inflammatory cytokine suggesting an immune modulating role of the organism.

Whilst the cause is unknown it is thought to be due to increased sensitivity of the gut and problems digesting food.
Emetics

**Ipecacuanha:** actives constituents are the alkaloids emetine and cephaline. These irritate the lining of the stomach producing vomiting.

**Apomorphine:** D₂ dopamine agonist which acts centrally in the chemical trigger zone. This works best as a subcutaneous injection.

Diarrhea

About 9L of water is reabsorbed by the bowel everyday - if we can’t reabsorb all of this then we get diarrhea.

The bowel reabsorbs water and electrolytes in the following way. Sodium is in high concentration in the lumen of the gut. The gut epithelium use Na/Glucose transporters, which use active transport, to uptake sodium and water. Sodium also enter via sodium channels. On the basolateral side sodium is pumped into the blood whilst K⁺ is pumped into the cell. Glucose is driven into the cell by sodium and then is pumped into the blood. This creates an osmotic pressure that pulls water across such that it is reabsorbed. If this fails, such as in diarrhea, we loose water. With this loss of water bicarbonate can enter the lumen of the gut and thus be lost. This leads to acidosis.

Diarrhea can be caused by infection, toxins, chronic inflammation and dietary imbalance. This is most dangerous in neonates and elderly patients due to dehydration and acidosis. Principles of treating diarrhea: symptoms; correct the fluid and electrolyte loss, withdraw food. Give antibiotics if a bacterial cause at heart. Use absorbents such as charcoal, kaolin, pectin and bismuth salts.

Cholera needs live saving rehydration by IV or inter arterial lines. Symptoms include severe diarrhea, sunken eyes and wrinkly skin. Cholera produces a pentameric toxin made of A and B parts. This binds to the cell surface receptor which is then internalized by the cell. The cell then cleaves the protein into single A and B parts. A is the toxin and acts on the G protein Gₛ so as to activate adenylate cyclase and thus increase cAMP. This then activates PKA which phosphorylates the chloride channel which activates it. Chlorine is secreted into the lumen which leads to sodium and water secretion leading to diarrhea. For this we can use antibiotics to target the infection. We can use drugs that stop the breakdown of enkephalins. These molecules stimulate GI which inhibits adenylate cyclase. Such drugs include racecadotril. **Crofelemer:** this acts on the chrolide channel [CFTR] to stop chloride secretion.
Lecture 8: GI Tract Physiology 4: Gastric Secretion

The stomach is the first site in which protein degradation occurs. This occurs with the help of pepsins and occurs in the corpus of the stomach. To activate pepsinogen to pepsin you need HCL. Intrinsic factor is made in the stomach and this is essential to protect vitamin B12 in the small intestine. The secretions of the stomach as isosmotic to plasma. The mucus and bicarbonate protect the stomach epithelia. The secretion has anti microbial properties.

The fundus produces mucus. The corpus makes HCL, intrinsic factor, pepsinogen, mucus and histamine. G cells produce gastrin and D cells produce somatostatin. The antrum makes mucus, gastrin [G cells] and somatostatin [D] cells. G cells produce gastrin and D cells produce somatostatin

There are various mucosal cells:
- Surface epithelia make mucus and bicarbonate.
- Mucous neck cells make mucus.
- Parietal cells make HCL and intrinsic factor.
- Chief cells (which have nucleus at the bottom of the cell) make pepsinogens.
- Endocrine or D cells make histamine and somatostatin.

HCL has various functions. It activates pepsin from pepsinogen. It kills or inhibits microbes. It stimulates secretions in the small intestine (to prepare for the arrival of food) and it helps iron and calcium absorption in the small intestine. The stomach has a 100+mmol concentration of H+ ions where as the intracellular environment is about 60 nmmol. Thus, there is a large concentration gradient.

When HCL is secreted we see morphological changes. The resting parietal cell has abundant tubular vesicles under the apical membrane. When the cell is stimulated these vesicles fuse to the membrane to become canaliculi. These acts to increase the surface area. They hold transporter proteins: H/K+ ATPase, K+ and Cl- transporters. Thus, fusion increases the number of transporters needed for acid secretion.

Secretion of HCL

The H/K+ ATPase on apical membrane pumps out H+ in exchange for K+. To block this clinically we use omeprazole. Ovabain is a drug that will act to inhibit the Na/K+ ATPase. The H/K ATPase works with the K+ channel on the apical side to get the K+ out of the cell. Water and bicarbonate moves on the basolateral surface. Carbon dioxide diffuses in and water enters via aquaporin’s. Water and CO2 will react to form carbonic acid at first but this then forms H+ and bicarbonate. This is catalyzed by carbonic anhydrase. On the basolateral membrane bicarbonate leaves in exchange for a Cl into the cell. This alkalizes the blood vessels of the stomach; this is called the alkaline tide. There is a Cl selective channel on the apical membrane to remove to the Cl. Basolateral membrane K+ channels maintain the driving force for Cl exit across the apical membrane.
Products of digestion [critically fat but also hyperosomatic solution in the duodenum] are detected by I and K cells. I and K cells are in the wall of the duodenum. I cells make CKK which inhibits parietal cells; K cells make GIP [gastric inhibitory protein] which acts on parietal cells and G cells of the antrum.

All of these different ways give us fine control and redundancy.

Persistalsis occurs in the body and antrum to mix food with the secretions. There is tonic contraction of the pylorus which controls emptying into the duodenum.

Food acts on mechanoreceptors, which via the vagal nerves, leads to movement of the stomach. The stomach has a pacemaker zone (in the upper corpus on the right). This makes waves of electrical, and ultimately muscular, excitability to churn up the stomach.

Persistalsis: contractions begin in the body and travel towards the pylorus. The increase in force and velocity as they approach the gastro-duodenal junction. Mixing occurs mainly in the antrum. Repropulsion (moving backwards) is very effective at mixing and breaking down gastric contents. There is tonic contraction over minutes or hours controlling the pylorus.

Carbohydrates are emptied from the stomach quickest, then proteins and slowest are fats.

The emptying of gastric contents:
- Gastric phase controlled by neural and hormones. Food activates receptors leading to gastrin release increasing motility and reducing tone to sphincter.
- Intestinal. When chyme delivered to small intestine then the rate of emptying is slowed by: hypertonic solution, HCL, fatty acids and monoglycerides and amino acids/proteins. Receptors detect these and release secretin GIP and CCK to reduce motility and close sphincter to slow emptying. If you add acid into the duodenum, then we see an increase in the contraction of the duodenum; but the stomach sees reduced activity. I.e. the duodenum is feeding back to stop the stomach pushing more acid in. as a result of control then gastric emptying does not exceed the rate at which; acid can be neutralized, fat can be emulsified and the small intestine can process chyme.
Lecture 11: Pharmacology of Gastric Acid Secretion

Other drugs used in diarrhea include motility modifying drugs:

- **Anti-muscarinics.** These reduce peristalsis and segmental contractions. But ideally we would increase segmental contraction. This, coupled with the fact the drugs have broad effects, means they are seldom used. The aim is to increase the time spent by food in the GI tract to increase water reabsorption.
- **Opioids** are a better choice as they reduce peristalsis and increase segmental contraction by having a direct effect on GI smooth muscle via the opioid receptors. Some opioids also increase fluid and water absorption. Examples include loperamide.
- **Anti-inflammatories** such as sulphasalzine which is broken down by gut bacteria into sulphonic acid [anti-inflammatory] and an antibiotic. These are used in treatment of inflammatory bowel disease and severe ulcerative colitis.

For morning sickness, we want to give promethazine, the H1 antagonist.

Laxatives can be a treatment for constipation. Constipation can occur due to slow motility of the colon; to much water removed by the colon and weak abdominal muscles. Laxatives accelerate the passage of contents through the intestine. Drugs include lubricants, bulk-forming drugs, intestinal stimulants and osmotics [to reduce water absorption since the more osmotic the environment the less water will be reabsorbed].

**Lubricants**

e.g. liquid paraffin. General safe. Special care; lubricant laxatives line the mucosal surface thus they might prevent the absorption of fat-soluble vitamins and other nutrients.

