The Burden of Alimentary Disease
Professor Mark Thursz (m.thursz@imperial.ac.uk)

Organs of the gastrointestinal tract (GI tract)
- Mouth + oesophagus
- Stomach
- Small intestine (duodenum, jejunum + ileum)
- Liver
- Biliary system
- Pancreas
- Large intestine (colon, rectum + anus)
  - Colon consists of caecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon

Components of burden of disease (details on pp)
- Patient burden
- Epidemiological statistics
  - Incidence – more important for acute diseases
  - Prevalence – more important for chronic diseases
- Health economic
  - Morbidity
  - Mortality
  - QUALYs/DALYs
- Societal burden
  - Health Cost – taxpayer vs individual

Symptoms of GI disease (examples on pp)
Symptoms are what the patient may complain of. They may be divided into general and regional symptoms.

- **General** (many GI diseases are difficult to diagnose specifically do to the frequency of general symptoms)
  - Anorexia
  - Weight loss
  - Anaemia

- **Upper GI tract**
  - Haematemesis – vomiting blood
  - Melaena – blood in stool
  - Nausea
  - Vomiting
  - Dysphagia – inability to swallow food
  - Odynophagia – pain on swallowing
  - Heartburn – burning sensation in epigastric region that moves upwards
  - Acid regurgitation
  - Belching
  - Chest pain
  - Epigastric pain – pain in the epigastric region (upper central region above TPP and between mid-clavicular lines)

- **Liver + Biliary system** (majority of liver disease does not present with symptoms until very advanced)
  - Right upper quadrant pain
  - Biliary colic – term used to describe when biliary tree is obstructed by a gallstone → abdo pain
Icterus - jaundice
- dark urine
Cholestasis – pale stool
Ascites – abdominal distension; may be associated with liver OR luminal GI tract disease

- **Mid GI tract + pancreas**
  - Abdominal pain
  - Diarrhoea
  - Steatorrhoea – abnormal amounts of fat in the faeces, due to malabsorption of fat in the gut
  - Distention – abdo swelling

- **Lower GI tract**
  - Abdominal pain
  - Bleeding
  - Constipation
  - Diarrhoea
  - Incontinence – inappropriate involuntary passing of urine, i.e. wetting yourself

**Signs of GI disease (on pp)**
Again, these may be divided generally and regionally

- **General**
  - Cachexia – a condition of abnormally low weight, weakness + general bodily decline
  - Obesity
  - Lymphadenopathy – disease of the lymph nodes
  - Anaemia
  - Jaundice
  - Stigmata of chronic liver disease

- **Hands**
  - Koilinychia – the development of thin, brittle, concave nails
  - Leuconychia – white discolouration of the nails
  - Clubbing – increased convexity of the nail fold, with associated increased softening and loss of the normal angle between the nail-bed and fold
  - Dupytrens contracture – a flexion deformity of the fingers (usually ring and little) with increased contracture of the palmar fascia (think of work experience!! Saw this in surgery)
  - Tachycardia
  - tremor

- **Abdomen**
  - Organ enlargement
  - Mass
  - Tenderness
  - distension

- **Anus + rectum**
  - Haemorrhoids – enlargement of the normal spongy blood-filled cushions in the wall of the anus
  - Fistula – an abnormal communication (i.e. hole/pathway) between two hollow organs/one hollow organ and the surface of the skin, i.e. an anal fistula is an opening between the anal canal and the surface of the skin
  - Fissure – a break in the skin lining the anal canal → pain during bowel movements and sometimes bleeding
  - Rectal masses
  - Proctitis – inflammation of the rectum
**General Statistics about GI diseases**
- 5% UK adults suffer chronic illness e.g. pancreatic, liver, inflammatory bowel disease
- Drug prescriptions >£4 billion
- Responsible for 12% UK deaths
- 1/8 hospital admissions
- ¼ main operations

**Major GI Diseases**
- **Worldwide**
  - Malnutrition
  - Enteric infections
  - Viral hepatitis + consequences
  - Gastric cancer
- **UK**
  - Dyspepsia
  - Liver disease (due to alcohol + obesity)
  - Colon cancer

**NB: Mortality rates** – the mortality rates of respiratory infections, infectious diseases and circulatory-related diseases are all relatively decreasing. Mortality rates of cancer are also stabilising. However deaths from liver-related diseases are increasing. 4-6% of UK population have abnormal LFTs (liver function tests). The main causes of these abnormal LFTs include:
  - Chronic HepB
  - Chronic HepC
  - Alcohol-related steato-hepatitis (this is hugely increasing due to increasing alcohol consumption)
  - Obesity-related steato-hepatitis

**GI Diseases**

**Hepatitis**
- **HBV**
  - 32nm virus
  - 350 mil chronically infected
  - 1 mil deaths/yr
  - Most prevalent in northern south America, Africa and Asia, and least prevalent in southern south America, UK and Australia – however due to increasing UK immigration, rates in the UK are rising
  - Outcome of HBV infection
    - <1% fulminant infection
    - 90% self-limiting infection
    - 10% persistent infection – with 70% being asymptomatic and 30% having cirrhosis +/- hepatocellular carcinoma
- **HCV**
  - Most prevalent in inner cities
  - Highly stigmatized – as associated with sexual transmission
  - Outcome of HCV infection
    - 20% self-limiting infection
    - 80% persistent infection – with 20% progressive and 80% of cases being non-progressive

**Dyspepsia**
- I.e. indigestion
Common reason for primary/secondary consultations
High risk for complications
40% prevalence in adults, with 26% experiencing symptoms on a weekly basis but only 2% consulting their GP
£100 million for OTC medication
Related to GORD (gastro-esophageal reflux disease)
  - associated with gastric reflux
  - GORD may potentially lead to the development of complications such as strictures (4-20%), oesophageal ulceration, bleeding + perforation
  - 2-7% of GORD patients will go on to develop an oesophageal ulcer → chronic oesophagitis
  - Chronic oesophagitis is generally regarded as the primary cause of Barrett’s oesophagus, and the epithelial changes that occur have been linked to a substantially increased risk of oesophageal carcinoma
    ▪ Barrett’s oesophagus occurs in 10-15%, and results in epithelial changes in which the squamous-cell epithelium of the oesophageal mucosa is replaced by metaplastic columnar-cell (i.e. metaplasia occurs)
  - There is also an association between symptomatic GORD and oesophageal adenocarcinoma, independent of Barrett’s oesophagus
    ▪ The development of oesophageal adenocarcinoma instead of oesophageal carcinoma is linked to an increased frequency, severity and duration of GORD symptoms
    ▪ However the absolute risk of developing adenocarcinoma is still very low (1/2 mil)

Helicobacter pylori related
  - Helicobacter pylori
  - Gram-negative, spiral bacterium which colonises the gastric mucosa
  - Infection persists for life unless treated
  - Found in 50% of the world’s population – geographic distribution is closely linked socio-economic development (i.e. in better socio-economic developed countries → decreased prevalence)
  - Helicobacter related disease – chronic gastritis
    ▪ 85% no long-term effects
    ▪ 14% peptic ulceration
    ▪ 1% gastric adenocarcinoma/lymphoma
  - Duodenal ulcer – caused by helicobacter pylori + NSAIDs
    ▪ Affects up to 10% of the population
    ▪ Estimated to cause up to 2000 UK deaths
    ▪ Main complication = perforation + bleeding

Cancer in the GI tract
  - Prevalent in the UK: colorectal, oesophageal, pancreatic, stomach + liver
  - Liver cancer
    ▪ May be primary or secondary
    ▪ Primary liver cancer arise in liver cells, e.g. hepatocellular + cholangio carcinomas – more prevalent in association with cirrhosis
    ▪ Secondary liver cancer is metastatic cancer from other primary locations; is more common in the UK but results in later detection
    ▪ Primary liver cancer can be detected at an early stage by ultrasound scanning, with an associated 50% 5 yr survival
    ▪ Cholangiocarcinoma – no treatment
  - Pancreatic cancer
95% adenocarcinoma of the pancreatic duct, which is difficult to diagnose early there has one of the poorest survival rates (2% at 5yrs)

Inflammatory conditions
- **Ulcerative colitis + Crohn’s disease**
  - UK prevalence 150,000 people
  - 8,500 new diagnosed cases/yr
  - Ulcerative colitis only affects the colon and rectum, and may have an acute presentation; ulcerative colitis with associated toxic megacolon (rapid dilation of the colon)
  - Crohn’s disease results in transmural inflammation, structures and fissures at any part of the GI tract
- **Coeliac disease**
  - Common in the west
  - Prevalence of 1/1000
  - Caused by gluten sensitivity, with an HLA related aetiology
  - Results in subtotal villi atrophy, with associated malabsorption

Biliary diseases
- Gallstone prevalence 1/10
- Most prevalent in middle-aged overweight women

Pancreatic diseases
- **Acute pancreatitis**
  - Mid to life-threatening
  - Blockage of the pancreatic duct results in a back-up of pancreatic enzymes causing severe inflammation
  - Ethanol accumulation + gallstones also present in 80% cases
- **Chronic pancreatitis**
  - Results in permanent damage to the pancreas, which may greatly impair quality of life
  - Main cause alcoholism

Intestinal diseases
- Diarrhoea prevalence worldwide = 200 mil
- Water + foodborne infections caused by viruses, bacteria + parasites – clean water supply essential!

Large bowel diseases
- Irritable bowel syndrome (IBS)
- Affects 1/3 population
- Only about 1 in 10 people seek GP

Anal diseases
- Faecal incontinence (soiling) may affect 1/20 people
- By age 50, about ½ population have haemorrhoids
- Over half of the >70yr old population have diverticula of the large intestine

Economic burden of GI diseases

Morbidity
  - GI diseases accounted for 5.51 million bed-days (6.1% of the total, 90 million); equivalent to 1.36 billion p.a.
- Out-patient care
  - 6.9% attributable to GI causes
  - costs £0.28 billion p.a.
- Primary care (GP visits)
  - 3.85% attributable to GI causes
  - £0.24 billion p.a.
- Community health & social services
  - GI attributable in 3%
  - £0.32 billion

**NHS prescription costs**
- Classes of drug (BNF)
  - Antacids
  - Antispasmodics
  - Ulcer-healing
  - Chronic diarrhoeal agents
  - Laxatives
  - Haemorrhoid treatment
  - Stoma care
  - Intestinal secretion drugs
- Total cost to NHS in 1995/6 was £0.83 billion

**NOTE:** Other economic factors to consider include the cost of not working, as well as further NHS costs (in-patients, out-patients, primary care, drugs + community services) which have a combined cost of £8 billion
Introduction to the small intestine – the Duodenum, Jejunum and Ileum

Alimentary System 2 - Dr Caroline Small (c.small@imperial.ac.uk)

1. List the main functions of the small intestine.
2. Distinguish between the duodenum, jejunum and ileum.
3. Describe the nature of villi and crypts.
4. Describe the source & process of enterocyte renewal in the small intestine.
5. Explain how enterocytes are adapted for absorption.
6. Compare turnover time of intestinal epithelium with epithelia from other sites.
7. Describe the structure/function relationship of the digestive epithelium.
8. Describe the structure/function relationship of the circular muscles.
9. Explain digestion and absorption of carbohydrates, proteins and lipids in the small intestine.

The small intestine can be sub-divided into three separate areas: the duodenum, jejenum and ileum. The primary function of all three areas is absorption of nutrients, salt and water (ie ingested substances) from the lumen to the blood.

Structure + Cell types

Size: the small intestine is ~6m long, with a 3.5cm diameter. The **duodenum** is ~25cm long, **jejunum**=2.5m and **ileum**=3.75m.

Basic organisation

- The **mesentery** surrounding the small intestine is folded, and has a large blood supply to support the metabolic functions of the cells, as well as aid absorption.
- There is no sudden transition between the different areas; all have the same basic organisation but may have slightly different histological features.
- Digestive epithelium: lies on an external muscular wall (consisting of longitudinal + circular muscles), with an internal circular-folded mucosa (consisting of different cell types). The mucosa are covered in **villi** (~1mm tall – increase surface area for absorption), with invaginations known as **crypts of lieberkuhn**.
- Intestinal villi: can be classified as a **simple epithelium** (1 cell thick) consisting of columnar absorptive cells (**enterocytes**), with interspersed secretory cells (**goblet cells**) and **enteroendocrine cells**
  - The villi are motile, have a large blood supply, good lymphatic drainage and good innervation from the **submucosal plexus**
- Between the villi, are crypts of lieberkuhn – epithelium which include **paneth cells** and **stem cells**.

Cell types

**Enterocytes**

- Most abundant
- Tall columnar cells with apical microvilli, basally located nuclei
- Specialised for absorption from the apical lumen to the basal blood supple
- They have a short life-span (1-6 days) – therefore have a dynamic environment with a rapid cell turnover
- There are tight junctions between the cells – important for intercellular communication
  - **Microvilli** – make up the brush border overlaying the apical membrane of the enterocytes (#0.5-1.5 micrometres). There are several thousand microvilli/cell – thus greatly increasing the surface area for absorption.
Glycocalyx - rich carbohydrate layer lies on the apical membrane, serves as protection of both the microvilli and enterocytes from the digestive enzymes, yet provides an environment in which efficient digestion can occur. It traps a layer of water + mucous known as the “unstirred layer” – many enzymes are present within this layer, thus it regulates the rate of absorption from the lumen.

NB: Surface area – the the mucosal folds, villi and microvilli act to increase the cylindrical internal surface area of the small intestine by 500x (from 0.4 → 200m²). This provides the maximum opportunity for nutrient absorption.

Goblet cells
- 2nd most abundant epithelial cell type, containing mucous filled-granules which accumulate at the apical end (leading to the characteristic goblet shape). The polarity of the granule accumulation also ensures secretion is unidirectional (ie goes into lumen, and not blood)
- Mucous – large glycoprotein that facilitates the passage of digested material through the bowel
- The abundance of goblet cells increases along the length of the small intestine, ie the duodenum contains relatively few compared to the colon.

Enteroendocrine cells
- Again, these are columnar epithelial cells which are scattered among the absorptive cells
- In the intestine, these are most commonly found in the lower parts of the crypts
- Hormone-secreting cells (also known as chromaffin cells) which influence gut motility (see Regulation of function lecture)

Paneth cells
- Are found in the bases of the crypts
- Contain large acidophilic granules
- The granules contain the antibacterial enzyme lysozyme (which protects the stem cells from any bacterial pathogens), as well as glycoproteins + zinc (trace metal is essential for function of a number of enzymes)
- Also engulf some bacteria and protozoa, therefore may have a role in regulating intestinal flora.

Stem cells
- Enterocytes and goblet cells have a short life-span, therefore continuous cell proliferation, differentiation + death occurs (ie there is rapid turnover of cells)
- Pluripotent cells continually divide by mitosis and migrate to the apical membrane of the villus tip, where they are shed off (regulated process by which the cells become senescent – ie they die and are sloughed into the lumen) and digested
This rapid turnover process is commonly known as the “escalator” of epithelial migration, and acts as the first line of defence against GI pathogens, ensuring any infections and lesions are short-lived. If the escalator-like transit of enterocytes is interrupted through impaired production of new cells (e.g. radiation), severe intestinal dysfunction will occur.

E.g. of rapid epithelial turnover in defence against Cholera
- Link to water-transmission established in 1854 by John Snow
- The cholera enterotoxin results in a prolonged opening of the chloride channels in the small intestine allowing uncontrolled secretion of water into the lumen → watery diarrhoea
- This can lead to massive dehydration and death
- It is treated with ORT to rehydrate the patient; however treatment against the bacterium is not required as the body itself will expel the bacteria and enterotoxin via its rapid turnover when the epithelial cells are replaced.

Differences in Histological Organisation of the Duodenum, Jejunum + Ileum

**Duodenum** – distinguished by the presence of Brunner’s glands which have alkaline secretions
- These are submucosal coiled tubular mucous glands which open into the base of the crypts
- The alkaline secretions neutralise the acidic chime from the stomach, protecting the epithelium and providing the optimum pH for the action of pancreatic digestive enzymes

**Jejunum** – characterised by the presence of taller + thinner plicae circulars (also known as valves of Kerckring – present in the duodenum + ileum, but as shorter and fatter)
- The jejunum also has a frilly interior formed by the circular folds in the mucosa

**Ileum** – like the large intestine, the ileum has Peyer’s patches (large clusters of lymph nodeules in the submucosa)
- These act to prime the immune system against intestinal bacteria and are well positioned to prevent bacteria from the colon migrating up into the small intestine

Motility of the small intestine

**Function** of small intestine motility:
- To neutralise the stomach chime and mix food with the digestive secretions/enzymes
- To facilitate contact between contents of the intestine + intestinal mucosa
- To propel intestinal contents along the alimentary tract

**Processes** of small intestine motility
- **Segmentation** – mixes the contents of the lumen by frequent stationary contractions of the circular muscles at intervals (With net movement of contents towards the colon)
- **Peristalsis** – propels chime towards the colon through sequential contraction of adjacent rings of smooth muscle, with most waves travelling about 10cm
- **Migrating motor complex** (rumbling stomach) – waves of smooth muscle contractions which occur predominantly during fasting (occurs in less ordered/more frequent fashion in fed state) that prevents the migration of colonic bacteria into the ileum and cleans the intestine of residual food. Each cycle begins in the stomach, and on reaching the terminal ileum, the contraction of the adjacent segment begins in the duodenum.

Digestion + Absorption

- Digestion in the duodenum occurs in an alkaline environment, and involves digestive enzymes and bile which enter from the pancreatic duct and bile duct respectively.
  - The duodenal epithelium also produces its own digestive enzymes
  - Digestion occurs both in the lumen, and in the unstirred layer of the membrane
There are 4 mechanisms of absorption, which all occur in the gut: passive diffusion, facilitated diffusion, primary active transport and secondary active transport.

