Digestion and Digestive Secretion from Mouth and Stomach

**The Mouth**

**Ingestion:** In the mouth food is ground, moistened and lubricated by saliva (secreted by three pairs of salivary glands).

**Digestion:** Salivary glands secrete α-amylase, which digests starch into small segments of α-dextrins and into individual soluble sugars. Salivary glands also secrete lysozyme, which kills bacteria but is not classified as a digestive enzyme.

Then the resulting bolus of food is swallowed into the esophagus and carried by peristalsis to the stomach.

**The Stomach**

Foodstuffs entering the stomach have been, crushed and reduced in size by mastication, with saliva. The stomach provides four basic functions that assist in the early stages of digestion and prepare the ingesta for further processing in the small intestine:

1. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly and dealt with over an extended period.

2. It is in the stomach that substantial chemical and enzymatic digestion is initiated, particularly of proteins.

3. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food, a prerequisite for delivery of the ingesta to the small intestine.

4. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing.

The wall of the stomach is lined with millions of gastric glands (appearing as gastric pits extended into the mucosa as straight and branched tubules) which together secrete 400–800 ml of gastric juice at each meal. Several kinds of cells are found in the gastric glands.
Four major types of secretory epithelial cells cover the surface of the stomach and extend down into gastric pits and glands:

1. **Mucous cells**: secrete an alkaline mucus that protects the epithelium against shear stress and acid.
2. **Parietal cells**: secrete hydrochloric acid.
3. **Chief cells**: secrete pepsin, a proteolytic enzyme.
4. **G cells**: secrete the hormone gastrin.
Gastric secretions

1. Mucosal Protection

Mucus layer on gastric surface forms a mucosal barrier to damage against several forms of potential injury to the gastric mucosa.

1. A gel 0.2mm thick; 80% CHO; 20% protein
2. Secreted by neck cells, surface epithelium
3. Can be cleaved by pepsin, so continual production is required
4. Release is stimulated by acetylcholine from nerve endings
5. Also rich in bicarbonate
   a. $\text{HCO}_3^-$ content creates a "micro-environment" around surface cells to prevent acid damage
   b. $\text{HCO}_3^-$ secretion is inhibited by adrenergic input (prominent in stress)

2. Acid Secretion

Hydrochloric acid is secreted from parietal cells into the lumen where it establishes an extremely acidic environment. This acid is important for activation of pepsinogen and inactivation of ingested microorganisms such as bacteria.

2.1. Function of Gastric acid

1. To kill micro-organisms: (but H. pylori survives by making ammonia (basic) from urea using urease).
2. to provide the optimal pH for pepsin action
3. to activate pepsinogens (cleaved to form pepsin)
4. Facilitating absorption of iron by converting colloidal iron into ionic form.
5. stimulating duodenum to liberate secretin
6. breaks down connective tissue in food
2.2. Mechanism of gastric acid secretion

- The parietal cells of gastric glands are capable of secreting HCl into the gastric lumen.
- Luminal $H^+$ concentrations of up to 0.14 M (pH 0.8) have been observed.

As the plasma pH = 7.4, the parietal cell transports protons against a concentration gradient of $10^{6.6}$. The free energy required for HCl secretion under these conditions is minimally 9.1 kcal mol$^{-1}$ of HCl (= 38 J mol$^{-1}$ of HCl). That is why parietal cells are stuffed with mitochondria and uses huge amounts of energy as they carry out this three-million fold concentration of protons.

Acid secretion mechanisms in the parietal cell
The key player in acid secretion is a H+/K+ ATPase or "proton pump" located in the cannalicular membrane. This ATPase is magnesium-dependent. This enzyme is unique to the parietal cell and is found only in the luminal region of the plasma membrane. It couples the hydrolysis of ATP to an electrically neutral obligatory exchange of $K^+$ for $H^+$, secreting $H^+$ and taking $K^+$ into the cell.

As the $K^+/H^+$ATPase generates a very acidic solution, protein reagents that are activated by acid can become specific inhibitors of this enzyme. This fact is a key in most drugs used to treat peptic ulcers.

