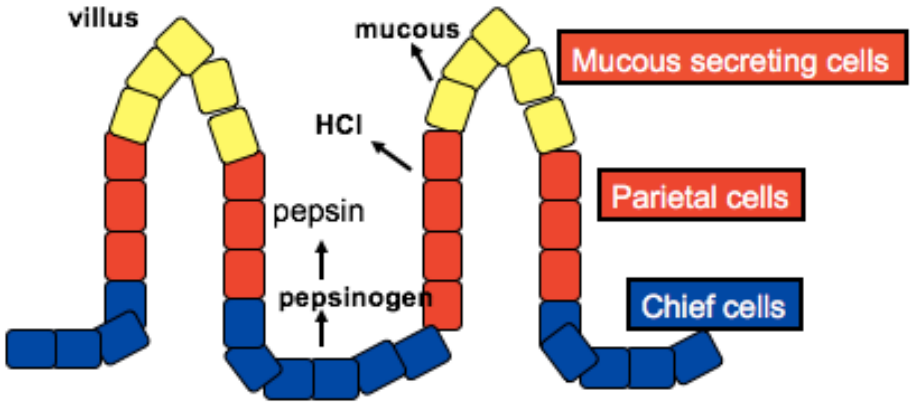
Module 3: Drug Treatment of Allergy and Gut Disorders

Gastrointestinal Drugs

The blood vessel and the glands that comprise the GIT are under both neuronal and hormonal control. There are two principal intramural plexuses in the tract: the **myenteric plexus**, which lies between the outer longitudinal and middle circular muscle layers, and the **submucosal plexus** on the luminal side of the circular muscle layer.

- Plexuses are interconnected – their ganglion cells receive preganglionic parasympathetic fibres from the vagus, which are mostly cholinergic and excitatory. Incoming sympathetic fibres are mostly postganglionic.
- Neurons within the plexuses constitute the **enteric nervous system**, and secrete ACh as well as NA.
- Plexuses also contain sensory neurons, which respond to mechanical and chemical stimuli.
- The endocrine secretions involved in the GIT are mainly peptides synthesised by endocrine cells in the mucosa, including gastrin and cholecystokinin.



The stomach secretes approximately 2.5 litres of gastric juice daily. The principal exocrine components are proenzymes such as **prorennin** and **pepsinogen** (produced by the chief or peptic cells), and **HCl** and **intrinsic factor** (secreted by the parietal cells).

- Acid production promotes proteolytic digestion of food, iron absorption, and pathogen killing.
- Mucus-secreting cells also lie among the surface cells of the gastric mucosa. Bicarbonate ions are secreted and trapped in the mucus, creating a gel-like protective barrier that maintains the mucosal surface at a pH of 6-7 i.e. protects from acid.
- HCl and intrinsic factor are important to denaturing the food proteins that enter the GIT by exposing their bonds for degradation.
- Pepsinogen is transformed into **pepsin**, which is involved in the degradation of proteins into peptides.

Regulation of Acid Secretion by Parietal Cells

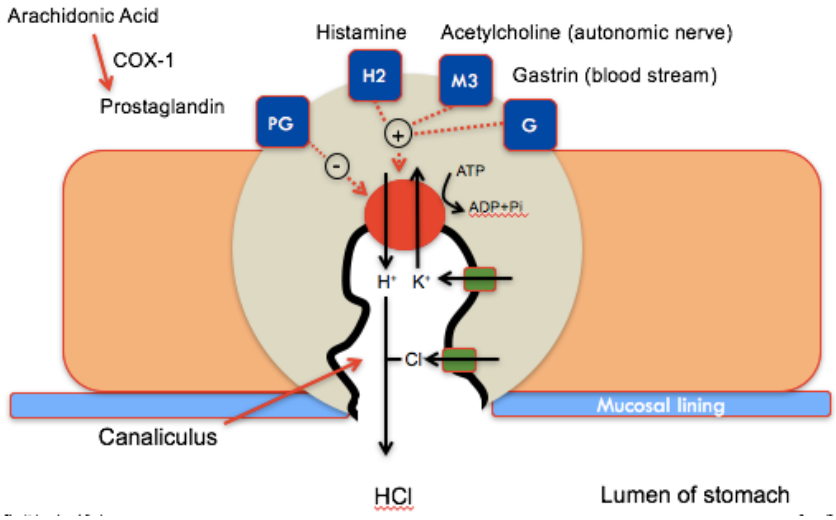
The regulation of acid secretion is important in the pathogenesis of **peptic ulcers**, and constitutes a particular target for drug action.

