Salivary Glands
Esophagus
Stomach
1. An understanding of the physiologic role of salivary glands, the esophagus, and the stomach.
2. An understanding of the physiologic defects in esophageal reflux and dysmotility.
3. An understanding of how our knowledge of gastric physiology is exploited in the therapy of gastric disorders.
4. An understanding of the mechanisms underlying the treatment of peptic diseases.

Salivary gland; esophagus; stomach; antacids
Secretry

Absorptive
Salivary Glands

- Gross anatomy
  - parotid
  - submandibular
  - sublingual

- Histology
  - serous
  - mucus
  - mixed
Salivary Gland Functions

- Lubrication
  - Swallowing
  - Speech
  - Prevention of dental caries
- Digestion
• Secretory Products (1,500 mls/day)
  ◦ Amylase
  ◦ Lipase
  ◦ Mucin
  ◦ Growth factors
    • Nerve growth factor
    • EGF
  ◦ Fluid and electrolytes
End-pieces

Amylase-containing
PRIMARY SECRETION
(nearly isotonic; levels of Na⁺, K⁺, Cl⁻ and [probably] HCO₃⁻ similar to plasma)

Modication of ionic content

Striated and excretory ducts

Na⁺
K⁺
Cl⁻
HCO₃⁻
Adapted from Am J Physiol 178:155 (1954)
Regulation of Secretion

Regulation is via both the sympathetic and parasympathetic nervous systems
Achalasia

- Loss of primary peristalsis
- Elevated lower esophageal sphincter pressures
Spastic Esophagus
Endoscopic Photograph Showing Traditional, or Long-Segment, Barrett's Esophagus

Enteroendocrine cells - Ghrelin

- Esophagus
- Cardia
- Lesser curvature
- Duodenum
- Pylorus
- Antrum (Gastrin)
- Fundus
- Body
  - Parietal cells:
    - HCl
  - Intrinsic factor
  - Chief cells:
    - Pepsinogen
  - Greater curvature
  - Enteroendocrine cells - Ghrelin
Stomach Anatomy

- **Cardia**
  - mucus cells

- **Fundus and Body**
  - mucus cells
  - parietal cells
    - acid secretion and intrinsic factor
  - chief cells
    - Pepsiniogen
  - enteroendocrine cells
    - ghrelin

- **Antrum**
  - mucus
  - enteroendocrine cells
    - gastrin, somatostatin
Gastric Functions

- **Storage**
- Mechanical breakdown of food
- Exocrine secretion (~2,500 mls/day)
  - Acid
  - Pepsinogen
  - Intrinsic Factor
- Endocrine secretion
  - Gastrin
  - Ghrelin
Receptive Relaxation

- Stomach exhibits high compliance
  - 1.5 L of air results in an increase of 10 mm Hg in intraluminal pressure
- Dependent upon the vagus nerve
  - Non-adrenergic, non-cholinergic control
  - Dependent on nitric oxide
Gastric Functions

- Storage
- **Mechanical breakdown of food**
- Exocrine secretion (~2,500 mls/day)
  - Acid
  - Pepsinogen
  - Intrinsic Factor
- Endocrine secretion
  - Gastrin
  - Ghrelin
300 ml starting volume
Gastric Functions

- Storage
- Mechanical breakdown of food
- Exocrine secretion (~2,500 mls/day)
  - Acid
  - Pepsinogen
  - Intrinsic Factor
- Endocrine secretion
  - Gastrin
  - Ghrelin
Acid Secretion

- No acid, no ulcers
- Peptic ulcer disease affects up to 10% of the population
H⁺-K⁺:ATPase

- Expressed by parietal cells
- Intraluminal pH = 0.8
- Cytosolic pH = 7.3
- Proton gradient = 2,400,000
\[ E = E_0 - \left( \frac{0.05915}{z} \right) \log \left( \frac{[\text{red}]}{[\text{ox}]} \right) \]
Enzyme requirements

- ATP
  - 1 ATP > 2 H⁺
- Potassium
  - Required on the luminal side
- Hydrogen
  - Produced via carbonic anhydrase
Figure 26–8. Composite diagram of a parietal cell, showing the resting state (lower left) and the active state (upper right). The resting cell has intracellular canaliculi (IC), which open on the apical membrane of the cell, and many tubulovesicular structures (TV) in the cytoplasm. When the cell is activated, the TVs fuse with the cell membrane and microvilli (MV) project into the canaliculi, so the cell membrane in contact with gastric lumen is greatly increased. M, mitochondrion; G, Golgi apparatus. (Reproduced, with permission, from Junqueira LC, Carneiro J, Kelley RO: Basic Histology, 7th ed. Appleton & Lange, 1992.)
Light (A,B) and electron (C-E) micrographs of isolated rabbit gastric glands stimulated with histamine for 30 min

Fundus

Intrinsic factor

Parietal cells

HCl

Body

Chief cells

Antrum

G cells

gastrin

G cells

gastrin

pepsinogen

Parietal cells

HCl

Chief cells

Antrum

G cells

gastrin

Fundus

Intrinsic factor

Parietal cells

HCl

Body

Chief cells

Antrum

G cells

gastrin

G cells

gastrin

pepsinogen
Regulation of Acid Secretion

- Acetylcholine - vagal input
- Gastrin - G cells
  - pH > 3, amino acids Phe, Trp
- Histamine
- Inhibition of any one pathway will also significantly affect stimulation by other agents.
Ach  
Muscarinic Receptor  
Atropine  
IP$_3$, Ca$^{2+}$  
H$^+$ secretion  
Omeprazole  
(inhibits H$^+/K^+$ ATPase)

Histamine  
H$_2$ receptor  
Cimetidine  
cAMP  

Gastrin  
IP$_3$, Ca$^{2+}$

H$^+$ secretion
Why doesn't the stomach digest itself?