<table>
<thead>
<tr>
<th>Type of Transport</th>
<th>Carrier Proteins</th>
<th>Against/With Gradient</th>
<th>Energy Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive Diffusion</td>
<td>No</td>
<td>With</td>
<td>No</td>
</tr>
<tr>
<td>Facilitated Diffusion</td>
<td>Yes</td>
<td>With</td>
<td>No</td>
</tr>
<tr>
<td>Primary Active Transport</td>
<td>Yes</td>
<td>Against</td>
<td>Yes (hydrolysis of ATP)</td>
</tr>
<tr>
<td>Secondary Active Transport</td>
<td>Yes</td>
<td>Against</td>
<td>Yes (Electrochemical Gradient)</td>
</tr>
</tbody>
</table>

Carbohydrates

- Contain ~50% of ingested calories
- Digestion – begins in the mouth by salivary alpha-amylase, but this is destroyed in the acid pH of the stomach. Most digestion occurs in the small intestine, primarily on the unstirred layer of membrane.
- Structure – may be simple monosaccharides (e.g. glucose + fructose) and disaccharides (sucrose + maltose), or complex sugars bonded together to form a chain (e.g. starch, cellulose + pectins)
- Pancreatic alpha-amylase – secreted into the duodenum in response to a meal, requiring Cl- and slightly alkaline pH for optimum activity (provided by Brunner’s glands in duodenum)
- Absorption – different mechanisms are used for different sugar molecules:
  - Glucose + galactose – absorbed by secondary active transport on carrier protein SGLT-1 on apical membrane
  - Fructose – by facilitated diffusion on carrier protein GLUT-5 on apical membrane
  - GLUT-2 facilitates the exit at the basolateral membrane

Proteins

- Digestion – begins in the stomach by pepsin, which is then inactivated in the alkaline duodenum
  - Pancreatic proteases are secreted into the small intestine as precursors (e.g. trypsinogen), which is then converted on the duodenal brush border by enterokinase to trypsin. Trypsin then continues digestion and activates other proteases involved in digestion.
- Absorption – following breakdown of the proteins into large polypeptides, brush border peptidases break down the peptides further into di/tri-peptides, and free amino acids.
  - Free amino acids are then absorbed by facilitated diffusion and secondary active transport
  - Di/tri-peptides are absorbed using distinct carrier proteins, followed by breakdown into amino acids by cytoplasmic peptidases before they cross the basolateral membrane

Lipids

- Digestion of lipids in more complicated, as they are poorly soluble in water. It consists of a four stage process in the small intestine:
  - Secretion of bile + lipases
  - Emulsification
  - Enzymatic hydrolysis of ester linkages
  - Solubilisation of lipolytic products in bile salt micelles
- **Emulsification** – required as lipids are poorly water soluble; function is to increase the surface area of the fat for digestion
  - Bile salts facilitate the emulsification into a suspension of lipid droplets, which then allows pancreatic lipase to split triglycerides into two fatty acids and a monoglyceride
- **Bile salts** – molecule is amphipathic; consist of a steroid-nucleus and bile acid hydrophobic face, and a hydrophilic face consisting of OH groups and carboxyl/sulfonic acid. The hydrophobic face dissolves in fat, and the hydrophilic face dissolves in water.
- **Micelles** – bile salts form micelles consisting of the hydrophilic head regions in contact with the surrounding solvent, sequestering the hydrophobic tail regions of monoglycerides in the micelle core.
- **Pancreatic lipase** – initially breaks down triglycerides into monoglycerides and free fatty acids, as well as forming complexes with colipase; preventing bile salts from displacing lipase from the micelle.
- **Other lipid enzymes** – phospholipase A2 hydrolyses fatty acids at the 2 position in many phospholipids, resulting in lyso-phospholipids and free fatty acids + pancreatic cholesterol esterase hydrolyses cholesterol ester to free cholesterol and fatty acids
- **Absorption** – micelles allow transport across the unstirred layer, and present the fatty acids + monoglycerides to the brush border
  - The whole micelle is not absorbed together; the bile salts are absorbed in the ileum, but lipid absorption is complete by mid-jejunum
  - Bile-salts are then transported back to the liver for recycling, through the enterohepatic circulation
- **Lipid metabolism** – involves the re-synthesis of triglycerides in enterocytes by two pathways:
  - Monotglyceride acylation (major) – fatty acids bind to the epical membrane, where fatty acid binding proteins (FABP) facilitate their transfer to the smooth ER (where they are esterified into triglycerides)
  - Phosphatidic acid (minor) – triglycerides are synthesised from CoA fatty acid and alpha-glycerophosphate
- **Chylomicrons** – after the re-synthesis of triglycerides in the enterocytes, lipoprotein particles are synthesised as an emulsion.
  - These consist of 80-90% triglycerides, 8-9% phospholipids, 2% cholesterol, 2% protein and trace carbohydrate
  - These are transported to the golgi and secreted across the basement membrane by exocytosis, where they enter lacteals (lymph channels) instead of blood vessels due to their large size

**Note:** the ileum is separated from the colon by the ileocaecal sphincter. Relaxation and contraction of this sphincter controls the passage of material into the colon, as well as preventing the backflow of bacteria into the ileum
Malnutrition I – Undernutrition
Dr Gary Frost (g.frost@imperial.ac.uk)

1. Demonstrate a basic understanding of the role of nutrition in health and disease
2. Demonstrate a basic understanding of the role of gastrointestinal tract in maintaining nutritional status
3. Have a basic understanding of the role of the macro-nutrients in health and disease

Introduction to malnutrition

- There are two extreme ends of malnutrition: under nutrition + obesity
- The gut acts as a barrier that allows the movement of nutrients across it. It is highly adapted for this function, and most nutrients are efficiently absorbed in the small intestine (therefore states of malabsorption have disastrous effects on bowel function)
- Undernutrition results from inadequate consumption, poor absorption, or excessive loss of nutrients
- Malnutrition most commonly refers to undernutrition, but the term can also encompass overnutrition (leading to obesity); results from overeating or excessive intake of specific nutrients.
- Malnutrition poses a major health problem:
  - 1/3 global population live below the recommended nutritional needs (1200kcal)
  - 25% of western society is obese, which accounts for most of T2DM, 30-40% of CVD + is a large risk factor for many cancers

Maslow’s Heirarchy of Needs

- Social/psychological way of ranking things that are important for human survival; represented as a pyramid which illustrates the five levels of human needs.
- The most basic needs are physiological + safety/security, which are shown at the base of the pyramid
- The biological systems of the body will NOT perform without meeting nutritional needs (water + food – base of the pyramid), therefore adequate nutrition is vital for human survival
- NB: malnutrition is also associated with a reduction in life expectancy (both undernutrition during childhood and obesity/overnutrition in adulthood)
  - Malnutrition thus forms a dual problem, which exists side-by-side

Nutrition: the basics

BMI (body mass index)

- Way of assessing body composition, in order to estimate adiposity
- BMI = Weight (kg) / height (m)
- Also considers waist measurement
• Considers 5 ranges, with a desirable range of 20-25 (healthy weight)
• BMI is more important in considering obesity/overweight, as obesity leads to increased risk in many diseases including all cancers (except melanoma + bladder cancer)
  o BMI less relevant when considering patients who are undernourished; severely undernourished patients may have a fluid imbalance, which will result in an inaccurate weight measurement
• Arm circumference and corresponding arm skin-folds are used as surrogate measurements for undernourished patients
• When considering children, growth and weight development charts are used

Dietary reference values
• Estimate the nutritional needs of a population, therefore can be used clinically to assess nutritional adequacy
• Values based on the normal distribution of requirements for different people needed to maintain health and reduce the risk of diet-related diseases
• The amount of each nutrient is called the nutritional requirement, and may vary between individuals (and different life-stages) and for each nutrient
• Dietary recommendations are based on the estimated average requirement, which considers the intake:
  o Need in order to maintain circulating levels or tissue concentration
  o Associated with the absence of disease
  o Need to maintain balance
  o To cure sign of deficiency
  o Associated with an appropriate biochemical marker of adequacy
• Nutrient requirements = the amount which must be consumed by an individual to maintain optimal health and function/avoid deficiency
  o Must take into account the variation between individuals in the nutrient requirements
  o Must also consider the efficiency of utilisation of the nutrient, e.g. only 20% of iron is absorbed
  o Methods used to determine the requirements include:
    ▪ Observation of intakes
    ▪ Balance studies
    ▪ Physiological estimates
    ▪ Clinical studies
    ▪ Functional tests
• 3 reference values are considered for each nutrient (plotted on a normal distribution curve)
  o Estimated average intake (EAR) = mean requirement
  o Lower reference nutrient intake (LRNI) = 2.5 SD below EAR
  o (Upper) reference nutrient intake (RNI) = 2.5 above EAR
• E.g. Vitamin C
  o Ascorbic acid (Vit C) is an essential vitamin, with antioxidant roles + important in the formation of collagen
  o Deficiency in Vitamin C = Scurvy
  o The dietary reference value for vitamin C (mg/day) increases with age (from 15 at 0-6 months → 25 at 15-50+ years)
  o The link between Vitamin C and scurvy (i.e. the discovery of the treatment) can be considered to be the first systematic trial (James Lind)
    ▪ Involved 12 sailors suffering from scurvy, who were segregated and treated with either cider, seawater, garlic mustand + horseradish, vinegar, and organges/lemons
    ▪ Those fed citrus fruits experienced a remarkable recovery (other 5 groups; 2/ garlic, died)
Before considering nutrient requirements, the body's demand for energy in order to meet metabolic needs must be considered. If this is not met, nutrients are not used effectively, but rather are used to meet energy demands.

- **Energy demands** - based on the 1st law of thermodynamics (energy cannot be created nor destroyed)
  - Thus when weight is stable, energy in = energy out + energy stored
  - Weight gain, energy in > energy out
    - Increased intake
    - Decreased expenditure
    - Decreased metabolic rate

- **Energy out** can be divided into 3 components:
  - Adaptive thermogenesis
  - Physical activity
  - Obligatory energy expenditure (BMR)

- **Energy intake** - made up of fat, carbohydrates, protein + alcohol
  - The estimated average requirements for energy depend on sex + age
  - The composition of the energy is also important, i.e. there are specific dietary reference values for protein, carbohydrate + fat

### Average daily intake of energy and macronutrients and intakes compared with Dietary Reference Values (DRVs) by sex and age of respondent*

<table>
<thead>
<tr>
<th>Energy and macronutrients</th>
<th>Men aged (years):</th>
<th>All men</th>
<th>Women aged (years):</th>
<th>All women</th>
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<tr>
<td></td>
<td>19-24</td>
<td>25-34</td>
<td>35-49</td>
<td>50-64</td>
</tr>
<tr>
<td>Total energy intake (MJ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (average value)</td>
<td>9.44</td>
<td>9.82</td>
<td>9.93</td>
<td>9.55</td>
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<tr>
<td>% of Estimated Average Requirements **</td>
<td>89%</td>
<td>93%</td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td>Protein</td>
<td></td>
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<tr>
<td>Mean (average value)</td>
<td>77.8</td>
<td>90.6</td>
<td>90.1</td>
<td>88.8</td>
</tr>
<tr>
<td>% of RNI</td>
<td>140%</td>
<td>163%</td>
<td>162%</td>
<td>166%</td>
</tr>
<tr>
<td>Total carbohydrate***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (average value)</td>
<td>273</td>
<td>277</td>
<td>279</td>
<td>269</td>
</tr>
<tr>
<td>% of food energy</td>
<td>49.0%</td>
<td>47.7%</td>
<td>47.5%</td>
<td>47.4%</td>
</tr>
<tr>
<td>Non-milk extrinsic sugars*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (average value)</td>
<td>96</td>
<td>80</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>% of food energy</td>
<td>17.4%</td>
<td>13.9%</td>
<td>13.1%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Non-starch polysaccharides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (average value)</td>
<td>12.3</td>
<td>14.6</td>
<td>15.7</td>
<td>16.4</td>
</tr>
<tr>
<td>% with intakes &lt; 18g</td>
<td>94%</td>
<td>77%</td>
<td>70%</td>
<td>61%</td>
</tr>
<tr>
<td>Total fat**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (average value)</td>
<td>85.8</td>
<td>87.1</td>
<td>88.3</td>
<td>84.5</td>
</tr>
<tr>
<td>% of food energy</td>
<td>36.0%</td>
<td>35.8%</td>
<td>35.9%</td>
<td>35.6%</td>
</tr>
<tr>
<td>Saturated fatty acids**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (average value)</td>
<td>32.3</td>
<td>32.2</td>
<td>33.4</td>
<td>32.0</td>
</tr>
<tr>
<td>% of food energy</td>
<td>13.5%</td>
<td>13.2%</td>
<td>13.5%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Base</td>
<td>108</td>
<td>219</td>
<td>253</td>
<td>253</td>
</tr>
</tbody>
</table>
- **Energy metabolism** – all centred around acetyl CoA, and its possible fates which adapt to nutritional status; in a good nutritional state, Acetyl CoA enters the TCA cycle. In a starved state, ketone body production is more prevalent.

- **Energy store**
  - Glycogen – stored in the liver + muscle (short term store)
  - Adipose tissue – major store (long term)
  - Muscle tissue – store used during prolonged starvation

- NB: there is an oxidation hierarchy of macronutrient balance, which leads to fat sparing. This is due to the fact that with alcohol, carbohydrate + protein intake, there is an automatic adjustment of oxidation which does not occur after intake of fat.

### Energy Intake and Expenditure

<table>
<thead>
<tr>
<th>Intake</th>
<th>Expenditure</th>
<th>Stores</th>
<th>Auto regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Alcohol</td>
<td>Alcohol</td>
<td>Perfect</td>
</tr>
<tr>
<td>CHO</td>
<td>CHO</td>
<td>CHO</td>
<td>Excellent</td>
</tr>
<tr>
<td>Protein</td>
<td>Protein</td>
<td>Protein</td>
<td>Excellent</td>
</tr>
<tr>
<td>Fat</td>
<td>Fat</td>
<td>Fat</td>
<td>Poor</td>
</tr>
</tbody>
</table>

### Body composition (e.g. 70kg man)

- Should be:
  - 42kg water
  - 12kg fat
  - 12kg protein
  - Glycogen, phosphates, ions + other make up remaining mass

- Importance of body composition – dictates:
  - Energy expenditure
  - Response to disease
  - Risks to many chronic diseases
  - Sporting ability

- **Growth**
  - The human body increases in weight approx. 20-fold from baby-adult
  - All the material in this weight gain enters the human body as food, therefore you are effectively what you eat!
  - Grossly abnormal diets will cause changes in body weight, configuration + composition

- Age – body composition will change dramatically from fetus to adult:
NOTE: Ageing

There are also associated changes that occur with aging:
- Decline in body size
- Increase in body fat
- Decline in muscle mass
- Decline in total body water
- Decline in liver mass
- Effects on required drug dosages + toxicity of drugs
- Can often lead to a downward spiral into undernutrition (more commonly known as malnutrition)

Regulation of feeding
- Average human eats ~900,000kcal/yr
- 3% error → 27,000 calorie change → 10lb weight change (however this does NOT happen)
- Feeding is not just under voluntary control, also under control from peripheral signals to the hypothalamus:
  - Leptin, Ghrelin, PYY<sub>3-36</sub>
  - PYY<sub>3-36</sub> = GI hormone with anorexic effect
  - Ghrelin = stomach + pancreatic hormone with orexigenic effect
  - Leptin = long term regulatory hormone released from adipocytes with anorexic effect
  - Leptin through to be treatment for obesity, but obesity → increased leptin resistance therefore not effective therapy
  - Leptin is responsible for the additional coordinated effects of under nutrition e.g. cessation of menstrual cycles

Undernutrition

Causes

<table>
<thead>
<tr>
<th>In the developing world</th>
<th>In the developed world</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Politics</td>
<td>• Age</td>
</tr>
<tr>
<td>• Climate</td>
<td>• Change in social circumstances, e.g. isolation, death of partner + poor housing</td>
</tr>
<tr>
<td>• Poor water</td>
<td>• Illness</td>
</tr>
<tr>
<td>• Poor agricultural policy</td>
<td>• Aging – 10% of free living elderly people are undernourished to a degree with impaired function</td>
</tr>
<tr>
<td>• Demand of the developed world</td>
<td></td>
</tr>
<tr>
<td>• Often in developed countries, the variety of foods is generally worse, providing less energy and worse nutrition</td>
<td></td>
</tr>
</tbody>
</table>

Specific nutrient deficiencies
- **BERIBERI** – caused by Thiamine (Vitamine B1 derivative) deficiency
  - Thiamine
    - Occurs in the body as free thiamine + various phosphorylated forms: monophosphate (TMP), triphosphate (TTP) + pyrophosphate (TPP)
    - Critical for the release + utilisation of energy from food (involved in the breakdown of energy molecules e.g. glucose) + nerve function (found on neuron membranes)
    - Occurs naturally in unrefined cereals + fresh foods (especially whole grain bread, fresh meat, legumes, green vegetables, fruit + milk)
  - Beriberi
    - Ailment of nervous system
    - Symptoms include sever lethargy + fatigue
    - Complications affect cardiovascular, nervous, muscular + GI systems
May be found in people whose diet consists mainly of polished white rice (thiamine-bearing husk removed)

Prevalent in chronic alcoholics with inadequate diet (Wernicke-Korsakoff syndrome) + post gastric-bypass patients

- **PELLAGRA** – caused by Niacin (vitamin B3 derivative synthesised from troptophan) deficiency
  - **Niacin**
    - Nicotinamide is the derivative of niacin and is used by the body to form coenzymes:
      - nicotinamide adenine dinucleotide (NAD)
      - nicotinamide adenine dinucleotide phosphate (NADP)
    - niacin coenzymes required
  - **Pallagra**
    - Initially thought to be an infectious disease
    - Noted that appeared after staple crop was replaced by maize

### Complications (relating to loss of lean body mass)

<table>
<thead>
<tr>
<th>Lean Body Mass (% loss of total)</th>
<th>Complications (related to lost LBM)</th>
<th>Associated mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Impaired immunity, increased infection</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>Decreased healing, weakness, infection</td>
<td>30</td>
</tr>
<tr>
<td>30</td>
<td>Too weak to sit, pressure sores, pneumonia, no healing</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>Death, usually from pneumonia</td>
<td>100</td>
</tr>
</tbody>
</table>

### Childhood malnutrition
- Decreases fat mass (therefore energy stores)
- Increase in water, decrease in nitrogen (protein composition may remain constant)
- Delays in chemical maturation
- Delays development
- Can affect IQ

### Starvation
- Ketones begin to supply energy to brain as free amino acids decline
- Body begins energy conservation measures
- Brain still dependant on glucose, therefore gluconeogenesis must occur (from protein catabolism)

### Signs of undernutrition
- Weight loss
- Loss of subcutaneous fat (loose skin on extremities)
- Muscle wasting
- Peripheral oedema (no cardiac disease)
- Glossitis, cracking edges of mouth
- Hair loss
• Chronic infections
• Poor wound healing, chronic wounds, pressure sores
• Listless, apathetic
• Recurrent pulmonary infections

Adoptions to weight loss
• In response to energy restriction/starvation, the RMR (resting metabolic rate) is reduced by both passive and active methods
  • **Passive response** to negative energy balance (hormonal)
    o Decrease insulin
    o Decreased thyroxine → decreased T3
    o Glucagon release
    o Growth hormone release
    o Leads to substrate mobilisation of free fatty acids and amino acids → weight loss + change in body composition
  • **Active response** to reduced energy flux
    o Decrease SNS activity
    o Increase catecholamine production
    o Leads to decreased metabolic flux + energy expenditure → decrease in metabolic activity of the FFM (fat-free mass – i.e. total body mass – fat mass)
• Short fasts lead to a loss of glycogen + associated water in liver, as well as loss of gut weight (water loss)
• Long fasts protect further liver + gut loss, therefore result in muscle and fat loss