- The secretion of the parietal cells is an isotonic solution of HCl, with a pH less than 1. The Cl^- is actively transported into **canaliculi** (invagination in the parietal cell), which communicate with the lumen of the gastric glands.
- This Cl^- secretion is accompanied by K^+, which is then exchanged for H^+ from within the cell by K^+-H^+-ATPase. Carbonic anhydrase catalyses the combination of carbon dioxide and water to give carbonic acid, which dissociates into H^+ and bicarbonate ions.
- The bicarbonate ions exchange across the basal membrane of the parietal cell for Cl^-.
- Essentially: the proton pump pumps proteins from the cytoplasm into the canaliculus via counter-transport of potassium from the extracellular environment, back into the cell. Potassium is then

pumped out by potassium channels (driven by hydrolysis of ATP to ADP). For every proton that is pumped out, a Cl^- is also pumped out.

Mediators of parietal cell output:

- **Prostaglandin R** – lipid molecule produced by metabolism of arachidonic acid by COX-1. This inhibits the proton pump and facilitates mucus production i.e. turns off acid secretion.
- **Histamine** – the enterochromaffin-like cells that lie close to the parietal cells sustain a steady basal release of histamine. Histamines acts on parietal cell H1 receptors to increase intracellular cAMP.
- **Gastrin R** – stimulation of acid secretion by ECL cells via gastrin receptors, and elevate intracellular Ca2+. Gastrin also stimulates histamine synthesis and indirectly increases pepsinogen secretion.
- **ACh** – stimulates muscarinic M3 receptors on the surface of parietal cells, elevating intracellular Ca2+ and stimulating proton release.
- Histamine, ACh and gastrin therefore all stimulate the proton pump.



Pathological Conditions Involving the GIT

Dyspepsia i.e. indigestion is characterised by upper abdominal pain or discomfort – this can be explained by insufficient tone within the lower oesophageal sphincter, which leads to acid regurgitation and heartburn. Symptoms can be unspecific, and may or may not therefore indicate underlying pathophysiology.

Peptic ulcers are localised erosions of the mucosal membrane in the stomach or duodenum. Pain is caused by the irritation of the exposed surface to stomach acid; this can lead to bleeding and death. Causes of dyspepsia and peptic ulceration:

- Use of **NSAIDs** (aspirin, ibruprofen, naproxen, diclofenac or indomethacin) – these drugs stop the metabolism of arachidonic acid into prostaglandins by inhibiting COX-1 action.
    - This therefore inhibits effective functioning of the proton pump, reducing mucus production and leading to a thinner mucosal lining which is susceptible to acid attack.
    - Treatment involves using an alternative to NSAIDs, or utilising a prostaglandin E2 analogue (**misoprostol**) to increase mucus and bicarbonate secretion and inhibit acid secretion.
- Helicobacter pylori (gram negative bacillus) – live in the protective mucosal lining close to the cell surface. It transforms the cells such that there is less mucus production, elevated acid secretion and therefore ulcer formation.

Treatments for dyspepsia are targeted at reducing acid production, and therefore reducing the pain and discomfort of irritation caused by acid regurgitation and ulcer formation.

1. H2 receptor antagonists (**cimetidine**, **ranitidine**) – both only bind specifically to H2Rs.
    - Ranitidine has longer-lasting action, and 10 times the intrinsic activity of cimetidine, as well as fewer adverse reactions.

- This is because it has 10% of the affinity of cimetidine for CYP450, leading to fewer drug interactions.
- These drugs block stimulation of the proton pump by inhibiting the stimulatory action of histamine, and may reduce acid production by up to 90%.

2. Proton pump inhibitors (**omeprazole**, **pantoprazole**, **rabeprazole**, **lansoprazole**) – similar mechanisms of action, but differ in their stability and reactivity.

- Omeprazole is an inactive pro-drug in normal physiological conditions, and is only activated in the low pH of the stomach. This property allows it to pass through various membranes until it reaches the stomach.
- In its active state, omeprazole can form covalent bonds with cysteine residues of the proton pump i.e. it is an irreversible inhibitor of the proton pump.
- Essentially, PPIs are administered orally and absorbed into the bloodstream; they do not demonstrate pharmacological activity until they pass into the canaliculus of the parietal cells. They accumulate in the canaliculus after activation, because the charged form can no longer cross back into the cell.
- Only activated when parietal cells are actively secreting acid i.e. inactive between meals. They are also highly selective for the proton pumps of parietal cells in the stomach, leaving them relatively free of side-effects.

Treatment of H pylori infections involves therapy of a PPI and two antibiotics from: **metronidazole**, **clarithromycin**, **amoxicillin**, and **tetracycline**. This combination: (i) reduces acid production and allows the ulcer to heal (PPI); and (ii) restores optimal pH for antibiotic activity to kill the bacteria. Bismuth chelate may also be added, as it is toxic to bacteria.