth dentine, cranial nerve peripheral neurons and glia
        - Transient templates
        - Sympathetic trunk and dorsal root ganglia

Pharyngeal arches 1-4

- Pharyngeal arch 1:
    - 2 prominences
        - Upper – smaller maxillary part
            - Forms maxilla, zygomatic bone and the squamous part of the temporal bone
            - Forms bones of the middle ear except stapes
        - Lower – larger mandibular part
            - Forms cartilage that ossifies and forms the mandible
- Pharyngeal arch 2:
    - The hyoid arch
        - Forms most of the hyoid bone
- Pharyngeal arches 3 and 4:
    - Neck structures
    - Rest of hyoid bone, thyroid and cricoid cartilages



Summary of pharyngeal arch derivatives

Arch	Nerve	Muscles	Skeletal	Artery
Maxillary/ mandibular (1)	Trigeminal (V)	Mastication (temporalis masseter, medial, lateral pterygoid)	Mandible model Malleus, incus Meckel's cartilage	Terminal branches of the maxillary artery
Hyoid (2)	Facial (VII)	Facial expression (buccinator, platysma stapedius, stylohyoid, digastric posterior belly	Stapes, styloid process, lesser cornua of the hyoid, upper part of body of hyoid Reichert's cartilage	Stapedial (embryonic) Corticotympanic
3	Glossopharyngeal	Stylopharyngeus	Greater cornua of hyoid, lower part of body of hoid	Common carotid, root of internal carotid
4 and 6	Superior laryngeal and recurrent laryngeal (branch of vagus)	Intrinsic muscles of the larynx, pharynx, levator palati	Thyroid, cricoid, arytenoid, corniculate and cuneiform cartilages	4 – aortic arch, right subclavian 6 – ductus arteriosus, roots of pulmonary arteries

Pouches

Pouch	Overall structure	Specific structures
1	Tubotympanic recess	Tympanic membrane, tympanic cavity, mastoid antrum, auditory tube
2	Intratonsillar cleft	Cryptos of palatine tonsil, lymphatic nodules of palatine tonsil
3	Inferior parathyroid gland, thymus gland	
4	Superior parathyroid gland, ultimobranchial body	
5	Becomes part of 4th pouch	

Grooves and membranes

- 1st groove becomes part of the external acoustic meatus
- 1st membrane forms the tympanic membrane

Summary

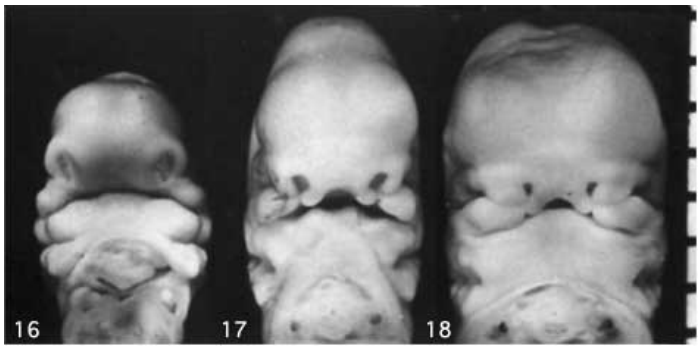
- 1st arch – about the mouth (chewing, jaw) and the external and middle ear
- 2nd arch – about the face, hyoid, and external and middle ear
- 3rd arch – about the neck and endocrine
- 4th arch – about the neck and endocrine

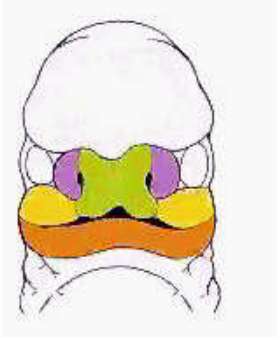
Abnormalities of the pharyngeal arches

- Sinuses – when a portion of a groove remains
- Fistula – a tract extending from pharynx to open on the side of the neck
- Cysts – remains of cervical sinus
- Vestiges – cartilaginous or bony developmental remnants under skin at side of neck

Face

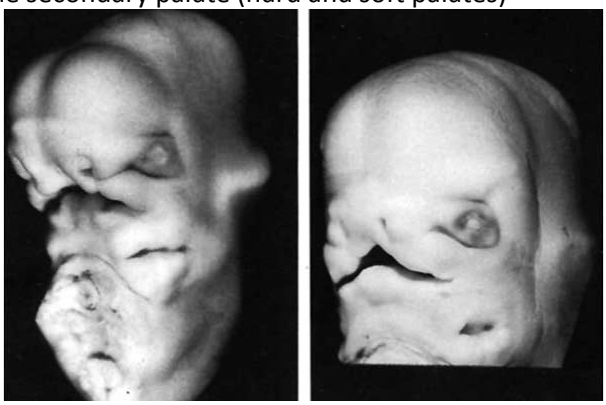
- Develops weeks 4-10
- Parts:
    - Frontonasal prominence
    - Maxillary
    - Mandibular
- Between maxillary and mandibular is the stomodeum, the floor of which is the buccopharyngeal membrane
    - Holes above the stomodeum are the nasal region (floor of the holes are the nasal placodes)





Palate

- Maxillary region is made up of two separate prominences that need to fuse together with the nasal prominence to form the upper lip
    - Failure of this mechanism (which is complex, so failure is common) results in cleft lip/palate
        - Complex because: need to break down the epithelium and fuse: an epithelial-mesenchymal interaction
    - Cleft palate can be related to >300 human abnormalities (detected weeks 4-8)
- Palatal development occurs from weeks 7-12 and involves formation of the primary palate (prolabium), premaxilla and cartilaginous septum then the secondary palate (hard and soft palates)

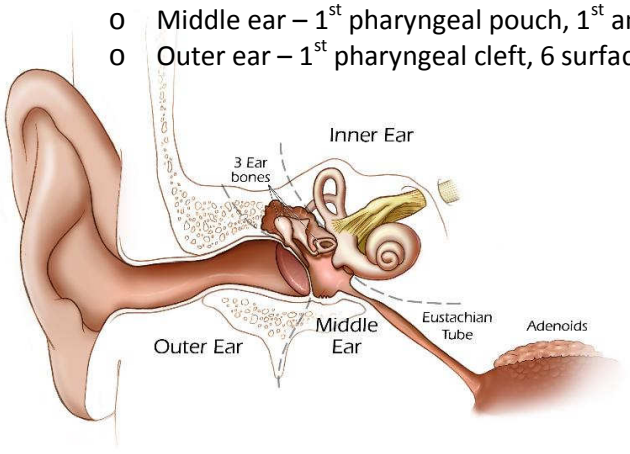


Tongue

- Has contributions from all arches
    - Somitomeres (unsegmented mesoderm from head region)
- Also:
    - Somites contribute tongue muscle cells

Ear – parts, an overview

- 3 regions:
    - Inner ear – otic placode then otocyst (for hearing and balance, embedded in bone at the skull base)
    - Middle ear – 1st pharyngeal pouch, 1st and 2nd arch mesencyme (3 bones)
    - Outer ear – 1st pharyngeal cleft, 6 surface hillocks (outer)

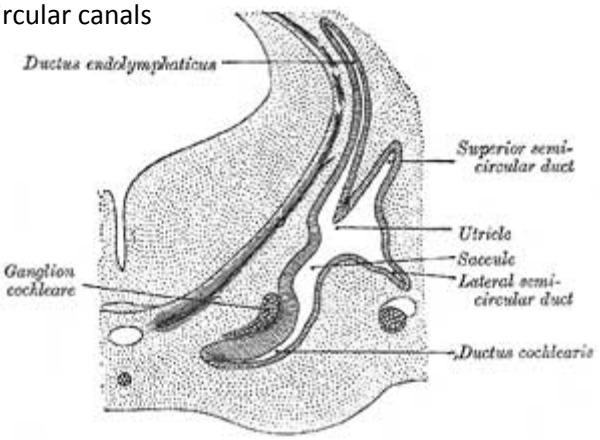


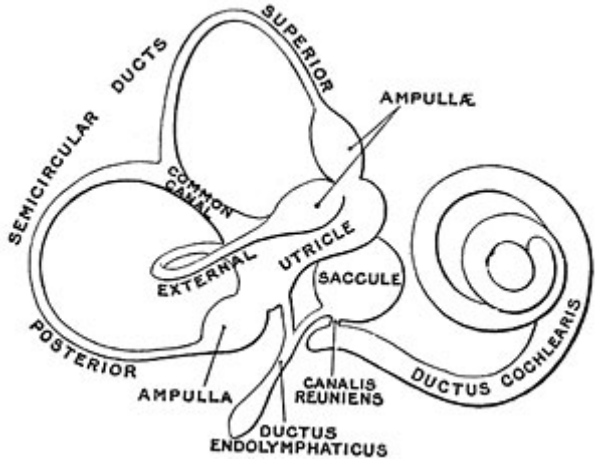
Overview continued

- Week 8: pinna, the external ear is present
    - Found at the level of the jaw – a relative position that changes with growth
        - Can be important clinically:
            - eg: position is a good marker for fetal alcohol syndrome because alcohol affects the cartilage. Ie it is structurally different, with a double “rail”
- Inner ear
    - Disc placode – the 1st identifiable sensory placode
        - Patch of ectoderm that buds off and enters the head (buds inwards)
        - Pinched off and lies in head region (otocyst)
- Middle ear
    - Pharynx, 1st pharyngeal pouch forms cavity
        - Pharyngeal arches 1 and 2 mesenchyme forms the bones
        - Tympanic membrane is formed from the membrane of the 1st arch
        - Cleft of the 1st arch forms the ear canal, undergoes recanalisation
- Outer ear
    - 1st pharyngeal cleft
    - 6 surface hillocks (arches 1 and 2)

Inner ear

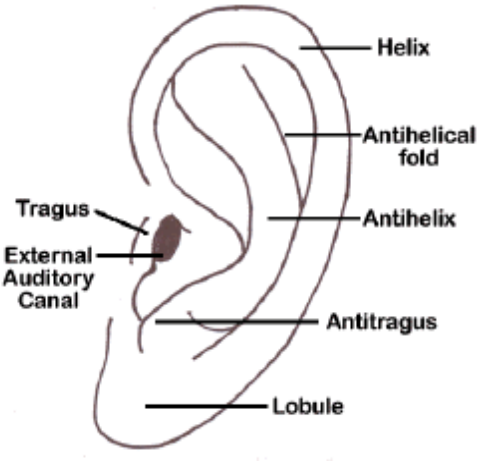
- Begin with a pair of sensory placodes (otic placodes) in the head region
    - Form from ectoderm on the surface then fold inwards to form a depression
    - Become pinched off entirely from the surface and become fluid-filled sacs (vesicles) – otocyst
        - Vesicles sink/migrate into the head mesenchyme
- Vesicles extend and fold
    - Form a membranous labyrinth
        - Upwards – cochlea, downwards, outwards – semicircular canals
        - Utricle and saccule
        - Endolymphatic duct
- Innervated by the vestibulocochlear nerve CN VIII

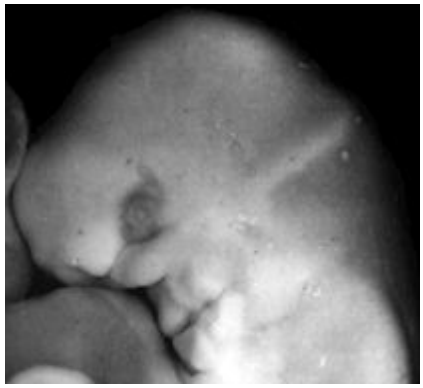




External ear

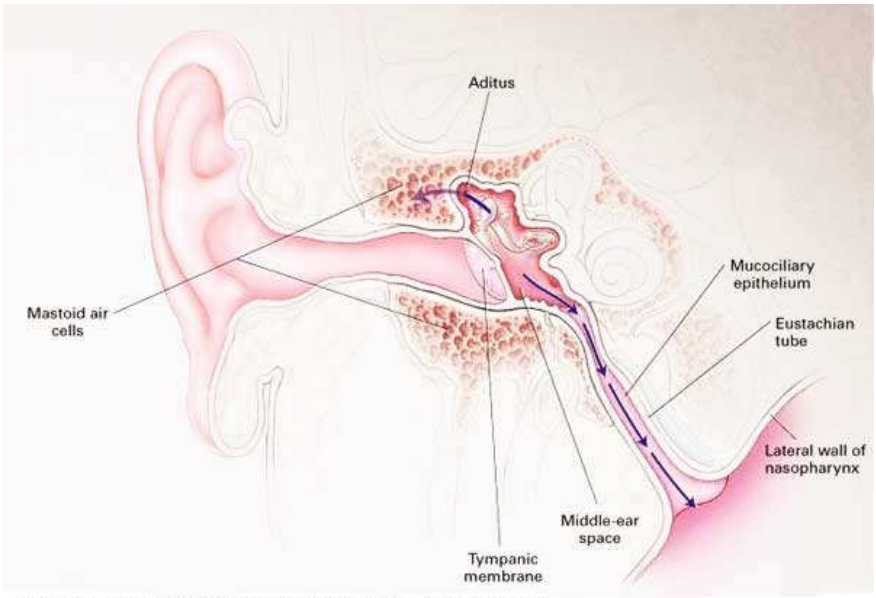
- 6 auricular hillocks form external ear
    - 3 on arch 1, 3 on arch 2
    - External auditory meatus (canal) formed from the 1st groove
    - Between arches 1 and 2 the pouch forms the tubotympanic recess





Middle ear

- Ossicles – bones
  - Arch 1 – malleus, incus
  - Arch 2 – stapes
- Muscles (mesoderm)
  - Arch 1 – tensor tympani
  - Arch 2 – stapedius
    - Protects tympanic membrane by relaxing in presence of loud noises
- Tympanic cavity
  - First pharyngeal pouch
  - Extends as the tubotympanic recess then the Eustachian tube
- Eustachian (otopharyngeal, pharyngotympanic) tube
  - Connects tubotympanic recess with nasopharynx
    - Allows pressure equalisation between middle ear and external environment and fluid drainage
  - Needs to be held open by muscles
    - Only tensor palati muscles at birth, as an adult, also have levator palati
  - Children: narrow, short, horizontal – thus an infection to the middle ear is common
    - Fluid can drain and accumulate into the middle ear, also can't hear
    - With growth, Eustachian tube gets longer, wider and a 45 degree angle, allowing draining from middle ear
  - Hearing is important for neural development



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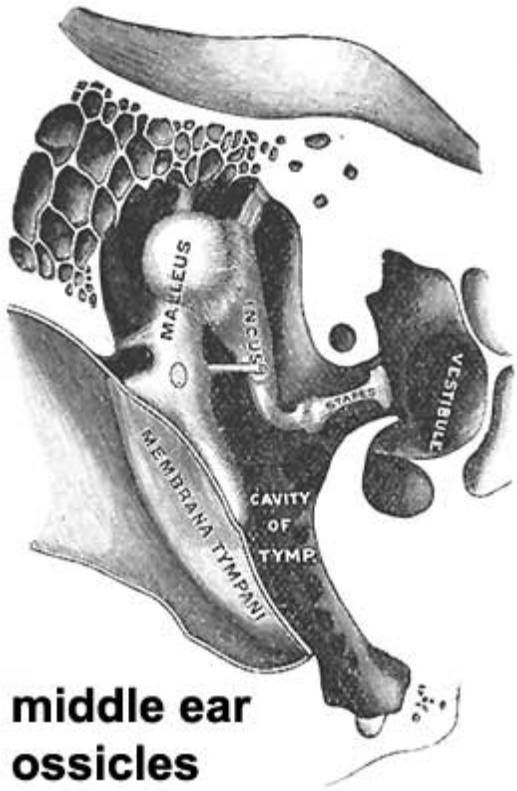


Timeline

- Week 3: otic placode, otic vesicle
- Week 5: cochlear part of otic vesicle elongated
- Week 9: mesenchyme around membrane labyrinth (otic capsule) chondrifies
- Week 12-16: capsule adjacent to membranous labyrinth forms the perilymphatic space and fills with perilymph
- Week 16-24: ossification forming petrous temporal and mastoid process of temporal
- 3rd trimester – vibration acoustically of maternal abdominal wall startles fetus

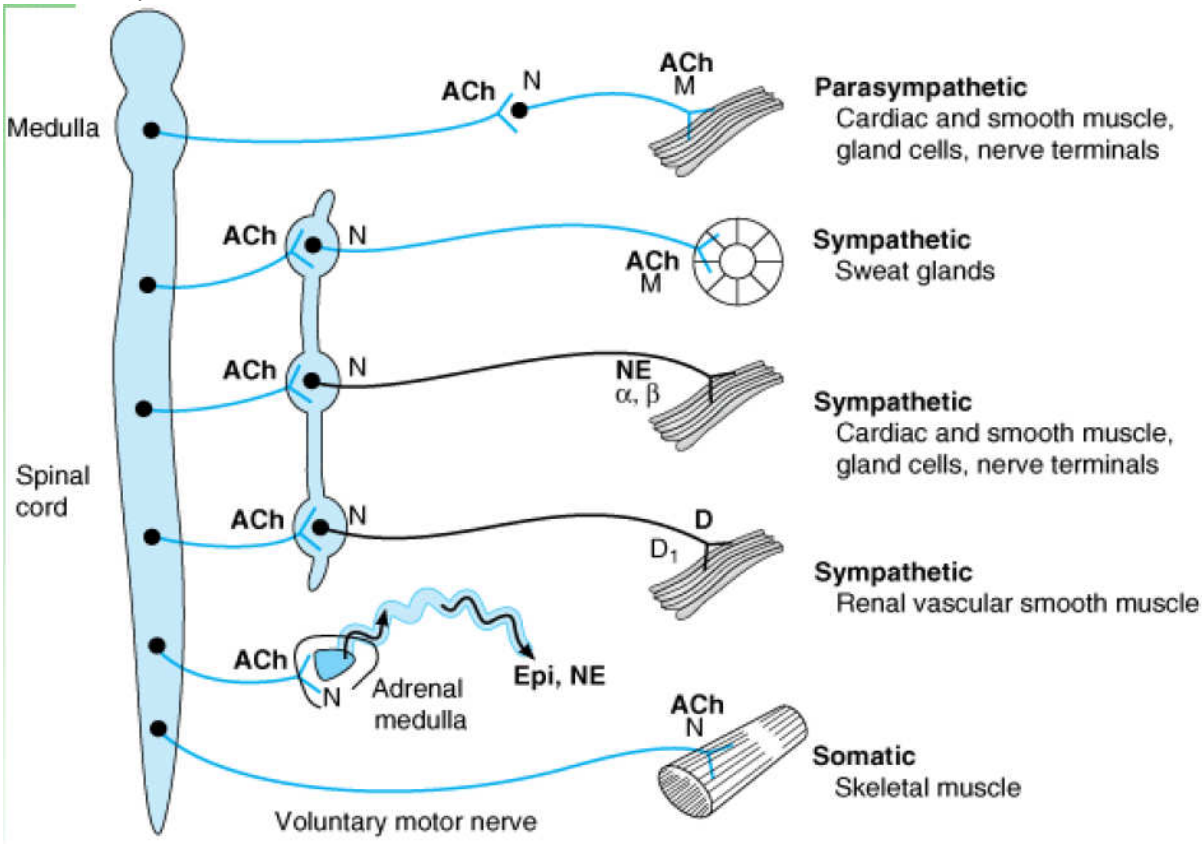
Summary

- Inner ear – epidermal otic placode at level of hindbrain
- Middle ear – 1st pharyngeal arch: cavity, arches 1 and 2 mesenchyme: ossicles
- Outer ear – 1st pharyngeal cleft: external auditory meatus, arches 1 and 2: 6 auricular hillocks

Overview of the nervous system - revision

- Nervous system
  - Central nervous system (brain and spinal cord)
  - Peripheral nervous system
    - Somatic nervous system (voluntary, skeletal muscle)
    - Autonomic nervous system (involuntary, body organs, smooth muscle)
      - Parasympathetic – body functions, rest and digest
      - Sympathetic – fight or flight response
      - Enteric – digestion

Autonomic nervous system



- Notes:
  - Parasympathetic has a long preganglionic fibre with synapse in the ganglion close to the target organ
  - Sympathetic has synapse in the dorsal root ganglion of the sympathetic trunk
  - Somatic only uses a single nerve
- Sympathetic vs parasympathetic

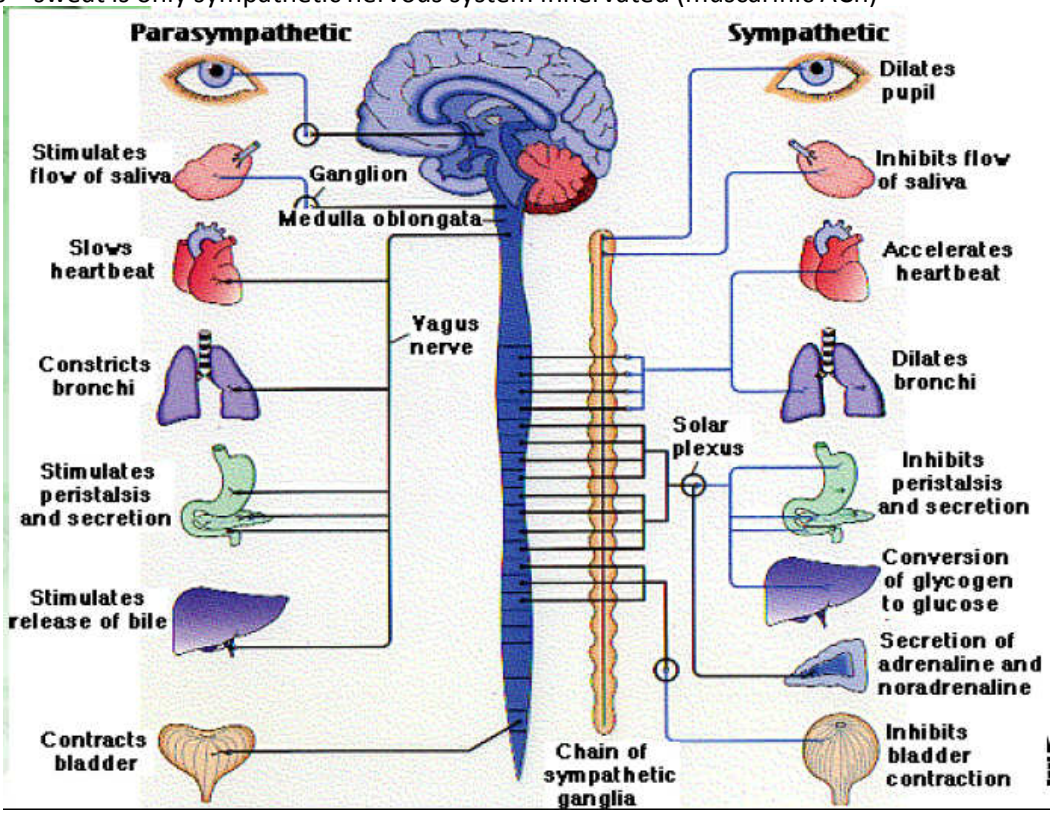
Sympathetic	Parasympathetic
Flight or flight	Rest and digest
Neurotransmitters: Acetylcholine at ganglia Noradrenaline/adrenaline at target tissues	Neurotransmitters: Acetylcholine at ganglia Acetylcholine at target tissues
Nicotinic receptors at ganglia α and β-adrenoceptors at target tissue	Nicotinic receptors at ganglia Muscarinic receptors at targets

Receptors of the ANS

- Cholinergic receptors – respond to ACh (parasympathetic and preganglionic)
    - Subclasses:
        - Nicotinic receptors
            - N_M – neuromuscular junction
            - N_N – autonomic ganglia, adrenal medulla and CNS
        - Muscarinic receptors
            - M_1 – CNS, glands (NT release, gastric acid secretion)
            - M_2 – heart and smooth muscle (slows heart rate)
            - M_3 – smooth muscle of BVs and lungs and glands (constriction of bronchi, relax of vessels)
            - M_4 – nerve cells (inhibitory effects via decreased cAMP)
            - M_5 – unknown
- Adrenergic receptors – respond to noradrenaline and adrenaline (sympathetic)
    - Subclasses
        - α-adrenergic receptors
            - α1 – blood vessels and other smooth muscle
            - α2 – presynaptic nerves (autoreceptors)
                - α1 and 2 stimulated by noradrenaline, inhibited by adrenaline
        - β-adrenergic receptors
            - β1 – heart (increases HR, vs M2)
            - β2 – smooth muscle (relaxes)
                - asthma: beta agonist treatment
            - β3 – fat tissue (lipolysis)

Autonomic function

- Involuntary control, self-governing
    - Most internal organs have dual innervation and antagonistic control to maintain homeostasis by physiological balance
- EGs of autonomic functions/regulation:
    - Contraction/relaxation of smooth muscle
    - All exocrine and some endocrine secretions
    - Heart rate, cardiac output
    - Energy metabolism in liver and skeletal muscle
- Exceptions:
    - BVs are mainly sympathetic nervous system
    - Glands – sweat is only sympathetic nervous system innervated (muscarinic ACh)



Autonomic activities summary

Organ	Parasympathetic Response (predominant)	Sympathetic Response "Fight or Flight"
Heart (baroreceptor reflex)	↓ heart rate M2 ↓ cardiac output	↑ heart rate β1 ↑ cardiac output
Bronchioles	Constriction M3	Dilation β2
Stomach and intestine	↑ secretion of HCl & digestive enzymes M1, M3 ↑ GIT motility M3	↓ secretion β2 ↓ motility
Urinary bladder	Contracts detrusor M3 ↑ urination	Constricts sphincter α1 Relaxes detrusor β2 ↓ urination
Rectum	Contracts smooth muscles M3 ↑ defecation	Constricts sphincter α1 Relaxes smooth muscles β2 ↓ defecation
Eye	Constricts pupil M3 Adjusts for near vision M3	Dilates pupil α1 Adjusts for far vision β2

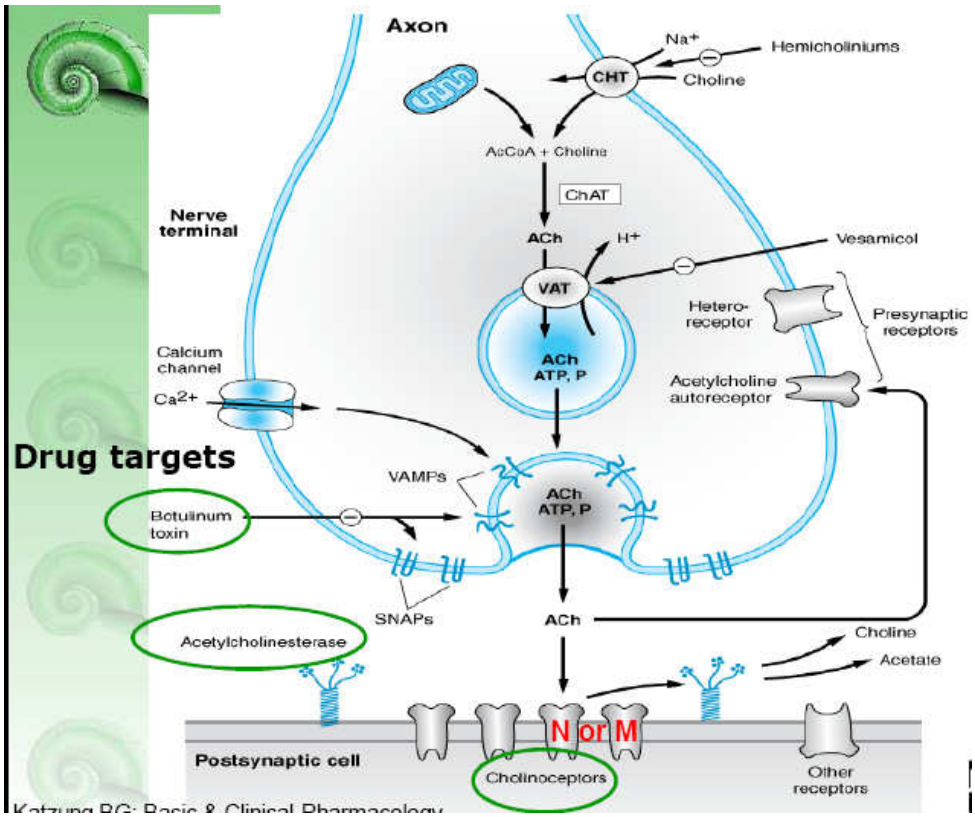
Cholinergic drugs

- Drug targets:
  - Botulinum toxin – inhibits release of ACh
  - Acetylcholinesterase – hydrolyses released ACh
  - Receptors – facilitate function

Parasympathomimetics

Stimulation/mimicking of ACh

- Muscarinic receptor agonists
  - Pilocarpine (topical treatment for glaucoma)
  - Bethanechol (postoperative urinary retention)
- Nicotinic receptor agonists
  - Nicotine (withdrawal)
- Acetylcholinesterase inhibitors
  - Physostigmine (glaucoma)
  - Neostigmine, pyridostigmine (myasthenia gravis – weak sk. muscle)

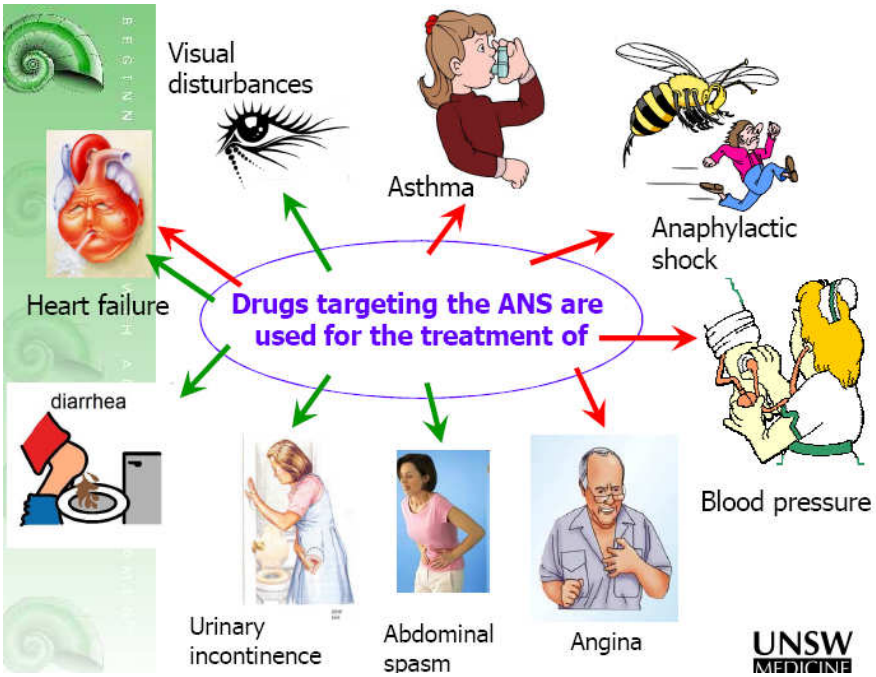


Anticholinergics

Reduce effects of ACh

- Antimuscarinic agents
  - Atropine (see later)
- Ganglionic blockers
  - Hexamethonium (useful antihypertensive but with profound side effects because blocks both SNS and PNS
- Botulinum toxin
  - Neurotoxin produced by Clostridium botulinum causing food poisoning (botulism)
    - Blocks exocytosis of ACh vesicles
  - Uses: dystonia (abnormal muscle contraction), cosmetic surgery, urinary incontinence

Drugs targeting the ANS



Atropine

- Muscarinic receptor antagonist, antimuscarinic
- Uses:
    - Ophthalmic
        - Topical – cycloplegic (paralyse accommodation reflex), mydriatic (dilate the pupils)
            - Effects degrade slowly, effects can last 2 days – 2 weeks
            - Tropicamide – preferred as a mydriatic because it has a short duration of effect
    - Resuscitation – treatment of bradycardia in cardiac arrest
    - Premedication in anaesthesia – inhibit bronchial and salivary secretions and reflexes, + bronchoconstriction
        - Thus prevent aspiration
    - Antidote for organophosphate poisoning – insecticides and nerve gases can destroy acetylcholinesterase
        - Atropine prevents prolonged action of ACh
    - Anti-spasmodic and anti-diarrhoea – GIT inhibition

Incontinence

- Different causes: stress 30%, urge 40%, mixed 30%
- Urge incontinence
    - When the bladder contracts without warning causing leakage (16% of population)
    - Symptoms:
        - Frequency (>8 times/day), urgency (sudden, unavoidable desire to void), nocturia (waking at night to void)
    - Treatment – antimuscarinics (oxybutynin and tolterodine)
        - Mechanism
            - ACh stimulates muscle contraction to initiate micturition, antimuscarinics block this
- Treatment with Tolterodine successfully reduces symptoms of frequency and urgency
    - Treatment is only successful in 60% of patients and there are severe side effects:
        - Dry mouth, constipation

Side effects of antimuscarinics

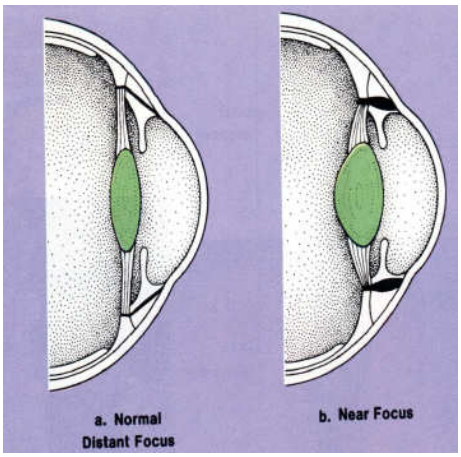
- Gut motility reduced – constipation
- Urine retention – UTI risk
- Blurred vision, photophobia
- Exocrine gland secretions inhibited – dry mouth, hyperthermia (decreased sweating)
- CNS excitation (agitation, disorientation, hyperactivity) – if given high doses that cross BBB
- Toxic doses can lead to depression, circulatory and respiratory failure – need to treat with AChE inhibitor, eg: physostigmine

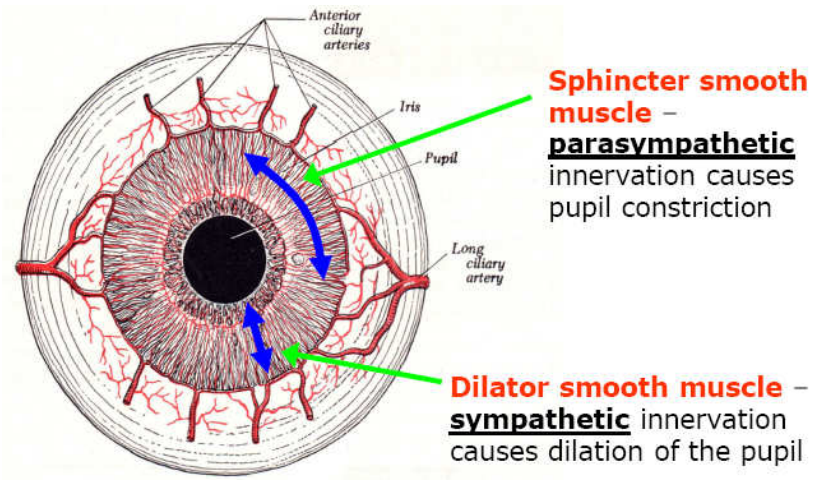
Botulinum toxin (BOTOX)

- Neurotoxin produced by Clostridium botulinum (bacteria that causes food poisoning, botulism)
    - Botulinum toxin A (BTX-A) used to treat dystonia: blepharospasm, hemifacial spasm, cervical dystonia, stuttering
    - Currently used in bladder disorders: neurogenic detrusor overactivity (NDO), idiopathic detrusor overactivity (IDO)
        - Given by local injection and effective for 6-12 months and dramatically increases quality of life

The eye

- The lens:
    - Focus on distant objects
        - Ciliary muscles relax suspensory ligaments and the lens is flattened
    - Focus on near objects
        - Accommodation – ciliary muscle contracts (muscarinic) and reduces tension on suspensory ligaments so the lens becomes rounded
- The pupil:
    - Sphincter smooth muscle – parasympathetic innervation causing pupil constriction
    - Dilatory smooth muscle – sympathetic innervation causing pupil dilation

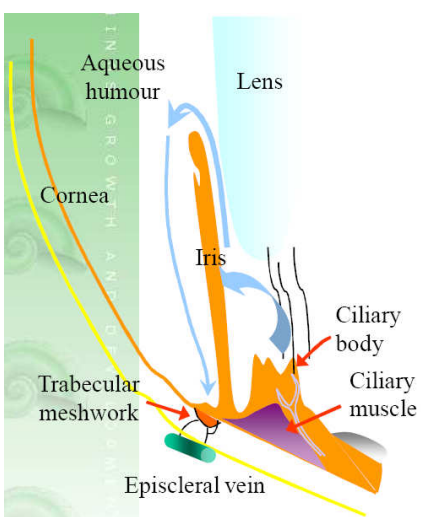




	Sympathetic	Parasympathetic
Ciliary muscle	Relaxes (focus on distance) β2 adrenoceptors	Contracts (focus on near) M3 receptor
Dilator smooth muscle	Contracts (see wide) α1 adrenoceptors	
Sphincter smooth muscle		Contracts (focus centre) M3 receptor

Glaucoma

- Aqueous humour (watery fluid in anterior chamber of eye) produced by ciliary body
    - Flows into anterior chamber and leaves via trabecular meshwork
- Glaucoma – pressure in aqueous humour raised due to trabecular meshwork blockage, damaged to optic nerve
- Therapy:
    - Muscarinic agonists (pilocarpine) or AChE inhibitors (physostigmine) relax ciliary muscle and episcleral vein
        - Thus increase outflow of fluid and reduce production of aqueous humour



ANS and the eye

	Sympathetic	Parasympathetic
Pupil	Dilates (wide focus)	Constricts (narrow focus)
Ciliary muscle	Relaxes (far vision)	Contracts (near vision)
Drug uses	β-receptor antagonists (propanolol, timolol), decrease intraocular pressure in glaucoma	Muscarinic agonists (pilocarpine) decreases intra-ocular pressure in glaucoma M antagonists (atropine, tropicamide) ophthalmic drops to dilate pupil for eye check

ANS and the heart

	Sympathetic	Parasympathetic
Effect	Increased force of contraction Increased heart rate	Decreased force of contraction Decreased heart rate
Receptor	β1 adrenoceptors	Muscarinic M2 receptors
Drug uses	Adrenaline – stimulates cardiac function following cardiac arrest Propanolol (β blocker), metoprolol (β1 blocker) – treat angina and cardiac arrhythmias	Atropine (M antagonist) – treat bradycardia (possibly following myocardial infarction)

Development

- Childhood development – progressive acquisition of skills as a child grows and matures
    - Occurs especially during the first 2 years
- Development is a complex process with spurts and plateaus
    - Development is affected by child-related factors and environmental factors
    - There is a wide range of normal development
        - (eg: 9-16 months, children learn to walk unaided – large range)
- Development is a continuous process
    - Sequence is the same, but rate varies
    - Related to maturation of the nervous system and opportunity via stimuli
- Through development:
    - Generalised activity is replaced by specific individual responses
    - Primitive reflexes are lost before the corresponding voluntary movement is acquired

Theories on development

- Darwin
- Measurement – Galton, Binet, Terman Gesell
- Learning – Pavlov, Watson, Skinner
- Emotional – Freud, Erikson, Bowlby
- Temperament – Hall, Jones, Carey
- Cognition – Piaget

Nature vs nurture

- Nature theory
    - The sequence and timing of development is pre-programmed
    - External stimuli has a marginal effect
- Nurture theory
    - Neurobiological substrate is necessary but environmental influences play major role in development
    - Quality and type of interaction/stimuli (environment) determine outcomes of development
- Present understanding
    - Development is a continual process involving interaction between genetic substrates/sequences and the environment
        - Can be influenced adversely and advantageously by the environment but the nature, degree and duration of change may be determined by biological factors

Domains of development

- Gross motor – posture and movement
- Fine motor – manipulation
- Speech/language – expression, communication
- Cognitive – understanding/compliance
- Personal/social – understanding social situations, picking up on social cues
- Self-help, independence – doing things for self

Developmental milestones

- Milestone – a particular behaviour/skill that a child has attained
    - Age milestones are acquired is compared to the normal range to ensure normal development
- Sequence of assessment:
    - History-taking – open ended questions, then specific questions (talk to parents + child)
    - Observation of child
        - Spontaneous play
        - Non-verbal tasks – block building, foamboards/puzzles, drawing
        - Verbal tasks – receptive, expressive (simple to complex)
        - Gross motor tasks
        - Return to spontaneous play
    - Physical examination – assess neurological development
    - Hearing – important for language
        - 80% of developmental problems are to do with language
    - Vision – helps assess fine and gross motor problems
    - Developmental screening/assessment
        - Denver 2
        - Australian Developmental Screening Test (ADST)
        - Ages and Stage Questionnaires (ASQ)
        - Brigance Screens
        - Parent's Evaluation of Developmental Status (PEDS)
    - Standardised developmental tests
        - Griffiths Mental Developmental Test
        - Bayley Scales of Infant Development
        - IQ Tests

Infant reflexes

- Moro reflex (startle reflex) – if infant's head moves suddenly, temperature changes abruptly or they are startled by a sudden noise
    - Legs and head extend while arms jerk up and outwards and then brought together and infant cries
    - Adaptive to allows infant to hold onto mother
- Walking/stepping reflex – if soles of feet touch a flat surface, foot will move upwards in a 'walking' motion
- Rooting reflex – infant turns head towards side if cheek is stroked to search for nipple and milk
- Tonic neck reflex – if head is turned to the side, infant assumes a 'fencing posture' with arms up
- Palmar grasp reflex – if an object is placed in palm, infant grips object

Summary of development from 0-6 years – SEE TABLE

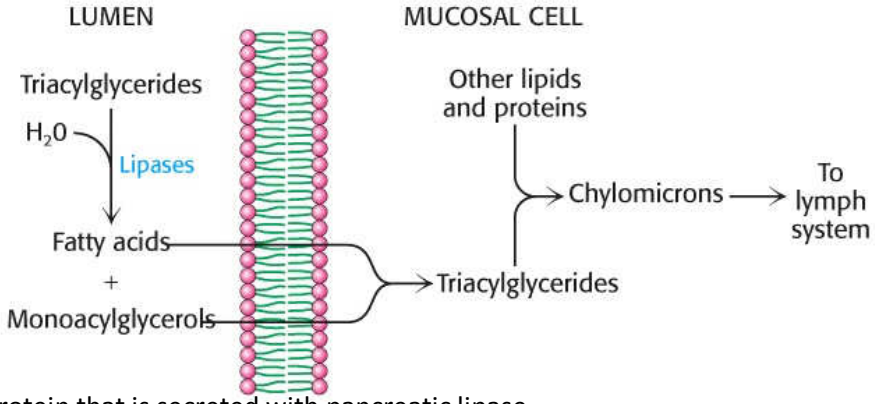
- 6 weeks
    - Resolution of primitive reflexes
    - Eyes can follow light/objects
    - "listens" and can vocalise in response
    - Smiles
        - Visually recognises mother
- 3 months
    - Fragile sitting, support on forearms
    - Hands together and to mouth
    - Laughs, searches for sound with eyes
        - Cooing – vowel sounds
    - Friendly with strangers
- 6 months
    - Rolls front to back, bears weight when held standing
    - Reaches for toys
    - Babbling, can localise sounds
    - Selective response to mother and familiars

- 9 months
    - Sits alone with lateral propping
    - Crawling (7-12 months), pull to stand (7-12 months)
    - Pick up objects with thumb and index finger
        - Looks for fallen toys
    - Echolalia, listens to conversations and babbles with double syllables
    - Takes objects to mouth, distinguishes strangers and familiars
- 12 months
    - Crawls well, shuffles, pulls to standing
    - Throws toys, can hold pencil
    - Knows name
        - Long strings of inflected babble → first single words, knows definitions by use
    - Finds hidden toys, displays affection to familiars
- 15 months
    - Walks alone, crawls upstairs, pushes trolley/pram
    - Builds tower of 2, points with index finger
    - 3-4 meaningful words, jargon (speak with speech-like sounds), obeys simple instructions
    - Helps with dressing, drinks from cup, active in exploring environment
- 18 months
    - Walks pulling toy on string, walks up stairs 2 feet/step, trotting
    - Towers of 3, single hand dominance, purposeful scribble
    - Jargon, start 2 word combinations, points to 2 body parts
    - Feeds self with spoon, parallel play
- 2 years
    - Walks backwards, runs
    - Tower of 6-7, “train without chimney”, circular scribble
    - 2-3 word short sentences, follows instructions, points to 4 body parts
    - Symbolic play, tries to dress/undress
- 2.5 years
    - Jumps off floor, stands on 1 foot
    - Tower of 8, train with chimney, vertical/horizontal strokes, single hand preference
    - Short sentences (4+ syllables), answer simple questions, knows first name
    - Cooperative play, takes off pants
- 3 years
    - Pedals tricycle, steps 1 foot/step, tiptoes
    - Towers of 9+, imitates bridge, mature pencil grip, scissors
    - Sentences 6 syallables, ask “what”, “where, uses pronouns
    - Dresses self, knows gender
- 4 years
    - Hops on one foot, kicks ball
    - Copies 6 block pyramid, man stage 1 (jellyfish man)
    - Compound sentences with because, but, if, asks “why”, tells stories and jokes, understands abstract language
    - Can do up front buttons, imaginative group play
- 5 years
    - Walk downstairs 1 foot/step
    - Copy square, draw house
    - Longer sentences (10 syllables), understands opposites, counts to 10
    - Dresses/undresses, brushes teeth
- 6 years
    - Run upstairs, skip, bounce/catch ball
    - 10 block stairs, write 1st name
    - Understand same and different
    - Know address, 1 special friend

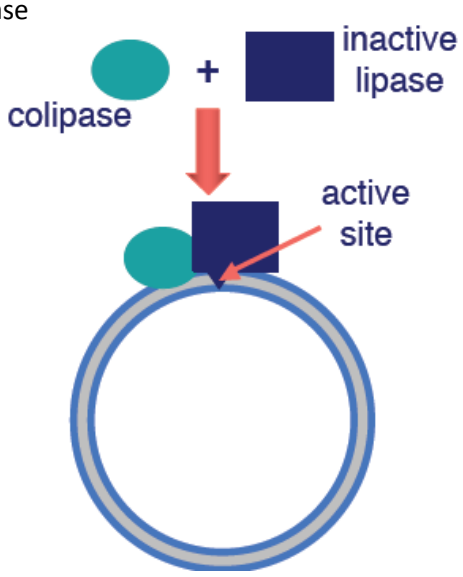
SEE LECTURES NOTES FROM BGDA (same lecture)

Fat digestion

- Process:
  - Triacylglycerides (main component of dietary fat) is broken down by pancreatic lipase forming fatty acids and monoacylglycerols
    - These are taken up by the mucosal cells and reassembled in to triacylglycerides
      - These are then combined with other lipids and proteins to form chylomicrons
        - Chylomicrons are thus transported via the lymph system
  - Bile salts are important for emulsifying the fat and facilitating digestion



- Colipase
  - A small protein that is secreted with pancreatic lipase
  - 2 functions:
    - Binds to inactive lipase and helps it bind to lipid micelles
    - Induces a conformational change in the lipase that exposes an active site at the region of the enzyme surface in contact with the micelle thereby activating lipase
  - Allows lipase to only be activated when it reaches the target site

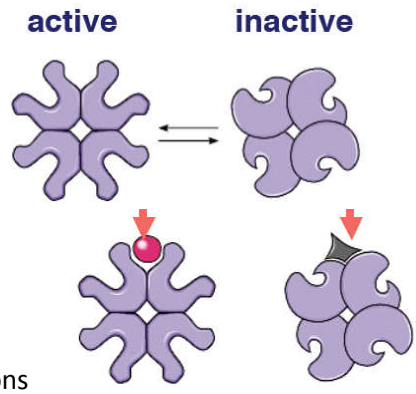


Controlling enzyme activity

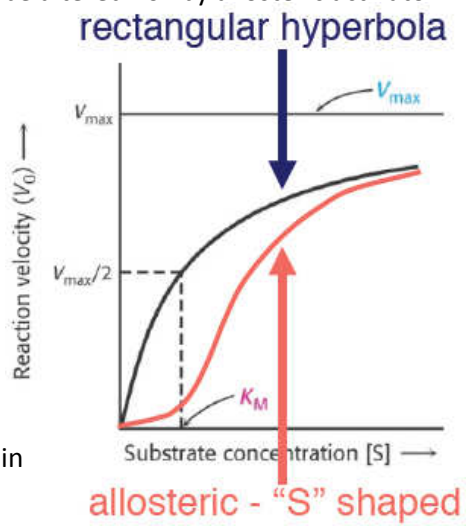
- 3 mechanisms:
  - Altering the activity of existing enzymes by reversible binding of molecules (small)
    - Eg: ion, organic molecule
    - Eg: colipase
  - Altering the activity of existing enzymes by covalent modification
    - More permanent and involves a catalysed reaction
    - Eg: turning on of zymogens by splitting peptide bonds
  - Altering the amount of enzyme present
    - Turning on/off enzyme secretion, breakdown or synthesis

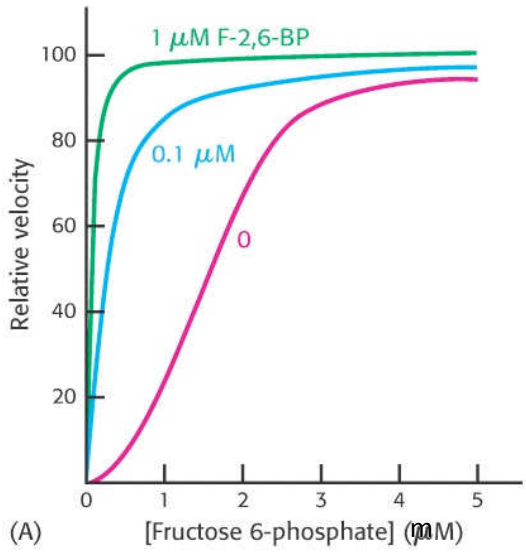
Reversible binding

- Competitive inhibitors
  - Substrate analogues can bind at the active site and prevent actual substrate binding
  - Not a common mechanism for intracellular enzymes
    - Common target for drug action
- Activation and inhibition of intracellular allosteric enzymes
  - Common general mechanism for controlling metabolism intracellular
    - There are no extracellular allosteric enzymes
- Allosteric enzymes
  - Properties:
    - Many intracellular enzymes that control metabolism are allosteric
    - Structure is quaternary with 2 or more subunits with active sites
  - Mechanism:
    - Allosteric enzymes oscillate between active and inactive conformations
    - Allosteric activators and inhibitors reversibly bind to the enzyme and lock it in the active/inactive conformation
  - Thus, allosteric activators and inhibitors modulate enzyme activity and regulate metabolic pathways



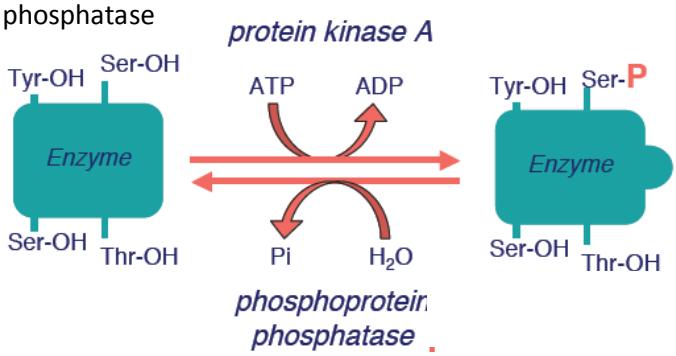
- Effect of allosteric enzymes
  - Reaction velocity vs substrate concentration curve:
    - Regular enzymes – rectangular hyperbola curve
    - Allosteric enzymes – sigmoid curve (S-shaped)
      - At a low substrate concentration, enzyme activity is lower, at a high concentration, similar
      - Curve can be changed with activation/inhibition of enzyme
  - Eg: glucose breakdown
    - Enzyme activity can be altered 20x by allosteric activator



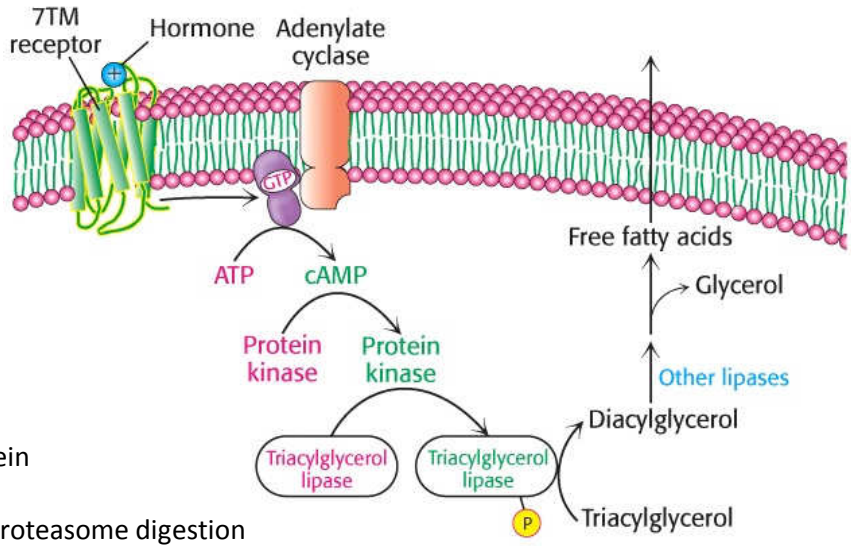


<u>Covalent modification</u>

- Cleavage of peptide bonds:
  - Zymogen activation in protein digestion
  - Blood clotting
- Chemical reaction with a particular amino acid side chain
  - Phosphorylation/dephosphorylation
- Phosphorylation
  - Occurs at hydroxyl (-OH) groups on amino acid side chains
    - Common mechanism for controlling enzyme activity, receptors and transporters
    - Ie, occurs at Serine, Threonine and Tyrosine residues
  - Activity can thus be turned on or off in different proteins by phosphorylation/ dephosphorylation
- Protein kinase A
  - Phosphorylates serines, enzyme is specific for serin side chains and only one (or a few) serines in a target enzyme
  - Process:
    - Binds ATP and target enzyme at the same time
    - Transfers a phosphate group
    - Phosphorylation of enzyme causes a conformational change that activates or inhibits the enzyme
  - Process can be reversed by phosphoprotein phosphatase

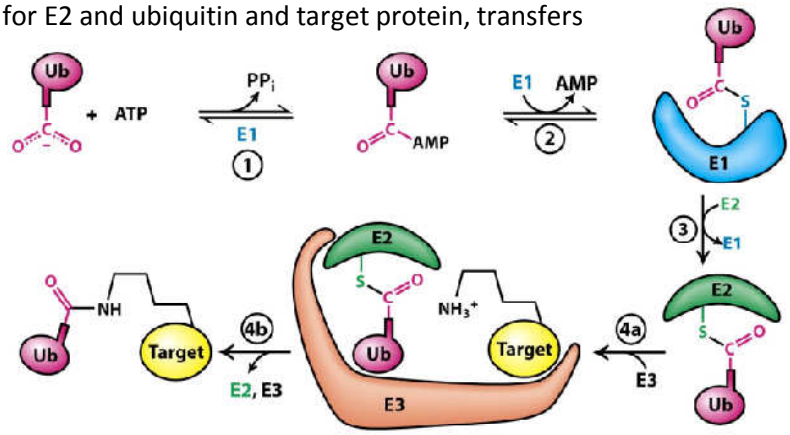


- Importance of protein phosphorylation
  - Often occurs as a response to external signals (eg: binding of hormones or neurotransmitters to receptors)
    - Modifies the function of cells in the context of the rest of the body, vs. allosteric that are purely intracellular
    - Allows external control of metabolism and other cellular processes
  - EG: triacylglycerol breakdown in adipose tissue
    - Hormone binds to a 7TM receptor which causes an influx of cAMP
      - cAMP activates protein kinase that then phosphorylates triacylglycerol lipase
        - this breaks down triacylglycerol (fat reserves) and leads to energy production
- Enzymes can have allosteric properties and changes with phosphorylation/dephosphorylation

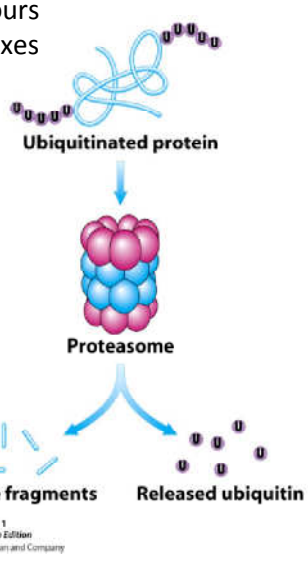


Amount of enzyme

- Gene expression – synthesis of new protein
- Rate of degradation and removal
    - Often via ubiquitin-tagging and proteasome digestion
    - Half lives of enzymes
        - Enzymes that are important in control have short half lives allowing their concentration to be changed readily
- Ubiquitin
    - Small protein (8.5kDa) used to tag intracellular proteins for destruction
    - C-terminal carboxyl group covalently bonds to amino groups in lysine side chains via isopeptide bonds
        - Process:
            - ATP converted to AMP and attached to ubiquitin (enzyme 1)
            - Ubiquitin is attached to enzyme 1 instead of AMP
            - Ubiquitin is attached to enzyme 2 from enzyme 1
            - Complex of enzyme 2 and ubiquitin is attached to enzyme 3
            - Ubiquitin is transferred to the target
        - Enzymes:
            - E1 – interactions with ubiquitin
            - E2 – transfers ubiquitin from E1 to E2
            - E3 – large, recognition site for E2 and ubiquitin and target protein, transfers ubiquitin to target protein

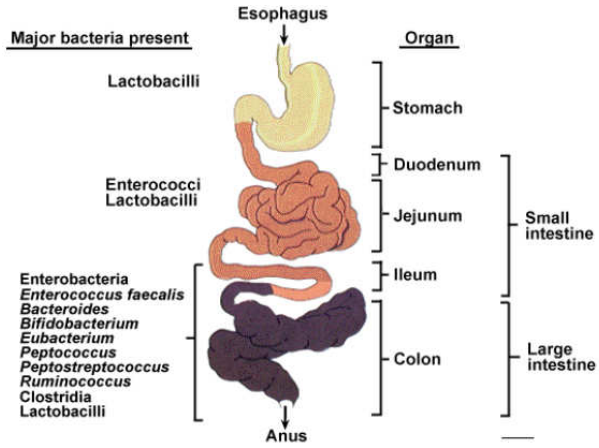


    - Signals for ubiquination
        - Half-lives of intracellular proteins are determined by amino terminal residues
            - Eg: in yeast, N-terminal arginine, $t_{1/2}$ ~2mins; methionine, $t_{1/2}$ ~20hours
        - PEST (proline, glutamate, serine, threonine) boxes and cyclin destruction boxes
            - Amino acid sequences in proteins
        - Multiple E2 and E3 proteins recognise different N-terminal amino acids and domains
            - The E3 family is one of the largest gene families in humans
- Proteosome
    - Made up of alpha and beta subunits
        - Beta-subunits split tagged protein into small peptides and ubiquitin (for reuse)
            - Subsequently, peptides can be broken down into amino acids by peptidases
        - Ubiquitin aids in directing the protein into the proteosome



Gastroenteritis

- Epidemiology
  - Gastroenteritis is one of the leading causes of death by infectious disease
    - 1/3 of children that die every year die form diarrhoea diseases
    - Most childhood deaths are in developing countries
  - About 1 case/person/year in Australia
- Symptoms: vomiting, diarrhoea, malaise, fever
- Aetiology: viruses, bacteria and parasites
  - Replicate in the gut, cause associated sequelae



The gut

- The largest mucosal surface and largest lymphoid organ
  - Fertile ground for viral replication
- Natural flora can protect to an extent, increases in number further down the tract
  - Thus, gastroenteritis more common in infants because gut hasn't developed natural flora yet

Faeces

- Waste/excrement from the digestive tract
  - Made up of water, food residue, bacteria, and secretions from the liver and intestine
- Diarrhoea – frequent passage of watery bowel movements
  - Causes death most commonly by dehydration

Viruses

- Gastroenteritis is caused by parasites (2.4%), bacteria (27.1%) and viruses (70.5%)
  - Of viruses, there are 4 main agents: **norovirus** (47%), **astrovirus** (5%), **adenovirus** (9%), **rotavirus** (39%)
- Morphology of viruses
  - DNA viruses
    - Enveloped – pox, herpes, hepatitis B
    - Naked capsid viruses – **adenovirus**, parvovirus-single strand
  - RNA viruses
    - +ve RNA strand: naked (**norovirus**, sapovirus, **astrovirus**), enveloped (rubella, SARS)
    - -ve RNA strand: enveloped (rabies, influenza)
    - +ve and –ve RNA: double capsid (**rotavirus**)
    - +ve RNA via DNA: enveloped (retrovirus: HIV)

Naked capsid viruses

- Environmentally stable, resistant to:
  - Acid, temperature, proteases, detergents, dessication
- Consequences of this:
  - Easily spread
  - Retains infectivity after drying
  - Resistant to detergents, and sewage treatment
  - **Survives in the gut**
  - Induces an immune response

Rotavirus (looks like a rotor)

- Vaccine available
- Properties:
  - 80-100nm diameter
  - 3 layers of protein
  - Enclosed double-stranded RNA genome
  - Incubation period 2-3 days
- Symptoms:
  - Severe dehydrating diarrhoea in infants and young children, otherwise moderate dehydration
  - Fever, vomiting, diarrhoea
    - Fever and vomiting generally decrease in 24-48 hours
- Detection
  - EIA (enzyme immunosorbent assay)
  - Latex agglutination
  - Samples are often not taken, because you get better without treatment and thus it's not worth finding out the cause + unpleasant taking stool sample
- Epidemiology
  - Peak at 1 year
  - More common in winter months

Adenovirus

- Properties
  - Double-stranded DNA genome with 30kbp
    - Many serotypes: 47, only 2 cause gastroenteritis (40 and 41)
  - May enter via respiratory tract or alimentary tract and cause gastroenteritis
- Epidemiology
  - Causes diarrhoea in infants throughout the world
    - Causes 2-3% of infant diarrhoeal disease in developing world
  - 90% of symptomatic disease occurs in <2 year olds
- Comparison vs rotavirus:
  - Rotavirus commonly causes fever, adenovirus less commonly
  - Rotavirus has a shorter duration: 5-7 days, adenovirus: 10-14 days

Astrovirus

- Properties:
  - Small round virus
  - Single stranded RNA genome
  - 8 human serotypes exist
- Epidemiology
  - Common in infants and young children
    - 3rd or 4th commonest infection in children
  - More common in cooler months – survives longer outside the body in cold weather
  - Outbreaks have occurred in nosocomial, day care facilities, military recruits, elderly
  - Immuno-deficient individuals at risk

Norovirus

- Began in Norwalk, Ohio
- Properties:
  - Non-enveloped ssRNA virus
  - 27-35 nm in size
  - Infectious dose is 10-100 virus particles – highly contagious
  - Drifts/mutates and thus there is limited immunity
- Highly contagious:
  - Multiple modes of transmission – vomit, diarrhoea
  - Stable in the environment and resistant to normal disinfection methods
  - Can be asymptomatic