Normal Metabolism
• Metabolic rate 25-30kcal/kg/d
• Hormones balanced
• Intact skin prevents heat + water loss
• Energy production for cell function, muscle function + tissue repair
  o 50-60% kcal = Carbohydrate (oxygen pathway to energy used)
  o 25-30% kcal = Fat (used as micronutrients)
  o 5-10% kcal = Protein (pathway to protein synthesis used)
• Energy production used in lean mass compartment + fat mass depot
• Lean mass compartment; involved in maintaining physical + metabolic machinery (with anabolic + catabolic stimuli)

Metabolic Response to starvation (short term)
The pancreas – structure & function

1. Distinguish between the exocrine + endocrine parts of the pancreas in structural + functional terms
2. Review the anatomical regions and main relations of the pancreas
3. Sketch the duct system of the pancreas
4. Define a pancreatic acinus
5. Describe the subcellular organisation of synthesis and secretion by the pancreatic acinar cells
6. Outline the embryonic development of the pancreas
7. List the most important components of the pancreatic (exocrine) secretions + define their roles in digestion
8. Explain the mechanism for bicarbonate secretion in terms of ion exchange pumps + membrane ion channels and the dependence on active transport
9. Understand that acinar cells synthesise enzymes for the digestion of carbohydrate, lipids and proteins + store these in an inactive form in zymogen granules, and explain how these enzymes are activated when they enter the duodenum
10. Explain how nervous stimulation and the hormones secretin + CCK regulate the release of pancreatic juice

Lecture outline: pancreatic development, endocrine + exocrine roles, pancreatic juice, control of secretion, stimulus interaction

Pancreatic development

- Pancreatic buds grow out into dorsal + ventral mesenteries of foregut at junction with midgut
- The ventral bud is part of the hepatobiliary bud
- The dorsal bud then expands on the left to form the head-neck-body-tail of the pancreas
  - Islets of Langerhans are most abundant in the tail of the pancreas
- The duodenum then rotate to form a C-shape; the ventral bud then swings posteriorly to the duodenum to fuse with the dorsal bud, forming the rest of the head + uncinate process of the pancreas
  - In some people, the two ducts remain separate
- The ventral duct then usually acquires drainage from the neck-body-tail of the pancreas to form the main pancreatic duct, which opens into the common bile duct just prior to entrance into the duodenum

Structure

- Can be divided into 5 regions: tail, body, neck, head, uncinate (hook-like structure)
- Lies mainly on the posterior abdominal wall extending from the C-shaped duodenum to the hilum of the spleen
- Pancreatic juice reaches the duodenum via main + accessory pancreatic ducts, which fuse with the common bile duct and enter into the 2 part of the duodenum
- The branches of the duct system of both the ventral and dorsal buds five rise to both exocrine (Acinar) and endocrine (islets) tissue

Anatomical relations

- Lies posterior to the duodenum, and anterior to the IVC and aorta
- Spleen lies supralaterally to the left, with the left and right kidneys posterolaterally on either side (each associated with their own adrenal gland)
- Also has close relations with (and supply from) the coeliac + superior mesenteric arteries

NB: Imaging – MRI scans can be used for imaging of pancreatic tumours, whereas angiography is more commonly used for assessing pancreatic disease
Endocrine + exocrine roles of the pancreas

- Endocrine: secretion of substances into the bloodstream to have effect on distant target organs – involves ductless glands
- Exocrine: secretion into a duct to have direct local effect
- The pancreas has 2 functional parts: endocrine and exocrine
  - The endocrine function of the pancreas makes up 2% of the gland; the islets of Langerhans
    - The islets are highly vascular, ensuring that all endocrine cells have close access to a site for secretion
  - Exocrine function makes up the remaining 98%: acini; involved in the digestive function of the pancreas; secretes pancreatic juices into the duodenum
    - Pancreatic juices are rich in digestive enzymes and \( \text{HCO}_3^- \)
- Endocrine secretions of the pancreas are from the islets of Langerhans, which consist of 3 different cells; each of which secrete a different hormone:
  - Beta cells (~60-80% of tissue) – secrete insulin: anabolic hormone which promotes glucose transport into cells + storage as glycogen thus reduces blood glucose, promotes protein synthesis + lipogenesis
  - Alpha cells (~15-20% of tissue) – secret glucagon: hormone which increases gluconeogenesis + glycogenolysis (thus increases blood glucose)
  - Delta cells (~5-10% of tissue) – secrete somatostatin: regulatory hormone which acts as endocrine “cyanide”
- Pancreatic disease may involve both exocrine + endocrine effects, e.g. cystic fibrosis

Pancreatic cell differentiation

- Acinar cells form grape-like spheroidal clusters of 10+ secretory epithelial units which secrete pro-enzymes into ducts
  - The enzyme precursor proteins are synthesised on RERE, glycosylated sorted + packed in the Golgi complex, stored in secretory granules + secreted by apical exocytosis
- The endocrine cells of the pancreas are derived from the branching duct system (predominantly in the tail of the pancreas), but eventually lose contact with the ducts to form separate islets and then different further to specialise into the different cell types
- Between the exocrine acini and endocrine islets are sepat of connective tissue, with columnar epithelium lining the interspersed minor pancreatic duct, which fuse to form the major pancreatic duct

Pancreatic juice

- There are 2 components of pancreatic juice:
  - Low volume, viscous solution rich in digestive enzymes – secreted by acinar cells
  - High volume, water solution rich in \( \text{HCO}_3^- \) - secreted by the centroacinar cells + duct cells
- Acinar cells are large with apical secretory granules
  - These granules store the inactive precursors in order to protect the tissue from auto-digestion
- Duct cells are small, pale, with few granules

Bicarbonate secretion

- Concentration 120mM
- pH 7.5-8.0
- Function: neutralises acid chime from the stomach (preventing damage to the duodenal mucose + providing the optimum range for pancreatic enzymes
- The bicarbonate secretion washes the low volume secretion out of the pancreas into the duodenum
• Effect of duodenal pH on bicarbonate secretion rate – (seen in graph)
  o When duodenal pH<5, there is a significant linear increase in pancreatic bicarbonate secretion
  o When duodenal pH<3, there is not much more increase in the bicarbonate secretion

• The reason that bicarbonate secretion stops even though the pH is still acidic is due to bile + Brunners glands in the duodenum
  o Bile also contains bicarbonate + helps neutralise the acid chime
  o Brunners glands (see small intestine lecture) also secretes alkaline fluid

• Mechanism of secretion
  1. Separation of H⁺ and HCO₃⁻
    - Catalysed by carbonic anhydrase
    - CO₂ diffuses into the duct cell from the blood, reacting with H₂O to form H⁺ + HCO₃⁻
    - CO₂ + H₂O ⇄ H⁺ + HCO₃⁻
    - Simultaneously, Na⁺ moves down a concentration gradient between tight junctions (paracellular transport), and H₂O follows
  2. Transport of H⁺ + HCO₃⁻ out of the duct cell – coupled exchange driven by electrochemical gradients (secondary active transport)
    - The HCO₃⁻ is exchanged with Cl⁻, which has a high lumen concentration compared to IC duct cell conc, therefore the bicarbonate is transported into the lumen, with Chloride going into the cell
    - H⁺ is exchanged with Na⁺, which has a higher blood conc compared with the cell conc, thus flows into the cell and H⁺ thus is transported into the blood
  3. Maintenance of the Na⁺ gradient – Primary active transport using ATP
    - In order to exchange H⁺ for Na in step 2, the Na⁺ gradient needs to be maintained. This is done using the Na/K exchange pump
  4. Returning of the K⁺ (to the blood) and Cl⁻ (to the duct cell) - via protein channels

• NOTE: the same reaction CO₂ + H₂O ⇄ H⁺ + HCO₃⁻ occurs in gastric parietal cells + pancreatic duct cells
  o In the stomach, the hydrogen goes into gastric juice and the bicarbonate into blood
  o In the pancreas, the bicarbonate is secreted into the juice and the hydrogen into the blood

Enzyme secretion
• Lipases, proteases + amylases are synthesised and stored in zymogen granules
• Zymogens are pro-enzymes
• This protects the acini + ducts from autodigestion
• Clinical correlate: acute pancreatitis – blockage of pancreatic duct may overload this protection and result in auto-digestion of the pancreas
• Digestion of proteins
  o Protein digestion is started in the stomach by pepsin, which acts in acid conditions
  o When chime enters the duodenum, the pepsin that is mixed into it comes as well, but is soon inactivated by the alkaline conditions
LSS Alimentary System

Alexandra Burke-Smith

- The pancreas produces a cocktail of proteases, all released as precursors e.g. trypsinogen (which is then activated to form trypsin)
- The pancreas contains a trypsin inhibitor to prevent trypsin activation of proteases, therefore ensuring the enzymes are only activated in the duodenum
- The duodenal brush border produces enterokines, which cleaves the trypsinogen between a valine + an isoleucine.
- Trypsin can then go on to activate other proteases in the same way.
- All the proteases are fairly short lives as they are digested themselves
- NB: trypsin also converts some lipolytic enzymes, but also requires colipase + the action of bile salts for effective action

**Altered pancreatic enzyme function**
- Pancreatic secretions adapt to diet, e.g. high protein, low carb
- Pancreatic enzymes are essential for normal digestion
- Lack of these can lead to malnutrition, even if the dietary input is ok
- ORLISTAT (anti-obesity drug) inhibits pancreatic lipases
  - Steatorrhoea – increased faecal fat by reducing intestinal fat absorption
  - Also occurs e.g. during cystic fibrosis + chronic pancreatitis

Control of pancreatic secretion

- Pancreatic secretion begins before food enter the duodenum via a vagal reflex in response to the smell/taste of food – this is known as the CEPHALIC PHASE, involving cholinergic synapses which only result in enzymatic secretion
- When food arrives in the stomach, the GASTRIC PHASE is stimulated. This involves the same mechanisms as the cephalic phase
- INTESTINAL PHASE - When acid chime enters the duodenum from the stomach, it stimulates the duodenal mucosa to release hormones (secretin + CCK: cholecystokinin) into the blood
  - This is responsible for 70-80% of pancreatic secretion, and stimulates both components of pancreatic juice
  - Secretin is released by the acid pH and stimulates bicarbonate secretion
    - Involves cAMP
  - CCK is released in response to fats/proteins + stimulates enzyme secretion
    - Involves Ca^{2+} and PLC via vagus reflex
- The cephalic phase ends when meal is eaten
- Ansorption of fats and peptides removes the local luminal stimulus for CCK release, thus ending the intestinal phase

Stimulus interaction

There is a synergistic interaction between CCK + secretin, i.e. CCK combined with secretin shows a marked increase in bicarbonate secretion compared to secretin alone. **Summary (what happens during a meal)**
- Food mixed, digested in stomach, pH 2
- Chyme squirited into duodenum
- H+ ions in duodenum stimulate release of secretin, stimulating release of pancreatic juice (plus bile and Brunner’s gland secretions) to raise pH to neutral/alkaline.
- Peptides + fat in duodenum cause sharp rise in CCK, vagal nerve, stimulating pancreatic enzyme release, peaks by 30 mins, continues until stomach empty.
- CCK potentiates effects of secretin on aqueous component (necessary because most of duodenum not at low pH).
1. Understand the production + excretion of bilirubin
2. Describe the features of pre-hepatic, hepatic + post-hepatic jaundice
3. Give two examples of each of these types of jaundice
4. Describe the pathogenesis of the symptoms + signs associated with jaundice

Lecture structure: bile composition/production, bile salts, anatomy of the biliary system, regulation of bile flow + secretion, gall bladder function, control of flow, bilirubin metabolism, jaundice

Bile

Why do we produce bile?
- Bile has 3 important roles:
  o Cholesterol homeostasis
  o Dietary lipid/vitamin absorption
  o Removal of xenobiotics/drugs/endogenous waste products
    - E.g. cholesterol metabolites, adrenocortical, other steroid hormones
    - Xenobiotics – exogenous compounds e.g. food additives, which we are exposed to

Composition of bile
- Water, bile salts, inorganic salts, bile pigments (bilirubin, bilivirden), fatty acids, lethicin, fat, cholesterol, alkaline phosphatase, drug metabolites + trace metals
- All components form an alkaline electrolyte solution
- There are also other substances excreted into bile:
  - Andrenocortical + other steroid hormones
  - Drugs/xenobiotics
  - Cholesterol
  - Alkaline phosphatase (ALP)
- Clinical correlation: in duct obstruction, there is an increase in cholesterol + ALP, which may result in jaundice. However in hepatic illness, the increase is NOT in ALP, but rather ALT + AST (alanine transaminase + aspartate transaminase)
- The golden-yellow colour of bile is due to gluconorides of bile pigments

Production of bile
- The liver is mainly made up of hepatocytes, with an intersperse biliary tree (duct system) lined by cholangiocytes
- 500-650ml produced + secreted daily
  - 60% by hepatocytes
  - 40% by cholangiocytes
- The bile drains from the liver into the duodenum at the duodenal papilla
- Role of the biliary tree:
  - The biliary epithelium is important in altering the pH + fluidity of bile. It modifies the bile as it flows through it. This includes:
    o Splitting of glutathione into constituent amino acids (which are reabsorbed)
    o Reabsorption of glucose + some organic amino acids
    o Contribution of IgA from cholangiocytes by exocytosis
    o CFTR mechanism (cystic fibrosis transmembrane regulator) – actively secretes bicarbonate and chloride ions into bile
Clinical correlation: mutation in CFTR gene in cystic fibrosis → reduction in this mechanism contributing to liver cirrhosis + fibrosis

Water is also drawn into bile by osmosis through paracellular junctions

Bile flow

- Is closely related to the concentration of bile acids + salts in the blood
- Biliary excretion of bile salts is performed by transporters expressed on the apical surface of hepatocytes and cholangiocytes, which govern the rate of bile flow as well
- Dysfunction of the transporters is a major cause of cholestasis – stasis of the biliary tree/bile duct which may lead to jaundice
- The main transporters include:
  - Bile salt excretory pump (BSEP) – responsible for the active transport of bile acids across hepatocytes into bile
  - MDR related proteins (MRP1 + 3)
  - Products of the familial intrahepatic cholestasis gene (FIC1)
  - Multidrug resistance genes (MDR1 + 3)
    - MDR1 mediates the canalicular excretion of xenobiotics + cytotoxins into bile
    - MDR3 encodes a phospholipid transporter protein that translocates phosphatidylcholine from the inner to outer leaflet of the membrane

Bile salts

- Bile salts are sodium + potassium salts of bile acids conjugated to glycine + taurine
- Bile acids are synthesis from cholesterol; 4 acids in humans
  - 2 primary acids are formed in the liver:
    - Cholic acid
    - Chenodeoxycholic acid
  - These are then converted by colonic bacteria:
    - Cholic acid → deoxycholic acid
    - Chenodeoxycholic acid → lithocholic acid
- The purpose of the conjugation is to make the initial compounds more easily absorbed + metabolised

Function

- Fats are water insoluble, and bile consists of predominantly water, therefore bile salts allow emulsion of the lipids in the water by reducing the surface tension of the fat and forming micelles in the water
- They are able to do this by forming micelles – due to their amphipathic nature they form a lipid hydrophobic core with a hydrophilic surface – allowing the lipids to be transported to the GI tract epithelial cells for absorption
- The detergent-like actions make bile salts potentially cytotoxic in high concentrations, but cell membranes are protected by other intraluminal lipids and their own membrane content of cholesterol + glycolipids. However they are thought to contribute to liver cancer at very high concentrations.

The biliary system

Anatomy

- Hepatocytes are the major functional cells of the liver, which form complex 3D arrangements called hepatic laminae (1 cell thick layers)
- Bile canaliculi are small ducts between hepatocytes that collect bile and drain into bile ductules – bile ducts and eventually the common hepatic duct.
- Hepatic sinusoids are highly permeable blood capillaries that receive oxygenated blood from branches of the hepatic artery + nutrient-rich de-oxygenated blood from branches of the hepatic portal vein. At a transit time of ~8.4s, these converge and deliver blood into a central vein, which flows into the hepatic vein which drains into the IVC.
- A bile duct, branch of the hepatic artery + branch of the hepatic vein together are referred to as a portal triad.
- The hepatocytes, bile duct system + hepatic sinusoids can be organised into units called hepatic lobules:
  - hexagonal structure with a central vein with radiating hepatic laminae + sinusoids. At the three corners of the hexagon is a portal triad.
- Hepatocytes at the extreme periportal zone (i.e. closest to the portal triads) make contact with the cholangiocytes lining the bile ducts. Here, there is a short stretch where bile flows in channels lined by both cholangiocytes + hepatocytes = Canal of Hering.
- The liver can also be organised into functional units called acini:
  - Each hepatic acinus is an approximately oval mass that includes portions of two hepatic lobules.
  - The short axis of the hepatic acinus is defined by the branches of the portal triads, that runs along the border of the hepatic lobules (i.e. marked by the border where the 2 lobules meet).
  - The long axis is two imaginary curved lines which join the two central veins.
  - The hepatocytes are then arranged in 3 zones around the short axis:
    - Zone 1 are first to receive incoming oxygen, nutrients + toxins from the blood, thus are last to die if circulation is impaired.
    - Blood flows outwards.
    - Zone 3 are last to receive incoming oxygen etc, and to show effects of bile obstruction.

**Regulation of bile flow & secretion**
- The right lobe of the liver drains into the right hepatic duct.
- The left lobe of the liver drains into the left hepatic duct.
- The R + L hepatic ducts coalesce just outside the liver to form the hepatic duct.
- The Gall bladder has cystic duct, through which stored bile is released when needed for digestion.
- The cystic duct + hepatic duct fuse to form the common bile duct, which lies posterior to the pancreas and opens into the duodenum at the ampulla of vater (controlled by the sphincter of Oddi).
- Between meals, bile is stored in the gall bladder as the sphincter of Oddi is closed.
- Eating causes the sphincter of Oddi to relax, and release of GI mucosal hormone CCK → gall bladder contraction + secretion of bile.

