Guide for use of these notes

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

The companion text I have predominantly used to compile these notes is "The Digestive System" by Margaret E. Smith in the system of the body series. The recommended text is Vander's but due to its smaller size and consistent clinical cases its quite a useful little book to have next to you when writing notes.

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

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

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

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

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

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

Good luck with first year

And listen when Kevin Murphy says somatostatin

Stuart Taylor
Learning Objectives

- List the names of the organs of the alimentary tract
- Describe symptoms and signs of alimentary tract disease
- List the main diseases of the GI tract and liver
- Be aware of the economic burden of GI and liver diseases

Describe symptoms and signs of alimentary tract disease

**Symptoms**

- **General**
  - Anorexia
  - Weight loss
  - Anaemia- due to poor iron absorption

- **Upper GI tract**
  - Haematemesis and Melaena- black tarry stool associated with GI bleed and thus haemoglobin oxidation.
  - Nausea and vomiting
  - Dysphagia - difficulty swallowing and Odynophobia- pain on swallowing
  - Heartburn, acid regurgitation and belching.
  - Chest pain
  - Epigastric pain

- **Liver and biliary**
  - RUQ pain
  - Bilary Colic- no relief no matter how they lie due to irritation of the viscera.
  - Jaundice/ icterus (of eyes)
  - Dark urine/ pale stool
  - Abdominal distensions

- **Mid GI Tract and Pancreas**
  - Abdo pain
  - Diarrhoea/ steatorrhoea
  - Distension

- **Lower GI Tract**
  - Abdominal Pain
  - Bleeding
  - Constipation
  - Diarrhoea
  - Incontinence

**Epidemiology**

- **Worldwide**
  - Malnutrition
  - Enteric infections
  - Viral hepatitis and consequences
  - Gastric cancer

- **UK**
  - Dyspepsia
  - Liver disease due to alcohol and obesity
  - Colon cancer

- **Main causes of chronic liver disease in UK**
  - 4-6% of population have abnormal LFTs
    - Chronic hepatitis B (0.5-1%)
    - Chronic hepatitis C (0.4-1%)
    - Alcohol related steato-hepatitis(?)
    - Obesity related steato-hepatitis (?)

- **Hepatitis B**
  - 350 million chronically infected with 1 million deaths per year.
  - 90% is self-limiting infection (immune system is able to clear up)
  - 10% is persistent infection
    - Of this 30% have cirrhosis + HCC
    - 70% asymptomatic carriage
  - 1% fulminant infection

- **Hepatitis C**
  - Has 80% persistent infection with then 20% having a progressive disease.
  - Asymptomatic -> Cirrhosis -> Cancer
  - Apparently spread iatrogenically by doctors.

Be aware of the economic burden of GI and liver diseases

- 12% of all deaths in UK are due to digestive diseases.
- 1 in 8 admissions to hospital.
- 1 in 4 main operations within general hospitals.
- Liver deaths are increasing in England and Wales.

- Mortality and lost years
  - Absence from work

List the main diseases of the GI tract and liver

- **Dyspepsia**
  - Indigestion characterised by chronic/ recurrent pain in the upper abdomen
  - Common reason for primary and secondary care consultations
  - NHS costs
  - Quality of life
  - Risk of complications

- **Gastro Oesophageal Reflux Disease**
  - Ulceration caused by low pH of stomach contents entering the oesophagus.
  - Increased risk of adenocarcinoma

- **Helicobacter pylori** - Gram negative spirilli bacteria that colonises the gastric mucosa whose infection persists for life unless treated.
  - Found within 50% of the world population, geographic distribution is closely linked to socio-economic development.
  - **Chronic gastritis** is related to helicobacter pylori with 85% having no long term effects, 14% have peptic ulceration and 1% have gastric adenocarcinoma or lymphoma.

- **Duodenal ulcer**
  - Peptic ulceration affects up to 10% of population and is estimated to causes 16,500 deaths per year in USA due to them bleeding.

- **Liver cancer**
  - This is mostly metastatic from other cancers in the body.
  - Primary liver cell cancer (Hepatocellular and cholangio carcinomas) has 2,000 cases per annum.
  - Primary liver cancer (HCC) is higher in cirrhosis.
  - Can be detected at an early stage by ultrasound scanning.
  - 50% 5 year survival.
  - Cholangiocarcinoma increases 20 fold in last 20 years but unfortunately there is no treatment.

- **Pancreatic cancer**
  - 95% adenocarcinoma of pancreatic duct
  - Difficult to diagnose early
Liver deaths are increasing in England and Wales.

Mortality and lost years
Absence from work
Morbidity
- Out patient care
  - 6.9% GI diseases
  - £0.28 billion p.a
- GP visits
  - 3.85%
  - £0.24 billion
- Community health and social services
  - 3%
  - £0.32 billion

NHS prescription costs
- 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.

Total overall economic burden of GI disease is approximately £8 billion.

Inflammatory conditions

Pancreatic cancer
- 95% adenocarcinoma of pancreatic duct
- Difficult to diagnose early
- One of the poorest survival rates of 2% at 5 years.

Ulcerative colitis and Crohn’s disease
- Affects 150,000 people in the UK and 8,500 new cases are diagnosed every year.

Coeliac disease
- Common in the West, but virtually unknown elsewhere in the world.
- UK 1 in 1000
- Caused by gluten sensitivity which is particularly bad in Western Ireland (1 in 200/250)

Biliary disease and conditions

About 1 in 10 in Britain have gallstones, especially women, overweight people, and those who are middle aged or over.

Female, fat and forty!

Pancreatic Diseases

Acute Pancreatitis
- Mild to life threatening
- Blockage of pancreatic duct
- Back up of pancreatic enzymes causing severe inflammation
- Ethanol and gallstones in 80%

Chronic Pancreatitis
- Permanent damage to pancreas
- Alcohol excess main causes
- Can greatly impair quality of life.

Intestinal Diseases and Conditions

Water and foodborne infections can be due to viruses, bacteria and parasites.

Large bowels diseases and conditions

Irritable bowel syndrome is a very common condition in our society. It affects a third of our population at one time or another. About 1 in 10 have symptoms bad enough to go to doctor.

Anal disease and conditions

Faecal incontinence (soiling) may affect 1 in 20 people.
About half the population has haemorrhoids by age 50
Over half the over 70’s population of the UK have diverticula of the large intestine.

Diverticula - Small outpouchings of the colon
The main functions of the oesophagus
- Muscular contractions (peristalsis) moves food down the oesophagus.
- Muscles undergo transition from skeletal to smooth between pharynx and stomach.
- Longitudinal and circular layers of muscle really helices of various pitches.
- Lowest part of inferior constrictor (cricopharyngeus) is upper oesophageal sphincter.
- Muscle coats of oesophagus are continuous with the laryngopharynx.
- Lower oesophageal sphincter is formed from a combination of skeletal (diaphragm?) muscles.
- Functional gastro-oesophageal sphincter depends on skeletal muscle of the diaphragm.
- Foregut derivative receiving blood from all 3 branches of coeliac axis.
- Oesophagus enters at the cardio region on lesser curvature between fundus and body.
- Antrum tapers to pyloric sphincter.
- Suspended in mesenteries (lesser and greater omenta and gastrosplenic ligament).
- Cardia and pyloric regions which are associated with only mucus secretions.
- Body and fundus regions secrete mucus, HCl, pepsinogen.
- Oesophagus and stomach link to anatomy:
  - Cardia and pyloric regions which are associated with only mucus secretions.
  - Body and fundus regions secrete mucus, HCl, pepsinogen.
  - Oesophagus enters at the cardio region on lesser curvature between fundus and body.
  - Antrum tapers to pyloric sphincter.
  - Functional gastro-oesophageal sphincter depends on skeletal muscle of the diaphragm.
  - Foregut derivative receiving blood from all 3 branches of coeliac axis.
  - Parasympathetic nerves from vagus, sympathetic from recurrent laryngeal nerve or perforate the pericardium.
  - Due to its positioning any surgery that is carried out on it can potentially sever the recurrent laryngeal nerve or perforate the pericardium.
  - Upper oesophageal sphincter is formed by skeletal muscle
  - Lower oesophageal sphincter is formed from a combination of skeletal (diaphragm?) and smooth muscle.
  - Muscle coats of oesophagus are continuous with the laryngopharynx.
  - Lower part of inferior constrictor (cricopharyngeus) is upper oesophageal sphincter.
  - Longitudinal and circular layers of muscles really helices of various pitches.
  - Muscles undergo transition from skeletal to smooth between pharynx and stomach.
  - Muscular contractions (peristalsis) moves food down the oesophagus.

Link to anatomy:
- There are a number of regions of the stomach which include:
  - Cardia and pyloric regions which are associated with only mucus secretions.
  - Body and fundus regions secrete mucus, HCl, pepsinogen.
  - Oesophagus enters at the cardio region on lesser curvature between fundus and body.
  - Antrum tapers to pyloric sphincter.
  - Functional gastro-oesophageal sphincter depends on skeletal muscle of the diaphragm.
  - Foregut derivative receiving blood from all 3 branches of coeliac axis.
  - Parasympathetic nerves from vagus, sympathetic from T6-T8 via coeliac plexus.

Demarcate the functionally distinct regions of the gastric mucosa:
- Sketch and label a typical acid- and enzyme-secreting gastric gland
- Summarize the functions of acid and enzyme secreting cells

List the main functions of the stomach:
- Break food down into smaller particles (due to acid and pepsin).
- Hold food and release at a controlled steady rate into duodenum.
- Kill parasites and certain bacteria.

NB - Stomach is lined by simple columnar epithelium with very tight junctions which acts to restrict bacterial entry.
Define the structural basis for the gastro-oesophageal sphincter

- The Zigzag Line (Z line) is the junction between the stomach and oesophagus epithelium which is clear anatomically as the oesophagus are pink whereas the stomachs are more red in colour.

Using simple diagrams, explain the mechanism of secretion of pepsinogen by the chief cells

**Gastric Chief Cell**
- Protein-secreting epithelial cell
- Abundant RER
- Golgi packaging and modifying for export
- Mass of apical secretion granules
- Secretes pepsinogen

Using simple diagrams, explain the mechanism of secretion of HCl by the oxyntic cells

- Many mitochondria are needed to provide the large amount of ATP required for secretion.
- Cytoplasmic tubulovesicles contain H+/K+ ATPase
- Internal canaliculi extend to apical surface
- Whilst secreting the tubulovesicles fuse with membrane and microvilli project into canaliculi.
- A canaliculus is an adaptation found on gastric parietal cells. It is a deep infolding, or little channel, which serves to increase the surface area, e.g. for secretion. The membrane of parietal cells is dynamic; the numbers of canaliculi rise and fall according to secretory need. This is accomplished by the fusion of canicular precursors, or "tubulovesicles", with the membrane to increase surface area, and the reciprocal endocytosis of the canaliculi (reforming the tubulovesicles) to decrease.

Summarize the control of gastric secretion and outline the basis for the use of H2 inhibitors and proton pump inhibitors in pharmacological control of gastric acid secretion

- There are 3 phases of gastric secretion:
  3) Cephalic phase: thought, sight, smell and taste of food

- The Zigzag Line (Z line) is the junction between the stomach and oesophagus epithelium which is clear anatomically as the oesophagus are pink whereas the stomachs are more red in colour.
- Gastric folds (rugae) allows an increase in the size of the stomach when food enters but not an increased pressure (which would happen if it was purely stretching of stomach mucosa).

- The acid concentration of the stomach is about 1.5 times that in the blood.
- Mucins = gel coating
- HCO3 trapped in mucus gel
  - pH at:
    - Epithelial surface = 6-7
    - Lumen = 1-2

- Stomach – Parietal Cell

- Pepsinogen
- HCl
- Mucus
- Gastrin
- HCO3
- Mucus

- The wall of stomach is rich in blood and lymphatic vessels which get nutrient and oxygen supply.
- Acid produced by stomach is about 10000 times that in the blood.
Potassium enters via a sodium potassium exchanger and is pumped into the lumen so that it can then be exchanged for H+ via the H/K+ATPase. It then leaves the lumen and enters back into the cell as shown above.

CO₂ enters and is combined with water to form Hydrogen Carbonate and a hydrogen ion by the enzyme carbonic anhydrase.

Energy from ATP is used to pump hydrogen into the cannaliculi which then will enter the gastric lumen.

Hydrogen carbonate is then exchanged for chloride ions, HCO₃⁻ ends up in the blood and causes a phenomenon known as the alkalic tide.

Enterogastrones:

- Stimulated by thought of food, taste/smell, food in stomach.
- Neural (vagal parasympathetic) and endocrine (gastrin) inputs
- Final common pathway is intramucosal histamine release from ECL cells.
- Histamine acts on parietal cells through H₂ receptors.
- Inhibited by H₂ receptors (Ranitidine) or by proton pump inhibitors (Omeprazole)

**Explanation of control of gastric acid secretion**

- Stimulated by thought of food, taste/smell, food in stomach.
- Neural (vagal parasympathetic) and endocrine (gastrin) inputs
- Final common pathway is intramucosal histamine release from ECL cells.
- Histamine acts on parietal cells through H₂ receptors.
- Inhibited by H₂ receptors (Ranitidine) or by proton pump inhibitors (Omeprazole)

**Basic Plan of Gut Wall**

1. **Mucosa**: epithelium
2. **Submucosa**: connective tissue (containing nerve plexus)
3. **Muscularis**: smooth muscle (containing nerve plexus)
4. **Serosa/Adventitia**: connective tissue +/ epithelium

**Qu. 1:** Which of the following statements about the generalised structure of the gut wall is incorrect?

- Circular muscle is closer to the lumen
- Myenteric plexus lies between the longitudinal and the circular muscles

**Qu. 2:** Which of the following statements about the gastrointestinal tract is correct?

- The rate of fluid secretion is typically approximately 1 litre / day
  Most of the fluid is reabsorbed in the large intestine
- The rate of fluid secretion is typically approximately 1 litre / day
  Most of the fluid is reabsorbed in the large intestine
- Absorption of ions / glucose / amino acids from the gastrointestinal tract is dependent on an Na⁺/K⁺ATPase in the apical membrane
- Absorption of ions / glucose / amino acids from the gastrointestinal tract is dependent on an Na⁺/K⁺ATPase in the apical membrane
- The cephalic phase in the control of gastrointestinal function depends on the presence of chyme in the small intestine
- The cephalic phase in the control of gastrointestinal function depends on the presence of chyme in the small intestine

**Best Option:**

**Page 65 The Digestive System by Margaret E. Smith**

- Motility is reduced which means that the pyloric sphincter is closed, this is so that food remains in stomach so it can be digested.

2. **Gastric phase** food in stomach - stretch and chemo receptors

**Three Phases of Gastric Secretion**

1. **Gastric Phase**
   - Acid in the duodenum causes the release of Secretin and fat within the duodenum causes the release of Cholecystokinin (CCK) and Gastric Inhibitor peptide (GIP) into the blood.
   - All of these are responsible for decreasing gastric juice secretion.
   - Motility is inhibited by distension of the duodenum via a quick enterogastric reflex via the vagus nerve and via a slower humoral mechanism utilising enterogastrones such as secretin and CCK.

2. **Intestinal Phase**
   - The intestinal phase is largely inhibitory with gastric secretion and motility both being inhibited.
   - Acid in the duodenum causes the release of Secretin and fat within the duodenum causes the release of Cholecystokinin (CCK) and Gastric Inhibitor peptide (GIP) into the blood.
   - All of these are responsible for decreasing gastric juice secretion.
   - Motility is inhibited by distension of the duodenum via a quick enterogastric reflex via the vagus nerve and via a slower humoral mechanism utilising enterogastrones such as secretin and CCK.

**Best Option:**

- Absorption of ions / glucose / amino acids from the gastrointestinal tract is dependent on an Na⁺/K⁺ATPase in the apical membrane
- Absorption of ions / glucose / amino acids from the gastrointestinal tract is dependent on an Na⁺/K⁺ATPase in the apical membrane
- The cephalic phase in the control of gastrointestinal function depends on the presence of chyme in the small intestine
- The cephalic phase in the control of gastrointestinal function depends on the presence of chyme in the small intestine
Learning Objectives

List the main functions of the small intestine.