**Bulk Forming Agents**

e.g. sterculla [a non digestible polysaccharide] and bran [has water insoluble fibres]. These increase the volume of non-absorbable food material in the colon. Special care needs to be taken to ensure adequate fluid intake occurs to avoid dehydration and consequent worsening of the constipation.

**Intestinal Stimulants**

e.g. bisacodyl, dantron and phenolphthalein. They stimulate the contraction of the intestine to aid fecal expulsion. The stimulate cAMP, cholecystokinin and vasoactive peptide synthesis. Have a direct effect on smooth muscle and also effect the myenteric plexus to increase peristalsis. These may cause abdominal cramps and should not be used when there might be an intestinal obstruction.

**Osmotic Laxatives**

e.g. MgSO_4 and lactulose. These are poorly absorbed solutes when remain in the GI tract and so promote the movement of water from the tissues into the lumen.
Lecture 12: GI Tract Physiology 6: Digestion in the Intestine

All foodstuffs are completely digested in the small intestine. All secretions in the small intestine are iso-osmotic i.e. they have the same osmolality as plasma. Secretions of the small intestine:

**Intestine:** makes 1 litre a day of pH 7.6 secretion composed of mucus, enteropeptidase [which activates pancreatic enzymes] and water.

**Liver:** makes 0.5 litres a day of pH 7.4 secretion composed of bile acids, cholesterol, phospholipids etc.

**Pancreas:** 1.5 litres a day of pH 7.4-8.4 secretion composed of salts and enzymes. The pancreas has a large capacity to synthesize proteins and secretes the most bicarbonate. Without a pancreas you need enzyme replacement therapy with every meal. Pancreas has both endocrine [insulin and glucagon] and exocrine functions [salts, water and enzymes (which are made in acinar cells)].

The pancreatic juice is composed of salts, water, bicarbonate, and sodium chloride, which acts to create the right environment for enzymes to work. The enzymes include proteases, lipases and a-amylase [which digests carbohydrates]. These enzymes are important for digestion of foodstuffs and are essential for life.

The roles of bicarbonate are four fold. Firstly, it buffers pH also neutralizes acid, it provides anti-microbial properties and finally it helps to give the physical properties to mucus. Mucus is stored in tight packets in the zymogen which calcium ions bound. The bicarbonate will bind to the calcium when the zymogen is secreted and flatten out the mucus polymer to one long thin chain of mucus. In cystic fibrosis patients lack bicarbonate and so the mucus doesn’t form its proper structure.

The pancreas has the same structure as the salivary glands with a main collecting duct, and lobules composed of an accinus and an intercalated duct. Acinar cells line the accinus and duct epithelial cells line the duct. The pancreas makes 5-15 grams of protein each day and makes over 20 enzymes.

Recall how in the salivary glands the ductal epithelial cells had tight junctions so that all movement was **transcellular**. The water and sodium movement occurs paracellulary in the accinus and this physically washes all the secretions away from the accinus i.e. down the duct. In the pancreas the duct lining epithelia lack these tight junctions. So sodium, water and bicarbonate can all enter the duct lumen and chloride can exit the lumen and enter the cell.

**Recall:** proteins are made and packaged into zymogen granules on the apical surface of acinar cells.

Zymogen granules sit at the apical pole of acinar cells. Lipases and a-amylase are secreted in their active form. But proteases must be secreted in their inactive form so as to avoid
junctions. Bicarbonate secretion into the duct draws the Na and water across to complete the isotonic NaHCO3- secretion.

The duct is regulated as follows. Secretin is the dominant player. This rises cAMP and thus phosphorylates the apical Cl channel. This is the defective channel in cystic fibrosis. The duct cells drive the movement of the secretions down the duct; there is high flow and low protein content [as all the protein is washed down the duct into the intestine]. But in CF there is poor modification to the secretion, as the channel is defective, and so protein accumulates in the duct and pathology occurs. In the CF patient the exocrine tissue is often replaced with fat. Thus if we stop the flow of ions protein will get stuck in the duct.
Recap: the duct lining epithelia need to remove H+; this is done with the Na/H exchanger [Na moves in via the electrochemical gradient and in returns removes H+]. This is secondary active transport.