**Enterohepatic circulation**
- Liver cells transfer various substances from plasma to bile; many of which are then concentrate in bile e.g. gluconuride, which is hydrolysed then reabsorbed into the circulation – i.e. the cycle repeats itself.
- This can prolong the action of different drugs, e.g. morphine
- Summary = GI tract – portal blood – uptake by hepatocyte + excretion into canaliculus – bile duct – GI tract – reabsorption into terminal ileum + transport out of enterocytes

Circulation of bile salts
- Bile salts enter the duodenum, are transported through the jejunum into the ileum
- 95% are then absorbed from the ileum + enter the enterohepatic circulation to return to the liver
- 5% are converted to secondary bile acids in the colon, with deoxycholate being absorbed into the venous circulation to the liver + lithocholate being excreted
- 3.5 grams of the bile salts recirculate in enterohepatic circulation
- Clinical correlations w/ enterohepatic circulation
  - Terminal ileal resection/disease – leads to a decrease in bile salt reabsorption + increase in excretion due to interruption of circulation
  - If bile is stopped from entering the GI tract, up to 50% of indigested fat appears in the faeces, along with malabsorption of soluble vitamins A,D,E + K – e.g. Crohn’s disease

The gall bladder

Functions
- Bile storage
- Bile acidification
- Bile concentration – reducing the volume of stored bile by absorbing Na, Cl, Ca + carbonate ions, with a net movement of water

Effects of cholecystectomy
- Definition: removal of the gall bladder
- May be required for gall bladder cancer or gall stones
- Gall bladder is not essential, as its periodic discharge of bile aids digestion but will require a reduction in fat intake

Bilirubin
- Water insoluble yellow pigment
- Source:
  - Hb breakdown in spleen
  - Catabolism of haem proteins
  - Ineffective bone marrow erythropoiesis
- Bilirubin is produced in spleen then bound to albumin where it dissociates in the liver and enters hepatocytes
- In the hepatocytes, it binds to cytoplasmic proteins and is conjugated to glucoronic acid to form diglucoronide-BR
  - This is more soluble than free bilirubin
- The conjugated molecule is then transported across conc gradient into bile canaliculi and into the GI tract
- Total BR = free unconjugated BR + conjugated BR

Urobilinogens
- Water-soluble colourless derivative of BR formed by the action of GI bacteria on bilirubin
- GI tract mucosa relatively impermeable to conjugated BR, but permeable to unconjugated + urobilinogens
- Therefore some urbilinogens are reabsorbed into the general circulation, and are excreted via the kidneys into the urine
The remaining 80% are not absorbed, therefore are excreted in faeces; first converted into stercobilinogen which is oxidised to give brown colour of faeces.

**Cholestasis + Jaundice (icterus)**
- Cholestasis = cessation of bile flow
- Jaundice = BR >34-50microM/L in blood (normal = 20)
- Cholestasis normally results in jaundice, but jaundice has other possible causes

**Causes**
- **Pre-hepatic**
  - Problem is before the liver, i.e. BR production in the spleen is too high
  - May be due to haemolysis, massive transfusion, haematoma reabsorption, ineffective erythropoiesis
  - BR production is too great for conjugation in the liver, therefore predominantly unconjugated BR in the blood
  - Look for HB drop without overt bleeding
- **Hepatic/hepatocellular**
  - Spleen production of BR normal, but the hepatocytes of the liver not functioning properly, either defective uptake, conjugation or excretion
  - May cause liver failure (which may be acute, chronic, caused by viral hep etc) and intrahepatic cholestasis
- **Post-epatic/obstructive**
  - Defect in the transport of conjugated BR by the biliary duct system e.g. in the common bile duct
  - Tends to be from obstructive cause, e.g. gall stonesm liver malignancy, pancreatic cancer, local lymphadenopathy
  - Bilirubin stasis → increased risk of infection + sepsis
  - Also leads to upstream dilatation of bile ducts
  - Treatment: obstruction removal via stent

**Specific causes**

<table>
<thead>
<tr>
<th>Pre-Hepatic</th>
<th>Hepatic</th>
<th>Post-Hepatic</th>
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<tr>
<td>Inherited disorders of BR metabolism:</td>
<td>Hepatitis due to:</td>
<td>Intrahep cholestasis 2ndary to drugs or virus</td>
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<tr>
<td>Crigler-Najjar</td>
<td>Viral</td>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Gilbert’s</td>
<td>Autoimmune</td>
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<td>Rotor</td>
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<td>Dubin-Johnson</td>
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<td>Haemolysis</td>
<td>Metabolic liver disease</td>
<td>Carcinoma head of pancreas</td>
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<td>Carcinoma ampulla</td>
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</table>
NB: Gilbert’s caused by AGT deficiency (polymorphism → less effective enzyme in 2% of population) → slightly increased BR which may spike during illness or stress

ALSO, other illnesses cause yellow skin discoloration, e.g. Addison’s, carotinaemia – however jaundice also presents with yellow discolouration of the eyes (important diagnostic tool)
Immunological mechanisms & infections of the alimentary tract

1. List the innate functions of the alimentary system which are part of our defence systems
2. Define MALT + GALT
3. Describe a Peyer’s Patch
4. Define the role of IgA in the GI tract
5. Describe the importance of colonic flora
6. Describe the circulation of lymphocytes within the alimentary system + how this relates to the immune system elsewhere
7. List 3 mechanisms of infectious diarrhoea
8. Describe the global importance of childhood diarrhoea

Why mucosal immunology? The alimentary system is exposed to many antigens on a daily basis. These antigens can be derived from food and from potential invaders such as bacteria + viruses. Recognition and appropriate handling of these antigens are vital to survival. If the immune system is poorly functioning then we are at risk of infections and if too vigorous can lead to hypersensitivity reactions and auto-immune disease.

Examples of GI Pathogens

- **Mouth**: oral candidiasis
- **Gastric**: Helicobacter Pylori
  - In the normal stomach, acid secretions maintain a low pH to aid food digestion
  - In response to H. infection, gastrin secreted by G cells stimulates excess acid production
  - Continued excess stomach acid → tissue damage + peptic ulcers
  - In some cases, chronic inflammation develops → atrophy of the stomach wall + malignant tumours?
- **Traveller’s diarrhoea** has multiple causes, which include:
  - **Escherichia coli** (E.coli)
    - Strains + toxins: enterotoxigenic (cholera-like w watery diarrhoea) enterohaemorrhagic, enteropathogenic (EPEC), enteroinvasive (shigella like w bloody diarrhoea + megacolon)
    - Routes of transmission: farms, unpasteurised milk, burgers
    - Treatment: usually supportive, but sever cases antibiotics are used
  - **Noravirus** – faeco-oral transmission with 24-48hr incubation period → acute gastroenteritis <3 days, but may be infectious for up to 2 weeks
  - **Cholera** – gram negative extracellular bacillus – targets Cl- channels → huge water + salt loss in rice-water like diarrhoea. Causes extreme dehydration + possible hypovolaemic shock
    - Treatment: supportive (fluid replacement, salt, water, sugar + IV fluids)
  - Also shigella, salmonella, rotavirus, giardia

“superbugs of the 21st C” - *Clostridium difficile* (C. Diff)

- The colon is colonized by large numbers of commensal gut bacteria + Antibiotics kill many of these
- C. Diff gains a foothold + produces toxins → mucosal injury
- Neutrophils + RBC leak into gut between injured epithelial cells
- Causes pseudomembranous colitis (antibiotic associated), bloody diarrhoea, mucous + abdominal pain
- Treatment: isolation, stop current antibiotics, metronidazole + vancomycin

NB: Food intolerance may also cause symptoms of GI disease e.g. diarrhoea – Nuts, Hen egg white, Cow’s milk, Wheat, sesame seeds, soya + shell fish
GI Immunology

Innate GI Defence
- Gastric acid
- Commensal oral flora
- Peristalsis
- Mucus secretion from goblet cells
- Proteases – intraluminal enzymes
- Protective shield of the enterocyte membrane + brush border

Gut immunity
We are exposed to thousands of antigens on a daily basis. There are two “immunological” defences of the GI tract, closely related to the prominent lymphatic supply/draining of the gut:
- **MALT** – mucosa associated lymphoid tissue
  - The oral cavity is rich in MALT, e.g. the tongue, palatine, lingual + pharyngeal tonsils
- **GALT** – gut associated lymphoid tissue
  - May be organised or not organised
  - *Not organised* GALT consists of **intra-epithelial lymphocytes** (mainly CD8) + lamina propria lymphocytes (antigen presenting cells)
  - *Organised* GALT consists of **cryptopatches** (tiny lymphoid aggregates present in the small intestine), **isolated lymphoid follicles** + mesenteric lymph nodes
  - Function: generated lymphoid cells + antibodies: IgA, IgG, IgM + induced cell mediated immunity
  - Within the Gut mucosa, there are regions of epithelium which are specialised to form “**dome epithelium**”
    - These are areas of M cells instead of mucosal epithelium; effectively areas which control the uptake of antigens
    - Formed by smaller epithelial cells with less goblet cells, less mucus + no secretory IgA
    - M cells form the portal of entry for antigens, where they are transported to lymphocytes, macrophages + dendritic cells
- **IgA** – the specialised immunoglobulin of the gut – transported from submucosa to lumen by transcytosis
  - Dimeric IgA secreted by plasma cells in the submucosa, which then binds to the poly-Ig receptor on the epithelial cell membrane
  - Receptor + IgA endocytosed to form vesicle, then undergo enzymatic cleavage to form secretory IgA which is secreted into the lumen
- **M cells** – present in dome epithelium
  - Unique ability to transcytose antigens, presenting them to plasma cells within organised lymphoid follicles of the submucosa
  - Alternatively, can present the antigens to a pool of cytokines + lymphocytes (predominantly T cells) in a pocket on their basolateral side
  - The pool of cytokines is known as a cytokine milieu + affects development of the unconventional resident T cells of the gut
    - The plastic response of T-cells to this milieu can lead to a proinflammatory environment, leading to an increase in Th1, Th\_17 with a decreased Treg cell count
- **Intraepithelial lymphocytes** – make up 20% of the intestinal epithelium, and consist of 2 different groups of T cells
  - Conventional T cells; migrated from other tissues
  - Unconventional T cells; resident T cells which express unusual combinations of CD4, CD8 or γδ TCR
  - Groups of CD4 cells:
    - Th1 – cellular immunity + autoimmunity
    - Th2 – humoral immunity, atopy, asthma + allergy
- Treg – immunoregulatory function
- Th_{IL}17 – inflammation + autoimmunity

- Adaptive immune response
  - M cells transport antigens into submucosal organised lymphoid tissue, present to plasma cells, which secrete IgA

- Innate immune response
  - Infection of an epithelial cell signals the synthesis of a series of stress-induced proteins, expressing 2 atypical MHC class I molecules known as MIC-A +MIC-B
  - T cells bearing the NK receptor NKG2D binds to the atypical molecules
  - Infected cell is then killed by induction of apoptosis + replaced by adjacent healthy cells

Clinical Correlates

- **Coeliac disease**
  - Subtotal villus atrophy with gluten intolerance
  - Pathogenesis: dendritic cells of the submucosa mature in a proinflammatory environment of increased Th1 + Th_{IL}17, with reduced Treg count

- **Crohn’s disease**
  - The gut has a dual immunological role: immunoreactivity + food tolerance (acquired tolerance to food “antigens” → suppression of humoral response)
  - Crohn’s is an acquired tolerance failure, in which individuals do not suppress humoral response to food, therefore become hypersensitive to the food antigen
  - Symptoms include structuring, ulceration + inflammation
  - Related to an increased TGF-beta – caused by either cytokine secretion of IL-10 (associated with a low dose exposure) or anergy deletion (associated with a high dose exposure)

- **Primary sclerosing cholangitis**
  - Inflammatory condition of the biliary tree associated with inflammatory bowel disease
  - May cause cholangiocarcinoma
  - Cause is T-cell misdirection to the liver whether they contribute to inflammation + biliary destruction
1. List the main functions of the liver
2. Review the organisation of the liver + biliary system at the level of gross anatomy
3. Describe the main features of the blood supply to the liver
4. Explain the organisation of liver tissue in relation to its microcirculation, making correct use of the terms portal triad, central vein, sinusoidal capillary, hepatocyte, lobule, periportal region + centrilobular region
5. Summarise the functional importance of main structural features of hepatocytes (RER, golgi, secretion granules, glycogen granules, mitochondria, smooth ER, junctional complexes)
6. Draw a simple diagram outlining the relationships of hepatocytes to bile canaliculi + sinusoidal capillaries, and use this to explain major hepatic functions
7. Define the position + main roles of Kupffer cells (fixed macrophages)
8. Outline the embryological origins of the liver
9. Explain the main structural + functional changes in the liver between the embryonic period + postnatal period

Summary of lecture structure: surface anatomy, morphological anatomy, blood supply, functional anatomy, biliary system, embryology, histological structure + ultrastructure

Surface anatomy

- The abdominal region can be divided into 4 quadrants
- The liver is a large solid organ which sits in the right upper quadrant (predominantly, also in left UQ)
- The superior border tends to lie at the level of the 5th costal cartilage
- Protected mainly by ribcage, superiorly by the diaphragm + inferiorly by the abdominal muscles + organs

Importance of surface anatomy

- The liver is a very friable organ, and any damage to the liver is very painful and may cause severe bleeding (capsule surrounding liver is very well innervated, and the liver itself is very vascular)
- Surface anatomy is used in liver biopsy, as knowledge of the location of the liver prevents damaging other organs
  - Percussion of chest inferiorly, and percussion of abdomen superiorly – when dull region is reached = liver
  - Large inspiration followed by expiration prior to insertion of needle
- Biopsy used to determine diagnosis + staging of liver disease

Morphological anatomy

- The liver consists of 2 lobes, separated by the falciform ligament
- The coronary ligament + left triangular ligament connect the liver to the abdominal wall + diaphragm
- The gall bladder lies inferiorly in the arch of the liver, therefore should not be palpable – if the gall bladder is palpable; indicates enlargement
Blood supply

- The liver is a very vascular organ, due to its importance in metabolism + homeostasis – thus receives 25% of the resting cardiac output
- Has a dual blood supply: arterial and venous
  - 20% artery blood from L + R branches of the hepatic artery – oxygen rich
  - 80% venous blood draining from the gut through the hepatic portal vein – nutrient rich
- This provides the liver with both a direct + indirect blood supply, which reduces the risk of acute ischemia if embolus present
- NB: hepatic lesions will receive arterial supply more rapidly than the venous supply, therefore contrast medium can be used in liver imaging to observe the effect on the arterial supply

Functional anatomy

- The morphological lobes of the liver correspond to the attachment of the mesenteries and the location of the falciform ligament
- However functionally, the liver is divided between the territories of the R + L branches of the hepatic artery
- Centrally, the liver is divided by the hepatic portal vein, hepatic artery + bile duct
- Peripherally, the liver is then divided into 8 functionally independent segments, all with their own hepatic vein branch, which coalesce into the R + L hepatic veins which drain into the IVC
- This means that each segment can be resected without bleeding + damaging the surrounding segments – this is known as a “bloodless” liver surgery, and is common for surgical tumour removal
- The segments are numbered clockwise from the posterior central caudate lobe, and this is important in radiology for locating hepatocellular carcinomas on CT scans

Functions of the liver

- Secretes bile into duodenum + synthesis of bile salts
- Phagocytoses + breaks down over-dates RBC
- Excretes bile pigments into bile
- Metabolises many natural + synthetic molecules to prepare them for excretion
- Synthesis + secretion of key blood proteins
- Key site of insulin dependent glycogen storage + of intermediary metabolism
- Many others

Embryological origins

- The liver + biliary system share a common origin with the ventral part of the pancreas at the junction between the foregut + midgut
- Arises from the septum transversum – point at which the ectoderm of the amnion meets the endoderm of the yolk sac
- The mesenchymal structure of the septum provides a framework on which the parenchymal (hepatocyte) cells + bile ducts with associated blood supply can develop
The biliary tract

- The biliary system as an important role in the excretion of toxins + secretion of fats
- Hepatocytes within the liver produce bile, and secrete this into bile canaliculi which drain into ductules – ducts and eventually drain into the hepatic duct
- The gall bladder serves as a reservoir of bile between meals, and has a cystic duct which fuses joins the gall bladder to the hepatic duct to form the common bile duct
  - The common bile duct has a spiral muscular structure which twists/untwists; on untwisting of the duct + sphincter of Oddi, it becomes patent + secreted bile into the ampulla in the 2nd part of the duodenum
  - At the ampulla, the CBD may also join the pancreatic duct
- Bile neutralises chime + aids digestion of fats, therefore structural abnormalities of the biliary tree may have devastating effects on digestion
- The biliary tree can be seen using ERCP (endoscopic retrograde choligraphic panreatography)
  - A wire is passed through the spinchter of Oddi (along with a scope), and dye is injected to the see the branches of the bile ducts
  - This can be used to see any obstructions, e.g. gall stones or tumours
  - Is also good because as it is invasive, provides opportunity to solve problem found, e.g. removing the obstruction
- MRI can also be used to observe the effects of gall stones or tumours on the biliary tree, e.g. dilation due to accumulation of bile, or constriction of the distal end of the bile duct

Histological structure

- The liver consists of unit known as lobules
- These consist of a central vein (which drains into hepatic veins – IVC) with radiating hepatocyte sheets
- Around the edges of adjoining lobules are portal triads consisting of:
  - Hepatic arteriole
  - Branch of the hepatic portal vein
  - Bile duct
- Between the sheets of hepatocytes + capillary sinusoids which eventually drain into the central vein
  - There are also bile canaliculi which drain the bile produced in the hepatocytes into ductules which flow outwards into the portal triad

Cell types

- Hepatocytes – are the main functional cells, bile producing, make up approx. 80% of liver cells
- Endothelial cells line all the blood vessels and sinusoids of the liver
- Cholangiocytes lining the biliary tree + branches, including bile canaliculi
- Kupffer cells are liver resident macrophages (larger, darker more flattened nuclei compared to hepatocytes) – these breakdown RBC + choreograph immune responses in the liver
- Hepatic stellate cells are Vit A storage which may be activated (by toxic insult, immune invasion, reactive oxygen etc) to form fibrogenic myofibroblastic phenotype – deposition of fibrous tissue causing liver fibrosis and eventually cirrhosis

Lobule vs acinus (see previous liver notes for more detail)

- Lobules are the histological units within the liver which are easily identified and are centred around central veins which drain into the hepatic veins
- Acini are functional units which are aligned around the portal triad, and divided into zones dependent on their proximity to arterial blood supply
  - These are less easy to visualise, but pattern of cell death related to acini zones which can be seen in microscopy
**Ultrastructure**

- Shown on EM
- The space between hepatocytes + their associated sinusoid endothelium = Space of Disse
- The endothelium is fenestrated to allow the movement of substances, and Kupffer cells reside in the space
- In a normal liver, the hepatocytes are healthy, covered in microvilli. The space of Disse is clear, with kupffer cells + stellate cells, and the endothelium of the sinusoids are fenestrated
- In liver disease, they hepatocytes lose their microvilli, endothelium lose fenestrae, the stellate cells deposite fibrous tissue into the space of Disse. There is also an upregulation of Kupffer cells which leads to the production of free radicals which cause further damage
- There are different stages of fibrosis: mild-moderate, moderate “bridging” and full cirrhosis
- Fibrous tissue affects the blood supply to healthy hepatocytes → energy supply/detoxification function loss
- Cirrhosis occurs when there is decomposition of surrounding liver tissue → failure, immunosuppression, hypertension (at location of portosystemic anastomoses), vomiting of blood
1. Define acute and chronic pancreatitis
2. List four causes of acute pancreatitis
3. List the symptoms and signs of acute pancreatitis
4. List blood tests and imaging modalities which are useful for patients with pancreatitis
5. List three causes of chronic pancreatitis
6. List the complications of acute and chronic pancreatitis

Introduction
Inflammatory disease of the pancreas has two different entities: acute and chronic. The pancreas is a long flat gland that lies horizontally behind the stomach. The head of the pancreas rests against the duodenum and the tail reaches towards the spleen. It has two main functions:
1) Exocrine: Production of digestive juices and enzymes for the metabolism of fats, carbohydrates and protein.
2) Endocrine: Secretion of insulin, glucagon and somatostatin. The pancreatitis has an incidence of 17 new cases per 100,000 people.