Distinguish between the duodenum, jejunum and ileum.

Describe the nature of villi and crypts.

Describe the source & process of enterocyte renewal in the small intestine.

Compare turnover time of intestinal epithelium with epithelia from other sites.

Describe the structure/function relationship of the digestive epithelium.

Describe the structure/function relationship of the circular muscles.

Compare turnover time of intestinal epithelium with epithelia from other sites.

Cholera

- Enterocytes and goblet cells of the small intestine have a short life span (36 hours).
- Enterocytes are the first line of defence against GI pathogens and may be directly affected by toxic substances in the diet.
- Effects of agents which interfere with cell function, metabolic rate etc which will be diminished.
- Any lesions will be short-lived.
- If escalator like transit of enterocytes is interrupted through impaired production of new cells (e.g. radiation) severe intestinal dysfunction will occur. Causes gut wall to fall apart.

Duodenum

- Distinguished by Brunner’s glands.
- Submucosal coiled tubular mucous glands secreting alkaline fluid.
- Open into the base of the crypts.
- Alkaline secretions neutralize acidic chyme and help optimise pH for action of pancreatic digestive enzymes.

Jejunum

- Characterised by the presence of numerous, large folds in the submucosa called plicae circulares (valves of Kerckring).
- NB these are also present in the duodenum and ileum but plicae in the jejunum tend to be taller, thinner and more frequent.

Ileum

- Shares some features with the large intestine.
- The ileum has a lot of Peyer’s patches - large clusters of lymph nodules in the submucosa.
- Prime immune response against intestinal bacteria.
- Well positioned to prevent sneaky bacteria from colon migrating up into small intestine.

Describe the structure/function relationship of the circular muscles.

Functions of small intestine motility

- a. To mix ingested food with digestive secretions and enzymes
- b. To facilitate contact between intestinal contents and the intestinal mucosa
- c. To propel intestinal contents along alimentary tract

Segmentation

- Mixes the contents of the lumen.
- Segmentation occurs by stationary contraction of circular muscles at intervals.
- More frequent contractions in duodenum compared to ileum and allows pancreatic enzymes and bile to mix with chyme.
- Although moves in both directions net effect is downwards.

List the main functions of the small intestine.

- To absorb nutrients, salt and water.

Distinguish between the duodenum, jejunum and ileum.

Structures and cell types

- Approximately 6m long and 3.5cm in diameter.
- Duodenum 25cm
- Jejunum 2.5m
- Ileum 3.75m

Describe the source & process of enterocyte renewal in the small intestine.

Explain how enterocytes are adapted for absorption.

Describe the nature of villi and crypts.

Digestive Epithelium

- External wall has longitudinal and circular muscles (important for motility).
- Internal mucosa arranged in circular folds.
- Mucosa covered in villi (1mm tall).
- Invaginations known as Crypts of Lieberkühn.

Describe the structure/function relationship of the digestive epithelium.

Cell types

- Mucosa lined with:
  - Primary enterocytes
    - Most abundant in small intestine.
    - Tall columnar with microvilli and a basal nucleus.
    - Specialised for absorption and transport.
    - Short lifespan of 1-6 days.
    - Tight junctions whose permeability changes as you move down the alimentary tract.
    - Picket fence model of proteins in cell membrane holds important proteins in place.

Chloride channels

- Cholera enterotoxin results in prolonged opening of the chloride channels in the small intestine allowing uncontrolled secretion of water.
- Bodily fluid moves freely into the lumen and hence out through the intestine, leading to rapid massive dehydration and death.
- Treatment is rehydration. Cholera bacteria will clear out and epithelium will be replaced.

 Describe the nature of villi and crypts.
**Digestion and Absorption of Carbohydrates, Proteins, and Lipids in the Small Intestine**

**Duodenum**
- In the small intestine digestion occurs in an alkaline environment.
- Digestive enzymes and bile enter the duodenum from the pancreatic duct and bile duct.
- Usually the enzymes are associated with the brush border.

**Motility**
- Cycles of smooth muscle contraction that mainly occurs in fasting.
- Each cycle = contraction of adjacent segments of small intestine.
- Begins in stomach, migrate through small intestine towards colon. On reaching terminal ileum, next contraction starts in the duodenum.
- Prevents migration of colonic bacteria into the ileum and may clean the ileum of residual food.
- Also occurs in fed state but is less ordered, more frequent and harder to distinguish from the other motile movements.

**Digestion and absorption of carbohydrates, proteins, and lipids in the small intestine.**

<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>

- Because a lot of food is water soluble which doesn’t pass well across membranes transporter proteins are needed.
- Secondary active transport: Coupling of sodium influx to export of other molecules.

**Carbohydrates**
- “50% of ingested calories in Western diet.
- Mucous is a large glycoprotein that facilitates passage of material through the bowel.
- Abundance of goblet cells along the entire length of the bowel increases.
- i.e. there are relatively few in the duodenum but very many in the colon.

**Peristalsis**
- Involves sequential contraction of adjacent rings of smooth muscle.
- Propels chyme towards the colon.
- Most waves of peristalsis travel about 10cm (not the full length of intestine)
- CNS is needed to be involved

**Bile salt molecule**
- Bile salt is amphipathic:
  - Hydrophilic hydroxyl and carboxyl face dissolves in water.
  - Hydrophobic nucleus and a methyl face dissolves in fat
- Steroid nucleus flat.
- Bile and lipases are secreted into the duodenum.
- The function of emulsification is to increase the surface area for digestion.

**Lipids**
- Bile salts facilitate the emulsification of fat into a suspension of lipid droplets (1 micrometre diameter)
- The function of emulsification is to increase the surface area for digestion.
- Allows pancreatic lipase to split triglycerides.

**Digestion of lipids**
- Bile and lipases are secreted into the duodenum.
- Bile salts facilitate the emulsification of fat into a suspension of lipid droplets (1 micrometre diameter)
- The function of emulsification is to increase the surface area for digestion.
- Allows pancreatic lipase to split triglycerides.
- Bile salt molecule:
  - Steroid nucleus planar - two faces amphipathic
  - Hydrophobic nucleus and a methyl face dissolves in fat
  - Hydrophilic hydroxyl and carboxyl face dissolves in water.
Secondary active transport: Coupling of sodium influx to export of other molecules.

**Carbohydrates**
- ~50% of ingested calories in Western diet.
- Digestion beings in the mouth by salivary alpha amylase but is destroyed in the stomach (acid pH).
- Most of the digestion of carbohydrates occurs in the small intestine.
- Possible evolutionary function to determine contains energy and therefore tastes "nice".
- Carbohydrates are either simple or complex. Simple contains monosaccharides and disaccharides. Complex contains sugars bound together to form a chain such as amylose and amylopectin.

**Digestion of carbohydrates**
- Secreted into duodenum in response to a meal.
- Continues digestion of starch and glycogen which is started by salivary amylase.
- Acts mainly in the lumen.
- Breaks down large carbohydrates.
- Disaccharides and oligosaccharides are broken down to monosaccharides by enzymes on the brush border such as maltase, lactase and sucrase.

**Absorption of carbohydrates**
- Absorption of glucose and galactose is by 2^o active transport (carrier protein and electrochemical gradient). Carrier protein = SGLT-1 on apical membrane.
- Absorption of fructose is by facilitated diffusion. Carrier protein = Glut-5 on apical membrane.
- Glut 2 facilitates exit at the basolateral membrane.
- The human small intestine can absorb 10kg of simple sugars per day.

**Absorption of lipids**
- Absorption of neutral lipids including triglycerides, cholesteryl esters and phospholipids.
- Absorption of chylomicrons.
- Micelles allow transport across the unstirred layer and present the fatty acids and monoglycercides to the brush border.

**Digestion of proteins**
- Protein digestion begins in the stomach by pepsin, but pepsin is inactivated by the duodenal alkaline duodenum.
- Trypsin is activated by enterokinase, an enzyme located on the duodenal brush border. Trypsin then activates other proteases by autocatalysis.
- Brush border peptidases break down the largest peptides prior to absorption.
- Amino acids are absorbed by facilitated diffusion and secondary active transport (similar to sugars).
- Di and tri peptides are absorbed using carrier proteins distinct from single amino acids.
- Cytoplasmic peptidases break down most of the di and tri peptides before they cross the basolateral membrane.

**Lipid metabolism**
- Monoglycerides and free fatty acids absorbed by enterocytes are resynthesized into triglycerides via 2 different pathways: 1. Monoglyceride acylation (major) 2. Phosphatidic acid pathway (minor).
- Fatty acids bind to the apical membrane.
- Fatty acid binding proteins (FABP) facilitate transfer of fatty acids from apical membrane to the smooth ER.
- In the smooth ER fatty acids esterified into diglycerides and triglycerides.
- Triglycerides are synthesised from CoA fatty acid and alpha glycerophosphate.
- These are lipoprotein particles synthesised in enterocytes as an emulsion.
- 80-90% triglycerides, 8-9% phospholipids, 2% cholesterol, 2% protein, trace carbohydrate.
- Chylomicrons are transported to the Golgi and secreted across the basement membrane by exocytosis.
- They are too big to enter blood capillaries of the villi so instead they enter the lacteals.

**Extra info**
- The ileum is separated from the colon by the ileocaecal sphincter.
- Relaxation and contraction controls the passage of material into the colon.
- Also prevents the back flow of bacteria into the ileum.
Learning Objectives

- List three mechanisms of infectious diarrhoea
- List the innate functions of the alimentary system which are part of our defence systems
- Define MALT and GALT
- Describe a Peyer’s patch
- Define the role of IgA in the GI tract
- Describe the importance of colonic flora
- List the innate functions of the alimentary system which are part of our defence systems

Our immune system needs to be tolerogenic of food because it is basically just a foreign antigen but it still needs to be able to mount an appropriate immune response when a proper pathogen invades.

Non-immune mechanisms

- Anatomical
  - Mucous layers
  - Peristalsis
  - Enterocyte membrane
- Chemical
  - Gastric acid
  - Enzyme (proteases)
  - Oral flora
  - Peristalsis
- Commensal bacteria
  - Oral and gut flora

Define MALT and GALT

Mucosa associated lymphoid tissue and Gut associated lymphoid tissue.

GALT

Not organised:
- Intra-epithelial lymphocytes
- Lamina propria lymphocytes

Organised:
- Peyer’s patches
- Cryptopatches
- Isolated lymphoid follicles
- Mesenteric lymph nodes

Generates lymphoid cells and antibodies
- IgA secretory and interstitial
- IgG
- IgM
- Cell mediated immunity

Describe a Peyer’s patch

Define the role of IgA in the GI tract

- IgA binds to pathogens and neutralises it, this is important because it stops the pathogen being able to penetrate into the gut mucosa.
- M cells take up antigen and contain pores on their surface to do so.

Immunological mechanisms of the alimentary tract

02 May 2012
10:01
Stuart’s Alimentary System Page 10
IgA is transported from submucosa to lumen by transcytosis.

Describe the importance of colonic flora.

Coeliac disease is an autoimmune disease.

A lot more immune cells destruction of villi demarcation.

Caused by an immune response to wheat in particular gluten.

Common screening mechanism is for antibody test.

Oral tolerance

- Nuts
- Hen egg white
- Cows milk
- Wheat
- Sesame seeds
- Soya
- Shell fish

Crohn’s disease

- NOD2 is involved in potentially causing Crohn’s disease
- Dysregulation and immune activation

Primary sclerosing cholangitis

- Inflammatory condition of the biliary tree
- Associated with IBD
- Leads to cholangiocarcinoma.

Immune cells

- Intra epithelial lymphocytes:
  - Make up one fifth of the intestinal epithelium
  - Conventional T cells (also lamina propria)
    - Migrated from other tissues
  - Unconventional T cells (innate)
    - Resident
    - Express unusual combination of CD4, CD8 or gamma delta TCR.

- IgA binds to pathogens and neutralises it, this is important because it stops the pathogen being able to penetrate into the gut mucosa.

- M cells take up antigen and contain pores on their surface to do so.

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- Crohn’s disease
  - NOD2 is involved in potentially causing Crohn’s disease
  - Dysregulation and immune activation

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Entero-hepatic lymphocyte homing under normal conditions

- MAdCAM-1
- VAP-1
- T cells
- Portal lymph node
- Liver

Entero-hepatic lymphocyte homing in IBD/PSC

- MAdCAM-1
- VAP-1
- T cells
- Portal lymph node
- Liver

- a4/77
- CCR9
- VAP-1
- MAdCAM-1
- CLS25
- VAP-1
- CLS25
- MAdCAM-1
- VAP-1
- Portal lymph node

- Shelf fish
Learning Objectives

- List the main functions of the liver
- Review the organisation of the liver and biliary system at the level of gross anatomy
- Describe the main features of the blood supply to the liver
- Outline the embryological origins of the liver
- 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, periporal region and centrilobular region
- Summarise the functional importance of the main structural features of hepatocytes (rough ER, Golgi complex, secretion granules, glycogen granules, mitochondria, smooth ER, junctional complexes)

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**List the main functions of the liver**

1. Secretes bile into duodenum (via gall bladder where bile is stored and concentrated) – bile salts are needed to emulsify dietary fats for efficient digestion and absorption
2. Phagocytoses and breaks down over-date red cells
3. Excretes bile pigments (Bile breakdown products) into bile
4. Metabolises many natural and synthetic molecules to prepare them for excretion
5. Synthesises and secretes key blood proteins (eg albumin and fibrinogen)
6. Key site of insulin dependent glycogen storage ("glucostat") and of intermediary metabolism of nutrients

- Most functions are carried out by the hepatocytes whereas the breakdown and recycling of red cells is carried out by the Kupffer cells in the endothelial lining of the blood sinusoids.

**Define the position and main roles of the fixed macrophages (Kupffer cells)**

- 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, periporal region and centrilobular region

**Outline the embryological origins of the liver**

- The liver and biliary system share a common origin with the ventral part of the pancreas at the beginning of the midgut.
- The septum transversum is a thick mass of cranial mesenchyme that gives rise to parts of the thoracic diaphragm and the ventral mesentery of the foregut in a developed human being.
- The septum transversum arises at an embryonic junctional site. This is where the ectoderm of the amnion meets the endoderm of the yolk sac (externally) and where the foregut meets the midgut (internally).
- Mesenchymal structure of the septum transversum provides support upon which the liver and blood supply can develop.

**Lobes of the liver**

- Anatomical lobes based on the attachment of the mesenteries
- Boundary between the territories of the left and right branches of the hepatic artery is important.
- This put the small lobes (caudate and quadrate) in with the functional left lobe.
- Couinaud classification divides the liver into 8 functionally independent segments .
- Centrally there is the portal vein, hepatic artery and bile duct.
- Peripherally there is the hepatic vein.
- Each segment can be resected without damaging those remaining.

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**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, periporal region and centrilobular region**

- The lobules of the liver consist of cords (sheets) of hepatocytes. These radiate from a central vein (draining via the main hepatic veins to the IVC).
- Round the edges of adjoining lobules are portal triads consisting of:
  - An arteriole
  - A branch of the portal vein
  - A bile duct
  - All come from the main triad entering the liver at the porta or hilum.

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80% of cells in the liver are hepatocytes.
Endothelial cells line blood vessels and sinusoids.
Cholangiocytes line biliary structures.
Kupffer cells are fixed phagocytes aka liver macrophages.
Hepatic stellate cells: These are Vitamin A storage cells (Ito cells) and may be activated to a fibrogenic myofibroblastic phenotype.

- Hepatocyte sheets near the central vein of a lobule.
- Flattened, dense cell nuclei belong to phagocytic Kupffer cells.
- Hepatocyte nuclei are paler and rounded.

**Describe the main features of the blood supply to the liver**

- There is a rich blood supply which is ~25% of the resting cardiac output.
- 20% arterial blood from the hepatic artery (left and right branches).
- 80% venous blood draining from the gut through the hepatic portal vein (HPV).
- HPV drains the gut which means that the liver is the first organ to have nutrient rich blood which is important for its function.