Norovirus: continued

- Symptoms – often last for 2 days, (0-3 days)
    - Vomiting
    - Diarrhoea
    - Nausea, abdominal cramps
    - Headache, muscle aches, fever
    - Dehydration
    - Up to 30% can be asymptomatic
- Transmission
    - Methods:
        - Faecal-oral: water, food
        - Person to person
        - Eg: hotel restaurant: vomit at table, 25% 4 tables away got sick, 90% at table
    - Food at risk
        - Shellfish (oysters, clams, mussels) – filter water and concentrate virus
        - Ready to eat foods that require handling but are not cooked
            - Eg: salads, sandwiches, fruit, finger foods, dips, communal foods
    - Places at risk:
        - Cruise ships, nursing homes, childcare centres, hotels
- Detection:
    - Reverse transcriptase polymerase chain reaction (RT-PCR) of stool
        - Thus, sequencing of genotype and strain identity
    - Direct electro-microscopy of stool samples
    - Enzyme immunosorbent assays (EIA)
- Infection control
    - Isolation
    - Emphasis on hygiene and PPE: eg. masks
    - Education, advice to relatives
    - Terminal clean room/ward
    - Maybe stop admissions to A and E for 24 hours
- Genome
    - 3 parts: capsid, structural protein, protease, RNA polymerase, helicase
    - 5 genogroups: group II is the most common in human outbreaks
- Historical outbreaks
    - US 95/96 strain (1997-2000)
    - Farmington Hills virus - 2002
    - Hunter out break – 2004
    - 2006a outbreak – 2006
    - 2006b outbreak – 2007
    - Since then, a network has been set up throughout Australia to track norovirus
- Treatment
    - Disease is self-limiting
    - In children, can lead to life-threatening dehydration
    - Intervention targets hydration and nutrition

Virus trends

- Gastroenteritis common among children
    - Norovirus affects children and adults
    - Astrovirus is common in domicillary settings
- Management:
    - Oral rehydration
    - Prevention and treatment of dehydration and nutritional compromise
    - Antidysmotility drugs

Bacterial non-colonisers

- Produce toxins
- Examples:
    - Staphylococcus aureus
    - Clostridium perfringens
    - Bacillus cereus
- Illness is a result of exposure to contaminated foods
    - Short incubation time (1-6 hours)
- Symptoms: vomiting, diarrhoea
- Treatment is generally supportive

Bacterial colonisers

- Examples:
    - Salmonella, Shigella, Campylobacter, Yersina, Escherichia coli, Clostridium difficile
- Laboratory analysis:
    - Microscopy looking at: white cells, red cells, food particles, fat globules, cysts, ova and parasites
    - Culture for bacterial pathogen

Salmonella

- Properties:
    - Gram negative bacilli with flagella
    - Adaptable to different environments – found in contaminated foods (milk and meat)
    - Serotyping is important
- Non-typhoid salmonella
    - Most common form of salmonellosis
    - Incubation period of 6-48 hours
    - Symptoms – last 2-7 days
        - Nausea, vomiting, diarrhoea
- Treatment
    - Symptomatic
    - Antibiotics if systemic infection

Shigella

- Epidemiology
    - Highly contagious but does not survive well in the environment
    - Increased risk: hygiene, sexual activity, closed populations
    - More common in developing countries
- Transmission
    - Faecal oral
    - Food and water
- Species:
    - Shigella sonnei, flexneri, dysenteriae
- Properties:
    - Low infectious dose – resistant to stomach acid
    - Incubation period of 1-3 days
    - Can invade cells of the colon if there is non-motility
        - Thus can lead to an inflammatory response and blood and mucus in the stools
- Treatment:
    - Supportive care
    - Treatment is recommended for all cases since it is a public health issue – causes infection with low inoculum
        - Antibiotics: norfloxacin, ciprofloxin, ampicillin, co-trimoxazole

Campylobacter

- Commonest bacterial pathogen
  - Egs: Campylobacter jejuni, coli
- Epidemiology
  - Warm weather in temperate climates
- Transmission
  - Faecal oral transmission
    - Infected people can shed for several weeks
  - Poultry is a common source
- Properties:
  - Incubation time of 1-7 days
  - Curved gram –ve bacilli, non spore forming
  - Can invade gut mucosa
  - Toxins: enterotoxin, cytotoxin
- Symptoms:
  - Fever
  - Leukocytosis
  - Abdominal cramp
  - Blood in the stool – due to mucosal invasion
- Treatment
  - Antibiotics are often unnecessary
    - Used in severe cases or in risk jobs (food handlers) – erythromycin

Bacterial trends

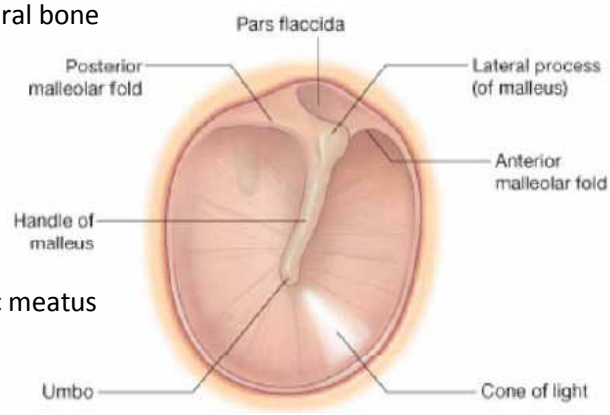
- Types:
  - Common: salmonella non-typhoid, campylobacter, shigella
  - Overseas: vibrio cholerae, vibrio parahaemolyticus, salmonella typhoid
  - Nosocomial: clostridium difficile
  - Less common: E. coli, aeromonas, plesiomonas shigelloids, yersina enterocolitica
- Treatment
  - Symptomatic unless systemic infection - then antibiotics

Parasites

- Giardia Lamblia
  - Obligate anaerobic protozoa that lives in the small intestines
  - Has two stages:
    - Trophozoite stage – causes disease
      - Binucleate with 8 flagella
      - Lives in host in this form
    - Cyst stage
      - Lives outside the host in this form
      - Can survive harsh environmental conditions
      - Transmitted faecal-oral
  - Clinical presentation:
    - Asymptomatic (carriers)
    - Intermittent diarrhoea and constipation
    - Weight loss, malaise
    - Malabsorption of fat – causes foul smelling flatulence and stools
  - Diagnosis – microscopy of stool sample, EIA, biopsy
  - Treatment – Metronidazole (Flagyl)
- Cryptosporidium
  - Oocysts are infectious
    - Complex lifecycle with sexual and asexual stages
    - Zoonotic potential
  - Water transmission important, filtration is best prevention method (resistant to disinfectant)
  - Important disease for immunocompromised, developing countries
  - Lack of effective therapy, maintenance of hydration is important

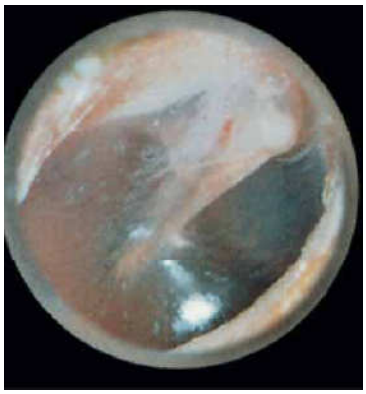
Introduction

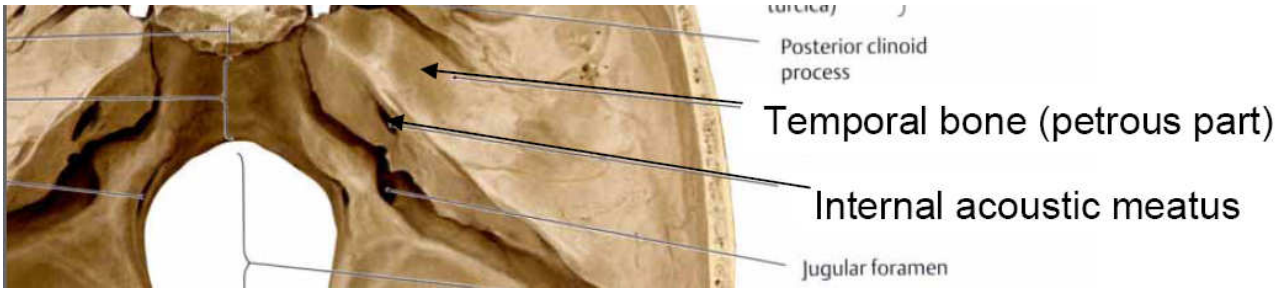
- The ear is located for the most part in the petrous part of the temporal bone
    - Has 2 functions: hearing and balance
    - Made up of 3 parts: outer, middle and inner

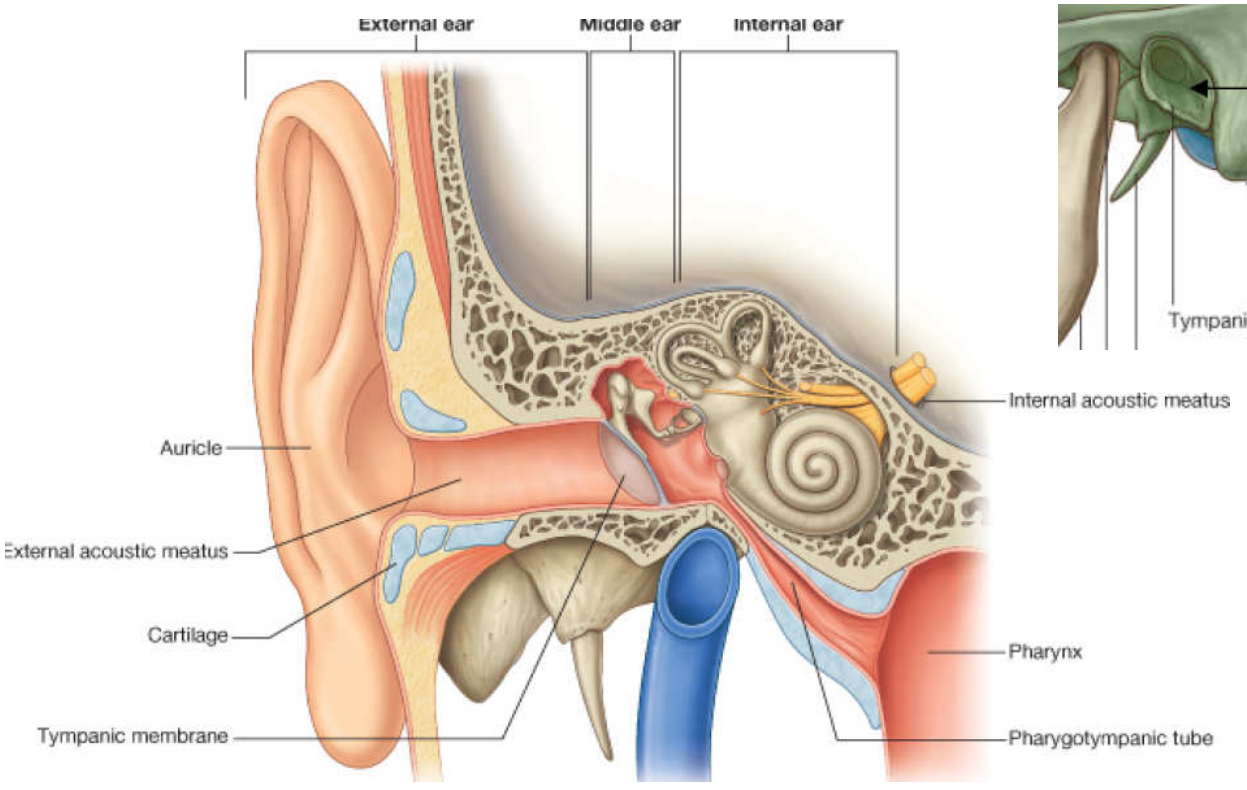


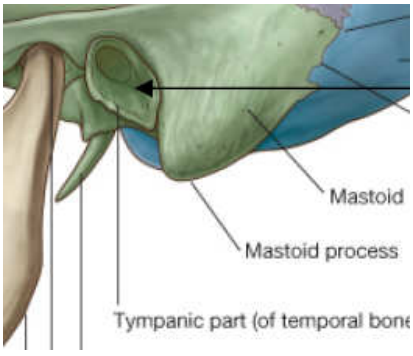
Outer (external) ear

- Auricle
    - Cartilaginous structure on the lateral head
        - Varies from person to person like a finger-print
    - Functions to channel sound waves into the external acoustic meatus
- External acoustic meatus (external auditory canal)
    - Curved tube extending from the auricle to the tympanic membrane
        - 2.5cm long
        - Directed downwards, forwards and medially
    - Outer 1/3 is cartilage, inner 2/3 formed by bone
    - Lined by hairy skin with glands
        - Glands secrete cerumen (earwax) that traps foreign objects
- Tympanic membrane (ear drum)
    - Semitransparent membrane that separates the external and middle ear
        - Outer surface (lateral) covered by skin
            - Concave appearance
        - Inner surface (medial) covered by mucous
        - Superior part is more flaccid
    - The first ossicle (malleus) attaches to the medial surface
    - Cone of light can be seen in a normal membrane in the antero-inferior quadrant via otoscope



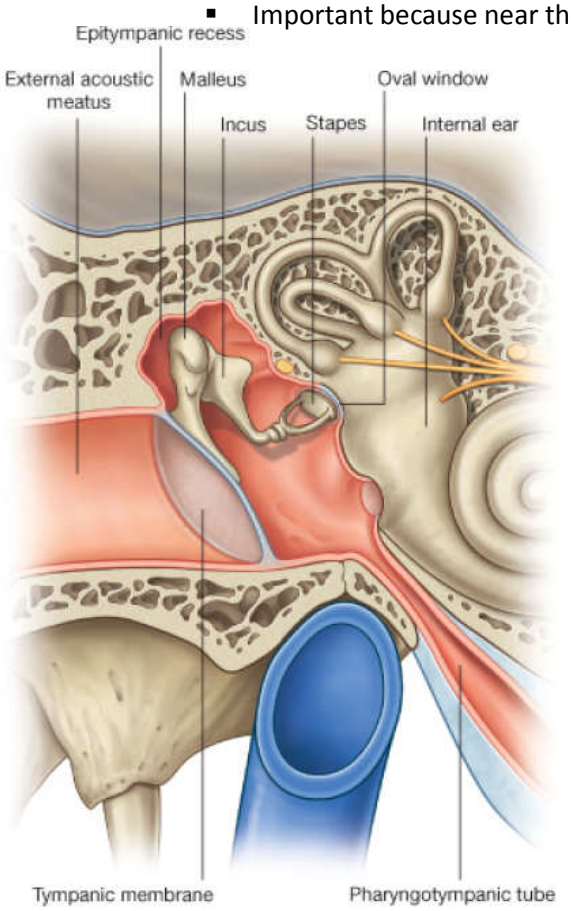


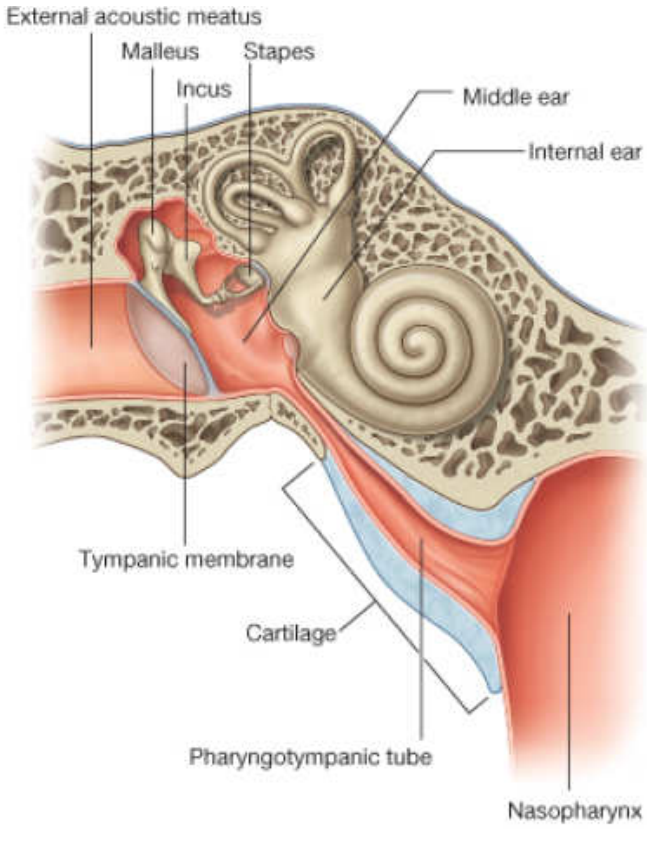




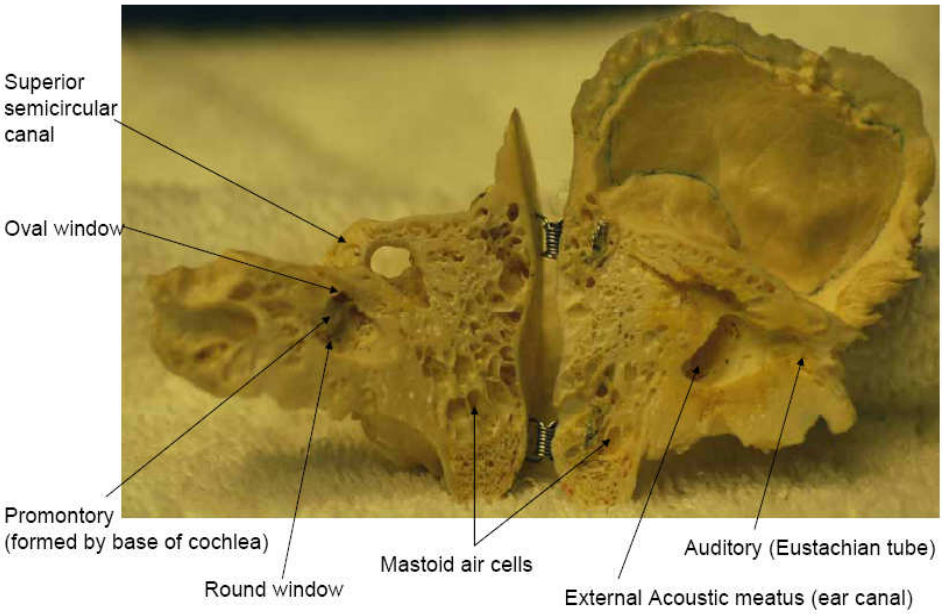
Middle ear

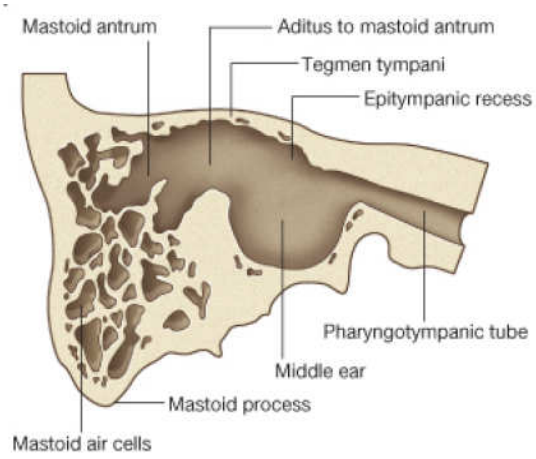
- Air-filled cavity found in the petrous part of temporal bone
    - 15mm high and 2-6mm wide
    - Lateral wall formed by the tympanic membrane
- 2 parts:
    - Epitympanic recess (above the level of the tympanic membrane)
        - Communicates with the mastoid antrum and air cells via the aditus in the posterior wall
            - Important because infection can spread from middle ear to mastoid air cells
    - Tympanic cavity proper
- Auditory tube
    - Passes forward from the anterior wall to the pharynx
    - Function:
        - Enables equalisation of pressure of middle ear with external environment (air pressure)
        - Normally closed, opens with swallow/yawn to allow air to pass (eg. popping sensation with altitude)
- Medial wall has 2 membrane covered openings that lead to the inner ear:
    - Oval window (fenestra vestibuli)
    - Round window (fenestra cochleae) – allows compensating of perilymph movement
- Ossicles are 3 tiny bones that form a chain from lateral to medial walls
    - Malleus (hammer) – attached to the internal surface of the tympanic membrane
    - Incus (anvil)
    - Stapes (stirrup) – covers the oval window
    - Articulations between these are via synovial joints
- 2 muscles prevent excessive vibrations of the ossicles and protect the tympanic membrane
    - Tensor tympani muscle – arises from a canal in the anterior wall of middle ear and attaches to malleus
    - Stapedius muscle – arises from a small pyramid of bone on the posterior wall and attaches to stapes
        - 2mm in size, controlled by the facial nerve (CNVII)
            - Damage to facial nerve can result in sensitivity to high sounds
- Other relations:
    - Internal carotid artery, internal jugular vein – inferior to middle ear cavity
    - Facial nerve
        - Arises from brainstem and enters internal acoustic meatus then facial canal
            - Facial canal passes along the medial wall of middle ear then passes inferiorly down posterior wall and leaves the skull via the stylomastoid foramen
                - Canal may be bony or membranous, needs care
        - Important because near the middle ear, it is susceptible to injury via infection or surgery

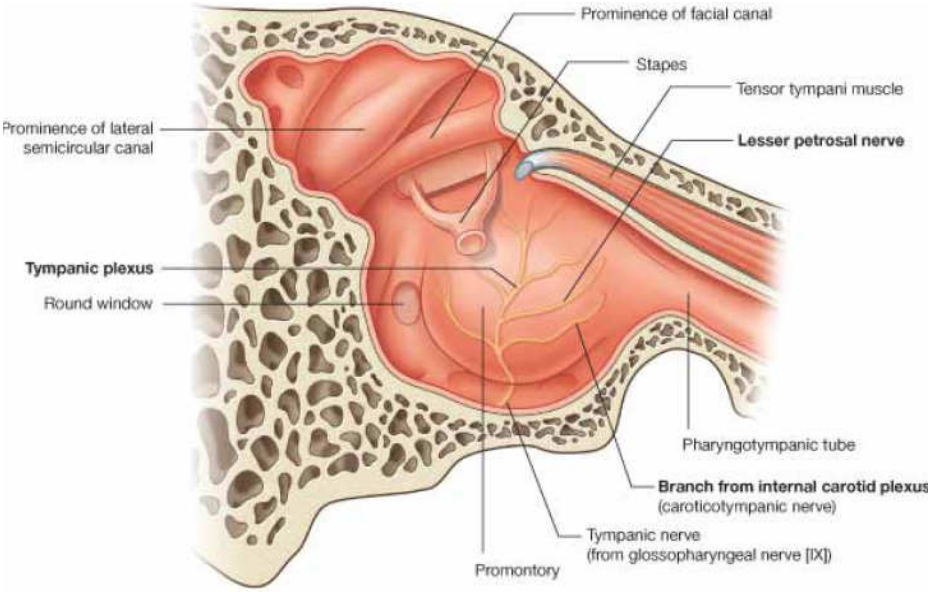




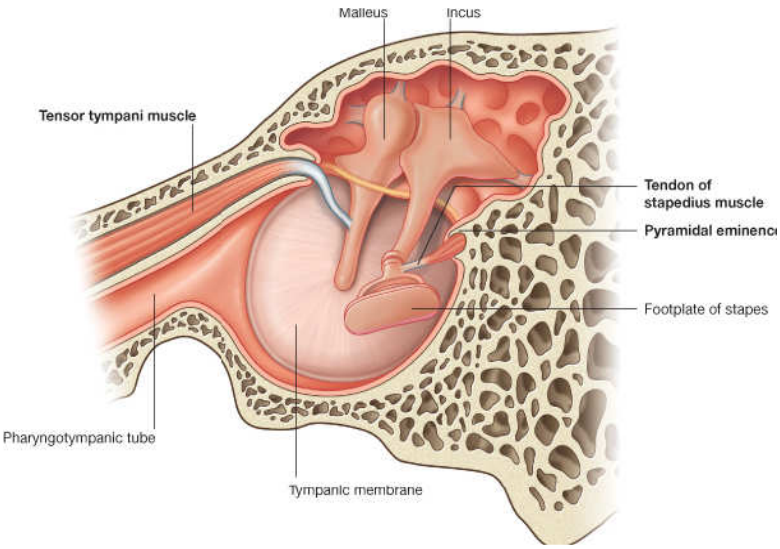
Split temporal bone showing middle ear cavity





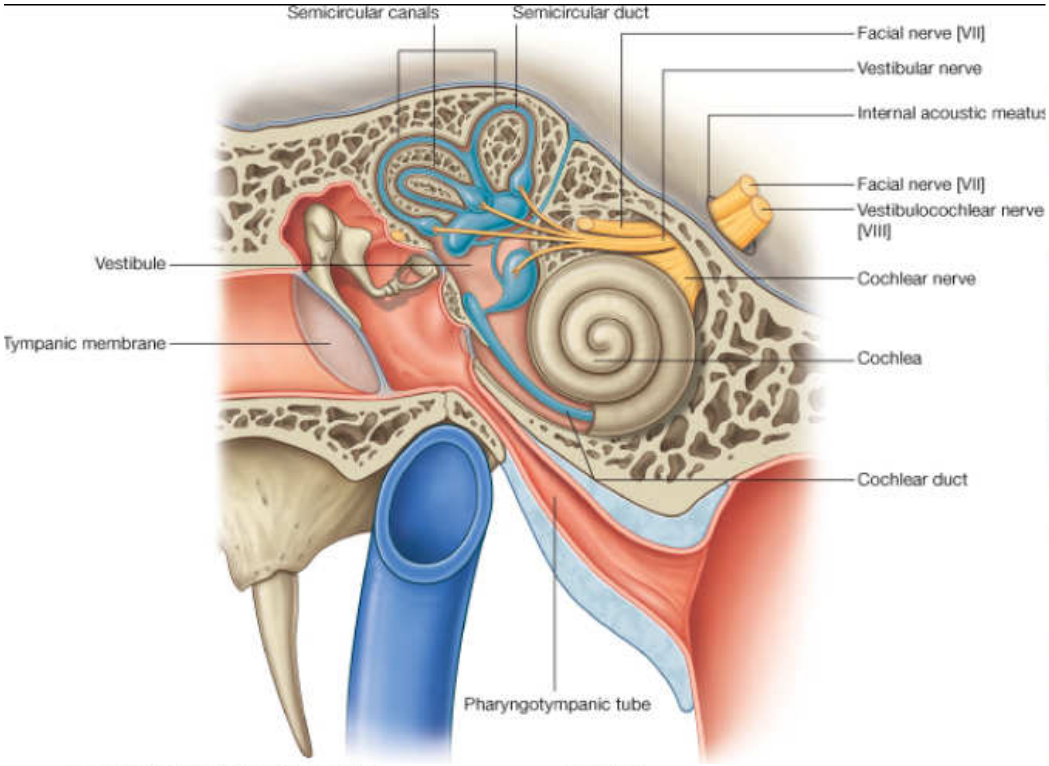


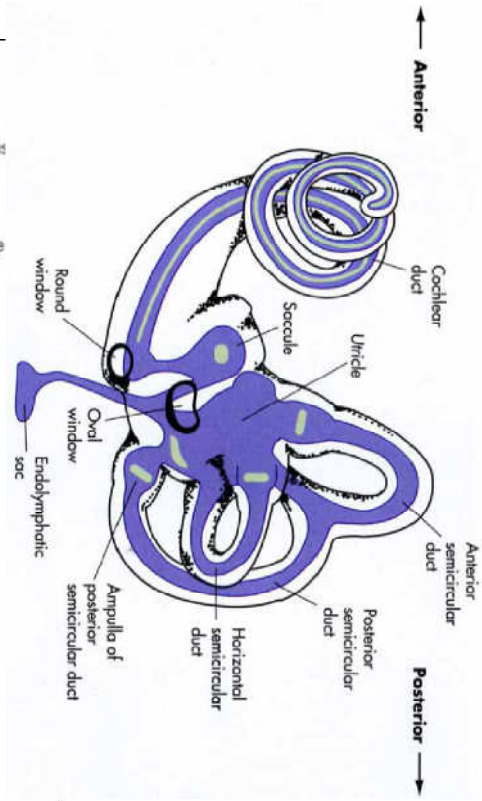
Medial wall of the middle ear

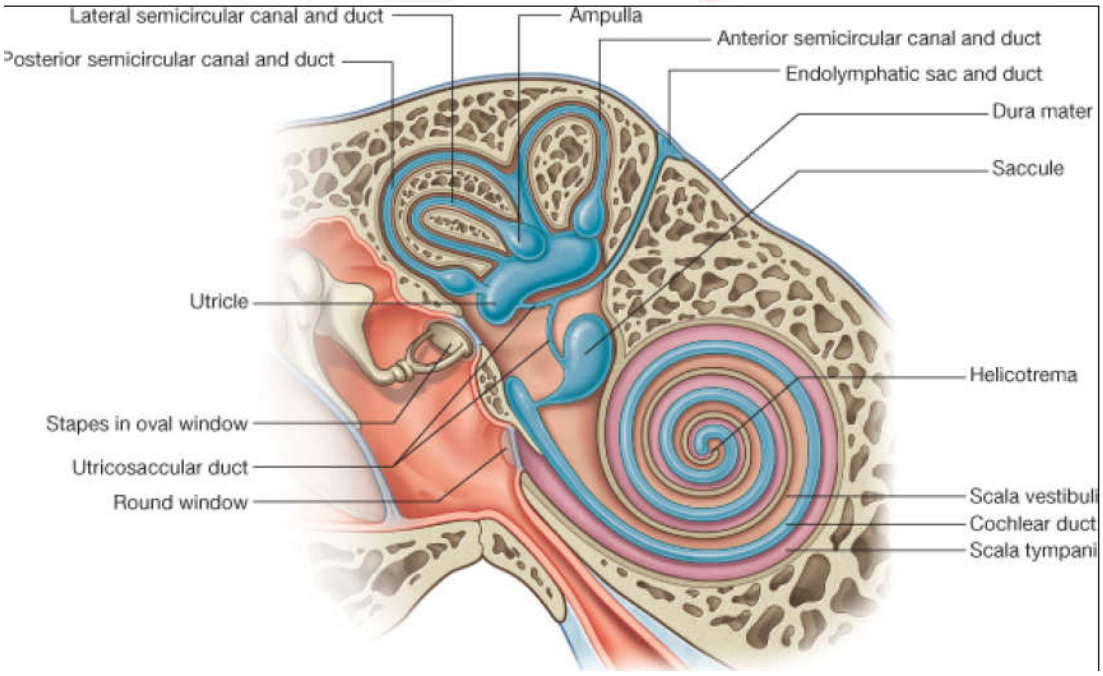


Internal (inner) ear

- Fluid-filled cavity divided into bony and membranous labyrinths
- Bony labyrinth
    - A network of interconnected spaces within the petrous temporal bone
        - Filled with perilymph – like extracellular fluid
    - 3 parts:
        - Vestibule (central), 3 semicircular canals, cochlea (spiral tube with snail shell appearance)
- Membranous labyrinth
    - Closed system of interconnected ducts that "float" inside the bony labyrinth
        - Filled with endolymph – like intracellular fluid
    - 3 parts (that directly correspond to the parts of the bony labyrinth:
        - Utricle and saccule – static labyrinth (within the vestibule)
            - Contain receptors for determining head position
        - 3 semicircular ducts (within the semicircular canals)
            - Ampulla of ducts is involved in detecting the direction of head movement and coordinating movement of the eyes with the head
        - Cochlear duct (within the cochlea)
            - Involved in hearing – see later
    - Contains specialised receptors for hearing and balance



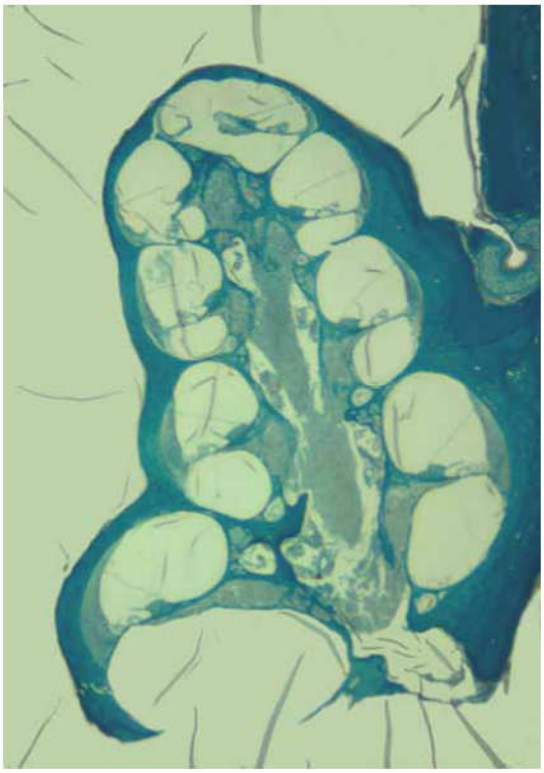


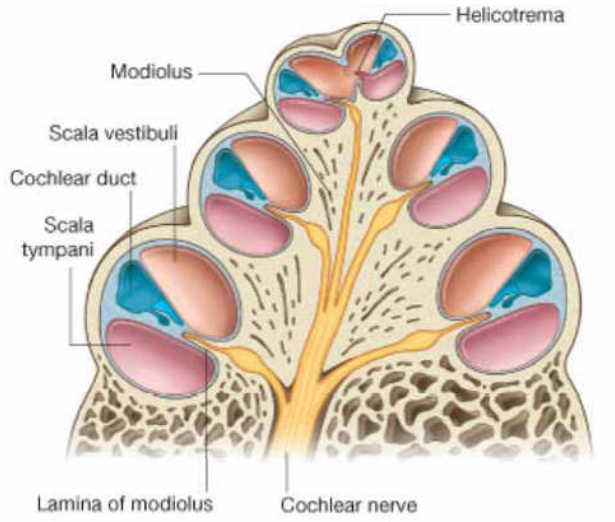


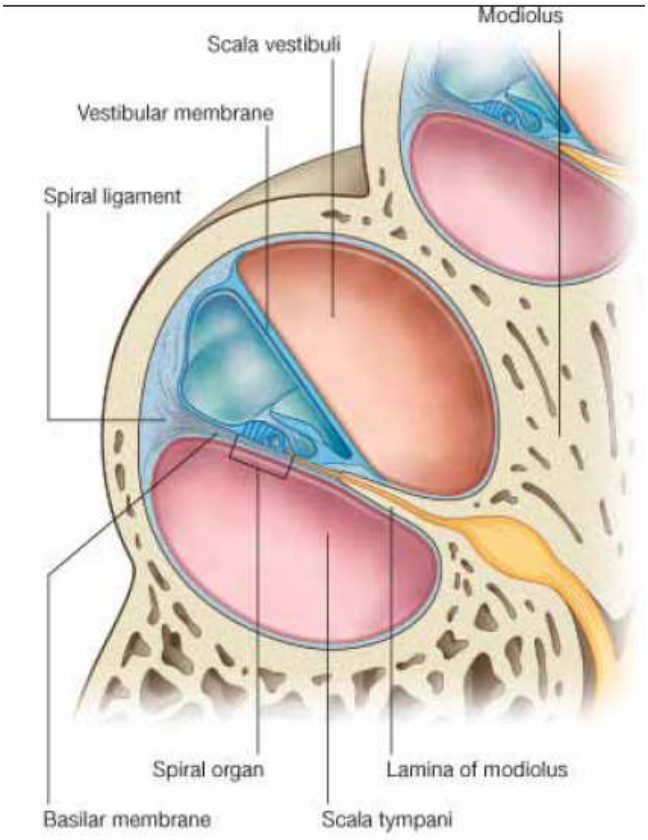
Hearing

- Receptors are located within the Cochlea
    - Structure of the cochlea:
        - A long tube that is coiled 2½ times around a central bone core – modiolus
            - Modiolus contains the cell bodies of CN VIII
    - Cross section shows 3 parts to the tube:
        - Cochlear duct, scala vestibuli and scala tympani
            - Vestibular membrane separates the scala vestibuli from the cochlear duct
            - Basilar membrane separates the scala tympani from the cochlear duct
        - Scala vestibuli and tympani communicate that the apex of the cochlea at the helicotrema
    - Stria vascularis – in the outer wall of the cochlea duct
        - Produces endolymph

The cochlear is a long tube coiled 2.5 times around a bony core (the modiolus)

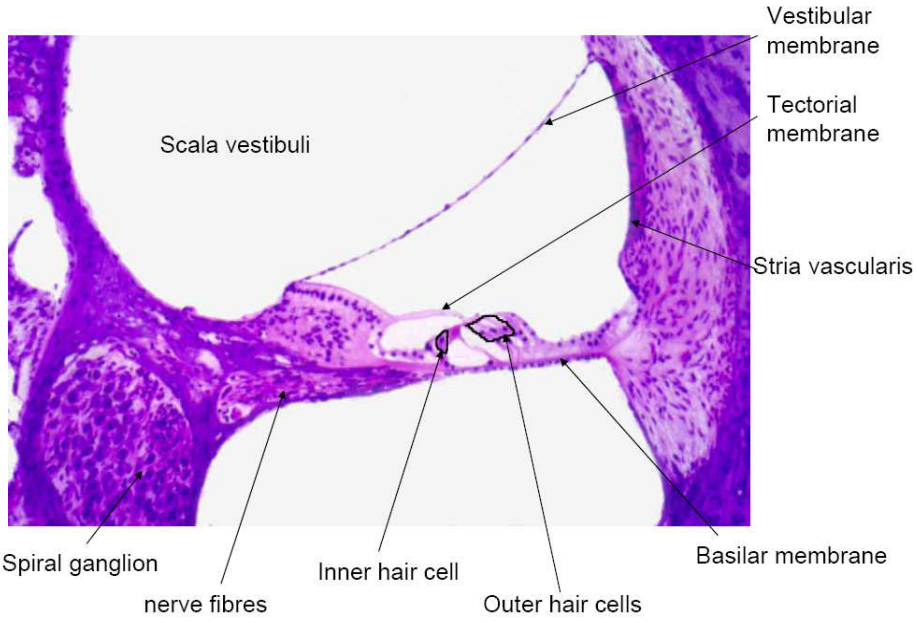


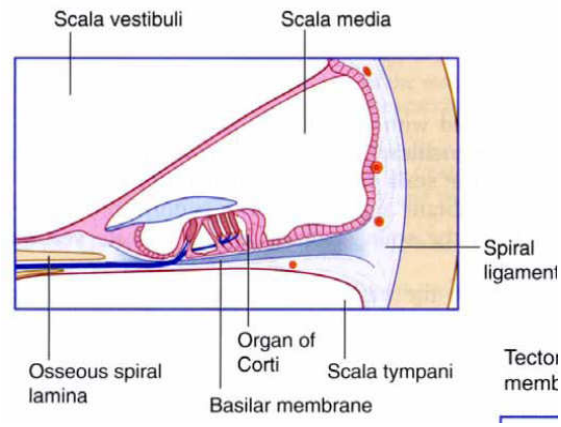


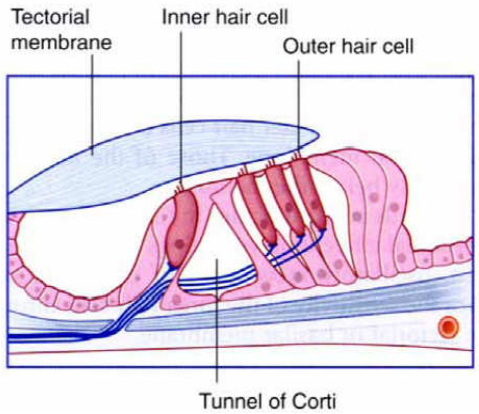


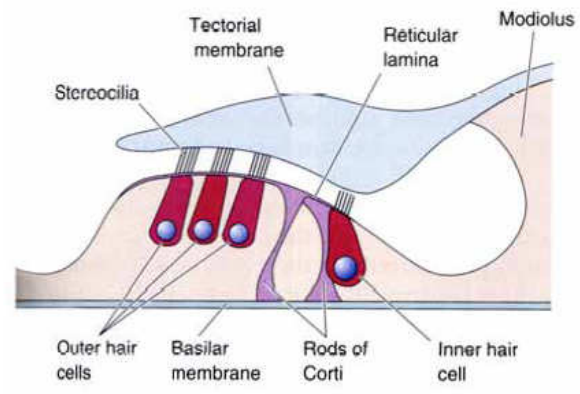
(Spiral) Organ of Corti

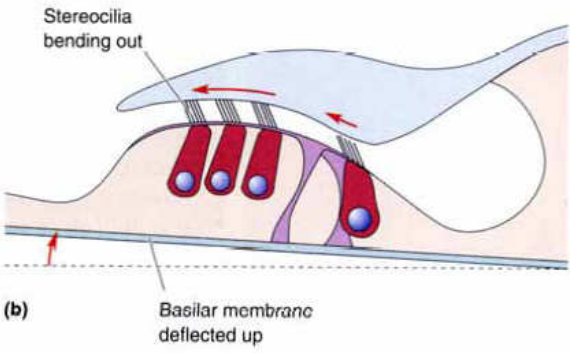
- Auditory receptor organ found within the cochlear duct
- Sits on the basilar membrane and is made up of:
    - Supporting cells
    - Tectorial membrane - gelatinous
    - 2 sets of hair cells (inner and outer)
        - Specialised neurons that are activated by "bending" of stereocilia (hairs) on surface
            - Stereocilia are in contact with the tectorial membrane
- 2 types of hair cells:
    - Inner hair cells
        - ~3500 cells in a single row in each ear – extend along the basilar membrane
        - Stereocilia not embedded in tectorial membrane
        - Provide 95% of input to auditory nerve (ie. 1 inner hair cell → auditory nerve fibre)
            - Allow differentiation of frequency and intensity of sound
    - Outer hair cells
        - ~15-20 000 cells in 3-5 rows in each ear
        - Stereocilia embedded in tectorial membrane
        - Provide 5% of input to auditory nerve
        - Can change length and influence the orientation of tectorial membrane and thus sensitivity of inner hair cells
            - Shorten: cause increased bending of hair cells and thus magnify input to cochlear nerve
                - Cochlear amplifier effect
        - Damage to outer hair cells can result in hearing loss





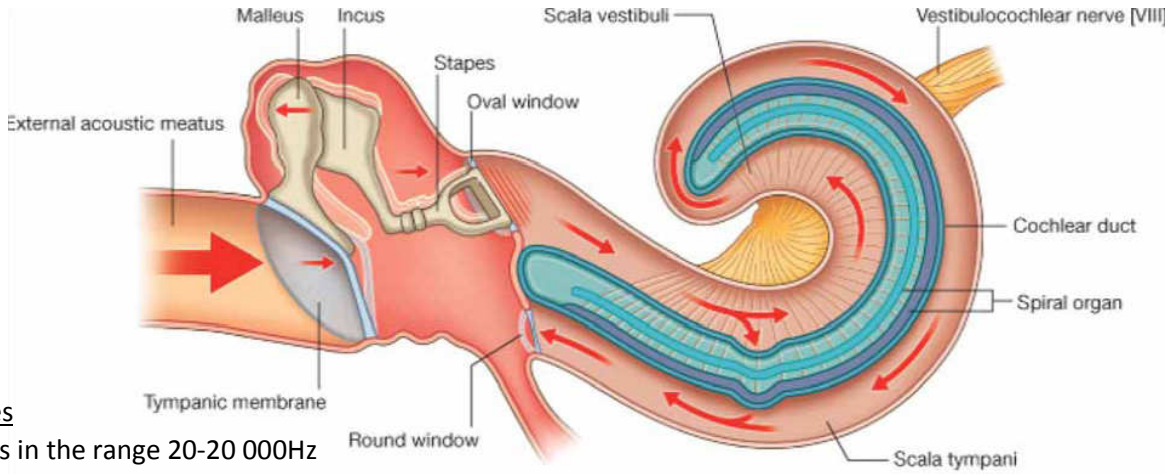






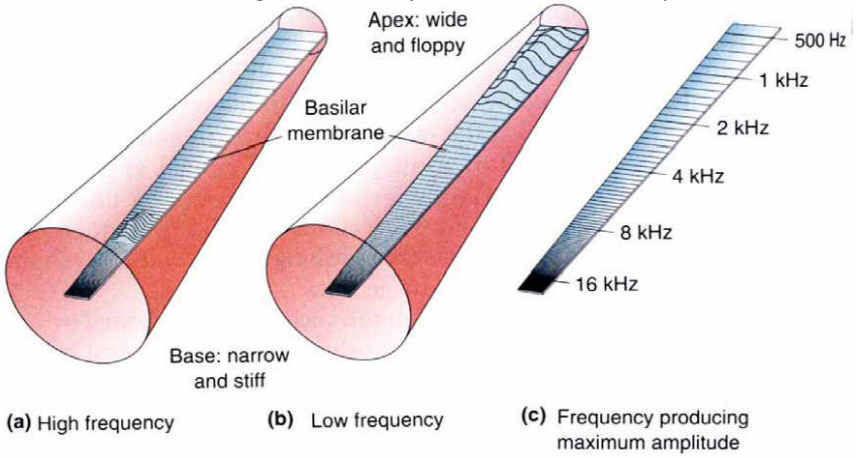
Mechanism of sound transduction

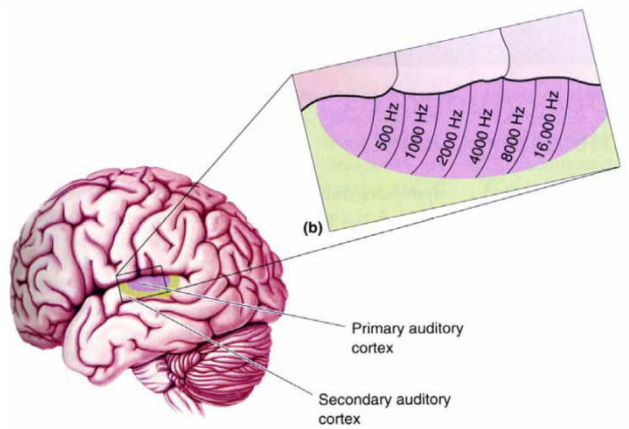
- Sound waves are directed by auricle into the external acoustic meatus
    - Tympanic membrane vibrates and resulting movement causes malleus to vibrate
    - In turn, incus and stapes vibrate
        - Ossicles form a lever system that amplifies the sound waves by 20x
        - Vibration of the stapes causes movement of the attached oval window thereby moving the perilymph in the scala vestibuli
            - This movement is transferred across into the cochlear duct and moves the basilar membrane
                - Thus, hair cells are bent and activate fibres of the cochlear part of CNVIII
                - CNVIII transmits information to brainstem → thalamus → primary auditory cortex
                    - Primary auditory cortex is located on the transverse temporal gyri
                    - Thus sound is perceived and interpreted

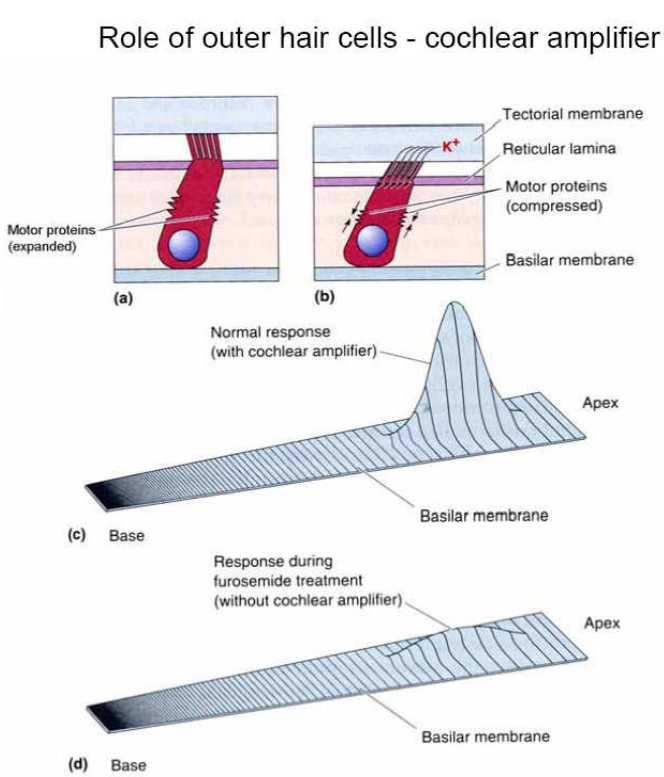


Distinguishing frequencies

- We can detect sounds in the range 20-20 000Hz
- Properties of the basilar membrane changes progressively along length – tuned for different frequencies
    - Base – cochlear is narrow and tight
    - Apex – wide and loose (500um)
    - Thus, high frequencies cause vibration at the base, and low frequencies at the apex
- Auditory nerve fibres that arise from different parts of the basilar membrane have tonotopic organisation
    - Thus, maintenance of this map to the auditory cortex allows mapping of frequencies
        - Ie: low frequencies anterior and high frequencies posterior
- Auditory cortex receives input from both ears
    - Damage to auditory cortex in one hemisphere doesn't result in significant hearing loss







The importance of hearing

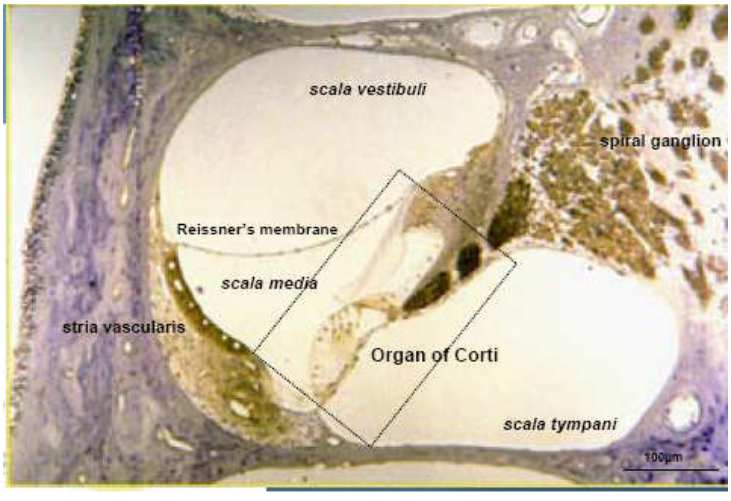
- Allows information transfer and coordinated action
    - Can motivate, inspire, eg: the Haka

Properties of hearing

- Sound localisation
    - We can locate sounds (see later also)
    - External ear channels sound into the external acoustic meatus and also aids this
        - Eg: bats
- Pitch range
    - Approximately 10 octaves from 20Hz to 20 00 Hz
        - Best range is between 500Hz (vowels) and 4000Hz (consonants)
- Pitch discrimination
    - We can distinguish between two frequencies of 0.2% apart (eg: 1000 and 1002Hz, a semitone is 6%)
        - 0.2% is equivalent to differentiating between 1 or 2 sensory hair cells
        - This is due to frequency mapping in the auditory cortex and cochlear
- Timing discrimination
    - We can hear sounds separated by 1/100 000th of a second, ie 10µs

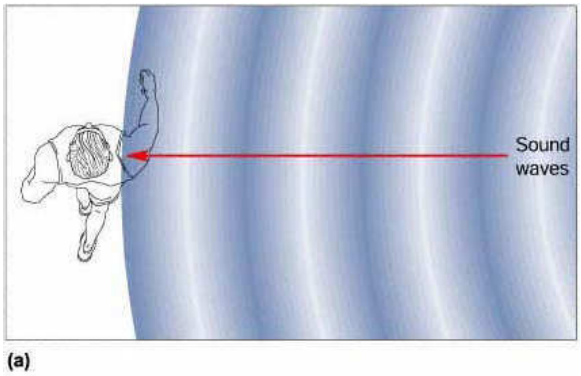
Sound transduction – forward and reverse

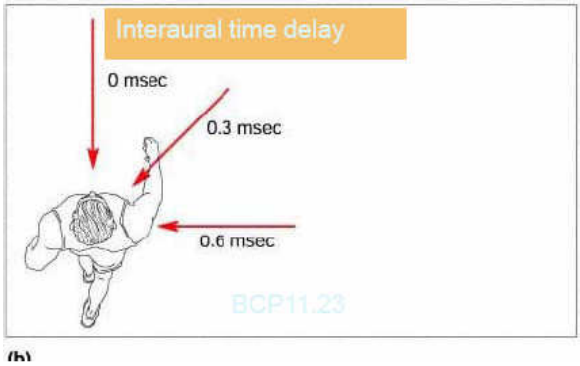
- Basilar membrane is moved by the fluid movement caused by the transduction of the sound through the middle ear
    - This causes stereocilia of inner hair cells (primary hearing cells) to bend
        - The tips of the stereocilia are attached to ion channels and with movement, the channels open/close
            - Ie: mechanoelectrical transduction
        - Endolymph is high in K^+ and has a resting potential of 100mV
            - Inside the hair cell, there is a resting potential of -70mV
            - Thus, with opening of ion channels, K^+ influx causes depolarisation and action potential
- From here the message is passed via sensory nerves to the auditory cortex
    - Each of the ~5000 inner hair cells has unique innervation from ~15-20 sensory nerves
- Outer hair cells (only mammals have)
    - Create reverse transduction (cochlear amplification)
    - Contain the protein prestin that undergoes conformational changes depending on the membrane potential
        - Fastest known form of biological motility
        - Thus, when the membrane potential changes with moving stereocilia, prestin changes and puts energy back into the cochlea by oscillating at the frequency of the incoming sound
            - Thereby it facilitates a wider range of hearing and better frequency discrimination
    - Can be demonstrated using otoacoustic emissions
        - If there is dysregulation of the cochlear amplifier, the ear can put out sound in response to hearing
        - Otoacoustic emissions are used to detect normal hearing function in babies and is evidence for reverse transduction

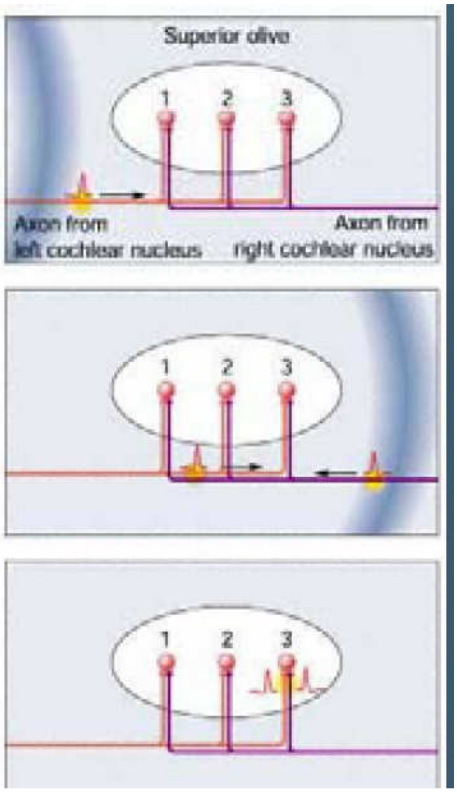


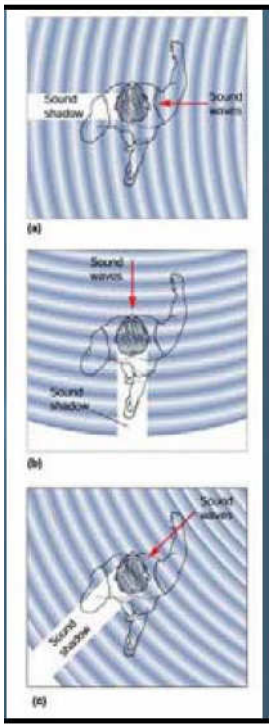
Auditory pathways

- Brain can learn to decode – remember demonstration
- Pathway:
    - Spiral ganglion → auditory nerve → ventral cochlear nuclei → Superior olive → lateral meniscus to midbrain/inferior colliculus → medial geniculate nucleus of the thalamus → auditory cortex in the transverse temporal gyri
- Sound localisation
    - Sound pathways from left and right ears unite in the superior olive
        - Thus, using interaural time delay, brain discriminates the location of the sound (works best <2kHz)
    - On a cellular level:
        - Sound from the left side activates activity first, then sound from right ear activates activity from the other direction
            - Thus, where they meet (eg. 3rd neuron) their summed depolarisations cause action potential
    - For higher frequencies, the interaural difference is not as great, but using the shadow the head, the same effect can work



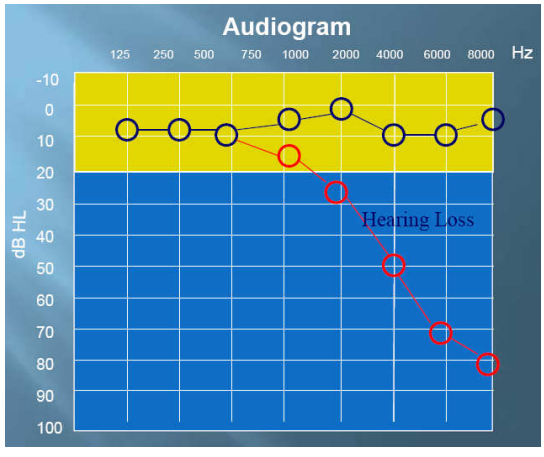






Losing our hearing

- Symptoms
    - Can't follow conversations in noisy environments
    - Think that people aren't speaking clearly
    - Have to ask people to repeat themselves (especially women and children: lose high frequency hearing first)
    - It help if people face you when speaking
    - Music sounds less clear and enjoyable
    - Other people tell you that you have the TV and radio up too loud
    - Can't work out where a sound is coming from
- Audiogram
    - Measures how good our hearing is
        - Not a straight line, we can hear better at different frequencies (best: 1-4kHz)



Losing our hearing (continued)

- Causes of hearing loss
  - Ear disease
    - Congenital, hereditary factors
      - Connexion 26 – GJB2: important pipeline protein for ion homeostasis in cochlea
    - Infections (glue ear) – otitis media
      - Conduction loss and sound becomes muffled
        - Can lead to infection of the inner ear
      - Strongly related to living conditions → higher prevalence in Aborigines
    - Fluid imbalance in the inner ear
      - Menieres disease – also affects vestibular system
    - Ageing (presbycusis)
      - Approx 60% of causes
    - Noise exposure ~30%
      - Accumulated exposure to high energy sounds thought to cause hearing loss
      - Problem because we very easily adapt: if high external noise, don't notice how loud music is
    - Ototoxic drugs
      - Eg: aminoglycoside antibiotics
  - Developmental and acquired disease of the central auditory pathways
- Epidemiology
  - WHO ranks adult-onset hearing loss as 15th most significant element of burden of disease
    - >7% of Australian population affected by debilitating hearing impairment
  - Most prevalent forms are noise-induced hearing loss (NIHL) and presbycusis
    - ¾ >70
  - 3/1000 children born with mild-profound deafness
  - Financial cost is 11.75 billion, 1.4% GDP 2005
    - ~half affected were working age (15-64) and many could not work because of deafness
  - Demographics:
    - Males higher than females at younger age: traditionally exposed to noisier environments
    - Possibly, hormonal effects become more important in later age
  - Indigenous people
    - High prevalence of chronic suppurative otitis media (CSOM)
      - Regarded as a disease of poverty
      - Can have a life long impact with delays in speech and language development
      - In class at school, approximately half the students can't hear properly due to middle ear infections
- Hearing problems can have a profound effect and delay intellectual development
  - <3 years, the auditory centre is very plastic and if there is conductive blockage, this can delay understanding and learning
  - May need speech therapy if hearing is impaired at this time
- Treatments
  - Reduce noise exposure
  - Improve rehabilitation from hearing loss
    - Improve development of hearing aids and cochlear implants
  - Hair cell transplantation or replacement – gene therapy
  - Supporting cochlear homeostasis and auditory neural plasticity

Cochlear implant

- Microphone picks up sound from environment
- Speech processor filter sound
- Transmitter transmits processed sound to internal device by electromagnetic induction
- Receiver and stimulator (electrodes in cochlea) converts signal to electrical impulses to directly stimulate the auditory nerves

Definitions
- Allergen – normally harmless environmental substance that induces an allergic immune response
    - Ie: an immune response where the IgE antibody is prominent
    - Allergens are a subclass of antigens
- Allergy, allergic reaction, type 1 hypersensitivity reaction – an inappropriate immune response to an allergen
    - Normally includes the IgE antibody
- Atopic individual – a person who makes an allergic reaction to one or more allergens
    - This person has atopy or is atopic
- Allergic disease – a clinical condition caused by allergy

Epidemiology
- 40% of Australians are atopic
- >20% of Australians have an allergic disease
    - Allergic disease is determined by many factors including IgE
    - 10% of Australians have asthma
        - 15% of children have asthma (2x since the 1970s)
- Allergic disease causes a huge burden in time loss from school, work and cost of medication
    - Also: visits to doctors, and emergency
- Death burden is not as severe as chronic diseases, but still significant
    - >300 deaths in Australia/year due to asthma, >10/year from anaphylaxis

Allergic diseases
- Types:
    - Allergic asthma
    - Allergic rhinitis (hay fever)
    - Allergic conjunctivitis
    - Atopic dermatitis (atopic eczema)
    - Allergic urticaria/angioedema
    - Food allergy (urticaria and/or vomiting)
    - Eosinophilic oesophagitis
    - Anaphylaxis
- Definitions:
    - Urticaria (hives)
        - Weal (swelling of skin by oedema) and flare (red skin around a weal) reactions in the dermis
    - Angioedema
        - Diffuse swelling of deeper skin and mucous membranes
    - Anaphylaxis (anaphylactic shock)
        - A response to an allergen that affects several systems
        - Typically:
            - Urticaria/angioedema
            - Hypotension and airway obstruction – life-threatening
- Note:
    - There are non-allergenic causes of these diseases
        - Eg: urticaria is most often not caused by allergens
        - Eg: occupational/intrinsic asthma
    - Diagnosis of allergic disease requires understanding of the disease process and its allergic basis
    - Many patients have more than 1 allergic disease
        - Eg: united airway disease – lower and upper airway allergic disease
            - 8/10 allergic asthmatics have allergic rhinitis
            - ¼ with allergic rhinitis have allergic asthma
    - Allergic march:
        - Infants most commonly develop atopic dermatitis and food allergies and then following in childhood, asthma and rhinitis

Allergens

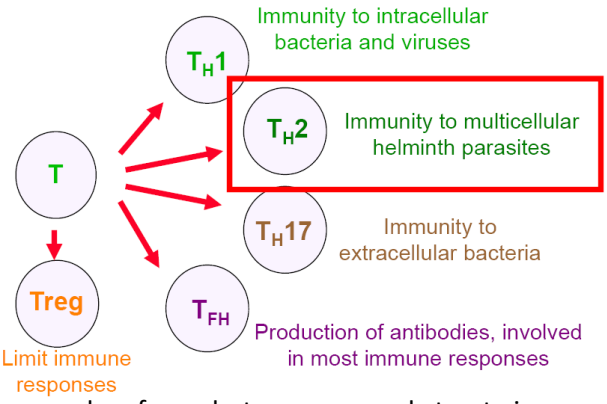
- Types:

Types	Symptoms	Examples
Inhaled	Asthma/rhinitis	House dust mite (faecal pellets) – commonest allergen associated with asthma
		Grass pollens – rhinitis
		Animal danders – skin flakes, cats: allergy is often to saliva – they lick themselves
		Moulds
Foods	GIT symptoms, urticaria, angioedema, anaphylaxis, atopic eczema	Peanuts, tree nuts
		Cows' milk
		Hens' eggs
Drugs	Anaphylaxis, urticaria, angioedema	Causes: any drug, especially antibiotics such as Penicillin, especially injected
Venom	Anaphylaxis	Bee venom
Contact	Anaphylaxis	latex – important because condoms, gloves for health professionals, gloves on surgeons in body of allergic person

- Properties:
  - Proteins
    - Immune system responds to them as if they were microbial proteins
  - Can be drugs (small molecules) – which are not proteins
    - Work by binding to and altering body proteins which are then treated like foreign proteins
  - Inhaled allergens often have enzyme activity
    - Digest tissue and thus increase access to mucosal cells (eg. in the airway)
  - Best treatment is reduction of exposure to allergen

CD4 T cells

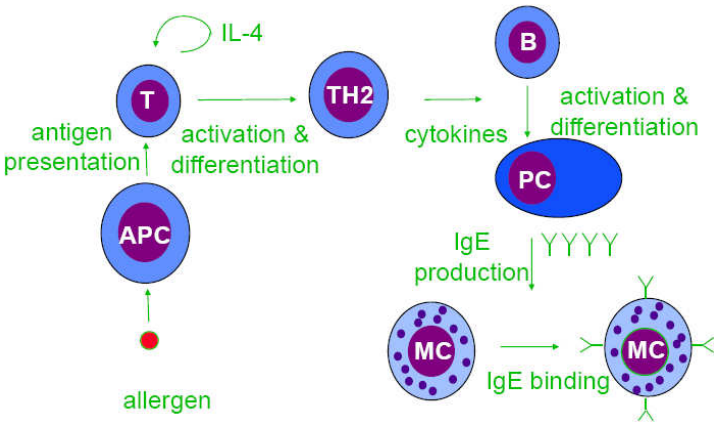
- Normal roles:



- In allergic immune responses, dealing with TH2 responses
  - Cause increase in:
    - IgE antibody production – ie definition of atopy
    - Eosinophils and basophils
    - Mast cells
    - Mucus production
      - Allows lowered adherence of allergens to mucosal surfaces, but mucus can obstruct airways
    - Smooth muscle contraction
    - All are factors in the pathogenesis of allergic disease and are characteristic of parasitic infection
  - Mediated by cytokines

Pathogenesis

- Process:
  - Allergen is taken up by an antigen presenting cell and presented to naïve T-cells
  - T-cells are activated and differentiate into TH2 cells (via IL-4, released by T-cells and other cells)
  - TH2 cells release cytokines that cause activation and differentiation of B cells into Plasma cells
  - Plasma cells produce IgE that attaches to tissue Mast cells at mucosal sites
- Reaction occurs on second exposure, after host has become sensitised and developed an immune response
  - Increased exposure increases the chance of developing specific IgE and thus an allergy



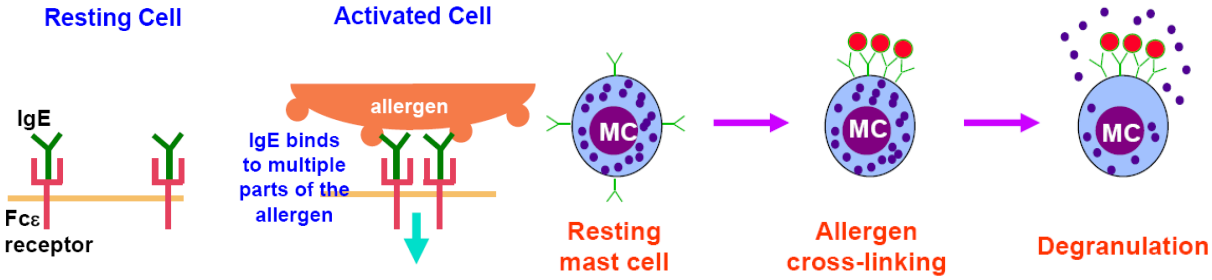
There are 2 phases to reaction

- Time course:
    - Particular diseases are defined by how prominent they are at immediate/late phase

	Immediate phase	**Late-phase reaction**
Time after allergen	Up to 30 minutes	4-24 hours
Major mediators	Histamine, granule components	Cytokines, leukotrienes, prostaglandins
Pathology	Oedema, hyperaemia	Leukocyte infiltrate, esp. eosinophils
Examples	Anaphylaxis, urticaria, angioedema	Asthma, allergic rhinitis, conjunctivitis

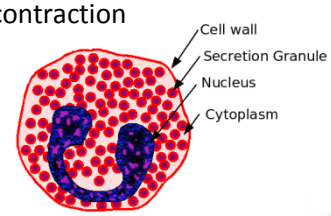
Immediate reaction

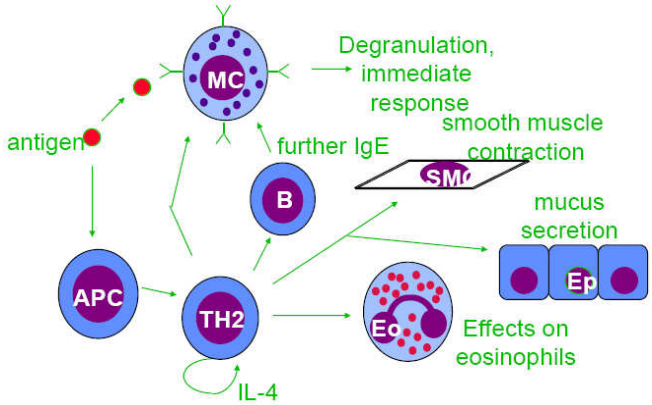
- Mast cells
    - High affinity surface receptors that bind IgE
        - Activated by allergen cross-linking of receptor-bound IgE
            - Activation causes release of granules (50% of cell) containing histamine and other mediators
            - Activation also causes synthesis of cytokines, leukotrienes and prostaglandins that contribute to late-phase reactions
        - Can be activated in other ways, eg: non-allergenic causes of urticaria



Late phase reaction

- TH2 also:
    - Activates eosinophils and stimulates their accumulation
    - Stimulates mucus secretion by epithelial cells
    - Stimulates smooth muscle contraction





- Eosinophilic inflammation
    - Cytokines (produced by T cells and mast cells) attract and activate leukocytes
        - Infiltration of leukoctyes (esp. eosiniphils) from the blood causing mucosal inflammation
            - Eosinophils may also be prominent in the blood and secretions
    - Eg: asthma: airway becomes sensitive to bronchoconstriction due to non-specific agents
        - Ie: cold, exercise, air pollution
        - Can be inhibited with glucocorticoids which is a general antiinflammatory agent

Management

- Diagnosis:
    - Establish the presence of the allergenic disease
        - Eg: diagnostic criteria for asthma
    - Determine whether patient is atopic and identify allergens using history or skin prick test
- Treatment:
    - Exclude allergens from diet and environment
    - Use drugs
        - Topical (at skin of mucous membranes) are better to minimise systemic exposure
    - Immunotherapy (desensitisation
        - Controversy about mechanism
        - Repeat administration of allergen subcutaneously or sublingual to modify immune response
            - Eg: useful in bee venom allergy or rhinitis due to pollen
    - If risk of anaphylaxis, patient should carry an epipen (adrenaline syringe)

Skin prick test

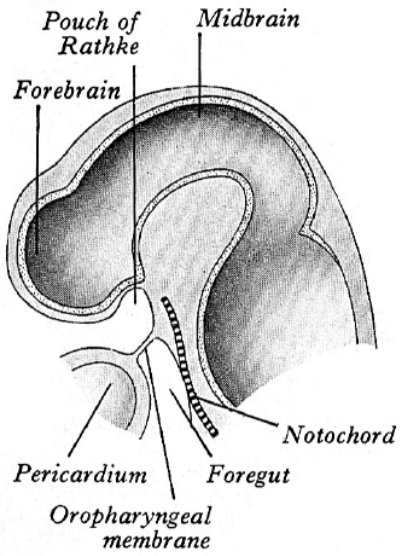
- Process:
  - Drops of allergen solution are placed on the skin
  - A needle is used to prick the skin underneath each drop to the epidermal=dermal level
    - If dermal mast cells have antigen-specific IgE, they degranulate and cause a local weal and flare
      - Diameter of weal is diagnostic
  - Needs a control sample because some people have a reaction to minor skin trauma (vs toxin)
  - Diameter of weal is measured at 20 minutes
  - Atopy is defined as a significant reaction to at least one of the common allergens
- Importance
  - Cheap, quick, sensitive
  - Patient can concurrently get counselling about allergen avoidance
- Not appropriate at certain situations:
  - Skin prick testing not available
  - Patient on antihistamines
  - Severe atopic dermatitis – not enough clear skin
  - Theoretical concern about anaphylaxis
    - Here: blood sample can be taken and specific IgE in serum measured using the RAST test
      - Eg: anti-house dust mite IgE

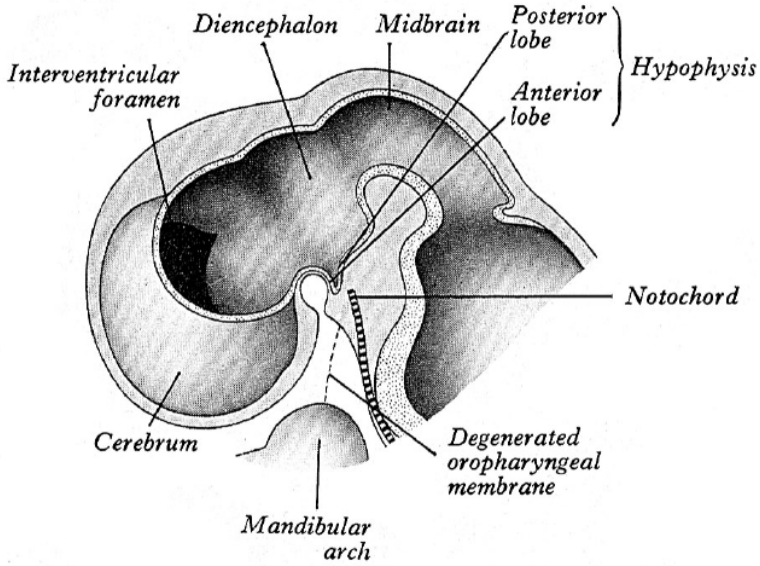
Ongoing questions

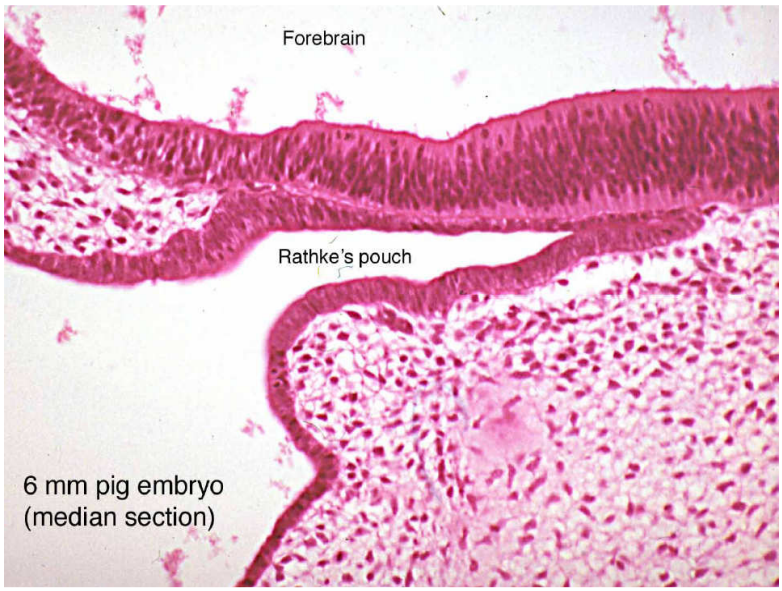
- Genes
- Environmental factors that have increased atopy in last few decades
- Prevention
- Treatment by targeting individual molecules

Embryonic development of the hypophysis

- Arises from the pouch of Rathke (ectoderm) and the diencephalon
    - Found where the roof of the buccal cavity (pouch of Rathke) meets the floor of the diencephalon
- Relations:
    - Internal carotid on either side
    - Stomodeum – primitive mouth
- Wraps around the hypothalamus
    - Produces hormones that cause generation of pituitary hormones
- Functions from the 12 week fetus







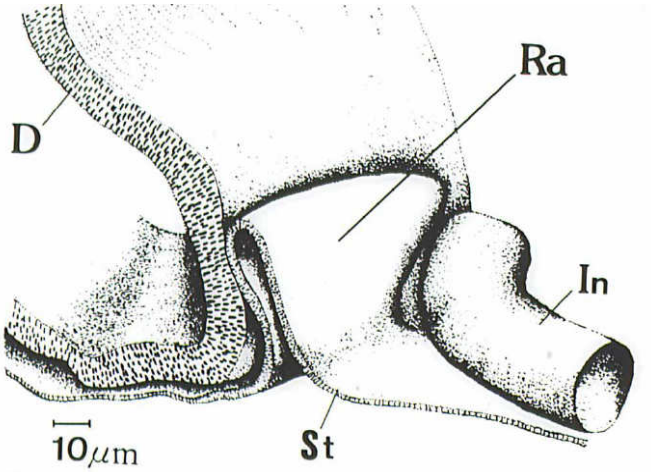
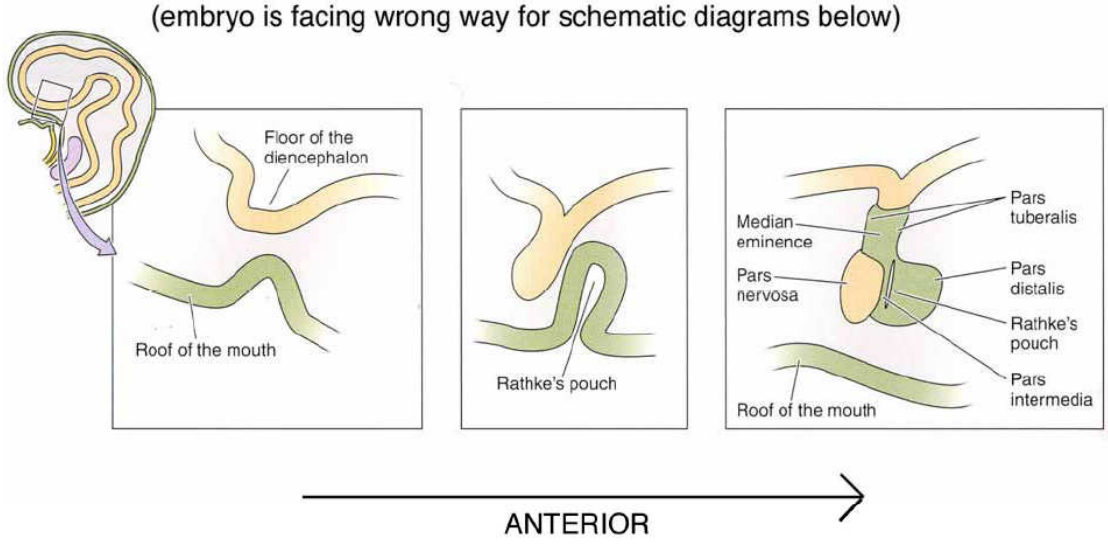


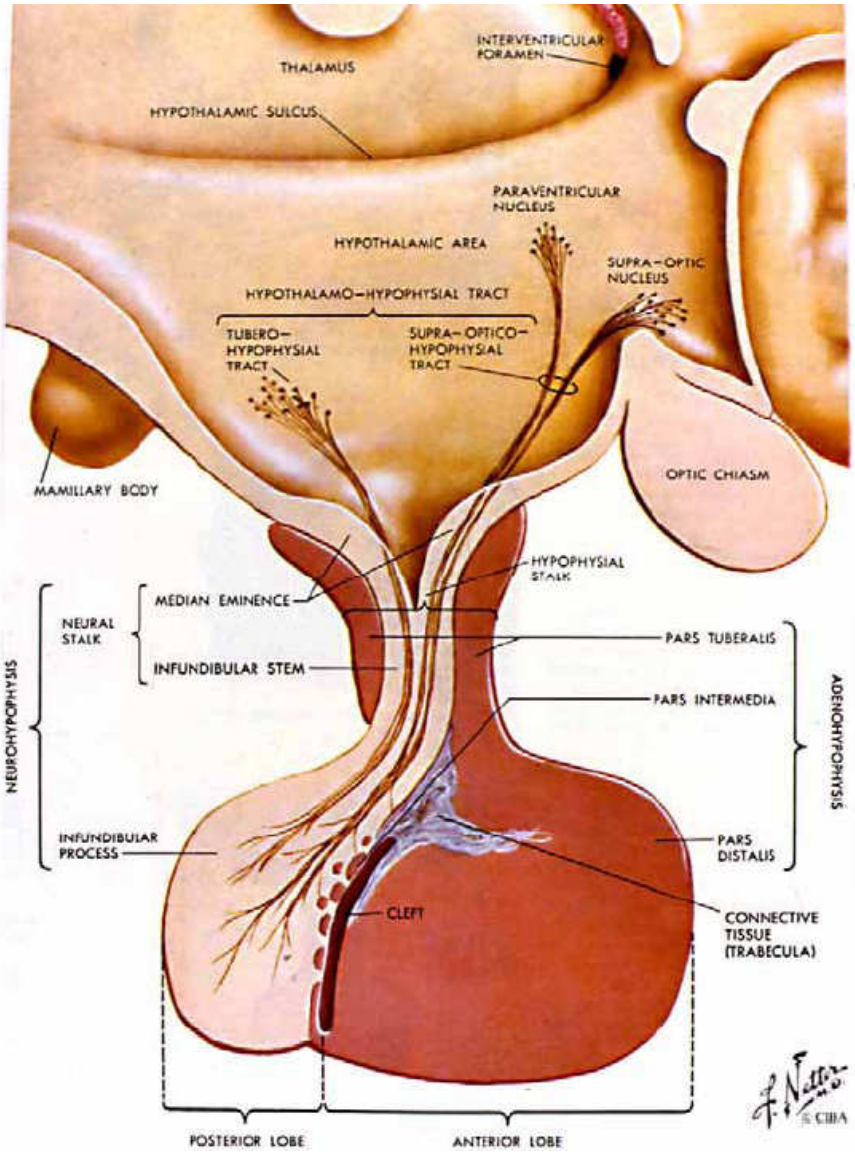
Fig. 1. Three-dimensional microstructure of a human embryo of 5 weeks gestation with a median sagittal section, viewed from the left side. Nasal end at left. *D*, diencephalon; *In*, internal carotid artery; *Ra*, Rathke's diverticulum; *st*, stomodeum

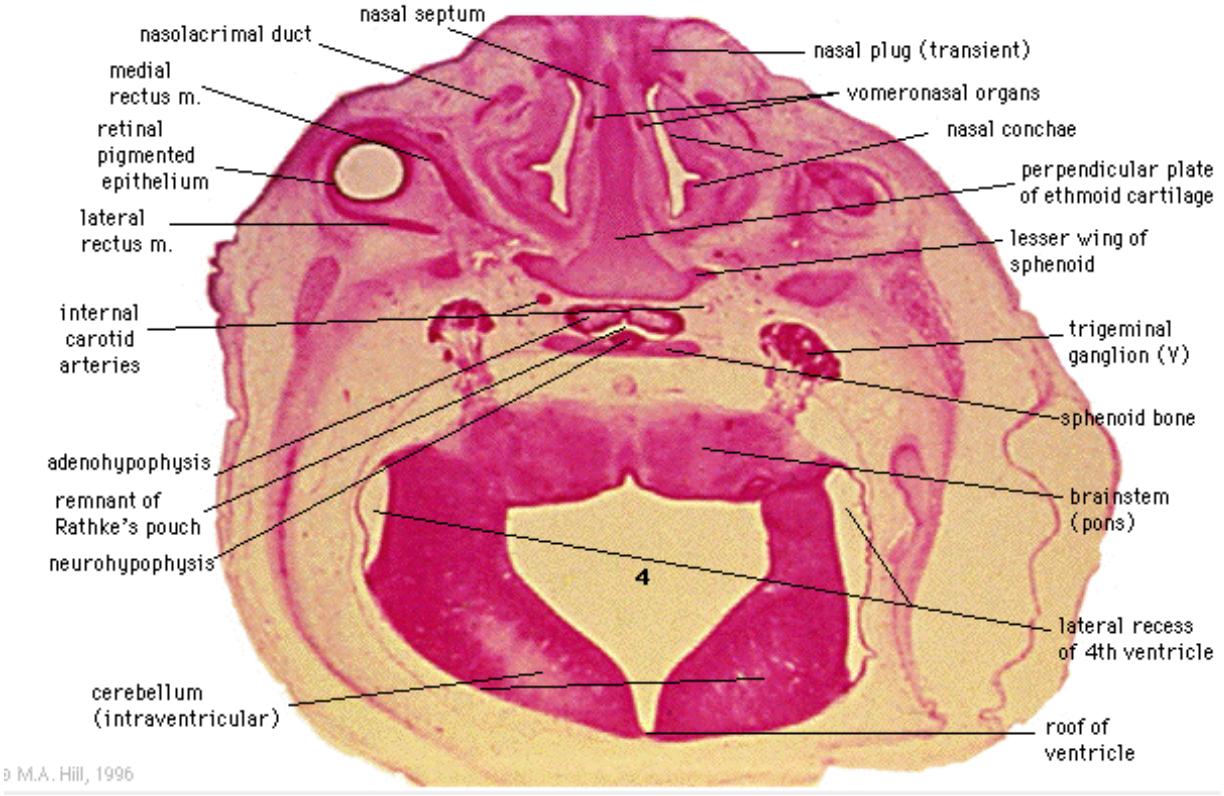
(embryo is facing wrong way for schematic diagrams below)



Anatomy

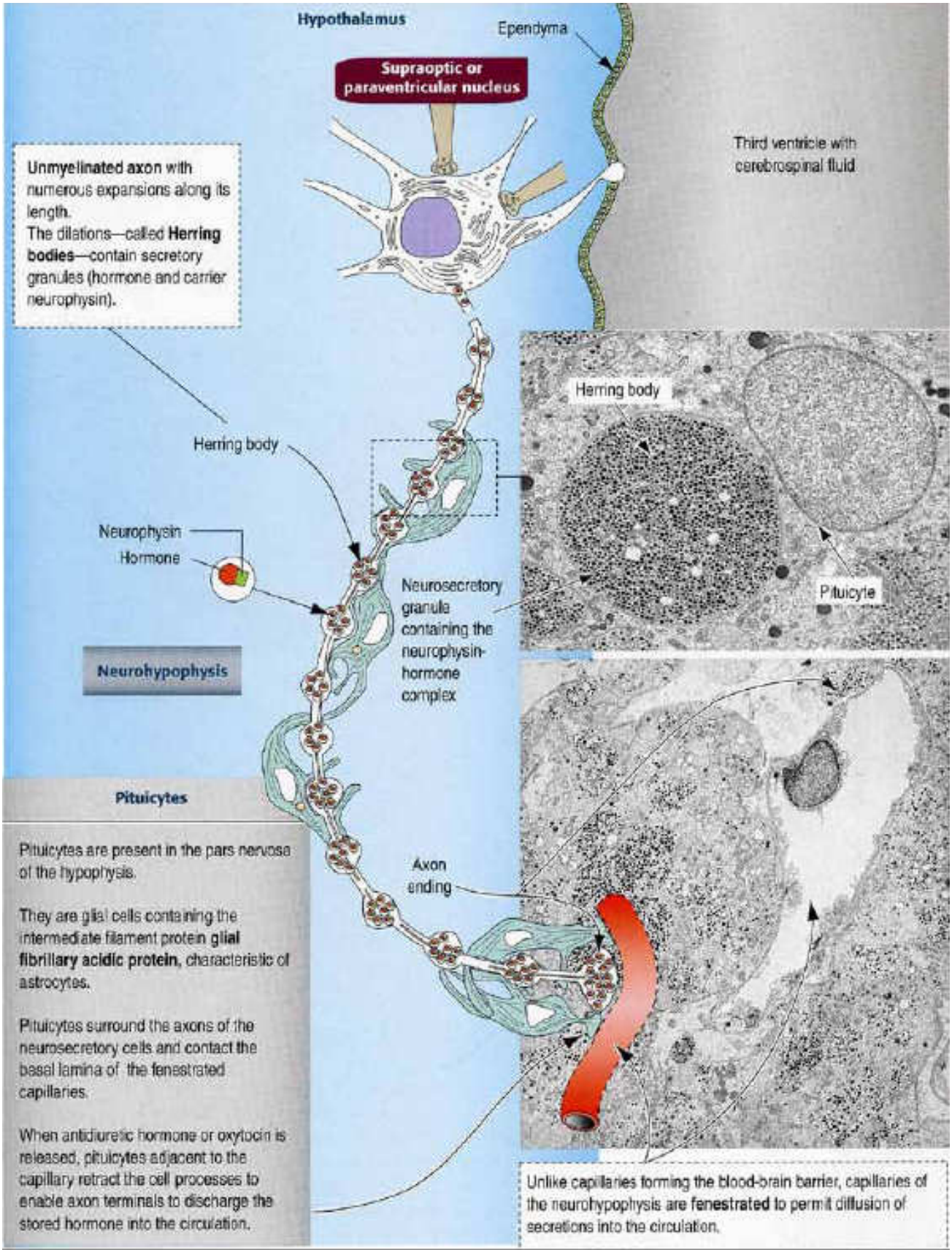
- Infundibulum
  - A tube connecting the hypothalamus with the pituitary
- Parts of the pituitary gland:
  - Pars tuberalis – part of the anterior lobe of the pituitary gland
    - Wraps around the pituitary stalk
  - Pars nervosa – posterior pituitary
  - Pars intermedia – boundary between the anterior and posterior lobes of the pituitary
- Paraventricular and supraoptic nuclei
- Hypothalamus releases hormones that stimulate cells to produce hormones, or hormones that are stored before release
- Rich vascular network between the hypothalamus and pituitary





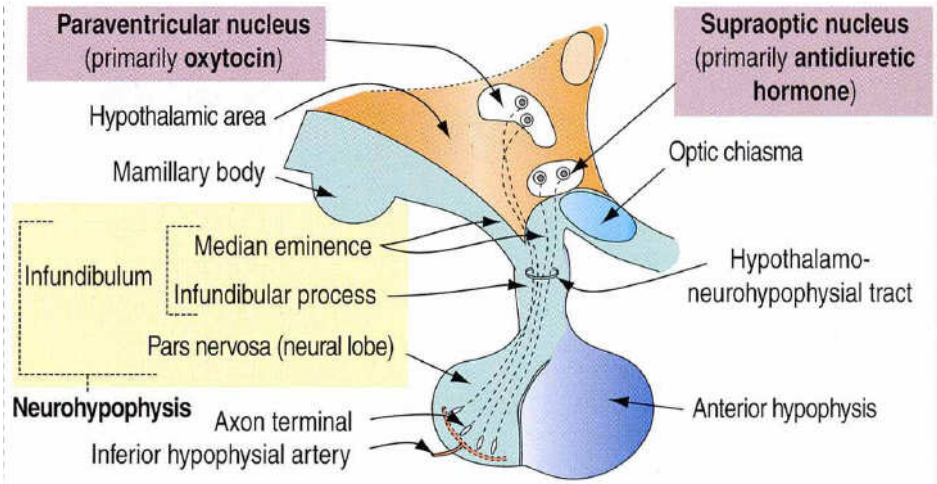
Pars nervosa – neurohypophysis (posterior pituitary)

- Receives axons from the hypothalamus
- Cells:
    - Herring bodies – used for the storage of oxytocin and vasopressin
    - Pituicytes – glial supporting cells
- Axons terminate on fenestrated capillaries



H-P axons

- Paraventricular nucleus in the hypothalamus makes oxytocin
    - Oxytocin is released down the axon and travels through the infundibulum to the pars nervosa of pituitary
    - At the axon terminal, it can be released directly into the blood stream via fenestrated capillaries
- Supraoptic nucleus in the hypothalamus makes antidiuretic hormone
    - ADH is released down the axon and travels through the infundibulum to the ars nervosa of the pituitary
    - At the axon terminal, it can be released directly into the blood stream via fenestrated capillaries
- Carrier protein neurophysin is important for transport
    - Collections containing hormone and this protein can form – Herring bodies



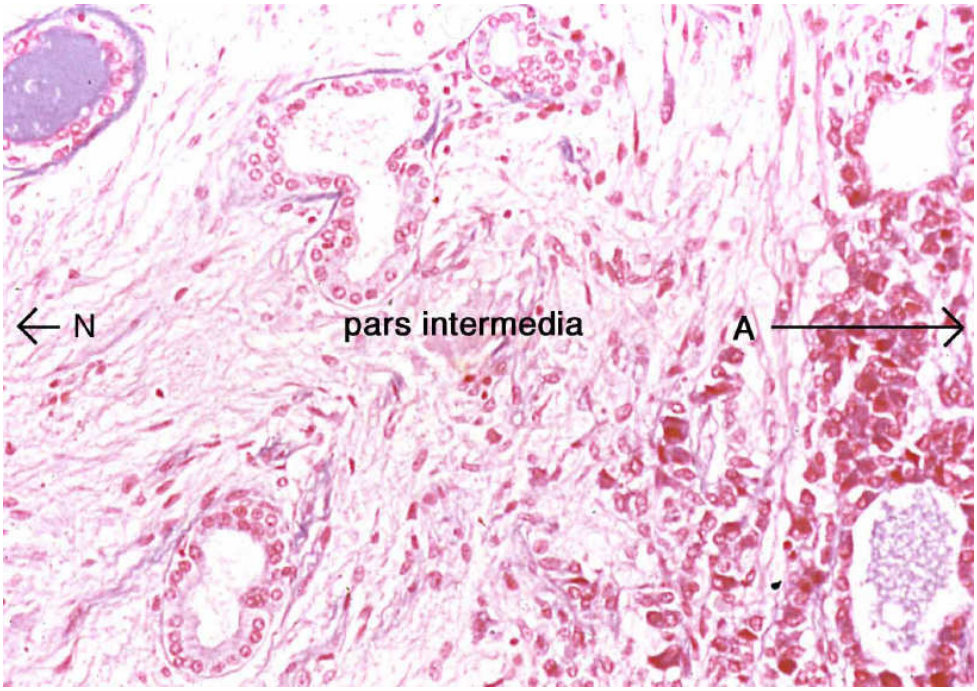
The hormones **antidiuretic hormone** (or **arginine vasopressin**) and **oxytocin** are synthesized in the neurons of the **supraoptic** and **paraventricular nuclei**, respectively. The hormones are transported along the axons forming the **hypothalamoneurohypophysial tract**, together with the carrier protein **neurophysin**, and are released at the axon terminals. The hormones enter **fenestrated capillaries** derived from the inferior hypophysial artery.

Hormones of the neurohypophysis

- Pars nervosa
    - Produced by hypothalamus itself and stored in the posterior pitutary
    - Antidiuretic hormone/Vasopressin
        - Increases water permeability of kidney collecting ducts and promotes vascular smooth muscle contraction
    - Oxytocin
        - Acts on contraction of uterine smooth muscle and the myoepithelial cells of the mammary gland
- Hypothalamus
    - Stimulate production/release of hormones in the anterior pituitary (adenohypophysis)
    - Thyrotropin-releasing hormone (TRH) – stimulates release of thyrotropin and prolactin
    - Gonadotropin-releasing hormone (GnRH) – stimulates the release of follicle stimulating hormone (FSH) and luteinising hormone (LH)
    - Somatostatin – inhibits release of growth hormone and thyrotropin
    - Growth hormone-releasing hormone (GRH) – stimulates release of growth hormone
    - Prolactin-inhibiting hormone (PIH) – inhibits release of prolactin
        - Also, dopamine
    - Corticotropin-releasing hormone (CRH) – stimulates release of both B lipotropin and corticotropin

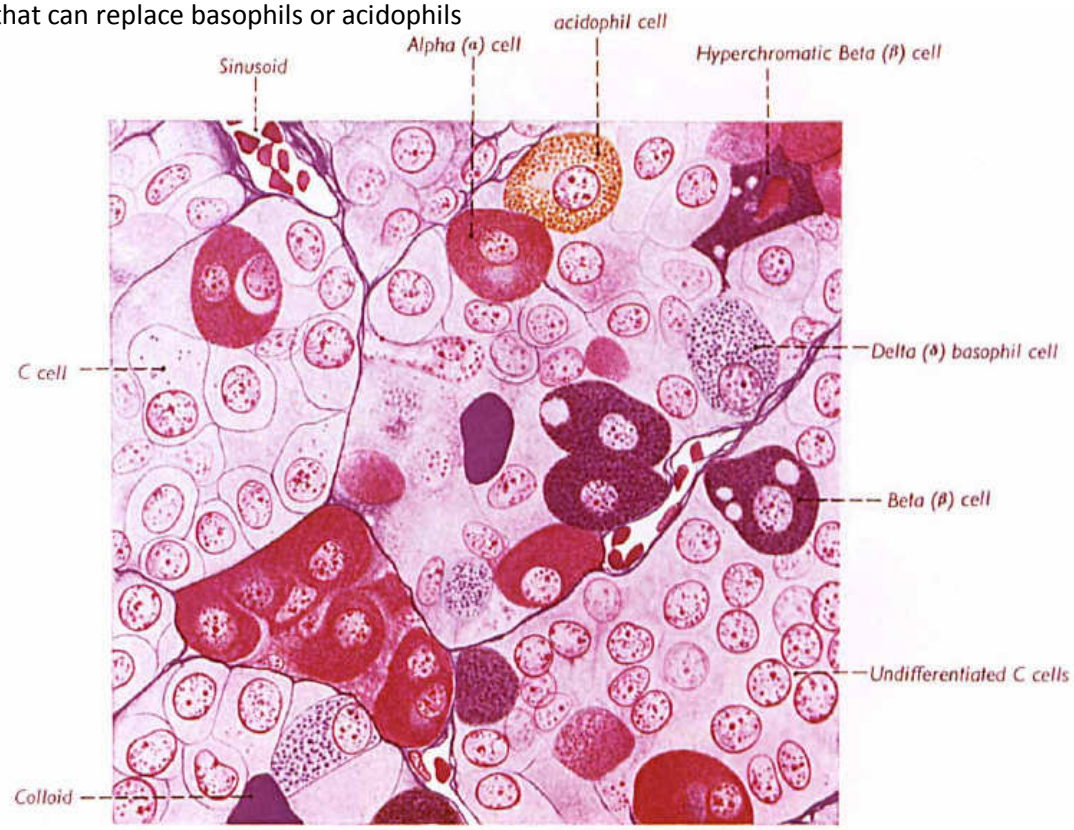
Pars intermedia

- Lies between the neurohypophysis and adenohypophysis
    - Contains:
        - Rathke cysts (colloid filled)– remnants of Rathke's pouch
        - Basophils
        - Chromophobes



Adenohypophysis (pars distalis, anterior pituitary)

- Contains cells that produce, store and release many hormones under hypothalamic stimulus
    - Acidophils
    - Basophils
    - Chromophobes (undifferentiated C cells)
        - Stem cells that can replace basophils or acidophils



- Acidophilic cells:
    - Somatotropic cell – produce somatotropin (growth hormone)
        - Acts on growth of long bones via somatomedians synthesised in the liver
        - Numerous round or oval secretory granules (300-400nm)
        - Released by somatotropin releasing hormone (SRH) and inhibited by somatostatin
    - Mammotropic cell – produce prolactin
        - Promote milk secretion
        - Granules increase in size (200-600nm) during pregnancy and lactation
        - Released by prolactin releasing hormone (PRH) and inhibited by Prolactin inhibiting hormone (PIH)

- Basophilic cells
    - Gonadotropic cell – produces FSH and LH
        - FSH promotes ovarian follicle development and estrogen secretion in women and spermatogenesis in men. LH promotes ovarian follicle maturation and progesterone secretion and Leydig androgen secretion in men
        - Granules are 250-400nm in diameter
        - Released by GnRH
    - Thyrotropic cell – produces thyrotropin (TSH)
        - Stimulates thyroid hormone synthesis, storage and liberation
        - Small granules (120-200nm)
        - Released by TRH
    - Corticotropic cell – produces Corticotropin (ACTH – adrenocorticotropic hormone)
        - Stimulates secretion of adrenal cortex hormones
        - Large granules (400-550nm)
        - Released by corticotropin releasing hormone (CRH)

<u>Vasculature</u>

- Superior and inferior hypophyseal artery
- Hormones are released by various pathways into these arteries:
    - Posterior pituitary stores and releases hormones produced by the hypothalamus
    - Anterior pituitary produces and releases hormones under stimulation from the hypothalamus
- The pituitary is like the coordinator of the orchestra

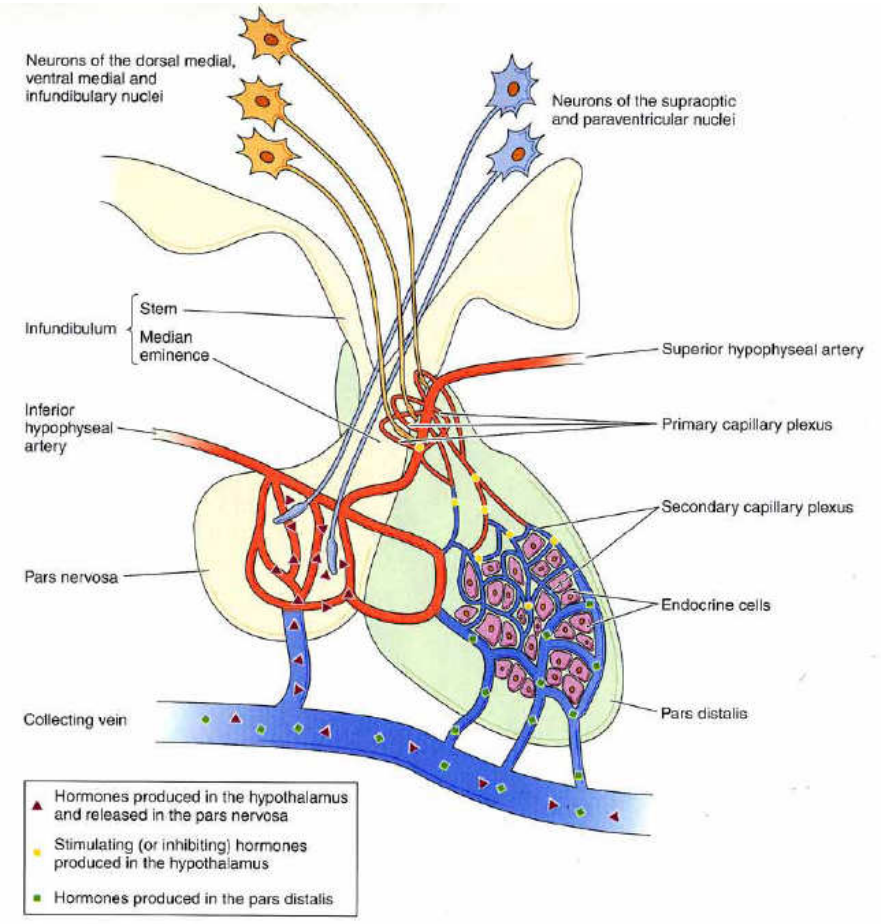


Figure 20–2. The hypothalamo-hypophyseal system, with its vascularization and sites of hormone production, storage, and release.

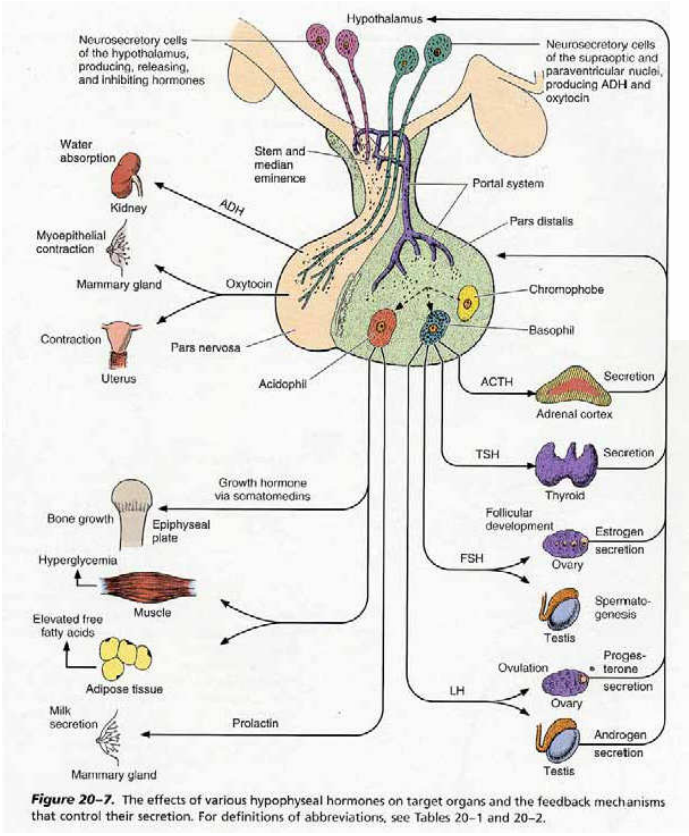


Figure 20–7. The effects of various hypophyseal hormones on target organs and the feedback mechanisms that control their secretion. For definitions of abbreviations, see Tables 20–1 and 20–2.

Adrenal gland

- Cortex – derived from mesoderm of the body wall
  - Produces glucocorticoids
- Medulla and extra-adrenal sites – derived from neural crest cells
  - Produce adrenaline and noradrenaline

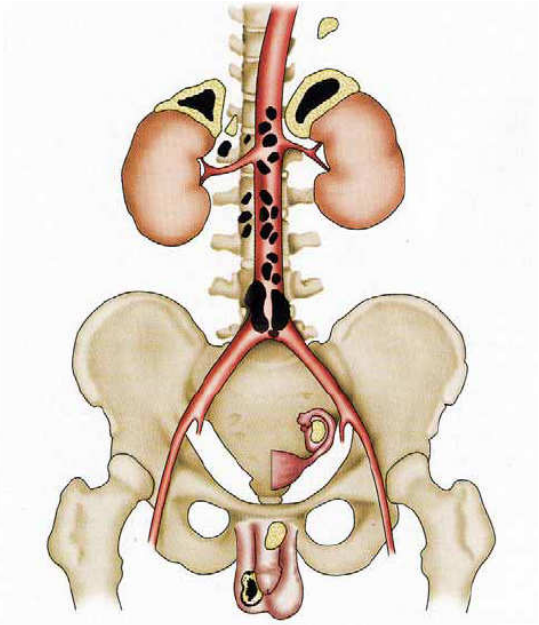
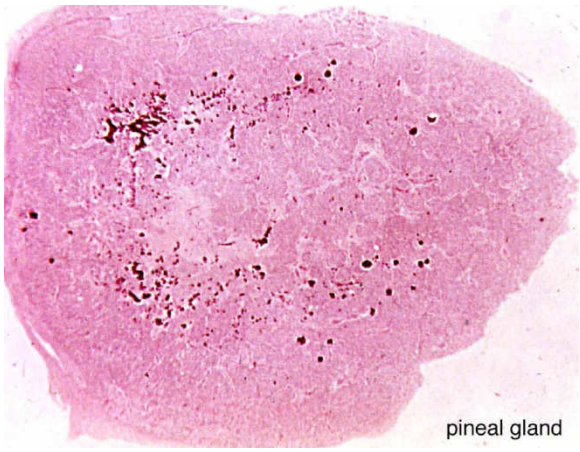
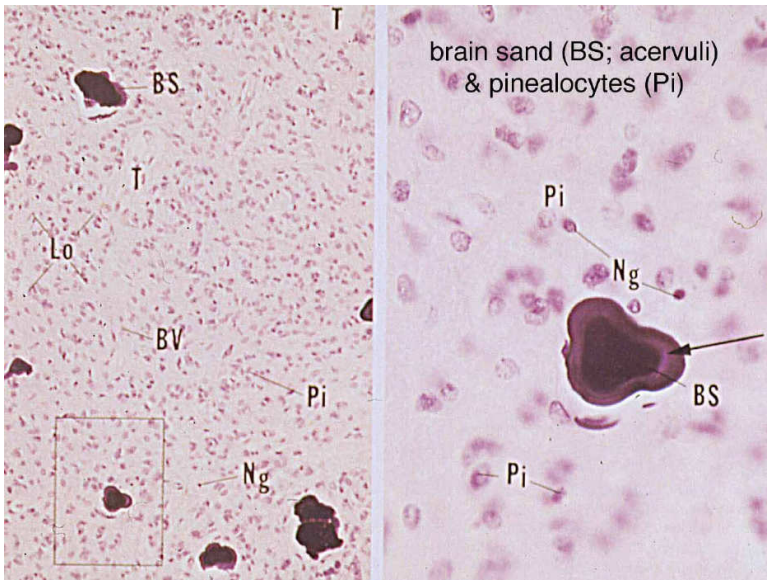


Figure 21–1. Human adrenal glands. Adrenocortical tissue is shown stippled; adrenal medullary tissue is shown black. Note the location of the adrenal glands at the superior pole of each kidney. Also shown are extra-adrenal sites where cortical and medullary tissues are sometimes found. (Reproduced, with permission, from Forsham in: *Textbook of Endocrinology,* 4th ed. Williams RH [editor]. Saunders, 1968.)

Pineal gland

- No BBB layer
- Outpocketing of the diencephalon on the dorsal side
  (vs the hypothalamus on the ventral side)
  - Enlarges in darkness, small in the light
  - Contains concretionary bodies: black sand (corpora arenacea)
    - These cells are lamellated
  - Pinealocytes – supporting cells





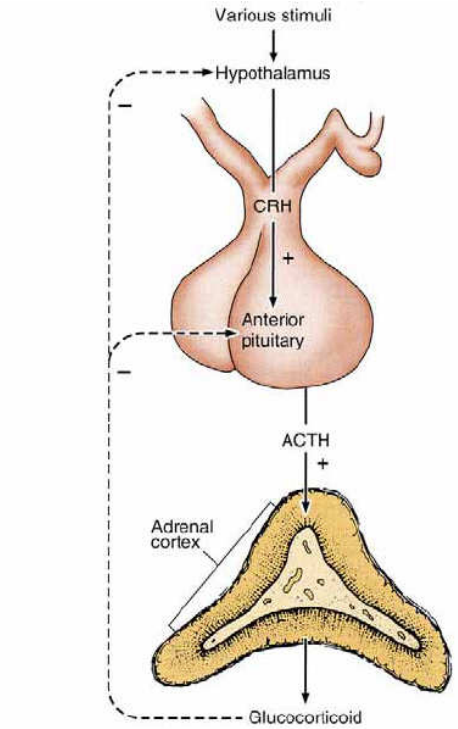
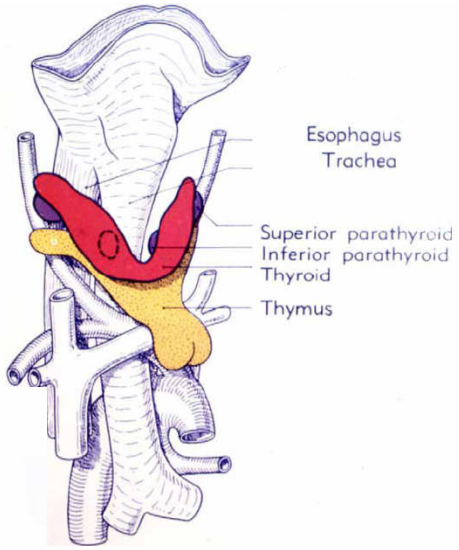
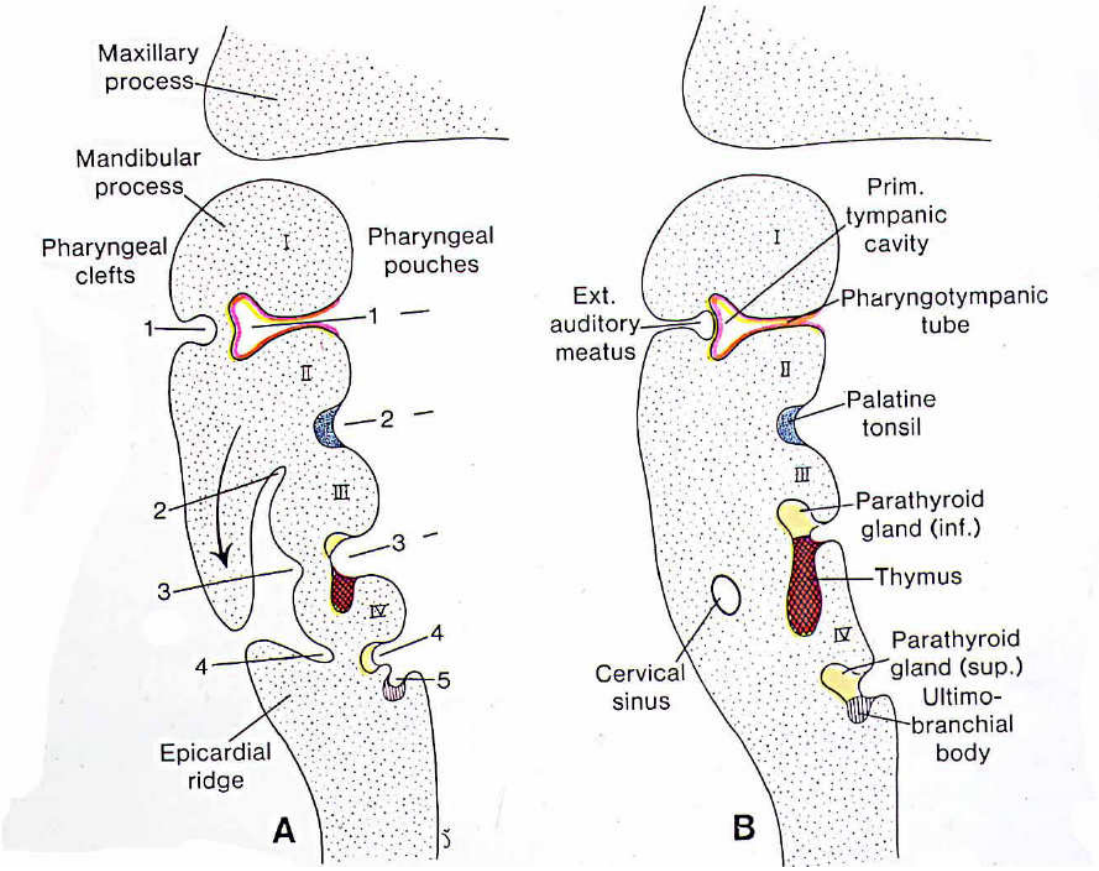


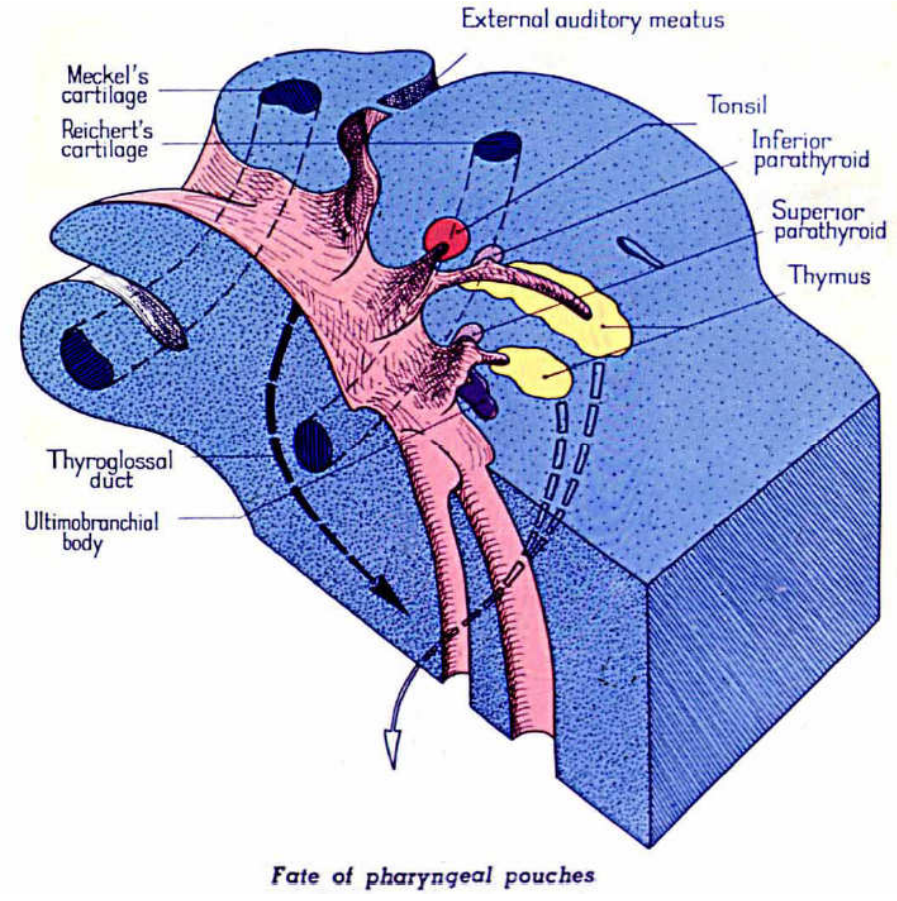
Figure 21–6. Feedback mechanism of ACTH and glucocorticoid secretion. Solid arrows indicate stimulation; dashed arrows, inhibition. CRH, corticotropin-releasing hormone, ACTH, corticotropin.

Embryonic development of parathyroid and thyroid

- Pharyngeal arches
  - Pouch 2 forms the palatine tonsil
  - Pouch 3 forms the thymus and inferior parathyroid
  - Pouch 4 forms the superior parathyroid
- Thyroid
  - Embryonic origin is the foramen caecum on the tongue
    - "migration" into adult position
    - Ie. all other parts around it grow and it is anchored in position







Fate of pharyngeal pouches

Introduction
- The indigenous population in Australia is not a homogenous group
    - 350 different cultures in 1788 when the Europeans arrived, most still exist
        - Eg: Sydney group is known as the Eora people: 29 different groups
- Social factors affect health, particularly important in the indigenous population

Aborigine spread
- At time of colonisation, thought to have a population f 750 000-1.5 million people
    - Spread all over Australia
- Disease was brought by the Europeans
    - Ie: measles, small pox, flu, typhoid, gastric disease
    - Reduced the population to ~80 000 people
- Children and land were dispossessed
    - Every aspect of life was dominated
- Infant mortality was high
    - 1950s, Aborigines were still considered a dying race
- Modern times
    - Aboriginal populations have gathered in cities
        - Many Aborigines live in Sydney
        - 2/3 live in Southern QLD and NSW

1960s onwards
- Infant mortality decreased in the 1960s
    - There was an increase in the number of young Aboriginal people
- 1990s, saw a number of ageing Aborigines for the first time
    - At 75 years, mortality becomes similar to that of non-indigenous people
        - Explanations: survive this long due to better childhood opportunities, health and nutrition
- Current population of Aborigines (by census) – 517 000

Changes 1960s onwards
- Access to human rights and self-determination
- Increased access to healthcare and services
- Opportunities for education and other development
    - However, up until 1978, in NSW, Aborigines could still be excluded from schools
    - Even now, access is different. Most Aborigines do not have equal access to education
- Voting, etc

The gap
- There are many differences in terms of health outcomes in the statistics for Aboriginal populations vs non-indigenous populations
- This gas is particular large, and doesn't follow the trend in other countries where their indigenous have a comparable level of health
    - Thought to be due to a lack of a treaty (a symbolic acknowledgement of what happened)
    - In Australia, there is no recognition that the land was not terra nullius, ie that the land did belong to the Aborigines before the European settlers arrived

Life expectancy
- The non-indigenous community has a large ageing population (population coffin)
    - By 2020, children born are likely to have a life expectancy of 100
- Indigenous population (population pyramid)
    - Not many people reach old age
    - Most people die in their 40s and 50s ("50% die by 50")
    - Those that reach 75+ had a nutritionally sufficient childhood
- Average life expectancy of an Australian baby is 82, indigenous baby: 62 (same as the 1930s Australian population)

Deaths

- Non-indigenous people
  - People die when they're old
- Aboriginal people
  - People die as children or in middle age (generally all ages except teens)
- This means that living in big cities doesn't necessarily protect you

Positives

- Old Aboriginal people are strong and well
  - Eg: 70 year olds are often the primary carers of babies (great grand children)
- The Aboriginal people is a resilient people
  - Overcame the hostile natural environment of Austrlaia
  - Overcame more recent abuse by European colonisers

Birth weight

- Aboriginal and Torres Strait Islander mothers have a lower mean birth weight than non-indigenous mothers
  - Not necessarily related to remoteness
- Aboriginal babies with non-Aboriginal mothers, show little inter-regional variation
- Aboriginal babies are 2x more likely to be low birth weight babies
- Other trends:
  - Overall increase in LBW babies can be attributed to teenage pregnancy
  - Mortality rates have decreased

Children

- 38% of Indigenous population are children 0-14, vs 19% of non-indigenous population
  - Indigenous children are 5% of all Australian children, vs Aborigines being 2.6% of entire population

Causes of child mortality

- Indigenous population vs non-indigenous population
  - Conditions in the perinatal period – 3x higher
  - Ill defined conditions like SIDS – 5x higher
  - Congenital mortality – 1.6x higher
  - Injury/poisoning – 3x higher
  - Respiratory disease – 7.2x higher (related to otitis media)

Disease 0-14

- Similar rates in: skin, musculoskeletal, eye, respiratory disease
- Different rates in ear diseases (this often can lead to long term developmental problems)
- 40% of all children have a long term condition (including asthma, allergies)
- Hospitalisations
  - Higher in Aboriginal kids, in particular to do with skin diseases
- NB: drug use is an important issue: especially Marijuana in adolescents

Methods for closing the gap

- Healthcare that is culturally appropriate and commensurate (equal) to need
- Increased health practitioners in indigenous health settings
- Increased responsiveness of mainstream healthcare to indigenous needs
- Increased maternal and child healthcare
- Increased funding for the basics of health:
  - Nutrition, physical activity, fresh food, healthy lifestyles, adequate housing, not smoking, drugs, drinking
- National targets and benchmarks – that can be monitored to achieve equity
- Increase education and opportunity, 1% of Aboriginal people are in the health workforce, vs 6% non-indigenous

Note

- To inspire change, need to capture the hearts and minds of individuals
- Decreasing stereotypes is of the most importance
- ¼ indigenous people don't know where their next meal comes from

Infectious diseases
- 2nd leading cause of death world wide (26% vs CVS 29%)
    - This is symbolic of a failure of the healthcare system, because the number of people who die from infectious disease is still very high despite immunisation and the treatments available
- Developed countries:
    - 3rd leading cause of death
    - Causes 1/3 of DALYs – morbidity

Definitions
- Infections in the fetus/newborn can be acquired:
    - In utero (congenital)
    - At the time of birth (natal) – eg: HSV
    - During neonatal period (post natal)
        - Eg: from other children, children are more infectious and have worse hygiene

Consequences of viral infection in pregnancy
- Generally, if fetus is infected vertically, viruses can cause fetal defects
    - Depends on the time of infection and the virus
- Congenital:
    - Varicella zoster virus (VZV), influenza, measles, rubella, CMV
        - Rubella/CMV – allows fetus to survive, but steals nutrients and causes malformations
            - Ie: blindness, deafness, diabetes, pneumonitis, hepatitis, mental disability
- Fetal defects:
    - VZV, CMV, Rubella, HSV, parvovirus
- Newborn:
    - VZV, CMV, rubella, HSV, Enteroviruses
- Illness later in infancy/childhood
    - HIV, HepB, HepC, CMV, Rubella, EBV

Viral infection in childhood
- Mortality used to be high, has since decreased
- Common causes:
    - Acute LRTI, TB, Diarrhoeal, HIV/AIDS, Malaria, Measles, Hep B
- Diarrhoeal disease is a common cause of death – rotavirus, norovirus
    - Illustrates difference between developing and developed countries
        - Developed countries – inconvenience
        - Developing countries – common cause of death

Causes of infection in childhood
- Bacterial
    - UTI – gram negative rods
    - Cellulitis – Streptococcus pneumoniae, staphylococcus aureus
- Fungi
- Viral (most)
    - Respiratory – RSV
    - GIT – rotavirus/norovirus
    - Systemic/skin rash, CV, CNS – enterovirus
    - Hepatitis – CMV

Determinants of perinatal infection
- Exposure of a large enough viral dose
- Maternal antibodies
    - Transferred transplacentally from week 35, + through breast milk
    - Malfunction can cause susceptibility to infection
- Immature immune response of newborn

Cutaneous manifestations of systemic infection

- 3 categories:
    - Dissemination of infections agents by blood, secondary to infection of skin
        - Eg: Neisseria meningitidis – purpura rash
    - Dissemination of toxin
        - Eg: SSSS (staphylococcal scalded skin syndrome), Scarlet fever, toxic shock syndrome
    - Systemic disease with exanthem (skin rash)
        - Probable immunological basis
            - Eg: Erythema nodosum, erythema multiforme (immune response manifesting in skin)

Tumour viruses

- Epstein-Barr virus can increase chance of developing Burkitt's lymphoma
    - Also, Burkitt's lymphoma is highly associated with malaria

Common infections: congenital infections

- Should test newborn if:
    - Hx:
        - Maternal illness, maternal exposure (childcare workers)
        - Premature (can be due infection)
        - Parents with STDs (eg: genital herpies, Chlamydia, gonorrhoea) – often indicative of other STDs
        - Parent in high risk category (drugs, prostitutes, prison)
        - Adolescent mother – high risk for pregnancy complications and congenital infection)
        - No antenatal care
    - Physical exam
        - Premature, microcephaly, unexplained hydrocephalus, ocular, unexplained jaundice
- CMV
    - Ubiquitous Herpes virus
    - Transmission
        - Fetus – maternal blood: in utero, cervix, breast milk
        - Children – day care centres (1/10 are secreting CMV in urine)
        - Adults – sexual transmission
            - Thus epidemiology: peaks in childcare age and late teens
        - Transplacental transmission – blood borne
            - 2/3 mothers are asymptomatic
            - Colonises placenta and moves to baby 2-3 months later
    - Most common viral cause of congenital malformation in Australia
        - Only causes malformations if infection during pregnancy is primary
            - If there is no immune response, virus can easily pass to baby before immune response is mounted
        - 350-500 born each year with malformations
            - Half are present at birth, half before the age of 5
    - Effects:
        - Hearing loss (1/8-1/5 get bilateral sensorineural loss)
        - Mental disability – calcification and microcephaly
        - Jaundice
        - Pneumonia
        - Hepatosplenomegaly
        - Microcephaly
        - Prematurity
        - Chorioretinitis
        - Petechiae – small haemorrhages under the skin

- Parvovirus B19
    - Infection comes and goes
        - CMV, EBV, HHV8, 7 are present in the body for life
    - Discovered 1974, related to parvovirus in animals
    - Targets rapidly dividing cells – fetus
        - Haemopoetic system: anaemia
            - Can get severe/fatal drop in red cells
        - May result in an outpouring of amniotic fluid, cells are swollen
    - Effects in most children:
        - Temperature
        - Slack cheek syndrome
        - Lacy rash for a few days to weeks
            - Exacerbated by heat, can be itchy
        - Exanthem
- Rubella – causing congenital rubella syndrome
    - Disastrous in early gestation (50% chance of death)
        - Now rare in developing countries due to vaccination
    - Reinfection often doesn't cause congenital malformation
    - Effect (depend largely upon the infection trimester):
        - T1: 40-50% defect, T2: *, T3: low chance
    - Australia: 4-5 cases/year unvaccinated
        - 1/few years CRS