The current model for explaining acid secretion is as follows:

- Hydrogen ions are generated within the parietal cell from dissociation of water. The hydroxyl ions formed in this process rapidly combine with carbon dioxide to form bicarbonate ion, a reaction catalyzed by carbonic anhydrase.

- Bicarbonate is transported out of the basolateral membrane in exchange for chloride. The outflow of bicarbonate into blood results in a slight elevation of blood pH known as the "alkaline tide". This process serves to maintain intracellular pH in the parietal cell.

- Chloride and potassium ions are transported into the lumen of the cannaliculus by conductance channels, and such is necessary for secretion of acid.

  Hydrogen ion is pumped out of the cell, into the lumen, in exchange for potassium through the action of the proton pump; potassium is thus effectively recycled.
2.3. Control of gastric acid secretion

Parietal cells bear receptors for three stimulators of acid secretion, reflecting a neural, paracrine and endocrine control:

- **ACETYLCHOLINE**
  - released from cholinergic nerve fibres
  - binds to (M3) receptor on cell surface
  - opens Ca\(^{++}\) channels in apical surface
  - promotes release of Ca\(^{++}\) from intracellular stores

- **GASTRIN**
  - binds to CCK-B receptor on cell surface
  - releases intracellular Ca\(^{++}\)

- **HISTAMINE**
  - released from mast cells
  - binds to parietal cell surface receptor
  - activates adenyl cyclase (increases cyclic AMP, an intracellular messenger)
Histamine's effect on the parietal cell is to activate adenylate cyclase, leading to elevation of intracellular cyclic AMP concentrations and activation of protein kinase A (PKA). One effect of PKA activation is phosphorylation of cytoskeletal proteins involved in transport of the H+/K+ ATPase from cytoplasm to plasma membrane. Binding of acetylcholine and gastrin both result in elevation of intracellular calcium concentrations.

**INHIBITORY CONTROL**

- acid at less than pH 2 is a direct inhibitor of acid release
- acid in duodenum releases secretin which inhibits gastric secretion
  - fatty acids, peptides stimulate release of GIF (gastric inhibitory polypeptide) and CCK (cholecystokinin)

Several additional mediators have been shown to result in gastric acid secretion when infused into animals and people, including e.g. calcium. Calcium simulates gastrin release. It is unclear whether these molecules have a significant physiologic role in parietal cell function.

**Alkaline tide during gastric secretion:** Owing to secretion of a large amount of H⁺ as HCl, there is surplus of OH⁻ in the parietal cell which is taken up not only by the CO₂ to form HCO₃⁻ but also by other buffer systems of parietal cell initially and later by those of plasma.

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\begin{align*}
\frac{HPO_4^{-2}}{H_2PO_4^-} & \quad \frac{HCO_3^-}{H_2CO_3^-} & \quad \text{Lactate} \\
& \quad \text{Lactic acid}
\end{align*}
\]

All tend to increase on the side of the base i.e.:\(\frac{HPO_4^{-2}}{H_2PO_4^-}\), \(\frac{HCO_3^-}{H_2CO_3^-}\) and lactate, with the result that the pH of plasma is raised and an alkaline urine is excreted for some hours following intake of food and gastric secretion. This is known as the alkaline tide.
3. Proteases:

Pepsinogen, an inactive zymogen, is secreted into gastric juice from both mucous cells and chief cells. Once secreted, pepsinogen is activated by stomach acid into the active protease pepsin, which is largely responsible for the stomach’s ability to initiate digestion of proteins, in young animals; chief cells also secrete chymosin (rennin), a protease that coagulates milk protein allowing it to be retained more than briefly in the stomach.

Pepsinogens and Pepsins

Pepsinogens are secreted in a form such that the activation peptide assumes a compact structure that occludes the active site. On exposure to an acidic (pH < 4) environment such as occurs in the lumen of the stomach, the activation peptide unfolds, allowing the active site to clip it off, yielding mature, catalytically active pepsin.