**Summarise the functional importance of the main structural features of hepatocytes (rough ER, Golgi complex, secretion granules, glycogen granules, mitochondria, smooth ER, junctional complexes)**

- The plasmalemma of adjacent hepatocytes shows irregularities with tight junctions, spot desmosomes and gap junctions. These separate the canaliculus from the rest of the intercellular space.
- Mitochondria are needed to provide the energy required for endocytosis and membrane ruffling.

**Draw a simple diagram outlining the relationships of hepatocytes to bile canaliculi and sinusoidal capillaries, and use this to explain major hepatic functions**

- Instead of forming simple sheets or glands facing a lumen on one side and the capillary bed on the other, hepatocytes are arranged as complex, anastomosing sheets separated by wide sinusoidal capillaries.
- The apical part of the hepatocyte is reduced to a narrow band surrounding the cell within the plane of the sheet of the hepatocytes. These apical domains bound a meshwork of narrow intercellular spaces called bile canaliculi. Bile is secreted into the canaliculi; tight junction on each side of the canaliculi prevent leak back to the circulation.
The portal vein, hepatic artery and bile ducts that enter the liver together retain their relationship even after multiple branching; these microscopic vascular bundles within the liver are termed portal triads. A region of liver parenchyma surrounded by a ring of about 5 or 6 portal triads is called a lobule. A tributary of the hepatic veins at the centre of each lobule receives the blood draining from the sinusoidal capillaries. In other words the lobule is a unit of vascular supply within the liver, the blood circulating from the peripheral triads to the central vein.

However the bile canalicular network drains towards the bile ductules within the triad, and the term acinus is used for a unit of bile secretion. These are simply different ways of looking at the same way.

Define the position and main roles of the fixed macrophages (Kupffer cells)

- One major function of the liver is not attributable to the hepatocytes. This is the phagocytosis and lysosomal breakdown of old red cells, which is handled by fixed macrophages called Kupffer cells that form part of the lining of the sinusoids.

• Bile secreted from the apical (canalicular) surfaces of the hepatocytes drains through the canalicular network to the bile ductules in the triads.
• All other liver secretion products such as albumin, fibrinogen and glucose are released at the non-canalicular surfaces of the hepatocytes into perivascular space (of Disse) and thus enter the very permeable sinusoidal capillaries.
• Canaliculus lumen is only 0.75 microns in diameter.
• Microvilli project from the canalicular membrane into the lumen providing a large surface area for secretion.
• Leaky tight junctions between hepatocytes permits paracellular exchange between the plasma and the canaliculus.
• Atony (lack of contraction of bile canaliculus) results in reduced bile flow (cholestasis).
Liver Function

Learning Objectives

Briefly describe how the liver is supplied with blood

Describe how the liver "buffers" the blood glucose concentration in terms of glycolysis storage/breakdown and glucose synthesis from non-carbohydrate sources (gluconeogenesis)

Describe the role of liver in protein and fat metabolism.

Describe how bile is stored and concentrated in the gall bladder, and reassorbed in the ileum, the main contents of bile and the role of bile in the digestion of fats. Are bile salts, bilirubin, cholesterol, phospholipids, bilirubin, cholesterol, phospholipids, bicarbonate ions and water

Define the term jaundice. Explain the difference between haemosylytic and obstructive jaundice

Briefly describe the role of the liver in metabolising/inactivating steroid and peptide hormones and various "foreign" chemicals (drugs) which are then excreted in bile, the storage of fat soluble vitamins (A,D,E,K), vitamin B, iron (as ferritin)

Describe how Kupffer cells in liver sinusoids destroy any bacteria which have entered the blood from the gut lumen

Describe how the liver performs the first hydroxylation step on vitamin D necessary to convert it to the biologically active form

Describe the role of liver in protein and fat metabolism.

Protein metabolism
- Synthesises 90% of plasma proteins (remainder are gamma globulins). Makes 15-50g/day.
- Importance of plasma proteins - binding/carrier function, plasma colloid osmotic pressure - oedema.
- Synthesis of blood clotting factors.
- Synthesis of dietary 'non essential' amino acids by transamination.

Transamination:
- Start with appropriate alpha keto acid precursor.
- Exchange of an amino group on one acid with a ketone group on another acid.
- E.g. Pyruvate+ glutamate -> Alanine+ alpha ketogluturate

- Essential amino acids (lysine, leucine, isoleucine, methionine, threonine, tyrosine, valine and phenylalanine) do not have appropriate keto acid precursors:
  - ILLMTVP
- Glutamic acid is a common intermediate in transamination reactions.

Deamination:
- De-amine amino acids prior to use as an energy source:
- Deamination is the conversion of an amino acid into the corresponding keto acid by the removal of the amine group as ammonia and replacing it with a ketone group.
- Deamination occurs primarily on glutamic acid because glutamic acid is the end product of many transamination reactions.
- Oxygen from water is used to create the keto group.
- Reducing agent co factor is needed:

Examples:
- Transamination: AA + alpha-ketoglutaric acid ---+ A-keto acid + Glutamic acid
- Deamination: Glutamic acid + NADH + H+ + H2O --- NAD + H+ + NH3 + a ketoglutarate

Blood supply
- There is a rich blood supply which is ~25% of the resting cardiac output.
- There is a dual blood supply:
  - 20% arterial blood from the hepatic artery (left and right branches)
  - 80% venous blood draining from the gut through the hepatic portal vein (HPV)
- HPV drains the gut which means that the liver is the first organ to have nutrient rich blood which is important for its function

Gluconeogenesis:
- The process of synthesising glucose from non-carbohydrate sources:
  - Lactate->Pyruvate->Glucose (lactate is produced in rbc metabolism anaerobic and also in muscle).
  - Also amino acids via deamination can be used to make glucose via the pathway
  - Alanine->Pyruvate->Glucose
  - From triglycerides->Glycerol->Glucose

Cori Cycle

Urea Synthesis
- Metabolism of NH3 leads to formation of NH3.
- Ammonia is NH3.

Muscle

Liver

Cori Cycle
Fat metabolism

- Fat is the main energy store in the body, 100x glycogen levels. Stored in adipose and the liver. When glycogen stores are full, liver can convert excess glucose and amino acids to fat for storage.
- Metabolises fats as energy source - converts FA’s to AcetylCoA -> TCA cycle in liver.
- Alternatively, liver can convert 2 Acetyl CoA -> Acetoacetic acid for transport in blood -> other tissues -> Acetyl CoA -> Energy.
- Synthesises lipoproteins, cholesterol, phospholipids.

Lipoprotein synthesis:
- There is a problem with transporting lipids in an aqueous medium therefore lipoproteins are formed which are triglycerides, cholesterol esters, phospholipid enclosed in a protein coat.
- Numerous types of phospholipid.
- Cholesterol ester transferase protein (CETP) shuttles cholesterol from HDL to LDLs.
- Inhibiting CETP of interest to drug companies.
- Most promising was Pfizer's CETP inhibitor, torcetrapib.
- However all development stopped due to increased systolic blood pressure, deaths and cardiovascular events.
- Are the bad and good labels too simplistic?

Cholesterol and phospholipid synthesis:
- Phospholipid - Fatty acid, phosphoric acid and a nitrogen containing base.
- Cholesterol - Synthesis of steroid nucleus from Acetyl CoA (also in diet). Used in Fatty acid, phosphoric acid and a nitrogen containing base.
- UV light converts cholesterol to Vitamin D precursor, which requires a where the store is small. Vit K is essential for liver sinusoids contain tissue macrophages (Kupffer cells). Bacteria may cross bile pigments gallstones. 

Urea Synthesis
- Metabolism of NH₂ leads to formation of NH₃.
- Ammonia is toxic
- NH₃ is toxic particularly to the CNS
- Liver converts NH₃ to urea.
- Urea is very water soluble, metabolically inert, non toxic. Excreted in water.
- 2 molecules of ammonia + 1 molecule of CO₂ gives water and Urea.

\[
2\text{NH}_3 + \text{CO}_2 \rightarrow \text{H}_2\text{N} = \text{NH}_2 + \text{H}_2\text{O}
\]

Bile metabolism

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Lipoprotein synthesis:
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- Numerous types of phospholipid.
from gut lumen to blood. Kupffer cells destroy these and prevent bacteria entering the rest of the body.

- Ca²⁺ metabolism - UV light converts cholesterol to Vitamin D precursor, which requires a double hydroxylation at position 25 and 1 to convert it to the active form. First is in the liver and second is in the kidneys. Liver disease therefore can cause rickets.

**Qu. 4:** Which of the following statements about the liver is incorrect?

- The digestion products of proteins, carbohydrates and lipids all travel from the gut to the liver primarily in the portal vein
- X Glycogen metabolism in the liver maintains blood glucose levels between meals
- The liver can use amino acids, glycerol or lactate as a substrate for gluconeogenesis
- Glutamic acid is a common intermediate in transamination reactions
- The liver is the main organ in which ammonia is converted to urea

**X Mark = -2 (conf=2)**

**Best Option:** The digestion products of proteins, carbohydrates and lipids all travel from the gut to the liver primarily in the portal vein

Chylomicrons (including the breakdown products of lipids) enter the lacteals and are transferred to the bloodstream via the lymphatic system.

*Pasted from: [https://www.ucl.ac.uk/lapt/laptlite/sys/run.htm?icl08_alimentary?f=clear?i=icl1?k=1?u=_st1511?i=Imperial]*
Liver Failure
17 May 2013 15:13

Learning Objectives

- Define Liver Failure and its main types
- Understand the important underlying pathophysiology
- Name important causes of acute and chronic liver failure
- Know the clinical features and complications of liver failure
- Be aware of possible treatments for liver failure

Define Liver Failure and its main types

Liver Failure: Insufficient hepatoic function to maintain homeostasis:
- Characterised by:
  - Rate of onset: manifestations and outcome
  - Cause
  - Clinical features.
- Rate of decline of function determines the way the syndrome manifests and the likely outcome.
- Main features are the consequence of the accumulation of toxins resulting from the loss of the detoxifying function of the liver.

To understand liver failure one must remind oneself of the functions of the liver:
- Detoxification
- Synthesis: plasma proteins (e.g. albumin, clotting factors), bile.
- Excretion: bilirubin, cholesterol, hormones, drugs.
- Enzyme activation
- Storage: glycogen, fat, vitamins (ADEK) and regulation of glucose.
- Immune regulation: Kupffer cells- antigens, immune complexes.

Main types are acute and chronic.

Acute liver failure- specific aetiologies.
- Develops in a previously normal liver and is subdivided according to interval between the onset of jaundice and encephalopathy:
  - Hyperacute- ≤7 days between jaundice and encephalopathy
  - Acute- 1-4 weeks
  - Subacute- 5-12 weeks

Aetiology= main influence on rate of deterioration and prognosis

<table>
<thead>
<tr>
<th>Time from jaundice to encephalopathy</th>
<th>Common aetiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute ≤7 days</td>
<td>Paracetamol</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A, B</td>
</tr>
<tr>
<td>Acute 1-4 weeks</td>
<td></td>
</tr>
<tr>
<td>Subacute 5-12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Other causes:
- Infection: HSV (herpes simplex), EBV, varicella.
- Drugs: Isoxandrin, ecstasy, halothane
- Metabolic: Wilson’s, Reye’s
- Vascular: Budd-Chiari, ischaemic
- Other: Fatty liver of pregnancy, lymphoma, amanita phalloides.

Amanita phalloides:
- This is a mushroom that tastes pleasant but the fatal dose is only 30g.
- Risk is not decreased by cooking and there is delayed presentation of liver and kidney failure and no known antidote.

Khat: this is a leaf that is chewed in eastern African and the Arabian peninsula and contains cathinone- amphetamine like substance. May cause chronic hepatitis.

Rarer Causes:

Budd-Chiari syndrome
- Obstruction of hepatic veins at any site from lobule of IVC to right atrium.
- Present with abdominal pain, hepatomegaly, ascites and histologically shows sinusoidal distension.
- Causes include thrombophilia, webs, veno-occlusive disease.

Understand the important underlying pathophysiology

- Centrilobular necrosis of hepatocytes.
- Mononuclear cell infiltrate: portal tract and lobules
- Fatty change
- Activation of macrophages
- Release of cytokines- TNF, interleukin 1,6.

Name important causes of acute and chronic liver failure

Acute liver failure:

- Metabolic: Wilson’s, Reye’s
- Drugs: Isoniazid, ecstasy, halothane
- Idiosyncratic drug toxicity
- Subacute Amebic liver abscess
- Hyperacute Amanita phalloides
- 1/3 of cases especially Staphylococcus but it can be any. Fungal infection is unrecognised in up to 1/3 of cases.
- There may also possibly be increased access for infection such as with endotracheal tubes, lines, catheters and ascites.
- Poor host defence can be caused by Kupffer cell failure and polymorphic mechanisms results in increased uptake of water into brain cells.
- Death actually results from brain stem herniation and cerebral hypoxia.

- Disruption of blood brain barrier and increased osmosis into brain.
- Death actually results from brain stem herniation and cerebral hypoxia.
- Multifactorial- vasogenic leads to disruption of blood brain barrier, cytotoxic mechanisms results in increased uptake of water into brain cells.

Clinical features include:
- i. Systolic hypertension
- ii. Increased muscle tone
- iii. Mydriasis: (Muscle twitching)
- iv. Decerebrate posturing
- v. Dysconjugate eye movements
- vi. Loss of pupillary reflexes
- vii. Respiratory arrest.

3. Coagulopathy
- Liver synthesises all coagulation except for Factor VIII. It also synthesises inhibitors of coagulation and proteins involved on the fibrinolytic system so coagulopathy is very complex.
- Platelet count falls and platelets dysfunctional
- Bleeding: mucous membranes, GIT, brain.
- Measure the prothrombin time.

4. Metabolic: hypoglycaemia, potassium, sodium and potential metabolic acidosis.
- Hypoglycaemia due to high insulin and low liver uptake.
- Decreased gluconeogenesis, potassium levels due to increased urinary loss.
- Decreased sodium and metabolic acidosis.
- Metabolic acidosis especially with paracetamol toxicity, also lactic acidosis due to reduced tissue perfusion by time of grade 3 encephalopathy. Also hyperphosphataemia, calcaemia and magnesaemia.

5. Infection
- Common in both acute and chronic liver failure.
- Poor host defence can be caused by Kupffer cell failure and polymorphic dysfunction. Which in turn causes a reduced conscious state.
- There may also possibly be increased access for infection such as with endotracheal tubes, lines, catheters and ascites.
- There may be both bacterial and fungal infections. Bacteria are mainly gram positive especially Staphylococcus but it can be any. Fungal infection is unreocgnised in up to 1/3 of cases.

Clinical features of acute liver failure include:

- Focal neurological deficits
Wilson’s Disease
- Autosomal recessive 1:30,000
- Copper accumulation in liver, basal ganglia and cornea.
- Can present with acute or chronic liver disease.
- Treatment is with penicillamine a copper chelator.
- It is due to failure of copper excretion into bile.

Acute Fatty Liver of Pregnancy
- Incidence 1:1000 UK
- Aetiology is inherited defects of fatty oxidation.
- Presents in the 3rd trimester with RUQ pain, vomiting then later with jaundice, encephalopathy, ascites and bleeding.
- Treatment is urgent delivery.

Chronic liver failure - can complicate virtually all forms of chronic liver disease.

Causes:
- Alcoholic liver disease
- Chronic viral hepatitis (C,B)
- Autoimmune chronic active hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Haemochromatosis
- Non alcoholic fatty liver disease

<table>
<thead>
<tr>
<th>Child-Pugh grade</th>
<th>Stage</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
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<tr>
<td>Bilirubin (umol/l)</td>
<td>&lt;17</td>
<td>17-34</td>
<td>&gt;34</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>&gt;35</td>
<td>30-35</td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1</td>
<td>Grade 2-4</td>
<td></td>
</tr>
<tr>
<td>Clotting (PT)</td>
<td>normal</td>
<td>&lt;1.4</td>
<td>&gt;1.4</td>
<td></td>
</tr>
</tbody>
</table>

Be aware of possible treatments for liver failure

1. Underlying causes
   - Remove toxic drug, N-acetylcysteine used to combat paracetamol overdose.

2. Supportive
   - Prevention/control of infection and or bleeding.
   - Nutrition
   - Early renal support
   - Recognition/management of raised intracranial pressure

3. Transplantation
   - In acute liver failure - Grade 3 or 4 encephalopathy
   - Chronic liver failure - Child-Pugh grade B/C
   - Survival: 12 month survival
     - 60% for acute
     - 90% for chronic

4. Artificial liver support
   - Artificial support is an attractive option due to the scarcity of organs and delays associated with transplantations.
   - There can be the potential for full recovery especially with paracetamol.
   - Can also be used as a bridge to either a transplant or recovery.
   - The system must:
     i. Replace necessary liver function: synthetic, eliminatory and metabolic.
     ii. Counter adverse effects of necrotic liver
     - e.g. Albumin and clotting factors in addition to other plasma proteins.
     - Metabolise fats, proteins, cholesterol and excrete drugs.
   - There are 2 approaches
     i. Biological: live hepatocytes

Clinical features of acute liver failure include:

1. Portal hypertension
   - Portal venous system:
     - Carries blood from abdominal alimentary tract (i.e. spleen, gall bladder, pancreas, bowel) to the liver.
     - Normal portal pressure is 7mm Hg.
   - Portal hypertension/ block (liver nodule development?)
     - Collaterals develop
     - Portal systemic shunting
       - Encephalopathy - lack of ammonia processing
       - Septicaemia
       - Impaired liver regeneration
     - Portal circulation can be blocked inside or outside of liver therefore collaterals develop to carry portal blood into the systemic circulation.
     - Portal pressure correlates particularly with nodule formation.

   - Portal vein runs posterior to pancreas: formed by union of superior mesenteric and splenic vein.
   - Inferior mesenteric brings blood from left colon and rectum.

2. Ascites
   - Extracellular fluid within the peritoneal cavity
     - Sodium retention
     - Portal hypertension
     - Hypoalbuminaemia
   - Complications
     - Spontaneous bacterial peritonitis
     - Renal failure, encephalopathy.
   - Sodium retention due to kidney response to perceived reduced circulating plasma volume (peripheral vasodilation, AV shunting) sodium retention mediated by renin-angiotensin-aldosterone system

3. Renal failure
   - Acute tubular necrosis-acute liver failure
   - Hepatorenal syndrome (functional renal failure): chronic liver disease
     - Renal vasosconstriction
     - Decreased renal prostaglandins
     - Sepsis
     - Bleeding and hypotension

Know the clinical features and complications of liver failure

- Portal hypertension:
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  - Portal systemic shunting
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- Inferior mesenteric brings blood from left colon and rectum.
- Oesophageal varices
  - Supplied by left gastric vein and drain into azygos system.
  - Deviation of blood into these channels leads to varicosities in lower end of oesophagus.
  - Bleeding leads to haematemesis, melena, encephalopathy.
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- Acute tubular necrosis-acute liver failure
- Hepatorenal syndrome (functional renal failure): chronic liver disease
  - Renal vasosconstriction
  - Decreased renal prostaglandins
  - Sepsis
  - Bleeding and hypotension
- Human or animal
- Immortal cell line

iii. Non-biological- blood purification - adsorption and dialysis techniques
- E.g. mars system: selectively eliminates toxins bound to albumin.
- Logistically easier and cheaper to target toxins that accumulate in liver.

- Or auxiliary liver transplant- donor liver placed alongside native liver.
Learning Objectives

- Understand the production and excretion of bilirubin
- Describe the features of pre-hepatic, hepatic and post-hepatic jaundice
- Give two examples of each of these types of jaundice
- Describe the pathogenesis of the symptoms and signs associated with jaundice

Jaundice

Understand the production and excretion of bilirubin

- Bilirubin is a H2O insoluble, yellow pigment.
- 75% BR from Hb breakdown
- 22% from catabolism of other haem proteins.
- 3% from ineffective bone marrow erythropoiesis.
- BR is bound to albumin with most dissociating in the liver.
- There is more free than conjugated.
- Free BR enters hepatocytes, binds cytoplasmic proteins and becomes conjugated to glucoronic acid (UDPGT from smooth ER) then to diglucoronide-BR which is more soluble and greater than free BR. It is transported across concentration gradient into bile canaliculi into the GIT.

Bile Overview/ Features

- Bile production is necessary for cholesterol homeostasis, dietary lipid/vitamin absorption and for the removal of xenobiotics/drugs/endogenous waste products e.g. cholesterol metabolites, adrenocortical and other steroid hormones.

Bile Production

- Cholesterol and Alkaline Phosphatase (ALP) will be raised if there is an obstruction.
- 500-600ml of bile is produced daily. It is golden yellow in colour resulting from the glucuronides of bile pigments.
- 60% bile secreted by hepatocytes (liver cells)
- Up to 40% secreted by cholangiocytes (biliary epithelial cells)
- Bile drains from liver, through bile ducts and into duodenum at duodenal papilla.
- Biliary tree called the bile ducts, they enlarge as they become further away from their origin.

Role of biliary tree

- Alters pH, fluidity and modifies bile as it flows through.
- H2O drawn into bile (osmosis through paracellular junctions)
- Glutathione split into constituent amino acids and reabsorbed.
- Luminal glucose and some organic acids also reabsorbed.
- HCO3 and Cl actively secreted into bile by CFTR mechanism.
- Cholangiocytes contribute IgA by exocytosis.

Bile Formation

- Urobilinogens: H2O soluble colourless derivatives of BR formed by action of GFR bacteria.
- GIT mucosa is relatively impermeable to conjugated BR but is permeable to unconjugated BR and Urobilinogens.
- Therefore some unconjugated BR enters enterohepatic circulation and some forms urobilinogens.
- Some bilirubin goes to the kidney (urobilinogen)
- 20% urobilinogens reabsorbed into general circulation and is excreted in urine.
- Some urobilinogens passed in stool as Stercobilinogen.

- Oxidation of stercolbilinogen to stercolbin causes brown colouration of faeces.

Describe the features of pre-hepatic, hepatic and post-hepatic jaundice

- Cholestasis is a cause of jaundice and means the cessation of bile flow.
- Jaundice: facing bilirubin in blood (the porphyrina)
- Yellow tinge to skin, sclera, mucous membranes.

Bile Flow:

- Bile flow closely related to concentration of bile acids and salt in blood.
- Biliary excretion of bile salts and toxins is performed by transporters expressed on apical surface of hepatocytes and cholangiocytes.
- These biliary transporters also govern rate of bile flow.
- Dysfunction of the transporters is a major cause of cholestasis
- Main transporters include the
  - Biliary salt excretory pump (BSEP) responsible for active transport of bile acids across hepatocyte canalicular membranes into bile, and secretion of bile acids is a major determinant of bile flow.
  - MDR related proteins (MRP1 and 3)
  - Products of the familial intrahepatic cholestasis gene (FIC1) and multidrug resistance genes (MDR1 and 3)
  - MDR1 mediates the canalicular excretion of xenobiotics and cytotoxins.
  - MDR3 encodes a phospholipid transporter protein that translocates phosphatidylcholine from the inner to outer leaflet of the canalicular membrane.
- When people have high levels of bile salts they can get high levels of inflammation in the bile duct due to bile salt detergent properties.

Bile salts

- Na and K salts of bile acids are conjugated in the liver to glycine and taurine (cysteine derivative)
- Bile acids synthesised from cholesterol
- 4 acids in humans
- Two primary ones are Cholic acid and Chenodeoxycholic acid which are converted by colonic bacteria to Deoxycholic acid and Lithocholic acid which are secondary acids.
- Remember that bile salts form micelles and are amphipathic with hydrophilic domain facing out and hydrophobic domain facing in which means that free fatty acids and cholesterol are inside.
- Detergent like actions make bile salts potentially cytotoxic in high concentrations but cell membranes are protected by other intraluminal lipids e.g. phosphatidylcholine in biliary tree and fatty acids in GIT, also by their own plasmalemma content of cholesterol and glycolipids.

Anatomy of the biliary system

- Canal of Hering: Hepatocytes of extreme periportal zone make contact with bile duct lining cells and there is a short stretch where bile flows in channels lined by a mixture of bile duct lining cells and hepatocytes.
- Sphincter of Oddi controls the release of bile when we're fasting, bile can’t pass into the gut and go up into the gall bladder. Cholecystokinin opens the sphincter, causes contraction of the gall bladder, and subsequent excretion of bile into the duodenum.
Cholestasis is a cause of jaundice and means the cessation of bile flow.

**Jaundice**

- Excess bilirubin in blood (>34-50 \(\mu\text{M/L}\))
- Yellow tinge to skin, striae, mucus membranes.
- Cholestasis normally results in jaundice.
- However jaundice does not necessarily mean there is cholestasis.

**Pre-hepatic jaundice**
- Increased quantity of BR from:
  - Haemolysis
  - Massive transfusion
  - Haematoma resorption
  - Ineffective erythropoiesis
- Look for HB drop without overt bleeding where BR>>> LFTs
- ic: blood film, haepatoglobins, LDH.

**Hepatic/Hepatocellular**
- Hepatocytes are malfunctioning.
- Defective uptake and conjugation.
- Defective BR excretion.

**Liver Failure:**
- Acute/ Fulminant
- Viral hepatitis, ETOH, AID, PBC, PSC
- Intrahepatic cholestasis: sepsis, TPN, drugs.

Amount of BR being made is normal and blood flow is normal. The problem is with the conjugation of the BR to make it bound and therefore inactive.

**Post hepatic/ Obstructive**
- Defective transport of BR by biliary duct system e.g. common bile duct stones, HepPancBil malignancy, local Lipathy.
- Lookout for sepsis (cholangitis)
- Cholangiocarcinoma is cancer of the bile duct themselves.

Give two examples of each of these types of jaundice

Describe the pathogenesis of the symptoms and signs associated with jaundice

**Pre-hepatic** - rate of formation of bilirubin> removal

**Hepatic**
- a. Damage to liver cells stop conjugation and or excretion. Associated with severe hepatocellular damage.
- b. Failure to uptake bile
- c. Reflux of bile between hepatocytes.

**Post hepatic**
- a. Damage to intrahepatic bile ducts
- b. Obstruction of intra or extrahepatic bile ducts.

<table>
<thead>
<tr>
<th>Pre-Hepatic</th>
<th>Hepatic</th>
<th>Post-Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited disorders of BR metabolism:</td>
<td>Hepatitis due to:</td>
<td>Intrahep cholestasis 2ndary to drugs or virus</td>
</tr>
<tr>
<td>- Crigler-Najjar</td>
<td>- Viral</td>
<td></td>
</tr>
<tr>
<td>- Gilbert’s</td>
<td>- Autoimmune</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>- Rotor</td>
<td>- Drugs</td>
<td>Gallstones in CBD</td>
</tr>
<tr>
<td>- Dubin-Johnson</td>
<td>- Alcohol</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>- Haemolysis</td>
<td>- Metabolic liver disease</td>
<td>Carcinoma ampulla</td>
</tr>
</tbody>
</table>

- Obstructive jaundice is associated with a pale stool and dark urine.
Learning Objectives

Outline the embryonic development of the pancreas

Review the anatomical regions and main anatomical relations of the pancreas

Distinguish between the exocrine and endocrine parts of the pancreas in structural and functional terms

Sketch the duct system of the pancreas

Define a pancreatic acinus

Describe the subcellular organisation of synthesis and secretion by the pancreatic acinar cells

List the most important components of the pancreatic (exocrine) secretions and define their roles in digestion

Explain the mechanism for bicarbonate secretion in terms of ion exchange pumps and membrane ion channels and the dependence on active transport

Understand that acinar cells synthesise enzymes for the digestion of carbohydrate, lipids and proteins and store these in an inactive form in zymogen granules, and explain how these enzymes are activated when they enter the duodenum

Outline the embryonic development of the pancreas

The pancreas develops as a part of the ventral foregut mesentery arising at the foregut-midgut junction. It is composed of both a dorsal and ventral bud with the ventral bud being part of the hepatobiliary bud.

Review the anatomical regions and main anatomical relations of the pancreas

Uncinate—Hooklike in Latin

Endocrine function is more concentrated in the tail.

Portal vein forms behind the head of the pancreas and gets trapped between uncinate process and neck region.

Portal vein formed by SMV + Splenic Vein

Associated with the 2nd part of duodenum at the ampulla of Vater.

Lies mainly on the posterior abdominal wall extending from C-shaped duodenum to hilum of spleen

Pancreatic juice reaches duodenum via the main and accessory pancreatic glands.

Distinguish between the exocrine and endocrine parts of the pancreas in structural and functional terms

Endocrine- Secretion into the blood stream to have effect on distant target organ (Islets of Langerhans)

Exocrine- Secretion into a duct to have direct local effect.

Insulin- Anabolic hormone, promotes glucose transport into cells and storage as glycogen, reduces blood glucose, promotes protein synthesis and lipogenesis.

Glucagon- Increases gluconeogenesis and glycogenolysis

Somatostatin- Endocrine cyanide, BRUTAL

Endocrine- 2% of the gland

• Secretes hormones into blood- Insulin and Glucagon in addition to somatostatin and pancreatic polypeptide.

Exocrine- 98% of the gland

• Secretes (Pancreatic Juice) into duodenum via pancreatic duct/common bile duct in addition to having a digestive function.

Sketch the duct system of the pancreas

<table>
<thead>
<tr>
<th>Exocrine</th>
<th>Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ducts</td>
<td>Derived from the branching duct system</td>
</tr>
<tr>
<td>Acini are grape-like clusters of secretory units</td>
<td>Lose contact with ducts-become islets</td>
</tr>
<tr>
<td>Acinar cells secrete pro-enzymes into ducts</td>
<td>Differentiate into alpha and beta cells secreting into the blood</td>
</tr>
<tr>
<td>More endocrine function from the tail of the pancreas than the head</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 4-2: Development of the Hepatic Ducts and Pancreas
Define a pancreatic acinus

- A small sac-like cavity in the pancreas containing acinar cells that secrete low-volume, high-viscous enzyme-rich fluid. There are also duct and centroacinar cells that secrete high-volume, watery, HCO₃⁻ into the lumen.

List the most important components of the pancreatic (exocrine) secretions and define their roles in digestion

**Bicarbonate**
- Duct and centroacinar cell.
- Juice rich in bicarbonate (~120mM where the plasma’s is only 25mM, pH 7.5-8
- Prevents damage to duodenal mucosa
  - Raises pH to optimum range for pancreatic enzymes to work
  - Neutralises acid chyme from the stomach
- Washes low volume enzyme secretion out of pancreas into duodenum.

**Effect of Duodenal pH on Bicarbonate Secretion Rate**

- Duodenal pH < 3 = not much more increase in bicarbonate secretion
- Duodenal pH < 5 = significant linear increase in pancreatic bicarbonate secretion

- It may seem strange that bicarbonate secretion stops at pH which is still acid. However bile also contains bicarbonate and helps neutralise the acid chyme.
- Brunner's glands secrete alkaline fluid.

Explain the mechanism for bicarbonate secretion in terms of ion exchange pumps and membrane ion channels and the dependence on active transport

- Simplified

Understand that acinar cells synthesise enzymes for the digestion of carbohydrate, lipids and proteins and store these in an inactive form in zymogen granules, and explain how these enzymes are activated when they enter the duodenum

- Some of the main enzymes that the pancreas releases are:
  - Trypsinogen a precursor of a powerful protease which is converted to trypsin by enterokinase, an enzyme present on the brush border of the small intestine.
  - Chymotrypsinogen which can be activated by trypsin.
  - Proelastase
  - Procarboxypeptidase
  - Prophospholipase A
- Zymogen means pro-enzyme.
Stimulus Interaction:

- CCK alone has no effect on bicarbonate secretion
- CCK can markedly increase bicarbonate secretion that has been stimulated by secretin.
- Vagus nerve has similar effect to CCK
- Secretin no effect on enzyme secretion.