Enteropeptidase activates the inactive enzymes [trypsinogen, chmotrypsinogen and precarboxypeptidase] into their active forms. The enteropeptidase is found in the wall of the villus of the enterocytes in the duodenum but there is also some free in the lumen of the duodenum [this is released from the apical membrane; bile salts promote their release]. Once some active forms are produced they feed back to make more of the inactive precursors. When trypsinogen is released by the acinar cells it is accompanied by trypsin inhibitor to protect from accidental activation prior to it reaching its target site.

Control of Pancreatic Secretion

**Cephalic phase:** vagal impulses are the major stimulus. This phase accounts for 25% of total volume of secretion. This is an enzyme rich secretion.

**Gastric phase:** distension from food acts on mechanoreceptors leading to a vagovagal reflex [here specifically it is the gastropancreatic reflex] that leads to release of an enzyme rich secretion. This phase accounts for about 10% of secretory volume.

**Intestinal phase:** accounts for 65% of secretory volume. Hormones are the major stimuli. The acid released from the stomach into the duodenum will act on chemoreceptors. This causes $S$ cells, in the wall of the duodenum, to release secretin. This travels in the blood to the ductal cells. This causes a large volume but low enzyme content secretion to be created. In addition, fatty acids, monoglycerides and peptides are detected by $I$ cells which release CCK. This travels in the blood and acts acinar and ductal cells to produce an enzyme rich pancreatic juice.

Also in this phase there is a change in distention and osmolality. This acts on mechanoreceptors via the enteropancreatic reflex [a vagovagal reflex] to cause pancreatic secretion.

Bile is secreted by hepatocytes and stored in the gall bladder. Bile is composed of:
- Bile acid [65%] which emulsifies lipids to improve their digestion.
- Cholesterol [4%] this is the only significant method of excretion of cholesterol.
- Phospholipids [20%] which form mixed micelles to allow the absorption of fatty acids.
- Bile pigments [0.3%] which are the breakdown products of haemoglobin (bilirubin). Also allows the removal of heavy metals and drugs.

Between meals bile is concentrated and stored in the gall bladder. The emptying of the gall bladder occurs as follows. In the cephalic and gastric phase there are vagovagal reflexes to contract the gall bladder and relax the sphincter of Oddi. The epithelium of the gall bladder absorbs NaCl to concentrate the bile. In the intestinal phase fatty acids cause the release of CCK from $I$ cells which will act to empty the gall bladder into the duodenum in the same
Lecture 18: Disorders of Absorption

**Malabsorption:** a state in which there is failure of the intestinal processes of digestion, transport or both of nutrients across the intestinal mucosa into the circulation.

**Malnutrition:** a state in which a deficiency of nutrients such as energy, protein, vitamins and minerals causes measurable adverse effects on tissue composition, function or clinical outcome.

**Intestinal failure:** a reduction in the functioning gut mass to below the amount required for adequate digestion and absorption of food. This can be temporary, permanent, acquired or congenital. It can be broadly grouped into 3 types of failure:

1. **Type 1** or self limiting. For example, with an ileus post surgery [this is when the gut stops working briefly].
2. **Type 2** – this is more severe and required temporary support. For example, following a major resection.
3. **Type 3** - chronic. This will require long term nutritional support. For example, following a small bowel infarction.

Absorptive mechanisms. There is luminal processing followed by mucosal absorption and then transfer of the nutrients into the circulation. Thus there many sites where this may fail. For example, the luminal processing may fail following a gastrectomy or following pancreatic insufficiency, the mucosal absorption may be damaged by diseases such a coeliac’s and the transfer to the circulation may fail following lymphatic disease such as lymphangiectasia.

**Clinical Presentation**

This can be varied and affect multiple systems and may indeed be asymptomatic. The signs and symptoms will lead to an indication of the location of the pathology.

**Diarrhea:** this is the most common symptom. Secretory diarrhea is seen in inflammatory conditions. There may also be fat and bile salt malabsorption. Bile is reabsorbed at the terminal ileum so if you resect this, which is often done for Crohn’s, then bile will get into the large colon where it is an irritant and cause diarrhea.

**Weight loss:** often indicates small bowel pathology. There may be dietary avoidance such as fatty foods. Inflammation occurs in addition to the malabsorption. An entero-colic fistula may have occurred- this is a small bowel to colon fistula. The can occur in inflammatory states, such as Crohn’s, where inflammation causes an ulcer that the pushes through to the large bowel. The food can go straight through and thus leading to malabsorption and rapid transit times of the bowel.

**Pain and bloating:** this may be caused by inflammation or obstruction. A stricture means that no food can pass through leading to colic pain [muscle pain]. There are no pain receptors in the bowel, hence it is possible to colonoscopically resect polyps etc. The
B12 is found in animal products. When it is ingested it is complexed with R factor in the stomach, it then travels to the small bowel where it is protected by intrinsic factor. It is then absorbed in the terminal ileum [in the last 2 feet]. B12 is important for RBC and integrity of the neurological system [Wernicke’s encephalopathy]. The stomach will make and release intrinsic and R factor.

Dietary insufficiency is rare other than in vegans. But people may lack intrinsic factor; such as in gastrectomy, pernicious anaemia. Bacteria may uncouple the complex in the jejunum or ileum. There may be disease or resection of the terminal ileum.

**Pernicious Anaemia.** This is also macrocytic anaemia. The RBC may contain nuclear material [megaloblasts] and we see hypersegmented neutrophils.

Clinical features: more common in females and there may be a family history. It is associated with autoimmune conditions; the symptoms are similar to anaemia. We may see neurological problems such as parasthesiae [pins and needles]. May also get vitiligo which is hyper pigmentation – an autoimmune reaction against melanocytes [pigment cells] leading to discoloration of the skin. Patients may also have fatigue, glossitis and gait changes.

Diagnosis: parietal cell or intrinsic factor antibodies in the blood. May do a small bowel study.

Other causes of malabsorption:
- Jejunal diverticulosis. This is when pockets are made in the bowel and this allows bacteria to sit and ferment in them which cause irritation. This is fine in the large colon but not the small.
- Pneumatisis.
- Amyloid deposits may deposit in the gut and block absorption.
- Whipples disease caused by *Trophera whippei* which is a tropical infection. Causes inflammation of the bowel but can be treated with antibiotics.
- Pancreatitis: gall stones. Note this is mainly caused by alcohol. Insufficiency of the pancreas leads to malabsorption and can cause steatorrhea. The pancreas can function normally with as little as 10% functional state left. We can measure pancreatic function with fecal elastase and can be treated with pancreatic enzyme replacement.
C. difficile

This is the most common hospital infection. Typically occurs post antibiotic use as this clears the flora allowing the pathogen to thrive. This can cause pseudomembranous colitis [covers the mucus membrane]. It is a gram negative infection that can cause bacteremia.

Severe cramping can indicate inflammatory process. Quick time to onset suggests food poisoning.
Lecture 21: **Drugs and the GI Tract: Absorption and Availability**

**Pharmacokinetics:** what the body does to the drug. It is important to know this for many reasons.

1. It is important to know if a drug is going to be absorbed if given by a particular route. For example, if we give insulin orally we know it will be degraded because it is a protein.
2. We need to estimate accurate plasma concentrations of drug as a fraction of time. This is so we can dose correctly. We need to ensure that we give doses above the therapeutic level but below the adverse effect level [i.e. within the therapeutic window]. This can also ensure we dose at the right times so as to ensure our patients stay within the therapeutic window at all times.
3. To know where the drug goes once inside the body. For example, piriton for hay fever crosses the BBB. This is a H1 antagonist. This causes drowsiness. Now we have loratadine which doesn’t cross the BBB but still antagonizes H1 receptors.
4. Need to know the drug metabolites such as for paracetamol.

Major routes of administration:

**Enteral [GI Tract]**

*Oral* - This is easy but the first pass effect is something to consider [see later].

*Sublingual* - such as GTN for angina. This has a rapid effect but most drugs take to long or are not absorbed across this membrane.

*Rectal* - diazepen in status epilepticus. Absorbed by the lower tract. This is good if people are vomiting.

**Parenteral [not via GI Tract]**

*General*

*IV* - thiopentone. This is to lose consciousness within 10 seconds. But there is a risk of air emboli and bacteria induction.

*IM* - fluphenazine. This is anti-psychotic. This lasts for 6 weeks because it is put in an oil vehicle to allow slow release. This ensures compliance. Some drugs are absorbed quickly in muscles such as morphine, this is delivered in a aqueous vehicle to allow rapid effect.

*Subcutaneous* - insulin. This is easy to administer.

*Inhalation* - such as isoflurane to maintain anesthesia. This is easy to control.

*Intranasal* - increasing use. Such as arginine vasopressin.

**Local**

*Epidural* - bupivcaine in labor.
trapping. Weak acids include aspirin, warfarin and benzylpenicillin. Weak bases include atropine, morphine and erythromycin.

The dissociation of a weak acid is: \[[HA] \leftrightarrow [A^-] + [H^+]\] I.E. Looses a proton

Whilst a weak base is: \[[B] + [H^+] \leftrightarrow [BH^+]\] I.E. gains a proton

The equation relating pH, pKa and ratio of ionized/unionized drug is the Henderson-Hasselbalch equation, which is:

\[
pH = pKa + \log \left[ \frac{\text{BASE}}{\text{ACID}} \right]
\]

thus for a weak acid this becomes \(pH = pKa + \log \left[ \frac{\text{ionized}}{\text{unionized}} \right]\) or:

**Weak acid:** \(pH = pKa + \log(10) \left[ \frac{\text{ionized}}{\text{unionized}} \right]\)

**Weak base:** \(pH = pKa + \log(10) \left[ \frac{\text{unionized}}{\text{ionized}} \right]\)

Note we need to change the equation every time the drug enters a new pH. For example, when it moves from the stomach to the plasma. For example, aspirin in the stomach is mainly in unionized form, whilst in the plasma it is ionized. If the drug is ionized, it will cross the membrane. This means the drug will be absorbed from the stomach but not go back to the stomach.

Note if the value on the bottom of the ionized/unionized ratio is less than 1 we have more of whatever is at the bottom of this ratio [the value underneath so here more unionized – i.e. whatever we are dividing by].

Weak acids tend to be unionized in the stomach so can be absorbed.

Drug distribution is the penetration of drugs into tissues and organs from the blood. The degree of distribution often depends upon lipid solubility and tightness/extent of plasma protein binding. Drugs bound to albumin are not functional as can’t be up taken by tissues. This is measured with apparent volume distribution (Vd)- which is the volume of water in which drug would have to be distributed to give its plasma concentration or:

\[
Vd = \frac{\text{amount of drug in the body}}{\text{plasma concentration}}
\]

It is not easy to measure the amount of drug in the body as the body begins to excrete it as soon as it is absorbed. This value is expressed as a volume or volume / mass (litres per kg). warfarin and heparin have small Vd’s whilst Prozac has high. This is useful to know as it partly determines plasma half life of the drug and can be used to design dosing schedules.
Lecture 22: Drugs and the GI Tract: Drug Excretion

Excretion and metabolism of drugs together constitute elimination i.e. the removal of the drug from the body. Excretion occurs in the urine [from kidneys], milk, vomit and bile [where metabolites are often concentrated and fed down the GI tract. Note that can be reabsorbed by the GI system here]. Metabolism mainly occurs in the liver and metabolites are usually excreted in the urine. A notable exception is suxamethonium, which is metabolized in the plasma.

$T_{0.5}$ is the plasma half life of a drug, which is the time it takes for the $C_p$ [plasma concentration of drug] to fall to half its initial value. A low $T_{0.5}$ means that the body eliminates the drug quickly.

**Rate of elimination = clearance x $C_p$**

Or clearance = rate of elimination / plasma concentration

The units are volume / time e.g. ml min$^{-1}$

Clearance is equal to the amount of plasma which is cleared of its drug content in unit time. It is a useful measure since the rate of elimination of most drugs varies with plasma concentration, but clearance stays fairly constant. Consider the following situation of a drug where the Vd is 10,000 ml containing 10,000 mg of drug and clearance is 1,000 ml per min:

- At minute 1 1000ml is eliminated, so we loose 10% i.e. 1000mg is eliminated leaving 9000mg of drug behind. Thus the rate of elimination is 1000mg per min.
- At minute 2 we lose another 1000mg. Thus we lose another 10%. But this time its 10% of 9000mg so we lose 900mg. Thus the rate of elimination is now 900mg per min leaving 8100mg behind.
- At minute 3 we lose another 1000ml meaning the rate of elimination is now 810mg per min.