Acute pancreatitis
Is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. Clinical presentations:

Causes: The most common causes of pancreatitis are alcoholism and cholelithiasis. Other causes are metabolic, infections, medications and vasculitis.

Clinical diagnosis: History of upper abdominal pain and vomiting with epigastric or diffuse abdominal tenderness. Occasionally body wall ecchymosis (Cullen’s sign at the umbilicus, Grey-Turner’s sign in the flanks) will be found.

Biochemical diagnosis: Elevated levels of pancreatic enzymes, amylase and lipase. Elevated white blood cell count, liver enzymes and bilirubin, hyperglycemia, hypocalcemia. C-reactive protein (CRP) concentration has independent prognostic value. A peak level of > 210 mg/l in the first four days of the attack or > 120mg/l at the end of the first week has a predictive accuracy of around 80%.

Radiological diagnosis: Plan x rays: Chest and abdominal plain x rays in order to detect local ileus (sentinel loop) and in case of the chest x ray the pleural effusion is the most common finding and the alveolar interstitial shadowing may suggest an adult respiratory distress syndrome (ARDS). Ultrasound: Is valuable in detecting free peritoneal fluid, gallstones, and dilatation of the bile duct. MRCP: Non-invasive investigation of the bile duct. ERCP: In patients thought to have a severe biliary pancreatitis secondary to gallstones.

CT-scanning: For the diagnosis and eventually for the drainage of fluid under radiological guidance. Severity stratification: Biochemical and objective criteria: Glasgow and Ramson scoring systems. Those scoring systems improve the accuracy of prognostication around 70-80%. The APACHE II scoring system can be used to assess the initial severity of disease and the chances of developing a subsequent complication.

Management of mild acute pancreatitis: Monitoring of temperature, pulse, blood pressure, and urine output. Line for IV fluids, nasogastric tube and urine catheter. Antibiotics should not be administered routinely as there is not evidence that their use in mild cases will affect outcome or reduce the incidence of septic complications. Nutritional recommendations: 2-5 days: fasting, 3-7 days: referring (diet rich in carbohydrates, moderate protein, moderate in fat). After 7 days may start a normal diet.

Management of severe acute pancreatitis: The initial management involves full resuscitation and a multidisciplinary approach. These patients should be managed in ITU. When cardiocirculatory compromise exists a Swan-Ganz catheter is required. The administration of intravenous antibiotics as a treatment of infections...
following severe acute pancreatitis is justified. CT scanning should be done. Nutritional support: enteral/parenteral. Enteral nutrition should be attempted in all patients.

The severe gallstone pancreatitis should be treated with ERCP and sphincterotomy urgently. Gallstones eradication should be done by cholecystectomy within two or four weeks. If local complications develop, such as pseudocyst or infected necrosis, cholecystectomy should be performed when the complications are treated surgically.

**Chronic pancreatitis**
The most common causes of chronic pancreatitis are alcoholism, microlithiasis and idiopathic. Rare causes are hereditary pancreatitis, hyperparathyroidism, and obstruction of the main pancreatic duct caused by stenosis, stones or cancer. Symptoms may be identical to those of acute pancreatitis. Although occasionally there is no pain, severe epigastric pain may last for many hours or several days. Possible causes include acute inflammation not recognised by conventional tests, distension of pancreatic ducts caused by strictures or calculi, a pseudocyst, or obstruction of either the duodenum or the common bile duct caused by fibrosis of the head of the pancreas. When lipase and protease secretions are reduced to < 10% of normal level, the patient will develop steatorrhea.

**Diagnosis:** Laboratory tests, including amylase and lipase, are frequently normal, probably because of significant loss of pancreas function. Inflammatory markers can be minimally elevated as well. Structural abnormalities can be visualised in plan x-ray abdomen, showing pancreatic calcifications, which indicates intraductal stones. Abdominal ultrasound, CT scan can show abnormalities in size and consistency of the pancreas, pancreatic pseudocysts, or dilated pancreatic duct. The ERCP can show abnormalities in the pancreatic duct. Tests to assess the endocrine function of the pancreas can show diabetes mellitus. The most sensitive tests of the exocrine function of the pancreas: is the secretin test. Other tests include measurement of serum trypsinogen, faecal chymotrypsin, and urinary p-aminobenzoic acid.

**Treatment:** A relapse of chronic pancreatitis may require similar management to that of acute pancreatitis. The supply of IV fluids, dietary restriction including fat and proteins in order to reduce stimulus to the pancreas secretion. H2 or PPI blockers to reduce acid stimulation and relieve of the pain. To treat the chronic pain, pancreatic enzymes (30,000 U of lipase) have been used with each meal. A pancreatic pseudocyst can be decompressed into a nearby structure eg. stomach or into a defunctionalized loop of jejunum via a Roux-en-Y. If the pain is refractory and the main pancreatic duct is dilated a lateral pancreaticojejunostomy (Puestow Procedure) may be indicated.

If the duct is not dilated a resection can be considered like a distal pancreatectomy or Whipple’s operation. These operative approaches may relieve pain in 60 to 80% of patients and should be reserved for patient with a nondilated duct who have discontinued using alcohol and who can manage diabetes that may be intensified by pancreatic resection. Steatorrhea can be improved with pancreas extracts containing lipase. H2 blockers can be used to reduce the intragastric acidity. Use of Insulin to treat the diabetes should be managed carefully due to the associated glucagon deficiency.

Patients with chronic pancreatitis are at increased risk for pancreatic cancer. Worsening of symptoms should prompt an examination for malignancy, including brushing of strictures for cytological analysis or measurements of serum markers (eg. CA 19-9, CEA).

**EXTRA NOTES**
- Pancreas is retroperitoneal. If enzymes are released in active form, self-digestion can occur...
- Exocrine function: ducts, released at particular times.
- Endocrine function: insulin + glucagon, into bloodstream
- Location of pancreas: sits under liver behind stomach above transverse colon. Lies at trans-pyloric plane.
- Duodenum encircles head + neck of pancreas. Important: if pancreas is inflamed, it affects the duodenum + halts peristalsis. Makes patient nauseous + vomit. Main symptom of pancreatitis: pain (inflammation + visceral spread via coeliac plexus). Inflammation can lead to choleostasis + jaundice, + auto-digesting enzymes can affect blood vessels + lead to bleeding.
- Pancreas: yellow, shiny organ.
- Parts of pancreas: see previous lecture.
- Back of pancreas: main pancreatic duct joins bile duct
• Blood supply: gland develops between foregut + midgut. It therefore gets blood supply from more than one artery
• Clinical importance: hypertrophy of head causes obstruction. Degeneration of islets of Langerhans leads to DM. Pancreatitis is an inflammatory condition of the exocrine pancreas. Cancer of the head is often fatal (poor prognosis).
• Microscopic anatomy: islets of langerhans

• PANCREATITIS: definition, epidemiology, causes, pathophysiology, diagnostics, prognostic markers, management, complications.
• Definition: ‘itis’ i.e. inflammation. Acute vs. chronic. Particular triggers.
• Acute pancreatitis is activation of all processes before digestive hormones have been released. Enzymes are normally released in precursor form. Substances within gut then activate these precursors, therefore preventing damage to structure of pancreas. However in pancreatitis, the pancreas is activated when you pass gall stones/drink too much alcohol etc.
• Incidence: 3% of cases of abdo pain. Lower prevalence in Japan (less alcohol). Can occur at any age, but major peaks are young males (alcohol) and older females (gall stones). No geographical predisposition but in reality a disease of the Western world.
• Most common causes:
  • “Get smashed” – gall stones, ethanol, trauma, steroids, mumps, autoimmune, scorpion bites, hypothermia/volaemia, OR hypertriglyceridaemia/calcaemia, ERCP (procedure), drugs (e.g. oestrogen, tetracycline, thiazide, metronidazole, simvastatin, sulfonamides)
• Pathology: microscopic (inflammation + autodigestion/autolysis + leakage), macroscopic (saponification, haemorrhage, fat necrosis, infection)
• Symptoms: RUQ/epigastic pain, vomiting, dehydrated/shock, jaundice (obstructive), indications of causes (alcohol, disease e.g. mumps)
• Signs: often look quite well, confused. 3 responses to trauma: body’s healing process is overwhelming, body’s healing process is underwhelming, body has a balanced healing process. Most unwell people tend to be the elderly, highly febrile, tachypnoea, tachycardia, shock, abdominal distension, tender/guarding/rebound, Grey-Turner’s (haemorrhagic), Cullen’s (bruising around umbilicus as blood tracks down falciform ligament), ascites, epicgastric mass, tetany (transient hypocalcaemia), ARDS
• Tests/investigations: assessment, full history + examination, urine, bloods (FBC, U&Es, LFTs, lipase, LDH, calcium, CRP), ABGs.
• Raised amylase: caused by many different disorders, so must fit with a history of pancreatitis.
• Other tests: CXR (to rule out acute abdomen – free air under diaphragm), ECG, AXR (gallstones, calcified pancreas, sentinal loop), USS (rules out gallstones), CT
• Other imaging modalities: EUS, ERCP, MRCP
• Prognostic indicators Ranson’s/Glasgow Criterior, APACHE
• Treatment: resuscitate, confirm diagnosis, admit, IV access, catheter, NGM/NGT, analgesia, DVT prophylaxis, central line, manage alcohol related problems, antibiotics, PPI, address feeding problems, treat the cause, treat complications, be prepared for problems (medical, surgical, social)
• Complications: local, general, early, late
• Local: necrosis, abscess, haemorrhage, pseudocyst/other fluid collections, exocrine/endocrine dysfunction, pancreatic fistulae, pseudoneuerysm, pancreatic ascites, chronic pain
• General: MODS, ARDS, renal failure, coma, liver failure, coagulopathy
1. Describe the principles of energy balance
2. Describe methods of assessment of energy stores + risks
3. Understand mechanisms of obesity
4. Describe complications of obesity
5. Understand the basics of obesity management

Energy Balance

- Maintaining weight reflects an energy balance between energy intake + expenditure
- Obesity reflects a positive energy balance, caused by an increased intake. However obesity leads to an increased total energy expenditure.
- Energy intake consists of protein, fat and carbohydrate
- Most of our energy expenditure = resting energy expenditure (i.e. BMR) but physical activity + thermogenesis also important
- Any increase in energy intake tends to be stored as fat (initially tipping the energy balance). However a new balance is then set at a higher value (reason that an obese individual will require more calories to maintain weight)
  - E.g. a 70kg weight = 56kg fat-free mass with 14kg fat mass. A 80kg weight will have 60kg of fat-free mass, with 20kg fat mass – the energy balance is then re-set to maintain this
- The ideal intake of energy is ½ complex carbs, followed by fat + protein. However the typical western diet has a higher fat intake.
- Energy expenditure – majority is resting energy expenditure, coming from maintaining temperature, ion concentration AND storing protein + carb (storage of protein + carb requires energy!)

Assessment of energy stores + risks

- Definition of obesity is in terms of weight/height² = BMI
  - 25-30kg/m² = overweight
  - >30kg/m² = obese
- However regional adiposity/energy partitioning is a better assessment for disease risk, morbidity + mortality
- NB: there is an increasing trend in obesity in both the UK + US
- Obesity can be considered a metabolic syndrome consisting of a constellation of risk factors which happen to cosegregate:
  - Waist circumference (men>102, women>88) – if omental fat > peripheral fat, there is a greater associated risk for CVD (especially CHD)
  - T2DM (it’s more than obesity → increased risk) – associated with microalbumin + insulin resistance
  - Hypertension (bp>135/80mmHg)
  - HDL count (men<1.0, women<1.3)
  - Fasting glucose (>6.0mmol)

Mechanisms of obesity

- Obesity can be seen as a multifactorial disease, with influences from genes, environment + society
- Causes to consider include energy intake/energy usage, genetics, brain/endocrinology, behaviour/culture
- Energy intake vs. energy usage
The intake of energy in the general population has been relatively constant, however there has been a change in dietary patterns of energy consumption (increased fat, decreased carbohydrate) – this has an important effect on energy storage + satiety (carbs make you feel full). Diet composition is important to weight gain as fat is the main storage fuel + autoregulation following fat is important. There is also an associated with increased fat/decreased carb → reduced satiety (although control of satiety has complex endocrinology). It is difficult to measure quantity of energy expenditure, but technological advances has led to a big reduction in overall energy expenditure – it is proven that maintaining a high physical activity reduces risk of obesity in both men + women.

- **Genes**
  - Most obesity is not monogenic, but the amount and site of weight gain is part genetic (shown by study of weight gain in twins).
  - The study of T2DM has led to the identification of a common variant in the FTO gene which is correlated to a 3kg weight increase in the 16% population who has homozygous genes may also influence preference for type of food, i.e. whether you choose junk or fruit.

- **Brain + endocrinology**
  - White adipose tissue makes a hormone called leptin, which signals to the hypothalamus that the body has sufficient energy stores + satiety.
  - Rare leptin deficiency → obesity as no satiety drive.
  - However most obese individuals have an increased leptin, due to increased white adipose tissue.
  - Leptin is actually more important in underweight individuals – signals need for food by choreographing additional body responses to reduced fat, e.g. stopping menstruation + reduced antibody count.
  - NB: insulin also has a role in satiety control.
  - Other hormones include grehlin (from stomach) + PYY (from intestine) which are important in the control of satiety + hunger respectively.
  - Leptin, grehlin + PYY are important targets for treatment of obesity, but are less important when considering the cause.

- **Behaviour + culture**
  - Individual behaviour + societal changes have contributed to obesity, e.g. driving to work instead of working.
  - Cost of healthy food also influences, therefore link between obesity + socio-economic class suggested.

Complications of obesity

- Obesity increases morbidity + mortality risks in both men + women.
- There are also economic + psychological costs associated with obesity.
- Obesity also has an associated increased risk for many diseases, including cardiovascular, GI disease, chest disease, endocrine, gynaecological + obstetric.
- With an increased BMI, there is increased mortality with reduced life expectancy in both men + women, e.g. BMI of 35 as opposed to 30 → reduction of life expectancy of 1 ¼ years.

Obesity management

- First, we need to establish the reason for obesity management – this should not be a personal opinion, but rather following EBM on associated morbidity + mortality.
- Firstly lifestyle, diet + exercise should be considered – pharmacological interventions + surgery should be a later resort.
• Benefits of moderate weight loss include psychological benefits, improvement of polycystic ovarian syndrome, oesophagitis, CHD, angina, osteoarthritis, liver function, pregnancy + diabetes
  o There is also an associated reduction in mortality, blood pressure, risk of T2DM, LDL count + increase in HDL count
• Diets – the atkins diet is associated with the greatest weight loss over 12 months. However EBM shows that diets are suited to individuals
  o However all support physical activity in conjunction with diet
• Problem with obese patients is that the difference between ideal + actual outcome of weight loss leads to a psychological barrier – making conventional weight management (including diet + activity changes) fail over the long term
  o For long term treatment, pharmacological intervention as supplementation of lifestyle changes more successful – however there is only one current licensed drug = orlistat; a GI lipase inhibitor which reduces fat absorption (other drugs have been taken off market due to adverse effects)
• surgery has now become a viable option for obese patients; including gastric bypass + gastric banding
  o gastric bypass prevents calories coming into contact with the duodenum, which reduces calorie absorption
  o gastric banding reduces the size of the stomach, promoting earlier satiety
  o surgery may become a more common treatment in the future
Liver failure

Summary of Functions of the Liver

- Excretion of
  - Bilirubin
  - Cholesterol
  - Hormones
  - Drugs
- Enzyme Activation
- Storage of
  - Glycogen
    - Regulation of glucose concentration
  - Vitamins
- Synthesis of
  - Plasma proteins such as albumin and clotting factors
  - Bile
- Detoxification
- Immune Regulations
  - Kupffer cells release antigens from the gut and remove immune complexes from the blood

NB: the wide variety of the functions of the liver are facilitated by the rich dual blood supply the liver receives (systemic + hepatic portal vein), and due to the close proximity of the highly permeable sinusoidal capillaries and functioning hepatocytes.