Orlistat:
- Increased faecal fat-occurs when pancreatic lipase secretion significantly reduced.
- Social anus cannot differentiate between oil and air.

**Gut is stimulated by the vagus nerve which is parasympathetic**

**Control of secretion**

- Cephalic phase
  - Mediated by cholinergic vagus nerve. The juice secreted during this phase is mainly enzyme rich containing very little HCO<sub>3</sub>⁻.
  - In response to vagal stimulation, the acinar cells also secrete kallikreins, which catalyse the production of bradykinin a vasodilator. This results in increased blood flow to the pancreas, and increased volume of secretion.

- Gastric Phase
  - The presence of food in the stomach stimulates the secretion of pancreatic juice via a hormonal mechanism.
  - Activation of chemoreceptors in the walls of the stomach by peptides, and the activation of mechanoreceptors causes the release of the hormone gastrin from G cells and the local circulation. Stimulation of cholinergic is also involved in this phase of control. During the gastric phase the secretion of both the enzyme-rich and the alkaline components of pancreatic juice is increased.

- Intestinal phase- 70-80% of pancreatic secretion.
  - Food material in the duodenum stimulates both the secretion of the alkaline and enzymatic components of the pancreatic juice.
  - Acid stimulates the release of secretin in the walls of the intestine and this hormone stimulates the duct cells to secrete the alkaline fluid. Note this is a feedback control mechanism which helps control the pH of the contents in the duodenum.
  - The enzyme rich juice is released during the intestinal phase in response to fat and peptides in the food. The fats and peptides cause release of CCK from the walls of the duodenum into the blood. CCK also stimulates the acinar cells to secrete enzymes.
  - Trypsin in the duodenum inhibits the release of enzymes via inhibition of CCK release.
  - Secretin exerts a permissive effect on the secretion of enzymes. It does not stimulate enzyme secretion on its own, but it enhances the effect of CCK.
  - Similarly CCK exerts a permissive effect on the secretion of the alkaline fluid by secretin.
  - Vagal stimulation causes release of mainly the enzyme rich secretion but if the vagi are sectioned, the alkal secretion elicited in response to secretin is reduced by 50%, indicating a functional overlap between the effects of vagal stimulation and secretin.
  - Thus the vagal mechanism may enhance the effect of secretin.

**Extra information**

- Bicarbonate rich component is controlled by release of a hormone Secretin (cAMP)
- Enzyme rich component secretion is controlled by vagal reflex and by a hormone Cholecystokinin (CCK) (Caz⁺/PLC)
- CCK also stimulates bile secretion.

**Switching off CCK**

- Cephalic phase ends when meal eaten.
- Absorption of fats and peptides removes local luminal stimulus for CCK release from mucosa.
- Possibly other mechanisms.

**Stimulus Interaction:**

- What does this show well is the role of the CFTR chloride channels in that it is important for chloride to be able to be pass out of cell into the lumen so that it can then be exchanged later for the bicarbonate.
• Potassium returns to blood via K channels.
• Cl⁻ returns to lumen via CFTR.
Learning Objectives

Define acute and chronic pancreatitis

List the symptoms and signs of acute pancreatitis

List four causes of acute pancreatitis

List blood tests and imaging modalities which are useful for patients with pancreatitis

List the complications of acute and chronic pancreatitis

List three causes of chronic pancreatitis

Define acute and chronic pancreatitis

Acute Pancreatitis

- Is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems.
- 150-420 per million population
- Severe pancreatitis has mortality rate of 20%
- Etiology of acute pancreatitis should be determined in 80% of patients (20% as idiopathic)
- Pancreas is retroperitoneal apart from tail.
- Located in C shape of duodenum
- Secretions from accessory duct enter duodenum at Ampulla of Vater.

Diagnosis of acute pancreatitis:

- Clinically (pain and vomiting) and elevated pancreatic enzymes (lipase lasts longer and has more specificity than amylase)
- CXR (to exclude perforated ulcer)
- US (for gall stones)
- CT (in doubtful cases and to exclude other pathology)

History:

- Previous gall stones
- Alcohol intake
- Family history
- Drug intake
- Exposure to viral causes or prodromal

List four causes of acute pancreatitis

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

List the symptoms and signs of acute pancreatitis

- Abdominal pain radiating to back
- Vomiting: near to stomach and duodenum inflammation can make you vomit.
- Organ failure (chest, kidney)
- Jaundice, cholangitis: due to proximity to duct and gall stones.
- The scope of clinical presentation also includes:
  a. Severe acute pancreatitis
  b. Mild acute pancreatitis
  c. Acute fluid collection
  d. Pancreatic necrosis and infected necrosis
  e. Acute pseudocyst
  f. Pancreatic abscess

List the complications of acute and chronic pancreatitis

- Multiple organ failure
- Necrotising pancreatitis, abscess
- Haemorrhage
- Biliary complications
- Pseudocyst: fluid collected in gland forms a cyst.

Management of pancreatitis

- Supportive
  - IV fluids, respiratory, active monitoring.
  - ERCP
    - Severe attack due to gall stones.
    - Jaundice, cholangitis, dilated CBD (cystic bile duct
  - Prophylactic antibiotics
    - Conflicting evidence
    - Maximum 14 days
  - PNA (fine needle aspiration) for 30% people with necrosis.
  - Interventional radiology
    - Embolisation for haemorrhage
    - Drainage of abscess
  - Surgical
    - Cholecystectomy during the same admission
    - Necrectomy
    - Drainage of pseudocyst

List three causes of chronic pancreatitis

- Biliary obstruction
- Alcohol
- Heredity

Chronic pancreatitis

Diabetes:

- Glycaemic control
- Nutritional therapy
- Pain management
- Antidepressants

Management:

- Diet and lifestyle changes
- Pain management
- Endoscopic ultrasound
- Percutaneous drainage
- Surgery

24H after admission:

- Glasgow score 3 or more
- CRP>150 (Normal range is about 5)

- After 48 hours you may be able to detect organ failure.
- Black on CT = necrotic.
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.

The picture above shows that in chronic pancreatitis episodes of acute pancreatitis are not cleared and they have repeated attacks of inflammation.

Symptoms may be very similar to acute pancreatitis but occasionally there is no pain or there may be severe epigastric pain that can last for many hours or multiple days.

When lipase and proteases secretions are reduced to <10% of normal level the patient will develop steatorrhoea.

**Management of chronic pancreatitis**

- Enzyme replacement
- Adequate nutrition
- Insulin supplement
- Management of secondary complications e.g. jaundice.

**Chronic relapsing cases:**

- Pain management
- Rehabilitation of the alcoholic patient
- Surgical intervention (pancreatectomy)
  - Intractable pain not responsive otherwise
  - Management of a secondary complication e.g. stricture CBD.
  - Strecthic nerves- coeliac plexus- cut the nerves so pain cannot be felt.

- Diffuse calcium stones= calcification of pancreas and thus chronic pancreatitis.
Learning Objectives

- To describe principles of energy balance
- To describe methods of assessment of energy stores and risks
- To understand mechanisms of obesity
- To understand the basics of obesity management
- To describe complications of obesity
- To describe methods of assessment of energy stores and risks

To describe principles of energy balance

1. In a steady state energy in must equal energy out
   - Overweight/obese individual has increased total energy expenditure
     - REE
     - Thermogenesis
     - Physical activity
   - CHO
   - FAT
   - PROTEIN
   - ENERGY INTAKE
   - ENERGY EXPENDITURE
   - 70kg Weight
   - 56kg FFM
   - 14kg Fat Mass
   - 20%

REE= Resting energy expenditure.

- Somebody who eats more just develops a new set point for their weight - they do not gain weight indefinitely.

- Thermogenesis is the cost of storing food

- Lean body mass (FFM) is proportional to resting energy expenditure

  - Really tells us how many mitochondria somebody has.

  - BMI is not as good as a predictor of cardiac events as waist to hip ratio.

To understand mechanisms of obesity

- Physiologically designed to protect against starvation.
- Humans with opposable thumbs were able to break open bones and suck out the marrow inside.
- 1st half of century energy expenditure was driving energy intake.
- Gradually in 1960's food became readily available, reduced in cost, driving decreased energy consumption.

Causes of obesity:

- Energy intake
  - Energy intake per person of food sold fairly constant. Increase in energy intake is not necessarily the main cause of obesity.
  - Although we are eating the same amount of calories we are eating more fat in comparison to carbohydrate.
  - Autoregulation following fat ingestion is difficult.
  - Satiety involves complex endocrine regulation.
- Energy Usage
  - Big reduction in energy expenditure over recent years.

To describe complications of obesity

- Mortality
- Morbidity
- Economic
- Psychological
- Cardiovascular
- Gastrointestinal
- Chest disease
- Endocrine
- Gynaecological- Poly cystic ovary syndrome
- Obstetric

Lean body mass (FFM) is proportional to resting energy expenditure

- FFM (lean body mass) is proportional to our energy expenditure.
- Really tells us how many mitochondria somebody has.

Fasting glucose

Metabolic Syndrome

HDL

Men<1.0

Women<1.3

Waist circumference

Men>102

Women>88

Hypertension

BP>135/80

Microalbumin

Insulin resistance

- We are very efficient at exercise so that not much energy is wasted.
- Thermogenesis is the cost of storing food

Dietary Energy:

- We are very efficient at exercise so that not much energy is wasted.
- Thermogenesis is the cost of storing food

- Fasting glucose

- Metabolic Syndrome

- HDL

- Men<1.0

- Women<1.3

- Waist circumference

- Men>102

- Women>88

- Hypertension

- BP>135/80

- Microalbumin

- Insulin resistance

BMI is not as good as a predictor of cardiac events as waist to hip ratio.

- Omental fat is more metabolically active and drains directly through the liver.

Lean body mass (FFM) is proportional to resting energy expenditure

- FFM (lean body mass) is proportional to our energy expenditure.
- Really tells us how many mitochondria somebody has.
comparison to carbohydrate.
- Autoregulation following fat ingestion is difficult.
- Satiety involves complex endocrine regulation.

**Energy Usage**
- Big reduction in energy expenditure over recent years.
  - Today we walk 3000 steps a day. Amish community walk 18-20,000 a day.

**Genes**
- Most obesity is not monogenic.
  - However obesity does have some major genetic factors. Weight gain and storage is predicted well by genetics e.g. twin pairs.
  - FTO gene - homozygous for this gene means you are 16% more likely to be obese.
  - Genetics loads the gun, the environment pulls the trigger. **BRUTAL**
- White adipose tissue - Stores most fat and produces leptin.
  - Leptin tells hypothalamus you have enough energy.
  - White adipose tissue is an endocrine gland in its own right.
  - Leptin isn’t about regulating excess calories, it’s the means by which low energy stores tell the body to stop menstruation and antibody production.
  - Insulin may have an effect on satiety intake.
  - Ghrelin from stomach tells us we are hungry.
  - PYY (Polypeptide Y) produced by small intestine that tells hypothalamus you have eaten a big meal.

**Endocrinology**
- White adipose tissue - Stores most fat and produces leptin.
  - Energy expenditure (Thermogenesis)
  - Hypothalamus
  - LEPTIN

**Energy (or fat) homeostasis**
- You have eaten big meal
  - LEPTIN
  - INSULIN
  - Ghrelin
  - PYY

**Insulin**
- Satiety (intake)

**White adipose tissue**

*To understand the basics of obesity management*

**Why?**
- Follow evidence base
  - Lifestyle diet and exercise
  - Pharmacological
  - Surgical
  - Weight loss
  - 100kg>>10kg weight loss

**Diet**
- Atkins associated with greatest weight loss over 12 months compared to Zone, Ornish and LEARN diets.

**Pharmacotherapy**
- Orlistat is a GI lipase inhibitor.
- Sibutramine - NA uptake had other effects.
- Rimonabant CBI - Cannabinoid receptor can cause depression.

**Surgery**
- Stomach is reduced to 20ml in size.

**Life span was reduced with a BMI of 35 or 30.**

**Diabetes and metabolic syndrome**

**Psychological morbidity**

**Cardiovascular disease**

**Chest disease**

**Gynaecologic disease**

**Rheumatological disease**

**Chest disease**

**Psychological morbidity**

**Cardiovascular disease**

**Chest disease**

**Psychological morbidity**

**Cardiovascular disease**

**Chest disease**

**Psychological morbidity**

**Cardiovascular disease**
• Both very safe and effective means of weight loss, recommended for people with a BMI > 40.

• Endobarrier: tube 30cm long and fits into the pylorus bypassing the duodenum and enters the small intestine. Food contact with the duodenum is important in satiety.

• Lifestyle change had best outcome for people who were going on to develop diabetes.

• Denmark taxed saturated fat in food.
Learning Objectives

To demonstrate a basic understanding of the role of nutrition in health and disease.

To demonstrate a basic understanding of the role of the gastrointestinal track in maintaining nutritional status.

To have a basic understanding of the role of the macro-nutrients in health and disease.

Energy

- If you don’t supply the body with enough energy then nutrients will be misused e.g. deamination of amino acids to generate glucose and energy.

- Obligatory energy expenditure= Basal Metabolic Rate
- Adaptive thermogenesis- Amount of energy needed to keep warm and absorb nutrients
- As you get older you lose muscle mass which drives down energy intake.

Energy Metabolism:

- Nutrient Requirements- Metabolic demand/ Efficiency of utilization
  - Also can be thought of as the intake associated with absence of disease, needed to cure sign of deficiency or needed to maintain circulating levels or tissue concentration.
  - Amount which must be consumed by an individual to maintain optimal health and function and or avoid deficiency.
  - Methods used to determine requirements:
    - Observation of intakes
    - Balance studies
    - Physiological estimates
    - Clinical studies
    - Functional tests

Vitamin C- Ascorbic Acid

- Essential
- Roles as an anti oxidant (Fe$^{3+}$ to Fe$^{2+}$)
- Important in formation of collagen.
- Deficiency is scurvy.

MASLOW’S HIERARCHY OF NEEDS- GCSE BUSINESS STUDIES

Physical needs: supply of water and food.
Density of malnutrition is directly related to low life expectancy.
Gambia: obesity and malnutrition side by side.
Underweight
Monitoring body weight can be complicated by fluid balance.
Arm circumference- can be used to measure subcutaneous fat.
Undernourishment in children can be determined by using growth charts.

Dietary reference values
- Reference Nutrient Intake- This is 2.5SD above the Estimated Average Intake (the amount actually needed).

- Only absorb 30% of iron from diet

- There are different needs for each nutrient which also vary before individuals and life stages, e.g. women of childbearing age need more iron than men.

Energy Metabolism:

Fates of Acetyl CoA

- Pyruvate
- Amino Acids
- Free Fatty Acids
- Acetyl CoA
- TCA
- Ketone Bodies
- Fatty Acids
- Acetyl C5A
Growth
- The human body will increase in weight twenty fold from a baby to an adult.
- All material in weight gain enters the human body as food and drink.
- Grossly abnormal diets will cause changes in body weight, configuration and composition.
- Example: height 100 years ago limit related to energy intake, now we possibly reach our genetic maximum.

Regulation of feeding
- Average human eats 900,000 kcal per year.
- A 3% error would result in an extra 27,000 kcal per year.
- This would result in an extra 10lb weight gain per year.
- Leptin levels are high in the morning.
- PYY tells you to stop eating.
- There are far more signals that tell you to eat then to stop eating in the human body.

Changes in Ageing
- Decline in body size, liver and kidney mass.
- Increase in body fat
- Decline in muscle mass
- Decline in total body water.

Causes of under nutrition in the developing world
- Politics
- Climate
- Poor water
- Poor agricultural policy
- Demand of the developed world
- Food security will become the biggest public health issue in the coming years.

To have a basic understanding of the role of the macro-nutrients in health and disease

Thiamine- Vitamin B1
- Thiamine occurs in the human body as free thiamine and as various phosphorylated forms.
- Beriberi is a nervous system ailment caused by a deficiency of thiamine in the diet.
- Thiamine is involved in the breakdown of energy molecules such as glucose, and is also found on the membranes of neurons.
- Symptoms of beriberi include severe lethargy and fatigue, together with complications affecting the cardiovascular, nervous, muscular and gastrointestinal symptoms.
- Berberin can almost be man made because thiamine bearing husks of white rice have been removed in polished white rice.