Optimal activity of pepsins is at pH of 1.8 to 3.5, depending on the isoform, They are reversibly inactivated at about pH 5 and irreversibly inactivated at pH 7 to 8.

The mature, active enzymes are roughly 325 amino acids with a mass of approximately 35 kDa.

Pepsin initiates protein digestion by splitting certain amino acid linkages in proteins (Cleaves preferentially C-terminal. It does not cleave at V, A or G. Other residues may be cleaved, with very variable rates) to yield peptide fragments.

Because pepsin can digest protein, it must be stored and secreted in an inactive form so that it does not digest the cells in which it is formed.
In general, secretion of pepsinogens is coupled to secretion of acid from the parietal cell. In vitro studies have demonstrated that secretion is effectively stimulated by agents that stimulate either of two conditions:

1. Elevated intracellular levels of cyclic AMP: examples include secretin, vasoactive intestinal peptide and epinephrine.
2. Elevated intracellular calcium: the principal mediators investigated include acetylcholine and peptides of the gastrin/cholecystokinin family

Pepsin was discovered by Theodor Schwann in 1836. It was the first animal enzyme to be discovered.

Chymosin (Rennin) and the Coagulation of Milk

Chymosin, known also as rennin, is a proteolytic enzyme synthesized by chief cells in the stomach. Its role in digestion is to coagulate milk in the stomach, a process of considerable importance in the very young animal. If milk were not coagulated, it would rapidly flow through the stomach and miss the opportunity for initial digestion of its proteins.

Chymosin efficiently converts liquid milk to a semisolid like cottage cheese, allowing it to be retained for longer periods in the stomach. Chymosin secretion is maximal during the first few days after birth, and declines thereafter, replaced in effect by secretion of pepsin as the major gastric protease.

Chymosin is secreted as an inactive proenzyme called prochymosin that, like pepsin, is activated on exposure to acid. Chymosin is also similar to pepsin in being most active in acidic environments, which makes sense considering its mission.
4. Hormones

The principle hormone secreted from the gastric epithelium is gastrin, a peptide that is important in control of acid secretion and gastric motility. Gastrin is secreted by G-cells and released into the blood where it travels to the parietal cells to stimulate acid secretion, and to Enterochromaffin-Like (ECL) Cells to stimulate histamine secretion.

The net result of gastrin secretion is increased acid production through two mechanisms:
1. Direct stimulation of the parietal cells,
2. Tropic action on parietal cells increasing their number.

N.B. in gastrinoma (Zollinger-Ellison syndrome) increased production of gastrin causes hypersecretion of acid which is not subject to normal inhibitory mechanisms.

A number of other enzymes are secreted by gastric epithelial cells, including a lipase and gelatinase. One secretory product of considerable importance in man is intrinsic factor, a glycoprotein secreted by parietal cells that is necessary for intestinal absorption of vitamin B₁₂.

**Intrinsic Factor**

Intrinsic factor is a glycoprotein secreted by parietal (humans) of the gastric mucosa. In humans, it has an important role in the absorption of vitamin B₁₂ (cobalamin) in the intestine, and failure to produce or utilize intrinsic factor results in the condition pernicious anemia.— as a result of an autoimmune attack against parietal cells. In all mammals, vitamin B₁₂ is necessary for maturation of erythrocytes, and a deficiency of this vitamin leads to development of anemia. Since efficient absorption of vitamin B₁₂ in humans depends on intrinsic factor, diseases which decrease the secretion of intrinsic factor (e.g. atrophic gastritis), interfere with cleavage of the binding proteins (e.g. pancreatic exocrine insufficiency) or decrease binding and absorption of the intrinsic factor-vitamin B₁₂ complex (e.g. ileal disease or resection) can result in this type of anemia.
Absorption in the Stomach

The stomach absorbs very few substances, although small amounts of certain lipid-soluble compounds can be taken up, including aspirin, other non-steroidal anti-inflammatory drugs, and ethanol.

Notably, these substances are also well-recognized causes of gastric irritation and their use (especially overuse) is commonly associated with development of gastritis and gastric ulcers.