<u>Skin rashes in children</u>

- Measles
    - Epidemiology:
        - Significant problem despite vaccine
            - 30-40 million cases/year
            - 750 000 deaths/year
        - Major preventable problem, especially in developing countries
    - Vaccine prevents, but disease is not treatable
    - Can cause viraemia
        - 10-12 day incubation
    - Effects:
        - Sore throat, conjunctivitis
        - Rash: maculopapular – confluent
        - Koplik's spots
    - Complications (often cause death)
        - Pneumonia, diarrhoea, malnutrition, diarrhoea
        - Blindness (measles is the major cause)
- Varicella zoster virus
    - Causes an itchy rash if infected in childhood
    - Attenuated strain vaccine
    - Causes congenital malformations if spread in utero
        - If virus infects baby, immune system prevents baby dying
        - Virus lodges in ganglia and reactivates later
        - In utero – causes scarring of the skin/wasting of limbs – if affecting nerves
    - Complications
        - Bacterial super infection of skin lesions
        - Thrombocytopaenia
        - Arthritis, hepatitis
        - Cerebellar ataxia
        - Encephalitis
        - Meningitis, glomerulonephritis

Gastroenteritis in children

- Symptoms:
  - Children are quiet, decreased skin retraction
  - Hypotension, decreased eyeball pressure (late stage)
  - Dry mucous membranes
  - Dehydration – shutting down of brain/kidneys
- Viral agents (most common)
  - Rotavirus (vaccine available, previous to vaccine, caused 70%)
  - Norovirus, adenovirus (also causes respiratory disease, strains 40 and 41), astrovirus (5%), others

Respiratory disease in children

- RSV – respiratory syncytial virus
- Influenza A
  - 4-5 million/year
    - Winter
    - Children are often infected because they shed more and acquire more
- Often don't know the cause
  - Corona viruses, rhinovirus – not tested for
- Rhinovirus
  - Most common cause of the cold
  - Epidemiology:
    - Year-round infection, peak in autumn/spring
  - Hundreds of types
    - Immunity may not be cross-reactive (often protection is in the form of local IgA)
  - Pathogenesis
    - Likes lower temperatures ($33^{o}C$)
  - Can be associated with asthma
- Influenza
  - 4-5 million get influenza, 2 million die (especially elderly and children
  - H3N2

Early development
- Emotional development – expression and recognition of emotions
- Social development – bonding and attachment, relating to others
    - Development and expression of emotion is important for early bonding and attachment

Attachment
- The strong emotional ties that bind individuals to an intimate companion
    - aided by innate reflexive behaviours (eg: following with eyes, clinging, sucking, vocalising)
- Caring and bonding is promoted by specific attributes
    - They are cute
    - They do cute things

Facial expression
- Can express basic emotions
    - By 36 hours can mimic facial expressions
- Proportions and appearance emphasises cuteness

Emotions and social development
- Communicative function (use emotion)
    - Cries of distress – summons caregiver
    - Smiling – rewards caregiver
    - Crying – comfort from caregiver
    - Overall promotes social contact between infant and carer
- Secure attachment requires ongoing, consistent and reciprocal interaction
    - Failure of secure attachment can result in psychological disorders
        - Separation can cause rejection and failure of attachment
            - Eg: hospitals, babies in intensive care (past practices)
        - Ie: failure of emotional development can lead to social problems

Talking to babies
- Music-like, dance-like vocalisations
- Gestures of body and facial movements
    - These actions are often automatic with the baby
    - If someone doesn't like this, there can be adverse reactions
- PND – post natal depression
    - Talk at baby, not to it
        - Less music/dance
        - Flat, negative vocal/facial affect
        - Less active/playful, no turn taking
    - Less likely to elicit positive affect attention and learning for infant
    - Need another person in the house to take over

Basic trust
- Primary emotional task to learn
    - If not developed, has many effects down the track
        - Stress response
        - Can't trust later on, formation of relationships impaired

Impairment of attachment formation

- Causes:
    - Parental lack sensitivity to infant needs
    - Illness/handicap of infant
    - Abuse and neglect
    - Separation and abandonment
    - Physical/psychological illness of parent
- If attachment fails, when child is a mother herself, can not know what to do with child
- Long term effects:
    - Can't form meaningful relationships
    - Personality – manipulative/charming
    - Difficulty with empathy
    - Change in neural pathways (decreased hippocampal volume, hyper-reactivity of stress regulation areas)
    - Psychiatric illness (depression/anxiety)

Chronology of emotional expression

- Simple emotions
    - Birth – distress, interest, disgust (primary emotions)
    - 4-6 weeks – joy (1st social smile, maybe earlier)
    - 4-5 months – sadness, anger, surprise, fear (responsive emotions)
    - Complex emotions:
- Complex emotions
    - 1-2 years – embarrassment, shame, guilt, pride (self-conscious, self-aware, some idea of social context)
    - 18-24 months – fake emotions
    - 3 years – hide emotions

Humans are social animals

- Social isolation and abandonment is equivalent to a cruel punishment → a strong predictor of mortality
    - Eg: past practice was to leave child alone by themselves in their room to sleep
        - Now: sleep between mother and father
- There are many social rules, roles, norms and behaviours to learn and understand
    - Also need to understand social hierarchies and power structures to allow socialisation
    - Socialisation requires an understanding of social etiquette appropriate to context
- Social development is important for other broader development
    - Secure attachment is important for social development

Social development

- Facilitated by:
    - Instrumental and observational learning
    - Modelling
    - Playing – makes kids healthy, happy, human and smarter (can be alone or with others, cooperation)

Altruism vs aggression

- Altruism – selfless concern for others
    - Developed at age 2
    - Related to moral development and empathy
- Aggression – behave intending to hurt
- These behaviours have been found to be hard-wired (genetic)
    - Also draw on what parents do (environment) and media

Moral reasoning – Kohlberg's model

1. Punishment
2. Naïve reward
3. Good boy/girl – approval
4. Authority – society's rules/laws
5. Social contract – society's rules viewed as fallible rather than absolute
6. Individual principles and conscience – abstract ethical principles (beyond concrete thinking), equity and justice

Summary
- Cognitive development doesn't occur in isolation
    - Occurs concurrently with neurological, social and others
    - However, it is broadly consistent with neurological
- Piaget and Vygotsky
    - Stage models for cognitive development
    - Highlight aspects of age-appropriate learning
- Understanding the basic stages is important for interaction with children

Definitions
- Cognition – broad term referring to thinking/knowing
- Cognitive development – development of the ability to think and know
    - The process of how a person perceives, thinks and gains an understanding of their world through interaction and influence of genetic and learned facors

Cognition
- Characteristics:
    - Attention – sustained (finite time), divided (multitask), alternating (mixture)
    - Learning/memory – immediate, short term, long term, working, prospective
    - Language – comprehension, expressive, written, verbal
    - Executive functions – problem solving, reasoning, decision making
    - Theory of mind

Neurological development
- Seeing and hearing develop
    - Receptive language area and speech production
        - Higher cognitive functions
- Myelination → increases velocity from 2-50m/s
- EG: testing language skills
    - Naming animals in a minute
    - Age correlates with performance
        - Age also correlates with an increase in standard deviation (greater variation in ability)
    - Skills needed for task (combination of these):
        - Vocabulary (language)
        - Retrieval (memory)
        - Attention (concentration)
        - Organisation (executive function)
    - Skills needed are related to age

Models of cognitive development
- 2 influential models in history (start of last century:
    - Piaget – cognitive development
    - Vygotsky – social and cognitive development
- Stage based
- Provide a structure for understanding childhood cognitive development

Piaget – Child prodigy

- Observed 1000s of children
- Proposed that a child's increase in ability to understand the world was equivalent to the cognition maturing
    - Created a 4 stage linear model
    - Further, thought that learning occurred through:
        - Assimilation – experience fits in with existing knowledge
        - Accommodation – new information causes existing knowledge to be modified
        - Two processes are often simultaneous
    - Encouraged people to let children teach themselves, and learn for themselves because childhood reasoning is dependent on experience and pre-existing knowledge

TABLE 2.1 THE FOUR STAGES OF COGNITIVE DEVELOPMENT

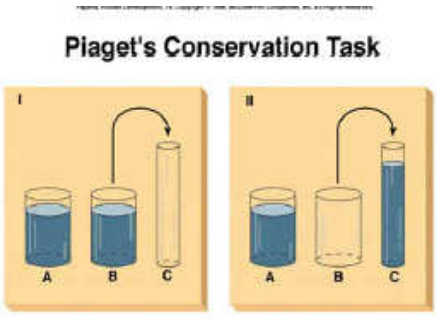
Stage	Approximate Ages	Chief Characteristics
Sensorimotor	Birth–2 years	Discovery of relationships between sensation and motor behavior
Preoperational	4–7 years	Use of symbols to represent objects internally, especially through language
Concrete operations	7–11 years	Mastery of logic and development of "rational" thinking
Formal operations	11 years +	Development of abstract and hypothetical reasoning

Sensorimotor (0-2 years)

- Child learns about the environment using motor, fine motor and sensory abilities to explore
- Sub stages:
    - 0-6 weeks – reflexes: feeding, sleeping, sucking
    - 6 weeks-4 months – habits, conditioned responses (eg. special response for mother)
    - 4-9 months – connection between vision and touch, repetitive behaviours with toys etc to explore environment
    - 8-9 months – object permanence
    - 9-12 months – connections between means and ends, interested in parts of objects
    - 12-18 months – strategic behaviour, can generate new ways to achieve goals, knowledge of function

Preoperational stage (4-7 years)

- Cognitive functions:
    - Symbolic representation
    - Concentration and memory
    - Intuitive thought vs logical
        - Can believe things but not explain them
- Egocentric – can't think from another's perspective
- Can't understand 'class inclusion'
    - Eg: cats, dogs, monkeys, doesn't understand species, mammals, animals
- Can't understand mass, volume – conservational shape



Concrete logical operations (7-11)

- De-centering (working memory), increased frontal lobe functions
    - Take several aspects of a problem into account
- Reversibility: 4+4 = 8, 8-4 = 4
- Conservation – mass, volume shapes
- Serialisation – arrange objects in order
- Classification – can understand classes
- Delimitation of egocentrism, can understand what other people can think

Formal logical operations (12-adult)

- Abstract thinking
  - Can understand concepts (eg: justice, love)
  - Idealistic thinking – what should be done
- Coincides with adolescence: sexual and moral maturity
- Not all adults reach this stage
  - 5% don't complete skills of this stage

Summary

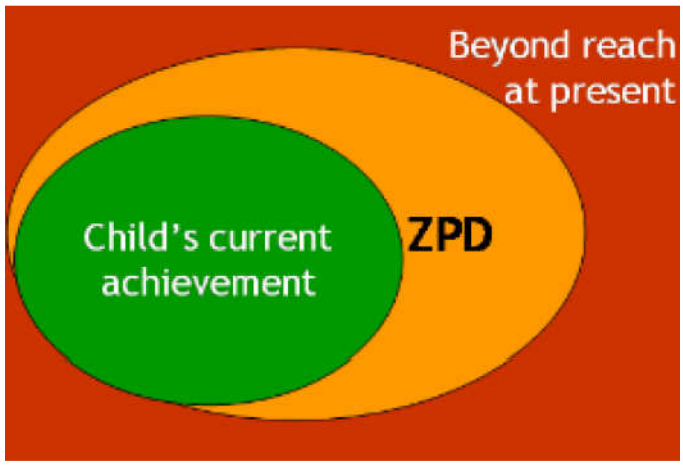
- Timing can vary, sequencing supposedly doesn't vary
- Not culturally specific
- Stages are logical and hierarchical – qualitative and quantitative

Criticisms

- Poor methodology
- Recent work suggests that scheme is too rigid, ie that children develop a mix of skills from a mix of stages

Lev Vygotsky

- Proposed that child's cognitive development was dependent on social interaction (with family and other people)
  - Ie, children need interaction with people and problem solving to properly develop
- Held the idea that language was fundamental to cognitive development
  - Language is the primary tool of adaptation
    - This can be then internalised to regulate own behaviour
- Proposed the zone of proximal development
  - That is, what a child can do alone vs unaided is different
    - This difference is the zone of proximal development, and the best zone for learning
  - From this, if we teach things just beyond a child's current ability, get best results
- Summary:
  - Emphasised relations to others
  - Held an importance in the role language
  - Zone of proximal development – need to be aware of this for optimum development

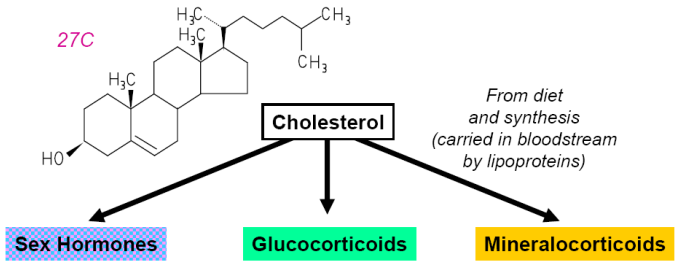


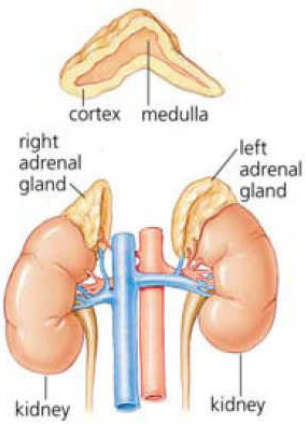
Introduction

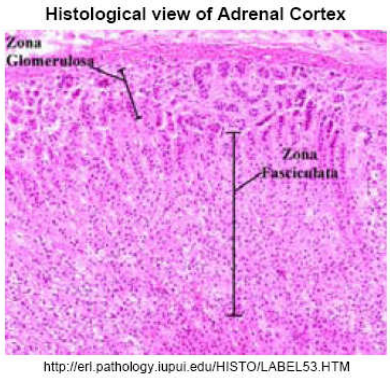
- Nature always finds away
  - The endocrine system is the solution to solve the problem of coordinating a multicellular organism
    - Uses chemical messengers (hormones)

Synthesis of steroid hormones

- Steroid hormones are synthesised from cholesterol
  - Cholesterol is obtained from the diet and through endogenous synthesis
  - Carried in the blood as lipoproteins
- Progesterone is converted into mineralocorticoids and glucocorticoids in the adrenal glands
  - Located above the kidneys, cortex:
  - Cortex:
    - Zona glomerulosa produces mineralocorticoids
    - Zona fasciculata produces glucocorticoids







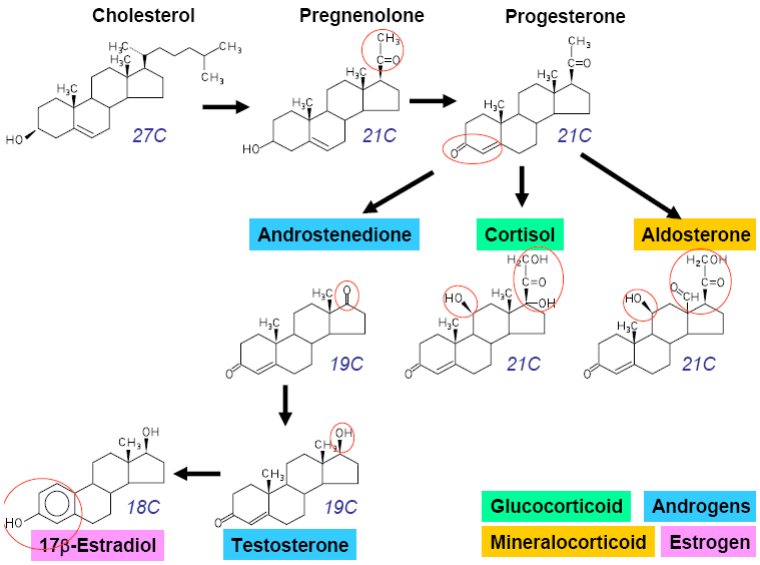
Types of steroid hormones

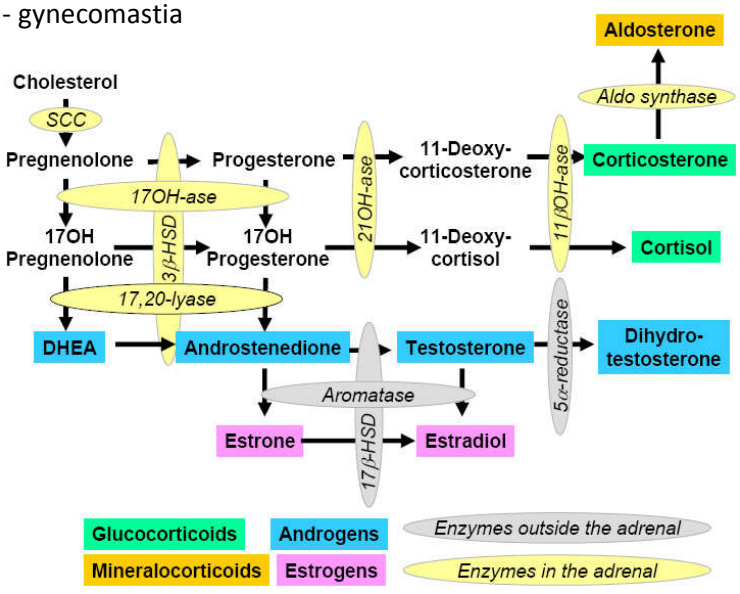
- Mineralocorticoids (aldosterone, 21C)
  - Produced from progesterone in the zona glomerulosa (outer zone of adrenal)
  - Effects:
    - Increases Na^+ uptake
      - Raises blood volume and thus blood pressure
    - Secreted in response to elevated angiotensin II or plasma potassium
- Glucocorticoids (cortisol, 21C)
  - Synthesised from progesterone in the zona fasciculata (mid-zone of adrenal cortex)
  - Secreted when stimulated by ACTH (adrenocorticotrophic hormone) from anterior pituitary
  - Effects:
    - Stress adaptation:
      - In response to - Hypoglycaemia, fear, pain, heavy exercise, infection
    - Elevates blood pressure and Na^+ uptake
    - Immune system effects
  - Production follows a diurnal pattern – helps us get out of bed in the morning (peaks at 8am)
    - Obesity: diurnal pattern is lost (high all the time)
- Sex hormones
  - Testosterone (19C)
    - Androgen produced from progesterone in the testes
    - Principle male sex hormone
      - Responsible for secondary male sex characteristics
  - Estradiol (18C)
    - Estrogen produced in the ovary
    - Principal female sex hormone
      - Responsible for secondary female sex characteristics
- Other major steroid hormones
  - Pregnenolone
    - Produced from cholesterol
    - Acts as a precursor for C18, 19, 21 steroids
  - Progesterone
    - Progestin produced from pregnenolone
    - In females: secreted from corpus luteum (ovary)
      - Important for luteal phase of menstrual cycle
      - Also involved in differentiation of mammary glands

Steroid hormone metabolism/synthesis

- Cholesterol breakdown into various hormones is facilitated by many enzymes
  - All belong the to same class: CYP450
    - Ie. they take a lipophilic compound and add oxygen
    - This class of enzyme is also important in drug detoxification
- List of enzymes and pathway diagrams:
  - Note: aromatase is in adipose tissue
    - Obesity: more estrogen, less testosterone - gynecomastia

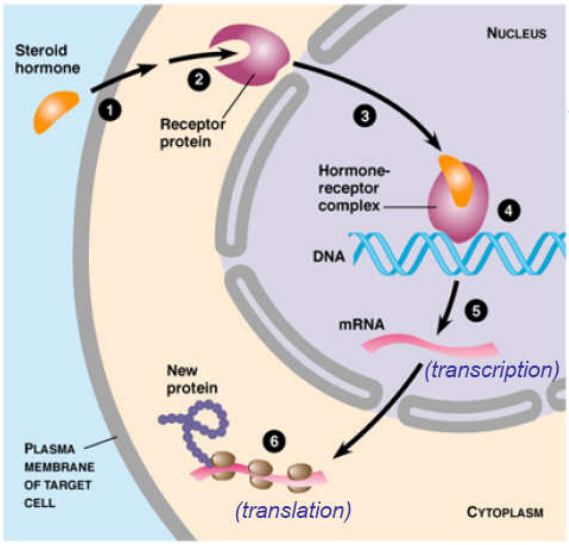
Common name	"Old" name	Current name
Side-chain cleavage enzyme; desmolase	$P450_{SCC}$	CYP11A1
3 beta-hydroxysteroid dehydrogenase	3 beta-HSD	3 beta-HSD
17 alpha-hydroxylase/17,20 lyase	$P450_{C17}$	CYP17
21-hydroxylase	$P450_{C21}$	CYP21A2
11 beta-hydroxylase	$P450_{C11}$	CYP11B1
Aldosterone synthase	$P450_{C11AS}$	CYP11B2
Aromatase	$P450_{aro}$	CYP19

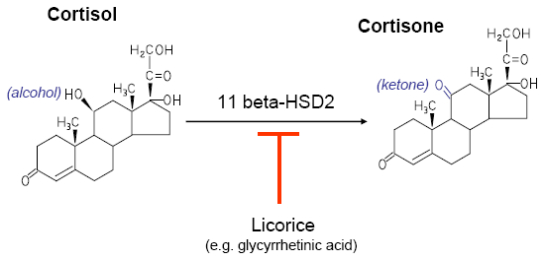




Mechanism for steroid function

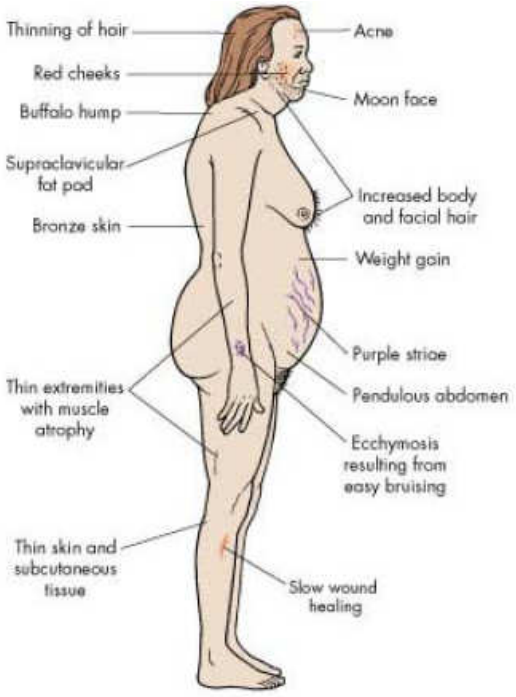
- Steroid hormones are part of the endocrine system
  - Specialised cells release steroid hormones (chemical messengers) into the blood stream to target cells
- Effects are via Steroid Hormone Receptors (SHR)
  - These are hormone-activated transcription factors
  - Contain a DNA binding domain, activation domain and a hormone binding domain
- Ligands – steroid hormones (eg. glucocorticoids, androgens, estrogens)
  - DNA promoters have SHR element upstream for SHR binding
- Process:
  - Steroid hormone bind to nuclear receptors
  - Receptors migrate into the cell nucleus
  - Receptors bind to cell DNA and influence transcription and thus cell function
- Each steroid has its own receptor:
  - Androgen receptor – testosterone
  - Estrogen receptor – estradiol
  - Progesterone receptor
  - Glucocorticoid receptor – cortisol, dexamethasone (exogenous)
  - Mineralocorticoid receptor – aldosterone, cortisol (cross-reactivity, promiscuity)
- Cortisol is particularly promiscuous, so an enzyme is needed to allow mineralocorticoid receptor specificity
  - 11 beta-hydroxysteroid dehydrogenase type 2 (11 beta- HSD2) → converts cortisol to inactive cortisone
    - Liquorice (eg. glycyrrhetinic acid) blocks 11 beta-HSD2 and prevents deactivation of cortisol
      - In large dose, results in hypertension, change in the distribution and deposition of fat





Overdose of corticosteroids – Cushing's syndrome

- Epidemiology
  - Incidence 10-15/million people per year
    - ~= 1/100 000
  - Normally in adults 20-50
- Causes:
  - Non-cancerous tumour in the pituitary (pituitary adenoma) causing over production of ACTH
    - Induces adrenal cortex hyperplasia
      - Thus, increased cortisol production
    - Treatment is surgical correction
  - Tumour in the adrenal gland (zona fasciculata) causing over production of cortisol
  - Use of steroid-containing medications
    - Used to treat inflammatory conditions
      - Eg: asthma, rheumatoid arthritis, allergies, lupus, Crohn's and other autoimmune diseases
        - Dampens the immune response and decreases autoimmune damage
    - If given in large doses for a long time, may develop Cushing's syndrome
      - Also, have a long half life, thus stay in body for a long time
- Cushing's syndrome effects:
  - High blood pressure
  - High blood glucose
  - Menstrual irregularity
  - Lipodystrophy – fat distribution changes, loss of fat from limbs
  - Irritability, depression, aggression, psychosis

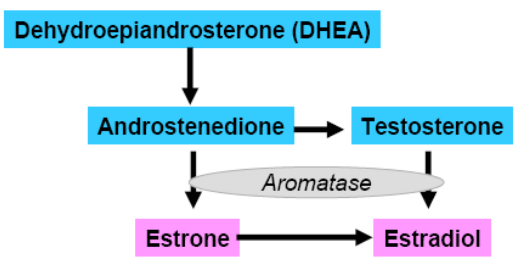


Adrenal insufficiency (underdose) – Addison's disease

- Epidemiology
  - Prevalence – 1/100 000
- Cause:
  - Gradual destruction of the adrenal cortex by the immune system
- Effects (due to adrenal glands under-producing cortisol and maybe aldosterone):
  - Weight loss
  - Muscle weakness
  - Fatigue
  - Low blood pressure
- Treated with oral glucocorticoids

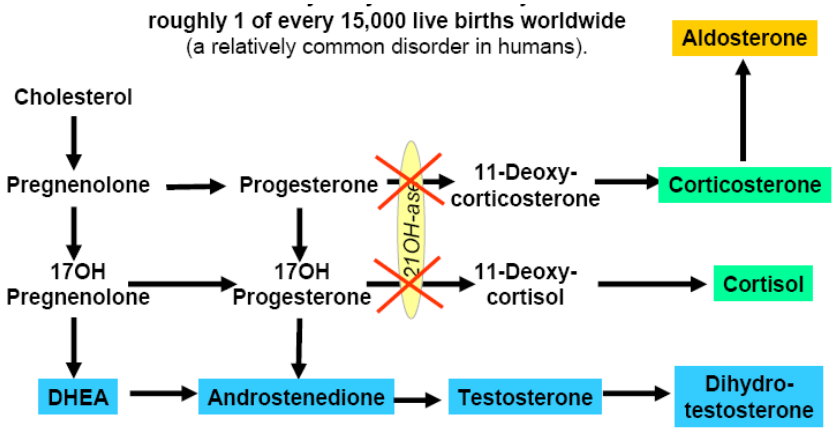
Androgens

- DHEA and androstenedione are weak androgens
  - Converted to sex hormones testosterone and estrogens in other tissues
    - Testosterone and estrogen are also produced de novo in gonads
  - Males produce some estrogen (fat tissue has high aromatase) and females some testosterone (sex drive)
- Androgens have been linked to male-pattern baldness
  - 5 alpha reductase converts testosterone to DHT (more potent)
- The more testosterone present during gestation, the longer your ring finger vs your index finger
  - Related to sporting prowess, mathematical ability and autism



Congenital adrenal hyperplasia

- Epidemiology
  - Relatively common: 1/15 000 live births
- Cause:
  - 21-hydroxylase deficiency causing no production of aldosterone or cortisol (mineralocorticoids, glucocorticoids)
- Effects of insufficiency/excess
  - Glucocorticoid (insufficiency):
    - Hypotension
    - Hypoglycaemia
    - Impaired response to infection
    - Elevated ACTH (feedback mechanism)
  - Mineralocorticoid (insufficiency):
    - Hypotension
    - Salt-wasting crisis in infancy – life threatening vomiting and dehydration in 1st weeks of life
  - Androgen (excess):
    - Virilisation (ambiguous genitalia in girls, clitoromegaly)
    - Precocious puberty (early puberty)
    - Hirsutism
    - Infertility (no menstruation)



Androgens and sex differentiation

- Androgens facilitate the development of human external genitalia
  - Without androgen, female genitalia begins to develop
  - With androgen, male genitalia begins to develop
- Testosterone masculinises and defeminises rats
  - Castrated rat given estrogen would exhibit female behaviour, given testosterone exhibit male behaviour
  - Female rate given estrogen would exhibit female behaviour, given testosterone exhibit male behaviour

Lack of androgen effects

- XY androgen insensitivity
  - Androgenous look, male but looks female

Steroid hormones and cancer

- Some tumours need steroid hormones for survival and growth
  - Eg: estrogen – breast cancer, ovarian cancer, uterine cancer
  - Eg: androgens – prostate cancer
    - However, not every of these cancer types is hormone-sensitive
- Treatment
  - Reduction of hormone levels – cut off hormone supply for cancer
  - Changing cancer's ability to use hormones – synthetic hormones blocking cancer receptor sites
    - Eg: Tamoxifen – drugs that binds to estrogen receptors and prevents binding
  - Thus can make tumours shrink, ie not grow

Overview of genital system development

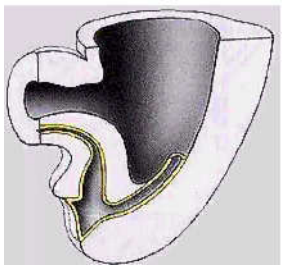
- 3 stages
    - Differentiation of gonad (testes, ovaries) – sex determination
        - Depends on X, Y chromosome
    - Differentiation of internal genital organs
    - Differentiation of external genital organs
        - Endocrine of gonad causes internal and external organs to differentiate
- Time-course
    - Long maturation process – large potential for malformation
        - Begins in embryonic period, continues through fetal period and finishes in puberty

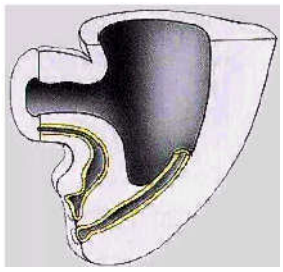
Embryonic genital system development

- Gastrulation
    - First cells to migrate through the primitive streak are primordial germ cells
        - Associated with endoderm
    - Eventually develop into the gonads

Urinary tract

- Develops from the endoderm:
    - The yolk sac, yolk stalk and gastrointestinal tract all contribute
- At the hindgut region, near cloacal membrane rectum and urinary area are continuous
    - At week 6, cloaca is divided by the urorectal septum
        - Forms:
            - Posterior rectal area
            - Anterior urogenital sinus (continuous with allantois – extends into connecting stalk)
        - Bladder develops – urachus, median umbilical ligament



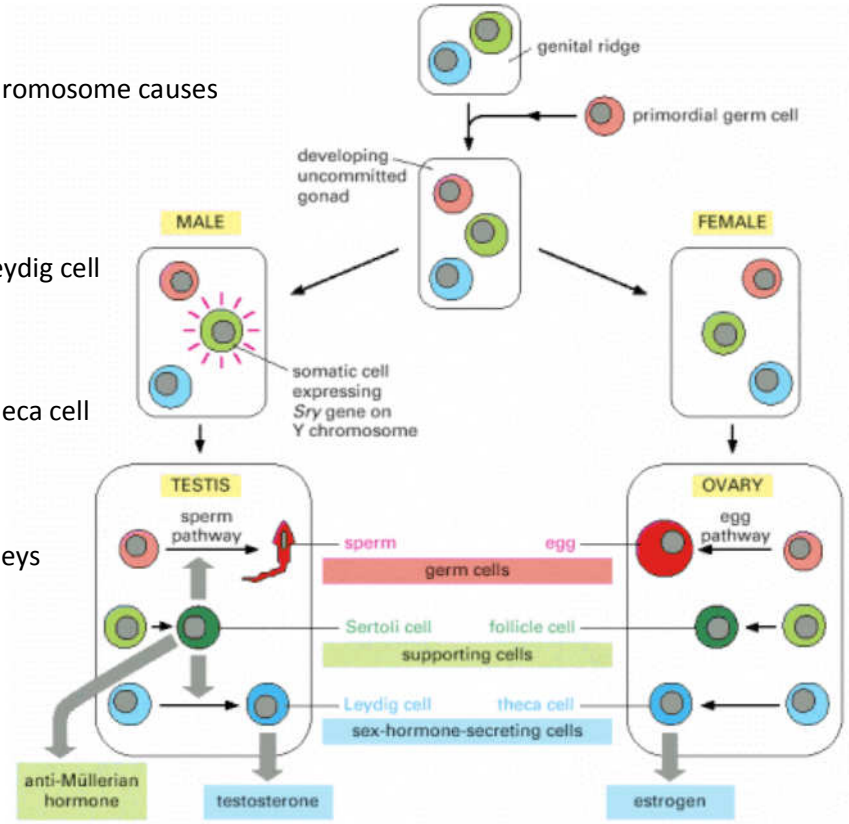


Sex determination

- Chromosomes
    - X
        - 1400+ genes
            - Contains many genes required for regular functioning
        - 150 million base pairs
        - 95% determined
    - Y
        - 200+ genes
            - Contains the SRY region
        - 50 million base pairs
        - 50% determined
- SRY gene, if present, causes production of SRY protein
    - This binds DNA and causes production of testes determining factor (TDF), a transcription factor
        - Causes DNA of target cells to bend 70-80 degrees and changes cell function
- Sex determination
    - Week 5-6, germ cells migrate into the gonadal ridge
        - At this stage, male and female gonads are identical
        - From here, gonads develop depending on sex chromosome and SRY gene
            - Ie, Y present, testes, no Y: ovary

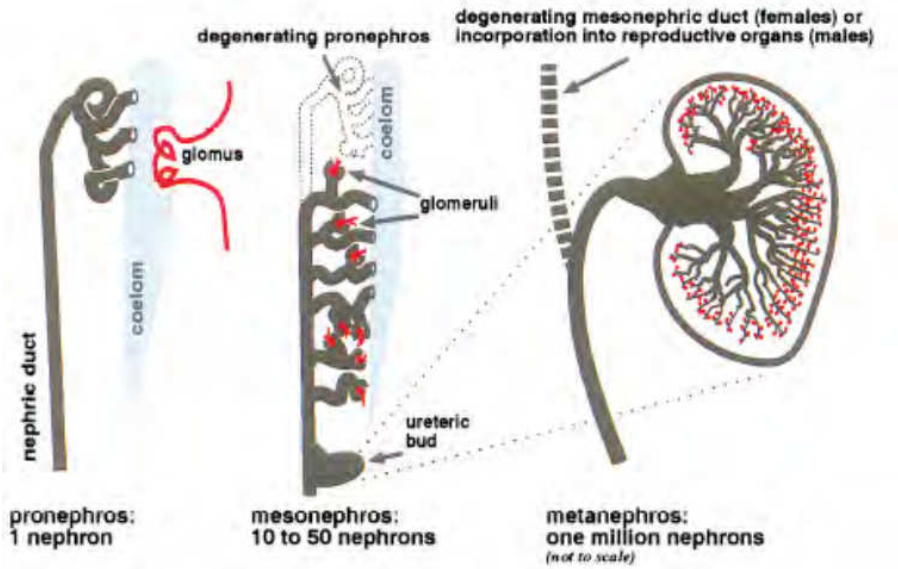
Gonad development

- After gastrulation, cell signalling by neighbours causes formation of primordial germ cells
  - These migrate into genital ridges and becomes the gonads
    - Genital ridges become gonads and primordial germ cells become eggs or sperm
  - Gonad will be an ovary unless somatic cells contain a Y chromosome
- Process:
  - Primordial germ cell enters genital ridge
  - Somatic cell expressing SRY gene on Y chromosome causes differentiation of ridge into testis
  - Differentiation (male):
    - Primordial germ cell → sperm
    - Somatic cell → Sertoli cell
    - Sex hormone secreting cell → Leydig cell
  - Differentiation (female):
    - Primordial germ cell → egg
    - Somatic cell → follicle cell
    - Sex hormone secreting cell → theca cell



Kidney development

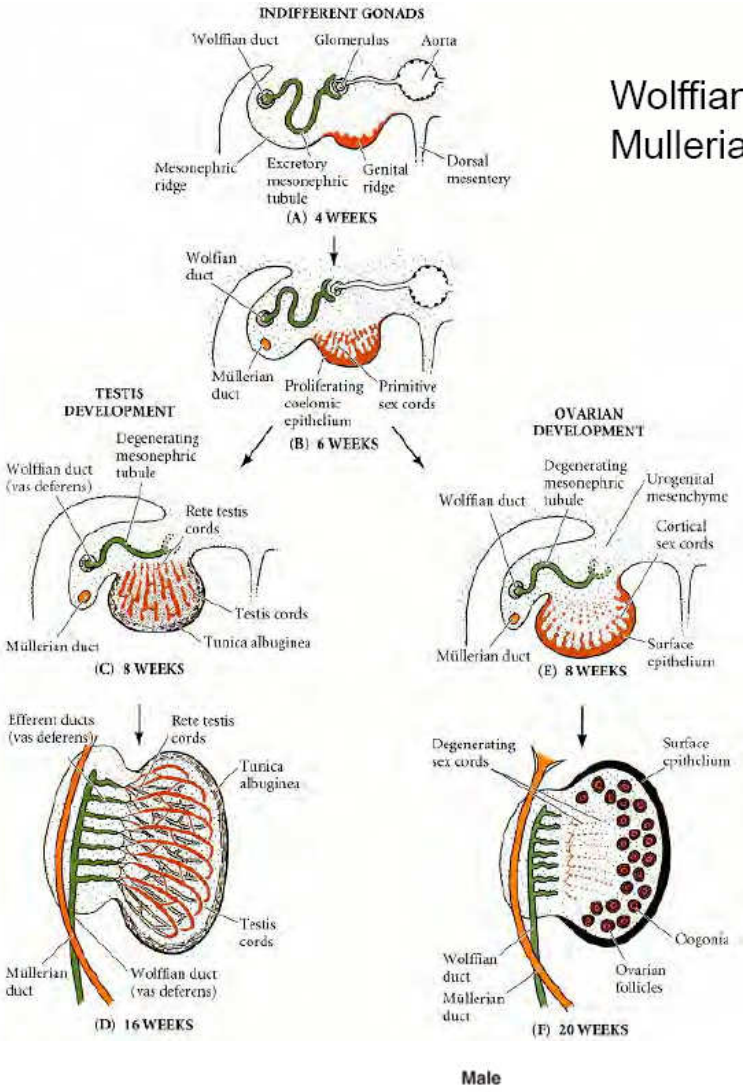
- Pronephros → mesonephros → metanephros
  - Transient structures in formation of kidneys
- Nephric duct (connected to the cloaca)
  - Formed from intermediate mesoderm
  - Becomes the mesonephric duct that eventually forms the internal male genital tract
- In same area, a 2nd set of ducts: paramesonephric ducts
  - Form the internal female genital tract
  - In women, the lack of anti mullerian hormone causes degeneration of the mesonephros
- Kidneys form from the ureteric bud



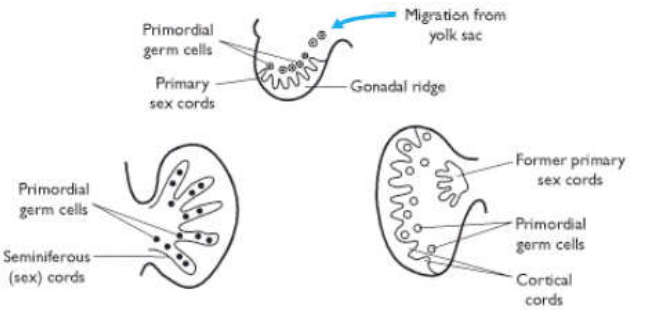
Internal genital organs

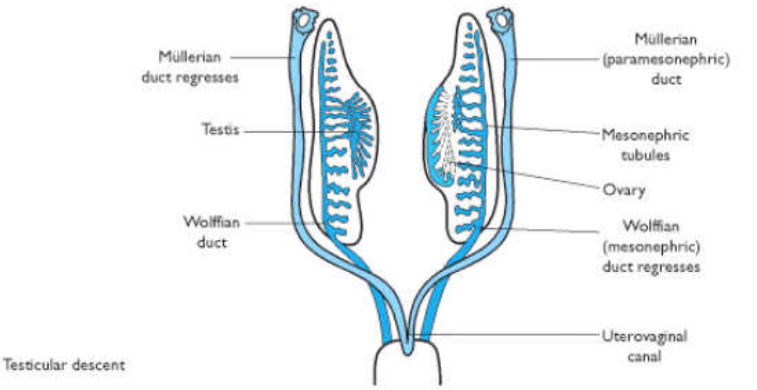
- Form from a duct system (paired)
  - Nephric duct
  - Mesonephric duct (Wolffian)
  - Paramesonephric duct (Mullerian)
    - Develops in the 7th week
    - An invagination of the coelomic epithelium
    - Cord grows and terminates on the urogenital sinus
- Testes secrete:
  - Mullerian duct inhibitory factor (MDIF)
    - Causes regression of the paramesonephric duct
  - Testosterone
    - Maintains the mesonephric duct
- Ovaries secrete:
  - Mullerian hormone
    - Causes regression of mesonephric duct
  - Estrogen
    - Maintains the paramesonephric duct
- Paramesonephric duct becomes the uterus
  - External epithelial plate at the junction region between uterus and cloaca thickens and vagina forms
- Mesonephric duct becomes the ductus deferens

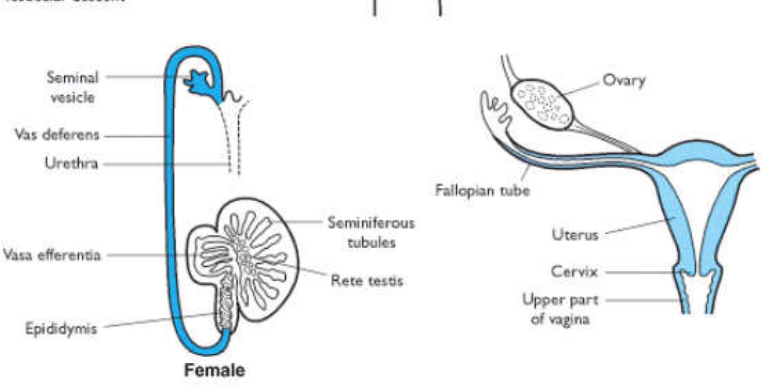
Diagrams of internal genital organ development

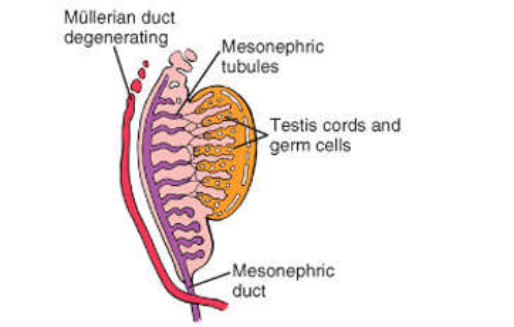


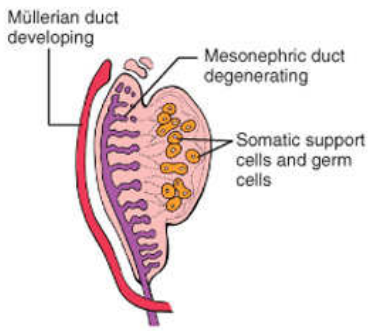
Wolffiar
Mulleria

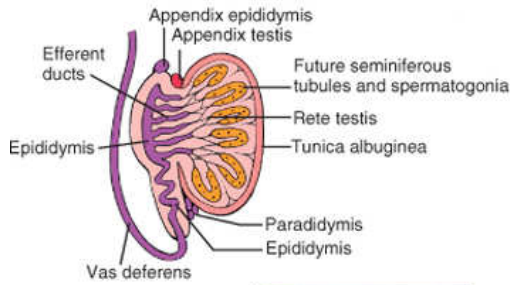


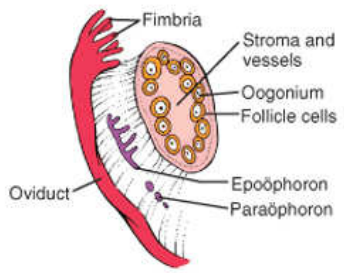


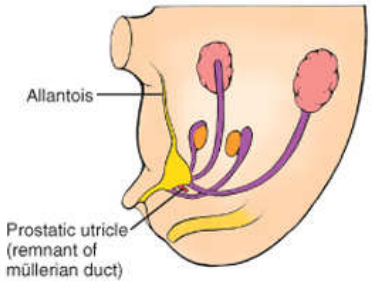


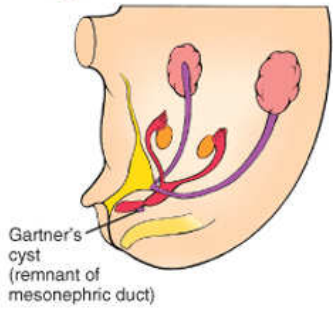






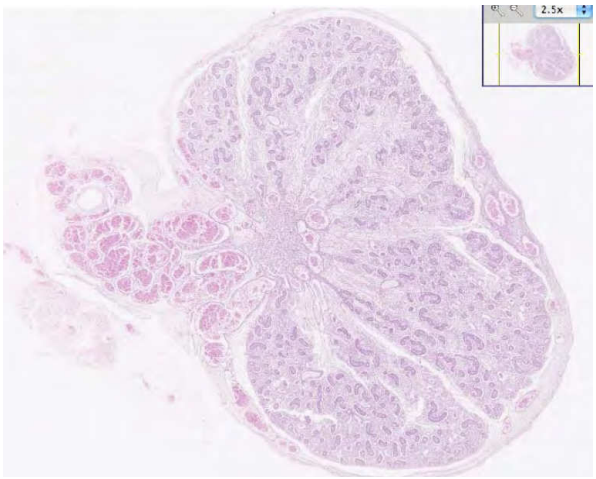


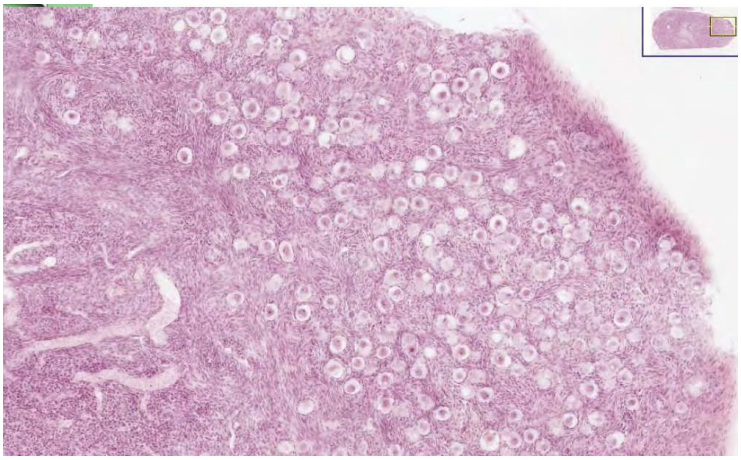


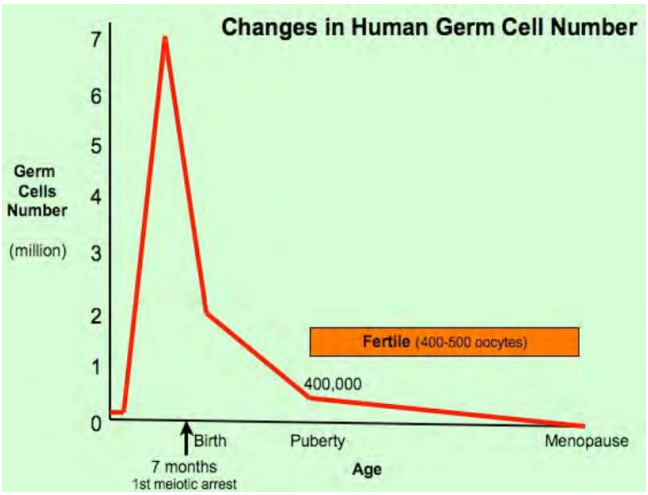


Histology slides

- Fetal testis:
  - Similar to adult
- Infant ovary:
  - Cortex is thicker – more primordial oocytes (follicles)
    - After birth, germ cells lost
    - At puberty, 400 000 oocytes left
    - Release ~400-500 eggs in lifetime

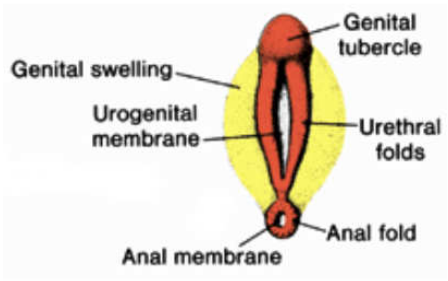


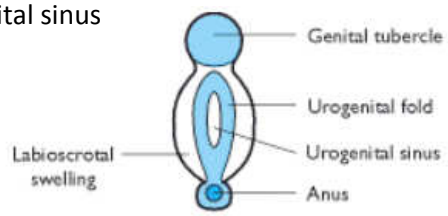


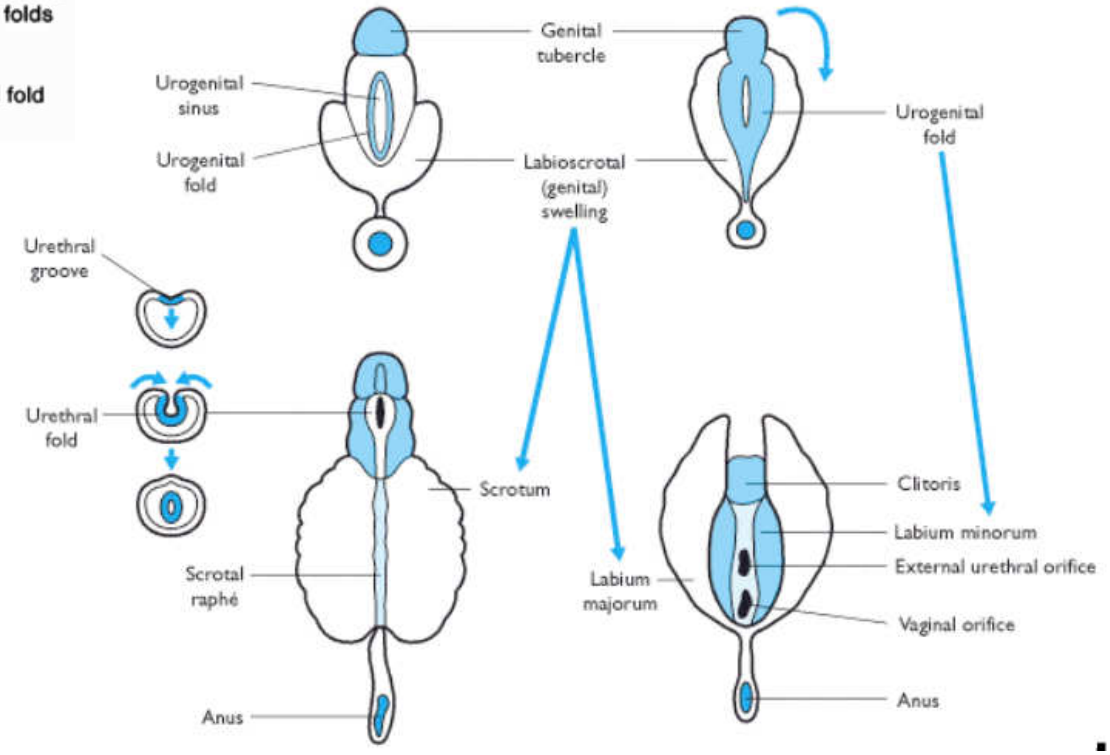


External genitalia

- At stage 23, can't differentiate male and female
  - Standard external genitalia
- Parts:
  - Genital tubercle becomes the clitoris/glans penis
  - Genital swelling becomes scrotum, labial folds
  - Male: urogenital folds fuse to enclose the urogenital sinus
  - Female: folds do not fuse but form labia minora
- Comparison:

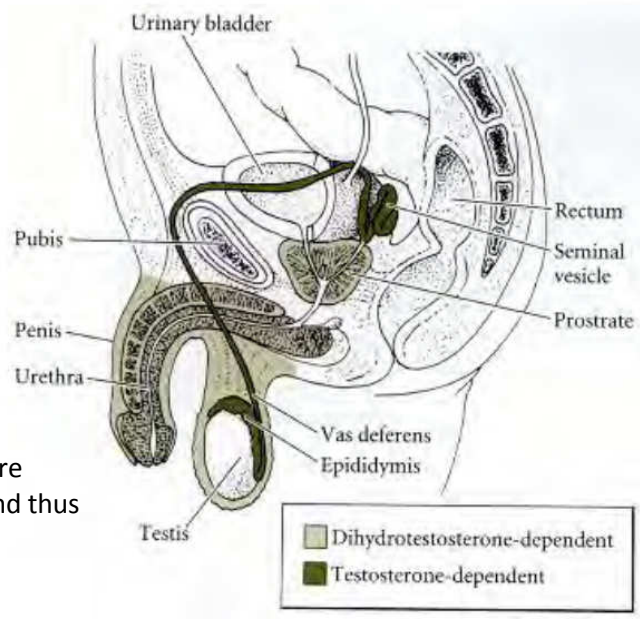






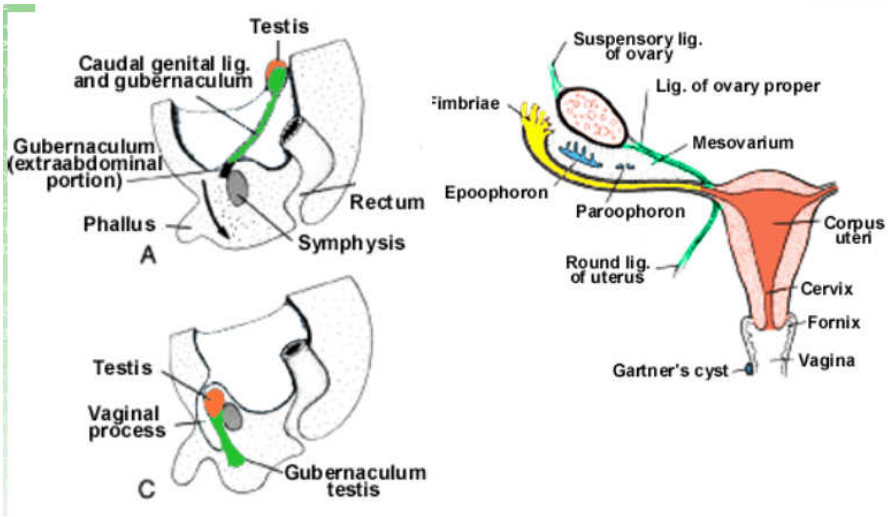
Male anatomy is dependent on hormones:

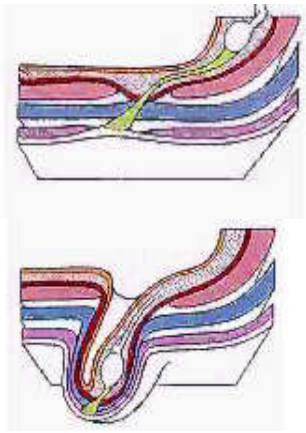
- Testosterone
- Dihydrotestosterone
    - 5alpha reductase conversion of testosterone
    - Differentiates external genitalia and prostate



Descent of the testes

- Gubernaculum has a role in testes migration into the scrotum
    - Thought to be a shortening or a relative change in position
    - May be a postnatal change
- Where the testes leaves the body cavity is a major site of herniation because there is a weakening of the musculature here
    - Hernia can lead to intestines etc, losing blood supply and thus ischaemia and necrosis



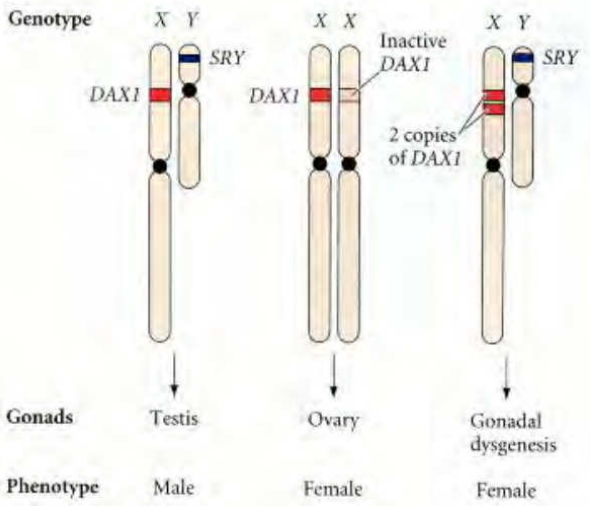


Puberty

- Timing differs for males and females
    - Induced by gonadotrophin secretion and stimulation of gonadal maturation
- Hormones:
    - Males – increase in testosterone
    - Females – increase in estradiol – has positive feedback
- External genitalia develop
- Mammary glands develop
- Tanner stage 1-5
    - Stages (1-5)
        - Female: no breast tissue → areolar enlargement with breast bud → enlargement with breast and areola as single mound → projection of areola above breast as single mound → papilla
        - Male: prepubertal → testes enlarge → penis enlarges, initially length, growth of testes, scrotum → continued growth, pigmented scrotum → testes, penis and scrotum adult size
        - Also pubic hair development

Genetic abnormalities (genital, 12% of total)

- Chromosomal
    - EGS:
        - Turner's syndrome (monosomy XO)
            - 99% non-viable embryos
            - Fail to sexually mature at puberty
        - Klinefelter's syndrome (47, XXY)
            - Begin normal male, infertile
            - Tall, mental dullness, behaviour problems
        - Male sex reversal (46, XX)
            - Develop as male, infertile adults
            - Part of SRY gene located on one X



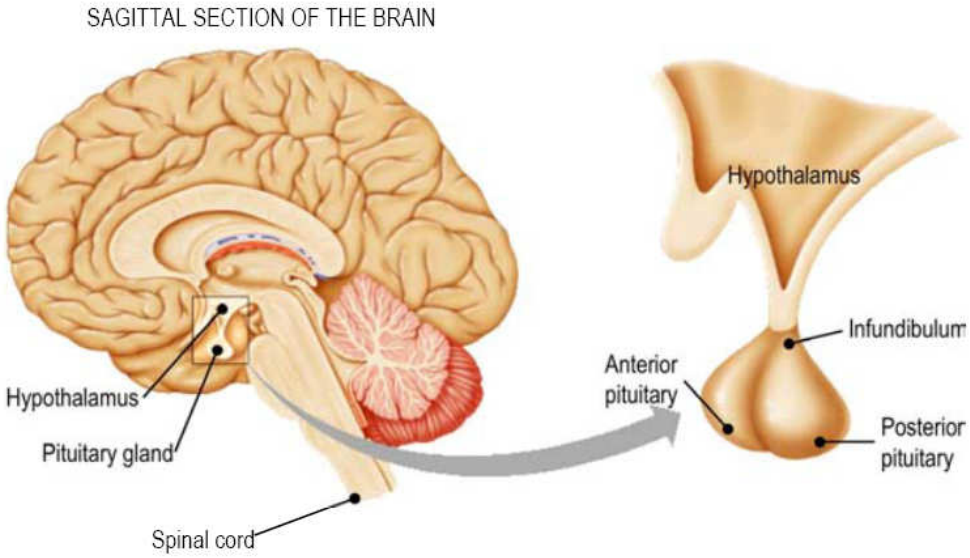
- Hermaphroditism
    - Transgenic appearance of sex characteristics
    - True (46, XX)
        - Gonads both ovary and testes tissue
        - Ovotestes or ovary and testes
    - Male pseudohermaphrodites (46, XY)
        - Gonads of one sex, external genitalia of opposite
        - Various causes
    - Female pseudohermaphrodites (46, XX)
        - Gonads are ovaries, external genitalia ambiguous
        - Hyperplastic adrenals could secrete androgens
- Gonadal dysfunction
    - Improper germ cell formation
    - Gonadal dysgenesis
        - Swyer's syndrome (46, XX)
    - Mixed gonadal dysgenesis (45, X/46, XY)
    - Primary hypogonadism
        - Affected females (46, XX)
        - Defective anterior pituitary production of gonadotropin
            - Prevents development of genitalia
- Tract abnormalities
    - Many different forms
    - Uterine
        - Often associated with other abnormalities
        - Problem with paramesonephric duct
        - Unicornuate, bicornuate
    - Vagina
        - Agenesis, atresia
    - Ductus deferens
        - Uni or bilateral absence, possible due to mesonephric duct not differentiating
- External genitalia
    - Multi-factorial – chromosomal, single gene, environmental
        - Developmental arrest can give ambiguous
    - Hypospadias (common, 1/300)
        - Failure of urogenital folds ot fuse
        - Thus, get proximally displaced urethral meatus, can be corrected surgically
- Gonadal descent
    - Cryptorchidism – one or both testes haven't descended into the scrotum
        - 1/30 live male births, more common in prematures
        - Can be associated with other abnormalities
    - Undescended ovaries – rare, but can be associated with other uterine abnormalities
- Virilisation of genetic female with ovaries (too much androgen)
    - Fetal androgens – congenital adrenal hyperplasia, adrenal adenoma or hyperplasia
    - Maternal androgen – ovarian, adrenal tumours
    - Latrogenic – exogenous androgens
- Androgen insensitivity (too little androgen effect)
    - XY karyotype and presence of testes
    - External – female secondary sex characteristics
    - Internal – lack of mullerian duct derivatives, undescended testes

<u>Sex and brain differentiation</u>

- Brains of males and females differ:
    - Reproductive regions and other regions (where sex differences not necessarily expected)
- Different susceptibility to neurological and psychiatric disease
- Sources of these differences
    - Sex chromosome genes, gonadal hormones, XX and XY differentiation before influence by gonadal hormones