Niacin- Vitamin B3
- Nicotinamide is the derivative of niacin and used by the body to form the coenzymes NAD and NADP.
- Deficiency state is Pellagra.
- Thought initially to be an infectious disease as it spread rapidly around far east and Europe. It was noted this occurred as staple crops were replaced with maize apart from in Mexico where crops were softened with lime.

Complications relative to loss of LBM

<table>
<thead>
<tr>
<th>Lean Body Mass (% loss of total)</th>
<th>Complications (related to lean LBM)</th>
<th>Expected mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Increased infection</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>Decreased healing, weakness, infection</td>
<td>35</td>
</tr>
<tr>
<td>30</td>
<td>Too weak to sit, pressure sores, no healing</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>Death, usually from pneumonia</td>
<td>100</td>
</tr>
</tbody>
</table>

- Severe malnutrition in children can affect IQ.
- 7% of people over age of 70 are in malnutrition.

Signs of under nutrition
- Weight loss
- Loss of subcutaneous fat
- Muscle wasting
- Peripheral oedema
- Glossitis, cracking edges of mouth
- Hair loss
- Chronic infections
- Poor wound healing, chronic wounds, pressure sores
- Listless, apathetic
- Recurrent pulmonary infections.
Normal Metabolism
nonstressed, normal nutrient intake

CHO 55%-60% kcal
Pathway to energy
oxygen used

FAT 25%-30% kcal
Micronutrients

PROTEIN 5%-10% kcal
Pathway to protein synthesis

ENERGY DEPOT
Lean Mass
Compartment
Protein synthesis adequate to maintain physical and metabolic machinery

ENERGY PRODUCTION
For Cell function, Muscle function, Tissue repair

Hormones are balanced
Anabolic and catabolic stimuli

Intact skin
Prevents heat & water loss

Normal metabolic rate
25-30 kcal/kg/d

For: Cell function,
Muscle function,
Tissue repair

Protein synthesis adequate to maintain physical and metabolic machinery
Learning Objectives

- To recognise the clinical presentation of malabsorption
- To understand the disease mechanisms leading to malabsorption
- To learn about the clinical importance, presentation, complications and treatment of coeliac disease
- To understand the disease mechanisms leading to malabsorption

**Causes of malabsorption**

<table>
<thead>
<tr>
<th>Common</th>
<th>Coeliac disease</th>
<th>Gluten sensitive enteropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel bacterial overgrowth</td>
<td>Gastric surgery and achlorhydra</td>
<td>Intestinal blind loops post-surgery</td>
</tr>
<tr>
<td>Intestinal strictures</td>
<td>Fistulae (as in Crohn's disease)</td>
<td>Impaired peristalsis (fibrosis)</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>Chronic pancreatitis</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Less common</td>
<td>Short bowel syndrome</td>
<td>Intestinal resection for Crohn's disease, mesenteric vascular disease or injury</td>
</tr>
<tr>
<td>Chronic infections</td>
<td>Tropical sprue</td>
<td>Giardiasis, Other parasites (e.g. Strongyloids)</td>
</tr>
<tr>
<td>Tuberculosis, AIDS, Whipple's</td>
<td>Lymphoma</td>
<td>IPSID, EATL, refractory sprue &amp; ulcerative jejuno-ileitis</td>
</tr>
<tr>
<td>Radiation enteritis</td>
<td>Fibrosis, Atrophy, Strictures, Lymphangiectasia</td>
<td></td>
</tr>
<tr>
<td>Intestinal lymphangiectasia</td>
<td>Congenital, Infective, Fibrotic, Malignant, Cardiac</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Orlistat, Laxatives, Neomycin</td>
<td>Cholecystokinin (and certain others with specific interactions)</td>
</tr>
<tr>
<td>Allergic</td>
<td>Eosinophilic enteritis, Milk and soya enteropathy</td>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Congenital, acquired</td>
<td></td>
</tr>
</tbody>
</table>

**Frequent Clinical features**

- Malaise
- Coeliac disease - Inflammatory disease of upper small intestine resulting from genetic susceptibility.

**Malabsorption of specific nutrients**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Lactase non persistence</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Pernicious anaemia (loss of intrinsic factor)</td>
</tr>
<tr>
<td>Bile salts</td>
<td>Bile salt diarrhoea</td>
</tr>
</tbody>
</table>

- Hypolactasia in the small intestinal brush border membrane is usual adult human phenotype (non-persistence of neonatal lactase)
- Malabsorption of lactose in small intestine gives symptoms from breakdown in colon (H2, CO2, SCFA, lactate)

**Iron deficiency:** "Hyper or hypothyroidism can cause pretty much any GI condition" GI tumour could cause an intestinal bleeding but does not necessarily exit from the rectum.

**Nutrition**

- Fats
- Amino acids and proteins
- Carbohydrates
- Electrolytes and water
- Minerals
- Trace elements
- Vitamins

**Malnutrition Universal Screening Tool**

- BMI score
- Weight loss score
- Acute disease effect score
- Scores are assigned to each individual section and divides people into low, medium and high risk categories.

- Muscle wasting
- Loss of fat
- Oedema/ascites low albumin
- Anaemia, skin lesions, poor wound healing
- Anthropometry

**Malabsorption and malnutrition**

- Abnormal digestion
  - Reduced gastric tissue/secretion
  - Loss of pancreatic tissue
  - Impaired bile secretion

- Abnormal absorption
  - Loss of functioning enterocytes
  - Pre and post mucosal effects
  - Single gene disorders

- Steatorrhoea
  - Pale poorly formed stools with an offensive smell which is difficult to flush away.
  - Faecal fat content should be less than 6g a day.
  - Rarely lasts longer than 2 weeks.
  - Chronic diarrhoea has many causes:
    - Osmotic
    - Secretory
    - Inflammatory

- Weight loss
- Signs and symptoms of nutrient deficiencies
- And in children growth failure

**Malabsorption**

- Usual after surgery for Crohn's disease
- Less than 200cm of small intestine causes malabsorption, malnutrition, electrolyte imbalance, progressive weight loss.

**Short bowel syndrome**

- Usually after surgery for Crohn's disease
- Less than 200cm of small intestine causes malabsorption, malnutrition, electrolyte imbalance, progressive weight loss.

**Nutrient**

- Lactose
- Vitamin B12
- Bile salts

- Hypolactasia in the small intestinal brush border membrane is usual adult human phenotype (non-persistence of neonatal lactase)
- Malabsorption of lactose in small intestine gives symptoms from breakdown in colon (H2, CO2, SCFA, lactate)

**Iron deficiency:** "Hyper or hypothyroidism can cause pretty much any GI condition" GI tumour could cause an intestinal bleeding but does not necessarily exit from the rectum.
Coeliac disease: Inflammatory disease of upper small intestine resulting from gluten ingestion from genetically susceptible individuals.

- Pre and post mucosal effects
- Single gene disorders

**Frequent Clinical features**
- Malaise
- Fatigue
- Steatorrhoea
- Diarrhoea
- Weight loss
- Anaemia

**Common Clinical Features**
- Anorexia
- Abdominal pain
- Oral ulcers
- Osteopenia

**Rare Clinical Features**
- Tetany
- Oedema
- Rashes

**Changing presentation of coeliac disease**
- Under-diagnosis in the community may be related to change in presentation in coeliac disease
  - Possible decline in severity of illness
  - Less reliance on wheat-based diet.

**Autoantibodies**
- IgA class
- Tissue transglutaminase is the autoantigen recognised by endomysial antibodies and allows the production of anti- ttG antibodies.

**Dermatitis herpetiformis**
- Vesicular rash
  - Intense pruritus
  - Blisters rarely present
- Skin biopsy
  - IgA

**Gluten**
- Fraction of cereals that binds
- Proteins found in wheat, barley, rye.
- There are HLA association: HLA-A1 and HLA-DR
- Enteropathy- Inflammatory damage with cell death. Hyperplastic crypts results from stimulated regeneration.
- Main method of treatment is to avoid gluten and may be combined with nutritional supplements.

**Complications**
- Nutrient malabsorption and impaired nutritional status - slow growth, anaemia, neurological disorders
- Small bowel malignancy
  - Lymphoma- enteropathy associated T-cell lymphoma
  - Adenocarcinoma
  - Osteoporosis/ osteopenia.

**Common tests**
- Fats- faecal elastase
- Protein and nitrogen- urinary excretion, albumin
- Minerals- ions, calcium
- Also xylose absorption test of intestinal integrity/function
- Pancreolauryl test of pancreatic esterase activity

**Faecal Pancreatic Elastase**
- Enzyme stable during passage through GI tract and thus a small sample of stool is tested.
- High sensitivity and specificity for diagnosing pancreatic insufficiency
Enteric Nervous System

Learning Objectives

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

ANS
- Regulates smooth muscle, cardiac muscle and glands.
- Has both sympathetic and parasympathetic nervous system.

Enteric nervous system regulates:
- Motility
- Blood flow
- Water and electrolyte transport
- Secretion
- Absorption
- GI system.
The enteric nervous system integrates the motor and secretory activities of the GI system. If the sympathetic and parasympathetic nerves to the gut are cut many motor and secretory activities continue as they are controlled by the enteric nervous system.

Enteric neural dysfunction/regeneration
- Inflammation (ulcerative colitis; Crohn’s disease)
- Post-operative injury
- Irritable bowel syndrome
- Ageing (constipation)

Cell bodies of preganglionic parasympathetic neurons are in the brainstem and sacral spinal cord.
- Preganglionic neurons interact directly with enteric nervous system.

Sympathetic innervation
- Majority of sympathetic fibres do not directly innervate structures in the GI tract instead they terminate on neurons in the intramural plexuses.
- Vasconstrictor sympathetic fibres do directly innervate the blood vessels of the GI tract - coeliac, superior and inferior mesenteric.

Enteric plexus (Auerbach’s plexus)
located between the circular and longitudinal smooth muscle layers. Controls activity of muscularis externa.

Motility
Circular Muscle
Longitudinal Muscle
Minor plexuses including deep muscular plexus (inside circular muscle), and the ganglia supplying biliary system and pancreas
Submucosal Plexus
- Mucosa
- Muscularis Mucosa

Submucosal plexus (Meissner’s plexus). Sensing environment within lumen
Blood flow, epithelial and endocrine cell function

- Submucosa is closer to the surface than the muscle layers.
- Myenteric and submucosal plexuses respond and co-ordinate each other. Allows a specific type of response.

Migrating myoelectric complex
- Waves of electrical impulses moving through the gut. Trying to sweep the undigested food out. Begins at stomach then gradually moves down the GI tract. Explained well in Vander’s page S42.

Describe how gut hormones control GI function.
- Pretty major endocrine gland.

The Gut Hormones
- Secretin
- Gastrin
- Insulin
- Glucagon
- Somatostatin
- Cholecystokinin
- Pancreatic Polypeptide
The Gut Hormones

Describe how gut hormones control GI function.

Secretin
- Secreted by the S cells of the upper duodenum and jejunum.
- Major stimulus is the presence of acid in the duodenum (pH falls below 4.5).
- Stimulates pancreatic bicarbonate secretion (effect potentiated by CCK).
- High concentrations: inhibition of gastric acid and gastric emptying.

Cholecystokinin
- Secreted by cells most densely located in the small intestine.
- Release stimulated by fat and peptides in upper small intestine.
  - Actions:
    - Stimulates pancreatic enzyme release
    - Delays gastric emptying
    - Stimulates gall bladder contraction
    - Decreases food intake and meal size.

Gastric inhibitory peptide
- Secreted by mucosal K cells (predominantly in the duodenum and jejunum).
- GIP released following ingestion of a mixed meal.
- Fat is more potent stimulus than carbohydrate.
- Stimulates insulin secretion.
- GIP receptor antagonists reduce postprandial insulin release.

Peptide YY (PYY)
- Cells found throughout the mucosa of the terminal ileum, colon and rectum.
- Released from L cells post prandially (particularly fat).
- Actions:
  - PYY reduces intestinal motility
  - Reduces gall bladder contraction
  - Reduces pancreatic exocrine secretion.
  - Inhibitor of intestinal fluid and electrolyte secretion.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Location</th>
<th>Stimulated by</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>G cells of gastric antrum and</td>
<td>Mechanical distension of stomach</td>
<td>Release of gastric acid from oxyntic/parietal cells</td>
</tr>
<tr>
<td></td>
<td>upper duodenal mucosa</td>
<td>Direct vagal stimulation</td>
<td>Release inhibited when pH falls below 3 in the stomach</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>D cells of duodenal and jejunal</td>
<td>Released in response to a mixed meal</td>
<td>Inhibits gastric, intestinal and pancreatic secretions</td>
</tr>
<tr>
<td></td>
<td>mucosa, pancreas and hypothalamus</td>
<td></td>
<td>Growth and proliferation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Release of GI hormones</td>
</tr>
<tr>
<td>Secretin</td>
<td>S cells of upper duodenum and</td>
<td>pH below 4.5 in the duodenum</td>
<td>Intestinal nutrient and electrolyte transport</td>
</tr>
<tr>
<td></td>
<td>jejenum</td>
<td></td>
<td>Motility</td>
</tr>
<tr>
<td>CCK</td>
<td>Cells located mostly densely</td>
<td>Stimulated by fat and peptides in the</td>
<td>Stimulates pancreatic enzymes</td>
</tr>
<tr>
<td></td>
<td>in small intestine.</td>
<td>small intestine</td>
<td>Delays gastric emptying</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stimulates gall bladder contraction</td>
</tr>
<tr>
<td>GIP</td>
<td>K cells of upper duodenum and</td>
<td>Ingestion of a mixed meal - fat is a</td>
<td>Decreases: Motility</td>
</tr>
<tr>
<td></td>
<td>jejenum</td>
<td>large stimulus</td>
<td>Gall bladder contraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pancreatic exocrine secretions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluid and electrolyte transport</td>
</tr>
</tbody>
</table>

These are produced predominantly in the mucosa layer but with some also made in the submucosa.

- Act on secretory cells located in the wall of the GI tract, pancreas and liver to alter the rate or the composition their secretions.

Paracrine
- Histamine released from stomach wall cells is a key physiological stimulus to HCI secretion by gastric parietal cells.
- Somatostatin from the stomach can inhibit acid secretion by paracrine mechanisms.

Functions of the gastrointestinal endocrine system include:
- Regulation of the mechanical processes of digestion
- Regulation of the chemical and enzymatic processes of digestion.
- Control of post absorptive processes involved in the assimilation of digested food and CNS feedback regulating intake.
- Effects on the growth and development of the GI tract.

Gastrin:
- Synthesised in gastric antrum and upper small intestine.
- Release stimulated by:
  - Amino acids and peptides in the lumen of the stomach.
  - Gastric distension
  - Vagus nerve directly acetylcholine.
- Gastrin stimulates gastric acid secretion.
- Release inhibited when pH of stomach falls below pH 3.

Somatostatin
- Endocrine cyanide.
- Synthesised in endocrine D cells of the gastric and duodenal mucosa, pancreas (also hypothalamus).
- Somatostatin is a universal inhibitor.
- Release in response to a mixed meal.
- Inhibition of:
  - Gastric, intestinal and pancreatic secretions
  - Growth and proliferation.
  - Release of gut hormones
  - Intestinal nutrient and electrolyte transport
  - Motility
- G that's GRIM
- Analogues used to treat neuroendocrine tumours: Octreotide has a much longer half life.
- Gastric hormones have a very short half life less than 10 minutes.

Insulin
- Glucagon
- Somatostatin
- Pancreatic Polypeptide

GLP-1
- GLP-1 (glucagon-like peptide 1) functions in the upper small intestine.
- Major stimulus is the presence of amino acids and peptides in the lumen of the stomach.
- Inhibits release of gastric acid from oxyntic/parietal cells.
- Stimulates the release of bicarbonate from the duodenum, increasing bicarbonate concentration and intestinal fluid and electrolyte secretion.
- Stimulates intestinal nutrient and electrolyte transport.
- Motility.
- Increases food intake and meal size.
- Stomach secretion.
- Intestinal nutrient and electrolyte transport.
- Motility.