Liver Failure

- Definition = insufficient hepatocyte function to maintain normal homeostasis
- Liver Failure can be characterised by
  - Rate of Onset – the rate of decline of function determines the way in which the syndrome manifests + the likely outcome
  - Cause
  - Clinical Features – the main clinical features are a consequence of the accumulation of toxins resulting from the loss of the detoxifying function of the liver

Pathophysiology

- Histologically, the liver can be divided into polyhedrons of hepatocytes called lobules. Sinusoidal capillaries drain the hepatocytes into the middle central vein (branch of hepatic vein), and there are peripheral portal triads (branch of the hepatic artery, portal vein + bile duct)
- Liver failure can thus be seen as centrilobular necrosis of hepatocytes – it has no constant hepatic pathology but rather it is a functional syndrome
- May be associated with:
  - Mononuclear cell infiltrate – e.g. monocytes + macrophages, which affect the portal tract and lobules
  - Fatty change – seen depending on the aetiology
  - Activation of macrophages
  - Release of cytokines such as TNF. IL-1 and IL-6 (proinflammatory)

Aetiology

- The cause of the liver failure dictates the rate of onset, clinical presentation and eventual outcome
- Acute liver failure - This develops within 6 months in a previously normal liver and is further divided into three groups according to the rate of onset, the interval between the onset of jaundice and encephalopathy; hyperacute, acute and subacute
- **Chronic liver failure** - failure may develop due to the gradual progression of a pre-existing underlying liver disease or may be precipitated by an additional new insult in a patient with a previously compensated liver disease

**Amanita phalloides (Death Cap)**
- They taste pleasant
- They have a fatal dose of 30g
- Risk is not decreased by cooking
- It has delayed presentation
  - Liver and kidney failure
- No antidote

**Clinical features + possible complications**
- General ill-health and fatigue
- Jaundice
- Hyperdynamic circulation
- Fever and sepsis
- Muscle wasting
- Skin and endocrine changes

- **Hepatic encephalopathy (acute)**
  - This occurs with both acute and chronic liver failures
  - Reversible neuropsychiatric state due to the brain being exposed to increased levels of ammonia and other neurotransmitters.
  - Impairs cognition + consciousness
  - Caused by hepatocellular dysfunction + hepatocellular dysfunction
  - Has 4 grades: 1= confused, 2=drowsy, 3=sleeping but rouseable, 4= coma, unrouseable

- **Cerebral oedema (acute)**
  - Disruption of blood brain barrier and increased osmosis into brain.
  - Caused by increased carotid artery pressure (> intracerebral pressure → increased ICP)
  - Cause of death in 30-50% of acute liver failure
  - May cause death by brain stem herniation or cerebral hypoxia
  - Clinical features include systolic hypertension, increased muscle tone, myoclonus, decerbrate posturing, dysnconjugate eye movements, loss of pupillary reflexes, respiratory arrest

- **Ascites** (chronic)
  - This is another common feature of chronic liver failure
  - Extracellular fluid within the peritoneal cavity
    - Due to perceived reduced circulation plasma volume → sodium retention, postural hypertension + hypoalbuminaemia
  - Complications include spontaneous bacterial peritonitis, renal failure + encephalopathy

- **Coagulopathy (acute)**
  - Failure causes synthesis of coagulation inhibitors + proteins involved in fibrinolytic complex → increase fibrinolysis (breakdown of clot)
  - Platelet count falls and platelets dysfunctional
  - Bleeding of mucous membranes, GIT and brain

- **Metabolic Effects (Acute)**
  - Decrease in glucose (hypoglycaemia) due to high insulin and decreased liver uptake and gluconeogenesis.
  - Decrease in potassium due to increased urinary loss
  - Decrease in sodium
  - Metabolic acidosis
LSS Alimentary System

Alexandra Burke-Smith

- **Infection (acute)**
  - Common in both acute + chronic liver failure
  - Poor host defences due to kupffer cells + polymorphonuclear dysfunction
  - Increased access fr infection biproduct of endotracheal tubes, lines etc
  - Bacterial infection includings gram positive e.g. staph
  - Fungal infections common, but often unrecognized (pyrexia unresponsive to antibiotic)

- **Renal Failure**
  - **Acute Tubular Necrosis**
    - Caused by acute liver failure
  - **Hepatorenal Syndrome**
    - A feature of chronic liver failure and refers to a functional renal failure
    - Can be caused by
      - Renal vasoconstriction
      - Decreased renal release of prostaglandins
      - Sepsis
      - Bleeding and hypotension

- **Portal Hypertension(chronic)**
  - **The Portal Venous System**
    - It carries blood from the abdominal alimentary tract, including the spleen, gallbladder, pancreas and bowel, to the liver
    - The normal portal pressure is **7mmHg**
  - **Portal Hypertension or Block**
    - This is equivalent to liver nodule development
    - Collaterals develop
    - Portal-systemic shunting also occurs leading to
      - Encephalopathy
      - Septicaemia
      - Impaired liver regeneration
  - **Oesophageal Varices**
    - The lower oesophagus is supplied by the left gastric vein but could drain into the azygous system
    - The deviation of blood leads to **caricosities** in the **lower end of the oesophagus**
    - Bleeding will lead to **haematemesis** (vomiting of blood), **melena** (black, haemorrhagic faeces) or **encephalopathy**
    - This can be treated by the **Sengstaken Blakemore tube**

**Acute Liver failure**

Can be further subdivided into:

- **Hyperacute** refers to less than **7 days** between jaundice and encephalopathy
- **Acute** refers to an **interval of 1 to 4 weeks** between jaundice and encephalopathy
- **Subacute** refers to an **interval of 5 to 28 weeks** between jaundice and encephalopathy
- This usually has **specific aetiologies** providing the cause of the liver failure
  - Hyperacute = paracetamol, Hep A + B
  - Acute = Hep A, B +E, Idiosyncratic drug toxicity
  - Subacute = Non A non B hepatitis

**Underlying Physiology**
The principle clinical manifestations results from disturbances in the hepatic functions, relating to

- Coagulation
- Salt and water homeostasis
- Vasodilatation
- Removal of toxins
- Infection control
Nitrogen and glucose metabolism
Portal pressure
Bilirubin metabolism

Causes

- **Infection**
  - Viral hepatitis is the most important cause for acute liver failure worldwide
  - Hepatitis A and B cause hyperacute and acute liver failures
  - Hepatitis E can cause acute liver failure
  - NANB (Non-A, Non-B) Hepatitis can cause subacute liver failure
  - Herpes Simplex Virus
  - Epstein-Barr Virus
  - Varicella virus
  - *Amanita phalloides* is a death cap toadstool fungus

- **Drugs**
  - Paracetamol overdose is the most common cause and responsible for 70% of acute liver failure cases in the UK
  - Paracetamol causes hyperacute liver failure
  - Idiosyncratic drug toxicity would cause acute liver failure
  - Isoniazid
  - Ecstasy
  - Halothane

- **Metabolic**
  - Wilson’s Disease
  - Reye’s Syndrome

- **Cardiovascular**
  - Budd-Chiari Syndrome
  - Ischaemic heart disease

- **Miscellaneous**
  - Fatty liver of pregnancy
  - Lymphoma
  - Idiopathic

Clinical features

- Hepatic encephalopathy
- Cerebral oedema
- Coagulopathy
- Metabolic
- Infection

Rare causes

- **Budd-Chiari Syndrome**
  - Obstruction of hepatic veins at any site from lobule to right atrium
  - Presents with abdominal pain, hepatomegaly, ascites
  - Histology shows sinusoidal distention
  - Causes include thrombophilia, veno-occlusive disease

- **Wilson’s Disease**
  - Autosomal recessive disease → Copper accumulation in the liver, basal ganglia + cornea
  - Caused by failure of copper excretion in bile
  - Can present with acute or chronic liver disease
Treatment is simple = penicillamine = copper chelator

Symptoms include CNS effects, renal bone + haemolytic effects + Kayser Fleischer rings surrounding cornea (usually accompanying neuro problems, but may be absent in acute presentation)

- **Acute fatty liver of pregnancy**
  - Inherited defects of fatty acid oxidation
  - Incidence 1:1000 UK
  - Presents in 3rd trimester with RUQ pain, vomiting unrelated to morning sickness
  - Later leads to jaundice, encephalopathy, ascites, bleeding
  - Treatment – urgent delivery with supportive care

**Chronic Liver Failure**

**Causes**

It develops in a patient with existing advanced liver disease thus the causes reflect the common causes of cirrhosis of the society:

- Alcoholic Liver Disease
- Chronic Viral Hepatitis B and C
- Autoimmune and Cholestatic Liver Disease
- Primary Biliary Cirrhosis
- Primary Sclerosing Cholangitis
- Metabolic Liver Diseases
  - Haemochromatosis – inherited blood disorder that causes the blood to retain excessive amounts of iron
  - Non-alcoholic fatty liver disease

**Clinical features**

- Portal hypertension and its associated complications
- Oesophageal varices
  - May cause hematemesis (vomiting blood), melaena (blood in stool) + encephalopathy
  - Treated with senstaken-Blakemore tube
- Ascites

**Treatment of Liver Failure**

- **Treatment**
  - **Treatment of the Underlying Liver Condition**
    - Remove toxic drug etc
  - **Supportive Care**
    - Prevention or control of infection
    - Prevention or control of bleeding
    - Nutrition
    - Early renal support
    - Recognition or management of raised intracranial pressure
  - **Liver Transplantation**
    - Occurs in acute liver failure with grade 3 or 4 encephalopathy
    - Occurs in chronic liver failure with a Child-Pugh grade of B or C (point system used based on bilirubin + albumin levels, as well as presence of ascites + encephalopathy)
    - 12 month survival rate is 60% of those with acute liver failure and 90% for those with chronic liver failure
    - Success depends on the primary disease causing the liver failure – most commonly virus related or alcoholic
  - **Artificial (Biological or Non-Biological) Liver Support**
    - Artificial liver support is an attractive option, especially due to
- The scarcity of organs
- Delays in transplantation
- The potential for full recovery, especially for livers damaged due to paracetamol overdose
  - It could be a bridge to either transplant or recovery
- The system must
  - Replace necessary synthetic, eliminatory and metabolic functions
  - Counter adverse effects of necrotic liver
- **Biological Approach**
  - Involves live hepatocytes from human or animals
  - The cell lines are immortal
- **Non-Biological Approach**
  - Blood purification by adsorption and dialysis techniques
  - The MARS system is an example
- **Auxiliary Liver Transplant**
  - The donor liver is placed alongside the native liver
Regulation of function: enteric nervous system + gut hormones

1. Describe the major features of the enteric nervous system.
2. Explain how the autonomic nervous system and the enteric nervous system interact.
3. Describe how gut hormones control GI function

Introduction - Regulatory signal systems

- Nervous stimulation – NT released from neurones innervating target cells
- Paracrine – hormones released by cells in the vicinity of the target cell + reach target cell by diffusion
- Endocrine – hormones released into the blood where they reach their targets via the circulation
- The GIT is regulated by the nervous system (intrinsic + extrinsic), as well as paracrine + endocrine factors

Intrinsic control: The Enteric NS

- GIT wall: concentration of neurones 2nd to only the NCS. Rich plexus of ganglia connected by unmyelinated nerve fibres
- Function: integration of motor + secretory activities (control independent of CNS). Regulates:
  - Motility
  - Blood flow
  - Water + electrolyte transport
  - Secretion
  - Absorption
- Consequence of enteric dysfunction: inflammation (ulcerative colitis, Crohn’s disease), post-operative injury, IBS, ageing (constipation)
- Types of neurones: sensory (respond to variety of stimuli), motor (innervate smooth muscle, secretory cells or blood vessels), interneurons (integrate effector output + sensory input)

Nerve Plexuses

- **Myenteric (Auerbach’s) plexus** – continuous throughout the GIT between the circular + longitudinal smooth muscle layers. Controls the activity of the muscularis externa → control of gut motor function:
  - Peristalsis during feeding
  - Migrating motor complex during fasting
- **Submucosal (Meissner’s) plexus** – continuous between the duodenum and large intestine; in the submucosa beneath the muscularis mucosa. Senses environment within the lumen, and thus controls:
  - Gut secretions
  - Gut epithelial + endocrine cell function
  - Blood flow
- **Minor plexi** – including the deep muscular plexus (within circular smooth muscle) + the ganglia supplying the biliary system + pancreas
- NB: there is inter-communication between the myenteric + submucosal plexuses.

Motility in the GIT

- Migrating motor complex – occur independently of the CNS, but require autonomic input
  - MMC is a sequence of movements within the small intestine – function of which is to sweep the GIT clean between meals
- Peristalsis – the directional movement of food through the GIT during digestion, involving the circular and longitudinal smooth muscles; achieved by the myenteric plexus
Extrinsic control: The Autonomic NS

The sympathetic branch
- Thoraco-columnar outflow
- Cell bodies of post-ganglionic neurones in pre/para-vertebral ganglia
- Splanchnic nerves carry the postganglionic fibres to the viscera. Most do not directly innervate structures within the GIT, but terminate on neurones in the intramural plexuses.
  - However they do directly innervate the blood vessels of the GIT (coeliac, SMA + IMA) – act as vasoconstrictor fibres which allow the blood supply of the GIT to act as a reservoir which needed (e.g. during exercise, pumped to skeletal + cardiac muscle)
- NT = noradrenaline

The parasympathetic branch
- Cranio-sacral outflow
- Cell bodies of post-ganglionic neurones close to target organs – the preganglionic neurones synapse on ganglia close to gut wall/directly with enteric plexi
- NT = acetylcholine
- Usually reaches GIT via vagus nerve; after the transverse colon, innervated by pelvic splanchnic nerves
- Excitation usually stimulates motor + secretory activity of GIT (rest + digest)

Afferent pathways
- Local + higher feedback loops present
- Sensory input = chemo/mechanoreceptors in the wall of the GIT
- Local afferents directly feeds back to the intrinsic/enteric NS
- Splanchnic + vagal afferents feed back to the CNS – these include the feelings of pain, nausea + satiety

Paracrine + Endocrine control: the Gut Hormones
- Produced by endocrine cells in the mucosa/submucosa of stomach, intestine + pancreas
- Act on secretory cells in wall of GIT, pancreas + liver to alter rate of production/concentration of their secretions
- Some hormones may act on smooth muscle, e.g. GI sphincters + gall bladder
- Paracrine e.g. = Histamine release from the stomach wall is key to HCl secretion from the gastric parietal cells, and somatostatin from the stomach can inhibit this secretion.

Functions of the GI endocrine system
- Regulation of mechanical processes of digestion
- Regulation of chemical + enzymatic processes
- Control of post-absorptive processes e.g. assimilation of digested food + CNS feedback regulating intake
- Effects on GIT growth + development
Gastrin
- **Synthesised** in gastric antrum + upper small intestine
- Release **stimulated by** amino acid peptides in the stomach, gastric digestion + vagal input
- Release **stimulates** gastric acid secretion
- Release **inhibited by** stomach pH<3

Somatostatin
- **Synthesised** in the endocrine delta cells of the gastric/duodenal mucosa, pancreas (+hypothalamus)
- Release **stimulated by** ingestion of a mixed meal
- Release **inhibits** gastric secretion, motility, intestinal + pancreatic secretions, release of gut hormones, intestinal nutrient/electrolyte transport + growth/proliferation
- I.e. acts as endocrine cyanide. Analoges e.g. octreotide used to treat neuroendocrine tumours

Secretin
- **Synthesised** by S cells of upper duodenum + jejunum
- Release **stimulated by** pH<4.5 in duodenum
- Release **stimulates** pancreatic HCO₃⁻ secretion (potentiated effect via CCK),
  - High concentrations **inhibit** gastric acid + gastric emptying

Cholecystokinin (CCK)
- **Synthesised** by most cells densely located in the small intestine
- Release **stimulated by** fat + peptides in the upper small intestine (independent of vagal input)
- Release **stimulates** pancreatic enzyme release, delayed gastric emptying, gallbladder contraction + satiety

Gastric Inhibitory Peptide (GIP)
- **Synthesised** by mucosal K cells in duodenum + jejunum
- Release **stimulated by** ingestion of a mixed meal, especially fat
- Release **stimulates** insulin secretion
- GIP receptor agonists reduce postprandial insulin release

Peptide YY (PYY)
- **Synthesised** by L cells throughout ileum, colon + rectum
- Release **stimulated** post prandium (after eating)
- Release **inhibits** motility, gallbladder contraction, pancreatic exocrine secretion, intestinal fluid/electrolyte secretion, further food intake
- PYY experimentally reduces a person’s calorie intake
Liver functions
Alimentary System 12 – Dr Kevin Murphy (k.murphy@imperial.ac.uk)

Outline of lecture: the liver, glucose metabolism, protein metabolism, fat metabolism, bile production, other functions

Overview of the liver
• Large, multifactorial organ
• Function carefully regulated to meet body requirements
• Summary of main functions:
  o Digestion
  o Biosynthesis
  o Energy metabolism
  o Degradation + detoxification
  o NB: all functions are carried out by hepatocytes EXCEPT the breakdown + recycling of RBC, which is carried out by Kupffer cells (fixed macrophages) in the endothelial lining of the capillary sinusoids
• The biliary system includes drainage from ductules into the R + L hepatic duct, into the common hepatic duct, which joins with the cystic duct to form the common bile duct
• Hepatic blood flow - ~25% resting cardiac output
  o Dual blood supply
  o 20% arterial blood from R+ L hepatic artery
  o 80% venous blood draining from gut through hepatic portal vein (absorbs many nutrients, except lipids which are mainly absorbed into the lymph as chylomicrons)

Glucose metabolism
• It is important to control blood glucose. After a meal, the levels increase and must be taken up into tissues (stored mainly as glycogen in muscle + liver)
• Between meals, liver glycogen breakdown (glycogenolysis) maintains blood glucose concentration. However a 24hr fast will deplete the glycogen store (only 80g). Blood glucose must then be increased by another pathway:

Glucconeogenesis
• The process of synthesising glucose from non-carbohydrate sources
• Cori cycle – glucose is broken down anaerobically in muscles into lactate. This lactate can then be used by the liver to synthesis glucose (via a pyruvate intermediate, requires 6ATP + LDH)
• Glucose can also be synthesis from amino acids via deamination, or from triglycerides:
  o Alanine → pyruvate → glucose
  o Triglycerides → glycerol → glucose

Protein metabolism

The liver synthesises 90% of plasma proteins (imp. Binding/carrier functions required in maintaining plasma volume), blood clotting factors + dietary non-essential amino acids (via transamination)

Transamination
• The synthesis of dietary non-essential amino acids from an alpha-keto acid precursor
• Involves the exchange of an amino group (NH₂) one acid with a ketone group (=O) on another acid
• E.g. pyruvic acid (keto-acid) + glutamic acid (amino acid) → alanine (amino acid) + α-ketoglutaric acid
Glutamic acid is a common intermediate
- Essential amino acids (lys, leu, ile, met, thr, val + phe) do not have an appropriate keto acid precursor

Deamination
- The conversion of an amino acid into the corresponding keto acid by the removal of the amine group as ammonia + replacing it with a ketone group
- Occurs primarily on glutamic acid, as glutamic acid is the end product of many transamination reactions
- E.g. Glutamic acid + NAD$^+$ + H$_2$O $\rightarrow$ NADH + H$^+$ + NH$_3$ + α-ketoglutaric acid
- NADH can then be used to generate ATP
- Ammonia is toxic, therefore need to be careful with the levels within the body following deamination $\rightarrow$ synthesis of UREA
  - The liver converts NH$_3$ to urea involving CO$_2$ (urea = NH$_2$C(O)NH$_2$)
  - Urea is very water soluble, metabolically inert + non-toxic
  - Urea is then excreted in the urine

Fat metabolism
- Fat is the main energy store in the body (stored in adipose + liver tissue)
- When glycogen stores are full, the liver can convert excess glucose + amino acids to fat for storage
- The fats can then be metabolised as an energy source converting fatty acids to acetyl-CoA
  - Acetyl-CoA can then be used to produce energy in various forms, entering the TCA cycle

Lipoproteins
- Synthesis of lipoproteins required for lipid transport in aqueous environment; contain triglycerides + cholesterol core, with a phospholipid + protein coat (stabilising the lipid)
- There are various types of lipoproteins depending on their composition:
  - VLDL = lots of triglycerides
  - (IDL = intermediate density lipoprotein)
  - LDL = high cholesterol + phospholipids (bad cholesterol)
  - HDL = high protein coat
- Lipoproteins decrease in density HDL > LDL > IDL > VLDL – the lower density = larger diameter
- Good vs. Bad cholesterol
  - Cholesteryl ester transfer protein (CETP) shuttles cholesterol from HDL to LDLs – since a high HDL/LDL ratio is important in prevention of atherosclerosis, inhibition of CETP is of interest to drug companies
  - However most promising drug = torcetrapib – had to stop manufacture due to large number of adverse effects.