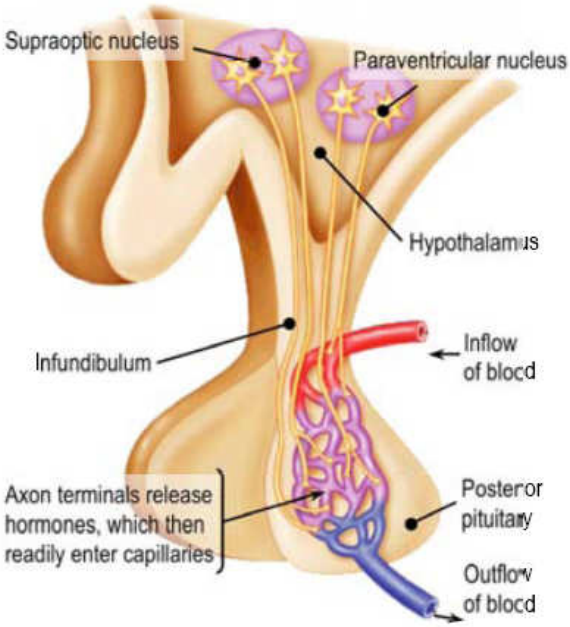
Anatomy

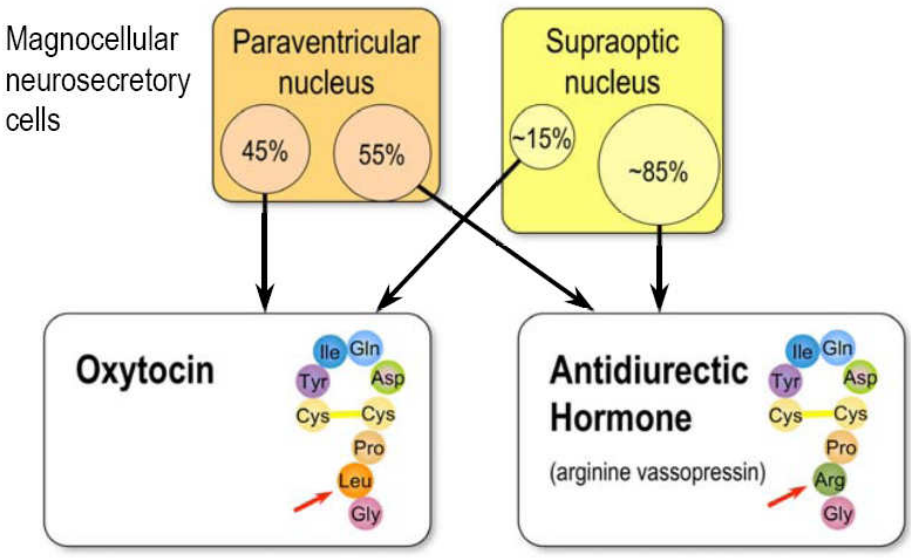
- Hypothalamus contains neurons that send axons down into the pituitary



Posterior pituitary

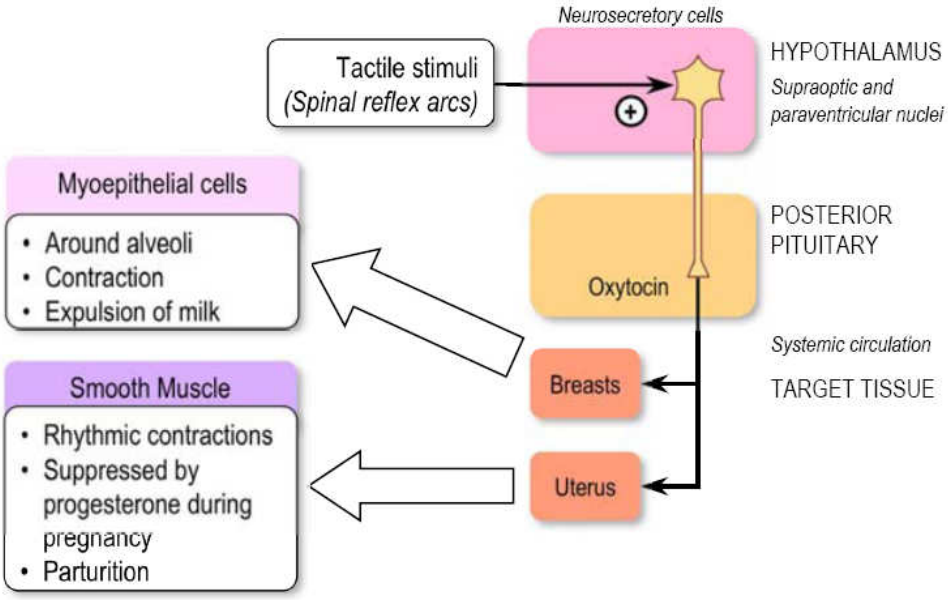
- Process:
  - Magnocellular neurosecretory cells (neurons) in the hypothalamus (paraventricular and supraoptic nuclei) synthesise hormones
    - Hormones are packaged into vesicles that are transported down the axon
    - Hormones in vesicles are released by exocytosis (like neurotransmitters) into fenestrated capillaries
- Produces oxytocin and antidiuretic hormone
  - Paraventricular nucleus: 45% oxytocin, 55% antidiuretic hormone
  - Supraoptic nucleus: 15% oxytocin, 85% antidiuretic hormone
- Oxytocin vs antidiuretic hormone
  - Very different effects, differ from each other by a single amino acid: Leucine (oxytocin) vs Arginine (ADH)





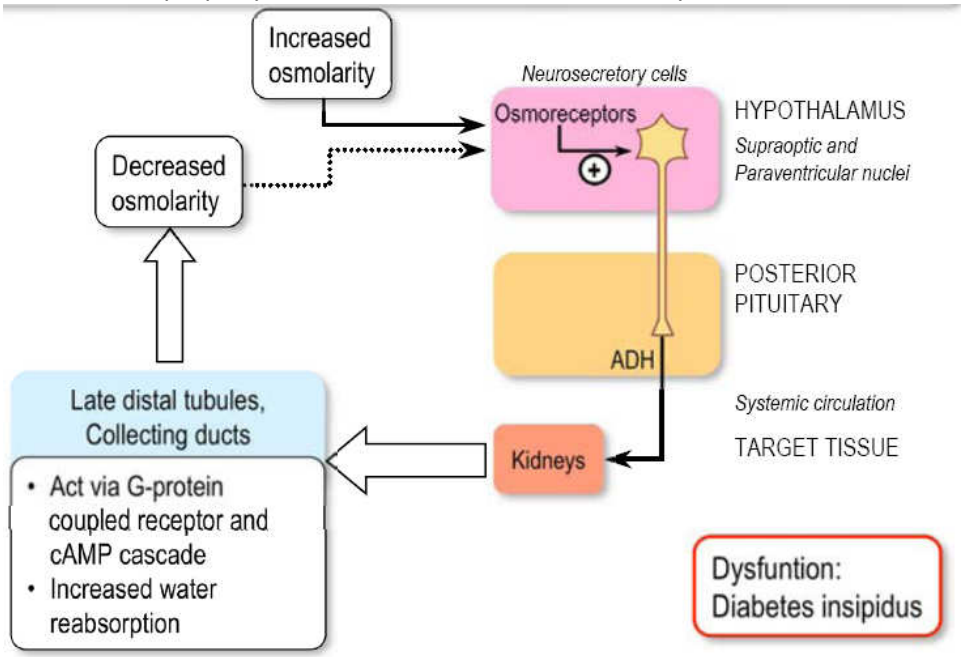
Oxytocin

- Tactile stimuli (stimulation of the breasts/sexual organs) causes increased release of oxytocin from the hypothalamus and further release through the posterior pituitary
    - Has different effects on different tissues:
        - Breasts – myoepithelial cells
            - Contraction to expel milk from alveoli
        - Uterus – smooth muscle
            - Rhythmic contractions
            - Suppression during pregnancy by progesterone
            - Important during parturition (enhanced)



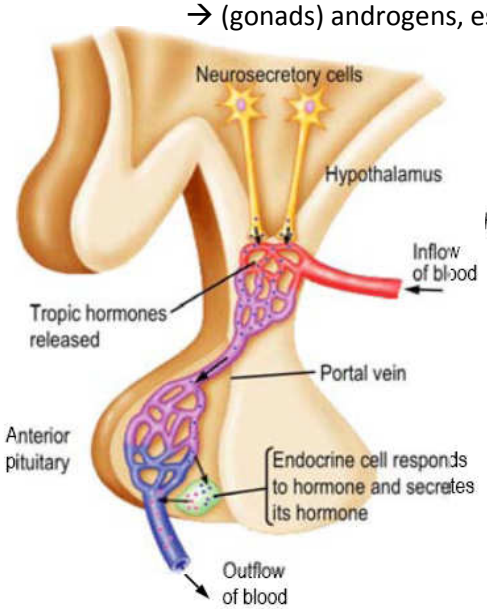
Antidiuretic hormone (ADH)

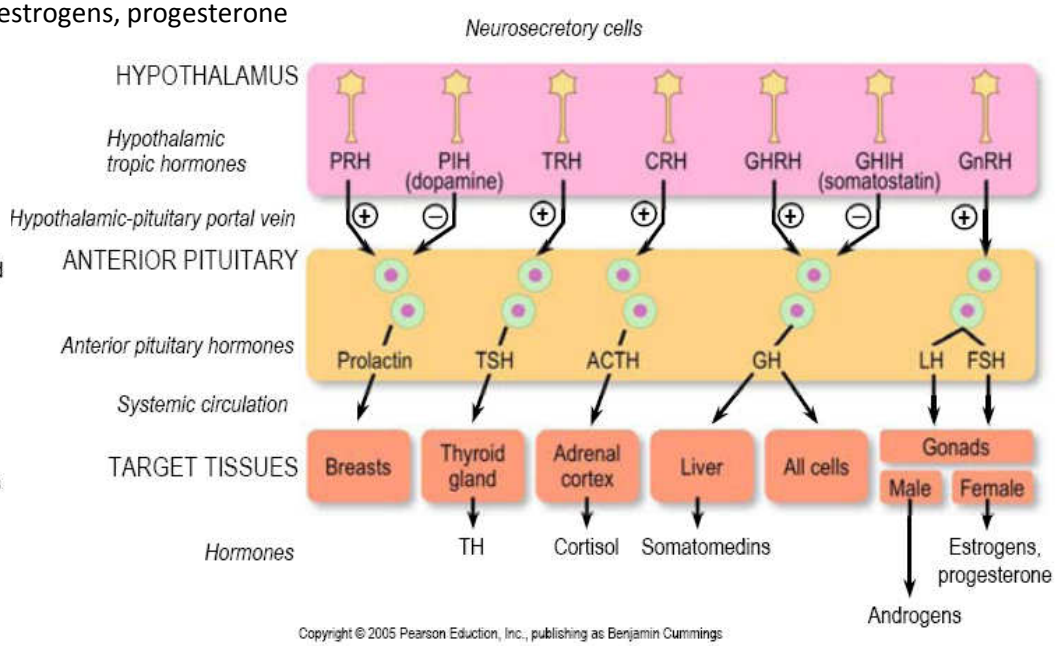
- Controls osmolarity
- Increased osmolarity causes simulation of osmoreceptors that cause increased release of ADH from hypothalamus
    - Passes through posterior pituitary and into circulation
    - Effects:
        - Kidneys – last distal tubules, collecting ducts
            - Acts via a G-coupled protein receptor and a cAMP cascade
            - Increases water reabsorption
    - Negative feedback
- Dysfunction can lead to diabetes insipidus
    - Can’t reabsorb water properly and thus can’t decrease osmolarity of blood



Anterior pituitary

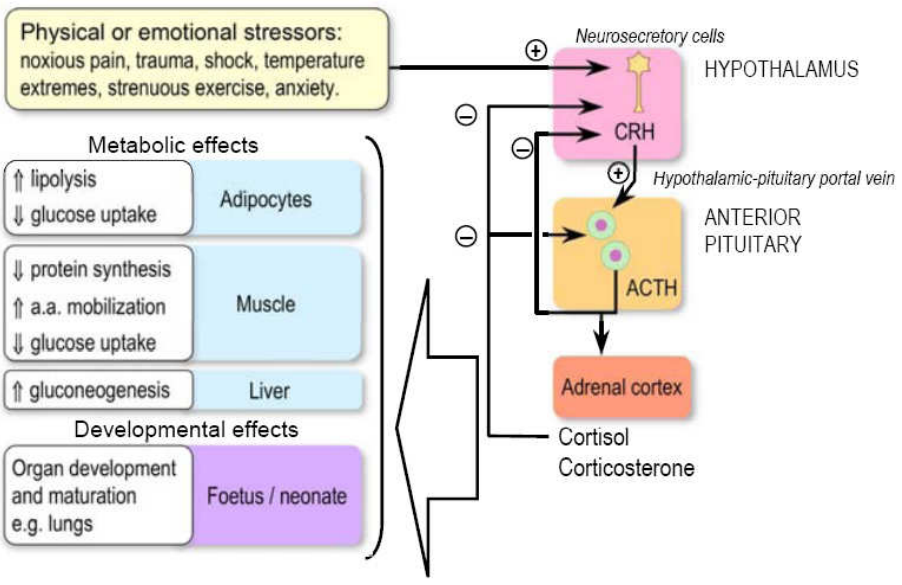
- Process – hierarchical control:
  - Neurosecretory cells release tropic hormones from the hypothalamus
    - These are transported via the hypothalamic-pituitary portal vein to the anterior pituitary
      - These hormones act on endocrine cells in anterior pituitary and stimulate hormone release
      - Anterior pituitary hormone enter the blood and circulate
- Hormones:
  - Prolactin releasing hormone vs prolactin inhibiting hormone (dopamine) → prolactin → breasts
  - Thyrotropin releasing hormone → thyroid stimulating hormone → (thyroid gland) thyroid hormone
  - Corticotropin releasing hormone → adrenocorticotropic hormone → (adrenal cortex) → cortisol
  - Growth hormone releasing hormone vs growth hormone inhibiting hormone (somatostatin) → growth hormone → (liver) somatomedins, all cells
  - Gonadotropin releasing hormone → luteinising hormone, follicle stimulating hormone → (gonads) androgens, estrogens, progesterone





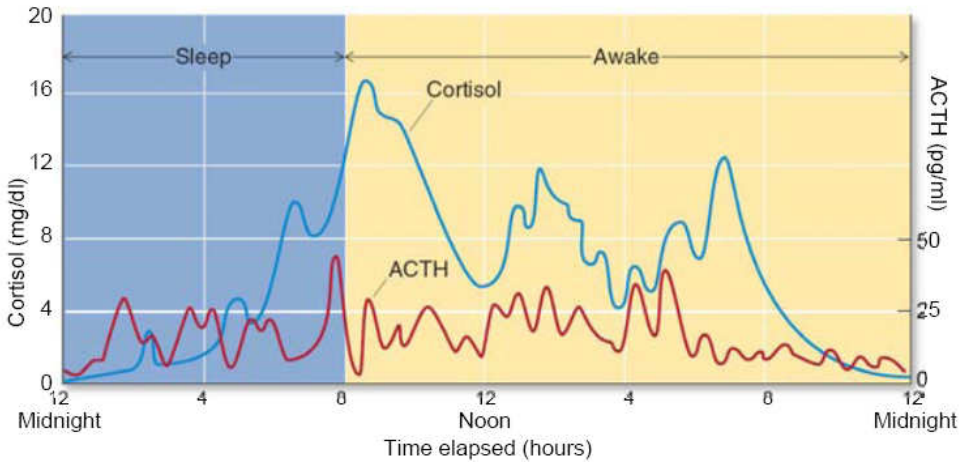
Adrenocorticotropic hormone

- Peptide hormone produced by cleavage of a larger pro-hormone
- Acts on the adrenal cortex (zona fasciculata, zona reticularis)
  - Produces glucocorticoids: cortisol and corticosterone from cholesterol
- Dysfunction
  - Cushing's syndrome due to adrenal defect or ACTH over secretion at anterior pituitary
- Stimulated by corticotropin releasing hormone which is simulated by physical or emotional stress:
  - Noxious pain, trauma, shock, temperature extremes, strenuous exercise, anxiety
- Cortisol effects:
  - Metabolic – increased energy in blood (available)
    - Adipocytes – increased lipolysis, decreased glucose uptake
    - Muscle – decreased protein synthesis, increased AA mobilisation, decreased glucose uptake
    - Liver – increased gluconeogenesis
  - Developmental
    - Fetus/neonate – organ development and maturation, eg: lungs
- Feedback control – self-regulated



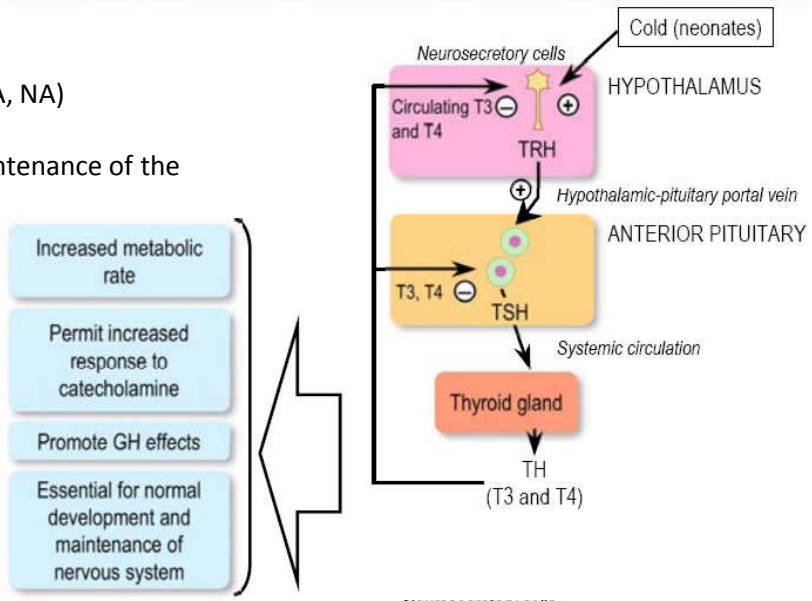
Adrenocorticotropic hormone (continued)

- Diurnal variation
  - Important role in waking us up
    - Levels drop as we sleep, increase as we wake
  - Responds to meal times, linked to energy metabolism
    - Increased glucose in the blood stream, works with other hormones to maintain balance
- Half life: 60-90 minutes (vs adrenaline: 10-15seconds)
- Regulates enzymes and thus causes longer acting changes
  - Alters gene expression, vs: peptide hormone that alter cell surface receptors



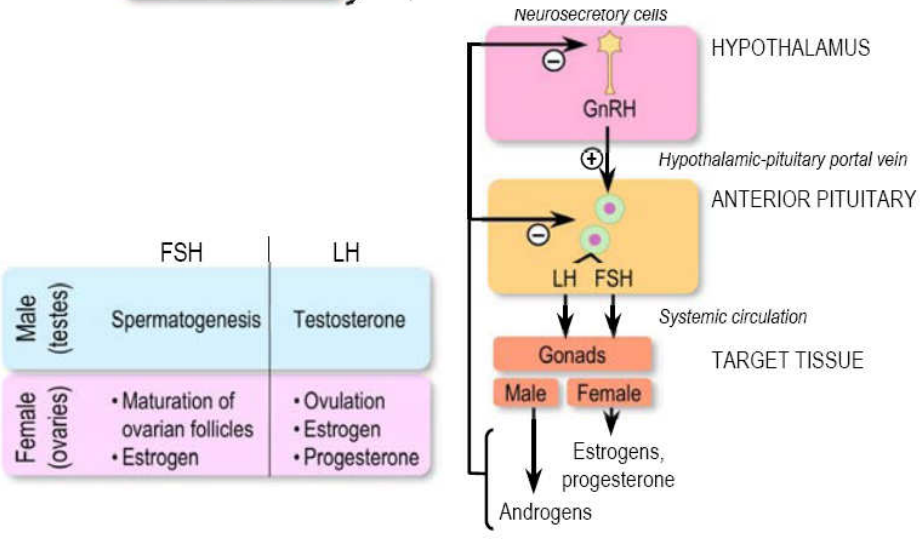
Thyroid stimulating hormone

- A large glycoprotein with an alpha and beta chain
- Acts on almost all cells in the body
- Stimulated by thyrotropin releasing hormone (TRH)
  - TRH is stimulated by the cold in neonates (can't regulate temperature very well)
- T_3 and T_4 Effects:
  - Increased metabolic rate
  - Increased response to catecholamine (eg: A, NA)
  - Facilitates growth hormone effects
  - Essential for normal development and maintenance of the nervous system

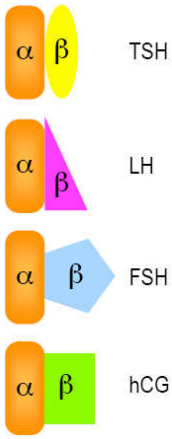


Gonadotropins: LH and FSH

- Glycoproteins made up of alpha and beta chains, related to TSH
- Stimulated by GnRH that has a pulsatile release
  - Changes with menstrual cycle and other inputs from the CNS
  - Hypothalamus receives input from many parts of the brain and stimulates GnRH release



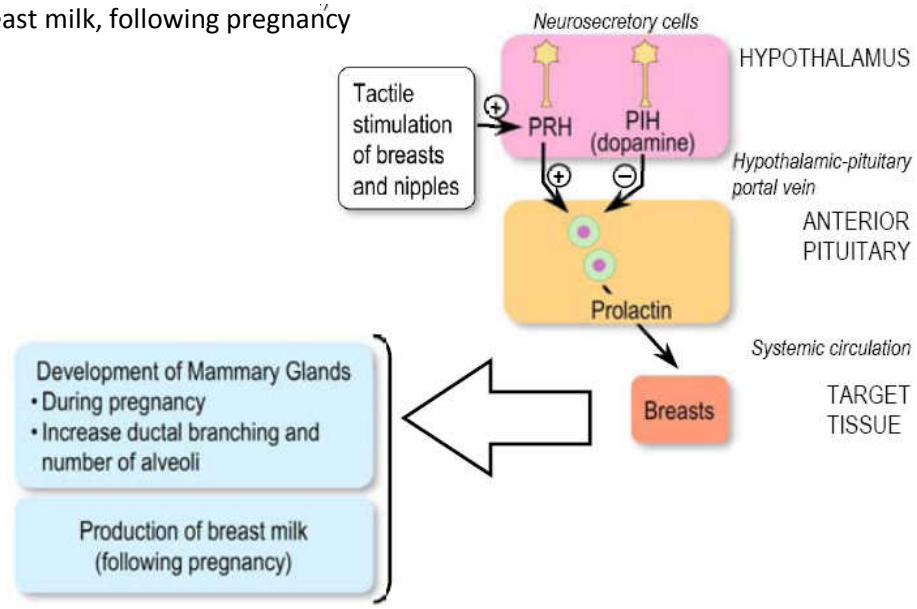
<u>Glycoprotein hormones</u>



- TSH, LH FSH and hCG (human chorionic gonadotropin) are related
  - Made up of 2 subunits
    - Share the same alpha chain, have a different beta chain (allows specificity of hormone)

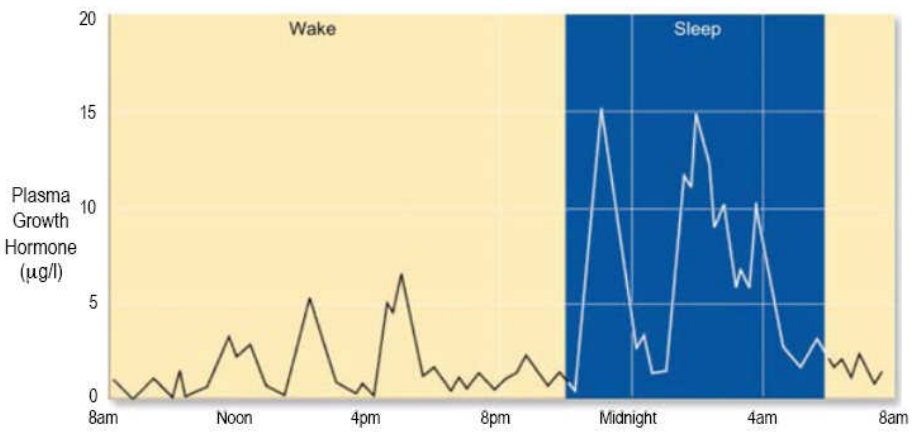
<u>Prolactin</u>

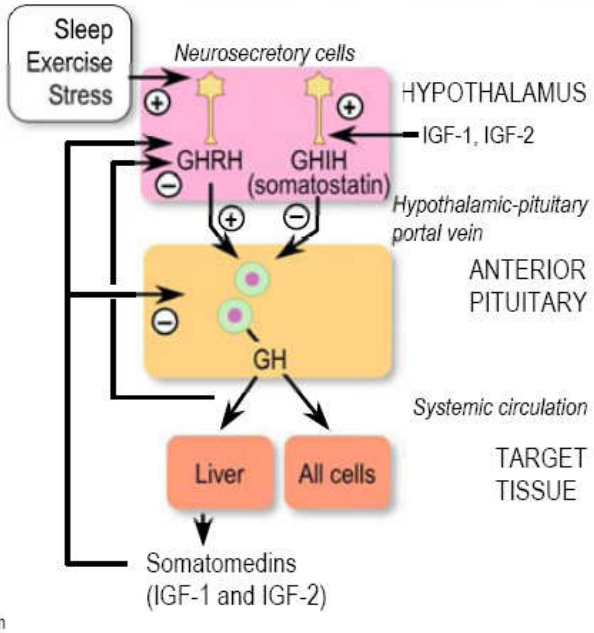
- Single-chain protein related to growth hormone
- Default state is inhibition
  - Release is stimulated by a change in the balance between prolactin releasing hormone and prolactin inhibiting hormone
    - The existence of PRH is disputed, PIH is dopamine
  - Release can also be stimulated by tactile stimulation of breasts and nipples
- Effects
  - Breasts
    - Development during pregnancy: increased ductal branching and alveoli number
    - Production of breast milk, following pregnancy



<u>Growth hormone (somatotropin)</u>

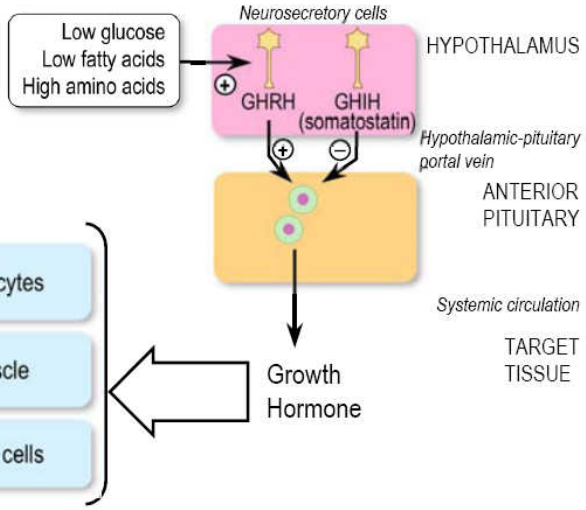
- Protein hormone (191 aa) produced by cleavage from a pro-hormone
- Release from the anterior pituitary is stimulated by GHRH and GHIH balance
  - GHRH is stimulated by sleep, exercise and stress, (low glucose, low fatty acids, high amino acids)
  - GHIH (somatostatin) is stimulated by IGF-1 (insulin-like growth factor) and IGF-2
- Effects
  - Liver
    - Production of somatomedins (IGF-1 and IGF-2) that facilitate indirect cellular growth effects
  - All cells: metabolic effects
- Diurnal variation
  - Pulsatile release with high releasing during sleep and pubertal growth spurt
- Half life is 20-50 minutes





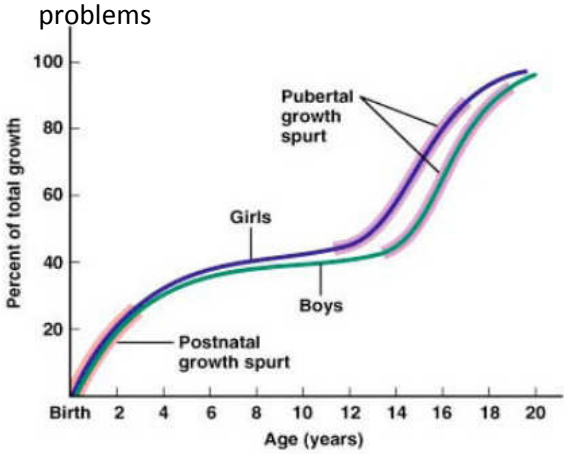
Growth hormone (continued)

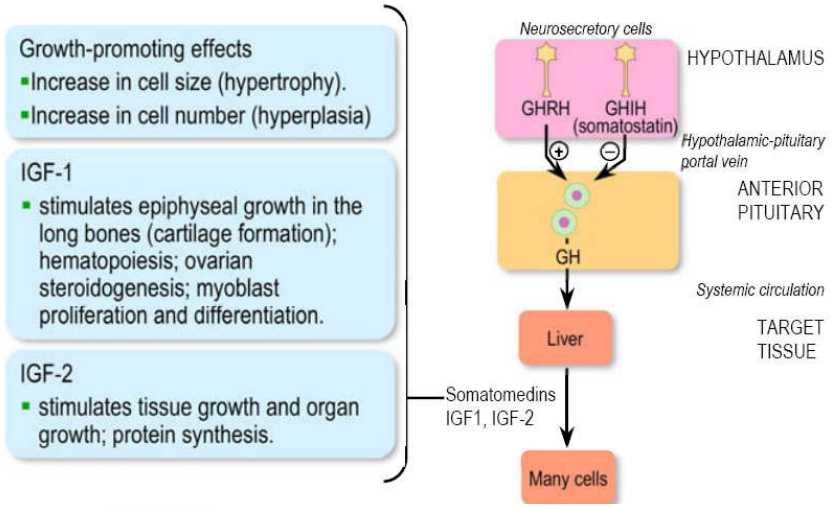
- Effects on all cells
  - Metabolic – want glucose available and protein available for growth
    - Adipocytes – increased lipolysis, decreased glucose uptake
    - Muscles – increased protein synthesis (important for growth), decreased glucose uptake
    - Other cells – increased protein synthesis
  - Cell growth – indirect
    - Cause liver to produce somatomedins: IGF-1 and IGF-2, act on every cell in the body
      - Promote growth: hypertrophy (cell size) and hyperplasia (cell number)
    - IGF-1, stimulates:
      - Epiphyseal growth in long bones (cartilage formation)
      - Haematopoiesis, ovarian steroidogenesis (menstrual cycle)
      - Myoblast proliferation and differentiation
    - IGF-2, stimulates:
      - Tissue growth and organ growth
      - Protein synthesis
- Long bone growth: IGF-1
  - Process:
    - Young chondrocytes undergo cell division
    - Chondrocytes enlarge
    - Chondrocytes are trapped during calcification and die

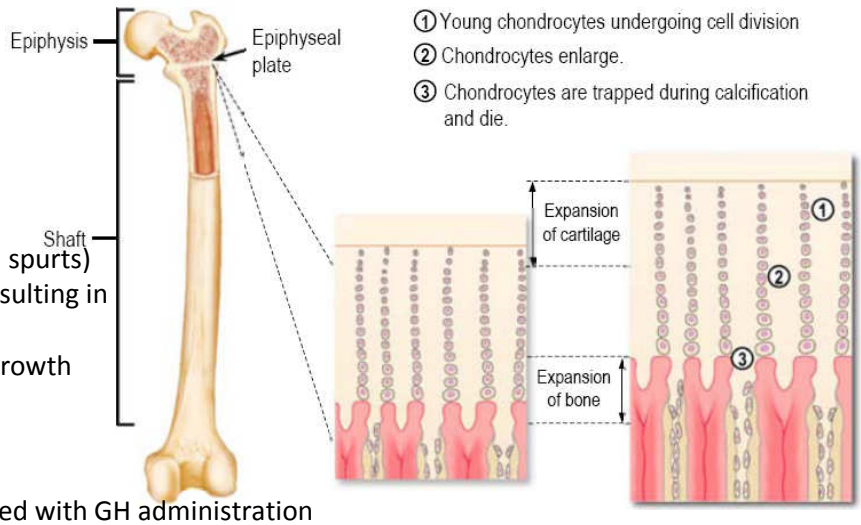


Growth and development

- Involves an interplay/interaction of several molecules:
  - Thyroid hormones
  - Glucocorticoids (cortisol, corticosterone)
  - Sex steroids
  - Growth hormone
  - Somatomedins
- Defects in these can cause growth problems





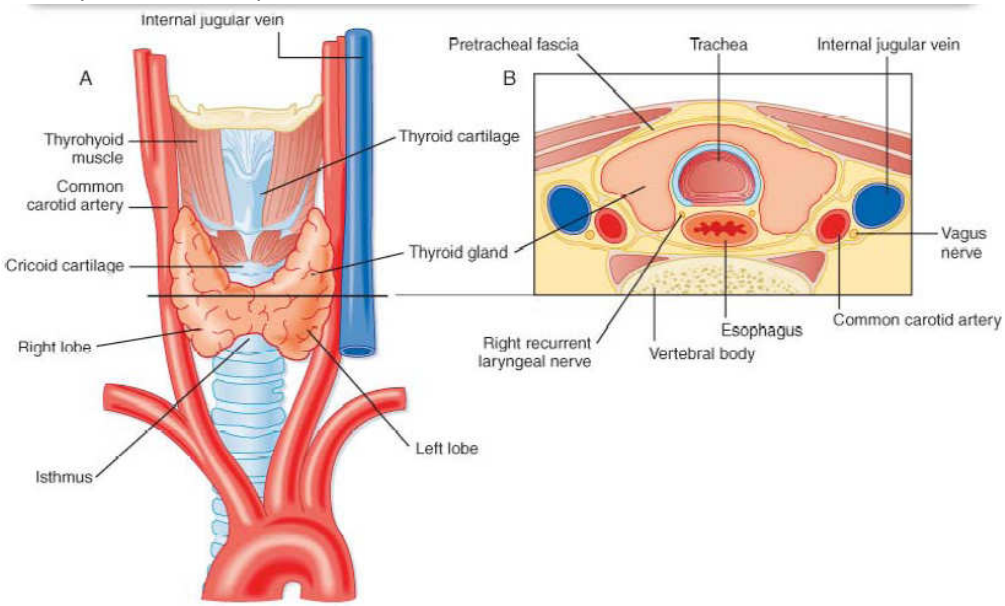


Growth hormone dysfunction

- Giantism
  - Excess growth hormone (during growth spurts)
    - Due to hypersecretion of GH resulting in excessive elongation of bones (epiphyseal plates) and tissue growth
- Dwarfism
  - Too little growth hormone
  - Causes:
    - GH hyposecretion, can be treated with GH administration
    - IGF-1 impairment, or a lack of tissue response to IGF-1 (Laron dwarfism)

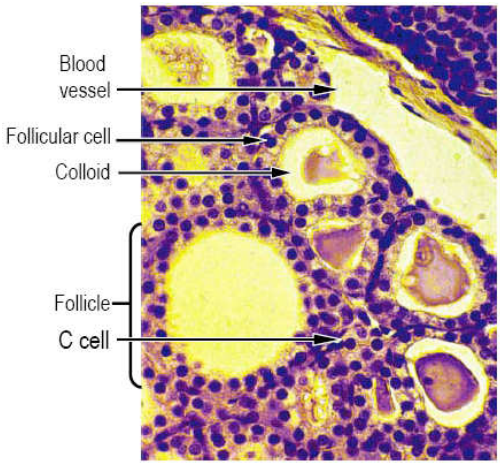
Anatomy

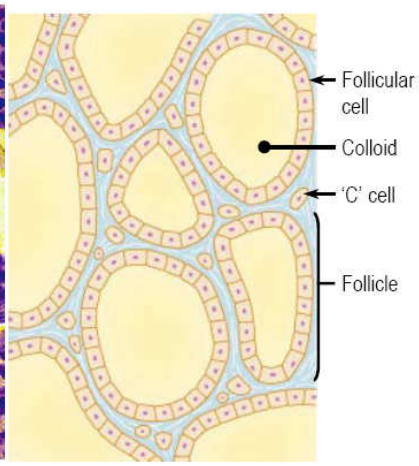
- The thyroid is shaped like a bow-tie or butterfly and is located in front of the trachea
    - Like all endocrine organs, it is richly innervated with BVs
        - Process: vessel into gland → capillaries → vessels out of organ
        - Thus allows hormones to be distributed into the blood stream
- Hormones are carried in the blood directly or via carrier proteins

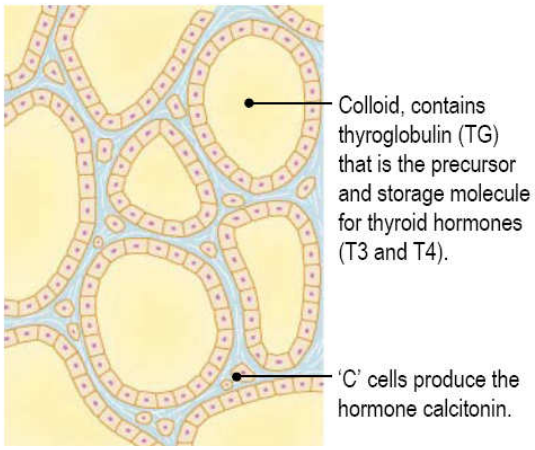


Thyroid follicles

- Follicle is made up of follicular cells around a colloid of fluid
    - Follicular cells:
        - Regulate production and release of hormones
        - Produce precursor proteins like thyroglobulin
        - Store iodide
    - Colloid stores thyroglobulin – the precursor and storage molecule for thyroid hormones
    - 'C' cells (parafollicular cells)
        - Produce hormone calcitonin

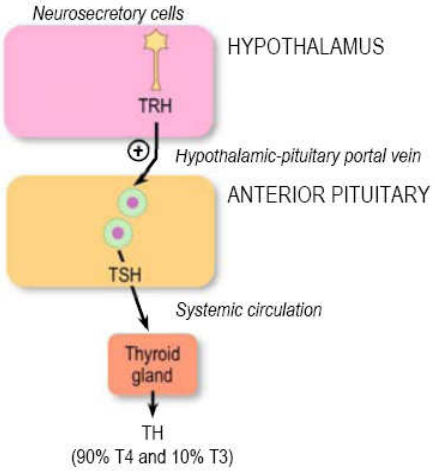






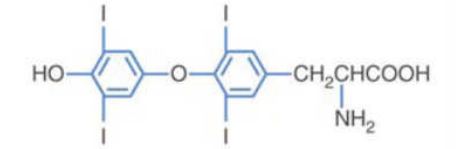
Pathway – control of thyroid hormone secretion

- Thyrotropin releasing hormone (TRH) – tripeptide hormone (pyro-Glu-His-Pro) is released from the hypothalamus and stimulates cells in the anterior pituitary to release Thyroid stimulating hormone (TSH)
    - TSH is a large glycoprotein with an alpha and beta chain
        - TSH:
            - Promotes iodide uptake – short term receptor
            - Promotes synthesis of thyroglobulin and thyroid hormones – long-term transcription regulation
            - Stimulates secretion of T_3 and T_4 – fast altering action of proteins involved in secretion

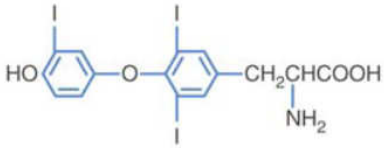


Thyroid hormones

- Synthesised from tyrosine
  - Amine hormones, but are lipophilic
    - Not dissolvable in water and can cross cell membranes
    - However, thus need help with transport around body
  - Iodinated ring structures
- T4 and T3 are determined by the number of iodide molecules attached
  - T4 is synthesised at a rate 10x greater than T3
    - T3 is more potent at target tissues
  - T4 is converted to T3 by cleavage at target tissues by enzyme deiodinase



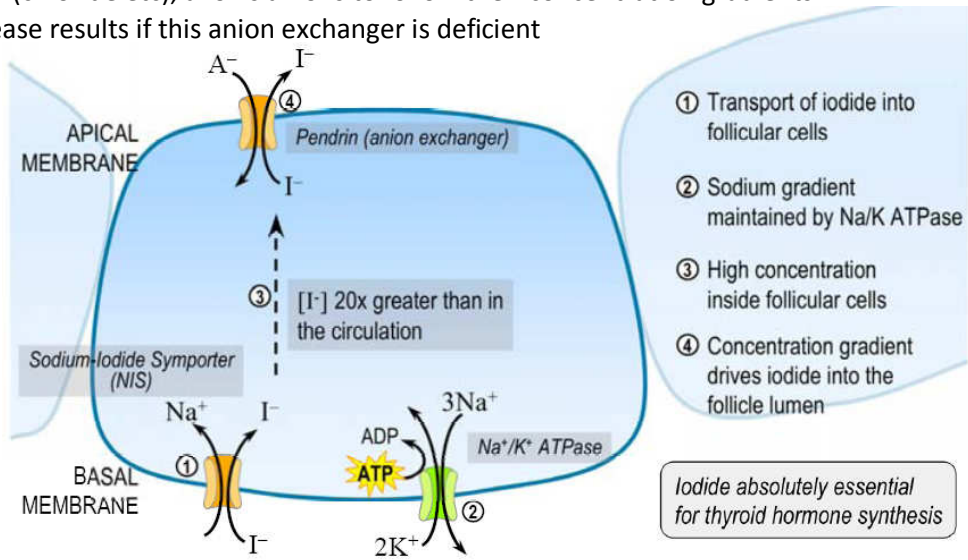
3,5,3′5′-Tetraiodothyronine (thyroxine, or T_4)



3,5,3′-Triiodothyronine (T_3)

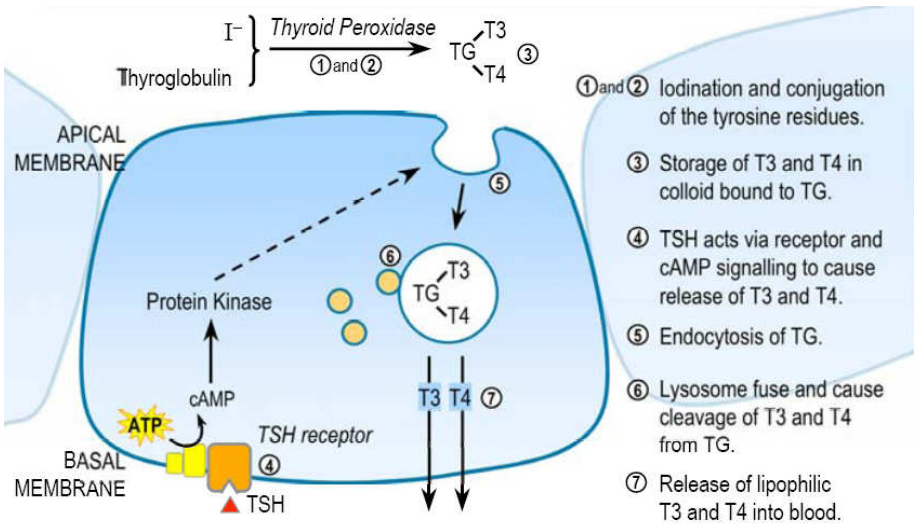
Production: iodide accumulation

- Process:
  - Iodide is taken up from the blood into follicular cells by secondary active transporters
    - Ie: Sodium-iodide symporter (NIS)
      - Uses concentration of gradient of Na^+ to move against the iodide gradient
      - Iodide concentration is 20-100x greater inside follicular cell than outside
    - Na^+ concentration is maintained by Na^+/K^+ ATPase
  - Iodide diffuses out of the cell following the concentration gradient
    - Some diffuses into the follicle lumen
    - Also assisted by Pendrin (anion exchanger)
      - Trades I^- for A^- (chloride etc), allows anions to follow their concentration gradients
      - Pendrin's disease results if this anion exchanger is deficient



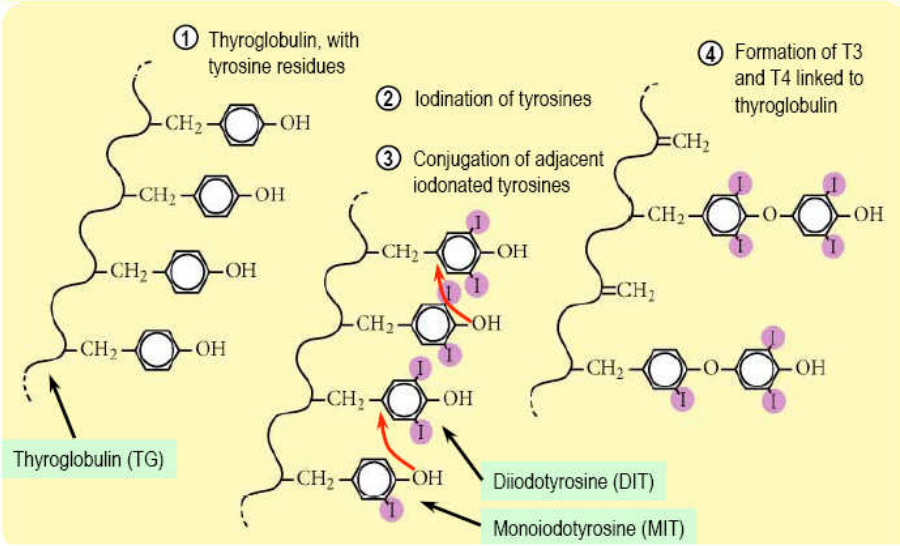
Production: thyroid peroxidase

- Thyroid peroxidase is a very efficient enzyme that causes iodination and conjugation of tyrosine residues
- Process:
  - TP oxidises iodide to iodine (so that it doesn't contribute to the concentration gradient) - iodination
    - Iodine is added to thyroglobulin – conjugation
      - Allows storage of T_3 and T_4 in a colloid, bound to TG
  - TSH activates a G-coupled receptor and initiates a cAMP cascade
    - This leads to endocytosis of TG
  - Lysosome (endopeptidases) fuses with endosome and causes clevage of T3 and T4 from TG
  - Thus, T3 and T4 diffuse out of the cell into the blood stream



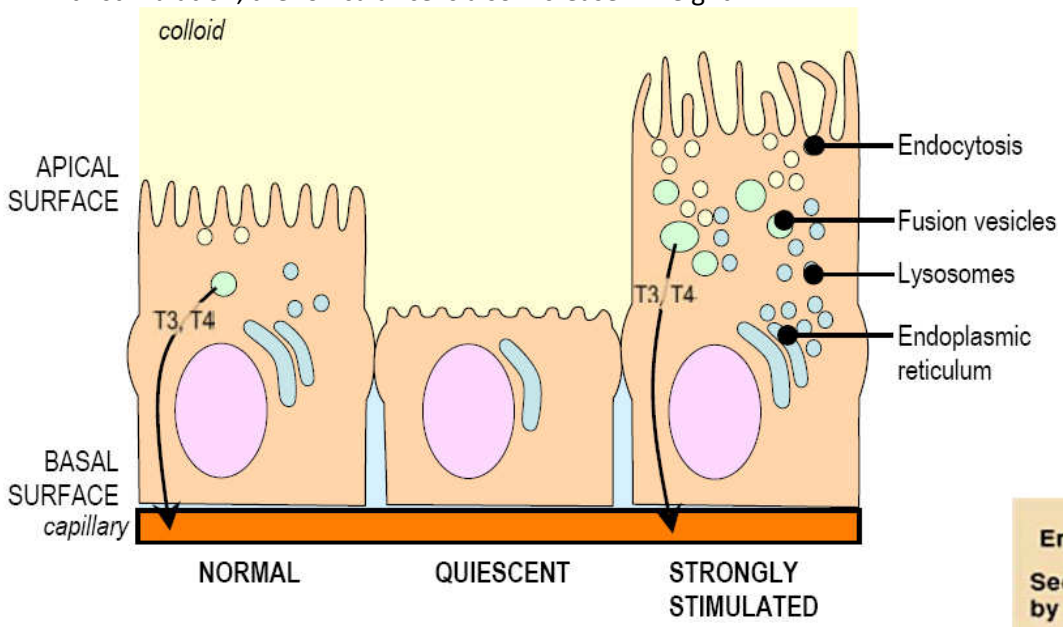
Iodination and conjugation

- Facilitated by thyroid peroxidase
    - Iodide molecules are oxidised and attached to tyrosine residues of thyroglobulin
        - 1 or 2 iodines can be attached
            - 2 – diiodotyrosine
            - 1 - monoiodotyrosine
    - Adjacent iodinated tyrosines are conjugated to form T4 or T3 linked to thyroglobulin peptide backbone



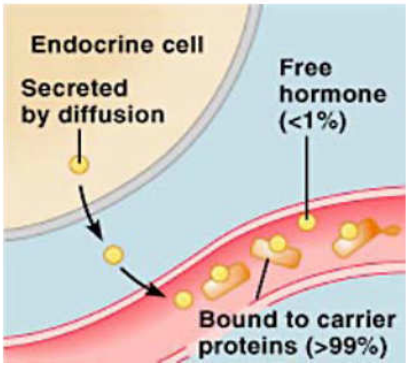
Endocytosis and lipolysis

- TSH causes endocytosis (pinocytosis) of thyroglobulin with T3 and T4 attached
    - Lysosome fuses with the endosome and endopeptidases break peptide bonds and form free T3 and T4
    - These diffuse into the blood via the basal surface of the follicular cell
- With stimulation, the follicular cells also increase in height



T3 and T4 transport

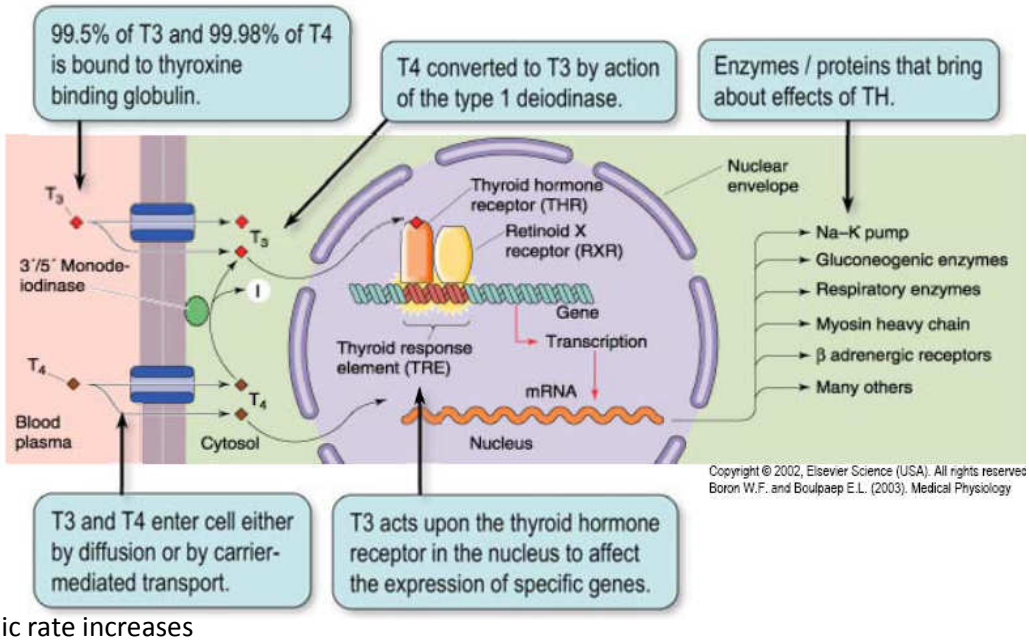
- T3 and T4 are lipophilic and thus need transport proteins to get around in the blood
    - Transported bound to specific carrier proteins:
        - Thyroxine-binding globulin (TBG)
        - Transthyretin
    - Also bound non-specifically to albumin



- Binding and length of binding is based on probability, so hormones come off binding proteins everywhere
    - Only has effect in various places if the appropriate receptors are present
    - T3, 99.5% bound to TBG, half life = 24 hours, T4, 99.98% bound to TBG, half life = 8 days
- T4 provides a reserve pool available for conversion to T3 by deiodinases in the periphery
    - T3 is biologically active

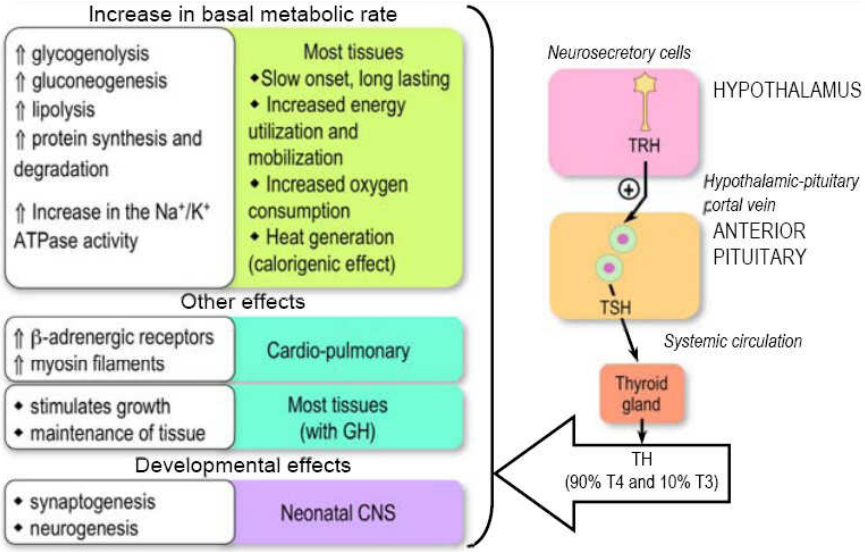
Action of thyroid hormones

- T3 and T4 are released by probability and enter cells by diffusion or carrier-mediated transport
    - T4 is converted to biologically active T3 by type 1 deiodinase
    - T3 moves to the nucleus, binds to receptors (thyroid hormone receptor, THR)
        - Thus binds to the thyroid response element (TRE) and modifies gene expression
    - Transcription leads to changes in:
        - Metabolic enzymes
        - Structural, receptor proteins



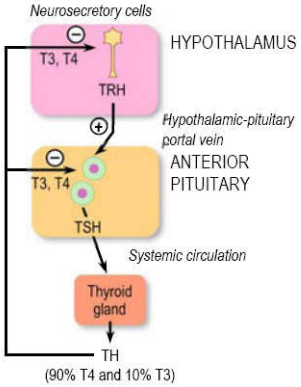
Effects of thyroid hormones

- Most tissues – basal metabolic rate increases
    - Increased glycogenolysis – energy source
    - Increased gluconeogenesis (liver)
    - Increased lipolysis
    - Increased protein synthesis and degradation – generates heat, caloric effect
    - Increased Na^+/K^+ ATPase activity (heat generation)
    - Increased oxygen consumption, due to increased production of ATP in mitochondria
- Cardiopulmonary
    - Increased beta-adrenergic receptors
    - Increased myosin filaments
- Most tissues (with GH)
    - Stimulates growth
    - Involved in maintenance of tissue
- Neonatal CNS – developmental effects
    - Synaptogenesis
    - Neurogenesis
        - Therefore, lack can lead to cretinism



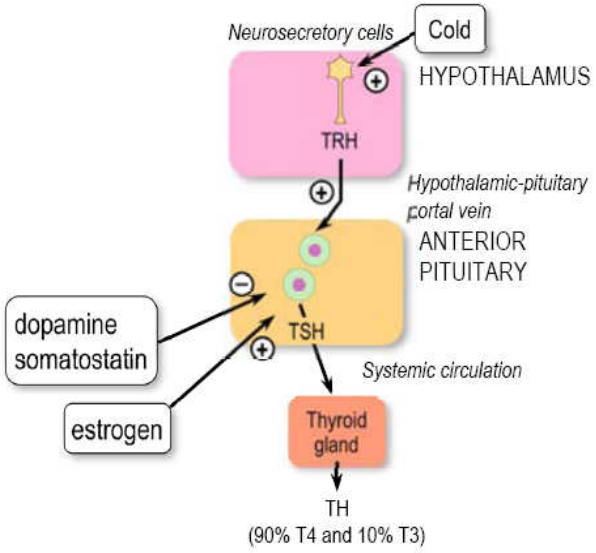
Control of thyroid hormone secretion

- Negative feedback control
    - Circulating T3 and T4 have negative feedback on the hypothalamus and anterior pituitary
    - T4 is converted to T3 by type to deiodinase in the hypothalamic and thyrotrophic cells



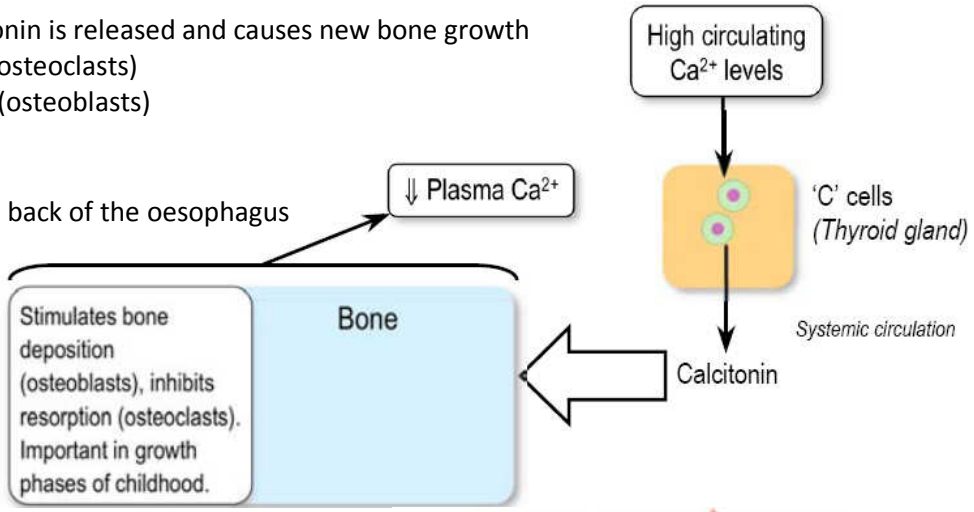
Control of thyroid hormone secretion (continued)

- Inhibition
  - Dopamine and somatostatin (like with GH) inhibit
- Stimulation
  - Extreme cold in neonates (children have poor temperature regulation)
  - Estrogen causes upregulation of TRH receptors because TSH is needed to support changes in the menstrual cycle/pregnancy



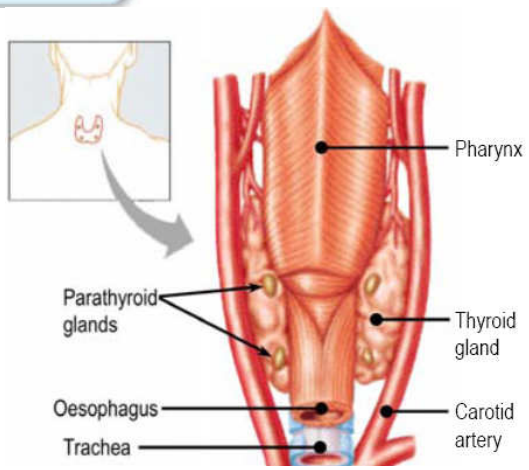
"C" cells – parafollicular cells

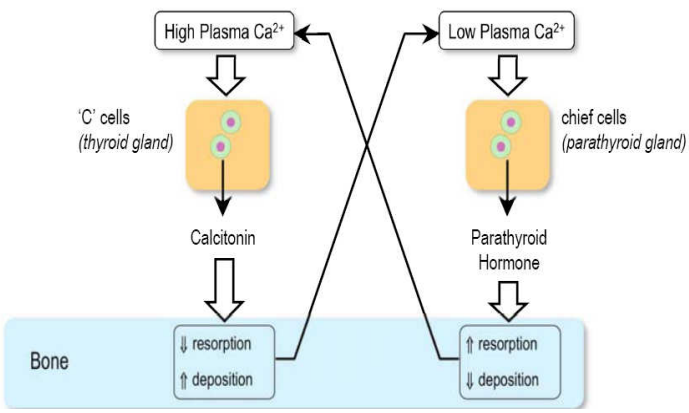
- Secrete calcitonin
  - A peptide hormone (32aa)
- Process:
  - Calcium sensing receptor protein (CasRP) on 'C' cells detects calcium levels
  - With increased calcium, calcitonin is released and causes new bone growth
    - Inhibits reabsorption (osteoclasts)
    - Stimulates deposition (osteoblasts)

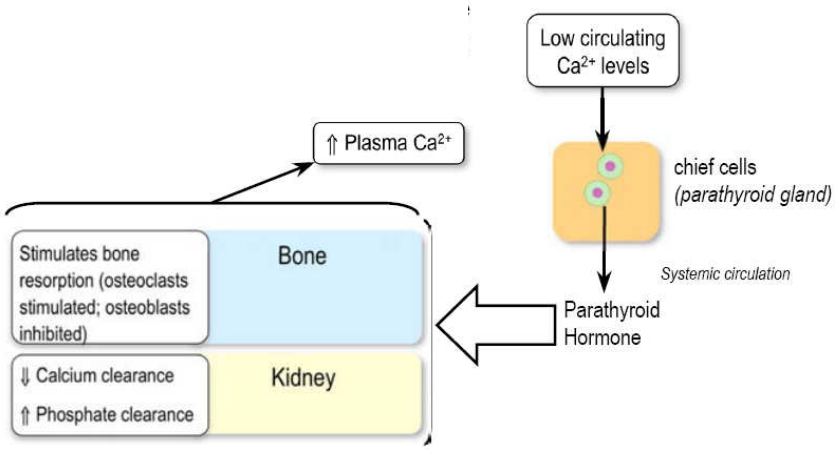


Parathyroid gland

- Four, small ovoid bodies located at the back of the oesophagus
  - Embedded in the posterior surface of each lobe of the thyroid gland
  - Separated from thyroid by connective tissue
- 2 cell types
  - Chief cells (most)
  - Oxyphilic cells
- Chief cells secrete parathyroid hormone (PTH)
  - Single chain protein formed from pro-hormone
- Process:
  - Calcium sensing receptor protein (CasRP) on chief cells detects calcium levels and modulates release of PTH
  - With low circulating calcium levels, PTH has effects:
    - Bone: stimulates bone reabsorption (osteoclasts) and inhibits bone deposition (osteoblasts)
    - Kidney: decreased calcium clearance, increased phosphate clearance
- Forms an integrated, dynamic system between parathyroid and PTH, 'c' cells and calcitonin to regulate calcium levels
  - Important for muscle contraction and release of synaptic vesicles

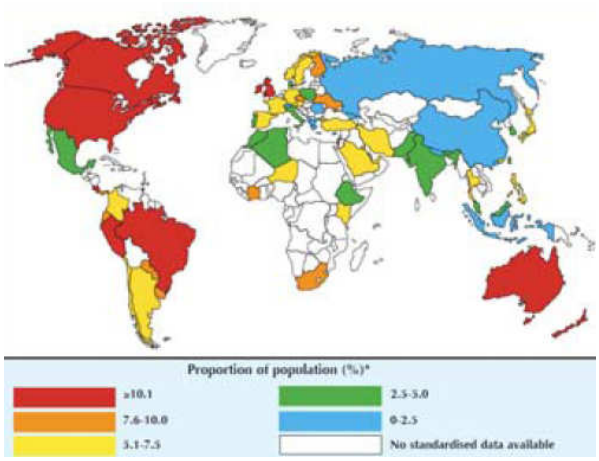






Epidemiology

- Globally, Australia is a 'hot spot' for asthma
    - However, there is no data available for much of the developing world
- Australia has one of the highest asthma prevalence rates in the world
    - 10.2%: 2 million Australians (2005)
        - Rising in the last 25 years, since stabilised
    - 2nd most common self-reported illness in indigenous people
    - In the top 10 reasons for seeing the GP
        - Especially boys 10-14 and women >65
- 2006, 402 deaths from asthma, however, mortality decreasing, 70% in last 20 years
    - Most deaths are >65 and due to complications
- Important cause of morbidity and burden of disease
    - Affects work, school and other normal activities