Insulin
- Stimulates glucose uptake by muscle and fat tissues.
- Inhibits release of gastric acid from oxyntic/parietal cells.
- Stimulates the release of bicarbonate from the duodenum, increasing bicarbonate concentration and intestinal fluid and electrolyte secretion.
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- Intestinal nutrient and electrolyte transport.
- Motility.
Learning Objectives

- Review the anatomical sections and main anatomical relations of the large intestine and related structures.
- Compare the structure and functions of the small and large intestines.
- Describe how the motility of the large intestine is regulated.
- Describe the control of defaecation.
- Describe the main functions of the large intestine.

Large Intestine

- Consists of the colon, cecum, appendix, rectum and anal canal.
- The cecum is a blind pouch just distal to the ileocaecal valve - larger in herbivore for the breakdown of food with bacteria.
- The appendix is a thin, finger-like extension of the cecum - not physiologically relevant in humans. Escape pod for good bacteria - hide in their during a diarrhoeal infection and helps with repopulation.
- The colon is the principal functions of the colon are the reabsorption of electrolytes and water and the elimination of undigested food and waste.

- 1.5m long, 6cm in diameter.
- The ascending colon is on the right side of the abdomen, runs from the cecum to the hepatic flexure (the turn of the colon by the liver).
- The transverse colon runs from the hepatic flexure to the splenic flexure (turn of the colon by the spleen).
- The descending colon runs from the splenic flexure to the sigmoid colon.
- Sigmoid (s-shaped) colon runs from descending colon to the rectum.

- Taenia coli - Bands of LONGITUDINAL muscle that leads to a pouched appearance.
- Taenia coli shorter than small intestine.
- They cause the formation of pouches or segments called haustra (singular hastrum).

Goblet Cells

- Higher number of goblet cells than small intestine.
- More prevalent in the crypts than along the surface, number increases distally toward the rectum.
- The mucus facilitates the passage of the increasingly solid colonic contents, and covers bacteria and particulate matter.
- Acetylcholine (parasympathetic and enteric nervous system) stimulates Goblet Cell secretion.

Paneth cells

- No Paneth cells in the large intestine this is because we want to keep the commensal bacterial.
- Reminder that the function of Paneth cells is to release acidophilic granules containing bacterial lysozyme, glycoproteins and zinc and to engulf some bacteria.
- Glycocalyx does not contain digestive enzymes.

Microvilli

- ~0.5-1.5um high and they make up the brush border
- There are several thousand microvilli per cell
- The surface of the microvilli are covered with glycocalyx
  - Rich carbohydrate layer on apical membrane
  - Protection from digestive lumen on apical membrane, yet allows for absorption
  - Traps a layer of water and mucus known as the "unstirred layer" which regulates rate of absorption from intestinal lumen.

Describe how the motility of the large intestine is regulated.

- Like the small intestine muscularis externa consists of an inner circular and outer longitudinal layer.
- Circular muscles are segmentally thickened.
- Longitudinal layer concentrated in three bands known as the taenia coli.
- Between the taenia coli the longitudinal layer is thin.
- Bundles of muscle from the taenia coli penetrate the circular layer at irregular intervals.
- Taenia coli shorter than circular muscle layer, ovoid segments called haustra can contract individually.

Describe the control of defaecation.

- Enterocytes and goblet cells are abundant.
- Abundant crypts.
- Stem cells found in crypts.
- Mucosa appears smooth at the gross level because it has no villi (smaller SA than small intestine).
- Enterocytes have short, irregular microvilli and primarily concerned with resorption of salts.
- Water is absorbed as it passively follows the electrolytes, resulting in more solid gut contents.

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- Water is absorbed as it passively follows the electrolytes, resulting in more solid gut contents.
Describe the main functions of the large intestine.

Large Intestine Motility
- 5-10cm per hour moving along the large intestine.
- Kneading process designed to absorb salt and water.
- Try to keep it up in the top of the large intestine due to the top being able to absorb more.
- Hastrual contraction-thickened circular muscle causes back and forth mixing.
- Short propulsive movements every 30 mins which increase in frequency following a meal.

Control
- Parasympathetic vagus nerve controls most of large intestine.
- External anal sphincter controlled by somatic motor fibres in the pudendal nerves.
- Afferent sensory neurons detect pressure.
- Hirschsprung’s disease: No enteric intramural ganglia.
- Myenteric plexus ganglia concentrated below taenia coli.
- Hormonal/paracrine control e.g. aldosterone can affect sodium and water absorption.

Mass movement
- 1.5 times daily- mass movement which resembles a peristaltic wave.
- Can propel contents 1/3-3/4 of length of large intestine in few seconds.
- Food that contains fibre promotes rapid transport through the colon.
- Stimulated to some degree whilst eating

Reabsorption
- Colon absorbs electrolytes and water.
- More is absorbed in the proximal colon.
- Na and Cl absorbed by exchange mechanisms and ion channels.
- Water follows by osmosis.
- K+ moves passively into lumen - loses potassium into the gut.
- Large intestine can reabsorb approx. 4.5 litres water (usually 1.5 litres). Above this threshold you have diarrhoea.

Large Intestine Flora
- All mammals have symbiotic relationships with their gut microbial community.
- Stomach and small intestine have few bacteria.
- Large intestine contains many, essential to normal function.
- Average weight of live bacteria is 1.5kg.

Roles
- Synthesis and excretion of Vitamin K- germ free animals can have clotting problems.
- Prevent colonization by pathogens by competing for attachment sites or for essential nutrients.
- Antagonise other bacteria through the production of substances which inhibit or kill non-indigenous species. Stops bad bacteria getting a foothold
- Stimulate the production of cross reactive antibodies. Antibodies produced against components of the normal flora can cross react with certain related pathogens and thereby prevent infection or invasion.
- Stimulate the development of certain tissues, including cecum and lymphatic tissues.
- Change in gut morphology.

Species:
- Bacteroides- Gram negative, anaerobic, non-sporeforming bacteria.
- Bifidobacteria are gram positive, non-sporeforming, lactic acid bacteria. Thought to stop colonisation by pathogens.

Links between gut bacteria and
1) Drug metabolism
2) Insulin resistance
3) Bile acid metabolism
4) Lipid metabolism
5) Obesity

Yakult- Just executing a bottle full of bacteria.

Describe the control of defaecation.
- Rectum filled with faeces by mass movement in the sigmoid colon.
- Stores until is convenient to void.
- Defaecation reflex controlled primarily by the sacral spinal cord both reflex and voluntary actions.

Rectum
- Dilated distal portion of the alimentary canal.
- Histologically similar to the colon but distinguished by transverse rectal folds in its submucosa and the absence of taenia coli.
- Terminal portion is the anal canal. Surrounded by internal (circular muscle) and external (striated muscle) anal sphincters.

Reflex
- Reflex to sudden distension of walls of rectum.
- Pressure receptors send signals via myenteric plexus to initiate peristaltic waves in descending, sigmoid colon and rectum. Internal anal sphincter inhibited.
- Weak intrinsic signal augmented by autonomic reflex.
- External anal sphincter under voluntary control.
- Urge resisted, sensation subsides.

Social rectum- Can distinguish between solid, liquid and gas. Cannot tell the difference between gas and oil very well.

Faeces
- 150g/day adult.
- Two thirds water.
- Solids: cellulose, bacteria, cell debris, bile pigments, salts (K+).
- Bile pigments give colour- oxidation of Sterobilinogen to stercobilin.
- Bacterial fermentation gives odour.

- 4.5 litres water (usually 1.5 litres)
- Loses potassium into the gut.
- Antibodies produced against thickened circular muscle causes back and forth mixing.
- Movements of large intestine more complicated then small intestine.
Specific issues in alimentary absorption

Learning Objectives

- Briefly describe the processes of diffusion and osmosis.
- Describe the different protein-mediated transport systems that move substances across membranes.
- Explain the mechanisms involved in absorbing water, Na⁺, K⁺, Ca²⁺, Cl⁻, HCO₃⁻, and vitamins in the alimentary tract.
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Calcium:
- Duodenum and Ileum absorb Ca²⁺
  - Think DIC
  - Ca²⁺ deficient diet increases gut’s ability to absorb.
  - Vit D and parathyroid hormone stimulate absorption.
  - Diet 1-4g/day, secretion 0.6g. Absorb 0.7g.
  - Calcium is a secondary messenger, lies on top of sodium channels etc.

Method:
- Calcium carried across apical membrane by Intestinal calcium-binding protein (IMcal) facilitated diffusion.
- Binds to calbindin in cytosol.
- Calcium pumped across basolateral membrane by Plasma Membrane Calcium ATPase (PMCA) and Na/Ca exchanger.
- PMCA has a high affinity for Ca²⁺ but low capacity. Maintains the very low concentrations of calcium normally observed within a cell.
- The Na/Ca exchanger has a low affinity for Ca but a high capacity. Requires large concentrations of calcium to be effective.

Vitamin D
- Essential for normal Ca absorption.
- Deficiency causes rickets, osteoporosis.
- Increases transport of Ca across the brush border although the exact mechanism is unclear.
- Enhances the transport of calcium ions across the cytosol.
- Increases the levels of calbindin.
- Increases rate of extrusion across basolateral membrane by increasing the level of Ca ATPase in the membrane.

Iron
- Essentially iron is toxic; if over absorbed there are serious pathophysiological effects.
- Adults ingest approx 15-20mg/day
  - But only absorbs 0.5-1.5 mgs.
- Iron forms insoluble salts with
  - Hydroxide
  - Phosphate
  - Bicarbonate ions
- Vitamin C increases iron absorption by converting Fe³⁺ to Fe²⁺ which we can absorb. (It prevents formation of insoluble complexes)

- Iron is present as
  - Inorganic iron (Fe³⁺ = ferric and Fe²⁺ = ferrous)
  - As a heme group (haemoglobin, myoglobin and cytochromes)

- Home is smaller part of diet, but more easily absorbed (20% of presented, rather than 5%)
- Cannot absorb Fe³⁺, only Fe²⁺ can be absorbed.

- Home
  - Dietary heme is highly bioavailable
  - Heme is absorbed intact into the enterocyte.

Process of absorption
- Takes place in duodenum: Duodenum + Iron = Die of too much iron

Water
- 99% of H₂O presented to the GI tract is absorbed.
- Greatest amount of water is absorbed in the jejunum.

Standing Gradient Osmosis
- Driven by Na⁺
- Transport of Na from lumen into enterocyte complex and varies between species.
  - Counter transport in exchange for H⁺ (proximal bowel)
  - Co-transport with amino acids, monoosaccharides (ileum)
  - Restricted movement through ion channels (colon)

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are transported into the intercellular spaces due to electrical

B12 + Ileum = BI
Calcium
Water
Vit B12 in the ileum and exchanged with HCO
Iron
Duodenum + Iron = DI = Die of too much iron

Brush border membrane bind the IF B12 complex and allow Vitamin

Divalent

Wall is incorrect?
Mechanism
Intrinsic factor
Vitamin B12
Vitamins

• Schilling test used to be used to check for B12 reabsorption.

Qu. 4: Which of the following statements about transport across the gut wall is incorrect?

• Takes place in duodenum: Duodenum + Iron = DI = Die of too much iron
• Heme is internalised into the enterocyte via Heme Carrier Protein 1 (HCP-1) and via receptor mediated endocytosis.
• Fe2+ liberated by Heme oxygenase.
• Duodenal Cytochrome B (Dcytb) catalyses the reduction of Fe3+ to Fe2+ in the process of iron absorption in the duodenum of mammals.
• Fe2+ is transported via Divalent Metal Transporter 1 (DMT-1), a H+ coupled cotransporter.
• Fe2+ binds to mobile ferritin, and is carried to the basolateral membrane and moves via Ferroportin ion channel into blood.
• Hepcidin, the major iron regulating protein, suppresses ferroportin function to decreases iron absorption
• Hephaestin is a transmembrane copper-dependent ferrooxidase that converts Fe2+ to Fe3+
• Fe3+ travels in blood bound to transferrin OR!
  ○ Binds to apoferritin in cytosol to form ferritin micelle.
  ○ Ferritin is globular protein complex. Fe2+ is oxidised to Fe3+ which crystallises within protein shell.
  ○ A single ferritin molecule can store up to 4,000 iron ions.
  ○ In excess dietary iron absorption you produce more ferritin.

Vitamin B12 appear in the plasma bound to
B12 to be taken up into epithelial cells.
Receptors on the
transferrin.
Transported into blood by
In the epithelial cells majority of iron is bound to ferritin and is unavailable for absorption.
Hephaestin so it can bind to transferrin.

Vitamin B12
• Takes place in ileum: Ileum + B12 = Ileal B12
• User contains a large store (2-5mg)
• Most Vitamin B12 in food is bound to proteins.
• Low pH and the digestion of proteins by peptic releases free vit B12.
• binds to R proteins.
• Can actually be destroyed in GI tract therefore bound to R proteins, which are later digested in duodenum.

Intrinsic factor
• Vitamin B12 binding glycoprotein
• Secreted by Gastric parietal cells
• VitB12/IF is resistant to digestion
• No IF then no absorption of vit B12
• VitB12/IF complex binds to cubulin receptor, taken up in distal ileum mechanism unknown, but thought to involve receptor mediated endocytosis.

Mechanism
• Once in cell, Vit B12/IF complex broken down—possibly in mitochondria.
• B12 binds to protein Transcobalamin II (TCI), crosses basolateral membrane by unknown mechanism.
• Travels to liver bound to TCI
• TCI receptors on cells allow them to uptake complex.
• Proteolysis then breaks down TCI inside of cells.

Vitamin B12 deficiency
• Impaired absorption of vit B12 retards the maturation of red blood cells.
• Pernicious anaemia

Prevention of iron toxicity
• Irreversible binding of iron to ferritin in the epithelial cells stops too much absorption of iron.
• Iron/ferritin is not available for transport into plasma.
• Iron/ferritin is lost in the intestinal lumen and excreted in the faeces.
• Increase in iron concentration in the cytosol increases ferritin synthesis and decreases its synthesis of transferrin receptors.

Vitamins
• Organic compounds that cannot be manufactured by the body but vital to metabolism.
• Passive diffusion predominant mechanism
• Fat soluble (ADEK) transported to brush border in micelles. K taken up by active transport.
• Specific transport mechanisms for vitamin C (ascorbic acid), folic acid, vitamin B1 (thiamine), vitamin B12.

Summary: Water
• Ingests about 2L/day
• 7L enters the gastrointestinal tract in various secretion.
• 99% of the H20 presented to the GI tract is absorbed.
• The absorption of water is powered by the absorption of ions.
• The greatest amount of water is absorbed in the small intestine, esp. the jejunum.

Summary: Hydration
• Prevents dehydration
• Glucose and amino acids move against a concentration gradient
• Active transport of Na+ into lateral intercellular spaces by Na+K+ATPase transport in the lateral plasma membrane.
• Cl and HCO3 are transported into the intercellular spaces due to electrical potential created by the Na+ transport.
• High conc of ions in the intercellular spaces causes the fluid there to be hypertonic.
• Osmotic flow of water from the gut lumen via adjacent cells and tight junctions into the intercellular space.
• Water distends the intercellular channels and causes increased hydrostatic pressure.
• Ions and water move across the basement membrane of the epithelium and are carried away by the capillaries.
• Cl is co-transported with Na+ in the ileum and exchanged with HCO3 in the colon. Both are types of secondary active transport.
• K+ diffuses in via paracellular pathways in the small intestine, leaks out of cells in colon. Passive transport.

Diarrhoea
• In secretory diarrhoea the secretion of CI, Na and water into the intestinal lumen - by cells in the crypts of Lieberkühn is elevated.
• Cholera toxin permanently activates adenyl cyclase, elevating cAMP in the crypt cells and thus enhances the secretion of Cl (and therefore also of Na and water)
• Cholera patients may produce up to 20 litres per day of watery stool. Such patients are likely to die unless they are promptly and adequately rehydrated.