Thus the rate of elimination changes with concentration [highest at high concentrations] but clearance remains constant. Thus, clearance is easier to use.

Drug elimination can be of different orders:
of which comes from aspartate and the other from glutamate. Urea is a small non toxic compound that can be excreted.

**Urea Cycle**

The glutamate and glutamine feed into the cycle to produce ammonia and bicarbonates. Carbamoyl phosphate synthase then makes carbamoyl phosphate, which is the rate limiting step. This feeds into the cycle by combining with ornithine. Aspartate feeds into the cycle later. The cycle produces urea and regenerates ornithine which acts as the carrier molecule for nitrogen. Genetic defects in the cycle are rare but lead to Hyperammonaemia which causes mental retardation due to the build up of ammonia.

The periportal cells have high amounts of urea cycle activity. But some free ammonia will escape these cells. This is washed down to the perivenous cells. These cells have a large capacity to synthesise glutamine. This is fed to the kidneys. There are two isoenzyme of glutaminikinase. 1 is found in the kidney and one in the liver. In the kidney this breaks down glutamine to produce ammonia. This ammonia can then be directly excreted as it does not re-enter the circulation but instead passes to the bladder. In the liver however the enzyme makes N-acetylglutamate. This is an allosteric activator of the urea cycle by acting on carbamoyl phosphate [the rate limiting step].

**Liver and pH Homeostasis**

Urea synthesis is inhibited by acidosis. Urea synthesis uses bicarbonate and so when the body is acidic it is useful to stop the urea cycle. Glutamine synthase is stimulated by acidosis however. This is because more ammonium is escaping the periportal cells and washing down the perivenous cells. Glutaminase is regulated by pH. Liver enzyme is inhibited by acidosis to stop the urea cycle. The kidney version is activated by acidosis to promote glutamine breakdown and release of ammonia for secretion and generate bicarbonate. Glutamine breakdown will produce bicarbonate in the kidney. So in acidosis we slow the urea cycle to persevere bicarbonate and stop the production of hydrogen ions, which occurs in the cycle.

**Bilirubin Metabolism**

Heamoglobin and other heam compounds need to be broken down. They are complex as they are prosthetic. They are broken down by the reciculodenothelial system in the spleen. This make bilirubin. This is hydrophobic and so must bind to albumin to be transported in the blood. The bilirubin enters the liver where it is conjugated by enzymes on the ER. This helps to increase the solubility. A key enzyme is UDP-Glucuronyl transferase. This forms bilirubin-glucuronide. This is exported via the bile duct and converted to urobilinogen, urobilins and final stercolins by gut bacteria. Stercolins give feces its brown colour. Note some urobilinogen is reabsorbed by the entero-hepatic circulation and is excreted in the urine as urobilin, which gives the yellow colour to urine.

The build up of bilirubin causes jaundice. it is yellow and causes discoloration of the eyes and skin when above 35um. Hepatic jaundice may be the result of reduction of liver bilirubin
Truelove and Witts set out criteria, grading the severity of the disease. It accounts for the number of bloody stools a day, temperature, heart rate, haemoglobin and ESR. We can also use criteria, such as the Lennard-jones system to predict the likelihood of colectomy.

Mortality is about 1.5% from UC which is higher than Crohn’s. This is high for a young person, non malignant condition.

Treatment: steroids, Cyclosporin A/infliximab, surgery and azathioprines. Azathioprines are long term oral drugs, but they take at least 6 weeks to work. We use cyclosporins or infliximab for severe patients.

Steroids are effective but have systemic severe side effects.

Ciclosporin is affective but not in the long term. It also has side effects- especially renal toxicity, BP and infection risk. Infliximab is preferred as it can be used long term and has less side effects.

Surgery removes the whole large bowel. This needs a ileostomy bag which will fill with liquid. We can now do a ileoanal pouch to make a rectum like structure. But the bowels will still open 6-8 a day, pouchitis can occur and there is malignancy risk at the anal margin. Some patients choose to go back to the ileostomy bag.

Mortality before steroid use was 75%.

For milder states we can use other medication such as the 5 ASAs which belong to the class mesalazine. They have a fairly flat dose response curve but oral therapies can work. Higher dose may bring about earlier remission. Once daily therapy is effective. Those will left sided restricted disease tend to do well on these medications.

Suppositories are used for proctitis [when disease it at the bottom end of the colon only]. We use enemas for disease extending beyond the rectum but not past the splenic flexure. Consider dual topical therapy of suppositories and enemas of different drugs.

For mild-moderate UC there is a limited dose response to 5-ASA therapy in outcomes, though response is quicker with higher doses. Topical therapy is effective for left disease disease. Combination improves remission rate and rate of recovery (e.g. for bleeding).

For poorly controlled disease [such as if they have needed 3 or more steroids this year] we used immunomodulators such as azathioprine. These have side effects and require blood monitoring. These drugs take a long time to take affect [6 weeks – 3 months].

Thus 10% of patients have severe UC. 80% of people respond to steroids but consider 2nd line agents. Combination therapy works best.

Inflammatory bowel disease can present in kids and tends to have more severe presentations. A problem is that many medications have restricted licensing in children.
passes into the urine making it dark. The conjugated form is normally metabolised by gut bacteria, and so when the bile duct is blocked this doesn’t happen and so we get pale stools [the dark colour of stools is caused by one the metabolites].

<table>
<thead>
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<th>Symptoms</th>
<th>Unconjugated</th>
<th>Conjugated</th>
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<tbody>
<tr>
<td>Dark urine</td>
<td>No</td>
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</tr>
<tr>
<td>Pale stools</td>
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<td>Yes</td>
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<td>Cause kernicterus?</td>
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<td>Yes</td>
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<td>Pathological in neonates?</td>
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</tbody>
</table>

If the conjugated form is in excess, it can cross the BBB and thus cause kernicterus (damaging the brain). Unconjugated forms can’t enter the brain as they are not water soluble so can’t cross the BBB.

Traumatic births can lead to extensive hematomas [bruises]. As these are metabolised [hemolysis] we can see a rise in bilirubin leading to jaundice.

Gilbert’s syndrome is when there is a problem with the conjugating enzymes. You are fine most of the time but if you face a stress [such as illness] when patients may go jaundice. It can also be a problem if you are on drugs that could affect liver function; we need to know about the disease to be sure its not the drugs causing the jaundice. Now there is genetic testing for this reason.

With cancers the profile tends to get worse over time: i.e. if obstructing the biliary tree then we see worsening of results as this wont clear.

Note with ALP we can do electrophoresis to determine the isoenzyme make up; i.e. can see if the liver of bone enzyme forms is raised. This can help us determine disease type.

Example Cases

See overleaf.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Bilirubin</th>
<th>Enzymes</th>
<th>Other results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert’s</td>
<td>↑↑</td>
<td>Normal</td>
<td>Genetic tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[unconjugated]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal Jaundice</td>
<td>↑↑</td>
<td>Age specific</td>
<td>Split bilirubin (ratio of unconjugated to conjugated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[conjugated usually]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary Spherocytosis</td>
<td>↑↑</td>
<td>Normal</td>
<td></td>
<td>This is when blood is sphere shaped and fragile</td>
</tr>
<tr>
<td></td>
<td>[unconjugated]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>↑↑</td>
<td>Deranged (ALP at first)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[conjugated]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer in Head of Pancreas</td>
<td>↑↑</td>
<td>Deranged (ALP at first)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[conjugated]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Hepatitis</td>
<td>↑↑</td>
<td>Deranged ALP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[unconjugated]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Normal</td>
<td>Deranged ALP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deranged LFT with No Liver Disease</td>
<td>Normal</td>
<td>ALP rise – is it from bone?</td>
<td>Do YGT to see if bone or liver.</td>
<td></td>
</tr>
<tr>
<td>Alcohol Abuse</td>
<td>Normal</td>
<td>May be deranged: ALT and or AST:ALT ratio</td>
<td>YGT will be raised</td>
<td>Cirrhosis will cause a rise in enzymes but not fatty liver. AST:ALT ratio raised.</td>
</tr>
</tbody>
</table>