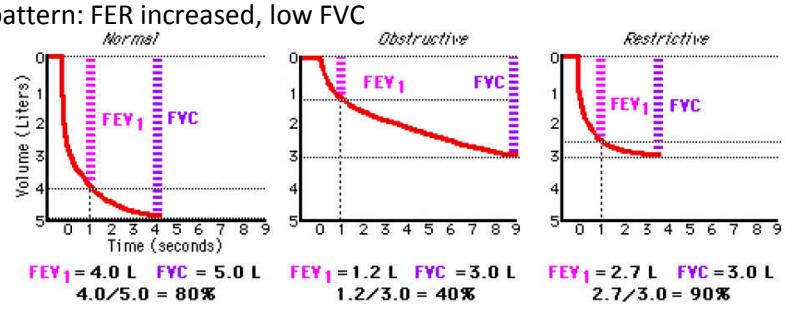


Definition/description

- Length of definition is inversely proportional to the degree of understanding
    - Thus we don't really understand the underlying mechanism/process of asthma
- Things we do know:
    - Extremely common syndrome (aggregation of symptoms, signs)
        - Figures are uncertain due to under/over reporting, but they are still very high with this uncertainty
    - Commonly associated with atopy
        - Ie. the developed IgE response to antigenic challenge and thus allergies
    - There is no single pathognomonic feature
        - There is no way to definitively test for asthma
    - Diagnosis is normally based on clinical manifestations
        - Patients are normally given a trial of therapy and if this works, diagnosis is confirmed

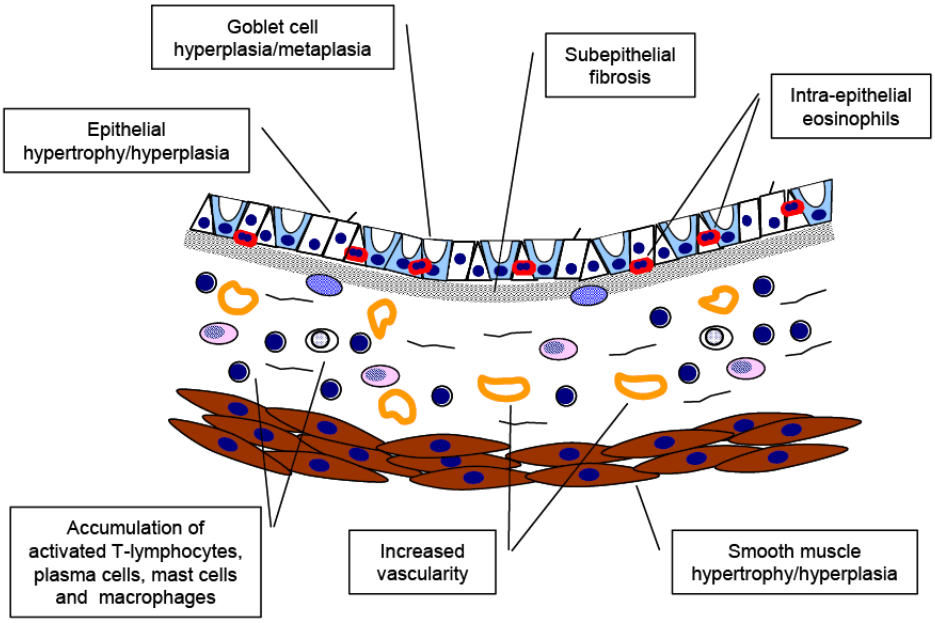
Characteristics of asthma

- Functional abnormalities
    - Increased resistance to airflow (often reversible) – ie, it is harder to breathe
        - Bronchoconstriction
            - Contraction of bronchiole smooth muscle
            - Relieved by β2 agonist
        - Airway wall oedema
            - Inflammation results in vasodilation and exudate efflux into tissue thus decreasing bronchiole lumen
        - Obstruction by mucus
            - Air movement dries out the mucus making it sticky and obstructive
    - Airway hyper-reactivity (hyper-responsiveness)
        - Ie. asthmatics respond worse to irritants than non-asthmatics
            - Irritants can be: bronchoconstrictors or non-specific irritants
    - Asthma is an obstructive disease
        - Can be diagnosed by spirometry
            - FER (forced expiratory ratio)
              = FEV_1 (forced expired volume in 1 second)/FVC (forced vital capacity
        - Obstructive pattern: low FER, normal FVC
        - Restrictive pattern: FER increased, low FVC

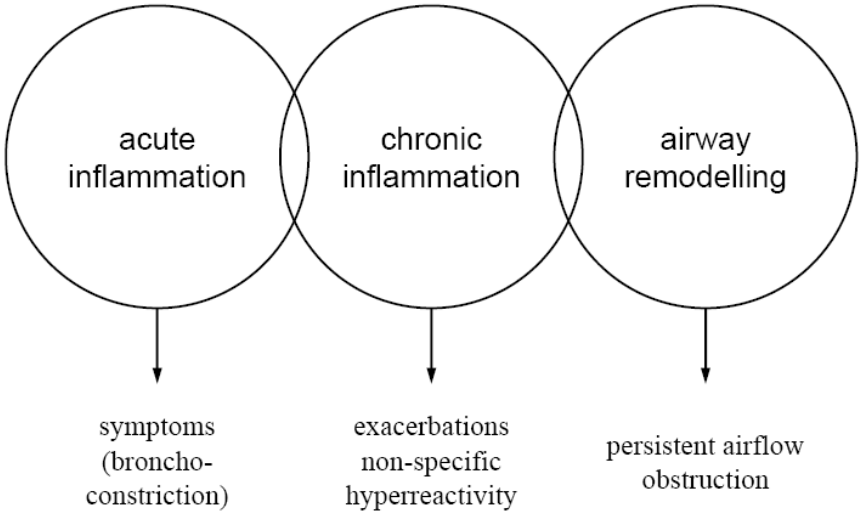


Characteristics of asthma (continued)

- Inflammation of the airways
  - Recruitment of eosinophils (normally only seen in allergic inflammation and parasitic infection)
  - Accumulation and degranulation of mast cells
  - Accumulation of activated T-cells and macrophages
- Airway wall remodelling
  - Metaplasia and hyperplasia of goblet cells
    - Lining of the epithelium changes
    - Mucus is normally made by bronchiole glands, now goblet cells and mucus overproduction
  - Subepithelial fibrosis – fibrosis layer underneath epithelium
  - Hypertrophy and hyperplasia of smooth muscle
    - Increase in smooth muscle mass thus increasing bronchoconstriction for the same stimulus
  - Angiogenesis – increased vascularity
    - Increased leakage of fluid into the tissue with inflammation

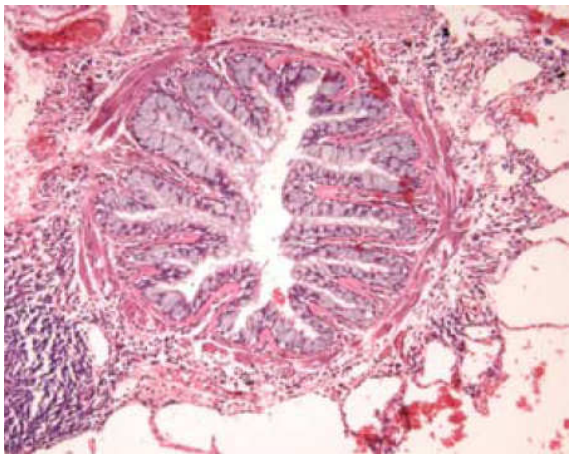


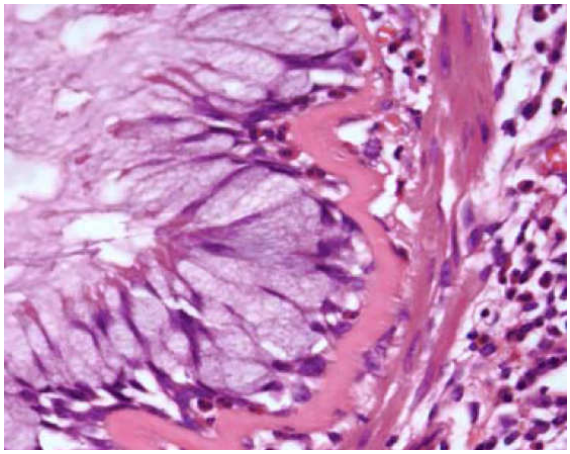
- Theories to relate different features of asthma to pathological processes are incomplete
  - Often over simplified
  - Eg:
    - Acute/chronic inflammation/airway remodelling all linked
      - Acute inflammation causes symptoms – like bronchoconstriction and airway wall oedema
      - Chronic inflammation causes exacerbations – like non-specific hyper-reactivity
      - Airway remodelling causes persistence of the airflow obstruction

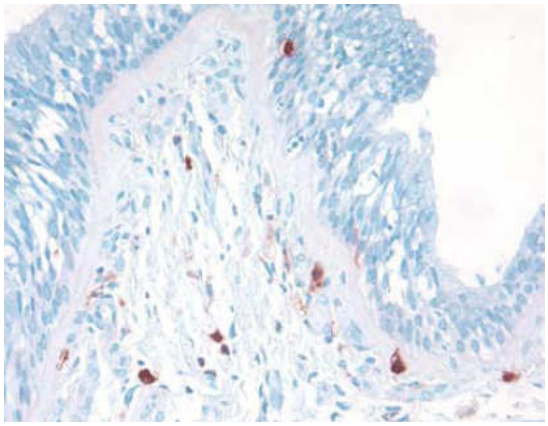


Histology slides

- (pic 1) Asthmatic bronchiole with low power
    - Features:
        - Prominent band of smooth muscle
        - Airway has collapsed
        - Epithelium is almost entirely made up of goblet cells
        - Inflammatory cells → eoseinophils/lymphocytes present
            - Lymphoid follicle present
        - Mucus in lumen
- (pic 2) Asthmatic bronchiole – high power
    - Features
        - Intraepithelial eosinophils + other eosinophils
        - Subepithelial fibrosis
        - Goble cells
        - Mucus
- (pic 3) Immunohistochemical (immunoperoxidase) staining of mast cells (tryptase)





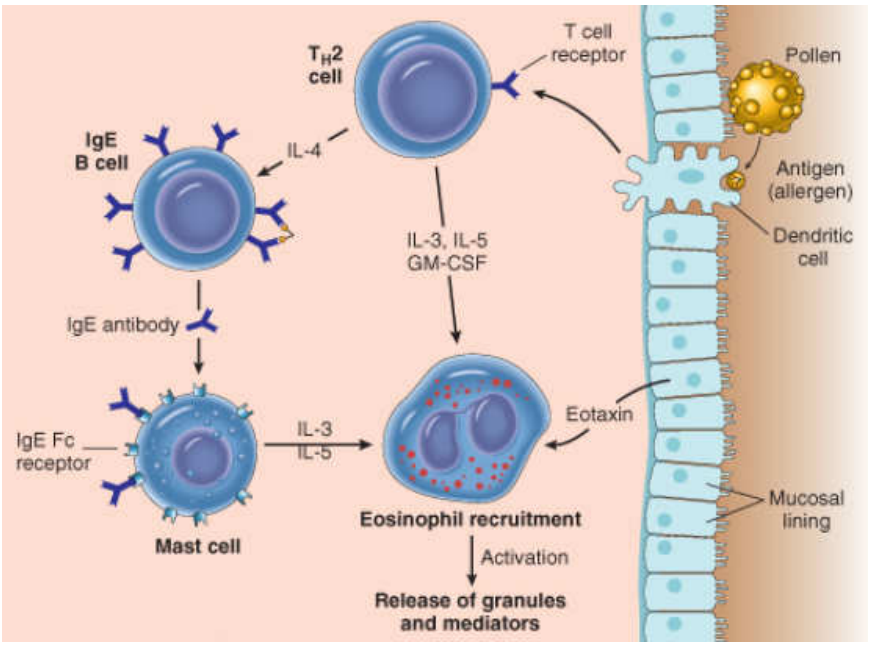


Allergens

- Important allergens
    - House dust mite (most common in Australia)
    - Pollens (eg. rye grass)
    - Animal fur and features
    - Insects (eg. cockroaches)
    - Fungal spores, organic dusts, low molecular weight chemicals
- Non-allergic triggers
    - Chemicals (esp. occupational exposure, food additives)
    - Drugs (eg. aspirin – inhibits cyclooxygenase, causes increased production of leukotrienes)
    - Particulate pollutants (eg. tobacco smoke, air pollution)
    - Viral infections (acute exacerbations of asthma)
    - Exercise (increased airflow, airway wall dehydration)
- Most asthma that develops in childhood is allergic
    - In adulthood, many are non-allergic stimuli
- Allergic asthma can commonly be triggered by non-specific triggers

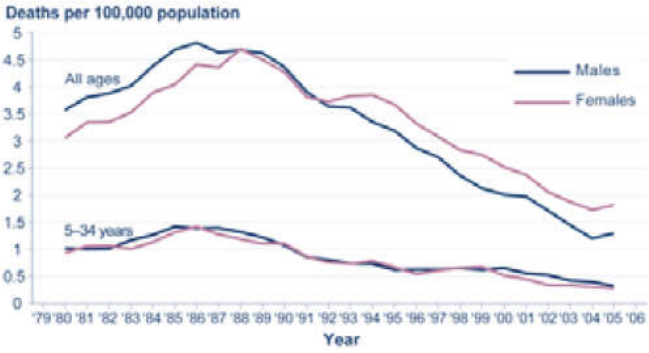
Pathogenesis

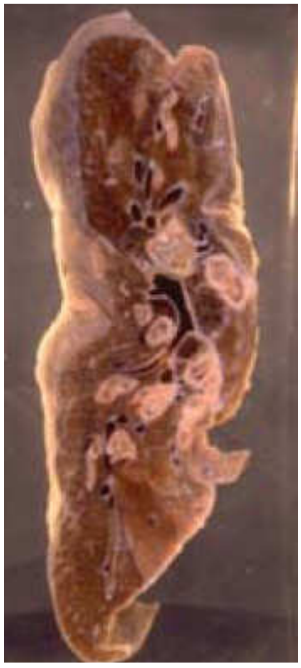
- Antigen presentation causes T-cells to differentiate into TH2 and release IL4, 5
    - These induce differentiation of B lymphocytes that release IgE
    - IgE attaches to mast cells
        - On repeat presentation, IgE is cross-linked and histamine degranulation occurs
        - Mast cells also release leukotrienes that mediate some of the allergic response

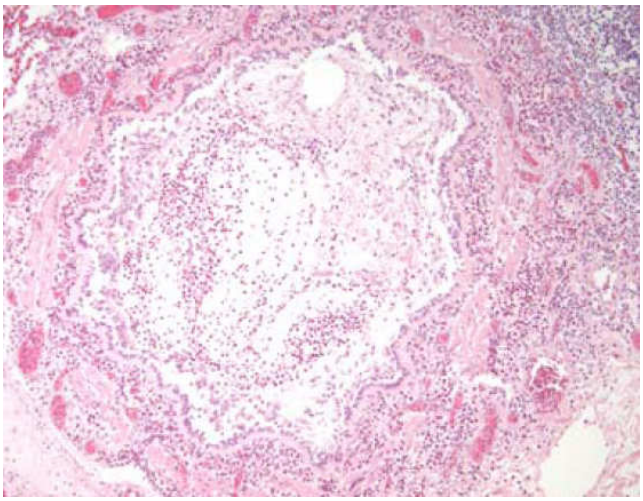


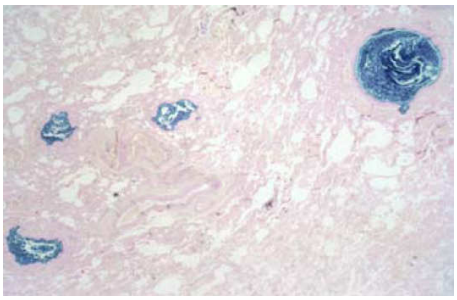
Mortality

- Mortality has decreased in recent times
- In the early 80s, there was a spike in the mortality
    - Possibly due to inappropriate use of bronchodilators causing cardia arrhythmias
- (pic 1) Mucus plugging in fatal asthma
    - Death during acute asthmatic exacerbation
    - Notice prominent mucus filled airways
- (pic 2) Fatal asthma with inflammation plugging
    - Notice:
        - Vascularity leading to air wall oedema
        - Lymphocytes
        - Mucus plug + inflammatory cells (eosinophils) + sloughed off epithelium
        - Basal epithelium thin because cells sloughed off
- (pic 3) Mucus plug alcian blue stain for mucin
    - Notice mucus plugs









Treatment

- Anti-inflammatory drugs
    - Inhaled glucocorticosteroids
        - Non-specific and can also block other things (like the immune system)
    - Long acting β2 agonists
        - Preventers, don't understand why has positive outcome if used concurrently with glucocorticoids
    - Leukotriene receptor antagonists
        - Limited uses because only effective in aspirin/exercise induced
    - Other agents (cromones, anticholinergics (inhibit mucus), novel anti-inflammatory drugs)
- Inhibition of specific mediators
    - Humanised monoclonal anti-IgE
        - Effective, but expensive
    - Anti-cytokine antibodies
    - Soluble cytokine receptors
- Immunoprophylaxis and immunotherapy
    - Native or modified allergens
    - Peptide epitopes
    - DNA vaccines
    - Nice in theory, none yet effective
- We don't have a good understanding of the pathogenesis (asthma is a complex syndrome), thus treatment is symptomatic

Epidemiology

- Prevalence
  - 1% of children have a major disability
    - Ie. an ongoing disability that affects life in every aspect and requires life-long support
  - 5% of preschoolers have developmental problems and need formal intervention
    - Commonest is speech/language delay
  - 15% of school children have learning problems, need intervention
    - In particular, may have problems reading

Implications of developmental delay

- Child
  - Education, social, support, health
- Family
  - Bereavement, social support, expectations, aetiology, genetics, finances, planning for the future, worries about problems that extend beyond the life of the parent
  - With significant disability, one parent may not be able to work full time
    - Financial problems
- Society
  - Social policy, funding, inclusion, need an increase in generic services, special services, consumer advocacy and participation
  - Old policy – children were gathered and put in institutions
    - New – all people in the community are valued
      - Everyone has the right to participate in determining their own lives and who their peers are

Definitions

- Developmental delay definition is applicable to children under 5 only
  - After this age (school age), other standards exist for assessing children and for diagnosing disability
- Definition – child is attaining usual milestones of development later than expected for age
  - Most milestones are variable, but quite consistent and sequential
    - Eg. walking 9-18 months, sitting unaided: 6-8 months
  - Delay can be confined to 1-2 specific developmental areas
    - Can include all areas – global developmental delay

When is it delayed?

- Sufficiently behind for age to give rise to concern or need for further assessment/intervention
  - Take action if attainment is ¾ or less of expected for delay
    - Based on bell shaped curve – 2 SD

Early diagnosis

- Advantage to early diagnosis? Is it worth the parental anxiety?
  - Yes
    - Plasticity of brain development – brain wiring at these times is easily changed
    - Sensitive periods of developmental aspects
    - Prevention of secondary disability and handicap
      - Prevent worsening – eg. cerebral palsy, encourage motor development instead of nothing
    - Can result in increased competence, self-sufficiency and increased quality of life
      - Worthwhile in the long term
    - Allows planning/provision of family support
    - Allows investigation of aetiology and genetic counselling if necessary

Sensitive periods of developmental aspects

- Phases in development of children when brain development, sensory input and environment act together to facilitate acquisition of a particular skill
    - If skill development is interrupted at the time, skill learning may be harder and imperfect later
        - eg: hearing impairment can result in language problems
        - eg: turn in the eye – development of visual pathway may be impaired
            - lack of use of one or both eyes can result in permanent loss of vision even though eye recovers
            - treatment is to put an eye patch on good eye to prevent this adaptation

Determinants

- Development is a continuous process affected by interaction between genetics and the environment
    - Ie: development can be adversely and advantageously influenced by environment
    - While: degree, nature and duration of change are genetic

Presentation

- Developmental delay can present at birth – Down's syndrome
- Risk factor – in history
- Screening
- Failure in milestones
- Parental concern – nearly always right
    - Can be about behaviour/emotions rather than development necessarily

Presentation and diagnosis and assessment

- 12-18 months
    - Delay in motor milestones
    - Feeding problems
    - Irritability
    - Irregular on handling
- 18-36 months
    - Speech delay, hearing concerns
    - Severe, frequent tantrums
    - Non compliance, persistent overactivity
    - Clumsy, poor coordination
- 36-60 months
    - Delay in speech, disruptive behaviour
    - Slow acquisition of skills, poor social and peer relationships
- Diagnosis:
    - Observation, screening
    - Definitive requires multi-disciplinary assessment and should lead to appropriate services
- Assessment
    - Psychologist (cognitive), medical (aetiology), social worker (family support), speech pathologist (language)
    - Medical role:
        - Aetiology diagnosis, exclusion of other problems, health surveillance, medical aspects of management, coordination, collaboration

Specific developmental delays

- Most common are speech/motor delays
    - Motor
        - Often presents with child not walking by 18 months
        - Mild delay can be familiar, associated with decreased muscle tone
            - Can often improve
        - More severe or unusual pattern (eg. pedalling on back) needs further investigation
            - may be neurological or neuromuscular (eg. cerebral palsy, muscular dystrophy)
        - Motor delay is not closely related to overall cognitive developmental delay

- Speech
  - Often presents with child not speaking by 2.5 years
    - Ie. not joining words or not having a wide vocabulary
    - Present in 12-15% of 3 year olds
  - Needs assessment by a speech pathologist
    - Speech or comprehension assessment
    - May need cognitive assessment
  - Speech delay is the presenting sign in many cognitive disorders
    - Eg. Autism
    - There is a large difference between understanding and comprehending (receptive language)
  - Causes
    - Sensorineural hearing impairment – hearing music doesn't mean can hear speech
    - Expressive language delay – delay in speech, normal comprehension
    - Expressive/receptive delay
    - Global developmental delay
    - Autistic spectrum disorder
    - Rare – specific epilepsy syndrome

<u>Global developmental delay</u>

- Causes:
  - 65% are prenatal
    - Genetic – chromosomal, microdeletions, single gene defect (X-linked etc)
    - Dysmorphic syndromes of unknown origin
    - Acquired – infection (eg. rubella), teratogens
  - Perinatal <10%
    - Hypoxia, infection
  - Postnatal
    - Infection, trauma (eg. head injury), hypoxia

<u>Down syndrome</u>

- Trisomy 21
  - Whole extra chromosome 21 often due to non-disjunction in the ovary
  - Translocation (parent has normal number of chromosomes, but part of chromosome 21 is found translocated on chromosome 14 or 15
    - When passed to child, have extra part of chromosome 21
  - Mosaicism – some cells are euploid and some are trisomic
    - With Down's syndrome, mosaic children tend to be more normal than full Downs
  - Huge individual variation in effect of disease
- Epidemiology
  - Same incidence throughout all ethnic groups worldwide
  - 1/750 live births
  - Risk factors
    - Increased maternal age, esp. >37
    - Most DS are born to young mothers – more young mothers have children
  - Prenatal screening/diagnosis is available
- Cognitive impairment
  - DS, most have intellectual disability, adaptive learning is less affected
  - Good social/independence skills (esp with other DS people)
    - Can often function well in social groups/with peers

Environmental factors

- Nutrition
  - Maternal – iodine (lack: cretinism)
  - Infant (calories, FA – important in brain development, other)
- Pre-natal infection
  - Rubella, CMV, toxoplasmosis
- Pre-natal toxins
  - Alcohol, drugs, anti-epileptic drugs
- Peri-natal factors
- Post-natal injury, hypoxia, infection
- Deprivation
  - Abuse and neglect
- Other
  - Socioeconomic factors
  - Language – multi/bilingual

In 40% of severe and 70% of mild, no cause of disability can be found

Aetiology investigation

- Allows definition of cause
  - Allay blame/guilt, information on expected outcome, and thus specific treatment/management
- Can exclude, define known genetic disorders
  - Thus define risk of recurrence and facilitate pre-natal diagnosis advice
- Disadvantages:
  - Doesn't lead to cure, often can provide no answers and not change disability management, fear, pain

Examination/history etc

- History:
  - Family history
  - Pregnancy, birth and neonatal period
  - Infancy (esp. hearing, vision, immunisation)
  - Developmental history
  - Social history
- Examination
  - Stature, head circumference
  - Dysmorphic features
  - Neurological, motor signs
- Observation
  - Of play, behaviour
- Investigations
  - Chromosomes, DNA studies, TFT,
  - Possible neuroimaging
    - Esp: micro/macrocephaly, cns signs, parental anxiety/assurance

What can be done

- Early intervention
  - Organised program of educational support and other activities (speech therapy, physiotherapy)
    - Doesn't reverse impairment
    - Can improve condition
  - Support to family: counselling, information, support networks
  - Support for social integration
- Medical role in particular involves coordination of a multi-disciplinary team for interventions and support

Long term outcomes

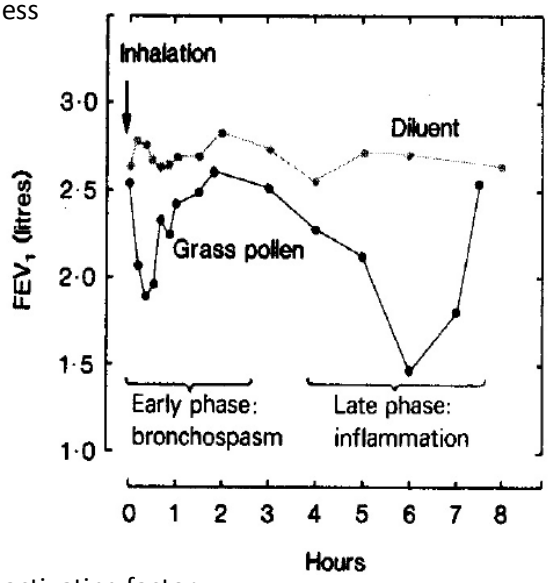
- Some can resolve (eg. expressive language delay), some predispose to difficulties later (receptive language delay)
- Delay due to abuse/neglect can resolve with environment
- Global tends to correlate with intellectual and learning difficulties

Facts about asthma

- Australia has one of the highest prevalence rates of asthma in the world
  - 2.2 million people
    - 1/6 children, 1/10 adults
  - Higher prevalence in indigenous people and older women
- Most common reported long-term illness < 15 years
  - In top 10 common reasons for visiting the GP
- Problem is mostly to do with morbidity
  - Mortality has dropped in recent years due to treatment

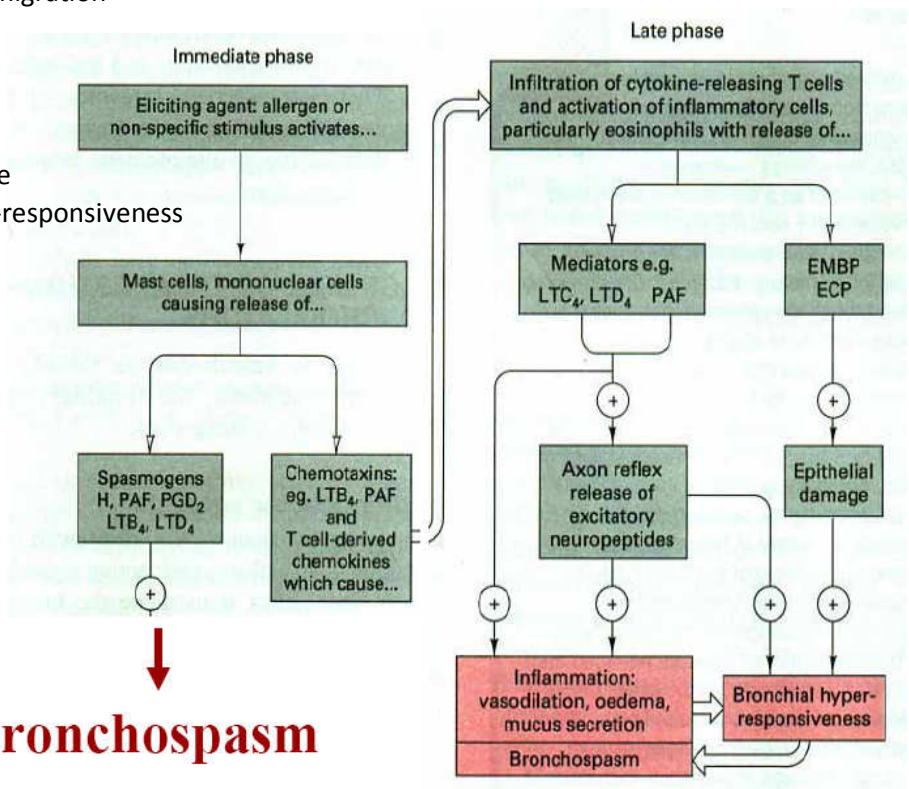
Definition

- Recurrent reversible airway obstruction caused by airway hyper-responsiveness to stimuli
  - Increased airway resistance → muscle contraction, increased mucus secretion, airway wall swelling
  - Decreased FEV_1
- Characterised by inflammatory changes and bronchial hyper-responsiveness
- Not a single disease
  - Childhood/adult onset
  - Environmental factors and genetic component
    - Associated with atopy
  - Triggers
    - Pollution
    - Cold air
    - Exercise induced
    - Allergen induced
    - NSAID induced



Phases

- Early phase – bronchospasm
  - Allergen activates mast cells and mononuclear cells
    - These release:
      - Histamine, prostaglandins, leukotrienes, platelet activating factor
      - Chemotaxins – induce late phase
- Late phase – inflammation
  - Chemotaxins induce eosinophil migration
    - Releases mediators
      - Vasodilators
      - Mucus
      - Bronchospasm
    - Causes epithelial damage
      - Bronchial hyper-responsiveness



Receptors that affect airway smooth muscle

- Adrenergic β2 receptors
  - Activated by circulating adrenaline from the adrenal medulla
  - Causes bronchodilation
- Muscarinic M 1, 2, 3 receptors
  - Activated by parasympathetic ACh
  - M1 and M3 act postsynaptically to cause bronchoconstriction
  - M2 acts presynaptically as an autoregulator and inhibit NT release (ACh)
- Nonadrenergic noncholinergic nerves (NANC)
  - Inhibitory – NO
  - Stimulate – substance P, neurokinin A

Viral infections

- Acute exacerbations of chronic inflammation
- Mechanism
  - Virus activates eosinophils that inhibit M2 receptors
    - This means less inhibition of ACh release and thus increased M1 and M3 action → bronchoconstriction

Management of asthma

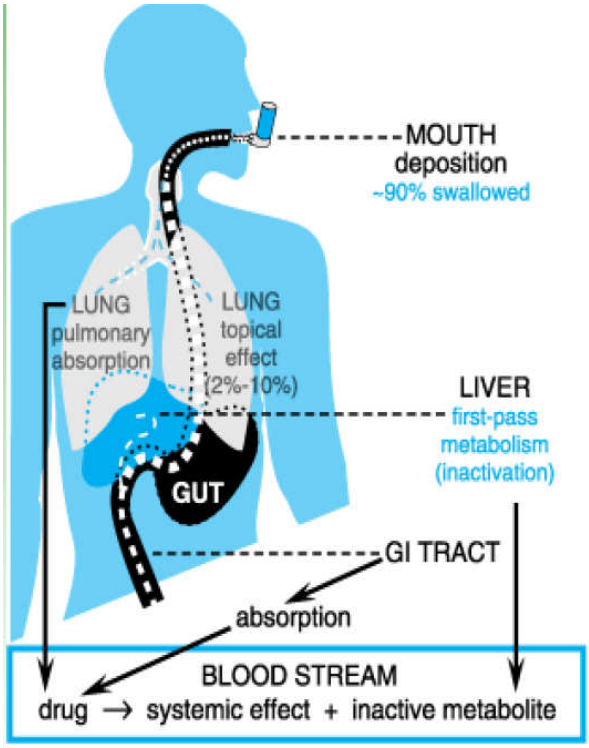
- Aims
  - To decrease symptoms and increase lung function
  - Identify triggers
  - Minimise side effects from treatment
- And thus:
  - Increased quality of life
  - Decrease morbidity
  - Decrease mortality
    - Decreased over 30-40 years due to bronchodilator therapies
    - Spike in the 80s due to overuse, tolerance and possible linked cardiac arrhythmias
  - Prevent permanent abnormal lung function

Anti-asthmatic drugs

- Bronchodilators – reliever
  - β2 agonist, muscarinic antagonist, Xanthines
  - Acute treatment
- Symptom controllers – preventer
  - Long acting β2 agonist
- Antiinflammatory drugs – preventer (current standard treatment)
  - Glucocorticoids, oral steroids, leukotriene receptor antagonists, sodium cromoglycate, Nedocromil sodium
  - Long acting – long term treatment

Route of administration

- Inhalation
  - Allows deposition of drugs in the lungs and absorption into blood stream
  - Still has 90% swallowed, however
    - Drugs need to be poorly absorbed in the gut or inactivated in the liver (travel via blood from gut to liver) – thus prevent systemic side effects



β2 adrenergic agonists

- Cause bronchodilation
- Physiological antagonist of bronchospasm in smooth muscle
    - Inhibits release of inflammatory mediators from mast cells
- Administration
    - Inhaler/nebuliser (acute asthma)
    - IV in serious attacks (status asthmaticus)
- Length of action:
    - Short acting – salbutamol, terbutaline
        - Reliever, used to calm acute exacerbations
        - Duration of action 4-6 hours, max effect at 30 minutes
        - Resistant to degradation, excreted largely unchanged in urine
    - Long acting – salmetrol
        - Takes 12 hours to act, more a preventer than reliever
- Side effects
    - Tremor, tachycardia
    - Overuse can be a major problem – tolerance develops and there is downregulation of receptors
        - Should only be used by need
    - The use of preventer antiinflammatory agents minimises need for overuse
    - Cardiovascular disorders
        - May be a problem if patient is also on non-selective β blockers

Xanthines

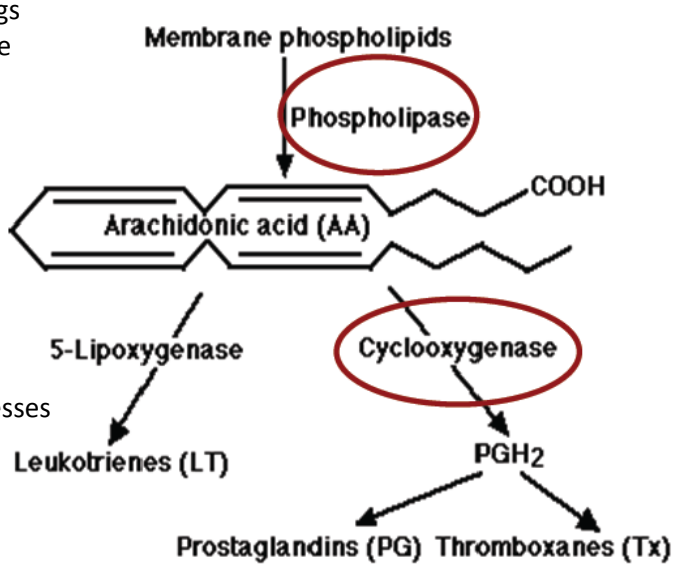
- No longer in use
    - Previously used as bronchodilators when β2 agonist don't work
- Theophylline
    - Pharmacodynamics
        - Well absorbed, thus given orally
        - In slow release preparations, can sustain blood levels for 12 hours
    - Mechanism of action:
        - Thought to inhibit phosphodiesterase that metabolises cAMP
            - Thus, increased intracellular cAMP which inhibits the activation of inflammatory cells
        - Bronchodilator due to increased cAMP
    - However, dose required to get these effects is higher than therapeutic dose, so mechanism is not understood
        - Poor therapeutic index, therapeutic dose is close to toxic dose
- Side effects
    - CNS stimulation – reduction inf fatigue, increased mental and motor performance
    - Tremor, nervousness, sleep interference
    - Inotropic, chronotropic effects – cardiac arrhythmias
    - Diuresis (increased urine production), GIT – nausea, vomiting, link to anorexia
- Interactions with other drugs:
    - Oral contraceptives, antibiotics (erythromycin), calcium channel blockers, cimetidine
    - These inhibit CYP450 and thus theophylline is not metabolised and action persists longer

Muscarinic receptor antagonists

- Ipratropium bromide
- Antagonises bronchoconstriction mediated by ACh
    - Mainly used for irritant stimulus asthma
    - Also inhibits mucus production
- Maximum effect is after 30-60 minutes, onset of action is slow
- Can be used on combination with β2 agonists

Glucocorticoids

- Antiinflammatory agent
- Given prophylactically (preventer)
    - Continuously given and decreases hyper-reactivity
    - Inhibits late phase responses
- Main preventable therapy
    - Eg: Beclomethasone, beudesonide, fluticasone (2x more potent than others)
- Mechanism
    - Broad – antiinflammatory, immunosuppression
    - Inhibits:
        - Platelet activating factor
        - Allergic influx of inflammatory cells into the lungs
        - Activation of macrophages and mediator release from eosinophils
        - Inhibits eicosanoid biosynthesis
            - Inhibits enzymes including COX2 which causes formation of prostaglandins
        - Inhibits IL-3 formation



- Side effects
    - Local effects: oral thrush, hoarseness
    - Systemic effects: bruising, dermal thinning, adrenal suppression affecting bone metabolism (osteoporosis)
        - Causes growth suppression, asthma also suppresses
            - Thus important to balance benefit vs risk in each individual case
- Oral treatment, eg. prednisolone
    - Used when inhaled therapy is ineffective
        - Short course treatment in acute/severe/deteriorating condition
    - Increased side effects

Leukotriene receptor antagonism

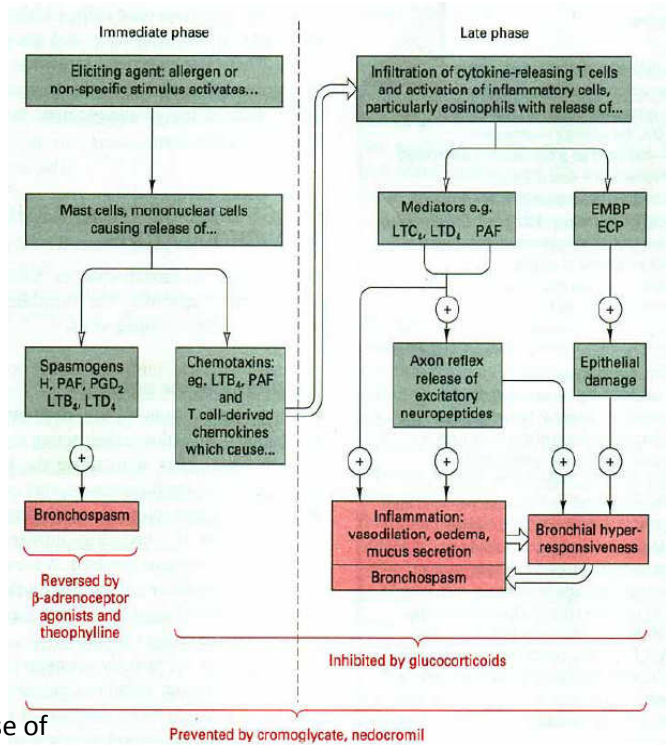
- Leukotrienes amplify the inflammatory response and act as bronchoconstrictors
    - Competitive antagonism blocks LTC4, D4 and E4
- Act by bronchodilation – eg. Montelukast, Zafirlukast
    - Used in prophylactic treatment
    - Used in antigen/exercise induced asthma
- Useful in combination with glucocorticoids allows reduction of glucocorticoid dose
- Useful in aspirin sensitive asthma
    - NSAIDS inhibit cyclooxygenase, thus increased production of other pathway – leukotrienes
        - Thus, antagonists block NSAID induced asthma in particular

Leukotriene synthesis inhibitors

- Block synthesis of leukotrienes by blocking 5-lipoxygenase that catalyses reaction forming leukotrienes
    - Eg: Zileutin (short acting)
        - Used as a short acting treatment for antigen, exercise, aspirin induced asthma
            - Not direct, however, so not used to relieve

Sodium cromoglycate, nedocromil sodium

- Used prophylactically (preventer)
    - Useful in antigen, exercise, irritant asthma
    - More often effective in children than in adults: not all asthmatics respond
- Administration is inhaled or via nebuliser
- Mechanism is unknown, not bronchodilators
    - May block mast cell degranulation



Death from asthma

- Common cause – status asthmaticus
    - Post mortem appearance
        - Airways clogged with thick mucus
        - Shedding of airway epithelium
        - Inflammation – inflammatory cells, eosinophils
        - Hypertrophy of smooth muscle
    - Treatment
        - Combination of drugs, immediate and urgent:
            - β2 agonist, IV and nebuliser
            - Oxygen
            - Hydrocortisone IV, prednisone oral
            - Ipratropium nebuliser

Allergen immunotherapy

- Standard therapy suppresses inflammatory response
    - Doesn't act on the initiating event
- Allergen immunotherapy acts on IgE
    - IgE disease is treated by administering an increasing dose of allergen to decrease patient sensitivity to particular allergen
    - Studies have shown a reduction in inflammatory response and hyper-reactivity
- Adverse effects
    - Mild swelling of injection site
    - Sneezing, bronchospasm
    - Anaphylaxis – severe, rapid allergic reaction, hypotension, collapse
- Therapy takes 30 minutes to work
    - Needs to be given in a controlled environment to ensure safety
    - Treatment for anaphylaxis:
        - Adrenaline – adrenergic agonist (physiological antagonist)
            - Causes bronchodilation and increased BP (HR, TPR)
        - Oxygen, mask ventilator

Anti-IgE therapy

- Monoclonal antibody, eg. Omalizumab – targeted agent of IgE
    - Prevents IgE binding to mast cells/basophils, thus preventing allergic reaction at early stage
- Not often used – not a bronchodilator, shouldn't be used in acute asthmatic attack
- Side effects: reaction at injection site (redness, stinging, bruising); anaphylaxis in 0.1% of patients

Cytokine modulators – novel therapies

- Inhibits cytokine synthesis, like glucocorticoids
- Mechanisms
    - Antibodies block cytokines or receptors
    - Soluble receptors → mop up secreted cytokines
    - Receptor antagonists
- Drugs that inhibit synthesis of multiple cytokines may be the most effective, less specific

Peptides

- T-cell - peptide protein complex interaction results in:
    - Inactivation of T-cell response antigen and thus mediated effects don't occur
- Thus, there is a decrease in the immune responsiveness to allergen and asthmatic response
    - Eg: Cat Peptide Allergen Desensitisation (Cat PAD) to treat cat allergies
- Very specific – specific T-cell

DNA vaccines

- Splice genes for allergens into plasmid DNA
    - DNA is injected and induces and immune response
- Thus, with later introduction of allergen, immune system prevents sensitisation to allergens

What is narrative ethics

- Stories that have take-home messages
  - Learning through vicarious experiences (others' experiences)
  - Increase moral perception
  - Ie. stories where people want us to not make the same mistakes they did
- Allow discovery of mortality through choice and context
  - Our choices depend on:
    - Options
    - Personal position
  - These are shaped by social conditioning and personal experience/context

In medicine

- Listening to patients
  - How patient gives history is more important and gives us more information than symptoms/signs alone
- Teaching by narrative, anecdotes
  - Eg. clinical tutors
- In future → we will develop our own narratives
  - Ie. our own constellation of experiences or practical wisdom
- The art of medicine
  - Combining science and narrative

Narrative

- Captures inextricable and intangible necessity of freedom in human life
  - Life is a story
  - Learn moral lessons form our won story and others'
- Realise multitude of options:
  - Eg. life story → possible outcomes
  - Eg. illness story → possible diagnoses
  - Eg. choices in medical dilemma → teenage pregnancy

Ethical dilemmas

- Always asking ourselves: what's going on in this situation?
  - Need to appreciate social/moral/personal contexts
- Need to look at the options – narrative options
  - Also need to consider different perspectives – narrative subplots
- Can be difficult
  - Stories conflict
  - Stories can be in opposition and have different values

Listening to stories

- Important to understand the patient's story, rather than simply taking a history
  - Listening to story allows consideration of the broader context and the patient's personal narrative
  - Story can go anywhere, need to follow rather than stick to strict structure
- Listening to silences – can be important
- Appreciate non-verbal, symbols, metaphor communication
  - Often used by patients because it is easier to express feelings in this way

Patients are our best teachers

- If we listen and understand patients' narratives, we can get a patient's history as part of the process
  - Case presentation is translating a story into a formulaic tale
- Competence requires:
  - Gathering/interpretation of complex stories
  - Retelling/writing down of our interpretation

Ethical issues

- Storytelling events (narratives)
    - Different plots, goals
    - Different pas experiences/beliefs/moral judgements

How is narrative useful to medical ethics?

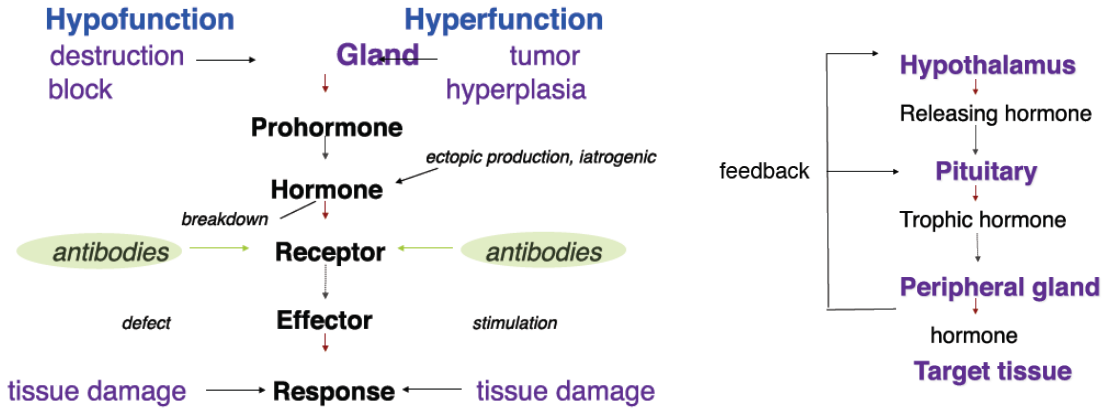
- Ethics are not clearly defined or delineated, neither are narratives
    - Narratives and ethics function in shades of grey
- Aids us in deciding what is right and wrong
    - Interaction of ethical principles, narratives POVs) and background beliefs (own opinion)

Identity

- Defined by gender, culture, social status
- Sex and gender – one of the greatest polarisations in society
    - Determined early
    - Social/biologically determined and constructed
- Problems with in-between cases
    - Intersex
    - Castration vs mastectomy – still a woman/man?
- Intersex:
    - Example to demonstrate importance of individual narrative and how it changed policy
    - Definition – ambiguous sex polarisation due to many different disorders
    - Old policy:
        - Establish sex and determine early on
        - Secrecy
    - New policy:
        - Delay surgery to allow choice and consent
        - Recognition that premature establishment may cause psychological problems later in life

Endocrine disorders

- A hormone imbalance due to:
  - Oversupply of a hormone
    - Eg. benign or malignant tumour
  - Deficiency of a hormone
    - Eg. congenital lack, damage by autoimmune disease (eg. type 1 diabetes, immune system destroys beta cells)
- Hormones can be of different classes, this is important to remember in pharmacotherapy
  - Classes:
    - Amines – eg. NA
      - Rapidly broken down in the gut
    - Peptides – eg. insulin
      - Also destroyed in gut, thus given IV
    - Steroids
      - Stable, can be taken orally
- Summary of causes:

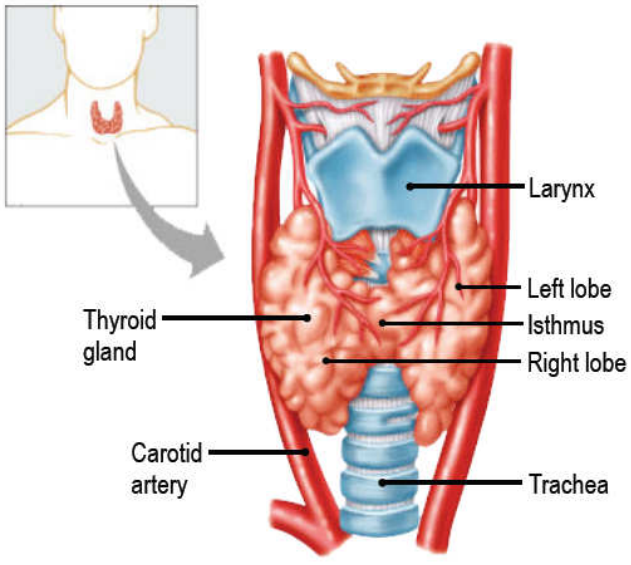


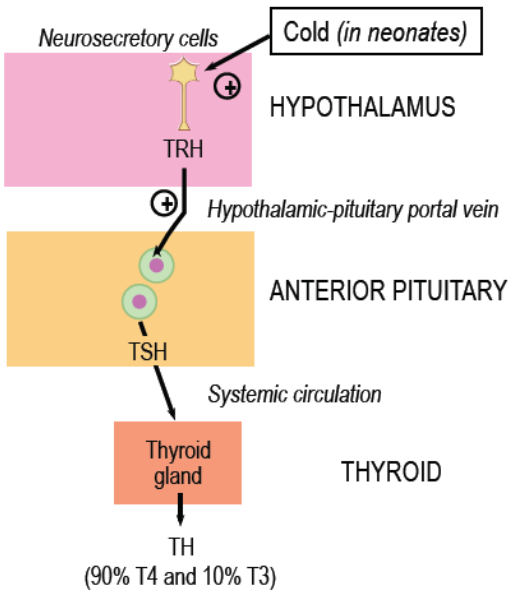
Feedback loops

- In regular hormone release, there are 3 levels of control
  - Hypothalamus, pituitary, peripheral gland, these also can be possible defect locations
    - Measurement of different releasing hormones can diagnose source of lesion

Thyroid gland

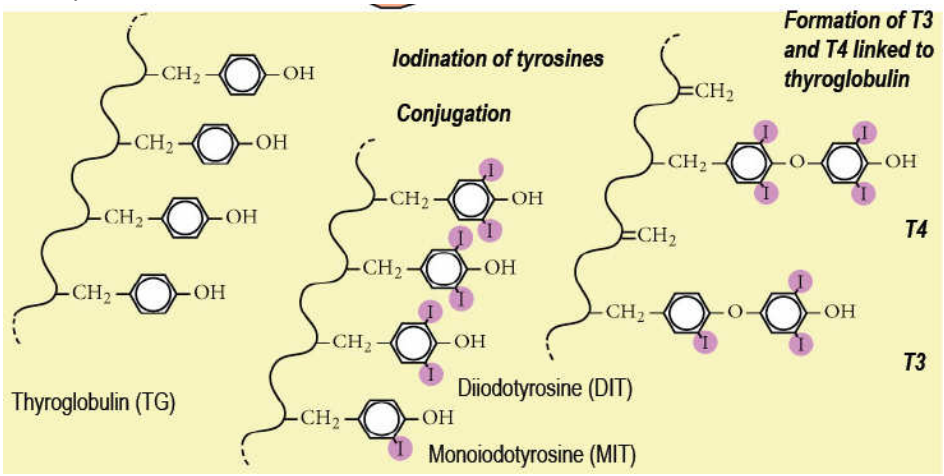
- Anatomy
  - Butterfly-shaped structure in front of trachea
    - Secretes T3, T4 and calcitonin
  - Associated with the parathyroid and vagus nerves
  - Large tumours can obstruct the trachea, and affect the vagus nerves
- Hormone production (diagram, same as other lecture)





Thyroid gland (continued)

- Thyroid peroxidase catalyses the reactions to:
  - Attach iodine to tyrosine subunits of thyroglobulin
  - Conjugate diiodotyrosine and monoiodotyrosine to form T3 and T4 linked to peptide backbone
- TSH causes the pinocytosis of T3 and T4 attached to TG
  - T3 and T4 are separated by a lysosome and released by diffusion from the cell
- T3 is more potent and biologically active
  - T4 can be activated at target tissues by deiodinase
- In pregnancy, the placenta and mammary glands also take up iodine
  - If low iodine, can't make thyroid hormones → disease



Hyperthyroidism

- High circulating T3 and T4
- Epidemiology
  - Higher rates in women, especially middle age ~40
- Most common cause: Grave's disease (2/3 of hyperthyroidism)
  - Autoimmune response to TSH receptor causing over-stimulation
  - Other causes:
    - Toxic multinodular goitre
    - Toxic adenoma
    - Sub-acute thyroiditis (often resolves)
- Diagnosis can be confirmed with thyroid function tests
  - Results: low TSH with high free T4 or T3
- Presentation
  - Goitre – enlargement of the thyroid gland
  - Localised oedema
  - Swelling around the eyes and upper lid retraction
    - Exophthalmos – autoimmune damage to the periorbital area, especially the muscles around the eye
      - eye pushed forward → can lead to blindness
  - Clubbing of fingers and toes
  - Others: increased basal metabolic rate, increased temperature, increased HR, increased appetite, increased weight loss, sweating, menstrual irregularity, increased bowel movements

Treatment

- Options
  - Surgery
  - Radiotherapy – Iodine-131
  - Drugs
    - Symptom relief
    - Restore euthyroid status (normal thyroid function)
- Choice of treatment is highly dependent on the individual: age, sex, etc

Surgery

- Subtotal thyroidectomy – leave some to maintain thyroid function
    - Effective in treating Graves/multinodular goitre
- Before surgery:
    - Antithyroid drugs to control symptoms
    - Iodine (NaI) to stop release of hormone in the short term
        - Increased iodine causes decreased vascularity of gland and thus a reduction in release
- Thyroid supplementation may be required after surgery

Radioactive iodine

- Iodine-131 is taken orally and is selectively uptaken by the thyroid gland
    - Here, it can destroy a tumour etc that is excessively uptaking iodine using gamma emission
- Useful in Graves' disease
- Half life of 8 days
    - Dose is standardised to BMI
    - Takes a few months to work because iodine stores may be high in the colloid
- Contraindicated in pregnancy and young women of childbearing age
    - Radiation can cause defects
- Post-treatment
    - May need treatment with antithyroid drugs for 3-6 months
    - May cause a person to by hypothyroid, further treatment

Antithyroid drugs

- Uses
    - Control hyperthyroidism
        - Long term treatment: years and then follow up
    - In conjunction with radioactive iodine
    - To control hyperthyroidism before surgery

Examples: Carbimazole, Propylthiouracil

- Given orally
- Mechanism of action
    - Block thyroid hormone synthesis by blocking thyroid peroxidase
    - PTU also blocks de-iodination of T4 to T3
- Pharmacokinetics:
    - A long term treatment
        - These drugs can take months to have an effect because body has large stores of TG
    - Half lives:
        - Carbimazole – 4-6 hours
        - PTU – 2 hours
- Adverse effects:
    - Vomiting, anorexia, itching, rash
    - Agranulocytosis – in the 1st 3 months
        - Loss of granular white blood cells
            - Should watch for infection
- Considerations
    - Both drugs cross the placenta, but PTU has a high chance of causing fetal injury, thus carbimazole used in pregnancy
        - Use lowest effective dose
        - Perform a maternal vs fetal risk assessment
    - Overall, however, PTU is preferred
        - If given during pregnancy, can induce fetal hypothyroidism, and goitre
        - During lactation, PTU is preferred

Examples: Carbimazole, Propylthiouracil (continued)

- Regimens:
  - Adjusted regimen
    - High dose for 3-4 weeks
    - Reduce dose by 50% to retain thyroid function (based on T3/4 levfels)
    - Review every 4-6 weeks with gradual reduction
  - Block-replacement regimen
    - Long term high dose
    - Thyroxine added at 6 weeks to maintain euthyroid thyroid function
    - Follow up analysis and monitoring every 3 months
  - Block-replacement regimen is easier to monitor, but has more possible AEs
- Subsequent therapy
  - Monitoring of thyroid function and other vitals
    - Thyroid function analysed using assays for TSH, T4, T3
    - Vitals: BMI, etc
  - May be able to cease drug at 24 months
    - Varies person to person, everyone responds differently to drugs

Drugs for symptomatic relief

- Beta blockers
  - Reduce tachycardia, tremor, sweating
  - avoid in asthma – may be on beta agonist relievers
- Eye drops
  - Lubricate eyes
  - Prednisolone acetate – reduces eye swelling

Hypothyroidism

- Low circulating levels of free T3 and T4
  - Historically linked to low dietary iodine and treated with dietary supplements
- In pregnancy, endemic iodine deficiency often can lead to cretinism or goitre in child
  - In Australia, we get sufficient iodine from crops, fish, soil
    - In some places, however, it is hard to get enough iodine
- Causes
  - Hashimoto's thyroiditis
    - Autoimmune disease where antibodies to TSH receptor cause an inflammatory response and inhibit receptor function
  - Iodine-131 treatment
  - Surgery to fix hyperthyroidism

Treatment

- Aims of treatment
  - Restore euthyroid state
  - Relieve symptoms
  - Maintain growth and development
    - Newborns are tested – Guthrie-Heel prick
- Before treatment
  - Thyroid function test – elevated TSH, low free T4
    - Examine possible secondary hypothyroidism – low TSH, low T4
      - Pituitary/hypothalamic disease
  - Consider drug precipitants
    - Eg. Li for bipolar treatment can cause thyroid dysfunction

Treatment (continued)

- Hormone replacement
  - Thyroxine: T4 administered and converted to T3 as necessary inside cells
    - Pharmacokinetics:
      - Long duration ($T_{1/2}$ = 7 days), replacement of choice
      - Taken orally
    - Suppresses TSH
  - Liothyronine (T3) has a more rapid onset, but a shorter duration
    - Possible cardiotoxic side effects
- Regimen
  - Once daily – life long
    - Therapy and clinical signs monitored so that dosage can be adjusted
  - Stabilising time of 6 weeks before dose adjustment
  - Metabolism in the liver may be slowed down, reducing the metabolism of other drugs
    - Thus doses should be carefully monitored and updated
- Adverse effects
  - Related to action of hormone
    - Tachycardia, sweating, weight loss
  - Drug interactions – reduces the effect of digoxin

Special cases

- The newborn
  - Screening is routine
    - If hypothyroidism found, replacement therapy implemented
    - Allows normal physical and intellectual development, needs monitoring
- Pregnancy
  - Thyroid function monitored each trimester
    - Dose adjusted as required
- Elderly
  - Maintenance dose may be lower

Iodine

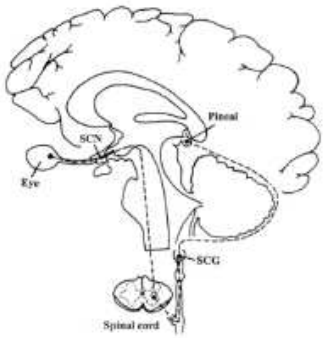
- In a normal diet, we get enough iodine
  - If bad diet, and not enough iodine can get increased TSH levels and goitre
- 50 years ago, severe iodine deficiency was the main cause of thyroid dysfunction
  - Lead to goitre and mental retardation
  - Iodised salts were introduced to decrease incidence
- Study in Australian children iodine levels
  - Almost half were found to be iodine deficient
    - Explanations:
      - Changes in the processing of milk
      - Reduced salt in diets (iodised slat)
- Generally, too much iodine probably won't hurt, but iodine deficiency can cause severe mental retardation in children, and various symptoms in adults

Hormones

- Types:
  - Amino acid derivates – NA, A, Thyroid hormone
  - Proteins, small peptides – TSH, LH, FSH
  - Steroids – androgens, glucocorticoids, mineralocorticoids
- Types of action
  - Autocrine – acts on self (extracellular fluid)
  - Paracrine – acts locally (extracellular fluid)
  - Endocrine – acts by secretion into the blood stream
    - Consequently, endocrine organs are richly vascularised

Endocrine organs

- Ductless glands - hypothalamus, pituitary, pineal, thyroid, parathyroid, thymus, pancreas, adrenal, gonads
- Accessory endocrine glands – heart, digestive tract, kidney, adipose
- Transient – placenta, maternal

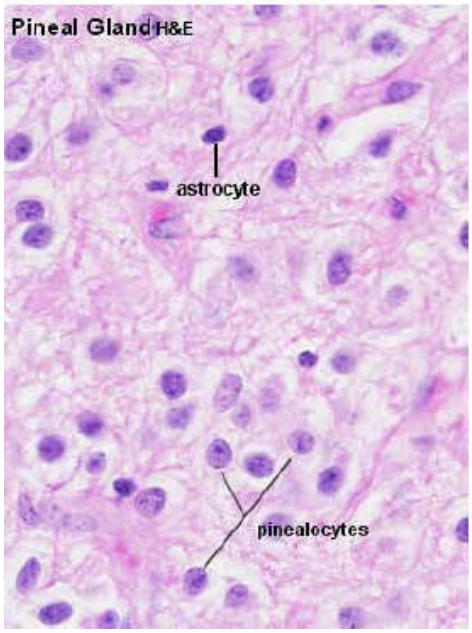


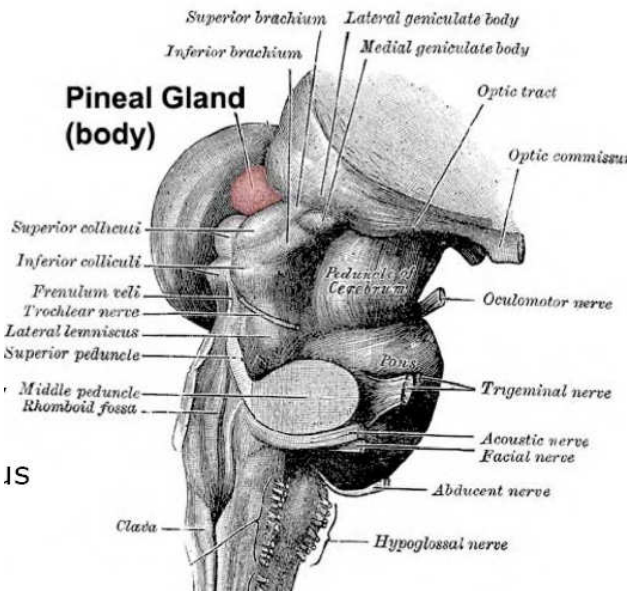
Overall origins

- Derived from epithelia
  - Embryo covering - ectoderrm
  - GIT lining – endoderm
  - Coelomic cavity lining – mesoderm

Pineal gland

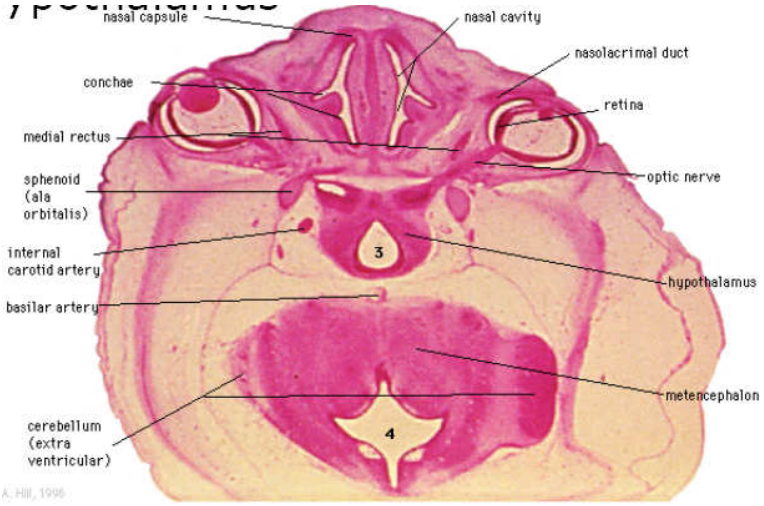
- Part of the epithalamus (part of the diencephalon)
  - Made up of neurons, glia, pinealocytes
- Hormone – melatonin
  - Secreted by pinealocytes
  - Has a cyclic nature that corresponds to diurnal rhythms
    - Low during daylight, high during night
    - Thought to be a remnant from before we had bony skulls and sunlight affected our rhythms
  - Thought to be involved in gamete maturation – delays puberty
  - Possible antioxidant effect to protect neurons
- Embryonic development
  - Prosencephalon neuroectoderm becomes the diencephalon
    - Median diverticulum in the caudal roof buds off
    - Diverticulum proliferates and goes from hollow to solid
      - Pinealocytes form from neuroglia
      - Cone shaped (pine) gland forms
        - Innervated by epithalmus