Cholesterol + Phospholipid synthesis
- Phospholipid – compound containing fatty acid, phosphoric acid + nitrogen containing base
- Cholesterol – sterol nucleus synthesised from acetyl CoA (+dietary intake)
  - Used in the synthesis of various compounds including steroid hormones + bile salts
- Both have important role in cell/organelle membrane structure

Bile production
- Bile is continued formed + secreted by the liver (unregulated), then stored + concentrated in the gall bladder (holds ~15-60ml)
- Secretion of bile in the liver occurs through narrow canaliculi between adjoining hepatocytes into the biliary system
  - All other transactions (i.e. other secretion/absorption) occurs via the capillary sinusoids
The major components of bile: 50% dry weight = bile salts, cholesterol, lethicin (phospholipid), pigments (bilirubin + biliverdin), bicarbonate ions + water

Separately, some components would be insoluble, but together, bile is a stable solution

**Bile acids/salts**
- Primary bile acids are made from the oxidation of cholesterol into cholic + chenodeoxycholic acids
  - Carboxyl + hydroxyl groups then added so water soluble
- They are then conjugated with taurine or glycine → taurcholic + glycocholic acids
  - This increases the water solubility further
- NB: secondary bile acids are de-conjugated + de-hydroxylated primary bile salts – involves GI bacteria
- **Bile salt molecule:** planar steroid nucleus; 2 phases (amphipathic)
  - Hydrophobic face (nucleus + methyl groups) – dissolves in fat
  - Hydrophilic face (hydroxyl + carboxyl groups) – dissolves in water

**Bile functions**
- Digestion/absorption of fats
- Excretion of variety of substances via GIT
- Neutralisation of acid chime from stomach

**Bile release**
- Released into the ampulla of Vater (2nd part of duodenum) during digestion
- Small amounts are released during cephalic + gastric phases due to vagal nerve + gastrin influence
- However the majority of bile release occurs during the intestinal phase, under the influence of CCK which causes contraction of the gallbladder + relaxation of the sphincter of Oddi

**Digestion of lipids**
Lipids are poorly soluble in water, which makes them more complicated to digest. Digestion in the small intestine is a 4 stage process:

1) **Secretion of bile (from liver/gallbladder) + lipases (from pancreas)**
2) **Emulsification**
   - Bile salts facilitate the emulsification of a fat into a suspension of lipid droplets, increasing the surface area for digestion
3) **Enzymatic hydrolysis of ester linkages**
   - Pancreatic lipase then splits the triglycerides into 2 fatty acids and a monoglyceride at a fat/water interface
   - Lipases complexes with colipase preventing the bile salts from displacing the lipase from the fat droplet
4) **Solubilisation of lipolytic products in bile salt micelles**
   - Bile salts form micelles with the released fatty acids + glycerol
   - Each micelle has a diameter ~5nm, and contains ~30 molecules
   - Hydrophilic “head” of bile salt in contact with surrounding solvent, sequestering the hydrophobic tail regions with the monoglycerides in the micelle core

**Absorption of lipids**
- Micelles present the fatty acids and monoglycerides to the brush border (small enough to diffuse between microvilli).
- The whole micelle is not absorbed together... bile salts are absorbed in the ileum, but lipid absorption is usually complete by the middle of the jejunum.
- Bile salts are transported back to the liver for recycling (enterohepatic circulation)

**Lipid metabolism**
- Monoglycerides + free fatty acids absorbed by enterocytes are resynthesized into triglycerides by 2 different pathways:
Monoglyceride acylation (major)

Phosphatidic acid pathway (minor)

- The triglycerides are then combined with proteins, cholesterol, phospholipids + trace carbohydrate forming chylomicrons
- Chylomicrons are transported to the Golgi and secreted across the basement membrane by exocytosis to enter lacteals (lymph channels – too large to enter blood capillaries)

**Enterohpatic circulation**

- Active reabsorption bile salts in terminal ileum. In addition, de-conjugation and de-hydroxylation by bacteria make bile salt lipid soluble. Lose <5% (15-35% per day) through excretion
- Recirculate via HPV back to liver. Hepatocytes avidly extract bile salts, clearing all from the HPV
- Bile salts are re-conjugated and some re-hydroxylated before reuse.
- Bile salt pool secreted twice per meal.

**Bile detox + excretory functions**

- Liver breaks down/inactivates steroid and peptide hormones. Secreted into bile for excretion
- Also performs similar role with variety of “foreign” compounds - usually drugs
- Excretory route for excess cholesterol - lecithin (phospholipid) allows more cholesterol in micelles (stabilises the high cholesterol content).
  - Too much cholesterol may lead to gall stones
- Also involved in the excretion of bile pigments e.g. bilirubin (product of haem of old RBC breakdown in spleen)
  - Porphyrin group from haem reduced to bilirubin in spleen
  - Conjugated to glucoronic acid in liver – excreted in bile
  - Liver disease may lead to bile pigment gall stones

**Other functions**

**“Larder” functions = storage**

- Storage of fat soluble vitamins (A,D,E,K)
  - Stores are sufficient for 6-12 months except Vit K where store is small
  - This poses a problem as Vit K essential blood clotting
- Storage of iron as ferritin.
  - Available for erythropoeisis
- Storage Vit B₁₂
  - Insufficient Vit B₁₂ - pernicious (megaloblastic) anaemia, nerve demyelination
- Glycogen and fat store

**Protection**

- Resident macrophages in liver sinusoids (Kupffer cells) destroy pathogens that may be absorbed from the lumen of the gut into the enterohpatic circulation
- This prevents the pathogens (especially common with bacterial infections) from entering the rest of the body

**Ca²⁺ metabolism**

- UV light converts cholesterol to a Vit D precursor
- The precursor then requires a double hydroxylation to convert it into the active form of Vitamin D
- The first hydroxylation occurs in the liver (the second is in the kidneys)
The oesophagus + stomach
Alimentary System 13 – Dr Chris John (c.john@imperial.ac.uk)

Basic plan of the Gut wall

- The gut wall can be divided into 4 layers:
  - **Mucosa** – consists of epithelium, lamina propria, loose connective tissue + muscularis mucosae
  - **Submucosa** – consists of connective tissue + nerve plexuses
  - **Muscularis** – consists of smooth muscle + nerve plexuses
  - **Serous/adventitia** – consists of connective tissue (+/- more epithelium)

Oesophagus

- Conduit from getting food from the mouth to the stomach; important in control of swallowing
- Food comes in through the mouth, the tongue forces food posteriorly to the pharynx (soft palette raised to close nasal cavity) into the pharynx. This is under neural control
- Where the pharynx becomes the oesophagus is C5, then ends T10 (piercing the diaphragm)
- The oesophagus passes very close to the recurrent laryngeal nerves + the pericardium. These may be damaged in excessive oesophagus extension.
- Design specifically for function; the lining needs to be designed for “wear and tear” existence = stratified squamous epithelium
  - Non-keratinising – therefore moist
  - Lubricated by mucus secreting gland
  - Many layers act as protective layer if surface layer damaged
  - 2 sphincters – most of the pressure within the oesophagus is <atm (which means food wants to backtrack up) so these prevent this
- The swallowing centre within the medulla opens the upper oesophageal sphincter under parasympathetic control via vagus
- There is a fair amount of skeletal muscle in the upper oesophagus, but this decreases as it descends – this leaves an element of voluntary control within the upper half
- When food has entered and the upper oesophageal sphincter is closed, the bolus of food is moved down the oesophagus by peristalsis (purely under muscular control, gravity has no effect)
  - Circular muscle is major driver of the movement. The muscle just superior to the bolus contract, whereas the one in front/inferior relaxes → rhythmic contraction down the oesophagus
- If food gets stuck half way down, the swallowing centre can start a wave of 2nd peristalsis
- Cycle takes ~9seconds to move food ~30cm long

Gastro-oesophageal junction

- At the Z-line, stratified squamous lining of the oesophagus gives way to the simple columnar epithelium of the stomach
- Lower sphincter resides here – the sphincter isn’t really one as such; there are 3 contributing mechanisms which lead to the sphincter action
  - The pressure difference between the abdominal oesophagus + stomach
  - Contraction of the diaphragm
  - As the stomach expands, it compresses the Z-line
- Heartburn – the acidic content being ejected into the oesophagus – this is because the mechanism of the lower sphincter is not foolproof
In pregnancy, the stomach is forced upwards, and the lower oesophagus is forced back into the thorax → loss of pressure difference + contractile element of diaphragm

- When the stomach is empty, there are gastric folds = rugae. As the stomach distends, there is not great change in pressure but the rugae expand. This is important in preventing reflux

**Stomach**

- **Function** = break down bolus of food, hold food and release it at a controlled rate into the duodenum + kill parasites/certain bacteria
- **Structure** – several regions: cardia, fundus, body, antrum + pyloris
- The sphincters of the stomach remain closed post-eating for about 4 hours before it is released into the duodenum. During this period the bolus is churned steadily
- **Secretions:**
  - Cardia + pyloric – mucus only
  - Body + fundus – mucus, acid, pepsinogen
  - Antrum – gastrin
- The slightly different secretory functions of the different regions of the stomach – the epithelium may be slightly different
- All regions have mucus producing cells – mucin “mops up” excess acid
- HCl produced by parietal cells. Endocrine cells produce gastrin
- **Acid production** – 2L/day, 150mM [H+]
  - Epithelial surface pH=6-7 (neutralised by bicarbonate ions trapped in mucus)
  - Lumen pH 1-2
- **Chief cell** - Pepsinogen producing cell
  - Well designed for protein synthesis – large amounts of RER, golgi + secretion granules
  - Pepsinogen passes through gastric pit into stomach
- **Parietal cells** – acid producing cell
  - Seen in the resting state, many mitochondria (requires vast ATP to conc H ions by 3mil X than blood – very active process)
    - ATP used predominantly by H/K ATPase within cytoplasmic tubulovesicles
    - Important structure = internal canaliculi – internal reservoirs
  - Active state – tubular vesicles fuse with canaliculi, which also fuse to form large open reservoir extending to the apical surface; H+ then diffuses out through the stomach lumen
    - On basolateral membrane, there is a Na/K pump which pumps K into cell; this passively diffuses into lumen
    - H+ ions generated by carbonic anhydrase (and bicarbonate ions) from the readily available CO2 + H2O
    - The H+ ions are actively secreted into the reservoir in exchange for K
    - All of the bicarbonate ions are exchanged out of the cell for Cl entry, which also diffuses into the reservoir
    - The H+ and Cl- ions then bond to form HCl
LSS Alimentary System

Alexandra Burke-Smith

Protein concentrations – HIGH H/K ATPase + carbonic anhydrase
  - H/K ATPase in huge conc within gastric glands
  - Carbonic anhydrase in high conc

• Pepsinogen – interacts with HCL to form pepsin, via autocatalytic process
  - The pepsinogen on its own has conformation with internal active site which is protected
  - Acidic environment of the stomach exposes the active site
  - Pepsin itself then further catalyses its own production once the active site is exposed (positive feedback)
  - Pepsin is a protease

• Gastrin – endocrine product of the stomach (predominant one)
  - Produced predominantly in the pyloric antrum
  - One of its major action is to stimulate histamine release from the chromafin cells within the lamina propria
  - Together, these then increase acid production in the stomach
  - There is a sort of negative feedback system, as the stomach gets more acidic – gastrin secretion is inhibited
    - A protein rich meal acts against this, as proteins make very good buffers for acid

Gastric secretion

1) Cephalic phase – thought/sight/smell + taste of food – central effect
  - Central effect mediated by the efferent vagus nerve, which leads to production of Ach
  - Ach can directly act on parietal cells to increase acid, or indirectly activate chromaffin cell to increase histamine
  - Prepares for arrival of food

2) Gastric phase
  - When food enters stomach, distension activates stretch receptors
  - Contents activate chemoreceptors – local enteric response
  - Ach + gastrin release (more profound than cephalic)

3) Intestinal phase
  - Largely inhibitory effect on secretion of acid
  - As food leaves the stomach and enters the small intestine – pH must be increased, thus acid secretion should be reduced
  - E.g. PYY
  - Even within the SI, if the food entering is still very protein rich, acid secretion may be increased – this is because protein acts as a very good buffer for acid
The large intestine
Alimentary System 14 – Dr Kevin Murphy (k.murphy@imperial.ac.uk)

Outline of lecture: anatomy + function, mucosal structure, muscles + motility, regulation, flora

Anatomy and function

- The large intestine consists of the cecum, appendix, colon, rectum + anal canal
- The cecum is a blind pouch just distal to the ileo-cecal valve
- The appendix is a thin, finger-like extension of the cecum

Colon

- Principle functions: reabsorption of electrolytes/water + elimination of undigested food/waste
- Dimensions: 1.5m long, 6cm diameter
- Ascending colon – on the right side of the abdomen, runs from cecum to hepatic flexure
- Transverse colon – hangs off the stomach (attached by mesocolon), running from hepatic flexure to splenic flexure
- Descending colon – on the left side of the abdomen, runs from splenic flexure to sigmoid colon
- Sigmoid colon – s shaped colon running from descending colon to rectum
- Structural features:
  - Appendices epiploicae – fatty tags of the peritoneum surrounding colon
  - Taenia coli – 3 longitudinal bands running along length of colon
  - Haustra – pouchings of the colon wall
  - Solitary nodules – nodules of lymphoid tissue in the wall of the colon
- Reabsorption:
  - More electrolyte/water reabsorption occurs in the proximal colon, with Na+ and Cl- ions being absorbed by exchange mechanisms + ion channels
  - Water then follows by osmosis
  - K+ moves passively into the lumen
  - The large intestine can reabsorb up to 4.5litres of water, above this diarrhoea occurs

Rectum

- The dilated distal portion of the alimentary canal
- Histology is similar to the colon, but is distinguished by transverse rectal folds in is submucosa + the absence of taenia coli in its muscularis externa
- The terminal portion of the rectum is the anal canal. This is surrounded by the internal (circular muscle = involuntary) + external (striated muscle = voluntary) anal sphincters

Mucosal structure

- Like the small intestine, the large intestine has abundant enterocytes, goblet cells + crypts (with associated stem cells)
- At the gross level, mucosa appears smooth (no villi). The enterocytes have short, irregular microvilli and are primarily concerned with the reabsorption of salts (with water following → more solid gut contents)
Goblet cells
- There are a higher number of goblet cells in the LI than the SI – they are more prevalent in the crypts than along the surface, with the numbers increasing distally toward the rectum
- The mucus facilitates the passage of the increasingly solid colonic contents, and covers bacteria + particulate matter
- Acetylcholine (from parasympathetic + enteric NS) stimulates goblet cell secretion

Paneth cells
- Found only in the bases of the crypts of the SMALL INTESTINE (NONE IN LARGE INTESTINE)
- Contain large, acidophilic granules containing:
  - antibacterial enzyme lysozyme (protects stem cells),
  - glycoproteins, and zinc (essential trace metal for a no.of enzymes).
- Also engulf some bacteria and protozoa.
- May have a role in regulating intestinal flora.

Microvilli
- Microvilli (~0.5-1.5µm high) make up the “brush border”.
- There are several thousand microvilli per cell
- The surface of the microvilli are covered with glycocalyx
- **Glycocalyx**
  - rich carbohydrate layer on apical membrane
  - offers protection from the digestional lumen, yet allows for absorption.
  - traps a layer of water & mucous known as the “unstirred layer” which regulates rate of absorption from intestinal lumen
- glycocalyx DOES NOT CONTAIN DIGESTIVE ENZYMES like it does in the small intestine

Muscles and motility

**Muscle layers**
- Like the small intestine, muscularis externa consists of an inner circular + outer longitudinal layer
  - The circular muscles are segmentally thickened
  - Longitudinal layers are concentrated in 3 bands – the taenia coli
    - Between the taenia, the longitudinal layer is thin
- Bundles of muscle from the taeniae coli penetrate the circular layer at irregular intervals, forming segments called haustra – these can contract individually
- Apart from the rectum + anal canal, muscle layers of the large intestine are more substantial + continuous
  - The movement of the large intestine is also more complicated than the small intestine

**Motility**
- Colonic contracts like a kneading process - it is minimally propulsive, with a max propulsion ~5-10cm/hr
- Motility promotes absorption of electrolytes + water
- In the proximal colon, “antipropulsive” patterns dominate to retain chime
- In the transverse + descending colon, localised segmental contractions of haustra cause back and forth movements, with short propulsive movements every 30 mins
  - These increase in frequency following a meal

**Mass movement**
- 1-3 times daily, there is a mass movement which resembles a peristaltic wave – this can propel contents 1/3 – ⅘ of the length of the large intestine in a few seconds
- Food that contains fibre promotes this rapid transport
**Regulation**

- **Parasympathetic innervation**
  - Vagus nerve innervates the ascending and most of transverse colon
  - Pelvic nerves innervate more distally
- **Sympathetic innervation**
  - Thoracolumbar outflow
- **External anal sphincter** controlled by somatic motor fibres in the pudendal nerves
- **Afferent sensory neurons** detect pressure
- **Enteric NS** important in Hirschspring’s disease, where there are no enteric intramural ganglia
- **Endocrine/paracrine control**
  - E.g. aldosterone promotes sodium + water absorption
  - This is via the synthesis of Na⁺ ion channels + Na/K pumps

**Defecation**

- The rectum is filled with faeces by mass movement in the sigmoid colon – here food is stored until convenient to void
- The defecation reflex is controlled primarily by sacral spinal cord – includes both reflex + voluntary actions
- The filling of the rectum → reflex response to distension of the walls
- Pressure receptors send signals via myenteric plexus to initiate peristaltic waves in the descending, sigmoid colon + rectum
- The internal anal sphincter is inhibited
- The external anal sphincter is under voluntary control
- The urge can be resisted, and the feeling subsides
- **Rectum**
  - The last few cm of the rectum = “social part” – this can distinguish between solid, liquid + gas
  - This is important in knowing what can be passed appropriately in what circumstances
- **Faeces**
  - 150g/day in an adult; 2/3 water
  - Solids include cellulose, bacteria, cell debris, bile pigments + salts (K+)
  - Bacterial fermentation gives odour

**Flora**

- All mammals have symbiotic relationships with their gut microbial community = microbiome
- The stomach and small intestine have few bacteria, but the large intestine contains many which are essential to its function (~1.5kg of live bacteria present in healthy adult)
- Intestinal flora is a diverse, highly metabolically active community of bacteria

**Roles**

- Synthesize + excrete vitamins
- Prevent colonization by pathogens by competing for attachment sites or for essential nutrients
- Antagonize other bacteria through the production of substances which inhibit/kill non-indigenous species
- Stimulate the production of cross-reactive antibodies, which prevent infection or invasion
- Stimulate the development of certain tissues, including cecum + lymphatic tissues

**Types**

- **Bacteroides** – most prevalent, gram negative, anaerobic, non-sporeforming bacteria
  - Implicated in the initiation of colitis + colon cancer
- **Bifidobacteria** – gram positive, non-sporeforming, lactic acid bacteria
  - Often described as “friendly”; thought to prevent colonization by potential pathogens
1. To recognise the clinical presentation of malabsorption
2. To understand the disease mechanisms leading to malabsorption
3. To learn about the clinical importance, presentation, complications and treatment of coeliac disease

**Diarrhoea**

- The normal frequency of bowel movements ranges from 3x/day → 3x/week
- Normal weight of bowel movement <200g/day
- Bristol stool form scale: 1 (constipation) → 7 (liquid diarrhoea)
- When to investigate diarrhoea? Chronic diarrhoea; many possible causes e.g. osmotic, secretory, inflammatory

**Malabsorption**

- Leads to malnutrition
- Key presenting features: diarrhoea/steatorrhoea, growth failure, weight loss
- Steatorrhoea: pale, poorly formed stools (offensive smell, difficult to flush, oil rings + faecal leakage)
  - Normal weight + frequency, but abnormal fat content >6g/day

**Assessment**

- The malnutrition universal screening tool consists of 3 steps:
  1) BMI
  2) Weight loss
  3) Acute disease effect score
  4) Overall risk
- Examination of muscle wasting, loss of fat, oedema + ascites
- Things to look for: anaemia, skin lesions, hair loss, poor wound healing, purpura (petechiae >3mm diameter)
- Anthropometry: measurements of the body e.g. height, weight, BMI, arm circumference

**Nutrient requirements**

- Macronutrients (FACE)
  - Fats
  - Amino acids/proteins
  - Carbohydrates
  - Electrolytes + water
- Micronutrients (MTV)
  - Minerals
  - Trace elements
  - Vitamins

**Tests for malabsorbed nutrients**

- Fats – steatorrhoea
- Proteins + nitrogen – urinary excretion + albumin
- Minerals – plasma iron, calcium, magnesium, zinc etc
- Vitamins – B₁₂ (cobalamin), D (calciferol), folate, Vitamin K, carotene
- Tubeless tests are rarely used, detail not needed
- Faeces Pancreatic Elastase 1 (FPE1) – value <200mg/g stool indicates exocrine pancreatic insufficiency
• Wireless capsule enteroscopy – 2 frames/sec, disposable, 8hr battery

Causes

• **Mal digestion**: consequence of - reduced gastric tissue/secretion, reduced pancreatic tissue, impaired bile secretion, reduced intestinal brush border enzymes

• **Malabsorption**: consequence of – loss of enterocyte function, pre + post-mucosal effects, single gene disorders

• **Common causes**:
  o Coeliac disease: gluten sensitive enteropathy
  o Small bowel bacterial overgrowth e.g. strictures (abnormal narrowing), diverticulae (outpuchings), impaired perstalsis, fistula (abnormal connection between two cavities, e.g. Crohn’s)
  o Pancreatic insufficiency e.g. chronic pancreatitis, CF

• **Less common causes**:
  o Short bowel syndrome – due to chronic infections, lymphoma, radiation, enteritis, intestinal lymphangiectasia, drugs, allergy, immunodeficiency
  o Disorders associated with non-functional transporters (often present in childhood)
  o Nutrient associated conditions
    ▪ Lactose – lactase non-persistence
    ▪ Vitamin B12 – pernicious anaemia
    ▪ Bile salts – bile salt diarrhoea
  o NB: short bowel syndrome usually presents post-op for Crohn’s, trauma or infarction
    ▪ A loss of <200cm of small intestine leads to failure, with associated well loss. This requires nutritional support.

Coeliac disease

• “inflammatory disease of the upper intestine resulting from gluten ingestion in genetically susceptible individuals”

• Histologically presents as subtotal villus atrophy

• Variety of presentations: typical, atypical + asymptomatic

• Frequent features (>30%) – malaise, fatigue, steatorrhoea, diarrhoea, weight loss, anaemia, decreased folate + decreased iron

• Common features (~25%) – anorexia, abdominal pain, PMH/FH, decreased B12 albumin + Vit D, osteopenia

• Occasional features (<25%) – muscle/bone pain, rashes, oedema, lymphoma, further micronutrient imbalance

• Changing epidemiology: was once a disease of childhood; now 85% of diagnoses made in adults

• Changing presentation: there a many non-specific symptoms. This may be due to a possible decline in severity of symptoms, or change in diet

• Diagnosis: autoantibodies (high specificity + sensitivity), IgA count, tissue transglutaminase count + endomysial antibodies

• The coeliac iceberg:
  o Complications: lymphoma
  o Clinically active: nutritional deficiencies
  o Subclinical: dermatitis herpetioforms, villous atrophy, subtle histology
  o Potential: latent disease

• Screening: prevalence ~1% in general population, but this prevalence is increased in T1DM, thyroid disease, anaemic blood donors, IBS + osteoporosis

Gluten sensitive enteropathy

• GLUTEN – binding element found in wheat (A-gliadin), barley (hordein) + rye (secalin)
These elements are polypeptides rich in P + Q

- Normally tTG crosslinks proteins to prevent proteolysis and this often occurs at the active site of tTG. However in coeliac tTG crosslinks glutamine residues from gliadin (this is your Q) on a site other than the active site. This results in a permanently covalently bonded molecule (this is E). Your immune system doesn’t like this E therefore antibodies form against it i.e. anti-tTG antibodies. This then eventually results in coeliac disease

- SENSITIVE – immunological reaction (see above) is due to genetic predisposition (70% concordance in monozygotic twins)
  - Genes involved: HLA-DQ2 (present in 95% of Coeliacs, 20% of controls)
  - Other genes contribute

- ENTEROPATHY – inflammation, apoptosis, subtotal villous atrophy, hyperplastic crypts
  - Leads to nutrient malabsorption

Principles of treatment
- Gluten-free diet
- Maintain adequate nutrition
- Prevent complications, including:
  - Nutrient malabsorption + impaired nutritional status
  - Small bowel malignancy (T-cell lymphoma, adenocarcinoma)
  - Osteoporosis/osteopenia
Importance of lecture: Liver disease rising, and 5th biggest killer in the UK (Overtaken respiratory diseases, cardiovascular diseases etc.)

The biochemistry of alcohol

- **Ethanol** – practically insoluble in fats + oils
  - The concentration in a tissue is dependent on the relative water content + reaches equilibrium quickly with the concentration of ethanol in the plasma
  - Ubiquitous organic compound – essentially carbon dioxide + water
  - Not bound to plasma proteins, dissolves in the water content of the body

- **Metabolism** – enzymes present in the body (because alcohol exists in the body regardless of intake):
  - ADH (alcohol dehydrogenase)
  - Catalase
  - CYP2E1 (cytochrome P450 enzyme 2E1)

- Metabolism in 2 steps: ethanol converted to acetaldehyde by alcohol dehydrogenase. Acetaldehyde converted to carbon dioxide + water by aldehyde dehydrogenase.
- Genetic polymorphism exists in the enzymes that catalyse the breakdown of alcohol, e.g. Asians have the inability to metabolise alcohol quickly due to ineffectiveness of ALDH (causes nausea, vomiting, headaches)
- However much alcohol is put into the system, the body continues to metabolise it, despite the metabolic limits of the enzymes in this direct pathway. Two alternative pathways to the first step: CYP2E1/catalase

- CYP2E1: inducible. The more alcohol put in, the more CYP2E1 produced. This explains the presence of tolerance to alcohol, which disappears when you stop drinking (lag phase)
- CYP2E1 problem: the bi-product of this pathway is reactive oxygen species (toxic free radicals), trivalent oxygen molecules with spare electrons, which may trigger processes such as inflammation. This may explain why heavy alcohol usage leads to inflammation

The psychology of alcoholism

- There is a difference between alcohol liver disease (ALD), alcohol addiction (alcoholism) + alcohol misuse (problem drinking) – however there is an overlap between these 3 things
- There is in fact a genetic component to drinking
- Management is different:
  - ALD - hepatologists, Gastroenterologists + A/E
  - Addiction – psychiatrists, drugs/alcohol workers
  - Misuse – police, social workers, judiciary + prison service
- **Definition of addiction**: continued use of a substance that will probably lead to harmful consequences to the user in the form of impaired psychological or social functioning, tissue damage or mental illness in the particular person” (WHO memorandum)
- **Alcohol misuse**: failure to carry out major obligations at work, home, or school because of repeated alcohol use. Repeated use of alcohol even when it is physically dangerous to do so. Repeated experience of legal problems. Continued use of alcohol despite knowing that it has caused or worsened social or other situations.

- **Alcohol dependence**: evidence of tolerance and/or withdrawal. Amount or duration of use often greater than intended. Repeated failure to control or reduce alcohol use. Abandoning important activities. Continued use of alcohol despite knowing the consequences.

- **Nature vs. nurture**: MZ/DZ twin studies show concordance rates with alcohol-related problems are much higher in MZ twins. Scandinavian adoption studies showed that babies taken away from alcoholic mothers had a greater chance of having alcohol-related problems. Genetic input has a greater influence than environmental input.

**Alcohol + the liver**

- **LT effects of alcohol**: myocardial + pancreatic injury, fatty liver, hypoxic liver damage, carcinogenesis, ongoing cell damage, enhanced toxicity.
- Important to remember: it is not only the ethanol, but the metabolites, which can lead to hepatocyte cell death.
- **Progression of ALD**: normal liver...70% develop steatosis (fatty liver) & steatohepatitis (fatty with inflammation). Under the microscope, fat droplets are deposited. Occurs in up to 60% of heavy drinkers, and reversible if alcohol reduced. Steatohepatitis leads to raised LFTs.
- Fatty liver = foie gras!
- Steatosis & steatohepatitis leads to fibrosis.
- Hepatic fibrosis: hepatocytes lie in plates, blood vessels run in sinusoids, in between the capillaries + hepatocytes is the space of Disse containing hepatic stellate cells. Chronic inflammation leads to transformation of hepatic stellate cells into fibroblasts, which begin to lay down collagen fibres which condense into fibrous bands.
- Cirrhosis (10%) irreversible scarring of liver with fibrous bands + regenerative nodules. Eventually develops. Macroscopically, as collagen fibres contract, the liver looks shrunken and knobbly.
- Liver disease does not normally present until very late e.g. haematemesis, ascites.

**Alcohol + the rest of the body**

- **GI tract**
  - Increased inflammation + risk of cancer in oesophagus + stomach
- **Chronic pancreatitis** → chronic pain (often leads to high dose opiate addiction), diabetes + weight loss
- **Cardiovascular system** – alcohol cardiomyopathy (heart hypertrophies, but becomes baggy)
  - Also increases blood pressure → increases risk of haemorrhagic + ischaemic stroke
- **Brain function** – over time, the effect on the neurological system = long term problems
  - E.g. Wernicke’s encephalopathy etc.
- **Immunity** – leads to immunosuppression + increased autoimmunity
- **Cancer** – increases incidence of diff cancers, and is associated with breast + colon cancer – this is due to immunosuppression
- **Foetal alcohol syndrome** – significant effect on unborn child, some effects seen at birth, but also some seen later in life e.g. social functioning, success in school etc.

**Alcohol + society**

- Incidence of cirrhosis decreased during prohibition in the 1930s, and during alcohol taxes in UK in 1960s.
- Incidence of cirrhosis increased during termination of alcohol rationing in Sweden in 1955, and after economic prosperity in Germany in the 1970s.
• Alcohol has never been cheaper in the UK.
• 5% of UK population consumes 50% of the countries alcohol.
• Hidden effects: social, financial, friends, self-esteem, family, productivity.
• Medical costs: 20-60% of all hospital admission, £3 billion a year treating alcohol-related sickness. Car crashes linked to drink driving cost £300 million. 863,257 patients sought treatment for alcohol-related harm. 560,000 people admitted to hospital with conditions caused directly by their drinking, most commonly cirrhosis or overdose.
• Problem continues: drinking-related attendances to A&E have topped 1 million
• Paddington Alcohol Test: most you will drink in any one day? How often you drink more than 8 units? Do you feel your current attendance at A&E is alcohol related?
• Symptoms of acute alcohol withdrawal: moderate (hyperthermia, tachycardia/tachypnoea, hypertension, nausea + vomiting, tremor + sweating, anxiety + agitation) + severe (disorientation, hallucinations, convulsions)

Drinking & You
• You’re OK as long as you steer clear of spirits...fiction
• What is a unit: 8g of ethanol. % solution is g/100ml. Know how to calculate it!!! (Dr Brown Youtube video)
• How much does it cost?
• Never drink on an empty stomach: fact. IV alcohol raises blood alcohol concentration by a huge amount in comparison to oral alcohol. This is the first pass metabolism of ethanol, as if you drink at a rate which your liver can metabolise, you wont get drunk, but your blood alcohol concentration will rise.
• Fatty foods stop the stomach from emptying, therefore slowing alcohol metabolism, slowing alcohol absorption.
• The alcohol in the liver is what causes disease. This depends on the amount you drink, not how quickly you drink it.
• Clinical features of acute alcohol poisoning: ataxia, anaesthesia, dysarthria, nystagmus, drowsiness + coma, vomit inhalation, hypoglycaemia.
• Effects of alcohol on male reproductive system: alcohol is a direct testicular toxin, causing atrophy of seminiferous tubules.
• Women cannot handle alcohol as much as men. Why? Possibly because of under-reporting and the social change. Women also weigh less than men, and a greater % of fat, meaning that the volume + distribution of women is possibly 60% of a man’s.
• Hangover: headache, nausea + vertigo, retching + vomiting.
• Hangover cure: fluids, glucose, sleep.
Diarrhoea in Children
Alimentary System 17 – Dr Jethro Herberg (j.herberg@imperial.ac.uk)

Importance

- 1 billion people worldwide lack access to clean water
- 2.5 billion do without adequate sanitation
- Sanitation: “collection, treatment + disposal/reuse of human excreta, domestic wastewater + solid waste, as well as associated hygiene”
- Diarrhoeal disease result in an estimated 2.5 million deaths p.a. in children <5yrs
- Accounts for 21% of all deaths in children, and 17% of all malnutrition-related deaths

Diarrhoea

- Definition: an increase in stool frequency with change to loose/watery stool
- In breast-fed infants, this definition is adapted to encompass any departure from normal stool pattern with increased volume + frequency
- Classification of diarrhoea:
  - Acute (<2 weeks) – may be result of infection, and the major complication = dehydration
  - Chronic (>2 weeks) – large differential diagnosis, and the major complication = growth failure

Types

- **Secretory**: active secretion, or inhibited absorption, without structural damage.
  - Cholera & some E.coli toxins: switches on chloride pump
- **Osmotic**: water drawn to gut lumen passively
  - Malabsorption (e.g. pancreatic disease)
  - Osmotic laxatives
- **Inflammatory**: damaged mucosa cannot absorb
  - Infections
  - Inflammatory diseases eg Crohn’s
- **Hypermotility**
  - eg toddler diarrhoea, hyperthyroidism

Assessment

Firstly, assess whether diarrhoea is persistent, acute or dysentery. For acute diarrhoea, dehydration needs to be assessed asap, whether severe moderate or not dehydrated.

**History:**

- Still eating/feeding?
- Still passing urine? If not – SEVERE dehydration
- Poo – blood? Mucus? Freq?
- Food eaten - new? Off?
- Travel – changes spectrum of dd
- Swimming
- Pets
- Immunodeficiency

**Examination**

- ABC
- Any other focus for infection?
- Degree of dehydration
Clinical features
- Dark, sunken eyes (no tears)
- Low turgor (when skin pinched remains raised)
- Delayed capillary refill time
- Dry mucous membranes
- Decreased conscious level
- Sunken fontanelle (gap between skull in babies/infants)

Clinical assessment of dehydration

<table>
<thead>
<tr>
<th></th>
<th>Moderate: 5-10%</th>
<th>Severe: &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Drowsy</td>
<td>Limp, sweaty, cold, cyanotic</td>
</tr>
<tr>
<td>Pulse</td>
<td>Tachycardic</td>
<td>Rapid, weak</td>
</tr>
<tr>
<td>BP</td>
<td>May be normal</td>
<td>Low</td>
</tr>
<tr>
<td>Urine output</td>
<td>Reduced</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Rehydration
- ORT – oral rehydration therapy: 1 litre of water, 8 teaspoons sugar + 1 teaspoon salt
- Salt + sugar are required because of the sodium-glucose cotransporter in the small intestine
- For severe dehydration, saline infusion may be required
- The predominant cause of the dehydration is hypernatraemia (elevated plasma sodium as a result of fluid loss) – this must be corrected through rehydration
  - However, rapid rehydration may also result in cellular swelling, therefore this needs to be avoided too

Viral causes of diarrhoea
- Rotavirus
- Caliciviruses - Noroviruses + Sapporo virus
- Adenovirus
- Enteroviruses

Rotavirus
- Every child infected before age 5
- Faecal-oral spread
- Enterocyte destruction: osmotic diarrhoea
- Rehydration is key
- Followed by temporary lactase insufficiency
- Vaccines in roll-out

Bacterial + Protozoal causes of diarrhoea

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Protozoa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Sigellae spp</td>
<td>Giardia</td>
</tr>
<tr>
<td>Enteroinvasive E. coli</td>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td></td>
</tr>
</tbody>
</table>
Salmonella
Campylobacter
yersinia

Acute diarrhoea

Top causes
- In rich countries: rotavirus, salmonella, campylobacter
- In poor countries: rotavirus, shigella, E. coli

Investigations
- Always look for viruses
- Fever: look for salmonella, Shigella, campylobacter
- Blood: look for enteroinvasive types eg E.coli O157
- Persistent, or after travel: look for parasites (Giardia, cryptosporidium, schistosomiasis)
- Recent hospital stay: rotavirus, norovirus, C. difficile

Management of acute diarrhoea
- Nutrition (breastmilk, vitamin A, zinc)
- Rehydration
- NOT anti-diarrhoea drugs
- NOT antimicrobials

NB: there has been a decline in mortality rates for acute diarrhoeal disease, this is due to:
- Use of ORS
- Promotion of breast-feeding
- Improved supplemental feeding/nutrition
- Female education
- Measles immunisation, and future vaccines
- The infrastructure of this decline is the improvement in water, hygiene + sanitation!

Chronic diarrhoea

Causes
- Infections, and post infection syndromes
- Carbohydrate intolerance
- Food sensitivities
  - permanent (eg Coeliac Disease)
  - temporary ( eg Cow’s milk protein intolerance)
- Motility disorders (including toddlers’ diarrhoea)
- Inflammatory bowel disease
- Pancreatic disease (eg. Cystic fibrosis)
- Intestinal lymphangiectasia

Consequences
- Malnutrition
- Susceptibility to infection
- Poor growth, delayed puberty
- Anaemia, ricketts
- Cognitive impairment

NB: chronic diarrhoea is associated with a higher mortality than respiratory + other infections