Summary: Calcium
• Absorbed in the small intestine.
• Calbindin (a calcium binding protein) facilitates the transport of Ca++ through the cytosol of the intestinal epithelial.
• Ca++ is transported across the basolateral membrane by Ca ATPase and the Na+/Ca++ exchange protein.
• Vitamin D stimulates the absorption of Ca++ by enhancing the synthesis of calbindin and Ca-ATPase.

Summary: Iron
• About 5% of inorganic iron ingested is absorbed by the small intestine.
• Approximately 20% of the heme iron is absorbed.
• Inorganic iron is transported across the brush border via DMT-1 (Divalent Metal Transporter-1).
• In the epithelial cells majority of iron is bound to ferritin and is unavailable for absorption.
• Transported into blood by ferroportin, converted to Fe3+ by Hephaestin so it can bind to transferrin.

Summary: Vit B12
• Receptors on the ileal brush border membrane bind the IF B12 complex and allow Vitamin B12 to be taken up into epithelial cells.
• Vitamin B12 appear in the plasma bound to Transcobalamin II

Summary: Intrinsic factor
• Vitamin B12 binding glycoprotein
• Secreted by Gastric parietal cells
• VitB12/IF is resistant to digestion
• No IF then no absorption of vit B12
• VitB12/IF complex binds to cubulin receptor, taken up in distal ileum—mechanism unknown, but thought to involve receptor mediated endocytosis.

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Vitamin B12 deficiency
• Impaired absorption of vit B12 retards the maturation of red blood cells.
• Pernicious anaemia
All other things being equal, net osmotic water movement will occur from a solution of low tonicity to a solution of high tonicity.

Potassium is actively transported into enterocytes across the lateral membrane.

Paracellular transport involves movement through tight junctions.

Absorption of galactose across the apical membrane takes place by secondary active transport.

\( \text{Ca}^{2+} \) crosses the basolateral membrane by facilitated diffusion.

Best Option: \( \text{Ca}^{2+} \) crosses the basolateral membrane by facilitated diffusion.

\( \text{Ca}^{2+} \) cross the apical membrane via a facilitated diffusion mechanism involving intestinal calcium-binding protein and is then pumped across the basolateral membrane. The sodium/potassium pump on the lateral membrane both pumps Na\(^+\) ions out of the cell and K\(^+\) ions in; Galactose (and glucose) enter the cell via a Na/sugar co-transporter. This depends on a sodium gradient developed as a result of active transport elsewhere (i.e., the basolateral membrane pump) and is therefore secondary active; paracellular transport is between cells and therefore must pass though the tight junctions.
Learning Objectives

To understand the biochemistry and metabolism of ethanol

To understand the physiological effects and disease processes that alcohol can bring about in the various organ systems, with particular reference to liver disease and cirrhosis.

To appreciate the psychological and material impact of alcohol on both the individual and society as a whole

To develop the knowledge and skills to advise on how to enjoy alcohol responsibly and to identify and deal with problem drinking.

To appreciate the psychological and material impact of alcohol on both the individual and society as a whole

- Addictive element that is associated with alcohol.
- Alcohol misuse (Problem drinking)
- Alcoholic liver disease
  - Alcohol addiction (Alcoholism)
    - These three are arranged in a Venn diagram.
- Addiction is dealt by psychiatrists and drug and alcohol workers.

Alcohol misuse:
- Failure to carry out major obligation at work, home, or school because of repeated alcohol use.
- Repeated use of alcohol even when it is physically dangerous to do so.
- Continued use of alcohol despite knowing that it has caused or worsened social or interpersonal problems.

Alcohol dependence
- Evidence of tolerance and/or withdrawal
- Amount of duration of use often greater than intended.
- Repeated failure to control or reduce alcohol use.
- Withdrawal symptoms

Nature vs nurture
- Suggestion that there must be a genetic component to alcohol addiction.
- Alcohol and heroin addicted mice get clever. "Sleep with dirty old men mice to get it is an inducible enzyme so people who drink heavily can still have a lot more side effects and migrating macrophages, chronic inflammation causes them to develop a lot more mortality.

To understand the physiological effects and disease processes that alcohol can bring about in the various organ systems, with particular reference to liver disease and cirrhosis.

Alcohol and the upper GI tract
- Oesophagus
  - Cancer
  - Reflux
  - Oesophagitis
- Stomach
  - Gastritis
  - Ulcers
  - Cancer
- Chronic Pancreatitis
  - Up to 45% due to alcohol.
  - Exocrine insufficiency
    - Steatorrhoea, vitamin deficiencies, hypocalcaemia
  - Endocrine insufficiency
    - Diabetes
- Evidence that no alcohol whatsoever leads to a slight increased risk of stroke.

Neurological effects
- Wernicke's encephalopathy
- Korsakoff's psychosis
- Optic toxicity
- Autonomic dysfunction
- Peripheral neuropathy.

Alcohol and Immunity
- Alcohol leads to immunosuppression.
  - Increased incidence of infectious disease
  - Bacterial pneumonia, Septicaemia, TB, Hepatitis C.
- Alcohol leads to an increased incidence of autoimmunity.
  - Contributes to liver disease and renal dysfunction.
  - Alcoholic hepatitis, liver cirrhosis, renal disease associated with IgA deposition.

Fetal alcohol syndrome
- Fetal alcohol syndrome is among the most commonly known causes of mental retardation and is a major public health problem.
- Other interesting information
  - Significantly improves life expectancy if you detox alcoholics.

Clinical features of Acute Alcohol Poisoning
- Death and anaesthesia leading to accidental injury

To understand the physiological effects and disease processes that alcohol can bring about in the various organ systems, with particular reference to liver disease and cirrhosis.

- Alcohol dehydrogenase.
- Aldehyde is very toxic - increases blood pressure, nausea, headache.
- Aldehyde dehydrogenase (ALDH)- genetic polymorphisms for this gene.
- Asia - capacity to breakdown alcohol is significantly reduced - a lot more side effects and more prone to liver disease.
- Cytoschrome P452E1 - it is an inducible enzyme so people who drink heavily can still metabolise effectively.
- Reactive Oxygen Species are generated via the CYP2E1 pathway, tissue damage, inflammation and stimulation of the immune system which leads to fibrosis and cirrhosis.

Progression of ALD
- Normal liver → Fatty liver → Fibrosis → Cirrhosis → Hepatocellular carcinoma.

Fatty Liver
- Fat droplets deposited in the liver.
- Occurs in up to 60% of heavy drinkers.
- Leads to steatohepatitis and abnormal LFT's.
- Reversible if alcohol reduced.
- Fat sets up an inflammatory reaction which stimulates the immune system and cytokines causing damage.

Hepatic Fibrosis
- Space of Disso - migrating macrophages, chronic inflammation causes them to develop into fixed hepatic stellate which lay down collagen fibres.

Cirrhosis
- Asymptomatic.
- Irreversible scarring of liver with fibrous bands and regenerative nodules.
- Eventually develops in 20% after 15 years.
- Mortality common, associated with jaundice, ascites, bleeding, cachexia, infections and encephalopathy.
- 3-5% per annum risk of developing liver cancer.
- Death in most within 10 years.

To develop the knowledge and skills to advise on how to enjoy alcohol responsibly and to identify and deal with problem drinking.

- Useful link to check you are doing the calculations right
  - http://www.drinkaware.co.uk/tips-and-tools/drink-diary/

Calculating units by mass
- % alcohol is the number of g of alcohol in 100ml.
- Gs of alcohol = percentage mass of alcohol x volume drunk/100
- Annoyingly to make it more complicated most drinks don’t give the percentage of alcohol by mass they instead do it by volume.

Calculating units by volume
- Gs of alcohol= (Percentage volume x 0.789 x volume drunk)/100
- The problem is when calculating percentage by volume is that ethanol’s density is not the same as water. Therefore 10g of alcohol does not have a volume of 10ml. In order to be able to do the calculation we need to multiply by ethanol’s density which is 0.789.

Worked example
- Last night I drank 1 pint of lager at 5% alcohol by volume. Calculate how many units I consumed.
- Gs of alcohol= (5 x 0.789 x 568/100=22.4076 g of alcohol
Worked example

Last night I drank 1 pint of lager at 5% alcohol by volume. Calculate how many units I consumed.

\[ \text{Gs of alcohol} = \frac{5 \times 0.789 \times 568}{100} = 22.4076 \text{ g of alcohol} \]

- 8g of alcohol = 1 unit
- \[ \frac{22.4076}{8} = 2.801 \text{ units} \]

I wouldn’t think that they would ask you to do it by volume as they didn’t teach us about the density of ethanol causing problems, however it may crop up and is useful to know.

Food in the stomach dramatically reduces the amount that gets absorbed into the blood.

You can have liver disease without getting drunk.

Alcohol is very rapidly absorbed into the duodenum.

- Ataxia and anaesthesia leading to accidental injury.
- Dysarthria (slurring of words) and nystagmus - weird eye twitching.
- Drowsiness which may progress to coma.
- Inhalation of vomit which can be fatal - maintain airway by keeping patient in the recovery position.

Effects of Alcohol on Male Reproductive System

- Alcohol is a strong Leydig cell toxin, it can have an adverse effect on the synthesis and secretion of testosterone and is one of the commonest causes of male impotence.
- Hangover - end up dehydrating yourself. Altered osmolarity of endolymphatics.

Alcohol induced hypoglycaemia is one of the serious complications of acute alcohol poisoning.

First Pass Metabolism of Ethanol

Oral Alcohol

IV Alcohol

Alcohol induced hypoglycaemia is one of the serious complications of acute alcohol poisoning.
Learning Objectives

- To understand that diarrhoea is a very significant contributor to global morbidity and mortality in children under 5 years. You should be familiar with the size of the problem.
- To understand the critical differences between acute and chronic presentations of diarrhoea in children.
- To be aware of the major advances in prevention and management that have lead to reductions in mortality from diarrhoea in the last 25 years.

One billion people worldwide lack access to clean water.
- 2.5 billion do without adequate sanitation.
- Median episodes per year of diarrhoea = 3.2

Diarrhoea: Increase in stool frequency with change to loose or watery stool.

Viral causes of diarrhoea
- Rotavirus
  - Virtually every child infected by age of 5 years.
  - Faecal-oral spread
  - Enterocyte destruction: osmotic diarrhoea
  - Rehydration is key
  - Caliciviruses
    - Noroviruses
    - Sapovirus
  - Adenovirus
  - Enterovirus

Bacterial causes
- Enterotoxigenic E.Coli (ETEC) traveller’s diarrhoea
- Shigellae spp. Invasive. Dysentery
- Vibrio cholerae
- Salmonellae
- Campylobacter
- Yersinia

Protozoa
- Cryptosporidium
- Giardia
- Entameoba histolytica

Types of diarrhoea
- Secretory: active secretion, or inhibited absorption, without structural damage
  - Cholera and some E.coli toxins: switches on chloride pump.
- Osmotic: water drawn to gut lumen passively
  - Maldigestion (e.g. pancreatic disease)
  - Osmotic laxatives
- Inflammatory: damaged mucosa cannot absorb
  - Infections
  - Inflammatory disease e.g. Crohn’s

History
- Still eating/feeding
- Still passing urine
- Poo-blood? Mucus? Freq?
- Food eaten- New? Off?
- travel
- Swimming
- Pets
- Immunodeficiency

Examination
- ABC (airway, breathing, circulation)
- Any other focus for infection?
- Degree of dehydration.

Clinical features
- Dry mucous membranes
- Sunken fontanelle
- Dark, sunken eyes
- Low turgor
- Delayed capillary refill time

Moderate: 5-10% Severe: >10%

General
- Drowsy
- Limp, sweaty, cold, cyanotic

Pulse
- Tachycardic
- Rapid, weak

BP
- May be normal
- Low

Urine output
- Reduced
- Absent

- Percent of body weight water loss.
- Oral rehydration needs glucose in order to help with sodium absorption.
- Intra-osseus: if you cannot get the vein you go for flat bit of the tibia as this will be rapidly become part of the circulation.

Diarrhoea, malnutrition, & pediatric mortality in regional referral hospital
Francistown Botswana, Nov 2005 - April 2006

Diarrhoea accounts for 20% of mortality < 5 years.

Chronic Diarrhoea
- Use height/weight measurement.
- Coeliac disease: destruction of enterocytes brush border.
- Infections, and post infection syndromes.
- Carbohydrate intolerance.
- Food sensitivities
  - Permanent (e.g. Coeliac disease)
  - Temporary (e.g. Cow’s milk protein intolerance)
- Mother can pass on enough cow’s milk protein just by drinking it herself.

Complications:
- Malnutrition
- Poor growth, delayed puberty
- Anaemia, rickets
- Cognitive impairment.
Learning Objectives

- How blood osmolality and pressure regulate thirst.
- The major hypothalamic circuits regulating appetite.
- The role of leptin in the regulation of body weight.
- How gut hormones can influence short term appetite.
- The major hypothalamic circuits regulating appetite.

How blood osmolality and pressure regulate thirst.

- A person feels thirsty when:
  - Body fluid osmolality is increased
  - Blood volume is reduced
  - Blood pressure is reduced

- The increase of the plasma osmolality is the more potent stimulus as just a 2-3% change induces a strong desire to drink.
- A decrease of 10-15% in blood volume or arterial pressure is required to produce the same response.
- As covered in other sections antidiuretic hormone acts on the kidneys to regulate the volume and osmolality of urine. High levels of ADH cause the kidneys to retain more water and a small volume of urine is excreted.
- Osmoreceptors that measure the osmolality of the blood are located in the Organum vasculosum (of the lamina terminalis (OVLT) or supraoptic crest) and the Subfornical organ (SFO)
- These osmoreceptor cells shrink or swell in response in changes to osmolality. They then send signals to the ADH producing cells of the hypothalamus to alter ADH release.

Sensation of thirst

- The feeling of thirst is decreased by drinking even before sufficient water has been absorbed by the GI tract to correct plasma osmolality (PO)
- Receptors in the mouth, pharynx, oesophagus seem to be involved.
- Relief of thirst sensation via these receptors is short lived.
- Thirst is only completely satisfied once PO is decreased or blood volume or arterial pressure is corrected.
- Once again the renin-angiotensin-aldosterone system. Angiotensin II invokes the sensation of thirst, this is important because one of its important functions is to raise blood pressure and therefore it is released when blood pressure falls. Angiotensin II activates SFO neurons to contribute to the homeostatic response to maintain body fluids at the correct levels.

Can leptin cure obesity?

- 3 ways in which leptin regulatory loop could lead to obesity
  - Leptin is a circulating hormone produced by adipose cells.
  - They hypothalamus sense the concentration of the hormone then alters neuropeptides to increase or decrease food intake.
  - Leptin is low when there is low body fat
  - Leptin levels are high when there is high body fat.
  - Hormone that decreases food intake and increases thermogenesis.

**Stuart's Alimentary System Page 49**
No NPY or AgRP mutations associated with appetite have been discovered in humans.

POMC deficiency and MC4-R mutations cause morbid obesity.

- A drug company paid a lot of money to commercial rights to leptin hoping that mechanism A or B would be leptin’s involvement in obesity. Instead obese people have high levels of leptin because they have leptin resistance.

- There are a small number of cases of congenital leptin deficiency which results in severely hyperphagic and obese individuals.

How gut hormones can influence short term appetite.

- We feel less hungry after a meal not due to the bulk in the stomach or the nutrients in the circulation but because of the release of hormones from the gut.
  - These hormones are:
    - Peptide YY
      - 36 amino acid peptide with a tyrosine at both ends that is released into the circulation after a meal.
      - Directly modulates neurons in arcuate nucleus
        - Inhibits NPY release
        - Stimulates POMC neurons
      - Decreases appetite
      - PYY3-36 reduced food intake 36%.
    - Ghrelin
      - Ghrelin is a gastric hormone that is 28 amino acids long (peptide hormone) and has an octanyl at the 3rd position. High when fasting and falls after eating.
      - Stimulates NPY/AgRP neurons
      - Inhibits POMC neurons
      - Increases appetite

- Gut hormones may represent a novel treatment for obesity.