Hypothalamus

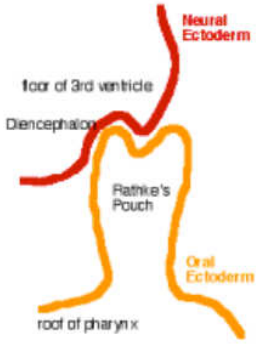
- Embryonic development
  - Prosencephalon neuroectoderm becomes the diencephalon
    - On the ventro-lateral wall the intermediate zone proliferates (thickens)
      - Develops into the hypothalamus behind the optic stalks
    - Associated formation of the pituitary gland
    - Associated with mamillary bodies – pea-sized swellings on ventral wall of hypothalamus
- Adult function:
  - Links the CNS to the pierpheral endocrine system
  - Stimulates the pituitary via the HP portal circulation via 'releasing hormones'

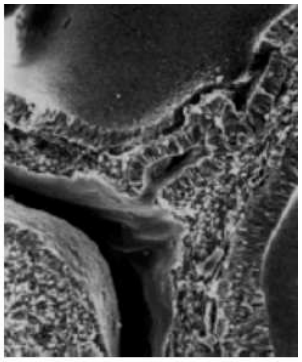


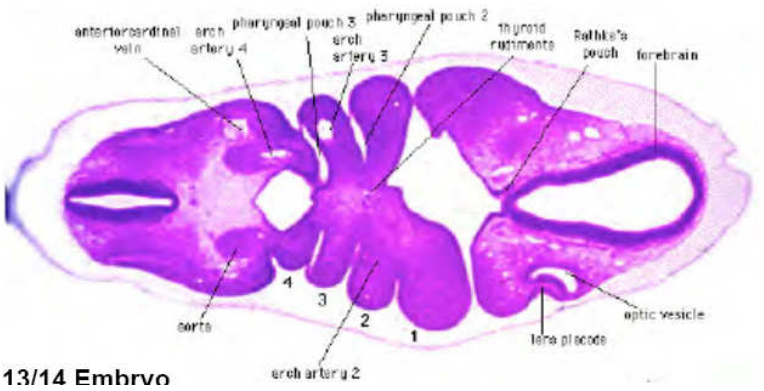
Stage 22

Pituitary gland

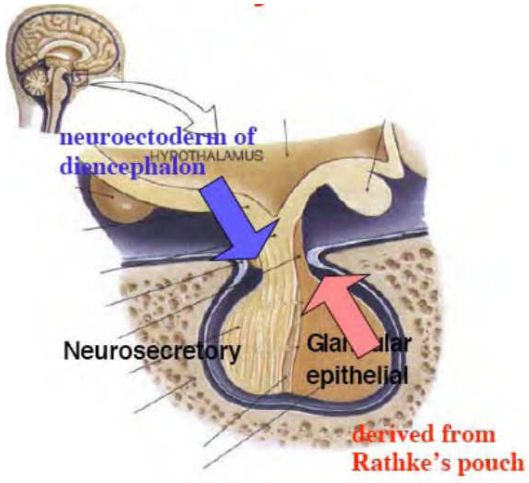
- Located in the sella turcica
  - Anterior to the lamina terminalis (neuropore closure)
- Develops from:
  - Ectoderm roof of the stomodeum
  - Neuroectoderm of the diencephalon
- Adenohypophysis
  - Anterior wall proliferates – pars distalis
  - Posterior wall doesn't grow – pars intermedia
  - Rostral growth near infundibular stem – pars tuberalis
- Neurohypophysis
  - Infundibulum – median eminence, infundibulum, pars nervosa
- Rathke's pouch
  - Embryonic structure, folding of stomodeum ectoderm
- Timeline
  - Week 4
    - Hypophysial pouch, Rathke's pouch, diverticulum from roof
  - Week 5
    - Elongation, contacts infundibulum, diverticulum of diencephalon
  - Week 6
    - Connecting stalk between pouch and oral cavity degenerates
  - Week 10 (early fetal)
    - GH and ACTH detectable → pituitary functioning
      - Thought to drive 2nd trimester growth
  - Week 16
    - Adenohypophysis fully differentiated
  - Week 20-24
    - Growth hormone levels peak then decline





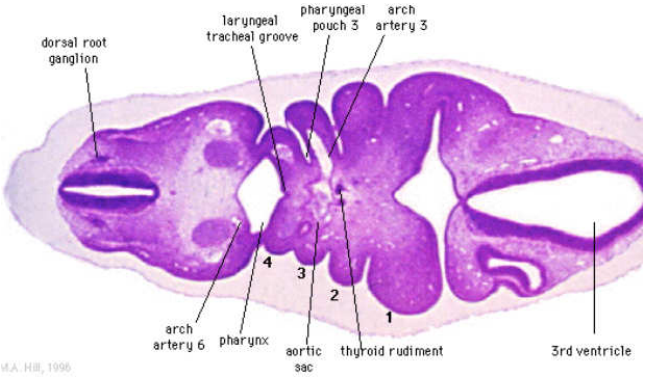


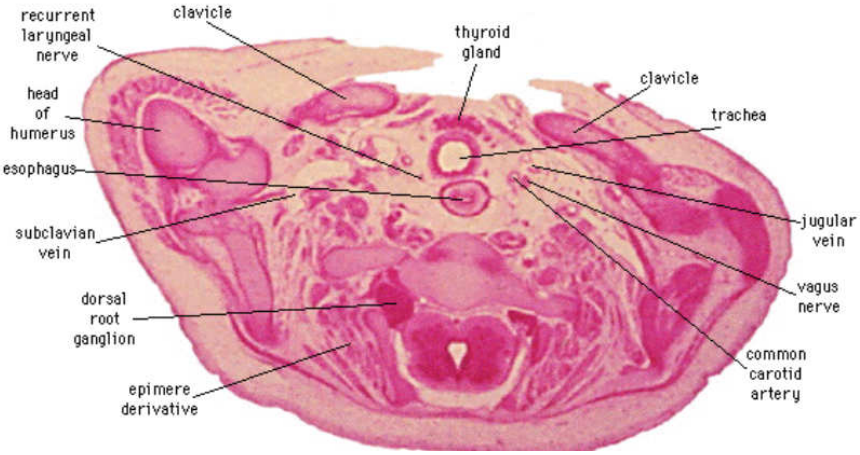
13/14 Embryo



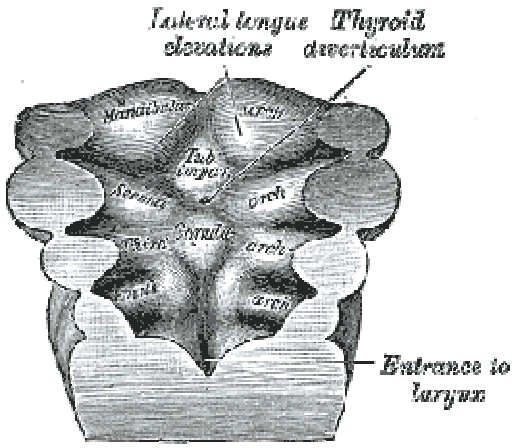
Thyroid

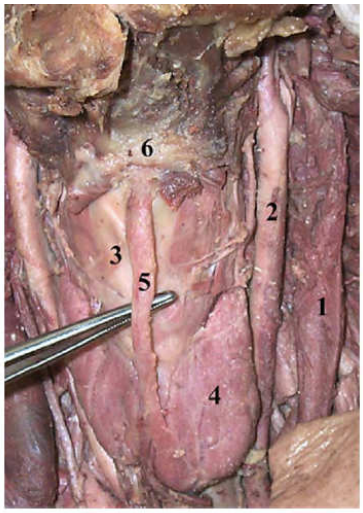
- Functions in the embryo
  - Begins releasing hormones from week 10
    - Required for neural development (absence, reduced = cretinism)
  - Stimulates metabolism of protein, carbohydrate, lipid
- Embryonic development
  - Median endodermal thickening on floor of pharynx
  - Formation of outpouching – thyroid diverticulum
    - As the tongue grows, thyroid descends into neck
    - Becomes the thyroglossal duct, proximal end is the foramen cecum on the tongue, distal end is final site of thyroid
      - Normally atrophies and closes off before birth
    - Diverticulum proliferates and becomes solid
      - Right and left lobes proliferate further forming lobes and isthmus in centre





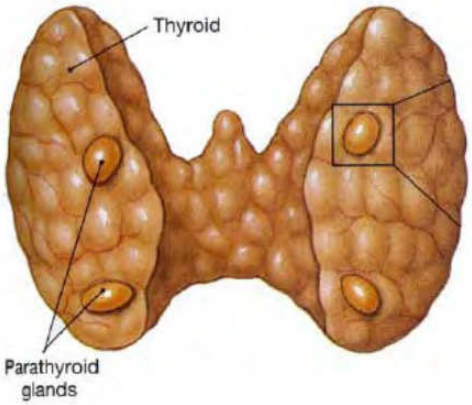
- Timeline
  - 24 days
    - Thyroid median endodermal thickening is in the floor of the pharynx
    - Outpouching – thyroid diverticulum
  - Week 11
    - Colloid appearance in thyroid follicles, iodine and thyroid hormone synthesis
    - Growth factors (insulin-like, epidermal) stimulate follicular growth
  - Fetal thyroid hormone
    - Secreted initially in a biologically inactivated form, later causes development of brown fat
      - After birth, thyroid hormone surge is thought to activate brown fat
    - Iodine deficiency in this period causes neurological defects – cretinism
  - Birth
    - TSH levels increase, then T3 and T4 at 24 hours → decline to normal in 5-7 days
- Abnormalities
  - Incomplete/excessive descent
  - Persistent thyroglossal duct
    - May form cysts and fistulas
  - Pyramidal lobe (50% of people)
    - Isthmus attachment to hyoid bone
    - Failure of distal thyroglossal duct to degenerate





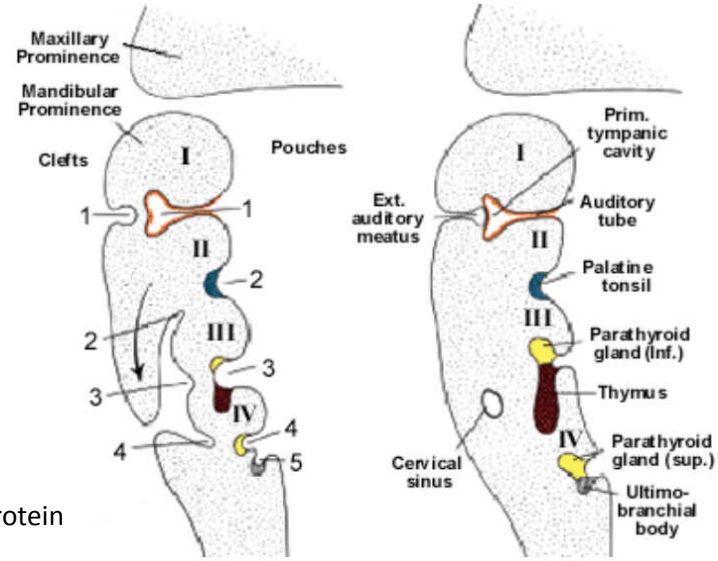
(5) Thyroglossal duct connects thyroid gland (4) inferiorly with foramen cecum of tongue superiorly
Hyoid bone (6)
Thyroid cartilage (3)

<u>Parathyroid</u>



- Function
  - Not part of the thyroid gland
    - Made up of 4 small glands at the back of the thyroid gland
  - Chief cells secrete parathyroid horone
    - Increases Ca^{2+}, works in the opposite way to calcitonin
      - Stimulates osteoclasts and inhibits osteoblasts
      - Increases Ca GIT absorption
- Embryonic origin
  - Forms from the endoderm of pharyngeal pouches 3 and 4
    - Also may have ectoderm and neural crest contributions
  - Reversal of pouches:
    - 3rd pharyngeal pouch – forms inferior parathyroid – descends with thymus
    - 4th pharyngeal pouch – superior parathyroid
  - Week 6
    - Diverticulum elongates, hollow then becomes solid with proliferation, dorsal cell proliferation
  - Fetal parathyroids
    - Respond to calcium levels
    - Fetus has higher calcium levels than mother, and thus needs own regulatory system – PTH

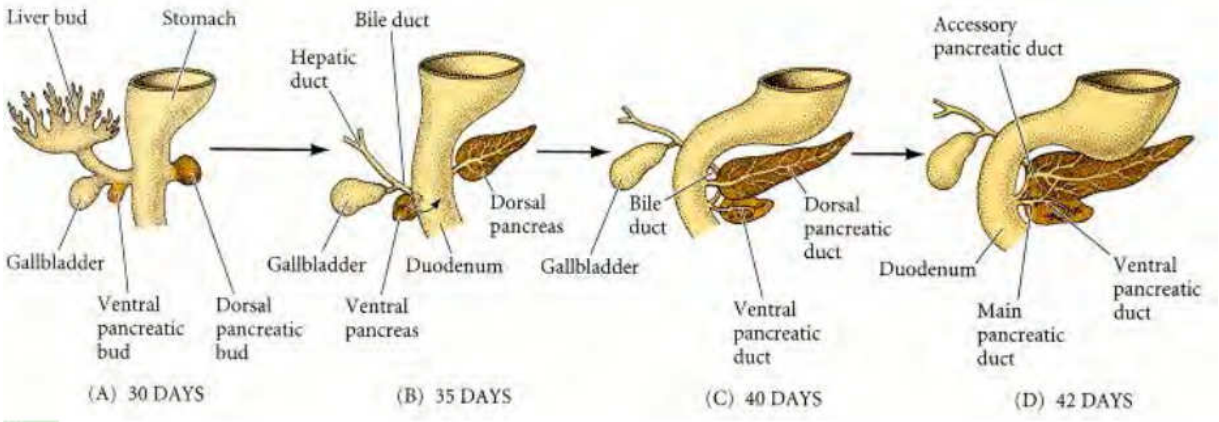
<u>Thymus</u>



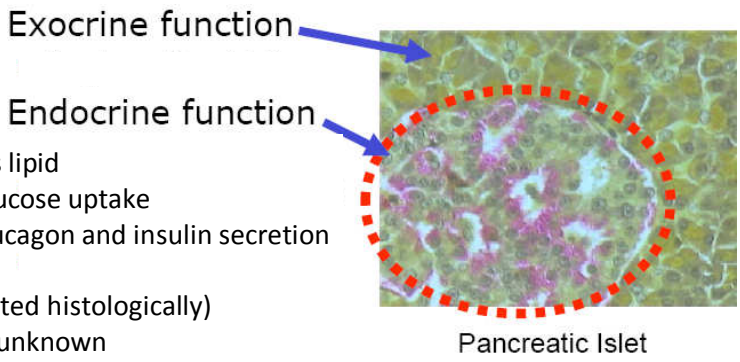
- Originates from the third pharyngeal pouch endoderm
  - Week 6
    - Diverticulum elongates
    - Hollow to solid
    - Ventral cell proliferation
  - Thymic primordia
    - Surrounded by neural crest mesenchyme
  - Final development induced by epithelia/mesenchyme interaction

<u>Pancreas</u>

- Functions
  - Exocrine (99% by volume) – amylase, alpha-fetoprotein
  - Endocrine (1% by volume) – pancreatic islets
- Embryonic origin
  - Pancreatic buds
    - Endoderm covered by splanchnic mesoderm
    - Form from endoderm at the level of the duodenum
      - Dorsal bud – larger, forms first
      - Ventral bud – smaller, forms later
    - Splanchnic mesoderm forms dorsal and ventral mesentery
  - Growth of duodenum and stomach rotation cause ventral and dorsal buds to come together and fuse
    - Ventral bud duct and distal part of dorsal bud fuse for exocrine function
      - Forms pancreatic duct (+ accessory pancreatic duct if present)
  - Endoderm extends into the splanchnic mesoderm to form endoderm islets (Islets of Langerhans)
    - Budding of these islets of endoderm allow dual endocrine and exocrine function



Pancreas continued

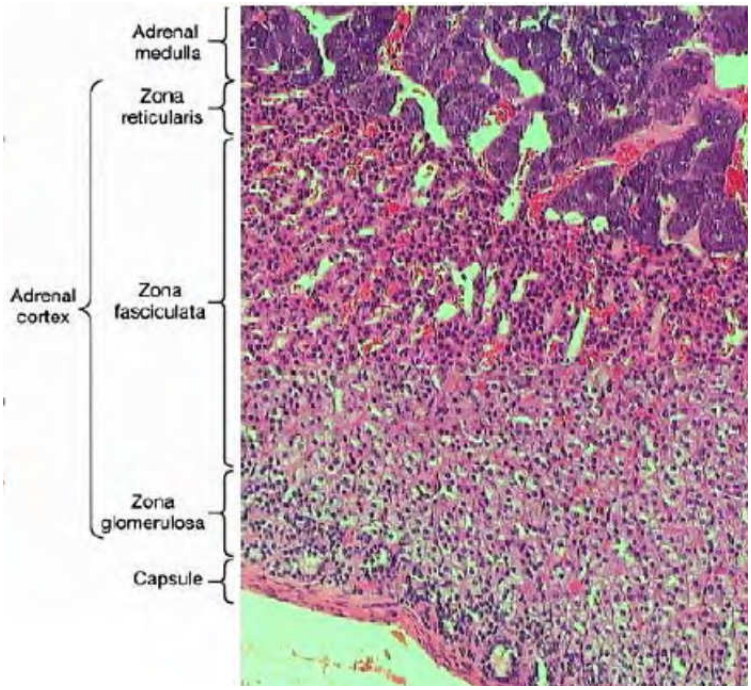


Pancreatic Islet

- Endocrine Islets of Langerhans
  - 4 cell types:
    - Alpha – produces glucagon that mobilises lipid
    - Beta – produces insulin that decreases glucose uptake
    - Delta – produce somatostatin, inhibits glucagon and insulin secretion
    - F-cells – produce pancreatic polypeptide
  - Function begins from 10-15 weeks onward (detected histologically)
    - Exact role of hormones in fetal growth is unknown
      - Do know that insulin/glucagon are important for glucose levels
  - Exocrine function begins after birth
- Timeline
  - Week 7-20
    - Pancreatic hormone secretion increases, some maternal insulin present
  - Week 10
    - Alpha, delta and beta cells differentiate – begin of insulin secretion
  - Week 15
    - Glucagon is detectable in plasma
  - Beta cells (most abundant)
    - Stimulate fetal growth, proliferate into infancy
  - Maternal diabetese mellitus
    - Can result in hypertrophy of fetal beta cells
      - Interaction of maternal and fetal glucose status: high maternal glucose causes high levels of insulin secretion in fetus
    - Pre-gestational diabetes or gestational diabetes + faster hyperglycaemia
      - 3-4x increased risk of infant malformations, teratogenic:
        - Heart, NS, skeleton malformations
        - Large baby – high birth weight
      - Known as fuel-mediated teratogenesis
        - Degree of malformation is related to diabetic control
    - Mild gestational diabetes – no effect on fetus

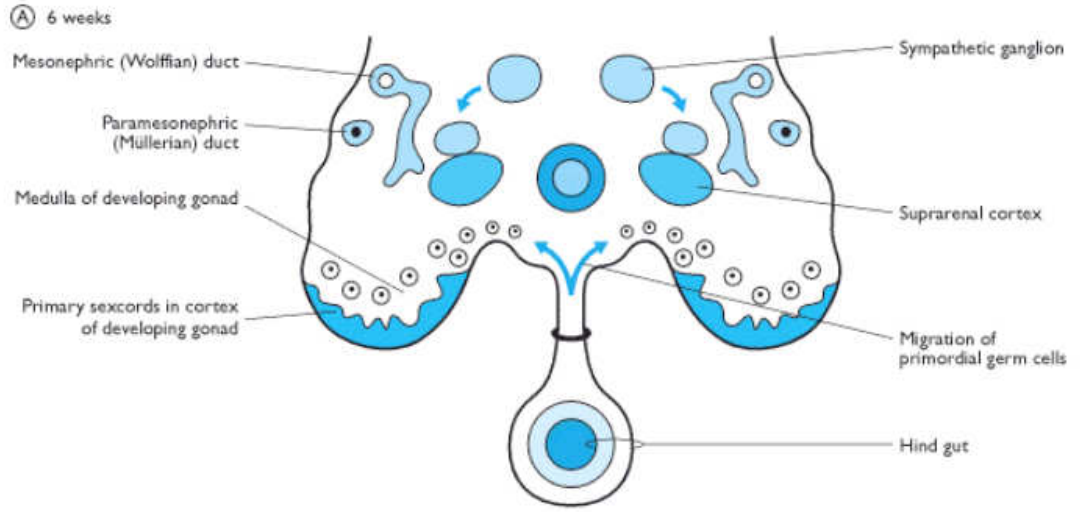
Adrenal gland

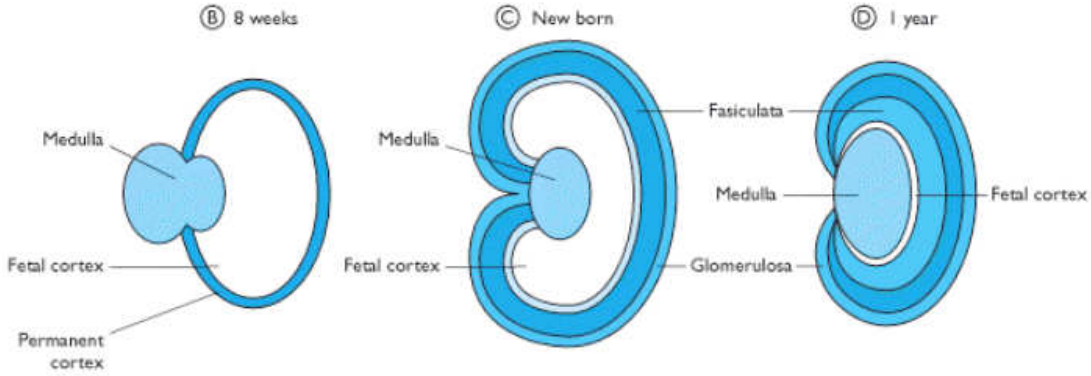
- Anatomy:
  - Cortex and medulla
  - Cortex: Zona reticularis
    - Narrow band with small cells and capillaries
    - Produces androgens
  - Cortex: Fasciculata
    - High lipid content, pale foamy cells
    - Cortisol, corticosterone, cortisone
  - Cortex: Glomerulosa
    - Small cells, cords or oval groups
    - Aldosterone
  - Medulla:
    - Fight-flight
    - Systemic adrenaline and noradrenaline
- Richly vascularised
  - Arterioles pass through the cortex
  - Capillaries pass from the cortex to the medulla to reach the arterioles

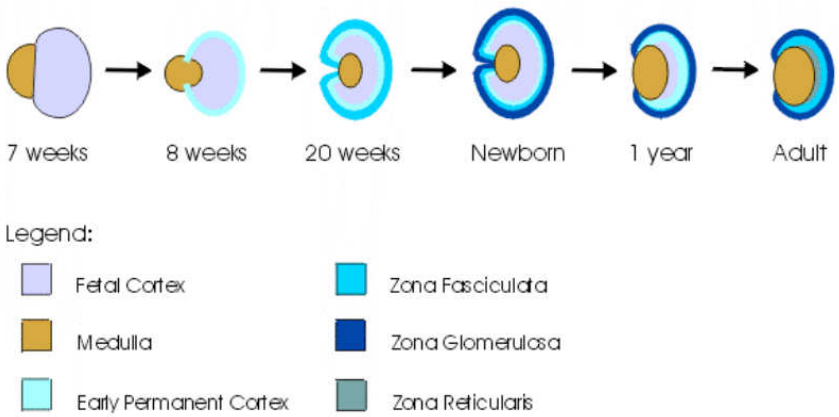


Adrenal gland (continued)

- Embryonic development, timeline
  - Initially larger than kidney
  - Week 6
    - Fetal cortex forms from mesothelium adjacent to dorsal mesentry
    - Medulla forms from neural crest cells migrating from the adjacent sympathetic ganglia
  - Late fetal period
    - Differentiates to form cortical zones
  - Birth – zona glomerulosa, zona fasciculata present
  - Adult cortex – mesothelium mesenchyme encloses fetal cortex
  - Year 3 – zona reticularis present
- Medulla
  - Neural crest origin
  - 2 types of cells:
    - A (80%)
    - NA (20%)
- Hormones:
  - Fetal cortex produces a steroid precursor (DEA)
    - This is converted by the placenta into estrogen
  - Adult medulla produces A and NA
  - Fetal adrenal hormones – influence lung development (cortisol)







Gonads

- Covered in sexual differentiation lecture/prac
- Derivations:
    - Gonads are derived from mesothelium and underlying mesenchyme
    - Primordial germ cells – first cells to migrate through the primitive streak
        - Migrate initially to the yolk sac, then to the mesentery of the hind gut before the genital ridge of the developing kidney
    - Gonadal ridge
        - Mesothelium thickening
        - Medial mesonephros
- Testis
    - 8 weeks
        - Mesenchyme, interstitial cells of Leydig secrete testosterone, androstenedione
    - 8-12 weeks
        - hCG stimulates testosterone production
    - Sustentacular cells (somatic cells)
        - Produce AMH to puberty
- Ovary – X-chromosome genes regulate development

Placenta

- Endocrine functions
    - Protein hormones
        - Human chorionic gonadotrophin (hCG)
            - Like LH, supports corpus luteum in ovary preserving pregnancy state
            - Found in maternal urine – pregnancy test
            - Found up to 20 weeks, maintains fetal adrenal cortex growth and maintenance
        - Human chorionic somatommotropin (hCS, placental lactogen, hPL)
            - Stimulates mammary gland development
            - Rises through pregnancy and stimulates maternal metabolic processes/breast growth
        - Human chorionic thyrotropin (hCT)
            - Like TSH in fetus
        - Human chorionic corticotropin (hCACTH)
            - Like ACTH
        - Relaxin
    - Steroid hormones
        - Progesterone
            - Support maternal endometrium and maintain pregnancy
        - Estrogens – produced in the fetal adrenal/placenta
- Formed from maternal decidua and fetal trophoblastic cells and extraembryonic mesoderm

Endocrine Functional changes through life

- Puberty (increased activity)
- Menopause (decreased activity)
- Disease (diabetes, thyroid, kidney)
    - Dependent on genetics, health, nutrition, lifestyle
- Pharmaceuticals (birth control, steroids, hormone replacement therapy)

Endocrine disruptors

- Exogenous chemicals that interfere with hormone function
    - Mimic – binds receptors (eg. diethylstilbestrol, potent estrogen, affects reproductive tracts of male/female)
    - Block – preventing hormone (eg. finasteride, anti-androgen: dihydrotestosterone, male genital dev arrest)
    - Interfere – transport/elimination (eg. polychlorinated biphenyl pollutants, thyroid hormones secreted)

Note:

type 1 diabetes – juvenile onset, autoimmune (T-cell dependent) destruction of islets of Langerhans
type 2 diabetes – adult onset, insensitivity to insulin

Parenting

- Definition – the parents' capacity to meet the infant's physical emotional and social needs
    - Ie: raising a child
    - No qualifications required
    - Normal life experience and a significant event
- Overwhelming and rewarding
    - Demanding with many responsibilities
- Parenting is a 2 way relationship
    - Relationship between caregiver and child has a significant role in child outcome
    - Failure of this relationship – insecure attachment, may result in various consequences

Parenting style

- Determines child development and behaviour
- 2 models
    - Dimensional
        - Scale between restrictive and permissive; loving and hostile
    - Categorical
        - Permissive – warm, caring, liberal and relaxed about behaviour and discipline
        - Authoritarian-restrictive – highly controlling, less emotionally close, strict, non-negotiable ideas
        - Authoritative – loving, warm, enforces rules and demands achievement

Challenges for infant/mother

- Birth
    - Infant communication
    - Babies develop attraction to human beings
        - Show this by smiling, gurgling
- Birth-3 months
    - Infant comforts self
    - Infant develops trust for mother
        - Mother meets basic needs
    - Are social, enjoy social interactions
- 4-6 months
    - Indiscriminate attraction – can tell between familiar and strange, smile at familiar
    - Allow care by strangers
    - Reciprocal exchanges with mother
    - have a feeding, sleeping, waking routine
- Physical development:
    - Sit without support – 6 months
    - Stands holding on – 7 months, pulls to standing – 9 months
    - Turns to a voice, puts food in mouth
    - Waves bye-bye – 8 months
- 7 months onwards
    - Discriminate attachment – have specific attachments
    - Separation anxiety
        - Clinginess, important form other to encourage independence
    - Object permanence
    - Avoid closeness with strangers
- 1 year on:
    - Walk, simple commands, simple words: mama, dada, drinks from cup, finger feeds
- 1-2 years
    - Wary of strangers, socially responsive
    - Multiple attachments
    - Tantrums, individualisation

Attachment

- Definition: an intense emotional relationship between 2 people that endures through time and causes stress and sorrow with prolonged separation
    - An evolving process that begins in pregnancy and strengthens over next 2 years
    - Occurs in all children to some degree

Maternal sensitivity and infant responsiveness

- A key determinant in the development of attachment
    - Sensitive mother:
        - Interprets infants communications, responds to infant's needs, accepting, cooperating, accessible
        - Promotes secure attachment
    - Insensitive mother:
        - Interacts on own terms and wishes
        - Promotes insecure attachment
- Infant responsiveness – other key determinant in development of attachment
    - Refers to the ability of the infant to respond to and interact with the mother
    - Requires intact neurodevelopmental function

Attachment theory :John Bowlby

- Considered attachment of infants to mother as a biological safety mechanism to allow infant to stay close to mother
    - From here, mother supplies a base from which to explore
    - Psychological development is formed by this parent-child relationship
- Parent-child relationships are important in the child's development, personality and future relationships

Strange situation experiment: Mary Ainsworth

- Examines infant reactions to separation from mother
- Method:
    - Child enters room with mother and plays with toys
    - Stranger enters room and tries to interact with infant
    - Mother leaves room – **first separation**
    - Stranger tries to interact with infant
    - Mother returns – **first reunion**
    - Infant is alone, stranger enters and tries to interact – **second separation**
    - Mother returns, stranger leaves – **second reunion**
- Allows determination of 4 patterns of attachment:
    - Secure attachment: 55-65% normal samples (normal)
        - Infant uses mother as a base from which to explore
        - Separation doesn't induce undue stress
        - Reunites actively and positively with mother
        - Prefers mother to stranger
    - Insecure –avoidant attachment – 20-30% of normal samples (self sufficient, distance)
        - Avoids parents and caregiver
        - Muted distress in absence of mother
        - Minimal response on reunion
        - No preference to stranger or mother
    - Insecure-ambivalent attachment – 5-15% of normal sample
        - Suspicious of strangers
        - Extreme distress on separation
        - Resists reunion and distress continues
    - Disorganised attachment – 10-20% normal, 45-80% maltreating samples
        - Lack of clear attachment behaviour on separation/reunion with mother
        - Passive, disconnected, dazed
        - Can be confused/apprehensive with mother
            - Has been both comforted and frightened by mother
- Cross-cultural:
    - Secure attachment is most common everywhere, others vary
    - Need to keep in mind child-rearing customs

Barriers to optimal parenting/attachment

- Postnatal mental illness
- History of inadequate parenting
- Lack of support
- Psychosocial stressors
- History of trauma

Postnatal mental illness

- Parent may not be able to meet the demands on the child and thus can affect bonding and attachment
- Types:
    - Postpartum 'blues'
        - Majority of new mothers: 50-80%
        - First week after birth to about day 10, transient mood, disturbed sleep, feeling of attachment to baby
            - No suicidal thoughts, hopelessness, worthlessness
            - May lead to PND,
        - Care of baby is not impaired
    - Puerperal psychosis
        - Psychiatric emergency
        - Uncommon: 1/1000
        - Occurs within 1 month of pregnancy
    - Postnatal depression
        - Very common. 1/7 women who give birth, many are unrecognised
        - Diagnosis:
            - 5 or more in a 2 week period of:
                - Depressed mood, diminished interest/pleasure, appetite, sleep disturbance, agitation, retardation, drained energy, worthlessness, guilt, decreased concentration, suicidal, thoughts of death
        - Sequelae
            - Mother:
                - Untreated, 50-70% still depressed, 6 months later
                    - ¼ chronic, ¼ recurrent
                - Adverse consequence on maternal confidence and parenting skills
                - Often results in insecure attachment
            - Infant:
                - Social, emotional, cognitive, behavioural development impaired
                - Attachment compromised
            - Other
                - Family disintegration, public costs
        - Detection can be hard because:
            - Mother hides symptoms
            - Poor sleep is seen as normal
        - Predicting
            - Antenatal:
                - Previous psychiatric treatment, mental illness (past, present), family history
                - Screening in pregnancy and postpartum
                - Triage and monitor
            - Edinburgh PND scale
                - Brief 10 item questionnaire
                - Not diagnostic, but identifies people who may need further assessment

Epidemiology

- Incidence of STDs is increasing
  - UK, 96-05, 60% increase in STDs
  - Causes:
    - Increased density and mobility of populations
    - It's hard to change human sexual behaviours (lack of education, misinformation)
    - Absence of vaccines against STDs
    - Increased sexual activity
- Top STDs worldwide:
  1. Genital warts – Papilloma viruses
  2. Non-specific urethritis – Chlamydia trachomatis
  3. Lymphogranuloma venereum (systemic) – Chlamydia trachomatis
  4. Vaginal thrush, balanitis – Candida albicans
  5. Vaginitis, urethritis – Trichomonas vaginalis
  6. Genital herpes – Herpes simplex I and II
  7. Gonorrhoea – Neisseria gonorrhoeae
  8. AIDS – HIV
  9. Syphilis – Treponema pallidum
  10. Hepatitis – Hepatitis B virus
  11. Chancroid – Haemophilus ducreyi

Genital warts

- Common – 440 million cases in the world
- Cause: papilloma viruses
  - Icosahedral capsule, naked virus (no envelope)
  - Double-stranded DNA
  - >40 different papilloma viruses cause warts
    - Some are specific to causing cervical cancer
- Induce papillomas
  - Benign growths of the epithelium of skin of mucous membranes – warts
- Diagnosis
  - Clinical
    - Cauliflower lesions on the penis, vulva, peri-anal region, throat
    - Many are asymptomatic
  - PCR from cervical swab or biopsy
  - Can be found on the cervix at colposcopy
    - With 5% acetic acid, can see white plaques
- Treatment
  - Chemical removal – podophyllin (genital)
  - Physical removal – cryocautery (liquid nitrogen)
- Cervical cancer
  - Prevalence of cervical cancer with HPV – 99.7%
    - High risk subtypes: 16, 18 (these two associated with 70% of cervical cancers)
  - Pap-smear can detect pre-cancerous lesions
  - Vaccine now available
    - Gardasil, prevents HPV types 16, 18, 6 and 11 (6&11 cause genital warts)
    - 4.7 million distributed in Australia
  - Common: >700 new cases/year, 2005, 216 deaths – hard to treat once diagnosed
- HPV typing can use PCR

Chlamydia trachomatis

- Common – 92 million new cases in 1999
- Cause: Chlamydia trachomatis
    - Types:
        - Serotypes A, B1, B2 and C – Trachoma (eye infection)
        - Serotypes D-K – Genital infection (non specific urethritis), ocular and respiratory infection
        - Serotypes L1, 2, 3 – systemic infection, lymphogranuloma venereum
            - Not common in Australia, more in Asia, Africa, S America
    - Small bacterium (200-800nm), obligate intracellular parasite
        - Growth only in mammalian cell lines
    - Life cycle:
        - Elementary body
            - Extracellular spaceship form, initiates infection by binding to epithelial cells
        - Reticulate body
            - Intracellular replication
        - Process:
            - EB attaches to cell → endocytosis, vesicle fusion with lysosomes inhibited (unknown mech) →differentiation to RB →multiplication → differentiation to EB → release into extracellular
- Disease
    - Entry to host is via minute mucosal abrasions
        - Organism attaches to columnar and transitional epithelial cells
    - Men – urethritis, proctitis (inflam of rectum lining), epididymitis
        - Discharge, 25% asymptomatic
    - Women
        - Discharge, 70% asympatomatic
        - Pelvic inflammatory disease: salpingitis
            - Inflammation of the fallopian tubes
                - Can lead to scarring of the tubes and infertility (+ ectopic pregnancy)
    - Peri-natal infection
        - 10-30% born to infected mothers develop purulent conjunctivitis
        - 10% develop pneumonitis
- Sampling
    - Swab of epithelium (cervix, urethra, rectum), pus or urethral exudate is inadequate
    - Transport – viral transport medium, or a fixed smear
- Diagnosis
    - Direct detection in smears
    - Tissue culture
    - ELISA, PCR (now, main is urine PCR)
- Treatment
    - Extended required
        - Slow growing bacteria
        - Antibodies kill reticulate bodies
    - Doxycycline (tetracycline) or Roxithromycin (macrolide)
- Contact tracing is important

Vaginal thrush (females), balanitis (males)

- Causative agent: Candida albicans (yeast)
    - Reproduces by budding
    - Can be sexually transmitted, but often isn't
- Epidemiology
    - 75% women have at least one occurrence of vulvovaginal candidiasis in their life
    - Penile colonisation in 20% of male partners of women with recurrent Candida
        - Men are often asymptomatic
- Risk factors
    - Pregnancy, oral contraceptives – higher glycogen content in vaginal environment
    - Broad spectrum antibiotics – eliminates normal flora
    - Diabetes, steroids

- Diagnosis
  - Clinical
    - Females – cheesy, thick, curd-like discharge
    - Males – usually asymptomatic, can have a patchy, red appearance
  - Sampling: lower vaginal swab
  - Laboratory
    - Wet mount, gram stain, culture (Saboraud's medium)
    - Look for appearance of pseudohyphae
- Treatment
  - Only if symptomatic → topical anti-fungals
    - Nystatin, cream or pessary
  - In males, test for diabetes (predisposing)

<u>Trichomoniasis</u>

- Causative agent: Trichomonas vaginalis
  - Protozoan with four anterior flagella and a posterior flagellum attached to an undulating membrane
    - Axostyle protrudes posteriorly
- Site of colonisation
  - Vagina – women, urethra – men
- Epidemiology
  - Women – main carriers, 50% asymptomatic
  - Men – low prevalence, usually asymptomatic
    - Found in 23-40% of male sexual partners of infected women
    - Asymptomatic men are an important vector/reservoir
  - Prevalence correlates with sexual activity
- Symptoms
  - Acute inflammation
  - Frothy, foul smelling discharge containing PMNs
  - Can cause haemorrhages in the cervix → strawberry cervix
- Diagnosis
  - Sample: high vaginal swab, transport – needs to be kept moist
  - Lab
    - Wet mount examination, cannot be cultured
    - PCR now available
- Treatment
  - Metronidazole, Tinidazole (single dose)
    - Nitroimidazole (treat anaerobic bacterial infections)
  - Partners need treatment

<u>Genital herpes</u>

- Most common cause of genital ulceration
- Cause: Herpes simplex virus (HSV)
  - HSV1 – oral Herpes (cold sores)
  - HSV2 – genital herpes
  - HSV1 and 2 are frequently found in both sites (oral sex may contribute)
- Lesions
  - Occur 3-7 days after infection
  - Blisters, pain on urination
    - Healing can take up to 2 weeks
  - Recurrences are common, often less severe
- Associated symptoms: fever, headache, malaise, swelling of local lymph nodes
- Diagnosis
  - Sampling – scrape lesion, transport in viral transport medium
  - Polymerase chain reaction – can tell if HSV 1 or 2, treatment is the same, however
  - ELISA – seroconversion can take 12 weeks
- Treatment

No curative, anti-virals (acyclovir) can shorten episode if started in first 72 hours

Gonorrhoea

- Gonorrhoea, Chlamydia and Syphilis are common worldwide, especially Sub-Saharan Africa and SE Asia
- Cause: Neisseria gonorrhoeae
    - Gram negative cocci, fastidious (needs enriched media: CBA)
    - Human pathogen
- Epidemiology
    - Women have 50% chance of infection after single sexual encounter with infected man
    - Men have 20% chance of infection after single sexual encounter with infected woman
- Disease
    - Incubation 2-7 days
    - Development:
        - N. gonorrhoea attaches to epithelial cells of urethra/cervix, or throat (oral sex)
            - Facilitated by pili and other surface proteins (afimbral adhesion)
        - Taken up by PMNs
        - Cellular damage due to lipopolysaccharide
            - Induces TNF-alpha, and host cell damage
    - Males:
        - Urethral gonorrhoea – >90% develop symptoms and seek treatment
            - Symptoms – purulent urethral discharge, severe pain and burning on urination
        - Rectal gonorrhoea – 18-34% develop symptoms
            - Symptoms – mild burning on defecation, itching ,mucopurulent discharge, blood in faeces
        - Throat infection
    - Females:
        - Urethral and cervical infections – <50% develop symptoms within 2-7 days and seek treatment
            - Symptoms – purulent vaginal discharge, severe pain and burning on urination
            - Often asymptomatic
        - Rectal gonorrhoea – occurs in 30% of women with cervical gonorrhoea
            - Symptoms – asymptomatic in 95%
        - Throat infection
    - Complications
        - Pelvic inflammatory disease
            - Occurs in 10-20% of women with gonorrhoea, can cause sterility
        - Bacteraemia
        - Gonococcal arthritis
            - Most common joint infection in sexually active adults
        - Dermatitis-arthritis syndrome
            - Fever, chills, skin lesions and arthralgia in the hands, feet, elbows
    - Neonatal
        - Exposure in the birth canal can lead to ophthalmia neonatorum
            - Untreated → blindness
- Diagnosis
    - Specimens – swab of discharge (urethra, cervix, rectum)
        - Needs non-toxic swab, and transport medium
    - Direct gram stain – gram negative diplococci (intracellular)
    - Bacterial culture – chocolate blood agar
    - Antibiotic sensitivities (using culture)
    - PCR – using urine sample
- Notifiable disease
- Treatment
    - Treat all sexual contacts:
        - ceftriaxone (cephalosporin III) + azithromycin (macrolide) or doxycycline (for Chlamydia)

Syphilis

- Cause: Treponema pallidum
  - Thin coiled organism, spirochaete bacterium, 10-13um long, sluggishly motile
  - Not grown in vitro, cell line and can't gram stain
    - Only can be grown in rabbit testis (silver stain)
  - Transmitted with 10% efficiency
- Disease course
  - **Infection**: bacteria has a cork-screw movement that allows it to penetrate skin/mucous membranes
    - Multiplies extra-cellularly and induces an immune response:
      - Infiltration of plasma cells, PMN and macrophage
  - Causes a painless ulcer (chancre) at initial site of infection – **primary syphilis**
    - Heals in 3-6 weeks untreated
  - **Secondary syphilis**
    - Organism escapes the lesion and is trapped in draining lymph nodes and multiplies
      - Spreads systemically – esp: joints, muscles, skin, mucus membranes, liver, lymph nodes
    - Symptoms – flu-like illness, myalgia, headache, fever, muco-cutaneous rash
      - Severity differs person to person
  - **Latent syphilis**
    - Treponemes remain dormant, possibly in the liver or spleen
  - **Tertiary syphilis**, 3-30 years later
    - Re-awakening and multiplication of Treponemes
    - Further dissemination and invasion
      - Host: Cell mediated hypersensitivity – gummas (soft, non-cancerous growth) in skin, bone and testis
    - Clinical signs and symptoms: neurosyphilis, CV syphilis (aortic lesions, heart failure), progressive destructive disease
  - Summary:
    - Incubation period of 2-6 weeks (slow growing)
    - Primary syphilis – chancre, regional lymphadenopathy
      - Some patients clear disease, 1-3 months
    - Secondary syphilis – rash, generalised lymphadenopathy
      - Some patients clear disease, 1-3 months
    - Latent: 2-50 years, no symptoms
      - 70% lifetime latency
      - 30% tertiary syphilis → CNS, Gummas, CVS
    - Highly contagious at primary and secondary stages
- Congenital syphilis
  - Untreated pregnant women can transfer infection to baby at any stage of disease
    - Can lead to: abortion, still birth, multiple organ failure, CNS defects, deformed skull and teeth, rash and jaundice
  - Completely preventable, routine antenatal testing
- Diagnosis of primary syphilis
  - Definitive:
    - Dark field microscopy, direct fluorescent antibody
  - Presumptive diagnosis
    - Non-treponemal (screening) – serological detection of cardiolipin
      - VDRL
      - Rapid plasma reagin (RPR)
    - Treponemal (confirmation)
      - Fluorescent treponemal antibody absorbed (FTA-ABS)
      - Microhaemagglutination assay for antibody to T. pallidum (MHA-TP)
    - Treponema pallidum specific PCR
      - Currently being validated, lacks sensitivity
- Treatment (all sexual contacts)
  - Antibiotic therapy – benzathine penicillin(Pen G) IM
  - Later stages require long term treatment and follow up
- Notifiable disease

STDs in general

- Genital lesions/ulcers increase risk of acquiring infections (like HIV)
- STDs can often occur not in single
    - Eg: Syphilis and Gonorrhoea, Gonorrhoea and Chlamydia, Genital herpes can be reactivated by Gonorrhoea

Summary table

Pathogen	**Diseases and symptoms**	**Treatment**
Human papillomavirus	Genital warts, cervical cancer	Surgical removal of pre-cancerous or cancerous lesions
Chlamydia trachomatis	Urethral infection, pelvic inflammatory disease, ectopic pregnancy, infertility	Antibiotics – azithromycin
HIV	AIDS	Suppression of virus with antiviral drug therapy
Neisseria gonorrhoea	Gonorrhoea, urethral infection, pelvic inflammatory disease, ectopic pregnancy, infertility	Antibiotics – cephalosporins
Treponema pallidum	Syphilis, genital ulcers, neurological damage, heart disease	Antibiotics – penicillin
Haemophilus ducreyi	Chancroid, genital ulcers	Antibiotics – azithromycin
Herpes simplex virus	Genital lesions	Suppression of virus with antiviral drug therapies
Hepatitis B virus	Hepatitis, liver cancer	Limited
Hepatitis C virus	Hepatitis	Limited
Trichomonas vaginalis	Vaginal discharge	Antibiotics - metronidazole

Epidemiology

- Respiratory tract infections make up half of all symptomatic illness
    - Have significant morbidity and direct and indirect health care costs
        - Health care, time off work took look after kids
    - Occasionally fatal

Host defences

- IgA
- Nasal filtration
- Ciliated epithelium
- Saliva – flushing, lysosyme
- Normal flora
    - Streptococcus species, Corynebacterium species, Neisseria species, Anaerobic cocci, Haemophilus influenzae, Staphylococcus aureus (in nose of 15% of population), Candida albicans
- Disease depends greatly on location in the host

The common cold

- Infection of the nasopharynx
- Children have ~8 episodes/year, adults 1-2
- Diagnosis is clinical:
    - Sneezing, sore throat, cough, acute rhinorrhea, malaise, headache, fever (often low fever)
- Aetiology
    - Rhinoviruses (>100 serotypes, no cross-reactivity)
        - Prefers lower temperature, thus stays in upper repiratory tract
    - Coronaviruses
    - Parainfluenza viruses
    - Respiratory syncytial virus
    - Unknwn causative organisms
- Treatment
    - Symptomatic
    - No vaccine – so many types
- Complications
    - Otitis media
    - Bacterial pharyngitis
    - Pneumonia

Influenza

- Influenza virus
    - 3 types:
        - A – epidemics and pandemics, moderate to severe
            - Further sub-typed: H5N1 (avian), H1N1 (swine)
        - B – epidemics, moderate
        - C – mild
- Influenza vs cold
    - Onset abrupt vs gradual
    - Fever, myalgia, arthralgia, anorexia, headache **severe vs uncommon**
    - Cough, malaise – more severe
    - Fatigue, weakness
    - COLD: stuffy nose, sneezing, sore throat
- Complications
    - Secondary bacterial infection
    - Pneumonia (most common)

Pharyngitis and tonsillitis

- Inflammation of pharynx, and tonsils (often concurrent)
- Cause:
    - Viruses (80%)
    - S. pyogenes (10-20%)
    - Epstein-Barr virus (<5%)
        - Infectious mononucleosis, glandular fever
        - Increased incidence in teenagers, infection primarily of B-lymphocytes
- Diagnosis:
    - Clinical
        - Sore throat, pain on swallowing, fever, enlarged lymph nodes, runny nose and post-nasal drip, headache
        - Tonsillitis may have exudate
    - Laboratory diagnosis
        - Microscopy of throat swab is useless – natural flora
        - Rapid strep antigen test – detects group A streptococcus (GAS) antigen
        - Throat culture (gold standard)
            - >95% sensitivity
        - Serological test for EBV (blood)
- Streptococcus pyogenes
    - Gram negative cocci in chains
    - Most acute bacterial pharyngitis
    - Complications:
        - Complications (suppurative) – peritonsillar abscess, otitis media, sinusitis
        - Indirect (non-suppurative) – rheumatic fever, acute glomerulonephritis
            - May need lifelong penicillin to prevent rheumatic fever
- Treatment
    - Severe tonsillitis with clinical features suggestive of bacterial aetiology – acute onset, anorexia, fever
    - Patients in groups at risk of acute rheumatic fever (aboriginal communities in central and N Australia)

Otitis media

- Inflammation blocks the Eustachian tube and fluid builds up in the middle ear
- Types:
    - Acute OM
        - Fever and pain, effusion
    - OM with effusion
        - Glue ear (thick/watery fluid in middle ear)
        - Absence of fever, inflammation
        - Possible perforation
    - Recurrent OM
        - >3 episodes in 6 months
    - Chronic OM
- Epidemiology
    - 83% children at least 1 episode by 3 yo
        - Peak age group is at 6-12 months
    - More common in ATSI or non-english background
- Why more common in younger children
    - Eustachian tube is shorter, more horizontal and straighter and medial orifice is more open
    - Young children get more viral respiratory infections
    - Supine feeding
- Examination
    - Fluid accumulation, bulging opaque eardrum
    - Older children may touch ear, feels irritable
- Aetiology
    - ~50% viral
    - Of non-viral: 38% streptococcus pneumoniae, 27% Haemophilus influenzae, 28% unknown, 10% Moraxella catarrhalis, 3% strep pyogenes

        - Streptococcus pneumoniae
            - Alpha haemolytic, sensitive to optochin
            - Gram positive diplococci
        - Haemophilus influenzae
            - Cultured on CBA (heated HBA)
            - Gram negative rod
            - Types:
                - Encapsulated (serotypes A-F)
                    - Type B most virulent – causes meningitis, vaccine available
                    - Nasopharyngeal carriage, 5-10% of people, type b, 1-5%
                - Non-encapsulated (naked)
                    - Nasopharyngeal carriage: 25-80%
- Microbiological Investigations
    - Tympanocentesis culture
        - Routinely not done, risky
    - Culture often only done if rupture occurs
- Treatment
    - If: systemic signs (vomiting and fever) – antibiotics
    - Otherwise: symptomatic
        - Wait and see approach, give prescription and tell parents to give if symptoms persist
            - <2 year: 24 hours, >2 years: 48 hours
- Consequences
    - Permanent hearing loss (young children) – conductive hearing loss
    - Problems with speech and language development (+ classroom behaviour)

<u>Sinusitis</u>
- Inflammation/infection of one or more paranasal sinus
    - Acute, chronic, recurrent
- Symptoms
    - Purulent rhinorrhea and nasal congestion, cough, facial pain
- Cause
    - Pathogens (same as AOM)
        - S. pneumoniae, M. catarrhalis, Non-typable H. influenzae

<u>Laryngitis</u>
- Inflammation of the larynx
- Symptoms: sore throat, dysphonia (hoarseness), loss of voice, cough, low-grade fever (maybe)
    - Physical exam – hard to visualise larynx on standard examination
    - Associated symptoms – rhinitis, pharyngitis, cough
- Cause: mostly viral, occasionally bacterial

<u>Croup – Acute laryngo-tracheo-bronchitis</u>
- Symptoms: fever, hoarseness of voice, no productive cough, inspiratory stridor
- Cause: mostly viral
    - Parainfluenza virus type 1, 2
    - Influenza A or B
    - RSV

<u>Diphtheria</u>
- Acute bacterial disease affecting tonsils, nose and/or skin
    - Uncommon, vaccination
- Cause: cornynebacterium diphtheriae
- Symptoms:
    - Pharyngitis
    - Obstruction (epithelial cells, blockage, suffocation)
    - Toxic myocarditis, congestive heart failure
- Transmitted by respiratory droplets

Epiglottitis

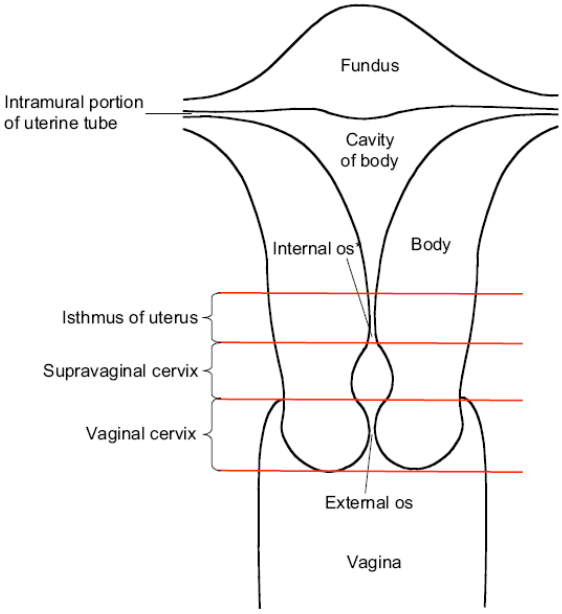
- Often in young children (large epiglottis)
    - Vaccine has meant decrease in incidence
- Symptoms: severe inflammation and oedema, trouble breathing/talking/swallowing
    - Emergency, potential blockage and quick death
    - Need intubation, otherwise don't examine in case cause blockage
- Cause: Haemophilus influenzae

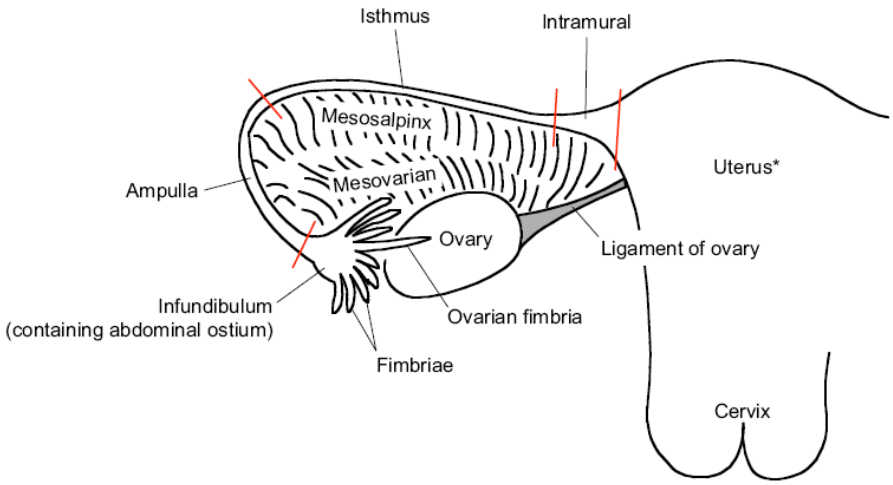
Whopping cough (Pertussis)

- Symptoms (one or more):
    - Paroxysms of coughing
    - Inspiratory whoop without other apparent cause
    - Post-tussive vomiting
    - Persistent cough > 2 weeks
        - Episodes every few hours
- Cause: Bordetella pertussis
- Stages (1-3 weeks each):
    - Catarrhal stage
        - Infectious stage
        - Cold, dry cough
        - Treat here, can stop spread
    - Spasmodic/paroxysmal stage
        - Whooping cough appears
    - Convalescent stage
        - Gradual decline in frequency and intensity of coughing fit
- Diagnosis
    - Difficult in catarrhal stage
    - Culture
        - Only isolated in 30-50% of cases
            - Organism is fragile and fastidious
            - Throat swab not suitable
            - Needs 2-3 days to culture
    - Serology – IgA concentration
    - PCR
- Treatment
    - Early antibiotic may be beneficial
        - Can limit spread
    - Symptomatic
        - Antitussives, antispasmodics, sedatives
    - Notifiable disease
        - Antibiotic prophylaxis to contacts
        - Immunisation status checked for children in household

Female reproductive system

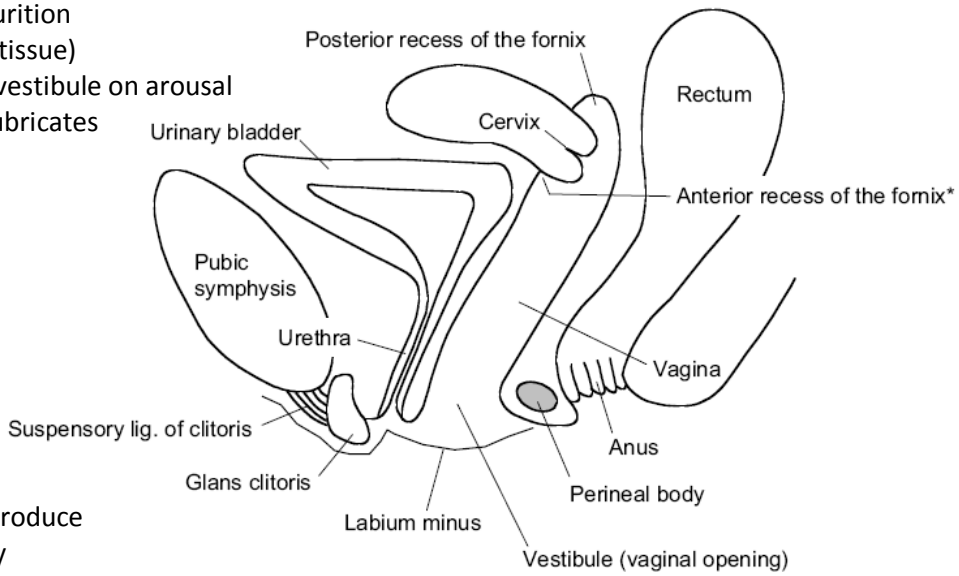
- Made up of internal organs (pelvic cavity) and external genitalia (lower part of the vagina)
- Ovaries (female gonads)
  - Egg and hormone production
  - Located on the lateral pelvic wall in the ovarian fossa
- Uterus (womb)
  - Located between the bladder (anterior) and rectum (posterior) in the lesser pelvis (not pregnant)
  - Covered by peritoneum on posterior (intestinal) and anterior (vesical) surfaces
  - Parts:
    - Body, fundus, uterine tube attachments, isthmus, cervix
- Cervix
  - Meets the vagina at right angles, bulges into the anterior vaginal wall
  - Vaginal wall divides into vaginal and supravaginal parts
    - Supravaginal has a cavity of the uterine cervix (cervical canal)
      - Fusiform, palmate mucosal folds facilitating canal closure
      - Communicates with the vagina via the internal os, the uterus via the internal os
- Uterine tubes
  - Carry spermatozoa to the ovum and the fertilised (and unfertilised) ovum to the uterus
  - 10 m long, extends from upper lateral uterus to ovarian region
  - Parts:
    - Uterine ostium, peritoneal/abdominal ostium
    - Infundibulum, ampulla (fertilisation, dilated), isthmus (narrow), intramural parts
  - Infundibulum is shaped like a trumpet
    - Rim has fimbriae (finger-like projections), one is longer and attaches to the tubal end of the ovary (ovarian fimbria)
    - Contains abdominal ostium





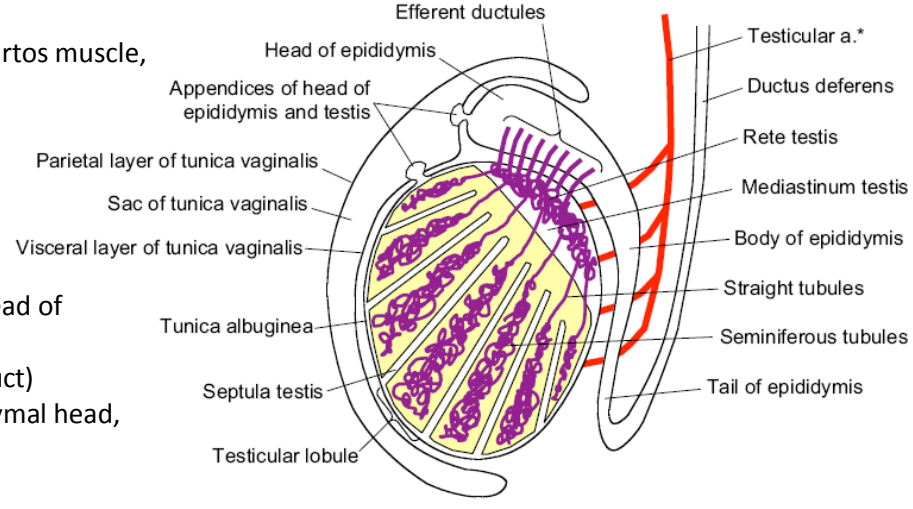
- Ligaments
  - Ligament of the ovary – derived from the gubernaculum
  - Broad ligament: mesometrium, mesosalpinx, mesovarium
    - Wide fold of peritoneum attaching uterus to peritoneal wall

- Vagina
  - Fibromuscular tube lined by stratified squamous epithelium
  - Extends from the vestibule (cleft between labia minora) to cervix of the uterus
    - Recess around the cervix is the fornix – anterior, posterior, lateral recesses
  - Inner walls normally in contact, forming H shape on cross section
  - Anterior wall related to the urethra
    - Posterior wall covered by peritoneum in upper quarter and lower is related to perineal body (central anchor point for pelvic floor muscles) and anorectal canal
- External genitalia
  - Urogenital diaphragm and Levator ani (anal diaphragm)
    - Important in micturition
  - Bulb of vestibule (erectile tissue)
    - Opens up vaginal vestibule on arousal
  - Greater vestibular gland lubricates

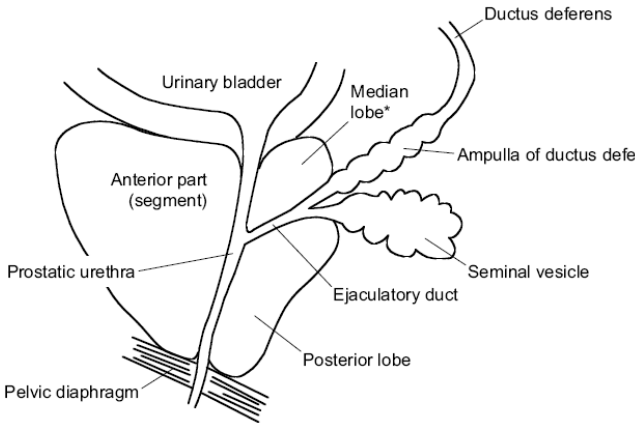


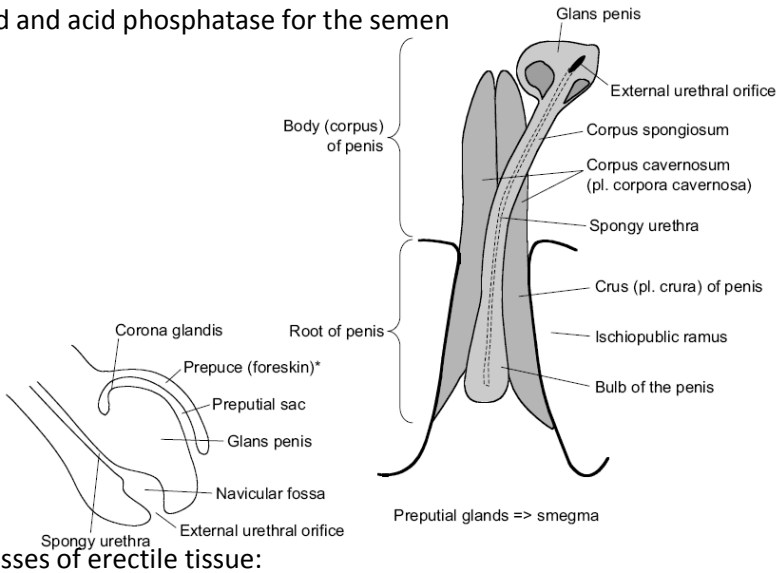
<u>Male reproductive system</u>

- Testes
  - Paired ovoid organs that produce spermatozoa after puberty
  - Outer fibrous covering – tunica albuginea with septa that divides testis into wedge-shaped lobules
    - Each lobule has 1-4 seminiferous tubules, about 800 in whole testis
    - Lobules and septa converge near posterior margin to form mediastinum testis (mass of fibrous tissue continuous with tunica albuginea
      - Seminiferous tubules converge on 20-30 straight tubules approaching the mediastinum
        - These become a network of tubules in the mediastinum: fete testis
          - 15-20 efferent ductules leave the rete testis entering the head of the epididymis
  - Tunica vaginalis covers tunica albuginea
    - Remnant of fetal processus vaginalis peritonei (precedes the descent of the testis from abdomen to stomach)
      - Proximal part closes off and obliterates leaving tunica vaginalis as a closed sac
    - Has parietal and visceral (covers scrotum, medial, posterior surfaces of epididymis, sinus of epididymis) layers
    - Abnormalities: persistent processus vaginalis, hydroceol
- Spermatic duct
  - Layers from abdominal cavity: dartos muscle, scrotum, cremaster muscle
- Epididymis
  - Attached to posterior testis
  - Parts: head, body, tail (pointing)
- Appendices:
  - Appendix of the testis – upper pole of testis inferior to head of epididymis (remnant of paramesonephric duct)
  - Appendix of epididymis – epididymal head, pedunculated appendage (remnant of meonephric duct)



- Ductus deferens
    - Continuation of the tail of the epididymis
    - Initially tortuous, ascends in posterior spermatic cord, becomes straighter
        - Traverses inguinal canal, exists the deep inguinal ring entering lesser pelvis
            - Crosses the ureter, passes between the posterior surface of bladder and upper pole of seminal vesicle
            - Ampulla of ductus deferens – dilated section)
            - Enters the prostate, joins the duct of the seminal vesicle forming ejaculatory duct
                - Ejaculatory duct is 2cm long and opens into the prostatic urethra
- Seminal vesicles
    - Coiled tubular glands
        - Produce fructose and coagulating enzyme (vesiculase) for seminal fluid
    - Sperm is stored in epididymis and possible ampulla of ductus deferens, not here
- Prostate
    - Parts:
        - Base (adjacent to bladder neck), apex (facing downwards), posterior, anterior and inferolateral surfaces
        - 4cm transverse, 3cm vertical, 2cm anteroposterior
        - Median lobe between prostatic urethra and ejaculatory ducts
            - Can enlarge into the bladder in later life preventing urination
    - Prostatic enlargement
        - Can compress urethra to prevent flow, make initiation of micturition difficult
    - Produces alkaline fluid containing citric acid and acid phosphatase for the semen

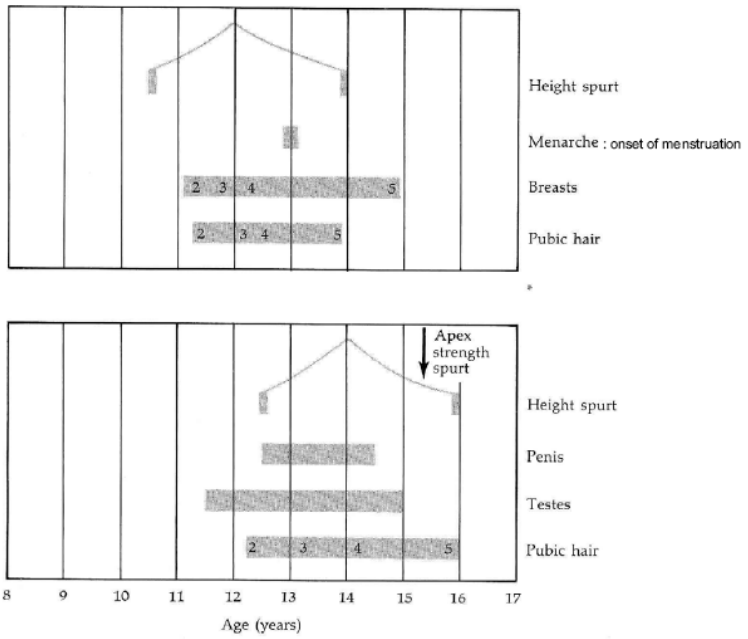




- Penis
    - Parts:
        - Root attaching to perineum – 3 masses of erectile tissue:
            - 2 crura attaching to ischiopubic ramus
            - Bulb of penis (between 2 crura, attached to inferior urogenital diaphragm – fascia)
        - Body (corpus, pendulous)
            - Spongy urethra passes through
            - Has a dorsum (posterosuperior during erection) and urethral surface
                - Made up of:
                    - 2x corpus cavernosa – crura are continuous with corpora cavernosa
                    - Corpus spongiosum – bulb is continuous with corpus spongiosum
    - Corpora cavernosa
        - Enclosed in a strong fibrous tunica albuginea – meet in midline as septum of the penis
        - Interior contains cavernous spaces (also seen in spongiosum, but not as much)
            - These have numerous trabeculae arising from fibrous sheaths thus creating spaces for filling with blood during ererction
    - Corpus spongiosum
        - Expanded distally as the glans of the penis
        - Has the corona glandis – overhanging ridge at the neck of the penis
        - Contains the spongy urethra, opens into the navicular fossa at the apex of the glans
            - Glans is covered in a prepuce (foreskin) that arises from the body of the penis
                - On the urethral surface, a fold of skin passes from prepuce to the glans – frenulum

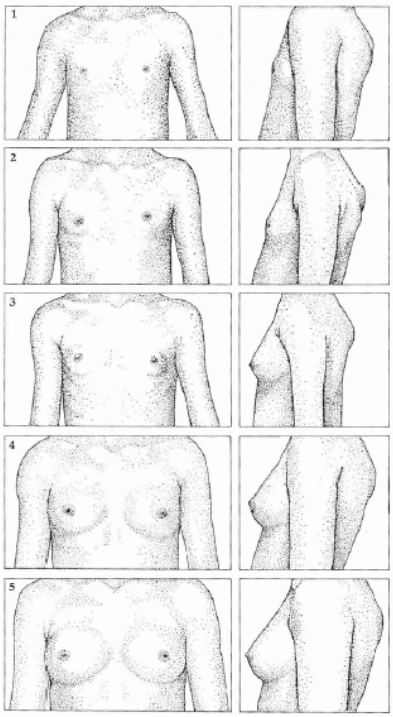
Changes at puberty – summary

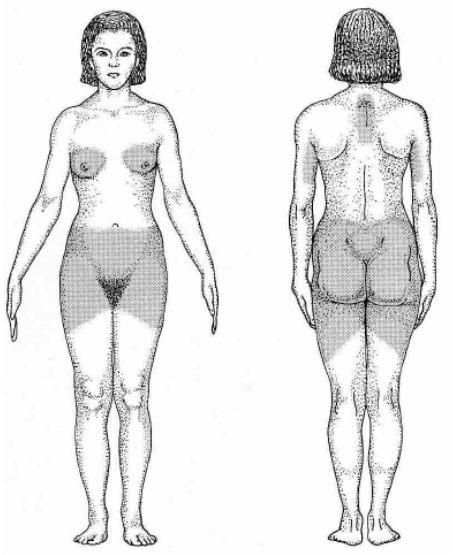
- Males and females develop at different rates and at different ages

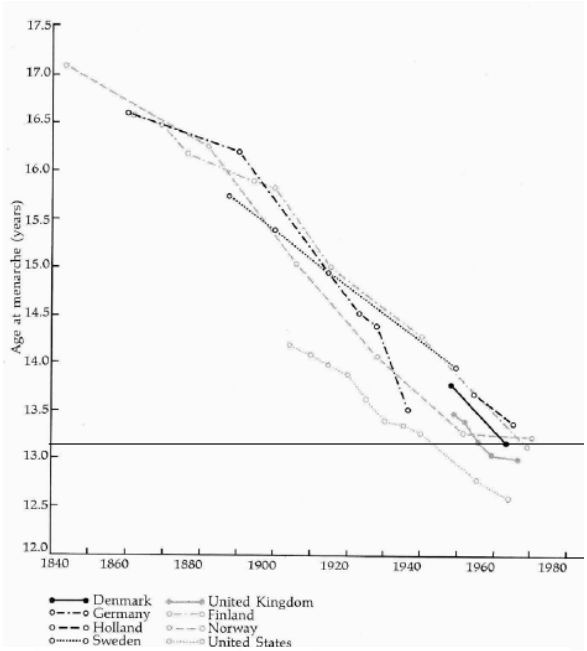


Physical changes at puberty: female

- Considerable variation between individuals in the age puberty is reached
- Tanner stages: breasts
  - 1: prepubertal, flat – like child
  - 2: small, raised breast bud
  - 3: general enlargement and raising of breast and areola
  - 4: areola and nipple form contour separate from breast
  - 5: adults breast – areolar in same contour as breast
- Menarche
  - Age has been declining by ~4 months/decade since 19th century
    - Decline is possibly due to: better nutrition (caloric, protein) and improved infant/child health
    - Age of onset has steadied in rest times, measured by menarche
- Fat redistribution:
  - Fat loss from: limbs, but not net loss
  - Redistributed to: breasts, hips, buttocks, upper thighs, upper back, backs of upper arms
  - Face: fat deposits soften the contours and allow distinguishing between faces of men and women

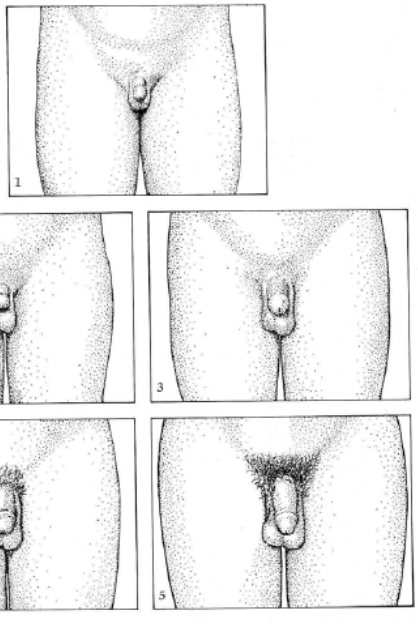




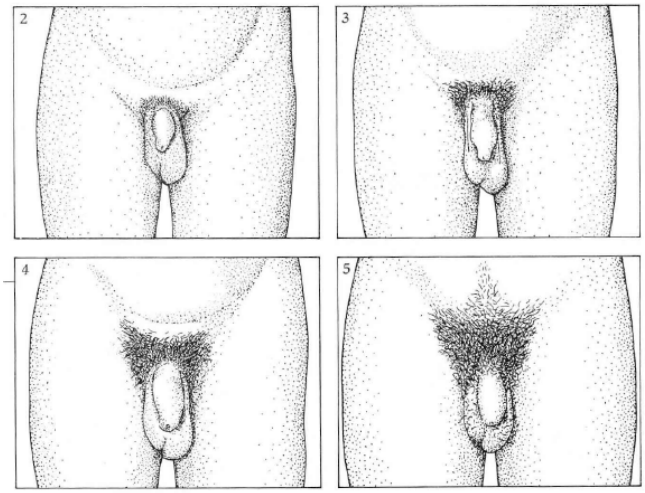


Physical changes at puberty: males

- Considerable variation between individuals in the age puberty is reached
- Tanner stages: genitalia:
  - 1: prepubertal, testes and penis size of early childhood
  - 2: testes become larger, scrotal skin reddens/coarsens
  - 3: continuation with lengthening of penis
  - 4: penis enlarges in size and scrotal skin becomes pigmented
  - 5: adult genitalia

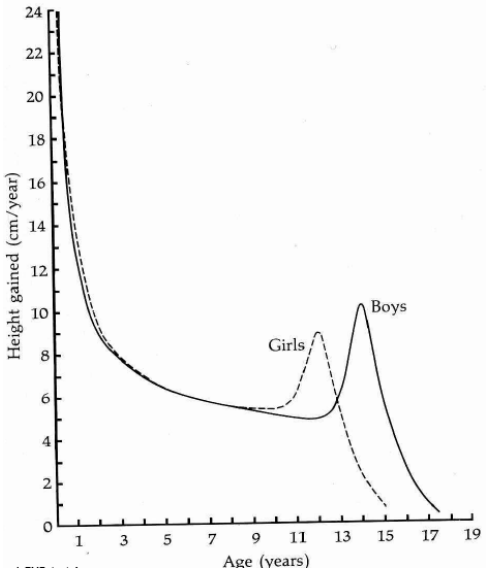


- Tanner stages: pubic hair (male and female)
    - 1: no pubic hair
    - 2: sparse growth of downy hair at base of penis
    - 3: pigmentation, coarsening and curling with increased hair
    - 4: adult hair, limited area
    - 5: adult hair with horizontal upper border and spread to thighs



<u>Growth rates</u>

- Growth spurt of boys is later than girls, but faster and longer
- Primapes don't have a growth spurt in skeletal growth, only in muscle mass, humans do



<u>Muscle mass</u>

- Both girls and boys have an increase in muscle mass, testosterone causes boys to have a larger increase
    - measured using creatinine excretion

<u>Blood pressure</u>

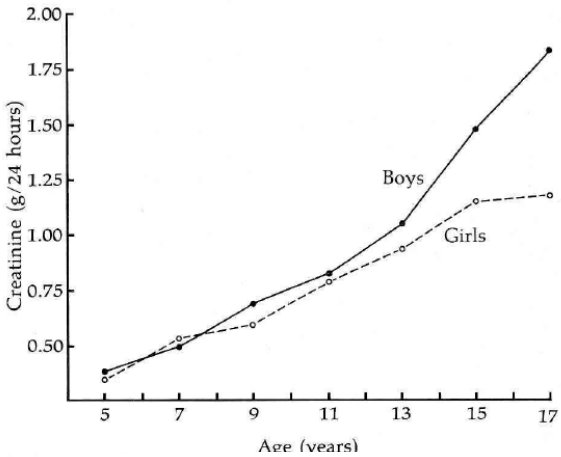
- Elongation of the trunk + aorta and an increase in muscle mass means BP increases
    - Thus also boys > girls in terms of BP

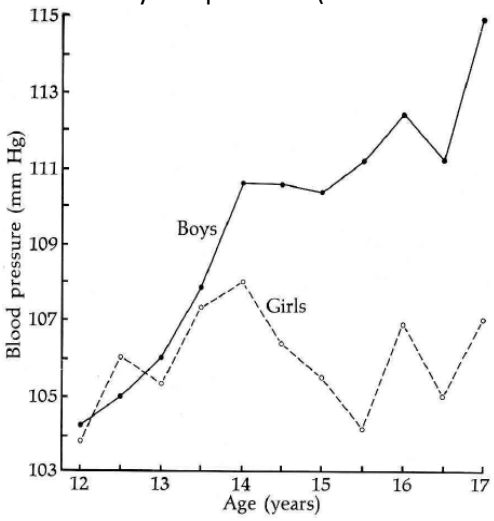
<u>Red blood cells</u>

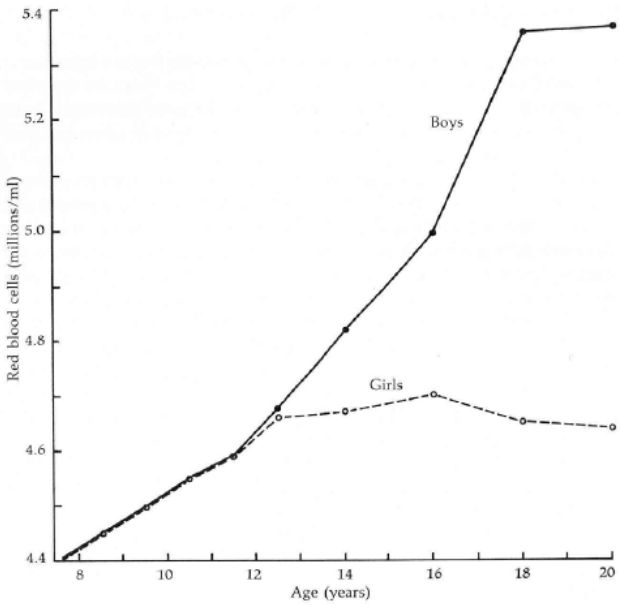
- Blood volume, haemoglobin and RBC number increases markedly in boys, not as much in girls
    - Due to muscle mass/size
    - Thus boys have an increased exercise capacity

<u>Non-reproductive physical changes</u>

- Body fat redistribution
- Increase in stature
- Increase in weight (skeleton, muscle, internal organs, fat)
- Increase in musculature and strength
- Improvement in coordination (cerebellum)
- Growth of larynx and deepening of voice
- Changes in body proportions (in order): facial, feet/hands, hips, chest, shoulders, trunk length
- Increase in cardiac mass (males 2x females)
- Rise in blood pressure, decrease in HR
- Increase in RBC number and blood volume
- Increase in lung size and vital capacity
- Decline in basal body temperature (mech unknown)





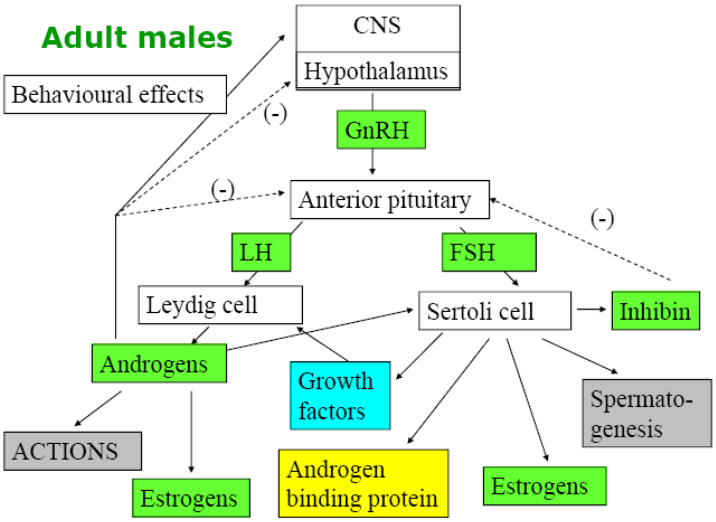


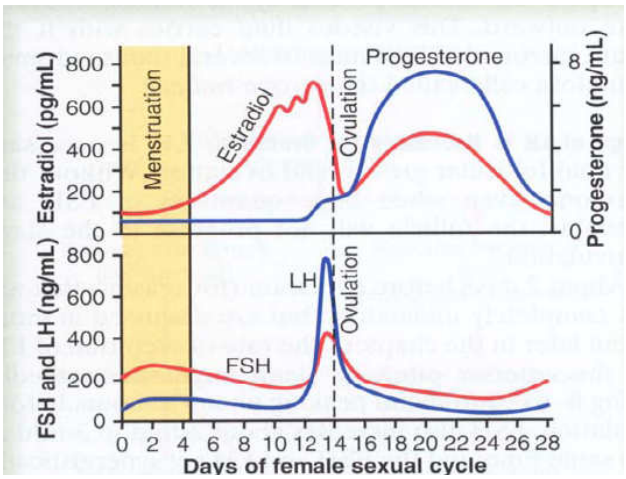
Introduction

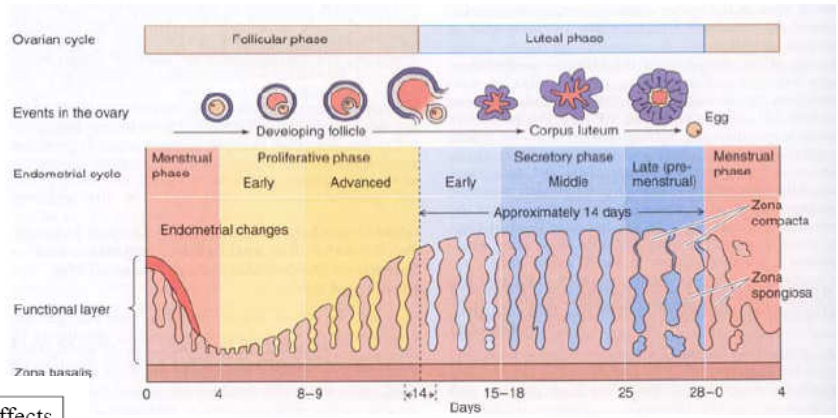
- Puberty is the period where gametogenic and endocrine functions have developed to the point where reproduction is possible
    - Ie: development of gonads, dual function:
        - Production of germ cells (ova, spermatozoa)
        - Secretion of sex hormones (estrogens, androgens: testosterone)
        - Dependent on gonadotropins from anterior pituitary

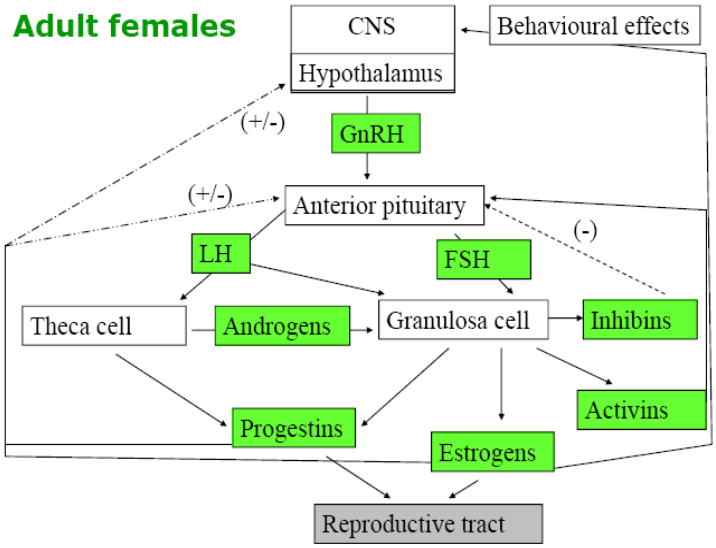
Adult physiology

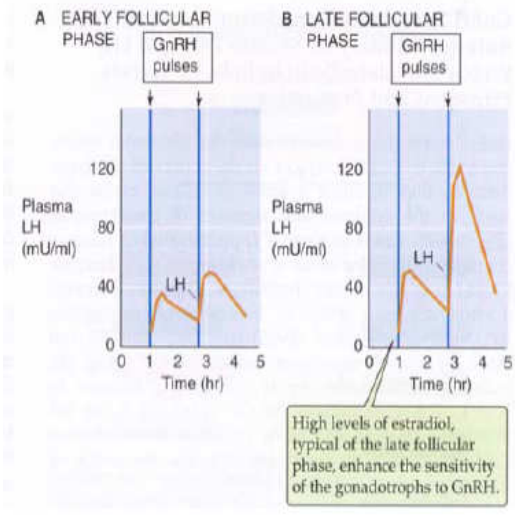
- Males
    - GnRH secretion is pulsatile, with a short half life (2-4 minutes)
        - Thus Gonadotropin (LH, FSH) secretion is pulsatile
            - LH: 8-14 pulses/24 hours, FSH pulses less prominent (amplitude) but longer half life
    - Castration results in a rise in pituitary content and secretion of LH and FSH (removal of testosterone inhibition)
    - Continuous GnRH suppresses gonadotrophin release
- Notes:
    - m/f both produce estrogen and testosterone but one is more predominant
    - inhibin is a polypeptide
- Females:
    - GnRH release is pulsatile (~hourly)
        - Amount varies throughout the cycle
- Notes:
    - Estrogen normally inhibits GnRH, and gonadotropins, but right before ovulation, provides positive feedback causing late follicular rise in FSH and LH





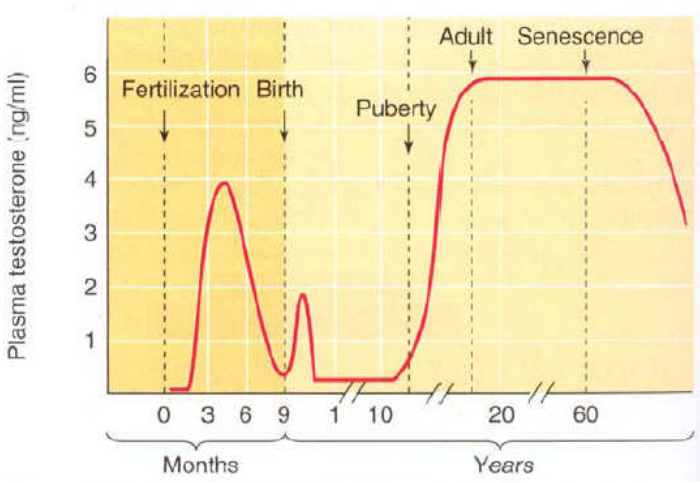






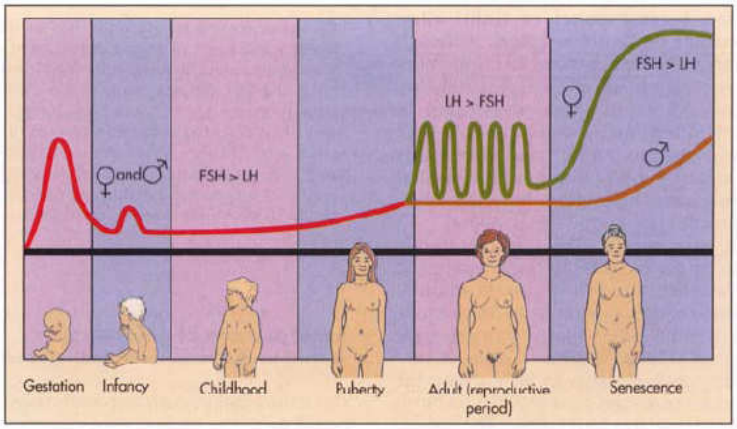
Fetus and infancy

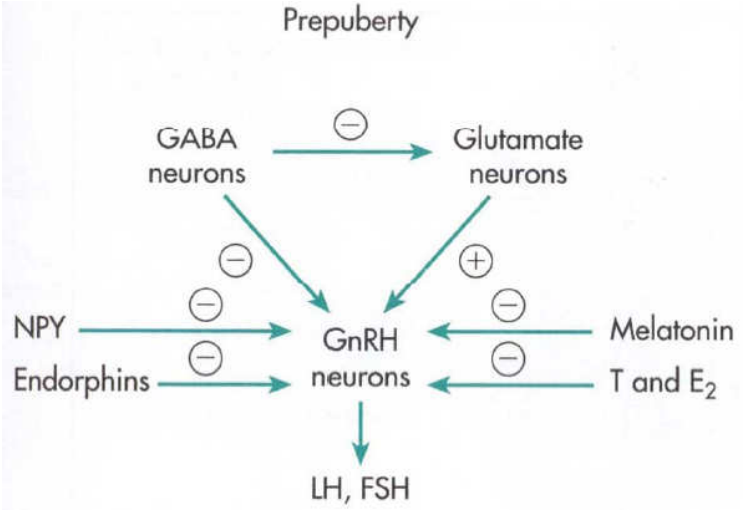
- Fetus:
  - GnRH is present in the hypothalamus 14-16 weeks gestation
  - Gonadotrophs present in anterior pituitary form 10 weeks
  - Hypothalamuc-pituitary system functional by 23 weeks
- Gonadotroph surges
  - Surge in LH, FSH occurs in utero
  - Second peak in post-natal (neonatal) period
    - Possible due to withdrawal from high steroid environment
      - Ie, levels of sex hormone are low, thus no inhibition
      - High steroid environment explains why newborn baby may have a large scrotum, breast buds, enlarged labia minorum and possible a withdrawal bleed
  - These cause corresponding sex hormone peaks



Childhood

- Release of GnRH is prevented
  - Thus plasma gonadotropin levels are low
  - Consequently, gonads are quiescent and sex steroid levels are low
- Thus, removal of gonads at this time doesn't cause a massive elevation of LH, FSH
  - Because, LH, FSH release isn't limited by estrogen and progesterone negative feedback
- However, system is functional because pulsatile injections in monkeys can bring on normal menstrual cycles
- Control is thought to be due to a high GABA tone
  - Also note: NPY, melatonin (pineal gland)





Pubertal development

- Progression:
  - 7-10 there is a slow increase in estrogen, androgens
  - Early teens, rapid rise
- Development can be defined by the Tanner stages
  - Genital development (boys), breast development (girls), pubic hair (both)
- See anatomy lecture

Order of events

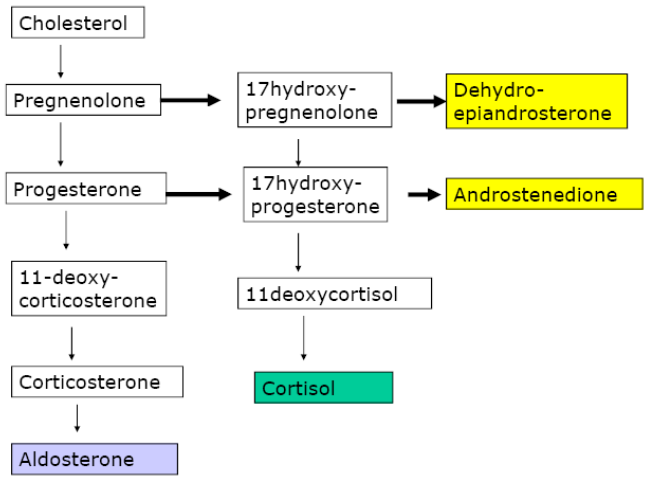
- Girls
  - Thelarche – breast development
  - Pubarche – axillary and pubic hair development
  - Menarche – first menstrual period, a defined day
    - Initial periods are generally anovulatory, regular ovulation begins a year later
  - General development:
    - Estrogen:
      - Thickens vaginal mucosa, enlarges uterus and cervix,
      - Iincreases number and length of uterine glands, induces proliferation in stroma and endometrium
      - Induces production of cervical mucus
    - Breasts – progesterone (alveoli), estrogen (ducts) +other hormones
- Boys
  - Testes enlarge to greater than 2.5 cm (3ml)
    - Means there is an increase in seminiferous tubules
    - Measured using callipers, ruler or Prader Orchidometer (chain of wooden 'eggs')
  - Spermachy – first appearance of spermatozoa in early morning urine
    - Mean age: 13.4, genital stage 3-4, pubic hair stage2.4
  - Androgen effects (testes begin producing testosterone)
    - Lengthening of penis
    - Enlargement of scrotum, prostate and seminal vesicles
    - Development of pubic, axillary hair

Puberty, male changes

- External genitalia
- Internal genitalia – seminal vesicles enlarge, secrete and form fructose, prostate, bulbourethral glands enlarge and secrete
- Voice – larynx enlarges (50%), vocal cords increase in length/thickness, voice deepens
- Body confirmation – shoulders broaden, muscles enlarge
- Hair – facial hair, temporal hair recession, pubic hair grows male pattern (triangle with apex up), chest, axillae, anus
  - + general body hair
- Skin – sebaceous gland secretion thickens/increases – acne
- Mental – aggression, active attitude, interest in opposite sex

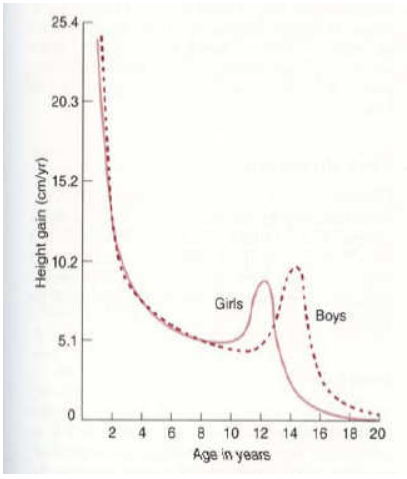
Andrenachy

- Onset of secretion of adrenal androgens
  - 8-10 years in girls, 10-12 years in boys
  - Due to increased activity in 17-alpha hydroxylase
- Causes:
  - Increase in conversion of pregnenolone to 17 alpha hydroxypregnenolone
  - Increase in conversion of progesterone to 17 alpha hydroxyprogesterone
    - Thus, increased formation of androgens
- Peak of androgen release is at age 25 for males and females



Growth spurt

- Due to growth hormone, estrogens and androgens
  - Turned off by closure of the epiphyseal plates in long bones by estrogen
- Girls: lasts 3 years, peaks tanner stage 3, boys, lasts 4 years, tanner stage 3-4

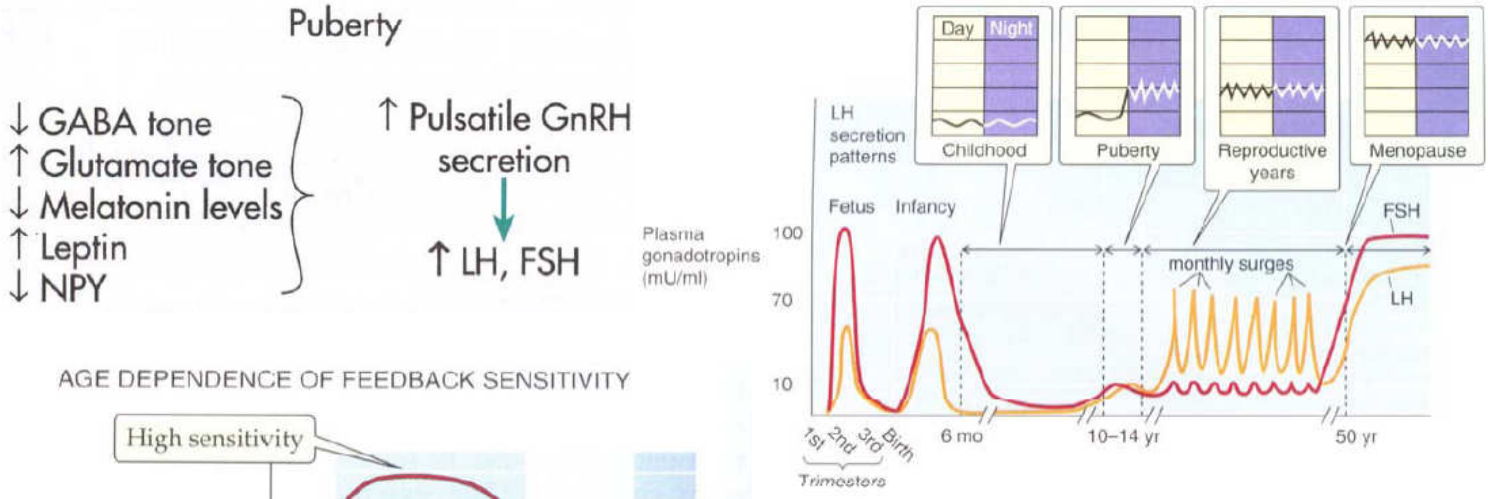


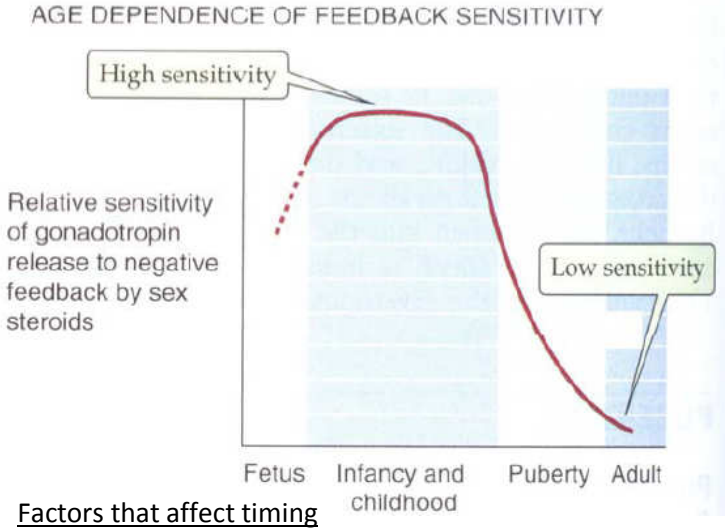
Body composition

- Before puberty, boys and girls have similar lean body mass, skeletal mass and body fat
    - After:
        - Men – 150% average woman's lean and skeletal body mass
        - Women – 200% body fat of men
            - + different distribution: thighs, breasts etc
        - Men have 2x number of muscle cells and 1.5x the muscle mass
        - Men have a higher haematocrit

Controlling the onset of puberty

- Onset of puberty varies greatly with age
    - Europe and USA, age of onset has been decreasing at a rate of 1-3 months/decade for last 200 years
    - Rate has slowed in recent times
        - Measured using age of menarche, age voice breaks
- Average:
    - Males – 9-14, females – 8-13
- Begins with onset of pulsatile gonadotropin secretion during sleep (due to GnRH pulses)
    - GnRH is controlled by GABA, glutamate, melatonin, leptin, NPY
    - Also related to GnRH negative feedback from sex steroids
        - Front infancy to puberty, negative feedback is highly sensitive
        - At puberty onwards, sex steroids don't have strong negative feedback and thus levels increase





Factors that affect timing

- Genetic (50-80%)
    - There is a loose association between mother and daughter menarche
- Nutrition
    - Critical body weight is necessary for puberty to occur
        - Ie. athletes, anorexia nervosa stop menstruating (eg. also ballerinas)
    - There is a link between weight and puberty – leptin (mice studies)
        - Leptin is secreted by fat cells and produces satiety
            - Ie: if you're fat, you have higher leptin, puberty earlier
        - Immature female mice, if given leptin can induce precocious puberty
        - Special breed of mice: fat. No leptin
            - Infertile, give leptin, become fertile
- Geographical location and exposure to light (earlier in the tropics, later at altitude)

Early puberty

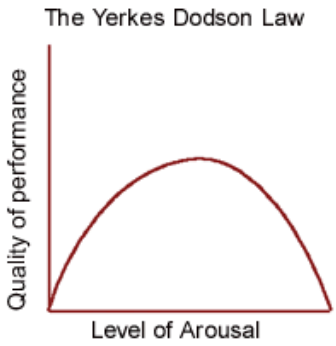
- Precocious puberty – true early puberty
    - Constitutional – more common in girls
    - Hypothalamic disease
        - Tumours, infections causing increased release of GnRH
        - Interruption of a pathway that inhibits GnRH
        - Lesions in experimental animals, have shown this
    - Gonadotropin-independent
        - Occurs without pubertal pattern of gonadotropin secretion
        - Causes:
            - Increased sensitivity of LH receptors due to activating mutation in the G-protein that couples receptors to adenyl cyclase
    - Cases:
        - 9 years old, tanner stage 5 breasts
        - Age 2 years 9 months, tanner stage 3 breasts, menstrual period
            - Cysts in brain compressing hypothalamic region and increasing GnRH
- Pseudo precocious puberty
    - Early development of secondary sexual characteristics without gametogenesis
        - Due to abnormal early exposure to androgens/estrogens
    - Causes:
        - Congenital adrenal hyperplasia (enzyme deficiency)
        - Adrenal tumours
        - Gonadal tumours

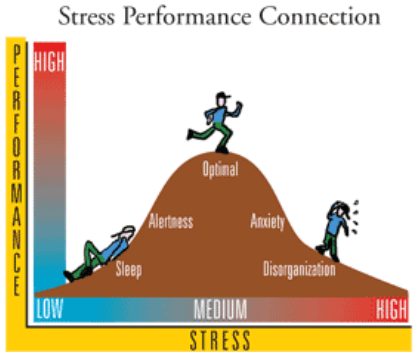
Late (delayed or absent) puberty

- Pathological delay if:
    - Menarche not occurred by 17, testicular development not occurred by 20
- Panhypopituitarism (anterior pituitary insufficiency)
    - Broader disease that may involve delayed puberty/absent puberty
    - Eg: dwarfism, endocrine abnormalities
- Kallmann's syndrome
    - Hypogonadotropic hypogonadism + hyposmia/anosmia
        - Small gonads and can't smell things
    - Due to disordered migration of GnRH cells during development – related to migration of olfactory cells
- Turner's syndrome: XO
    - Webbing of neck, low hairline, streak ovary
- Isolated abnormality in otherwise normal individuals (gonads and endocrine normal)
    - Eunuchoidism – males
        - Leydig cell deficiency from childhood
        - Appearance:
            - Tall adults – epiphyseal plates remain open, growth continues longer than normal
            - Narrow shoulders, small muscles: female body configuration
            - Small genitalia
            - High pitched voice
            - Pubic/axillary hair present (adrenal androgens) but sparse and female pattern
    - Primary amenorrhoea – females

Anxiety
- Mental state in anticipation of a threat
  - Evolved to protect us from danger
- Disorder, if this mental state in anticipation of a threat is inappropriate
  - Due to a genetic and environmental interaction
  - Susceptibility is determined early in life – upbringing
    - Median ages of onset:
      - Specific phobias: 6, social phobias (scared of social judgement): 10-12
      - OCD, panic disorders: late teens
      - Post-traumatic stress disorder, generalised anxiety disorder: late 20s-30s
- Disorders of young people
- Models of internalising and externalising fear can explain various manifestations

Symptoms – fight or flight
- Varied
- Anxious anticipation
- Shortness of breath – increased respiration
- Nausea – blood to muscles away from gut
- Cold sweats – increased sweating
- Palpitations – increased heart rate
- Shaking/trembling – increased muscle tension
- Selective intension/inattention – mental arousal
- Light too bright – pupils dilate





Yerkes-Dodson curve
- Anxiety can be facilitating and debilitating depending on its level
  - Can be used to examine performance, judgement of complex situations, perceptions of new information
- Ie. it's good to have a small amount of anxiety to increase function, but too much can lead to dysfunction

State anxiety
- How anxious you feel at the present time
- Determined by:
  - Level of threat/challenge – ie. no threat, no anxiety
  - Trait anxiety/neuroticism – personality, how 'anxious' a person you are
  - Ability to cope – managed by appraisal, problem solving, de-arousal, social support

Trait anxiety
- Stable across lifespan
  - Correlation with 4, 8, 12 month and 20 year surveys
- Largest single risk factor for anxiety disorders
  - Brain structures are different
  - Under genetic control

Coping
- Methods:
  - Appraising accurately
  - Preparing to combat, confront, don't avoid
  - Control fear
  - Recruit social support
- Ability to cope depends on the level of threat and trait anxiety

Note: symptoms can facilitate further anxiety

**** flow diagram trait anxiety ****

Fear circuits

- Potential threat/challenge → Thalamus
  - → amygdala → hippocampus
  - → amygdala → frontal cortex
- Parts:
  - Striatum – to do with active coping
  - Periaqueductal grey – to do with passive fear
- ~50% of anxiety (neuroticism) is under genetic control

Serotonin

- ss polymorphism in serotonin transporter
  - Associated with:
    - Depression
    - Anxiety
    - Neuroticism, increased trait anxiety
    - Occurs in up to 30% of the population

Maternal influences

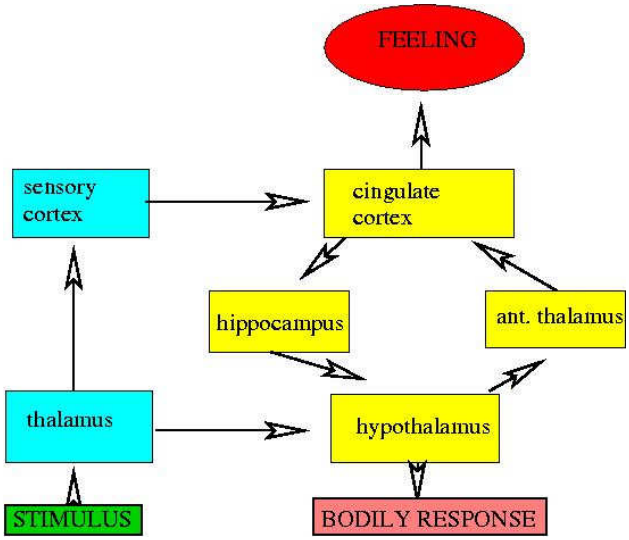
- Maternal anxiety can lead to anxiety in the adult offspring
  - Genetics is thought to be more important than environment, however in some cases, the environment can override
    - Anxious mother mouse with anxious mother mouse kids = anxious kids
    - Normal mother mouse with normal mother mouse kids = normal kids
    - Anxious mother mouse with normal mother mouse kids = normal kids (genetics)
    - Normal mother mouse with anxious mother mouse kids = normal kids (environment)

Children

- Sexual abuse is associated with increased anxiety, and in particular increased rates of post-traumatic stress disorder
  - + morphologically, decreased hippocampal size
- Post-traumatic stress disorder (PTSD) – instrinsic memories of trauma
  - Due to trauma and biology
    - 15% of people who experience a traumatic event get PTSD
  - Have smaller hippocampus
    - Vulnerability factor or effect of trauma? cause or effect?
    - Reduced hippocampus with reduced ability to cope with trauma and reduced with trauma
  - Twin study
    - Small hippocampus before trauma, one trauma → PTSD; other no trauma, no PTSD
- Much unknown

Adult life

- Neuroticism decreases with:
  - Age
  - Treatment with SSRIs
    - Suppress propensity to arousal
  - CBT
    - Teaches how to cope
  - Repetitive exposure to controlled stressors
    - Eg. exchange students vs non-exchange students
      - Mature, emotional age of 28, increased coping due to controlled stress exposure
- Trait anxiety, if reduced, greatly reduces symptoms
  - Thus trying to treat with CBT the 'risk factors' for trait anxiety



History
- Darwin 1872
  - Book: expression of emotions in man and animals
  - Had pictures following emotions and expressions across different animal species and humans
- Papez circuit →

Anger
- A strong feeling that makes you want to hurt someone or be unpleasant because something unfair or hurtful has happened
- Neurobiology - serotonin
  - CSF 5-IAA reflects presynaptic serotonin
    - Shown to be low in violent men, prisoners, violent suicide cases, impulsive firestarters, violent offenders, aggressive psychiatric patients
    - Ie: aggressive people who can't control emotions or regulate anger
- Case: Bella, affective instability
  - ADHD
    - Anger, tantrums
    - Impulsivity, destructive
    - Episodic aggressive behaviour – suggestive of bipolar spectrum disorder
      - Bipolar is hard to diagnose in children because cognitive control mechanisms are still developing
  - Poor social skills, but charismatic following
  - Treatment with Ritalin (focuses attention and helps concentration)
    - Further treatment: CBT to control aggression + alternative outlet for anger (martial arts?)
- Genetics:
  - Anger scores have been linked to:
    - DARPP32 genotypes
      - Phosphoprotein related to dopaminergic systems
    - Left amygdala volume

Impulsivity
- Failure to resist impulse/drive/temptation
  - Result: rapid, unplanned reactions to internal and external stimuli
  - Inability to delay reward, think before acting
    - Choose small immediate rewards instead of larger delayed rewards
  - Impaired executive function
- Linked with novelty/sensation seeking behaviour
  - A personality style, linked with MAO that breaks down catecholamine NTs
- Case: Alex, impulsive
  - Does things without thinking
    - Responds to challenges and doesn't think about consequences
  - Treatment:
    - SSRI – serotonin is implicated in impulsive tendencies
    - CBT:
      - Strategies to stop and think about the consequences of actions
      - Alcohol – disinhibitor, impairs judgement
        - Motivational interviewing to make aware of alcohol effects + family hx

Regions of the brain

- fMRI with monetary incentive task
    - if performance (speed/accuracy) is better than previously, earn money
    - people who do better are those with impulsive reaction styles
        - correlation with ventral striatum and orbital frontal cortex – impulsivity
- Areas correspond to different emotions/actions:
    - Orbital frontal cortex, ventromedial prefrontal cortex – impulsivity
    - Dorsolateral prefrontal cortex – executive function, goal setting, ordering of acitons
    - Amygdala – facial emotion recognition, anger management
    - Anterior cingulate cortex – control of attention and inhibiting behaviours

Social exclusion experiment

- Cyberball
- Dorsal anterior cingulate cortex activity
    - With increased trait aggression, greater degree of activation
- Decreased platelet MAO related to sensation seeking

Phineas Gage

- Model citizen, good worker, family with children
- Working with tamping rod, uncontrolled explosion forced it through his head
    - Destroyed some of the prefrontal cortex
    - → personality changed
        - Impulsive, aggressive
        - Forgot about work, family fell apart, turned to alcohol
- Ie. prefrontal brain systems are important in the regulating of impulsivity/aggression

Important factors

- Genotype leading to multifactorial brain elements, and chemical elements
    - Thus individual variation

Many people have depression

- Churchill, Lincoln, Gallop, Goodes
- Books
    - Lewis Wolpert
    - Antonio Damasio
    - Joseph LeDoux
- Depression is a distortion of normal sadness

What are emotions? (Damasio)

- A continuum
    - A state of emotion → non-conscious (biology)
    - A state of feeling → non-conscious "feeling"
    - A state of feeling made conscious → conscious experience
- Primary (universal) emotions:
    - Happiness, sadness, fear, anger, surprise, disgust
- Secondary emotions:
    - Embarrassment, jealousy, guilt, pride
- Background emotions:
    - Well being vs. malaise
    - Calm vs. tension

Shared biology of emotion

- Emotions are complicated collections of chemical and neural responses
    - Have a regulatory role that creates circumstances that are advantageous to an organism and assists it in the maintenance of life
    - Can be helpful – ie: the Yerkes Dodson curve
- Learning and culture alter the expression of emotion and give it new meanings
    - The biology, however, is due to innate brain devices and is evolutionarily the same
- Biology:
    - Neural devices are limited to specific areas of the brain
        - Don't often involve conscious awareness
    - Emotions are stereotyped (predictable, replicated)
        - Individual variation is changed by culture and learning
- Analogy:
    - Emotions use the body as their theatre to alter, eg:
        - Internal milieu
        - Visceral vestibular systems
        - Musculoskeletal systems
    - Manifest as an interplay between different body systems

Conscious and subconscious

- Subconscious:
    - Basic life regulation
    - Emotions → body systems (preconscious level)
    - Feelings
- Conscious
    - Feelings
    - Behaviours/responses to emotions

Areas of the brain

- Amygdala, ventromedial prefrontal, brainstem, hypothalamus, basal forebrain
- Limbic system – primitive brain
    - Comprises a large part of the brain in animals (reflexes, instincts)
    - As higher cortical function has evolved, limbic system has decreased in relative size
- Papez circuit:
    - 2 steps, 1st is before conscious awareness
        - Part 1: emotional stimuli → thalamus → hypothalamus → **bodily responses** (eg. cortisol with stress)
            - Thus response occurs in the body before aware, eg. snake, HR increases, muscles tense before visual sends message to register there is a snake
        - Part 2: thalamus → sensory cortex → cingulate cortex (integrates feelings etc), input from hypothalamus, hippocampus → **feelings**

Depression

- Adults, 3.2% experienced depression in the last month, 6.3% in the last year (1/17)
    - Not just sadness, this is clinical depression where there is interference with people's lives and functionality
- 20% chance of experiencing depression throughout life
- Symptoms:
    - Emotional
        - Depressed mood
        - Reduced interest/pleasure
        - Despair
    - Physical
        - Changes in weight/appetite
        - Agitation/retardation
        - Sleep problems
        - Difficulties concentrating, thinking clearly
        - Reduced energy levels
    - Cognitive
        - Feelings of worthlessness
        - Suicidal thoughts
        - Indecisiveness
- Global burden of disease:
    - Economic loss (mainly due to loss of function)
    - Depression ranks highest, >10% of total disability
        - Other mental health problems also in the top 10
        - Depression hits people in their formative years and recurs, thus induces high economic loss/disability
    - If project disease burden (ie. premature death and disability)
        - 2020, depression goes from 4th to 2nd highest worldwide

Brain systems – sadness/depression

- Only higher species experience
    - Anxiety and fear, other less complex animals can experience
    - Maybe sadness/depression is associated with our sense of consciousnesss?
- How is it natural/adaptive?
    - Advanced species are social beings, we relate and have relationships
        - Part of being human
    - Thus, it may be an adaptation to help us cope with loss of relations and allow for **social healing**
        - Other sadness is an elaboration of this as we became able to think more abstractly: conceptual loss
- Sadness is normal
    - Depression is the same process gone awry, a distortion of normal sadness
- Genetic associations:
    - Process:
        - Initial factors:
            - Genetics
            - Social support
            - Childhood experiences
            - Cognitive thinking styles, personality – genetics?
        - Progression:
            - Anxiety, sub-clinical depression
            - Self-esteem
        - Later:
            - Life events, chronic difficulties
            - Social support
        - Leading to depression

Stressful life events

- **Loss** events ie. relationship loss, death, unemployment, ill health
- Sense of entrapment → **loss** of control
- Humiliation/stress

Genes and the environment

- Genetics: thought to explain 30-40% of the cause of depression/anxiety
    - Strong association between genetic risk and likelihood of stressful life events leading to depression
        - Ie. family history closely showed risk in presence of a stressful life event
- Environmental factors also important
    - Ie. if we don't experience stressful life events, won't get depressed

Serotonin

- Serotonin reuptake transporter takes up serotonin and removes from synapse
    - Polymorphisms:
        - Short/short, long/short, long/long
            - Long/long is normal
            - short/short doesn't do well with stress
                - associated with amygdala neuraonl activity
- s/s with increased life events has increased rates of depression vs l/l

Introduction
- Depression is hard to define
  - A disorder, disease, syndrome, mood state?
  - Disorder – when there is an impact on functioning
  - Disease – underlying pathological process
    - Abnormal condition of the body/mind causing discomfort dysfunction, distress
  - Syndrome – collection of symptoms
- Health
  - A state of complete physical, mental, and social well-being
    - Can lead to a socially and economic productive life
  - More than: not having a disease
- Mental health
  - Independence, competence
  - Able to deal with normal stress
  - Able to bounce back and recover from stress
  - Able to form satisfying relationships
- Mental illness
  - Particular syndromes/disorders
    - Often result in impaired cognitive function, atypical behaviour etc
  - Episode – transient period of mental illness
  - Not an exact opposite of mental health, mental health requires more than just: not disease

Moods
- Happiness – social bonding, promoting well-being
- Anger – attack, giving us the energy ot push through something
- Sadness – coping mechanism, dealing with loss
- Fear – avoid danger
- Disgust – expel something
- Surprise – dealing with the unexpected

Normal
- Mood swings
- Can get self out of bad moods

Abnormal
- Mood is too intense/long lasting relative to trigger
- Mood is inappropriate
- Unable to recover, get self out of mood

Personality styles – for dealing with stress (attributional styles)
- Internalisers – serotonin seekers
  - Anxious/worrying, socially avoidant, sensitive to rejection, perfectionistic
- Externalisers – adrenaline junkies
  - Irritable, hostile, violent
- Some genetic/neurobiology, some environmental

Emotional dysregulation
- Internalisers
  - Go quiet, stew, withdraw
  - Take on selves, take sedatives
- Externalisers
  - Quick tempered
  - Take it out on others, prefer stimulants
- Dependent on culture, family, personality, previous experiences

Episode of clinical depression

- DSM-IV (diagnostic and statistical manual)
    - > 2 weeks with 5 or more of:
        - Depressed, sad
        - Loss of interest in pleasurable things
        - Appetite change, weight change
        - Trouble sleeping
        - Agitation, retardation
        - Fatigue, lack of energy
        - Feel worthless, excessive guilt
        - Trouble concentrating, thinking clearly, making decisions
        - Suicidal thoughts
    - These symptoms disrupt your daily routine and interfere with work/relationships

Melancholic depression

- Observable psychomotor disturbance
    - Cognitive processing problems (poor concentration)
    - Retardation/agitation
    - Depressive symptoms (severe)
- Disruption of cognitive circuits linking basal ganglia (planning, thinking ahead, executive functions) and prefrontal cortex
    - Leads to cognitive/psychomotor symptoms
    - Putamen shown to shrink – problems initiating actions
- Symptoms:
    - Anhedonia, non-reactive mood, “emptiness”, low energy in the am, sleep problems
- Psychomotor:
    - Cognitive problems, suicidal thoughts, can’t change the processes, retardation, agitation, change in behaviour

Introduction
- Treatment depends on the level of depression
    - Mood state, disease, syndrome, disorder
- People tend to behave 3 ways about their problems:
    - Normalise – I'm ok
    - Somatise – there's something wrong with my body
    - Psychologise – something wrong with my thinking

Approaches to treating
- Acute symptom relief
- Maintaining, improving
- Prevent relapse/episodes
- Biological/social/psychological vulnerabilities
    - Social – dealing with emotions, strategies for de-arousal

Depressive episodes
- Process
    - Predisposing factors + precipitants
        - + psychological factors, personal meaning of event
            - → how depression is experienced
                - → protective factors → outcome

Treatment – general
- Diagnosis
- Symptom relief
- Current issues
- Long-term issues + relapse

Mood
- Diagnose distress related disorders, check health/hx + triggers
- Teach coping strategies
    - Dealing with stress – relaxation, mindfulness, exercises, emotional intelligence
    - Assertiveness training
    - Drug/alcohol, controlled drinking
    - Relationships issues

Depression - internalisers
- Diagnosis
- Teach coping strategies
    - Education
    - Problem solving, CBT interpersonal therapy
    - Consider personality style
- Relapse prevention
- Antidepressants?

Externalisers
- Deal with irritability
- Coping strategies:
    - Lifestyle factors/education
    - Anger management
    - Alcohol, smoking education/therapy
    - GPs, health practitioners involved
    - Relationship advice

Clinical depression

- Diagnosis
- Education about depression and treatment
- Counselling, improve coping
    - Cognitive therapy (challenge thinking)

Roy

- Psychiatric assessment
- Medication – antidepressants, CBT, electroconvulsive therapy, monitor regularly
- Hospitalisation – psychiatric emergency (high suicide rates), may need voluntary hospitalisation

Extra material

- Mood charts
- Mindfulness – premediation (watch 1 minute, clear mind)
- Men's issues sheet
- Goal setting
- Exercise

Introduction

- Ages 18-59, 31% of men, and 43% of women have sexual dysfunction
    - Few get treatment
- Response cycle:
    - Desire → arousal → organism → resolution
- Counselling
    - PLISSIT
    - P – permission (to give information, etc), LI – limited information (sex ed), SS – specific suggestions (ideas) IT – intensive therapy (relationship counselling, psychotherapy etc)
    - ¼ women have been sexually abused

Desire

- 16-59, 55% females lacked desire for sex for a month in the last year, 25% of males
    - Ie. desire fluctuates based on inhibitors and enhancers
        - Physical, emotional, relationship, sexual, lifestyle, hormonal
    - Female desire is more distractible
        - If conditions are bad for reproduction, sex drive decreases
        - Enhancers are gender specific
- Limerance – courtship period (6-18 months)
    - Desire is maximised
- Maximising desires involves removing inhibitors and maximising enhancers

Arousal

- Difficulty
    - Education, self-examination, maximising enhancers
- Can't reach organism
    - Clitoral stimulation often necessary
- Uncomfortable intercourse
    - Psychological or biological
        - Biological until proven otherwise
    - Treat cause
        - Woman controls position, pace, penetration
    - Reactive pelvic floor spasm – vaginismus
        - Fear response, poor sexual education
        - Treat with CBT

Introduction
- Men think they're invulnerable
    - Iceberg concept: problem builds up under surface before men go to see the doctor

Metabolic syndrome
- Defined by: diabetes, hypertension, obesity, cholesterol
    - Closely related to erectile dysfunction and hypogonadism (low testosterone)
- Presenting symptom is often erectile dysfunction
    - This can more generally be the presenting symptom of a lot of conditions

Males issues
- Weight circumference
- BMI
- Alcohol – now recommended max 2/day, 4 on a binge
- Exercise – 30 minutes everyday
    - Moving should be an opportunity rather than an inconvenience
- Smoking – causes impotence

Sexual function
- Process of:
    - Desire → erection → ejaculation → resolution
- Stages:
    - Excitement (arousal)
    - → plateau
        - Increased HR, glans engorged, ejaculation inevitable
    - → organism
        - Endorphins, ejaculation, muscle contraction
    - → resolution
        - Relaxation
    - → refractory period
        - How long before we can have sex again
        - Increases with age

Erection and erectile dysfunction
- Erection
    - Stimulation → neural changes (reduced symp, increased parasymp) → cellular changes (cGMP, NO)
- Dysfunction
    - Penile is the smallest major artery
        - may be the first presenting sign of other problems
    - 1/5 people >40 and 1/3 over 60 have erectile dysfunction
    - Definition – persistent inability to maintain sufficient erection
    - Causes – social, lifestyle, medical
- Sexual history → important to characterise dysfunction
    - Psychological (generally young) → sudden, varied dysfunction
    - Physical (generally old) → gradual, consistent
- During sleep: penile aerobics
- Treatments for erectile dysfunction:
    - Drugs – Levitra, Cialis, Viagra
    - Lifestyle intervention
    - Self-injection, implant, vacuum
    - Problems: priapism – erect penis does not return to flaccid state, medical emergency
- Sex in older people → negative societal image
    - Problems are associated with increasing age
- Testosterone drops from age 30
    - Treatments: Testogel, Reandron

Premature ejaculation

- Lack of control of ejaculation
    - Median time is 5.4 minutes
    - Less than 1 minute is PE, 1-2 suspected PE
- Treatments
    - SSRIs, techniques, pelvic floor exercises

Teenage sexuality

- Physiological, psychological, social changes during adolescence
    - Independence and making own mistakes are important
- Parents talking to children:
    - Assume that education will encourage experimentation, or that the media/school does all the teaching

Prostate

- Checking – rectal, blood test
- Problems especially after 50
- Symptoms:
    - Weak urination flow due to enlargement of the prostate pressing/obstructing the bladder/urethra
- Benign prostatic hyperplasia
    - Men more commonly have obstructive urinary problems, women normally storage (increased frequency)
- Cancer
    - Most common male cancer
    - Most asymptomatic
    - 10% lifetime risk, 3% mortality if get cancer
- PSA
- Treatments → radiotherapy

Testicles

- Examination for lumps
    - May be different sizes, at different levels
- Easily treatable if found early

Important:

- **Doctors think: I hope he brings it up**
- **Patients think: I hope he asks me**

Websites

www.sydneymenshealth.com.au
www.m5project.com.au
www.andrologyaustralia.org
www.reachout.com.au