Protecting the Earth from asteroids
Resistance to severe malaria
Closed cages without carbon

Microscopy product review
Aspirin/NSAID ulcers

- Increase risk of ulcers with aspirin or NSAID (non-steroidal antiinflammatory drugs)
  - Mechanism of action may include the inhibition of prostaglandin synthesis, which normally promotes mucus production.
  - Analogs of prostaglandin E (misoprostil) are used to reduce the incidence of NSAID ulcers. Acid inhibition is more commonly used now.
Gastric Exocrine Protein Secretion

- Mucus - lubrication and mucosal protection
- Intrinsic factor - binding and absorption of vitamin B12. Produced by the same cells (parietal cells) that secrete acid.
- Pepsinogen - activated by acid to pepsin, an endoprotease. Produced by the chief cells.
Vitamin B12

- Methylation-facilitates 1-carbon transfers
  - conversion of homocysteine to methionine
- Intramolecular rearrangement
  - isomerization of methylmalonyl coenzyme A to succinyl CoA
• Intrinsic Factor represents the only major essential factor produced by the stomach
  ◦ Intrinsic Factor is essential for vitamin B12 absorption.
  ◦ Patients who undergo a gastrectomy must have vitamin B12 replaced.
    • Deficiency results in CNS and peripheral neuropathic problems, megaloblastic anemia, etc.
Pepsinogen

- Secreted by the chief cells as an inactive proprotein.
- Activated by cleavage in an acid environment.
- Cleaves at aromatic amino acids.
Gastric Endocrine Protein Secretion

- Gastrin
- Ghrelin
Ulcer Disease Therapy

Ulcers occur only in the presence of acid
Oral Antiacids

- Advantages of the oral antacids include their low cost, rapid onset of action and absence of systemic adverse reactions. Disadvantages include that short duration of beneficial effects
Oral Antacids

- Sodium bicarbonate (baking soda, Alka Seltzer)
- Calcium carbonate (Tums, Os-Cal)
- Magnesium hydroxide (Mylanta)
  - side effects: diarrhea
- Aluminum Hydroxide
  - side effects: constipation
Anticholinergics

- Inhibit neural stimulation of acid secretion
- High incidence of side effects
**Table 51-1. PERCENTAGE OF PATIENTS WITH SYMPTOMS REFERABLE TO THE ALIMENTARY TRACT AFTER OPERATION**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Vagotomy and Gastroenterostomy n=122</th>
<th>Vagotomy and Antrectomy n=126</th>
<th>Subtotal Gastrectomy n=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric fullness</td>
<td>37</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>Early dumping</td>
<td>12</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Late dumping</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Food vomiting</td>
<td>5</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Bile vomiting</td>
<td>11</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Heartburn</td>
<td>17</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Flatulence</td>
<td>18</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>21</td>
<td>11</td>
</tr>
</tbody>
</table>

H2 receptor antagonist

- imidazole ring - related to histamine
- Competitive antagonists for histamine
- Rapidly absorbed with peak levels in 90min. Not protein bound.
- $T_{1/2} = 4$-$12$ hours depending on formulation
- Excreted largely in the urine, which requires dosage adjustments in renal failure
Cimetidine

• Adverse reactions
  ◦ Anti-androgenic effects: gynecomastia
  ◦ Diarrhea, headache, dizziness
  ◦ inhibits the hepatic cytochrome P450 such that the half-life of warfarin-containing anticoagulants, phenytoin, propranolol, nifedipine, and others may be longer
Figure 37-3. Inhibitors of the gastric \( \text{H}^+\cdot\text{K}^-\cdot\text{ATPase} \).

A. Structures of lansoprazole and omeprazole. B. Mechanism of irreversible inhibition of \( \text{H}^+\cdot\text{K}^-\cdot\text{ATPase} \) by pump inhibitors. In the acidic environment of the parietal cell canaliculi, these “pro-drugs” are converted to sulfinamides that interact covalently with sulphydryl groups in the extracellular thiol-rich domain of the proton pumps.
Stimulation
PPI - Omeprazole

- Covalently binds to the pump in low pH
- First pass effect in the liver after intestinal absorption
  - Excreted in the urine (70%) and feces
- Few significant adverse reactions
  - Elevated risk of osteoporosis with chronic use.
Press Release: The 2005 Nobel Prize in Physiology or Medicine

3 October 2005

The Nobel Assembly at Karolinska Institutet has today decided to award

The Nobel Prize in Physiology or Medicine for 2005

jointly to

Barry J. Marshall and J. Robin Warren

for their discovery of

"the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease"